Overview

Auditory Sensing Systems: Overview

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Detailed Description

This second edition of the Encyclopedia of Computational Neuroscience includes updates to the first edition's entries based on new findings in the field, and publishes several new reviews on recent topics of interest and modelling techniques for the study of auditory sensing systems. We thank the authors for their willingness to contribute to this section and thus provide a rich scientific resource on auditory neuroscience, for young and senior researchers alike.

Auditory sensing, or the sense of hearing, is concerned with detecting and extracting information from pressure waves in the surrounding medium, typically air or water. Since waves are generated by movements or collisions, this primarily tells the perceiver about things happening in the environment. In addition, since pressure waves can be reflected, absorbed, and refracted by other objects, these pressure waves also contain a great deal of contextual information about the environment and the objects in it. A fundamental challenge for the auditory system is to segregate the contributions of individual sound sources to the sound pressure waves received by the sensors as these are made up of a combination of all concurrent sources and their various reflections. Sounds unfold in time, so modelers of auditory processing cannot ignore time and the need to process signals within time; this becomes especially challenging when considering the multiscale nature of the information contained within sounds.

Possibly due to the complexity of the problem, many aspects of auditory processing have not yet been modeled at a detailed neurocomputational level. In addition, a great deal of processing occurs even before the incoming signals reach cortex; with the result that there are more models related to subcortical processing, than to higher level, putatively cortical, functions. The articles commissioned for the auditory sensing systems section therefore span a range of topics from qualitatively different point of view, with a strong focus on the functionality of the auditory system. Together they provide an interesting and insightful view of current understanding of auditory processing, with a great deal of useful information for modelers regarding the neuroanatomy and

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neurophysiology of the auditory system, methodological approaches to studying the auditory system, and functional requirements and perceptual constraints on auditory processing.

A well-illustrated overview of the anatomy and physiology of the auditory system, including the extensive but poorly understood efferent system is covered by ▶ "Anatomy and Physiology of the Mammalian Auditory System." A detailed account of efferent control of the auditory sensor, the cochlea, is presented in the article on the ▶ "Physiology and Function of Cochlear Efferents." It is in the cochlea that the biological system begins to analyze the pressure waves over multiple time scales and to do so within the time constraints of the ongoing multiscale information flow.

Another point of major transformation occurs at the gateway to the cortex, described in the article ▶ "Auditory Thalamocortical Transformations." Three further overview articles dealing with electrophysiological correlates of auditory perception: ▶ "Auditory Event-Related Potentials," ▶ "Auditory Brainstem Responses," and ▶ "Electrophysiological Indices of Speech Processing" document methodological approaches to studying high-level perceptual functions. Specific aspects of the functional neurophysiology of the thalamocortical auditory system are addressed in a number of articles. The articles ▶ "Associations and Rewards in the Auditory Cortex" (revised) and ▶ "Context-Dependent Processing in Auditory Cortex" (revised) demonstrate that the auditory cortical code needs to be viewed in more complex terms than simple acoustic feature representations. For example, neural correlates of reward are found even within primary auditory cortex (▶ "Associations and Rewards in the Auditory Cortex"). In contrast, the articles ▶ "Spectrotemporal Receptive Fields," ▶ "Stimulus-Specific Information," and ▶ "Stimulus Reconstruction from Cortical Responses" show how auditory cortical activity can in some circumstances be usefully interpreted in terms of acoustic feature combinations.

An overview of theories and models of higher-level aspects of auditory perception are presented in ▶ "Auditory Perceptual Organization," ▶ "Music Processing in the Brain," ▶ "Neural Coding of Speech Sounds," ▶ "Pulse-Resonance Sounds," ▶ "Auditory Memory" (revised), ▶ "Acoustic Timbre Recognition" ▶ "Pitch Perception, Models," ▶ "Rhythm Perception: Pulse and Meter," and ▶ "Sound Localization in Mammals and Models." These diverse topics emphasize the different ways in which sound is interpreted by the brain, while the article ▶ "Tinnitus, Models" shows how modelling may help advance understanding of a perceptual phenomenon that plagues 10–15% of the population.

The section also contains articles which present more detailed neurocomputational models and theories more closely related to the biology. These tend either to relate to very specific functions (▶ "Sound Localization in Mammals and Models" (revised), ▶ "Stimulus-Specific Adaptation, Models," ▶ "Auditory Precedence Effect," and ▶ "Masking and Masking Release" (revised)), or relate to processes at or near the sensor (▶ "Auditory-Nerve Response, Afferent Signals" (revised) and ▶ "Cochlear Inner Hair Cell, Model").

Finally, new entries in the Auditory Sensing Systems section focus on neural features of sound perception such as neuronal phase-locking to the spectrotemporal components of the acoustic signal (▶ "Auditory Frequency-Following Responses"), enhancement of the cortical representation of auditory signals in the presence of noise at moderate signal-to-noise ratio (▶ "Auditory Cortex: Separating Signal from Noise"), and perceptual organization of environmental sounds (▶ "Environmental Sound Perception: Effects of Aging and Hearing Loss"). They also present recent advancements in mathematical and computational modeling of auditory processing in the auditory pathway and auditory perceptual representation. The articles review modeling of the interaural and internal time and level differences (▶ "Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms"), modeling of sound-evoked extracellular voltages in the auditory brainstem (▶ "Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of"), as well computational and statistical methods

used to study auditory stream segregation (▶ "Computational Models of Auditory Stream Segregation").

Cross-References

- ▶ Acoustic Timbre Recognition
- ▶ Anatomy and Physiology of the Mammalian Auditory System
- ▶ Associations and Rewards in the Auditory Cortex
- ▶ Auditory Brainstem Responses
- ▶ Auditory Cortex: Separating Signal from Noise
- ▶ Auditory Event-Related Potentials
- ▶ Auditory Frequency-Following Responses
- ▶ Auditory Memory
- ▶ Auditory Perceptual Organization
- ▶ Auditory Precedence Effect
- ▶ Auditory Thalamocortical Transformations
- ▶ Auditory-Nerve Response, Afferent Signals
- ▶ Cochlear Inner Hair Cell, Model
- ▶ Computational Models of Auditory Stream Segregation
- ▶ Context-Dependent Processing in Auditory Cortex
- ▶ Electrophysiological Indices of Speech Processing
- ▶ Environmental Sound Perception: Effects of Aging and Hearing Loss
- ▶ Extracellular Voltage Recordings in the Medial Superior Olive, Modeling of
- ▶ Internally Coupled Ears (ICE): Biophysical Consequences and Underlying Mechanisms
- ▶ Masking and Masking Release
- ▶ Music Processing in the Brain
- ▶ Neural Coding of Speech Sounds
- ▶ Physiology and Function of Cochlear Efferents
- ▶ Pitch Perception, Models
- ▶ Pulse-Resonance Sounds
- ▶ Rhythm Perception: Pulse and Meter
- ▶ Sound Localization in Mammals and Models
- ▶ Spectrotemporal Receptive Fields
- ▶ Stimulus Reconstruction from Cortical Responses
- ▶ Stimulus-Specific Adaptation, Models
- ▶ Stimulus-Specific Information
- ▶ Tinnitus, Models

Basal Ganglia: Overview

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Definition

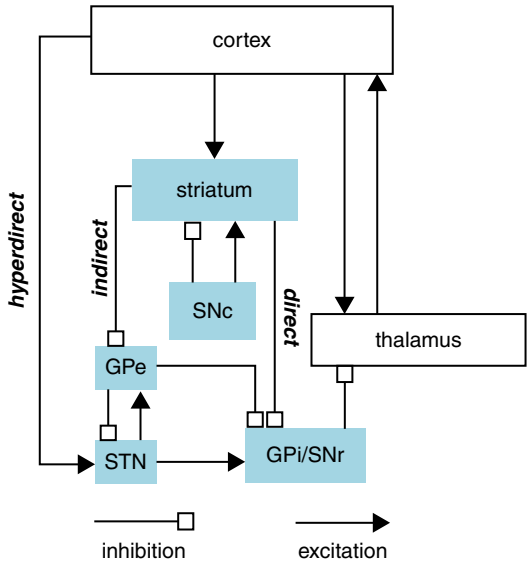
The basal ganglia are a collection of four subcortical nuclei, the striatum, substantia nigra, globus pallidus, and subthalamic nucleus. They are components of several apparently segregated circuits that can be classified according to function as motor, oculomotor, associative, and limbic. Certain neurons in the basal ganglia are major sources of the neurotransmitter dopamine, associated with reward, while others receive dopaminergic inputs; thus, the basal ganglia have received considerable attention in the context of learning. Imbalances in activity across the basal ganglia nuclei within the motor circuit are associated with various motor disorders.

Detailed Description

This section considers on the motor aspects of the basal ganglia, which have been the focus of most computational studies. The articles can be classified as those concentrating on activity within particular areas of basal ganglia, those concerning basal ganglia function, and those about the roles of basal ganglia in motor disorders, predominantly parkinsonism.

Basal Ganglia Structure

While the structures of the basal ganglia (Fig. 1) appear to be common across a wide range of vertebrate animals, from primates to lamprey (Stephenson-Jones et al. 2011), there are somewhat different naming systems used in different species, and there are some structural differences across species (e.g., mammals versus birds). Following the nomenclature used in primates, the striatum, encompassing the caudate nucleus and the putamen, is the predominant recipient of



Basal Ganglia: Overview, Fig. 1 Major structures and pathways of the basal ganglia. Basal ganglia areas are colored in blue. Connecting arrows and lines represent the existence of direct synaptic interactions between areas. A projection from GPe to the striatum recently discovered in rats is omitted here

cortical inputs. There are several types of neurons within the striatum, most of which release the neurotransmitter GABA, which has an inhibitory effect on its targets (see entry ▶ "Basal Ganglia: Striatal Models Cellular Detail"). Striatal neurons are also major recipients of dopamine. Different types of dopamine receptors arise in different striatal neurons, and this variability translates into diverse impacts of dopamine release. In coarse terms, dopamine promotes activity in some striatal neurons and inhibits it in others, but specific effects may be more complicated and may depend on ongoing activity levels.

The substantia nigra has two main parts, the substantia nigra pars reticulata (SNr) and the substantia nigra pars compacta (SNc). The former sends inhibitory output to areas outside of the basal ganglia that may be related to oculomotor activity (see entry ▶ "Basal Ganglia: Control of Saccades") or other motor activity, particularly in rodents. The latter releases dopamine to the striatum and other basal ganglia areas (see entry ▶ "Basal Ganglia: Dopaminergic Cell Models").

The globus pallidus is also a dichotomous structure, with segments that are referred to as external (GPe) and internal (GPi). Both parts predominantly contain GABAergic neurons that exhibit high firing rates, although with diverse firing patterns, under baseline conditions (see entry ▶ "Basal Ganglia: Globus Pallidus Cellular Models"). The GPe receives projections from a subset of striatal neurons as well as from the subthalamic nucleus (STN), and it innervates both the striatum and the STN in return, although it appears that the subpopulations of GPe neurons targeting these areas are distinct (Mallet et al. 2012). The GPi is subject to inputs from a different subset of striatal neurons, from the STN, and from the GPe and in turn projects to thalamic areas outside of the basal ganglia.

The STN stands out as the only basal ganglia area that releases the excitatory neurotransmitter glutamate. STN neurons exhibit intrinsic firing, albeit with heterogeneous properties (see entry ▶ "Basal Ganglia: Subthalamic Nucleus Cellular Models"). Besides participating in a reciprocal loop with GPe (see entry ▶ "Subthalamopallidal Loop and Oscillations"), the STN projects directly to GPi. The STN also receives direct glutamatergic input from the cortex and some dopaminergic input from the SNc.

The routes along which activity flows through the basal ganglia have been classified into the direct pathway, the indirect pathway, and the hyperdirect pathway (Fig. 1). This nomenclature refers to the number and types of steps between the cortex, which provides input to the basal ganglia, and the GPi, the primary source of motor outputs from the primate basal ganglia. The direct pathway is the stream from the cortex to the striatum to GPi. In net, the direct pathway inhibits basal ganglia output, since the cortex excites the striatum, which inhibits GPi. Since GPi inhibits downstream areas, reductions in its output can be pro-kinetic. The indirect pathway goes from the cortex through the striatum to GPe and continues on to STN and then GPi; the GPe-GPi connection may also be included in this pathway. Overall, the indirect pathway is believed to promote basal ganglia output and hence suppress movement. This view is based

on the idea that the cortex excites the striatum and thus inhibits GPe and disinhibits its target STN, which in turn excites GPi; the reduction in GPe activity also lowers its inhibition of GPi, yielding additional enhancement of GPi firing. This reasoning omits the complication of feedback pathways, such as the excitation that STN sends to GPe, however. The hyperdirect pathway, like the direct pathway, includes only one intermediary between the cortex and GPi: it refers to the cortical projection to STN together with the STN link to GPi. Presumably, this pathway is called "hyperdirect" because it features excitatory transmission via glutamatergic synapses from STN to GPi that is faster and has a more immediate effect than the direct pathway's inhibitory signaling via GABAergic synapses from the striatum to GPi. Like the indirect pathway, the hyperdirect pathway promotes basal ganglia output.

Finally, note that in rodent, which is a useful experimental model, the output structure analogous to the GPi is called the entopeduncular nucleus, and the major motor output structure is thought to be the SNr.

Basal Ganglia Function

The basal ganglia have been postulated to have a wide range of functions related to motor learning and other steps contributing to goal-directed movements (Chakravarthy et al., 2010). Models have been developed to represent and make predictions about the mechanisms involved in several of these functions. In the Basal Ganglia section of this encyclopedia, articles discuss background information and computational work on the mechanisms for action selection, habit formation, decision-making, and control of saccades. Furthermore, additional articles treat the role of the basal ganglia as an exploration engine and the learning and production of songs by birds.

Several lines of evidence point to the basal ganglia as a major site of action selection (see entry ▶ "Basal Ganglia: Mechanisms for Action Selection"). In particular, the basal ganglia are well positioned anatomically to orchestrate action selection by integrating inputs from a broad range of cortical areas and providing outputs to downstream motor-related sites. The basic idea of how action selection might work rests on the observations that under rest conditions, the output nuclei of the basal ganglia, GPi and SNr, exhibit high activity levels and that these areas release inhibitory neurotransmitters, which are well suited to block motor activity. To perform a movement, this inhibitory "gate" must be opened but only in a way that allows the desired action while maintaining a blockade on all other movements. Models of action selection position the direct pathway as the agent that removes inhibition and suggest that the indirect and hyperdirect pathways can act to suppress behavior and to participate in behavior switching (see entry ▶ "Basal Ganglia: Mechanisms for Action Selection"; Nambu et al. 2002).

Gradually, particular actions can become habits, which are actions that are elicited by certain stimuli in a way that lacks flexibility. Although established habits are less dependent on external rewards than are other learned behaviors, rewarding feedback that leads to striatal activation and associated plasticity of corticostriatal synapses are central to their being formed, and the corresponding learning process has been considered in computational models (see entry ▶ "Basal Ganglia: Habit Formation"). Dopamine is central to this form of plasticity and learning, and impairments in habit formation and performance are noted in subjects with Parkinson's disease.

A basal ganglia function that is distinct from pure action selection and habit learning arises in perceptual decision-making. In this process, in abstract terms, it is thought that evidence favoring each of a number of choices accumulates until one option becomes sufficiently supported to elicit a corresponding behavior. The evidence is presumably represented by firing of various sets of cortical neurons that can influence basal ganglia activity, and basal ganglia activity is involved in setting the selection threshold (see entry ▶ "Basal Ganglia: Decision-Making"). In this view, the dopamine-based reward induced by a behavior is involved in threshold adjustment and thereby influences future choices. Computational models consider how the activity in the pathways of the

basal ganglia interacts with dopaminergic reward signals to drive and adjust the decision-making process, positing various roles for particular brain areas in evidence accumulation, stimulus detection, threshold adjustment, and decision-making and cancelation. Some also treat impairments in parkinsonian conditions and alterations under deep brain stimulation (see entry ▶ "Basal Ganglia: Decision-Making").

Unlike other actions to which the basal ganglia contribute, rapid eye movements known as saccades in primates are gated by outputs from SNr rather than GPi. Issues under investigation relating to saccade generation, which have been treated in computational models, include mechanisms of target selection, of learning of target priorities, and of interactions of these processes with working memory (see entry ▶ "Basal Ganglia: Control of Saccades").

A less thoroughly investigated function of the basal ganglia is the generation of variability in motor responses. Such variability is certainly observed in the behaviors of many species and seems to be essential for optimizing behavior and attaining maximal rewards. There is significant experimental evidence implicating the basal ganglia as a source of such motor exploration, and some computational modeling work to instantiate these ideas and study their implications has been performed (see entry ▶ "Basal Ganglia System as an Engine for Exploration"). In relevant models, while the direct pathway takes on the traditional role of implementing action selection, the indirect pathway, and particularly the STN, injects variability into this process. Learning based on reward signals is critical to such models and helps control the relative dominance of direct and indirect pathway signals.

One example of the prominence of behavioral variability arises in song production by songbirds. Songs must be learned, which involves exposure to the song of another bird, trial-and-error behavior, and auditory feedback. This process appears to heavily involve a basal ganglia analogue that participates in learning, in the introduction of behavioral variability, and in the selection of rewarding behaviors. Certain songbird experimental preparations are advantageous for studying this combination of processes, and corresponding models of associated reinforcement learning and song production have been informed by observations from these preparations (see entry ▶ "Basal Ganglia: Songbird Models").

Basal Ganglia and the Motor Symptoms of Parkinsonism

The loss of dopaminergic neurons in the SNc appears to be the critical trigger for a slew of changes in neuronal activity within areas of the basal ganglia that result in the motor symptoms of parkinsonism. This loss is typically gradual, and the causes appear to involve a complex combination of environmental and genetic factors that are still under intensive investigation.

Classical models of parkinsonism attribute its motor signs to an imbalance in direct and indirect pathway outputs stemming from the loss of dopaminergic input to the striatum (Albin et al. 1989). The loss of dopamine removes a source of excitation to the striatal neurons with D1 receptors, which project to GPi. Less firing by these striatal neurons, viewed as a weakening of the direct pathway, results in disinhibition of GPi. Meanwhile, diminished dopamine translates to reduction in inhibition of the striatal neurons with D2 receptors, which in turn inhibit GPe. As a result, GPe output is suppressed, which relieves GPe inhibition of STN and allows enhanced STN firing. The increased STN activity provides more drive to GPi, viewed as a strengthening of the indirect pathway. Together, these changes tip the balance of direct and indirect pathway effects in a way that favors the indirect pathway and promotes GPi activity. GPi outputs inhibit the pallidal recipient areas of the thalamus and are believed to represent an inhibitory gate that shuts down movement. Thus, pathologically enhanced GPi firing could interfere with initiating and carrying out movements in a way that translates into some motor signs of parkinsonism.

The complete explanation for the emergence of parkinsonian motor signs likely involves phenomena that are omitted from this classical description. It has become clear that loss of dopamine leads to widespread modifications of neuronal

activity patterns, rather than just changes in firing rates, in the basal ganglia. These effects include an enhanced prevalence of bursting, altered oscillation structure, and increased correlation in outputs of neurons within, and across, basal ganglia areas (Rubin et al. 2012).

One potential source of oscillations within basal ganglia is the reciprocal excitatory-inhibitory loop between the GPe and the STN (see entry ▶ "Subthalamopallidal Loop and Oscillations"). Oscillations in the beta band (broadly taken as 10–30 Hz) appear to be particularly prevalent in parkinsonian conditions and may be particularly effective at hijacking activity in thalamic areas downstream from the basal ganglia, and several different sources for such oscillations have been posited (see entry ▶ "Basal Ganglia: Beta Oscillations").

While oscillations observed in the activity of basal ganglia neurons seem like a natural candidate to contribute to parkinsonian tremor, the link between altered neuronal firing and other parkinsonian symptoms may be less explicit. In particular, the slowing of movement known as bradykinesia may emerge from the interactions of all of the motor signaling pathways through the basal ganglia, or it may be necessary to consider basal ganglia interactions with corticospinal-muscular pathways to explain its source (see entry ▶ "Basal Ganglia: Bradykinesia Models").

The predominant treatments for Parkinson's disease in its early stages are pharmacological, aimed at replacing lost dopamine. In cases where pharmacological treatments gradually lose efficacy or induce substantive side effects, deep brain stimulation therapy represents a treatment option that, while highly invasive, is at least partially adjustable (by tuning of stimulation parameters) and reversible (by cessation of stimulation). Deep brain stimulation for Parkinson's disease typically is targeted at STN or GPi and proves effective for many patients; although the mechanisms underlying its efficacy are not known, theories have honed in on its potential impact on patterns of basal ganglia activity and outputs and their downstream effects (see entry ▶ "Computational Models of Deep Brain Stimulation (DBS)"; Rubin et al. 2012).

Cross-References

- ▶ Basal Ganglia System as an Engine for Exploration
- ▶ Basal Ganglia: Beta Oscillations
- ▶ Basal Ganglia: Bradykinesia Models
- ▶ Basal Ganglia: Control of Saccades
- ▶ Basal Ganglia: Decision-Making
- ▶ Basal Ganglia: Dopaminergic Cell Models
- ▶ Basal Ganglia: Globus Pallidus Cellular Models
- ▶ Basal Ganglia: Habit Formation
- ▶ Basal Ganglia: Mechanisms for Action Selection
- ▶ Basal Ganglia: Songbird Models
- ▶ Basal Ganglia: Striatal Models Cellular Detail
- ▶ Basal Ganglia: Subthalamic Nucleus Cellular Models
- ▶ Computational Models of Deep Brain Stimulation (DBS)
- ▶ Subthalamopallidal Loop and Oscillations

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Bayesian Approaches in Computational Neuroscience: Overview

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Definition

Bayesian approaches in Computational Neuroscience rely on the properties of Bayesian statistics for performing inference over unknown variables given a data set generated through a stochastic process.

Detailed Description

Given a set of observed data $d_{1:n}$, generated from a stochastic process $P(d_{1:n}|X)$ where X is a set of unobserved variables, the posterior probability distribution of X is $P(X|d_{1:n}) = P(d_{1:n}|X)P(X)/P(d_{1:n})$ according to Bayes' theorem. X can be a set of fixed parameters as well as a series of variables of the same size as the data itself $X_{1:n}$.

Based on the posterior probability and a specified utility function, an estimate of X can be made that can be shown to be optimal, for example, by minimizing the expected variance.

One common use of this principle within computational neuroscience is for inferring unobserved properties (hidden variables X) based on observed data, d. These techniques can be used for inference on any data sets but has in neuroscience mostly been used for neurophysiological recordings, imaging, and behavioral data.

By their nature electrophysiological recordings are noisy and stochastic. Given the stochastic responses of neurons to stimuli, Bayesian methods can be used to infer the underlying stimuli or activation of the neurons, $X_{1:n}$ (Bayesian Electrophysiology Analysis).

For imaging data an underlying neural activity $X_{1:n}$, for example, firing rate at the level of individual columns of cortex, is assumed to give rise to measured responses $d_{1:n}$, for example, the blood flow measured by fMRI, through a stochastic process. Inverting the process through the Bayesian inference allows for estimating the unknown neural activity (Bayesian Imaging Analysis).

The ideas can also be useful for inferring properties about the behavior of individual human subjects, X, by the assumption of a stochastic process, $P(d_{1:n}|X)$, through which characteristics of each individual subject lead to individual choices in an experimental task, $d_{1:n}$ (Bayesian Behavioral Analysis).

The abovementioned techniques all use Bayesian inference to infer underlying properties of recorded data but are essentially used as very effective tools for data analysis. An alternative line of research takes as the working hypothesis that the human brain has evolved to the point of itself approximating an ideal Bayesian observer (sometimes referred to colloquially as the Bayesian Brain Hypothesis). Accordingly, this line of research compares human behavior to the output of such an ideal observer within, for example, perceptual (Bayesian Models of Perception) or cognitive tasks (Bayesian Models of Cognition).

A related effort has proposed that the computations necessary to perform the steps of Bayesian inference can be done through populations of biological neurons (Bayesan Inference with Spiking Neurons). Recent works on artificial neural networks have also reignited interest in combining ideas from the two areas of research including means of designing artificial networks able to perform Bayesian inference.

There is a continued effort to translate ideas on Bayesian inference from Machine Learning and Computer Science into Computational Neuroscience, including, for example, recent advances in sampling techniques for inference.

Cross-References

- ▶ Bayesian Inference with Spiking Neurons
- ▶ Behavioural Analysis, Bayesian
- ▶ Cognition, Bayesian Models of
- ▶ Electrophysiology Analysis, Bayesian
- ▶ Imaging Analysis, Bayesian
- ▶ Perception, Bayesian Models of

Biochemical Signaling Pathways and Diffusion: Overview

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Detailed Description

Signaling pathways modulate the function of neurons and neuronal networks through diverse processes. The most well-known function of signaling pathways is synaptic plasticity, which controls neuronal networks via modulation of the strength of synaptic connections. Signaling pathways also are critical for neuronal development, axon guidance, and regulation of transcription and translation. Signaling pathways are activated by the G protein-coupled transmembrane receptors, such as metabotropic glutamate receptors or noradrenergic receptors; by the receptor tyrosine kinases; and by calcium influx through NMDA receptors or voltage-dependent calcium channels.

Calcium

Due to the importance of calcium, its concentration is tightly regulated by buffers and pumps. One of these calcium buffers, known as calmodulin, is not inert; rather, it can activate diverse enzymes such as adenylyl cyclase, calcineurin, phosphodiesterase type 1B, and calcium-calmodulin-dependent protein kinase II. In addition to calcium influx through plasma membrane channels, both the mitochondria and the smooth endoplasmic reticulum (SER) are sources of calcium. Two types of calcium permeable channels reside on the SER: the inositol trisphosphate receptor channel and the ryanodine receptor channel. Calcium-dependent calcium release through these channels can lead to oscillations or waves of calcium, depending on various factors.

Kinases

The second messengers activated through transmembrane receptors have multiple downstream targets, including ionic channels, kinases, and phosphatases. Of the thousands of kinases and phosphatases in the proteome, several have a demonstrated role in synaptic plasticity, though their relative importance depends on the brain region and cell type. Protein kinase type C is a calcium- and lipid-activated kinase which is critical for LTP in the cerebellum. Protein kinase type A is a cAMP-activated kinase, which is critical for LTP in the striatum, and for several long-lasting forms of LTP in the hippocampus. Gene transcription and protein translation are required for both memory and for long-lasting forms of synaptic plasticity. One kinase that appears to bridge these other kinases and transcription is the ERK1/2 forms of MAPK (mitogen-activated protein kinase).

Modeling Techniques

Calcium dynamics and signaling pathways are modeled as cascades of biochemical reactions, both bimolecular reactions and enzyme reactions, and diffusion. Many special purpose simulators are available to implement these signaling pathways, either using stochastic techniques or deterministic approaches. Modeling calcium influx requires the simulator to have capabilities for modeling membrane potential. Due to the diversity in temporal and spatial scale involved in modeling neuronal electrical activity coupled to reaction-diffusion pathways, very few models

incorporate signaling pathways in entire neurons, though the number of such models is increasing as computational power increases.

Cross-References

- ▶ Bimolecular Reactions, Modeling of
- ▶ Biophysical Models of Calcium-Dependent Exocytosis
- ▶ Calcium Buffering: Models of
- ▶ Calcium Dynamics in Neuronal Microdomains: Modeling, Stochastic Simulations, and Data Analysis
- ▶ Calcium Pumps, Models of
- ▶ Calcium Release, Models of
- ▶ Calcium Waves, Models of
- ▶ Calmodulin, Models of
- ▶ Cerebellum: Overview
- ▶ Deterministic Reaction-Diffusion Simulators
- ▶ Diffusion Equation
- ▶ Enzyme Kinetics, Modeling of
- ▶ Extracellular Signal-Regulated Kinases, Models of
- ▶ Gillespie Algorithm for Biochemical Reaction Simulation
- ▶ High-Voltage-Activated Calcium Channels
- ▶ Metabotropic Receptors (G Protein Coupled Receptors)
- ▶ N-Methyl-D-Aspartate (NMDA) Receptors, Conductance Models
- ▶ Particle-Based Stochastic Simulators
- ▶ Protein Kinase A, Models of
- ▶ Protein Kinase C, Models of
- ▶ Signaling Pathways, Modeling of
- ▶ Stochastic Simulators

Brain Imaging: Overview

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Synonyms

Functional neuroimaging

Definition

Brain imaging constitutes a set of techniques used to measure functional activity in networks of interacting brain cells as well as to reveal the major underlying structural properties of these networks. Functional data obtained with these techniques reflect local changes in brain perfusion, metabolism, and extracellular electric/magnetic potentials originated from the activity of these brain cell networks. Brain imaging has been traditionally used to explore both normal and pathological brains in a large variety of species ranging from rodents to primates. In principles, brain imaging could be applied for both in vitro and in vivo situations.

Detailed Description

Techniques for brain imaging have been developed for two major physical brain scales, i.e., the mesoscale and the macroscale. Theoretical models useful to interpret how these two physical scales interact have been developed in the past (see ▶ "Multiscale Brain Connectivity"). Brain imaging modalities have been combined with specific stimulation techniques to study brain activity in both mesoscopic (e.g., uncaging methods, optogenetics – see ▶ "Optogenetics") and macroscopic (e.g., transcranial magnetic stimulation, TMS) levels. Brain imaging constitutes one of the most important building blocks in the development of brain-machine interfaces (see ▶ "Brain-Machine Interface and Neuroimaging").

Neuroimaging at the Mesoscale

Functional refers to observations reflecting the activity of populations of cells (e.g., neurons, astrocytes) in a particular brain structure with the resolution of single cells. Examples of functional neuroimaging for this particular scale are confocal/multiphoton (MP) microscopy, current source density (CSD) analysis from intracranial recordings using MEA, intrinsic optical signal (IOS), optical coherence tomography (OCT), and

voltage-sensitive dye imaging (VSDI). These imaging techniques are based on either in vitro or very invasive in vivo experimental protocols. Some of the imaging techniques based on optical phenomena (confocal/MP microscopy, VSDI – see ▶ "Voltage Sensitive Dye Imaging, Intrinsic Optical Signals") provide the ideal spatial resolution to explore the activity of single cells, but their temporal resolution is in the order of hundreds of milliseconds. In contrasts, images resulting from the CSD analysis could reflect electrical phenomena happening in the order of a few milliseconds, but they are associated with the activity of synchronized population of neurons in extended brain regions. IOS and OCT are employed mainly to record changes in blood flow/volume in the brain as well as alterations in blood oxygen concentration (see ▶ "Voltage Sensitive Dye Imaging, Intrinsic Optical Signals").

Anatomical refers to static pictures of the cellular networks directly reflecting structural properties. These images are obtained using different modalities of sectioning microscopy (see ▶ "Physical Sectioning Microscopy").

Neuroimaging at the Macroscale

Functional refers to observations reflecting the activity of large regions inside the brain. Examples of functional neuroimaging for this particular scale are functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission tomography (SPECT), functional near-infrared spectroscopy (fNIRS), and electro (EEG)/magneto (MEG) –encephalograms. The spatiotemporal profiles of these brain imaging techniques are quite different (Riera and Valdes-Sosa 2010). Deciphering the origin and nature of signatures in the functional neuroimaging imprinted by abnormal brain activity is important while using them for diagnosing, monitoring, and treating brain diseases and disorders (see ▶ "Connectivity Analysis in Normal and Pathological Brains"). To that end, it is crucial to understand the physiological mechanisms underlying these brain imaging techniques (see ▶ "Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism," ▶ "Kinetic Models for PET/SPECT Imaging," and ▶ "Forward and Inverse Problems of MEG/EEG"). These techniques classify either as slightly invasive (i.e., fMRI, fNIRS, EEG/MEG) or extremely invasive because of the use of radioisotopes (i.e., PET, SPECT, see ▶ "Radiopharmaceuticals in Molecular Imaging"). A variety of methods have been developed for the preprocessing and analysis of brain imaging data, with resulting software and platforms currently available (see ▶ "Software for Neuroimaging Data Analysis," ▶ "Statistical Analysis of Neuroimaging Data," and ▶ "Meta-analysis in Neuroimaging").

Anatomical refers to static pictures of the entire brain, or part of it, directly reflecting structural properties. Example of imaging modalities used to study morphometric characteristics of brain tissues are the T1/T2 magnetic resonance imaging (MRI) and the computed tomography (CT). Diffusion tensor imaging (DTI) has been commonly employed to study the strengths of connections between different brain regions.

Cross-References

- ▶ Applications of Information Theory to Analysis of Neural Data
- ▶ Biophysical Models: Neurovascular Coupling, Cortical Microcircuits, and Metabolism
- ▶ Brain Atlases
- ▶ Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery
- ▶ Brain-Machine Interface and Neuroimaging
- ▶ Connectivity Analysis in Normal and Pathological Brains
- ▶ Current Source Density (CSD) Analysis
- ▶ Electrophysiology Analysis, Bayesian
- ▶ Forward and Inverse Problems of MEG/EEG
- ▶ Imaging Analysis, Bayesian
- ▶ Independent Component Analysis of Images
- ▶ Kinetic Models for PET/SPECT Imaging
- ▶ Local Field Potential, Relationship to BOLD Signal
- ▶ Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG)

- ▶ Meta-analysis in Neuroimaging
- ▶ Multiscale Brain Connectivity
- ▶ Neuroimaging, Neural Population Models for
- ▶ Noninvasive Brain-Computer Interfaces
- ▶ Optogenetics
- ▶ Physical Sectioning Microscopy
- ▶ Radiopharmaceuticals in Molecular Imaging
- ▶ Reconstruction, Electron Microscopy
- ▶ Software for Neuroimaging Data Analysis
- ▶ Statistical Analysis of Neuroimaging Data
- ▶ Voltage Sensitive Dye Imaging, Intrinsic Optical Signals

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Brain-Machine Interface: Overview

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Abbreviations

AP	Action potentials
BCI	Brain-computer interfaces
BMI	Brain-machine interface
ECoG	Electrocorticogram
EEG	Electroencephalogram
EMG	Electromyogram
FES	Functional electrical stimulation
LTD	Long-term depression
LTP	Long-term potentiation
MIMO	Multi-input multi-output
NI	Neural interfaces
SCI	Spinal cord injury
SISO	Single-input single-output

Synonyms

Brain-computer interfaces; Neural interfaces

Definition

A brain-machine interface (BMI) is a direct communication pathway between the nervous system and a man-made computing device. This communication is *unidirectional* in BMIs that either record neural activity in the nervous system to affect the state of an external device or stimulate neural activity to affect the state of the nervous system. It can also be *bidirectional*, such as BMIs that record activity from certain parts of the nervous system and use this activity – or features extracted from it – *in real time* to stimulate activity in other parts of that system. This communication can occur at multiple levels, which may include muscles, peripheral nerves, spinal cord, or the brain.

Detailed Description

BMIs fundamentally rely on the concept of causation between electricity and movement or between electricity and cognition. The causal link between electrical current injection into the body and movement of parts of that body was first established in the late eighteenth century by Galvani (1791), Fowler and Galvani (1793), who could evoke muscle twitches in the frog legs by direct current injection into the muscle ex vivo. A similar discovery in the central nervous system was made in 1870 by Fritsch and Hitzig (1870), in which electrical stimulation of different areas of the cerebral cortex caused muscular contractions of specific parts of a dog's body in vivo. It was not until 1928 that recording of the all-or-none electrical discharge of single neurons in the optic nerve of the toad was made by Adrian (Adrian

and Bronk 1928) and was found to be strongly correlated with light stimuli. Ever since, countless studies have revealed numerous mechanisms of neural coding of sensory stimuli or movement parameters, such as orientation tuning by V1 neurons (Hubel and Wiesel 1962), spatial position by hippocampal place cells (Ranck 1973; O'Keefe 1979) and movement direction by primary motor cortex neurons (Georgopoulos et al. 1986).

The early 1990s nonetheless has witnessed a paradigm shift in the way recording and stimulation of neural activity is achieved. In particular, microwire bundles have been used to record the activity of a handful of neurons in awake behaving animals (McNaughton et al. 1983). Striking advances in the microfabrication technology of high-density microelectrode arrays (HDMEAs) (Drake et al. 1988; Normann et al. 1999) have later permitted large-scale simultaneous recording of many neurons (tens to hundreds) in awake behaving subjects, which eventually paved the way for these arrays to become a key element in BMIs development in subsequent years (Nicolelis 1999).

Unidirectional BMIs

Afferent BMIs

Afferent BMIs (ABMIs) rely on transforming features of sensory stimuli (e.g., auditory, visual, etc.) to electrical pulse trains in order to stimulate neural activity in the central or the peripheral nervous systems to cause artificial sensation to compensate for some form of sensory loss (e.g., deafness or blindness) (Fig. 1). Auditory prosthesis, such as cochlear implants (CIs) – dating back to the first implant in 1957 by Djorno and Eyries – is the first example of an afferent BMI that was approved by the FDA in 1984 (House and Urban 1973). CIs transform sound features (e.g., intensity or pitch) recorded through a microphone to pulsatile currents in the spiral ganglia. This eventually elicits action potentials from residual hair cells in the auditory nerve of hearing-impaired subjects.

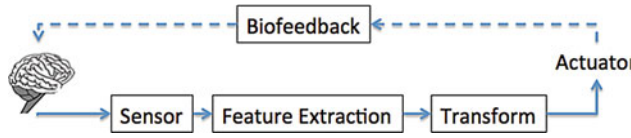
Likewise, visual prosthesis rely on transforming features of the visual scenes recorded through a video camera to stimulate different parts of the visual pathway in legally blind subjects. The site of stimulation along this pathway is a function of where neural degeneration occurs, but the most promising demonstration of visual prosthesis thus far has been through the stimulation of the retinal ganglion cell layer that provide input to the optic nerve in patients with retinitis pigmentosa and age-related macular degeneration (de Balthasar et al. 2008).

Efferent BMIs

EBMIs rely on extracting features from recorded neural activity in real time that are subsequently transformed into control signals for actuating an external device (e.g. a paralyzed limb) (Fig. 2). They can be categorized based on the recorded signal modality, which is predominantly neural (but see (Sitaram et al. 2009) for an example of metabolic activity that utilizes blood-oxygen-level dependent (BOLD)).

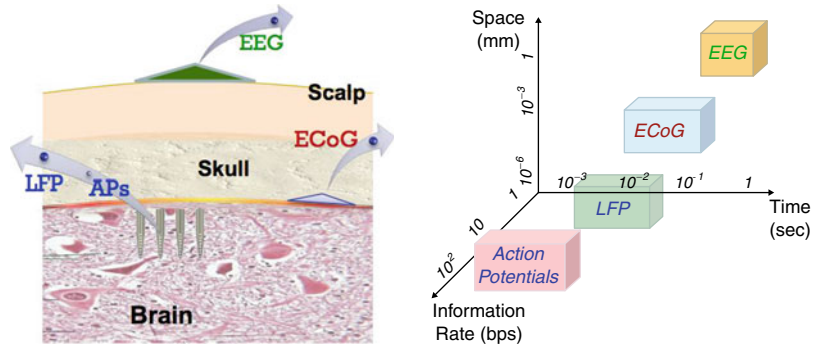
In EBMIs, the neural readout may differ in the temporal and spatial scales of variations, as well as in information content, as shown in Fig. 3. While the 1–2 ms APs elicited by individual neurons are known to contain large information about behavioral covariates (typically measured in bits per second), they tend to be highly variable and can only be recorded thus far using penetrating microelectrodes (McNaughton et al. 1983; Drake et al. 1988; Normann et al. 1999; Nicolelis 1999), or using voltage-sensitive dye-based calcium imaging at shallow cortical depths (Koester and

Brain-Machine Interface: Overview, Fig. 1 Basic elements of an afferent BMI. Features are extracted from the sensory stimuli and then converted to electrical pulses that stimulate target areas in the afferent pathway of the corresponding sensory modality



Brain-Machine Interface: Overview, Fig. 2 Basic elements of an efferent BMI. The read out of neural activity can be a single signal source recorded from a target area within an efferent pathway – or multiple sources fused together within the transform block, aka the "decoder" – to actuate an artificial device. The user is able to continuously monitor changes in the state of the actuator in real time, typically through visual feedback

Brain-Machine Interface: Overview, Fig. 3 Spatial, temporal, and information characteristics of neural signals recorded from the brain for efferent BMI operation. (Adapted from Oweiss 2010)



Sakmann 2000; Stosiek et al. 2003) – although the latter signals have not been used in BMIs. While local field potentials (LFPs) can also be recorded using penetrating electrodes, they contain less information than spike trains and are believed to provide a glimpse over the synchronized activity of large populations of neurons within a few 100 microns from the electrode tip (Mitzdorf 1985; Katzner et al. 2009). Macroelectrodes, either implanted subdurally to record ECoG or fixed extracranially to record surface EEG, offer another less risky alternative for EBMI since they are less- or noninvasive (Wolpaw et al. 2002; McFarland et al. 2005; Thongpang et al. 2011).

Historically, work in efferent BMIs (EBMIs) is more recent than ABMIs. The first EBMI dates back to the pioneering work of Fetz (1969) and was based on a single-neuron recording from a monkey's precentral "motor" cortex. In this setting, the BMI was a single-input/single-output (SISO) system where the firing rate of a single neuron was integrated over small time intervals and used to control an illuminated meter whose pointer deflection was proportional to the activity integrator's output. The animal had to volitionally modulate the firing rate of the selected neuron in order to bring the meter to a predetermined threshold for reward. This operant conditioning paradigm constitutes the first proof of concept of an EBMI, though was not used to actuate any limbs. This approach has been extended in modern EBMIs to involve the simultaneous recording and use of hundreds of neurons that are subsequently transformed through a "decoding" filter to generate control signals that actuate multiple degrees of freedom (DOFs) (Hochberg et al. 2012). As such, these BMIs are considered multi-input/multi-output systems (MIMOs).

Cerebral BMIs

Another class of unidirectional BMIs – neither designed to directly cause sensation nor produce movements – is designed to stimulate neurons in the central nervous system to directly inhibit pathological behavior in subjects with neurological impairment. An example of such systems is deep brain stimulators (DBS), in which an electrode array is implanted in the subthalamic nucleus (STN) of a Parkinsonian patient, and macrostimulation of the STN through a few electrode leads ameliorates the disease symptoms by reducing bradykinesia and tremor (Coffey 2009). Similar designs are intended to regulate mood disorders (Mayberg et al. 2005; Hajcak et al.

2010) or abate epileptic seizures (Theodore and Fisher 2007; Halpern et al. 2008; Boon et al. 2009; Jones 2010).

Bidirectional BMIs

Bidirectional – or sometimes referred to as "recurrent" – BMIs differ from unidirectional BMIs in that neural measurements are used in the input to the transform to compute stimulation parameters *in real time*. As such, they are considered "closed loop" compared to unidirectional BMIs that are "open loop." This specific feature allows stimulation to be dynamic and to follow the dynamics of the neural input to the transform, which may be volitionally modulated by the subject in certain applications (Fig. 4).

Sensorimotor BMIs

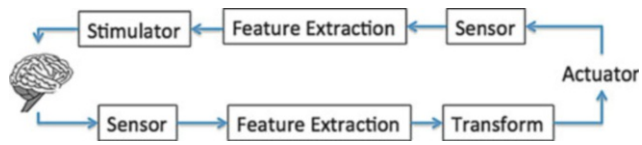
This class of bidirectional BMIs combines recording and stimulation to restore one or more functions. For example, motor signals can be recorded from cortical areas and used to directly control muscle contraction or hand grasp via FES (Moritz et al. 2008; Ethier et al. 2012). These signals can also be used to stimulate the spinal cord below the injury site using parameters extracted from cortical signals in real time (Harkema et al. 2011; Moritz et al. 2007; Shanechi et al. 2014) or via stimulation of peripheral nerves (Navarro et al. 2005; Micera and Navarro 2009). In that respect, this is a class of bidirectional BMIs that restores motor function through FES.

Another class of bidirectional BMIs combines efferent and afferent BMIs to restore movements as well as sensory feedback in the form of touch and proprioception. The importance of such design is the indispensible role that somatosensation plays in the integration and coordination of limb movements, particularly for complex upper limb functions such as reaching and grasping. There is debate over which site(s) to stimulate to restore somatosensory feedback, but the majority of approaches have focused on stimulation of peripheral nerves (Raspopovic et al. 2014). Peripheral stimulation, however, is not feasible in patients with spinal cord injury (SCI). Recent reports devised protocols for these patients based on subcortical (Daly et al. 2012; Liu et al. 2011) or cortical stimulation (Berg et al. 2013; Tabot et al. 2013).

A third class of bidirectional BMIs aims to induce plastic changes in neural circuits by using patterns of activity recorded from one brain site to stimulate activity in another distal brain site in real time (Jackson et al. 2006). Key to induce this plasticity is to ensure stimulation is delivered within a few milliseconds of recording spike events so as to promote LTP and LTD of synaptic connections, consistent with Hebbian plasticity (Hebb 1949). It is contended that this type of plasticity triggers functional as well as structural changes in the targeted neural circuits (Lucas and Fetz 2009); the longevity of this plasticity, however, is yet to be demonstrated, since neurons return to their original encoding properties shortly after stimulation is terminated.

Cognitive BMIs

Certain brain areas have specific cytoarchitectonic architecture with known role in cognitive functions, such as the hippocampus role in the formation and maintenance of long-term episodic memory (Bliss and Collingridge 1993). This knowledge is critical to the ability to restore



Brain-Machine Interface: Overview, Fig. 4 Basic elements of a bidirectional – or recurrent – BMI. Neural activity is read out to control an actuator. In turn, changes in the actuator state are measured and used to provide information back to the nervous system through stimulation patterns of relevant areas in the peripheral nerve, the spinal cord, or the brain

inter-areal as well as intra-areal information exchange by means of artificial devices. In this setting, neural activity is recorded from one upstream region (e.g., hippocampus CA3) known to provide feedforward information to downstream regions (e.g., CA1) (Yeckel and Berger 1990). When the communication between the two regions is disrupted due to malfunctioning neural tissue, eventually causing memory loss, activity recorded from CA3 is "decoded" to predict the input to the CA1 region. The BMI then uses this prediction to derive the stimulation patterns needed to evoke biomimetic activity at the output of the CA1 region. Thus, the transform model in this BMI design lumps both a "decoder" of the input neural activity in CA3 and an "encoder" of the patterns to be evoked in CA1 through stimulation in one block (Song et al. 2007).

Bidirectional BMIs for Neurological Disorders

This class of BMIs extends cerebral BMIs to include a closed loop design that records neural activity and uses features extracted from this recordings to dynamically adjust stimulation patterns in real time (Rosin et al. 2011) (Carlson et al. 2013; Afshar et al. 2012). A similar approach is used to reduce or prevent seizures from occurring in drug-resistant epileptic patients (Nagel and Najm 2009) (Morrell and RNS System in Epilepsy Study Group 2011). This strategy is more advantageous compared to resection of the parts of the brain where hypothesized epileptic foci reside, which has been the standard clinical treatment for many years. Other examples use a similar concept to treat brain injury or psychiatric diseases, such as traumatic brain injury (Schiff et al. 2007), major depression (Malone et al. 2009), obsessive compulsive disorders (Goodman et al. 2010), among others (Mohr 2008).

The Computing Device

A key element in BMI design is the computational capability of the device and the corresponding number of inputs and outputs. For example, in SISO BMIs, computations can be as simple as the detection of APs presence in a noisy electrode recording followed by a spike count within a fixed time interval (usually 50 ms). They can also consist of complex time varying (Kalman 1965) – and sometimes nonlinear (Hampson et al. 2013) – transformation of multiple electrode recordings in MIMO BMIs. EBMIs in particular are designed to have the decoder extract neural features (typically the firing rate of individual cells) to determine the "state" of the population. Because this state varies in time, it can be described by a "trajectory" in a neural state space (Oweiss 2010; Badreldin et al. 2013; Churchland et al. 2012). The transform then filters this state to reduce its dimension to a smaller number of variables that can be subsequently used to control the actuator (Gilja et al. 2012). As such, the subject is required to learn this transformation with extended practice.

