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Neuronal network modelling of the effects of anaesthetic agents on somatosensory pathways

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Abstract. The whole question of consciousness, awareness and depth of anaesthesia is both timely, little understood and deeply challenging. Models of the underlying neural pathway mechanisms/dynamics are necessary for understanding the interactions involved and their structure and function. A neuronal network of the somatosensory pathways is proposed in this paper based on experimental information and physiological investigation into anaesthesia. Existing mathematical neuronal models from the literature have been modified and then employed to describe the dynamics of the proposed pathway network. Effects of anaesthetic agents on the cortex were simulated in the model which describes the evoked cortical responses. By comparison with responses from anaesthetised rats, the model's responses are able to describe the dynamics of typical responses. Thus, the proposed model promises to be valuable for investigating the mechanisms of anaesthesia on the cortex and the effects of brain lesions.

1 Introduction

The aim of anaesthesia is to temporarily and reversibly disrupt the function of the central nervous system in order to render the patient unconscious, to block all sensory appreciation during surgery and produce a temporary amnesia (Angel 1991). All of the approaches to monitoring the state of anaesthesia attempt to "open a window" on the anaesthetised brain using electrophysiological signals such as electroencephalograms (EEG), heart-rate variability and evoked potentials (Angel 1991; Pomfrett 1999; Bischoff et al. 2000). If anaesthesia is inadequate and the patient actually experiences the pain of surgery, this is followed by nightmare symptoms leading to psychological trauma (Hanning and Aitkenhead 1994). The somatosensory cortex, from which somatosensory evoked potentials (SEPs) can be elicited, performs the role of interpreting external somatic stimuli and is actively involved in pain processing in the humans (Angel 1993b; Kanda et al. 2000).

The literature discusses extensively the structure and functioning of the somatosensory cortex and its role in anaesthesia processing (Angel 1977, 1993a; Knight et al. 1999; Treede et al. 1999; Kaas and Collins 2001). However, mathematical modelling of the somatosensory pathway from an engineering aspect and hence for technological applications has been explored less. This unbalanced development means that the study of monitoring and control of anaesthesia relies mainly on trials on human patients. Hence, from the point of view of engineering, it is worth developing mathematical models for the somatosensory pathway to unveil the mechanisms of anaesthesia in the brain.

The concept of neural network modelling for describing nerve cells and the nervous system was proposed by McCulloch and Pitts (1943). Application of this concept did not expand until the 1990s, when it began to be widely employed in many aspects of engineering. Though it was originally proposed for consideration of biological neurons, it is much more common in engineering applications than in biological studies. A few applications of artificial neural networks (ANNs) can be found in biological modelling for systems such as the visual cortex (Jansen and Rit 1995; Dow and Anastasio 1998), the olfactory system (Freeman 1987) and holistic networks (Ermentrout 1998).

Motivated by the success of ANN in engineering, the objective of this study was to develop a model of the somatosensory pathway based on anaesthesia experimental exploration, with the concept of ANN being employed to construct a neuronal network model. The model uses both a spatial distributed modelling approach (Lopes da Silva et al. 1974) and lumped-parameter modelling (van Rotterdam et al. 1982) together with existing physiological information from studies relating to the somatosensory nervous system,

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especially in anaesthesia. The model forms an integral part of the nervous structures being studied to elucidate the effect of anaesthetic agents on patient awareness (Angel 1993b, 2002).

2 Somatosensory neuronal pathway

The EEG alpha-rhythm activity can be modelled by combining the thalamus and cortex as a single thalamocortical relay cell with an inhibitory interneuron feedback (Lopes da Silva et al. 1974). This is a spatially distributed model, since the distribution of neurons in a specific area is considered. Lumped parameters which treat physiological properties as several single parameters have been adopted in the model developed in this paper. This technique has also been applied to model the visual nervous system (Jansen and Rit 1995). This methodology is suitable because of the lack of sufficiently detailed physiological knowledge and a high degree of redundancy in the cortex.

The microstructures of the cortical connections can be determined by analysing the post-stimulus cellular activity (Gerstein and Perkel 1972) and evoked cortical cellular responses recorded from the cortex with microelectrodes (Angel 1977). Figure 1 illustrates the proposed network model of the somatosensory pathway in the brain based on physiological investigation and experimental information (Angel 1993a,b). In this model each cell at its respective cortical layer is treated as an independent module but networked via interneurons or collateral direct connections. The number of either excitatory or inhibitory synapses per neuron is represented using a connectivity coefficient (Wilson and Cowan 1972) which can be partially derived from histological literature (White 1989; Jansen and Rit 1995). The source of the evoked response is not a single neuron but is the nearby synchronous response of a large population of cortical cells to a specific afferent input (Angel 1977). For simplicity, in this paper each neuronal module represents a population of cells in a specific region, identified in the figure legend.

Pyramidal cells represent the most abundant and characteristic neuronal type in the cerebral cortex (Thomson and Deuchars 1994). Thus, the cortical cells and interneurons represented in Fig. 1 are considered as pyramidal cells. All cortical cells are assumed to have identical physiological properties because of the lack of sufficiently detailed physiological knowledge (Lopes da Silva et al. 1974; Tsodyks et al. 1998). Interneurons connecting different cortical cells are believed to have physiological properties different from those of the cortical cells (Jansen and Rit 1995), and are represented in the proposed model. Many sensory cells show spontaneous activity in the absence of external inputs (Angel 1993a). Thus, it is reasonable to assume that every cortical cell in the network receives spontaneous activity from its surrounding cells.

