Comparing Epileptiform Behavior of Mesoscale Detailed Models and Population Models of Neocortex

Sid Visser,† Hil G. E. Meijer,*† Hyong C. Lee,‡ Wim van Drongelen,‡ Michel J. A. M. van Putten,†§ and Stephan A. van Gils*†*

Abstract: Two models of the neocortex are developed to study normal and pathologic neuronal activity. One model contains a detailed description of a neocortical microcolumn represented by 656 neurons, including superficial and deep pyramidal cells, four types of inhibitory neurons, and realistic synaptic contacts. Simulations show that neurons of a given type exhibit similar, synchronized behavior in this detailed model. This observation is captured by a population model that describes the activity of large neuronal populations with two differential equations with two delays. Both models appear to have similar sensitivity to variations of total network excitation. Analysis of the population model reveals the presence of multistability, which was also observed in various simulations of the detailed model.

Key Words: Modeling, Neocortex, Epilepsy, Oscillation, Delay differential equation, Bifurcation analysis.

(*J Clin Neurophysiol* 2010;27: 471–478)

Epilepsy is a neurologic disease, characterized by an increased risk of recurring seizures, that affects nearly 1% of the world population. This disease can be controlled pharmacologically in approximately two third of the cases, although a multidrug regimen, with all the side effects resulting from drug-drug interactions, is often required to adequately control these patients. The remaining third of patients has an intractable epilepsy that cannot be controlled adequately with drug treatment (Kwan and Brodie, 2000). Despite the introduction of many novel drugs throughout the last decades, the prevalence of intractable epilepsy has not decreased. One possible explanation for this observation is that the existing antiepileptic drugs target only a few specific mechanisms of epileptogenesis, whereas other etymologies, yet unidentified, may require different treatment.

As most patients with epilepsy remain seizure-free most of the time, it can be time consuming to collect enough pathologic data for analysis. This is partially due to the limitations in spatial and temporal resolution of recording equipment. For instance, scalp EEG mainly displays collective phenomena of cortical dynamics with a very limited sensitivity for subcortical circuits that are presumably relevant in certain types of epilepsies (e.g., absence epilepsy).

Modeling may improve our understanding of epileptogenesis and provide clues for novel treatments. Such models exist at many levels of abstraction, ranging from describing the brain as a black box with a certain input/output relation to a detailed description of the individual neurons in the brain. To reveal new mechanisms behind seizures, any useful model should have a succinct connection with physiology to relate observed (neurologic) behavior to the pathologic condition of the patient.

A straightforward approach to model neuronal activity in the brain is to model individual neurons in the brain and their mutual interactions. We refer to models of this type as detailed models. As individual cells and connections can be modeled with various levels of complexity, different types of detailed models exist. Several detailed models have been proposed of the complete brain (Izhikevich and Edelman, 2008; Markram, 2006), but these do not focus on pathologic behavior. Detailed models of the brain primarily intended to study epileptiform activity have been developed as well, but these consider only a limited number of neurons (Lytton, 2008; Traub et al., 2005; van Drongelen et al., 2004, 2005, 2006). This limitation, however, does not preclude the possibility of formulating important, testable hypotheses. For instance, predictions regarding epileptiform activity have been made with a detailed model that were subsequently confirmed *in vitro* (van Drongelen et al., 2005).

Because these detailed models are substantial in both size and complexity, analyzing their behavior is a hazardous task. For that reason, we are interested in studying a more abstract class of models that gives a more concise description of neuronal activity than detailed models, so-called population models. Rather than describing properties of individual neurons, these models describe the dynamics of population-averaged quantities, such as the mean membrane potential of all neurons in the populations, the mean firing rate, or the fraction of active neurons within the population.

Most population models are based on the original work done by Wilson and Cowan (1972) who derived a model for two generic interconnected populations; one population containing only excitatory and the other only inhibitory neurons. Potential mechanisms for transitions between normal and epileptic activity have been studied with population models in absence epilepsy (Breakspear et al., 2006; Lopes da Silva et al., 2003; Rodrigues et al., 2009) and mesial temporal lobe epilepsy (Wendling et al., 2002).

A fundamental problem of population models, however, is that they are based on averaging procedures that cannot be justified rigorously. For that reason, it is difficult to relate parameters of population models to physiological properties of the neurons within the populations. Therefore, one should be cautious during analysis of the model and continuously investigate the physiological relevance of the parameters considered.

We do not favor one modeling approach over the other, because we believe that both types of models should be analyzed simultaneously

From the *Department of Applied Mathematics and †MIRA-Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands; ‡Department of Pediatrics, The University of Chicago, Chicago, Illinois, U.S.A.; and §Department of Clinical Neurophysiology, Medical Spectrum Twente, Enschede, The Netherlands.

Supported by The Netherlands Organization of Scientific Research (NWO) grant 635.100.019: "From Spiking Neurons to Brain Waves" and Dr. Ralph and Marian Falk Medical Research Trust.

Presented at Tools for Epilepsy Research: Tutorials and Updates, Chicago, IL, August 6–8, 2009.

Address correspondence and reprint requests to Sid Visser, EWI-AAMP, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands; e-mail: s.visser-1@math.utwente.nl.

ISSN: 0736-0258/10/2706-0471

to study new mechanisms for seizure onsets. In our opinion, hypotheses should be formulated through bifurcation analysis of simpler population models and then subsequently tested in a detailed model. This step, which to our knowledge is rarely performed, is crucial because it gives the lumped parameters of the population model a relevance and clinical significance by mapping them onto a set of physiological parameters in a detailed model. Similarity between both models should ideally be determined by quantitative measures.

We present two models of the neocortex, one detailed model and the other based on the population approach. We consider changes of parameters and show that both models have similar sensitivity to these parameters.

