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Studies of stimulus parameters for seizure disruption using neural network simulations

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Abstract

A large scale neural network simulation with realistic cortical architecture has been undertaken to investigate the effects of external electrical stimulation on the propagation and evolution of ongoing seizure activity. This is an effort to explore the parameter space of stimulation variables to uncover promising avenues of research for this therapeutic modality. The model consists of an approximately $800\text{ }\mu\text{m} \times 800\text{ }\mu\text{m}$ region of simulated cortex, and includes seven neuron classes organized by cortical layer, inhibitory or excitatory properties, and electrophysiological characteristics. The cell dynamics are governed by a modified version of the Hodgkin-Huxley equations in single compartment format. Axonal connections are patterned after histological data and published models of local cortical wiring. Stimulation induced action potentials take place at the axon initial segments, according to threshold requirements on the applied electric field distribution. Stimulation induced action potentials in horizontal axonal branches are also separately simulated. The calculations are performed on a 16 node distributed 32-bit processor system. Clear differences in seizure evolution are presented for stimulated versus the undisturbed rhythmic activity. Data is provided for frequency dependent stimulation effects demonstrating a plateau effect of stimulation efficacy as the applied frequency is increased from 60 Hz to 200 Hz. Timing of the stimulation with respect to the underlying rhythmic activity demonstrates a phase dependent sensitivity. Electrode height and position effects are also presented. Using a dipole stimulation electrode arrangement, clear orientation effects of the dipole with respect to the model connectivity is also demonstrated. A sensitivity analysis of these results as a function of the stimulation threshold is also provided.

1. Introduction

Mechanisms of epilepsy both in the mesial temporal lobe as well as neocortex have been explored in both animal models and human pathologic tissue (Jefferys 2003; Engel et al. 2003). This has led to enormous success in the description of histological and electrophysiological changes apparent in epilepsy in man, as well as providing reproducible and stable correlates in comparable mammals. The parameter space of variables describing epilepsy is vast and complex, and ultimately the origins of the most common types of seizures are not completely understood. Investigators in the last century began to use computational modeling to study epilepsy, utilizing its important ability to rapidly change descriptive variables such as ion channels and synaptic properties, connections between neurons, the relative importance of different neuronal compartments, and the temporal characteristics of synaptic messaging (Traub et al. 1994; Traub et al. 1999; Kudela et al. 1997; Kudela et al. 2003a; Traub et al. 2005).

Modeling efforts in the past in our laboratory have focused heavily on simple one-compartment neuronal representations arranged in very large arrays of several thousands of inhibitory and excitatory neurons to investigate the temporal and gross spatial properties of developing epileptic activity (Kudela et al. 1997; Kudela et al. 2003a). Efforts have also been made to explore the differences in somatic and dendritic inhibitory influences and their effects on seizures in a multicompartment format (Yang et al. 2003). We have explored the role of intracellular calcium dynamics on seizure evolution as well (Kudela et al. 2003b). Most recently, we have begun to explore a therapeutic effort at stopping or altering seizure development via cortical stimulation (Franaszczuk et al. 2003). Our previous modeling work has now been adapted into a simulation of a more realistic cortical architecture. On a layer by layer basis, several classes of neurons are simulated including pyramidal and stellate cells (excitatory types) as well as several inhibitory classes. Connections between cells as well as synaptic and channel properties are guided by available histological and electrophysiological data. As described below, these efforts have resulted in some general conclusions regarding the timing, frequency, and spatial characteristics of an applied time-varying electric field and their influence on epileptic activity.

Over the last three decades, excitation of the central nervous system in the form of deep brain stimulation via thin cylindrical electrodes or induction coupled stimulation of the vagus nerve has become an effective and accepted form of therapy for a variety of neurological diseases (Benabid et al. 1994; Benabid et al. 1996; Siegfried and Lipitz 1994; Penry and Dean 1990; Uthman et al. 1990). Patients with epilepsy frequently undergo surgery for the placement of subdural monitoring electrodes to help with seizure localization. These are sometimes also used as stimulation leads to better delimit eloquent cortex. Lesser et al. (Lesser et al. 1999) demonstrated, in a set of patients undergoing preresection evaluation, that afterdischarges which occur during stimulation for localization could be aborted by a train of neighboring brief pulse stimulation. Reports from Penfield and Jasper demonstrated evidence for this as early as 1954 (Penfield and Jasper 1952). There is even some evidence that the timing of the stimulation pulses relative to the cellular network activity might be critical in terminating cortical afterdischarges (Motamedi et al. 2002). Concurrent with the recent work stopping cortical afterdischarges was the development of fast preictal seizure prediction algorithms (Echauz et al. 2001; Litt and Echauz 2002) which made it possible to conceive of a device which could both predict the onset of a seizure as well as attempt to stop it, all in a closed loop format. Such a device is currently undergoing clinical trial (FDA 2005).

Computational modeling of stimulation techniques applied to nervous tissue has a long history as well. Recent efforts include the development of the activation function for excitation of

nerve fibers developed by Rattay (Rattay 1986; Rattay 1988; Rattay 1989), multicompartment fiber models (Warman et al. 1992; Richardson et al. 2000; Moffitt et al. 2004), and several analyses of deep brain stimulation electrodes (McIntyre et al. 2004; Butson and McIntyre 2005). Of relevance to this work, simulations of central nervous system neurons in the context of the cortex as well as the spinal cord have also been performed (McIntyre and Grill 1999, McIntyre and Grill 2002), and indicate along with experimental studies that the primary location of action potential (AP) generation induced by applied electric fields is at the axon initial segment (Nowak and Bullier 1998a, Nowak and Bullier 1998b). Of interest, recent reduced experimental models examining planar patterns of cultured neurons grown over a microelectrode array also exhibit reductions and cessations in bursting behaviour for a variety of imposed stimulation fields (Wagenaar et al. 2005).

The simulation effort described below has adapted our previous simple model consisting of single inhibitory and excitatory classes into a more architecturally realistic cortical representation. The minicolumn hypothesis of Buxhoeveden et al. (Buxhoeveden and Casanova 2002a), or a size-scaled version of that concept has been used to come up with a spatially repeating local circuit, which is then used as a skeleton to fashion together longer range connections. The total number of neurons per minicolumn (16 neurons) as well as the size scale is similar to that found by Buldyrev et al. (Buldyrev et al. 2000) and Buxhoeveden and Casanova (Buxhoeveden and Casanova 2002b). We have chosen specific paradigms to pattern the intrinsic connections of the excitatory cells utilizing elements of both the visual cortex model of Douglas and Martin (Douglas and Martin 2004), as well as the more general cortical connectivity provided by Nieuwenhuys (Nieuwenhuys 1994). As outlined in detail, electrophysiological properties were derived from modified Hodgkin-Huxley excitable cells in a one-compartment format (Hodgkin and Huxley 1952; Av-Ron 1994).

Recent efforts to adapt network models to exhibit more realistic electrophysiologic behaviour range from those with few adjustable parameters and compartments (Park et al. 2005; Izhikevich 2003), to elaborate computationally intensive efforts (Bower and Beeman 1998; Howell et al. 2000; Hines and Carnevale 1997; Markram 2006). To the best of knowledge, this is the first time a dynamically realistic cortical simulation has been used to examine the effects of external stimulation in a reduced one compartment format. This will provide a useful tool to compare with the ongoing clinical efforts as well as provide a bridge for more elaborate and accurate cortical simulations.