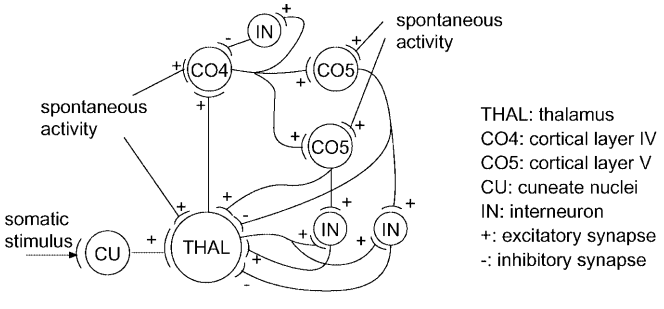

Fig. 1. Proposed network model of the somatosensory pathways

Somatic stimuli from a sensory receptor are transmitted along the axonal pathway ascending through the cuneate nuclei to the thalamus. The sensory inputs further ascend to layer IV and then layer V of the cortex (primary somatosensory area). The real contribution of one of the neurons of cortex layer V is not well understood. The presence of inhibitory inputs as well as excitatory inputs affects the network properties considerably. An inhibitory connection works as a negative feedback to a cortical cell and introduces stability into the network. Physiologically, the signals emanating from each neuron project to the scalp and can be picked up on the human scalp with suitable electrodes (Dawson 1947). In simulation, we are able to monitor membrane potentials of a specific cortical cell.

3 Modelling the neuron cells

3.1 Background

In physiology, the nervous system is a network of single neurons interconnected by interneurons and collateral direct connections. The neurons by themselves are not very powerful in terms of information processing or representation, but their interconnection enables a neuronal network to process complex tasks (Freeman 1987). A neuron can be seen as the construction of synapses, cell body and axon hillock based on the concept of lumped modelling (van Rotterdam et al. 1982). The synapses convert incoming signals into membrane potentials. Fluctuations in membrane potentials, either temporally or spatially distributed, are integrated by the cell body. The integration is then transcribed to nerve impulses at the axon hillock if the integrated membrane potential reaches a threshold potential. Finally, the nerve impulses are transmitted through the axons. Figure 2 illustrates the physiological and mathematical models of a neuron describing its structure and manipulations.

3.2 Neuronal components

3.2.1 Synaptic transmission. The selection of synaptic dynamics is an important factor in generating different states of cortical activity as reflected by EEG recordings (Tsodyks et al. 1998). Physiological experiments show that the excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs) have impulse responses as

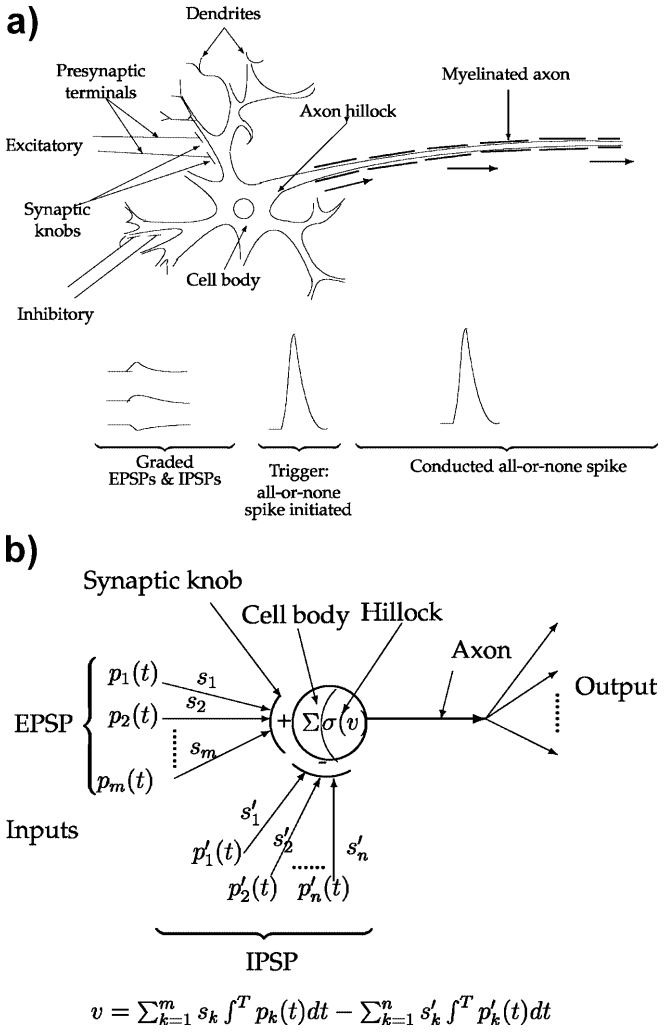

Fig. 2a,b. Physiological (**a**) and mathematical (**b**) models of a neuron. *EPSP*, excitatory post-synaptic potential; *IPSP*, inhibitory post-synaptic potential