METHODS

Areas of the neocortex make numerous connections with each other and with deeper subcortical brain regions such as the thalamus. These regions of neocortex are organized into a collection of macrocolumns that each perform an elementary task (Churchland and Sejnowski, 1999). These macrocolumns can then be split into mesocolumns that are in turn split into microcolumns within which the activity of neurons is strongly correlated. Such a microcolumn contains roughly 1,000 neurons and covers an area of approximately 100×100 μm of neocortex. The local structure of a microcolumn consists of several layers that are tightly connected with each other. In this article, we focus on modeling a small area of neocortex without long-range interactions to either thalamus or other neocortical columns.

Two modeling approaches are used: the first being a detailed neuron model analyzed at a mesoscale of 656 neurons and the other a simpler two-population model.

Detailed Model

Description

A small patch of the neocortex is modeled by connecting detailed models of individual neurons with artificial synapses, similar to that in the study by van Drongelen et al. (2004, 2005, 2006).

Briefly, the model describes the activity of pyramidal neurons in layers 2/3 and 5/6 of the neocortex, referred to as superficial cells and deep cells, respectively, and four types of inhibitory interneurons: three types of basket cells (each of a different size) and chandelier cells. All neurons are discretized into several compartments that describe the physiological structure of a cell with a soma and a dendritic tree. The interneurons consist, due to their limited size, of two compartments, whereas the superficial and deep pyramidal cells are described by five and seven compartments, respectively. Cells are placed randomly in a three-dimensional space, complying with the following depth ranges for each cell type. The depth of the superficial pyramidal cells varies between 250 and 750 μm, whereas the depth of the deep pyramidal cells varies between 1000 and 1500 μm and the interneurons between 250 and 1500 μm. The minimal separation between two cells is 2 μm.

Voltage-gated sodium and potassium channels and maximal conductances for ion channels are the same as that used in the study by van Drongelen et al. (2006). Superficial pyramidal cells contain persistent sodium channels that cause the cells to burst intrinsically.

Action potentials are assumed to have a constant conduction velocity of 0.08 m/s through axons, inducing a time lag for synaptic transmission proportional to the distance between cells. After arrival of an action potential, an exponentially decaying postsynaptic current is generated, which has two time constants (Bower and Beeman, 1998).

Connections of neurons are randomly determined in a way such that the connection probability depends on the cell types (both sending and receiving neurons) as well as the distance between the cells. Both types of pyramidal neurons can connect to all neurons within a certain range. Basket cells will only inhibit pyramidal cells and other basket cells. Chandelier cells make inhibitory connections to initial segments of pyramidal cells exclusively. The model contains neither gap junctions nor long-range connections to other columns.

Mesoscale Implementation

A realization of this model with 656 neurons (2×256 pyramidal cells and 4×36 interneurons) is implemented in C++, making it a mesoscale simulation. We randomly generate one network, consisting of 43,124 connections, and we only consider simulations with this specific network topology.

Next, an interface is developed that converts the neuronal activity of the network to a local field potential, representing a small electrode placed on or nearby the network, e.g., an EEG or an electrocorticogram electrode. The algorithm is based on the method of "sinks and sources" as described in the study by Nunez and Srinivasan (2005), except that only the superficial pyramidal neurons are considered rather than all neurons, because these large cells are closest to the electrode. Therefore, they will have the largest contribution to the EEG compared with the smaller interneurons and the deep cells that lie farther away. The obtained signal is unfiltered and should be interpreted as a DC recording.

Population Model

Description

The activity of a neuron in a microcolumn is strongly correlated with the activity of nearby neurons because of tight connectivity and synchronization. It is therefore a natural step to consider the average activity of a large group of neurons rather than the behavior of individual neurons.

Here, a microcolumn of the neocortex is modeled using two populations, representing the average activity of the superficial and the deep pyramidal cells, respectively. First, it is assumed that neither of the populations can exhibit self-sustained activity in the absence of activity of the other population; hence, the activity of the populations is modeled to decay exponentially over time. Next, when the activity of a layer increases, more action potentials are sent to neurons in the other layer where excitatory synapses are activated after some time lag. This increases the activity in that layer. Rather than modeling a population of inhibitory interneurons, we model the inhibition caused by pyramidal cells that excite interneurons that in turn inhibit the pyramidal cells (see also Fig. 1).

The above-described model leads to the following set of delayed differential equations:

$$\begin{aligned} \frac{dx_1}{dt} &= -\mu_1 x_1(t) - F_1(x_1(t-\tau_i)) + G_1(x_2(t-\tau_e)), \\ \frac{dx_2}{dt} &= -\mu_2 x_2(t) - F_2(x_2(t-\tau_i)) + G_2(x_1(t-\tau_e)), \end{aligned} \tag{1}$$

with x_1 and x_2 the activity of the neuronal populations of superficial and deep pyramidal cells, respectively. The constants μ_1 and μ_2 represent the intrinsic rate of exponential decay of neuronal activity within a population. The functions $F_i(x)$ and $G_i(x)$ are both sigmoidal functions that determine the activation of the inhibitory and excitatory synapses, respectively. The delay τ_e is the time needed for action potentials to travel from one layer to another, whereas τ_i is the time lag for the inhibitory feedback loop. Both delays include the extra time lag caused by activation of the synapses.

The two-population network given in Eq. 1 is an example of a graded Hopfield network with delays. Several of these networks have been analyzed in the study by Belair and Campbell (1994) and

Shayer and Campbell (2000), but their analysis focused mainly on studying steady states rather than (periodic) oscillations.