2. Materials and Methods

2.1 Model Cell-Types

The model used in this study consists of an array of one-compartment neurons, with four different classes of cells representing excitatory pyramidal cells in cortical layers II and III (treated as one layer), layer V, and layer VI, as well as excitatory stellate cells in layer IV. There are also three classes of inhibitory interneurons represented as basket cells, double-bouquet cells, and chandelier cells. Each cell type has a defined location within the vertical layers and has distinct electrophysiologic properties. The cells are organized around a square minicolumn array of 25 μm center-to-center spacing in both cortical tangential directions (the x- and y- axes in our coordinate system). This dimension is similar (23 μm) to the spacing between vertically oriented bundles of myelinated axons in monkey visual cortex observed by Peters and Sethares (Peters and Sethares 1996). The total size of the simulated array is 800 $\mu\text{m} \times 800 \mu\text{m}$ (or 32 by 32 minicolumns). Each minicolumn consists of 12 pyramidal cells, 1 stellate cell, and 1 each of the inhibitory subtypes, making a total of 16 neurons per minicolumn or 16,384 cells for the whole model. There are internal axonal connections involving the members of a given minicolumn, as well as external connections to neurons in other minicolumns at a range of distances away.

Data for the actual height of the various layers above the white matter come from human data for agranular cortex, specifically region 24a (human anterior cingulate cortex) (Gittins and Harrison 2004). The total height of the cortex above the white matter was taken as 2340 μm , with the center of layer I taken at z-position 2185 μm , the center of layers II was 1940 μm , the center of layer III was 1540 μm , the center of layer IV at 1230 μm (taken as the transition between layers III and Va in the agranular data). The location of layer V was taken as the center of the Va band at 1130 μm , and the location of layer VI was taken as 488 μm (Gittins and Harrison 2004). The layer II/III pyramidal cells were also placed at height 1940 μm (layer II), the stellate cells at 1230 μm (layer IV), the layer V pyramidal cells at 1130 μm (layer V), and the layer VI pyramidal cells at 488 μm (layer VI). For the purposes of stimulation, all basket cells were organized in a band at 1940 μm (layer II), corresponding to the rich collection of basket cells in layers II/III. Ample connections guided by anatomic data between these basket cells and the layer V/VI pyramidal cells do exist in the model as outlined in the circuit diagrams below. The double bouquet cells are organized in a band at 1940 μm as well since most of these cells are supragranular (Peters and Sethares 1997). The chandelier cells are placed at mid-position in the cortex in layer IV at 1230 μm .

The specific electrophysiology properties of the cells as a function of class are described below. The basic connectivity pattern was drawn from a variety of histology data sources and is provided in the next few subsections (i–vii). This data driven set of connection probabilities will be denoted as connection pattern A. Variations on this pattern derived via multiplicative factors on the total numbers of connections were investigated to find those patterns that reproduced physiologic bursting behaviours at reasonable frequencies (2–20 Hz). Five of these patterns were explored in detail, and these are referred to as patterns B–F. The multiplicative factors used to derive these patterns from pattern A are presented in Table 1. The pattern A connection probabilities are:

- i. Layer II/III pyramidal cells make isotropic connections to several of the cortical layers out to 300 μm . Longer range connections were explored in the dipole stimulation studies described below involving the connections of patch regions similar to those observed histologically in cat visual cortex (Kisvárdy et al. 1986). Thomson and Deuchars estimated a lower limit of 5% for probability of connection between layer II/III pyramidal cells for cells of typical separation <250 μm (Thomson and Deuchars 1997). We use a 5% probability of connection between layer II/III pyramidal cells within this model out to a radius of 300 μm , and 5% of the possible layer IV stellate cells are contacted as well. 9% of the possible layer V pyramidal cells available are contacted by the layer III cells, again a lower limit provided by (Thomson and Deuchars 1997). The surrounding basket cell and chandelier cell inhibitory classes are also contacted by layer II/III pyramidal cells in an isotropic fashion, and an attempt is made to keep the total number of excitatory to inhibitory connections at 5% of the excitatory to excitatory numbers following from (Melchitzky et al. 2001). Only sparse connections between layer II/III pyramidal cells and double bouquet cells are observed histologically (Lewis et al. 2002). All of the layer II/III pyramidal cells or of the regular-spiking variety, and exhibit spike adaptation (Figure 1a)(Connors and Gutnick 1990).
- ii. Layer IV stellate cells make no external connections outside of their own minicolumn in the model, as guided by the sparser stellate connections demonstrated in the cortical wiring model of Douglas and Martin (Douglas and Martin 2004). They are configured as regular spiking cells as well (Figure 1a)(Connors and Gutnick 1990).
- iii. Layer V pyramidal cells contact approximately 1% of the available layer II/III pyramidal cells within a radius of 300 μm (Thomson and Deuchars 1997), and 2.4% of external layer V pyramidal cells. Connections to available inhibitory cells are kept

at 5% of the excitatory connections, with double bouquet cells now included (Melchitzky et al. 2001; Lewis et al. 2002). Thomson and Deuchars discovered that 80% of layer V pyramidal cells contacted by layer II/III pyramidal cells were of the intrinsic bursting variety, and we have made all of them intrinsically bursting in this model (Figure 1b)(Thomson and Deuchars 1997; Connors and Gutnick 1990).

- iv. Layer VI pyramidal cells make approximately half the connections as the layer V cells do to the layer II/III pyramidal cells (0.5% of the available cells within 300 μm) within the model. And no connections are provided externally to layer V pyramidal cells or layer VI pyramidal cells in the spirit of Douglas and Martin (Douglas and Martin 2004). Contacts to external inhibitory cells are kept at 5% of the excitatory connections. These cells are kept as regular spiking cells (Figure 1a)(Connors and Gutnick 1990).
- v. Basket cells are represented as single compartment inhibitory cells with isotropic connection distributions out to a radius of 50 μm , which then decreases in detection probability as a dying exponential having a characteristic length of 50 μm (Budd and Kisvárdy 2001). Connections can extend as far as 1 mm away within the model. Small basket cells can contact up to 450 neighboring pyramidal cells, and larger ones can reach up to 960 pyramidal cells in histologic data (Kisvárdy et al. 2002). In our model, a total of 700 contacted cells is used, split evenly between the available stellate cells, and the three classes of pyramidal cells. Basket cells are typically found in layers II/III and V (Kisvárdy et al. 1993), and in this simulation they are all kept at the layer II/III position. Basket cells can contact up to 50 other basket cells (Kisvárdy et al. 1993), and in the model this number is split between external basket cells (25 cells) and chandelier cells (25 cells). Double bouquet cells are also probably contacted by basket cells, with estimates of 30% of calbindin and calretinin positive interneurons being contacted by parvalbumin positive cells (Peters and Sethares 1997), we include a 30% contact probability for available cells in our model. These inhibitory cells are all considered fast spiking in our model (Figure 1c)(Connors and Gutnick 1990).
- vi. Double bouquet cells in the model represent an intracolumnar acting inhibitory influence, with little external connectivity. The axonal connections extend out to approximately 100 μm (Lund and Wu 1997). It is known from histology studies that very few double bouquet axons reach down as far as layer V, and virtually none to layer VI, but the axons encounter many layer V pyramidal cell dendrites within layers II/III and IV (Peters and Sethares 1996). We provide for 3.2% contact out to 100 μm to available layer II/III and layer V pyramidal cells, as well as to stellate cells with no good data to support this. It has been estimated that 30% of parvalbumin positive cells (most chandelier and basket cells) are innervated by calretinin positive cells (double bouquet cells), and a figure of 30% of available cells within the 100 μm connection radius is included (DeFelipe et al. 1999). The double bouquet cells are treated as fast spiking interneurons (Figure 1c)(Connors and Gutnick 1990).
- vii. Chandelier cells are a type of inhibitory cell which innervates specifically the outgoing axonal initial segments of neighboring neurons. This acts to raise the threshold on the amount of synaptic current required to generate an action potential (Douglas and Martin 1990). Their axonal arbors are 300–400 μm in diameter (200 μm in the model) (Kawaguchi and Kubota 1998), and they synapse with approximately 20% of pyramidal cells encountered, primarily in layers II/III and IV (DeFelipe et al. 1985). There are no contacts to inhibitory cell-types in this model. These cells are represented as regular spiking inhibitory cells (Kawaguchi and Kondo 2002).

