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# Biophysical Modeling of Alpha Rhythms During Halothane-Induced Unconsciousness*

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## Abstract

During the induction of general anesthesia there is a shift in power from the posterior regions of the brain to the frontal cortices; this shift in power is called anteriorization. For many anesthetics, a prominent feature of anteriorization is a shift specifically in the alpha band (8–13 Hz) from posterior to frontal cortices. Here we present a biophysical computational model that describes thalamocortical circuit-level dynamics underlying anteriorization of the alpha rhythm in the case of halothane.

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Halothane potentiates $GABA_A$ and increases potassium leak conductances. According to our model, an increase in potassium leak conductances hyperpolarizes and silences the high-threshold thalamocortical (HTC) cells, a specialized subset of thalamocortical cells that fire at the alpha frequency at relatively depolarized membrane potentials (>−60 mV) and are thought to be the generators of quiet awake occipital alpha. At the same time the potentiation of $GABA_A$ imposes an alpha time scale on both the cortical and the thalamic component of the frontal portion of our model. The alpha activity in the frontal component is further strengthened by reciprocal thalamocortical feedback. Thus, we argue that the dual molecular targets of halothane induce the anteriorization of the alpha rhythm by increasing potassium leak conductances, which abolishes occipital alpha, and by potentiating $GABA_A$, which induces frontal alpha. These results provide a computational modeling formulation for studying highly detailed biophysical mechanisms of anesthetic action in silico.

## I. Introduction

As humans are induced into a state of general anesthesia there is a shift in EEG power from posterior regions of the brain to frontal regions of the brain. This shift in spatial power is called anteriorization [1]–[3]. A prominent aspect of anteriorization for certain anesthetics is a shift in alpha power (8–13 Hz) from posterior regions to frontal regions –the disappearance of quiet awake occipital alpha and the emergence of an anesthetically-induced frontal alpha. This shift in alpha power has been carefully characterized in the case of propofol [3]–[6]. In addition, a biophysically-based computational model has been developed to explain the circuit-level mechanisms that underlie the shift in alpha power during propofol-induced anesthesia [7].

Here we employ a related model to understand the physiological mechanisms underlying the anteriorization of alpha power for halothane, which potentiates $GABA_A$ conductances and increases potassium leak conductances [8]–[11]. We show that when we mimic the physiological actions of halothane in our model, alpha activity disappears from the posterior component, while alpha activity emerges in the frontal component. This dual effect is achieved by the multifaceted action of halothane. First, halothane increases potassium leak currents, silencing high-threshold thalamocortical cells (HTC), the putative generators of occipital quiet awake alpha. These specialized cells generate alpha activity at relatively depolarized membrane potentials (>−60 mV), and an increase in potassium leak conductances cause them to become hyperpolarized and move out of the operating range at which they are able to generate quiet awake alpha activity. While occipitally projecting thalamic nuclei contain HTC cells, these specialized cells are thought to be absent from frontally projecting thalamic nuclei. The second relevant effect of halothane we consider is the potentiation of $GABA_A$. As described in [7], [12] this potentiation imposes an alpha time scale on both the cortical and thalamic components of the frontal model that is reinforced by reciprocal thalamocortical feedback. We show here that the frontal alpha persists even after an increase in potassium leak conducatances. By using a mathematical modeling formulation, we are able to provide a detailed characterization of the neuronal dynamics induced through the introduction of both propofol and halothane. This computational approach offers a highly efficient means of evaluating the effects of competing actions of

anesthetics and may ultimately serve as a useful tool for engineering new means of dosing or delivering these drugs.

## II. Methods

We use the baseline conditions (i.e., before the administration of propofol) of the propofol model described in [7] as a starting point for the model presented here. Here we include the critical methodological details directly from [7], with minor alterations and the addition of details pertinent to halothane. The model consists of single-compartment Hodgkin-Huxley neurons. In this formalism, the membrane potential of each neuron is governed by the nonlinear differential equation

$$C_M dV/dt = -\Sigma I_M - \Sigma I_{Syn} (1),$$

where $I_M$ denotes membrane currents, $I_{Syn}$ denotes synaptic currents, and $C_M$ denotes the specific membrane capacitance. To capture the dynamics of anteriorization we combine a thalamocortical circuit that can account for the properties of propofol-induced frontal alpha [12] with a thalamic circuit that has the properties needed to generate occipital alpha [13]. We briefly describe each in turn below.

