Anesthetic-Induced Transitions by Propofol Modeled by Nonlocal Neural Populations Involving Two Neuron Types

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Abstract The present work derives the spatiotemporal field equation of neural populations considering two types of neurons. The model considers pyramidal cells, which may excite or inhibit other neurons, and GABAergic interneurons inhibiting terminal neurons. Additionally, taking into account excitatory and inhibitory synapses, the neural population obeys a vector-field equation involving nonlocal spatial interactions. The work studies the effect of the anesthetic agent propofol, which increases the decay time of inhibitory synapses. In addition, it explains the bifurcation mechanism in some detail and finds a saddle–node bifurcation subject to the propofol concentration. This bifurcation may model the transition between consciousness and nonconsciousness and vice versa during the administration of general anesthetics in medicine.

Keywords Neural fields · Integral-differential equation · General anesthesia

1 Introduction

Several studies in recent years have shown that the brain exhibits phenomena known from complex physical systems [1], e.g., complex pattern formation [2, 3], localized structures [4], or phase transitions of second order [5, 6]. Moreover, theoretical studies have elaborated that the loss of consciousness induced by anesthetic agents may be modeled as phase transitions of the first order [7, 8]. In corresponding models, one stable branch in the corresponding bifurcation diagram represents the stationary resting state of consciousness, while the loss of consciousness occurs by a saddle–node bifurcation to a

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second stable branch at lower brain activity. This transition originates from the change of synaptic properties induced by the anesthetics. In this context, experimental studies show that different anesthetic agents differ in their action on excitatory and inhibitory synapses. For instance, the induction agent *propofol* does not affect the excitatory synapses, but prolongs the decay phase of inhibitory synapses only [9, 10]. The present work will examine this effect of propofol.

Anesthetic-induced transitions cause characteristic effects in encephalographic activity [11], indicating macroscopic neural activity of neural populations. This work introduces a spatio-temporal neural population model, which allows for the mathematical description of the observed loss of consciousness while administering anesthetic agents. Our model treats general spatial connectivities; i.e., both diffusive and nonlocal interactions are treated. Thus, the work extends similar models, as the ground-breaking model of Steyn-Ross et al. [7], by considering nonlocally interacting neural populations. In addition, the proposed model presumes the somatic conversion of the sum of excitatory and inhibitory postsynaptic potentials (EPSP/IPSP) to firing rates, which has been found experimentally [12]. This detail is in contrast to previous models [7, 13, 14], which treat the conversion of EPSP and IPSP at the soma separately. The subsequent paragraphs derive the applied model and explain the transition from consciousness to nonconsciousness by a saddle-node bifurcation induced by propofol.

2 The Model

The proposed model considers an ensemble of neurons, which is coarse-grained in space and time [15, 16]. Furthermore, it accounts for two types of neurons, namely, pyramidal cells exciting and inhibiting terminal neurons and GABAergic interneurons, e.g., stellate cells, which inhibit terminal neurons only [17]. Hence, we distinguish synapses at pyramidal cells and at interneurons, while synapses may be excitatory or inhibitory. More detailed, the mean postsynaptic potentials (PSPs) $V_{Ab}(x, t)$ at spatial location x at time t are evoked at pyramidal cells ($A = P$) or interneurons ($A = I$) and originate from excitatory ($b = e$) or inhibitory ($b = i$) synapses by incoming neural firing activity $P_{P,I}$ from pyramidal cells (P) or interneurons (I). Experiments [12] show that PSPs may be modeled as the linear response to incoming firing activity and subsequently obey

$$\begin{aligned} V_{Pe,Ie}(x, t) - V_{P,I}^r &= \int_{-\infty}^t h_e(t-t')(1-\eta)P_P(x, t') dt' \\ V_{Pi,Ii}(x, t) - V_{P,I}^r &= \int_{-\infty}^t h_i(t-t')(P_I(x, t') + \eta P_P(x, t')) dt' \end{aligned} \quad (1)$$

where $h_e(t) = \alpha_1\alpha_2/(\alpha_2 - \alpha_1)(\exp(-\alpha_1 t) - \exp(-\alpha_2 t))$ and $h_i(t) = \beta_1\beta_2/(\beta_2 - \beta_1)(\exp(-\beta_1 t) - \exp(-\beta_2 t))$ are the synaptic impulse response functions. The weight η accounts for the fact that pyramidal cells (P) may terminate at excitatory (e) or inhibitory (i) synapses while the interneurons terminate at inhibitory synapses only. This aspect is taken into consideration by the parameter η giving the percentage of terminal inhibitory synapses of pyramidal cells. A typical value is $\eta = 0.8$ [18].