2.2 Connection Patterns

Figure 2. demonstrates the pattern of connectivity for both internal connections between neurons within a given minicolumn as well as external connections between neurons in separate minicolumns. The connection pattern relies heavily on the visual cortical model of Douglas and Martin (Douglas and Martin 2004). For some of the external connections left out of that model description the simulation includes connections described by Nieuwenhuys (Nieuwenhuys 1994) in his summary of the anatomic data. Specifically, these additional external connections are from the layer II/III pyramidal cells to distant layer V pyramidal cells. The visual cortical model wiring was used for the minicolumns because it has been widely studied over a long period of time, and seems to have analogs in other regions of somatosensory cortex (Douglas and Martin 2004).

2.3 Differential Equations and Numerical Integration

The numerical simulation used in this study utilized the excitable membrane model of Hodgkin and Huxley (Hodgkin and Huxley 1952) as modified by Av-Ron et al. (Av-Ron 1994; Av-Ron et al. 1993). Each cell in the simulation is influenced by a set of synaptic inputs as well as ion channel currents, with the membrane potential varying as:

$$C_m \frac{dV}{dt} = I_{syn} - I_{Na} - I_{Ca} - I_K - I_{K(Ca)} - I_A - I_L.$$

Where the individual currents are the input synaptic current I_{syn} , the inward sodium and calcium currents I_{Na} and I_{Ca} , outward potassium currents including a delayed rectifier current I_K , a calcium dependent potassium current $I_{K(Ca)}$, and a transient potassium current I_A , and lastly the leak current I_L . The individual ohmic conductances, activation and inactivation variables, cellular calcium dynamics, and synaptic connections are described in equation form in the appendix

2.4 External Field Stimulation

The external field is simulated by applying a current to either one or two circular disks with radii of 1mm. With two disks, the current is applied with opposite polarity to the two electrodes to create a dipole field. For a homogenous medium of conductivity σ , the potential distribution from a single disk of radius a receiving a current, I , varies as

$$\Phi(\rho, z) = \left(\frac{I}{4\pi\sigma a} \right) \sin^{-1} \frac{2a}{[z^2 + (\rho - a)^2]^{1/2} + [z^2 + (\rho + a)^2]^{1/2}}$$

where ρ is the radial distance from the center of the disk, and z is the vertical height from the disk (Atkinson et al. 1983). No account is made of any anisotropies in the conducting medium (gray matter), and a value of $\sigma = 0.3S/m$ is used after Ranck (Ranck 1963). The applied stimulation pulse takes the form of a square-wave train, lasting for 0.1 sec. The square wave shape is charge-balanced, with equivalent size and duration (200 μ sec) positive and negative lobes. Applied frequencies range from 60 Hz to 200 Hz. Two different voltage threshold criteria were used to investigate the induction of action potentials within the excitable elements of the model. The first involved looking at the voltage distributions along the axon initial segments (AISs) of the modeled neurons. Using a typical value for the AIS ($\delta = 30 \mu m$) as a characteristic length scale, the characteristic function involving the second difference of the voltage along the AIS was formed (McIntyre and Grill 1999; Rattay 1986; Rattay 1988; Warman et al. 1992; McIntyre et al. 2004):

$$\Delta^2 V = V(z_{AIS} + \delta) + V(z_{AIS} - \delta) - 2V(z_{AIS}).$$

From previous simulation studies of electric field effects near the AIS (McIntyre and Grill 1999), a threshold value of 3 mV was set for this quantity. When the stimulation threshold criteria is met, a single injection of current into the presynaptic cell approximately equivalent to 10 times that of a pyramidal cell excitatory synapse is administered (conductance 0.056 mS/cm²). This produces a resultant action potential in the cell with high efficiency.

Similarly, one may consider action potential production in the horizontal portions of the axon branches depicted in this simulation. For myelinated axons, this takes place at the nodes of Ranvier (Warman et al. 1992; McIntyre and Grill 1999), and the characteristic length used to calculate the second difference of the potential is on the order of $\delta = 500 \mu\text{m}$ for a $5.7 \mu\text{m}$ diameter myelinated axon. The vast majority of axons within the central gray matter providing local connections are much smaller than this diameter however, by a factor of 10 (McIntyre et al. 2004), and many of them are unmyelinated. The threshold value of $\Delta^2 V$ for $5.7 \mu\text{m}$ myelinated axons from McIntyre et al. ranges from 8–12 mV (McIntyre et al. 2004). To investigate an upper limit of distal axonal stimulation in our model, several stimulation runs were made with the sole point of AP production occurring in the middle of the horizontal axon branches based on an 8 mV $\Delta^2 V$ threshold criteria. The characteristic length used for these calculations was the individual horizontal axon branch length. These studies were performed without any AIS stimulation. When the stimulation threshold criteria is met, a single injection of current corresponding to the conductance of one excitatory pyramidal cell synapse (0.056 mS/cm²) is applied to the postsynaptic cell after a synaptic delay time of 1 msec.

2.5 Computational System

The code for the simulation was written in C and developed in a Linux environment. Currently the simulation runs on a cluster of 16 32-bit x86 architecture computers implemented as a distributed system. Each computer in the cluster performed the numerical integration calculations on a specific subnetwork, with data transfers between processors (representing neuronal connections crossing nodal boundaries) accomplished with Linux-based interprocessor communication commands. The computational loop consisted of the numerical integration of the model equations for each neuron as well as an updating of the synaptic currents for each synapse. The forward Euler method was used for the numerical integration routine with a time step of 0.01 msec. Time-binned network activity data files were saved to disk as well as membrane voltages and intracellular calcium concentrations from select subsets of neurons. The simulation software package as a whole consisted of three separate modules. The first module generated the descriptive parameters of the neurons, patterns of connectivity, and the stimulation parameters; the second module performed the numerical integration loop; and the third module acted as an interface into MatlabTM for data analysis. Typical 2 second simulation runs on a 32×32 minicolumn model typically take 2 hours to run. The simulation code is available via email as well as MPEGs of the resultant network activity (Anderson 2006).

2.6 Data Analysis

In order to compare the different model configurations, a figure of merit was derived to investigate the effects of stimulation on ongoing network activity. This amounted to timing the first peak in the network activity as it returned following the stimulation. The time of this peak was derived by plotting the summed network activity (total number of action potentials), in bins of 100 msec. Model parameters that were varied included the frequency of stimulation, connection numbers between neurons, electrode height in the monopolar situation, and the electrode location in the plane parallel to the cortical surface.

Studies were also performed on the efficacy of stopping seizures in spontaneously active networks using single pulses, and the effect of stimulation timing with respect to the underlying rhythm of the network. Finally, discrete connections between isolated patches of cortex were included to simulate longer range modular connections, and the alteration of network activity with dipolar stimulation was investigated. This was to look for differences in stimulation effects due to dipole orientation changes.

