



Epileptic seizures from abnormal networks: Why some seizures defy predictability

William S. Anderson^{a,*}, Feraz Azhar^{b,1}, Pawel Kudela^{c,2},
Gregory K. Bergey^{c,3}, Piotr J. Franaszczuk^{d,e,4}

^a The Johns Hopkins University School of Medicine, Department of Neurosurgery, Meyer 5-109E, 600 North Wolfe Street, Baltimore, MD 21287, USA

^b The Johns Hopkins University School of Medicine, Department of Neurosurgery, Meyer 5-157, 600 North Wolfe Street, Baltimore, MD 21287, USA

^c The Johns Hopkins University School of Medicine, Department of Neurology, Meyer 2-147, 600 North Wolfe Street, Baltimore, MD 21287, USA

^d The Johns Hopkins University School of Medicine, Department of Neurology, USA

^e U.S. Army Research Laboratory, Human Research and Engineering Directorate, Aberdeen Proving Ground, 2800 Powder Mill Road, Adelphi, MD 20783, USA

Received 15 June 2011; received in revised form 19 October 2011; accepted 18 November 2011

Available online 12 December 2011

KEYWORDS

Computational simulation;
Neural network model;
Seizure prediction;
Seizure generation

Summary Seizure prediction has proven to be difficult in clinically realistic environments. Is it possible that fluctuations in cortical firing could influence the onset of seizures in an ictal zone? To test this, we have now used neural network simulations in a computational model of cortex having a total of 65,536 neurons with intercellular wiring patterned after histological data. A spatially distributed Poisson driven background input representing the activity of neighboring cortex affected 1% of the neurons. Gamma distributions were fit to the interbursting phase intervals, a non-parametric test for randomness was applied, and a dynamical systems analysis was performed to search for period-1 orbits in the intervals. The non-parametric analysis suggests that intervals are being drawn at random from their underlying joint distribution and the dynamical systems analysis is consistent with a nondeterministic dynamical interpretation of the generation of bursting phases. These results imply that in a region of cortex with abnormal

* Corresponding author. Tel.: +1 443 287 4561; fax: +1 443 287 6423.

E-mail addresses: wanders5@jhmi.edu, wanderso68@gmail.com (W.S. Anderson), fazhar1@jhmi.edu (F. Azhar), pkudela@jhmi.edu (P. Kudela), gbergey@jhmi.edu (G.K. Bergey), pfranaszczuk@gmail.com (P.J. Franaszczuk).

¹ Tel.: +1 443 287 4561; fax: +1 443 287 6423.

² Tel.: +1 443 287 8295; fax: +1 410 955 0751.

³ Tel.: +1 410 955 7338; fax: +1 410 502 2507.

⁴ Tel.: +1 410 278 8003; fax: +1 410 278 8828.

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 2011		2. REPORT TYPE		3. DATES COVERED 00-00-2011 to 00-00-2011	
4. TITLE AND SUBTITLE Epileptic seizures from abnormal networks:Why some seizures defy predictability				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) U.S. Army Research Laboratory,Human Research ,and Engineering Directorate, Aberdeen Proving Ground,,2800 Powder Mill Road,,Adelphi,,MD,20783				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES See also ADA610492,Epilepsy Research, 99(3), 202-213 (2012)					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Same as Report (SAR)	18. NUMBER OF PAGES 13	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

connectivity analogous to a seizure focus, it is possible to initiate seizure activity with fluctuations of input from the surrounding cortical regions. These findings suggest one possibility for ictal generation from abnormal focal epileptic networks. This mechanism additionally could help explain the difficulty in predicting partial seizures in some patients.

© 2011 Elsevier B.V. All rights reserved.

Introduction

Epileptic seizures are brief, episodic phenomena. Partial seizures, the most common seizure type, arise from focal brain regions (e.g. temporal, parietal) (Niedermeyer, 2005).

While in some instances there may be an identifiable cause for the seizures (e.g. tumor, cavernoma, hippocampal sclerosis), in other instances no clear pathology is determined. The hallmark of an epileptic seizure is the involvement of local or regional neural networks; repetitive firing of a single neuron does not produce symptoms without this network involvement. What causes the interictal to ictal transition? A typical partial seizure lasts less than 2 min plus any postictal state (Afra et al., 2008). Therefore, even if a patient has very frequent seizures, the majority of time is spent in the interictal state. While some seizures can be provoked or are more likely to occur under certain situations (e.g. sleep deprivation, photic stimulation), the majority of seizures appear to occur spontaneously without known association with definable influences.

