Dynamical Aspects of Pharmacokinetic/ Pharmacodynamic & Quantitative Systems Pharmacology Models

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Introduction

Dynamical Aspects of Homeostasis and Disease

The realization that organisms maintain a dynamic equilibrium in face of constant internal or external stressors, is embedded in the term "*homeostasis*" and the observation of Claude Bernard that the purpose of diverse physiological mechanisms is to maintain a stable "*Milieu intérieur*" (interior milieu) against growing, aging, disease, operation, accident, stress etc. Successful adaptation to a constantly changing environment consists of a variety of body reactions that work towards counteracting the effect of natural development or internal/external stress to re-establish homeostasis [18, 28]. Long before the brilliant insights of Claude

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Bernard, in classic era, *Heraclitus* with his famous quote "*everything flows*" suggested that all systems retain the intrinsic capacity to undergo constant changes rather than being static. *Empedocles* had also proposed that all matters consist by the dynamic opposition and alliance of basic elements, and *Hippocrates* argued that health results from a balanced relationship of elements, whereas disease is indicative of a disharmony among them. Evidently, the notion that homeostasis is a complex, dynamic equilibrium with multiple levels of organization and control is not new.

Physiological complexity in humans spans from molecular and cellular networks to tissue functions and organs [16]. One of the most important manifestations of intrinsic complexity is a nearly 24 h (*circadian*) temporal coordination of biological processes that enables body to anticipate daily changes and optimize fitness. The 2017 Nobel Prize in Physiology or Medicine to Jeffrey Hall, Michael Rosbash, and Michael Young for their work on organism's inner circadian clocks indicates the paramount value of circadian rhythms [11]. The circadian timing mechanism consists of cell-autonomous molecular clocks present in almost all cells of the body, that are entrained by periodic environmental cues the most pervasive of which is the light-dark cycles. The suprachiasmatic nucleus (SCN) of the brain responds to light/dark cycles by regulating systemic signals, such as body temperature, hormone secretion, and activity and then transmits the 24 h light-dark information to the periphery of the body and synchronize the function of peripheral tissues [10]. Loss of entrainment between SCN and peripheral oscillators has been linked with several diseases such as obesity, diabetes, cardiovascular disease and cancer [77, 82, 117]. This hierarchical organization of circadian rhythms along with the clinical outcomes resulting from their disruption, represents a characteristic example of how organism's well-being emerges from the system's characteristics rather than its isolated parts' behavior.

Physiological variability and multiscale organization confers advantages not only to the homeostatic function of the body, but also to body's response to external stimuli such as injury or infection. In response to a stressor, body mounts an inflammatory response aiming to resolve the effects of the stressor and restore homeostasis. The inflammatory response involves multiple levels of organization such as transcriptional activation of inflammatory genes in multiple cell types, autonomic neural signaling, secretion of hormones and production of hormone-like inflammatory mediators (cytokines/chemokines) [36, 85, 132]. These intercommunicating systems are designed to confer a time-restrained return to homeostasis. However, when anti-inflammatory mechanisms fail to adequately counterbalance pro-inflammatory activity, the body can reach a state of prolonged, unresolving systemic inflammation. This dysregulated inflammatory state can cause significant harm to the body, even in the absence of any exogenous stressor. The inherent complexity of the inflammatory response and its multi-level organization necessitate a systems biology view to study how the individual parts interact to ultimately produce a self-regulated restoration of homeostasis.

Despite the established appreciation of human body complexity, drugs even today aim to fix certain physiological parameters to nominal values on patient's behalf. Many times, the notion that organism's stability and well-being could emerge as a property of the network is missing, and incorporation of systems dynamics in drug development is often limited. With the advances of systems theory and data analysis, our era urges the use of systems understanding in pharmacology [142].

Dynamical Aspects in PK/PD and Quantitative Systems Pharmacology

Maintenance of homeostasis usually involves a convolution of positive and negative feedback loops at multiple levels of body's organization, that function as control systems to counteract changes of various signals (negative feedback) or enhance system's response to a certain stimulus (positive feedback). Since early 80's, the emerging literature indicating that chaotic functions can accommodate the abundance of positive and negative feedback controls in physiological systems, particularly in EEG and ECG analysis, propelled van Rossum & de Bie to put forward the involvement of nonlinear dynamics by suggesting that chaotic behaviours could underlie pharmacological mechanisms [108–110]. These authors were the first to introduce the concept of attractor of a dynamical system in pharmaceutical sciences i.e., geometric forms that characterize long-term behavior in the phase space of the dynamical system. Alternatively, an attractor can be defined as a set of numerical values towards which a system tends to evolve, for a wide variety of starting conditions of the system. These geometrical forms correspond to predictable systems (point, limit cycle and torus attractor), while the strange attractor corresponds to unpredictable motions i.e. chaotic systems (Figure 1).

In general, pharmacotherapy assumes a reasonable degree of predictability and that usually variability in the observed systems arises from pure randomness. However, biological systems, including human body, are complex dynamic systems with a large number of variables and regulating mechanisms which operate simultaneously. A relatively simple mathematical presentation, the logistic map for population growth, has been used to explain the route to chaos of the variable x_n assigning different values to the control parameter α, based on the following difference equation (Eq. 1):

$$x_{n+1} = f[x_n] = a \cdot x_n \cdot [1 - x_n] \tag{1}$$

An illustrative example of the use of logistic map to reveal if the observed irregular behavior of observations arise from noise or chaos is shown in Fig. 2.