Furthermore, the synaptic response functions may be interpreted as Green's functions of corresponding temporal operators $\hat{L}_e$ and $\hat{L}_i$ obeying $\hat{L}_{e,i}h_{e,i}(t) = \delta(t)$, and we find operators $\hat{L}_{e,i}$ of second-order. The variables V_P^r and V_I^r are the mean resting potentials at pyramidal cells and interneurons, respectively, while $\alpha_{1,2}$ and $\beta_{1,2}$ are the time scales of the

excitatory and inhibitory synapses, respectively. After the additional rescaling of the time by $\tau = \sqrt{\alpha_1 \alpha_2} t$, we have

$$\hat{L}_e (V_{Pe,le}(x, t) - V_{P,I}^r) = (1 - \eta) P_P(x, t) \quad (2)$$

$$\hat{L}_i (V_{Pi,li}(x, t) - V_{P,I}^r) = P_I(x, t) + \eta P_P(x, t), \quad (3)$$

with $\hat{L}_e = \partial^2 / \partial t^2 + \gamma_e \partial / \partial t + 1$, $\hat{L}_i = \partial^2 / \partial t^2 + \gamma_i \partial / \partial t + \omega_0^2$, $\gamma_e = \sqrt{\alpha_1 / \alpha_2} + \sqrt{\alpha_2 / \alpha_1}$, $\gamma_i = (\beta_1 + \beta_2) / \sqrt{\alpha_1 \alpha_2}$, and $\omega_0^2 = \beta_1 \beta_2 / \alpha_1 \alpha_2$. Here, τ has been renamed as t for convenience.

Further assuming a spatial domain Ω , the firing activity evoked at pyramidal cells and interneurons reads

$$P_P(x, t) = \int_{\Omega} K_P(x - y) S_P [V_{Pe}(y, t) - V_{P,I}^r] dy \quad (4)$$

$$P_I(x, t) = \int_{\Omega} K_I(x - y) S_I [V_{Ie}(y, t) - V_{I,I}^r] dy. \quad (5)$$

Here, $S_P[\cdot]$ and $S_I[\cdot]$ represent the somatic conversion function of pyramidal cells and interneurons, respectively, and $V_{P,I}^r$, $V_{I,I}^r$ denote the corresponding mean firing thresholds. In contrast to other models, e.g., [7, 13, 14], the conversion function considers both excitatory and inhibitory PSPs. Moreover, the kernel functions K_P and K_I give the spatial synaptic connectivities from neurons of type P and I , respectively. These kernels introduce the spatial nonlocal interactions and include the specific case of diffusion models [15]. To show this, we rewrite the convolution integral in (4) and (5) for infinite spatial domains in the general form

$$\int_{-\infty}^{\infty} K(x - y) f(u(y, t)) dy = \int_{-\infty}^{\infty} \tilde{K}(k) \tilde{f}(k, t) e^{ikx} dk.$$

Here, $\tilde{K}(k)$ and $\tilde{f}(k)$ are the Fourier transforms of the spatial kernel $K(x)$ and the nonlinear function $f(x, t)$, respectively.

For the specific kernel $K(x) = \exp(-|x|/\sigma)/2\sigma$ with spatial interaction range σ , we find $\tilde{K}(k) = 1/(1 + \sigma^2 k^2)$. Subsequently, for small σ , i.e., short spatial interactions, we find by a Taylor series expansion

$$\begin{aligned} \int_{-\infty}^{\infty} K(x - y) f(u(y, t)) dy &= \int_{-\infty}^{\infty} (1 - \sigma^2 k^2 + \sigma^4 k^4 - \dots) \tilde{f}(k, t) e^{ikx} dk \\ &= (1 + D\Delta + D^2\Delta^2 + \dots) f(u(x, t)) \end{aligned} \quad (6)$$

with $D = \sigma^2$ and the Laplacian Δ . This is valid in one-, two-, and three-dimensional space. The first term in (6) gives the self-interaction, the second term represents the diffusive interactions, while the subsequent higher terms show the nonlocal interactions. In other words, the integral formulation in (4) and (5) in some way generalizes spatial interactions [15, 19].

Fig. 1 The temporal impulse response function of inhibitory synapses subject to various values of p , i.e., the propofol concentration

Combining (2), (3), (4) and (5), the final field equations read

$$\hat{L}_e(V_e - V_e^r) = \int_{-\infty}^{\infty} (1 - \eta) K_P(x - y) S_P \left[V_e(y, t) - V_i(y, t) - V_P^f \right] dy \quad (7)$$

$$\begin{aligned} \hat{L}_i(V_i - V_e^r) = & \int_{-\infty}^{\infty} \eta K_P(x - y) S_P \left[V_e(y, t) - V_i(y, t) - V_P^f \right] \\ & + K_I(x - y) S_I \left[V_e(y, t) - V_i(y, t) - V_P^f \right] dy \end{aligned} \quad (8)$$

with the abbreviations $V_e = V_{Pe}$, $V_i = V_{Pi}$.

