Computing a percolation model of information transmission for modeling general anesthesia

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***Abstract*—The study of general anesthesia lacks a systems-level mechanism to explain phenomenal properties such as loss of consciousness and network disintegration in the brain. The use of connectivity measures in the study of anesthesia inspires an application of a statistical mechanical theory known as percolation. In this report, we devise a simple, layered network with a unique topology to process input signals, as well as algorithms to compute the activity at all regions in the network. With such a model, it may be possible to develop a more detailed mechanistic theory of general anesthesia, as well as generate hypothesis about neural function during anesthetic induction.**

I. Introduction

A. Problem Description

While much is known about the cellular and molecular targets of anesthesia, not much is known about the systems-level mechanism of general anesthesia. The general anesthetic proposal, for instance, is a GABA-A receptor agonist, which excites GABA inhibitory interneurons. Such inhibition provides the neurological basis for considering the effect of general anesthesia as a process of cutting information transmitting connections between neural populations.

Loss of consciousness during anesthetic state transitions is, therefore, likely an emergent phenomenon due to disruption of functional communication between nodes of a large-scale neural network. In anesthetic state transitions, neural network properties are known to change as the brain loses consciousness. Therefore, it would be valuable to devise a model which degrades the connectivity of neural networks in silica as anesthesia is applied. To do so may would be an advance toward a mechanism for general anesthesia that relates the graph properties of neural networks with the phenomenology underlying loss of consciousness.

The aim of the work herein is to develop a model that assesses the information flow through a neural network representing a thalamocortical sensory pathway as its connections are being inhibited by general anesthesia. As a model of a sensory pathway in the nervous system, the network should be able to input an ascending thalamocortical sensory signal and output a cortical signal. The signal should be represented by neural activity as an agent transmitting between each node of the network. Such a network is an abstract representation of the graph structure of the thalamocortical network; each node represents neural populations and each edge represents connections between them. The network should possess the divergent and layered graph properties that characterizes such a system in neurobiology. At a critical threshold of connectivity, the system should undergo a mechanistic switch from conscious sensory transmission to unconsciousness.

Such a model enables investigation of system properties near the critical state of the network, allows hypothesis testing about the electrophysiological properties of such a perturbed system, and accommodates hypothesis generation for in vivo work in the future.

B. Related Work

It is well established that connectivity is degraded in a neural system during the transition between consciousness and unconsciousness, in anesthesia. A comparison of electroencephalography (EEG) responses to transcranial magnetic stimulation before and after anesthetic induction revealed that current propagation across the cortex is more local under anesthesia. [1] Spectral analysis of EEG during loss of consciousness also reveals network connectivity changes between signals measured at various cortical nodes. [2] [3] Lastly, functional magnetic resonance imaging has characterized connective differences between cortical and subcortical activity during conscious and unconscious states. [4]

This body of work motivates the network level modeling of general anesthesia. Various models have already been proposed. Models have been created to recreate many of the characteristic electroencephalographic features of anesthesia. [5] [6] [7] [8] A cellular automaton model has been proposed to abstract cortical EEG during anesthesia. [9]

However, most of these models are primarily concerned with reproduction of the electrophysiological features of cortical systems undergoing anesthetic induction with rigorous biological constraints and specifications. None of these models employ an information theoretic or signal processing approach to assessing sensory propagation through a thalamocortical network. Instead, they are merely a set of possible realities for large-scale inhibition during general anesthesia. As a result, it is difficult to relate such models to claims about the phenomenological loss of consciousness as a matter of information flow that is lost during propagation through a neural system.

II. Approach

To develop a mechanism to account for the loss of information flow through a neural system during general anesthesia,

we look to percolation theory as a process to simulate the effect of a general anesthetic drug. Such inhibition provides the neurological basis for considering the effect of general anesthesia as a process of cutting connections of information transmission between cortical nodes.