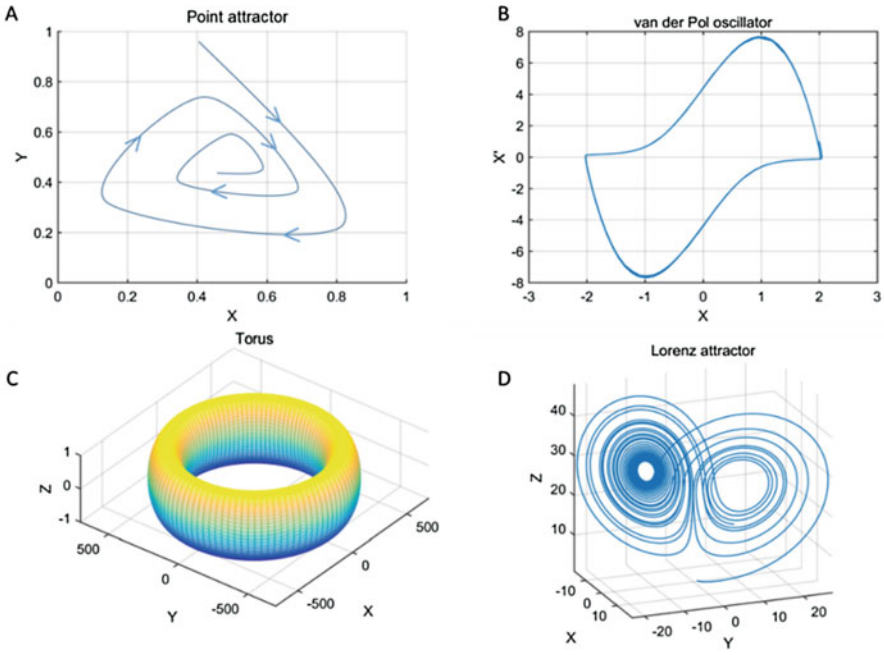

Fig. 1 A schematic representation of the various types of attractors. A: the point attractor. Regardless the initial conditions, the system ends up to the same steady state. B: Cycle attractor (van der Pol oscillator). The system always ends up doing a specific oscillation. C: A torus attractor. The torus is the two-dimensional (2D) equivalent of a circle. In fact, a circle can be called a 1-torus, the 2D torus can be called a 2-torus and there is also the 3-torus and generally the n-torus. The trajectory on a 2-torus is a 2D oscillation with the ratio of the frequencies of the two oscillations being non-rational. Because the trajectory never passes from the same point twice, in infinite time fills the entire surface of the torus. This type of trajectory is called quasiperiodic. Being an attractor, the torus attracts all trajectories to fall on its surface and follow the quasiperiodic behavior. D: Strange attractor (Lorenz attractor)

For a detailed mathematical analysis on the logistic map and a concise review on the principles of nonlinear dynamics including their applications in PD, the reader is referred to the publication by Dokoumetzidis et al. [29].

Danhof [25] classified dynamical systems into adaptive and non-adaptive. The former have changing system properties over time, particularly through emergence of self-organization, whereas the latter are characterized by functionally constant properties over time. The author suggested that the behaviors of complex biological systems are governed by the fundamental properties of hysteresis, non-linearity, individuality, variability, interdependency, convergence, resilience and multi-stationarity. Additional fundamental properties include emergence, robustness, self-organization and degeneracy [51, 141]. Multi-stationarity refers to the biological systems' phenomenon of existence of multiple, more or less stable, states and it is

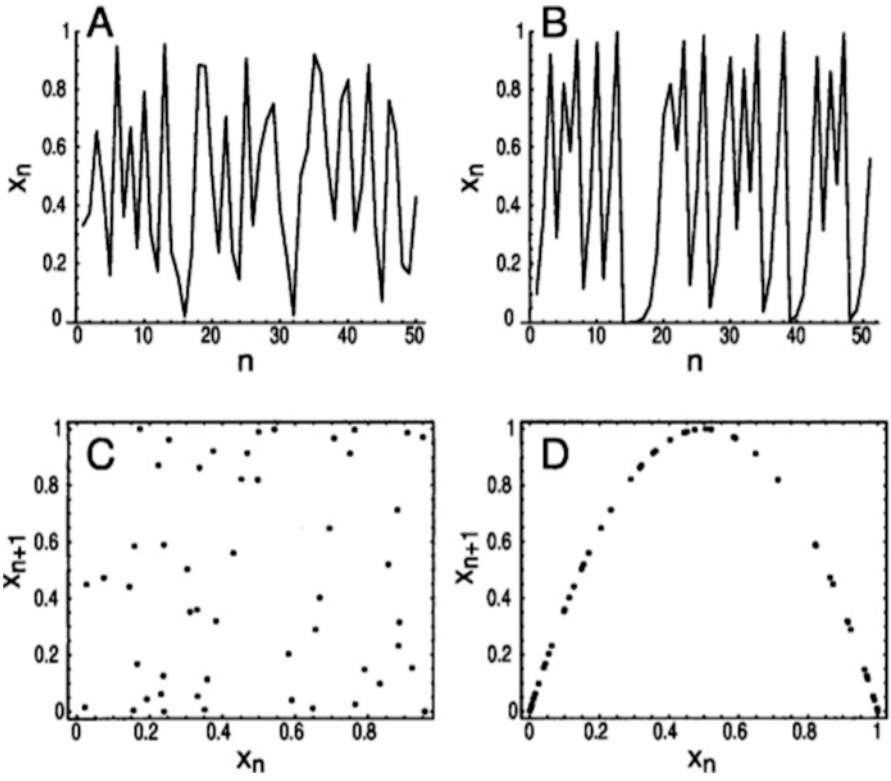

Fig. 2 (**A**) A series of uniformly distributed random numbers between 0 and 1. (**B**) Plot generated by the logistic map, a deterministic system of the form $x_n + 1 = 4x_n \cdot (1 - x_n)$. It is impossible to distinguish them visually (**A** or **B**). (**C** and **D**) The pseudophase plots of the two sequences of plots A and B, respectively. Each x_n is plotted against its consequent x_{n+1}. The random sequence (**A**) produces a pseudophase space of scattered points (**c**) showing that there is no correlation between successive points. On the contrary, the points of the deterministic sequence (**B**) lay in a well formed line (**D**). (Reproduced with permission from Ref. 29)

also characteristic of chaos theory. However, multi-stationarity is not a self-evident property. It is rarely immediately apparent through ordinary differential equations (ODEs)-based modeling and simulation, unless advanced mathematics techniques, like bifurcation analysis, are applied. Multi-stationarity can often confound the simulations, but the cause cannot be identified directly by visual inspection.