To model the effect of propofol, we introduce the scaling factor $p \geq 1$ by $\beta_1 = \beta_1^0/p$. This factor is strongly related to the blood concentration of propofol. In other words, for $p > 1$, propofol increases the inhibitory time constant $1/\beta_1$, which is in accordance with experiments [10]. Figure 1 illustrates the corresponding impulse response function $h_i(t)$ subject to p .

3 The Resting State and its Linear Stability

To investigate the existence of stationary resting states in the neural population, we assume the resting state as spatially constant and not time-dependent. To this end, $\bar{V}_e$, $\bar{V}_i$ are constant in space and time, and thus, (7) and (8) yield

$$\bar{V}_- = \kappa_P (1 - \eta - \eta/\omega_0^2) S_P \left[\bar{V}_- - V_P^f \right] - \kappa_I/\omega_0^2 S_I \left[\bar{V}_- - V_P^f \right] \quad (9)$$

$$\bar{V}_+ = \kappa_P (1 - \eta + \eta/\omega_0^2) S_P \left[\bar{V}_- - V_P^f \right] + \kappa_I/\omega_0^2 S_I \left[\bar{V}_- - V_P^f \right] + 2V_P^r, \quad (10)$$

with $\bar{V}_+ = \bar{V}_e + \bar{V}_i$, $\bar{V}_- = \bar{V}_e - \bar{V}_i$ and the constants $\kappa_P = \int K_P(x) dx$, $\kappa_I = \int K_I(x) dx$. Here, $\bar{V}_-$ represents the stationary somatic membrane potential. From (9) and (10), we observe that solving (9) suffices to obtain $\bar{V}_-$ and to obtain, subsequently, $\bar{V}_+$ by inserting

$\bar{V}_-$ into (10). Then, the stationary excitatory and inhibitory PSPs read $\bar{V}_e = (\bar{V}_+ + \bar{V}_-)/2$, $\bar{V}_i = (\bar{V}_+ - \bar{V}_-)/2$. In other words, the number of roots of (9) gives the number of stationary solutions for $\bar{V}_e$, $\bar{V}_i$.

Figure 2 illustrates the conditions for three roots of (9) for various propofol parameters p . It turns out that the right-hand side of (9) needs to have a minimum subject to $\bar{V}_-$. This condition is fulfilled only if there are two different neuron types with different somatic conversion functions, i.e., different mean firing thresholds or different shapes. Moreover, increasing p from $p = 1$ yields a downshift of the asymptote for large $\bar{V}_-$, which thus generates from one to three and, again, one solution. Hence, increasing the time scale of inhibitory synapses yields different numbers of stationary solutions, and p represents a suitable control parameter.

The obtained stationary solutions are given in Fig. 3. It turns out that there is a parameter regime $p \in [p_B; p_A]$ revealing two or three stationary states, while low or high values $p < p_B$ or $p > p_A$ yield single stationary solutions only. Now, to gain further information on the stability of these states, a linear stability analysis is applied to (7) and (8). The Fourier transforms of the small deviation equations from the stationary solutions yield

$$\hat{L}_e \tilde{u}_e(k, t) = A(k) \tilde{u}_e(k, t) - A(k) \tilde{u}_i(k, t) \quad (11)$$

$$\hat{L}_i \tilde{u}_i(k, t) = B(k) \tilde{u}_e(k, t) - B(k) \tilde{u}_i(k, t) \quad (12)$$

Fig. 2 Construction of solutions of (9). The panels show the left-hand side (thin solid diagonal) and the right-hand side (other lines) of (9), and the crossing points of the lines give the stationary solutions $\bar{V}_-$. **a** The dashed-dotted line denotes the right-hand side of (9) for $p = 1$, while the other lines correspond to $p > 1$. **b** A zoom of **a** to illustrate the mechanism of the saddle-node bifurcation. Here, we assume excitatory synapses emitting glutamate to NMDA-receptors, i.e., $\alpha_1 = 1430$, $\alpha_2 = 13$ Hz, while the inhibitory synapses emit GABA to GABA(type A)-receptors, i.e., $\beta_1^0 = 44$, $\beta_2 = 1000$ Hz. In addition, we choose $V_p^f = -40$ mV, $V_i^f = -50$ mV, $V_p^r = -70$ mV, $\kappa_P = 1.0$ mV s, $\kappa_I = 0.8$ mVs, and $S_{P,I}[x] = P_{\max}/(1 + \exp(-cx))$ with $c = 0.74$ /mV and the maximum firing rate at rest $P_{\max} = 30$ /s