Percolation defines a mathematical phenomenon by which a cluster, or subset of connected nodes, in a graph is connected if there exists an open path between its nodes. The probability that a path is open between two adjacent nodes is called the edge probability. If an open path exists between two noes, percolation is said to occur between the nodes that the edge joins. The probability that percolation occurs, or the percolation probability, can be considered dependent of the edge probability. The percolation probability can be seen to increase precipitously following a corresponding increase in edge probability past a critical threshold, or p_c. Other parameters of such a network may be investigated as well, such as the size of the giant cluster, which is the largest subset of nodes, each of which is connected by open edges to any other node in the cluster. [10]

Percolation is particularly useful for assessing the loss of information transmission during anesthetic states. Information transmission is known to occur as propagation of signals through a neural network. It is clear that propagation through such a neural network (as in visual pathways, for example) is disrupted during loss of consciousness. Because percolation describes the behavior of a graph that varies in connectivity, we may model transmitted information as an agent that travels, or percolates, along the open edges through a neural network.

Percolation is well defined for any network or lattice. Critical probabilities have been computed in mathematics for various common lattices. In nature, however, network topologies do not occur in well-ordered lattices, but occur with some randomness in their structures. One of the unknowns in implementing such a theory is the network topology that is able to abstract the connective structure of the thalamocortical sensory pathways that support conscious sensation. Then, being able to simulate information transmission across this network can be a great tool for computational scientists seeking a graph-theoretical approach to studying the behavior of such networks during anesthetic state transitions.

Percolation theory is classically defined where nodes and edges possess binary states of open or closed, and graph properties are analyzed as edge probability is lowered from 1 to 0. Because a model of information transmission hopes to simulate the transmission of time series of neural activity, it is advantageous to have the nodes of our network to possess activity values, not just binary states, and to model how the network handles the activity at output, not to model network properties solely through, for example, Monte Carlo sampling. The agent percolating through the network, therefore, are activity values, integrated at each node from the activities from the "presynaptic" nodes from which activity is passed.

This theory provides novel measures and algorithms for assessing the behavior of a neural network at varying degrees of connectivity, such as size of the largest cluster in a graph, or the fit between a plot of transmission probabilities versus the classic anesthetic does response curve. [11] Connectivity of networks matters especially to anesthesiology, where the precision of neural network analyses vary inversely with the scale at which they can be conducted. A statistical mechanical theory such as percolation may aid in the description of a systems-level mechanism of general anesthesia. [12] Percolation has already been posited as a measure of connectivity in neural networks. [13] Percolation has been investigated previously in living neural networks. [14]

A. Objectives

We seek a computational method which implements the following characteristics to modeling transmission of information coded neural activity through a thalamocortical network: (i) defines an network with an input layer and an output layer through which a time series is percolated as information flow; (ii) proposes a topology for such a network which abstracts the biological principles of neural network topology; (iii) cuts the edges of the network randomly as a function of the edge probability of the system, adhering to a set of functions for random sampling of edge probability values; (iv) defines an equation to calculate the activity at a node as an integrated value of presynaptic activities; (v) provides analytical tools to compare the inputs and outputs of a network to assess the integrity of information flow.

B. Theory

In our percolation model, the percolation of a signal through the graph begins at the input node, whose activity is set to a predefined input time series. At each time step, the activity of every other node in the network is computed as a weighted average of activity values at presynaptic nodes. The weight of each presynaptic activity value is determined by the magnitude of the edge weight that has been sampled from the edge probability. The computation is described by

$$A_k = \frac{\sum_j^n A_j * e_{jk}}{\sum_j^n e_{jk}} \tag{1}$$

for n presynaptic nodes j, the activities of which are weighted by their edges jk.

The weights of the edges are distributed between $[0, 1]$ and define how much of a presynaptic signal is weighted into the activity of the postsynaptic terminal. A high weight, then, is indicative of an open edge across which signals can percolate, and a low weight of a closed edge. Weight values are generated using a transformation with the normal cumulative distribution function with a standard deviation σ centered at $1 - p_e$, where p_e is the edge probability of the system. By initially assigning pseudorandom numbers uniformly distributed between $[0, 1]$ to each edge, a transformation with such a cumulative distribution function allows each edge to be approximately open or closed with a probability equal to p_e. This method can be represented by

$$e_i = \Phi_{1-p_e,\sigma^2}(U[0, 1]) \tag{2}$$

where Φ is the normal cumulative distribution function with standard deviation σ, p_e is the edge probability of the system, and each edge i is given a uniformly distributed random number from $U[0, 1]$. For n edges in the network, approximately $n*p_3$ edges have values close to 1, representing of open edges. At $p_e = 1$, nearly all of the edges have open weights close to 1; at $p_e = 0$, nearly all of the edges have weights close to 0.