There has been considerable interest in seizure prediction in recent years. Obviously if seizures could be reliably predicted, then the option for targeted therapy exists (e.g. stimulation), or at least the patient could remove themselves from potentially dangerous situations. The underlying hypothesis for seizure prediction is that there are changes in cerebral dynamics that may precede the clinical seizure by minutes to hours (reviewed in Sackellares, 2008). These changes may be local (i.e. near the seizure focus) or remote. These changes are not apparent with visual analysis of the EEG, even with intracranial recording arrays. Some groups have identified high frequency activity that may signal the onset of neocortical partial seizures, but this is an example of improved seizure detection, not prediction (Worrell et al., 2004, 2008; Bragin et al., 2010). Reliable seizure prediction has been challenging and even the most enthusiastic proponents of the prediction hypothesis acknowledge the difficulties with current algorithms (Lehnertz et al., 2007; Mormann et al., 2007; Andrzejak et al., 2009).

Seizure prediction may be difficult due to rapid bistable state changes at the time of ictal onset in the neocortex (Suffczynski et al., 2006; Lopes da Silva et al., 2003).

The mechanisms underlying a bistable state change may be quite different between primary generalized (e.g. absence) and partial epileptic seizures. A bistable state change may be more applicable to these primary generalized seizures which have abrupt bilateral cerebral onset. In this paper, a different possible mechanism is presented under which seizure prediction would be difficult in some patients with focal seizure onset.

Knowing, as we do, that partial seizures are a reflection of transient abnormal regional network activity, it is reasonable to postulate that these seizures in at least some (perhaps many) patients result from abnormal neural

networks (e.g. the epileptogenic zone) (Jacobs et al., 2000). We describe here a model of the epileptogenic zone where the epileptic focus is represented by an abnormal neural network that has very slightly altered connectivity so that, while seizures only occur infrequently, they can be triggered by normal background activity originating from outside the epileptogenic zone. This background activity could be influenced by various physiologic factors (e.g. sleep), but nevertheless this background activity would not result in seizure activity in the non-epileptic brain. This does not discount the possibility that some changes in neural network synchrony may occur in the "normal" brain since the cumulative lifetime incidence of unprovoked seizures approaches 4% (Hauser et al., 1993). Often these seizures are provoked (e.g. medications and alcohol) and less than half of these patients have recurrent seizures. The lifetime cumulative risk of developing epilepsy only ranges from 1.4% to 3.3% (Krumholz et al., 2007; Berg and Shinnar, 1991). In this model, however, where normal background activity, occasionally or rarely produces a seizure in abnormal regional networks, seizure prediction would be difficult since detectable preictal changes would not be present; the first changes would in fact be seizure initiation.

Epileptic networks in neocortex or the hippocampus show anatomical changes compared to normal tissue (Jacobs et al., 2000; Sallin et al., 1995). These changes can progress with time (Sallin et al., 1995; Arellano et al., 2004). This could result in neuronal networks more amenable to seizure generation (electrical or clinical) over large regional areas. There is a complex interrelationship, much of it not well understood, between neurons which are dysfunctional and the neural networks which can promote seizures (Leussis and Heinrichs, 2007; Kumar et al., 2007; Swann et al., 2007). Even in the non-epileptic brain, excitatory connections predominate with 80–90% of synapses being excitatory (Braitenberg and Schüz, 1998).

With neuronal network simulations it is possible to control, study, and quickly change the various influences on network behavior. Recently, we presented the results of computational simulation studies examining the role of external field stimulation on ongoing bursting activity in a neural network (Anderson et al., 2007, 2009). The cortical model used in these studies consists of discrete single compartment Hodgkin–Huxley type cells which are spatially arranged in a realistic fashion having both a layered and columnar structure. Since neural network behavior reflects the aggregate output of the component neurons, single compartment neurons allow greater computational efficiency and the ability to model larger networks in studies of network behavior. Arrangements of connected simulated neurons in this manner can demonstrate spontaneous bursting phases and have spatial characteristics similar to seizures recorded from humans (Anderson et al., 2007, 2009; Kudela et al., 1997, 2003a,b, 2005; Franaszczuk et al.,

2003). We now present the results of a similar neuronal network model with random surrounding background inputs. The goal of this study was to investigate the statistical structure of the resulting bursting network activity to seek the presence or absence of predictable patterns in the behavior.