### A. Model for frontal thalamocortical network

The structure of the network is shown schematically on the left-hand side of Fig. 1. Specifically, we consider a thalamic network model of 10 thalamocortical (TC) neurons reciprocally connected to 10 thalamic reticular (RE) neurons. The RE cells provide inhibition both to TC cells, mediated by both $GABA_A$ and $GABA_B$, and to other RE cells, mediated by $GABA_A$. The TC cells in turn provide excitatory inputs to the RE cells by means of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). This configuration is a standard thalamic model structure [14]. The cortical model consists of 8 pyramidal (PY) cells connected to 4 inhibitory interneurons (IN). The thalamocortical loop is formed by excitatory connections from TC cells onto PY and IN cells and reciprocal excitatory connections from PY cells onto RE and TC cells. Notable membrane currents include a T-type calcium current (in the TC and RE cells), a hyperpolarization-activated cation current $I_h$ (in the TC cells), and a potassium leak current $I_{KL}$ (in the TC cells). The baseline parameterization of all currents are specified in [12].

### B. Model for posterior thalamic network

The structure of the thalamic network is shown schematically on the right-hand side of Fig. 1. The network consists of 10 RE cells, 8 TC cells, and 2 specialized thalamocortical cells (HTC cells). HTC cells are thought to generate awake alpha and make up only 15–25% of the TC cell population [15], [16]. While HTC cells have been reported in the lateral geniculate nucleus, to the best of our knowledge they have not been reported in frontally projecting thalamic nuclei and so they are not included in the frontal model. The connectivity between RE and TC cells (including HTC cells) is the same as for the frontal network, except that HTC cells are connected via gap junctions [17]. A critical feature of the HTC cells is that at depolarized membrane potentials (>−60 mV) they burst with the timing

between bursts occurring at the alpha frequency. The bursts are mediated by a channel we refer to as $I_{THT}$, an $I_T$ calcium channel variant that operates at more depolarized membrane potentials than does the standard $I_T$ channel; the use of this channel is based on experimental findings [13], [15]. The ionic currents and basal parameterizations are similar to those listed in [13] for muscarinic acetylcholine receptor (mAChR) agonist-induced alpha. The occipital alpha model does not have a cortical component since more experimental work would be needed in order to construct it accurately. Furthermore, experimental work suggests that disrupting alpha in the lateral geniculate nucleus, disrupts quiet awake occipital alpha [18]; thus a thalamic alpha model is sufficient for our purposes. Please see [7] for further details about this modeling choice.

### C. Halothane Simulation

To model the effects of halothane on both the frontal and posterior networks, two perturbations were introduced to the baseline conditions. First, the $GABA_A$ inhibitory synaptic current was potentiated by a factor of three [8], [9], [19]. Second, the conductance of the potassium leak current current, $I_{Kleak}$, was increased by a factor of two over the baseline value [10], [11].

The simulated EEG for the posterior model was computed as a function of the membrane potential of HTC cells. This is in accordance with experimental findings that show awake thalamic alpha cannot be abolished by blocking synaptic currents [15]. For the frontal model the EEG was simulated as a sum of pyramidal AMPA currents. Our results hold if the EEG is simulated using the membrane potential of pyramidal cells instead.

## III. Results

During anesthetic induction, while subjects are in a quiet awake state with their eyes closed, alpha activity is observed over the occipital cortex. Both *in vivo and in vitro* studies have shown that the introduction of mAChR agonists to the lateral geniculate nucleus (LGN) can induce alpha activity in the LGN [16], [18]. The *in vivo* studies show that the introduction of mAChR agonists to the LGN also results in the induction of quiet awake alpha-like activity at the EEG level over the occipital cortex [18]. Furthermore, mAChR antagonists introduced to the LGN disrupt alpha activity not only in the LGN, but also in the occipital cortex. Since we wanted to model the type of alpha activity seen during the early part of anesthetic induction, which is similar to awake alpha, we adjusted the parameters of the baseline model to mimic the effects of mAChR agonists. This adjustment results in HTC cells firing at the alpha frequency (Fig. 2e), and alpha power is observed in the simulated occipital EEG (Fig. 2h). Under these model conditions, the RE cells are relatively quiet (Fig. 2g), in accordance with what is seen in experimental studies [18]. At the same time all cell types in the frontal component fire irregularly, resulting in the simulated EEG power being relatively flat (Fig 3.a–d).