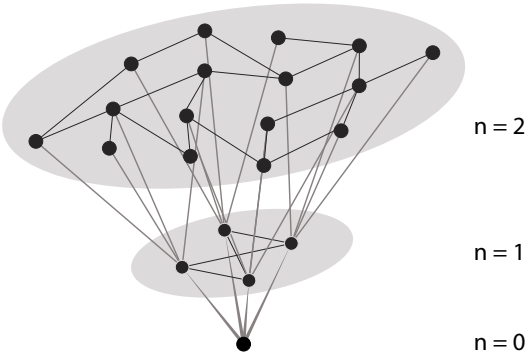


Fig. 1. Diagram of a two layer network.

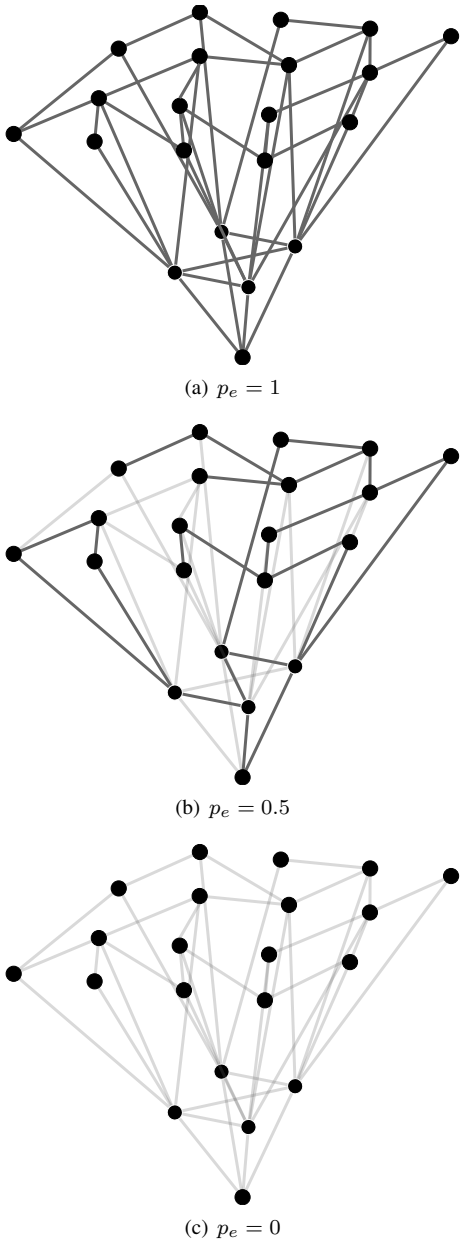
This method allows an efficient method of randomly sampling edge weights that has an approximate openness with a certain probability. Sampled using this method at $p_e = 1$, the network is almost completely connected. As p_e is lowered from 1 to 0, edges randomly start to close, or be cut, in the network. Such cutting is an abstraction of the effect of anesthetics on neural transmission, which with a certain property can be inhibited from firing.

C. Model Topology

We propose a graph embodying the thalamocortical loop, composed of nodes and edges that each have probabilities of being open or closed. Since the notion of effective connectivity makes no claims about the structural connections between brain regions in the form of axons and synapses, our model assumes that neural activity is depressed or excited during various brain states, including anesthetic states, without structural changes. The critical probability p depends on the underlying structure of the graph. Therefore, selecting the network topology with which to model the cerebral cortex is not a trivial question, both for neurobiological and computational reasons.

Our topology must fit two primary specifications. First, it must involve layers of connected graphs, in order to model the laminar hierarchical nature of thalamocortical information processing. [15] In the brain, information between the sensory layer and the cortical layer must pass through a set of layer connected in between, with some amount of processing occurring at each layer as a matter of distributed processing. Second, the topology must exhibit some degree of divergent behavior as the signal proceeds from layer to layer. This is made to reflect the high degree of divergence in sensory pathways, where the number of neurons at each layer projects to an increased number of neurons at the following layer. For example, it is well established that there are more neurons at the layer of the visual cortex than in the thalamus. The size of processing layers in a neural system increases as well.