Materials and methods

Computational model format

The individual neurons in this neocortical model were represented by single compartment neurons bearing synaptic connections from the rest of the network, and embedded with a fixed set of ionic conductances. The membrane potential varies as:

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

The individual currents include the input synaptic current I_{syn} , 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 $I_{K(\text{Ca})}$, a transient potassium current I_A , and a leakage current I_L (Av-Ron, 1994). The minicolumns used in the simulation consist of 16 cells with intrinsic intracolumnar wiring, adapted from the neocortical work of Douglas and Martin (2004), as described more fully in previous studies (Anderson et al., 2007, 2009). This is both for its ease of implementation computationally and for its experimental support in somatosensory and visual cortex (Douglas and Martin, 2004). The geometry imposed on a computational model becomes relevant when studying any spatially dependent effects on the resultant spreading activity. The minicolumns in this simulation have a 25 μm center-to-center spacing in a square lattice repeating structure. The total number of cells examined was 65,536, representing a simulated cortical surface area of 1.6 mm $\times$ 1.6 mm. Fig. 1 demonstrates a schematic of the intracolumnar excitatory cell connections and the organization of the minicolumns in planar space as well as snapshots of the resultant activity in the layer II/III pyramidal cell component during model bursting activity. The model connectivity and synaptic currents are described further in the [Supplementary material](#).

The base connection pattern studied in this report is representative of one that can produce robust bursting as previously studied (Anderson et al., 2007). The numbers of extra-columnar connections formed by each cell class are presented in [Supplementary Table 1](#). There are seven cell classes modeled: four classes of excitatory cells including layer II/III pyramidal cells, layer IV stellate cells, layer V pyramidal cells, and layer VI pyramidal cells, and three classes of interneurons including basket cells, double bouquet cells, and chandelier cells. Most of the model changes described in the described studies involve alterations in connection numbers between layer II/III pyramidal cells, one of the known robust horizontal connections systems in the cortex supporting epileptic propagation (Telfeian and Connors, 1998). The base connection for this system, $N_{2/3:2/3} = 178$, is defined as the number of layer II/III pyramidal cells a given layer II/III pyramidal cell contacts in its axonal distribution.

The model in general illustrates consistent bursting behavior, with epochs of spontaneous bursting onset and cessation given a random background input of Poisson based charge injection to 1% of the cells in the model. This is an effort to treat the underlying cortical activity as input from neighboring cortex, with the model itself treated as the epileptic focus given its ability to produce network bursting epochs. The synaptic input used for the background was not periodic in nature. Average rates for these Poisson distributions are described in "Activity changes with mean background frequency" section and Fig. 2. The synaptic activations used for the

background inputs were the same used in the cell to cell connections, and followed the same rise and decay times appropriate for postsynaptic potentials.

The pseudo-random number generator used for the application of the noise pulses was a linear congruential generator implemented with the C-function *drand48*, with an intrinsic period of 281×10^{12} . For a 30s simulation and 10^{-5} s time-step, this function was called 1.966×10^9 times for 1% of the cells undergoing background input. The period length for the pseudo-random generator is 143,000 times larger than this number.

Statistics and analysis

The interbursting phase intervals in the model were fit with a gamma distribution (Suffczynski et al., 2005, 2006). The functional form of this distribution $f(\dots)$ is given by

$$f(\Delta\tau) = (\beta^\alpha \Gamma(\alpha))^{-1} \Delta\tau^{\alpha-1} \exp\left(\frac{-\Delta\tau}{\beta}\right),$$

where $\Delta\tau$ is the interbursting phase interval, α is the shape parameter, β is the scale parameter, and $\Gamma(\dots)$ represents the gamma function. Parameters were estimated using the MATLAB function *gamfit* which returns maximum likelihood estimates and 95% confidence intervals for the shape and scale parameters. A non-parametric test of randomness was used to attempt to establish whether intervals were being drawn at random from their underlying joint distribution. This was based on the circular definition of the lag-1 serial correlation coefficient (Wald and Wolfowitz, 1943). *p*-Values were computed under the assumption of asymptotic normality of the test statistic.

A method for the detection of unstable periodic orbits (of period-1) in successive interbursting phase intervals was applied (So et al., 1996, 1997). A period-1 orbit is a fixed point of the nonlinear map expressing the evolution of the state of a system, iterated a single time (Guckenheimer and Holmes, 1983). Intervals were embedded in a two dimensional state space and 10^4 sets of transformed intervals were obtained after randomization. Dimensional reduction was instituted using circles of radius 9.4ms centered along the diagonal of the state space (Le Van Quyen et al., 1997). One hundred surrogates were produced to test the significance of peaks which appeared along this diagonal. The surrogates were generated using the amplitude adjusted Fourier transform algorithm (Theiler et al., 1992). This shuffles the original sequence of interbursting phase intervals, maintaining the original amplitude distribution of the data while approximately matching its Fourier power spectrum.

