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Modeling the dynamical effects of anesthesia on brain circuits

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General anesthesia is a neurophysiological state that consists of unconsciousness, amnesia, analgesia, and immobility along with maintenance of physiological stability. General anesthesia has been used in the United States for more than 167 years. Now, using systems neuroscience paradigms how anesthetics act in the brain and central nervous system to create the states of general anesthesia is being understood. Propofol is one of the most widely used and the most widely studied anesthetics. When administered for general anesthesia or sedation, the electroencephalogram (EEG) under propofol shows highly structured, rhythmic activity that is strongly associated with changes in the patient's level of arousal. These highly structured oscillations lend themselves readily to mathematical descriptions using dynamical systems models. We review recent model descriptions of the commonly observed EEG patterns associated with propofol: paradoxical excitation, strong frontal alpha oscillations, anteriorization and burst suppression. Our analysis suggests that propofol's actions at GABAergic networks in the cortex, thalamus and brainstem induce profound brain dynamics that are one of the likely mechanisms through which this anesthetic induces altered arousal states from sedation to unconsciousness. Because these dynamical effects are readily observed in the EEG, the mathematical descriptions of how propofol's EEG signatures relate to its mechanisms of action in neural circuits provide anesthesiologists with a neurophysiologically based approach to monitoring the brain states of patients receiving anesthesia care.

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Introduction

General anesthesia is a fascinating man-made, neurophysiological phenomenon that has been developed empirically to enable safe and humane performance of surgical and non-surgical procedures. The state consists of unconsciousness, amnesia, analgesia, and immobility along with maintenance of physiological stability. In the United States, more than 60,000 patients receive general anesthesia daily [1,2]. General anesthesia has been used in the United States for more than 167 years. Now, using systems neuroscience techniques, including, neurophysiology experiments with behavioral testing, detailed signal processing analyses and mathematical modeling, how anesthetics act in the brain and central nervous system to create the states of general anesthesia is being understood. Mathematical modeling has been used in anesthesiology to study the dynamics of anesthetic binding at specific receptor sites, to provide pharmacokinetic and pharmacodynamic descriptions of anesthetic behavior within the body [3–5], and to describe specific brain states such as burst suppression [6•,7]. The advent of systems neuroscience studies is fostering a growing interest in using modeling studies to describe anesthetic actions in neural circuits [8,9,10•,11,12•,13–18].

Propofol, 2,6-di-isopropyl-phenol, is one of the most widely used anesthetics. This drug is administered for induction of general anesthesia, maintenance of sedation, and in combination with a narcotic and a muscle relaxant for maintenance of general anesthesia. Propofol acts enhances inhibition at $GABA_A$ receptors, which are widely present throughout the brain and central nervous system [19]. Binding of propofol to the post-synpatic $GABA_A$ receptors on pyramidal neurons helps maintain chloride channels in the open state, thus enhancing the inward chloride current, which hyperpolarizes the post-synaptic cell and leads to inhibition [19]. The behavioral effects of propofol depend critically on how much and how rapidly the anesthetic is administered, in addition to the physiological state of the patient, such as, age, weight and co-morbidities [20], and the presence of other arousal potentiating medications.

Propofol's behavioral effects are strongly associated with highly structured oscillatory patterns in the electroencephalogram (EEG), local field potentials and in neural spiking activity [21,22••,23•]. The highly reproducible nature of these patterns suggest that they relate to the mechanisms through which propofol's binding at $GABA_A$ receptors leads to strong coordinated network activity throughout major portions of the brain. Because much is known about brain circuit architecture, the highly rhythmic features in these patterns suggests that mathematical modeling research can make important contributions to our understanding of propofol's actions in neural circuits, and as a consequence, how this anesthetic produces its altered states of arousal.

In this review, we summarize recent work using mathematical models to investigate the dynamical effects of propofol on brain circuits.

