Computational Aspects of Anesthetic Action in Simple Neural Models

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THE VOLATILE and intravenous anesthetics modulate activity of a variety of voltage-gated and ligand-gated ion channels. However, the mechanism(s) by which one or more of these effects produces general anesthesia and the specific site(s) of action which produce this state are presently unknown. There is growing recognition of the need for integrative approaches in order to relate anesthetic effects on ion channels with systems level behavior. However, the difficulty of determining how modulation of ion channel activity can produce general anesthesia is compounded by the relative paucity of information as to what constitutes general anesthesia at the systems level. Here, neural models are used to link anesthetic modulation of ion channel activity with overall systems level behavior using computer simulation and the analysis of the mathematical structure of some of these models. This complements recent work focusing primarily on anesthetic modulation of network interactions in more abstract and more complex models.

It has been hypothesized that the in vitro concentration-effect curve of the receptor responsible for general anesthesia should be similar to that seen in vivo at the systems level, where attention is generally paid to the slope and midpoint of such curves. An important feature of the in vivo concentration-effect curve that must be accounted for is its threshold-like behavior as anesthetic concentration is increased. Since anesthetic concentrations that lead to immobility lie well below the EC50 of the relatively shallow concentration-effect curves for volatile anesthetic suppression of voltage-gated ion channel activity, the above hypothesis has been used to implicate the ligand-gated ion channels as the site of action for the volatile anesthetics.

The ligand-gated ion channel thought to be most involved in the mechanism of action of the volatile anesthetics is the GABA_A receptor which, with greater certainty, is the site of action for the intravenous anesthetics thiopental, propofol, etomidate, and the neurosteroids. Yet, volatile anesthetic action may not be completely understood in terms of anesthetic modulation of GABA_A. Knockout mice lacking a component of the GABA_A receptor are readily anesthetized with volatile anesthetics, although this may simply reflect that the component of the GABA_A receptor necessary for volatile anesthetic action is still present in the knockout. Furthermore, the nonhalogenated anesthetics cyclopropane and butane have little effect on the GABA_A receptor which may also be true for the gaseous anesthetic xenon. However, if voltage-gated ion channels are relevant in general anesthesia, it is necessary to appreciate how relatively modest anesthetic effects at the ion channel are integrated to produce general anesthesia.

A model which links anesthetic action at the ion channel with systems level effects requires specific hypotheses as to the nature of general anesthesia at the systems level. Clinically, general anesthesia consists of at least loss of consciousness, amnesia, immobility, and blunting of autonomic reflexes. For inhalational anesthetics, anesthetic potency is generally quantified by using immobility as the endpoint. However, other attributes of general anesthesia appear at anesthetic concentrations that differ from those that lead to immobility. Moreover, immobility requires much greater anesthetic concentrations in preparations which provide anesthetic to only the brain and not the spinal cord. Thus, anesthetic effects at the systems level may be multimodal and associated with particular regions of the central nervous system.

Quantifying anesthetic effects at the systems level has been limited to analysis of the electroencephalograph and functional imaging of brain activity. Use of the electroencephalograph to characterize anesthetic depth has been complicated because electroencephalographic signals are not invariant with respect to anesthetic agent, and are not readily associated with specific endpoints such as immobility, though some progress has been made. Nonetheless, several features of the electroencephalograph are generally observed. For the intravenous anesthetics (barbiturates, propofol, and etomidate) a rather characteristic pattern is observed. At lower, generally subanesthetic, concentrations there is an increase in the fundamental frequency of the raw electroencephalographic signal, followed by slowing and increasing amplitude of the electroencephalograph with increasing anesthetic depth and, ultimately, burst suppression and isoelectric behavior are observed. Administration of benzodiazepines leads to loss of the α rhythm.
which is replaced by a higher frequency β rhythm in the human electroencephalograph, but does not eliminate the γ oscillations present in hippocampal slices. The volatile anesthetics are generally associated with increased slowing as anesthetic concentration is increased, followed by burst suppression and isoelectric behavior. Exceptions to this include seizure activity associated with enflurane, and lack of burst suppression or isoelectric electroencephalograph with the usual clinical concentrations of halothane. Increased variability is seen in the electroencephalograph during low dose ethanol consumption, and detailed analysis of the electroencephalograph under these conditions suggests a loss in the nonlinear structure of the electroencephalographic signal which permits an increased level of randomness. Functional imaging of human brain activity reveals that subanesthetic doses of isoflurane increase regional brain activation during specific tasks. During general anesthesia, the relative metabolism of the basal forebrain, thalamus, limbic system, cerebellum, occiput and midbrain reticular formation has been noted to decrease, and decreases in cerebral metabolic activity have been linked to measures derived from electroencephalographic activity. Regional differences in cerebral metabolic activity have been invoked to support the hypothesis that general anesthetics produce unconsciousness by modulation of the reticular nucleus of the thalamus. Thus, regional oscillatory activity as reflected by the electroencephalograph may be an important systems level correlate of anesthetic action.

Systems neurobiology has focused increasingly on the presence and role of correlated oscillations in the neocortex and other brain regions. Certain types of oscillations have been hypothesized to solve the “binding problem” of systems neurophysiology, the problem of linking the activation of multiple brain regions by related information. A neocortical layer of fast-spiking interneurons connected by inhibitory GABA_A and electrical synapses may be responsible for generating γ frequency oscillations (40–80 Hz), which are hypothesized to solve the binding problem and appear to play an important role in attention. Other types of oscillations occur at lower frequencies, and have been associated with the level of consciousness. For example, the spindle oscillations (7 to 14 Hz) that originate in the thalamus and appear with the onset of sleep or with barbiturate anesthesia are probably generated in the reticular nucleus of the thalamus with modulatory input from thalamocortical relay cells. Thus, through modulation of the voltage- and ligand-gated ion channels, anesthetics could interfere with neural oscillations and the neurophysiologic processes regulated by these oscillations.

A number of relatively simple computational neural models are now examined to help conceptualize the integrated effects of general anesthetics on the behavior of individual neurons and larger networks.

Methods

Computational models of single neurons and networks of neurons were modified to permit modulation of the voltage-gated and ligand-gated ion channels by volatile and intravenous anesthetics. The effects of volatile anesthetics on neural activity were then evaluated as a function of anesthetic concentration and other model parameters. The impact on model behavior was assessed by computer simulation and, where possible, examination of the mathematical structure of the models using analytic techniques.

Models

Four computational models of individual neurons and networks of neurons were examined. These were the Morris–Lecar model of oscillation in the barnacle muscle fiber, the Pinsky–Rinzel simplification of the 19-compartment model of the CA-3 hippocampal neuron by Traub et al., the Golomb–Rinzel network model of the reticular nucleus of the thalamus, and the Wang–Buzsáki model of hippocampal interneurons. These models were selected because of their relative simplicity and to illustrate specific aspects of anesthetic action. The Morris–Lecar and Pinsky–Rinzel models were used to examine the behavior of individual neurons as voltage-gated channel activity is modulated by anesthetics. The Golomb–Rinzel and Wang–Buzsáki models were used to examine anesthetic effects on simple oscillating networks.

