Consideration of the effect of anesthesia in the thalamocortical assemblies

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***Abstract*— Despite intensive research efforts, the effects of anesthesia on brain physiology and function have not been satisfactorily explained yet. Nevertheless, from what has been discovered up to now, we can attribute the effect of the anesthetics to changes in calcium(Ca^{2+}) channels and in Gamma-aminobutyric acid type A($GABA_A$) synaptic receptors. In this paper, we investigate through simulations the consequences of such changes in a Hodgkin-Huxley-based model of thalamocortical assemblies.**

I. Introduction

Modeling the effects of anesthesia upon the brain is a very challenging problem, since even the origin of the electroencephalogram (EEG) oscillations, which are presently used in clinical surgery to estimate the depth of anesthesia, remains a mystery despite more than 100 years of research. Nevertheless, from our literature study about the rhythmic activity of the brain, we deduce that it is generally accepted in the neuroscience community that the slow rhythms of the EEG are created by the interaction between the cortex and the thalamus[1].

During the early stages of sleep or under anesthesia, low frequency oscillations are mostly observed in the EEG. The generation of these slow oscillations is associated with the formation of an ensemble of significantly hyperpolarized neocortical neurons. Intracellular studies have shown that the hyperpolarizing phase of the slow oscillation is associated with disfacilitation, a temporal absence of synaptic activity[2]-[4]. A computational model of thalamocortical networks was investigated to test possible mechanisms for large-scale synchrony [5]. It also made predictions about the influential role of the cortex in triggering and synchronizing oscillations generated in the thalamus through corticothalamic feedback projections[6]. Intracortical mechanisms may be responsible for synchronizing oscillations over cortical distances of several millimeters through cortex-thalamus-cortex loops, even though the generators of the oscillations are in the thalamus. According to this view, the neocortex shapes and controls the spatial pattern of thalamic oscillations.

Because of this importance of the interactions between thalamus and cortex for brain rhythms, in order to simulate brain signals, we choose the model of Bazhenov et al.[7] which considers thalamocortical assemblies. This model includes four layers of neurons, where two of them are for the thalamus (RE: thalamic reticular neurons, TC: thalamic relay neurons) and the other two are for the cortex (PY: pyramical neurons, IN: interneurons). One of the advantages of this network is that each neuron follows the Hodgkin-Huxley formalism[8] that describes the behavior of ion channels using quantities as activation functions and time constants. Another positive point is the investigation of the transformation from slow waves to higher frequency waves which also takes place in the transition from deep anesthesia to light anesthesia.

Concerning the effects of anesthesia, it is known that both volatile and intravenous anesthetics modulate the activity of a variety of ion channels and synaptic receptors of neurons[9]. However, because of the lack of basic understanding of the workings of general anesthesia at the system level, it is very difficult to determine how microscopic modulation of ion activities can produce general anesthesia. Moreover, the effects of anesthesia differ from one kind of anesthetic to the other. Intravenous anesthetics act on the synaptic receptors, especially on the $GABA_A$ receptors. Volatile anesthetics also seem to act on this $GABA_A$ receptors, but their effect is not completely understood.The modulation of ion channels, among which Ca^{2+} channels are most prominent, is also considered relevant for general anesthesia. However, it is necessary to investigate how the different anesthetic effects are integrated to produce it.

Neural models are used to link the modulation of ion channel activity due to anesthetics with overall behavior at the system level using computer simulations and analysis of their mathematical structure[10]. Gottschalk and Haney[11] examined the response of four simple neural models to the concentration of anesthetics. In each of the models, the inhibitory effects under general anesthesia which decrease the influx of the Ca^{2+} channels are approximated by a decrease in the maximal Ca^{2+} conductance, and an increase of the inhibitory chloride current which evokes the prolongation of the open time of the $GABA_A$ channels by a decrease of the rate of channel closure or an increase of the rate of channel opening in the equations describing $GABA_A$ channel dynamics(eq.5). According to the results of [11], we deduced that we can not attribute the effects of anesthetics to one simple change of parameter. In fact, one single neuron model shows a decrease in the frequency of neuron activity as a function of a decrease in maximum conductance of Ca^{2+} channels, while another model shows an increase in frequency accompanied by a change from a bursting pattern to tonic firing. One network model