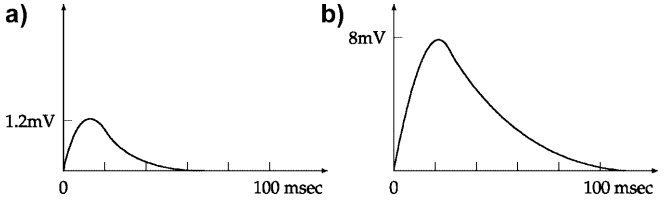

Fig. 3a,b. EPSP (**a**) and IPSP (**b**) impulse responses

shown in Fig. 3 and can be mathematically described as follows (van Rotterdam et al. 1982):

$$h_e(t) = \begin{cases} Aate^{-at}, & t \geq 0 \\ 0, & t < 0 \end{cases} \quad (1)$$

$$h_i(t) = \begin{cases} Bbte^{-bt}, & t \geq 0 \\ 0, & t < 0 \end{cases} \quad (2)$$

where $A = 3.25\,\text{mV}, B = 22\,\text{mV}, a = 100\,\text{s}^{-1}$ and $b = 50\,\text{s}^{-1}$, which are the parameters values used by van Rotterdam et al. (1982) in their work on EEG alpha-rhythm modelling. A and B represent the amplitude gains of the post-synaptic-potential functions, and a and b are interpreted as being the lumped transmission lags and all other spatially distributed delays, including temporal dispersion in the afferent tract, synaptic diffusion and resistive–capacitive delay in the dendritic network.

3.2.2 Interneuron. The interneuron has its own transfer function:

$$h_d(t) = \begin{cases} Aa_d te^{-a_d t}, & t \geq 0 \\ 0, & t < 0 \end{cases} \quad (3)$$

where $a_d \approx a/3$ as used by Jansen and Rit (1995) in visual cortex modelling means that the interneuron has a transmission lag that is 3 times longer than that of the cortical cells.

3.2.3 Axon hillock. The axon hillock model has the transfer function introduced by Freeman (1987) in olfactory system modelling:

$$\sigma(v) = \frac{2e_0}{1 + e^{\gamma(v_0 - v)}} \quad (4)$$

where $\gamma = 0.56\,\text{mV}^{-1}, e_0 = 2.5\,\text{Hz}$ and $v_0 = 6\,\text{mV}$, which are the parameter values used by Jansen and Rit (1995). Because of the lack of sufficient physiological information, both cortical cells and interneurons are assumed to have the same hillock model. This approach is used by Jansen and Rit (1995) in modelling the visual nervous pathway. Figure 4 shows the conversion curve of the hillock transfer function with parameter values as above.

4 Mathematical model of the somatosensory pathway

4.1 State-space representation

A mathematical representation of the physiological pathway of Fig. 1 is obtained by applying the linear synaptic transfer functions and the nonlinear hillock activation function to each cell in the pathway. Figure 5 shows the resultant block diagram of the mathematic model. Since the pathways with cells of cortical layer V are not well understood, both of these cells are modelled