We then adjusted the parameters of our model to mimic the actions of halothane by increasing both $GABA_A$ and potassium leak conductances. These changes result in the silencing of HTC cells in the occipital component (Fig. 3e) and in the simulated occipital EEG power being relatively flat (Fig. 3h). The bursts in the HTC cells are thought to be

mediated by $I_{THT}$ channels, a variant of $I_T$ channels that tend to be active at more depolarized membrane potentials [15]. Increasing potassium leak conductances results in the hyperpolarization of HTC cells, moving them to an operating range where $I_{THT}$ channels are relatively inactive. This disrupts the awake-alpha generating mechanisms of HTC cells and therefore silences them. At the same time the potentiation of $GABA_A$ imposes an alpha time scale on both the cortical and the thalamocortical portion of the frontal component of the model (See [12] for more details). Due to the potentiation of $GABA_A$, cortical interneurons impose a rhythmic firing onto the pyramidal cells at the alpha time scale (Fig. 3a,d). Also, the $GABA_A$ potentiation in the thalamus hyperpolarizes TC cells via RE cells, thus engaging intrinsic currents in TC cells, namely $I_T$ and $I_h$, which are more active at hyperpolarized membrane potentials. This results in the circuit firing at the alpha frequency (Fig. 3b,c). The alpha activity in both the thalamic and the cortical components is reinforced by the thalamocortical loop (See [12] for more details). Our contribution here is that this mechanism for the generation of frontal alpha via $GABA_A$ potentiation remains intact even when the potassium leak conductances are increased by the actions of halothane.

## IV. Discussion

In our previous work we demonstrated how propofol induces the anteriorization of the alpha rhythm via its molecular targets, $I_h$ and $GABA_A$, using a thalamocortical model. In particular the reduction of $I_h$ silences HTC cells, and $GABA_A$ potentiation induces frontal alpha. Here we demonstrate through modeling how halothane, which acts on potassium leak conductances and potentiates $GABA_A$, can also induce the anteriorization of the alpha rhythm. Our model shows that an increase in potassium leak conductances hyperpolarizes HTC cells, thus silencing them and abolishing occipital alpha. Futhermore, the model shows that this increase in potassium leak conductances does not disrupt the induction of frontal alpha by $GABA_A$ potentiation. We caution, however, that if halothane acts on additional currents, additional spectral characteristics may result during the induction of anesthesia.

It is thought that the induction of anesthesia via halothane results in the anteriorization of the alpha rhythm [1], [20]. Our model provides circuit-level insights into the possible mechanisms underlying the anteriorization of the alpha rhythm during the induction of general anesthesia via halothane. The model also highlights the general advantages of a computational approach towards investigating mechanisms of general anesthetic drugs within neuronal circuits. Such an approach is a powerful use of mathematical and systems-level modeling to describe both normal, pathological and drug-induced brain dynamics.

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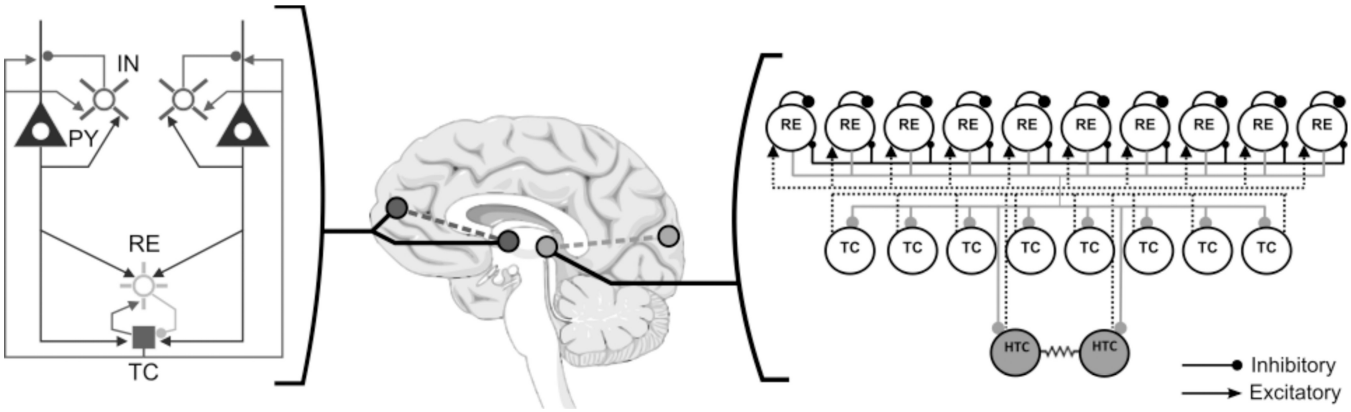