Fig. 3 Bifurcation diagrams showing the stationary solutions $\bar{V}_-$ of (9) and the corresponding excitatory and inhibitory PSPs $\bar{V}_e$ and $\bar{V}_i$, respectively. The points A and B mark the saddle-node bifurcation points, i.e., the transition between the stable and unstable solutions. The parameters are the same as in Fig. 2

where $\tilde{u}_e$, $\tilde{u}_i$ are the Fourier transforms of the small deviations and we have $A(k) = \delta_e(1 - \alpha)\tilde{K}_e(k)$, $B(k) = \delta_i\tilde{K}_i(k) + \delta_e\alpha\tilde{K}_e(k)$ with the kernel Fourier transforms $\tilde{K}_e$, $\tilde{K}_i$. Then, the ansatz $\tilde{u}_e(k, t)$, $\tilde{u}_i(k, t) \sim \exp(-\lambda t)$ with $\lambda \in \mathbb{C}$ yields the implicit equation

$$g(\lambda) = \lambda^4 + C\lambda^3 + D\lambda^2 + E\lambda + F = 0, \quad (13)$$

with real coefficients, while $C = C(p)$ and D , E , F depend both on p and the wavenumber k . This result is valid for all spatial interaction kernels $K_e(x)$, $K_i(x)$ and typical synaptic response functions. At first, to obtain the stability conditions for the constant stationary states shown in Figs. 2 and 3, we choose $k = 0$ and apply parameters corresponding to NMDA- and GABA_A receptors. We find C , $D(0)$, $E(0) > 0$ for all $p \geq 1$, while $F(0)$ may be positive or negative. Furthermore, the separation of the real and the imaginary parts of λ reveals $\lambda \in \mathbb{R}$, and thus, the rule of Descartes gives us conditions on the number of positive roots of (13). To be more specific, the number of sign changes in the coefficients of $g(\lambda)$ gives the maximum number of positive roots. Hence, in case of $F(0) > 0$, there are no sign changes and, thus, no positive roots. For $F(0) < 0$, there is a single sign change in $g(\lambda)$, yielding a single positive root. That is, $F(0) = 0$ represents the stability threshold for the stationary states.

Fig. 4 The eigenvalue λ and the function $F(0)$ subject to the propofol concentration p . The characters A , B , and C mark the parameter regime of the multiple stabilities, cf. Fig. 4

Figure 4 presents the eigenvalues λ and the function $F(0)$ as a function of the propofol concentration factor p . The comparison to Fig. 3 reveals the accordance of the stability thresholds $\lambda = 0$, $F(0) = 0$ with the onset and offset of the multiple solutions. We find that the upper and lower branches in Fig. 3 are stable, while the middle branch in the three-solution regime is unstable.

The latter stability study on $k = 0$ can be extended to the case $k \neq 0$, which may yield Turing instabilities. However, the corresponding discussion is beyond the scope of the present work, and will be discussed in a forthcoming paper.

Finally, to gain some insights to oscillatory behavior, the separation of real and imaginary parts of λ in (13) yields the conditions for the Hopf bifurcation $\Omega^2 = E(p, k)/C(p)$, $\Omega^4 - D(p, k)\Omega^2 + F(p, k) = 0$ with angle frequency Ω . Because the necessary more detailed study of the oscillatory behavior is beyond the scope of this paper, we refer to the reader to our future publications for investigation of this problem.

4 Discussion

To interpret these results, please recall that increasing $p \geq 1$ reflects an increased concentration of the anesthetic agent propofol. Subsequently, starting from a nonanesthetic stable state at $p = 1$ at a high (low) excitatory (inhibitory) PSP, the increase of p results in the bistability of the system, and the system might jump to the stable state at lower excitatory and inhibitory stationary PSPs due to the presence of intrinsic/extrinsic fluctuations. This jump from the upper branch to the lower branch reflects the loss of consciousness of the anesthetized subject. In case the system remains on the upper branch, the stationary state finally loses stability at point A in Fig. 3 by a saddle–node bifurcation, i.e., the system becomes monostable. Now, reducing the concentration of propofol, e.g., just waiting for the subject's body to decrease the concentration, the system becomes bistable again and fluctuations may evoke the jump back to the upper branch, i.e., the anesthetized subject becomes conscious again. At point B in Fig. 3, the system passes through a saddle–node bifurcation and becomes monostable again. Moreover, it is interesting to note that the state of unconsciousness exhibits a lower level of excitation and a higher level of inhibition compared to the state of consciousness, cf. Fig. 3.

5 Concluding Remarks

The presented work derives novel evolution equations for neural populations, which consider two neuron types, two types of chemical synapses with corresponding time scales, and general synaptic spatial connectivities. It turns out that the two coupled integral-differential equations suffice to describe mathematically the loss of consciousness of subjects under administration of the anesthetic agent propofol for realistic physiological parameters. Subsequent work shall study power spectra of the neural activity in the presence of noise, as these allow for an additional comparison of the proposed model and experimental results.

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