Likewise, in ABMIs, the computing device extracts features from signals measured in the outside world to influence the "trajectory" of the stimulation parameter(s) in a stimulation parameter space. Because the mapping between the trajectory of natural stimuli in the task space and the evoked response in the neural state space – which is typically of much higher dimension – is unknown, methods for finding the "best" stimulation strategies in "open loop" BMIs are far from optimal. As such, the experimenter/clinician assumes the role of finding an optimal "tune-up" of stimulation parameters to restore a specific function by trial and error. For example, stimulation parameters (e.g., pulse frequency) in DBS systems are manually adjusted to fit each patient and reduce tremor (Kuncel et al. 2006). The lack of selectivity of electrical stimulation and the absence of knowledge of the dynamics of the neural circuits affected by stimulation, however, make this approach a real challenge. As such, characterizing the dynamics of stimulation-evoked neural activity in upstream or downstream circuits becomes important in order to optimize the stimulation "dose" for restoring a desired function and to minimize any side effects over the long term (Liu et al. 2010, 2011; Kuncel et al. 2008). Thus, studying the neural system being stimulated by an artificial device may offer advantages in clinical BMI applications.

Cross-References

- Auditory Prosthesis
- Cortical Motor Prosthesis
- Decoding Field Potentials
- Deep Brain Stimulation (Models, Theory, Techniques): Overview
- Hippocampal Memory Prosthesis
- Memory Decoding Model
- Neural Decoding
- Noninvasive Brain-Computer Interfaces
- Recurrent Brain-Computer Interfaces
- Somatosensory Prosthesis
- Vestibular Prosthesis, Interface
- Vision Prosthesis

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Brain-Scale Networks: Overview

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Definition

The brain is composed of many neurons, functional areas, and layers. Together these components work as a network to produce behavior. At minimum, the network behavior is determined by four things: (1) the network inputs, (2) the dynamics of the individual nodes, (3) the coupling functions between the nodes, and (4) the topology. This encyclopedia section will provide a brief overview on characterizing brain-scale networks. Often the coupled system will have emergent behaviors, behaviors that could not be predicted from analysis of the individual components alone. Understanding how the brain functions requires an understanding of how components work together in a network. In many diseases the cause cannot be pinpointed to dysfunction or failure of a single component, such as an ion channel mutation. Instead, subtle changes in cellular behavior may lead homeostatic mechanisms to alter the coupling between the neurons and brain areas, resulting in pathological activity such as synchronous population oscillations or unchecked excitability. The ultimate goal in applying the network theory to understanding connections within the brain is to develop a measure that can explain the emergence of pathological behaviors and to perhaps develop approaches to treating diseases.

But first, we will introduce a few common terms. A **network** is a collection of coupled components. Generally, when the components coupled together are different elements, it is referred to as a **system**. If the components of the system are similar and interchangeable, it is instead called a **network**. The components in the network are referred to as **nodes**, which can be individual neurons or brain regions. The coupling between the nodes is referred to as **edges**, which can be synapses or fiber paths. Coupling in the nervous system is generally through chemical synapses which are **directional**, where the coupling of neuron or region A onto B will be different than B onto A. However, for networks of neurons coupled through electrical synapses, the coupling can be undirected. Networks are considered **weighted** if the strengths of coupling between nodes have a distribution and **unweighted** if they are all the same.

Generally, the dynamics of the nodes and coupling function are highly nonlinear. **A linear response** is defined as given twice the input, the output will be twice as strong. However, because neurons have thresholds and synapses are plastic, the responses are very nonlinear. Furthermore, neurons are a mixture of **deterministic** behavior, where its behavior can be determined from its past and its inputs, and **stochastic**, where the activity is also due to some noise in the system which cannot be accounted for.

The statistics of the coupling within a network is called the **topology**. A list of all the connections within a network is called the **graph.** If nodes have a physical location in space, such as brain regions, and coupling is dependent on the

distance, the network is considered to have a **geometry**.

In summary, neuronal networks are nonlinear, directional weighted graphs with a geometry. These networks are called complex networks, and few tools have been developed to analyze them. The development of these network analysis tools is at the cutting edge.

Detailed Description

The goal of these encyclopedia entries is to provide an introduction into the network theory. In the first entry (▶ "Network Theory in Neuroscience"), there is an overview of the network theory and its applications to diseases. In ▶ "Functional Network Observations of Diseased Brain States," there is an introduction to functional networks in neuroscience. In ▶ "Determining Network Structure from Data: Nonlinear Modeling Methods," we will introduce methods for reconstructing networks from the data using nonlinear measures. In ▶ "Master Stability Function for Globally Synchronized Systems," we introduce a universal approach to determining if a network will synchronize given the dynamics of the individual components and the network topology, through the analysis of the master stability function. In ▶ "Connectionist Models of CPG Networks," we will provide an introduction to non-synchronous network behaviors, such as seen in central pattern generators. In ▶ "Neuropathologies and Networks," we will introduce pathological network function to characterize diseases.

Cross-References

- ▶ Connectionist Models of CPG Networks
- ▶ Determining Network Structure from Data: Nonlinear Modeling Methods
- ▶ Functional Network Observations of Diseased Brain States
- ▶ Master Stability Function for Globally Synchronized Systems
- ▶ Network Theory in Neuroscience
- ▶ Neuropathologies and Networks

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Brainstem Processing: Overview

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Detailed Description

The brainstem has received considerably less attention by computational neuroscientists than other regions of the mammalian brain. This section highlights key areas that have received attention: neural circuitry underlying the generation and control of the respiratory rhythm, the baroreflex underlying the regulation of blood pressure, and pathways for pain processing. Entries in this section cover all three of these areas.

The article titled ▶ "Baroreflex Models" reviews over two decades years of computational models focused on neural pathways where blood flows in response to pressure changes in the circulatory system mediated by the baroreflex pathway.

Much attention has been given to the modeling of respiratory rhythm generation. The generation

and control of breathing is covered by two entries in this section. The entry titled ▶ "Pre-Botzinger Complex Rhythm Generation" surveys computational models of rhythmic activity in the pre-Bötzinger complex, which underlies the inspiratory component of respiratory rhythm generation and is a central pattern-generating circuit itself when isolated. The article titled ▶ "Control of Breathing, Integration of Adaptive Reflexes" describes computational models of adaptation and plasticity of the respiratory rhythm in response to external perturbations. There are also relevant articles in other sections of this encyclopedia, including ▶ "Computational Models of Mammalian Respiratory CPG" and ▶ "Brainstem Motoneurons, Models of".

The area of pain processing has received much less attention by computational neuroscientists. The article titled ▶ "Pain Processing Pathway Models" summarizes computational efforts in this area.

Cross-References

- ▶ Baroreflex Models
- ▶ Brainstem Motoneurons, Models of
- ▶ Computational Models of Mammalian Respiratory CPG
- ▶ Control of Breathing, Integration of Adaptive Reflexes
- ▶ Pain Processing Pathway Models
- ▶ Pre-Botzinger Complex Rhythm Generation

Cable Theory: Overview

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Detailed Description

Cable theory has a prominent place in neuroscience as it forms the basis of models of single neurons, axons, and dendrites and has led to an understanding of intraneuronal signaling. Starting with the conceptual model of a patch of membrane as an electric circuit, application of basic principles from physics leads to a mathematical equation, the cable equation. We start this section with an article on the cable equation, discussing the history of the cable equation in neuroscience, showing the derivation of the cable equation, providing solutions for the infinite cylinder, steady-state solutions for semi-infinite and finite cables and branched dendritic trees and transient solutions, concluding with a discussion of insights from cable theory. Several parameters play key roles in intraneuronal signaling including membrane capacitance, axial resistivity, the space (length) constant, and the time constant, and there are articles on each of these topics. From there we have two articles describing work done by Wilfrid Rall, widely regarded as the father of computational neuroscience. The first describes how Rall applied cable theory to dendritic trees and showed that given certain conditions a highly branched dendritic tree could be reduced mathematically to an equivalent cylinder. The simplicity and elegance of the equivalent cylinder model permitted mathematical analyses and insights regarding signaling in otherwise morphologically complex dendritic trees. The second describes various formulas Rall derived to estimate the electrotonic length of dendritic trees from simple voltage transients, formulas that have been applied in hundreds of studies. Finally, there are three articles that discuss extensions of cable theory in various ways. The first presents the morphoelectrotonic transform, a procedure that addresses the issue that attenuation of voltage from a synaptic input from the dendrite to the soma is not simply given by the electrotonic distance because of the effect of boundary conditions. The morphoelectrotonic transform provides a graphical means to visualize voltage attenuation both toward the soma and away from the soma, directly and intuitively. The second introduces the continuum theory for modeling dendritic spines. While there are various ways to incorporate the effect of dendritic spines in models, the continuum theory describes a novel way of doing this within the cable equation. Lastly, insights can be obtained from the

quasi-active approximation of a nonlinear cable. Here classic passive cable theory is extended by linearizing voltage-dependent conductances around a given membrane potential cable allowing the effect of voltage-dependent conductances on dendritic filtering to be studied mathematically. Almost all of these articles assume membrane is passive, but it is clear that both dendrites and axons contain voltage-dependent conductances. Nevertheless, cable theory is important for providing a basic understanding of intraneuronal signaling that forms the basis for understanding what happens with active conductances.

Cross-References

- ▶ Cable Equation
- ▶ Capacitance, Membrane
- ▶ Dendritic Spines: Continuum Theory
- ▶ Electrotonic Length, Formulas and Estimates
- ▶ Equivalent Cylinder Model (Rall)
- ▶ Morphoelectrotonic Transform
- ▶ Quasi-active Approximation of Nonlinear Dendritic Cables
- ▶ Resistivity, Axial
- ▶ Space (Length) Constant, Lambda, in Neuronal Signaling
- ▶ Time Constant, Tau, in Neuronal Signaling

Cerebellum: Overview

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Definition

The cerebellum processes sensory and motor information. Structurally is divided in the cerebellar cortex network and the deep cerebellar nuclei. Inputs to the cerebellar cortex arrive via the mossy fibers from multiple sources; mossy fibers contact granule cells, Golgi cells and unipolar brush cells. The second input to the cerebellar cortex comes from the inferior olive in the form of climbing fibers that synapse Purkinje cells. The output of the cerebellar cortex is provided by Purkinje cells that integrate the synaptic activity of climbing fibers, granule cells, and inhibitory interneurons. Golgi cells provide an inhibitory feedback mechanism to the granule cell layer. The deep cerebellar nuclei are the final integrator of cerebellar information. Cells in the deep cerebellar nuclei receive input from Purkinje cells, mossy fibers and climbing fibers.

Detailed Description

Cerebellar Cortex

The widely studied cerebellar cortex is composed, mainly, of four types of neurons: Granule cells, Purkinje cells, inhibitory interneurons (stellate and basket), and Golgi cells. There are two inputs to the cerebellar cortex provided by mossy fibers and climbing fibers. Climbing fibers are axons from inferior olivary neurons. Mossy fibers are a collection of axons from multiple areas that can carry direct sensory or cerebro cortical information. The arrangement of the cerebellar cortical neurons is regular across the cortex. Mossy fibers contact granule cells and Golgi cells. Granule cells send an axon into the molecular layer that bifurcates. The bundle of bifurcated axons is known as the parallel fibers. Parallel fibers contact Golgi cells, inhibitory interneurons and Purkinje cells as they traverse the cerebellar cortex. Climbing fibers synapse onto Purkinje cells.

The particular arrangement of granule cell-to-Purkinje cell connectivity was very attractive to computational scientist early on. The 'Beam Hypothesis' stated that a focal stimulation of the granule cells would be transformed into a sequential activation of Purkinje cells along the path of the parallel fibers (Braitenberg and Atwood 1958). The evoked inhibitory activity from parallel fiber to inhibitory interneurons would reduce the activity of the Purkinje cells on either side of the beam of activated Purkinje cells. The feedback mechanism provided by Golgi cells on to granule cells would then reduce over-excitability. The central mechanism of information processing in

this model is the existence of a beam of activated Purkinje cells following the local stimulation of granule cells.

The lack of beams of Purkinje cell activity reported by multiple teams over the years has prompted a discussion on how the cerebellar cortex processes information. Several reports have shown that Purkinje cells are activated only when they are directly above the cluster of stimulated granule cells. The Purkinje cells along the parallel fiber path are either inhibited or show no change in firing rate. Experimental and computational evidence has shown that this is due to fast feed-forward inhibition from the inhibitory interneuron on Purkinje cells concomitantly stimulated by parallel fibers. In fact, blocking of inhibition reveals a beam of Purkinje cell activity as predicted by the Beam Hypothesis (Santamaria et al. 2007). Thus, the emergent understanding is not that different from a center surround receptive field model. Under this perspective, granule cell synapses are effective in driving Purkinje cells to fire only when the Purkinje cells are close to the site of stimulation. Parallel fibers provide excitatory and feed forward inhibitory input to Purkinje cells far from the site of stimulation without this stimulation being reflected in changes of the Purkinje cell firing rate. However, the dendritic stimulation results in activation of voltage sensitive calcium channels and calcium activated potassium channels, modifying the excitability of the dendrite. This dendritic activation can then modify the response of the Purkinje cell to direct granule cell stimulation. Therefore, the long range effect of parallel fibers is to provide contextual information.

The Purkinje cell was one of the first neurons to be studied using the compartmental modeling approach. The large amount of information on somatic and dendritic conductances permitted to develop detailed compartmental models. These models have been reused and enhanced over the years to study different aspects of cerebellar function (De Schutter and Bower 1994; Steuber et al. 2007). There are also several models of inhibitory interneurons, Golgi cells and granule cells. Recent work suggests that the Purkinje cell might be simplified to a perceptron (Clopath et al. 2012).

Synaptic Plasticity

Long term depression (LTD) in the parallel fiber-to-Purkinje cell synapses is a model of learning and memory (Ito 2006; Feil et al. 2003). LTD is induced by the concomitant activation of the climbing fiber input and stimulation of a small bundle of parallel fibers. It is widely assumed that the climbing fiber stimuli carries a training or error signal, while the encoding signals, e.g., motor command, is encoded in the parallel fiber activity. The biochemical transduction cascade is very well understood and has been modeled using mass action and Monte Carlo models (Doi et al. 2005). These models and their experimental tests have pointed out to positive feedback biochemical loop that triggers and sustains LTD. Briefly, LTD is induced by the influx of calcium ions through voltage sensitive channels and release from intracellular stores. Calcium ions activate protein kinase C (PKC) which eventually activates mitogen associated protein kinase (MAPK). MAPK interacts with other substrates to produce arachidonic acid which in return activates more PKC. PKC then continues working in the feedback loop or phosphorylate AMPA receptors. Phosphorylated AMPA receptors are then internalized and the synaptic strength is reduced. The activation of the feedback loop is not a linear integrator of calcium concentration, instead it acts as a leaky integrator, thus the total amount and the temporal release of calcium determines the expression of LTD (Tanaka et al. 2007; Xia et al. 2000.).

Other Cells in the Cerebellar Cortex

There are other types of cells not traditionally included in cerebellar models. Lugaro cells are interneurons that are located in the granule cell layer (Lainé and Axelrad 1996). These neurons receive input from Purkinje cells and could be connected among themselves with gap junctions. These cells seem to be inhibitory and hypothesized to work in the burst frequency response of the granule cell layer. Another type of neuron,

primarily located in the vestibulo cerebellum, is the unipolar brush cell. These cells receive inhibitory inputs from Golgi cells and excitatory inputs from mossy fibers. Unipolar brush cells have multiple excitatory targets in the granule cell layer (Mugnaini and Floris 1994).

The Deep Cerebellar Nuclei

The deep cerebellar nuclei (DCN – dentate, interpositus, and fastigii) receive inhibitory inputs from Purkinje cells and excitatory activity from mossy fibers and climbing fibers. The cell from the cerebellar nuclei generates the bundles of axons that go to other areas of the brain. The cells of the DCN can be thought as the final and global integrator of the input and output signals to the cerebellum. DCN cells integrate inputs from the brain stem, inferior olive, and spinal cord with the Purkinje cell output from the cerebellar cortex. There are excitatory and inhibitory DCN neurons with their electrophysiological and computational contributions still being studied. The precise spike timing control of DCN spiking by Purkinje cell is believed to be the mechanism of the precise motor skills (Gauck and Jaeger 2000).

Summary

Although the function of the cerebellum is still being debated, how it processes information is becoming clearer due to vast amount of experimental information from ultra-structure to electrophysiology and behavior. Altogether, this large amount of data allows computational scientist to build realistic models at different levels of detail that can be experimentally tested.

Cross-References

- ▶ Deep Cerebellar Nuclei
- ▶ Long Term Depression in the Granule Cell-Purkinje Cell Synapse
- ▶ Modeling Cerebellar Learning: Input Minimization
- ▶ Multiscale Modeling of Purkinje Cells
- ▶ Olivocerebellar Pathway

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Computational Neuroanatomy: Overview

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Definition

Computational neuroanatomy is a subfield of neuroscience that aims to create functionally and structurally accurate models of the nervous system. These models are based on a wide range of input data, including microscopy and electrophysiology. These data acquisition methods encompass the broad scales across which neuroanatomy plays a role: (1) nanostructure describing individual connections between cells, (2) microstructure describing neuronal shape and cell type, and (3) gross structure describing cross-brain connectivity patterns. Computing in this field draws largely from the need to synthesize multiple modalities to statistically generate accurate models of morphology. For example, properties such as morphological structure, connection topology, wiring principles, and growth rules are statistically drawn from multiple sources and combined into motifs representing large-scale connectivity. High-performance computing can then be leveraged to simulate and verify the resulting models, with the end goal of studying neural behavior in silico.

Detailed Description

Computational neuroanatomy deals with the development of structural and functional models of the nervous system. The structural data forming the basis for these models are collected across multiple scales using a variety of data-acquisition and imaging modalities. Electron microscopy is used to acquire ultrastructural information of synapses, axon terminals, and dendritic spines at the nanometer scale. Advances in serial sectioning electron microscopy have enabled the investigation of whole neurons at this scale, with large-scale efforts focused on three-dimensional reconstruction. Optical microscopy (bright field and fluorescence) is often leveraged at the micrometer scale to study neuronal morphology, local circuits, and long-range projections. Both physical and optical sectioning is routinely used to obtain 3D volume data. Magnetic resonance imaging (MRI) and other noninvasive techniques are frequently employed for mapping cortical areas, major nuclei and fiber tracts, as well as functional data across the entire brain network.

Topics of study in computational neuroanatomy focus largely on model reconstruction and generation. This includes data mining from multimodal images using segmentation algorithms, morphometry, and statistics. This raw reconstructed data must also be analyzed to establish fundamental rules for constructing viable large-scale models. This requires topological analysis (small world, scale-free, etc.), growth and development models, organizational and optimization principles (e.g., wiring length minimization, self-organization, etc.), representation and ontology, and neuroinformatics. In addition, tools must be designed to enable viable exploration of neuroanatomical structures across multiple scale, integrating visualization, and comparative analysis. One of the major goals of comparative tools is the study of diseased versus healthy neuroanatomy, as well as inferring function from structure. Early studies in computational neuroanatomy, especially at the cellular level, were strongly motivated by the need for morphologically detailed multicompartmental models for use in neuron simulators such as NEURON (Carnevale and

Hines 2006), GENESIS (Bower and Beeman 2012), and others (Ascoli 2002).

Overview of Chapters

The computational neuroanatomy section features chapters that touch upon the topics listed above. The chapters can be roughly grouped into four categories: (1) brain atlases and the connectome, (2) imaging, (3) geometric reconstruction, and (4) wiring principles and synthetic models.

The first group includes four chapters: (1) ▶ "Brain Atlases," a collection of pointers to other chapters that describe in detail available brain atlases; (2) ▶ "Connectome, *Drosophila*," a chapter with a detailed survey of the known partial connectomes of the *Drosophila*, with perspectives on the utility, progress, and future of *Drosophila* connectome research; (3) ▶ "Connectome, Mouse," with a survey of publicly available mouse connectome data; and (4) ▶ "Connectome, General," a general survey of connectomics, its potentials, and its challenges.

The second group includes imaging related chapters: (1) ▶ "Imaging, Electron Microscopy" discusses the use of electron microscopy for computational neuroanatomy, and (2) ▶ "Imaging, Specimen Preparation" presents methods for brain specimen preparation for subsequent sectioning and imaging. (There are other imaging modalities that are relevant to computational neuroanatomy such as ▶ "Physical Sectioning Microscopy" and others discussed in the Brain Imaging section.)

The third group of chapters includes reconstruction algorithms for the extraction of geometrical information from the raw image volumes: (1) ▶ "Reconstruction, Electron Microscopy" discusses reconstruction techniques for densely packed neurons in electron microscopy image stacks; and (2) ▶ "Reconstruction, Techniques and Validation" talks about general reconstruction methods and validation techniques.

Finally, the fourth group of chapters consists of theoretical insights and computational simulation methods that analyze and utilize the quantified neuroanatomical data: (1) Networks/Networks discusses various methods for automated generation of realistic neurons and neuronal circuits for use in computer simulations (also see ▶ "NeuroMorpho.org"); and (2) ▶ "Wiring Principles, Optimization" presents optimization principles that could potentially be underlying neuronal morphology and connectivity patterns found in the brain.

Other Related Chapters and Resources

There are several chapters beyond this section (and sometimes whole sections) in this encyclopedia that are directly relevant to computational neuroanatomy: (1) Brain Imaging (▶ "Connectivity Analysis in Normal and Pathological Brains," ▶ "Multiscale Brain Connectivity"), (2) Brian Scale Networks (▶ "Network Theory in Neuroscience," ▶ "Neuropathologies and Networks"), (3) Databases in Computational Neuroscience (▶ "NeuroMorpho.org" and many other chapters in this section are relevant), and (4) Model Reproducibility (▶ "NeuroML").

Also see the following edited books and monographs on computational neuroanatomy: (Ascoli 2002; Capowski 2012; Chung 2013).

Notable omissions at the moment include (1) dendritic spine morphology and statistics (Bourne and Harris 2008), (2) delay (axonal conduction delay and integration time) and delay statistics (Lamme and Roelfsema 2000; Nowak and Bullier 1997), and (3) how to utilize gene expression data combined with structural information to infer function (Toledo-Rodriguez et al. 2004).

Conclusion

Computational neuroanatomy provides the foundational framework for building, quantifying, and visualizing comprehensive models of large neurological tissues. These models form the foundation for understanding neural computation by providing the ability to validate hypotheses in silico as well as compare networks for the study of aging and neurodegenerative diseases. Computational neuroanatomy also forms the backbone of connectomics (Sporns et al. 2005), enabling the eventual understanding, replication, and repair of neurological tissues.

Cross-References

- Brain Atlases
- Connectivity Analysis in Normal and Pathological Brains
- Connectome, *Drosophila*
- Connectome, Mouse
- GENESIS, the GENeral NEural SImulation System
- Imaging, Electron Microscopy
- Imaging, Specimen Preparation
- Multiscale Brain Connectivity
- Network Theory in Neuroscience
- NeuroML
- NeuroMorpho.org
- NEURON Simulation Environment
- Neuropathologies and Networks
- Physical Sectioning Microscopy
- Reconstruction, Electron Microscopy
- Reconstruction, Techniques and Validation
- Wiring Principles, Optimization

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Cortex: Overview

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Detailed Description

Anatomically, the cerebral cortex is the outermost neuronal tissue of the brain, and it is believed to play a key role in sensation, perception, higher cognitive functions, and motor control. It is a layered structure referred to as the gray matter, because it contains largely cell bodies as compared to the white matter containing largely myelinated axons. The evolutionary origin can be traced back to reptiles, but it first appeared as a uniform structure in early mammals. The increase in the size of this layered cortical sheet during evolution is believed to be crucial for the development of human cognition and ultimately human culture during human brain evolution. Even though many entries in this section on "Cortex: Models and Computation" are applicable to the **[hippocampus]** as well, the focus is on the phylogenetically younger six-layered neocortex.

Why is it so interesting and important to investigate the cortex using modeling? If the co-occurrence of the expansion of the neocortex during evolution of the emergence of human cognition and culture is more than a suspicious coincident, then understanding the cortex is essential to understand the human condition. Identifying brain and mind is certainly a too naïve approach, but it is now widely accepted that – whatever the relation between mind and brain is – an understanding of cortex will at least constrain theories of how the mind works. Testable theories and predictive models are needed to complement conceptual modeling and colloquial talk on that matter. Moreover, understanding how the cortex operates may help to diagnose neurological diseases earlier, to develop more efficient treatments,

and to construct **[brain-machine interfaces]**. Models in general, and patient-specific models in particular, will be useful to link measurements of macroscopic brain activity obtained with brain imaging techniques to the underlying causes. This rather practical justification for modeling cortex is becoming even more relevant today as a "deliverable" of computational neuroscience. However, accurate and faithful modeling has to deal with the complexity of the neural circuits and the cellular and synaptic heterogeneity. Multiple large-scale initiatives currently address this by collecting massive amounts of data to facilitate the development of faithful models of the cortex. Here, the role of cortical models is in organizing and summarizing the data, and they could even be integrated into (semi)automatic data-driven modeling pipelines with little intervention of a "modeler." I argue that modeling cortex is interesting and exciting, because despite massive amounts of available data, the activity of modeling will remain in large parts an art: Finding the right level of abstraction to arrive at insights for the question at hand can hardly be automated.

On the one hand, the neocortex is an umbrella for a set of distinct structures that differ, for example, in terms of their function, connectivity, and cytoarchitecture. On the other hand, Mountcastle (1978) suggested that similarities of these neocortical regions point to a common computational machinery in the sense that each region has the same basic architecture and operates according to the same computational principles. This is also the guiding idea of this section, without accepting it as a truism or dogma. It is indeed conceivable that different regions of the neocortex operate according to fundamentally different principles, or that conventional notions of "computation" are not suited as a metaphor to understand the cortex. The philosophy of science is not conclusive regarding a clear distinction of theory vs. model. However, as a tentative distinction for modeling cortex, we may adopt the short-hand definition that theory provides meaning to models, while models explain data. Computational principles come close to the notion of a theory. With that reading, the entries assembled in this section cover the whole spectrum between theories and models of cortex.

Robert Legenstein (▶ "Recurrent Network Models, Reservoir Computing") summarizes the state of the art in how artificial recurrent neural networks (RNNs) address demanding learning tasks. RNN researchers can be thought of as being in the luxurious position to investigate computations in cortex-inspired architectures without the burden to comply with all the constraints set by experimental neuroscience. The performance of these architectures and learning algorithms can serve as a yardstick for existing biologically more faithful models and as a guideline for constructing new models. Jochen Triesch's contribution on ▶ "Cortical Function, Normative Models of" gives a bird's eye perspective on how to derive models from computational principles. Cortical modeling involves determining model structure and parameterization, and for data-driven approaches, computational neuroscience has developed a **[rich repertoire of methods]**. The normative approach endorsed by Triesch is a complementary addition for doing this, which applies in particular to explaining cortical networks in terms of their genesis via **[learning mechanisms]**. The contributions of Sophie Deneve (▶ "Bayesian Inference with Spiking Neurons") and Walter Senn and Jean-Pascal Pfister (▶ "Reinforcement Learning in Cortical Networks") are instances of this normative approach. Deneve shows how Bayesian inference can be carried out by spiking neurons. The Bayesian approach turned out to be very fruitful for understanding computations in the cortex as evident by a whole section in this encyclopedia being dedicated to the **["Bayesian brain"]**. It should be noted that both Deneve's and Senn's and Pfister's entries explicitly address computation with spiking neurons and thus represent an explicit formal link between computational principles and experimentally testable predictions at the level of individual neurons. Both of these

mutually compatible approaches make explicit a notion of optimality as required within the normative approach: The Bayesian approach is based on a principled way of conducing logical inference under uncertainty, whereas reinforcement learning is based on Bellman optimality, i.e., **[decision making]** in dynamic and often only partially observable environments.

In a similar way, Udo Ernst (▶ "Center-Surround Processing, Computational Role of") addresses the phenomenon of center-surround processing (CSP) from a computational point of view. Even though CSP has been investigated mainly in the visual system, where it is exemplified, e.g., by the phenomenon of end stopping already described by Hubel and Wiesen (Hubel and Wiesel 1965), it is also a candidate for a canonical cortical computation to be found in various cortical regions. Ernst links CSP to the laws formulated by Gestalt psychologists in the early twentieth century but also to modern normative approaches that utilize the statistics of natural visual scenes in explaining physiological and perceptual phenomena. He points out that CSP has been successfully implemented in **[cortex-inspired artificial vision systems]**, where it improved object detection and recognition of natural scenes. Such real-world tests of cortical models are excellent yardsticks modelers may want to consider in addition to reproducing physiological or perceptual phenomena that are usually observed in rather artificial laboratory settings with less naturalistic stimuli. Michael Spratling (▶ "Predictive Coding") reviews the concept of predictive coding. This is an instance of a theory (in the sense defined above), but models derived from this theory can predict CSP as a by-product. The distinctive feature of predictive coding is that downstream areas in the hierarchically organized cortex continuously predict activity in areas at a lower level of the hierarchy. Given that downstream areas in sensory cortices integrate signals from neuronal populations with adjacent receptive fields (RFs), the predictions carry not only information about anticipated future inputs but also from the neighboring RFs as in CSP. Models derived from predictive coding are candidates for a canonical cortical computation. Applications to sensory cortices may be relatively straightforward, but the crucial test for a theory is its predictions when extrapolated beyond the *postdoc* explanations of already known phenomena. Let me point out three selected such extrapolations: First, it has been applied to explain mirror neuron activity as the natural consequence of predictive coding in the hierarchically organized "social brain" (Kilner et al. 2007). Second, it has been applied to interoception from which predictions about bodily self-consciousness could be derived (Seth et al. 2011). Third, it has been suggested that it may also be applicable to the **[motor system]** with the surprising consequence that the actual motor acts are carried out to fulfill predictions about sensory consequences of just these acts (Hawkins and Blakeslee 2004) as compared to being only the output stage of a sensory-to-motor transformation. Future experimental studies will need to further test these predictions. Interestingly, Spratling has shown that predictive coding and the concept of biased competition can be thought of as being just variants of the same mathematical model. Thus, while the interpretation of models derived from the predictive coding theory in terms of "prediction of inputs" may be unusual in some cases, as in the case of the motor system, the theory is still a rich framework to systematically derive mathematical models and testable predictions.

Computation cannot be considered in isolation. Communication engineers and designers of processors know this too well. Matthias Bethge (▶ "Efficient Population Coding") considers how much information is communicated by cortical networks. Bethge introduces the psychometric and neurometric functions and highlights that the information contained in the spiking activity of populations of neurons is often enough to predict the behavioral responses of the whole organisms. This is an empirical finding, but computational neuroscience also needs to ask more fundamental questions such as "how

much information can be transmitted?" Only this allows for assessing how close to optimality the cortical circuits are actually operating. To address such questions, he reviews how the concepts of Fisher and Shannon's mutual information can be applied to quantify the information content of population activity. Combining the approaches that focus on computation introduced so far with these studies of communication and information content could be a very fruitful direction for future studies, in particular when factoring in limitations due to fiber bottlenecks between cortical areas and energy expenditure.

RNNs are Turing-complete, which means that finite RNNs could, in principle, approximate any computation. However, to determine the computations actually performed by the cerebral networks, it is imperative to develop mechanistically plausible models that explicitly respect the anatomical and physiological constraints set by experimental neuroscience. Sean Hill (▶ "Cortical Columns, Models of") presents models of the so-called cortical column, which itself is a theoretical concept motivated by early experimental studies that showed smooth variation of functional properties tangential to the cortical surface but an invariance across cortical layers at a given position. The notion of a cortical column remains controversial, but for computational neuroscience it is certainly a goal to deliver predictive mechanistic models of signal propagation across cortical layers within an area. Probably the most prominent example of mechanistic network modeling to explain a physiologically observed phenomenon is the models for orientation tuning in primary visual cortex (V1), which are reviewed by Nicholas Priebe and Benjamin Scholl (▶ "Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling"). Hubel and Wiesel discovered orientation tuning (Hubel and Wiesel 1959) and formulated a first model, namely, that the tuning derives from the pattern of afferent connections from the thalamus onto neurons in V1. The subsequently developed models emphasized the role of intracortical connections to account for experimentally observed properties of orientation tuning such as contrast invariance. Interestingly, the original feedforward model by Hubel and Wiesel is still a guiding idea, even though it had to be refined. This highlights that such more informal and conceptual models remain valuable today, even though computational neuroscience has to show explicitly when and how models fail as reviewed by Priebe and Scholl.

In my first entrie (▶ "Center-Surround Processing, Network Models of"), I take a similar approach and address the question of how the CSP in V1, as introduced by Ernst, may be realized by cortical circuits. More specifically, I review network models of CSP that are distinct in terms of the assumed pathways. Early models emphasized the role of long-range connections within an area, but later models came to acknowledge the role of feedback from downstream areas. The cortical operating mode in vivo is characterized by strong recurrent excitation and balanced inhibition that affect how single neurons integrate and propagate signals (reviewed in my second short contribution ▶ "Balanced State"). Interestingly, more recent modeling studies investigated the role of short-range local connections in CSP and found that the properties of strongly connected recurrent networks in a balanced state need to be considered in models of CSP. Adaptation is another phenomenon that seems to be omnipresent in the cerebral cortex. Klaus Wimmer (▶ "Adaptation in Sensory Cortices, Models of") reviews models of adaptation and considers both their role in perception and how plausible mechanisms such as short-term synaptic depression mediate them. Since strongly recurrent networks in a balanced state with static synaptic connections may already exhibit counterintuitive phenomena, Wimmer argues for systematic modeling studies of structured networks with adaptation mechanisms as an important approach to understand adaptation in sensory cortices.

Selected examples of higher cognitive functions are attention and working memory. Cortical models of these functions are reviewed by Philipp Schwedhelm and Stefan Treue (▶ "Attentional Top-Down Modulation, Models of") and Gianluigi Mongillo (▶ "Working Memory, Models of"). Schwedhelm and Treue review

models of attentional top-down modulation. They highlight how phenomenological models have guided experiments and how those fed back into refining the models. Some of the models assume the mechanism of gain modulation but remain intentionally agnostic regarding the biophysical mechanisms. This exemplifies that cortical modeling with a properly chosen level of description could be integrated closely with experimental investigations. Working memory has also been studied experimentally in great detail, but most early network models of the persistent activity that is characteristic for the physiological correlate of working memory were variants of attractor networks, where a self-sustained "bump" of activity was identified with the content of working memory. Only more recent modeling studies suggested that self-sustained activity may not be restricted to the spiking activity of groups of neurons, because the state of synapses with short-term dynamics can also be considered as an activity variable that could be exploited to store self-sustained activity. The idea that synaptic variables, which are by multiple orders of magnitude more numerous than single cell state variables, may be crucial for cerebral information processing has been around in the computational neuroscience community for a long time. However, explicit formal models need to spell this out and show the potential benefit in, for example, systematic simulation studies even if the models are speculative and experimentally very hard to test as in the case of the synaptic theory of working memory. This also applies for models of attention: Given that after 50 years of the discovery of orientation tuning in V1, there is still no agreement on network models of even such a basal response property, it may not come as a surprise that the mechanisms of attention remain elusive. While, for example, mechanistic models of top-down gain modulation via synchronizing the discharges of inhibitory interneurons may be consistent with the available anatomical, physiological, and biophysical knowledge, recording multiple identified inhibitory interneurons in vivo in attentional demanding tasks remains to be achieved.

Another currently only poorly understood phenomenon is how the so-called resting state of the brain is generated and maintained. Computational Neuroscience research has already identified the problem of explaining mechanistically the ongoing low-activity state in recurrently connected *local* networks (Brunel et al. 2013) and derived models to explain them as a stable attractor. Joana Cabral and Gustavo Deco (► "Spontaneous Activity, Models of") review models of the *global* spontaneous activity that exhibits characteristic temporal properties and is found in the so-called default mode network. This activity (and the default mode network) has been studied intensively using functional magnetic resonance imaging (fMRI), but Cabral and Deco correctly point out that a deeper analysis of the network models is still needed to provide insights into the dynamical properties of the resting state.

The entries in this section cover computation and modeling of the cortex using different approaches and models at various levels of abstraction. Certainly, the cortex cannot be considered in isolation but needs to be modeled and understood in concert with other structures, such as the **[thalamus]** and **[basal ganglia]**. Will it be possible to understand cortex without modeling the whole brain or even closed sensory-motor loops within an "enactive" approach (Noe 2006) that states that to understand the brain – in our case, only the cortex – one needs to look at more than just the brain? This is indeed an open question that is of special interest for philosophers of science and mind. However, I argue that the cortex considered as a complex and self-assembled adaptive structure will remain a challenge for any kind of modeling conducted by Computational Neuroscientists who are open to empirical findings and brave enough to ignore irrelevant details without throwing out the baby with the bath water. The reward shall be motivating: to gain an insight into how the cortex works. Relevance and irrelevance of details needs to be decided on a case-by-case basis, which also depends on the taste of the modeler (or theoretician). Unfortunately, despite a multitude of models and some promising candidates for theories of cortical function, one needs to attest that we are not yet there: A unified theory of cortical computation with associated models still

needs to be derived *and* thoroughly tested. My own requirement for accepting such a theory is that it will cover at least the topics addressed by the entries in this section.

Cross-References

- ▶ Adaptation in Sensory Cortices, Models of
- ▶ Attentional Top-Down Modulation, Models of
- ▶ Balanced State
- ▶ Bayesian Inference with Spiking Neurons
- ▶ Center-Surround Processing, Computational Role of
- ▶ Center-Surround Processing, Network Models of
- ▶ Cortical Columns, Models of
- ▶ Cortical Function, Normative Models of
- ▶ Efficient Population Coding
- ▶ Emergence of Orientation Selectivity in the Cerebral Cortex, Modeling
- ▶ Predictive Coding
- ▶ Recurrent Network Models, Reservoir Computing
- ▶ Reinforcement Learning in Cortical Networks
- ▶ Spontaneous Activity, Models of
- ▶ Working Memory, Models of

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Databases and Data Repositories in Computational Neuroscience: Overview

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Definition

Computational neuroscience research often produces models that help explain empirical data and provide predictions about the biological systems that produce the data. Empirical and theoretical researchers can benefit from resources that facilitate model publication and exchange and provide neuroscience data that informs and contains these existing and future models.

Detailed Description

Databases of Computational Models

One category of databases in computational neuroscience is those that focus on computational models. The BioModels Database (Li et al. 2010; Vijayalakshmi et al. 2013) is a general repository of computational models of biological processes that includes some models from neuroscience. The SenseLab database, ▶ "ModelDB" (Migliore et al. 2003), provides a resource for published neuroscience models in a variety of formats. Many of these were developed specifically for simulating the electrophysiological and neurochemical properties of single neurons and networks of neurons, for example, with multicompartment Hodgkin-Huxley type

conductance-based models (Hodgkin and Huxley 1952). The Physiome Model Repository (see ▶ "Physiome Repository") (Yu et al. 2011) is a software suite that facilitates storage and management of models, focusing on those described in ▶ "CellML," a standard markup language for biological models. Similarly, ▶ "Open Source Brain" (Gleeson et al. 2010b) is a community platform for collaborative development of computational neuron and network models that utilizes open standards such as ▶ "NeuroML" (Gleeson et al. 2010a) to facilitate interoperability and visualization of neuroscience models developed by different researchers. Thousands of models at multiple scales (ion channels, neurons, circuits) have been converted to the NeuroML standard, and these can be obtained at NeuroML-DB (Birgiolas et al. 2015), which also reports the results of many standard physiological, morphological, and computational measurements and experiments on these models to better understand how they behave.

Databases of Neuron Morphology and Physiology

A second category of databases that are important for the computational neuroscience community includes those that contain structured information specific to neurons and their properties. For example, information on the detailed shapes of neurons (morphology) is compiled by NeuroMorpho (see ▶ "Neuromorpho.org") (Ascoli et al. 2007) which contains user-submitted neuron morphological reconstructions made, for example, using the Neurolucida application (Glaser and Glaser 1990). Similarly, other SenseLab databases (see ▶ "SenseLab: Integration of Multidisciplinary Neuroscience Data") including NeuronDB and CellPropDB (Crasto et al. 2007), contain information on the ionic currents and neurotransmitters expressed by each neuron and how these are distributed with respect to neuronal morphology.

Measured electrophysiological properties of neuron types, and the metadata associated with these measurements, are cataloged in the ▶ "NeuroElectro Project" (Tripathy et al. 2014). Detailed information on ion channel subtypes, including voltage and temporal dynamics, genetic homology, and corresponding literature references, is available at Channelpedia (Ranjan et al. 2011, http://channelpedia.net), a subproject within the Blue Brain Project (Markram 2006).

Information about neurons in specific brain areas, including many representative examples, are also publicly available. For example, the Neocortical Microcircuit Collaboration Portal contains information about primary somatosensory cortex (citation), The Allen Institute for Brain Science Allen Brain Atlas includes a Cell Types Database that covers primary visual cortex (Sunkin 2013), and ▶ "Hippocampome.org" covers hippocampus (Wheeler et al. 2015).

Relevant to these databases that provide data that are helpful for constraining computational models, the performance of models on experimental-data-driven unit tests is reported at SciDash.org, enabling direct model comparison on properties or predictions of interest.

Resources for Brain Connectivity

Another category of databases focuses on the anatomical organization of the brain. Here we provide some widely used examples, focusing on those that could provide quantitative constraints for modeling efforts. ▶ "BrainInfo" provides general information about brain areas, including what they do, where they are located, and what they contain. The Allen Institute for Brain Science provides brain-wide gene expression atlases, where the expression of each of the genes in the mammalian genome has been systematically quantified throughout the brain for a number of animal species and across stages of neural development, as well as anatomical connectivity of different brain regions (Lein et al. 2007, http://brain-map.org).

Parallel to this effort is the ▶ "Human Connectome Project" (Marcus et al. 2013), a large-scale effort to map complete structural and functional neural connections in vivo in individual humans. ▶ "BrainMap" (Laird et al. 2004) consists of a database and related software to search published functional and structural human neuroimaging experiments. In contrast, CoCoMac (Stephan et al. 2001; Bakker et al. 2012) is focused on the primate brain, containing records of tracing studies in the macaque. Finally, the ▶ "Cell Centered Database" (Martone et al. 2003, 2009) focuses on images

from light and electron microscopy, ranging from whole brain areas to subcellular compartments.

Other Resources

In addition to these neuroscience domain-specific databases are federated databases that provide linking facilities for cross-resource data integration. For example, NeuroLex (Larson and Martone 2013) provides a platform for community annotation of neuron types on the basis of morphological, neurochemical, or electrophysiological properties. Given this wealth of neuroscience resources, the ▶ "Neuroscience Information Framework (NIF)" provides tools for semantic search across these diverse databases (Gardner et al. 2008) through the development and incorporation of neuroscience domain-specific ontologies (Bug et al. 2008; Larson and Martone 2009; Hamilton et al. 2012; Imam et al. 2012). For example, in NIF, the search query "mitral cell" returns a number of database records including relevant research literature from PubMed, computational models from ModelDB, and connectivity information from BAMS.

The number and size of these databases continue to grow with the collection and contribution of ever more models and data. These databases give computational neuroscientists a powerful tool for constraining data-driven models and serve as an alternative to conventional literature searches.

Cross-References

- ▶ BrainInfo
- ▶ BrainMap
- ▶ Cell Centered Database
- ▶ CellML
- ▶ Hippocampome.org
- ▶ Human Connectome Project
- ▶ ModelDB
- ▶ NeuroElectro
- ▶ NeuroML
- ▶ NeuroMorpho.org
- ▶ Neuroscience Information Framework (NIF)
- ▶ Open Source Brain
- ▶ Physiome Repository
- ▶ SenseLab: Integration of Multidisciplinary Neuroscience Data

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Decision-Making: Overview

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Detailed Description

Much of computational neuroscience begins and ends with the responses of individual neurons. The field itself sprang from work in the 1950s aimed at uncovering the biophysical mechanisms underlying spike generation (Hodgkin and Huxley 1952), and other classic studies focus on the computational capabilities of dendritic trees and on how neural activity encodes sensory stimuli or statistical information about the world, to mention a couple of well-known examples (Dayan and Abbott 2001). A different point of view, however, is one in which neurons are the intermediaries between a subject and its environment. As the engines of behavior, neurons need to be computationally powerful for the express purpose of giving the subject an advantage, and hence their efficiency or performance should be measured with respect to the subject's success. So the computational neuroscience of decision-making is computational neuroscience in this context; it is the quest to understand how single-neuron activity contributes to nonreflexive actions, actions that cannot be predicted from a subject's history alone.

The idea of quantitatively explaining a person's subjective experiences based on the responses of specific groups of neurons goes back to the 1960s, with the work of Vernon Mountcastle and colleagues in the somatosensory modality. They found, for instance, that when a small probe, similar to the tip of a ballpoint pen, vibrates at a frequency of 2–40 Hz, the intensity of the evoked sensation reported by a person is directly related to the neural responses of a particular type of mechanosensory receptor under the skin, now known as a Meissner corpuscle (Talbot et al. 1968). Many design elements and analytical

techniques used in contemporary experiments were already laid out in those pioneering studies: they applied information theory to determine the coding capacity of sensory neurons (Werner and Mountcastle 1965) very much as is done today, except for the rudimentary computers, and they recognized neuronal variability, as well as rate versus temporal coding, as fundamental issues for neural computation (Werner and Mountcastle 1963). This early work was limited, however, because it compared psychophysical performance in one system (behaving humans) with neural activity in a different system (e.g., anesthetized monkeys). It was later, with studies like those of William Newsome and colleagues (Salzman et al. 1992), that vision became the more popular modality and that both behavioral and neuronal responses were simultaneously recorded in the same subjects during the performance of perceptually based tasks. That became the standard and a cornerstone for investigating the neural basis of decision-making (Parker and Newsome 1998).

Thus, decision-making involves the study of neurons and neural circuits as a subject captures information about the sensory world; analyzes it; combines it with other stored information about current goals, priorities, and possible courses of action; and makes a response. In the laboratory, researchers attempt to simplify this as much as possible while still maintaining the essence of the process – an internal evaluation that is not fully predictable – and while measuring three quantities as accurately as possible: the sensory stimuli, the relevant neuronal activity, and the subject's behavior (Parker and Newsome 1998). So even the simplest possible decision-making task requires various types of neural computations, and indeed, one common strategy in the field has been to try to break down the problem into temporally discrete steps (e.g., fixation, stimulus presentation, response selection, reward delivery), to investigate how neurons in various areas participate in specific aspects of the decision-making process (Romo and Salinas 2003). The articles that comprise this section of the Springer Encyclopedia of Computational Neuroscience review key components of any such decision-making process.

Three of the entries (▶ "Decision-Making Tasks"; ▶ "Choice Behavior"; ▶ "Categorical Decisions") emphasize the repertoire of tasks and associated mathematical models that have been successfully used to characterize and quantify behavior. This provides a foundation for understanding how primary factors, such as reward availability or the quality of sensory information, drive a subject's actions and how different tasks place demands on different cognitive functions, such as perceptual discrimination, conflict resolution, or working memory capacity, to name a few. Selection of a particular behavioral task thus determines both the specific cognitive function and the corresponding neural circuits under investigation. In this context, it has become clear that individual choices are often influenced by a variety of subtle factors that superficially may appear inconsequential (▶ "Decision-Making, Bias"). Such sources of bias are likely to attract increasingly more attention in the future, as our ability to correlate neuronal activity and behavior becomes more sophisticated.