General Principles of Computational Neural Models

Each of the biophysical models presented is built around the formalism developed by Hodgkin and Huxley. Membrane potential \( V_m \) is obtained from the differential equation for membrane potential:

\[
C \frac{dV_m}{dt} = I_{app} - I_{ion}
\]

where \( C \) is the membrane capacitance, \( I_{app} \) is the externally applied current, and \( I_{ion} \) is the sum of the currents resulting from the ion fluxes through the membrane ion channels. Essentially, this equation is a statement that the sum of the currents across the cell membrane must equal the externally applied current. Individual ionic currents whose sum comprises \( I_{ion} \) are modeled as a potential across a conductance. Thus, the individual currents \( I_i \) are expressed as

\[
I_i = g_i(V_m - V_i)
\]

where \( g_i \) is the conductance of the channel and \( V_i \) is the potential due to the ion conducted by the \( i \)-th channel (reversal potential). The conductance is a highly nonlin-
ear function of time and membrane potential. A general expression for \( g_i \) is
\[
g_i = \tilde{g}_i p_i^m q_i^m
\]
where \( \tilde{g}_i \) is the maximal conductance of the i-th channel and is proportional to the channel density, \( p_i \) and \( q_i \) represent gates which must both be in a permissive state for current to flow, and \( l_i \) and \( m_i \) are the corresponding exponents which can be thought of as the number of gates in one ion channel. Both \( p_i \) and \( q_i \) range between 0 and 1 to represent the fraction of gates in the permissive position. For both \( p_i \) and \( q_i \), this fraction is typically governed by an equation of the form
\[
\frac{dp_i}{dt} = \alpha_p(V_m)(1 - p_i) - \beta_p(V_m)p_i
\]
where \( \alpha(V_m) \) is the voltage-dependent rate constant governing the rate that the gate transitions from the non-permissive to the permissive state and \( \beta(V_m) \) is the voltage-dependent rate constant governing the rate that the gate transitions from the permissive to the non-permissive state. Typically, \( \alpha(V_m) \) and \( \beta(V_m) \) are highly nonlinear functions of membrane potential that must be empirically determined for each channel. For some systems calcium concentration can be a particularly important determinant of \( \alpha \) and \( \beta \). Temperature dependence of the model can be introduced through the system of equations defined by Eq. 4. This requires the use of a function \( \phi(T) \), such that
\[
\frac{dp_i}{dt} = \phi(T)[\alpha_p(V_m)(1 - p_i) - \beta_p(V_m)p_i]
\]
where \( \phi(T) \) is often of the form
\[
\phi(T) = Q_{10}^{(T - T_0)/10}
\]
where \( T \) is the new temperature, \( T_0 \) is the temperature for which the system was originally configured, and \( Q_{10} \) is the coefficient describing the increase in rate of the i-th process for a 10-degree increase in temperature. Thus, the rates, but not the steady state solutions of the system of equations defined by Eqs. 5 and 6 will be altered by temperature.

The above system of differential equations is a general description of a single compartment that can be considered the fundamental building block for constructing biophysical neural models. Often, a single compartment is sufficient to capture the behavior of interest as in the original Hodgkin-Huxley model or the Morris-Lecar model described below. To capture more elaborate neural behavior, particularly when investigating an anatomically complex neuron with a heterogeneous distribution of ion channels, multiple compartments can be electrically coupled together as in the Pinsky-Rinzel model, described below, and the more complex models which motivated it. Networks of single or multiple-compartment neurons can be generated by coupling them with one or more excitatory or inhibitory synapses as with the Golomb-Rinzel and Wang-Buzsáki models, below. Typically, synaptic currents are modeled beginning with equations like those of Eqs. 2–4, in which the conductance is governed by the presynaptic potential and the kinetics of the specific neurotransmitter. The contribution of each neuron in the network to the synaptic current(s) must be considered, and the connection geometries governing neural interactions can range from all-to-all, to random, to highly specific.

Specific Computational Models

Barnacle giant muscle fiber. The Morris–Lecar model (Appendix A)\(^49\) is useful for demonstrating the effects on individual neural activity of anesthetic modulation of voltage-gated ion channels. Although rather simple, this model displays many behavioral modes seen in more complex neural models and, therefore, is often used to demonstrate these different modes of behavior.\(^56\) Moreover, its relative simplicity permits more analytical approaches. It consists of a single compartment containing a nonactivating high voltage activated (HVA) \( Ca^{2+} \) channel, a \( K^+ \) channel, and a leak current.

Hippocampal CA3 neuron. The hippocampus plays an important role in memory and, because its anatomy is well suited for slice preparations, has been studied extensively in the laboratory. In addition, it has been the motivation for multiple computational modeling studies of increasing complexity, where this complexity extends to more realistic descriptions of ion channel activity, dendritic anatomy, distribution of ion channels over the dendrites, and network interactions.\(^57,58\) The Pinsky–Rinzel\(^50,51\) (Appendix B) reduction of Traub et al.’s 19-compartment hippocampal neuron model\(^19\) is used to illustrate the consequences of volatile anesthetic modulation of ion channel activity in hippocampal neurons. The two-compartment Pinsky–Rinzel model consists of single somatic and dendritic compartments that are electrically coupled. The somatic compartment contains a fast \( Na^+ \) channel, a fast \( K^+ \) channel, and a leak current. The dendritic compartment contains an HVA \( Ca^{2+} \) channel, two \( Ca^{2+} \) activated potassium channels (BK and SK), and a leak current.

Thalamic reticular nucleus. Although the thalamus is primarily known for its multiple nuclei relaying afferent sensory input, the reticular nucleus of the thalamus is thought to be the source of the spindle oscillations (7–14 Hz) seen during drowsiness, at sleep onset, and barbiturate anesthesia, and is the source of the electroencephalographic \( \alpha \) rhythm (8–12 Hz).\(^43,47,48\) The behavior of this nucleus is thought to be modulated by excitatory input from thalamocortical neurons which, themselves, receive several types of inhibitory input...
from the neurons of the reticular nucleus. Computational models of this system vary in complexity with respect to the description of the ion channels of the individual neurons as well as the nature and complexity of the interactions of the reticular nucleus with thalamocortical neurons. A simplified model of the reticular nucleus of the thalamus was developed by Golomb and Rinzel (Appendix C) in which membrane potential is controlled by the dynamics of fast-sodium and fast-potassium channel and a leak current, and neural interactions are mediated by GABA \(_\text{A}\) inhibitory interactions. Since modulation of GABA \(_\text{A}\) receptor activity is thought to be the basis for the action of a number of anesthetics, this model provides the opportunity to computationally examine the effects of anesthetics on a physiologically important neural system that may be related to consciousness. The model in Appendix C has been modified slightly from the original to permit partial connectivity between neurons in the network.

**Fast-spiking interneuron network.** As delineated in the Introduction, interactions of the neocortex may be regulated by a network of fast-spiking interneurons. These fast-spiking interneurons may also contribute to the behavior of the hippocampus. Wang and Buzsáki (see Appendix D) have constructed a model of this network in which neural interactions are modulated by GABA \(_\text{A}\) inhibitory interactions. Because the voltage-gated ion channels that define the properties of the individual neurons in this network are different from those of the reticular nucleus of the thalamus, the network properties also differ. This difference arises primarily because the output of the thalamic neurons described above is a burst controlled by Ca\(^{2+}\) entry as opposed to spikes controlled by the dynamics of fast-sodium and fast-potassium channels.

**Anesthetic Modulation of Ion Channel Activity**

The volatile anesthetics are known to modulate both voltage-gated and ligand-gated ion channels. Of the voltage-gated ion channels, the effect on the Ca\(^{2+}\) channel is most pronounced, although other types of receptors may play a role. Inhibitory effects on both the LVA and HVA Ca\(^{2+}\) channels decrease Ca\(^{2+}\) influx under general anesthesia. Effects on the T- (LVA), L- (HVA), and N- (HVA) type Ca\(^{2+}\) channels have been demonstrated. The decrease in Ca\(^{2+}\) current as volatile anesthetic concentration is increased appears to be relatively voltage insensitive. Consequently, as a first approximation which neglects transient effects upon activation of the channel, it is reasonable to model volatile anesthetic modulation of Ca\(^{2+}\) channels as a decrease in the maximal Ca\(^{2+}\) conductance \(g_{\text{Ca}}\) in Eqs. A.1, B.2b, and C.1) which varies with volatile anesthetic concentration. The extent that a channel is inhibited as anesthetic concentration is increased is frequently modeled with the Hill equation

\[
\text{Inhibition} = \frac{[A]^n}{[A]^n + EC_{50}^n}
\]

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 modification of Eq. 3:

\[
g_i = g_{i0} \frac{EC_{50}^n}{[A]^n + EC_{50}^n} p_i q_i m_i
\]

where, effectively, the maximal conductance is now modulated as a function of anesthetic concentration. Volatile anesthetic effects on ion channels other than the Ca\(^{2+}\) channels do occur. However, the effects on the fast-sodium and fast-potassium channels occur at much higher concentrations than for the Ca\(^{2+}\) channels.

Meaningful volatile anesthetic effects on the Ca\(^{2+}\)-activated potassium channels may occur at anesthetic concentrations close to the \(EC_{50}\) for the Ca\(^{2+}\) channels. A variety of intravenous and volatile anesthetic effects are known for the ligand-gated ion channels. Most of these involve the GABA \(_\text{A}\) inhibitory channel that controls neural interactions in the Golomb–Rinzel model of the reticular nucleus of the thalamus and the Wang–Buzsáki model of the fast-spiking interneuronal network. The GABA \(_\text{A}\) inhibitory channel is the only ligand-gated ion channel in these models.