reflects a decrease of the closing rate of $GABA_A$ channels in the increased amplitude and decreased frequency of the average membrane potential, indicating stronger synchrony of the neurons. Meanwhile, another neural network model doesn't show an increase of synchrony with a decrease of the closing rate but it does show greater degrees of synchronous behavior when the rate of $GABA_A$ channel opening is increased.

Consequently, it is imperative to investigate the reaction of our simulation model to changes of the parameters reflecting the effect of anesthesia. In this paper, we perform simulations on the thalamocortical assembly model varying the parameter of maximal conductance of Ca^{2+} channels or closing/opening rate of $GABA_A$ receptors from one simulation to another, and try to figure out how the global behavior of PY neurons, which should be interpreted as a field potential analogous to the EEG that is measured from experiments can be modified according to these parameter changes .

II. Model Description

A. Thalamocortical assemblies

The network consists of 100 PY, 25 IN, 50 TC, 50 RE neurons, and synaptic connections between neurons are represented in Fig.1. The numbers in this figure indicate the outdegree of each neuron for each kind of synapse, while "External" represents a fixed current stimulating the neurons. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and the N-methyl-D-aspartate (NMDA) receptors mediate fast and slow excitatory synaptic interactions respectively, while $GABA_A$ and $GABA_B$ receptors mediate fast and slow inhibitory synaptic interactions. The lower case d which is next to NMDA connections in Fig.1 indicates that short time depression[7] is included in the model. Moreover, the lower case dm next to some AMPA and $GABA_A$ connections means that spontaneous miniature EPSPs or IPSPs[7] are included in addition to the short term depression.

The kinetics of the thalamic neurons, RE and TC cells, are

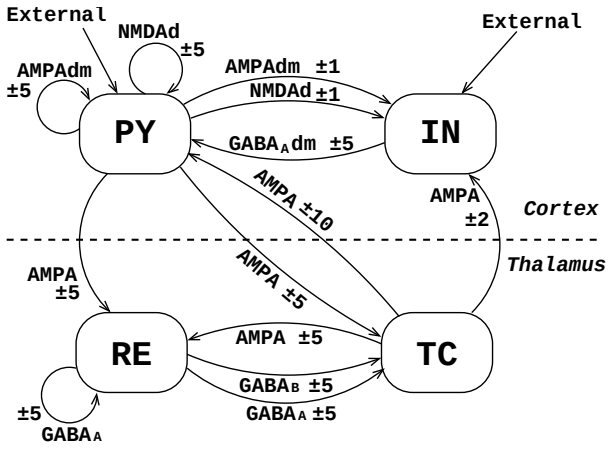

Fig. 1. Synaptic connection between four kinds of neurons

described by a single-compartment model as follows:

$$C_m \frac{dV}{dt} = -I_{leak} - I^{int} - I^{syn}, \tag{1}$$

where C_m is the membrane capacitance, V is the membrane potential, I_{leak} is the leakage current, I^{int} is the sum of active intrinsic currents and I^{syn} is the sum of synaptic currents. As intrinsic currents, for both RE and TC cells, a fast sodium(Na^+), a fast potassium(K^+), a low-threshold $Ca^{2+}(I_T)$ and a potassium leak current are considered. A hyperpolarization-activated cation current is also included in TC cells[12].