Most decision-making tasks have at least two components: a perceptual step during which current sensory information is analyzed (e.g., is that spot red or green?) and a motor report whereby the result of the perceptual judgment is indicated (e.g., push a left or a right button). The rest of the articles in the section focus either on perception (▶ "Accumulation of Evidence in Decision-Making"), motor planning (▶ "Decision-Making, Motor Planning"), or their interface and interaction. Although some neurons clearly relate to either perceptual or motor processing, it is often the case that the cells that correlate most strongly with a subject's choices have elements of both (▶ "Perceptual Decision-Making"). In fact, determining the degree to which a neural response encodes perceptual information versus a motor plan turns out to be surprisingly difficult (▶ "Target Selection vs. Response Selection"); the ambiguity arises even at the psychophysical level (▶ "Perceptual-Motor Dissociation"). In spite of this, a number of principles describing how neurons participate in the generation of perceptual judgments and ultimately produce choices have been identified (▶ "Perceptual Decision-

Making"). Furthermore, relatively simple quantitative models have been highly successful at reproducing not only the traditional behavioral metrics of performance and reaction time but also key aspects of neuronal activity (▶ "Accumulation of Evidence in Decision-Making"; ▶ "Decision-Making, Models"). Because of this, there is a relatively thorough understanding of at least some of the computations that are key to perceptual decision-making (▶ "Accumulation of Evidence in Decision-Making"; ▶ "Speed-Accuracy Tradeoff"; ▶ "Decision-Making, Threshold"). This trend is expected to continue.

Cross-References

- ▶ Accumulation of Evidence in Decision-Making
- ▶ Categorical Decisions
- ▶ Choice Behavior
- ▶ Decision-Making Tasks
- ▶ Decision-Making, Bias
- ▶ Decision-Making, Models
- ▶ Decision-Making, Motor Planning
- ▶ Decision-Making, Threshold
- ▶ Perceptual Decision-Making
- ▶ Perceptual-Motor Dissociation
- ▶ Speed-Accuracy Tradeoff
- ▶ Target Selection vs. Response Selection

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Deep Brain Stimulation (Models, Theory, Techniques): Overview

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Detailed Description

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for medically refractory patients with advanced Parkinson's disease (PD) (Benabid et al. 1991; Blond et al. 1992; Benabid et al. 2002; Deuschl et al. 2006) as well as for patients with early motor complications (Deuschl et al. 2006; Schuepbach et al. 2013). Several neurological diseases, such as Parkinson's disease (PD) or essential tremor, are characterized by pathological synchronization (Nini et al. 1995; Brown et al. 2001). Parkinsonian resting tremor, for example, seems to origin from a pacemaker-like population of neurons of the basal ganglia firing in a synchronized and oscillatory manner (Hutchison et al. 1997; Hurtado et al. 1999; Magill et al. 2001; Trottenberg et al. 2007). In contrast, under healthy conditions these neurons are active in an uncorrelated and desynchronized manner (Nini et al. 1995; Magill et al. 2001).

The standard DBS protocol employs permanent high-frequency (>100 Hz) pulse train stimulation (Benabid et al. 1991, 2002; Blond et al. 1992). Symptom suppression by DBS is strongly dependent on stimulation frequency – with only high frequencies (>100 Hz) being effective and effects being rapidly reversible (Birdno and Grill 2008). High-frequency DBS was developed empirically, mainly based on clinical observations and experimental results (Volkmann et al. 2006), and the mechanism of high-frequency DBS is still a matter of debate (Benabid et al. 2005).

Experimental observations indicate that during high-frequency DBS, a regular bursting mode is induced (Beurrier et al. 2002), and after a reduction of stimulation artifacts, robust bursting activity in STN neurons was observed in slice experiments (Beurrier et al. 2001). In the same experiments, the offset of stimulation was followed by a blockade of activity, i.e., a depolarization blockade (Beurrier et al. 2001). These observations were made in anesthetized animals and are contradicted by measurements in awake behaving primates (Anderson et al. 2003; Hashimoto et al. 2003; Dorval et al. 2008) and rats (McConnell et al. 2012). Other groups argue that high-frequency DBS blocks neuronal activity in relevant target areas during stimulation and therefore mimics the effect of tissue lesioning (Benabid et al. 2002). In 2005, Benabid and coworkers summarized different hypothetical mechanisms: membrane inhibition, excitation of excitatory and inhibitory afferents, jamming, excitation of efferents, and plasticity (Benabid et al. 2005). Novel experimental techniques, such as optogenetics, enabled to further reveal the mechanism of DBS and, in particular, of the stimulation of afferent axons projecting to the target region (Gradinaru et al. 2009).

Spatially extended single- and multi-compartment neuron models were used to evaluate the contribution of these different mechanisms (Grill and McIntyre 2001; Terman et al. 2002; Rubin and Terman 2004). For example, Grill and McIntyre (2001) showed that depending on the stimulation amplitude and the shape of the stimulation pulses, cells were either activated directly or fibers mediating excitatory or strong inhibitory action were activated. The activation of a larger number of structures takes place on the single-neuron level with different and possibly conflicting impacts on single-neuron dynamics (Grill and McIntyre 2001). For example, in the same neuron, the cell body (soma) is inhibited as a result of activation of presynaptic axons and GABA release, while the efferent axon is activated by the stimulation pulses on an approximately one for one basis (McIntyre et al. 2004). The various reactions of neurons toward stimulation on the network level further add complexity that is important for the creation of a sound model: cells responding differently to external inputs, such as somatosensory stimulation or stimulation owing to active movements, are present in the target tissue together with so-called no-response cells (Lenz et al. 1994). Therefore, high-frequency stimulation has a complex impact on these structures (Benabid et al. 2002; Shen et al. 2003). However, surprisingly, even single STN model neurons – lacking synaptic dynamics, neural circuitry, and contributions of glial cells – subjected to high-frequency stimulation reproduce clinically observed response characteristics (Pyragas et al. 2013).

To study another aspect of DBS, several groups use physical models based on Maxwell's equations to investigate the neuronal activation profile depending on electrode geometry and stimulation parameters (Butson and McIntyre 2005, 2006; Miocinovic et al. 2009; Yousif et al. 2008; Chaturvedi et al. 2010; Buhlmann et al. 2011).

While the standard DBS protocol was developed empirically (Volkmann et al. 2006), novel stimulation approaches are based on electrophysiological as well as computational concepts. Personalizing and optimizing high-frequency stimulation in real time by demand-controlled, adaptive DBS might constitute a superior high-frequency stimulation mode, as shown in an acute study in externalized patients (Little et al. 2013). In addition, modeling studies are used to further develop the stimulation algorithm, beyond standard high-frequency DBS, in order to finally establish superior stimulation mechanisms. For example, coordinated reset (CR), a patterned

stimulation protocol specifically targeting the reduction of synchronized activity, was developed by means of mathematical models (Tass 2003) and essentially aims at an unlearning of both abnormal synaptic connectivity and synchrony (Tass and Majtanik 2006). CR was successfully tested in a preclinical study, where 5 days of low-dose CR stimulation induced long-lasting therapeutic effects for 30 days (Tass et al. 2012). Another example is a closed-loop approach, which was controlled by the extent of oscillatory beta-band activity. During stimulus delivery, this approach resulted in a better reduction of akinesia as well as pallidal firing rates as compared to classical DBS in parkinsonian nonhuman MPTP-treated primates (Rosin et al. 2011). Finally, modifications of the standard HF protocol might offer a novel approach to improve the efficacy of deep brain stimulation (Brocker et al. 2013; Hess et al. 2013).

The combination of all these modeling and experimental and technological approaches plays a vital role in shaping our understanding and helps to improve the promising therapeutic intervention DBS.

Cross-References

- ▶ Computational Model-Based Development of Novel Stimulation Algorithms
- ▶ Computational Models of Deep Brain Stimulation (DBS)
- ▶ Computational Models Supporting Parameter Finding for Deep Brain Stimulation
- ▶ Computational Models to Optimize the Electrodes and Waveforms for Deep Brain Stimulation

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Dynamical Systems: Overview

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Definition

Many models of computational neuroscience are formulated in terms of nonlinear dynamical system (sometimes the dynamical system with noise) and include a large number of parameters. Therefore, it is difficult to analyze dynamics and find correspondence between parameter values and dynamical mode. Mathematical theory of dynamical systems and bifurcations provide a valuable tool for a qualitative study and finding regions in parameter space corresponding to different dynamical modes (e.g., oscillations or bistability). Thus, the dynamical systems (or nonlinear dynamics) approach to analysis of neural systems

has played a central role for computational neuroscience for many years (summarized, e.g., in recent textbooks, Izhikevich (2007) and Ermentrout and Terman (2010)).

Detailed Description

Theory of dynamical systems and bifurcations provides a list of universal scenarios of dynamics changes under parameter variation. For example, one scenario explaining the onset of oscillations is described by Andronov-Hopf bifurcation. In terms of neuroscience, this theory provides insight into the mechanisms underlying different neural response properties and firing patterns. Even more importantly, it allowed to elucidate the underlying mathematical structure that might be common to whole classes of firing behaviors. Thus, conclusions of such studies can be wide ranging, even if specific biophysical details of implementation may differ from case to case.

A common theme in all articles in this section is that they use concepts from nonlinear dynamics, especially geometrical methods like phase planes and bifurcation diagrams. Many exploit time scale differences to reduce dimensionality by dissecting the dynamics using fast-slow analysis, i.e., to separately understand the behaviors on the different time scales and then patch the behaviors together.

The articles in this section for the most part exploit the idealized model of neuron localized at one point (i.e., electrically compact neuron), focusing on the nonlinearities of spiking dynamics, and using biophysically minimal but biologically plausible description of neural dynamics. An article on ▶ "Fitzhugh–Nagumo Model" describes one of the first examples where dynamical systems approach has been applied to analysis of neural dynamics (Fitzhugh 1955). Although "Fitzhugh-Nagumo Model" is not biologically grounded and formulated in terms of the cubic nonlinearity, the model is still considered as one of the prototype models for excitable systems.

An article on ▶ "Morris–Lecar Model" describes the rich dynamic repertoire of the two-variable Morris-Lecar model, as its biophysical parameters are varied. The original detailed analysis of this model (Rinzel and Ermentrout 1998) has laid ground for similar approaches in many different contexts and provided a theoretical justification for influential Hodgkin's classification of "excitability types" (Hodgkin 1948, described in ▶ "Excitability: Types I, II, and III").

The articles on ▶ "Integrate and Fire Models, Deterministic" and ▶ "Theta Neuron Model" models target the most idealized end of the modelling spectrum where the spiking activity is represented by simple mathematical models. This approach to modelling of spiking times is fruitful for implementation in the large neural network and when mathematical analysis (in addition to numerical simulations) is desired.

Somewhat more intricate features of single cell dynamics are described in articles on modelling of ▶ "Postinhibitory Rebound and Facilitation" and ▶ "Spike-Frequency Adaptation" phenomena. Finally, the fast-slow dissection and bifurcation analysis really shine in the description of bursting behavior. The bursting dynamics (of individual cells or of population activity) is dissected into active and silent phases when trajectories are restricted to lower dimensional manifolds, and transitions between these phases correspond to reaching the manifold's boundary and jumping to a different manifold.

While most of these examples are for single-cell dynamics, the qualitative mathematical study is also applicable to the dynamics of neuronal networks and structures, especially in the mean-field approximations. One such example for network-generated rhythms is presented in the article on ▶ "Spike-Frequency Adaptation."

Of course, the models presented in this section are rather idealized and simplified for mathematical study compared to many other neuronal models that are designed to investigate the biophysical details of action potential generation: interaction of many known ionic currents, or the spatial propagation of activity, etc. Such minimalistic models however are invaluable when the problem or question at hand require only qualitative or semiquantitative characterizations of spiking activity. This is especially important in studies of large networks of interacting cells.

Cross-References

- ▶ Excitability: Types I, II, and III
- ▶ Fitzhugh–Nagumo Model
- ▶ Integrate and Fire Models, Deterministic
- ▶ Morris–Lecar Model
- ▶ Postinhibitory Rebound and Facilitation
- ▶ Spike-Frequency Adaptation
- ▶ Theta Neuron Model

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Dynamics of Disease States: Overview

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Synonyms

Dynamical diseases; Periodic diseases

Definition

Computational neuroscience provides insights into the mechanisms that underlie dynamic diseases of the nervous system. Neurocomputationally inspired therapeutic devices that replace functions lost due to disease offer tangible hope to many for a better life.

Detailed Description

The evolution of an illness is one of the clues that a physician uses to arrive at a diagnosis and treatment strategy for diseases that affect the nervous system. Is the onset acute or subacute? the clinical course self-limited, relapsing-remitting, cyclic, chronic progressive? and so on. The impetus for studying disease dynamics comes from the mathematics and physics communities: their long experience has shown that insights into mechanism often derive from examining how dynamics change. Consequently, the time evolution of a disease is modeled using differential equations and disease processes are described in terms of the stability and nature of the model's dynamical behaviors. In 1977, Michael Mackey and Leon Glass associated changes in physiological dynamics from healthy to unhealthy with changes in underlying control parameters (Mackey and Glass 1977). Subsequently, this concept of a *dynamical disease* was extended to that of a *dynamic disease* to account for the possibility that mechanisms other than those associated with changes in parameters may be involved (see entry ▶ "Dynamic Diseases of the Brain").

Computational neuroscience extends dynamical approaches to neurological disease in two ways (Erdi et al. 2017). First, by making it possible to include anatomical, physiological, and molecular details, computational models provide insights into how mechanisms acting at the level of molecules and individual neurons translate into phenomena manifested clinically at the bedside (see entry ▶ "Modeling of Disease: Physical and Molecular Level, Overview"). Historically, the two neurological diseases which provided the most insight into cortical function were temporal lobe epilepsy and classical migraine. Indeed the study of the geometry of migraine, drug, and flicker-induced visual fortification patterns (see entries ▶ "Stochastic Neural Field Theory," ▶ "Visual Hallucinations and Migraine Auras," and ▶ "Flicker-Induced Phosphenes") and their propagation (see entry ▶ "Migraines and Cortical Spreading Depression") has provided deep insights into the functional architecture of the visual cortex. Surgical approaches for the

treatment of patients with medically intractable epilepsy provided the impetus to directly record from cortex of awake humans. This, in turn, motivated studies into the ability of large populations of neurons to synchronize and generate seizures (see entry ▶ "Neural Population Models and Cortical Field Theory: Overview"). Moreover, computational models are now making it possible to gain insights into diseases ranging from blood pressure control (see entry ▶ "Baroreflex Models") to the nature of cognitive, functional, and psychiatric diseases of the nervous system that up to now have largely remained mysterious (see entry ▶ "Computational Psychiatry").

Second, by having "a disease in a computer model," it is possible to efficiently evaluate and refine treatment strategies in silico before applying them to humans (Jirsa et al. 2017). Computational challenges remain because of the presence of multistability (see enties ▶ "Multistability in Seizure Dynamics" and ▶ "Multistability: Stopping Events with Single Pulses") and time delays (see entry ▶ "Time-Delayed Neural Networks: Stability and Oscillations"). Indeed time-delayed, multistable dynamical systems have a tendency to generate transient oscillations that can be easily mistaken for limit cycle oscillations thus causing confusion (see entry ▶ "Delay-Induced Transient Oscillation (DITO) and Metastable Behavior").

Although the ultimate goal of medicine is cure, one cannot overlook the need to improve the patient's quality of life when cure cannot be achieved. The electrical properties of neurons make it possible to use electrical stimuli as a treatment modality. Applications range from aborting seizures with electrical stimuli (see entry ▶ "Multistability: Stopping Events with Single Pulses") to improving the quality of movements of patients with Parkinson's disease with deep brain stimulation (see entries ▶ "Parkinson's Disease: Deep Brain Stimulation", ▶ "Computational Models of Deep Brain Stimulation (DBS)", and ▶ "Deep Brain Stimulation (Models, Theory, Techniques): Overview"). Even noisy stimuli can benefit the function of cochlear implants in the hearing impaired or balance control in those with peripheral neuropathies by making it easier for the sensory nervous system to detect weak signals (see entry ▶ "Stochastic Resonance: Balance Control and Cochlear Implants"). In the last few years alone, these ideas have been translated into devices that can be used by patients, e.g., NeuroPace RNS® system for patients with epilepsy, Microsoft's Emma Watch® for patients with essential tremor, shoes with vibrating insoles to improve gait and balance in the elderly (Lipsitz et al. 2015).

As insight increases in our understanding of neural encoding, it is becoming possible to replace broken parts with electronic ones that perform the same function. The large number of articles in this encyclopedia point to the current enthusiasm in this therapeutic approach. Applications include restoring vision to the visually impaired (see entry ▶ "Retinal/Visual Interfaces (Models, theory, Techniques): Overview"), hearing to those who cannot hear (see entry ▶ "Peripheral Nerve Interface Applications, Cochlear Implants"), continence to those incontinent (see entry ▶ "Methodologies for the Restoration of Bladder and Bowel Functions"), and relief from pain to those who suffer (see entries ▶ "Pain Processing Pathway Models" and ▶ "Peripheral Nerve Interface Applications, Neuropathic Pain"). Dramatically it has become possible to interface the brain directly with electronic devices and make it possible for a patient to move robotic limbs by thought alone (see entries ▶ "Cortical Motor Prosthesis" and ▶ "Functional Neuroscience: Cortical Control of Limb Prostheses"). Even direct brain-to-brain interfaces are possible (Rao et al. 2014).

The frontier for dynamic disease is to understand the collective behaviors of the nervous system that emerge over the time scale of years. Can the development of an epileptic focus (epileptogenesis) be halted early so that an individual at risk never experiences a seizure? Can the rate of learning of a complex voluntary skill, such as the golf swing, by a patient with a robotic or stem cell-derived limb prosthesis be sped up to the point that the individual could enjoy the use of these limbs throughout a lifetime? Large, complex physical systems tend to self-organize dissipative structures, namely dynamical entities whose existence is maintained far-from-equilibrium by a

supply of energy. Already dynamical signatures of this self-organization, including power laws, have been observed in the bursting propagating activities of living neural populations (see entry ▶ "Neuronal Avalanches") and the dynamics of human balance control (see entry ▶ "Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights").

Computational neuroscience provides the tools for understanding how the nervous system learns to exert control thereby bringing to many tangible hope of a better life.

Key Entries

- Computational Psychiatry
- Dynamic Diseases of the Brain
- Epilepsy: Computational Models
- Flicker-Induced Phosphenes
- Functional Neuroscience: Cortical Control of Limb Prostheses
- Human Balancing Tasks: Power Laws, Intermittency, and Lévy Flights
- Migraines and Cortical Spreading Depression
- Multistability: Stopping Events with Single Pulses
- Neuronal Avalanches
- Parkinson's Disease: Deep Brain Stimulation
- Stochastic Resonance: Balance Control and Cochlear Implants
- Time-Delayed Neural Networks: Stability and Oscillations
- Visual Hallucinations and Migraine Auras

Cross-References

- ▶ Baroreflex Models
- ▶ Computational Models of Deep Brain Stimulation (DBS)
- ▶ Cortical Motor Prosthesis
- ▶ Deep Brain Stimulation (Models, Theory, Techniques): Overview
- ▶ Delay-Induced Transient Oscillation (DITO) and Metastable Behavior
- ▶ Intermittent Control of Movement and Balance
- ▶ Intermittent Control Strategy for Stabilizing Human Quiet Stance, A Model of the
- ▶ Methods for Optimizing Stimulus Waveforms for Electroceutical Control
- ▶ Modeling of Disease: Physical and Molecular Level, Overview
- ▶ Multistability in Seizure Dynamics
- ▶ Pain Processing Pathway Models
- ▶ Peripheral Nerve Interface Applications, Cochlear Implants
- ▶ Role of Delayed Feedback in Human Balancing
- ▶ Stochastic Neural Field Theory

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Gamma and Theta Oscillations, Hippocampus: Overview

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Detailed Description

The brain expresses several rhythms that are associated with normal and pathological states. The hippocampus is arguably the most heavily studied

structure in the brain for many reasons including its importance in learning and memory, and it generates several population activities that include theta and gamma rhythms. Many modeling studies have focused on these oscillatory activities, and the entries in this section detail much of this work. To develop and build models of any biological system, an in-depth appreciation of the biological and physiological basis of what is being modeled is required. This is provided in the ▶ "Hippocampus, Theta, Gamma, and Cross-Frequency Coupling" entry, where functional and experimental aspects are described, along with data analysis aspects in ▶ "Theta-Gamma Cross-Frequency Analyses (Hippocampus)." In developing models, the cellular units and how they are connected need to be examined. Three entries on ▶ "Hippocampus, Model Inhibitory Cells," ▶ "Hippocampus, Model Excitatory Cells," and ▶ "Hippocampus, Model Network Architecture" provide these details, and the challenges and complexities in these aspects are laid bare. Three theoretical entries on ▶ "Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models," ▶ "Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities," and ▶ "Mixed-Mode Oscillations in Single Neurons" provide the reader with the types of theoretical approaches that can be used to help understand how these subthreshold and mixed-mode activities that are present in hippocampal cells may contribute to theta and gamma rhythms. Gamma rhythms have been extensively studied both theoretically and experimentally, and as such, there are well-developed mechanistic understandings for their generation. These mechanisms are described and illustrated in the entry ▶ "Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)." This is not the case for theta rhythms or nested theta/gamma rhythms. However, network models have been developed and these are described along with the many considerations that arise in developing such network models in ▶ "Hippocampal Theta, Gamma, and Theta/Gamma Network Models."

In combination, the entries in this section provide the reader with a solid basis to learn about theta and gamma oscillations in hippocampus considering mathematical modeling and experimental perspectives. An appreciation of the many aspects that are involved, both general and specific, can be gained from reading these entries.

Cross-References

- ▶ Hippocampal Oscillations, Mechanisms (PING, ING, Sparse)
- ▶ Hippocampal Theta, Gamma, and Theta/Gamma Network Models
- ▶ Hippocampus, Model Excitatory Cells
- ▶ Hippocampus, Model Inhibitory Cells
- ▶ Hippocampus, Model Network Architecture
- ▶ Hippocampus, Theta, Gamma, and Cross-Frequency Coupling
- ▶ Mixed-Mode Oscillations in Single Neurons
- ▶ Quadratization: From Conductance-Based Models to Caricature Models with Parabolic Nonlinearities
- ▶ Subthreshold Antiresonance and Antiphasonance in Single Neurons: 3D Models
- ▶ Subthreshold Resonance and Phasonance in Single Neurons: 2D Models
- ▶ Theta-Gamma Cross-Frequency Analyses (Hippocampus)

General Overview of Spinal Anatomy and Physiology Organization

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Abbreviations

CNS	Central nervous system
CPG	Central pattern generator
CST	Corticospinal tract
DRG	Dorsal root ganglion

DSCT	Dorsal spinocerebellar tract
H-reflex (Hoffmann reflex)	Electrical analogue of the monosynaptic stretch reflex
PRV	Pseudorabies virus
RV	Rabies virus
SCI	Spinal cord injury
STT	Spinothalamic tract
VSCT	Ventral spinocerebellar tract

Definition

Organization of the mammalian spinal cord and activity-dependent and injury-induced plasticity of spinal pathways.

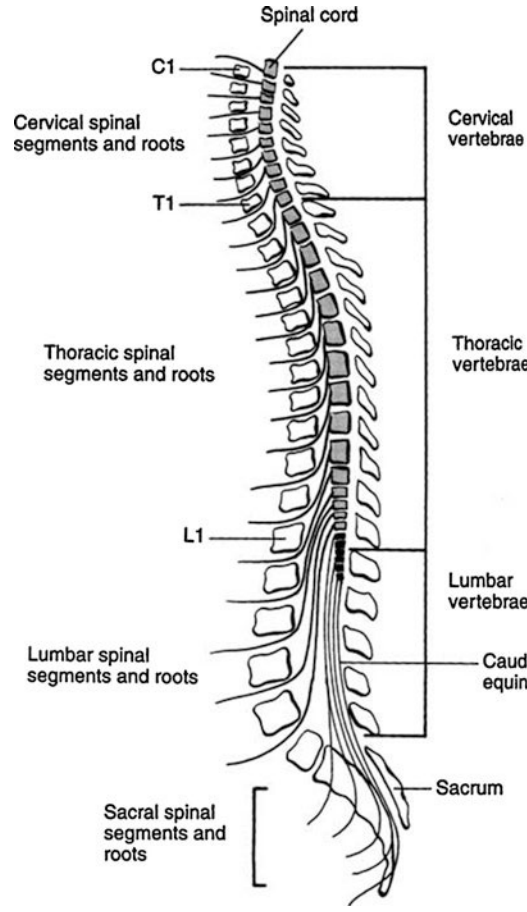
Detailed Description

Somatic perceptions, coordinated movements, and autonomic functions depend on the integrity of the spinal cord and its projections. In Part I of this entry, we describe the classic organization of the human spinal cord which is similar in most respects, except size, to other vertebrate spinal cords (see Sengul et al. 2012; Watson et al. 2010). The organization of the cord determines the accessibility of the neural structures for delivery of stimulation aimed at reengaging or modulating spinal neuronal output. In Part II, consideration is given to how spinal pathways may be modified by activity, injury, and injury followed by activity/stimulation, which is increasingly important in the development and application of rehabilitation protocols. Both type of activity and severity of injury are important in determining the optimal protocols for rehabilitation of individuals with spinal cord injury.

The Spinal Cord Is Organized Segmentally

The human spinal cord is comprised of 31 continuous spinal segments (Fig. 1). These are divided into cervical (C1 through C8) segments that supply the neck and arms, thoracic (T1 through T12) segments innervating the trunk and sympathetic ganglia, lumbar (L1 through L5) segments supplying the legs, and sacral (S1 through S5) and coccygeal (one segment) segments, supplying the saddle region, buttocks, pelvic organs, and parasympathetic ganglia. Dorsal and ventral roots enter and leave the vertebral column through intervertebral foramina at vertebral segments corresponding to the spinal segment. At its caudal end, the cord tapers to form the conus medullaris and the lumbar, sacral, and coccygeal roots extending to their appropriate vertebral levels to form a bundle, the cauda equina ("horse's tail").

The spinal cord is divided into cervical, thoracic, lumbar, and sacral segments. Note the exit of the lumbar and sacral roots through intervertebral foramina located caudal to the spinal segment with which the roots are associated.



General Overview of Spinal Anatomy and Physiology Organization, Fig. 1 Organization of the spinal cord

A segment is defined by dorsal roots that enter the cord carrying sensory information and ventral roots that exit the cord carrying motor commands (Fig. 2). The axons in the dorsal roots arise from dorsal root ganglion (DRG) cells located in paired ganglia lateral to the vertebral column. The axon from each DRG cell bifurcates to give rise to a centrally directed process (dorsal root axon or primary afferent) which projects into the spinal cord to terminate on neurons within the CNS. The peripherally directed axonal process enters a spinal nerve. Some of these peripheral sensory axons transmit information from sensory receptors in the skin; the strip of skin supplied by the peripheral process from cells in one dorsal root ganglion is known as a dermatome (Fig. 3). Other peripherally directed axons innervate the muscle spindles, sensory organs within muscles that mediate proprioception.

In this diagram of two segments of spinal cord, three dorsal roots enter the dorsal lateral surface of the cord, and three ventral roots exit. The dorsal root ganglion contains dorsal root ganglion cells whose axons bifurcate; one process enters the spinal cord through the dorsal root and the other extends peripherally to supply the skin and muscle of the body. The ventral root is formed by axons from motor neurons located in the spinal cord.

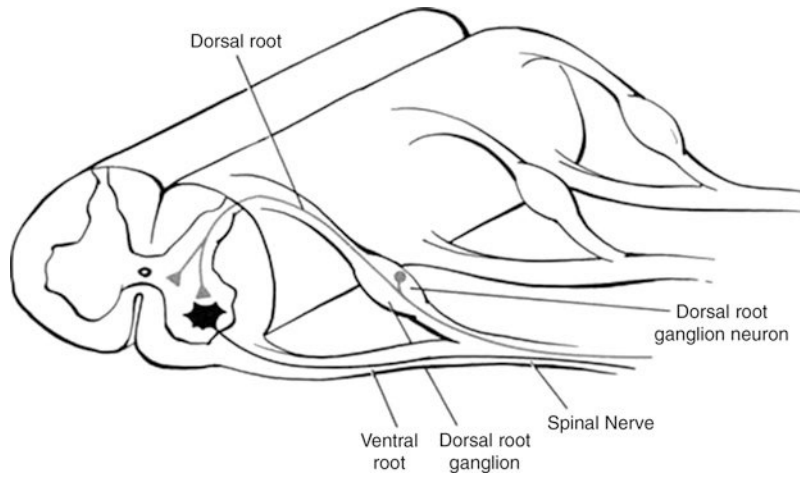
Axons from motor neurons in the spinal cord exit in the ventral roots and innervate skeletal muscles or autonomic ganglia. These ventral root axons join with the peripheral processes of the DRG cells to form spinal nerves, which contain both sensory and motor axons. Several spinal nerves may join to form a peripheral nerve.

Spinal Neurons Are Organized into Nuclei and Laminae

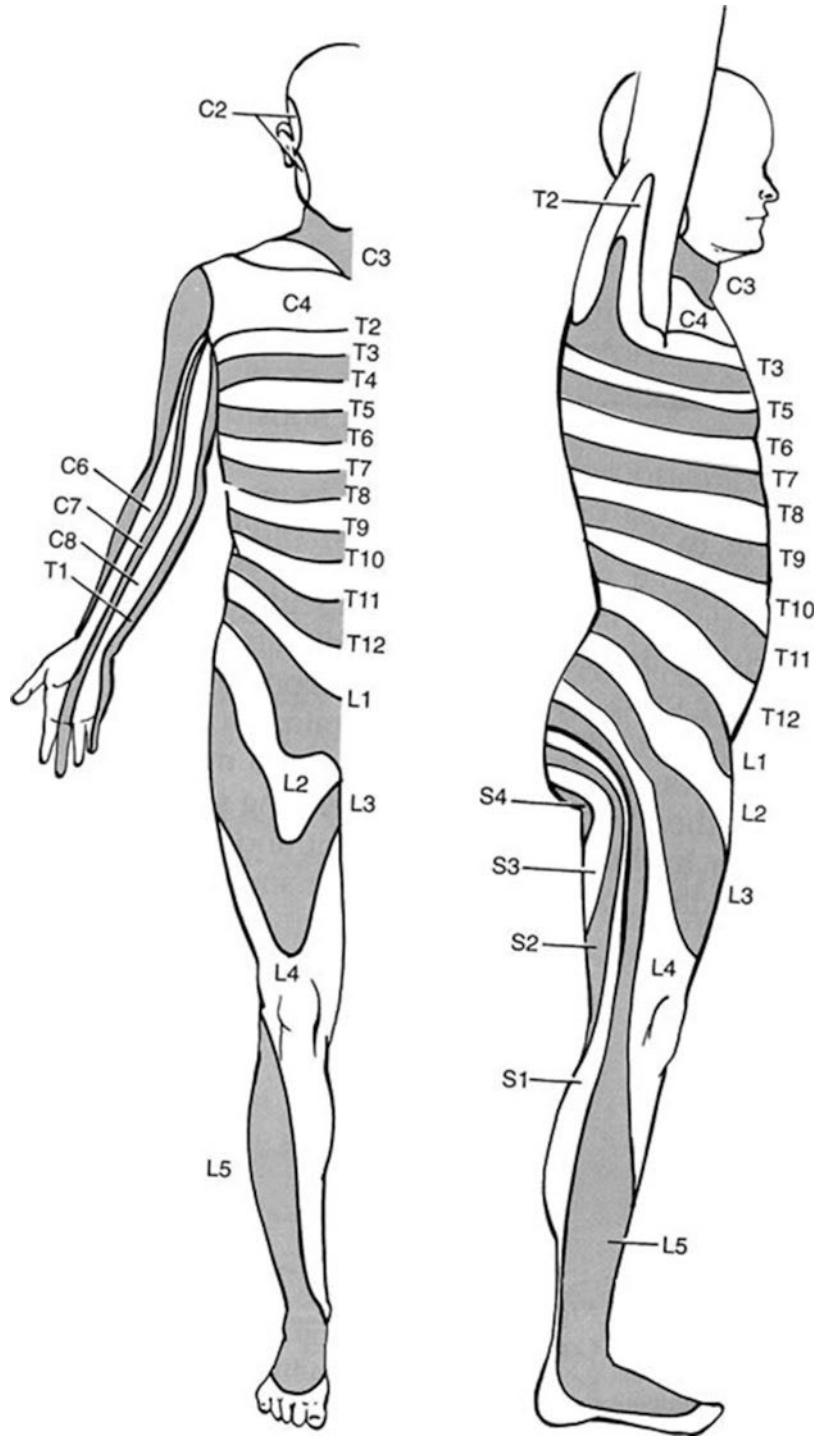
In cross sections, the spinal cord is composed of a butterfly-shaped core of gray matter, containing neuronal and glial cell bodies and their processes that is surrounded by white matter, composed of axons and their associated glial cells. The gray matter is subdivided into a sensory portion, the dorsal (or posterior) horn, and a motor portion, the ventral (or anterior) horn, separated by the intermediate zone (Fig. 4, Table 1).

Comparison of the classification schemes for the neurons in the gray matter of the spinal cord. On the right, a section stained to show cell size, distribution, and location of neurons in the lumbar spinal cord and, on the left, the related laminar boundaries.

The neurons in the spinal gray matter are also classified according to their projections. These include sensory relay neurons, which receive dorsal root input and whose axons project into ascending pathways that terminate in the brain or spinal cord, motor neurons whose axons exit in the ventral roots to synapse on muscle fibers or on neurons in autonomic ganglia, and propriospinal neurons, spinal interneurons whose cell bodies



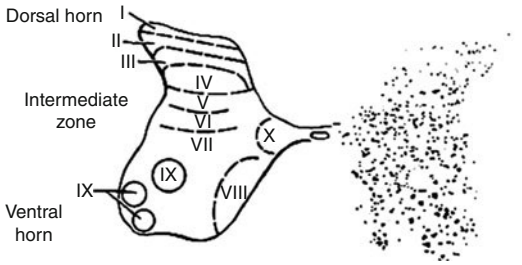
General Overview of Spinal Anatomy and Physiology Organization, Fig. 2 Spinal segments



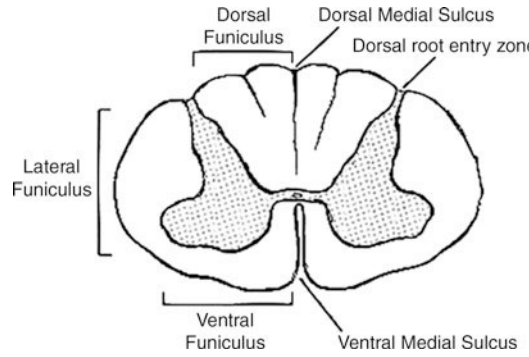
General Overview of Spinal Anatomy and Physiology Organization, Fig. 3 Dermatome. A dermatome is the area of skin supplied by axons from a single dorsal root ganglion

and axons are confined to the spinal cord. Propriospinal neurons are by far the most numerous, accounting for about 90% of all spinal neurons, and the most poorly understood.

Many of the neurons in the gray matter are clustered in functionally related nuclei. These nuclei may extend much of the length of the spinal cord, forming columns of cells, e.g., Clarke's



General Overview of Spinal Anatomy and Physiology Organization, Fig. 4 Organization of the spinal gray matter



General Overview of Spinal Anatomy and Physiology Organization, Fig. 5 External landmarks of the spinal cord

General Overview of Spinal Anatomy and Physiology Organization, Table 1 Classification of spinal neurons

Gray matter subdivision	Lamina	Nuclei included in laminae
	Lamina I	Marginal nucleus
Dorsal horn	Lamina II	Substantia gelatinosa
	Lamina III, IV	Nucleus proprius
	Lamina V	Reticular nucleus
Intermediate zone	Lamina VI	Commissural nuclei
	Lamina VII	Clarke's, intermediolateral
		Nuclei
Ventral horn	Lamina VIII	Medial motor nuclei
	Lamina IX	Lateral motor nuclei
Commissure	Lamina X	Central gray

nucleus, the intermediolateral nucleus, and motor neurons. In cross sections, the neurons in the gray matter can also be seen to be distributed in a laminar arrangement, particularly in the dorsal horn. Because the histologic differences among laminae reflect functional differences, the spinal gray matter is sometimes also classified into laminae.

The dorsal horn and intermediate zones (laminae I through VII) contain sensory relay nuclei and include the marginal nucleus (lamina I), the substantia gelatinosa (lamina II), and the nucleus proprius (laminae III, IV). Motor neurons are subdivided functionally into somatic and visceral motor neurons. Somatic motor neurons are located in the ventral horn (laminae VIII and IX) at all spinal levels and innervate striated muscle. All visceral motor neurons are located in the intermediate zone (lamina VII) at C8 through L3 (sympathetic) or S2 through S4 (parasympathetic) and innervate neurons in autonomic ganglia. Commissural neurons whose axons cross to the contralateral side of the spinal cord are located primarily in lamina X. These schemes for classifying spinal neurons are compared in Fig. 4 and Table 1.

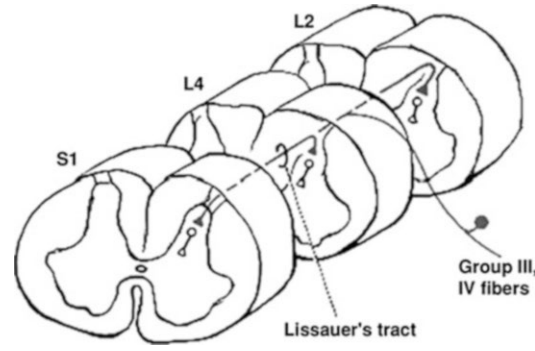
Ascending and Descending Tracts in the White Matter

The white matter is subdivided into three funiculi: dorsal (ascending pathways), lateral (ascending and descending pathways), and ventral (descending pathways), demarcated by the dorsal medial sulcus, the dorsal root entry zone, the ventral roots, and the ventromedial sulcus (Fig. 5). Propriospinal axons ascend and descend in the fasciculus proprius bordering the gray matter. Short propriospinal axons are located medially, immediately adjacent to the gray matter, and longer propriospinal axons ascend and descend, adjacent to the shorter axons.

Cross section of cervical spinal cord shows major landmarks and divisions of white matter.

Cells in the dorsal root ganglia and spinal gray matter give rise to the axons that form the ascending pathways that transmit sensory information to the brain. Cell bodies whose axons course in descending tracts are located in many parts of the brain. Their axons descend in the lateral and ventral funiculi and terminate on motor neurons or, more often, on propriospinal neurons that

project to premotor or motor neurons within the spinal gray matter. Descending systems provide central control of movement and posture. Some descending axons terminate on sensory relay neurons in the dorsal horn and can therefore modify sensory input to the brain. Propriospinal axons may be very short, connecting one cell with its neighbor, others (commissural fibers) cross the midline dorsal or ventral to the central canal, and long propriospinal axons ascend or descend in the white matter to connect distant segments of the cord (e.g., segments supplying upper and lower limbs).



General Overview of Spinal Anatomy and Physiology Organization, Fig. 6 Lissauer's tract

Sensory Pathways

The sensory input to the CNS from the body is organized according to information about the type of sensation (modality) and location of the stimulus. This information is used to produce appropriate spinal reflexes and is transmitted to appropriate parts of the brain for sensory processing. Information about a noxious stimulus to the skin is distributed in pathways that are different from those that transmit information about non-painful stimuli, such as light pressure or proprioception.

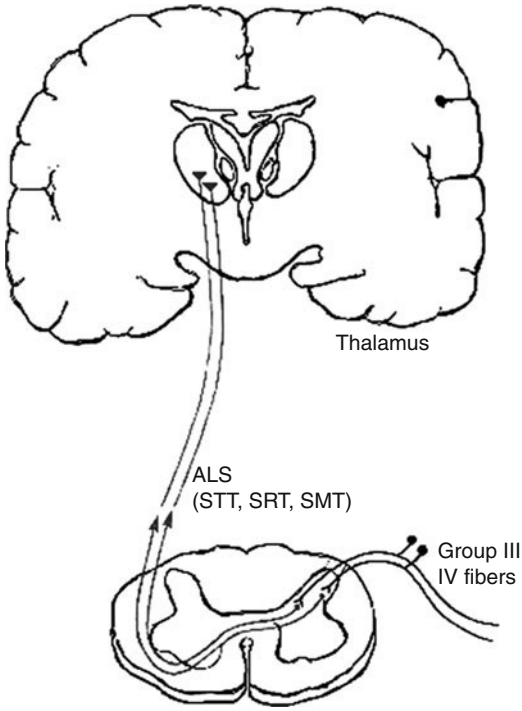
Upon entry into the spinal cord, the dorsal root fibers separate into a lateral and a medial division. The lateral division (Lissauer's tract) contains finer myelinated and unmyelinated fibers, originating from small dorsal root ganglion cells, and transmits responses to nociceptive (painful), nondiscriminatory or crude touch and thermal stimulation of the skin and viscera. The medial division contains large-caliber fibers from large dorsal root ganglion cells, whose peripheral receptors lie in muscle, joints, and skin. These fibers relay information about muscle length and tension to motor neurons and to propriospinal neurons, at segmental levels and to Clarke's and the lateral cuneate nuclei more rostrally. These pathways provide respectives the basis for spinal reflexes and information about somesthesia and joint position relayed to the brain, providing the basis for stereognosis (i.e., identification of shape and size of an object).

The Lateral Division

Lissauer's tract (Fig. 6) contains small-diameter axons that convey the modalities of pain, temperature, and crude or nondiscriminatory touch. Some axons branch and the branches ascend or descend in Lissauer's tract for several segments before entering into the lateral portion of the dorsal horn to synapse on cells in the dorsal horn (marginal nucleus, substantia gelatinosa, nucleus proprius, laminae I to IV). This distribution of collaterals rostrally and caudally means that activation of axons in one segment of the lateral division may stimulate dorsal horn cells over several adjacent segments. Neurons in the dorsal horn relay sensory information received from dorsal root axons to nuclei in the brain. These second-order neurons transmit this information through axons that cross and ascend in the lateral funiculus. Sensory relay neurons also receive input from various descending tracts, either directly or via interneurons. In this way, the neuron's ability to respond to sensory input is modified by the brain.

Entry and central course of axons of the lateral division from one dorsal root ganglion. These unmyelinated and thinly myelinated axons may branch and ascend or descend several segments in the tract of Lissauer before entering the gray matter and synapsing on second-order neurons in the dorsal horn.

The formation of the spinothalamic tract (STT) is shown in Fig. 7. Most axons in the STT arise from the marginal cells in lamina I and from the nucleus proprius in laminae III and IV and transmit nociceptive and thermal information. The axons of these second-order neurons cross to the contralateral spinal cord through the ventral



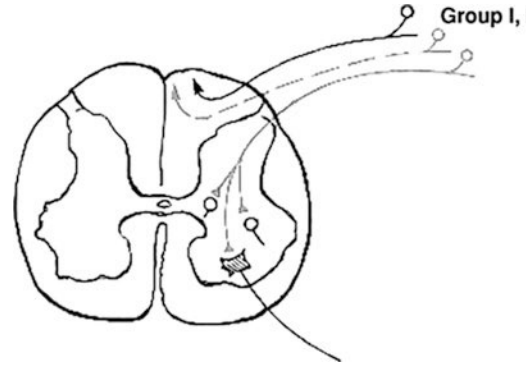
General Overview of Spinal Anatomy and Physiology Organization, Fig. 7 Formation of the spinothalamic tract (STT)

commissure and ascend in the white matter as the spinothalamic tract to terminate in the thalamus and other targets in the brain. They travel with other sensory spino-brainstem pathways in the anterolateral system (ALS).

Lateral division axons entering the dorsal root synapse on second-order neurons giving rise to axons that cross the spinal cord. Some axons form the spinothalamic tract (STT) and ascend to terminate in the thalamus. Some of these axons ascend to terminate in the reticular formation (spinoreticular tract, SRT) or mesencephalon (spinomesencephalic tract, SMT). These pathways travel together in the ventrolateral white matter to form the anterolateral system (ALS).

The Medial Division

Dorsal root axons in the medial division have local targets at their segments of entry. They may also give off collateral axonal branches that ascend to terminate in more distant targets in somatosensory relay and cerebellar relay nuclei.

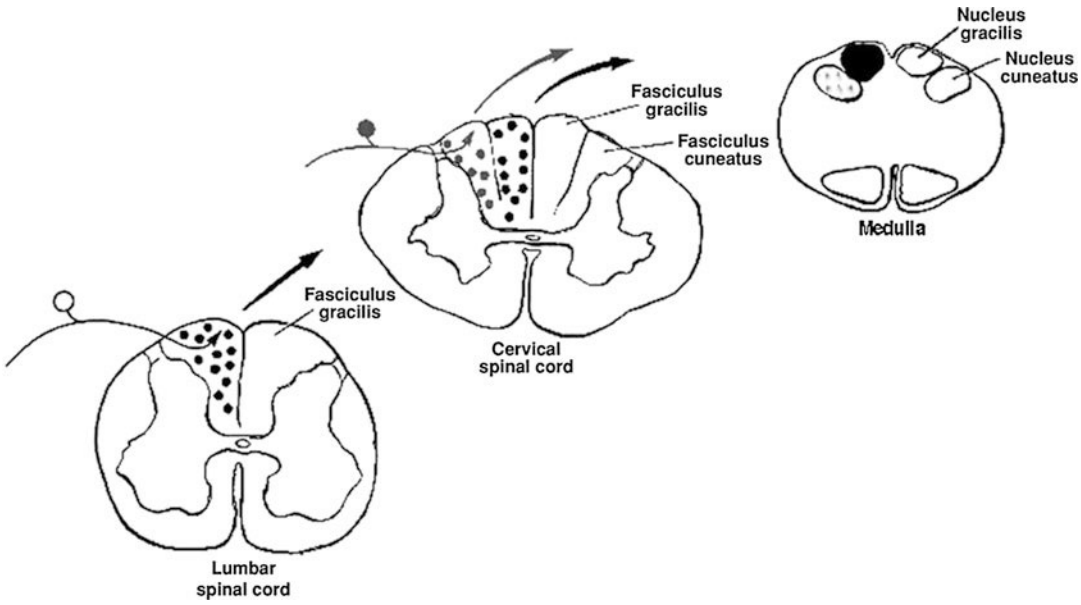


General Overview of Spinal Anatomy and Physiology Organization, Fig. 8 Medial division

Axons with local segmental targets enter the gray matter, synapse on propriospinal or motor neurons at that segmental level, and subserve reflex organization (Fig. 8). The Ia fibers of the medial division whose peripheral processes innervate stretch receptors in muscle spindles send central processes into the ventral horn, to synapse on the dendrites of motor neurons and propriospinal neurons. The monosynaptic connection between sensory axons and motor neurons is the anatomical basis for an important reflex, the stretch reflex. Other medial division axons, including collaterals of axons with segmental targets, enter the white matter in the dorsal funiculus, where they ascend to terminate in relay nuclei for somatosensory or cerebellar pathways. These relay nuclei receive sensory information from the skin, muscles, joints, fascia, and other tissues and then transmit the information to nuclei in the thalamus. The thalamus relays information to the cortex, where it is consciously appreciated or to the cerebellum, where it contributes to the control of posture and movement, without being consciously perceived.

Axons forming the medial division enter the spinal cord and ascend in the dorsal columns or make local reflex connections on motoneurons or propriospinal neurons or contact spinocerebellar nuclei.

Dorsal root fibers that project to somatosensory relay nuclei enter the dorsal funiculus at each segment, displacing medially the fibers originating from more caudal ganglia. As a result, these fibers become laminated, i.e., topographically

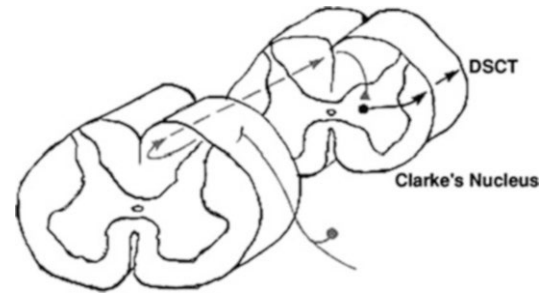


General Overview of Spinal Anatomy and Physiology Organization, Fig. 9 Dorsal column system

organized. In the cervical region, fibers from sacral dorsal roots are found nearest the midline and those from cervical roots nearest the dorsal root entry zone. Fibers representing the lower half of the body (sacral to T5) ascend in the gracile fasciculus; those from the upper half (T5 to C2) comprise the cuneate fasciculus. Axons in both bundles terminate ipsilaterally in nuclei of the medulla for which they are named, the nucleus gracilis and cuneatus. The gracilis and cuneate nuclei (dorsal column nuclei) then relay information to the thalamus (Fig. 9).