3. Results

In general, all of the frequency variation studies as well as studies investigating the location of the monopolar stimulation element were performed with a variety of neuronal levels of connection. A central noise source was used constantly during the simulation to provide robust ongoing activity, and to reinitiate activity after the stimulation period. This involved random current injection at a low probability of 3×10^{-5} per 10 μ sec time step (3 Hz) into the 16 most central layer II/III pyramidal cells in the model. The random number seed used to generate the noise current injections was kept constant within each experimental paradigm described below, but could vary between them. This was to produce the same temporal noise pattern within a given set of experiments, and provided the experimental substrate to examine alterations in the model behaviour as a function of applied pulse timing or electrode orientation. Regardless of the connection pattern or noise timing, all of the simulations demonstrated constant bursting behaviour.

Five levels of connectivity based on multiples of the inhibitory and excitatory cell connection numbers from pattern A were explored, described as patterns B–F in Table 1. This table also lists the base frequency of the noise induced activity achieved by each connectivity pattern as measured in the layer II/III pyramidal cells. Patterns B and C exhibited self-sustaining activity such that if the noise was shut off after 0.5 sec, the models continued to show continuous excitatory behaviour at least to 2 seconds. Longer simulation runs, and post-stimulation activity can exhibit both altered time frequency behaviour and spontaneous periods of activity cessation. In general network activity is robust in every cell class except for the Layer VI pyramidal cells which are less active. Plots of the instantaneous activity for all of the cell classes as a function of time is demonstrated in Figure 3 before, during, and after stimulation.

3.1 Monopolar Stimulation Frequency Studies

In this set of experiments, an electrode with radius 1 mm was used to provide the excitation stimulus. A series of 2-second trials was undertaken at each level of connection, with the central noise running continuously. The stimulation period was from 0.5 sec to 0.6 sec in each trial. The figure of merit used to compare different frequencies and different connectivities was the time required until the end of stimulation to the first action potential peak in the summed layer II/III pyramidal cell activity. This is demonstrated in Figure 4 as a function of stimulation frequency for each of the examined connectivity patterns. Overall there is a plateau effect, with longer return to activity times at higher stimulation frequencies. These studies assumed action potential solely in the vertical portion of the exiting axon on a given cell, at the axon initial segment. A characteristic function $\Delta^2 V$ threshold of 3 mV was assumed.

3.2 Single Electrode Stimulation Spatial Studies

This set of experiments examined the effects of moving the stimulation electrode in space over the network in both the same plane as the cortex, and perpendicular to it. Figure 5 demonstrates the delays to return of activity (layer II/III pyramidal cells) as a function of electrode position relative to the center of the network, taken all at the same height (155 μ m above the cortex). The central position of the electrode disk ranges from 0 to 1270 μ m with respect to the network center. As demonstrated, there is a central ring of enhanced stimulation under the electrode

(Figure 3), that produces the longest delays to return of activity and produces the peak in effect as it passes over the model. The pattern B data was continued to the other side of the model to show this symmetric ring-nature. In Figure 6, the sharp decay in height of layer II/III activity is demonstrated as the electrode is moved vertically above the cortex for the various connectivity patterns. This demonstrates the very sharp cutoff of activity provided by the artificial single threshold value for inducing action potentials. The addition of a distribution function for this threshold value greatly softens this effect as described below.

3.3 Modular Connection and Dipole Electrode Studies

In this set of experiments, two opposite corners of the network (the upper right and lower left in Figure 7) were preferentially wired to each other, specifically between the layer II/III pyramidal cells in each zone and the layer II/III to layer V connections. This crudely represents the longer range discrete patch connections observed in mammalian somatosensory cortex (Kisvárdy et al. 1986; Lund and Wu 1997; Melchitzky et al. 1998), and serves to add an element of anisotropy in the network.

The stimulation electrode geometry was altered to consist of two 250 μm radius circular electrodes separated by 1.6 mm center to center. The stimulation protocol was the same as in the monopolar case with a charged balanced waveform, but the polarity between the two dipolar electrodes was always the opposite sign. The dipolar geometry for stimulation was then examined within the discrete patch model, and rotated around the network within the plane of the cortex to look for any additional effects related to underlying connectional asymmetries. A plot of the time for activity return (layer II/III pyramidal cells) is presented in Figure 7a as a function of the dipole position. The percentage of total layer II/III pyramidal cell connections involved in the patch connections was 22%. There was a strong orientation effect related to the position of the dipole electrodes as exhibited by the finer rotational plot in Figure 7b. Orientations such that the dipole axis was aligned with the two connected patch regions were much more effective at delaying the return to activity. The time delay was also studied as a function of electrode separation in Figure 7c.

3.4 Distal Axonal Branch Stimulation

The horizontal action potential requirement invoked by insisting on action potential production in the horizontal axon branches at a characteristic function value of Δ^2V of 8 mV is demonstrated for the monopolar electrode system in Figure 8, as a function of frequency. In this stimulation paradigm, there is much less suppression of overall network activity, but there is certainly an alteration in the time-frequency characteristics of the resulting bursting, and this appears to be frequency dependent. This particular bursting mode consists of couplets of activity peaks with longer intercouplet separation due to the pattern of activity spread across the model during each periodic burst. As observed in Figure 8, this particular temporal pattern of spread can be altered by stimulation. The last plot in Figure 8 demonstrates a return to the predominantly observed bursting behaviour after stimulation at 200 Hz. This study was performed using a single 2 mm diameter electrode. A dipole electrode arrangement study using this horizontal action potential requirement was also performed in the patch connected paradigm, and using the dipole electrode geometry discussed in Section 3.3. Figure 9 demonstrates the modest effects on the underlying layer II/III pyramidal cell activity as a function of dipole orientation with respect to the connected patches, there were no clear orientation effects for this action potential requirement.

3.5 Single Pulse Timing Studies

The timing of the 0.1 sec stimulation onset with respect to the phase of the underlying network rhythm is investigated in Figure 10, specifically for connectivity pattern C. There is a transition in delay times and in the layer II/III pyramidal cell activity as the pulse time is varied with

respect to one peak in the underlying rhythm. Overall, delay times for single pulses in many instances could be comparable to the trains of pulses used in the frequency variation studies.

3.6 Threshold Sensitivity Analysis

The threshold for axon initial segment action potential was adjusted in a series of experiments for the monopolar geometry with fixed position of the electrode disk. Time to return of activity (layer II/III pyramidal cells) for 200 Hz stimulation as a function of the threshold condition on the characteristic function, Δ^2V is presented in Figure 11. The stimulation electrode height study for pattern C was also repeated using a Gaussian distribution for the threshold values of the characteristic function Δ^2V , with a mean of 2 mV and a standard deviation of 1mV. Including this distribution extended the stimulation effects out to a height of almost 10 mm above the cortex, assuming no impedance changes as the electrode is raised. This is unphysical in that the electrode would break any low impedance fluid interface as it is raised above the cortical surface, but it does point out that by stimulating a small number of neurons in the low threshold tail of the distribution, seizure activity can still be altered. Time to return of activity (layer II/III pyramidal cells) as a function of height in this situation is presented in Figure 12.