We propose a topology of layered small world networks, connected to each other in a tree-like fashion. (Figure 1.) Reductively, our model topology looks like an inverted tree in which every vertex has k children. The connections between the parents and children model ascending interlaminar thalamocortical projections in a sensory network. Such a tree defines



(a) $p_e = 1$

(b) $p_e = 0.5$

(c) $p_e = 0$

Fig. 2. Cutting of edges

layers of nodes which can be described by their distance away from the initial or input node at which inputs begin their ascent through the network. Among the nodes of a given layer, we add intralaminar edges between a random set of nodes following the Watts-Strogatz algorithm of generating small-world random graphs. Intralaminar neuronal networks have been claimed to exhibit the properties of small-world graphs, and the connectivity of small world networks have been attributed to conscious level during anesthesia. [16] [17] Such a network which we propose is designed to approximate the the general structure of a thalamocortical network.

As connections are randomly cut from the network, the percolation probability of a signal from the input node to the output layer decreases. Figure 2 shows what network connectivity looks like as it undergoes random cutting. However, the

decrease should be associated with a range of edge probability probability values where random cutting is sufficient to block percolation. One could imagine that cutting just a few connections do not have a large effect on the percolation probability across the entire system, just as allowing only a few connections to exist would not make it likely for signals to percolate at all.

D. Simulation

The steps of simulating activity through such a model are as follows. Broadly, simulation the percolation of a signal through our network requires initializing an unweighted graph of the desired topology, assigning random weights to each edge by the aforementioned sampling method, assigning an input activity, calculating the activity of all other nodes, and retrieving the output signal.

1) Generate adjacency matrix M defining the network with degree d and layer n.
2) Assign random weights E to each edge given an edge probability p_e, as in equation 2.
3) Calculate the activity at each node i over t time steps, with an input activity time series defined as the activity of the input layer, as in equation 1.
4) Retrieve output signal as a mean of activity time series of nodes in the final layer.

Generating the adjacency matrix of the network matching the specification required involves assigning d edges to the l nodes on each non-final layer, and then assigning intralaminar edges between the $d*l$ nodes created. The pseudocode for this algorithm is as follows.

1) For each layer in the network:
a For each node j in the layer:
i Add create d new nodes and add k edges from j to each new node k.
2) Arrange nodes j into a ring lattice.
3) For each edge in the layer:
a Rewire to a random node in the layer with some probability.

Assigning random weights to each edge can be done with the following pseudocode.

1) $R \leftarrow$ matrix with $size(M)$ of uniformly distributed pseudorandom numbers between $[0, 1]$.
2) $E \leftarrow R \cdot M$.
3) For every non-zero number e_{jk} in E:
a $e_{jk} \leftarrow \Phi_{p_e}(e_{jk})$

Percolating the signal through each node of the network can be done with the following pseudocode.

1) For each time step t:
a For each non-input node k in the network:
i Compute A_k with equation 1.

In our work, the output signal is defined as the mean signal of all nodes at the output layer. A signal percolates to the output layer if it plays any significant part in the computation of signals at the output layer, that is, if there are paths composed of edges with sufficient weight from input the output.

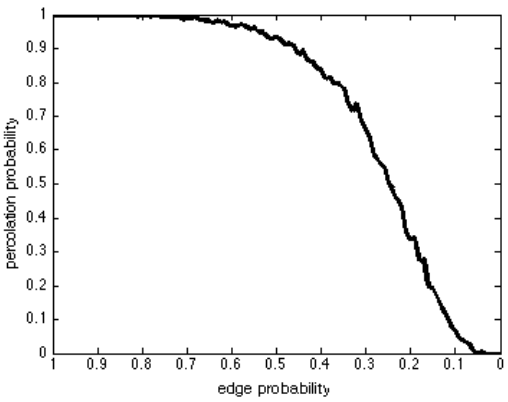


Fig. 3. Percolation probability versus edge probability as an abstraction of the anesthetic dose response curve.