Results

A total of 1600s of discontinuous 20- and 30-s data segments were obtained, holding the base connectivity of the layer II/III pyramidal cells to layer II/III pyramidal cells at $N_{2/3:2/3} = 178$. Only the random number seed supplied to the background input generator was varied for each of these runs. Additionally, five continuous segments of data were obtained with the base connectivity set at $N_{2/3:2/3} = 172$ of lengths 320s, 250s and $N_{2/3:2/3} = 178$ of lengths 195s, 140s, and 208s. These data were used for the dynamical systems analysis presented below. In addition to these data, sixteen 20-s runs were obtained with the model while varying the mean background input frequency at the base level of connectivity. Five 20-s runs were obtained at the base connectivity while varying the temporal pattern of the background input, and ten 20-s runs were obtained with a fixed

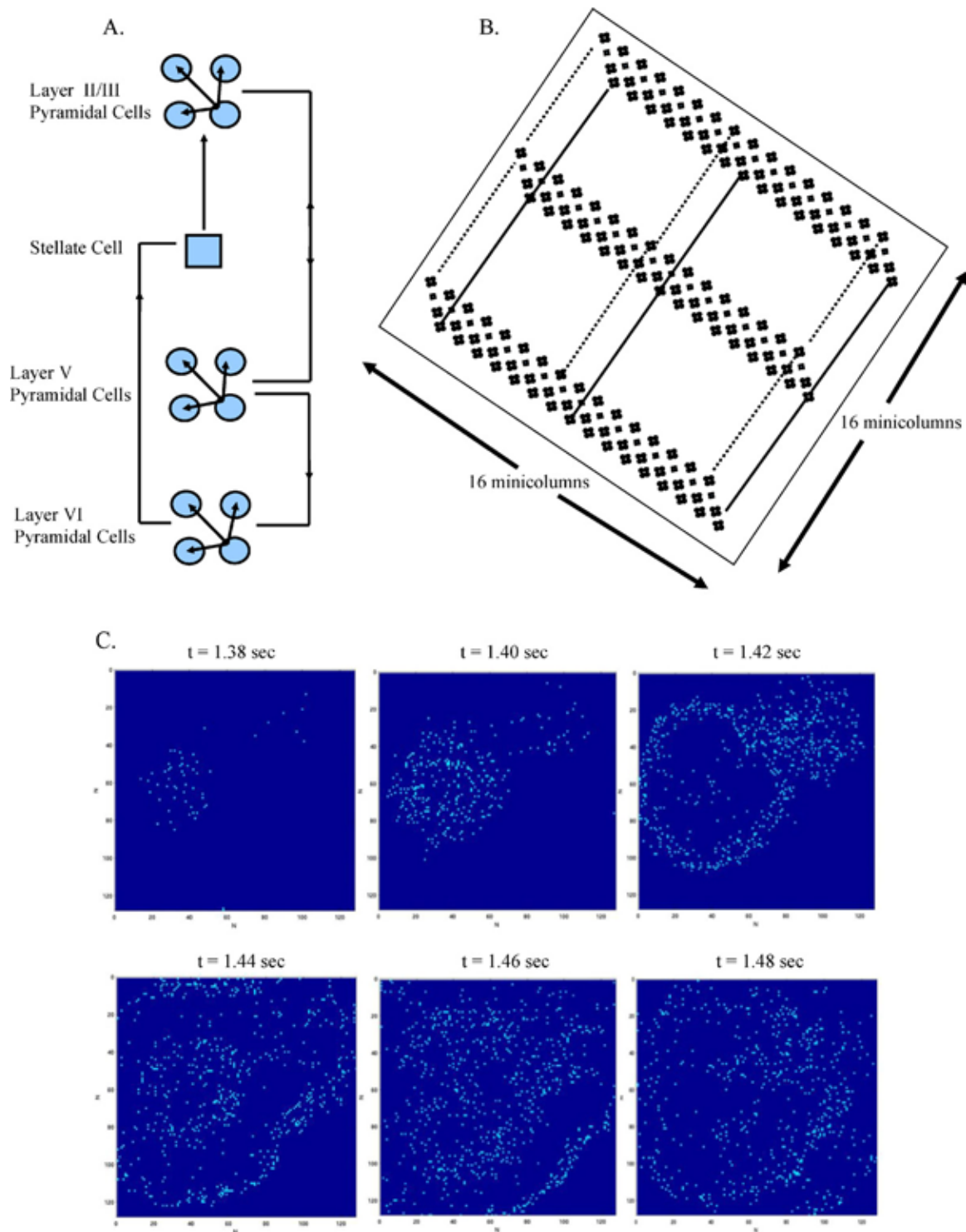