Additional studies of the total applied stimulation energy were made specifically for connectivity Pattern C. The energy delivered to the tissue during a given 0.1 sec long train of pulses will vary in our paradigm as:

$$E = I^2 R \cdot \Delta t \cdot N_{pulses},$$

With E being the total energy delivered during the 0.1 sec stimulation period, I the applied current, R the presumed constant contact impedance of the electrode on the pial surface, Δt the pulse length, which is held constant at 200 μ sec in our paradigm, and N_{pulses} being the number of applied pulses during the 0.1 sec stimulation period. The 200 μ sec pulse width is a good average excitable tissue chronaxie time used frequently in nervous stimulation systems, which is why we chose to use this value in our studies. We make the assumption that maintaining the current flow for this length of time will result in an action potential for the correctly located neuron with high efficiency. So the adjustable parameters in our model boil down to the number of stimulation pulses during the 0.1 sec interval, and the applied current. In our model, we assume a linear homogeneous isotropic medium that the neurons reside in to estimate the local current flow from the applied stimulation. Similarly, we ignore any CSF leakage effects and underlying white matter isotropy. Keeping the product $E \propto I^2 \cdot N_{pulses}$ constant at $(10 \text{ mA})^2 \times (6 \text{ pulses})$ while varying the applied frequency results in the time delay curve presented in Figure 13a, for the time delay to return of activity after stimulation. This demonstrates very little frequency dependence for the pattern C connectivity model, similar to the flat frequency dependence observed for pattern C in Figure 5. The product $E \propto I^2 \cdot N_{pulses}$ can also be kept constant by varying the applied current and number of pulses, while keeping the total stimulation time at 0.1 sec. This time delay curve is plotted in Figure 13b along with the applied current, demonstrating a sharp reduction in effect at higher frequencies as the current is reduced. This points out the applied current dependence in our model which is demonstrated for 200 Hz stimulation over 0.1 sec in Figure 13c, showing a quick falloff in effect below 8 mA.

4. Discussion

Previous computational studies of the effects of external electric fields on the excitable properties of the nervous system have dealt primarily with current and voltage threshold effects for action potential induction either in myelinated axons, soma, or the axon initial segment (Warman et al 1992; Richardson et al. 2000; Moffitt et al. 2004; McIntyre et al. 2004; Butson and McIntyre 2005; McIntyre and Grill 1999; McIntyre and Grill 2002). These have not been

performed in the context of active neural networks. Using order of magnitude values from these studies, we have derived voltage gradient criteria to determine where within the spatial confines of our model action potential production is taking place. Our previous investigations of stimulation within our model system involved current injection or action potential production within large contiguous blocks of simulated cells (Franaszczuk et al. 2003). This is the first time that a realistic field structure along with reasonable stimulation time-frequency characteristics have been applied to a dynamic seizure model. This model demonstrates cessation of epileptiform activity using a variety of connectional substrates secondary to the application of an external electric field (Figures 4–6).

Some discussion needs to be included on changes in network activity associated with the various connection patterns we studied (Patterns B–F). Clearly, alterations in relative numbers of inhibitory and excitatory connections affect the overall excitability of the system (compare the underlying bursting frequency in Table 1 for Patterns B and C). What is much more impressive is the sudden jump in bursting frequency observed by increasing the total number of connections in general (compare the bursting frequency between Patterns B–C with Patterns D–F). Increasing the total number of connections results in higher frequency behaviour, and greater numbers of cells undergoing action potentials at any given time point. One interpretation for this increase in connectivity could be the axonal branch sprouting behaviour that is observed in human and animal models in both neocortex and mesial temporal structures (Sutula 2002; Longo et al. 2003; Vijayalakshmi et al. 2005; Sutula et al. 1989; Carmichael et al. 2001). Future studies of epileptic foci might incorporate isolated regions of higher connectivity representing a seizure focus adjoining regions of less excitable modeled tissue to study the spread of epilepsy into normal brain. Our models additionally demonstrate spontaneous cessation of activity even during constant driving by a noise source, as in Figure 10b for stimulation at -0.06 sec relative to the activity peak. This effect is quite dependent on the timing of the stimulation pulse as demonstrated in the subsequent plots, but it is also present in unstimulated simulations as well where the activity does eventually recur due to the constant noise source. We find these features of our model quite encouraging, and more representative of real cortical epileptic activity which similarly demonstrates spontaneous cessation. Future studies in this regard might include stimulation induced bursting followed by phase dependent efficacy studies for a subsequent seizure disruption pulse, as in the experimental paradigm of (Lesser et al. 1999).

A frequent criticism of these types of modeling efforts is that either the model involves too much complexity or too little complexity to describe the phenomena at hand. One of our previous one-compartment neuronal simulations involved a simple array of only two classes of cells (inhibitory and excitatory), linked together in a random fashion. By changing the intracellular calcium dynamics it was possible to reproduce many of the time-frequency properties of an evolving temporal lobe seizure over several tens of seconds (Kudela et al. 2003b). The need to increase the complexity in our current studies was driven by the need for a more accurate spatial arrangement of the cells due to the inherent geometrical constraints of an external applied electric field. To keep the simulation as simple as possible, we instituted a repeating circuitry model based around the minicolumn hypothesis, which allowed us to adapt our single-compartment neuronal model into a spatial representation of the cortex. The total number of neurons currently represented is 16,384, and this will be expanded in future studies. At some point, to truly appreciate the effects of external stimulation, it might be necessary to make the model even more complex as in (Traub et al. 2005). We view the current effort as a middle ground, which allows for easy implementation of a computational representation of cortical stimulation.

We have now imposed a spatial scale on our model, which allows us to interpret evolution of activity in time and space. Transit speeds for organized waves of activity within the model

range from 13–30 mm/sec, which compares favorably with measured propagating wave speeds in neocortical slice preparations (30–50 mm/sec) (Wu et al. 1999; Bao and Wu 2003). Depending on the connectivity pattern used, our model also exhibits organized rhythmic activity within a physiologic range of 3–20 Hz. The external applied electric field supplied by either the monopolar or dipolar geometries produces underlying current densities in the cortex which range in value from 15 mA/cm² in layer VI up to 130 mA/cm² in the neighborhood of the electrodes. This is approximately a factor of 2–3 higher than the current densities calculated by Nathan et al. using a 3-dimensional finite element model of the cortex and underlying white matter for equivalent stimulation currents, and most likely represents our lack of accounting for CSF current shunting effects demonstrated by finite element models (Nathan et al. 1993).

Motamedi et al. reported in studies of stopping stimulation induced afterdischarges in subdural electrode monitored patients with brief pulses of electrical stimulation (BPS) that the BPSs were most effective if applied during the negative phase of the after depolarization (by a factor of 1.9) (Motamedi et al. 2002). We investigated the efficacy of stimulation with single pulses relative to the phase of the underlying rhythmicity in the layer II/III pyramidal cell activity measured during the simulation. This reveals a definite alteration in bursting behaviour as the stimulation pulse is varied across the underlying network peak in activity. Although it is difficult to correlate this result with the data of Motamedi et al. as far as the observed EEG phase, it certainly indicates that the phase of the external field pulse with respect to the network activity can play an important role.

There was a general trend in our results, more effective for certain connectivity patterns, to see a longer delay to return of network activity after stimulation at the higher stimulation frequencies. Specifically, we observe a plateau effect above 120 Hz in several of the connectivity patterns for the magnitude of the delay (Figure 3). In the small group of patients at our hospital center who have undergone implantation of the responsive neurostimulation system (RNS) for seizure control, most of them exhibit best control of their seizures with stimulation frequencies 100–200 Hz (4 out of 5 patients), with the poorly controlled fifth patient currently being treated at 50 Hz (GK Bergey, unpublished observations). It is not true that these patients have been consistently adjusted upwards in frequency; many of them were treated at 200 Hz, but found greater benefit at slightly lower frequencies. Our model is missing key information on stimulation induced effects at the higher frequencies, specifically, it is not well known how easily cortical neurons can follow an imposed 200 Hz stimulation for several stimulation cycles. One possible mechanism for higher frequency drop-out of stimulation induced effects might be from neurotransmitter depletion, which is one mechanism invoked for the lack of cortical effects observed in deep brain stimulation of the basal ganglia (Iremonger et al. 2006).