The intravenous anesthetics such as the barbiturates, etomidate, propofol, and neurosteroids are all known to increase the inhibitory chloride current by prolonging the open time of the GABA \(_\text{A}\) channel when it is stimulated with GABA. At higher concentrations of the intravenous anesthetics a decrease in the chloride current through the GABA \(_\text{A}\) channel is observed for at least several classes of the intravenous anesthetics which are known to prolong GABA opening. At somewhat higher concentrations the intravenous anesthetics listed above can activate chloride currents in the absence of GABA. The benzodiazepines, though exerting their action at the GABA \(_\text{A}\) receptor, differ from the intravenous anesthetics in that they appear to exert their effect by increasing the rate at which the GABA \(_\text{A}\) channel opens and are also distinguished by their inability to directly induce chloride currents through the GABA \(_\text{A}\) receptor. The effects of volatile anesthetics on the GABA \(_\text{A}\) channel share several similarities with the intravenous anesthetics. Their effect is characterized by prolongation of channel open time. However, at somewhat higher volatile anesthetic concentrations, the amplitude of the chloride current in the GABA \(_\text{A}\) channel is also decreased.

The above description of anesthetic effects on the GABA \(_\text{A}\) channel leads directly to a set of modifications to
the descriptions of \( \text{GABA}_A \) dynamics in the above computational models. An increase in the open time of the \( \text{GABA}_A \) channel, as seen with the intravenous and volatile anesthetics, can be modeled by decreasing the rate constant which governs the rate of channel closure in the equations describing \( \text{GABA}_A \) channel dynamics (\( \beta_{\text{syn}} \) in Eqs. C.3 and D.4 of the Appendices). This decrease in the rate constant as a function of anesthetic concentration has been measured experimentally for propofol and thiopental,\(^7\) and isoflurane, enflurane, and halothane.\(^6\) An increase in the rate of \( \text{GABA}_A \) channel opening, as seen with the benzodiazepines, can be modeled by increasing the parameter that governs the rate at which the channel opens (\( \alpha_{\text{syn}} \) in Eqs. C.3 and D.4 of the Appendices). A decrease in the amplitude of the inhibitory chloride current generated when the \( \text{GABA}_A \) is open can be modeled by decreasing the synaptic conductance (\( g_{\text{syn}} \) in Eqs. C.1 and D.1 of the Appendices). For some anesthetics,\(^6\) detailed quantitative descriptions of how these parameters vary with anesthetic concentration have been obtained and can be incorporated in the mathematical description of the model.

### Computer Simulation

The models presented in the Appendices were implemented with Mathematica 4.0.2.\(^2\)\(^8\) and were solved with the Runge–Kutta\(^9\) integration option. Additional simulations were also performed with the neural simulation language Genesis\(^3\) 2.0 that uses the exponential Euler integration scheme, where step size was progressively decreased and the stability of solutions with respect to chosen step size confirmed. All simulations were carried out until steady state behavior was achieved, and results from the terminal portion of the simulations are usually presented.

### Analytical Determination of Underlying Model Structure

Analytic approaches become less practical with increasing model complexity. Consequently, these are considered only for the Morris–Lecar model. The example given here follows a very typical approach for problems of this type,\(^6\) and was previously exemplified for the Morris–Lecar model.\(^5\) Here, this approach is adjusted to examine the alteration in model behavior as anesthetic concentration is varied.

Although more complex questions can be addressed, the most fundamental issue is when and how qualitative behavior changes as one or more parameters are varied. In this case, the parameter is, effectively, anesthetic concentration through its modulation of \( g_{\text{Ca}} \) (Eq. A.1 in the Appendices). The first step is to find the equilibrium point(s) of the system by setting the derivatives of Eqs. 1 and 4 to zero and solving for the variables \( V_m \) and \( p_f \). For each of the equilibrium points, the system is linearized and the stability of the linearized system examined. This is typically done by computing the eigenvalues of the matrix which characterizes the linearized system at the given equilibrium point. If the eigenvalues of the matrix are given as \( \lambda_i \), this corresponds to modes \( x_i(t) \) of system behavior in the vicinity of the equilibrium point of the form

\[
x_i(t) = e^{\lambda_i t}
\]

which indicates that the solution will tend to leave the vicinity of the equilibrium point for \( \text{Re}(\lambda_i) > 0 \), will head toward the equilibrium point for \( \text{Re}(\lambda_i) < 0 \), and exhibit a transition (bifurcation) in behavior for \( \text{Re}(\lambda_i) = 0 \), where \( \text{Re}(\lambda) \) denotes the real portion of the possibly complex eigenvalue. Thus, by examining \( \lambda_i \) as parameters of the system are varied important information can be obtained about the ability of given parameters to impact on fundamental aspects of system behavior. A typical behavioral change indicated by \( \text{Re}(\lambda_i) \) passing through zero would be a switch from quiescence (\( \text{Re}(\lambda_i) < 0 \)) to sustained oscillatory behavior (\( \text{Re}(\lambda_i) > 0 \)).

All analytic calculations were carried out using both the symbolic and numeric capabilities of Mathematica. The equilibrium points were obtained numerically, these results were substituted into the corresponding Jacobian matrix, obtained symbolically from the linearized system, and the eigenvalues of this matrix were then computed.

### Results

**Volatile anesthetic modulation of \( \text{Ca}^{2+} \)-current in the barnacle muscle fiber**

When parameterized as in Appendix A, the Morris–Lecar model produces sustained oscillations for injection currents from 33 to 42 \( \mu \text{A/cm}^2 \). In figure 1, for a fixed injection current of 35 \( \mu \text{A/cm}^2 \), the maximal \( \text{Ca}^{2+} \) conductance (\( g_{\text{Ca}} \) in Eq. A.1) is decreased, as might occur in the presence of a volatile anesthetic, until oscillations cease. Initially, as \( g_{\text{Ca}} \) is decreased, there is a graded decrease in the frequency of the oscillations (not shown). As illustrated in figure 1, for the given injection current, only a 10.8% decrease in the \( \text{Ca}^{2+} \) conductance is sufficient to prevent sustained oscillations, and the termination of oscillatory behavior occurs abruptly as \( g_{\text{Ca}} \) is decreased. The loci of injection current and \( g_{\text{Ca}} \) where oscillations cease is shown in figure 2A. Note that when \( g_{\text{Ca}} \) is decreased from its baseline value, larger injection currents are required for sustained oscillations. Conversely, larger injection currents will hyperpolarize the neuron unless \( g_{\text{Ca}} \) is decreased. The Morris–Lecar model was developed for a physiologic preparation maintained at \( 22^\circ \text{C} \) (room temperature). Volatile anesthetic sensitivity of HVA calcium channels at room temperature is known, and demonstrates a midpoint of approximately 0.85 \text{mM} and a Hill coefficient of 1.5 for...
halothane. Using these values to parameterize Eq. 8, the data of figure 2A can be used to construct the loci of volatile anesthetic concentration and injection current, shown in figure 2B, for which oscillations cease. Simultaneously incorporating volatile anesthetic sensitivity of the potassium channels by assuming that halothane suppression of potassium channel activity has a midpoint of between 3.063 and 6.4 mM and a Hill coefficient of 1.5 introduces no additional behavior. For the points shown in figure 2, the termination of oscillatory behavior as $\gca$ decreases corresponds analytically to a change in sign of the real component of one of the corresponding eigenvalues from positive to negative, demonstrating a basis for the abruptness of the transition.

Fig. 1. Behavior of the Morris–Lecar barnacle muscle fiber model, described in Appendix A, as $\gca$ conductance is varied with a fixed injection current. (A) The behavior of the model for the parameters of Appendix A is shown at the top for an injection current of 35 $\mu$A/cm$^2$. (B) When the $\gca$ conductance is decreased from its baseline value of 4.00 mS/cm$^2$ to 3.58 mS/cm$^2$ (10.5%), sustained oscillations persist. (C) However, decreasing the $\gca$ conductance to 3.57 mS/cm$^2$ (10.8% from baseline) prevents the emergence of sustained oscillations, demonstrating a threshold effect for behavior as $\gca$ conductance is modulated.