Figure 1 (A) Representative connectivity of the excitatory cellular component in a given modeled minicolumn, wiring after (Douglas and Martin, 2004). (B) Three dimensional arrangement of the 16×16 array of minicolumns in space. (C) Representative snapshots of evolving activity over 0.02s in the layer II/III pyramidal cell component. Each pixel represents one cell, color coded proportionally to the number of action potentials fired in bins of 1/100 of a second.

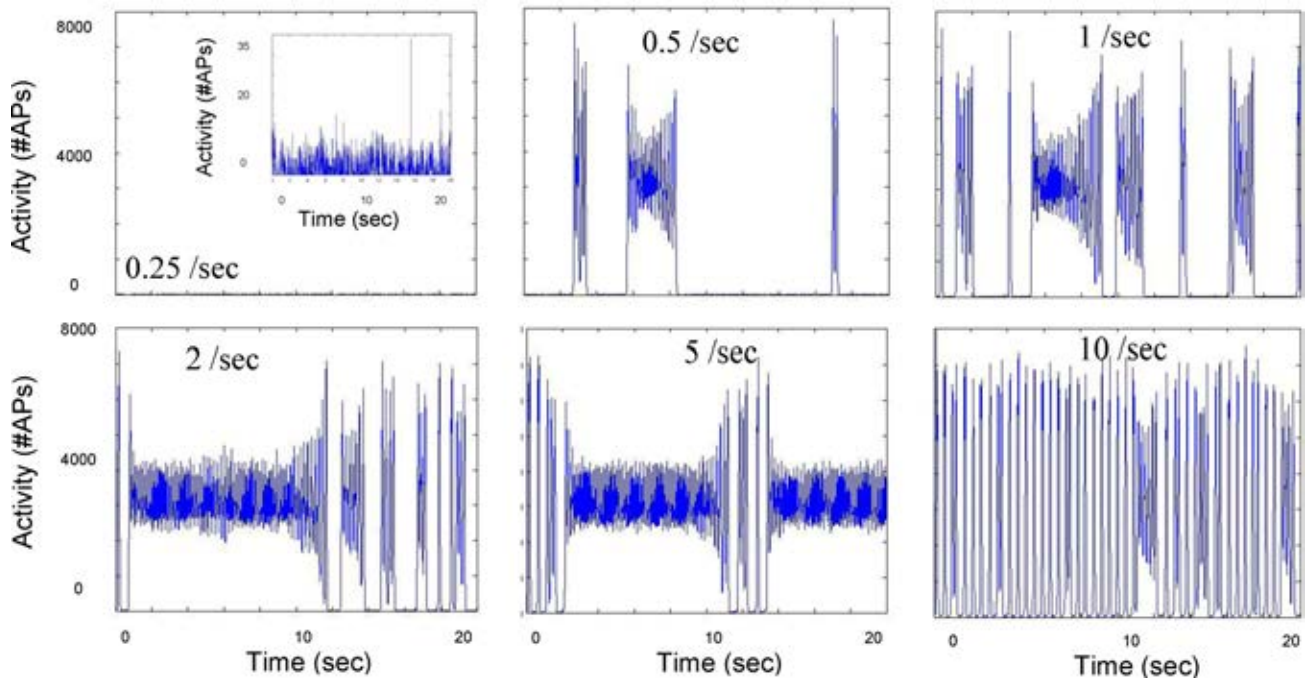


Figure 2 Network activity produced by sequential increases in the mean frequency of the applied background activity (background synaptic input provided to a fixed 1% set of the modeled cells, summed layer II/III pyramidal cell action potentials in 10 ms bins). The model exhibits a transition from episodic bursting to a very regular bursting behavior driven by the background input.

sequence of background input while varying the overall layer II/III to layer II/III connectivity ($N_{2/3:2/3}$).