The current modeling effort deals solely with local cortical effects of stimulation and self-excitatory behavior and ignores any effects due to the underlying white matter, which may be justified over such a small spatial scale (800 μ m $\times$ 800 μ m). It might be expected however, that any grossly organized white matter pathways passing under the region of stimulation will be more or less affected by the orientation of the stimulation system as well. Characteristic function thresholds for action potential production in passing axons do approach that of the axon initial segment, and stimulation of the underlying white matter may play a role in any propagated signal. We do see orientation effects in the dipole stimulation studies when two regions of the cortex are preferentially connected by longer distance axons, but this effect is from the extrinsic connectivity of the modeled regions and not to direct axonal stimulation. It is possible to observe some asymmetries in cortico-cortical evoked potentials (CCEPs), depending on the dipole orientation of the stimulation pair used, specifically in patients who have undergone grid placement for seizure monitoring (WS Anderson, unpublished observations). This might be an expression of differential stimulation of underlying white

matter tracks depending on electrode orientation. These effects have not been examined in detail in CCEP studies, since most activation is assumed to occur at the axon initial segment with anodal stimulation, and interneuron stimulation with cathodal stimulation (Matsumoto et al. 2004). Future CCEP studies should look for possible underlying white matter excitation effects as well.

This simulation study assumed axon potential production induced by stimulation arose primarily in the axon initial segment, and there are both experimental as well as simulation data to support this (McIntyre and Grill 1999; Nowak and Bullier 1998a; Nowak and Bullier 1998b). After action potential production occurs, all postsynaptic cells which a stimulated cell contacts receive a subsequent synaptic current injection. This represents a more efficient stimulation process than if only selected horizontally oriented axonal branches were being excited. Then the only postsynaptic cells affected (ignoring backpropagation and branch effects) would be the specific postsynaptic cell attached to this axonal branch. With fairly liberal axonal branch stimulation requirements used above in the dipole stimulation study (Figure 8), there is essentially no effect on the ongoing rhythmic activity. The threshold value of 8 mV used for the characteristic function is appropriate for 5.7 μm diameter axons, well above the size range of myelinated and unmyelinated cortical axonal branches (Bishop and Smith 1964). Distal axonal effects can become important when the field strength becomes appropriate for stimulating the underlying white matter, providing further impetus for exploring white matter effects in our modeling efforts. Additionally, as our time delay plots at constant stimulation energy demonstrate in Figure 13, there is a very sharp cutoff due to decreasing the stimulation current. This is present in Figure 13b, as the current is lowered to keep the applied energy constant when the stimulation frequency is increased, as well as in Figure 13c when the current is varied for a constant stimulation frequency. This threshold is also probably too sharp and will soften when a proper stimulation threshold distribution is incorporated.

Additionally, a distribution function for the axon AP initiation threshold needs to be more faithfully represented given the drastic alteration in height dependent results after implementing a very broad Gaussian distribution for this parameter. One might start with a similar form as the distribution of axon initial segment sizes observed in normal controls in motor neuron disease studies such as (Sasaki and Maruyama 1992). Including this will reveal how the stimulation effects are smeared outside the sharp boundary of the stimulation electrode providing information on the accuracy of placement near a seizure focus. Additionally, we seek improvements in our model to shorten the computational burden as we expand its geometric size scale. One possibility is by eliminating one of the neuron classes represented. The Level VI pyramidal cells might seem the best candidate, since their overall activity was low in the present model which possibly represents an artifact from the minicolumn wiring circuit that was chosen. Experimental studies show conflicting results regarding how important the deeper layers are in epileptic spread. The spread of activity via inhibitory networks seems to favor more superficial layers (I–III) (DeFazio and Hablitz 2005), while electrically isolating laminae in vitro seems to require the inclusion of the lower layers in certain experimental conditions (Telfeian and Connors 1998). As the accuracy of our modeling efforts improve, these are questions that can also be addressed in a model with architectural fidelity.

This model relies heavily on the monkey visual cortical wiring model of Douglas and Martin as the intrinsic minicolumnar wiring circuit. There is evidence from primate data as well as other animals that this particular circuit may have validity in other regions of somatosensory cortex (Douglas and Martin 2004). As we begin to focus this model on particular regions of cortex (frontal lobe, temporal neocortex), we will need to alter this intrinsic columnar wiring to better reproduce the architecture. Similarly, we have deemphasized the lateral connectivity of the Layer IV stellate cells as well as Layer VI pyramidal cells. This was in keeping with

current studies on epilepsy spread which seem to indicate the predominance of the Layer II/III and Layer V lateral connections (DeFazio and Hablitz 2005, Telfeian and Connors 1998). It is clear from histological studies that lateral projections from stellate cells as well as Layer VI play a functional role in the activity of primate visual cortex (Martin and Whitteridge 1984; Gilbert and Wiesel 1983; Lund et al. 1988; Schwark et al. 1992). Similar connections need to be added to this current neuronal model to investigate their effects on seizure evolution, especially as we plan on adding in thalamic interactions. Finally, we only very crudely included longer range patch connections in our simulations, as in the rotational dipole electrode studies in Figure 7. Cortical patch regions with separations on the order of 500 μm –1 mm add an extra layer of anisotropy to our simple lattice repetition of the underlying minicolumnar structure. Wadman and Gutnick demonstrated that these interconnected structures profoundly affect epileptiform propagation, and add a saltatory conduction element to the rate of spread (Wadman and Gutnick 1992). As we increase the size of the model from the current 800 μm $\times$ 800 μm , some realistic representation of these elements must be included.

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Appendix

Appendix

A1. Ohmic Conductances

The individual ohmic channel conductances are described by:

$$I_{Na} = g_{Na} m_{\infty}^3 (V)(1 - W)(V - V_{Na}) \text{ for the sodium current,}$$

$$I_K = g_K W^4 (V - V_K) \text{ for the potassium current,}$$

$$I_{K(Ca)} = g_{K(Ca)} \frac{C[7]}{K_d + C[7]} (V - V_K) \text{ for the calcium dependent potassium current,}$$

$$I_A = g_A A_{\infty}(V)B(V - V_K) \text{ for the transient potassium current, and}$$

$$I_L = g_L (V - V_L) \text{ for the leak current.}$$

The recovery and activation variables for these ohmic equations have time and voltage dependencies as well, and these are described by the equations:

$$\frac{dW}{dt} = \frac{W_{\infty}(V) - W}{\tau_w(V)} \text{ for the Na channel recovery variable,}$$

$$\frac{dB}{dt} = \frac{B_{\infty}(V) - B}{\tau_B} \text{ for the transient potassium channel inactivation variable.}$$

The voltage dependence for the steady state activation and inactivation variables $m_{\infty}(V)$, $A_{\infty}(V)$, $W_{\infty}(V)$, and $B_{\infty}(V)$ are modeled as sigmoidal curves parametrized with a half maximum voltage $V_{1/2}$, and a slope a as,

$$P_{\infty}(V) = (1 + \exp[-2a^P(V - V_{1/2}^P)])^{-1} \text{ for } P=W, m, A, B.$$

The sodium channel recovery variable time constant $\tau_w(V)$ is described as,

$$\tau_w(V) = \frac{1}{\lambda} (\exp[a^W(V - V_{1/2}^W)] + \exp[-a^W(V - V_{1/2}^W)])^{-1}.$$

The calcium current in the model is governed by the Goldman-Hodgkin-Katz electrodiffusion model (Hille 2001; Goldman 1943; Hodgkin and Katz 1949), with the current described as:

$$I_{Ca} = P_{Ca} X(V)^2 \left(\frac{K_c}{K_c + C[7]} \right) \left(\frac{z_{Ca}^2 VF^2}{RT} \right) \left(\frac{C[7] - C_o e^{-z_{Ca} FV/RT}}{1 - e^{-z_{Ca} FV/RT}} \right).$$

Where P_{Ca} is the calcium ion membrane permeability, $X(V)$ represents the calcium channel activation variable, K_c is the constant in the inactivation term, C_o represents the extracellular calcium ion concentration, and $C[7]$ represents the calcium concentration in the idealized intracellular shell just under the membrane. z_{Ca} is the charge on a calcium ion, F is Faraday's constant, R is the ideal gas constant, and T is the temperature. The time dependence of the calcium channel activation variable can be represented as:

$$\frac{dX}{dt} = \frac{X_{\infty}(V) - X}{\tau_X},$$

where the steady state value $X_{\infty}(V)$ is described as $P_{\infty}(V)$ above.