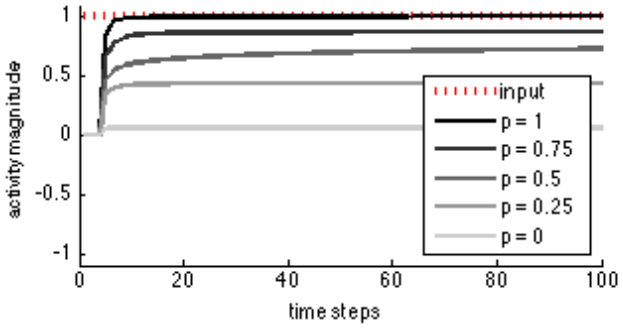
III. Results

One of the ways to assess the suitability of a a percolation model to a theory of general anesthesia is to reproduce a clinical feature of general anesthesia. Namely, the sigmoidal nature of the anesthetic dose response curve is important for our model because percolation theory deems that the percolation probability shares such a sigmoidal behavior. Figure 3 displays a plot of percolation probability versus edge probability using Monte Carlo methods on a network with three layers. In this data, however, inputs passed through the network are binary states, not activity time series. Nevertheless, the curve here presents the first data for the suitability of such a network toward modeling percolation, without drawing specific relations between the inhibition of edge probability and anesthetic inhibition.

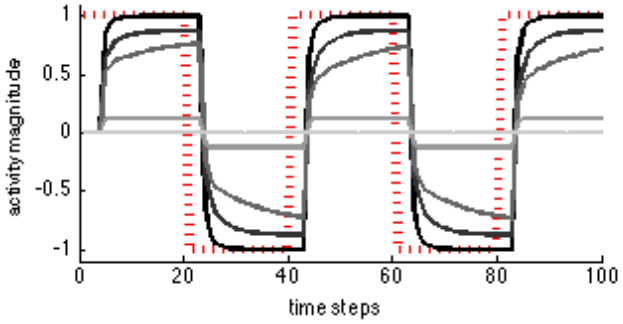
It is possible to examine the behavior of this network by passing in some simple inputs. In Figure 4, Simple tonic, stepping, sinusoidal, and random inputs are passed into the network and examined as edge probability is lowered from $p_e = 1$ to $p_e = 0$.

Several characteristics are of interest. First, signals reach the output layer with some amount of lag, as it takes multiple time steps for activity to traverse each set of edges in between the layers. Second, when p_e is lowered, the amplitude of the signal decreases, partly because the input signal percolates to a smaller proportion of the output layer nodes. Third, there may be spectral shifts seen when p_e is lowered. Observe that peaks are lost in the network output from the random input, which may result in frequency shifts for longer outputs. This is also observed in Figure 5, where new edge probabilities are given every 10 time steps. After some of these "resampling" events, activity does not change until the system resamples again, causing the oscillatory activity to lose peaks where they were in the input.

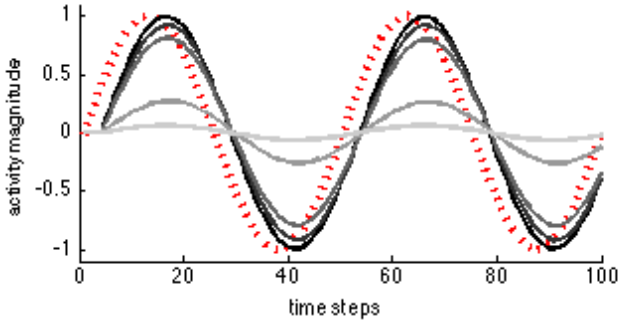
Note that at $p_e = 0$, some of the output activities simulated are not strictly constant at 0. Due to the sampling method described, a small subset of edges are still on, all with small weights, even when $p_e = 0$. This is because a normal cumulative distribution function centered at $1 - p_e$ still has a some area underneath its curve when $p_e = 0$. Signals that percolate along these edges may influence the output activity,



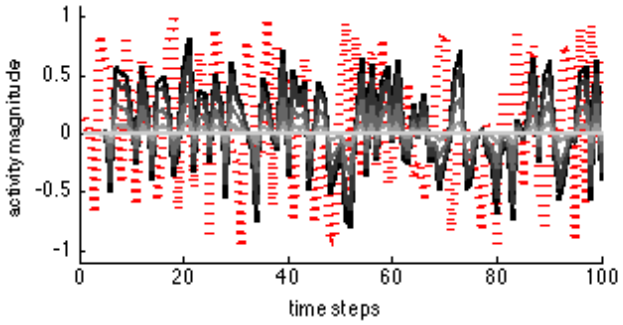
(a) Tonic input.



(b) Stepping input between 1 and -1.



(c) Sinusoidal input.



(d) Random input.

Fig. 4. Example output activity with simple inputs.

albeit slightly.