Fig. 2. Locus of injection current and $\gca$ conductance (A) or volatile anesthetic concentration (B) where sustained oscillation is not possible for the Morris–Lecar barnacle muscle fiber model. As described in the text, the plot in (B) was created from the data in (A) assuming that halothane decreases $\gca$ conductance according to the Hill equation where an halothane concentration of 0.85 mM decreases $\gca$ conductance by 50% and with a Hill coefficient of 1.5.

Volatile Anesthetic Modulation of Hippocampal CA3 Neurons

The response of the Pinsky–Rinzel model of the CA3 hippocampal neuron (see Appendix B) to steady current injection to the somal compartment is known to vary qualitatively with the magnitude of the injection current, as summarized in figure 3. Low levels of injection current lead to a bursting pattern (fig. 3A) mediated by calcium entry. Higher currents lead to complex patterns of spiking and bursting due to interactions between the somal and dendritic compartments (fig. 3B). Even higher currents lead to a somatic spiking pattern (fig. 3C), whose rate increases with increasing somal current injection (not shown) until the current is so great that the neuron remains in the depolarized state and cannot generate spike activity.

Halothane modulation of maximal $\gca$ conductance ($\gca$ in Eq. B.2b) was modeled using the same scheme.
concentrations because decreases in Ca\(^2+\) concentration still increase for a range of volatile anesthetic concentrations.


dendritic K\(^+\) current injected to the somatic compartment. A bursting pattern is present in (A) for \(I_s = 0.75\ \mu A/cm^2\). Increasing the injection current to \(I_s = 1.75\ \mu A/cm^2\) leads to a complex interaction between the somal and dendritic compartments and a correspondingly complex pattern of bursting and spiking (B). Higher injection currents lead to a spiking pattern generated by the somal compartment, shown in (C) for \(I_s = 2.5\ \mu A/cm^2\). For each case, a segment near the end of the panel on the left is shown in greater detail on the right.

and parameters as above. Modulation of the bursting pattern of figure 3A by halothane is shown in figure 4 for halothane concentrations of 0.10, 0.20, and 0.33 mM. Although a small increase in burst duration and frequency is seen in figure 4A for concentrations of 0.10 mM, most of the increase occurs between 0.15 mM and 0.2 mM (fig. 4B). Between 0.2 mM and 0.33 mM, irregular behavior composed of shorter bursts and spikes eventually gives way to the regular spiking behavior shown in figure 4C. For somal injection currents that produce the irregular pattern of figure 3B, halothane modulation of Ca\(^2+\) conductance produces a spiking pattern as halothane concentration is increased (not shown). Once the somal injection current is high enough to produce pure spiking behavior as in figure 3C, halothane modulation of Ca\(^2+\) conductance has no impact on the pattern and frequency of the spike train.

The alterations in burst duration and frequency occur as a direct result of decreases in the Ca\(^2+\) current. Although a decrease in Ca\(^2+\) current requires a smaller dendritic K\(^+\) current to repolarize the neuron, the burst duration still increases for a range of volatile anesthetic concentrations because decreases in Ca\(^2+\) accumulation delay production of sufficient dendritic Ca\(^2+\)-dependent K\(^+\) currents (primarily \(I_{K,C}\) of Eq. B.2a) to terminate the burst. The decreased rate of intracellular Ca\(^2+\) accumulation is due to both the decrease in the amplitude of the Ca\(^2+\) current and, indirectly, to the corresponding decrease in the membrane potential of the dendritic compartment, which then prevents full activation of the gating parameter of the Ca\(^2+\) channel (s in Eqs. B.2b, B.7 and B.8). The decrease in Ca\(^2+\) concentration achieved during a burst also contributes to the observed increase in burst frequency. A burst cannot be initiated until the dendritic K\(^+\) current (primarily \(I_{K,AHP}\) of Eq. B.2a) is sufficiently small, which occurs when the gating variable \(q\) for \(I_{K,AHP}\) decreases below a specific threshold. When the Ca\(^2+\) current is decreased by a volatile anesthetic, the decreased Ca\(^2+\) concentration decreases the activation variable \(\alpha_q\) (Eq. B.14a) and, hence, the maximal value of \(q\) achieved during a burst. Since the decay of \(q\) is relatively invariant with respect to membrane potential and Ca\(^2+\) concentration (Eq. B.14b), a smaller maximal value of \(q\) will require a shorter interval to reach the

Fig. 3. Representative behavior of Pinsky–Rinzel model of CA3 hippocampal neurons, described in Appendix B, during current injection to the somatic compartment. A bursting pattern is present in (A) for \(I_s = 0.75\ \mu A/cm^2\). Increasing the injection current to \(I_s = 1.75\ \mu A/cm^2\) leads to a complex interaction between the somal and dendritic compartments and a correspondingly complex pattern of bursting and spiking (B). Higher injection currents lead to a spiking pattern generated by the somal compartment, shown in (C) for \(I_s = 2.5\ \mu A/cm^2\). For each case, a segment near the end of the panel on the left is shown in greater detail on the right.

Fig. 4. Modulation of behavior of Pinsky–Rinzel model of CA3 hippocampal neurons by increasing concentrations of halothane during application of the relatively low somal injection current (\(I_s = 0.75\ \mu A/cm^2\)) used to generate Fig. 3A. It is assumed that halothane modulates Ca\(^2+\) conductance by decreasing the peak Ca\(^2+\) conductance according to the Hill equation where a halothane concentration of 0.85 mM decreases Ca\(^2+\) conductance by 50%, and with a Hill coefficient of 1.5. A modest increase in burst frequency and duration is produced when halothane concentration is 0.10 mM (A). This becomes more pronounced for a halothane concentration of 0.20 mM (B). Sustained spike activity appears with halothane concentrations of 0.33 mM (C) and greater (not shown). For each case, a segment near the end of the panel on the left is shown in greater detail on the right.
threshold where burst initiation becomes possible, leading to an increase in burst frequency. At higher volatile anesthetic concentrations, the Ca\(^{2+}\) conductance is diminished to the point where Ca\(^{2+}\) mediated voltage spikes do not occur in the dendritic compartment. Burst activity becomes impossible and is supplanted by rapid somatic spiking, effectively switching the behavioral mode of the neuron.

Incorporating volatile anesthetic effects on the sodium and potassium channels in the somal compartment adds little new behavior. The suppression of sodium channel activity by halothane has been reported to have a midpoint that ranges from 2.0\(^{66}\) to 2.6\(^{65}\) mM, and that for the potassium channel from 3.0\(^{65}\) to 6.4\(^{66}\) mM. Following earlier work, a Hill coefficient of 1.5 is assumed.\(^\text{19}\) When the more sensitive value of 2.0 ms is used for the sodium channel, the anesthetic concentration at which regular spiking behavior emerges will increase by about 0.01 ms, but only if the EC\(_{50}\) of the potassium channel is close to 6.4 mM. Once regular spiking appears, it persists with a decreasing amplitude as anesthetic concentration is increased to at least several times the value of the midpoint of the sodium channel sensitivity.

### Anesthetic Modulation of Inhibitory Interactions in the Reticular Nucleus of the Thalamus

The behavior of the Golomb–Rinzel model of the reticular nucleus of the thalamus as inhibitory interactions are modulated (fig. 5) for a network where, on average, each neuron interacts with 80% of the other network neurons. Here, the constant governing the rate at which neurons interact with 80% of the other network neurons.

In contrast to overall network behavior, the gross behavior of individual neurons is minimally affected by changes in \(\beta_{\text{syn}}\). As \(\beta_{\text{syn}}\) is decreased and GABA\(_A\) channels remain open longer, the frequency of the overall neural activity and the coherence of this activity are affected. \(^\text{55}\) The increased coherence as \(\beta_{\text{syn}}\) is decreased is reflected in the increased amplitude and decreased frequency of the average membrane potential, which should be interpreted as a field potential analogous to the electroencephalograph. In contrast to overall network behavior, the gross behavior of individual neurons is minimally affected by changes in \(\beta_{\text{syn}}\), as seen in figure 6.