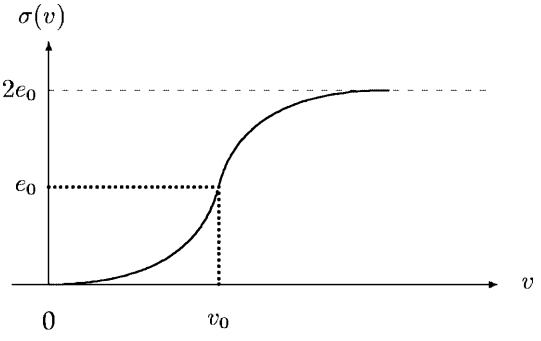

Fig. 4. Conversion curve of the hillock transfer function

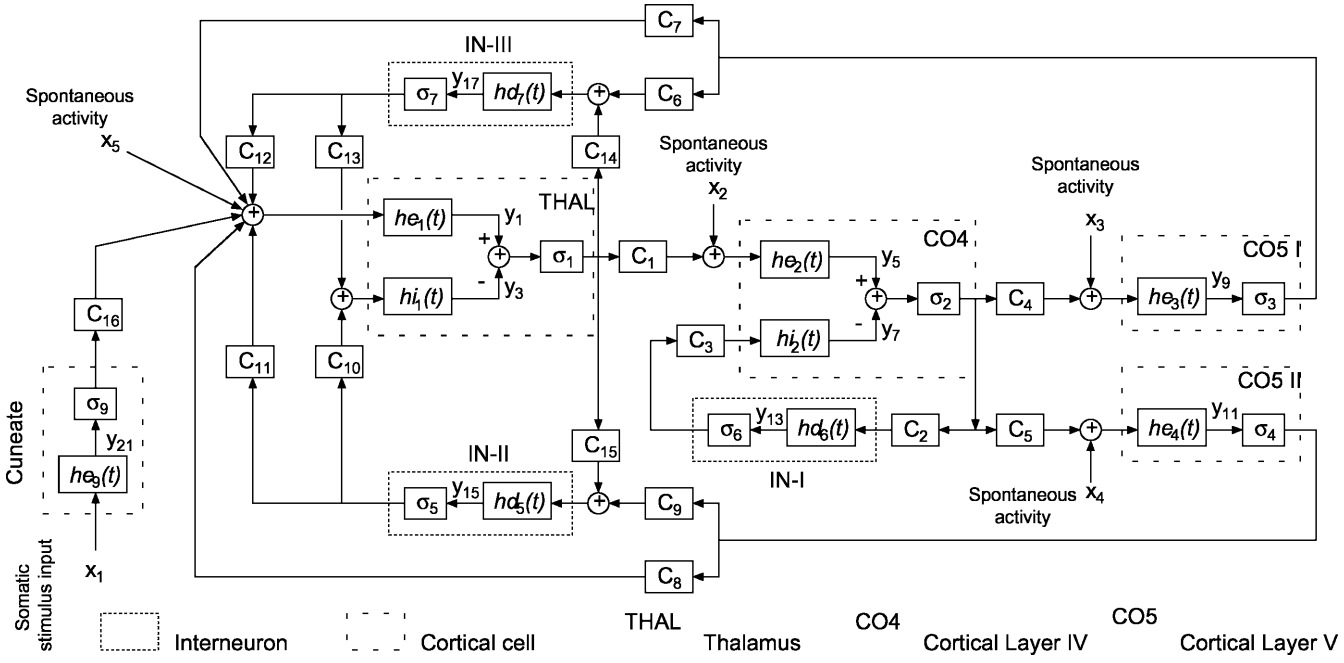

Fig. 5. Detailed block diagram of the proposed model for the somatosensory pathways of Fig. 1

with the same structure but with different connectivity coefficients accounting for their individual contributions to the model. Constants C_x represent the connectivity coefficients which account for the average number of synaptic contacts between the correlating cells (Wilson and Cowan 1972). The synaptic transmission can be described with signal convolution as

$$y(t) = h_e(t) \star u(t) \tag{5}$$

This is a linear system and can be decomposed into first-order ordinary differential equations (ODEs) ready for numerical integration. After some manipulations of forward and inverse Laplace transforms, we obtain the state-space representation for the synaptic transmission:

$$\dot{y}(t) = z(t) \tag{6}$$

$$\dot{z}(t) = Aau(t) - 2az(t) - a^2 y(t) \tag{7}$$

where $y(t)$ is the output, $z(t)$ is an internal state variable and $u(t)$ is xxx the incoming signal. Similarly, we can derive ODEs in this form for the IPSP and interneural transfer functions.

Applying the reduced-order ODEs to the block diagram we obtain the following state-space representation to describe the proposed pathway model:

For the thalamus

$$\begin{aligned} \dot{y}_1 &= y_2 \\ \dot{y}_2 &= A_1 a_1 \{x_5 + C_{16}\sigma(y_{21}) + C_{12}\sigma(y_{17}) + C_7\sigma(y_9) \\ &\quad + C_8\sigma(y_{11}) + C_{11}\sigma(y_{15})\} - 2a_1 y_2 - a_1^2 y_1 \end{aligned} \tag{8}$$

$$\begin{aligned} \dot{y}_3 &= y_4 \\ \dot{y}_4 &= B_1 b_1 \{C_{13}\sigma(y_{17}) + C_{10}\sigma(y_{15})\} - 2b_1 y_4 - b_1^2 y_3 \end{aligned} \tag{9}$$

For cortical layer IV

$$\begin{aligned} \dot{y}_5 &= y_6 \\ \dot{y}_6 &= A_2 a_2 \{x_2 + C_1\sigma(y_1 - y_3)\} - 2a_2 y_6 - a_2^2 y_5 \end{aligned} \tag{10}$$

$$\begin{aligned} \dot{y}_7 &= y_8 \\ \dot{y}_8 &= B_2 b_2 \{C_3\sigma(y_{13})\} - 2b_2 y_8 - b_2^2 y_7 \end{aligned} \tag{11}$$

For cortical layer V, cell I

$$\begin{aligned} \dot{y}_9 &= y_{10} \\ \dot{y}_{10} &= A_3 a_3 \{x_3 + C_4\sigma(y_5 - y_7)\} - 2a_3 y_{10} - a_3^2 y_9 \end{aligned} \tag{12}$$

For cortical layer V, cell II

$$\begin{aligned} \dot{y}_{11} &= y_{12} \\ \dot{y}_{12} &= A_4 a_4 \{x_4 + C_5\sigma(y_5 - y_7)\} - 2a_4 y_{12} - a_4^2 y_{11} \end{aligned} \tag{13}$$

For interneuron I

$$\begin{aligned} \dot{y}_{13} &= y_{14} \\ \dot{y}_{14} &= A_6 a_6 \{C_2\sigma(y_5 - y_7)\} - 2a_6 y_{14} - a_6^2 y_{13} \end{aligned} \tag{14}$$

For interneuron II

$$\begin{aligned} \dot{y}_{15} &= y_{16} \\ \dot{y}_{16} &= A_5 a_5 \{C_9\sigma(y_{11}) + C_{15}\sigma(y_1 - y_3)\} \\ &\quad - 2a_5 y_{16} - a_5^2 y_{15} \end{aligned} \tag{15}$$

For interneuron III

$$\begin{aligned} \dot{y}_{17} &= y_{18} \\ \dot{y}_{18} &= A_7 a_7 \{C_6\sigma(y_9) + C_{14}\sigma(y_1 - y_3)\} \\ &\quad - 2a_7 y_{18} - a_7^2 y_{17} \end{aligned} \tag{16}$$

For the cuneate nuclei

$$\dot{y}_{21} = y_{22}$$
$$\dot{y}_{22} = A_9 a_9 x_1 - 2a_9 y_{22} - a_9^2 y_{21} \quad (17)$$

The model equations can be solved using numerical techniques. Responses recorded on the scalp correspond to the integrated current generated by the membrane potential fluctuations of the cortical cells. Hence, the model validation signals are obtained by collecting results $y_5 - y_7$ (SEPs) for the output of the primary somatosensory cortex cells in layer IV.