The kinetics of the PY and IN cells are described by a two-compartment model as follows:

$$C_m \frac{dV_D}{dt} = -I_{leak} - \frac{g}{S_D}(V_D - V_S) - I_D^{int} - I^{syn},$$

$$\frac{g}{S_S}(V_S - V_D) = -I_S^{int}, \tag{2}$$

where C_m and I_{leak} are the membrane capacitance and the leakage current of the dendritic compartment, V_D and V_S are the membrane potentials of dendritic and axosomatic compartments, I_D^{int} and I_S^{int} are the sums of active intrinsic currents in each compartment, S_D and S_S are the areas of each compartment, I^{syn} is the sum of synaptic currents, and g is the conductance between the two compartments. As axosomatic intrinsic currents, for both PY and IN cells, fast Na^+ and fast K^+ currents are considered. For dendritic intrinsic currents in both cells, a slow voltage-dependent noninactivating K^+, a slow Ca^{2+}-dependent K^+, a high-threshold $Ca^{2+}(I_{HVA})$, and a K^+ leak current are included. For PY cells, a persistent Na^+ current is added to both compartments[13].

Each intrinsic current is modeled as

$$I_i^{int} = \bar{g}_i m_i^{M_i} h_i^{H_i} (V - E_i), \tag{3}$$

where $\bar{g}_i$ is the maximal conductance , m_i and h_i represent the fraction of open and non-inactivated gates respectively, M_i and H_i are exponents which indicate the number of gates in each ion channel, and E_i is the reversal potential of the i-th channel.

The synaptic currents through AMPA, NMDA and $GABA_A$ channels are also modeled similarly,

$$I_i^{syn} = \bar{g}_i r_i (V - E_i), \tag{4}$$

where $\bar{g}_i$ is the maximal conductance , r_i is the fraction of receptors in the open state, and E_i is the reversal potential of the i-th receptor. The activation parameter r follows the first-order kinetics

$$\frac{dr}{dt} = \alpha[T](1 - r) - \beta r, \tag{5}$$

where α and β are voltage-independent forward and backward rate constants, and $[T]$ is the transmitter concentration, represented by a pulse after each presynaptic spike. The $GABA_B$ receptors are modeled by a higher-order reaction scheme that takes into account the activation of K^+ channels by G-proteins.

B. Effect of anesthesia

The inhibitory effect on Ca^{2+} channels, which changes when anesthetic concentration is increased, is frequently modeled with the Hill equation

$$Inhibition = \frac{EC_{50}^n}{[A]^n + EC_{50}^n}, \quad (6)$$

where $[A]$ is the anesthetic concentration, n is the Hill coefficient, and EC_{50} is the anesthetic concentration at which channel activity is inhibited by 50%. This leads to the following modulation of maximal conductance which is now effectively modeled as a function of anesthetic concentration:

$$g_i = \bar{g}_i \frac{EC_{50}^n}{[A]^n + EC_{50}^n} m_i^{M_i} h_i^{H_i}, \quad (7)$$

Unfortunately, the effects on the $GABA_A$ receptors cannot be modeled uniquely like the Ca^{2+} channels as a function of anesthetic concentration because of the complex reaction to the anesthetic quantity which differs from kind to kind. The most pronounced effect, the prolongation of the open time of the $GABA_A$ channels, is modeled by a decrease of β and an increase of α in eq.5 as mentioned before. For some anesthetics, detailed quantitative descriptions of how these parameters vary with anesthetic concentration have been obtained, but still the descriptions for the anesthetics used in our experiments must be defined.

III. Results

A. Slow oscillations

One simulation is carried out implementing the model of Bazhenov et al.[7]. From Fig.2, we can observe the propagation of neuronal activity forming a striped pattern with respect to time. As mentioned at the end of the introduction, the EEG reflects the global synchrony of cortical neurons. More precisely, the amplitude of the EEG takes a high value when many PY neurons are spiking and, conversely, returns a low value during silent phases of activity. From the frequency of stripes in the figure, we can perceive that the frequency of EEG is about 0.2-3 Hz, which matches the frequency range of δ waves. We set the parameters used to obtain this result as a default and carry out other simulations changing parameters that concern the effect of anesthesia described in the previous section, using the same initial conditions.