Decreases in maximal Ca\(^{2+}\) conductance (\(I_{\text{Ca}}\) of Eq. C.1) of about 20–40%, as might occur in the presence of the volatile\(^\text{63}\) or intravenous anesthetics,\(^\text{92}\) permits network synchrony to occur at somewhat larger values of \(\beta_{\text{syn}}\) (not shown). The network behavior that is most prominent with decreased Ca\(^{2+}\) conductance is the increase in the value of \(\beta_{\text{syn}}\) where the fundamental frequency of the average membrane potential approaches that of the individual neurons, signifying relatively complete network synchrony. This occurs for \(\beta_{\text{syn}} = .01 \cdot \text{ms}^{-1}\) when \(I_{\text{Ca}} = .4 \text{ mS/cm}^2\), and \(\beta_{\text{syn}} = .02 \cdot \text{ms}^{-1}\) when \(I_{\text{Ca}} = .3 \text{ mS/cm}^2\). The decreased Ca\(^{2+}\) current permits a relatively greater impact of the inhibitory currents on membrane potential, effectively increasing the coupling between neurons, permitting synchronization to occur at larger values of \(\beta_{\text{syn}}\). Unlike the Pinsky–Rinzel model of the CA3 hippocampal neuron presented above, the relatively simple calcium dynamics of the Golomb–Rinzel model of the reticular nucleus of the thalamus precludes refinement of the calcium burst by delayed calcium entry. Consequently, the shape of the calcium burst and the burst frequency remain unaffected with the above decrements in Ca\(^{2+}\) conductance.

Both the volatile\(^\text{64,91}\) and intravenous\(^\text{83,84}\) anesthetics may decrease the amplitude of the inhibitory currents produced by GABA\(_A\) channels. As might be anticipa-
the above results are affected minimally by decreases of 10–20% in the conductance governing GABA_A synaptic interactions ($g_{syn}$ in Eq. C.1). Decreases of this magnitude might be observed at relatively high concentrations of the volatile anesthetics. An increase in the rate constant governing GABA_A opening ($\alpha_{syn}$ in Eq. C.3), as is hypothesized to occur in the presences of benzodiazepines, has little effect on the behavior of individual neurons or the entire network. This occurs because the onset of inhibitory currents is already very rapid when compared to the relatively slow time course of the individual neurons. Consequently, increasing $\alpha_{syn}$ does little to alter the time course or intensity of inhibitory interactions.

**Anesthetic Modulation of Inhibitory Interactions in a Fast-Spiking Interneuronal Network**

As emphasized by Wang and Buzsáki and illustrated in figure 7, the synchrony of the fast-spiking interneuronal network depends critically on the rate constant governing the closure of the GABA_A synapses. However, in marked contrast to the network model of the reticular nucleus of the thalamus, reduction in the value of $\beta_{syn}$ leads to decreased synchrony of the network. This is reflected by an increase in frequency and decrease in amplitude of the membrane potential when it is averaged over all neurons in the network as a network analog of the electroencephalograph. Importantly, this occurs for relatively modest reductions in $\beta_{syn}$, especially when compared to the reductions in $\beta_{syn}$ that were necessary to achieve network synchrony in the model of the reticular nucleus of the thalamus. The reduction in synchrony with reduction of $\beta_{syn}$ was seen for a range of values of $g_{syn}$. In contrast to the properties of the Golomb-Rinzel model depicted in figure 6, the frequencies at which individual neurons in the network oscillate decrease somewhat with decreasing $\beta_{syn}$.

The sensitivity of the fast-spiking interneuronal network to alterations in the rate at which the GABA_A channels open, as might occur in the presence of the benzodiazepines, is shown in figure 8. An increase in the rate at which GABA_A channels open can lead to greater degrees of synchronous behavior. Although the values of $\alpha_{syn}$ used to generate figure 8 are somewhat smaller than that of 12 · ms$^{-1}$, used to generate the simulations of figure 7, they demonstrate a sensitivity of the fast-spiking interneuron model to changes in the rate of GABA_A channel opening that are not present in the more slowly oscillating model of the reticular nucleus of the thalamus.

Incorporating volatile anesthetic effects on Na$^+$ and K$^+$ conductance as described for the model of the hippocampal neuron has minimal impact on the behavior of individual neurons within the network. However, the decreased spike amplitude as anesthetic concentration approaches the EC$_{50}$ of the Na$^+$ channel leads to decreased inhibitory interactions and loss of network synchrony for halothane concentrations of about 1.5 mM.
Although it is known that volatile anesthetics can suppress Ca\(^{2+}\) current, obtaining model behavior as a function of the concentration of a particular volatile anesthetic, as was done in figure 2 for the Morris–Lecar model, is still somewhat imprecise. First, the kinetics of the volatile anesthetic’s interaction with the Ca\(^{2+}\) channel are not well-established, nor is the effect of the volatile anesthetic on the kinetics of the Ca\(^{2+}\) current. Second, the full complement of necessary experimental data are unavailable. Minimally, this would include measurements of anesthetic modulation of ion channel activity for the same type of preparation as the model, obtained at the same temperature as the experimental data on which the model is based, and with sufficient measurements to describe channel behavior over the full range of anesthetic concentrations. The Morris–Lecar model was developed for a preparation of the barnacle giant muscle fiber at room temperature (22°C). Data obtained at room temperature from a different type of cell demonstrates values of 0.85 mS for the EC\(_{50}\) and 1.5 for the Hill coefficient (n in Eq. 7)\(^{63}\) which were used along with Eq. 7 to estimate volatile anesthetic effects for other anesthetic concentrations. Even though there is some imprecision in relating volatile anesthetic concentration to decreases in calcium current, this does not alter the fundamental observations of threshold-like behavior occurring for decreases in maximal Ca\(^{2+}\) conductance well below 50%, and that the threshold varies with the level of stimulation current.

**Hippocampal CA3 Neuron.** The Pinsky–Rinzel\(^{46}\) model of the CA3 hippocampal neuron was examined with the same computational approach used to examine the Morris–Lecar model of the barnacle giant muscle fiber. To determine the impact of volatile anesthetics on model behavior, the model incorporated the same quantitative relationship between anesthetic concentration and maximal Ca\(^{2+}\) conductance (g\(_{\text{Ca}}\) in Eqs. B.2b and B.8) used above in the Morris–Lecar model. Volatile anesthetic modulation of Ca\(^{2+}\) current leads to an increase in burst frequency, a lengthening of burst duration and, finally, a switch from bursting to spiking behavior as anesthetic concentration is increased (fig. 4).

As detailed in the Results, all of these effects occur in the model as a direct result of decreases in the Ca\(^{2+}\) current and the subsequent decrease in intracellular calcium concentration. The increase in burst duration is a consequence of the decrease in the calcium-activated potassium current (I\(_{\text{K–Ca}}\) in Eq. B.2a, also known as BK). Therefore, any decrease in this current by direct action of volatile anesthetics,\(^{73–76}\) should lead to additional burst duration. Because the increase in burst frequency is tied to reductions in the afterhyperpolarization current (I\(_{\text{KAHP}}\) in Eq. B.2a, also known as SK), it can be seen that if volatile anesthetics had the additional effect of reducing the afterhyperpolarization current, then burst frequency might be further increased.

Discussion

To help conceptualize the integrated response to anesthetic modulation of voltage-gated and ligand-gated ion channels and the contribution of this integrated response to general anesthesia, four computational neural models were modified to incorporate known features of anesthetic action on ion channel behavior. Models were chosen for their parsimony and their ability to illustrate integrative aspects of anesthetic action in systems with features that may be relevant to general anesthesia.

**Models and Their Limitations**

**Barnacle Giant Muscle Fiber.** The Morris–Lecar model of the barnacle giant muscle fiber,\(^{49}\) although of minimal clinical relevance, is an important model of calcium oscillations whose simplicity permits some degree of mathematical analysis which complements observations made from the simulations. The major finding with this model is that relatively modest decrements in maximal Ca\(^{2+}\) conductance, as might occur in the presence of the volatile anesthetics, can terminate the oscillations. Importantly, the Ca\(^{2+}\) conductance and, therefore, the anesthetic concentration at which neural quiescence emerges is a function of the level of stimulation provided by the amplitude of the injection current, consistent with the observation that general anesthesia is a function of the level of stimulation. An examination of the underlying mathematical structure of the model reveals not just a change in the nature of the oscillation, but the emergence of a perfectly stable system that is no longer capable of oscillation.
Again, these results demonstrate that relatively modest volatile anesthetic effects on voltage-gated ion channels could have important consequences for the behavior of the neuron. The prolongation of burst duration in the presence of volatile anesthetics is known to occur in vitro. A switch from a bursting mode to a tonic-spiking mode for isolated hippocampal neurons in the presence of volatile anesthetics is not as well established experimentally, where network considerations may predominate. However, in simpler systems, a sufficiently high Ca\(^{2+}\) conductance is necessary for bursting behavior to supplant spiking behavior. The ability of a volatile anesthetic to switch a neuron from a bursting pattern to a tonic spiking one whose rate is a function of the input current could have important consequences for information transfer in the brain. Switching of neural firing patterns is already used by the brain to regulate information flow through the thalamus where modulation of a T-type Ca\(^{2+}\) channel determines the mode of behavior and bursting is more likely to elicit cortical activity.