In pharmacokinetics/pharmacodynamics (PK/PD), simpler dynamics are associated with pharmacokinetic processes and this is the reason why pharmacokinetic studies, in general, are less variable than the pharmacodynamic ones [67]. Even when the system is simple, tools from dynamical systems theory can still be useful. When a system has only one variable, its behaviour can be studied by plotting the variable against its derivative. Such a plot is referred as phase plane (e.g. *dC/dt* vs. C in Michaelis-Menten kinetics). According to van Rossum and de Bie [109], the

phase space of a pharmacokinetic system is ruled by a point attractor since the drug leaves the body and consequently the drug concentration in plasma tends to zero. On the other hand, in pharmacodynamics there are several examples of systems exhibiting nonlinear dynamical nature. Traditionally, pharmacodynamics has been based on the receptor occupancy theory without feedback, which leads to the classical direct and indirect Emax models. This simplified representation of a pharmacodynamic response is not always physiologically relevant and deviations from that can be anticipated when feedback mechanisms, induced by the ligand-receptor complex formation and functioning to maintain a basal ligand value, are considered.

Ever since, PK/PD models not only have been addressed by dynamic sub-models linking nonlinearly time-concentration-effect, but they have also evolved over time to state-of –the-art mechanism-based PK/PD, disease progression and quantitative systems pharmacology (QSP) models under the umbreall of systems biology. Such models can account for whole biochemical signaling pathways and biological networks rather than single transduction pathways implemented in classical PK/PD (e.g. turnover models). In addition, they are able to mathematically describe the sum of involved physiological processes and characterize the functional interactions within the biological network, which are of great importance for agents acting in multiple target and/or when homeostatic (feedback) mechanisms are operative in the network. Therefore, systems pharmacology models can be advantageous for illuminating irregular patterns of drug action (e.g. oscillatory behaviour). Apart from commonly mentioned issues of such complex models, regarding robustness, identifiability and granularity, in depth investigation of the system's dynamics is often neglected. In this chapter, specific examples from simple PK/PD to complex and large quantitative systems pharmacology models were carefully chosen and briefly presented to illustrate the importance of applying tools from the nonlinear dynamical systems theory in mathematical modeling and simulation. These examples are categorized based on the respective physiological systems including the cardiovascular, the central-nervous, the endocrine and the immune system.

Cardiovascular System

Historically, cardiac physiology has been extensively studied and numerous applications of nonlinear dynamics and chaos theory associated with the healthy and/or diseased cardiac function have been published [24, 45, 46, 59, 137]. Analyzing electrocardiogram (ECG) with either statistical (like spectral analysis) or dynamical (like phase space reconstruction) techniques has clearly indicated that heartbeat, blood pressure or in general signaling in the cardiovascular system is essentially irregular [46, 47, 124, 136, 138, 143]. In fact, the ECG was one of the first biological signals studied with such tools, where concepts from chaos theory have been applied to the analysis of its variability [24, 46, 52, 91, 92, 135].

There are a number of studies investigating the pharmacologic effect of drugs on the dynamics of cardiac physiology. These examples include, but are not limited to, the attempt to control cardiac chaos using ouabain, the induction of cellular chaos during quinidine toxicity and the effect of atropine and anticholinergic drug on cardiac inter-beat intervals and heart rate variability, respectively [43, 58, 114, 128]. De Brouwer et al. [6] have successfully applied concepts of nonlinear dynamics using a simple model based on coupled oscillators to describe the dynamics of agonist-induced vasomotion, where the route to chaos in the presence of a class IV antiarrhythmic drug, verapamil, was investigated.

Modeling of the spatial evolution dynamics of the cardiac electrical activity under the prism of chaos theory is very promising. In this effort, the cardiac tissue is considered to be an excitable medium, the electrical activity of which is described not only in time but also in space by reaction-diffusion partial differential equations [84]. This way, the system is able to produce spiral waves, which serve as precursors of the chaotic behavior. Such spiral waves signal the transition from the normal heart rate to tachycardia, while the chaotic regime, observed after spiral waves have broken up, corresponds to the transition to fibrillation. The latter transition is often characterized as electrical turbulence, due to its resemblance to the respective hydrodynamic phenomenon. Although such approaches have not yet directly implemented to PK/PD or QSP models and integration of pharmacologic response in the excitable media models remains challenging, they provide valuable information for the pharmacologic effect of antiarrhythmic drugs. Agents belonging to the antiarrhythmic classes I and III such as flecainide and moricizine have been proven to potentially increase sudden death rate caused by ventricular fibrillation [31]. Simulations of two- and three-dimentional (2D, 3D) cardiac tissue have been attempted. In this case, the 3D equivalent of spiral waves is scroll waves [42, 105, 125]. These models were able to differentiate between the antiarrhythmic action observed in a single cell system, lacking spatial evolution, and the proarrhythmic effect in a whole cardiac tissue system of either two or three spatial dimensions.

This new approach has given rise to evaluation of antiarrhythmic drugs based on the chaotic dynamics governing the transition from tachycardia to fibrillation [42, 105, 139]. This is also supported by experimental evidence [42]. These findings have indicated that the limitations of the classical approach of premature ventricular polarization suppression (i.e. initiation of tachycardia) might be associated with the failure to predict long-term efficacy of class I and III antiarrhythmic compounds [139]. However, sudden cardiac death, due to ventricular fibrillation, is divided into two main components: a) the initiation of tachycardia and b) its degeneration to fibrillation. As a result, a revised antiarrhythmic drugs' classification, incorporating both anti-tachycardiac with anti-fibrillary profiles, has been proposed.

Several implications of cardiovascular drugs such as the increased risk of bioequivalence failure of antiarrhythmic generics could be attributed to the chaotic behavior of the cardiac signaling. It is evident that the oversimplified approach of Emax model, adopted most of the times in PK/PD modeling of antiarrhythmic compounds, might be neither sufficient nor appropriate. Overall, further research

to increase understanding of the high complexity degree of cardiac signaling, its association with disease and the effect of drugs acting on the cardiovascular system is required. Toward this direction, nonlinear dynamical systems analysis might be a very powerful, if not necessary, mathematical tool.

CNS-System

Evaluation of nonlinear dynamics in brain electrical activity has provided information about the underlying neuronal networks and brain disorders [81]. Most of studies applying tools from the nonlinear dynamical systems theory are based on experimental electroencephalogram (EEG) recordings and highlight the chaotic behavior of the brain electrical activity. Phase space reconstruction and fractality calculation of real time EEG recording are some of the techniques that have been used to assess the EEG variability [1]. These nonlinear systems tools demonstrate not only the underlying complexity of brain electrical activity, but also enrich the information obtained from classical techniques such as the Fourier analysis. In addition, they can be utilized to qualitatively distinguish between EEG recordings in different disease states like epileptic seizures, Alzheimer's and Parkinson's disease or schizophrenia [56, 57, 119, 123]. In the same context, reduction of the nonlinear structure of brain activity has been observed after administration of low doses of ethanol [33].