4.2 Selection of connectivity coefficients

The main difficulty encountered in dealing with the model parameters is the selection of the connectivity coefficients – sixteen coefficients are used in the model. It is hard to accurately identify such a large number of parameters because of either the nonexistence or the variability of physiological data. Therefore, parameters used here are mainly obtained from previous work and modifications from simulations.

The connectivity coefficient is defined as the average number of synaptic contacts of a neuron, so determination of the coefficients is based on counting the number of the synaptic contacts on a neuron. White (1989) reported a series of histological experiments on the synaptic organisation of the cerebral cortex. However, experimental results presented by White (1989) and other researchers are still far from the goal of identifying accurately the number of synaptic contacts. Hence, Lopes da Silva et al. (1974) treated the coefficients as ratios of synaptic connections between neurons. Jansen and Rit (1995) derived a set of ratios of the connectivity coefficients between thalamocortical neurons and interneurons based on histology-literature surveys for mimicking visual evoked potentials. They derived a set of realistic values based on existing histological data. Two sets of parameter values resulted from these studies. Thus, a compromise of ratios was chosen and the final numerical values were mostly dependent on simulation results. The aim of their parameter choice was to make the system oscillate stably and retain alpha-rhythm-like characteristics. The histological information adopted for their derivation relied more on studies of the somatomotor cortex than of the visual cortex; therefore, their derived coefficients are adopted with slight modifications in this paper. The selection of the connectivity coefficients significantly affects the system stability and responses (Zetterberg et al. 1978).

Based on the research by Jansen and Rit (1995) and our current simulation studies, we adopted the following connectivity coefficients: $C_1 = C, C_2 = 0.25C, C_3 = 0.1C, C_4 = C, C_5 = C, \quad C_6 = C, C_7 = C, C_8 = 0.25C, C_9 = C, C_{10} = 0.1C, C_{11} = 0.8C, C_{12} = 0.1C, C_{13} = 0.1C, C_{14} = C, C_{16} = C$ and $C_{16} = C$, where C is the base constant to be decided by trial and error. $C = 135$, which gave the best simulation results in the study of Jansen and Rit (1995), is also used in this work. Since large changes of the connectivity coefficients can make the system unstable, the above selection was maintained constant throughout all simulations. This is physiologically reasonable since the number of synaptic contacts should be a constant under normal conditions (Thomson and Deuchers 1994).

5 Simulation method and results

5.1 Basic activity

The system was implemented in GNU C++ on Linux workstations. The ODE equations were solved using the fourth-order Runge–Kutta–Fehlberg (RKF4) method with a fixed step length. A sweep is envisaged to consist of 500 samples at a sampling rate of 500 Hz. The sampling period in the RKF4 integration is divided into 50 steps for a better resolution. Fifty raw responses are averaged to give an evoked-potential response, this being the so-called *ensemble averaging* (Dawson 1947; Aunon et al. 1981). The responses representing the post-synaptic membrane potentials occur at the respective neuron.

Cellular discharge (spontaneous activity) in the central nervous system is never stable (Angel 1977), since firing behaves in a stochastic manner. Thus, interpreting the number of nerve impulses per second is influenced by the measurement technique. Rating the average of the instantaneous frequencies arrives at a higher value than rating the average frequency (Angel 1991). The spontaneous activities of each pyramidal cell are random numbers with a uniform distribution between 120 and 320 pulses/s, as suggested by Jansen and Rit (1995) and from an aggregate of their simulation results. This is reasonable as a basis for the average of instantaneous-frequency measurements. Based on the nominal model parameters, five typical runs of stimulus-free responses are illustrated in Fig. 6. The effect of many anaesthetic agents is to change the evoked cortical responses which corresponds to a change in the responses of cells at the cortical level (Angel 1993a). Hence, SEP responses are obtained from the signal of $y_5 - y_7$ which models the post-synaptic membrane potential of cortical layer IV (see Fig. 5).

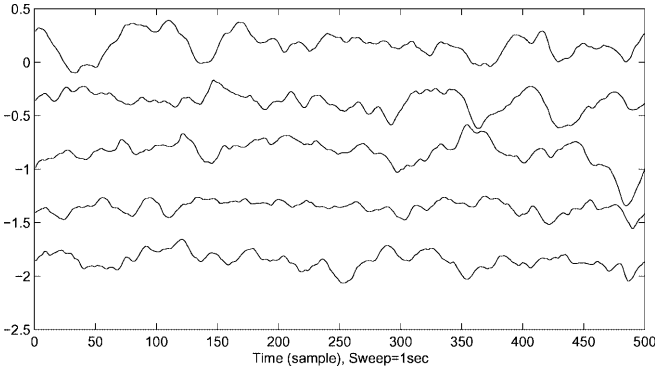

Fig. 6. Stimulus-free responses from cortical layer IV

A monotonic function (Fig. 7) was used to mimic the somatic stimulus (Jansen and Rit 1995):

$$u(t) = q \cdot \left(\frac{t}{w}\right)^n \cdot \mathrm{e}^{-t/w} \tag{18}$$

where $n = 7, w = 0.005$ and $q = 0.5$. Stimuli generated using the above function were applied to the cortical model at the 50th sample time of each sweep.