As with the Morris–Lecar model, the relationship between specific effects in the model and a given anesthetic concentration is imprecise for many of the same reasons. An additional issue with the model of the CA3 hippocampal neuron used here is the presence of only a single type of Ca\(^{2+}\) channel, when multiple HVA and LVA Ca\(^{2+}\) channels contribute to the membrane potential of CA3 neurons, each with a unique sensitivity to the volatile anesthetics. Ultimately, the full impact of the effects of volatile anesthetics on the model neurons may not be realized until they are incorporated in a network which also incorporates the volatile anesthetic effects on inhibitory interactions as well as the contributions to network dynamics from other inhibitory and excitatory interactions which may not be affected by the volatile anesthetics.

**Thalamic Reticular Nucleus.** An appreciation for the contribution of network interactions can be seen in the simulation of the Golomb–Rinzel model of the reticular nucleus of the thalamus. Here, a decrease in the rate at which the GAB\(_A\) channels close, which leads to prolongation of the inhibitory current, was used to incorporate the effects of intravenous or volatile anesthetic effects on inhibitory synaptic interaction. The anesthetic-induced reductions in the rate of GAB\(_A\) channel closure (\(\beta_{\text{syn}}\) in Eq. C.3) that are introduced in the model correspond to those found experimentally for clinically relevant concentrations of anesthetics. As the open time of the GAB\(_A\) channels increased, progressive slowing of overall network activity, but not that of individual neurons, was observed, reflecting a growing synchrony in network behavior. Although there is a level of conductance for the GAB\(_A\) channel (\(\overline{g}_{\text{syn}}\) in Eq. C.1) below which synchrony becomes impossible, for the most part decreases in this conductance only altered the range of the rate parameter governing closure of the GAB\(_A\) channels (\(\beta_{\text{syn}}\) in Eq. C.3) over which the transition to synchronous behavior is observed. As emphasized above for the model of the CA3 hippocampal neuron, volatile anesthetics may also affect the currents of the voltage-gated ion channels, particularly Ca\(^{2+}\) channels. Although the model of the reticular nucleus used here incorporates a T-type Ca\(^{2+}\) channel, many model features that might permit more elaborate interactions of volatile anesthetics with the individual neurons, particularly the Ca\(^{2+}\)-dependent potassium currents were not present. Despite this, decreases in Ca\(^{2+}\) current increased the ability to achieve network synchrony because this permitted a relatively greater influence of the inhibitory synaptic currents on membrane potential. Increasing the rate of GAB\(_A\) channel opening, as might occur with the benzodiazepines, did not affect model behavior since the time course of the opening was already quite fast relative to the time course of the membrane potential.

Additional aspects of anesthetic action on the behavior of the reticular nucleus of the thalamus could emerge with a more realistic model. Excitatory input from thalamocortical neurons, which are themselves inhibited by the reticular nucleus, is thought to contribute to regulation of the rhythm of the reticular nucleus. In addition, both GAB\(_A\) and GAB\(_B\) inhibitory interactions are present within the reticular nucleus and the inhibitory pathway from the reticular nucleus to the thalamocortical network. Moreover, the oscillations of both the thalamocortical neurons and the neurons of the reticular nucleus are driven in part by T-type Ca\(^{2+}\)-currents which are known to be affected by volatile anesthetics, and whose modulation increased the synchrony of the model of the reticular nucleus, as shown above. Although GAB\(_A\) receptors are not affected by volatile or intravenous anesthetics, the longer time constants associated with their activation and inactivation could impact on model behavior. When thalamocortical neurons and GAB\(_A\) inhibitory interactions are incorporated in models of the reticular nucleus, they appear to confer additional stability to the resulting oscillations.

**Fast-spiking Interneuron Network.** The Wang–Buzsáki model of a fast-spiking interneuron network, when stimulated with a level of input current sufficient to produce oscillations in the \(\gamma\) range (40–80 Hz), is notable for its paradoxical behavior when contrasted with the behavior of the reticular nucleus of the thalamus. Decreases in the rate constant governing closure of the GAB\(_A\) channels (\(\beta_{\text{syn}}\) in Eq. D.4), as occurs with many intravenous and volatile anesthetics, lead to a loss of synchrony (fig. 7), where the theoretical and computational basis for this behavior have been further elucidated elsewhere. Increases in the rate constant governing opening of GAB\(_A\) channels (\(\alpha_{\text{syn}}\) in Eq. D.4), which occurs with the benzodiazepines, may be more important to the behavior of this network (fig. 8) than in the relatively slower thalamic network. A much more
complex model of γ oscillations in a hippocampal slice preparation, which incorporates the interaction of detailed multicompartment models of hippocampal neurons modulated by fast-spiking interneurons, requires more than a decrease in the rate of GABA$_A$ channel closing to lose the synchrony of the γ frequency oscillations. An additional GABA$_A$ inhibitory leak current, as is documented to occur at higher concentrations of the intravenous anesthetics$^{80,81,85,86}$ must be incorporated to induce the loss of synchrony of the γ frequency oscillations. The addition of gap junctions to permit electrical coupling between the dendrites of interneurons is a model enhancement that can affect synchrony in certain types of networks.$^{104}$

**Implications for Anesthetic Action at the Ion Channel**

The specific molecular site(s) responsible for general anesthesia remain(s) controversial. Since many of the intravenous and volatile anesthetics are known to exert their effect at the GABA$_A$ receptor, it is tempting to implicate these actions at the GABA$_A$ receptor as the unitary mechanism of general anesthesia. However, the volatile and intravenous anesthetics also affect voltage-gated ion channel activity, though it has been postulated that the anesthetic concentration at which these effects occur and the nature of these effects render them clinically irrelevant.$^{10}$ The results presented above from the simulations with the Morris–Lecar model of the barnacle giant muscle fiber and the Pinsky–Rinzel model of the CA3 hippocampal neuron call this view into question. In each case, relatively modest reduction of Ca$^{2+}$ current corresponding to clinically relevant anesthetic concentrations brought about dramatic alterations in model behavior. Nevertheless, fundamental changes in network synchrony were observed when clinically relevant concentrations of intravenous or volatile anesthetics decreased the rate of GABA$_A$ channel closure, and network synchrony could be further modulated by concurrent effects at the voltage gated channels.

The behavior of all four models is summarized in figure 9, where the concentration-effect curves for halothane on the voltage- and ligand-gated ion channels are shown along with the halothane concentrations at which model behavior is fundamentally altered. Although relatively high concentrations of halothane are necessary to achieve network synchrony in the thalamic model, this may be consistent with known differences of halothane on the electroencephalograph compared with other volatile anesthetics. For example, if it is assumed that the maximal reduction in the rate of GABA$_A$ channel closing is twice as great for isoflurane as for halothane,$^{64,91}$ then network synchrony is achieved for isoflurane concentrations of 0.40 ms (as opposed to 0.70 ms) in the thalamic model, and synchrony is lost for isoflurane concentra-

![Fig. 9. Concentration-effect curves of multiple ion channels in the presence of halothane together with anesthetic concentrations at which model behavior qualitatively changes for each of the four models described in the text. Arrows depict the halothane concentration at which quiescence occurs in the barnacle muscle fiber model (a), bursting is supplanted by spiking in the hippocampal model (b), synchrony is achieved in the network model of the reticular nucleus of the thalamus (c), and synchrony is lost in the fast-spiking interneuron model (d). The inhibition of a high voltage activated Ca$^{2+}$ channel, a Na$^+$ channel, and a K$^+$ channel in the presence of halothane are depicted using the Hill equation (Eq. 7) using values for the EC$_{50}$ of 0.85 mM,$^{63}$ 2.0 mM,$^{66}$ and 6.4 mM,$^{66}$ respectively, and a Hill coefficient of 1.5.$^{10}$ The prolongation of the time constant governing closure of GABA$_A$ channels in the presence of halothane is depicted using the Hill equation assuming an EC$_{50}$ of 0.90 mM, a Hill coefficient of 1.5, and a maximal prolongation of 2.5 the baseline value.$^{64,91}$