Usually, PK/PD studies of centrally acting drugs rely on some quantitative measures of EEG parameters [73]. Analysis of time series of EEG data in PD studies with CNS drugs using techniques of nonlinear dynamics are very limited. Some examples include the effect of pregnenolone sulfate, penicillin and lorazepam on the electrophysiological activity of brain [35, 54, 55, 65, 74, 107].

Modeling in the brain aims to rather illuminate the qualitative principles underlying the various phenomena, such as epileptic seizures, than to quantify and forecast them [64]. Accounting for changes in brain activity using tools from chaos theory can provide important information about the underlying dynamics and possibly reveal irregular dynamical behavior as source of the high variability observed in the PD parameters of CNS drugs. In this chapter, we focus on tools from chaos theory applied in different models of a well-studied CNS disease, the Parkinson's disease.

Parkinson's Disease

Parkinson's disease (PkD) is the second most common, after Alzheimer's, progressive neurodegenerative disease with substantial and growing socioeconomic burden and its incidence is expected to increase with life expectancy. Parkinson's is a complex multifactorial disease resulting from aging, genetic predisposition and exposure to environmental stimuli and is characterized by tremors and movement

rigidity. Pathogenesis of PkD involves oxidative stress, aggregation of the a-synuclein (Asyn) protein and dysfunction of proteasomes as well as lysosomes. Both, positive and negative feedback motifs have been identified and all involve misfolding of Asyn. Even though the physiological proteolytic mechanisms are normally responsible for clearing misfolded proteins, misfolded Asyn is capable of partly inhibiting, through a double-negative feedback interaction, proteasomic and lysosomal function [70]. On the other hand, there are two double-positive feedback mechanisms, involving misfolded Asyn, that we put emphasis on: (1) increased cytosolic dopamine (DA) levels via permeabilization of DA-containing vehicles, which in turn induce the misfolding of native Asyn and (2) increased oxidative stress and as a result elevated levels of reactive oxygen and nitrogen species (ROS/RNS), due to mitochondrial damage. This leads Asyn to misfold even further. Of course, this is not an exhaustive list of the observed feedback mechanisms in Parkinson's disease, where several longer and more complex interaction pathways can take place, but outlines well identified pathways that have been utilized in mathematical models. Aside from the feedback mechanisms, the development and prognosis of Parkinson's disease is influenced by several other factors as well. This include, but are not limited to, increased brain concentrations of metal ions (like Fe^{2+}, Cu^{2+}), increased inflammation and age-related degenerative factors such as protein clearance and mitochondrial function attenuation.

Over the last decades, mechanism-based mathematical models of Parkinson's disease have been developed and improved with the increasing insight of brain physiology and experimental techniques. Recently, Bakshi et al. [2] carefully reviewed the mathematical biology models for Parkinson's disease. These mechanistic models were classified into three categories (i) Asyn aggregation, (ii) disease pathogenesis and (iii) pathology propagation models. The former category is typically ODE-based with the most parsimonious models and the greatest experimental support, whereas the latter has not gained much attention modeling-wise, apart from some limited attempts mainly by Kuznetsov and co-workers [61, 62, 126]. The pathogenesis models, in contrast, usually combine ODEs with network models, stochastic simulation algorithms, flux-balance analysis (FBA) and/or biochemical systems theory. In this chapter we focus on these models, since tools from the nonlinear dynamical systems theory have been more widely applied to their analysis.

Examples of pathogenesis models from three sub-categories: (a) reactive oxygen species (b) Ubiquitin proteasome pathway, chaperone-mediated autophagy and lysosomal clearance and (c) Dopamine metabolism models are summarized in this section.

Reactive Oxygen Species (ROS) Models

In 2009 a detailed brain energy metabolism model was proposed by Cloutier et al. [20] Glycolysis and mitochondrial energy metabolism in neurons and astrocytes were modelled and the predictions were compared with in vivo data from rat brains. The same authors in a later work updated their model by integrating the aging-related

effect and by adding time-dependent reduction in the mitochondrial complex 1 efficiency. Using metabolomics, energy-related metabolites data from brain slices in healthy and PARK2 knockout mice were used to train the model. The authors suggested that regardless of genetic mutation, the brain cells were able to robustly maintain control of ATP levels and the observed reduction of those may not be related with Parkinson's pathology [97, 140]. However, brain energy metabolism models have several limitation since they are lacking spatial details such as diffusion and locus synaptic activity effects, in regards to capillaries. Recent research has shown that implementation of such effects could influence the prediction and that averaging spatially detailed models with ODEs might be appropriate only under certain parametrizations [12, 13].

The aforementioned energy metabolism model was modified to account for feedback between ROS and misfolded Asyn, Asyn aggregation and minimal description of its proteolytic clearance. The final model consisted of 33 ODEs and demonstrated a bistable-switch-like behavior with respect to various factors like mutation, environmental toxins and aging. The lower and higher steady states were characterized by low and increased ROS and misfolded Asyn levels, representing the healthy and disease states, respectively [22]. To get insight into the bistability and bifurcation behavior, a reduced model with only as variables the ROS and misfolded Asyn levels was implemented and was able to reproduce the full scale model [21]. The bistable-switching behavior in short-time scale has been also supported by in vivo experiments in paraquat-induced oxidative stress in rat brains [39]. In simulations of the model by Raichur et al. bistability was present, even though the authors did not comment on it at that time [121].

Ubiquitin Proteasome Pathway, Chaperone- Mediated Autophagy, and Lysosomal Clearance

Models for the ubiquitin proteasome pathway and the negative feedback involved between misfolded Asyn and proteasomes have been recently presented. However, in these cases mainly stochastic simulations to qualitatively test hypotheses and/or experimental results have been used [89, 100, 101]. Recent work has also focused on lysosomes and autophagosomes, but this is not subject of this section [37, 96, 145].

