A thalamacortical feedback model to explain EEG during anesthesia

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Abstract. General anesthesia (GA) is a medical procedure which aims to achieve unconsciousness, analgesia, amnesia, and immobility. Although GA is commonly used in medical care for patients undergoing surgery, its precise underlying mechanisms and the molecular action of anesthetic agents (AA) remain to be elucidated. A wide variety of drugs are used in modern anesthetic practice and it has been observed that for many AAs, during the transition from consciousness to unconsciousness, the electroencephalogram shows biphasic effects in amplitude: an initial increase of the spectral power followed by a decrease at higher concentrations. Moreover during the administration of propofol, specific changes in EEG rhythms can be observed. The aim of this work is the extended discussion of a recent model by Hindriks and van Putten [8] that reproduces specific changes in EEG rhythms by the study of a neuronal population model of a single thalamocortical module. We illustrate specific features of the model, such as the physiological assumptions, the derivation of the power spectral density and the impact of the propofol concentration and of the stationary state. We show that the propofol-induced modification of the stationary state plays an important role in the understanding of the observed EEG.

Keywords: General anesthesia, Thalamocortical model, EEG, Power spectrum

1 Introduction

General anesthetics (GAs) include a large number of drugs which without them, modern medicine, especially surgery, would not have been possible. However, the mechanism underlying its anesthetic effects on human beings is not yet fully understood [1].

It has been observed that during the transition from consciousness to unconsciousness, by induction thippental, propofol, and sevoflurane, many derived EEG variables show biphasic effects, that is an initial increase of the spectral power followed by a decrease at higher concentrations [2]. Moreover, during the induction phase of propofol, enhanced oscillatory activity within several frequency bands can be observed [3]. For clinically relevant concentration of propofol specific changes in EEG rhythms include an increase in alpha peak frequency, over frontal regions, accompanied by increase in delta and theta power [4, 5].

Most of the previous studies on anesthetic phenomena have been done by considering a mean-field model to explain the biphasic behavior and describe some experimental feature of specific changes in electroencephalography (EEG) data recorded during anesthesia [6–9]. While some previous theoretical studies (Steyn-Ross 1999; Bojak and Liley et al. 2005; Hindriks and van Putten 2012) are based on the same type of continuous spatial mean-field model involving spatial partial derivatives [10], Hutt and Longtin have considered a neural populations model motivated by Wilson and Cowan [11] and Amari [12].

In this study we use a thalamocortical feedback model first developed by Rennie et al. [13] and recently extended to model general anesthesia by Hindriks and van Putten [8] to reproduce the specific changes in EEG activity that can be observed during the propofol-induced general anesthesia. The present work reviews this latter model and points out the importance of stationary states to understand EEG power spectra during anesthesia.

2 Methods

2.1 Model

The body of the model [8] is based on a population-level model of a single thalamocortical module consisting of four populations of neurons, namely excitatory (E) and inhibitory (I) cortical neurons, a thalamic relay nucleus (S), and a thalamic reticular nucleus (R). The average soma membrane potential for $a \in E, I, S, R$ is modeled by

$$V_a(t) = \sum_{b=E,I,R,S} \bar{h}(t) \otimes K_{ab}\phi_b(t - \tau_{ab}), \tag{1}$$

where ϕ_b is the pulse firing rate of the population b (units Hz). The constants K_{ab} are the strengths of the connections from population of type b to population of type a (units mVs). The delay term, τ_{ab} is zero if the both populations are in the thalamus or in the cortex. For thalamocortical or corticothalamic pathway, the delay is nonzero [14]. We point out that this model does not distinguish excitatory and inhibitory synapses in contrast to other models for general anaesthesia as [6, 7, 9].