The selection of the frequency of the spontaneous activities for each pyramidal cell affects the oscillatory characteristics of the model network significantly. Figure 8 shows the results of varying the range of the spontaneous activities from (180, 480) to (4, 10). Other model parameters used in the simulation had their nominal values unchanged. The spontaneous frequency range of (120, 320) gives the most realistic oscillatory response. Responses with spontaneous frequency ranges below (7, 20) have almost the same waveform and show no rhythmic characteristics.

In analogy to SEPs recorded from living subjects, we are able to define the usual terms relating to SEP analysis, as shown in Fig. 9. Figure 9a is a response recorded from a urethane-anaesthetised rat. In Fig. 9b, obtained from the model, the onset, initial positive peak and initial negative trough are also well defined. Hence we can easily estimate the onset latency and the relative amplitudes and use them as an index of anaesthesia.

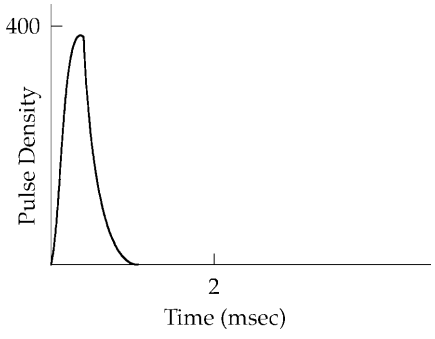

Fig. 7. Time response of the stimulus function (18)

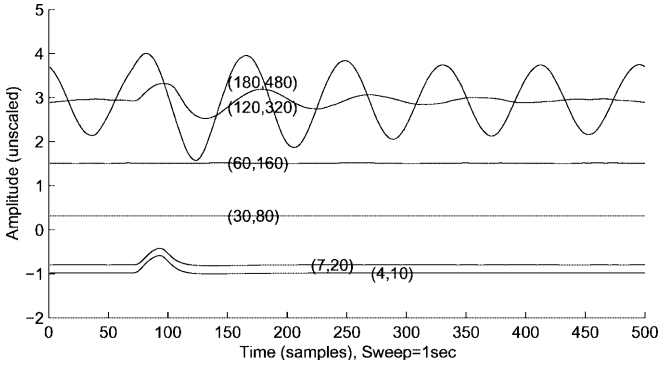

Fig. 8. Spontaneous activity and oscillatory characteristics of the network. Each *pair of numbers* represents the range of uniformly distributed random numbers used for the stimulus

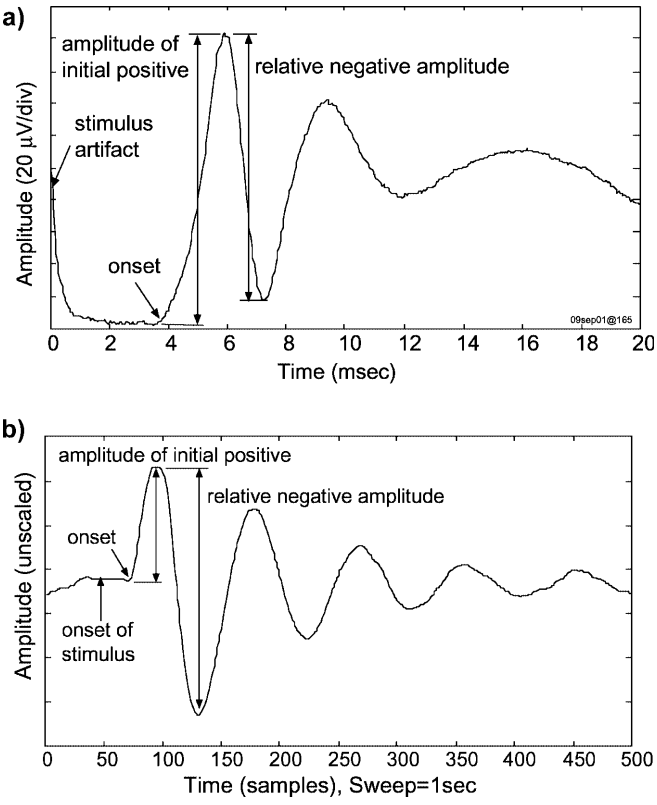

Fig. 9a,b. Definitions of terms used in somatosensory-evoked-potential analysis. **a** Response recorded from an anaesthetised rat. **b** Simulation result from the proposed model for the somatosensory pathways

5.2 Application to general anaesthesia

5.2.1 Mechanisms of anaesthetic agents in the nervous system. Anaesthetic agents acting on the somatosensory nervous system either attenuate or block signal transmission from the peripheral sensory receptors to the somatic sensory cortex (Angel 1993b). Laboratory research has revealed that the thalamic relay cell is a major site of anaesthetic action, and that the centripetal transmission of sensory information is decreased at this site by anaesthetic agents (Angel and LeBeau 1992). In propofol anaesthesia, for example, this behaviour may be due to an increase in the release of γ-aminobutyric acid (GABA) acting at $GABA_A$ receptors as proposed by Fiset et al. (1999) to explain the marked decrease in thalamic regional blood flow which occurs with propofol administration in human patients. For anaesthetic agents to affect axonal conduction requires considerably higher concentrations than the effect of synaptic transmission, and only occurs at lethal doses (Seeman 1972; Rang and Dale 1987). Hence, only the factors altering synaptic transmission are studied. These factors include reduction of neurotransmitter release, inhibition of the post-synaptic action of the transmitter or reduction of the electrical excitability of the post-synaptic cell. The first two are widely recognised to be the main factors (Langmoen et al. 1995), and based on them the effect of an anaesthetic agent is simulated in the model by

varying the amplitude gains and delay constants of suitable pyramidal cells of the model. The last factor can be modelled as an increase of the threshold value of the hillock.