Activity changes with mean background frequency

These experiments were performed with the base connectivity of the layer II/III pyramidal cell system set at the base value of $N_{2/3:2/3} = 178$. If the mean frequency of the applied background synaptic input is varied from 0.25/s up to 10/s, several patterns of activity become apparent (Fig. 2). At 0.25/s, only the low level set of activity produced with action potential production by the background input is observed, at the cells where the input takes place. This plot essentially demonstrates the Poisson-based random network activity between the bursting phases. At 0.5/s, sporadic bursting activity transmitted to the network as a whole can be observed, with long quiescent epochs. As the applied mean background frequency is further increased, longer and longer periods of constant bursting activity can be observed up to 5/s. After this, a second activity transition is observed, in which the activity changes from continuous bursting into short periods of very large amplitude bursting (in terms of numbers of active neurons) punctuated by brief periods of quiescence. At 10/s it appears to dominate the activity. This implies a saturation mechanism in this class of connected network, which comes into play after a critical percentage of cells are excited per time step. This saturation behavior is again an intrinsic property of the fixed network being probed. Additionally, these studies imply that seizure onset can be driven by neighboring cortical activity, albeit regular patterns that might not be typical of random background input activity utilized here.

Network activity altered with input pattern changes

Within the context of this model, it is possible to change the random pattern of connectivity between represented cells, and still keep the total number of connections between the various cell classes constant. By varying the random number seed supplied to the generator distributing the connections, different patterns of activity can be demonstrated, even with the same application of underlying cortical activity applied to the same cells. Examples of the changes in activity are presented in Fig. 3A. The pattern produced ranges from almost constant bursting throughout the 20s examined, to brief periods of on and off bursting. Similarly, the connectional pattern can be held constant along with the cells in which the background activity is applied, while varying the random number seed responsible for producing the order in which background pulses are injected into the cells. This produces similar alterations in network activity demonstrated in Fig. 3B, and can include several time scales of bursting epochs. These studies imply a rich dynamics of stochastic behavior in randomly connected neural networks receiving temporally uncorrelated background input, and again point toward difficulties in predicting when the bursting phases might begin.

Network activity is very sensitive to numbers of excitatory connections

Finally, changing the numbers of connections in this network model can produce substantial alterations in network behavior. Fig. 4 presents a sequence of plots of the layer