To simplify the model and decrease the number of parameters, we analyze the symmetric system:

$$\begin{aligned} \mu_1 &= \mu_2 := \mu, \\ F_1(x) &= F_2(x) := F(x), \\ G_1(x) &= G_2(x) := G(x). \end{aligned} \tag{2}$$

The following expressions are chosen for the synaptic activation functions:

$$\begin{aligned} F(x) &= \alpha_i(\tanh(\sigma_i x - 1) + \tanh(1))\cosh^2(1), \\ G(x) &= \alpha_e(\tanh(\sigma_e x - 1) + \tanh(1))\cosh^2(1), \end{aligned} \tag{3}$$

with α_i and α_e the strengths of the inhibitory and excitatory connections and σ_i and σ_e the rates at which their synapses saturate. For negative values of x, both $F(x)$ and $G(x)$ are negative, representing a suppression of the synaptic background activity.

We choose the following values for the parameters: $\mu = 3$, $\tau_i = 4$, $\tau_e = 7$, $\alpha_i = 0.2$, $\alpha_e = 1.5$, $\sigma_i = 2$, and $\sigma_e = 1.2$. The delays are chosen similar to the delays in the detailed model. Because the number of excitatory synapses in the detailed model outnumbers the inhibitory, α_e is chosen larger than α_i. For the same reason, we choose $\sigma_i > \sigma_e$ because the inhibitory synapses will saturate faster because of their low number.

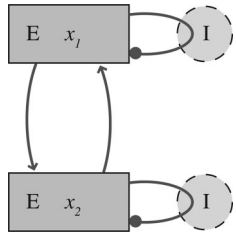

FIGURE 1. Schematic overview of the population model: two connected excitatory (E) populations are considered as well as the feedback of the inhibitory (I) populations that is modeled as an intrinsic property.

Simulating Epilepsy

Decreased Excitation

As shown in the study by van Drongelen et al. (2005), the neocortex can exhibit epileptiform activity when excitatory synapses in the network are weakened. Although verified experimentally, this opposes most expectations, and therefore we try to reproduce the results of this experiment with both models. In the detailed mesoscale model, the global levels of excitation can be modified by adding or removing excitatory synapses.

Modifying the levels of excitation in the population model can be achieved in several ways. The parameter α_e represents the excitation between layers and is therefore a proper candidate parameter. Nevertheless, the parameter μ determines the rate at which the activity within a layer decreases. If the network contains more excitatory synapses, more connections are made within the population, and the activity will therefore decrease at a lower rate. We have chosen to vary the parameter μ to modify the levels of excitation because we assume that more intralayer connections exist than interlayer connections. Using numerical continuation packages DDE-BIFTOOL and PDDE-CONT, we study all possible solutions of the population model.

RESULTS

Mesoscale Detailed Model

Validation

The mesoscale detailed model is evaluated for different levels of excitation, beginning at a high value of excitation and then decreasing excitation below the normal level.

For high levels of excitation, the network exhibits saturated, desynchronized activity in which all neurons fire action potentials at a high frequency with a very low correlation (Fig. 2). When the network excitation is set to normal physiological values, the microcolumn's behavior shows irregular bursts (Fig. 3). For low values of excitation, we observe fast oscillations in the EEG of 50 Hz (Fig. 4). A closer analysis of these oscillations reveals that the populations of superficial and deep pyramidal cells are alternately active, similar to that in the study by van Drongelen et al. (2007). After reducing the excitation to exceptionally low levels, one fifth of the normal level, the oscillations cease and the network reaches a state of burst suppression-like

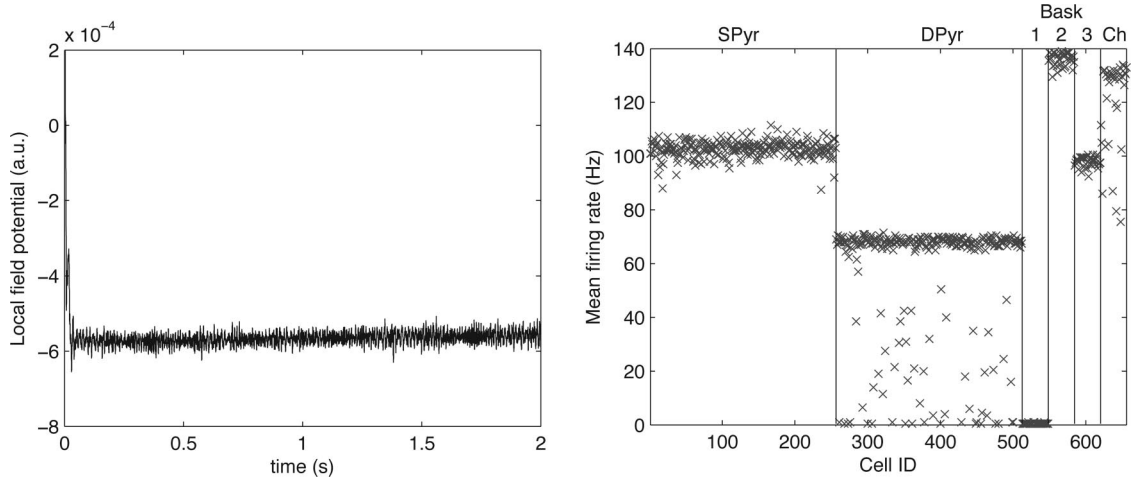

FIGURE 2. Simulation of mesoscale detailed model for high excitation. The local field potential in the left panel shows desynchronized activity. The right panel depicts mean firing rate of individual neurons (see text).