5.2.2 Attenuation of synaptic transmission. The excitabilities of the thalamic and cortical neurons are significantly sensitive to a variety of substances (McCormick et al. 1991). At the cellular level, anaesthetic agents inhibit the conduction of action potentials, and also inhibit transmission at synapses. In simulation studies, the nervous network was now considered to be anaesthetised with different doses. The dose is represented by a percentage change in the nominal parameter values. This was mimicked by attenuating the amplitude gain (A) and the time constant (a) of the EPSP function (1) of all cortical cells by the same percentage. The lower the percentage, the bigger is the dose, i.e. 10% of the nominal values is more intense than 20% of the nominal values in terms of attenuating synaptic transmission.

The doses were decreased from 100% to 5% of the nominal values in steps of 5%, and the results are shown in Fig. 10. From this figure we see that the onset latency increased and the relative amplitude decreased. This result coincides with experimental results on humans and animals (Sebel et al. 1985; Angel 1993a). For model parameters less than 25% of the nominal values, there are almost no oscillations within the sweep duration. This can be interpreted as the subject being over-anaesthetised, and might correspond to a lethal dosage.

5.2.3 Increase of the hillock threshold. The above simulations show that mimicking anaesthesia with the parameters of synaptic transmission is reasonable. An alternative is to use different threshold potentials to simulate different anaesthetic levels; this simulation is shown in Fig. 11. The different levels were simulated by increasing the threshold value of the sigmoid function (4) from v_0 to $2v_0$ in 5% steps. However, the changes of the threshold potential do not behave as well as those using synaptic transmission modulation. Hence, the synaptic transmission is adopted as the key parameter in the nervous system simulation.

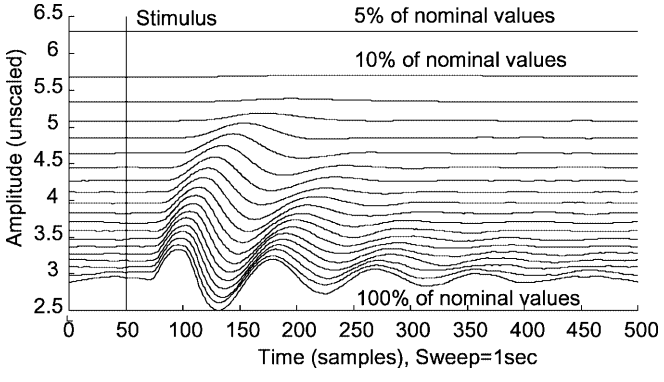

Fig. 10. Effects of varying the amplitude gain and delay constant to represent different depths of anaesthesia

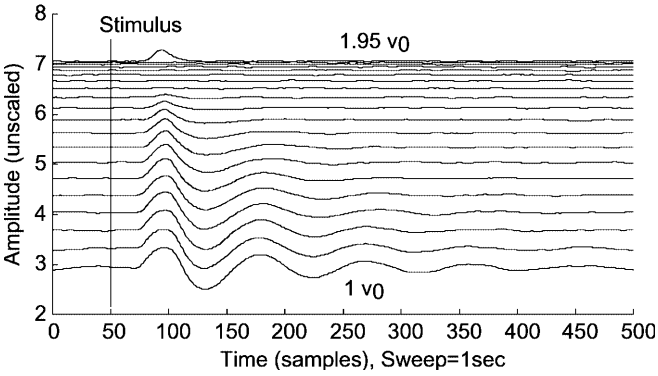

Fig. 11. Effects of varying the hillock threshold level and delay constant to represent different depths of anaesthesia

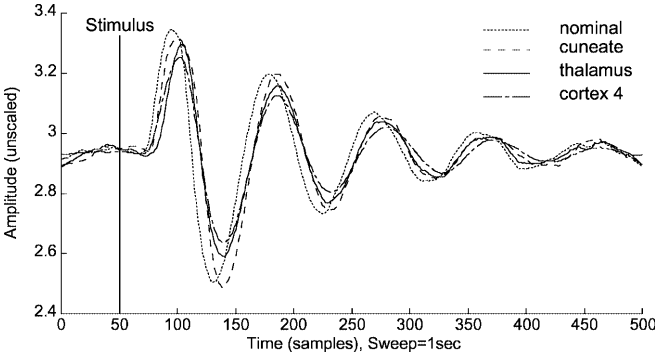

Fig. 12. How the evoked potentials recorded at cortical layer IV is affected by a single anaesthetised cell

5.2.4 Effects of individual cortical cells on the network. Several simulations on individual neurons were conducted to show how varying the parameters of an individual neuron affects the evoked potential responses (output of cortical layer IV). The synaptic parameters (amplitude gain and time constant) of a single cortical cell of the nervous pathway were halved from the nominal values, while the other cells were kept at their nominal values. Comparative results are shown in Fig. 12. Responses of the anaesthetised cortical layer V almost overlap with the nominal curve. The thalamus decreases the amplitude and onset latency significantly. Anaesthetising the cuneate only delays signal transmission. These effects are reasonable since the thalamus works as a relay to the whole system (Angel and LeBeau 1992; Fiset et al. 1999).