Axons mediating fine tactile sensibility contribute to the medial division. They ascend in the dorsal columns to the brainstem, where they terminate on second-order neurons in the dorsal column nuclei. The axons arising from lumbar and low thoracic dorsal root ganglia ascend in the fasciculus gracilis and terminate in the nucleus gracilis. Axons arising from upper thoracic and cervical ganglia ascend in the more laterally located fasciculus cuneatus and terminate in the nucleus cuneatus located lateral to the nucleus gracilis in the medulla.

Other dorsal root axons enter the dorsal funiculus to ascend for several segments before terminating in relay nuclei for cerebellar pathways.



General Overview of Spinal Anatomy and Physiology Organization, Fig. 10 Spinocerebellar systems

Axons arising from DRG cells in caudal thoracic, lumbar, and sacral regions ascend in the dorsal columns to terminate in Clarke's nucleus (Fig. 10), located in segments T1 to L2. Those arising from more rostral ganglia ascend in the dorsal columns to terminate in the lateral (also called the external or accessory) cuneate nucleus in the medulla. The dorsal spinocerebellar tract (DSCT) arises from neurons located in Clarke's nucleus; it ascends in the white matter ipsilaterally and is therefore uncrossed. The DSCT terminates in the cerebellum. Similarly, the cuneocerebellar tract carries information from the lateral cuneate nucleus to the cerebellum. Both nuclei therefore

relay sensory information from the periphery to the cerebellum. There is a third pathway to the cerebellum, the ventral spinocerebellar tract (VSCT). Cell bodies whose axons form the VSCT are distributed throughout the dorsal horn and intermediate zone; their axons cross in the ventral commissure to ascend in the contralateral VSCT, as part of the ALS, to the cerebellum, where they cross again before terminating. Although the course of the VSCT differs from that of the DSCT and cuneocerebellar pathways, their functions appear to be related.

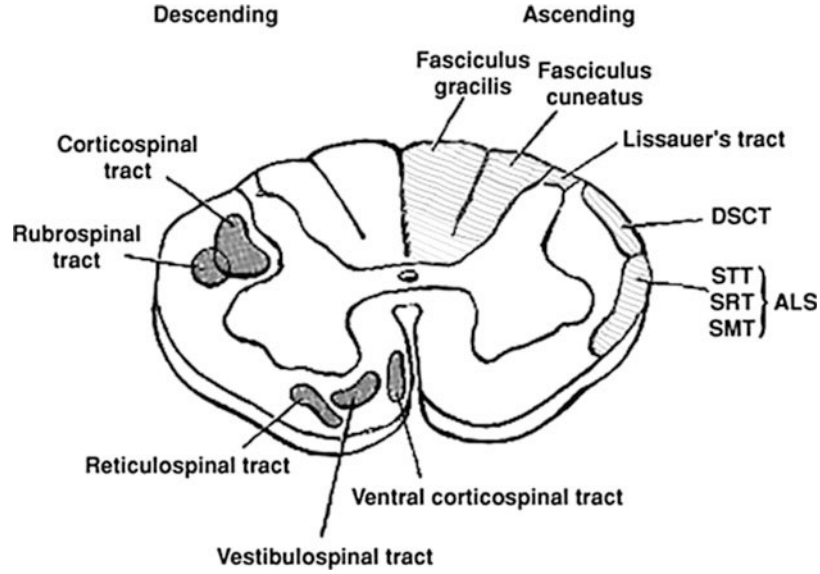
Axons conveying proprioceptive and muscle information also form part of the medial division. Axons from lumbar and caudal thoracic dorsal root ganglia enter the spinal cord and ascend ipsilaterally in the dorsal columns to the thoracic level where they terminate on second-order neurons in Clarke's nucleus. The axons of Clarke's neurons ascend in the lateral funiculus as the dorsal spinocerebellar tract (DSCT) which terminates on third-order neurons in the cerebellum. Axons from more rostral segments ascend synapse in the lateral cuneate nucleus (not shown), which then projects to third-order neurons in the cerebellum.

Motor Pathways

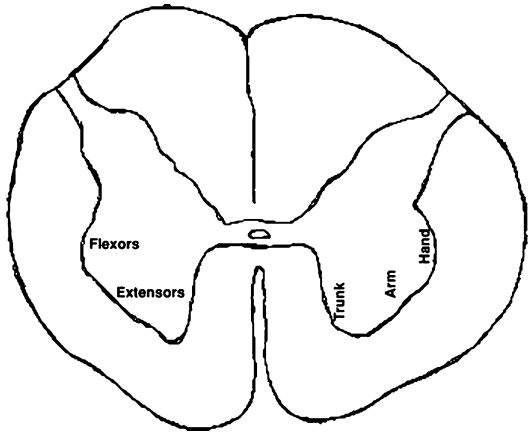
Descending tracts are located in the lateral and ventral funiculi. Most of the axons in these tracts terminate on propriospinal neurons, which then project to premotor or motor neurons; very few terminate directly on motor neurons. The location of four important descending tracts, the corticospinal, rubrospinal, reticulospinal, and vestibulospinal tracts, is shown in Fig. 11.

The corticospinal tract (CST) descends to the spino-medullary junction, where 90% of the axons cross, and then continues to descend as the lateral corticospinal tract in the lateral funiculus contralateral to the cell bodies of origin. Those axons that do not cross at the spino-medullary junction descend in the spinal cord as the ventral corticospinal tract but then cross in the spinal cord before their termination contralateral to their origin. In rodents, unlike primates and cats, the CST crosses at the spino-medullary but descends in the ventral portion of the dorsal columns within the spinal cord. The rubrospinal tract is also largely crossed and is located in the lateral funiculus. The reticulospinal tract, including the modulatory monoaminergic pathways (serotonergic and noradrenergic), contains axons that arise from reticular nuclei ipsilaterally and contralaterally. The vestibulospinal tract is almost entirely uncrossed.

Somatic motoneurons are somatotopically organized within the ventral horn (laminae VIII and IX). Their axons exit in the ventral roots and innervate striated muscle. A medial motor nucleus is present in the ventral horn throughout the length



General Overview of Spinal Anatomy and Physiology Organization, Fig. 11 Location of ascending (*right*) and descending tracts (*left*)



General Overview of Spinal Anatomy and Physiology Organization, Fig. 12 Somatotopic organization of ventral motoneurons

of the cord. These motor neurons innervate axial (trunk) musculature. There are also prominent groups of nuclei located laterally in the ventral horn, which are particularly well developed in the lumbar and cervical segments that supply the limbs. The lateral group of nuclei is subdivided functionally into ventral nuclei, which innervate extensor muscles, and dorsal nuclei, which innervate flexors. Within these two subdivisions, the neurons innervating proximal muscles are located medially and those that supply the distal muscles more laterally (Fig. 12).

Axial musculature is supplied by motor neurons located medially and limb musculature by motor neurons located laterally in the ventral horn. Those innervating extensors are more ventral and flexors more dorsal; neurons innervating proximal muscles are more medial than those innervating distal muscles.

Visceral motoneurons (preganglionic neurons) are located in the intermediate zone. They innervate neurons in autonomic ganglia and the autonomic ganglion cells (postganglionic neurons) innervate visceral organs. Those preganglionic neurons in the intermediolateral nucleus in lamina VII at C8 to L3 send axons to the ganglia in the sympathetic chain, providing central regulation of the sympathetic nervous system. Neurons in the intermediate zone at levels S2 through S4 form the more poorly defined sacral parasympathetic nucleus. Their axons innervate the sacral parasympathetic ganglia and thus provide central control of the sacral portion of the parasympathetic system that mediates bowel, bladder, and sexual reflexes. Central control of more rostral portions of the parasympathetic system is provided by groups of cranial nerve nuclei.

Propriospinal Systems

A great deal of detailed information is available about DRG cells, motor neurons, and their projections. The cell bodies of both motor neurons and DRG cells can be identified morphologically and by methods that label transmitters, receptors, or other cell-type specific molecules. Axonal projections can be visualized and traced by injecting dyes or viral vectors that are incorporated and transported retrogradely, anterogradely, or in both directions and can identify motor neurons that project to specific muscles and DRG cells, as reviewed in Lanciego and Wouterlood (2011).

Propriospinal neurons, however, make up the vast majority of spinal neurons. Because propriospinal neurons are engaged in complex spinal networks, e.g., the central pattern generator (CPG), and in pain transmission (see entry ▶ "Sensory Input to Central Pattern Generators," this volume), a fuller understanding of their connectivity will be important in appreciating how these complex circuits form, how they function, and how they may be modified by activity or injury.

In the last few years, new technologies have accelerated progress in understanding the connectivity and functions of propriospinal neurons (reviewed in chapters in Ziskind-Conhaim et al. 2010, 2013; Conta and Stelzner 2008). The advent of transsynaptic tracing using pseudorabies virus (PRV) and monosynaptic tracing using a genetically modified replication-deficient rabies virus (RV) has provided more detail about interneuronal pathways (Arber 2012; Stepien et al. 2010; Coulton et al. 2011). RV or PRV labeling can be combined with immunocytochemical or other methods to identify the phenotype of the premotor propriospinal neurons.

Developmental neurobiology and molecular genetics have combined to provide additional

ways of differentiating subpopulations of propriospinal neurons, based on lineage (time of origin, birthdate), and the expression of transcriptional markers that control neuronal differentiation and migration to specific positions in the adult CNS. Genetic deletion or pharmacologic blockade can identify the consequences of loss of function in these propriospinal neurons and suggest their roles during development and as adults in the organization of spinal networks (reviewed in Arber 2012; Grossman et al. 2010; Kiehn 2011). These advances have been particularly fruitful in understanding the connectivity of the central pattern generator (CPG). While the network of propriospinal neurons that comprise the CPG is normally modulated by supraspinal projections and afferent input, it can function in the absence of information from the brain or periphery to produce rhythmic, patterned neural activity or fictive locomotion (Hägglund et al. 2010).

The complexity of the propriospinal neuronal connections is still only incompletely understood. The combination and further development of these and other methods that can detect activity in ensembles of functionally related neuronal network and provide 3-dimensional and live imaging, promises a rapid acceleration of progress in this area (Di Maio et al. 2011; Ertuk and Bradke 2013; Hinckley and Pfaff 2013; Laskowski and Bradke 2013).

Spinal Pathways Are Plastic

While the first part of this entry describes the organization of the spinal cord as if it were static, we know that the spinal cord retains the ability to adapt to changes in its environment (plasticity) even in adults. Significant changes in spinal cord neurons and their environment occur as a result of active or passive exercise or training (activity-dependent plasticity). Changes induced by injury occur in afferent, descending, and propriospinal systems and include sprouting, receptor regulation, and alterations in neuronal properties, in addition to the inflammatory and degenerative responses resulting from the injury. When spinal cord injury is followed by a program of exercise, the functional and anatomical modifications in spinal organization may be further altered or even reversed sufficiently to support greater recovery of function. Understanding lesion-induced changes and promoting plasticity directed by activity can thus be exploited to improve function.

Activity-Dependent Plasticity

Activity-dependent plasticity refers to functional changes in response to activity related to movement. This may include exercise and specific training protocols (Harkema et al. 2012; Roy et al. 2012) or operant conditioning (Pillai et al. 2008; Wolpaw and Chen 2009; Chen et al. 2011) that modify motor output.

Plasticity Following Spinal Cord Injury (SCI)

An injury may be complete (transection spinalization), or it may spare some pathways and thus be incomplete (contusion, clip compression, hemisection, tractotomy). Contusion or clip-compression injuries are considered to be clinically more relevant, while hemisections or tractotomies are surgical injuries that allow evaluation of specific pathways. The consequences of an incomplete injury will depend on which pathways are spared. Spinal cord injury does not elicit substantial regeneration of axotomized neurons and will result in death of some short projecting propriospinal neurons in the vicinity of the injury (Conta Steencken and Stelzer 2010), structural changes in neurons located more distantly from the injury (Gazula et al. 2004), and apoptosis of oligodendroglia (Beattie et al. 2002). Axons that survive an incomplete injury may show long-lasting changes in transmission (Arvanian et al. 2009; Cote et al. 2012) and deficits (but perhaps not permanent) in conduction properties resulting from demyelination (James et al. 2011).

Incomplete SCI is often followed by some degree of spontaneous motor recovery, due in part to reorganization of spared spinal pathway mediated by sprouting and increased excitability of surviving neurons. While gain of function induced by injury may contribute to recovery, it

may also be maladaptive when it contributes to neuropathic pain (Ferguson et al. 2012; Tan et al. 2012), spasticity (Boulenguez and Vinay 2009; Edgerton and Roy 2010), and autonomic dysreflexia (Hou et al. 2008), disorders which often accompany SCI. Complete injury is likely to show little improvement of function in the absence of therapies and is more likely to be accompanied by maladaptive responses.

Activity-Dependent Plasticity After SCI

The functional benefits of treatment based on either exercise−/activity- or injury-induced changes may be modest by themselves, but they are noninvasive and can supplement traditional physical therapy. Consequently, locomotor training after spinal injury (Harkema et al. 2012) is now a widely used rehabilitative strategy to improve function after SCI in humans. Locomotor function on a treadmill can be recovered after spinal transection in experimental animals if training, combined with body weight support, is provided. The success of this therapy is based in part on the normalization of abnormal measures induced by injury when it is followed by training. This effect may relate to the relevance or predictability of the sensory stimulation (Ferguson et al. 2012). The mechanisms that contribute to training-mediated recovery include levels of neurotrophic factors or other molecules (Cote et al. 2011) or changes in gene expression in spinal neurons (Liu et al. 2012; Keeler et al. 2012) and also include changes in neuronal properties and sprouting where exercise/activity tend to ameliorate some of the effects of injury (Cote et al. 2011).

Summary

The spinal cord is contained within the vertebral canal and access to the cord limited by the vertebrae. The cord is somatotopically organized with sensory information being primarily processed in the dorsal horns and tracts, while motor information is mostly contained within the ventral horn and tracts. The intermediate region between the posterior and anterior halves of the cord contains the largest number of interneurons and is likely the site of most computation processing although the circuitry is still poorly understood. Targeting the activation to certain portion of the circuitry is complicated by both the proximity of the elements forming the circuit and our lack of understanding of its organization. A greater understanding of the anatomical and computational modifications in the spinal circuitry in normal function will be essential for developing ways of improving rehabilitative strategies after injury.

Cross-References

▶ Sensory Input to Central Pattern Generators

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Information Theory: Overview

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Definition

Information Theory started with Shannon's seminal paper "A Mathematical Theory of Communication" (Shannon 1948). Because its importance and flexibility were quickly recognized, there were numerous attempts to apply it to diverse field outside of its original scope. The entries in this section provide an overview of the current state of Information Theory in Neuroscience.

Detailed Description

When discussing a field, it is useful to review the basic concepts and their properties. That has been provided in multiple articles for Information Theory. To assist the reader, the entry ▶ "Summary of Information-Theoretic Quantities" provides a brief summary of the main information-theoretic quantities. For a more thorough investigation, we would direct interested readers to the most excellent introduction to Information Theory by Cover and Thomas (2006), now in its second edition.

Very soon after Shannon's initial publication (1948), a small number of manuscripts provided the foundations for the current use of information theory in neuroscience. MacKay and McCulloch (1952) applied the concept of information to propose limits of the transmission capacity of a nerve cell. This work foreshadowed future work on what can be termed "Neural Information Flow" – how much information moves through the nervous system, and the constraints that information theory imposes on the capabilities of neural systems for communication, computation and behavior. A second set of manuscripts, by Attneave (1954) and Barlow (1961) discussed information as a constraint on neural system structure and function, proposing that neural structure in sensory systems is matched to statistical structure of the sensory environment, in a way to optimize information transmission. This is the main idea behind the "Structure from Information" line of research that is still very active today. A third thread, "Information Estimates," started with a forward-looking article (Miller 1955), which pointed out many potential pitfalls of extracting information quantities from observations. Its significance penetrated the mainstream neuroscience research later; once information-theoretic analysis became more widespread, the biases noted by Miller were rediscovered, and corrected.

Subsequent Developments

The theme that arguably has had the widest influence on the neuroscience community is that of "Neural Information Flow". The initial works of MacKay and McCulloch (1952) showed that neurons are in principle able to relay large quantities of information. That research also started the first major controversy in the field, which still resonates today: the debate about timing versus frequency codes (Stein 1967). A steady stream of articles followed, both discussing these hypothesis and attempting to clarify the type of information relayed by nerve cells (Abeles and Lass 1975; Eagles and Purple 1974; Eckhorn and Pöpel 1974; Harvey 1978; Norwich 1977; Poussart 1971; Stark et al. 1969; Taylor 1975; Walloe 1970). After the initial rise in interest, the application of Information Theory to neuroscience was extended to a few more systems and questions but did not spread too broadly. This was presumably because, despite strong theoretical advances in Information Theory, its applicability was hampered by

difficulty in measuring and interpreting information-theoretic quantities.

The work of de Ruyter van Steveninck and Bialek (1988) started what could be called the modern era of information-theoretic analysis in neuroscience, in which Information Theory is seeing more and more refined applications. Their work advanced the conceptual aspects of the application of information theory to neuroscience and provided an impetus to removing biases in information estimates, discussed in detail in the entry ▶ "Estimating Information-Theoretic Quantities."

Current State

Information Theory found applications in the study of neural processing as a theoretical and practical system for the analysis of communicated signals. A variety of information-theoretic quantities are in use in Neuroscience. The entry ▶ "Applications of Information Theory to Analysis of Neural Data" provides a general overview of current applications of Information Theory, as an analysis tool of neural information flow.

The structure of neural activity often introduces challenges that have been of marginal interest to the engineering community. The entry ▶ "Metric Space Analysis of Neural Information Flow" exemplifies one such case, metrization. In a metric-space approach to analyzing neural response, the data is reduced from a set of complicated objects, spike trains, to a much simpler object, the matrix of distances between the spike trains. When applied to neural information, this matrix is used to estimate information theory quantities for the corresponding spike train data. The tools developed in that direction combine metric properties of spike trains with their information transmission function.

Several entries discuss specific applications in neuroscience stemming from more recent developments in Information Theory. ▶ "Directed Information Flow and Causality in Neural Systems" discusses developments based on the natural ideas of information flow in a causal direction. Surprisingly, this idea has taken quite some time to develop in the communication literature due to various technical difficulties. The works originates form the ideas of Granger (1969) on causal interactions. The information-theoretic perspective of (Massey 1990; Massey and Massey 2005) removed Granger's linearity assumptions.

And lastly, applications in neuroscience are also pushing the development of new tools in Information Theory. One of the examples presented here, ▶ "Information Measures of Redundancy and Synergy in Neural Activity," summarizes the progress made in that direction, for which the original definitions provided by Shannon proved inadequate.

In conclusion, Information Theory is thriving in the neuroscience community, and the long efforts are bearing fruit, as diverse research questions are being approached with more elaborate and refined tools. As demonstrated by several recent thematic journal issues (Dimitrov et al. 2011; Milenkovic et al. 2010), Information Theory is firmly integrated in the fabric of neuroscience research, and a progressively wider range of biological research in general, and will continue to play an important role in these disciplines. Conversely, neuroscience is starting to serve as a driver for further research in Information Theory, opening interesting new directions of inquiry.

Cross-References

- ▶ Applications of Information Theory to Analysis of Neural Data
- ▶ Directed Information Flow and Causality in Neural Systems
- ▶ Estimating Information-Theoretic Quantities
- ▶ Information Measures of Redundancy and Synergy in Neural Activity
- ▶ Metric Space Analysis of Neural Information Flow
- ▶ Summary of Information-Theoretic Quantities

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Invertebrate Pattern Generation: Overview

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Detailed Description

Central pattern generators (CPGs) are networks of neurons in the central nervous system (CNS) that produce patterned activity, usually as coherent oscillations, in the absence of external timing cues. CPGs provide timing input to motor neurons whose discharge dictates movements of muscles that control rhythmic behavior such as respiration or locomotion (Marder and Calabrese 1996). The long-held debate between scientists who believed half a century ago that rhythmic motor activity is generated by reflex chains and those who held the more radical view of centrally generated rhythms was resolved conclusively, in favor of the latter group, by demonstrating that neural networks generating rhythmic motor activity can do so in the isolated nervous system, in the absence of the body and therefore sensory feedback. In the early 1960s, these "fictive" motor patterns were first demonstrated to govern rhythmic activation in two invertebrate model systems: the movement of flight wings in locusts and the beating of swimmerets in crayfish (Wilson 1961; Ikeda and Wiersma 1964). The demonstration of fictive motor activity led to the development of in vitro preparations in search of the underlying CPG circuits. Although CPG networks have been

traditionally described in the context of controlling motor activity, a more contemporary viewpoint of CPGs includes networks that subserve brain oscillations connected to sensory, cognitive, and memory tasks (Yuste et al. 2005).

CPGs have historically led systems neuroscience in the understanding of neural circuit interactions, partly because of the ease of identification of neurons and networks whose activity correlates with a rhythmic motor activity. The identification of neural circuits has been more successful in invertebrates where the number of neurons involved in neural processing is lower, sometimes by orders of magnitude, and the ability of identifying synaptic connections among neurons is facilitated by dual recordings. Vertebrate and especially mammalian neural circuit analysis was, until recently, performed with cruder techniques such as lesions, but in the past decade or so, genetic tools and the identification of molecular markers have allowed for more precise circuit analysis in the large networks of vertebrate systems (Han 2012; Arrenberg and Driever 2013). However, neural circuits have been identified only in a few vertebrate model systems and simple behaviors (Issa et al. 2011; Cangiano and Grillner 2005). The knowledge of the neural circuits and the ability to record functionally identified neurons in invertebrates have allowed for the in-depth analysis of the mechanisms underlying circuit dynamics and plasticity (Marder et al. 2005) as well as a rigorous description of the computations performed by the neural circuits (Selverston 2010).

The computational description of pattern-generating circuits evolved in parallel with the in vitro experimental studies of cellular and synaptic mechanisms. The complexities of circuit analysis of invertebrate CPGs have led to numerous modeling studies, some of which have been influential in shaping our conceptual understanding of both single-neuron and network operations. For example, the computational description of bursting oscillations, led by models of invertebrate CPG neurons (Plant and Kim 1976), paved the way for the complete mathematical analysis of bursting mechanisms in neurons and other excitable cells (Rinzel 1987; Rinzel and Lee 1987). This section of the Encyclopedia of Computational Neuroscience provides an overview of the contributions of invertebrate pattern generators in the context of computational models.

Cross-References

- ▶ Automated Parameter Search in Small Network Central Pattern Generators
- ▶ Bifurcations Dynamics of Single Neurons and Small Networks
- ▶ Bursting in Neurons and Small Networks
- ▶ Gap Junctions in Small Networks
- ▶ Neuromodulation in Small Networks
- ▶ Sensory Input to Central Pattern Generators
- ▶ Short-Term Synaptic Plasticity in Central Pattern Generators
- ▶ Stability and Homeostasis in Small Network Central Pattern Generators

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Invertebrate Sensory Systems: Overview

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Definition

Invertebrate sensory systems specialize in gathering information from the surroundings allowing animals to locomote and behave appropriately given the current environmental conditions.

Detailed Description

Invertebrate neurobiology has long been at the forefront of computational neuroscience, starting with the mathematical model of the biophysical basis of the action potential by Hodgkin and Huxley in the squid giant axon almost 70 years ago (Hodgkin and Huxley 1952). Many invertebrate systems are highly suitable for detailed modeling because of their relatively compact size and the fact that their neurons can often be uniquely identified. This feature allows the formulation of precise descriptions of their behaviors and simplifies the interpretation of experimental results. Yet, as Hodgkin and Huxley's seminal analysis of action potential mechanisms has proved, invertebrate models possess characteristics similar to those of vertebrates, and the computational principles derived from either type of nervous systems have been found universally applicable, even if details of mechanistic implementations differ.

This section of the Encyclopedia focuses on the sensory systems of invertebrates, complementing the section on their motor systems. It presents an overview of computational modeling emphasizing salient topics in the field. While the coverage is far from exhaustive, it is our hope that these entries will provide the reader an overview and an entry point to the rich literature covering the modeling of invertebrate sensory systems and related topics.

Among the different sensory systems, vision has arguably been the most intensely investigated in invertebrates and vertebrates alike. The entry on ▶ "Phototransduction Biophysics" summarizes our understanding of the mechanisms by which invertebrate photoreceptors translate light signals into membrane potential changes. Most of the work on this topic has been carried out in flies and particularly the genetically tractable fruit fly, *Drosophila melanogaster*. The biochemical cascade mediating phototransduction has been studied in great detail and has recently led to a better understanding of the implications for neural coding. Another classical topic of insect vision has been the study of the mechanisms underlying directionally selective motion detection. This work originated in beetles and was later pursued in flies, leading to the correlation model of Hassenstein and Reichardt (1956). The neural circuits implementing this model, which is closely related to the motion-energy model of mammalian motion detection (van Santen and Sperling 1985), have long proven tricky to investigate due to difficulties in tracing the anatomical and physiological connections between the neurons that perform the computations of the correlation model.

Progress has been made by combining anatomical, electrophysiological, imaging, and genetic techniques in *Drosophila* that are summarized in the entry on ▶ "Visual Motion Detection in *Drosophila*." Although *Drosophila* has recently helped better understand the circuitry underlying motion detection, a large body of work on the topic was carried out in bigger flies, leading to detailed biophysical models of a class of neurons involved in motion detection. These models are introduced in the entry on ▶ "Fly Lobula Plate Tangential Cells (LPTCs), Models of." Local

motion detection is only the first step in processing visual information generated by an animal moving in its environment. Such information, often called "optic flow," is particularly important for flying animals. The strategies and constraints on the processing of such information are summarized in the two entries on ▶ "Optic Flow Processing" and ▶ "Visual Processing in Free Flight".

Another function of the visual system of critical importance to animals is predator evasion and collision avoidance. Our understanding of the neural mechanisms of collision avoidance has rapidly progressed over the past decades in a variety of invertebrate model systems, including locusts, crabs, and fruit flies. Similar collision avoidance mechanisms have been documented in vertebrate systems such as goldfish, zebrafish, pigeons, and mice. The entry on ▶ "Collision Avoidance Models, Visually Guided" describes our understanding of those systems. Animal navigation and migration relies on an internal representation of the external world allowing orientation over long distances. In insects, particularly in monarch butterflies, ants, and locusts, the detection of polarized patterns of light in the sky provides an internal compass for navigation. The detection and processing of polarized light patterns leads to a sort of "cognitive map" in the central nervous system akin to those studied in the rodent hippocampus. The entry on ▶ "Polarization Vision" provides a summary of our understanding of this fascinating and exotic sensory modality.

Olfaction is a prominent and important sense in invertebrates, particularly in insects. The mechanisms of insect olfaction and their close relation to vertebrate olfaction have been investigated intensely, culminating in a detailed understanding in several organisms, including moths, locusts, and fruit flies. Examples of models of olfactory coding are presented in the entry entitled ▶ "Insect Olfaction: A Model System for Neural Circuit Modeling". Another primary sense, audition, is used by animals to locate preys or predators and for communication with conspecifics. Because of their small size, invertebrates and insects such as crickets and locusts, which are among the best-studied auditory model systems, face physical constraints quite different from those applying to vertebrates. Their study has led to a wealth of information on how auditory information is processed, both at the level of the auditory periphery and in the brain. These results are summarized in the entry on ▶ "Auditory Processing in Insects".

Wind and air current sensing is carried out by a specialized sensory system called the cercal system in crickets and other orthopteran insects. This system provides a fascinating example of how information is processed by populations of sensory neurons, as summarized in the entry entitled ▶ "Cercal System". More broadly, the entry on ▶ "Computation with Population Codes" explains the role such neural codes play in a variety of other animals. The leech has proven to be one of the best models to study these topics because of the compact size of its nervous system, well-understood natural behaviors, and the applicability of large-scale imaging of neuronal activity using voltage-sensitive dyes and other electrophysiological techniques. Finally, invertebrate somatosensation is introduced in the entry on ▶ "Tactile Sensing in Insects".

Adaptation is a fundamental property of neuronal responses observed throughout sensory systems. The entry entitled ▶ "Biophysics of Adaptation in a Computational Model of the Leech T Neuron" details the ionic mechanisms of adaptation in one type of sensory neuron and its consequences for the processing of sensory stimuli.

In addition to the above-mentioned entries, the section includes one entry – entitled ▶ "Nitric Oxide Neuromodulation" – on a somewhat exotic and fascinating volume neuromodulator: nitric oxide. The computational properties of nitric oxide neuromodulation have been investigated in detail in several invertebrate systems, leading to models of its role in sensory processing and learning. Similar regulation of neuronal circuits by volume neurotransmission has been described in vertebrates as well (e.g., Oláh et al. 2009).

The last topic covered in this section is the efficient representation of neural information in the entry entitled ▶ "Sensory Coding,

Efficiency". The possibility that sensory neural codes may be efficient has been first raised in the 1960s (Barlow 1961). It has since then been investigated in several systems, including the visual system of invertebrates. The entry includes background information and a summary of results on efficient coding in these systems.

Cross-References

- Auditory Processing in Insects
- Biophysics of Adaptation in a Computational Model of the Leech T Neuron
- Cercal System
- Collision Avoidance Models, Visually Guided
- Computation with Population Codes
- Fly Lobula Plate Tangential Cells (LPTCs), Models of
- Hodgkin-Huxley Model
- Insect Olfaction: A Model System for Neural Circuit Modeling
- Nitric Oxide Neuromodulation
- Optic Flow Processing
- Phototransduction Biophysics
- Polarization Vision
- Spike-Frequency Adaptation
- Tactile Sensing in Insects
- Visual Motion Detection in *Drosophila*
- Visual Processing in Free Flight

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Learning Rules: Overview

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Definition

The title of this entry, namely, "Learning Rules," refers to several type of methods and procedures that have been used in different neuroscience research areas to quantify how previous experiences, training, and stimulations protocols affect brain response and behavior in different animals and at different levels of description. The concept assumes the such previous experiences produce changes or plasticity in the brain (i.e., the learning rule) that affect its posterior behavior, e.g., under the action of related stimuli (the retrieval of what is learned). Such "Learning Rules" concept has been also extended to neural networks modeling and artificial intelligence research, providing precise mathematical definitions for different learning rules, a fact that has helped to gain a better understanding of their consequences.

Detailed Description

Learning is the most important procedure by which different stimuli in the environment alter the behavior in animals and humans, and today its neurobiological base is widely accepted (Thompson 1986). In fact, neurobiological and computational studies have stressed the significance of synaptic plasticity in the learning process (Black et al. 1990; Fusi 2017): Experience and training leads to modifications of synapses, which in turn lead to changes in neuronal firing patterns,

causing changes in behavior. A full understanding of the processes underlying learning, therefore, requires an understanding on the neural as well as on the systemic level.

In the behavioral literature, learning is studied by means of different experimental procedures in which animals or humans are exposed to sensory stimuli and interact with the environment (Mackintosh 1974). The paradigms which have been used gave rise to a categorization into associative and nonassociative learning. In nonassociative learning an animal is repeatedly exposed to a single type of stimulus, and learning is described by the strength of its behavioral impact leading, for example, to the phenomena of habituation and sensitization (Thompson and Spencer 1966; Rankin et al. 2009). In associative learning animals learn predictive relationships in the presence of a reinforcement signal (Pearce and Bouton 2001). Historically, classical conditioning (where reinforcements are delivered independent of any action taken) is differentiated from operant conditioning (where reinforcements depend on the action and where behavior is associated with its outcome).

In the neural network literature (see, e.g., Haykin 2009), learning is often classified according to what kind of information is available in a particular learning scenario. In the so-called supervised learning, an agent (e.g., a neural network) forms associations between two sets of events with the goal to predict one by the other. Learning is based on a given set of correct pairings. Pairings between events are also formed in the so-called reinforcement learning; however, evaluative feedback about network performance is only provided in the form of reinforcements, for example, reward or punishment signals. Correct pairings imply high rewards; hence, learning is driven by maximizing returns. Reinforcement learning bears similarities with the abovementioned associative learning paradigms, and algorithms which were originally developed by the neural network community are now widely applied to quantify associative learning in animals and humans. In the so-called unsupervised learning, responses of an agent are modified when stimuli are presented but in a nonassociative way. In an artificial agent setting, supervised learning is often applied for solving pattern recognition problems, and reinforcement learning is used to learn action sequences. Unsupervised learning, on the other hand, is applied to learn internal representations of the outside world. Statistical regularities are extracted and are used to build representations of stimuli and actions which are better suited for recognition, planning, memorization, decision-making, and other cognitive tasks.

In many areas of neuroscience where "real" neurons and networks are studied, learning is linked to changes of neuronal and synaptic properties. Activity-dependent synaptic plasticity is widely believed to be the most important feature underlying learning. It also plays an important role during neural development, where the interplay of neural activity with the so-called intrinsic processes shapes the circuitry and the neural response properties. Learning at the neuronal level is characterized by how the activation history of pre- and postsynaptic neurons relates to the efficacy of the synaptic connection between them. Different stimulation protocols of neurons in (mostly) in vitro preparations uncovered a wealth of phenomena associated to learning processes, the most prominent ones being long-term potentiation, long-term depression, or spike-timing-dependent plasticity.

"Learning Rules," i.e., the title of this entry, refers to the quantification of the effects of experiences, training, and stimulation on the brain and behavior on all abovementioned levels of description. Learning Rules inserted into computational models then help to explore the consequences of the observed plasticity during different learning processes. Thus, one can explore, for example, how activity-dependent synaptic plasticity interacts with network responses which eventually induce behavior, how a network can adapt its parameters such that a desired function can be performed, or how interindividual differences in learning behavior can be related to interindividual differences in their objectives. Thus, learning rules serve as a computational tool to link experience-induced changes observed on a system level to the mechanisms operating on the level of neurons and networks and vice versa.

At the core of this entry are entries for activity-dependent learning rules, which quantify how pre- and postsynaptic activity changes the strength of a

synapse (see entries ▶ "Hebbian Learning," ▶ "Anti-Hebbian Learning," ▶ "Spike-Timing Dependent Plasticity, Learning Rules," and ▶ "Tempotron Learning"). Here, the learning rules are formulated in a more abstract setting, and the biophysical foundations are addressed in entry ▶ "Synaptic Dynamics: Overview" (cf. ▶ "Long-Term Plasticity, Biophysical Models," ▶ "Short-Term Plasticity, Biophysical Models," and ▶ "Spike-Timing Dependent Plasticity, Learning Rules"). The effects of learning rules in terms of network dynamics and computation are then addressed in a neural network setting (see entries ▶ "Boltzmann Machine," ▶ "Hopfield Network," ▶ "Perceptron Learning," and ▶ "Slow Feature Analysis") covering supervised and unsupervised learning paradigms. They are also addressed in a neural modeling setting, where the computational models are used to understand some of the mechanisms underlying neural development (see entries ▶ "Cortical Maps, Activity-Dependent Development" and ▶ "Cortical Maps, Intrinsic Processes"). The entry is complemented by one entry on reinforcement learning (see ▶ "Reward-Based Learning, Model-Based and Model-Free"), which summarizes current computational approaches for quantifying behavior for reward-based, associative learning paradigms. Possible neural implementations of reinforcement learning are discussed in entry ▶ "Cortex: Overview" (cf. ▶ "Reinforcement Learning in Cortical Networks").

Cross-References

- ▶ Anti-Hebbian Learning
- ▶ Boltzmann Machine
- ▶ Cortex: Overview
- ▶ Cortical Maps, Activity-Dependent Development
- ▶ Cortical Maps, Intrinsic Processes
- ▶ Hebbian Learning
- ▶ Hopfield Network
- ▶ Long-Term Plasticity, Biophysical Models
- ▶ Perceptron Learning
- ▶ Reinforcement Learning in Cortical Networks
- ▶ Reward-Based Learning, Model-Based and Model-Free
- ▶ Short-Term Plasticity, Biophysical Models
- ▶ Slow Feature Analysis
- ▶ Spike-Timing Dependent Plasticity (STDP), Biophysical Models
- ▶ Spike-Timing Dependent Plasticity, Learning Rules
- ▶ Synaptic Dynamics: Overview
- ▶ Tempotron Learning

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LFP Analysis: Overview

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Detailed Description

Local field potentials (LFPs) are low-frequency electrical potentials recorded with micro- or

macro-electrodes throughout the brain. The upper frequency cutoff of the LFP is often considered to be around 100 Hz but may be as high as 500 Hz in some studies. The normal amplitude of the LFP can range from a few microvolts (e.g., in the basal ganglia) (Goldberg et al. 2004) to hundreds of microvolts in the cortex. Perhaps the earliest recording of an LFP may be attributed to Renshaw, Forbes, and Morison in 1940, who described these potentials in the cortex and the hippocampus of a cat under various anesthetics (Renshaw et al. 1940). Extensive electrophysiological studies have formed the current view that cortical LFPs result from synaptic activity (Eccles 1951; Creutzfeldt et al. 1966; Elul 1971; Klee and Rall 1977; Mitzdorf 1985; Bedard et al. 2004). Correspondingly, the LFP fluctuations tend to have a strict phase relationship to cortical discharge: negative deflections in the LFP coincide with increases in the instantaneous firing rates of cortical neurons in both superficial and deep layers (Lass 1968; Gray and Singer 1989; Murthy and Fetz 1996a; Donoghue et al. 1998; Destexhe et al. 1999). In addition, these fluctuations are highly correlated across distances of several millimeters in the cortex (Eckhorn and Obermueller 1993; Sanes and Donoghue 1993; Murthy and Fetz 1996b; Contreras et al. 1997; Bullock 1999; Destexhe et al. 1999), indicating that LFPs are not always strictly local.

Theoretical attempts to account for the LFPs and model their generation date back to Lorente de Nó (1947) and include the seminal works of Ulla Mitzdorf (1985), who implemented the technique of current source density (CSD), and Wilfrid Rall, who calculated the potentials generated by various spatial organization of electrical dipoles (Klee and Rall 1977; Goldberg et al. 2004). These theoretical accounts relied on the large-scale repetitive columnar structure of the cortical circuitry to generate large potentials due to the summed contribution of many aligned neuronal dipoles (Elul 1971; Klee and Rall 1977; Abeles 1982; Mitzdorf 1985; Eggermont and Smith 1995).

This "LFP analysis" section, which has contributions from several leading authorities, covers the following topics: (a) methods for measuring the LFP; (b) modern accounts of how LFPs are generated; (c) the relationship between the LFP and other common measures of collective brain activity such as the EEG, the MEG, and the fMRI, as well as its relationship to and possible influence on single-cell membrane potentials; (d) the power spectral structure of the LFP, which often displays a *1/f* structure, or marked oscillation peaks under various physiological and pathophysiological conditions (e) LFP in the context of particular brain functions such as vision and olfaction; and (f) current modeling methods of the LFP. These various topics are overviewed below.

Neurophysiological Basis of LFPs

A first important aspect of the LFP is the relation between this signal and other well-known signals of the brain. In the entry ▶ "Local Field Potential, Relationship to BOLD Signal", Nikos Logothetis and Stefano Panzeri review the relation between the LFP signals and the BOLD (blood oxygen level dependent) signal, as recorded by MRI techniques. The entry also discusses multiunit activity in relation with the BOLD signal.

A similar large-scale approach is followed by Stephanie Jones in ▶ "Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG)". This entry reviews the biophysical bases of the genesis of EEG and MEG signals and how such signals relate to the LFP. The "inverse problem" of estimating neuronal sources from EEG and MEG signals is also reviewed.

The relationship to unit activity is further described in detail in ▶ "Local Field Potential, Relationship to Unit Activity" by Bartosz Teleńczuk and Alain Destexhe. This entry reviews the relation between extracellularly recorded unit activity and LFP, as a function of the frequency of the different rhythmical activities found in LFPs. It is shown that unit activity correlates with the high-frequency (>200 Hz) components of the LFP and, to a lesser extent, with the low-frequency components (<10 Hz), whereas the intermediate-frequency bands have a rather weak correlation with unit activity.

In the entry ▶ "Local Field Potential: Relationship to Membrane Synaptic Potentials", Aryeh Taub, Ilan Lampl, and Michael Okun go a bit more deeper in the neuron and review the relation between the intracellularly recorded membrane potential and the LFP signal. The entry considers different types of brain activity, such as up-down states, and discusses the role of inhibition.

In the entry "Local Field Potentials and Ephaptic Coupling", Costas Anastassiou discusses the hypothesis that the LFP is not merely an epiphenomenon of electrical brain activity but may actually serve as a global slow signal that can couple to other neural elements (e.g., axons, synapses). This ephaptic coupling results from the fact that the membrane voltages in these elements can be altered by fluctuations in the LFP simply because they are the difference between the intracellular potential and the extracellular (local field) potential.

Finally, in the entry ▶ "Local Field Potentials: LFP", Alain Destexhe and Claude Bedard review general properties of LFPs, such as their spatial coherence, namely, how LFPs recorded by neighboring electrodes relate to each other. They also review temporal (spectral) properties of LFPs, such as their typical *1/f* structure. The entry also overviews different approaches for modeling LFPs.

Oscillatory Properties of LFPs

A fundamental property of LFP signals is their propensity to display oscillations. In the entry ▶ "Local Field Potential and Deep Brain Stimulation (DBS)", Manuela Rosa, Sara Marceglia, Sergio Barbieri, and Alberto Priori review the use of LFPs in the treatment of DBS in humans. It describes how DBS provides LFP recordings in humans, how they are related to oscillatory activity, and how DBS may interfere with these (sometimes pathological) oscillations.

Pathological oscillations are further investigated in the entry ▶ "Local Field Potential and Movement Disorders" by Annaelle Devergnas and Thomas Wichmann. They review the use of LFP recordings in movement disorders and show that LFPs display various types of oscillations, at different frequencies, for different pathologies associated to movement disorders.

In the entry ▶ "Local Field Potentials in Olfaction", Leslie Kay review the LFP signals recorded in the olfactory system (olfactory bulb and pyriform cortex). Their review emphasizes the emergence of beta and gamma oscillations in olfactory structures.

The occurrence of LFP oscillations in the visual system is investigated in the entry ▶ "Local Field Potential in the Visual System" by Gregor Rainer. This entry reviews the occurrence of LFPs in visual cortex, with an emphasis on visually evoked potentials, and visually evoked oscillations in the gamma frequency band.

Finally, in the entry ▶ "Local Field Potential, Synchrony of", Ariana Frederick, Jonathan Bourget-Murray, and Richard Courtemanche review how LFPs can reveal the presence of network synchrony. Synchrony is here defined as the synchronization between different networks, which indicates a possible interaction between them, for example, using oscillations at different frequencies.

Modeling the Spectral Structure of LFPs

The modeling of LFP signals is first considered by Biyu Jade He in the entry ▶ "Electrocorticogram (ECoG)". This entry reviews models of the ECoG and how this surface signal relates to the LFP recorded in depth. The entry also discusses the spectral structure of these signals and their power-law frequency scaling.

The modeling of LFPs is further developed in the entry ▶ "Local Field Potentials: Interaction with the Extracellular Medium" by Claude Bedard and Alain Destexhe. This entry reviews models of LFPs by staying as general as possible and includes the electrical nature of an extracellular medium. Both microscopic and macroscopic (mean-field) models of the LFP are considered. It is shown that the frequency-filtering properties of the extracellular medium can fully explain the spectral properties of LFPs (such as power law or *1/f* scaling).

Methodological Aspects of the LFP

Different methods to record LFPs are described in the entry ▶ "Local Field Potential, Methods of Recording" by Andrew Sharott. This entry describes important factors such as the type of electrode, the role of the reference, and the recording conditions. The entry discusses how such factors can be determined to correctly interpret the LFP signal.

In the entry ▶ "Resistivity/Conductivity of Extracellular Medium", Scott Lempka and Cameron McIntyre review another set of important biophysical properties that contribute to LFP genesis: the electrical properties of neural tissue, the associated measurements of conductivity, the frequency-filtering properties, as well as the influence of volume conduction.

Finally, in the entry ▶ "Current Source Density (CSD) Analysis", Daniel Wójcik reviews the physical bases of the CSD analysis, which consists of estimating neuronal current sources from LFP measurements performed by electrodes located at equidistant points in space. Different variants of the CSD analysis are presented and discussed.

Cross-References

- ▶ Current Source Density (CSD) Analysis
- ▶ Electrocorticogram (ECoG)
- ▶ Local Field Potential and Deep Brain Stimulation (DBS)
- ▶ Local Field Potential and Movement Disorders
- ▶ Local Field Potential in the Visual System
- ▶ Local Field Potential, Ephaptic Interactions
- ▶ Local Field Potential, Methods of Recording
- ▶ Local Field Potential, Relationship to BOLD Signal
- ▶ Local Field Potential, Relationship to Electroencephalogram (EEG) and Magnetoencephalogram (MEG)
- ▶ Local Field Potential, Relationship to Unit Activity
- ▶ Local Field Potential, Synchrony of
- ▶ Local Field Potential: Relationship to Membrane Synaptic Potentials
- ▶ Local Field Potentials in Olfaction
- ▶ Local Field Potentials: Interaction with the Extracellular Medium
- ▶ Local Field Potentials: LFP
- ▶ Resistivity/Conductivity of Extracellular Medium

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Low Frequency Oscillations (Anesthesia and Sleep): Overview

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Synonyms

Delta oscillations; Relay mode; Sleep; Sleep oscillations; Sleep spindles; Slow oscillations; Slow rhythms; Thalamic bursting

Definition

The transition from waking to sleep or to anesthesia is characterized by an increase in the amplitude and a decrease in the frequency of the electrical activity recorded in the electroencephalogram (EEG). The spectral composition of the EEG changes from one dominated by low-amplitude fast frequencies in the beta gamma range to one dominated by the frequency ranges of slow (0.1–1 Hz), delta (1–4 Hz), and sigma (7–15 Hz, which corresponds with sleep spindles) oscillations (da Silva and Schomer 2011). The dramatic changes in the EEG during the transition from waking to sleep correlate with the deafferentation of the forebrain from the external world and the suppression of consciousness. This section describes cellular mechanisms and computer models of these oscillatory processes and their functional consequences. In this overview entry, some critical points are discussed about the organizations of these rhythms in slow wave sleep and anesthesia.

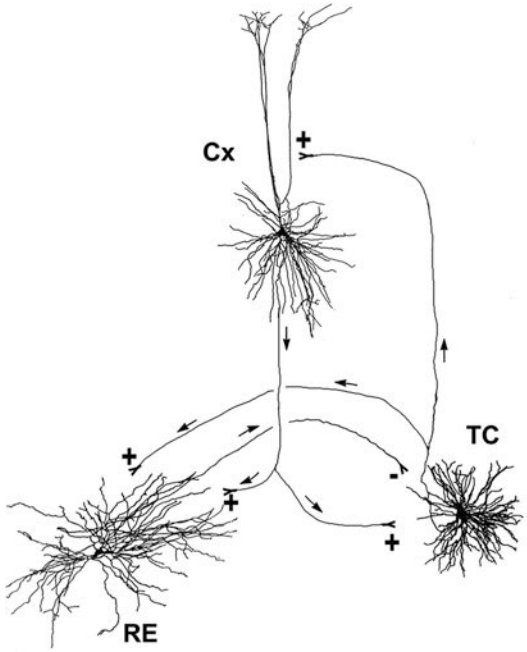
Detailed Description

Background

Slow sleep rhythms are generated within the vast networks connecting thalamus and cortex (Steriade et al. 1994; McCormick and Bal 1997). The main building blocks of thalamocortical circuits (Steriade 2003; Jones 2007), which are essential to understanding the basic principles of rhythm generation (Fig. 1), are (i) reciprocal excitatory glutamatergic connections between cortical pyramidal cells and thalamocortical neurons; (ii) collaterals of excitatory thalamocortical and corticothalamic axons onto reticular thalamic cells, which are established as these axons cross the reticular nucleus on their way in and out of the thalamus; and (iii) inhibitory connections from reticular thalamic cells onto thalamocortical neurons. Reticular thalamic neurons surround the thalamus in its dorsal and lateral surfaces and do not project to the cerebral cortex but project only back into all other thalamic nuclei (Ramon y Cajal 1911). The reciprocal excitation and feedback inhibition combined with various degrees of convergence and divergence are essential to the generation, distribution, and synchronization of the rhythms that characterize sleep and anesthesia (Jones 2001).