**Implications as to the Mechanism of General Anesthesia**

General anesthesia is not a single dichotomous state, and includes sedation, amnesia, loss of consciousness, immobility, and blunting of autonomic reflexes, with each of these features appearing once anesthetic concentrations reach a given threshold.$^{18–22}$ Threshold behavior appears in the models presented here as well as in a more abstract model of general anesthetic action,$^7$ and was the criterion used to generate figure 9. Clinically and encephalographically,$^{25}$ general anesthesia can be biphasic, with an initial excitement phase followed by increasing depth of anesthesia as anesthetic concentration is increased. Several of the models presented here exhibit behavior consistent with inhibition and several models exhibit behavior consistent with excitement. In the CA3 hippocampal model, the increase in burst frequency, increase in burst duration and, perhaps, the shift to a tonically spiking pattern of behavior as anesthetic concentration is increased could be considered examples of increased excitability. The loss of synchrony in the fast-spiking interneuron model as GABA$_A$ channels remain open longer could lead to less organized and, therefore, higher frequency electroencephalographic ac-

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tivity. Given the hypothesized role of this network in attention\(^{41,42}\) and in “binding” information from multiple cortical areas,\(^ {37}\) it is conceivable that loss of synchrony in this network could be associated with sedation, amnesia, and decreased levels of consciousness. In the model of the reticular nucleus of the thalamus, which is known to be associated with sleep and barbiturate anesthesia,\(^ {43-47}\) oscillations become more organized as GABA\(_A\) channels remain open longer. Smaller decrements in the closing rate of the GABA\(_A\) channels are necessary to desynchronize the fast-spiking interneuronal network, whereas larger decrements are necessary to achieve complete synchrony in the model of the reticular nucleus of the thalamus. Thus, different components of the central nervous system may contribute to the overall state, and these contributions, even if involving the same receptor system, may appear at different anesthetic concentrations.

It may be important to appreciate that all aspects of anesthetic action on ion channel behavior and the subsequent impact on individual neurons and the networks they comprise may not be directly related to aspects of the anesthetic state that are clinically recognized and are of direct clinical utility. There is a growing appreciation for the dynamic qualities of the central nervous system, where neurons are continually adjusting their response in accordance with the prevailing pattern of pre- and postsynaptic activity. In various systems, this manifests itself in the form of synaptic plasticity,\(^ {105}\) adjustments of dynamic range,\(^ {106}\) and alterations in the conductances of populations of ion channels.\(^ {107}\) It is conceivable that general anesthesia could affect these processes by altering the pattern of prevailing neural activity and through the dynamic adjustments in response to that activity. These changes could underlie some of the longer-term effects that have been reported following general anesthesia,\(^ {108}\) and represent additional features of systems level behavior that may be amenable to computational modeling.

**Conclusions**

In summary, computational approaches offer additional tools for considering the integrated neural response to anesthetic action, and have demonstrated how anesthetic modulation of ion channel activity could lead to more complex systems level behavior. Collectively, the models described here have exhibited behavior consistent with both excitation and inhibition once anesthetic concentration reaches a clinically relevant threshold. Future progress in this area will require the development of more detailed biophysical models that more realistically incorporate the action of anesthetics and other drugs that modulate anesthetic action. Apart from elucidating the process by which one or more actions at the ion channel lead to general anesthesia, these approaches may eventually pave the way for more rational drug design and use.

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**Appendix A**

Morris-Lecar model of the barnacle giant muscle fiber modified to permit volatile anesthetic modulation of Ca\(^ {2+}\) conductance.\(^ {49,56}\)

\[
\frac{dV}{dt} = - \frac{\bar{g}_c}{C} f_c(a)(V-V_{ca}) - \bar{g}_n n(V-V_k) - \bar{g}_l (V-V_l) + I
\]

\[
\frac{dm}{dt} = \lambda_m (V)(m(V) - m)
\]

\[
\frac{dn}{dt} = \lambda_n (V)(n(V) - n)
\]

\[
m_c(V) = 0.5[1 + \tanh((V - V_1)/V_2)]
\]

\[
\lambda_m (V) = \lambda_m \cosh(V - V_3)/(2V_4)
\]

\[
n_c(V) = 0.5[1 + \tanh((V - V_3)/V_4)]
\]

\[
\Lambda_c = \frac{\lambda_m \cosh(V - V_3)/(2V_4)}{\Lambda_m + \lambda_m \cosh(V - V_3)/(2V_4)}
\]

**Model Parameters:**

\[
V_1 = 0 \text{ mV} \quad \bar{g}_c = 4 \text{ mS/cm}^2 \quad V_{ca} = 100 \text{ mV}
\]

\[
V_2 = 15 \text{ mV} \quad \bar{g}_k = 8 \text{ mS/cm}^2 \quad V_c = -70 \text{ mV}
\]

\[
V_3 = 10 \text{ mV} \quad \bar{g}_l = 2 \text{ mS/cm}^2 \quad V_l = -50 \text{ mV}
\]

\[
V_4 = 10 \text{ mV}
\]

\[
C = 20 \mu \text{F/cm}^2, \quad \lambda_m = 1.0, \quad \bar{\Lambda}_m = 0.1
\]

**Initial Conditions:**

\[
V(0) = -20 \text{ mV}, \quad m(0) = 0.065, \quad n(0) = 0.002
\]

**Definition of Model Parameters:**

\[
I = \text{applied current (mA/cm}^2\)
\]

\[
\bar{g}_c, \bar{g}_k, \bar{g}_l = \text{maximal conductance for Ca}^{2+}, K^+, \text{and leak currents (mS/cm}^2\)
\]

\[
V = \text{membrane potential (mV)}
\]

\[
V_{ca}, V_{ck}, V_c = \text{equilibrium potentials for Ca}^{2+}, K^+, \text{and leak currents (mV)}
\]

\[
m, n = \text{fraction of open Ca}^{2+} \text{ and K}^+ \text{ channels}
\]

\[
m_c(V), n_c(V) = \text{fraction of open Ca}^{2+} \text{ and K}^+ \text{ channels in steady state for given membrane potential}
\]

\[
\lambda_m (V), \lambda_n (V) = \text{rate constant for opening of Ca}^{2+} \text{ and K}^+ \text{ channels (s}^{-1}\)
\]

\[
\bar{\lambda}_m, \bar{\lambda}_n = \text{maximal rate constant for opening of Ca}^{2+} \text{ and K}^+ \text{ channels (s}^{-1}\)
\]

\[
V_1, V_4 = \text{membrane potential at which m_c(V) and n_c(V) are equal to 0.5 (mV)}
\]

\[
V_2, V_4 = \text{reciprocal slope of m_c(V) and n_c(V) (mV)}
\]

\[
C = \text{membrane capacitance (} \mu \text{F/cm}^2\)
\]
\(a = \text{anesthetic concentration (mM)}\)

\(n_{\text{Ca}} = \text{anesthetic concentration at which Ca}^{2+}\text{-conductance is halved}\)

\(n_{\text{Ca}} = \text{Hill coefficient for anesthetic modulation of Ca}^{2+}\text{-conductance}\)