In this model, only the axons of excitatory cortical neurons are long enough to emit propagating pulses along axons and the ϕ_E obeys the damped oscillator equation

$$D\phi_E = S(V_a), \tag{2}$$

in which the operator D is defined as

$$D = \left(\frac{1}{\gamma}\frac{\partial}{\partial t} + 1\right)^2, \tag{3}$$

where γ is the ratio of propagation velocity to mean axonal length. It is assumed that the spatial spread of activity is very fast in other populations and the

activity variable can be approximated by a sigmoidal function as

$$\phi_a = S(V_a) = S_{max}[1 + \exp(-\frac{V_a - \theta}{\sigma})]^{-1}, \tag{4}$$

in which S_{max} is the maximal firing rate (units Hz), θ is the average activation threshold (units mV), and σ is proportional to the standard deviation of activation thresholds over the populations (units mV^{-1}).

In Eqs. (1), $\otimes$ denotes the convolution operator and $\bar{h}(t)$ denotes the mean synaptic response function

$$\bar{h}(t) = \frac{\alpha\beta}{\beta - \alpha}\left(e^{-\alpha t} - e^{-\beta t}\right), \tag{5}$$

where α and β are the synaptic decay and rise rate of synaptic response function, respectively.

External input to the system can be considered as a non-specific input to relay neurons as

$$K_{SN}\phi_N = \langle\phi_N\rangle + \sqrt{2\kappa}\xi(t), \tag{6}$$

where $\langle\phi_N\rangle$ indicates its mean value, $\xi(t)$ is a Gaussian white noise with average zero and κ is the intensity of the driving noise. For more details of model and the nominal parameter values see [8].

2.2 Effect of propofol on populations

It has been shown that propofol increases the decay time constant of $\mathrm{GABA_A}$ synapses, and hence increases the total charge transfer in these synapses but not that of excitatory synapses [15]. Interestingly propofol has been shown to have a negligible effect on the amplitude synaptic receptors in cortical neurons [15].

To integrate physiological observations into the model, the potentiation of synaptic receptors in anesthesia condition can be modeled by $\alpha \to \alpha/p$ with $p \geq 1$, which leads to a decrease in the decay rate constant α or equivalently, an increase in decay time constant of $\mathrm{GABA_A}$ receptors. The factor p indicates the target concentration of propofol in the neural populations. We take $p = 1$ for zero concentration i.e, baseline condition. Then we could replace the synaptic response $h(t)$ by

$$h(t) = \frac{H}{\eta(\alpha, \beta)}\bar{h}(t), \tag{7}$$

in which

$$\eta(\alpha, \beta) = \frac{\alpha\beta}{\beta - \alpha}\left[\exp\left(-\alpha\frac{\ln(\beta/\alpha)}{\beta - \alpha}\right) - \exp\left(-\beta\frac{\ln(\beta/\alpha)}{\beta - \alpha}\right)\right], \tag{8}$$

where the constant H indicates the synaptic efficacy [8]. The maximum height of $h(t)$ indeed is H and hence is independent of the rate constants α and β. The baseline value chosen for α and β; α=50 Hz, β=200 Hz leads to the value $\eta(\alpha, \beta) = 31.5$ Hz .

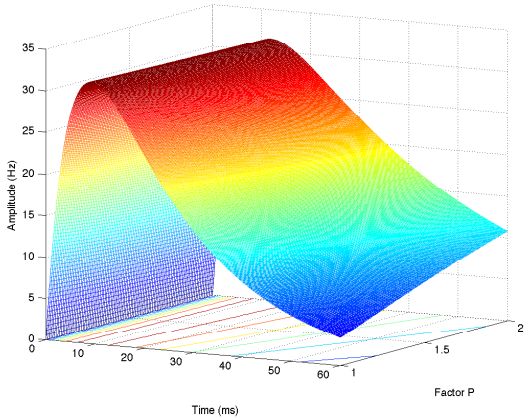

Fig. 1. The temporal synaptic response function $h(t)$ of inhibitory $GABA_A$ synapses subject to p. Parameters are set to α=50 Hz, β=200 Hz.