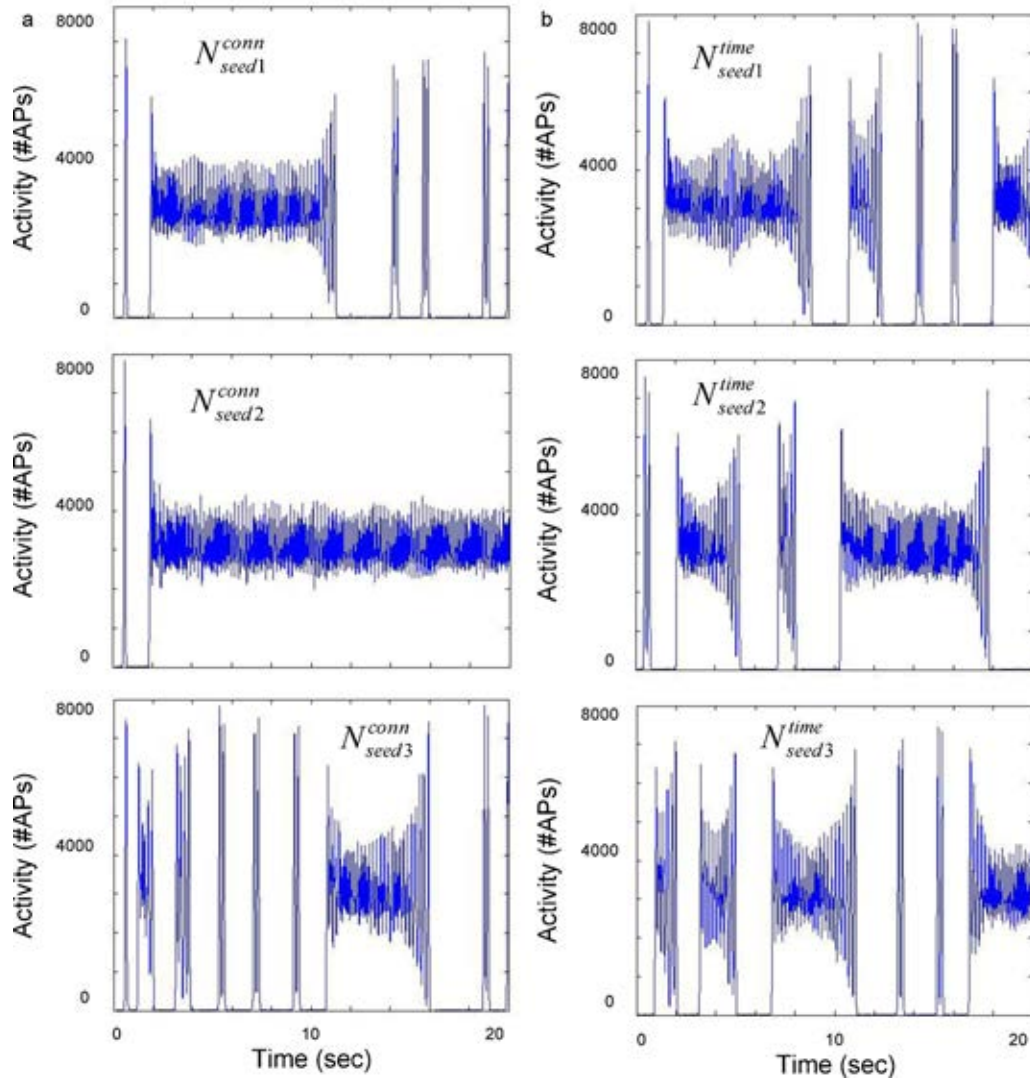


Figure 3 (A) Network activity induced by varying the random connectivity pattern between cell classes (different connectivity seeds, N_{seed}^{conn} , for the random number generator). Numbers of action potentials in layer II/III pyramidal cell component, 10 ms time bins. (B) Network activity induced by varying the random time sequence of background synaptic input, N_{seed}^{time} . In these experiments, all cellular connections remain fixed, and the identity of the cells undergoing background synaptic input remain fixed.

II/III pyramidal cell activity (time-binned action potential numbers) for various degrees of extracolumnar connectivity between the layer II/III pyramidal cells. The base activity explored in this manuscript is shown in the plot with total number of connections held at $N_{2/3:2/3} = 178$ (between extra-minicolumnar layer II/III pyramidal cells). A rapid reduction in network bursting is shown for a connection number reduced below this, and almost continuous activity is shown for connection numbers above this. Fig. 3A and B data were obtained with the connectivity set at $N_{2/3:2/3} = 178$. Only the random pattern of connectivity is varied in Fig. 3A and the time sequence of background input in Fig. 3B. These studies were performed in the context of a constant average level of surrounding background input, and imply the importance of internal connectivity in the development of uncontrolled bursting of the network.

Statistical analysis of interburst phase intervals

The statistical properties of the interburst phase intervals for five continuous runs of the model at connectivities of $N_{2/3:2/3} = 178$ and 172 were analyzed. This was motivated from a dynamical systems perspective, where periodicity in sequential intervals was sought for. Fig. 5A displays a histogram approximation to the probability density function for interbursting phase intervals for Continuous Run 1, which consisted of 163 intervals collected from a 320 s run of the simulation. Fig. 5D displays the same histogram approximation for Continuous Run 4, with a total of 58 intervals collected from a 140 s run of the simulation. Gamma distributions were used to fit these densities (Fig. 5A and D (blue traces)) (see "Materials and methods" section; Suffczynski et al., 2005, 2006). In the case of Continuous Run 1