The calcium concentration within the cell body is modeled as a diffusion process inside of a 20 μm radius spherical cell, see Figure 14. The inner core (shell #1) is a 17 μm radius sphere, and this is surrounded by six successive 0.5 μm thick shells out to a total radius of 20 μm (Kudela et al. 2005). The diffusion process includes calcium buffering effects with forward and backwards rate constants, a Ca^{2+} -ATPase pump, and the diffusion process discretized per

(DeSchutter 1989). The rate of change of the calcium concentration in the outer shell is governed by:

$$\frac{dC[7]}{dt} = \frac{-I_{Ca}}{2FV_{shell}} + bB_oU[7] - fC[7](1 - U[7]) - R_p\left(\frac{C[7]}{C[7] + K_p}\right) - J_{diff},$$

where $C[7]$ represents the $[Ca^{2+}]$ in the seventh shell, b and f represent the forwards and backwards rate constants for the buffering process, B_o is the total unbound buffer concentration, $U[7]$ is the fraction of bound buffer in the seventh shell, R_p and K_p are the kinetics constants of the pump process, and J_{diff} represents any gains or losses from diffusive $[Ca^{2+}]$ flow. In a given shell, the fraction of bound buffer will change as

$$\frac{dU[i]}{dt} = -bB_o + fC[i](1 - U[i]),$$

where $U[i]$ is the bound buffer fraction in the i^{th} shell, and $C[i]$ is the calcium concentration in the i^{th} shell. The calcium ion diffusion is governed by Fick's law in a spherically symmetric coordinate system:

$$\frac{\partial(rC[i])}{\partial t} = D \frac{\partial^2(rC[i])}{\partial r^2}.$$

A2. Model Parameters

The model parameters for the three different electrophysiology types simulated (regular spiking, intrinsic bursting, and fast spiking) are presented in Table 3. Figure 1 demonstrates single cell activity induced by a $5 \mu A/cm^2$ current injection for all three types, the injected current shuts off at 250 μsec . None of the neurons exhibit spontaneous activity after charge input ceases.

A3. Synaptic Properties

The synaptic currents in the model can be represented by

$$I_{syn}(t) = \sum_{j=1}^{N_{syn}} w_j g_j(t - \tau_j)(V - E_{syn}^j),$$

where N_{syn} is the total number of synapses on a given neuron, w_j is a weighting factor for that synapse, $g_j(t)$ is the synaptic conductance function, which can carry an intrinsic delay τ_j . E_{syn}^j is the reversal potential used in the driving function for the j -th synapse. The individual conductance functions can be represented as

$$g_j(t) = g_{syn}^j \sum_{i=1}^{N(t)} (e^{(t_i - t)/\tau_d} - e^{(t_i - t)/\tau_o}).$$

τ_d and τ_o are the onset and decay times for a given PSP. The individual synaptic conductance constants g_{syn}^j are adjusted to give each PSP an equivalent amount of injected charge integrated over time. At $\tau_d = 3msec$, and $\tau_o = 0.5msec$, it takes the value $g_{syn}^j = 0.01mS/cm^2$. The sum in this formula runs over the non-negligible past action potentials received by that synapse.

A scheme for deriving the relative synaptic weights can be obtained by considering the proportionality:

$$w_j \propto d_j n_{syn} R_j,$$

with d_j representing the reduction in size of the PSP due to distant synapsing in the dendritic arbor (Williams 2005; Williams and Stuart 2003). Pyramidal and stellate cells are assumed to synapse at 500 μm from the cell body, basket cells take a somal synaptic location, double bouquet cells synapse distally ($>500 \mu m$), and chandelier cells synapse immediately under the cell body. n_{syn} represents the total number of synapses for a given cell-cell connection and is taken from data when possible (Douglas and Martin 1990; Krimer and Goldman-Rakic 2001; Kalisman et al. 2003; Kisvárdy et al. 2002; DeFelipe 1985). R_j represents a factor for the relative receptor density, is taken as 1 for excitatory cells, and derived from (Paré et al. 1998) for the inhibitory cell types. Table 3 lists the relative weights for each type of possible cell-cell connection, along with the values of the individual synaptic conductance constants, g_{syn}^j .

Figure 1.

Single neuron simulations using modified Hodgkin-Huxley equations with calcium diffusion. A 5 μ A internal current injection is used to excite the cells, and the current source is shut-off at 250 msec to demonstrate the lack of self-excitatory behavior in each of the three cell-types. a) Regular spiking cell. b) Intrinsic bursting cell. c) Fast spiking cell. Table 3. presents the parameters for these three cell types.

Figure 2.

(a–c) Schematic diagram of the types of neurons within the simulation as well as their intrinsic connectivity within a minicolumn (darker shaded lines) and their local connectivity to neighboring neurons within other minicolumns (lighter shaded lines). d) Spatial size scale of axonal arborization pattern from a representative layer II/III.

Figure 3.

Snapshots of network activity for all seven cell classes as a function of time. Connectivity pattern C. Stimulation occurs from 0.5 to 0.6 sec. Classes 1–4 represent layer II/III pyramidal cells, stellate cells, and layer V and layer VI pyramidal cells respectively. Classes 5–7 represent basket cells, double bouquet cells, and chandelier cells respectively.

Figure 4.

Stimulation effects as a function of frequency and connectivity pattern. These plots demonstrate the time evolution of network activity with a constant central noise source present. Stimulation occurs from 0.5 sec to 0.6 sec (red arrows). The time delay to return of activity is defined as the time after 0.6 sec at which the first peak in the layer II/III network activity occurs. a) layer II/III pyramidal cell activity with stimulation at 200 Hz. b) layer II/III pyramidal cell activity with stimulation at 60 Hz. c) Delay to return of activity (layer II/III pyramidal cells) as a function of frequency for the tested connectivity patterns (B–F).

Figure 5.

Stimulation effects as a function of electrode position parallel to the cortical surface. The time to return of activity (layer II/III pyramidal cells) is plotted as a function of the stimulation electrodes distance from the center of the network for a variety of connectivity patterns. The pattern B data was continued through the center of the model to show the approximate dimension of the active central ring of stimulation under the electrode.

Figure 6. Stimulation effects as a function of height above the cortex for the tested connectivity patterns (A–F) (layer II/III pyramidal cells). The single vertical red line marks the cortical surface.

Figure 7.

(a) Study of the influence of stimulation on longer range patch connections in the network. Two opposite corners of the network, specifically between layer II/III pyramidal cells in each patch, and between layer V pyramidal cells in each patch, are preferentially connected. Stimulation is via the dipole electrode arrangement, and the plots of layer II/III pyramidal cell activity are presented as a function of the dipole orientation. Stronger stimulation induced effects are observed with the dipole axis parallel to the connected patches. The connected patches are shaded gray in the schematic, and the two dipole disks are represented as circles around the periphery of the model. Red arrows mark the onset and cessation of stimulation (Connectivity pattern C). The dipole marked with the '+' sign undergoes the positive lobe of stimulation first, the '-' electrode is switched in polarity. The figure should be read from left to right in a given row, the dipole is rotated in the clockwise direction around the model. (b)

Close up view of the time delay as a function of dipole rotation angle taken between the “0” orientation presented in the inset on the left side of the figure, and the “90” orientation shown on the right side. (c) Time delay dependence on the separation of the two electrodes, with the dipole system oriented along the connected patches. The red line marks the point of contact of the two electrodes.