2.3 Theoretical power spectrum

The stationary state of Eqs. (1) obeys $dV_a(t)/dt = 0$. We could linearize the Eqs. (1) about the stationary state and write them in a general matrix form of a linear DDE as

$$\hat{\boldsymbol{L}}\left(\frac{\partial}{\partial t}\right)\boldsymbol{X}(t) = \boldsymbol{A}\boldsymbol{X}(t) + \boldsymbol{B}\boldsymbol{X}(t-\tau) + \boldsymbol{I}(t), \tag{9}$$

with matrices $\boldsymbol{A}$, $\boldsymbol{B}$, the system activity vector $\boldsymbol{X}$ and the external input $\boldsymbol{I}$. The solution of system can be written as

$$\boldsymbol{X}(t) = \int_{-\infty}^{\infty} \boldsymbol{G}(t-t')\boldsymbol{I}(t')dt', \tag{10}$$

and the Green function obeys

$$\hat{\boldsymbol{L}}\left(\frac{\partial}{\partial t}\right)\boldsymbol{G}(t) = \boldsymbol{A}\boldsymbol{G}(t) + \boldsymbol{B}\boldsymbol{G}(t-\tau) + \mathbf{1}\delta(t), \tag{11}$$

in which $\mathbf{1}$ is unitary matrix. Applying the Fourier transform

$$\boldsymbol{G}(t) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{\infty} \tilde{\boldsymbol{G}}(\omega)e^{i\omega t}d\omega \tag{12}$$

yields

$$\tilde{\boldsymbol{G}}(\omega) = \frac{1}{\sqrt{2\pi}}[\hat{\boldsymbol{L}}(\omega) - \boldsymbol{A} - \boldsymbol{B}e^{-i\omega\tau}]^{-1}. \tag{13}$$

The power spectral density matrix $\boldsymbol{P}(\omega)$ of $\boldsymbol{X}(t)$ is the Fourier transform of the auto-correlation function matrix $\langle \boldsymbol{X}(t)^t \boldsymbol{X}(t-T)\rangle$ (Wiener-Khinchine Theorem) leading to

$$\boldsymbol{P}(\omega) = 2\kappa\sqrt{2\pi}\tilde{\boldsymbol{G}}(\omega)\tilde{\boldsymbol{G}}^t(-\omega),$$

where the high index t denotes the transposed vector or matrix [16].

At the end, the model assumes that excitatory activity generates the EEG and by virtue of the specific choice of external input the power spectrum of the EEG depends just on one matrix component of the Greens function by

$$P_E(\omega) = 2\kappa\sqrt{2\pi}\tilde{G}_{1,3}(\omega)\tilde{G}_{1,3}(-\omega) = 2\kappa\sqrt{2\pi}\left|\tilde{G}_{1,3}(\omega)\right|^2. \tag{14}$$

The stationary state of Eqs. (1) is given by

$$\begin{aligned} V_{0E} &= K_{EE}S(V_{0E}) + p_1K_{EI}S(V_{0I}) + K_{ES}S(V_{0S}),\\ V_{0I} &= K_{IE}S(V_{0E}) + p_2K_{II}S(V_{0I}) + K_{IS}S(V_{0S}),\\ V_{0S} &= K_{SN}\langle\phi_N\rangle + p_3K_{SR}S(V_{0R}) + K_{SE}S(V_{0E}),\\ V_{0R} &= K_{RS}S(V_{0S}) + K_{RE}S(V_{0E}), \end{aligned} \tag{15}$$

where $K_{SN}\langle\phi_N\rangle = 1\text{mV}$ and we take three different impact factors for the anesthetic effect of propofol as

$$\frac{H}{\eta_{ei}} = p_1, \frac{H}{\eta_{ii}} = p_2, \frac{H}{\eta_{sr}} = p_3,$$

in which we parametrize η_{ei}, η_{ii} and η_{sr} by

$$\eta_{ei} : \alpha \to \frac{\alpha}{p_1},\ \eta_{ii} : \alpha \to \frac{\alpha}{p_2},\ \eta_{sr} : \alpha \to \frac{\alpha}{p_3}.$$

This assumes a complete insensitivity of synaptic receptors located on cortical pyramidal neurons and reticular nucleus.