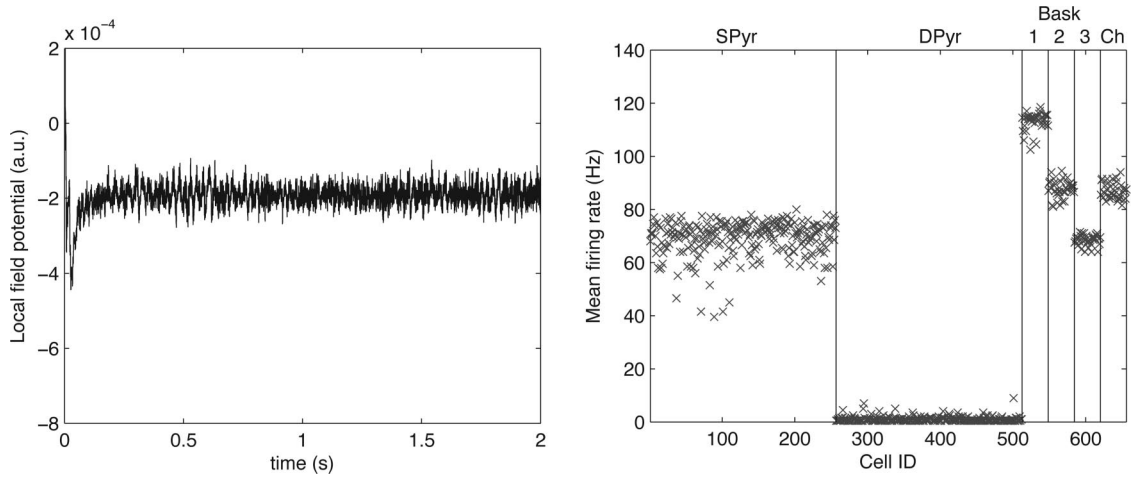

FIGURE 3. Simulation of mesoscale detailed model for moderate excitation. The local field potential shows irregular bursting, especially at 0.5 seconds.

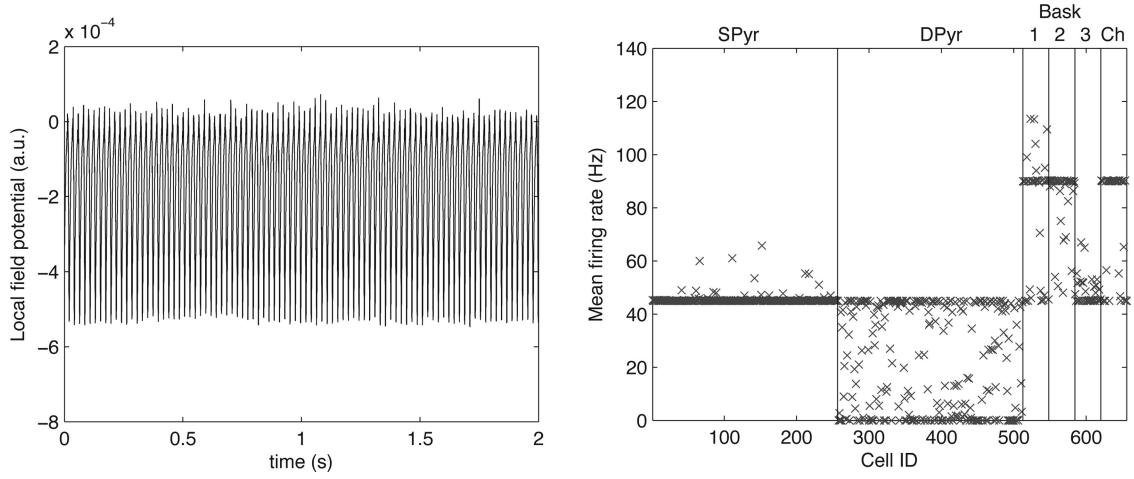

FIGURE 4. Simulation of mesoscale detailed model for low excitation. The local field potential shows oscillatory activity.

behavior (Fig. 5). These network bursts are initiated by the intrinsically bursting superficial pyramidal neurons that synchronize easily but fail to initiate activity in other layers because of the low level of excitation. Hence, the network remains silent apart from these short bursts of activity.

Oscillating and regular bursting behavior, typical epileptiform activity, are only observed in networks with weak excitatory synapses. Contrarily, desynchronized activity and irregular bursting are exclusively seen in simulations with high levels of excitation. These results are in correspondence with the findings of van Drongelen et al. (2005).

Activity of Populations

Next, we study the activity of individual neurons during simulations of the different types of network behavior. For each neuron in the network, the mean firing rate of action potentials is determined by dividing of the total number of action potentials of a neuron by the total simulation time. The results are shown in the right panels of Figs. 2 to 5, in which the mean firing rate is depicted for all neurons. The first group of 256 neurons represents the activity of the superficial pyramidal neurons (SPyr), whereas the second group depicts the activity of the deep cells (DPyr). The four other groups each contain 36 interneurons of different types: the first three columns contain basket cells of increasing size (Bask 1–3) and the latter column holds the chandelier cells (Ch).

As a first observation, we note that the variation of the mean firing rate of individual neurons is small for neurons within a population. For example, note the result for low excitation (Fig. 4) in which the firing rate of many neurons is identical to that of others. Furthermore, both the type 2 basket cells and the chandelier cells have similar firing rates as well as the superficial pyramidal cells and type 3 basket cells.

Generally, we observe that the activity of most neurons decreases gradually as the levels of excitation are reduced, except for the deep pyramidal cells whose activity drops suddenly for normal levels of excitation and recovers again for lower levels. As the levels of excitation are high, the small basket cells (type 1) experience an excitation block, indicating that the excitatory synapses remain continuously activated due to the absence of a rhythm. Hence, the neuronal activity is desynchronized.