In this section, we discuss in more detail a theoretical model involving feedback between proteolytic pathways and Asyn aggregation. In this model, a minimal description of Asyn aggregation and its interaction with proteasomes was described using three ODEs [121]. As function of the ratio between Asyn fibrils and free proteasomes, a bifurcation behavior was observed. It was predicted that homeostasis could be maintained at lower, but not at higher ratios, where free proteasome levels oscillated with prolonged periods of low concentration. Parkinson's pathogenesis was assumed to be associated with extended proteasome depletion leading to accumulation of Asyn oligomers [121]. The authors concluded that the model was able to predict Parkinson's pathogenesis, even without explicitly modeling the

proteasome inhibiting function of Asyn aggregates. In this case, similar to previously discussed ROS/NOS models, pathogenesis was predicted via systems undergoing bifurcation.

Dopamine (DA) Metabolism

Loss of functionality of dopaminergic neurons, which are involved in DA synthesis, storage, release and reuptake, causes DA depletion in brain. This results in increased DA cytoplasmic levels, which in turn lead to ROS generation and subsequently to Asyn misfolding. Using the biochemical systems theory (BST) formalism, Qi et al. developed a DA metabolism model to investigate the effects of key enzymes or transporters on DA homeostasis as well as the influence of rotenone and paraquat on DA metabolism [102–104]. Sass et al. [111] also adopted the BST approach with minimal kinetic information to understand the interplay between DA metabolism, Asyn and proteasomal/lysosomal athway. The authors showed that disruption of cellular pathways may result in Parkinson's disease.

Buchel et al. [9], using flux-balance analysis (FBA), in a model of the dopaminergic neuron, considered steady-state fluxes of several variables including DA, Asyn, ROS and proteasomal machinery. In a qualitative manner, it was shown that Parkinson's disease pathology can be associated with increased stressors levels (e.g. neurotoxins, Asyn). Tools from the nonlinear dynamical systems theory have been implemented in all the models discussed in this section. However, they all have several assumptions and limitations as well. The numerous variables and processes considered in BST and FBA models, given the limited kinetic information, has led the authors to use relative species concentrations and parametrization. In pathogenesis models the native Asyn concentrations used are of several orders of magnitude higher than the observed experimentally. This has a great impact for models exhibiting bifurcation or bistability, which are sensitive to native Asyn concentrations. In these models, recalibration of relevant parameter to reflect the physiological Asyn concentration range is mandatory. Furthermore, in models with bistability also other critical parameters may need to be revised. For example, whether the bistable behavior still remains at lower Asyn concentrations or not should be investigated. Quantitative comparisons of experimentally measured variables (such as misfolded Asyn) are necessary for calibration. Typically, the pathogenesis models only incorporate a single feedback system (e.g., ROS-Asyn feedback or Asyn-UPP feedback).

However, a dynamic model integrating multiple feedback loops to adequately capture the multifactorial nature of Parkinson's disease, provided that adequate parametrization is feasible, would be of interest. Such integrated models would not only provide further insight on the relative importance of various components involved in the pathogenesis, but they would also be helpful to compare effectiveness of different potential interventions and explore the synergistic value of combination therapies. System perturbation may be crucial to elucidate the link between disease biology and various aspects of the clinical manifestation. Last but not least, a multiscale model of Parkinson's, including molecular level and small timescale

changes to neuronal connectivity to evolution of clinical UPDRS scores, would require an approach that integrates diverse modeling formalisms such as a combination of differential equation-based molecular level, agent-based cell-level model and network-based neural connectivity models [2].

Secretion and Regulation of Hormones

Pulsatility is a widely appreciated characteristic of hormone secretion. Since the early 70's, Hellman et al. observed the episodical secretion of cortisol in man [50]. It was soon revealed that pulsatility is inherent to physiological processes. Indeed, the highly regulated hormone secretion through extensive feedback mechanism by the central and autonomous nervous system, the biological rhythms (e.g. circadian clock) and the complex between-hormones interactions are only some of the reasons for the pulsatile behavior and the chaotic nature governing the endo-, para- and autocrine systems. In this context, it has been evident that implementing tools from the dynamical systems theory in the study of hormonal systems is not only useful, but also fundamental to increase our understanding. This has been addressed so far bidirectionally; using experimental as well as modeling and simulation approaches.

Experimental studies have been focusing on the phase space reconstruction technique. In this approach, the concentration-time plasma profiles of various hormones have been utilized to evaluate the dimensionality and emerge the chaotic nature of the underlying systems' dynamics. Such examples include prolactin, cortisol, the parathyroid and the growth hormones [53, 90, 98]. In all these studies, the phase plane reconstruction produced attractors with fractal dimensions showing evidence for the presence of nonlinear dynamics. Based on the concept of Lyapunov exponents, Pincus developed the Approximate Entropy algorithm (ApEn) method to quantify the hormone pulsatility [95]. This method has been successfully applied to pulsatility quantification and its betwwen-groups differences identification (e.g diseased vs. healthy, young vs. elderly) of several hormones such as cortisol, prolactin, insulin, testosterone, the adrenocorticotropic (ACTH), the growth (GH) and the luteinizing (LH) hormones [14, 15, 26, 38, 41, 66, 68, 69, 120, 130, 133]. Therefore, experimental evidence of pulsatility origin and the chaotic nature underlying the dynamics of hormonal systems is abundant. This should serve as a guide to advance the experimental research and encourage physiologically- sound, mechanistical modeling, accounting for the dynamical aspects on a proper level.

That said, several mathematical models have been published in literature attempting to provide insight on the hormonal behaviour (secretion and regulation) and/or the effect of drugs on it. In 1980, Smith et al. [120] developed a model to qualitatively describe the interaction between LH-releasing hormone (LHRH), LH and testosterone. This model was then further elaborated by Cartwright and Husain [14] incorporating time-delayed terms and exhibiting limit cycle solutions.

Additional improvements have been implemented by Liu and Deng [68] as well as by Das et al. [26]. Specific examples include models of the hypothalamic-pituitary-adrenal (HPA) axis for the system of corticotropin-releasing hormone (CRH), ACTH and cortisol and the beta- cells mass system for insulin/glucose interplay [66, 130]. A dynamic, with chaotic behaviour, model for hormonal systems coupled by negative feedbacks has been also proposed by Londergan and Peacock-Lopez [69].