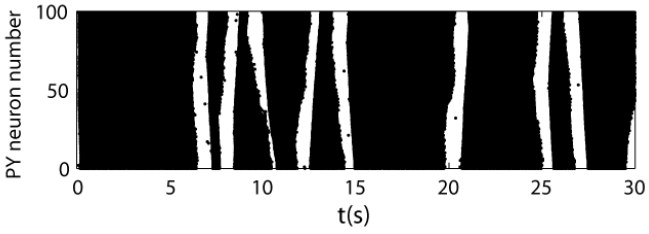

Fig. 2. Spontaneous activity of 100 PY cells for 30sec.

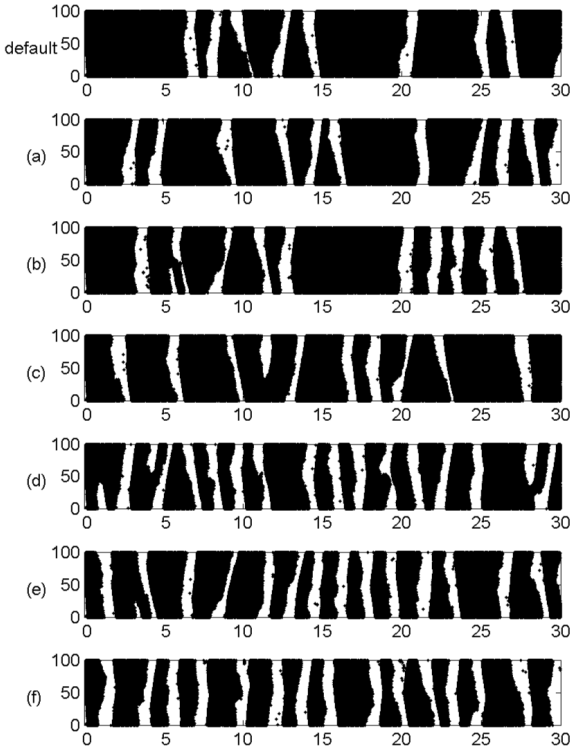

Fig. 3. Spontaneous activity of 100 PY cells depending on maximal conductance $\bar{g}$ of calcium channels ($\bar{g}_{T_{RE}}$, $\bar{g}_{T_{TC}}$, $\bar{g}_{HVA_{PY\&IN}}$). The x axis represents time(s) and the y axis is the PY neuron index. At the top, the default plot is shown for reference: (a)5% less than default $\bar{g}$, (b)10% less, (c)20% less, (d)40% less, (e)60%less, and (f)80% less.

B. Effects on Ca^{2+} channels

Since, for the moment, we don't have experimental measurements of the concentration of the anesthetics around the neurons, we simply change the maximal conductances of Ca^{2+} channels. More precisely, $\bar{g}_T$ in both RE and TC cells and $\bar{g}_{HVA}$ in PY and IN cells are decreased by the same percentage in each simulation. On Fig.3, we can remark that the number of white stripes increases as the values of $\bar{g}$ decrease, which makes sense because weakening Ca^{2+} currents has an inhibitory effect on neurons. This has as a consequence an increase in global frequency, which is not observed in the experiments. Therefore, further frequency analysis on the mean field of PY neurons is necessary to conclude about that. Moreover, we can also perceive that the synchrony among neurons becomes stronger with the change of this parameter since stripes are more limited by vertical lines when $\bar{g}$ is small.