For the linearization of Eqs. (1) one obtains

$$\boldsymbol{X}(t) = \begin{pmatrix} \phi_E(t)\\ V_I(t)\\ V_S(t)\\ V_R(t) \end{pmatrix},\ \boldsymbol{A} = \begin{pmatrix} K_1 & K_2 & 0 & 0\\ K_4 & K_5 & 0 & 0\\ 0 & 0 & 0 & K_8\\ 0 & 0 & K_{10} & 0 \end{pmatrix},\quad \boldsymbol{B} = \begin{pmatrix} 0 & 0 & K_3 & 0\\ 0 & 0 & K_6 & 0\\ K_7 & 0 & 0 & 0\\ K_9 & 0 & 0 & 0 \end{pmatrix},\ \boldsymbol{I}(t) = \begin{pmatrix} 0\\ 0\\ \sqrt{2\kappa}\xi(t)\\ 0 \end{pmatrix},$$

with

$$\begin{aligned} K_1 = K_{EE}\ , K_2 = p_1K_{EI}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0I}}\ ,\ K_3 = K_{ES}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0S}},\\ K_4 = K_{IE}\ ,\ K_5 = p_2K_{II}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0I}}\ ,\ K_6 = K_{IS}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0S}},\\ K_7 = K_{SE}\ ,\ K_8 = p_3K_{SR}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0R}}\ ,\ K_9 = K_{RE},\\ K_{10} = K_{RS}\frac{\partial S[V]}{\partial V}\,|_{V=V_{0S}}\ ,\ K_{11} = \frac{\partial S[V]}{\partial V}\,|_{V=V_{0E}}, \end{aligned}$$

and

$$\hat{\boldsymbol{L}}(\omega) - \boldsymbol{A} - \boldsymbol{B}e^{-i\omega\tau} = \begin{bmatrix} Ł\frac{\mathcal{D}}{K_{11}} - K_1 & -K_2 & -K_3e^{-i\omega\tau} & 0\\ -K_4 & Ł - K5 & -K_6 & 0\\ -K_7e^{-i\omega\tau} & 0 & Ł & -K_8\\ -K_9e^{-i\omega\tau} & 0 & -K_{10} & Ł \end{bmatrix} \tag{16}$$

where $Ł = (1 + i\omega/\alpha)(1 + i\omega/\beta)$ and $Đ = (1 + i\omega/\gamma)^2$.
We point out that the new constants $K_i,\ i = 2, 3, 5, 6, 8, 10, 11$ are proportional to the nonlinear gain $\partial S/\partial V$ computed at the stationary state. With Eq. (13) and (16), it turns out that the stationary state and the corresponding nonlinear gain play in important role in the power spectrum.

3 Results

This section shows that the model under study reproduce the specific changes observed in EEG data during the propofol-induced anesthesia. Figure 2 shows the theoretical EEG power spectrum in the baseline condition and after the administration of propofol. The spectrum resembles well experimental observation in EEG power spectrum, i.e. increases in delta and theta power as well as more pronounced alpha oscillations with increased peak-frequency.

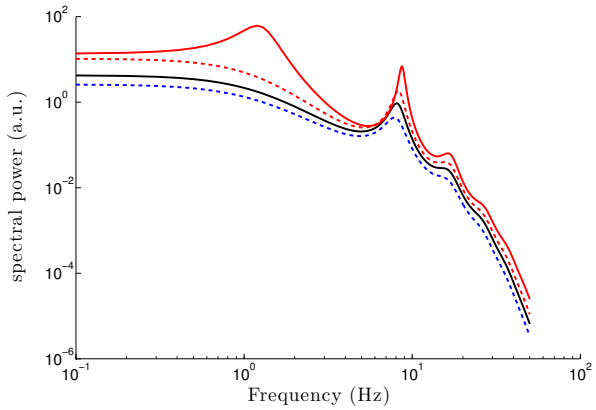

Fig. 2. Theoretical power spectrum of EEG in the baseline condition (solid black line) and three different sets of factor p in the anesthesia condition; p_1=p_3=1+0.5(p_2-1), p_2=1.1 (dashed red line), p_2=1.25 (solid red line) and p_1=p_2=p_3=1.05 (dashed blue line).