In pharmacokinetics/pharmacodynamics, often the physiological hormonal secretion is perturbed by the drug's effect either as primary target system of action or as side effect and as a result many studies have considered the hormonal secretion along with the dominant PK/PD aspects. In this section, some typical examples are summarized, whereas models involving thorough analysis of the underlying nonlinear dynamics for cortisol and prolactin are described in detail separately. Chakraborty et al. investigated the effect of corticosteroids on circadian cortisol levels, [15] while Fattinger et al. [38] studied the impact of a LHRH antagonist on testosterone and LH. Further examples include the dopaminomimetic, calcimimetic effect on prolactin and parathyroid hormone, respectively; as well as the ipamorelin-mediated effect on GH [41, 44, 63].

Of course, this is not an exhaustive list of modeling examples. However, these studies are mentioned, because of a common feature that they are sharing and this is not other than a minimum oversimplified implementation of hormone secretion, giving a smooth hormone baseline. In these cases, only the most obvious characteristics of hormone secretion, like circadian rhythms, have been integrated. The underlying physiological pulsatility, since it is considered as noise, it is practically ignored or phenomenologically implemented through spline terms or Fourier harmonics, [15, 41] but not through modeling of its dynamical origin. Last but not least, cases where the pulsatility can be omitted have been also identified. This refers to the effect of ipamorelin on GH, where the baseline of the hormone is wisely set to zero due to the multifold amplification of GH levels post drug-administration [44].

Melatonin

There is multiple evidence showing that melatonin participates in a number of physiological processes including the regulation of body's circadian rhythms, sleep, mood, immune response, aging, and cancer [8]. Melatonin is secreted by the pineal gland of the brain in response to the light/dark signals emanating from the retina and sympathetic nervous system. The synthesis of melatonin is stimulated by darkness and inhibited by light.

One of the most widely used model to mathematically describe the circadian secretion of melatonin in the body has been published by Brown et al. [7] In this model, two-dimensional linear differential equations were formulated in order to analyze plasma melatonin levels in 18 normal healthy male subjects during a

constant routine. The model includes two physiological compartments, namely pineal gland and plasma. Melatonin secretion to the pineal gland compartment was modelled through a step-wise function simulating pineal N-acetyltransferase (NAT) rise as a combination of two exponential processes with different time constants and plateau levels. Melatonin levels are then moved to the plasma compartment through a first order infusion and cleared from the plasma by a certain clearance rate. The model was successfully applied to describe melatonin physiological data and provided overall a more physiologically plausible estimate of the melatonin synthesis onset time. This model was further extended in a number of works in order to describe phase shifts observed upon exogenous melatonin administration [5, 122].

Depending on data availability and the question of interest, melatonin secretion and forward effects were simulated through various models. Sekula et al. [116] followed a statistical approach and fitted a linear beta-model to either healthy (control) or major depressive individuals shading light to probable differences on their onset, peak and offset times of melatonin secretion. In another study, Schwartz et al. [115] by using a simple model of two oscillators were able to represent melatonin secretion pattern and further predict amplitude changes in melatonin release under forced desynchronization. Finally, Scheff et al. modelled melatonin circadian secretion through a step-wise function by further considering its anti-inflammatory effects, which was ultimately included in a systems model of immune response [112, 113].

Cortisol

Over the last decades, as previously discussed, nonlinear dynamics have proved that deterministic systems even with few degrees of freedom can exhibit complex-random behaviors. Although only classical randomness is often involved in PK/PD, it has been shown variability can originate from the chaotic nature of the underlying dynamics. As indicated by numerous studies, hormone secretion is of chaotic nature and characterized by pulsatility [14, 26, 30, 68, 69, 90, 98, 120, 129, 130, 133].

In 2002, Dokoumetzidis et al. [30] described the erratic secretion of cortisol and its suppression by corticosteroids from a dynamical systems' perspective using a simple model. The model was relied on well-established concepts of hormonal erratic secretion and circadian rhythm [60]. Other factors controlling cortisol secretion have also been considered, but not explicitly modelled (e.g. negative feedback loops). The concentration of cortisol was described by a nonlinear time-delay differential equation with two terms, [48, 72, 84] particularly a first order term for disposition and elimination and a secretion rate term which adheres to the negative feedback mechanism and drives the pulsatile secretion as follows (Eq. 2):

$$\frac{dC}{dt} = k_1 \cdot \frac{a^n \cdot C_d}{a^n + C_d^n} - k_2 \cdot C \tag{2}$$

where C is the cortisol concentration, C_d is the value of C at time t-T, n is an exponent, k1 and k2 are the input and output rate constants, respectively. Phenomenological implementation of the circadian rhythm is achieved by the parameter alpha, which is a simple cosine function of a 24-h period, given by the following equation (Eq. 3):

$$a = A \cdot \cos\left[(t - f) \cdot \frac{2 \cdot \pi}{1440}\right] + B \tag{3}$$

where A and B are constants with concentration units, f is a constant with time units and t is time in min. A similar periodic function have been used by Rohatagi et al. [106] to describe the secretion rate of cortisol.

The time-delay equation (Eq. 2) has physical meaning because it is associated with cortisol auto-regulation and negative feedback loops and thus its own secretion. Since Eq. 2 has an infinite number of degrees of freedom, the authors constructed a pseudo-phase space for the system of Eqs. 2 and 3 using the model variables C(t), C (t-T/2), C(t-T) (Fig. 3) [4]. The attractor of the system was a strange attractor, shwoing that it had quite complex geometry. The use of three dimensions is also supported by the embedding dimension found by Ilias et al. [53]

The authors advocated that the extremely high variability often observed in experimental data (e.g. cortisol plasma concentration profiles) originates from