By counting the number of action potentials $n_{\mathrm{AP},i,j}$ of population i in time bin j, we define the instantaneous firing rate $f_{i,j}$ of neurons within population i as follows:

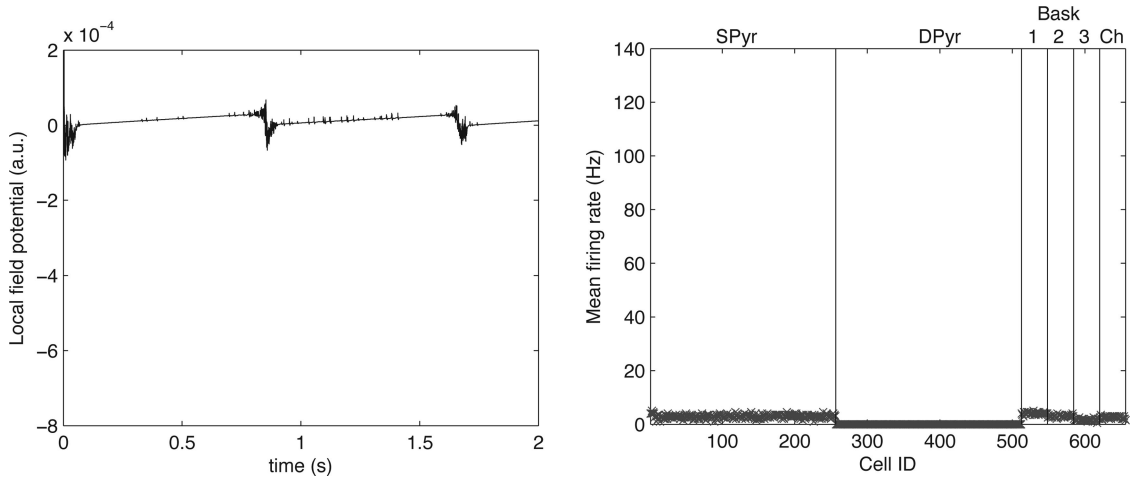

FIGURE 5. Simulation of mesoscale detailed model for very low excitation. The local field potential shows regular bursting.

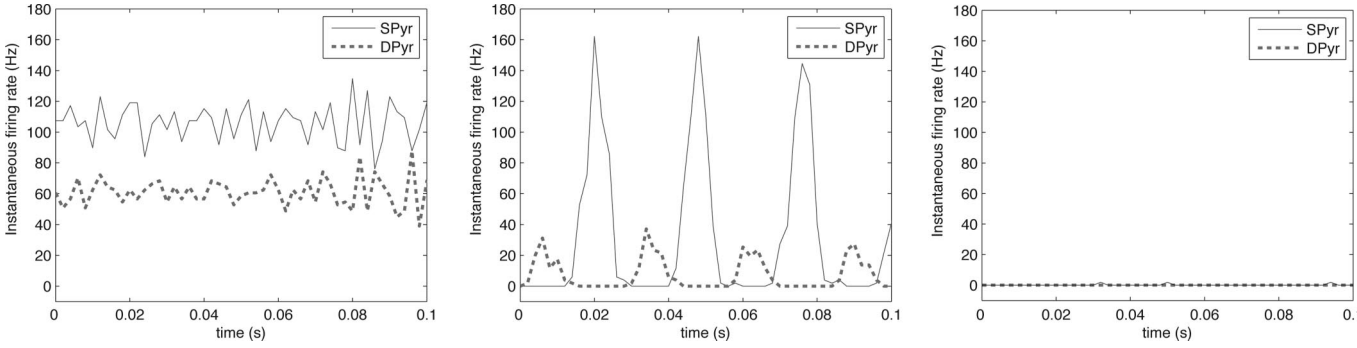

FIGURE 6. Instantaneous firing rate of both excitatory populations is plotted during simulations with high (left), low (center), and very low (right) excitation. Note the desynchronized activity in the left and the alternating activity in the center panel.

$$f_{i,j} = \frac{n_{\mathrm{AP},i,j}}{N_i T_j}, \tag{4}$$

with N_i the number of neurons in population i and T_j the size of time bin j. The size of the time bins is chosen to be 2 milliseconds. Figure 6 shows the instantaneous firing rate of the pyramidal neurons for several levels of excitation in the network. The desynchronized activity is now clearly visible as is the alternating activity during the oscillations.

Population Model

The above results, indicating that neurons of a given type in the detailed model have very similar behavior in the detailed model, encourage us to study a population model that describes the activity of these clusters rather than the individual neurons.

Analysis of Bifurcations

To understand the dynamics available to the population model, we performed the bifurcation analysis for the excitation parameter μ (cf. Appendix), which shows that the population model can display several different behavioral states. The model has equilibrium states corresponding to no activity and to high levels of activity in which both populations participate. More interestingly, the model displays three types of oscillatory behavior in which activity between populations is either in phase or in antiphase. Furthermore, substantial changes in frequencies can occur, which are caused by period-doubling bifurcations. Finally, for a range of decay parameter μ, the model may exhibit either periodic or equilibrium behavior depending on the initial conditions chosen for the system. In summary, the population model can, in principle, display all the basic types of behavior previously seen from the detailed model (cf. Validation section).

Behavior

Simulations are performed for the population model given in Eq. 1 for different values of μ to study the effects of altering excitation. For high levels of excitation ($\mu = 2$), the simplified model reaches a steady state with high-level constant activity (left panel of Fig. 7). At moderate levels of excitation ($\mu = 3$), the model manifests oscillations in which both populations are antiphasically active (middle panel of Fig. 7). For very low levels of excitation ($\mu = 4$), all activity dies out and both populations become quiescent (right panel of Fig. 7).

Comparison

Behavior

After analyzing both the detailed model and the population model individually, we compare their results in this section.