Figure 3 shows how the nonlinear gain and the stationary states dependent on the propofol concentration. We observe that the nonlinear gain may increase (a) or decrease (b) with increasing propofol dependent on the synapses that are modified. If the inhibitory synapses at cortical excitatory neurons (p_1) and at relay neurons (p_3) respond identically to a change of the propofol concentration in a specific relation to the response of synapses at cortical inhibitory neurons (p_2), then the nonlinear gain increases (Fig. 3(a)) reflecting an increased excitability and the power values increase as well (Fig. 2, red curves). In contrast, if the response of all three synapse types respond identically (as assumed in previous

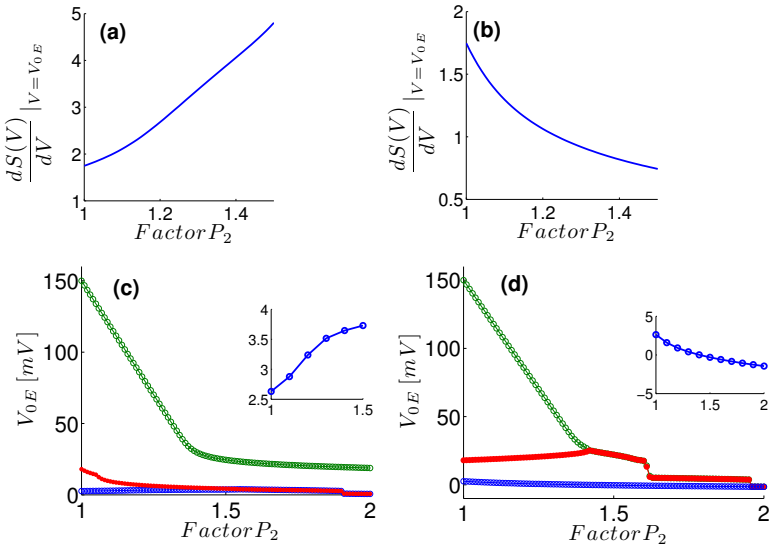

Fig. 3. The stationary states and the nonlinear gain dS/dV computed at the lowest stationary state of pyramidal neurons V_{0E} subjected to the factor p_2. **a, c)** p_1=p_3= 1+0.5(p_2-1), **b, d)** p_1=p_2= p_3. We observe three states in (c) and (d) for $p = 1$ where (c) the two lower states collide or (d) the two upper states collide. The center branch (red) is linearly unstable, whereas the other branches are linearly stable.

studies such as [9]), then the nonlinear gain decreases (Fig. 3(a)) and the decreased excitability diminishes the power spectrum values (cf. Fig. 2, blue curve).

Moreover, the stationary states behave differently in the two cases, cf. Fig. 3(c) and (d). Increasing (decreasing) the nonlinear gain is accompanied by an increasing (decreasing) value of the corresponding stationary state, see panels (c) and (d). It is also remarkable that in (c) the two lower stationary states collide to a single state whereas in (d) the two upper states collide. This difference indicates two fundamentally different mechanisms which may yield the different dynamics observed in the power spectrum. This link will be a research topic of future work.

4 Discussion

In the recent study of Hindriks and van Putten the authors have considered a high-dimensional mean field model to reproduce observed EEG changes during general anesthesia. The present work illustrates this work in some detail and highlights the important assumptions. We have extended the previous work by investigating the effect of the stationary state and have revealed the the increase or decrease of power seems to be strongly related the the increase or decrease of the stationary state of the system. This new finding proposes a more detailed study of the stationary state of neural population activity under anesthesia.

Acknowledgments.

The authors acknowledge funding from the European Research Council for support under the European Union's Seventh Framework Program (FP7/2007-2013) ERC grant agreement No.257253.

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