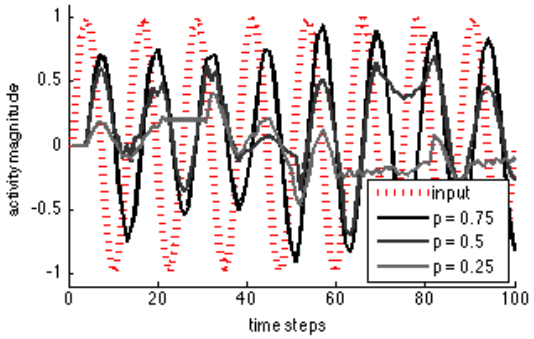


Fig. 5. Effect of resampling edges.

IV. Discussion

In this model, we propose a method to percolate an activity time series through a network in an effort to model inhibition in a neural system. In devising such a method as well as implementing the network through which to percolate such an input, we have developed hypotheses with which to investigate the phenomena surrounding loss of consciousness during general anesthesia as well as its systems-level mechanism.

This model is unique in the study of general anesthesia. Whereas previous models have simulated models with individual neurons possessing cellular or electrophysiological dynamics, this model employs abstract representations of whole neuronal populations. As such, we investigate the inhibition of a network and its handling of simple inputs on the basis of first principles.

It is evident from this work that the network handles each input differently based on its connectivity and may perturb the original signal in the spectral field. Such a finding is crucial, as it supports the motivation to investigate spectral shifts in the output signal based on the level of inhibition of the system. Spectral shifts are crucial to our understanding of the electroencephalography of anesthetic induction. Therefore, it may be valuable to perform spectral analysis on the output signals generated from a constant input signal, in an effort to reproduce some of the characteristic frequency shifts seen in general anesthesia.

For such analysis, it is reasonable to propose a class of inputs that produces the desired EEG signatures seen during of anesthetic induction, of which includes spectral and amplitude shifts. [18] The search for such an input or a set of possible inputs enables some degree of parameter searching that informs a reasonable hypothesis about the nature of ascending thalamocortical activity in our model. Sinusoidal of various frequencies as well as those mixed with random noise are among the inputs that may be considered.

There are a variety of other parameters that may be implemented into such a model. One such parameter involves the rate of edge weight resampling, as the weight of individual edges may change over the course of a simulation, sampled from the same distribution as in the beginning. Another such parameter may implementing scaling factors various edges relative to others in an effort to provide stronger ascending than descending transmission, or stronger feedforward than

feedback transmission. Such an implementation requires an asymmetrical system, which may aid in analyzing region-specific electrophysiological effects produced by such a system. Lastly, another parameter that may be investigated is the length previous activity from presynaptic nodes rather than a single time step in an effort to build some memory into the computation of activity at each node. These parameters may prove useful to generating hypotheses about how a neural system handles sensory information during anesthetic inhibition.

One of the main contribution of this research is the progress made toward a systems-level model of anesthetic inhibition that produces a critical threshold of conscious information transmission. As such, we have proposed the notion of the critical probability p_c, borrowed from percolation theory, which describes a narrow range of probabilities across which the content of a signal is lost precipitously when passed through an inhibited network. This is a theoretical formulation of the critical dosage necessary for loss of consciousness during general anesthesia, and allows us to make theoretical predictions about how the system handles informational inputs at various levels of inhibition using various parameters.

There are a variety of future directions for a percolation model of general anesthesia. First, this model is amenable to large-scale simulation with greater specificity. Second, parameter tuning might enable to generate specific hypotheses about the nature of a thalamocortical network that matches with clinical data from anesthesiology. Third, there are ideas to be gleaned in neural computing. While our model is simplistic and largely theoretical, there are a variety of networks that perform computational intelligence on inputs. For example, an analysis of random cutting in multi-layer perceptrons may provide some insights about the necessary connectivity of a system or a critical level of inhibition necessary for the network to lose certain intelligent capacities. Fourth, we propose that there exists a class of inputs which are likely to produce frequency shift and amplitude increasing behavior as p_e is cut. Because such behavior is characteristic of EEG shifts as anesthetic induction takes place, we may be able to validate this model further by finding such an input.

In summary, we have developed a series of algorithms and theory for the simulation of input activity signals in an inhibited neural system using percolation theory. This work is the starting point toward a systems-level mechanism of general anesthesia, validated by clinical EEG.

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