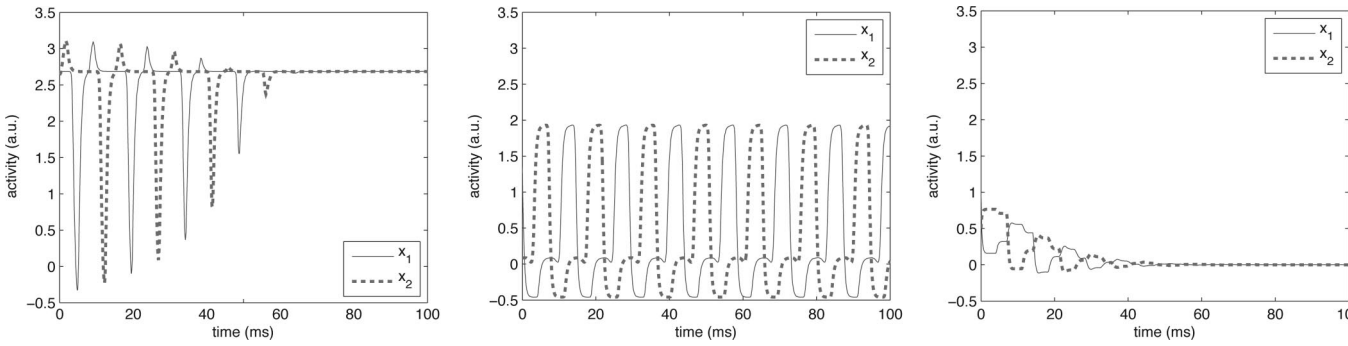

FIGURE 7. Simulation results for the population model for different levels of excitation. The excitation is changed in each of the panels $\mu = 2$ (left), $\mu = 3$ (center), and $\mu = 4$ (right).

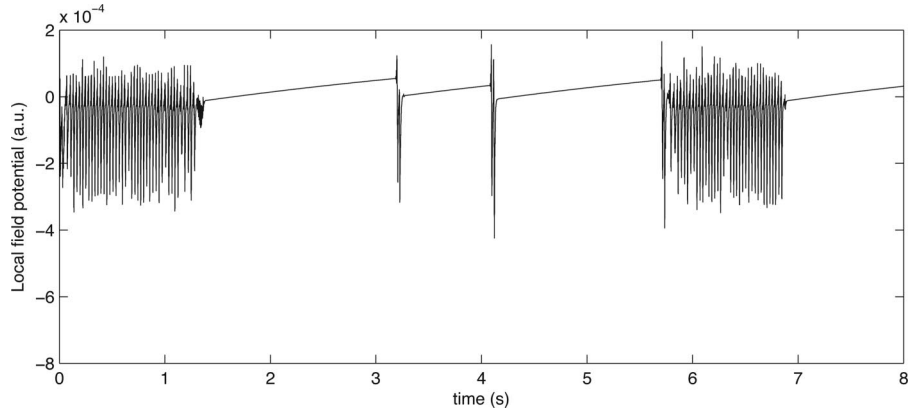

FIGURE 8. Simulation of the detailed model for values of excitation between low and very low, the model's behavior switches between oscillations and regular bursts. Compare with Figs. 4 and 5.

We note that the desynchronized behavior observed in the detailed model is similar to the high steady state in the population model, because the detailed model reveals that individual neurons in the excitatory populations are continuously active without a distinct rhythm. Both models exhibit this type of behavior for high levels of excitation.

For normal levels of excitation, the detailed model displays irregular bursts of activity, in which the superficial pyramidal cells are clearly more active than the deep cells (Fig. 3). This type of behavior, in which one population clearly dominates the other, can never be observed in the population model as no asymmetric steady states are found in the bifurcation analysis. In future work, we will break the symmetry of the population model and include specific properties of the excitatory neurons, such that asymmetric steady states, corresponding with the observed behavior, are likely to exist. Even though the population model is unable to exhibit this type of behavior, we may question the relevance of this result of the detailed model because of the, perhaps unnatural, dominance of the superficial population.

When the excitation in the network is low, the network shows oscillatory behavior in which neurons in the pyramidal populations are alternately active (Fig. 6, center). This corresponds extremely well with the family of asymmetric limit cycles observed in the population model (Fig. 7, center).

For very low values of excitation in the population model, we find that activity of both populations dies out eventually (Fig. 7, right). This behavior matches closely with the burst suppression of the detailed model, which is observed at very low levels of excitation, because it is quiescent for most of the time. We recall that the regular bursts occur on a long time scale (close to 1 second) and that the population does not contain such long time scales. Furthermore, the bursts of activity in the detailed model are initiated by the superficial pyramidal cells that burst intrinsically (van Drongelen et al., 2005). Because spontaneous activity is not included in the population model, we do consider these behaviors similar.

Multistability and Bifurcations

Bifurcation analysis of the population model reveals the presence of multistability of at most four attractors. These attractors and their stability are well defined in the population model but undetermined in the detailed model. For instance, if the detailed model is close to a bifurcation point, it can repeatedly switch from one type of behavior to another (see Fig. 8). This type of behavior, in which both states appear intermittently, is caused by the chaotic nature of the detailed model. The population model does not capture this intermittent behavior, but it describes the attractors to which switches can be made.

Moreover in the detailed model, we have found evidence for the occurrence of period-doubling bifurcations and the existence of multistability for synchronous and asynchronous neuronal activity.