5.2.5 Pharmacodynamics. The scheme presented in Sect. 5.2.2 can be envisaged as anaesthesia control using the target controlled infusion technique (Glen 1998). A system based on this technique aims to keep the drug concentration in the blood at predefined target levels. The effect (E) of the drug is usually described in terms of the drug concentration (C) using the Hill equation:

$$E(C) = \frac{E_{\max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \tag{19}$$

where E_{max} is the maximum possible effect, EC_{50} is the concentration at half-maximum effect and γ is a measure of the steepness of the curve. When monitoring the responses of anaesthesia using SEPs, the effect variable E can be the latency change, the relative amplitude or a combination of both (Sebel 1989; Angel et al. 2000).

Here we define the anaesthetic effect as the multiplication of the latency (θ) and the amplitude (ΔP) of the initial positive wave, i.e.

$$E = \theta(\Delta P_0 - \Delta P)/\Delta P_0 \tag{20}$$

where ΔP_0 is the amplitude at the control period, i.e. responses to the nominal model parameters.

Figure 10 shows that there is no distinctive initial negative wave if the concentration exceeds 75% (i.e. parameter at 25% of nominal value). Hence only responses to concentrations below 75% are utilised. The normalised contour of (20) together with its fitted Hill equation is depicted in Fig. 13. The simulation results show that the dose-versus-latency-change curve replicates the Hill equation as well as results from animal experiments. The simulation results are interesting not only because SEPs respond realistically to changes in the model parameters, but also because the mechanisms of the individual neurons respond characteristically to parameter variations.

6 Conclusions

The model proposed here does not consider synchrony properties of the EEG signals which were taken into account by Lopes da Silva et al. (1974) and Jansen and Rit (1995). Also, analytical studies were not undertaken due to the lack of physiological information and the complexity of the model. Instead, this paper concentrates on utilising existing neuronal models and physiological parameters in the proposed dynamics of the somatosensory nervous pathways.

The connectivity coefficients of the model were kept fixed during all simulations. This is justified by the fact that the number of synaptic contacts of a neuron should be constant in spite of changes of the nervous state, except when there are physical brain lesions. However,

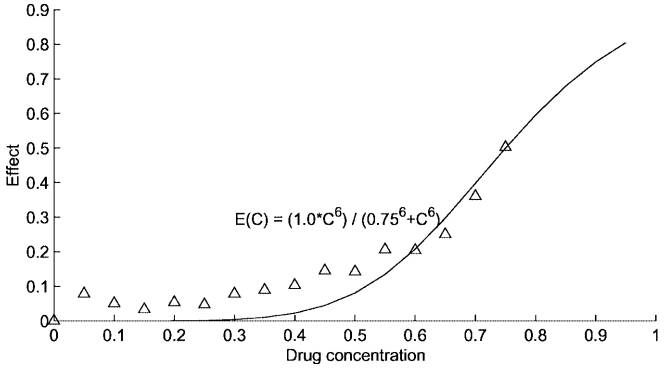

Fig. 13. Proposed pharmacodynamics for augmentation of the network

one of the major drawbacks of this cortical model is the unavailability of more realistic connectivity coefficients. Obviating this problem would require different approaches or more-specific histological examinations.

Anaesthetic drugs may influence the neurons at various sites, including the synapses, cell body, axon hillock and axon. Hence, we assumed that the parameters of synaptic transmission and the axon hillock changed due to administration of anaesthetic drugs. Evoked responses representing the post-synaptic membrane potentials recorded at cortical layer IV show that the model is able to reproduce these influences via parameter variation, although such a reproduction does not indicate uniqueness in physiological mathematical modelling.

The simulation results are interesting not only because of how the evoked potential responses are influenced by changes in the model parameters, but also by providing insight into the mechanisms of how the individual neurons respond to the parameter variation. McCormick et al. (1991) pointed out that the excitability of a neuron is quite sensitive to a variety of substances such as anaesthetic drugs, so simulation studies based on neuronal networks could be a potent approach for answering how electrophysiology behaves.

More realistic models, such as single-neuron models (Stein et al. 1974) which consider adaptation, refractory period and warm-up period, would be necessary for more-profound analysis. However, a major drawback in the development of those models is the lack of realistic model parameters. To use these neuronal network models in practice, we need more knowledge and experimental data from physiological studies. For example, the changes of excitability in the cortex are due not only to administration of drugs but also to changes in information processing within the cortex (Blom 1980; Angel 2002).

The proposed somatosensory neural model shown in Fig. 5 provides a framework for a wide range of hypothesis testing. The structure is realistic and parsimonious, and gives a paradigm on which a series of phenomena can be explored in a focused scientific manner. For example, the parameter set within the model gives a "best guess" nominal scenario which can be perturbed in simulation studies to provide a sensitivity analysis of second-order effects within the model. In turn, this can determine the high-sensitivity regions of the model, particularly relating to connectivity values, which could be explored via histological studies. If such studies were to show that these parameter sets invalidate the known SEP pattern behaviour, then changes via a principled approach could be made to the current model.

In addition to the validation of the model under quiescent conditions, the effects of drugs could be explored by testing different hypotheses on changes to parameters/dynamics. Further faults in the neural patterns can be explored via simulation, either by breaks in pathway connections or perturbations in parameter values. In these ways, the structure provides the basis for hypotheses testing which could guide and focus

physiological investigations in a systematic manner. This would then fulfil one of the major objectives in all modelling studies, while employing a simulation platform which for the proposed model requires only moderate computing recourses.

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