Figure 8.

Study of action potential production in the horizontal axonal branches as a function of frequency, solely in the monopolar format. Summed network activity for the layer II/III pyramidal cells is demonstrated as a function of time. Action potential production in the axon initial segment was ignored. Red arrows mark the onset and cessation of stimulation. Note the time-frequency alteration of this couplet bursting mode after stimulation (Connectivity pattern C).

Figure 9.

Patch connected study using the dipole electrode configuration (1mm diameter electrodes separated by 1.6 mm). The horizontal axon branch action potential requirements are used to determine the stimulated branches. Very little delay is observed for the return of the underlying layer II/III pyramidal cell activity. Red arrows mark the onset and cessation of stimulation (Connectivity pattern C). The dipole marked with the '+' sign undergoes the positive lobe of stimulation first, the '-' electrode is switched in polarity. The figure should be read from left to right in a given row, the dipole is rotated in the clockwise direction around the model.

Figure 10.

Study of timing of single pulse stimulation with respect to the underlying network rhythmicity, as demonstrated by the connectivity pattern C design. Time to return of layer II/III pyramidal cell activity as a function of delay time relative to the network peak activity peak is shown in A. A red line and arrow mark the stimulation point. The plots of network activity for each stimulation time are presented in B, demonstrating the phase sensitive alterations in post-stimulation network activity.

Figure 11.

Sensitivity of stimulation effects to threshold requirement on characteristic function, Δ^2V . Plot is for monopolar stimulation at 200 Hz with fixed electrode position relative to the network. Time to return of activity (layer II/III pyramidal cells) is plotted as a function of the threshold value in mV.

Figure 12.

Time to return of activity (layer II/III pyramidal cells) as a function of height for pattern C connectivity given a Gaussian distribution for the characteristic function threshold condition. In this example, the mean threshold for axon initial segment stimulation is 2 mV, and the Gaussian has a standard deviation of 1 mV. The single vertical red line marks the cortical surface.

Figure 13.

(a) Time to return of activity (layer II/III pyramidal cells) for pattern C connectivity, keeping the quantity $E \propto I^2 \cdot N_{pulses}$ constant at $(10 \text{ mA})^2 \times (6 \text{ pulses})$ as the applied stimulation frequency is varied as a measure of applied stimulation energy. Stimulation starts at 0.5 sec for a 2 sec run. (b) Time to return of activity (layer II/III pyramidal cells) for pattern C connectivity, keeping the quantity $E \propto I^2 \cdot N_{pulses}$ constant at (600 mA^2) by varying the stimulation current, and number of stimulation pulses. Total stimulation time is 0.1 sec starting at 0.5 sec for a 2 sec run. The stimulation current is also plotted. (c) Time to return of activity

(layer II/III pyramidal cells) for pattern C connectivity, simply as a function of stimulation current for 200 Hz stimulation from 0.5 to 0.6 sec in a 2 sec run.

Figure 14.

Diagram of shell structure used to model the $[\text{Ca}^{2+}]$ diffusion with the relative sizes of the simulated shells demonstrated.

Table 1

Table of model parameters for all three electrophysiology types used in the simulation (regular spiking, intrinsic bursting, and fast spiking).

Pattern Code	Excitatory Factor	Inhibitory Factor	Base Frequency
A	1	1	na
B	0.5	0.5	20.0 Hz
C	0.5	1	12.5 Hz
D	0.25	0.5	2.0 Hz
E	0.25	0.25	2.0 Hz
F	0.25	1	2.0 Hz

Table 2

Table of synaptic weights for each type of possible cell-cell connection in the model. In parenthesis, the value for the individual synaptic conductance constants, g_{syn}^j , is provided in units of mS/cm^2 .

Model Parameter	Regular Spiking	Fast Spiking	Intrinsic Bursting
$a^A (mV^{-1})$	.02	.02	.02
$V_{1/2}^A (mV)$	-20.0	-20.0	-20.0
$a^X (mV^{-1})$	0.2	0.2	0.2
$V_{1/2}^X (mV)$	-45.0	-45.0	-45.0
$a^B (mV^{-1})$	-0.1	-0.1	-0.1
$V_{1/2}^B (mV)$	-70.0	-70.0	-70.0
$a^W (mV^{-1})$	.055	.055	.055
$V_{1/2}^W (mV)$	-35.0	-35.0	-35.0
$a^m (mV^{-1})$	.065	.065	.065
$V_{1/2}^m (mV)$	-31.0	-31.0	-31.0
$\lambda (msec^{-1})$	.08	.08	.08
$\tau_X (msec)$	3.0	12.0	15.0
$\tau_B (msec)$	1.0	10.0	0.2
$V_{Na} (mV)$	55.0	55.0	55.0
$V_K (mV)$	-72.0	-72.0	-72.0
$V_L (mV)$	-50.0	-53.0	-50.0
$V_{Ca} (mV)$	124.0	124.0	124.0
$g_{Na} (mS/cm^2)$	120.0	120.0	120.0
$g_K (mS/cm^2)$	15.0	15.0	15.0
$g_L (mS/cm^2)$	0.3	0.3	0.3
$g_A (mS/cm^2)$	12.5	9.0	12.5
$g_{K(Ca)} (mS/cm^2)$	3.5	0.0	3.0
$K_c (\mu mol/L)$	2.0	2.0	2.0
$K_d (\mu mol/L)$	0.5	0.5	0.5
$P_{Ca} (cm/sec)$	0.12	0.0	0.15
$C_o (\mu mol/L)$	2.0	na	2.0
$R_p (\mu mol/L \cdot sec)$	3.0	na	3.0
$K_p (\mu mol/L)$	0.5	na	0.75
$b (m \text{ sec}^{-1})$	0.1	na	0.1
$f (m \text{ sec}^{-1})$	0.3	na	0.3
$B_o (\mu mol/L)$	60	na	60
$D (cm^2/msec)$	2.0×10^{-9}	na	2.0×10^{-9}

Table 3
Table of connection variations used in the frequency and electrode location simulations demonstrating the multiplicative factors used to vary the overall levels of excitatory and inhibitory connections. The base frequency of the resultant activity as measured in the layer II/III pyramidal cells is also listed.

	Post- Layer II/III Pyramid	Post- Layer IV Stellate	Post- Layer V Pyramid	Post- Layer VI Pyramid	Post- Basket Cell	Post- Double Bouquet Cell	Post- Chandelier Cell
Pre-Layer II/III Pyramid	3(.0056)	3(.0056)	3(.0056)	0	1(.0056)	0	1(.0056)
Pre-Layer IV Stellate	3(.0056)	0	0	0	1(.0056)	0	1(.0056)
Pre-Layer V Pyramid	3(.0056)	0	3(.0056)	3(.0056)	1(.0056)	1(.0056)	1(.0056)
Pre-Layer VI Pyramid	3(.0056)	3(.0056)	0	3(.0056)	1(.0056)	1(.0056)	1(.0056)
Pre-Basket Cell	-4 (.0056)	-4 (.0056)	-4 (.0056)	-4 (.0056)	-4 (.0056)	-4 (.0056)	-4 (.0056)
Pre-Double Bouquet Cell	-2 (.0033)	-2 (.0033)	-2 (.0033)	0	-2 (.0033)	0	-2 (.0033)
Pre- Chandelier Cell	-43 (.0112)	-43 (.0112)	-43 (.0112)	0	0	0	0