Finally, two simulations were also performed in which the conduction velocity of action potentials through axons varied slowly over time (Fig. 9). As the conduction velocity slowly increases (Fig. 9, left) the frequency of the oscillations seems to double at $t \sim 0.6$ seconds. If the conduction velocity is slowly returned to its original

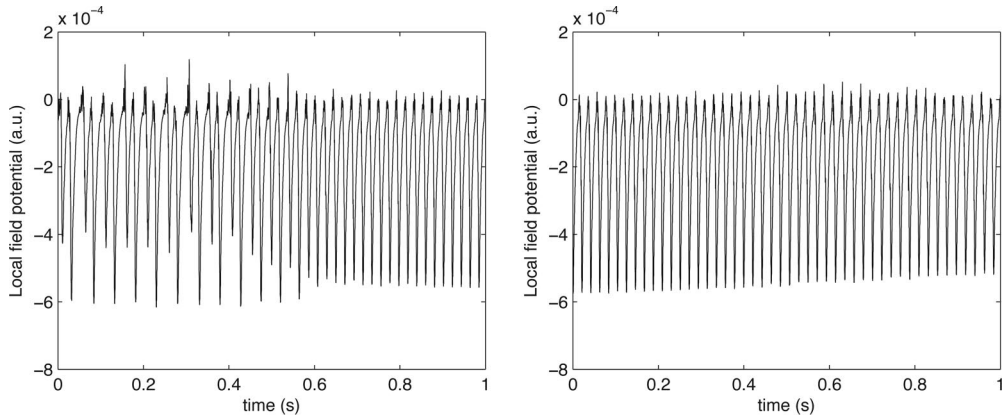

FIGURE 9. Simulation of the detailed model reveal a period doubling bifurcation with hysteresis. Left, The conduction velocity of action potentials increases slowly from 0.08 to 0.088 m/second due to which the system undergoes a period-doubling bifurcation. Right, The conduction velocity in decreased continuously from 0.088 to 0.08 m/second and the fast oscillations persist.

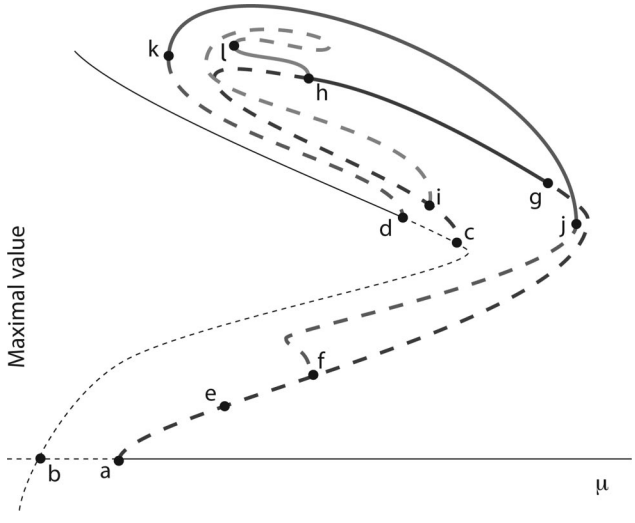

FIGURE 10. Bifurcation diagram of the population model, representing possible solutions of the system. Curves represent steady states (thin lines) and periodic orbits (thick lines). Solid lines indicate stable solutions and dashed lines correspond to unstable solutions. See text for a description of the curves and bifurcation points a to l.

value (Fig. 9, right) then these fast oscillations persist. This hysteresis confirms the multistability predicted by the bifurcation analysis of the population model, in which we found both symmetric and asymmetric stable limit cycles for a wide range of values for μ.

DISCUSSION

In this work, we studied two models of neocortex to examine neuronal activity during epileptiform network behavior. The first model is based on a detailed description of 656 neurons, consisting two types of pyramidal cells and four types of interneurons. For validation, we compared this model with the model by van Drongelen et al. (2005), because the network shows similar types of behavior (i.e., desynchronized, irregular bursting, oscillatory, and regular bursting) when the network excitation is changed. The second model is a population model, consisting two delay differential equations, that represents the activity of pyramidal neurons in both superficial and deep layers of the neocortex. Analysis of this model reveals comparable behavior with the detailed model for corresponding changes of excitation levels in the network. Determination of the bifurcation diagram of the population model yields an understanding of the more exotic types of behavior observed in the detailed model, such as multistability, intermittency, and period doublings (Figs. 8 and 9).

Although several hypotheses have been formed using population models (Lopes da Silva et al., 2003; Rodrigues et al., 2009), none of these have been further confirmed in a detailed model. This impedes any attempt to put these results into a physiological and clinical relevant perspective.

However, the fact that both the studied models exhibit similar behavior reveals, in our opinion, an efficient way to analyze transitions of network activity in the brain dependent on properties of individual neurons. First, bifurcations of an associated population model with lumped parameters can be studied, from which new hypotheses can be formulated regarding emergent epileptiform network behavior. Next, values of the lumped parameters of the population model should be translated into physiological parameters in the detailed model to gain physiological insight into the role these parameters play in inducing epileptiform behavior in the detailed model. This would allow for hypotheses generated from the population model to be verified in a more realistic model, which incorporates details of single neurons, and eventually validated in in vivo/in vitro model of epilepsy. This step is important because drug therapies are developed for targets at subcellular level.

We are aware of the limitations of both of our models (for instance omitting the thalamocortical feedback loop by only considering neocortical structures), and we present this work merely as a starting point for future work. Both models can be expanded by including thalamocortical connections, enabling us to study other types of epilepsy as well. The proposed population model is not fully examined for the presence of bifurcations with respect to parameters other than the level of excitation μ, and we expect further study to reveal new predictions for mechanisms behind the generation of epileptiform activity.

APPENDIX

Figure 10 shows a caricature of the bifurcation diagram of the population model for varying decay rate μ of the population's

activity. Every curve in the diagram represents a specific type of limiting behavior of the model: either a fixed point or a limit cycle. Fixed points are depicted with a thin line of which the vertical component is the population's activity at that fixed point. Limit cycles are indicated with a thick line that corresponds with the maximal activity reached by a population during a period. Solid lines are used to mark stable limiting behavior, meaning that it will force nearby orbits to exhibit similar behavior as the limiting behavior itself, whereas dashed lines designate unstable types of behavior that will repel nearby orbits.