Cellular Mechanisms

The single most important cellular mechanism underlying the dramatic transformation in brain

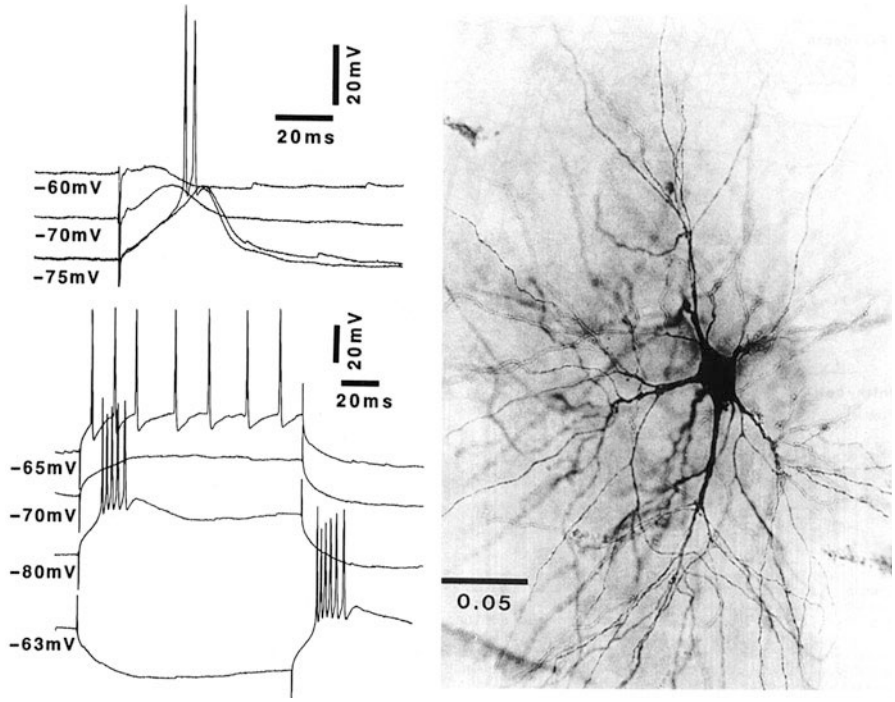


Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 1 A summary of the basic thalamo-cortico-thalamic circuit: *1*. Reciprocal excitatory (glutamatergic) connections between thalamocortical (TC) and cortical (Cx) neurons. *2*. Both ascending and descending axons leave collaterals in the reticular nucleus (RE). *3*. RE neurons are exclusively GABAergic and project topographically only back into the dorsal thalamus (not to cortex). The three cells used for the schematic were recorded intracellularly in vivo and filled with biocytin

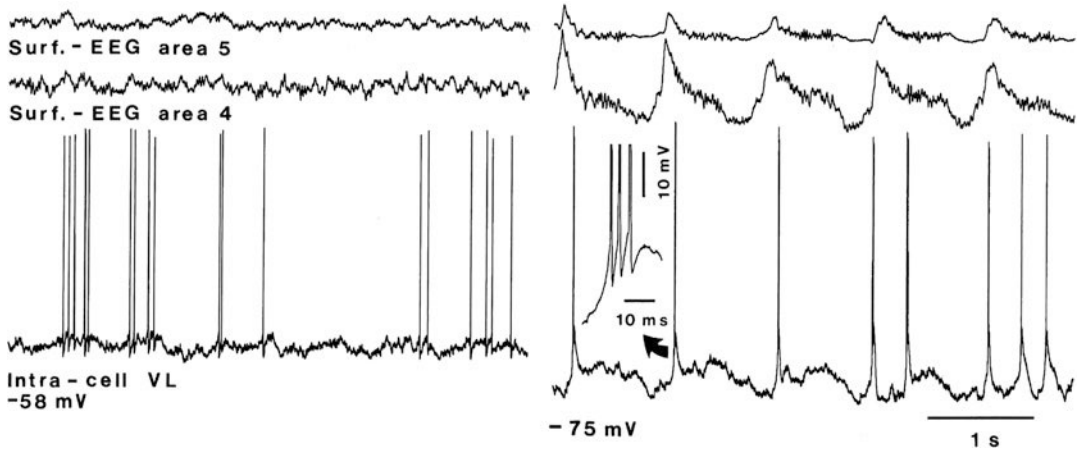
state during the transition from waking to sleep, or to anesthesia, is the change in firing mode of thalamocortical cells (Fig. 2) from tonic to bursting (Llinas and Jahnsen 1982; Jahnsen and Llinas 1984c; Steriade and Llinas 1988; Steriade et al. 1994; McCormick and Bal 1997). At depolarized membrane potentials (Vm) during activated brain states, such as waking, thalamocortical neurons respond to inputs with spike trains that reflect the amplitude and time of the inputs (Deschenes et al. 1984; McCormick and Feeser 1990; McCormick and Huguenard 1992). The membrane hyperpolarization that results from the reduction in cholinergic and adrenergic input during the transition from waking to sleep (Oakson and Steriade 1982; Steriade et al. 1982, 1990; Lu et al. 1993; Steriade 1993) removes inactivation of T-type calcium channels (Jahnsen and Llinas 1984a; Nowycky et al. 1985; Coulter et al. 1989; McCormick and Huguenard 1992; Gutierrez et al. 2001). When fully de-inactivated, T-channels are capable of generating an all-or-none calcium spike, known as a low-threshold spike (LTS) because it is triggered at thresholds 10 mV lower than the sodium action potential (Deschenes et al. 1982; Llinas and Jahnsen 1982). The LTS in turn generates sufficient depolarization to trigger a high-frequency (100–300 Hz) burst of sodium action potentials (Llinas and Jahnsen 1982; Deschenes et al. 1984; Jahnsen and Llinas 1984b).

The amplitude of the LTS and, therefore, of the resulting burst of sodium action potentials depend on the proportion of T-channels that are de-inactivated (Deschenes et al. 1982, 1984; Coulter et al. 1989; McCormick and Huguenard 1992), which reaches 100% at the hyperpolarized Vm of late stages of sleep and deep anesthesia.

The mechanism by which LTS bursts are triggered changes throughout the progressive stages of sleep. This is due to the progressive hyperpolarization of thalamocortical cells as sleep (Hirsch et al. 1983) or anesthesia (Contreras and Steriade 1997a) deepens and EEG activity becomes larger and slower (Fig. 3). At early sleep stages, when sleep spindles are the most conspicuous feature of the EEG, thalamocortical cells are still relatively depolarized and T-channels are not fully de-inactivated. De-inactivation depends on the phasic strong chloride-dependent GABAA IPSPs generated by the inhibitory input from reticular thalamic cells during sleep spindles (von Krosigk et al. 1993; Bal et al. 1995; McCormick and Bal 1997). During spindles, LTS bursts are generated as rebound bursts at the offset of these large GABAA IPSPs. At later, deeper (defined by the higher threshold to wake up) stages of sleep, thalamocortical cells are further hyperpolarized and T-channels are fully de-inactivated. At this stage, T-channels are activated by the depolarization caused by the cationic inward rectifier current IH (McCormick and Pape 1990). IH is voltage dependent and activated at the hyperpolarized levels of deep sleep and deep anesthesia. This IH-dependent depolarization, which is a ubiquitous property of thalamocortical cells (Dossi et al. 1992), triggers an LTS and a spike burst, at the



Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 2 This figure shows a thalamocortical neuron, filled with biocytin (*right*) in vivo, responding to synaptic activation (*top three traces*) and direct current injection (*bottom four traces*) through the microelectrode. Hyperpolarization switches firing mode from tonic to bursting in both cases. *Bottom* trace shows a rebound burst, a burst generated at the termination of a hyperpolarizing pulse (From Contreras and Steriade 1995)



Low Frequency Oscillations (Anesthesia and Sleep): Overview, Fig. 3 The transition from waking to sleep is characterized in the EEG by a transition from high-frequency (~40 Hz) low-amplitude activity to low-frequency (<15 Hz) high-amplitude oscillations. TC cells recorded simultaneously with the EEG show the transition from tonic, relay mode of firing during the waking state to the bursting, all-or-none mode of firing, incompatible with information transfer to the cerebral cortex. In addition, as shown in the figure, the bursting mode of firing is associated with the presence of global slow oscillations that are synchronized and widespread over large cortical and thalamic territories (the figure shows how activity is synchronized only during sleep between areas 4 and 5, for example). The high-amplitude, synchronized oscillatory activity together with the thalamic bursting mode of firing disconnect the cortex from the outside world during sleep (From Contreras and Steriade 1997a)

end of which, the membrane returns to its hyperpolarized level and reactivates IH, thus restarting a rhythmic cycle at the delta frequency range (McCormick and Pape 1990; Dossi et al. 1992; Nunez et al. 1992a). At the deep stage of sleep where thalamocortical cells generate delta oscillations, the EEG is also dominated by large amplitude rhythmic waves at the delta frequency. However, it is not clear what the relationship is, if any, between the intrinsically generated delta oscillations of thalamocortical cells and the cortical generators of delta oscillations when this rhythm is the predominant feature of the EEG (Amzica and Steriade 1998; da Silva and Schomer 2011; Carracedo et al. 2013).

A fundamental consequence of the progressive hyperpolarization of the Vm of thalamocortical cells throughout sleep (Fig. 3) is that, at the deep sleep stages when delta oscillations dominate the EEG (Fig. 3), the Vm is at or below the reversal potential for chloride, and therefore sleep spindles cannot occur. This leads to an incompatibility of sleep and delta rhythms in thalamocortical cells, with sleep spindles characterizing early stages when the Vm is still relatively depolarized and delta oscillations characterizing late stages when the Vm is very hyperpolarized (Nunez et al. 1992b).

Functional Consequences of Slow Rhythms

Three main consequences result from the transition in firing mode from tonic to bursting during the transition from waking to sleep or anesthesia:

1. *Unreliability of Responses*. Rather than reliable and predictable responses to sensory, motor, or cortical input, thalamic cells respond to inputs with all-or-none bursts of spikes which bear little information about the incoming input. Furthermore, because voltage-dependent inactivation of T-channels lasts tens of milliseconds, bursting responses to depolarizing inputs can only occur at low frequencies and therefore represent a strong frequency filter to incoming inputs (McCormick and Feeser 1990).
2. *Rhythmicity*. The transition to burst firing brings about slow rhythmic activity in thalamocortical networks. Three main slow rhythms characterize sleep and anesthesia: sleep spindles (7–15 Hz), delta oscillations (1–4 Hz), and slow oscillations (0.1–1 Hz). Such oscillatory activity requires participation of burst firing by thalamocortical cells and therefore extends the role of thalamic burst firing to the deafferentation of the forebrain. Indeed, in addition to the bursting properties described above, most thalamic spike bursts occur NOT in response to stimuli but, instead, as part of large oscillatory networks, further hindering thalamocortical relay of inputs (Steriade et al. 1994; Steriade 2000).
3. *Synchronization*. An inevitable consequence of thalamic burst firing and slow rhythm generation is the broad synchronization of thalamocortical networks (Contreras and Steriade 1997a, b). By virtue of the divergence and convergence of connections between reticular thalamic and thalamocortical cells, between thalamocortical and cortical neurons and within cortical networks, the strong bursting activity entrains large networks into the slow oscillations of sleep and anesthesia (Amzica and Steriade 1995).

As a result of the above three factors, the reliably responding, rapidly engaged thalamocortical networks that sustain information processing and consciousness in the awake state are transformed into networks that are slow and unreliable in responding and are engaged mostly in slow and synchronized oscillations. These oscillations are incompatible with information processing and ultimately determine the deafferentation of the forebrain during slow wave sleep and anesthesia (Steriade 2000).

Anesthesia and Slow Waves

In contrast with the organized and sequential arrangement of oscillations during sleep, anesthetics mimic and exaggerate one or more rhythmic patterns of sleep in different proportions. For example, during barbiturate anesthesia, the EEG shows spindles most prominently and virtually no delta or slow oscillations. Furthermore, under barbiturate anesthesia, spindle frequency is reduced and

duration increased with respect to naturally occurring sleep spindles. In contrast, ketamine-xylazine generates a strong and exaggerated slow oscillatory pattern on top of which rapid spindles may be triggered. In addition, the slow rhythm during ketamine-xylazine may reach frequencies above 1 Hz and may be confused with EEG delta waves. Urethane anesthesia generates a very stable pattern of slow oscillations with prolonged depolarizing and hyperpolarizing phases but very little spindle or delta oscillations. The combination of propofol and fentanyl produces a rich combination of rhythms including slow oscillations, occasional spindles, and delta waves. Detailed descriptions of oscillatory patterns under different anesthetics are far beyond this section.

Cross-References

- ▶ Corticothalamic Feedback: Large-Scale Synchrony
- ▶ Delta Rhythms: Models and Physiology
- ▶ Slow Oscillations and Epilepsy: Network Models
- ▶ Slow Oscillations: Models
- ▶ Slow Oscillations: Physiology
- ▶ Spindle Oscillations: Models

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Model Reproducibility: Overview

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Definition

The ability to reproduce an experimental result is the foundation of scientific inquiry. Similarly, computational studies need to be reproducible to serve the advance of science. However, computational scientists often find it difficult to reproduce published computational results. Here we provide an overview of efforts to support model reproducibility in computational neuroscience.

Detailed Description

Reproducing the simulation results of computational models and establishing the provenance of results should be straightforward given that computational studies do not suffer from the measurement errors seen in the experimental sciences. However, computational science has its own challenges for reproducibility, which are described well by Crook et al. (2013). In particular, issues such as the sensitivity of a model to numerics or the publication of models that are computationally under-specified lead to the need for criteria for successful model reproduction in many cases. These authors also make distinctions among:

- *Replicability*, where the same code and tools are used to reproduce results
- *Cross-replicability*, where the same model is used but implemented using different software
- *Reproducibility*, where a new model is implemented and produces the same scientific result

As noted in Crook et al. (2013), the boundary between cross-replicability and reproducibility is not always clear, but all efforts along this continuum of reproducible research contribute to advances in the computational sciences.

Model Sharing

Model sharing provides a means for promoting replicability and transparency in the computational sciences. For many reasons, the best infrastructure for sharing models involves curated model repositories such as ModelDB (Migliore et al. 2003), the BioModels Database: a Public Repository for Sharing Models of Biological Processes (Li et al. 2010; Vijayalakshmi et al. 2013), the Physiome Repository (Yu et al. 2011), and Open Source Brain (Gleeson et al. 2019).

Simulator Independent Specification of Models and Simulations

There are a number of ongoing efforts in support of cross-replicability with the aim of providing declarative descriptions of models that are simulator independent. Many of these efforts focus on the use of Extensible Markup Language (XML) technology (Bray et al. 1998) as an ideal representation for complex models.

The Systems Biology Markup Language (SBML) (Hucka et al. 2003) and CellML (Lloyd et al. 2004) are two popular languages for describing systems of interacting biomolecules that comprise models that are often used in systems biology. Both languages also can be used for describing more generic dynamical models, including those in neuroscience. FieldML follows a similar approach but focuses on multivariate spatiotemporal models and models based on the finite element method. NeuroML (Goddard et al. 2001; Crook et al. 2007; Gleeson et al. 2010) differs from these languages in that it is domain specific, where neuroscience concepts like cells, ion channels, and synapses form the basis for objects described in the language. NineML is another domain-specific language that focuses on descriptions of spiking neural networks. Additionally, the Simulation Experiment Description Markup Language (SED-ML) (Köhn and Le Novère 2008) provides a language for describing the details of simulation experiments. These different markup languages are complementary, and together they cover the different spatial scales for the majority of models in neuroscience.

Other efforts focus on code-based approaches for simulator independent model descriptions. PyNN is a Python-based, simulator independent language for building neuronal network models then simulating the model on any simulation platform that PyNN supports such as NEURON, NEST, and Brian (Davison et al. 2009).

The International Neuroinformatics Coordinating Facility, or INCF, advocates for FAIR (Findable Accessible Interoperable Reproducible) principles across all of their projects and activities including neuroscience data and models. In support of this effort, the organization provides a process for the formal endorsement of community standards, including two for describing models, NeuroML and PyNN.

Improved Research Reporting

In the systems biology community, MIRIAM (Minimum Information Required in the Annotation of Models, http://co.mbine.org/standards/miriam) is a community-level effort to provide a set of guidelines for use with any structured format for sharing models. The idea of using best practices and some required metadata for sharing and publishing models is outlined by Novère et al. (2005). All of these requirements can be adapted readily to models in neuroscience. Nordlie et al. (2009) conducted a survey of neuronal network models in the literature and found that current approaches are diverse and inadequate. These authors propose the adoption of best practices for model descriptions in publications, recommending the inclusion of the hypothesis, model derivation, model description, implementation details, model analysis, and model justification. They also provide a concise tabular format for summarizing network models in publications. Publication standards such as those discussed by Le Novère et al. and Nordlie et al. ensure that all possible model details are provided; however, it is important to be aware of the limits of replicability and the impact on reproducibility.

Cross-References

- CellML
- FieldML
- NeuroML
- NineML
- PyNN: A Python API for Neural Network Modelling
- Simulation Experiment Description Markup Language (SED-ML)
- Systems Biology Markup Language (SBML)

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Modeling of Disease: Physical and Molecular Level, Overview

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Definition

Physical-, molecular-, and cellular-scale understanding is not only the first step in the long ladder of multiscale modeling for clinical translational application, it is also the critical scale: "Where the rubber meets the road." The idiom from automotive engineering refers to the critical endpoint where all the ancillary engineering – fuel system, chassis, pistons, etc. – is finally tested. In the realm of translation, this point comes when we translate basic research results to the clinical setting. The physician intervenes at the molecular scale, using pharmacological agents to alter physiological activity only observed at far higher scales: the macroscopic realms of clinical tests and of signs and symptoms. The surgeon intervenes at a physical scale, for example, tying off or filling up a vascular aneurysm to prevent its bursting in the brain.

Given the vast scale gap between molecular or physical treatments and macroscopic outcome, there is enormous difficulty in understanding causal relations, so as to design better drugs and better drug combinations. Multiscale modeling can help make these connections in order to provide a basis for rational pharmacological or surgical treatment.

Detailed Description

This section includes entries of three types:

Techniques: These simulations are performed largely using techniques used elsewhere in computational neuroscience. However, some techniques have been introduced or expanded in the context of their use in translational studies.

Locations: Partitioning of the nervous system can be done at many scales, from organelle to major brain area.

Diseases: We make note of a few neurological and psychiatric illnesses that have been examined at this scale.

Techniques

The standard techniques of molecular and cellular computational neuroscience are utilized for clinical and translational modeling. The techniques that are applicable to simulation at the molecular and cellular level are listed here by their coverage in the entries of this encyclopedia (loosely grouped from micro to macro):

Stochastic Simulators

- ▶ Gillespie Algorithm for Biochemical Reaction Simulation
- ▶ Deterministic Reaction-Diffusion Simulators
- ▶ Bimolecular Reactions, Modeling of
- ▶ Equivalent Cylinder Model (Rall)

In this section, we add three additional methods that have been applied to clinical translational problems.

▶ "Polypeptide and Protein Modeling for Drug Design" takes us down to the lowest of the multiple scales used in computational neuroscience. Polypeptide modeling largely utilizes ball-and-spring modeling, staying above the level of quantum mechanical representations. Individual atoms or atomic groups (e.g., amino acids) are represented as moving in a force field largely determined by the chemical bonds connecting them. This research has direct importance for clinical translation because the lock-and-key fit of a ligand (a drug) to a target is dependent on the physical relations of the interacting species.

"Application of Declarative Programming in Neurobiology to Decipher Normal and Pathological Processes" demonstrates the novel use of a declarative programming language to address problems in Alzheimer's disease and in fear conditioning. Declarative programming is distinguished from the familiar imperative programming languages which we commonly utilize. Imperative programs implement an algorithm. Declarative programs describes relationships between elements, defining what computations are possible among these elements.

▶ "Biomechanical Modeling of Traumatic Brain Injury" provides physical-level models that consider the material properties of tissue, its geometry, and boundary conditions for stresses applied to the head, using finite element methods to predict injury from impact.

Locations

Disease strikes at many locations and at many scales. Parsimony and clinical efficacy depend on finding the proper scale and proper locus for clinical investigation and for clinical intervention – in some cases these are not the same location. A recent example from oncology is illustrative: a renal cancer and a leukemia were previously classified according to organ system and therefore treated by different subspecialists with different therapeutic approaches. These cancers have now been found to share the same tumor mutation and to benefit from similar treatments. As in this oncology example, protean neurological diseases will also express widely. For example, diseases of mitochondria such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers; the ragged fibers

being broken mitochondria) produce neurological disorders across many neural systems, beyond the already broad scope of their acronyms (DiMauro et al. 2013).

In addition to connoting locations in the brain and body (macroscale), disease localization also needs to consider the locus in the cell: particular organelles such as mitochondria, particular classes of molecules such as ion channels, and particular specialized subcellular spaces such as synapses and spines. Some of these locations are covered elsewhere in these volumes: see ▶ "Synaptic Dynamics: Overview" and ▶ "Dendritic Spines". It is to be expected that disorders of spine shape, and of proteins involved in synaptic plasticity, will produce neurological or psychiatric disorders. In this section, we consider the modeling of pharmacotherapeutic manipulation of ion channels in ▶ "Neuropharmacological Modeling Alterations in Ionic Homeostasis" and ▶ "Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation".

A literal route to clinical application is described here in ▶ "Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery". The blood-brain barrier and the extracellular space represent the major pathways for delivery of pharmacological agents. Due to therapeutic index (therapeutic concentration/toxic concentration ratio), it is important to consider how a particular drug can be delivered so as to arrive at adequate concentrations at the site of disease, without being present at excessive concentration at other locations (Brick and Erickson 2013).

At the cellular level, neurological disease has substantial overlap with disease in other excitable tissues. It is particularly valuable to consider the extensive work that has been done in cardiology, here represented by ▶ "Cardiac Excitable Tissue Pathology (Ion Channels)" and ▶ "Cardiac Excitable Tissue Pathology (Ischemia)". Cardiology models are generally more mature than those in neurology. They also have direct analogies to diseases of the brain, e.g., myocardial infarction and stroke, arrhythmias, and epilepsies. Similarly, excitable tissue is important in the islets of the pancreas and in other endocrine systems, where production and release of hormone are directly analogous to production and release of neurotransmitters: see entry on ▶ "Endocrine Cell Function and Dysfunction". A broader physiological perspective, relevant to many of these cell types, is presented here in ▶ "Neuropharmacological Modeling Alterations in Ionic Homeostasis".

Many neurological diseases present outside of the brain or involve the brain in its association with the body. In particular, the enteric nervous system (ENS) and autonomic nervous system (ANS) are prone to disorders (Rao and Gershon 2016) and will be important areas for modeling in the future. In the present section, we feature an entry on ▶ "Pathological Changes in Peripheral Nerve Excitability", to consider disorders in the peripheral nervous system (PNS). It is important to note that myopathies (muscle diseases) also fall within the bailiwick of neurology and will benefit from modeling, some of which can be borrowed from the cardiology literature.

At the subcellular level, signaling occurs through second and third through nth messengers. There has been considerable modeling at this scale (Blackwell 2013), but not as much looking at dysfunction. These topics are covered in detail in the entry on ▶ "Biochemical Signaling Pathways and Diffusion: Overview". Particular note should be made of the major role of calcium as a second messenger, covered in eight entries in that section. Certainly, dysregulation of calcium control will play a major role in the production and expression of disease that has yet to be elucidated by modeling. A review of the key role of calcium in Alzheimer's disease, Parkinson's disease, and Huntington's disease and the current modeling efforts are presented in the entry on ▶ "Calcium Dysregulation in Neurodegenerative Diseases".

At the subcellular and intracellular level, neurons metabolic dependence on astrocytes is modeled in ▶ "Brain Energy Metabolism". The entry details how dysfunction, particularly glucose hypometabolism in neurodegenerative diseases, could lead to cognitive impairments. It includes a detailed example of a three-compartment metabolic network model of energy metabolism and the challenges of developing a spatial model.

A multiscale model of neuroinflammation is described in the entry ▶ "Neuroinflammation,

Glia, and Cytokines: Networks of Networks". It involves modeling networks of molecular interactions at the subcellular level, which influence a network of cell states that then feed into a network of inflammation states at the tissue level. Complex network interactions can lead to unexpected results. The entry describes several modeling approaches including machine learning, dynamic systems, and control theory that reveal underlying properties of the system.

All disease is to a greater or lesser extent multifactorial. Patient susceptibility is determined in substantial part by the genome and its control, as well as by the epigenome (and metagenome, representing additional genomes that are involved (mitochondrial, bacterial – commensal or pathological, viral). In a neuron, communication between genome and synapse is particularly complex, insofar as this is information flow between the organism's two primary loci of information storage. Synaptic changes depend on elaboration, transport, and insertion of membrane proteins, which start with signals at the synapse that trigger changes in transcription. In the present section, we cover the role of second messengers in providing communication with the cell nucleus: ▶ "Transcriptional Control Dysfunction, Modeling", evaluating potential pathology in the linkage between the cell and its nucleus at the molecular and organelle scales.

Diseases

Evaluation of individual diseases is the natural approach for clinical translation – as an end goal we want to know how to treat a particular disease or even a particular patient (personalized medicine) or subgroup of patients (precision medicine). We highlight here four diseases, although there are several others where some cellular/molecular modeling progress has been made and many more where such progress is greatly needed.

A model of molecular dependencies in Alzheimer's is presented in "Application of Declarative Programming in Neurobiology to Decipher Normal and Pathological Processes". Examples of modeling the role of calcium in this disease are given in ▶ "Calcium Dysregulation in Neurodegenerative Diseases".

As a lens through which to view computational neuroscience, disease modeling presents a number of difficulties. First, diseases are generally multiorgan, both in production and in expression. For example, we present here an entry on ▶ "Brain Ischemia and Stroke". Stroke is most often caused by atherosclerosis, a disease of blood vessels. A translational model would ideally include the cellular changes of the arterial wall and the changes in hemodynamics, along with factors that include the blood-brain barrier (which breaks) and the role of a broad dispersion of harmful neurohumoral agents. Stroke frequently co-occurs with myocardial infarction (MI). These coincident disorders, in the brain, heart, and local microvasculature, affect one another, e.g., MI reduces cardiac output and therefore increasing the extent of an incipient stroke (Gan and Ramani 2008). Another difficulty in providing a unified model of a disease is that the disease may involve many disparate variants: hemorrhagic vs. bland stroke, thrombotic vs. embolic stroke, and cortical stroke (gray matter) vs. internal capsule (white matter) stroke.

As mentioned in the "Definition" section above, modeling at physical, molecular, and cellular levels is only the lowest rung in the multiscale ladder of both downward and upward causality. Disparate viewpoints at different scales represent a challenge but are a necessary stage in the development of future unified multiscale views, as can be illustrated by the case of epilepsy – contrast the entry in the section: ▶ "Epilepsy: Abnormal Ion Channels" with the perspective presented in entries on ▶ "Epilepsy: Computational Models", ▶ "Slow Oscillations and Epilepsy: Network Models", and ▶ "Epilepsy, Neural Population Models of".

How are we to build multiscale models out of these disparate pieces? Ideally it would be possible to embed one scale within the model for the higher scale, thereby creating a single unified multiscale model. In many cases this is not possible, so that the models remain separate, with each level informing the other via emergent properties discovered at the lower level. In the case of epilepsy research, emergences from the effect of a drug on a detailed model of an ion channel can be used to change the parameterizations of an ion

channel, which could then be directly embedded in a compartmental model. Emergences from the compartment model can then be used in a reduced model or to modify an integrate-and-fire model. Either of these models (or both as in a hybrid network) can be directly embedded to produce large network models. Emergences from the network can then be used to modify a mean-field model. While this upward sequence is difficult, the downward sequence is even more difficult: we want to follow the scales back down in order to apply lessons learned from the population model in order to eventually suggest changes to drug effect at the polypeptide level.

Conclusions

These initial efforts aimed at understanding the base scale of physical, molecular, and cellular interactions for understanding brain disease should be considered in the context of the wider field of computational systems biology, a field concerned with multiscale modeling across organ systems and medical specialties. Systems biology has been catapulted forward with the realization that the massive amounts of data being collected as genomes, proteomes, and other omes will not be interpretable without contexts, contexts that can only be provided by sophisticated computational models. Further future hope springs from the potential of computer simulation to provide personalized or precision medicine; physiological data from a particular patient would be used to adapt simulation parameters for simulation, just as anatomical data for a particular patient is currently used to provide specifics of beam targeting in radiation therapy.

Cross-References

- ▶ Biochemical Signaling Pathways and Diffusion: Overview
- ▶ Biomechanical Modeling of Traumatic Brain Injury
- ▶ Bimolecular Reactions, Modeling of
- ▶ Brain Energy Metabolism
- ▶ Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery
- ▶ Brain Ischemia and Stroke
- ▶ Calcium Dysregulation in Neurodegenerative Diseases
- ▶ Cardiac Excitable Tissue Pathology (Ion Channels)
- ▶ Cardiac Excitable Tissue Pathology (Ischemia)
- ▶ Dendritic Spines
- ▶ Deterministic Reaction-Diffusion Simulators
- ▶ Endocrine Cell Function and Dysfunction
- ▶ Epilepsy, Neural Population Models of
- ▶ Epilepsy: Abnormal Ion Channels
- ▶ Epilepsy: Computational Models
- ▶ Equivalent Cylinder Model (Rall)
- ▶ Gillespie Algorithm for Biochemical Reaction Simulation
- ▶ Neuroinflammation, Glia, and Cytokines: Networks of Networks
- ▶ Neuropharmacological Modeling Alterations in Ionic Homeostasis
- ▶ Neuropharmacological Modeling, Pharmacogenomics and Ion Channel Modulation
- ▶ Pathological Changes in Peripheral Nerve Excitability
- ▶ Polypeptide and Protein Modeling for Drug Design
- ▶ Slow Oscillations and Epilepsy: Network Models
- ▶ Synaptic Dynamics: Overview
- ▶ Transcriptional Control Dysfunction, Modeling

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Motoneurons and Neuromuscular Systems: Overview

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Definition

Motoneuron models are mathematical representations of motoneuron structure and function. Neuromuscular models represent computational models of neural components integrated with muscle models at various levels of detail and complexities. These models provide a computational framework for investigating neural control of movement. Together, motoneuron and neuromuscular models can guide the development of biomimetic neuromuscular control systems and neural prostheses.

Detailed Description

Motor neurons (or motoneurons) are the final common pathway for all neural drive to the skeletal musculature. Each motoneuron innervates one or more muscle fibers and the cell bodies of motoneurons are somatotopically organized in both vertebrates and invertebrates. Motoneurons were among the first neurons to be studied in great detail by experimentalists largely due to their unique position as output neurons of the nervous system. The rich tradition of the experimental work dates back to the early 1900s beginning with the historical work by Sir John Eccles (1903–1997) and Sir Charles Sherrington (1857–1952), followed by a host of physiologists to date whose work has laid the foundations for realistic models of motoneurons.

Like many neurons in the nervous system, motoneurons show repetitive firing behavior in response to excitation. However, like no other neurons in the nervous system, their frequency of spike discharge directly dictates the degree of muscle contraction. In this way, they mediate control of complex behaviors. At the cellular level, they possess complex morphologies that strongly influence their integrative function. They house a rich assortment of intrinsic membrane-bound ion channels that dynamically interact with a wide range of synaptic inputs to produce unique nonlinearities in their membrane properties. The heterogeneity of cellular properties within a motor pool further confers complex population dynamics. Taken together, motoneurons are an important class of neurons in the nervous system that are attractive candidates for modeling in order to gain a deeper understanding of the neural basis of motor control.

In this section, we discuss principles and methodologies used to develop models of motoneurons and motor effectors at various levels of complexities and scales. At the single cell level, articles presented describe two-compartment models (▶ Algorithmic Reconstruction of Motoneuron Morphology), more complex multi-compartment models (▶ Brainstem Motoneurons, Models of), and morphologically realistic models (▶ Compartmental Models of Spinal Motoneurons). Among vertebrate motoneurons, we explicitly address models of spinal (▶ Brainstem Motoneurons, Models of) and brainstem motoneurons (▶ Computational Models of Motor Pools). We further describe novel algorithms that can generate realistic motoneuron morphologies given a simple set of experimentally derived morphometric parameters (▶ Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons). At the population level, we describe motor pool models (▶ Mammalian Motor Nerve Fibers, Models of). We also describe the computational principles underlying models of the muscles (▶ Morphologically Detailed Motoneuron Models). Since motor fibers traverse long distances to provide electrochemical signals for these effectors, models of motor nerve fibers and propagation

of electrical signals along them are described (▶ Neuromuscular Control Systems, Models of). Lastly, systems-levels models of the neural control systems that enable us to perform tasks by providing suitable input to motoneurons are described (▶ Physiology and Computational Principles of Muscle Force Generation).

Cross-References

- ▶ Algorithmic Reconstruction of Motoneuron Morphology
- ▶ Brainstem Motoneurons, Models of
- ▶ Compartmental Models of Spinal Motoneurons
- ▶ Computational Models of Motor Pools
- ▶ Conductance-Based Models of Nonlinear Dynamics in Vertebrate Motoneurons
- ▶ Mammalian Motor Nerve Fibers, Models of
- ▶ Morphologically Detailed Cellular and Pool Motoneuron Models
- ▶ Neuromuscular Control Systems, Models of
- ▶ Physiology and Computational Principles of Muscle Force Generation

Multistability in Neurodynamics: Overview

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Synonyms

Bistability; Coexistence; Fold bifurcation; Hysteresis; Subcritical bifurcation

Definition

Multistability in neurodynamics is the coexistence of two or more observable regimes of activity, i.e., attractors, in the phase space of a neuronal system. In the absence of noise or perturbation, the neuronal system permanently exhibits one of the regimes. Multistability suggests that by an appropriate choice of perturbation or by resetting the initial state of the system, one could induce a switch from one regime into another.

Detailed Description

Multistable neuronal system can exhibit two or more regimes of activity, depending on its initial state. Both isolated neurons and neuronal networks can exhibit coexistence of several activity regimes. The coexistence of silence, subthreshold oscillations, tonic spiking, and bursting regimes with each other has been observed in a number of theoretical and experimental studies. A multistable neuronal system can show long-lasting responses to short transient signals. Such systems also may respond to perturbations in a state-dependent fashion, demonstrating hysteresis, which is the hallmark of (Nadim et al. 2008). Multistability has clear implications for dynamical memory and information processing in neurons (Marder et al. 1996; Egorov et al. 2002; Durstewitz and Seamans 2006). In the area of motor control, multistability could be a major mechanism of operation of multifunctional central pattern generators (Getting 1989; Venugopal et al. 2007; Briggman and Kristan 2008). On the other hand, multistability can be a pathological feature; for example, seizure regimes can coexist with normal regimes (Ziburkus et al. 2006; Cressman et al. 2009; Frohlich et al. 2010). For the latter, the electrogenic pump has been implicated to play a crucial role (Cressman et al. 2009; Krishnan and Bazhenov 2011).

Multistability can be categorized in terms of the regimes of activity which coexist, e.g., coexistence of tonic spiking and silence (Rinzel 1978; Guttman et al. 1980; Forger and Paydarfar 2004; Hahn and Durand 2001), coexistence of bursting and silence (Malashchenko et al. 2011a, b), coexistence of different bursting regimes (Wang 1994; Butera 1998; Newman and Butera 2010), and

coexistence of bursting activity and tonic spiking (Canavier et al. 1994; Frohlich et al. 2010; Cymbalyuk et al. 2002; Shilnikov et al. 2005; Malashchenko et al. 2011a). These regimes can coexist in the phase space of a neuronal system if some unstable regime creates a barrier, i.e., a separatrix demarcating a border between the basins of attraction. The mechanism underlying multistability can also be described and classified in terms of the unstable regime that forms the barrier (Rinzel 1978; Guttman et al. 1980). One of the key ingredients of such descriptions is the identification of the transitions, i.e., bifurcations, at which the unstable regimes appear and disappear. Ubiquitously, a separating regime is either a saddle equilibrium or a saddle orbit (Rinzel 1978; Malashchenko et al. 2011a; Barnett et al. 2013; Marin et al. 2013). For example, the stable manifold of the saddle equilibrium separates tonic spiking and silence observed in the simplified model of the cerebellar Purkinje neurons (Loewenstein et al. 2005; Fernandez et al. 2007), and the stable manifold of the saddle periodic orbit is a cause of bistability of spiking and silence in the giant squid axon (Rinzel 1978; Hahn and Durand 2001).

The methods developed in the bifurcation theory allow one to investigate stability of, evolution of, and transitions between the silent and oscillatory regimes of neuronal models in response to variation of the system's parameters (Kuznetsov 2004; Terman and Ermentrout 2010; Izhikevich 2010). Application of these methods identifies and explains the mechanisms supporting multistability under normal and pathological conditions (Rinzel 1978; Guttman et al. 1980; Forger and Paydarfar 2004; Gutkin et al. 2009; Hahn and Durand 2001; Krishnan and Bazhenov 2011; Shilnikov et al. 2005; Fröhlich and Bazhenov 2006; Cressman et al. 2009; Cymbalyuk and Shilnikov 2005; Malashchenko et al. 2011a, b).

Cross-References

- ▶ Coexistence of Bursting Regimes
- ▶ Multistability Arising from Synaptic Dynamics
- ▶ Multistability in Perception Dynamics
- ▶ Multistability in Seizure Dynamics
- ▶ Multistability of Coupled Neuronal Oscillators

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Neural Population Models and Cortical Field Theory: Overview

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The term neural population models (NPMs) is used here as catchall for a wide range of approaches that have been variously called neural mass models, mean field models, neural field models, bulk models, and so forth. All NPMs attempt to describe the collective action of neural assemblies directly. Some NPMs treat the densely populated tissue of cortex as an excitable medium, leading to spatially continuous cortical field theories (CFTs). An indirect approach would start by modelling individual cells and then would explain the collective action of a group of cells by coupling *many* individual models together. In contrast, NPMs employ collective state variables, typically defined as averages over the group of cells, in order to describe the population activity directly in a *single* model. The strength and the weakness of his approach are hence one and the same: simplification by bulk. Is this justified and indeed useful, or does it lead to oversimplification which fails to capture the phenomena of interest?

In ▶ "Mesoscopic Anatomy and Neural Population Models," Liley explains that the anatomy of the brain is organized into connected modules at the mesoscopic level, which can serve as a biological substrate for NPMs. In ▶ "Neuropercolation and Neural Population Models" and ▶ "Neural Mass Action," Kozma describes how this undergirds coherent neural activity. Brunel and Hakim demonstrate in ▶ "Population Density Model" and ▶ "Fokker-Planck Equation" how NPMs can be derived mathematically from existing descriptions of individual cells, and in ▶ "Stochastic Neural Field Theory," Bressloff shows this for the CFT variant as well. Liley then introduces the general NPM approach in ▶ "Neural Population Model," and Hutt the CFT variant in ▶ "Neural Field Model, Continuum."

Some historically important and/or particularly popular NPMs are showcased in ▶ "Amari Model" by Potthast, ▶ "Down Under Neural Population Models" by Liley, ▶ "Jansen-Rit Model" by Knösche, and ▶ "Wilson-Cowan Model" by Kilpatrick.

The modelling of connectivity in NPMs has been a topic of considerable development over the years and is covered in ▶ "Propagator, Axonal" and ▶ "Synaptic Connectivity in Neural Population Models" by Jirsa, as well as in ▶ "Gap Junctions, Neural Population Models and" by Sleigh and the Steyn-Rosses. The dynamical properties of NPMs are key for their application to various brain phenomena. The quasi-linear and noise-driven mode is described in ▶ "Transfer Function, Electrocortical" by Molaee-Ardekani and Wendling. Transitions in dynamics, for example, to self-sustained oscillations, are discussed in ▶ "Bifurcations, Neural Population Models and" by Knösche and ▶ "Phase Transitions, Neural Population Models and" by Sleigh and the Steyn-Rosses. Whereas the emergence of spatial structure is presented in ▶ "Pattern Formation in Neural Population Models" by Hutt and the chaotic regime in ▶ "Chaos, Neural Population Models and" by Knösche.

A fundamental strength of NPMs is their ability to predict the data generated by neuroimaging modalities like the electro- and magnetoencephalogram (EEG/MEG) and functional magnetic resonance imaging (fMRI), as described in ▶ "Neuroimaging, Neural Population Models for" by Bojak and Breakspear. This allows the comparison of model predictions with experimental data, be it for normal brain function as in ▶ "Gamma Rhythm, Neural Population Models of the" by Bojak and ▶ "Sleep, Neural Population Models of" by Phillips, under the influence of drugs as in ▶ "Anesthesia, Neural Population Models of" by Sleigh and the Steyn-Rosses or in disease as in ▶ "Epilepsy, Neural Population Models of" by Wendling and Molaee-Ardekani. While many of the methods used to predict the recorded signals are sound and even sophisticated, some of the basics still require substantial improvements, as Einevoll reminds us in ▶ "Extracellular Potentials, Forward Modeling of" Much of the work so far has been in forward prediction with NPMs; however, increasingly it is important to estimate the NPM state and parameters directly from the data. This is elucidated by Moran in ▶ "Dynamic Causal Modelling with Neural Population Models" and by Potthast in ▶ "Inverse Problems in Neural Population Models." Finally, it is exciting that NPMs, and CFTs in particular, can be used to model perception and motor control, as Schöner describes in ▶ "Embodied Cognition, Dynamic Field Theory of," with additional remarks by Schöner and Nowak given in ▶ "Coordination Dynamics."

To answer the question that was posed in the beginning, not only is the NPM approach justifiable and has shown itself to be useful; we expect that within a decade or two, NPMs will take their rightful place as the primary means for describing mesoscopic brain activity. The central problem we face at this description level will not be to simulate millions of brain cells in a reasonable amount of time; the central problem is now, and will be then, that we cannot *specify* the properties and interactions of so many brain cells in a biologically meaningful manner and cannot generate actual *human insight* into principles of function from the plethora of individual cell activities. Once the computational power becomes readily available, this realization will be unavoidable. The way forward will be multi-scale descriptions wherein higher levels discard irrelevant detail of lower levels for an effective and efficient description that remains accessible to the human mind. And given their intimate connection to (noninvasive) neuroimaging, we expect that NPMs will play a privileged role in such a future scheme. This section provides a mere snapshot of a field that is currently growing rapidly and will continue to do so in the foreseeable future.

Cross-References

▶ Amari Model
▶ Anesthesia, Neural Population Models of
▶ Bifurcations, Neural Population Models and
▶ Chaos, Neural Population Models and
▶ Coordination Dynamics

- ▶ Down Under Neural Population Models
- ▶ Dynamic Causal Modelling with Neural Population Models
- ▶ Embodied Cognition, Dynamic Field Theory of
- ▶ Epilepsy, Neural Population Models of
- ▶ Extracellular Potentials, Forward Modeling of
- ▶ Fokker-Planck Equation
- ▶ Gamma Rhythm, Neural Population Models of the
- ▶ Gap Junctions, Neural Population Models and
- ▶ Inverse Problems in Neural Population Models
- ▶ Jansen-Rit Model
- ▶ Mesoscopic Anatomy and Neural Population Models
- ▶ Neural Field Model, Continuum
- ▶ Neural Mass Action
- ▶ Neural Population Model
- ▶ Neuroimaging, Neural Population Models for
- ▶ Neuropercolation and Neural Population Models
- ▶ Pattern Formation in Neural Population Models
- ▶ Phase Transitions, Neural Population Models and
- ▶ Population Density Model
- ▶ Propagator, Axonal
- ▶ Sleep, Neural Population Models of
- ▶ Stochastic Neural Field Theory
- ▶ Synaptic Connectivity in Neural Population Models
- ▶ Transfer Function, Electrocortical
- ▶ Wilson-Cowan Model

Neuromodulation: Overview

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Definition

Neuromodulation refers to the regulation of neural and synaptic function by regulatory extrinsic or intrinsic substances.

Detailed Description

Computational modeling of neural substrates provides an excellent theoretical framework for the understanding of the computational roles of neuromodulation. Neuromodulation can be defined as biophysical processes that serve to modify – or modulate – the computation performed by a neuron or network as a function of task demands and behavioral state of the animal. These modulatory effects often involve substances such as acetylcholine (ACh), norepinephrine (NE), histamine, serotonin (5-HT), dopamine (DA), and a variety of neuropeptides. Modulatory effects are difficult to define, because they often originate from different structures and have different spatial distributions and time courses of action. Because of the wider use of modeling techniques and growing interest in systems neuroscience, the computational role of neuromodulation in information processing has helped elucidate neuromodulatory function, and predictive theories have arisen from computational approaches.

Neuromodulation can be described by its spatial and temporal characteristics, as well as the specific computational function ascribed to it. Spatial characteristics include extrinsic, originating from an area extrinsic to the network under study, or intrinsic, originating from processes within the area under study. The computational functions of extrinsic neuromodulation, such as ACh, NE, 5HT, and DA, are usually considered somewhat global, because they modulate many areas of the brain simultaneously. Classically, ACh has been associated with attentional processes, NE with signal-to-noise modulation, DA with reward learning, and 5HT with sleep-wake transitions. In other cases, modulation is specific to the network under investigation and an integral part of the computations performed within. Second messenger systems, plasticity processes, and gene regulation are examples of such intrinsic modulation. From a functional point of view, neuromodulation is often regulatory, for example, in the cases of second messenger systems or activity-dependent regulation of conductances. In the sensory

systems, neuromodulation is often linked to tuning of receptive fields (ACh) and regulation of signal-to-noise ratio. A third highly important function of most neuromodulators is the regulation of plasticity, via excitability of neurons, synaptic plasticity, and broader modulation of network dynamics.

Exactly how neuromodulation is integrated in computational studies depends widely on the details of implementation of the computational model itself. Effects of neuromodulators can be implemented from the detailed biophysical level, to broader regulation of network parameters in case of more abstract large-scale models. For example, specific effects on voltage-gated channels may be implemented in a biophysical model by changing channel parameters, in a simplified integrate and fire model by changing a related parameter such as firing threshold. Each study chooses the level of detail appropriate to the question asked and data available. For a comprehensive review of levels of implementation of neuromodulation in computational models, we refer the reader to Fellous and Linster (1998). The chapters in this section cover overviews of neuromodulatory computation divided by substance, nature of task, as well as overviews of types of network implementations and specific examples.

Cross-References

- ▶ Computation with Dopaminergic Modulation
- ▶ Computation with Serotonergic Modulation
- ▶ Computational Models of Modulation of Oscillatory Dynamics
- ▶ Computational Models of Neuromodulation

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Further Reading

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Neuromorphic Engineering: Overview

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Definition

Neuromorphic engineering is a recent interdisciplinary field involving biologists, physicists, mathematicians, computer scientists, and engineers to design hardware/physical models of neural systems. It aims at designing silicon-based neural systems for computational or biomedical purposes. The term "neuromorphic" relates to the computational architecture, shaped to model biological neural systems: neuromorphic engineering is by essence strongly linked to computational neuroscience.

Detailed Description

Neuromorphic engineering offers an interesting alternative to computer simulations of neural networks: while main components of computers are high-precision high-speed digital hardware with high-power dissipation, neural components are slow asynchronous computational elements which use a combination of analog and digital signal representations. Neuromorphic systems are hardware implementations that operate in physical time; they are inspired by the structure, function, and plasticity of biological nervous systems. Their design is facilitated by similarities between VLSI (very large-scale integrated circuits) hardware and neural bioware.