**Appendix B**

Pinsky-Rinzel Model of hippocampal CA3 Neuron.\(^{30,51}\)

\[
\frac{dV}{dt} = -I_{\text{Na}} - I_{\text{Ca}} - I_{\text{L}} + (g_{\text{L}}/\rho)(V_T - V) + I_{\text{L}}/\rho
\]  
\[\text{Equation (B.1a)}\]

\[
\frac{dV}{dt} = -\tilde{g}_{\text{Na}}m^2h(V_T - V_{\text{Na}}) - \tilde{g}_{\text{Ca}}c(V_T - V_{\text{Ca}}) - \tilde{g}_{\text{AHP}}m(V_T - V_{\text{AHP}}) + (g_{\text{L}}/\rho)(V_T - V) + I_{\text{L}}/\rho
\]  
\[\text{Equation (B.1b)}\]

\[
\frac{dV}{dt} = -\tilde{g}_{\text{Na}}m^2h(V_T - V_{\text{Na}}) - \tilde{g}_{\text{Ca}}c(V_T - V_{\text{Ca}}) - \tilde{g}_{\text{AHP}}m(V_T - V_{\text{AHP}}) + (g_{\text{L}}/\rho)(V_T - V) + I_{\text{L}}/\rho
\]  
\[\text{Equation (B.2a)}\]

\[
\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h
\]  
\[\text{Equation (B.3)}\]

\[
\frac{dc}{dt} = \alpha_c(1 - c) - \beta_c c
\]  
\[\text{Equation (B.4)}\]

\[
\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n
\]  
\[\text{Equation (B.5)}\]

\[
\frac{dq}{dt} = \alpha_q(1 - q) - \beta_q q
\]  
\[\text{Equation (B.6)}\]

\[
\frac{ds}{dt} = \alpha_s(1 - s) - \beta_s s
\]  
\[\text{Equation (B.7)}\]

\[
\frac{dCa}{dt} = -1.3\tilde{g}_{\text{Ca}}m^2h(V_T - V_{\text{Ca}}) - 0.075Ca
\]  
\[\text{Equation (B.8)}\]

\[
\alpha_v(V) = \frac{0.32(13.1 - V)}{\exp\left(\frac{(13.1 - V)}{4}\right) - 1}
\]  
\[\text{Equation (B.9a)}\]

\[
\beta_v(V) = \frac{0.28(V - 40.1)}{\exp\left(\frac{(V - 40.1)}{5}\right) - 1}
\]  
\[\text{Equation (B.9b)}\]

\[
\alpha_m(V) = \frac{0.128\exp\left(\frac{(17 - V)}{18}\right)}{\exp\left(\frac{(17 - V)}{18}\right) - 1}
\]  
\[\text{Equation (B.9c)}\]

\[
\beta_m(V) = \frac{1.6}{1 + \exp\left(\frac{(40 - V)}{5}\right)}
\]  
\[\text{Equation (B.10a)}\]

\[
\alpha_C(V) = \frac{0.016(35.1 - V)}{\exp\left(\frac{(35.1 - V)}{5}\right) - 1}
\]  
\[\text{Equation (B.10b)}\]

\[
\beta_C(V) = \frac{0.25\exp(0.5 - 0.025V)}{1 + \exp(0.5 - 0.025V)}
\]  
\[\text{Equation (B.11a)}\]

\[
\alpha_v(V) = \frac{1.6}{1 + \exp[0.02(V - 51.1)]}
\]  
\[\text{Equation (B.11b)}\]

\[
\beta_v(V) = \frac{0.02(V - 51.1)}{1 + \exp[0.072(V - 65)]}
\]  
\[\text{Equation (B.11c)}\]

\[\text{Model Parameters}\]

\[\tilde{g}_{\text{Na}} = 30 \text{ mS/cm}^2, \quad V_{\text{Na}} = 120 \text{ mV}\]

\[\tilde{g}_{\text{Ca}} = 10 \text{ mS/cm}^2, \quad V_{\text{Ca}} = -15 \text{ mV}\]

\[\tilde{g}_{\text{Kc}, \text{c}} = 15 \text{ mS/cm}^2, \quad V_{\text{Ca}} = 140 \text{ mV}\]

\[\tilde{g}_{\text{Kc}, \text{c}} = 15 \text{ mS/cm}^2, \quad V_{\text{Ca}} = -15 \text{ mV}\]

\[\tilde{g}_{\text{Kc}, \text{c}} = 0.8 \text{ mS/cm}^2, \quad C = 3 \mu\text{F/cm}^2\]

\[\tilde{g}_{\text{Kc}, \text{c}} = 0.1 \text{ mS/cm}^2, \quad g_c = 2.1 \mu\text{m}^2/\text{cm}^2\]

\[\rho = 0.5, \quad \rho(0) = 0.01, \quad \text{Ca} = 0.2\]

\[\text{Initial Conditions:}\]

\[V_{\text{Na}} = 120 \text{ mV}, \quad V_{\text{Ca}} = -4.6 \text{ mV}\]

\[V_{\text{Ca}} = 140 \text{ mV}, \quad V_{\text{Ca}} = 140 \text{ mV}\]

\[n(0) = 0.001, \quad s(0) = 0.009\]

\[c(0) = 0.007, \quad q(0) = 0.010\]

**Appendix C**

Golomb-Rinzel model of reticular nucleus of thalamus.\(^{55}\)

\[
\frac{dV}{dt} = -\tilde{g}_{\text{Na}}m^2h(V_T - V_{\text{Na}}) - \tilde{g}_{\text{Kc}}h(V_T - V_{\text{Kc}})
\]  
\[\text{Equation (C.1)}\]

\[
\frac{dh}{dt} = k_dh(V_T - l_h)
\]  
\[\text{Equation (C.2)}\]
Appendix D

Wang-Ružsík model of hippocampal interneuronal network.54

\[
\frac{dV}{dt} = -g_{m} h (V - V_{m}) - g_{k} n (V - V_{k})
\]

\[
- g_{l} (V - V_{l}) - \frac{g_{n}}{N} (V - V_{n}) \sum_{i=1}^{N} S_{i} h_{i} + I
\]

\[
\frac{dh}{dt} = \phi_{h} (1 - h) - \beta_{h} h_{i}
\]

\[
\frac{dn}{dt} = \phi_{n} (1 - n) - \beta_{n} n_{i}
\]

Model Parameters:

\[
V_{Na} = 55 \text{ mV}, V_{K} = -90 \text{ mV}, V_{L} = -65 \text{ mV}, V_{syn} = -75 \text{ mV},
\]

\[
g_{Na} = 35 \text{ mS/cm}^2, g_{K} = 9 \text{ mS/cm}^2, g_{l} = 0.1 \text{ mS/cm}^2,
\]

\[
g_{syn} = 0.1 \text{ mS/cm}^2, \phi = 5, \Theta_{syn} = 0 \text{ mV}, C = 1 \text{ \mu F/cm}^2,
\]

\[
\alpha_{syn}, \beta_{syn} = \text{forward and backward rate constants controlling}
\]

\[
\text{dynamics of gating variable } s \text{ which represents the fraction of open GABA}_A \text{ channels (ms}^{-1})
\]

\[
\phi = \text{parameter governing time constant of gating variable for calcium channel}
\]

\[
C = \text{membrane capacitance (\mu F/cm}^2)
\]

Initial Conditions:

\[
V_{i}(0) \text{ randomly and uniformly distributed between } -90 \text{ and } -50 \text{ mV (hyperpolarized initial conditions) or } -50 \text{ and } -10 \text{ mV (depolarized initial conditions). } s_{i}(0) \text{ and } h_{i}(0) \text{ obtained from steady state solutions of Eqs. C.2 and C.3 for the corresponding value of } V_{i}(0).
\]

Definition of Model Parameters:

\[
V_{i} = \text{membrane potential of } i\text{-th neuron (mV)}
\]

\[
N = \text{number of neurons in network}
\]

\[
\gamma = \text{fraction of total number of neurons connected to an individual neuron}
\]

\[
S_{i} = \text{connection matrix of either zeros or ones, with zeros on the diagonal, where connections were generated randomly so that, on average, } \gamma N \text{ connections were made to each neuron}
\]

\[
V_{Na}, V_{K}, V_{L}, V_{syn} = \text{equilibrium potential of sodium, potassium, leak, and synaptic currents (mV)}
\]

\[
\bar{g}_{Na}, \bar{g}_{K}, \bar{g}_{syn} = \text{maximal conductance of calcium, potassium, leak, and synaptic currents (mS/cm}^2)
\]

\[
h_{i}, s_{i} = \text{gating variable for calcium and synaptic currents for the } i\text{-th neuron, representing the fraction of channels that are open}
\]

\[
\alpha_{syn}, \beta_{syn} = \text{forward and backward rate constants controlling}
\]

\[
\text{dynamics of gating variable } s \text{ which represents the fraction of open GABA}_A \text{ channels (ms}^{-1})
\]

\[
\phi = \text{parameter governing time constant of gating variable for calcium channel}
\]

\[
C = \text{membrane capacitance (\mu F/cm}^2)
\]
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