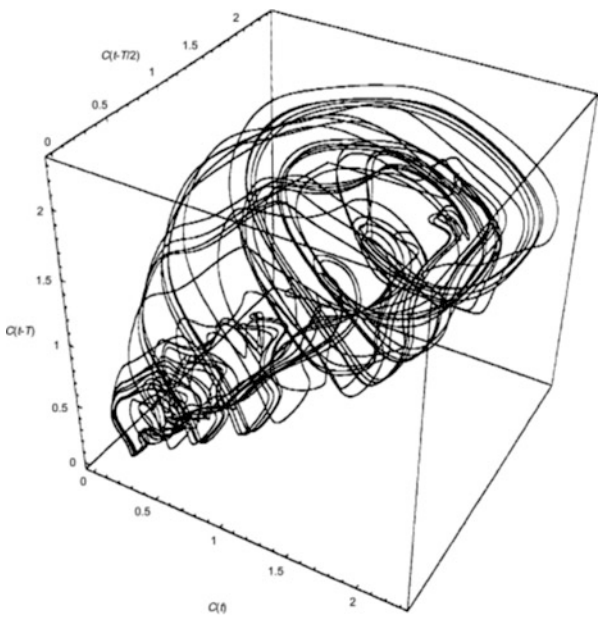

Fig. 3 A pseudo-phase space for the model of Eqs. 2 and 3 using the variables C(t), C(t-T/2) and C(t-T) expressed in mg 100 ml-1. The real phase space is of infinite dimension, however, trajectories may be considered to lie in a low dimensional space (attractor). The model parameters take the same values as in Fig. 1 and time runs for 10 days. (Reproduced from Ref. 30)

chaotic dynamics and not from pure randomness and therefore measures of central tendency should be questioned in these case and averaging might not be appropriate. Due to the erratic nature of the secretion, they suggested that an instantaneous, instead of average, secretion rate should be reported. It was also shown that the final simulated profiles with this model differed remarkably depending on the initial conditions and the sampling design.

Furthermore, the initial model was extended to allow for perturbation of the system due to external oral administration of corticosteroids. The pharmacokinetics of the external corticosteroids were assumed to be as simple as one-compartment disposition with first-order absorption, coupled with an effect compartment. Then, the effect-site concentration (C_e) was linked to the initial model so that it suppresses cortisol secretion (Eq. 4):

$$a' = a \cdot \left(1 - \frac{C_e}{C_{e50} + C_e}\right) \tag{4}$$

where C_{e50} is a coefficient that expresses the concentration of the drug when $\alpha' = \alpha/2$.

The final extended model was able to adequately capture the experimental cortisol plasma concentration profiles, generated after exogenous administration of fluticasone propionate, published by Chakraborty et al. [15] Based on the aforementioned discussion, the authors concluded that their analysis under the light of nonlinear dynamics provides mechanistical insight on cortisol secretion and that this approach should be more widely applied in PK/PD modeling, when supported by experimental and physiological evidence. They also highlighted that nonlinear dynamics construes a fundamentally new rational in PK/PD and that the clinical pharmacologists should be aware of the limitations of chaotic models for long-term predictions.

Interestingly, in recent studies Pilai et al. [93, 94] combined adaptive chaos synchronization and grid search to estimate physiological and pharmacological systems' parameters by exploring deterministic methods that are more appropriate and potentially perform better than classical numerical approaches (e.g. minimization of sum of squares, likelihood maximization). To illustrate these issues, they used the previously described cortisol model. They showed that chaos synchronization could help to avoid ending up in local minima, which is often observed with the gradient-based optimization algorithms. The hybrid adaptive chaos synchronization could be applied iteratively and was able to accurately estimate nonlinear parameters and track trajectories for a wide class of noisy chaotic systems. The authors concluded that their method could effectively estimate the parameters of the cortisol chaotic system and that its robustness against noise and data sampling rate effect may be of benefit for modeling nonlinear dynamical physiological systems.

Prolactin

Prolactin (PRL) is a polypeptide hormone with a primary role in the regulation of lactation in humans. It is predominantly secreted by specialized cells in the anterior pituitary gland, the lactotrophs [18]. In PK/PD, the response of prolactin to antipsychotic drugs has been studied by the classic precursor-pool model. Precursor-pool models have been used several times in the past to explain the tolerance and rebound effects induced by drug response [34, 49, 83, 118]. These are precursor-dependent indirect response models, which assume that the tolerance (or rebound) is the result of depletion (or accumulation) of finite pools of precursors that are responsible for the drug effect. The pool model has been applied to the PRL response after administration of antipsychotic drugs with the aim to explain the tolerance developed after repeated drug administration at narrowly spaced intervals. The original pool model by Movin-Osswald & Hammarlund-Udenaes was modified to account for the effect of remoxipride in rats [83]. By including a positive feedback (PF) component, Stevens et al. [127]. extended the already modified model, which had become nonlinear. Simulations, after using the model to investigate the effect of risperidone, predicted two separate baselines depending on dose. However, since no mathematical analysis of the underlying dynamics had been performed, such findings relied only on serendipitous discovery through simulations.

Recently, Bakshi et al. [3], using both the original and modified precursor-pool models for PRL, analyzed the systems' dynamics mathematically in an informative tutorial. The classic precursor-pool model consists only of two linear turnover equations in the dependent variables, and thus it has a unique steady state. However, the PF model it was shown that undergoes trans-critical bifurcation, meaning that the system changes from stable to unstable steady state or vice versa. The convergence to different steady states was also dose-dependent.

Through steady-state and phase-plane analysis they demonstrated that the nonlinearity of the model has resulted in multistationarity and that the higher of the two steady-states remains always stable In contrast, the lower one is stable only from below. In addition, under a parametric condition the desired steady state has been observed to be the higher and thus, always stable. However, in the parametrization by Stevens et al. the desired steady state is the lower one, which is unstable and reachable only from below. Simulations and plotting of the orbits in the phase plane illustrated that the parametric condition leading to the higher steady state is activated only by some orbits and this is the reason why the model exhibited convergence to two discrete steady states in response to different doses. Activation of the "if" condition depends not only on the relative timescale of drug clearance and the PRL endogenous elimination and secretion rate, but also on the accuracy of the numerical solver. Nevertheless, the authors concluded that even if the numerically solver was perfectly accurate, this irregular behavior would persist as structural property of the model.

Overall, the authors summarized the basic steps in dynamical systems analysis of ODE-based models, with the phase plane analysis being of particular interest for 2-ODE models allowing for comprehensive analysis of the underlying dynamics.

Immune System & Inflammatory Response

Immune response has triggered significant interest in systems-based approaches to understand the involved complexities and the individual interactions of a response [134]. In particular, systems modeling was applied to quantitatively evaluate not only the onset but also the resolution of the inflammatory response.