**Fig. 1.**

Schematic of model. The frontal portion of the model is depicted on the left-hand side. At the thalamic level it consists of inhibitory reticular nucleus cells (RE) reciprocally connected to excitatory thalamocortical cells (TC). The cortical component consists of reciprocally connected interneurons (IN) and pyramidal cells (PY). There are excitatory connections between the thalamic component and the cortical component via the PY and TC cells. The occipital component is depicted on the right-hand side. It consists of RE and TC cells interconnected in the same manner as the frontal component. It also includes a specialized subset of TC cells, HTC cells, which fire at depolarized membrane potentials at the alpha frequency. The HTC cells are coupled via gap junctions. This is a modified version of Fig. 1 in [7].

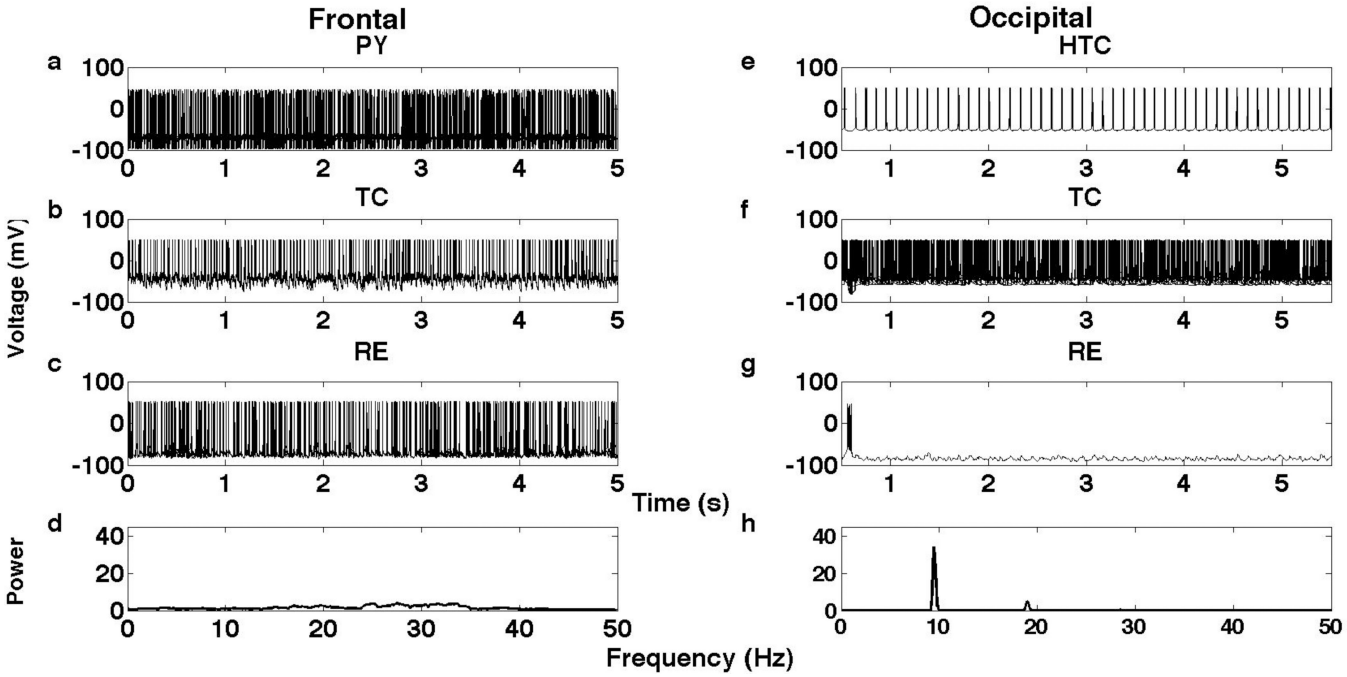


**Fig. 2.**

Activity patterns under baseline conditions. The firing patterns of PY cells (a), TC cells (b), and RE cells (c) and the power spectrum of the simulated EEG (d) of the frontal component. The firing patterns of HTC cells (e), TC cells (f), and RE cells (g) and the power spectrum of the simulated EEG (h) of the occipital component.

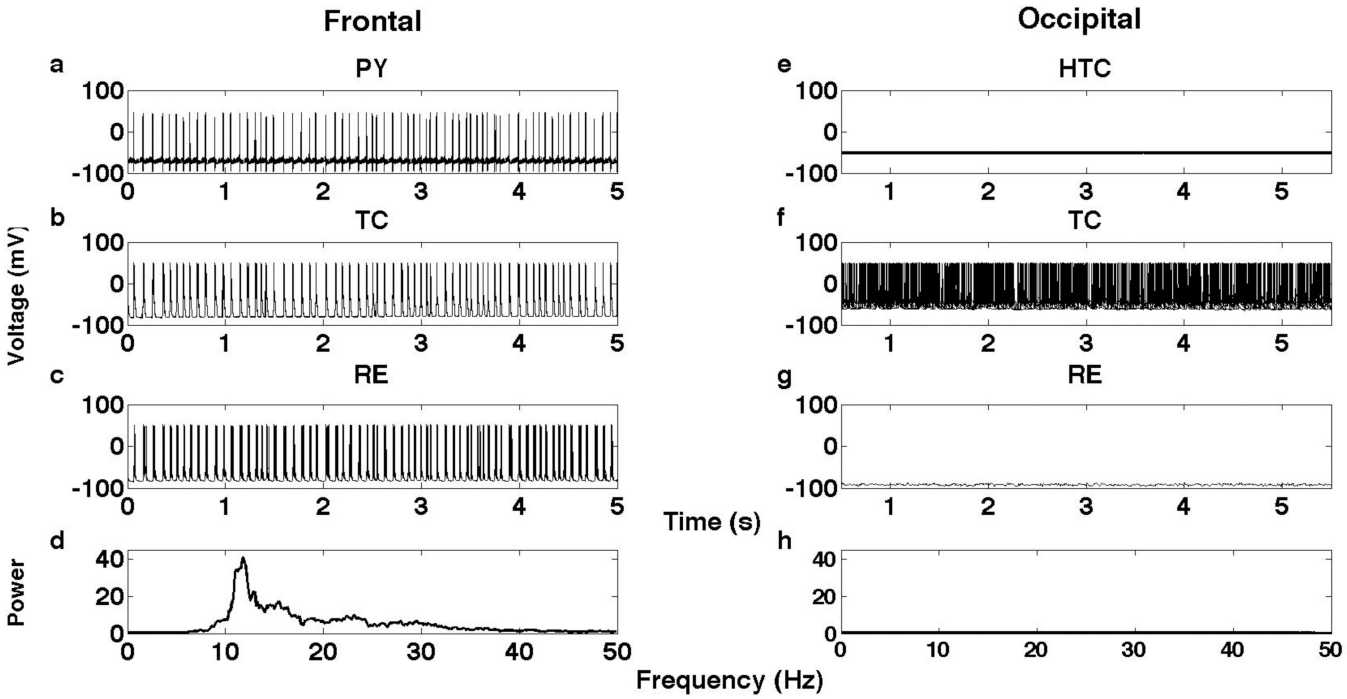


**Fig. 3.**

Activity patterns during halothane-induced anesthesia. The firing patterns of PY cells (a), TC cells (b), and RE cells (c) and the power spectrum of the simulated EEG (d) of the frontal component. The firing patterns of HTC cells (e), TC cells (f), and RE cells (g) and the power spectrum of the simulated EEG (h) of the occipital component.