Since decades, researchers have been implementing electronic models of neural circuits, following the long history of artificial neural networks that started in the 1950s. Original neuromorphic circuits (Mead 1989) were VLSI systems that used the nonlinear and graded properties of transistors to emulate protein channels in neurons. More recently the term neuromorphic

has been used to describe analog, digital, and mixed analog-digital VLSI as models of neural computation.

Neuron model computation can be either analog, with a continuous-time and continuous-value representation, or digital using numerical algorithms. In both cases, neuromorphic devices classically use spiking (asynchronous binary signal analogs to neural spikes) representation for neuronal communication and learning mechanisms. At the neural network level, synaptic modification mechanisms are usually introduced to model learning and adaptation in neural systems. Furthermore, similar to robustness of neural networks to changes in the environment, dynamic synaptic modification in neuromorphic systems allows gaining a remarkable robustness against transistor-level variations. Whatever the technological support of the neuromorphic electronics, real-time computation is mandatory for systems interacting with a biological environment (sensory or motor).

To date, widely known neuromorphic systems are highly integrated VLSI that emulate sensory transduction (vision, olfaction, audition) or more sophisticated and multimodal neural systems like the head-direction system. Larger neuromorphic systems emerged in the last decade, emulating complex or cognitive biological functions and suggesting new research directions for robotics by the means of biomorphic engineering.

According to the VLSI technology road map, promising low-power and high-density nanoscale technologies, including organic electronics, memristors, or 3D technologies, are expected to fulfill the need for large-scale neuromorphic systems, currently implemented using standard CMOS VLSI technologies. Large neuromorphic systems have performance measures (high density, high speed, low power) that are good enough to enable the study of large-scale and biologically inspired neural networks. Such large networks represent a challenge for computational neuroscience. Researchers have recently started investigating cognitive neuromorphic systems that are able to perform adaptive behaviors and that merge neural fields and single-neuron representations courtesy of the increased computational power of microelectronic devices.

Entries in this section review state-of-the-art neuromorphic engineering computational principles, technologies, and applications. This transdisciplinary research field, at its heart, combines the physics of electronics and biology and algorithms and then engineers it for solving tasks. Despite the many challenges, neuromorphic engineering may hold great promises for a new generation of medicine or industry technologies.

Cross-References

- ▶ Brain-Machine Interface: Overview
- ▶ Dynamical Systems: Overview
- ▶ Neuromorphic Cognition
- ▶ Neuromorphic Hardware, Large-Scale
- ▶ Neuromorphic Sensors, Cochlea
- ▶ Neuromorphic Sensors, Head Direction
- ▶ Neuromorphic Sensors, Olfaction
- ▶ Neuromorphic Sensors, Vision
- ▶ Neuromorphic Technologies, Memristors
- ▶ Spike-Timing Dependent Plasticity, Learning Rules
- ▶ Spiking Network Models and Theory: Overview
- ▶ Synaptic Dynamics: Overview

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Neuronal Model Optimization: Overview

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Synonyms

Neuronal model hand-tuning

Definition

Neuronal Model Parameter Optimization is the process of adjusting the parameters of a computational model of a neuron or neuronal network in order to achieve model activity that mimics that of the living neuron or network being modeled.

Detailed Description

This section contains entries that explain the need for neuron and network model parameter optimization, discuss various optimization methods, describe existing software tools for optimization and visualization of the model databases that result from some of the optimization methods, and discuss related concepts that have emerged from model optimization and exploration efforts over the last few years.

Why Do Neuronal Model Parameters Need to Be Optimized?

Computational models of neurons and neuronal circuits are important investigative tools that allow the study of neuronal signaling and information processing mechanisms that would not be experimentally accessible. However, constructing a model neuron or network requires the specification of numerous parameters, such as maximal conductances, half-activation voltages, and time constants of ionic membrane currents, as well as the strength and dynamical properties of synapses. A complete set of parameters to describe a given neuron or network is virtually never available from experimental data, because some of the parameters cannot be directly measured. Combining parameters measured from different animals is also problematic because almost all parameters vary between animals, and the distributions in the space of parameter sets obtained from different animals are often nonconvex, leading to ▶ "Failure of Averaging," i.e., the problem that the set of parameter averages obtained from a distribution of parameter sets can fall outside that distribution in parameter space.

Neuronal models initially constructed from incomplete and averaged parameter sets therefore usually generate activity that does not match that of the living system to be modeled. Such dysfunctional models then require parameter optimization, either through ▶ "Neuronal Model Hand-Tuning" by an expert employing educated guessing and trial-and-error parameter adjustments, or through one of the optimization methods described in this section.

Neuronal Model Optimization Methods

One approach that allows the identification of neuronal model parameter regimes that produce qualitatively different model behaviors (for example, spiking versus bursting versus silence) is ▶ "Bifurcation Analysis," i.e., the use of dynamical systems analysis to determine critical parameters that cause transitions from one behavior to another. Bifurcation analysis is most powerful for models of low dimensionality. For models with many dynamic variables and parameters, the use of bifurcation analysis may therefore require prior model simplification through ▶ "Neuronal Model Reduction," ideally without the loss of essential features of model activity.

A more agnostic approach to studying the dependence of neuronal model activity on the underlying model parameters is ▶ "Neuronal Parameter Space Exploration," i.e., the brute-force computational exploration of many – often tens of millions – of parameter combinations that cover the model's high-dimensional parameter space. Characteristics of the simulated model activity for each parameter combination are then stored in ▶ "Neuronal Model Databases" that can be mined for model versions with the desired activity, and to address general questions about the relationship between model parameters and output.

Less exploratory, more targeted model optimization methods are based on ▶ "Evolutionary Algorithms." They require the definition of a ▶ "Neuronal Model Output Fitness Function," which is a measure for how well a neuron or network model's activity replicates that of the living system to be modeled. ▶ "Multi-objective Evolutionary Algorithms" constitute a class of evolutionary algorithms that simultaneously

optimize models to meet several different objectives, rather than maximizing a single fitness measure. An implementation of evolutionary neuronal model optimization is available in the software tool ▶ "Neurofitter."

Finally, ▶ "Hybrid Parameter Optimization Methods" combine several of the above methods of neuronal model optimization to benefit from their respective advantages.

Visualization of Neuronal Model Parameter Spaces

Several of the model optimization methods described in this section produce long lists of parameter sets and their corresponding neuronal model activity that are often collected in ▶ "Neuronal Model Databases." Because the underlying models and their parameter spaces are high-dimensional, it is difficult to analyze how the activity of a model varies across parameter space. This problem is addressed by recently developed methods of ▶ "Neuronal Parameter Space Visualization," including the visualization tool ▶ "NDVis-Neuro," which is designed for the visualization of model databases that cover parameter space with a regular grid of parameter sets.

Beyond Optimization

A number of recent neuronal model optimization efforts, as well as a growing body of experimental data, have revealed concepts that go beyond model optimization in the sense of identifying a single "optimal" model parameter set. Neuronal models and the living systems they mimic display ▶ "Neuronal Parameter Non-uniqueness," meaning that different parameter sets can produce similar and functional neuron or network activity. The subset of parameter space that contains such functional parameter sets is called the "Neuronal Solution Space." Analysis of the structure of neuronal solution spaces has revealed that parameters do not necessarily vary independently within the solution space, but often show ▶ "Neuronal Parameter Co-regulation."

Apart from asking whether a given parameter set does or does not support functional model activity, parameter space exploration also allows for the analysis of ▶ "Neuronal Parameter Sensitivity," that is, in which direction and how strongly activity characteristics such as spike frequency depend on model parameters.

Together, the realization of ▶ "Neuronal Parameter Non-uniqueness" and the connected concept of "Neuronal Solution Space" have led to the strategy of "Ensemble Modeling," i.e., the approach of analyzing an entire ensemble of parameter sets and model versions that produce functional activity, rather than focusing on a single "optimal" model version.

Cross-References

- ▶ Bifurcation Analysis
- ▶ Evolutionary Algorithms
- ▶ Failure of Averaging
- ▶ Hybrid Parameter Optimization Methods
- ▶ Multi-objective Evolutionary Algorithms
- ▶ NDVis–Neuro
- ▶ Neurofitter
- ▶ Neuronal Model Databases
- ▶ Neuronal Model Hand-Tuning
- ▶ Neuronal Model Output Fitness Function
- ▶ Neuronal Model Reduction
- ▶ Neuronal Parameter Co-regulation
- ▶ Neuronal Parameter Non-uniqueness
- ▶ Neuronal Parameter Sensitivity
- ▶ Neuronal Parameter Space Exploration
- ▶ Neuronal Parameter Space Visualization

Olfaction: Overview

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Definition

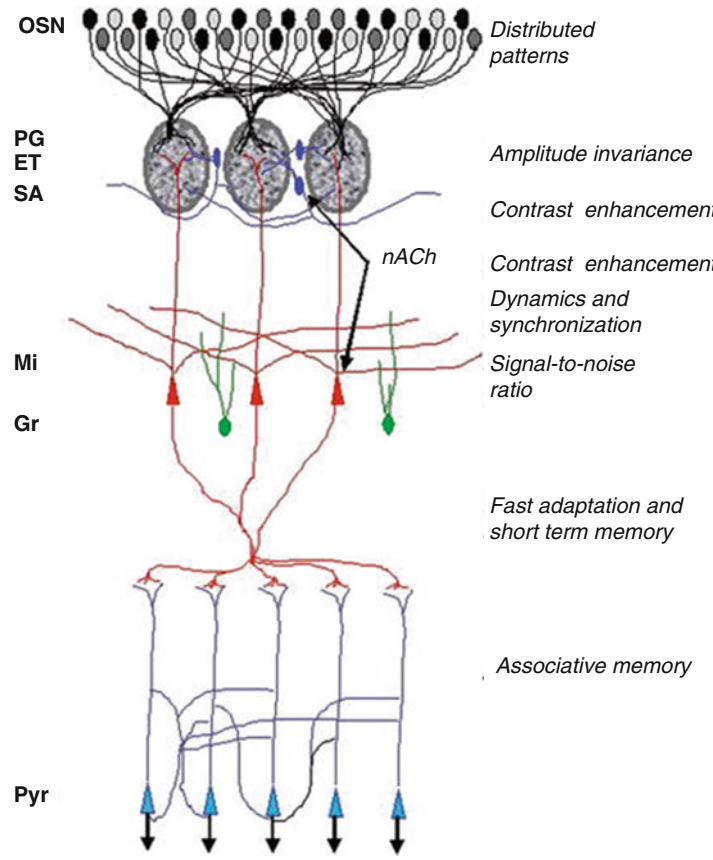
Olfaction refers to the sense of smell and the perception of odorants. This process involves

multiple peripheral and central structures of the nervous system, i.e., the olfactory pathway, and ultimately results in the creation of odor images in the brain as well as the generation of motor and behavioral responses. In several decades, olfaction has been investigated experimentally and theoretically, integrating physiological, behavioral, and computational studies. Here we focus on computational models of olfactory processing, showing how they can promote an understanding of olfaction that goes beyond the mere collection of experimental data.

Detailed Description

In natural environments, airborne chemicals stimulate continually the olfactory system, with unpredictable occurrence in time and space. The olfactory system enables the detection of these odorants out of a chemically noisy environment, extracting relevant odor features, and making a comparison with previously memorized odors.

The multiple circuits forming the olfactory system are thought to contribute distinct computations to odor processing. Figure 1 shows a schematic representation of the most prominent olfactory circuits in mammals. The short-axon (SA), external tufted (ET), and periglomerular (PG) cells form a subnetwork in the juxtaglomerular area, which has been proposed to transform a disorganized odor representation into a concentration invariant and contrast-enhanced one (Cleland and Sethupathy 2006; Cleland 2010). In the next layer, mitral (Mi) and granule (Gr) cells form a reciprocal



Olfaction: Overview, Fig. 1 *Schematic description of olfactory structures*. The olfactory sensory neurons (*OSN*) expressing a common receptor converge onto the common olfactory glomeruli, where they make excitatory synapses with the mitral (*Mi*), periglomerular (*PG*), and external tufted (*ET*) cells. ET, PG, and superficial short-axon (SA) cells are interconnected, forming a subnetwork in the glomerular layer. The high convergence between OSNs and glomerular cells can increase signal-to-noise ratio in the system (Linster and Cleland 2009). PG cells make inhibitory connections with Mi cell primary dendrites, allowing for contrast enhancement of the olfactory signals ahead of the Mi cell response (Cleland and Sethupathy 2006)

excitatory/inhibitory loop, which has been hypothesized to implement the neural substrate for fast oscillations and synchrony (Freeman 1974; Brea et al. 2009). Mi cell axons project to secondary olfactory structures, including the piriform cortex, in a non-topographically organized fashion. In the cortex, Mi axons make distal synapses with pyramidal (Pyr) cells, displaying short-term plasticity (Wilson and Linster 2008). The extensive excitatory connections between cortical pyramidal (Pyr) cells, known to undergo synaptic plasticity, have long been proposed to implement an associative memory for odor storage (Hasselmo et al. 1990).

Computational models of olfactory processing have provided mechanistic and functional insights into odor perception and learning. Mechanistical models have long focused on generation and maintenance of fast oscillations in the olfactory system, and particularly in the gamma range (e.g., Freeman 1974; Lagier et al. 2004; Li and Cleland 2013). Functional models have focused on computations such as signal-to-noise ratio modulation (e.g., Hasselmo et al. 1997; Linster et al. 2011), contrast enhancement (e.g., Linster and Hasselmo 1997; Urban 2002; Cleland and Sethupathy 2006; Cavarretta et al. 2016), and odor learning (e.g., Hasselmo et al. 1990; Wilson and Linster 2008; Cavarretta et al. 2016, 2018). A prominent subclass of functional models consists of biophysically detailed models, which accounts for diverse neuron types and mechanisms (e.g., Li and Cleland 2013; Gilra and Bhalla 2015; Cavarretta et al. 2018). Many models have focused on linking neural and perceptual processes (e.g., Mandairon et al. 2006), while others have stayed abstract and predictive (e.g., Brea et al. 2009).

In this section, most entries are about computational modeling of the olfactory bulb. Here, different models address the biophysical mechanisms and network properties of the system (see entries ▶ "Biophysical Models of Olfactory Mitral and Granule Cells", ▶ "Olfactory Computation in Mitral-Granule Cell Circuits", ▶ "Large-Scale Models of the Olfactory Bulb", and ▶ "Olfactory Computation in Glomerular Microcircuits"), and explain how glomerular and granule cell microcircuits organize odor response in specific patterns of spiking activity (see entries ▶ "Olfactory Computation in Mitral-Granule Cell Circuits", ▶ "Large-Scale Models of the Olfactory Bulb", and ▶ "Olfactory Computation in Glomerular Microcircuits"). Similarly, one entry is dedicated to a model of the insect olfactory system that gives insight into its basic functioning (see ▶ "Olfactory Computation in Antennal Lobe and Mushroom Bodies"). The olfactory sensory neurons are treated in one entry, where a mathematical model is proposed to predict the dose-response relationship for generic odor mixtures (see ▶ "Olfactory Sensory Neurons to Odor Stimuli: Mathematical Modeling of the Response"). All these entries are then complemented by a short review on information processing in the olfactory bulb (see ▶ "Information Processing in the Olfactory Bulb"), and a more speculative entry on the functional implication of neurogenesis in these olfactory areas (see ▶ "Olfactory Computation and Adult Neurogenesis"). The olfactory cortex is discussed in the setting of associative networks (see ▶ "Olfactory Cortical Associative Memory Models"), providing a review of the existing literature. Furthermore, three examples show of how to cellular and neuromodulatory data can explain behavior (see ▶ "Computational Modeling of Olfactory Behavior"), integrating computational modeling of olfactory areas and behavioral data.

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Peripheral Nerve Interfaces: Overview

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Definition

The peripheral nervous system (PNS) comprises nerve fibers and ganglia located outside of the brain and spinal cord, including 11 pairs of cranial nerves and 31 pairs of spinal nerves. The spinal (or somatic) nerves originate as dorsal and ventral spinal nerve rootlets at their junction with the spinal cord. The dorsal spinal nerve roots contain afferent (sensory) nerve fibers and their cell bodies, which are located in the dorsal root ganglia (DRG). The ventral spinal nerve roots contain efferent (motor) fibers whose cell bodies are located in the ventral horn of the spinal cord. The dorsal and ventral roots merge to form the spinal nerve, which exits the spinal column through the intervertebral foramen. Upon exiting the spine, the nerve divides into dorsal and ventral rami, which may branch further and mix with other nerve fibers to form plexuses (e.g., brachial plexus) and eventually form distinct peripheral nerves and their branches.

Detailed Description

This section begins with background information on the anatomy and physiology of the peripheral nervous system (▶ "Peripheral Nerves, Anatomy and Physiology of") and mathematical models for simulating the biophysical properties of peripheral nerves (▶ "Peripheral Nerve Models"). Subsequent entries describe devices and signal processing methods for acquiring and analyzing electrical signals from peripheral nerves.

Techniques for stimulating activity in peripheral nerve fibers are also described. This section also describes several research and clinical applications based on peripheral nerve recording and stimulation techniques.

Peripheral Nerve Interface Methods and Applications

Interfaces to the peripheral nervous system have long been considered of medical value, beginning in ancient Egypt where the pain-relieving properties of the electric catfish were discussed and continuing with the Mediterranean electric ray and torpedo fish. The nineteenth century saw renewed interest in electrical stimulation of the PNS due to dramatic advances in the understanding of electricity. Only relatively recently, however, through the pioneering modeling work of researchers like Hodgkin and Huxley, and those that have expanded and continued their work, have we begun to understand the PNS well enough to design safe and effective interfaces to it.

A wide variety of interface technologies has been developed to record or stimulate activity in peripheral nerves. Most interfaces rely on electrodes placed on the nerve surface (epineural) or penetrate the interior of the epineurium (intraneural) of the nerve (▶ "Peripheral Nerve Interface, Intraneural Electrode"; ▶ "Peripheral Nerve Interface, Epineural Electrode"; ▶ "Peripheral Nerve Signal Processing, Multipole Cuff Methods"; ▶ "Peripheral Nerve Interface, Regenerative").

Peripheral nerve interface technologies have been applied to the diagnosis or treatment of a wide range of medical conditions. Examples of diagnostic applications include electromyography and nerve conduction tests used to identify and localize nerve damage caused by carpal tunnel syndromes, diabetic neuropathies, and other injuries or diseases (▶ "Peripheral Nerve Interface Applications, EMG/ENG").

Electrical stimulation of peripheral nerve fibers is used to evoke activity in sensory, motor, and autonomic fibers. The cochlear implant is a highly successful example of a sensory prosthesis that restores hearing to people with profound hearing loss due to damage to the hair cells in the cochlea (▶ "Peripheral Nerve Interface Applications, Cochlear Implants"). Electrical stimulation of cutaneous nerve fibers with TENS/PENS devices is used to treat a variety of pain syndromes (▶ "Peripheral Nerve Interface Applications, Neuropathic Pain"). Other types of sensory prostheses are being developed (▶ "Peripheral Nerve Interface Applications, Sensory Restoration"), for example, to provide tactile and proprioceptive sensations to users of prosthetic limbs.

Summary

The highly structured nature of the peripheral nervous system makes it amenable to computational modeling. Advances in these interfaces have already made a profound impact on modern medical technology including cochlear implants (▶ "Peripheral Nerve Interface Applications, Cochlear Implants"); techniques to support bladder, bowel, and sexual function; and vagal nerve stimulation (▶ "Peripheral Nerve Interface Applications, Vagal Nerve Stimulation"). New techniques currently being investigated will address a variety of disorders throughout the body including obesity (▶ "Peripheral Nerve Interface Applications, Obesity"), neuropathic pain (▶ "Peripheral Nerve Interface Applications, Neuropathic Pain"), sleep apnea (▶ "Peripheral Nerve Interface Applications, Sleep Apnea"), and sensory restoration in amputees (▶ "Peripheral Nerve Interface Applications, Sensory Restoration"). The interfaces themselves come in a diverse array of forms from simple cuff electrodes (▶ "Peripheral Nerve Interface, Epineural Electrode") which wrap around the nerve to more complex regenerative electrode arrays (▶ "Peripheral Nerve Interface, Regenerative"), and utilize many advanced stimulation and signal processing techniques (▶ "Peripheral Nerve Signal Processing, Denoising").

Peripheral nerve interface technologies hold great promise in the diagnosis and treatment of a wide range of neurological disorders. Research in this area requires significant collaboration between researchers in computational modeling, neuroscience, biomedical engineering medicine, and physiology.

Cross-References

- ▶ Peripheral Nerve Interface Applications, Cochlear Implants
- ▶ Peripheral Nerve Interface Applications, EMG/ENG
- ▶ Peripheral Nerve Interface Applications, Neuropathic Pain
- ▶ Peripheral Nerve Interface Applications, Obesity
- ▶ Peripheral Nerve Interface Applications, Respiratory Pacing
- ▶ Peripheral Nerve Interface Applications, Sensory Restoration
- ▶ Peripheral Nerve Interface Applications, Sleep Apnea
- ▶ Peripheral Nerve Interface Applications, Vagal Nerve Stimulation
- ▶ Peripheral Nerve Interface, Epineural Electrode
- ▶ Peripheral Nerve Interface, Intraneural Electrode
- ▶ Peripheral Nerve Interface, Regenerative
- ▶ Peripheral Nerve Models
- ▶ Peripheral Nerve Signal Processing, Denoising
- ▶ Peripheral Nerve Signal Processing, Multipole Cuff Methods
- ▶ Peripheral Nerve Signal Processing, Source Localization
- ▶ Peripheral Nerve Stimulation Technique, Nerve Block
- ▶ Peripheral Nerves, Anatomy and Physiology of

Phase Response Curves: Overview

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Detailed Description

Phase response curves (PRCs, alternatively phase-resetting curves) are a powerful way of characterizing and explaining the behavior of nonlinear oscillators without knowing anything about their specific internal dynamics. The phase response curve represents the shortening or lengthening of the cycle period caused by an input depending upon at what point (phase) within the cycle an input is received. In contrast, for a linear time invariant system, the effect of an input is independent of when it is applied. No matter whether the oscillations represent the flashing of fireflies, a pendulum-based clock, a cardiac cell, or a neural oscillator, the phase response curve predicts the phasic relationship of the oscillator to periodic forcing or to coupling within a network of other oscillators. Each oscillator can be reduced to a phase oscillator whose angular velocity on a circle is constant, except when it receives an input that resets (advances or delays) its phase on the circle. In a neural context, there is usually a threshold event, often the action potential or spike, which is used to demarcate the boundaries of a cycle. If an input shortens the cycle, the next spike occurs sooner than it otherwise would have, and so the next spike is advanced. Conversely, if the next spike occurs later than it otherwise would have, the spike is delayed.

The phase-resetting curve is sometimes presented as the response to a specific input. We have called this the general PRC. One example might be to perturb the oscillator underlying the circadian rhythm by exposing an animal to a period of light during its usual period of darkness; another example might be to stimulate a particular synaptic input or set of synaptic inputs to a neural oscillator. The ▶ "Spike Time Response Curve" is a way to plot the phase response to a specific input, that is, a spike in the presynaptic neuron, in a way that preserves information about time intervals. Phase-resetting theory is generally applied to neural circuits under a simplifying assumption; two common assumptions are that of pulsatile (brief) coupling or weak coupling. The entry on ▶ "Pulse-Coupled Oscillators" uses the information in the spike-time response curve (or the information in the general phase-resetting curve combined with the intrinsic period information) to predict the response of an oscillator to periodic forcing or mutual coupling, under the pulse-coupled

assumption that the effect of each input dissipates quickly compared to the cycle period.

A second use of the term phase-resetting curve is to represent the response of the oscillator to an infinitesimal input, in other words as a change in the period per unit of the input, called the infinitesimal PRC or iPRC. The entry on ▶ "Phase Response Curve, Measurement of the Infinitesimal" explains how to measure the infinitesimal phase response curve (iPRC). The iPRC is useful mostly in the context of the weak-coupling assumption, which assumes that the phase resetting due to two brief, sequential pulses summates linearly, and the phase resetting due to a single brief pulse rescales linearly with the height of the pulse. Thus, a complicated input like a postsynaptic current waveform can be conceptually broken up into a series of shifted and scaled pulses (Dirac delta functions). The entry on ▶ "Weak Coupling Theory" explains the connection between the iPRC and the general PRC. That is, if the coupling is sufficiently weak, the general phase resetting due to any arbitrary input waveform can be computed by summing the phase resetting due to each individual pulse: the timing of each pulse gives the phase, and the height of the pulse gives the scale factor for the resetting. This amounts to convolving the iPRC with the input waveform. Since the coupling is weak, the assumption is that the relative phases of the oscillators change very slowly. Weak coupling can be used to predict the synchronization tendencies of networks of oscillators. The entry on ▶ "Phase Models, Noisy" explains the effect of noise under the assumption of weak coupling.

Many factors, including the underlying bifurcation structure and the particular set of conductances expressed by the neuron, influence the PRC shape as described in the entry on ▶ "Phase Response Curve, Measurement and Shape of General". The influence of the underlying bifurcation structure described in that entry led to the classification of all PRCs with a single sign (all advances or all delays) as type 1 and those with both advances and delays as type 2. A completely separate, classification scheme into type 0 and type 1 PRCs is described in the entry on ▶ "Phase Response Curve, Topology of".

The two schemes are a potential source of confusion because of the similar terminology, but these schemes are unrelated. In the topology-based scheme, which was developed first, weak resetting leads to type 1 phase resetting, in which the phase immediately after an input can take on any value, but strong resetting leads to type 0 resetting in which only a limited set of phase values are allowed immediately after a strong input. This approach to classifying phase-resetting curves makes minimal assumptions, including pulse coupling, and is based on simple topological considerations.

In summary, phase response curves have been defined for both infinitesimal and general inputs. PRCs have been classified using separate, unrelated schemes based on bifurcation analysis or topology. Finally, PRCs have been used to analyze synchronization under assumptions of either weak or pulsatile coupling.

Cross-References

- ▶ Phase Models, Noisy
- ▶ Phase Response Curve, Measurement and Shape of General
- ▶ Phase Response Curve, Measurement of the Infinitesimal
- ▶ Phase Response Curve, Topology of
- ▶ Pulse-Coupled Oscillators
- ▶ Spike Time Response Curve
- ▶ Weak Coupling Theory

Retinal/Visual Interfaces (Models, Theory, Techniques): Overview

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Synonyms

Artificial vision; Prosthetic vision; Visual neuroprosthesis

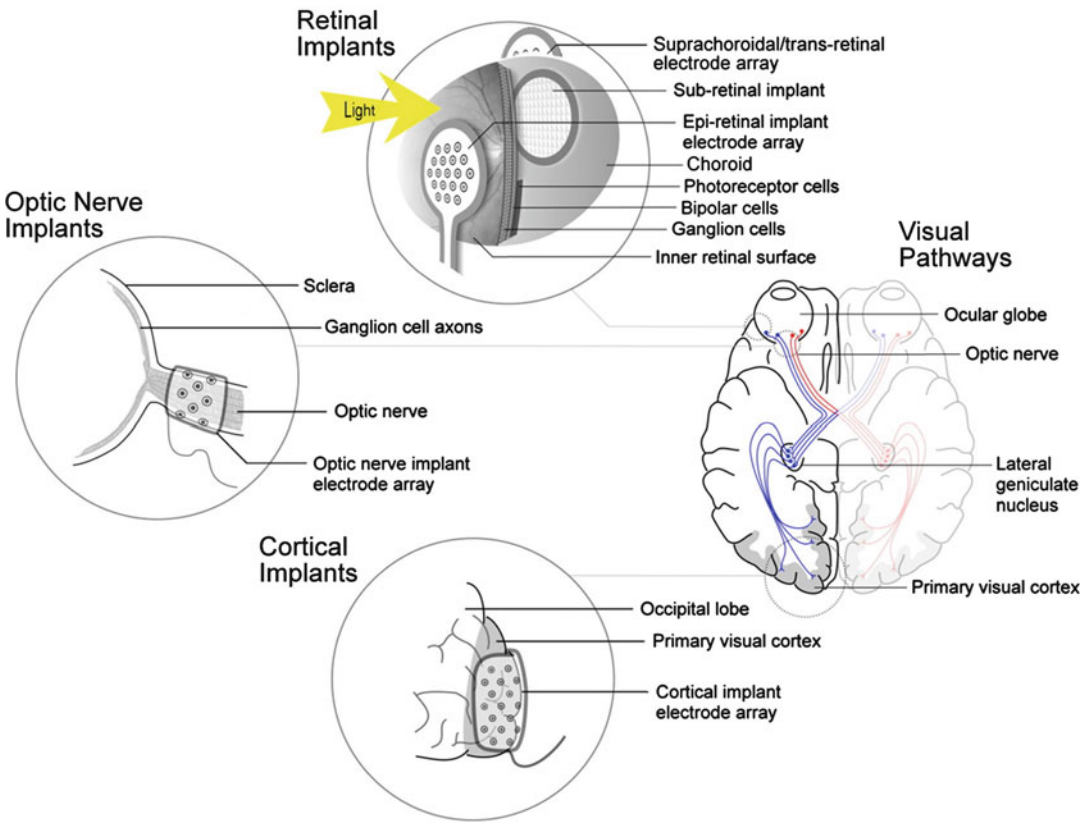
Definition

Retinal and visual interfaces encompass a range of approaches and technologies with the most common being that of a visual prosthesis, which is a subclass of sensory neuroprostheses. Such technologies can be used as a device therapeutic to restore some form of patterned vision to those suffering from profound vision impairment. Other approaches to vision restoration can also be included under the broad umbrella of a retinal/visual interface. These include optogenetic methods that use tissue engineering techniques to transfect remaining pathways in the visual system with photosensitive properties. Simulated prosthetic vision, methods to assess prosthetic vision, and computation models of the neural retina play important roles in increasing our understanding of how such approaches function and can best be optimized.

Detailed Description

Vision is arguably the most feature rich and complex of the senses, with visual cues being critical to most activities of daily living. Vision impairment results in momentous personal and economic burdens to individuals and to society with global estimates of 285 million persons impacted (Pascolini and Mariotti 2012).

Figure 1 illustrates the human visual pathways. Pathology or trauma to various elements of the visual pathway results in vision impairment or profound vision loss. In retinal degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), the



Retinal/Visual Interfaces (Models, Theory, Techniques): Overview, Fig. 1 *Right panel*: an axial section of the human brain outlining a trace of the visual pathway from the retina to the primary visual cortex. *Other panels*: possible intervention sites for artificial vision are categorized by retinal, optic nerve, and cortical placement locations. (Adapted from Lovell et al. 2010)

photoreceptors in the retina progressively die. In response to such diseases, there can be large-scale reorganization of the retina with substantial gliosis (Jones et al. 2003). Despite this, studies have shown that human retinal ganglion cells (RGCs) maintain their viability after the onset of these degenerative diseases, that the surviving retinal neurons are capable of being electrically stimulated (Humayun et al. 1996), and that rudimentary phosphene vision is achievable in humans with advanced retinal degeneration.

The etiology and/or site of insult to the visual pathway will dictate the range of possible target locations for a visual prosthesis (Guenther et al. 2012; Lovell et al. 2010). Possible sites for introducing a visual prosthesis include retinal (epiretinal (Humayun et al. 2012), subretinal (Zrenner et al. 2011; Palanker et al. 2005), suprachoroidal (Matteucci et al. 2013), trans-retinal (Fujikado et al. 2012)), optic nerve (Veraart et al. 2003), and cortical (Fernandez et al. 2005) locations (Fig. 1). In cases of trauma and diseases such as glaucoma, the RGCs can also be destroyed. As the RGC axonal processes form the optic nerve, in these cases electrical stimulation of visual pathways distal to the lateral geniculate nucleus (LGN) of the thalamus is ineffective.

In the case of retinal prostheses, to effectively replace vision with the same resolution as that of normally sighted humans would require an image capturing device to replace the function of the photoreceptor cells, of which there are approximately 125 million in each eye, converging to some one million RGCs. Current retinal devices, depending on placement and design, have electrode numbers from tens to several thousand at most.

The desired outcome is to have the electrode array placed in close proximity to the neural targets with the implanted components remaining securely fixed, even in the presence of rapid head and eye movements performed by the recipient. The device should maintain its position, integrity, and functionality for several decades of everyday usage, cause minimal injury, inflammation, or risk of infection to nearby tissue and cause minimal discomfort to the recipient. Also important in visual prosthesis design are aspects of size and battery life in the case of external componentry.

A typical vision prosthesis system comprises an external unit which using a camera and microprocessor performs the image capturing and processing and an implanted unit consisting of the microelectronic stimulator and the electrode array. Power and communication between the external and implanted units are normally facilitated by a transcutaneous radio-frequency (RF) link. The exceptions to this approach are typically subretinal devices that usually have photodiodes designed into the implantable component and thus have no need for an external camera.

Other more experimental approaches, in terms of readiness for human trials, are based around optogenetic techniques (Degenaar et al. 2009). This involves the use of viral transfection of rhodopsins to target various remaining cells in the visual pathway, making them photosensitive.

Common to all device therapies and target locations in the visual pathway are a list of challenges that must be overcome to improve efficacy and ensure device safety and longevity. These include maintaining a viable and stable neural interface over the long-term, device hermeticity and safe stimulation paradigms that allow concurrent stimulation at numerous electrode sites.

Cross-References

- ▶ Computational Models of Neural Retina
- ▶ Prosthetic Vision, Assessment
- ▶ Prosthetic Vision, Perceptual Effects
- ▶ Retinal Disease and Remodeling
- ▶ Retinal Neurophysiology
- ▶ Retinal Prosthesis
- ▶ Visual Prosthesis, Cortical Devices
- ▶ Visual Prosthesis, Epiretinal Devices
- ▶ Visual Prosthesis, Optic Nerve Approaches
- ▶ Visual Prosthesis, Optogenetic Approaches
- ▶ Visual Prosthesis, Subretinal Devices
- ▶ Visual Prosthesis, Suprachoroidal and Trans-retinal Devices

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Software Tools for Modeling in Computational Neuroscience: Overview

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Definition

A number of software tools have been made freely available to the neuroscience community to assist in building and analyzing biologically constrained computational models of neuronal systems. This overview will present a number of the most widely used applications for model development in computational neuroscience.

Detailed Description

Modeling in computational neuroscience is becoming a crucial tool for understanding how experimentally observed properties of neural systems emerge from lower-level biophysical processes. In the same way that processing of information happens at multiple physical scales in the nervous system, software applications have been created which specialize in modeling different aspects of neurons and networks.

This overview deals primarily with simulators of spiking neural networks, but other applications for modeling at lower levels (e.g., for biochemical signaling networks or reaction–diffusion within spines or whole cells) or higher scale (e.g., models of cognitive processes) have also been developed. There is also a focus on freely available, open-source applications.

Simulators

Abstract Neuron Simulations

The emergent properties of networks are frequently studied using highly simplified neurons with complex network connectivity and synaptic dynamics. NEST (chapter ▶ "NEST") is a widely used simulator for large neuronal models (e.g., 100,000 neurons and millions of synapses). It is highly optimized to run in a parallel computing environment. Another popular simulator of abstract neuronal networks is Brian (chapter ▶ "Brian Spiking Neural Network Simulator"), which is Python based and allows definition of new neuron and synapse models by writing the equations for their dynamics in a simple string-based format. Topographica (chapter ▶ "Topographica") is a simulator which deals primarily with neural maps. It facilitates investigation of the transformation of information between layers of topographic maps as are found in sensory

and motor systems. XPP (http://www.math.pitt.edu/~bard/xpp/xpp.html) is a widely used tool for simulation and analysis of dynamical systems and has frequently been used to build and investigate neuronal systems. Nengo (http://nengo.ca) is a simulator for large-scale neuronal systems. It has been used for creating the Spaun (Semantic Pointer Architecture Unified Network) simulation (Eliasmith et al. 2012).

Conductance-Based, Multicompartmental Simulators

Single neurons possess a range of features enabling them to perform computational transformations on inputs, including complex morphological structures and a host of active membrane conductances. A number of simulators have been developed which allow researchers to construct neuron models at this level of detail and potentially link such cells together into networks inspired by anatomical circuits. NEURON (chapter ▶ "NEURON Simulation Environment") is a general purpose neuronal simulation environment, which allows simulation of networks of neurons of varying levels of detail, from artificial/abstract cells to complex, morphologically detailed neurons. A key feature of NEURON is its extension language NMODL, which allows new ion channel and synapse models to be defined. An important recent addition to NEURON's functionality has been the ability to run large scale network models across multiple processors. A number of other Python based applications have been created on top of NEURON, including NetPyNE (http://netpyne.org), which facilitates the creation of biophysically detailed network models, and LFPy (chapter ▶ "LFPy: Multimodal Modeling of Extracellular Neuronal Recordings in Python"), which allows the generation of higher level brain signals such as electroencephalography (EEG) and magnetoencephalography (MEG) from NEURON simulations.

GENESIS (▶ "GENESIS, The GEneral NEural SImulation System") has also been widely used creating and analyzing detailed models of single cells and networks. MOOSE (▶ "MOOSE, the Multiscale Object-Oriented Simulation Environment") was initially based on GENESIS version 2 but has been further developed with a Python-based scripting interface, a new graphical user interface, and greater support for interacting with standardized modeling languages like SBML (▶ "Systems Biology Markup Language (SBML)") and NeuroML (▶ "NeuroML"). PSICS (▶ "PSICS: The Parallel Stochastic Ion Channel Simulator") can simulate multicompartmental, conductance-based cell models. Its particular strength is allowing efficient simulation of stochastic ion channels using a kinetic scheme-based approach.

Reaction–Diffusion Modeling

Modeling of the diffusion and reaction of biochemical substances in complex 3D structures can be useful for helping to understand the physical processes by which inputs are transformed in neurites and at synapses. Some of the applications available to create such models include MCell (MCell), STEPS (▶ "STEPS: STochastic Engine for Pathway Simulation"), and NeuroRD (▶ "Stochastic Simulators"). The NEURON simulator has also recently added support for reaction–diffusion simulations (McDougal et al. 2013).

Interoperability Frameworks

A diversity of simulation tools is beneficial from the point of view of offering greater choice to users and encouraging diverse approaches to neuronal simulation. There are a number of initiatives which aim to make it easier to use computational models across these simulators. PyNN (▶ "PyNN: A Python API for Neural Network Modelling") is a Python library for building neuronal networks, which was inspired by an increasing number of neuronal simulators using the Python language as a scripting interface. A neuronal network can be created using PyNN and then can be simulated on (and the behavior compared across) multiple simulators. NeuroML (▶ "NeuroML") is an XML-based language for describing models in computational neuroscience. This has been mainly used to encode 3D networks of multicompartmental, conductance-based neurons, but the recently developed version 2.0

increases its scope to more abstract neuron models. NineML (http://incf.github.io/nineml-spec) is another initiative to create an XML language for describing spiking neural networks. neuroConstruct (▶ "neuroConstruct") is a graphical application which allows the construction of complex 3D networks of biophysically detailed neurons. Simulation scripts can then be automatically generated to execute the model in different simulation environments.

Neuronal Morphology Databasing and Generation

Many modeling studies use detailed neuronal morphologies to examine how information is processed and transformed by single neurons, through active membrane conductances and integration of synaptic input. Neuromorpho.Org (▶ "NeuroMorpho.org") is the primary resource for obtaining neuronal morphologies which have been digitally reconstructed. It has contributions from many labs worldwide and covers a wide range of species and neuron types.

Detailed neuronal morphologies can also be automatically generated, based on data obtained from real neurons, for use in neuronal simulations. TREES Toolbox (▶ "TREES Toolbox: Code for Neuronal Branching"), CX3D (▶ "Cx3D: Cortex Simulation in 3D") and NeuGen (http://atlas.gcsc.uni-frankfurt.de/~neugen) are just some of the applications which can be used for this purpose. More details on initiatives for generating artificial neurons which could be used in neuronal simulations can be found in the entry ▶ "Synthetic Neuronal Circuits/Networks."

Useful Resources

Other useful resources where models, experimental data, and other software tools for computational neuroscience can be obtained include:

- ModelDB (▶ "ModelDB"): an archive of simulation scripts for published models in the format originally used by the model developers.
- Open Source Brain (▶ "Open Source Brain"): a resource for sharing and collaboratively developing neuronal models. Models reside in open-source repositories, and reusing, modifying, and converting the models to standardized formats such as NeuroML and PyNN are actively encouraged.
- Channelpedia (http://channelpedia.epfl.ch) is a resource developed by the Blue Brain Project which provides structured information on ion channels, and many of its entries have downloadable computational models of the channels.
- NeuroElectro (▶ "NeuroElectro Project") provides structured information on electrophysiological properties of neurons obtained from the literature.
- NeuralEnsemble (http://neuralensemble.org) is a resource which aims to promote open, collaborative software development in computational neuroscience and hosts a number of related software packages (e.g., Brian and PyNN).

Other Software for Neuronal Simulation

Population-Based Modeling

While most of the simulation packages mentioned already use spiking neuron models, a significant amount of modeling work takes place in computational neuroscience using population-based models and mean-field approaches to model large-scale cognitive processes. Examples of software packages which allow this type of modeling are MIIND (▶ "MIIND: A Population-Level Neural Simulator Incorporating Stochastic Point Neuron Models"), a simulator for high-level population based modeling, and The Virtual Brain (▶ "The Virtual Brain (TVB): Simulation Environment for Large-Scale Brain Networks"), which provides a simulator and a web-based interface for constructing neural population models.

Hardware-Based Modeling Solutions

In addition to software-based neuronal simulators, many groups are investigating hardware-based

solutions to enable faster and larger-scale neuronal simulations. Many of these use off-the-shelf hardware like Graphics Processing Units (GPUs), for example, NeMo (http://nemosim.sourceforge.net) and GeNN (http://genn-team.github.io/genn), but other initiatives are developing new hardware, customized to simulate large-scale neuronal networks, for example, SpiNNaker (http://apt.cs.man.ac.uk/projects/SpiNNaker).

Systems Biology/Bioinformatics Tools

\The Systems Biology community has been actively developing applications and model description languages in recent years to facilitate building and exchanging models of biochemical reactions, signaling pathways, and gene regulatory networks. SBML (▶ "Systems Biology Markup Language (SBML)") and CellML (▶ "CellML") are two widely used standards in this area, and many models in these formats, including neuronal models, can be obtained from the BioModels database (▶ "BioModels Database: A Public Repository for Sharing Models of Biological Processes") and the CellML Model Repository (http://models.cellml.org).

Conclusions

The development of tools for modeling in computational neuroscience is a dynamic field. The overview here has no doubt left out a number of simulators and applications, which would be of use to the wider community. The author encourages developers to get in contact with details of their work for inclusion in future versions of this entry.

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Somatosensory System: Overview

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Detailed Description

Somatosensation includes multiple senses: pain (nociception), temperature (thermoreception), touch, and the sense of our limb position in space (proprioception). Each submodality of somatosensation relies on different types of receptors embedded in the skin, muscle, and joints and involves different structures in the spinal cord and in the brain.

Pain

Pain is arguably one of the most vital senses as it signals when our body is liable to being damaged. There are many different types of receptors in the skin that signal a potentially harmful stimulus. Some receptors respond to intense mechanical deformations of the skin, others to extreme temperatures, and still others to different kinds of chemicals. Pain comprises a sensory discriminative component, which provides information about the location, duration, intensity, and quality of the pain; an affective one, which signals its unpleasantness; and a cognitive-evaluative one, which is associated with cognitive variables such as attention, which can modulate the sensory experience.

Thermoreception

Our ability to sense whether an object is warm or cold relies on two types of thermoreceptive fibers – so-called "cold" and "warm" fibers – embedded in the skin. As their names suggest, "cold" fibers are activated when the skin is cooled

and "warm" fibers are activated when the skin is warmed. In contrast to thermosensitive nociceptive fibers, which respond at extreme temperatures, thermoreceptive fibers only respond at intermediate, non-noxious temperatures (with the exception of the paradoxical response of some cold fibers to high temperatures).

Touch

The sense of touch plays a critical role in our ability to grasp and manipulate objects. Indeed, cutaneous signals provide information about the forces we exert on objects and whether these are slipping from our grasp. Without these signals, we would routinely crush or drop objects. Touch also plays an important role in emotional communication: We touch the people we care about and wish to be touched by them. Finally, our sense of touch plays a key role in embodiment, making our body feel as a part of us.

The skin is innervated by several types of mechanoreceptive afferents, each of which conveys different information about skin deformations (link: sensory innervation of the skin) and conveys different types of information about events impinging upon the skin. Merkel cells convey information about the shape of objects grasped in the hand (link: cutaneous mechanoreceptive afferents: neural coding of shape), Meissner corpuscles about motion of objects across the skin, and Pacinian corpuscles about surface texture (link: cutaneous mechanoreceptive afferents: neural coding of texture). Afferents produce highly repeatable and temporally patterned responses to skin stimulation (link: somatosensory neurons: spike timing), and models have been developed that predict with high accuracy the responses of somatosensory neurons to spatiotemporal skin deformations (link: mechanotransduction: models).

When we palpate an object, we obtain information about its shape (link: somatosensory cortex: neural coding of shape), its texture (link: cutaneous mechanoreceptive afferents: neural coding of texture), and its motion across the skin (link: somatosensory cortex: neural coding of motion).

Proprioception

Proprioception (link: proprioception) plays a critical role in guiding motor behavior. Individuals with intact motor systems but compromised proprioception have difficulty planning and executing movements, almost as if they had a motor impairment. Proprioception, like touch, is also important for our sense of embodiment.

There are several types of proprioceptive receptors, located in muscles, in the skin, and in joint capsules. Two types of muscle proprioceptors, muscle spindles and Golgi tendon organs, are thought to be the primary contributors to proprioception. One population of receptors in the skin is sensitive to skin stretch and can convey information about joint angle. Another type of proprioceptor, the joint capsule receptor, fires at the extreme ends of the joint's range and may be involved in preventing overextension of the joint.

Proprioceptive and cutaneous signals are then processed in the dorsal column nuclei, then in the ventroposterior lateral nucleus in the thalamus, and then in primary and secondary somatosensory cortices (link: somatosensory cortex: organization).

Cross-References

- ▶ Cutaneous Mechanoreceptive Afferents: Neural Coding of Texture
- ▶ Mechanotransduction, Models
- ▶ Proprioception
- ▶ Somatosensory Cortex: Neural Coding of Motion
- ▶ Somatosensory Cortex: Neural Coding of Shape
- ▶ Somatosensory Cortex: Organization
- ▶ Somatosensory Neurons: Spike-Timing

Spectral Methods in Neural Data Analysis: Overview

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Detailed Description

Spectral analysis is a powerful and widely used approach to the study of time series data (Warner 1998; Bloomfield 2000). It provides a useful complement to other types of analysis in computational neuroscience. Spectral analysis refers to a host of techniques relating to transformed time series in the frequency domain. A spectral representation of a time series is a function of frequency, where frequency is expressed in units of cycles per second, or hertz (Hz). Although spectral analysis is applicable to deterministic time functions, neural data is typically stochastic and thus requires statistical spectral analysis (Brillinger 2001; Bendat and Piersol 2010). Neural data types that are subjected to spectral analysis commonly include continuous time series such as the electroencephalogram (EEG), magnetoencephalogram (MEG), electrocorticogram (ECoG), and local field potential (LFP) but may also include point process time series such as single-unit and multiunit spiking activity (Glaser and Ruchkin 1976; Dumermuth and Molinari 1987; Hesselmann 1991).

Spectral methods in neural data analysis provide a frequency-based representation of neural time series data. They may be used to identify discrete, narrowband oscillations in time series or to decompose a broadband time series into frequency-specific components. Spectral methods are also employed in the frequency-based analysis of neural data arrayed in space rather than time (see ► "Spatial Spectral Analysis"). Spatial spectra are representations of spatial data, and spatial frequency is expressed in units of cycles per unit distance.