C. Effects on $GABA_A$ synaptic receptors

As a first exploration of the effects on $GABA_A$ channels, we performed simulations decreasing the channel closing rate β in all $GABA_A$ connections by the same ratio. From Fig.4, we can see that the effect of inhibition is so powerful that at a certain value of β the coherent spiking activity in the

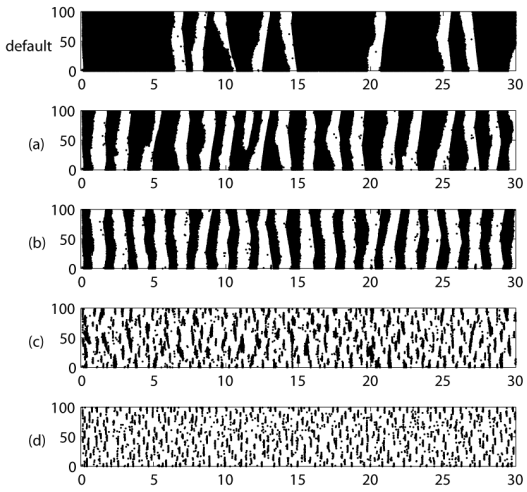

Fig. 4. Spontaneous activity of 100 PY cells depending on $GABA_A$ channel closing rate β. The x axis represents time(s) and the y axis is the PY neuron index. At the top, the default plot is shown for reference: (a)7/8 times default β, (b)3/4 times, (c)1/2 times, and (d)1/4 times.

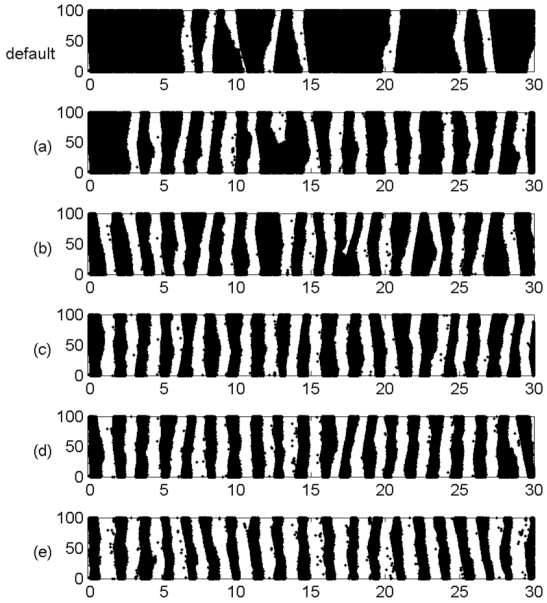

Fig. 5. Spontaneous activity of 100 PY cells depending on $GABA_A$ channel opening rate α. The x axis represents time(s) and the y axis is the PY neuron index. At the top, the default plot is shown for reference: (a)1.25 times default α, (b)1.5 times, (c)1.75 times, (d)2 times, and (e)5 times.

network becomes unsustainable. However, a small decrease of β actually increases the synchrony of neurons.

Fig.5 shows the results obtained in simulations in which we increase the $GABA_A$ channel opening rate α. As in the case of β, the network is inhibited by the prolongation of the opening time of the $GABA_A$ channels and duration of silent states which is represented by the white stripes increases. Moreover, we can observe that the neurons are more synchronized due to this increment for the same reason as before. However, the difference among the Fig.5(c)(d) and (e) is not large so that the change in the global reaction to the increase of α seems to have some kind of threshold effect.

IV. Conclusions

In this paper, the effect of anesthesia in a model of the thalamocortical system was investigated. To begin with, thalamocortical assemblies were taken as the origin of the slow waves in EEG signals, and a model based on the Hodgkin-Huxley formalism was chosen, implemented and simulated. Furthermore, the reaction of this model to changes of the parameters related to anesthetics was tested. The results have shown that supression of the inhibition that suppresses the spiking activities was effectively induced by all changes of the parameters, but the degree of this reaction was different in each case. Future tasks would be to test the reaction to parameter changes depending on the kinds of neurons or receptor positions, and also to consider the time evolution of the concentration of anesthetics. The final goal is to create a reliable model that allows to explain the effect of anesthesia, and compare the mean field of PY neurons with the EEG obtained from the experiments.

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