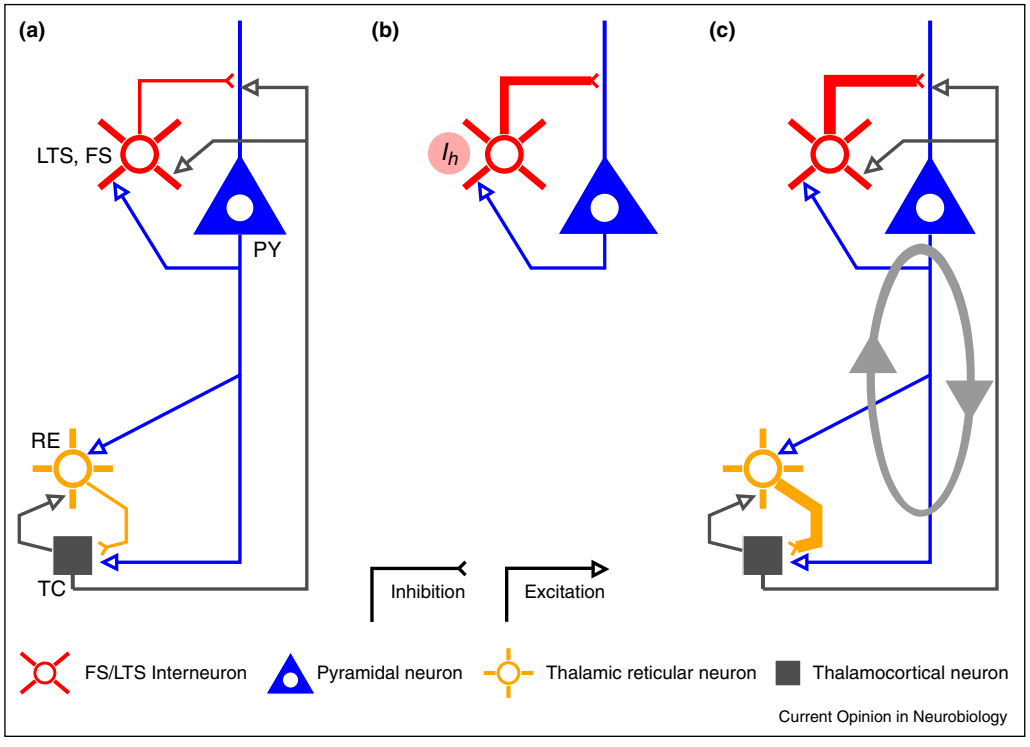
Paradoxical excitation

Propofol is well-known to induce paradoxical behavioral and electrophysiological manifestations of excitation, rather than sedation, at low doses [24–27]. A common EEG marker for this paradoxical excitation is elevated power in the beta (12.5–25 Hz) frequency band [25]. Despite these long-standing characterizations, the neuronal mechanisms that underlie the low-dose effects of propofol were not well understood.

Recently, a detailed computational model was developed in order to elucidate these mechanisms [9]. The model attributes the generation of Beta-band activity at low doses of propofol to cortical dynamics involving the interaction of pyramidal neurons with two type of inhibitory interneurons. The model specifically focusses on the role of the M-current, a slow potassium current, in low-threshold spiking (LTS) interneurons [28]. Propofol is modeled as a potentiation of the conductance and time constant of the $GABA_A$ synaptic current [29]. A low dose of propofol is modeled as inducing up to a twofold increase in each of these parameters. At such levels, the interaction between the $GABA_A$ synaptic current and the M-current creates a dynamical transition from synchrony to antisynchrony in networks of cortical interneurons (see Figure 1a,b). At the population level, this antisynchrony manifests as an increase in the spiking frequency of pyramidal neurons into the beta range. By modeling the collective activity of these pyramidal neurons as a surrogate for the EEG [30], the model thus predicts paradoxical excitation as a collective state of cortical interneuron antisynchrony mediated principally by LTS cells. A detailed mathematical analysis of this model was subsequently performed in [31]. There, in a highly reduced version of [9], the authors used geometric singular perturbation theory to show how the M-current and $GABA_A$ interplay is highly specific to the low-dose regime. The essential dynamical mechanism in this regime was revealed to be the creation of post-inhibitory rebound spiking in LTS interneurons.

Other modeling efforts on propofol have used a mean-field models that describe neuronal dynamics at the scale of cortical macrocolumns [32,33]. These approaches focus

Figure 1



Thalamic and cortical dynamics for low-dose and anesthetic-dose levels. **(a)** In a baseline regime, the thalamocortical system functions through interactions between four principle cell types: Cortical pyramidal neurons (PY), Interneurons (LTS/FS), Thalamic Reticular Neurons (RE) and Thalamocortical neurons (TC). **(b)** At low doses of propofol, a moderate increase in $GABA_A$ interacts with the hyperpolarization-activated current I_h in interneurons to create a primarily cortical beta oscillation [9]. **(c)** At higher (surgical) dose levels, the effects on $GABA_A$ increase in both cortical and thalamic networks, creating alpha (10–13 Hz) time-scales paced by the decay-rate of the inhibition [10•]. The reverberant connections between thalamic and cortex reinforces this oscillation, leading to broad and coherent alpha oscillations in the EEG. Figure adapted from [10•].