The traditional approach to spectral analysis is based on the pioneering work of Joseph Fourier (1768–1830), the French mathematician who is credited with having first introduced the representation of a mathematical function as a sum of trigonometric functions. Nowadays, Fourier methods play a major role in a multitude of applications in mathematics, science, and engineering. Fourier analysis refers to the linear decomposition of a function into elemental trigonometric basis functions, whereas Fourier synthesis is the operation of rebuilding the original function from the component basis functions. Although functions subjected to Fourier analysis are often continuous and potentially infinite in length, they may also be discrete and finite in length. The wide availability of methods for Fourier analysis of digitized finite-length time series on digital computers has made spectral data analysis practical, rapid, and inexpensive (Marple 1987). As a result, spectral analysis of neural data has become increasingly popular in modern times, with a growing list of applications in theoretical, experimental, and clinical neuroscience.

Fourier analysis of a time series assigns values of amplitude and (absolute) phase to the trigonometric basis functions (sines and cosines) of the decomposition. For univariate time series, that is, from a single recording channel, Fourier analysis specifies a range of frequencies of the component basis functions, along with amplitude (or power, squared amplitude) and phase values for each frequency component. This (polar) representation in terms of amplitude and phase has an equivalent (Cartesian) representation in terms of the real and imaginary components of a complex quantity. The simplicity, symmetry, and facility of use of the complex Cartesian representation make complex algebra a useful mathematical tool in spectral analysis. However, complex algebra is not necessary. The polar and complex Cartesian representations are equivalent in providing a complete description of time series data, and Fourier synthesis can reconstruct the time series from either one.

Fourier analysis is often used to quantify interdependency relations between time series that are derived from different sources (see ▶ "Spectral Interdependency Methods"). Frequency-based interdependency measures may be derived from the complex-valued cross-spectrum. The cross-spectrum yields two important real-valued spectra. First is the relative phase (i.e., difference in phase) spectrum, given by the arctan of the ratio of imaginary to real components of the cross-spectrum. Second is the normalized modulus of the cross-spectrum, the coherence spectrum, which is the frequency domain equivalent of the time domain cross-correlation function. The relative phase spectrum reflects the mean, and the coherence spectrum reflects the variance, of the distribution of relative phase values of two time series. Coherence is roughly equivalent to the phase-locking value, defined as one minus the circular variance of relative phase, in that they both reflect relative phase variation. The difference is that coherence additionally reflects (to a lesser degree) amplitude covariation. Spectral methods are used to examine neural interdependency relations between continuous signals (e.g., between LFPs), or discrete signals (e.g., spiking activities), or between continuous and discrete signals (e.g., spike-field coherence).

Neural time series data are commonly multivariate, being derived from multiple sources, and their spectral analysis often involves the assessment of pairwise interdependency relations in the frequency domain. Some interdependency relations between time series are directional, meaning that the interdependency is directed from one time series to another. Directed spectral methods quantify directed interdependency in the frequency domain (see ▶ "Directed Spectral Methods").

Because neural time series data commonly evolve over time, time-frequency, or spectrographic, representations are often useful (see ▶ "Time-Frequency Analysis of Analog Neural Signals"). This type of representation, which allows one to independently examine the temporal evolution of different frequency components, may be used to track the time-frequency evolution of a range of time-varying neural processes, including sleep, sensory, motor, and cognitive processing. Spectrographic representations of the electroencephalogram (EEG) are heavily used in neuropharmacology to assess the actions of neuroactive drugs. A variety of different time-frequency methods, such as the short-time Fourier transform, Wigner-Ville distribution, Cohen's class distribution, or wavelet transform (see ▶ "Wavelet Analysis"), have been applied in neural data analysis.

One important application of spectral methods in neural data analysis is filtering, the transformation of neural time series by the selection of certain frequency components and the exclusion of others (see ▶ "Digital Filtering"). Digital filtering, which refers to filtering operations performed on discretely sampled data in a digital computer, has the advantage of allowing data at both past and future time points to be used in determining the filtered value of a current time point, unlike analog filtering, where the filtering operation depends only on past time points. Although digital filtering may be performed in the time domain, it is more easily performed in the frequency domain by the selection of a range of frequencies (the passband) and exclusion of another range (the stopband). Data smoothing is an important operation in neural data analysis that is accomplished by digital (low-pass) filtering. Digital filtering is also used to separate spike and field signals recorded from a common microelectrode.

Neural time series are rarely deterministic, where each time series value is exactly determined by past values. For this reason, statistical spectral methods are usually required for neural time series analysis (Jenkins and Watts 1968; Percival and Walden 1993). Statistical spectral analysis considers time series data to be generated by stationary stochastic (random) processes, and the various spectral quantities are treated as data-derived statistical estimates of unknown population variables, rather than as deterministic quantities. Unlike nonparametric spectral analysis, which computes spectra directly from time series data by Fourier analysis, parametric spectral analysis is an approach that derives spectral quantities from a statistical model of the time series (see ▶ "Parametric Spectral Analysis"). In the model, the variable at a particular time is expressed by statistical relations with variables from past times. The

parametric model is typically autoregressive, meaning that each time series value is modeled as a weighted sum of past values (the weights being considered as the parameters of the model) (Kay 1988; Chatfield 2004). Although parametric models may be nonlinear, those used in neuroscience are typically linear because neural time series are commonly locally linear. Parametric modeling has some distinct advantages in neural data analysis: It allows a precise time-frequency representation of time-varying neural time series (Ding et al. 2000), and it serves as a theoretically sound basis for directed spectral analysis (Ding et al. 2006).

Spectral methods of neural data analysis utilize frequency-based representations. Since rhythmic activity, mostly in time but also in space, is ubiquitous in neuroscience, frequency-based techniques are very important tools in computational neuroscience. Given that many good software options exist for performing spectral data analysis, these techniques are readily available to neuroscience researchers working with many different types of neural data.

Cross-References

- ▶ Digital Filtering
- ▶ Directed Spectral Methods
- ▶ Parametric Spectral Analysis
- ▶ Phase-Locking Methods
- ▶ Spatial Spectral Analysis
- ▶ Spectral Interdependency Methods
- ▶ Time-Frequency Analysis of Analog Neural Signals
- ▶ Wavelet Analysis

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Further Reading

Wikipedia

Stochastic (random) process. http://en.wikipedia.org/wiki/Stochastic_process

Spike Train Analysis: Overview

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Definition

A sequence of action potentials ("spike train") is the output of an individual neuron and is the input

to receiving neurons. It is assumed that neurons interact by sending and receiving spikes. Therefore, simultaneously observed spike trains are analyzed for correlations to identify neuronal interactions. This section presents analysis approaches for various statistical aspects of spike trains.

Detailed Description

The brain is composed of billions of neurons, the elementary units of neuronal information processing. The neocortex, which is critical to most higher brain functions, is a highly complex network of neurons, each of which receives signals from thousands of other neurons and projects its own output via sequences of spikes (▶ "Spike Train") to thousands of other neurons (Braitenberg and Schüz 2009). In order to observe neuronal activity in the active brain, a large variety of recording techniques are being employed, ranging from recordings of individual neurons (intra- or extracellularly) to recordings of neuronal populations on mesoscopic or macroscopic scales. Any particular choice of the recording technique reflects the hypothesis the researcher has in mind about the mechanisms of neuronal processing. The focus on spike recordings from individual neurons implies that one strives to understand the elementary units of neuronal processing. However, approaching the relationship of different signal types may provide a means of relating processing on different spatial scales (▶ "Spike Triggered Average").

Early electrophysiological experiments were bound to record from single neurons only. The resulting insights are now the basis for the "classical" view of sensory coding: firing rates are modulated in a feed-forward hierarchy of processing steps. Signals from sensory epithelia are assumed to eventually converge to cortical detectors for certain combinations of stimulus features (▶ "Neural Coding") or finally transferred to motor output. Specific percepts or motor actions would be represented by the elevated firing of a single nerve cell (▶ "Estimation of Neuronal Firing Rate") or by changes of firing rates of groups of neurons which can be assessed by different conceptual approaches (▶ "Neuronal Population Vector," ▶ "Population Encoding/Decoding," and ▶ "State-Space Models for the Analysis of Neural Spike Train and Behavioral Data").

An alternative concept of neuronal processing by groups of neurons was suggested by Donald Hebb (1949) who first demonstrated the conceptual power of a brain theory based on cell assemblies. Inspired by Hebb and driven by more recent physiological and anatomical evidence in favor of a distributed network hypothesis, brain theorists constructed models that rely on groups of neurons, rather than single nerve cells, as the *functional* building blocks for representation and processing of information. Despite conceptual similarities, such concepts of neuronal cooperativity differ in their detailed assumptions with respect to the spatiotemporal organization of the neuronal activity. To understand the principles of coordinated neuronal activity and its spatiotemporal scales, it is obligatory to observe the activity of multiple single neurons simultaneously. Due to recent technological developments in recording methodology, this can regularly be done. Coordinated activity of neurons is only visible in correlations of their respective spike trains, which typically admit no simple interpretation in terms of fixed synaptic wiring diagrams. Rather, it became evident that the correlation dynamics apparent in time-resolved multiple-channel measurements reflect variable and context-dependent coalitions among neurons and groups of neurons. Thus, the analysis of simultaneously recorded spike trains allows us to relate concerted activity of ensembles of neurons to behavior and cognition. Different analysis approaches are thereby relevant to distinguish different or even complementary spatio-temporal scales based on methods ranging from pairwise analysis (▶ "Spike Train Distance," ▶ "Correlation Analysis of Parallel Spike Trains," and ▶ "Joint Peri Stimulus Time Histogram (JPSTH)") to concepts for the analysis of multiple parallel processes (▶ "Gravity Analysis of Parallel Spike Trains," ▶ "Unitary Event Analysis," ▶ "Information Geometry as Applied to Neural Spike Data," ▶ "Spatial Temporal Spike Pattern Analysis," ▶ "Statistical Evaluation of

Spatio-Temporal Spike Patterns," and ▶ "Generalized Linear Models for Point Process Analyses of Neural Spiking Activity"). The evaluation of significance (▶ "Significance Evaluation") is a basic element in these analyses, in some cases based on nonparametric methods (▶ "Surrogate Data for Evaluation of Spike Correlation"). Analysis of parallel spike trains (Grün and Rotter 2010; Kass et al. 2014) is the logical next step to improve our understanding of the neuronal mechanisms underlying information processing in the brain.

Cross-References

- ▶ Correlation Analysis of Parallel Spike Trains
- ▶ Estimation of Neuronal Firing Rate
- ▶ Generalized Linear Models for Point Process Analyses of Neural Spiking Activity
- ▶ Gravity Analysis of Parallel Spike Trains
- ▶ Information Geometry as Applied to Neural Spike Data
- ▶ Joint Peri Stimulus Time Histogram (JPSTH)
- ▶ Neural Coding
- ▶ Neuronal Population Vector
- ▶ Population Encoding/Decoding
- ▶ Significance Evaluation
- ▶ Spatial Temporal Spike Pattern Analysis
- ▶ Spike Train
- ▶ Spike Train Distance
- ▶ Spike Triggered Average
- ▶ State-Space Models for the Analysis of Neural Spike Train and Behavioral Data
- ▶ Statistical Evaluation of Spatio-Temporal Spike Patterns
- ▶ Surrogate Data for Evaluation of Spike Correlation
- ▶ Unitary Event Analysis

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Spiking Network Models and Theory: Overview

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Definition

Spiking neuronal networks are a type of neural network model where the neurons interact by sending and receiving the so-called spikes, short pulses that are only defined by their time of occurrence. Biologically, spikes correspond to the action potentials of neurons.

Neuron models that produce spikes are called *spiking neuron models*. Examples are the Integrate and Fire Models, Deterministic; the *Izhikevich model*; and the Hodgkin-Huxley Model.

The term spiking network was introduced to distinguish these models from formal neuron models which have graded activation functions.

Detailed Description

Historical Background

The first spiking neuron models were developed at the beginning of the twentieth century and focused on explaining the electrical behavior of isolated neurons. In 1907, Louis Lapicque proposed an electrical circuit model to describe the change in membrane potential after applying a current step. He assumed a fixed firing threshold to explain the occurrence of action potentials (Lapicque 1907; Tuckwell 1988). Lapicque's model can therefore be seen as the first *integrate and fire model*. In 1936, Arthur Hill extended Lapicque's model by adding an adaptive threshold (Hill 1936). These models are phenomenological

since they did not explain the biophysical mechanisms producing action potentials. In the 1950s Hodgkin and Huxley explained with a series of experiments that action potentials are caused by ionic currents which result from ion channels with voltage-dependent conductances (Hodgkin and Huxley 1952). But because of its simplicity, Lapicque's original threshold model is still used by experimental and theoretical neuroscientists.

Theoretical network models initially focused on explaining experimentally observed interspike interval distributions of individual neurons as well as the origin of the observed high variability of neuronal responses. Recent theoretical research mainly focuses on understanding low-rate spontaneous activity as well as multistability in the context of learning and memory.

Theoretical analysis of spiking neuronal networks is only possible if the network model is sufficiently simple. In recent years, computer simulations have become increasingly important to support and complement theoretical analysis, because they allow the inclusion of more biological detail and the analysis of heterogeneous network architectures.

Spiking Neuron Models

Theoretical network models typically resort to simplified neuron models, such as the leaky integrate and fire model (LIF), some variant of it, or more abstract models such as pulse-coupled oscillators.

All of these neuron models have in common that they interact by sending and receiving the so-called spikes which are abstractions of the action potentials produced by excitable cells such as neurons.

Spikes are temporal point events, characterized by their time of occurrence $\hat{t}$ and mathematically expressed by the Dirac delta function $\delta(t)$.

A sequence of spikes $S = \{\hat{t}^1, \hat{t}^2, \ldots\}$ is called *spike train* and can then be written as

$$s(t) = \sum_k \delta\left(t - \hat{t}^k\right), \tag{1}$$

where the index k runs over all spikes in S.

Integrate and Fire Models

The leaky integrate and fire (LIF) model constitutes a whole class of models consisting of two parts. The first part consists of one or more differential equations, describing the subthreshold behavior of the neuron's membrane potential. The second part converts the continuous membrane potential into discrete spike events. Here we will present the LIF model in its most basic form and then discuss a number of common variations.

Subthreshold Dynamics

The subthreshold membrane potential V is described by the differential equation

$$\tau \frac{d}{dt} V(t) = V_0 - V(t) + RI(t) \tag{2}$$

where V_0 is the resting potential, τ the membrane time constant, and R the membrane resistance.

$I(t) = I_{\text{syn}}(t) + I_{\text{ext}}(t) + \ldots$ is the total current across the cell membrane and comprises all external influences on the neuron, such as synaptic currents I_{syn} and externally applied currents I_{ext}.

Spike Generation

Spikes are generated, when the membrane potential V crosses a threshold value V_θ from below. The time of spike is then given by the relation

$$V(t') = V_\theta \text{ and } \frac{d}{dt} V(t') > 0 \tag{3}$$

In the following, we use t' to denote the times of endogenous spikes and $\hat{t}$ to denote input spikes from other neurons.

After a spike is generated, the membrane potential is reset to V_{reset}, a value which is often chosen to match the resting potential V_0.

Immediately after a spike, neurons are unable to produce another spike for a short period of time t_r, called *refractory period*. Many models implement the refractory period by holding the membrane potential at its reset value, such that $V(t) = V_{\text{reset}}$ for $t \in (t', t' + t_r]$.

Threshold Adaptation

Many neurons adapt to sustained input by reducing their firing rate. In integrate and fire models,

this is often captured by a mechanism called *threshold adaptation*.

The spike threshold V_θ is then no longer constant, but increases with every spike by an amount a and decays back to its resting value θ with a time constant τ_θ:

$$\tau_\theta \frac{d}{dt} V_\theta = \theta - V_\theta + a \sum_k \delta\left(t - t'^k\right) \quad (4)$$

where the sum runs over all endogenous spikes t'^k of the neuron.

Synaptic Input

Synaptic input enters the membrane potential in the form of the synaptic current $I_{\text{syn}}(t)$. A presynaptic spike at time $\hat{t}$ causes a conductance change at the postsynaptic membrane, which in turn results in a postsynaptic current of the form

$$I_{\text{syn}}(t,V) = \left(E_{\text{syn}} - V\right) \cdot g_{\text{syn}}(t - \hat{t}) \quad (5)$$

where E_{syn} is the reversal potential of the synapse and $g_{\text{syn}}(t)$ the time course of the conductance change.

Many models implicitly assume that the synaptic conductance changes much faster that the membrane potential V. Then V in Eq. 5 can be treated as constant, and the synaptic current no longer depends on the membrane potential which greatly simplifies analytical and numerical analysis.

In recent years, the terms COBA and CUBA have become popular to distinguish the two cases. COBA refers to the original Eq. 5 and stands for *conductance based*, while CUBA stands for *current based* and refers to simplified synaptic currents of the form

$$I_{\text{syn}}(t) = \text{psc}\left(t - \hat{t}\right) \quad (6)$$

where the postsynaptic current psc(t) is only a function of time (Vogels and Abbot 2005).

Since Eq. 2 is a linear differential equation with constant coefficients, its solution for arbitrary postsynaptic currents psc(t) is given by

$$\text{psc}(t) = V_0 + \int_0^\infty \text{H}(t-s) \exp\left(\frac{-(t-s)}{\tau}\right) \cdot \text{psc}(s) ds \quad (7)$$

where H(t) is the Heaviside step function and psp(t) is the so-called postsynaptic potential.

In the case where the postsynaptic current is a delta function $\text{psc}(t) := \delta\left(t - \hat{t}\right)$, Eq. 7 reduces to

$$\text{psp}(t) = V_0 + \exp\left(\frac{-\left(t - \hat{t}\right)}{\tau}\right). \quad (8)$$

In response to a spike train $s(t)$, we obtain

$$\text{psp}(t) = V_0 + \sum_k H\left(t - \hat{t}^k\right) \exp\left(\frac{-\left(t - \hat{t}^k\right)}{\tau}\right). \quad (9)$$

Spike-Response Model

The spike-response model (SRM) is a generalization of the LIF model (Gerstner et al. 1996a; Gerstner and Kistler 2002). It exploits the linearity of Eq. 2 and expresses the membrane potential as convolution:

$$V(t) = \eta\left(t - \hat{t}\right) + \int_0^\infty k(t,\ t') I_{\text{syn}}(t - t') dt' \quad (10)$$

where $\eta(t - t')$ is a kernel that describes the action potential as well as the after hyperpolarization of the last spike of the neuron at $t = t'$. $k\left(t,\ \hat{t}\right)$ is a kernel that describes the response of the membrane potential to a presynaptic spike at time $\hat{t}$. Like in the LIF model, a spike is generated when the membrane potential $V(t)$ crosses a threshold value V_θ from below.

For theoretical analysis of large spiking network, the spike-response model is more convenient than the original LIF model, since it captures the effects of incoming as well as self-generated action potentials in a closed mathematical form (Gerstner and Kistler 2002).

Stochastic Spike Generation and Escape Noise

For most neuron models with a deterministic spike threshold, it is also possible to use a stochastic spike generation mechanism by adding the so-called escape noise (Plesser and Gerstner 2000). This is done by relating the variable $V(t)$ to the probability density for observing an action potential in the

infinitesimal time interval $(t, t + \delta t]$ (Plesser and Gerstner 2000; Mensi et al. 2012). In this picture, the spike generation is a random point process with a conditional density function

$$\lambda(t|V,\ V_\theta) = \lambda_0 \exp\left(\frac{V(t) - V_\theta}{\Delta V}\right), \qquad (11)$$

where λ_0 is a scaling factor with unit s^{-1}, V_θ is the firing threshold, and ΔV is a factor that determines the steepness of the exponential function and therefore also the sensitivity of the firing threshold to small fluctuations.

The spike-response model with escape noise belongs to the larger class of *generalized linear models* (GLM) which have recently been used successfully also in other areas of neuroscience (see, e.g., Pillow et al. (2008), Truccolo et al. (2011)).

Stochastic Models of Neural Activity

In many regions of the brain, neurons fire constantly at a low rate, even if they are not directly stimulated. In the cortex, this spontaneous activity is very irregular. Moreover, even if a cortical neuron in vitro or in vivo is stimulated repeatedly, its response will differ for each stimulus presentation.

One of the earliest approaches to explain this variability of neuronal firing is to consider the fluctuation of the membrane potential of a neuron, caused by randomly arriving spikes from the surrounding network. In the simplest case, each neuron in the surrounding network will fire at some constant rate ν. The network, thus, generates a noisy *background activity* which then influences the firing probability of our neuron.

The number of excitatory and inhibitory spikes which arrive at neuron i during the interval $(0, t]$ can be written as

$$n_E(t) = \sum_{j \in E_i} \int_0^t s_j(t' - d)dt',$$
$$n_I(t) = \sum_{j \in I_i} \int_0^t s_j(t' - t)dt'$$

where E_i and I_i denote the sets of all excitatory and inhibitory neurons projecting to neuron i, respectively. The membrane potential of a neuron can then be written as (Stein 1965; Tuckwell 1988)

$$\frac{dV}{dt} = -\frac{1}{\tau}V + J_E\frac{dn_E}{dt} + J_I\frac{dn_I}{dt}. \qquad (12)$$

For sufficiently large networks, we can assume that n_E and n_I are Poisson processes with rates ν_E and ν_I, respectively.

In the absence of a threshold, and for constant firing rates, the mean and variance of the membrane depolarization are (Tuckwell 1988; Stein 1965)

$$\mathrm{E}[V] = \tau(J_E\nu_E + J_I\nu_I) \qquad (13)$$

$$\mathrm{Var}[V] = \frac{1}{2}\tau\left(J_E^2\nu_E + J_I^2\nu_I\right). \qquad (14)$$

More generally, we can describe the randomly arriving spikes as a *shot noise* process (Papoulis and Pillai 2002). This allows us to compute the mean and variance of the resulting membrane potential as a function of the background firing rate $\nu(t)$ and the synaptic response kernel $\mathrm{psp}(t)$. The mean membrane potential is then

$$\mathrm{E}[V]_t = \int_0^{+\infty} \nu(t - s)\mathrm{psp}(s)ds \qquad (15)$$

with variance

$$\mathrm{Var}[V]_t = \int_0^{+\infty} \nu(t - s)\mathrm{psp}^2(s)ds \qquad (16)$$

When an embedding into a cortical region is considered, random input comes from excitatory and inhibitory populations. Due to the linearity of the equations, the contributions from both populations superimpose, and the mean and variance of the combined membrane potential are given by

$$\mathrm{E}[V]_t = \mathrm{E}[V_E]_t + \mathrm{E}[V_I]_t \qquad (17)$$

and

$$\mathrm{Var}[V]_t = \mathrm{Var}[V_E]_t + \mathrm{Var}[V_I]_{t'} \qquad (18)$$

respectively.

Connections

A network consists of a set of N neurons and their connections. In a connection between two neurons, the sending neuron is called *presynaptic* and the receiving neuron is called *postsynaptic*. We write the set of presynaptic neurons of neuron i as N_i.

Static Connections

In the simplest case, the synaptic current simply adds the spikes of all presynaptic cells:

$$I_{\mathrm{syn,i}}(t) = \sum_{j \in N_i} J_{ij} s_j\left(t - d_{ij}\right) \tag{19}$$

$$= \sum_{j \in N_i} J_{ij} \sum_{k=1} \delta\left(t - d_{ij} - \hat{t}_j^k\right) \tag{20}$$

where d_{ij} is the propagation delay between neuron j and neuron i and $\hat{t}_j^k$ the kth spike of neuron j. J_{ij} is the *weight* or *efficacy* of the connection between neurons j and i which is in many cases assumed to be constant.

Dale's Principle

Dale's principle states that the efferent synapses of a neuron are all of the same type. Thus, if one efferent synapse of a neuron is excitatory, we know that all other efferent synapses of this neuron will also be excitatory. The same applies to inhibition.

Dale's principle introduces correlations into the connectivity matrix of the network, which are visible in the eigenvalue distribution of the matrix in the complex plane (Rajan and Abbot 2006). Moreover, Dale's principle also affects the correlation structure of random spiking networks. In random networks without Dale's principle, correlations between neurons will vanish in the limit of infinitely large networks. In such networks, Dale's principle prevents the correlations from disappearing (Kriener et al. 2008).

Short-Term Plasticity

The weight of a connection can depend on the spike history of the presynaptic neuron such that the weight decreases or increases if several presynaptic spikes arrive in short succession. These effects are called short-term depression (STD) and short-term facilitation (STF), respectively. Both can be described by a system of kinetic equations that model the depletion and replenishing of synaptic resources (Tsodyks et al. 1998, 2000).

Assume that there is a finite amount of resources available and that each spike uses a certain fraction of these resources which are then unavailable for a certain amount of time. Depleted resources are replenished at a constant rate D. The second factor in the model is the ability of a synapse to use its resources, expressed by a variable $u(t)$. In stochastic models of synaptic transmission, u corresponds to the release probability of a synaptic release site (Fuhrmann et al. 2002). If u is a constant, the synapse will be depressing. For facilitating synapses, u increases with each spike up to a maximum and decays at a constant rate F.

In the context of the STP literature, the maximal synaptic efficacy is usually denoted by A which corresponds to the synaptic weight J, used throughout the rest of this entry. The effective weight for the nth spike can then be expressed as

$$A_n = A u_n R_n \tag{21}$$

with initial values

$$u_i := U, \tag{22}$$

$$R_1 := 1. \tag{23}$$

u and R are then iteratively updated according to

$$u_{n+1} = U + u_n(1 - U) \exp\left(\frac{-\Delta t_n}{F}\right), \tag{24}$$

$$R_{n+1} = 1 + (R_n - R_n u_n - 1) \exp\left(\frac{-\Delta t_n}{D}\right), \tag{25}$$

where $\Delta t_n := \hat{t}^n - \hat{t}^{n-1}$.

The relation of the time constants D and F determines whether a synapse will be

depressing, facilitating, or a combination of the two. However, closer analysis of the equations as well as experimental results shows that the detailed behavior of dynamic synapses depends also on the spike frequency of the presynaptic neuron (Fuhrmann et al. 2002).

Dynamic synapses have a strong effect on the behavior of a network. Networks with facilitating synapses can show collective synchronization of all neurons, called population bursts (Tsodyks et al. 2000). By contrast, in networks where the facilitating and depressing synapses are distributed as indicated by experimental results, activity is more stable as the synapses exert some gain control on the network (Sussillo et al. 2007).

Short-term plasticity has also been linked to the persistence of network states with elevated firing rates. These are thought to play an important role in working memory (Mongillo et al. 2008).

Short-term plasticity is not related to Hebbian plasticity, since it depends only on the activity of the presynaptic neuron rather than on the activity of both the pre- and postsynaptic neurons.

Spike-Timing-Dependent Plasticity

Spike-timing-dependent plasticity (STDP) is a form of synaptic plasticity where the synaptic efficacy changes according to the relative timing of pre- and postsynaptic action potentials.

A typical experimental protocol for spike-timing-dependent plasticity involves two neurons with a synaptic connection. Action potentials are induced in both neurons in a defined temporal sequence by injecting current pulses. At the same time, the strength of the synaptic potential is measured in the postsynaptic neuron. This procedure is called *pairing*. After a number of pairings, each with the same timing relation between pre- and postsynaptic neurons, a change in the amplitude of the PSP can be observed. Systematic variation of the relative timing between pre- and postsynaptic action potentials then reveals that the change in PSP amplitude depends on the timing relation.

The classical results of Markram et al. (1997) and Bi and Poo (1998) show that potentiation is largest if the postsynaptic neuron spikes shortly after the presynaptic neuron, while the synapse became depressed if the postsynaptic neuron fired shortly before the presynaptic neuron. This is captured by the following model (Gerstner et al. 1996b):

$$\Delta J_{ij} = \sum_{\hat{t}^j \in S_j} \sum_{\hat{t}^i \in S_i} W\left(\hat{t}^{\,i} - \hat{t}^{\,j}\right) \tag{26}$$

where the sums run over all pre- and postsynaptic spikes, respectively. $W(\Delta t)$ is the so-called learning window, with

$$W(\Delta t) = A_+ \exp\left(\frac{-\Delta t}{\tau_+}\right) \text{for} \Delta t > 0, \tag{27}$$

$$W(\Delta t) = -A_- \exp\left(\frac{\Delta t}{\tau_-}\right) \text{for} \Delta t < 0, \tag{28}$$

and

$$\Delta t := t_{\text{post}} - t_{\text{pre}}. \tag{29}$$

The learning window is modeled as an exponential function which scales the degree to which the weight changes, depending on the time interval Δt. If the spike of the presynaptic neuron precedes the spike of the postsynaptic neuron, Δt is positive and Eq. 27 will increase the weight W by a value that is largest for short and smallest for large intervals. If the postsynaptic neuron spikes first, Δt is negative and Eq. 28 will decrease W.

There are a number of variations to this model as well as a number of alternative models which incorporate hypothesized biophysical mechanisms, underlying STDP (Morrison et al. 2008; Sjöström and Gerstner 2010). But so far, the experimental evidence does not allow to identify one of the models as authoritative (Feldman 2012).

Spike-timing-dependent plasticity is a mechanism that acts in addition to the synaptic short-term plasticity, described in the previous section. To obtain the final synaptic efficacy which combines both short-term and spike-timing-dependent plasticity, we replace A in Eq. 21 with $J + \Delta J$:

$$A_n = u_n R_n (J + \Delta J) \tag{30}$$

where J is the equilibrium weight.

Network Topologies

In a spiking network, the weighted, directed graph of the connections defines the topology of the network. Common network topologies are feedforward networks, recurrent networks, and networks with spatial topologies.

Feedforward Networks

Feedforward networks can be broken down into disjunct groups or layers of neurons G_1, G_2, ... where each neuron in group G_i is only connected to neurons in group G_j with $j \geq i$.

The propagation of spiking activity in feedforward networks is directed and in the direction of ascending group numbers. As a result, the total number of spikes in feedforward networks is limited, and at any given time, only a fraction of the neurons are active (Griffith 1963).

Synfire Chains

Examples of feedforward networks are the complete *transmission line*, also known as *synfire chain* (Griffith 1963; Abeles 1991). It consists of l mutually exclusive groups G_i, with $1 \leq i, \leq G_l$, each containing w neurons. Each neuron in group i projects to a certain number of neurons in group $i + 1$, thus forming a chain of groups of neurons. If sufficiently many neurons in the first group fire near simultaneously, they will ignite the neurons in the second group and so on. The spikes of the first group will therefore travel along the chain until either the activity disperses or the chain comes to an end. Theoretically, this can be described by the so-called pulse packets, propagating from one group to the next (Diesmann et al. 1999). In the ideal case, that is, given a sufficient number of spikes with a sufficiently narrow temporal spread, the pulse packet will propagate unchanged from one group to the next. And due to the divergent-convergent connectivity, small deviations from this invariant shape are then automatically repaired. However, depending on the number of neurons in a group and the connections between the groups, the pulse packet may also win or lose spikes or change its temporal precision (Diesmann et al. 1999; Câteau and Fukai 2001).

Recurrent Networks

Networks with feedback connections are called *recurrent*. Recurrent networks are often random with mixed excitation and inhibition. In random networks with uniform connection probability, each neuron has an equal probability to be connected to another neuron. In other models, the connection probability between neurons i and j depends on their distance.

Neighborhood Preserving Topologies

Networks in which neurons have a well-defined position are called *topology networks*. In such networks, the connection probability of two neurons usually depends on their distance. For example, the closer two neurons are, the higher is their probability to be connected. The neuronal positions may correspond to the actual positions of the neurons within a brain region, but they may also correspond to positions in some abstract space, for example, the orientation angle of a visual stimulus or the direction of movement in a reaching task. Thus, neighboring locations in stimulus or response coordinates are mapped to neighboring neurons.

The simplest examples of topological networks are line or ring networks, where the neurons are aligned on a one-dimensional axis. If the two ends of the axis are connected back to each other, the line turns into a circle. This is useful for representing periodic coordinates such as orientation angle or simply to avoid boundary effects at the end of the line.

Models of visual processing often use two-dimensional sheets or layers of neurons. Here the coordinates can correspond to visual space, e.g., the center of the neuron's receptive field or cortical space, that is, the actual position of the neuron in the brain. To ameliorate processing at the boundaries of the sheet, the two pairs of opposing sides are often connected such that the rectangular sheet turns into a torus.

Typical models of visual processing will combine several sheets into a functional architecture (e.g., Masquelier and Thorpe 2007; Grossberg and Versace 2008). Topological networks can be feedforward, recurrent, or a combination of the two.

Network Dynamics

Spiking neural network model are an important tool to study the dynamics of cortical network activity and to understand physiologically observed phenomena such as spontaneous activity, neuronal synchronization, and network oscillations. These are macroscopic network phenomena which we call the *macro state* of the network. Each macro state usually comprises a large ensemble of *micro states*, defined by the individual states of all neurons and synapses.

Many macro states, observed in cortical networks, can be understood, using a simple network with randomly connected excitatory and inhibitory neurons (Brunel 2000). The model consists of three populations of neurons: one population of excitatory neurons, one population of inhibitory neurons, and a third population of excitatory neurons, representing the long-range input from other brain regions. The excitatory and inhibitory populations are mutually coupled, and both receive input from the background population. We can now study the activity patterns which emerge, depending on the ratio of inhibition to excitation and the strength of the background population.

If the amount of excitation and inhibition is roughly equal so that on average the respective synaptic currents cancel each other, we speak of *balanced* network. In this regime, network activity is highly irregular, since spikes are generated by the difference in fluctuations of the excitatory and inhibitory currents (Tsodyks and Sejnowski 1995).

If all neurons fire independently of each other and their spike patterns are essentially random, we speak of *asynchronous-irregular* activity. This state is of particular interest, because it corresponds best to the state of low-rate spontaneous activity, observed in cortical networks.

Networks in the asynchronous-irregular state exhibit chaotic activity (van Vreeswijk and Sompolinsky 1996). Thus, even small perturbation such as adding or removing one spike will quickly result in a completely different micro state. Whether this critical dependence on the initial conditions is useful or detrimental for spike-based processing is still under debate (Izhikevich 2006; London et al. 2010).

If the neurons fire independently, but each at regular intervals, we speak of *asynchronous-regular activity*. In this state, each neuron oscillates at a different frequency, and occasionally, large parts of the network will fire synchronously. The intervals of these population events depend on the common multiples of the individual firing periods. It is also possible that all neurons fire at the same frequency, but out of phase. In this case, neurons will not be able to occasionally synchronize their spikes.

If all neurons fire synchronously with the same frequency, the network essentially oscillates and we speak of *synchronous-regular* activity. Oscillatory states are also of interest since they can serve as models for epileptic activity or for stimulus-evoked synchronization.

Theoretically, there is also a state of *synchronous-irregular* activity, a state where each neuron produces the same irregular spike train. Then the spikes of all neurons will occur in synchrony, but the intervals between the spikes will be irregular. However, this state is very unlikely to occur in random networks because it requires a well-chosen connectivity.

Cross-References

- ▶ Bayesian Inference with Spiking Neurons
- ▶ Excitability: Types I, II, and III
- ▶ Fitzhugh–Nagumo Model
- ▶ Hodgkin-Huxley Model
- ▶ Integrate and Fire Models, Deterministic
- ▶ Morris–Lecar Model
- ▶ Multistability in Neurodynamics: Overview
- ▶ Neuronal Avalanches
- ▶ Pulse-Coupled Oscillators
- ▶ Recurrent Network Models, Reservoir Computing
- ▶ Spike-Frequency Adaptation
- ▶ Spike-Timing Dependent Plasticity, Learning Rules
- ▶ Spontaneous Activity, Models of
- ▶ Theta Neuron Model

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Further Reading

A thorough introduction to the theory of spiking networks can be found in the somewhat dated but still highly valuable textbooks *Introduction to theoretical neurobiology* by Tuckwell (1988). An equally thorough and more recent reference is the book *Spiking neuron models: Single neurons, populations, plasticity* by Gerstner and Kistler (2002) which also contains

extensive treatment of learning and plasticity in spiking networks. A broader overview is given in the textbook *Theoretical Neuroscience* by Dayan and Abbot (2001)
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Spinal and Neuromechanical Integration: Overview

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Detailed Description

To interact with the environment or other organisms, the nervous system must move. Whether it is a fundamental protective reflex, a stabilizing postural adjustment, a rapid prey strike, or an expressive dance gesture, the motor repertoire of an organism defines the nature of its environmental interactions. Structures in the periphery of the motor system, the musculoskeletal system and spinal cord, most directly mediate these environmental interactions. The actions of central brain regions such as cortex, cerebellum, or basal ganglia all ultimately have to pass through these peripheral structures. Understanding the properties of these peripheral systems is therefore critical for our understanding of the neural control of movement.

How should we consider these peripheral components of the motor system? In one common perspective, these systems are problems that the CNS must overcome. In this perspective, the complex properties of muscles, limb mechanics, motor neurons, and spinal circuits require that central motor systems develop strategies that invert, bypass, or suppress these complexities. Complexity could therefore lead to greater complexity: evolutionary changes to the periphery could require the co-evolution of more complex mechanisms to maintain performance.

In an alternate perspective, peripheral systems might simplify for motor control. The complexities of spinal systems or nonlinear properties of the musculoskeletal system might reflect adaptations that allow simplified control by descending systems. For example, passive mechanics can be used to assist movements (Collins et al. 2005), muscle properties can contribute to stability (Nichols and Houk 1973), basic reflexes allow for rapid control (Loeb et al. 1999), and defining adaptive muscle coordination patterns can potentially simplify movement (Tresch and Jarc 2009). In this perspective, energetic costs associated with inefficient, complex control might lead to evolutionary adaptations that simplify control and neural processing.

These two perspectives are not mutually exclusive, and both emphasize the importance of understanding the contribution of peripheral systems to motor control and brain function. Entries in other sections of this Encyclopedia and the *Encyclopedia of Neuroscience* describe the basic physiological properties of muscles (see Heckman et al. 2009), motor units (see Burke 2009), reflexes (see Grey and Nielsen 2009), and pattern generating spinal networks (see ► Vertebrate Pattern Generation: Overview). The entries in this section

expand on those descriptions, characterizing how these systems function and how they interact with descending systems. Spinal interneuronal systems have been studied extensively for more than a century, and although much remains unknown about their role in behavior, these studies have provided basic information that can be used to guide computational studies of motor control (▶ Spinal Cord, Integrated (Non CPG) Models of). Proprioceptors provide the nervous system with information about body state – the position of the limb, the forces produced by muscles, and the interactions with the environment. Understanding how these state variables are encoded in the activity of proprioceptor afferents is critical in understanding what information the nervous system has access to when interpreting and interacting with the environment (▶ "Proprioceptor Models"). Although spinal systems are capable of a great deal of motor coordination on their own, including central pattern generators for basic protective reflexes and for locomotion, voluntary behaviors are accomplished by descending pathways from the brain including the cortex. How these systems interact with one another to produce movement, however, remains poorly understood. One central computational issue in these interactions is how information about task goals (e.g., the location of food to be grasped) is translated into motor commands (e.g., the muscle activations that result in movement of the arm and hand to the food) (Coordinate Transformations, Role of Spinal Circuitry in).

Ultimately motor control is the result of a single dynamic system including both the nervous system and body, coupled together through intrinsic sensory feedback also through dynamic interactions with the environment. Neuromechanics is the field of study that seeks to understand how these two systems work together to produce behavior. Entries in this section examine the neuromechanics of postural control (Neuromechanics of Postural Control), characterizing how neural and musculoskeletal systems interact to stabilize the body to maintain upright stance, and the neuromechanics of joint coordination during locomotion (Neuromechanics of Joint Coordination), characterizing how task goals are accomplished through dynamic coordination of low level execution variables.

Cross-References

- ▶ Coordinate Transformations, Role of Spinal Circuitry in
- ▶ Decision-Making, Motor Planning
- ▶ General Overview of Spinal Anatomy and Physiology Organization
- ▶ Motoneurons and Neuromuscular Systems: Overview
- ▶ Neuromechanics of Joint Coordination
- ▶ Neuromechanics of Postural Control
- ▶ Neuromuscular Control Systems, Models of
- ▶ Proprioception
- ▶ Proprioceptor Models
- ▶ Spinal Cord, Integrated (Non CPG) Models of
- ▶ Vertebrate Pattern Generation: Overview

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Spinal Interfaces: Overview

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Definition

Spinal interfaces have traditionally focused on electrical stimulation of spinal cord tissue (i.e., white matter axonal tracts and/or gray matter neurons) or associated spinal roots (see ▶ "General Overview of Spinal Anatomy and Physiology Organization" in this Encyclopedia). Spinal interface applications have primarily centered about restoration of function lost to neurological impairment and study of spinal neural circuitry (organization, basic functions). More recently, spinal interfaces are being developed to record neural activity from large populations of spinal neurons and to deliver pharmacological agents to specific regions of the spinal cord. These interfaces may also be capable of simultaneously stimulating spinal tissue. Emerging application areas of spinal interfaces include chronic monitoring of neural transmission to serve as a biomarker of pathology/recovery and so-called closed-loop stimulation protocols, in which delivery of spinal stimulation is contingent upon real-time detection of salient neural activity. This latter category is particularly useful for studying and promoting neural plasticity in spinal circuits.

Methodologies to record and/or modulate neural transmission in spinal tissue can be divided on the basis of applications (bladder, movement restoration, pain reduction, etc.), electrode technology employed (electrical, optical, etc.), electrode position (e.g., epidural, intradural, intraspinal), or a number of other characteristics. In this entry, spinal interface techniques are presented based on the degree of invasiveness, and the similar technological methods used to record from or stimulate the neural tissue are highlighted. In increasing order of invasiveness, spinal interfaces can be divided into (1) transcutaneous (recording and stimulation), (3) epidural, (4) intradural or intrathecal, and (5) intraspinal.

Detailed Description

High-Density Surface Electromyography

Spinal alpha motoneurons have long been the only neuron in the human central nervous system from which it is possible to obtain direct recordings. This is because motoneuron action potentials occur in a one-to-one ratio with motor unit action potentials (MUAPs), which are discrete action potentials evident in muscle fibers that can be accessed via electromyography (i.e., recording muscle electrical activity, EMG). Because each MUAP waveform has unique spatiotemporal features and because each muscle fiber is innervated by only one motoneuron (together, a "motor unit"), neural firing patterns of individual motoneurons can be discriminated from one another based on the shape of a given MUAP. These firing patterns are referred to as spike trains. When EMG is used to discriminate individual motor units and/or spike trains, it can be considered a form of transcutaneous spinal interface.

Traditional approaches for recording MUAPs, and by extension for accessing spike trains of discrete motoneurons, have relied on percutaneous needle-style or fine-wire electrodes that penetrate the skin and anchor into the muscle fibers below (i.e., intramuscular EMG). In addition to its invasiveness, this technique results in an extremely low yield of detectable motor units (~2–5/muscle) and provides reliable information only during contractions of low force magnitude.

Over the last 5–10 years, however, a powerful new technology has emerged for accessing motoneuron spike trains: high-density surface EMG (HD-sEMG) decomposition (Del Vecchio et al. 2020). In this non-invasive technique, flexible skin-surface electrodes containing 10's of electrically and spatially isolated recording channels (typically 64 or 128) are placed over a muscle of interest. Surface EMG activity is recorded

simultaneously from each channel. Subtle differences in the spatiotemporal and spectral characteristics of each channel are then exploited by advanced statistical signal processing techniques (e.g., blind-source separation algorithms, independent components analysis) to decompose the multichannel surface EMG activity into individual MUAP waveforms and spike trains. This approach enables access to entire populations of discrete motor units (to date, ranging from ~10 to 40/muscle), providing a remarkably detailed window into descending neural drive and spinal motor output and distinguishing HD-sEMG decomposition from the general overview of motor unit function afforded by traditional intramuscular EMG. HD-sEMG decomposition is also substantially more robust than intramuscular EMG during contractions of increasing force magnitude, enabling studies of human motor unit recruitment and rate modulation that were previously either inferential or, more often than not, infeasible.

While the potential applications of HD-sEMG decomposition are near limitless, early examples have included advanced myoelectric control of prostheses (Kapelner et al. 2019), pathological neural control of movement following neurologic injury (Miller et al. 2014), and spinal motor output in the decerebrate cat (Thompson et al. 2018).

Transcutaneous Stimulation

Transcutaneous spinal stimulation refers to the activation of spinal tissue through the skin. It is broadly categorized either as magnetic stimulation or electrical stimulation. In the case of magnetic transcutaneous spinal stimulation, a magnetic field induces ionic currents within the spinal tissue (see ▶ "Paraspinal Magnetic and Transcutaneous Electrical Stimulation" entry in this Encyclopedia). The basic methodology involves inducing depolarization via a time-varying magnetic field delivered transcutaneously by a coil applied to the skin surface. This approach is similar in concept to transcranial magnetic stimulation (TMS) used to probe cortical circuits. The principal applications of transcutaneous spinal magnetic stimulation have been for the initiation of locomotion following spinal cord injury or in Parkinsonian patients and for the treatment of pain when stimulation is delivered over the dorsal columns (see ▶ "Paraspinal Magnetic and Transcutaneous Electrical Stimulation" entry in this Encyclopedia). Finite element model studies of the spinal cord indicate that the greatest site of activation is within the tracts due to the lower threshold of activation of myelinated fibers of the white matter versus the cells of the gray matter (see ▶ "Finite Element Models of Transcutaneous Spinal Cord Stimulation" entry in this Encyclopedia). Since activation is typically delivered dorsally, the largest site of depolarization typically involves posterior roots and dorsal columns, although the anterior motor roots are also hot spots of depolarization.

Transcutaneous *electrical* stimulation can be used to indirectly modulate neural transmission in spinal circuits. In this approach, skin-surface electrodes are placed dorsally over the relevant vertebrae and traditional, pulsatile electrical stimulation is delivered. Rather than passing current directly into the spinal cord, the electrical stimulation is used to modulate neural transmission in primary afferent nerve fibers providing sensory inputs to spinal circuits damaged or weakened by injury. Although rarely described as such, some variants of classical transcutaneous electrical nerve stimulation (TENS) for pain are examples of this approach. More recently, however, transcutaneous electrical spinal stimulation has been introduced as a possible means to aid locomotor and upper limb rehabilitation following spinal cord injury (Inanici et al. 2018). The efficacy of this approach has not been demonstrated in randomized controlled trials as yet, and efforts to characterize the neural mechanisms by which it exerts potential therapeutic effects are ongoing but remain incomplete (Benavides et al. 2020).

Transcutaneous electrical spinal stimulation can also be delivered as a form of direct current stimulation, referred to as spinal cord direct current stimulation or transcutaneous direct current spinal stimulation (sDCS, tDCSS). Its use for modulating neural transmission in spinal circuits has paralleled that of similar approaches for modulating neural transmission in the brain. In tDCSS, two adhesive skin surface electrodes are placed on either side of the abdomen, one ventrally and one

dorsally. These electrodes are connected to the anode and cathode of a constant current stimulator, which drives current between the two sites. Unlike traditional transcutaneous electrical stimulation approaches (above), in which current is delivered in discrete pulses or trains thereof, in tDCSS the current is continuous (i.e., non-pulsed). In this regard, it can be considered to polarize the neural tissue for a period of time. The potential applications of tDCSS and the mechanisms by which it modulates neural transmission remain a source of active research. However, tDCSS appears to modulate transmission in motor and sensory regions of the spinal cord, as well as primary motor and sensory cortices, in a polarity-dependent manner (Cogiamanian et al. 2008, Ahmed 2011, Song and Martin 2017). These effects are thought to be driven at least in part by facilitation of certain forms of activity-*independent* neural plasticity (Jankowska 2017). Given its modulatory capacity and relative lack of invasiveness, tDCSS may be useful for priming spinal circuits during rehabilitation interventions.