Because the origin is always a fixed point of the system in Eq. 1, we choose this point as initial point for our analysis. For high values of μ, the origin is a stable fixed point of the system. When decreasing the parameter μ, the origin retains its stability until the critical point (a) is crossed at which it undergoes a subcritical Hopf bifurcation and a family of (unstable) limit cycles arises. Continuation of the unstable equilibrium yields a branch point at (b) where it coincides with another unstable equilibrium. Analyzing the evolution of this new equilibrium reveals a fold bifurcation and two successive subcritical Hopf bifurcations at (c) and (d) after which it becomes stable.

Closer inspection of the limit cycles that appeared at (a) yields a family of symmetric oscillations representing synchronous neuronal activity. This branch passes a Neimark-Sacker bifurcation at (e) and a supercritical period-doubling bifurcation at (f) where it spawns a branch of asymmetric periodic solutions with its period initially doubled. The symmetric branch folds over and undergoes another period-doubling bifurcation at (g) where it becomes stable until it undergoes another period doubling at (h). Beyond (h), the branch folds over and experiences another period-doubling bifurcation at (i) until it terminates in the Hopf bifurcation (c).

Following the branch of asymmetric solutions that emerges at (f), we find that it folds twice to gain stability at (j). At the left end of the diagram, stability is lost in another fold bifurcation (k), and the branch eventually terminates at the Hopf bifurcation (d).

Next, we continue the branch of limit cycles spawned at the period-doubling bifurcation (h), at which the populations exhibit synchronous activity at half the original frequency. The branch is stable at first but loses stability in (l) because of three successive fold bifurcations after which it ends in the period doubling at (i).

We summarize the results of this bifurcation analysis. For large values of μ larger than (j), the origin is the only stable solution of the system, indicating that all activity eventually dies out. If μ is smaller than (a), only one stable equilibrium is present at a high level of activity at which both populations remain continuously activate. Either of these steady states is symmetric in the sense that both populations exhibit identical behavior. Asymmetric steady states, in which one population is continuously active and the other quiescent, are not present with the current choice of parameters.

If the value of μ lies between (j) and (k), the network can generate periodic behavior where both neuronal populations are alternately activated. Whenever μ takes values between (l) and (d), the system has four stable solutions: two equilibria and two types of oscillations. The network can exhibit fast oscillations for μ in the range of (h) and (g) because of a period-doubling bifurcation.

ACKNOWLEDGMENT

The authors thank Ingo Bojak, Jack Cowan, and Stan Gielen for giving useful directions. Discussions with Marc Benayoun, Mark Hereld, Marcel Lourens, and Edward Wallace provided helpful insights for this work.

REFERENCES

Belair J, Campbell SA. Stability and bifurcations of equilibria in a multiple-delayed differential equation. *SIAM J Appl Math.* 1994;54:1402–1424.

Bower JM, Beeman D. The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System. 2nd ed. New York, NY: Springer-Verlag; 1998.

Breakspear M, Roberts JA, Terry JR, et al. A unifying explanation of primary generalized seizures through nonlinear brain modeling and bifurcation analysis. *Cereb Cortex.* 2006;16:1296–1313.

Churchland PS, Sejnowski TJ. *The Computational Brain*. Cambridge, MA: MIT Press; 1999. ISBN 0-262-03188-4.

Izhikevich EM, Edelman GM. Large-scale model of mammalian thalamocortical systems. *Proc Natl Acad Sci USA.* 2008;105:3593–3598.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med.* 2000;342:314–319.

Lopes da Silva FH, Blanes W, Kalitzin SN, et al. Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. *Epilepsia.* 2003;44(suppl 12):72–83.

Lytton WW. Computer modelling of epilepsy. *Nat Rev Neurosci.* 2008;9:626–637.

Markram H. The blue brain project. *Nat Rev Neurosci.* 2006;7:153–160.

Nunez PL, Srinivasan R. *Electric Fields of the Brain: The Neurophysics of EEG*. 2nd ed. New York, NY: Oxford University Press; 2005.

Rodrigues S, Barton D, Szalai R, et al. Transitions to spike-wave oscillations and epileptic dynamics in a human cortico-thalamic mean-field model. *J Comput Neurosci.* 2009;27:507–526.

Shayer LP, Campbell SA. Stability, bifurcation, and multistability in a system of two coupled neurons with multiple time delays. *SIAM J Appl Math.* 2000; 61:673–700.

Traub RD, Contreras D, Cunningham MO, et al. Single-column thalamocortical network model exhibiting gamma oscillations, sleep spindles, and epileptogenic bursts. *J Neurophysiol.* 2005;93:2194–2232.

van Drongelen W, Lee HC, Hereld M, et al. Simulation of neocortical epileptiform activity using parallel computing. *Neurocomputing.* 2004;58–60: 1203–1209.

van Drongelen W, Lee HC, Hereld M, et al. Emergent epileptiform activity in neural networks with weak excitatory synapses. *IEEE Trans Neural Syst Rehabil Eng.* 2005;13:236–241.

van Drongelen W, Koch H, Elsen FP, et al. Role of persistent sodium current in bursting activity of mouse neocortical networks in vitro. *J Neurophysiol.* 2006;96:2564–2577.

van Drongelen W, Lee HC, Stevens RL, Hereld M. Propagation of seizure-like activity in a model of neocortex. *J Clin Neurophysiol.* 2007;24:182–188.

Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Epileptic fast activity can be explained by a model of impaired gabaergic dendritic inhibition. *Eur J Neurosci.* 2002;15:1499–1508.

Wilson HR, Cowan JD. Excitatory and inhibitory interactions in localized populations of model neurons. *Biophys J.* 1972;12:1–24.