Modeling efforts on immune response vary from statistical and correlational to mechanism-based, deterministic and stochastic [19, 40, 79, 86, 113]. Clearly, inflammatory response encompasses a high level of interconnections through multiple levels of physiological organization and control. Chow et al. [17] investigated the acute inflammatory response in diverse shock states by implementing a highly detailed realization that incorporates individual cytokines, different types of immune cells, and other key physiological parameters. This model showed that different inflammatory outcomes can result from the same model with different initial states indicating that diverse inflammatory shock states share the same underlying mechanisms, even when cytokine-concentration data may be heterogeneous. The level of detail and complexity of such models can increase until eventually reaching the level of description of the host response [27, 88, 99, 131]. Similar, using high-throughput microarray mRNA measurements from peripheral blood cells, it was possible to develop semi-mechanistic models by linking the ligand (lipopolysaccharide, LPS) recognition by appropriate (TLR4) receptors to activation of inflammation-specific signaling cascades (NF-kB) which drive the peripheral release of pro- and anti-inflammatory cytokines [40, 87]. In a subsequent work it was demonstrated that an extended model with adeqaute signaling cascades was able to describe the complex phenomenon of endotoxin tolerance [144]. The inflammatory response induces the involvement of the neuroendocrine system, which modulates the release of anti-inflammatory hormones and neurotransmitters. As such, cortisol and epinephrine lead to anti-inflammatory downstream effects, cortisol through glucocorticoid receptor-mediated signaling and epinephrine through the stimulation of adrenergic receptors, leading to elevated intracellular cAMP concentrations. Leveraging established models of hormone activity to account for the effects of cortisol and epinephrine, allowed for investigation of cellular-level transcriptional responses to inflammation. The mechanisms through which hormone levels influence whether the system exhibits a healthy self-limited inflammatory response or a persistent chronic inflammatory state were also explored.

Circadian rhythms are of importance in the context of the inflammatory response since they impose patterns on a wide range of inflammatory mediators [23]. Meyer-Herman et al. [80] developed a mathematical model to evaluate the neuroendocrine-immune system interactions in rheumatoid arthritis. This model describes mainly the

measured circadian responses of plasma levels of TNF, noradrenaline, and cortisol, making use of a set of ordinary differential equations. Based on their model, it was observed that treatment with glucocorticoids between 00: 00 and 02: 00 a.m. induced the strongest inhibitory effect on TNF secretion. In chronic inflammatory diseases, such as rheumatoid arthritis, where patients overexpressing inflammatory agents, significant reduction in pro-inflammatory mediators like the TNF is often a clinical target. Similarly, Scheff et al. [112] incorporated a multilevel mathematical modeling scope based on which they evaluated the interplay between inflammation and circadian rhythms. This model predicted that LPS administration during the night induces larger increase in inflammatory mediators and larger reduction in the heart rate variability (HRV) relative to administration in the morning. Finally, semi-mechanistic models were further explored to rationalize the potentially permissive-suppressive inflammatory effects of cortisol as manifestations of the balance between pro- and anti-inflammatory characteristics induced by circadian rhythms [75, 76, 78].

Conclusions & Future Directions

In this chapter, the presence of nonlinear dynamics and the chaotic nature of physiological systems is highlighted. Dynamical aspects in the analysis of the behaviour of PK/PD and QSP models are summarized with the aim to showcase the urge to implement toolz of nonlinear dynamics in it. Particularly, we have focused on dynamical aspects of: (a) the cardiovascular and (b) the central nervous, (c) the hormone secretion and regulation and (d) anti-inflammatory response, for which some case examples are analysed. At the same time, there are several other therapeutic areas where dynamic systems theory has been successfully applied and therefore this chapter should not be considered as an exhaustive literature review of all possible applications of nonlinear dynamics in PK/PD or QSP models. However, the reader is referred to Eftimie et al. [32] for a comprehensive review of mathematical models in immunology and to the book by Macheras and Iliadis [71] for a detailed explanation of fractal phenomena in biopharmaceutics, pharmacokinetics and pharmacodynamics.

From the above presentation, it is evident that significant progress has been made towards mechanism- and physiologically-based modeling. On the other hand, physiological systems are inherently nonlinear and chaotic. The chaotic behavior is often considered to be feature of healthy state, whereas periodic or non-chaotic states are associated with disease and pathological symptoms which can be attributed to a sudden qualitative change in the temporal pattern (e.g. bifurcation) [28]. This change can either be caused by endogenous factors or an external stimulus (e.g. drug administration) that alters one or more critical control parameters. In this context, integration of nonlinear dynamics might be also useful in the field of disease progression by introducing a new rationale for therapeutic strategies, which rather aims at restoring and maintaining the homeostasis than

eliminiating the symptoms. This general concept has been introduced by Mackey and Milton [72, 81] and it is known as dynamic disease.

The notions of sensitivity from the initial conditions and the qualitatively different behavior for, even slightly, altered values of the control parameters, have a major impact and should be taken into account in modeling activities, especially when also experimentally supported. Advanced computational methods play a key role in simulating complex models, but usually offer only a limited picture of model behaviors, especially when the dynamics are rich in nonlinearities and counterintuitive behaviors. Such behaviors can be very difficult, if not impossible, to be revealed solely through simulations. It is noteworthy that even the simplest 2-ODE models can exhibit unpredictable behaviors and addition of one ODE explodes the range of possible behaviors, including chaotic ones. Systems pharmacology models are expected to be larger and even more complex and their dynamical behaviors are likely to hide an even greater degree of complexity.

In pharmacology, the dynamics of the underlying system is often only partially understood and models are a blend of biological, mechanical, physiological and pharmacological information accompanied by experimentally data. This might raise questions about the validity itself, the applicability, the parametrization, the granularity and the potential extrapolations of such models. Nowadays, many large biological, physiological, pharmacological or combination of those systems networks are formed from modules or motifs of smaller networks. Thorough understanding of the behavior of all the individual components is not only crucial, but also imperative, to increase confidence on their value, usefulness and performance. This also underlines the importance of using mathematical analysis to gain insight into model behavior.

In summary, mathematical techniques of dynamical systems' analysis allow for exploration of multistationarity, with the possibility of rejecting a priori models that are structurally unstable, and better understanding of the overall model behavior. Furthermore, such analysis can inform and guide experimentally testable hypotheses for verification/falsification of a model. At the same time, other mathematical techniques, such as quasi-steady state analysis and model reduction may be useful to reduce the model size and complement the dynamical systems' analysis.

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