Epidural Stimulation

Epidural stimulation refers to electrical stimulation delivered via leads inserted within the vertebral canal but outside the dura. Surgery is involved, but no stimulating electrodes are actually placed within the central nervous system or in the cerebrospinal fluid (CSF). Epidural stimulation is currently employed in a number of applications. Sacral anterior root stimulation combined with posterior sacral rhizotomy has been used extensively to restore bladder and bowel continence and voiding following spinal cord injury (Brindley 1988). Although most electrodes are implanted intradurally around the sacral roots, epidural electrode leads are sometimes used to activate the anterior sacral roots (typically S2, S3, and S4) (Egon et al. 1998). The anterior root stimulator takes advantage of the different contraction and relaxation times of the sphincter and bladder muscles. While the muscle fibers that constitute the sphincter are mainly "fast-twitch" muscle fibers that fatigue easily and relax very quickly, the fibers that compose the detrusor muscles are "slow-twitch" fibers that contract gradually and maintain force for a longer period of time. With intermittent short bursts of high-frequency electrical pulses to the sacral nerve roots, bladder and sphincter muscles contract, but while the sphincter relaxes rapidly at the end of each stimulus burst, the pressure in the bladder is still sufficiently high to produce urination. Activation of the S2–S4 roots with longer stimulus trains is used to obtain defecation in a number of patients. Variations of the basic principles are still employed today, although advances in our knowledge of urogenital anatomy and electrode design have led to more sophisticated stimulation schemes (see ▶ "Methodologies for the Restoration of Bladder and Bowel Functions" in this Encyclopedia).

Epidural stimulation has also been used extensively for the restoration of locomotion following spinal cord injury in various animal models and humans (see ▶ "Epidural Stimulation" entry in this Encyclopedia). In all species, stimulation is delivered over the dorsal columns with the most efficacious segments for initiating locomotion varying between species. The stimulus train is typically a low-frequency (40 Hz) train of pulses delivered continuously over the dorsal columns at lumbar levels to produce activation of the locomotor circuitry. The exact mechanisms of activation or even the neuronal composition of the locomotor centers remains unknown, but the technique has been used clinically to restore standing and some locomotor movements in individuals with complete motor paralysis below the level of injury when coupled with highly intensive physical therapy (Edgerton and Harkema 2011; Harkema et al. 2011, Wagner et al. 2018). In animal models, the technique has also been combined with intrathecal delivery of targeted therapeutics to further aid restoration of locomotion and for upper limb rehabilitation, although these areas have yet to be realized clinically (Musienko et al. 2011, Barra et al. 2018). Epidural stimulation has also been employed to facilitate the initiation of locomotion in Parkinsonian patients (Fuentes et al. (2010), also see ▶ "Spinal Stimulation for Parkinson Treatment" in this Encyclopedia).

Finally, epidural stimulation of the dorsal columns has been applied for the treatment of chronic

and intractable pain arising from conditions such as failed back surgery syndrome, phantom limb pain, spinal cord injury, diabetic neuropathy, and ischemic limb pain (Kumar et al. 1998; Ramasubbu et al. 2013, Chari et al. 2017). Stimulation is delivered through electrode leads placed over the dorsal columns in an attempt to provide analgesia for a number of various chronic pain conditions. Success rate in the long-term relief of pain is variable, ranging from about 20% to 80% (Kumar et al. 1998). Similar to epidural electrical stimulation for locomotor rehabilitation, the mechanisms of analgesia remain unclear. In more recent implementations, which use stimulation frequencies in the KHz range, it is thought that the stimulation blocks neural transmission in ascending pain pathways (Crosby et al. 2017, Linderoth and Foreman 2017).

For both locomotor and analgesic applications, epidural stimulation has faced two particular challenges in clinical translation: off-target effects and the duration of therapeutic benefits. Off-target effects frequently take the form of parasthesias, which range from mildly irritating to painful in their own right. In some individuals, these effects limit the time that stimulation can be tolerated. A benefit of newer KHz-range stimulation paradigms is that they may evoke fewer or less intense parasthesias, although the efficacy of these paradigms for locomotor rehabilitation has yet to be investigated (Crosby et al. 2017). Regarding the duration of effects, in studies to date the therapeutic benefits of epidural stimulation often diminish rapidly upon cessation of stimulation. This phenomenon is presumably related both to the relatively nonspecific delivery of current to the spinal cord and to the non-physiological and asynchronous stimulus waveforms used to modulate neural transmission. While more targeted stimulation approaches and closed-loop stimulation paradigms may address some of these drawbacks, they are not without their own barriers to clinical translation (see below and other entries in this section).

Intradural Stimulation

Next in order of increasing invasiveness is intradural or intrathecal stimulation. Here, leads are placed within the dural sac itself. Surgical and infection risks increase with this approach, as the implant is now placed within the central nervous system space and CSF and the blood-brain barrier is breached. Dural closure remains a surgical difficulty. However, closer proximity to the spinal cord provides greater access to specific spinal structures, allowing stimulation to be delivered to particular roots. Thus, it is no surprise that the Brindley-Finetech (described in Epidural Stimulation above) sacral anterior root electrodes are mostly implanted intradurally over the divided (anterior separated from posterior) sacral roots to restore bladder and bowel functions.

Intraspinal Stimulation

Intraspinal microstimulation (ISMS) provides the greatest access to the spinal cord but is also the most invasive and thus riskiest stimulation technique in terms of the potential damage it may cause to the nervous system. Stimulation is delivered within the spinal cord, typically via microwires implanted within the white and gray matter, although new high-density microelectrode array and optogenetic techniques amenable to spinal cord applications are being developed (Alilain et al. 2008, Lu et al. 2017). A particular benefit of ISMS for rehabilitation purposes is that it preserves orderly, physiological recruitment of motor units based on Henneman's Size Principle and allows smooth grading of contraction magnitude. This is contrasted by the well-documented reversed recruitment order and ballistic contractions common to transcutaneous neuromuscular electrical stimulation (NMES) techniques. ISMS of motor pools also readily recruits groups of synergist muscles, which has fueled many advances in our basic science understand of spinal physiology but also provides an opportunity to cohesively restore grouped movements via a single stimulation site (which is not possible with transcutaneous NMES).

Applications of ISMS have included direct activation of motor pools/motor units to cause muscle contractions that aid locomotion (Bamford and Mushahwar 2011), bladder and bowel functions (Pikov et al. 2007), and respiration (Sunshine et al. 2018) (see ► "Intraspinal

Stimulation" in this Encyclopedia). Emerging applications include the induction and study of neural plasticity – particularly spike-timing-dependent plasticity – for rehabilitation using closed-loop neural computer interface approaches (McPherson et al. 2015, and see ▶ "Electrical Conditioning for Spike-Timing-Dependent Plasticity of Neural Circuits" in this Encyclopedia). And while the invasiveness of ISMS has presented a conceptual barrier to widespread translation, multiple efforts are currently underway to achieve regulatory approval for ISMS electrodes in humans. One need look no farther than deep brain stimulation electrodes as an example of the potential clinical translational path for efficacious but invasive neuromodulatory therapies.

Electrode Technologies: Issues and Potential Solutions

The electrodes used to deliver stimulation to the spinal cord are for the most part similar to the ones used to deliver electrical stimulation to peripheral nerves and/or the brain. They include cuff electrodes that use metalized contacts (typically platinum) encapsulated within silicone or other materials. These electrodes are typically used to stimulate roots (Brindley-Finetech anterior root stimulator electrode, and see Xiao et al. 2012 for more advanced designs). Metal disk or lead wires are typically used to deliver stimulation epidurally, and microwires are used to deliver stimulation intraspinally. New electrodes being developed and tested in animal models aim to increase the number of contacts and stimulation sites which would allow for greater selectivity in the delivery of stimulation. These include electrode designs for intraspinal microstimulation (Snow et al. 2006) and multi-contact surface electrodes for epidural stimulation (Gad et al. 2013).

Intraspinal microstimulation remains one of the toughest applications as the stiff metal- or silicone-based electrode presents a mechanical impedance mismatch compared to the higher compliance of the spinal tissue, leading to tissue damage. In addition, the spinal cord glides substantially within the vertebral canal during movements (Ranger et al. 2008), and the tension it produces in the cable attaching electrode to associated connector may cause further damage to the tissue unless the cable's flexibility is sufficient to dissociate the motions of the vertebral canal and spinal cord. A promising approach to minimizing mismatches in tissue and electrode material impedances is the braided electrode design of the Giszter group (see ▶ "Braided Electrodes" entry in this Encyclopedia). By braiding extremely fine wires, a very high overall compliance electrode and cabling technology is produced that can be inserted within the spinal cord with the help of a removable cannula guide and produce minimal histological damage to the central nervous tissue after long-term implantation (Kim et al. 2013a). As part of recent translation efforts, Mushahwar and colleagues have also begun development of ISMS implants for humans, performing initial mechanical testing of the implants in porcine models (Toossi et al. 2017). Wireless stimulators may also offer freedom from the cable tethering problem and potentially dura resealing. Miniaturized stimulators can be implanted close to the neural target and controlled via wireless approaches (radio frequency, optical, or acoustic waves, etc.). The approach can have the benefits of a cable-free approach like the transcutaneous stimulators but will allow much more precise targeting of the stimulation delivery (see ▶ "Wireless Microstimulators" entry in this Encyclopedia).

Other stimulation techniques have been used experimentally to activate the spinal cord, but to date no clinical application of these techniques has been pursued. Bizzi and colleagues have used iontophoresis to deliver an excitatory neurotransmitter locally within the gray matter (Saltiel et al. 1998), but since electrodes are pulled glass micropipettes, applications are limited to cases where the spinal cord can be securely immobilized. More recently, cell soma-sized microprobes have been developed to deliver electrical stimulation while simultaneously recording neurotransmitter release (Schwerdt et al. 2018). Although their mechanical impedance is encouraging for spinal cord applications, they have yet to be rigorously tested for this application.

Optogenetic methods have also been used to activate spinal tissue in the rat animal model (see ▶ "Intraspinal Stimulation" entry in this Encyclopedia). Stimulation is usually achieved with delivery of light from the surface, but delivery of light deep into tissue is possible through pulled optic fibers inserted into neural tissue (Gradinaru et al. 2009, Lu et al. 2017) and the development of new miniaturized optoelectronics (Kim et al. 2013b, Montgomery et al. 2015, Samineni et al. 2017). While earlier generations of optical fibers suffered from the same mechanical impedance mismatch issues as their metal electrode counterparts, these newer optrodes represent a substantial improvement in flexibility and compliance.

Finally, infrared light from lasers has also been used to elicit action potentials in peripheral nerve and cochlea of small (rodents and guinea pig) animal models (Izzo et al. 2006; Wells et al. 2005a, b; Xia et al. 2014). The methodology is termed optical stimulation, and action potential initiation appears to be caused by the induction of thermal transient within the axons or neurons (Wells et al. 2007). Depth of penetration of the light is a limiting factor attempting to activate deep tissue, and to date the technology has not been used in the spinal cord. Optical stimulation methods offer the advantage of producing no electrical stimulation artifacts, which facilitates neural recordings and closed-loop configurations because the amplifiers and analog-to-digital converters used in recordings are no longer saturated by the large electrical signal generated by the stimulus pulses.

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Synaptic Dynamics: Overview

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Definition

Synaptic dynamics describes the time-dependent changes in synaptic currents that alter the strength of coupling between neurons. Various mechanisms, both pre- and postsynaptic, contribute to ongoing changes of synaptic currents and modulate the overall network activity. These mechanisms operate on various time scales (milliseconds to years) and can lead to immediate changes in neuronal activity, ongoing adaptation of neuronal responses to changing inputs, and long-term learning and memory.

Detailed Description

Connections between neurons form network circuitry, and these connections are not static, but change in amplitude and timing. When a spike reaches a presynaptic terminal, processes are initiated that result in release of neurotransmitters that diffuse across the synaptic cleft to reach the postsynaptic receptors. Changes in these release dynamics can lead to short-term or lasting changes in the amount and timing of transmitter released. In addition, surrounding cells such as glia can influence the local synaptic dynamics in tripartite synapse. Neurotransmitters bind to postsynaptic receptors that may induce current to flow that changes the postsynaptic neurons membrane potential or initiates signaling pathways that affect various properties of the postsynaptic neuron.

Fast Dynamics

Changes of synaptic currents following a single synaptic transmitter release event are usually on the time scale of milliseconds to second and controlled by the dynamics of postsynaptic receptors. These fast dynamics follow a time course determined by transmitter diffusion, conformational changes in postsynaptic receptors that allows current to flow though the receptor pore, or changes that result in triggering second messengers that modify membrane currents. The resulting current flow is characterized by a sharp rise followed by a slower decay as the receptors inactivate and neurotransmitters unbind. The resulting currents can either excite or inhibit the activity of the postsynaptic neuron, depending on the selectivity of membrane channels for specific ions.

Ionotropic receptors. Receptors that allow direct current flow though a pore are called ionotropic receptors (Eccles and McGeer 1979) and provide the fastest synaptic dynamics. Mathematical representations of a synaptic current, $I_s(t)$, can be represented by a conductance $g_s(t)$ that regulates current flow across the membrane (Gerstner and Kistler 2002; Koch 2004),

$$I_s(t) = g_s(t) \cdot (V(t) - E_s), \qquad (1)$$

where $V(t)$ is the membrane potential and E_s is the reversal potential of the current. If E_s is greater than the membrane potential, then the synaptic excites the neuronal activity, and if E_s is less than the membrane potential, then the synapse inhibits the neuronal activity.

The time-dependent synaptic conductance may be based on double exponential functions (or similarly shaped functions for $t \geq 0$).

$$g_s(t) = g_s\left(-e^{-t/\tau_1} + e^{-t/\tau_2}\right) \qquad (2)$$

where τ_1 is the onset time constant and τ_2 is the decay time constant. More detailed representations of changes in synaptic conductances are developed in kinetic models of channels.

Two important types of excitatory currents are mediated by AMPA glutamate receptor and *N*-methyl-d-aspartate (NMDA) receptors that are excitatory in most neurons and have time constants for a risetime of a few milliseconds. They differ in two respects, time constants and dependence on postsynaptic voltage, but are often colocalized at the same synaptic zones. AMPA receptors usually have a larger peak conductance and decay with a few milliseconds (Trussell et al. 1993). NMDA receptors have a longer decay (Jahr and Stevens 1990), and the peak current is dependent on the postsynaptic membrane potential. NMDA receptors pass calcium ions that can initiate signaling cascades that may have a secondary effect on synaptic dynamics on a longer time scale such as long-term plasticity (Collingridge and Bliss 1987; Lisman 1989). Another important current is mediated by gamma-aminobutyric acid (GABA) receptors and is usually inhibitory in adult neurons.

Metabotropic receptors. Receptors that trigger second messengers to modify membrane currents are called metabotropic receptors (Eccles and McGeer 1979). These receptors are typically slower in their effect on the membrane potential than ionotropic receptors and can result in secondary long-lasting effects on the excitability of neurons. They can also help to initiate signaling cascades that lead to long-term synaptic plasticity. Their fast dynamics are mediated though changes in membrane currents, such as potassium currents, and the effects on membrane excitability can be either excitatory or inhibitory depending on the type of metabotropic receptor. In the simplest mathematical representations of these receptors, the conductance can be represented by a double exponential function (Eq. 2) with a long onset time constant (τ_1) of several milliseconds.

Short-Term Dynamics

The synaptic dynamics caused by a spike may be affected by the history of previous spikes due to short-term plasticity (Zucker and Regehr 2002; Blitz et al. 2004). If the second of two spikes has a larger postsynaptic current than the first spikes, then the plasticity is called facilitation, and if the second spike has a smaller postsynaptic current, then it is called short-term depression. The amount of facilitation and depression on further spikes in a series changes over time and may saturate and last up to several seconds. The duration of facilitation and depression may occur on different time scales leading to complex sequences of postsynaptic currents that could be unique to the pattern of spikes.

Both pre- and postsynaptic mechanisms can be responsible for short-term plasticity. An important presynaptic mechanism is based on the presynaptic probability of neurotransmitter release for each spikes combined with the rate of replenishment of presynaptic vesicles containing neurotransmitters. If the probability of release is high, then synaptic zones may not yet be prepared for the next spike leading to a reduced peak synaptic current observed in short-term depression. In contrast, if the release probability is low, then the first spike may have helped to prime the release so that the release probability is higher for the second spike. This increased release probability at each synaptic zone leads to an increase in peak synaptic current observed in facilitation.

Long-Term Dynamics

Changes in synaptic currents that last longer than several minutes are called long-term plasticity. Several mechanisms, both pre- and postsynaptic, may be responsible for these lasting changes that may increase or decrease the strength of synaptic currents. Increases in synaptic currents are called long-term potentiation (LTP) (Bliss and Lomo

1973), and decreases are called long-term depression (LTD) (Dudek and Bear 1993). Long-term plasticity may be dependent on the activity of pre- and postsynaptic neurons, and when the relative differences of timing of spikes between the neurons determine whether the change is potentiation or depression, then it is referred to as spike-timing-dependent plasticity (STDP) (Abbott and Nelson 2000). The processes of long-term depression and potentiation are balanced by synaptic scaling that adjusts the global input to neurons to maintain stable activity. Long-term plasticity is believed to form the basis of learning and memory as learned sensory cues, and behaviors are encoded in the strengths of synapse in neural circuitry (Hebb 1949).

Cross-References

- AMPA Glutamate Receptor (AMPA Receptor), Conductance Models
- Anti-Hebbian Learning
- Biochemical Signaling Pathways and Diffusion: Overview
- Bimolecular Reactions, Modeling of
- Enzyme Kinetics, Modeling of
- Facilitation, Biophysical Models
- Gamma-Aminobutyric Acid Type-A (GABA-A) Receptors, Kinetic Models
- Gap Junctions in Small Networks
- Gap Junctions, Neural Population Models and
- Hebbian Learning
- Ionotropic Receptors Dynamics, Conductance Models
- Kinetic Models of Postsynaptic Currents
- Learning Rules: Overview
- Long Term Depression in the Granule Cell-Purkinje Cell Synapse
- Long-Term Plasticity, Biophysical Models
- Metabotropic Receptors (G Protein Coupled Receptors)
- Metabotropic Receptors Dynamics, Conductance Models
- N-Methyl-D-Aspartate (NMDA) Receptors, Conductance Models
- Olfactory Computation in Glomerular Microcircuits
- SenseLab: Integration of Multidisciplinary Neuroscience Data
- Short-Term Plasticity, Biophysical Models
- Short-Term Synaptic Plasticity in Central Pattern Generators
- Signaling Pathways, Modeling of
- Spike-Timing Dependent Plasticity (STDP), Biophysical Models
- Spike-Timing Dependent Plasticity, Learning Rules
- Stability and Homeostasis in Small Network Central Pattern Generators
- Tripartite Synapse (Neuron–Astrocyte Interactions), Conductance Models
- Working Memory, Models of

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Further Reading

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Vertebrate Pattern Generation: Overview

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Synonyms

Central pattern generator; CPG; Neural oscillator; Rhythm generators

Definition

Central pattern generators (CPGs) are neural networks that can produce organized rhythmic patterns in the absence of rhythmic sensory and descending inputs from other parts of the nervous system (Marder and Calabrese 1996).

Detailed Description

Vertebrate Central Pattern Generators

The central nervous systems of vertebrates contain many types of central pattern generators (CPGs) that generate and control various rhythmic movements. These CPGs control important functions, including different forms of locomotion, such as swimming, walking, running, and flying, and non-locomotor processes and behaviors, such as breathing, swallowing, chewing, mastication, scratching, whisking (in rodents), singing (in birds), etc. This overview focuses on computational models of locomotion and breathing in mammals, which are briefly discussed below. Other known models of vertebrate CPGs include CPGs controlling swimming in *Xenopus* tadpoles (Wolf et al. 2009; ▶ "Rhythm Generation in Young Xenopus Tadpoles"), zebra fish (Hill et al. 2004; Knudsen et al. 2006), and lamprey (Grillner et al. 2007); CPGs controlling swimming and walking in salamander (Ijspeert 2001; ▶ "Control of Aquatic and Terrestrial Gaits in Salamander"); CPGs controlling locomotion and scratching in turtles (Hao et al. 2011; ▶ "Control of Locomotion and Scratching in Turtles"); CPGs responsible for rhythm generation in embryonic chick spinal cord (Tabak et al. 2001; ▶ "Rhythm Generation in Embryonic Chick Spinal Cord"); and others.

Locomotor CPG in Mammals

The *Half-Center* Concept of the Locomotor CPG

The ability of the spinal cord to generate coordinated locomotor-like rhythmic activity in the absence of rhythmic supraspinal and afferent inputs provides strong evidence for both the existence of locomotor CPGs in vertebrates including mammals and their location in the spinal cord (Grillner 1981; Rossignol 1986; Orlovsky et al. 1999; Stuart and Hultborn 2008; Guertin 2009). The first schematic of a locomotor CPG, called the "half-center" model, was proposed by Graham Brown (1914, see also Stuart and Hultborn 2008; Guertin 2009). This model consisted of two (flexor and extensor) half-centers that reciprocally inhibited each other. The mutual inhibitory interactions between the half-centers were mediated by corresponding inhibitory interneurons, which ensured that only one half-center could be active at a time. The activity of the currently active half-center reduced gradually because of some fatigue or adaptation mechanisms leading to the activation of the antagonistic half-center, inhibiting the currently active half-center, and switching the locomotor phase. It was suggested that the flexor and extensor half-centers project to and activate the flexor and extensor motoneurons, respectively. Studies on immobilized decerebrate cats demonstrated that continuous electrical stimulation of the midbrain locomotor region (MLR) can produce "fictive locomotion" – the rhythmic pattern of motoneuron activity characterized by alternating activation of flexor and extensor

motoneurons similar to that observed during normal locomotion in the intact animal (Rossignol 1986). Similar patterns of locomotor activity could be also produced by systemic administration of the noradrenergic precursor, L-DOPA (e.g., Jankowska et al. 1967a, b). The demonstrated possibility to produce either MLR-evoked or drug-evoked fictive locomotion in the cat spinal cord has provided strong evidence for the existence of locomotor CPGs in the mammalian spinal cord.

The *Unit Burst Generators* Concept

CPG half-center models can be theoretically analyzed and classified into categories such as intrinsic escape, intrinsic release, synaptic escape, and synaptic release depending on which half-center and which process associated with this half-center control the transitions between activity states (Wang and Rinzel 1992; Skinner et al. 1994; Ausborn et al. 2018b; ▶ "Comparative Analysis of Half-Center Central Pattern Generators (CPGs)"). At the same time, the classical half-center concept can only represent a simplified CPG organization and cannot reproduce and explain many features of the locomotor pattern observed in the mammalian spinal cord. Specifically, biological locomotor activity does not exhibit strictly alternating flexor and extensor activities (with all motoneurons clearly belonging to one of these two groups) as suggested by the classical half-center model. The real pattern is more complex and includes motoneuron pools (such as those controlling biarticular muscles) generating bursts during both the flexion and extension phases of the step cycle or during only a part of one phase. There are also noticeable differences in the timing of burst onset and/or offset between different flexor and/or between different extensor pools. To overcome these and other limitations of the classical half-center model, Grillner (1981) proposed a unit burst generator (UBG) concept suggesting the existence of several separate rhythmogenic modules (or unit burst generators) controlling each joint of the limb and interacting with each other as coupled neural oscillators. A simplified mathematical model of the mammalian locomotor CPG based on the UBG concept was proposed and analyzed by Sherwood et al. (2011; ▶ "Computational Analysis of Rodent Spinal CPG"). Despite many obvious advantages, this model showed a very slow recovery after applied perturbations. The analysis of sub-networks of this CPG revealed that the endogenous bursting properties of coupled neurons dominated over the phasing and synchronization properties of the CPG network, leading to the slow phase resetting and rhythm stabilization in response to applied perturbations.

The Two-Level Model of the Locomotor CPG

An important extension of the classical half-center model was suggested based on the analysis of (a) spontaneous deletions (missing bursts) in the rhythmic motoneuron activities and (b) effects of afferent stimulations on the locomotor pattern during fictive locomotion in the cat (Rybak et al. 2006a, b; McCrea and Rybak 2007, 2008; ▶ "Two-Level Model of Mammalian Locomotor CPG"). This analysis led to the suggestion that the locomotor CPG has a two-level architecture with a separate top-level, half-center rhythm generator (RG) and a pattern formation network (PF). While the RG defines the locomotor frequency, the PF network is controlled by the RG and defines and coordinates the more complicated firing patterns of different motoneuron pools. The two-level model was able to reproduce a number of features of the locomotor pattern observed during cat locomotion, including phase maintenance of motoneuron activities following spontaneous deletions or brief stimulation of some afferents, which would be difficult or even impossible to explain in the framework of the classical half-center architecture (see ▶ "Two-Level Model of Mammalian Locomotor CPG"). Some aspects of supraspinal and afferent control of the two-level locomotor CPG were analyzed using computational modeling approaches (Rybak et al. 2006a; Markin et al. 2010; Spardy et al. 2011a, b).

One advantage of the two-level model is a possibility to perform independent control (by supraspinal and afferent inputs) of the step cycle duration (locomotor speed) at the RG level and the activity of motoneurons and motor synergies at the PF level. This CPG model was used in

several studies focused on the development of CPG-controlled legged robots (Chen et al. 2007; Maeda 2008; Amrollah and Henaff 2010).

Rhythmic Activity in Isolated Spinal Cord Preparations of Rodents

The mammalian locomotor CPG was also studied in vitro using isolated spinal cord preparations of rodents (Smith and Feldman 1987; ▶ "Locomotor Pattern Generation in the Rodent Spinal Cord"). The locomotor CPG in these preparations can be activated in several ways, including pharmacological manipulations [by using solutions with specific combinations of *N*-methyl-D-aspartate (NMDA) and serotonin], stimulations of sensory afferents or dorsal roots, and brainstem stimulation. The elicited motor output shows alternation of activity in the left and right ventral roots (e.g., left L2 and right L2) combined with alternation of ipsilateral flexor (L2) and extensor (L5) activities on each side of the cord. Significant progress in the understanding of functional and structural organization of spinal circuits has been achieved using special combinations of genetic, molecular, and developmental approaches. Several classes of spinal interneurons were defined in the embryonic and early postnatal spinal cord based on the dynamic expression pattern of transcription factors (Goulding 2009; Whelan 2010; Gosgnach 2011; Kiehn 2011; Dougherty and Ha 2019; ▶ "Locomotor Pattern Generation in the Rodent Spinal Cord"). The new genetic techniques allow visualization of identified neurons as well as manipulation of their activity and their selective elimination. Several classes of inhibitory (CINi) and excitatory (CINe) commissural interneurons (CINs) have been identified. The axons of these cells cross the midline, project to the opposite side of the cord, and mediate interactions between left and right circuits. The role of different CINs in locomotion has been identified by using transgenic mice with mutations in, or knockout (KO) of, specific genes resulting in various abnormal locomotor phenotypes (Kullander et al. 2003; Lanuza et al. 2004; Akay et al. 2006; Lundfald et al. 2007; Crone et al. 2008, 2009; Zhang et al. 2008; Zagoraiou et al. 2009; Rabe et al. 2009; Restrepo et al. 2011; Talpalar et al. 2013). A two-level computational model of neural circuits in the spinal cord with left and right rhythm-generating populations interacting via inhibitory and excitatory CINs has been developed based on the analysis of spontaneous deletions in the isolated spinal cord preparation with rhythmic activity evoked by administration of NMDA and serotonin (Zhong et al. 2012; ▶ "Locomotor Pattern Generation in the Rodent Spinal Cord") and further refined in subsequent studies (Rybak et al. 2013, 2015; Shevtsova et al. 2015; Shevtsova and Rybak 2016; Danner et al. 2016, 2017).

Modeling the Effects of Genetic Transformations on the Locomotor Pattern

A representative example of how genetic manipulations can change the phase relationships between ipsi- and contralateral neurons involved in control of locomotion in mice is based on the genetic ablation of special molecules involved in guidance of CIN axons, such as Netrin-1 and DCC. Also, the spinal cord contains glutamatergic interneurons with ipsilateral projections, whose axon guidance involves the EphA4 receptor. In *EphA4* knockout (KO) and *Netrin-1* KO mice, the normal left–right alternating pattern is replaced with a synchronized hopping gait, and the spinal cord of *DCC* KO mice exhibits uncoordinated left and right oscillations (Rabe et al. 2009; Restrepo et al. 2011; Rabe Bernhardt et al. 2012; Vallstedt and Kullander 2013). To investigate the effects of these genetic transformations, Rybak et al. (2013) developed a computational model of the spinal circuits containing the left and right rhythm-generating neuron populations (RGs), each with a subpopulation of EphA4-positive neurons, and the CINi and CINe populations mediating, respectively, mutual inhibition and mutual excitation between the left and right RGs. In the *EphA4* KO circuits, half of the axons of EphA4-positive cells crossed the midline and excited the contralateral RG neurons. In the *Netrin-1* KO model, the number of contralateral CINi projections was significantly reduced, while in the *DCC* KO model, the numbers of connections from both CINi and CINe were reduced. In the simulations performed, the models of *EphA4* and *Netrin-1* KO circuits showed switching from the left–right alternating

pattern to a synchronized hopping pattern, and the *DCC* KO network exhibited uncoordinated left–right activity. The model was able to reproduce multiple experimental data on the effects of above genetic transformations on the locomotor pattern, providing important insights into the organization of the spinal locomotor network and was later build upon by subsequent studies (Shevtsova et al. 2015; Danner et al. 2016, 2017; Ausborn et al. 2019).

Respiratory CPG in Mammals

Respiratory Pattern and Spatial Organization of the Respiratory CPG

The respiratory motor pattern observed during quiet breathing in mammals ("eupnea") consists of three phases: inspiration (I), post-inspiration (post-I or E1), and late expiration (E2), which can be recognized in the integrated activity of the phrenic and cranial nerves. This pattern originates within a bilateral column of neurons, called the ventral respiratory column (VRC), located in the ventrolateral medulla and controlled by inputs from other medullary (retrotrapezoid nucleus, RTN, raphé, etc.) and pontine regions. The VRC includes several compartments arranged in the rostro-caudal direction: Bötzinger Complex (BötC), pre-Bötzinger Complex (pre-BötC), and rostral (rVRG) and caudal (cVRG) subregions of the ventral respiratory group (VRG). Respiratory neurons in these compartments are usually classified based on their firing pattern (e.g., decrementing, augmenting) and phase of activity relative to the breathing cycle, such as early inspiratory (early-I or I-DEC), i.e., inspiratory neurons with a decrementing discharge pattern; ramp-inspiratory (ramp-I or I-AUG), i.e., inspiratory neurons with an augmenting firing pattern; post-inspiratory neurons (post-I or E-DEC), i.e., neurons with a decrementing activity during expiration; augmenting or stage II expiratory (aug-E or E-AUG or E2), i.e., expiratory neurons with an augmenting pattern; and pre-inspiratory/inspiratory neurons (pre-I/I), i.e., the neurons whose activity starts before the onset of inspiration and continues throughout inspiration. The BötC, with predominately post-I and aug-E neurons, is considered to be a major source of expiratory activity. The adjacent, more caudal pre-BötC contains neural circuits essential for generating inspiratory activity (Cohen 1979; Bianchi et al. 1995; Richter 1996; Smith et al. 2013).

Computational models of the respiratory network have been in development for several decades. Early computational models of the respiratory CPG focused on the network interactions between different types of respiratory neurons and did not consider intrinsic biophysical rhythmogenic properties of single respiratory neurons and their possible contribution to rhythmogenesis. Generation of the respiratory rhythm in these models was based on the half-center concept suggesting that the respiratory oscillations result from sequential phase switching resulting from the reciprocal inhibitory interactions between different types of respiratory neurons (Botros and Brace 1990; Duffin 1991; Ogilvie et al. 1992; Balis et al. 1994; Rybak et al. 1997; reviewed by Lindsey et al. 2012).

The Pre-Bötzinger Complex and Rhythm Generation In Vitro

A fundamentally distinct concept of respiratory rhythm generation was derived from neonatal in vitro studies. An important discovery has been that a subregion of the VRC, called the pre-Bötzinger Complex, contains a population of excitatory interneurons that can intrinsically generate an inspiratory-like rhythm (Smith et al. 1991). This rhythm was shown to persist after blockade of synaptic inhibition, indicating that the pre-BötC may contain cells with intrinsic bursting properties. Butera et al. (1999a, b) developed and analyzed a series of computational models of bursting pacemaker neurons and populations of these neurons with mutual excitatory connections. In these models, the intrinsic bursting was based on a slowly inactivating persistent sodium current (I_{NaP}) as the essential burst-generating, inward cationic current. The rhythmic bursting cycle in these models was controlled by the slow kinetics of inactivation and recovery from inactivation of I_{NaP}. Simulations performed have shown that the excitatory synaptic

interactions coupled with I_{NaP} activation can readily synchronize cellular bursts and produce population bursting. Importantly, generation of this rhythm does not require inhibitory interactions, which can explain the persistence of the in vitro oscillations after inhibitory synaptic transmission was blocked. It was also shown that even a small fraction of intrinsically bursting cells (5–10%) can produce a synchronized bursting activity of the entire population. Moreover, synchronized population activity may occur even if none of the cells operate in the intrinsic bursting state. Elevation of tonic drive to the population reduces burst duration, increases burst frequency, and, finally, switches population activity from population bursting to a regime of sustained asynchronous activity (Butera et al. 1999a).

Network-Based Versus Pacemaker-Driven Mechanisms for Respiratory Rhythmogenesis and Hybrid Pacemaker–Network Models

The early network models were able to generate a realistic respiratory motor pattern and simulate various alterations of this pattern under different conditions. However, these models failed to reproduce some characteristic behaviors observed in the reduced in vitro preparations and, specifically, the maintenance of the respiratory rhythm following inhibition blockade. Alternatively, the pacemaker-based models, developed to fit to in vitro data, could not explain many respiratory behaviors observed in vivo, such as the Hering–Breuer and other respiratory reflexes as well as the independent control of the duration of each respiratory phase. Neither could these models reproduce apneusis, a well-known abnormal breathing pattern characterized by a significantly prolonged inspiration (up to several seconds) alternating with short expiratory intervals. Moreover, the rhythmic activity generated in the reduced in vitro preparations and reproduced by the pacemaker-driven models is characterized by a decrementing shape of inspiratory discharges that clearly differs from the augmenting shape of phrenic discharges generated during eupneic breathing in vivo; these discharges rather resemble the decrementing bursts observed during gasping.

The above contradictions between the network-based and the pacemaker-based concepts and models can be resolved by postulating that (i) the pre-BötC, while capable of intrinsic bursting when isolated and under some special conditions, is normally embedded in the larger brainstem respiratory network which makes its behavior dependent on its interactions with other brainstem structures and (ii) the respiratory rhythmogenesis is state dependent, and therefore the respiratory oscillations may be generated by either a network-based or pacemaker-driven mechanisms or their specific combinations depending on the conditions (Smith et al. 2000, 2007; Rybak et al. 2002, 2004, 2007; Lindsey et al. 2012; Smith et al. 2013; Koizumi et al. 2016; Ausborn et al. 2018a; ► "Computational Models of Mammalian Respiratory CPG").

The Respiratory CPG and Spatial and Functional Hierarchy of Multiple Rhythmogenic Mechanisms

Significant progress in understanding of spatial and functional organization of the respiratory CPG in the mammalian brainstem has been achieved by using an arterially perfused in situ rat brainstem–spinal cord preparation (Paton 1996) and applying sequential rostral-to-caudal microtransections through the brainstem while recording cranial and spinal motor outflow to observe transformations of network behavior (Rybak et al. 2007; Smith et al. 2007). This approach revealed the existence of a rostral-to-caudal stacking of network building blocks serving distinct circuit functions, which are fully integrated in the intact system, but can be revealed when particular compartments are removed or under special metabolic conditions (hypoxia, hypercapnia). These studies revealed that sequential reduction of the network progressively reorganizes network dynamics, such that new rhythmogenic mechanisms emerge. Specifically, starting from a transection at the pontine–medullary junction, the normal three-phase respiratory pattern is transformed to a two-phase rhythmic pattern lacking the post-I phase. With more caudal transections made close to or at the rostral boundary of the

pre-BötC, the respiratory activity transforms to "one-phase" inspiratory oscillations originating within the pre-BötC, without critical involvement of phasic expiratory inhibition (Rybak et al. 2007; Smith et al. 2007). These results led to the conclusion that (i) generation of the normal three-phase rhythmic pattern requires the presence of the pons (i.e., excitatory drive from pontine neurons to the VRC); (ii) generation of the two-phase pattern is intrinsic to reciprocal inhibitory synaptic interactions between the BötC and the pre-BötC and may also involve the RTN to provide excitatory drive to generate stable behavior; and (iii) the one-phase inspiratory oscillations are generated within the pre-BötC and rely on intrinsic cellular mechanisms operating in the context of the pre-BötC excitatory network. These data allowed the conclusion that there is a spatial and dynamical hierarchy of interacting pontine, BötC and pre-BötC circuits, each of which controls different aspects of respiratory rhythm generation and pattern formation, which can be revealed as the network is progressively reduced. The expression of each rhythmogenic mechanism is state dependent and produces specific motor patterns likely to underpin distinct motor behaviors (Smith et al. 2007, 2013; ▶ "Computational Models of Mammalian Respiratory CPG").

A minimal network configuration proposed to represent the above multiple rhythmic states and their transformations included (i) a mutually inhibitory circuit with a ringlike architecture composed of post-I and aug-E neurons of the BötC compartment and early-I neurons within the pre-BötC and (ii) a pre-BötC kernel of excitatory pre-I/I neurons, with intrinsic I_{NaP}-dependent bursting properties. The latter participate dynamically in the expiratory–inspiratory phase transition and generation of the inspiratory phase. The detailed description and computational model of this core network and the circuit elements participating in each rhythmic state can be found in a series of related publications (Rybak et al. 2007; Smith et al. 2007; Rubin et al. 2009b; for review see also Lindsey et al. 2012; Smith et al. 2013; ▶ "Computational Models of Mammalian Respiratory CPG").

Respiratory Rhythm Generation and Coupled Oscillators

As described above, the respiratory CPG is considered to comprise several interacting populations of respiratory neurons located in the pre-BötC and BötC circuits within the VRC. A distinct site of neural oscillations was identified in vitro in the isolated neonatal rat brain stem–spinal cord preparation (Onimaru and Homma 1987, 2003; Onimaru et al. 1988). This additional oscillator, called the parafacial respiratory group (pFRG), seems to reside within, or overlap with, the RTN. It was also found that RTN/pFRG oscillations in vivo drive abdominal motor activity, expressing late-expiratory (late-E, or pre-inspiratory) bursts or biphasic discharges (with pre-I and post-I components) in the abdominal motor output when the system operates in the active (forced) expiration regime (Janczewski et al. 2002; Janczewski and Feldman 2006; Feldman and Del Negro 2006; Abdala et al. 2009). Several competing concepts concerning the physiological role of RTN/pFRG oscillations have been suggested, including the dual oscillator concept that considers the RTN/pFRG as an independent expiratory rhythm generator coupled with a distinct inspiratory rhythm generator in the pre-BötC (Janczewski and Feldman 2006). However, the exact physiological role of pFRG oscillations, the specific conditions for their emergence, and the nature and mechanisms of the interactions between the BötC/pre-BötC and RTN/pFRG oscillators are not yet known.

Molkov et al. (2010; ▶ "Coupled Oscillations in Neural Control of Breathing") extended the previous respiratory CPG model (Rybak et al. 2007; Smith et al. 2007) to include the RTN/pFRG oscillator and consider interactions between the BötC/pre-BötC and RTN/pFRG oscillators. The extended model incorporates an additional late-E population in the RTN/pFRG compartment, representing a source of late-E oscillatory activity. In the proposed model, under normal metabolic conditions, the RTN/pFRG oscillator is inhibited by the BötC/pre-BötC circuits, and the late-E oscillations can be only released by either hypercapnia-evoked activation of RTN/pFRG or by hypoxia-dependent

suppression of RTN/pFRG inhibition by BötC/pre-BötC. The proposed interactions between the BötC/pre-BötC and RTN/pFRG oscillators allow the model to reproduce several experimentally observed behaviors, including *quantal acceleration* of abdominal late-E oscillations with progressive hypercapnia and *quantal slowing* of phrenic activity with progressive suppression of pre-BötC excitability, as well as to predict a release of late-E oscillations by disinhibition of RTN/pFRG under normal conditions (Molkov et al. 2010; ▶ "Coupled Oscillations in Neural Control of Breathing"). Rubin et al. (2011) performed thorough analysis of the reduced model and explained the regimes of quantal acceleration and quantal slowing in terms of synchronization of the BötC/pre-BötC and RTN/pFRG oscillators. They have shown that the dynamics of each oscillator can be represented by a stable limit cycle in some phase space. The phase space of a system of two coupled oscillators is a Cartesian product of the phase spaces of each oscillator. The behavior of this system can be represented by a trajectory on 2D invariant torus. If the ratio of oscillation frequencies of the two oscillators is rational (i.e., equal to N/M, for some integers N and M), then this trajectory is closed, indicating N/M synchronization between oscillators, where N and M represent numbers of rotations around two orthogonal circles that together span the torus (Rubin et al. 2011). These modeling studies provide mechanistic explanations for the emergence of RTN/pFRG oscillations and their interaction with the BötC/pre-BötC circuits representing the core of the respiratory CPG.

Intrinsic Neuronal Properties Involved in Rhythmic Bursting in the Brainstem and Spinal Cord

The mechanisms generating neural oscillations in the mammalian brainstem, particularly in the pre-Bötzinger Complex involved in control of respiration, and in the spinal cord (locomotor CPG), that persist after blockade of synaptic inhibition, remain poorly understood. Experimental studies in medullary slices from neonatal rodents containing the pre-BötC identified two mechanisms that could potentially contribute to generation of rhythmic bursting: one based on the persistent or slowly inactivating I_{NaP} (Butera et al. 1999a, b; Koizumi and Smith 2008) and the other involving the calcium-activated nonspecific cation current (I_{CAN}) activated by intracellular Ca^{2+} accumulated from extracellular (e.g., calcium currents, I_{Ca}) and/or intracellular sources (Pace et al. 2007). The involvement and relative roles of these mechanisms in rhythmic bursting are still under debate. Several related models combining the above two mechanism have been developed (Rubin et al. 2009a; Toporikova and Butera 2011; Dunmyre et al. 2011; Jasinski et al. 2013). Jasinski et al. (2013) investigated Na^+-and Ca^{2+}-dependent bursting generated in single cells and in a heterogeneous population of synaptically interconnected excitatory neurons with I_{NaP} and I_{Ca} randomly distributed within the population. They analyzed the possible roles of network connections, ionotropic and metabotropic synaptic mechanisms, intracellular Ca^{2+} release, and the Na^+/K^+ pump in rhythmic bursting activity generated under different conditions. They showed that heterogeneous populations of excitatory neurons with these properties can operate in different oscillatory regimes with bursting dependent on I_{NaP} and/or on I_{CAN}, or independent of both. The exact oscillatory regime and the operating bursting mechanism may depend on neuronal excitability, synaptic interactions, and relative expression of particular ionic currents. The existence of multiple oscillatory regimes and their state-dependency may provide explanations for different rhythmic activities observed in the brainstem and spinal cord under different experimental conditions.

Interestingly, the Na^+- and Ca^{2+}-dependent bursting mechanisms can be unexpectedly connected. Brocard et al. (2013) have shown that the evoked locomotor-like activity in the isolated neonatal rodent spinal cord reduces the extracellular calcium concentration ($[Ca^{2+}]o$) to 0.9 mM and increases the extracellular potassium concentration ($[K^+]o$) to 6 mM. Such changes in $[Ca^{2+}]o$ and $[K^+]o$ trigger a rhythmic bursting activity in spinal interneurons that may represent elements of the respiratory CPG. The performed experimental studies and modeling have shown that the

emergence of this rhythmic activity critically involves a $[Ca^{2+}]$o-dependent activation of the persistent sodium current (I_{NaP}). These results suggest that the locomotor oscillations in the spinal cord may relay on the I_{NaP} -dependent pacemaker properties in spinal interneurons, which can be turned on and off by activity-dependent changes in $[Ca^{2+}]$o and $[K^{+}]$o (Brocard et al. 2013).

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Vestibular System: Overview

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Detailed Description

The vestibular system is our sixth sense. Not only does it contribute to our sense of orientation and movement in space but, via the vestibulo-ocular reflex (VOR), it stabilizes our vision, especially during rapid unpredictable head movements. Without the VOR our visual world would appear to move every time we undertook an activity that involves head movement, such as during walking, running, climbing, or driving on a bumpy road.

The vestibular organ is located in the inner ear next to the cochlear. As our head movements consist of rotations (nodding in affirmation) and translations (jumping up and down when happy), the vestibular organ comprises two sensor systems. The semicircular canals sense angular head rotations while the otolith organs sense linear head translations (see ▶ "Vestibular Otoliths, Response to Vibration and Sound"). Both the semicircular canals and otolith organs rely on specialized hair cells and the inertia of fluid (canals) or a gelatinous mass (otoliths) to bend the sensory hairs. Because there are two types of hair cells and because individual vestibular afferents receive input from different combinations of these hair cells, the signals coming from the vestibular periphery contain a wealth of sensory information that includes head-rotation velocity and acceleration, head linear acceleration, or tilt angle (see ▶ "Peripheral Vestibular Signal Processing"). This information is encoded in the signals coming from the peripheral vestibular organs but further processing occurs centrally (see ▶ "Central Vestibular Signal Processing") to generate the appropriate three-dimensional (horizontal, vertical, and torsional) eye movements required to stabilize vision and the muscle responses that equilibrate balance. Some of this processing is very rapid. For example, the direct pathway of the VOR consists of a three-neuron arc that has a transmission delay of ~7 ms in primates. In fact, the VOR is our fastest neural reflex.

The central vestibular neural circuitry, located in the vestibular nuclei of the brainstem, receives input from the vestibulo-cerebellum to sustain, modify, and train the vestibular response (see ▶ "Vestibular Adaptation and Compensation"). Thus, the vestibular system is an exquisitely adaptable system during normal function. For example, the VOR response increases almost immediately when needed to view close objects or scenes, as if that context had been pre-programmed and can be trained to increase or decrease when wearing magnifying or minifying lenses. The vestibular system also has the ability to recalibrate to compensate for permanent injury to one (complete injury) or both (incomplete injury) of the vestibular organs and their associated nerves. There are many causes of damage to the vestibular end organ and associated nerves. The most common of these include age-related cell loss, tumors, head trauma, ototoxic injury (e.g., by aminoglycoside drugs), Meniere's disease, infection (meningitis and vestibular neuritis), and cochlear implantation (see ▶ "Vestibular Function After Cochlear Implantation"). About 1% of adults under 65 and 25% over 65 will have an injury to the vestibular organs. Other patients will have normal functioning vestibular organs and nerves but suffer from abnormalities of the vestibular organs that result in conditions such as benign paroxysmal positional vertigo or superior canal dehiscence syndrome. Because the vestibular system operates over a large range of head-rotation frequencies (0 to ~15 Hz) and comprises the canals and otolith organs, a range of diagnostic tests have been developed to test for the different conditions above including the following: head impulse testing (see ▶ "Vestibular, Canal Testing: The Head Impulse Test"), video (see ▶ "Vestibular, Eye Movement Testing"), imaging, and

vestibular evoked myogenic potential testing. For example, the head impulse test is used to determine the function of each of the six semicircular canals and their associated nerves during physiologically relevant rapid head rotations. For patients with complete vestibular organ loss, vestibular function can be restored by a vestibular prosthesis that senses head movements and transmits an appropriately encoded electrical signal to drive the vestibular nerves (see ▶ "Vestibular Prosthesis, Interface"). For prosthesis recipients and also patients with incomplete vestibular loss, vestibular rehabilitation is essential for maximum recovery (see ▶ "Vestibular, Rehabilitation"). Ideally, vestibular rehabilitation exercises are tailored for each patient so that compensatory mechanisms are best enabled. The accepted techniques developed to diagnose, cure, and rehabilitate vestibular injury have helped many patients because they are based on our fundamental understanding of vestibular signals and their processing. This is the focus of the articles in this section.

Cross-References

- ▶ Central Vestibular Signal Processing
- ▶ Peripheral Vestibular Signal Processing
- ▶ Vestibular Adaptation and Compensation
- ▶ Vestibular Function After Cochlear Implantation
- ▶ Vestibular Otoliths, Response to Vibration and Sound
- ▶ Vestibular Prosthesis, Interface
- ▶ Vestibular, Canal Testing: The Head Impulse Test
- ▶ Vestibular, Eye Movement Testing
- ▶ Vestibular, Rehabilitation