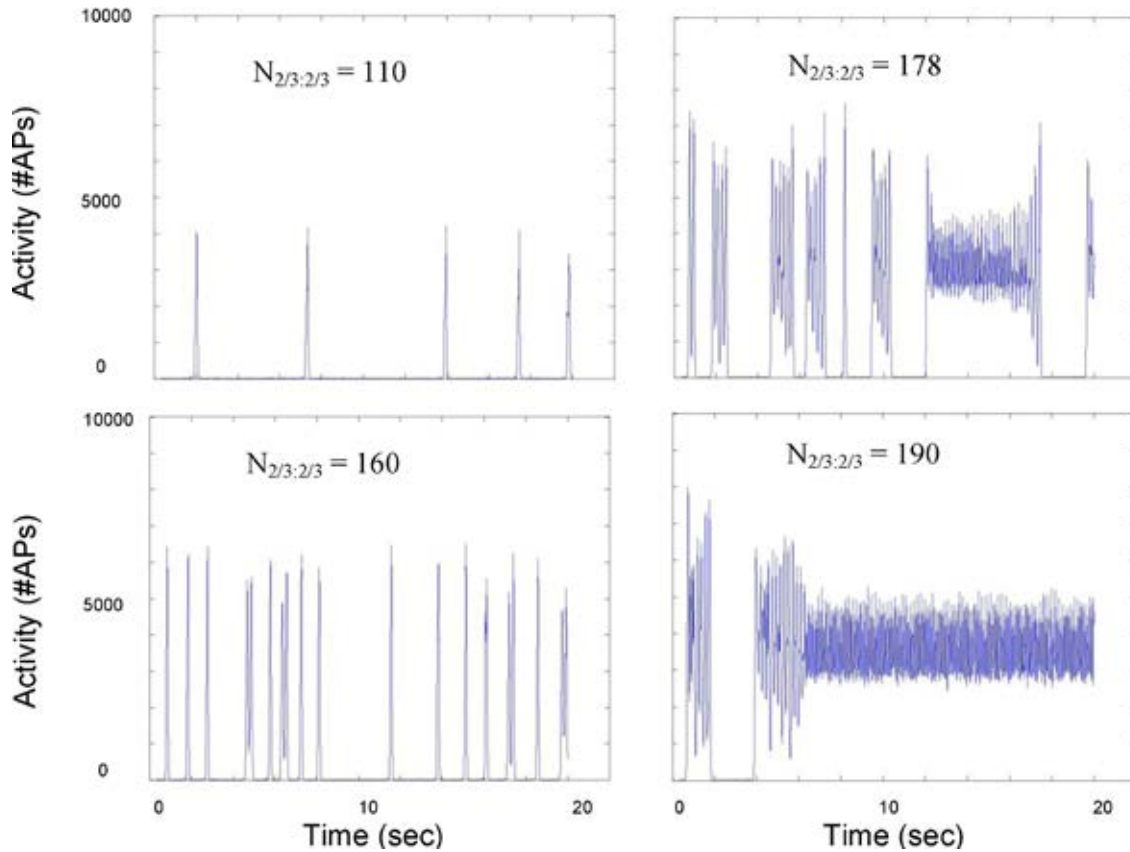


Figure 4 Changing the absolute connectivity in the layer II/III pyramidal cell component (number of layer II/III pyramidal cells contacted by a given layer II/III pyramidal cell, $N_{2/3:2/3}$) in the model produces alterations in the network bursting behavior. At very low absolute connectivity ($N_{2/3:2/3} = 110$) network bursting is brief and isolated, while at higher levels of absolute connectivity periods of constant bursting can be observed.

(Fig. 5A) we found $\alpha = 6.09$ (4.61–8.04) for the shape parameter of the distribution, and $\beta = 0.26$ (0.20–0.35) for the scale parameter (95% confidence intervals in parentheses). For Continuous Run 4 (Fig. 5D), the corresponding values were $\alpha = 7.14$ (5.00–10.19), and $\beta = 0.23$ (0.16–0.33) (similar results were obtained for 3 further continuous runs and one discontinuous run – results not shown). In accord with the interpretation of Suffczynski et al. (2005, 2006), the fact that the shape parameter α was larger than one in all runs, suggests the potential presence of periodicity in the generation of bursting epochs. To probe this link further, additional statistical tests were performed as described below.

To ascertain how intervals were being drawn from their underlying joint distribution, we applied a non-parametric test of randomness to the interbursting phase intervals (Wald and Wolfowitz, 1943). In the case of Continuous Run 1, we found that one cannot reject the null hypothesis of randomness at the 5% significance level (p -value 0.93). For Continuous Run 4, we found the same conclusion at the 5% significance level (p -value 0.29). This conclusion was also borne out for the remaining three continuous runs.

A method for the detection of unstable periodic orbits (of period-1) was then applied to test for the presence of deterministic dynamics in the generation of interbursting phase intervals (So et al., 1996, 1997). This method institutes a transformation of the sequence of intervals such

that the transformed sequence is clustered around locations of potential periodic orbits. One can compare the peaks of these clusters to those generated by surrogate data (Theiler et al., 1992), to compute the statistical significance of the peaks, and thereby ascertain the potential existence of periodic orbits in the data. Fig. 5C and F shows the peaks of the clusters were not significantly greater than those generated by surrogate data (see caption), and so no period-1 orbits were detected for either run (nor for the remaining three continuous runs), at the limit of detection in the current data set.

Discussion

Our results demonstrate that while holding the mean properties of the network stable (mean connectivity numbers, mean background excitation rates), very rich and strikingly different dynamics are produced by changing the model details. Epileptogenic behavior can be created in these networks, as described above, by changes in the random pattern of connectivity, while holding fixed the intrinsic active or passive membrane properties in the constituent neurons. Such changes in connectivity could be analogous to changes in underlying connectivity that might occur following cerebral insults, or repetitive seizures. Similar modeling

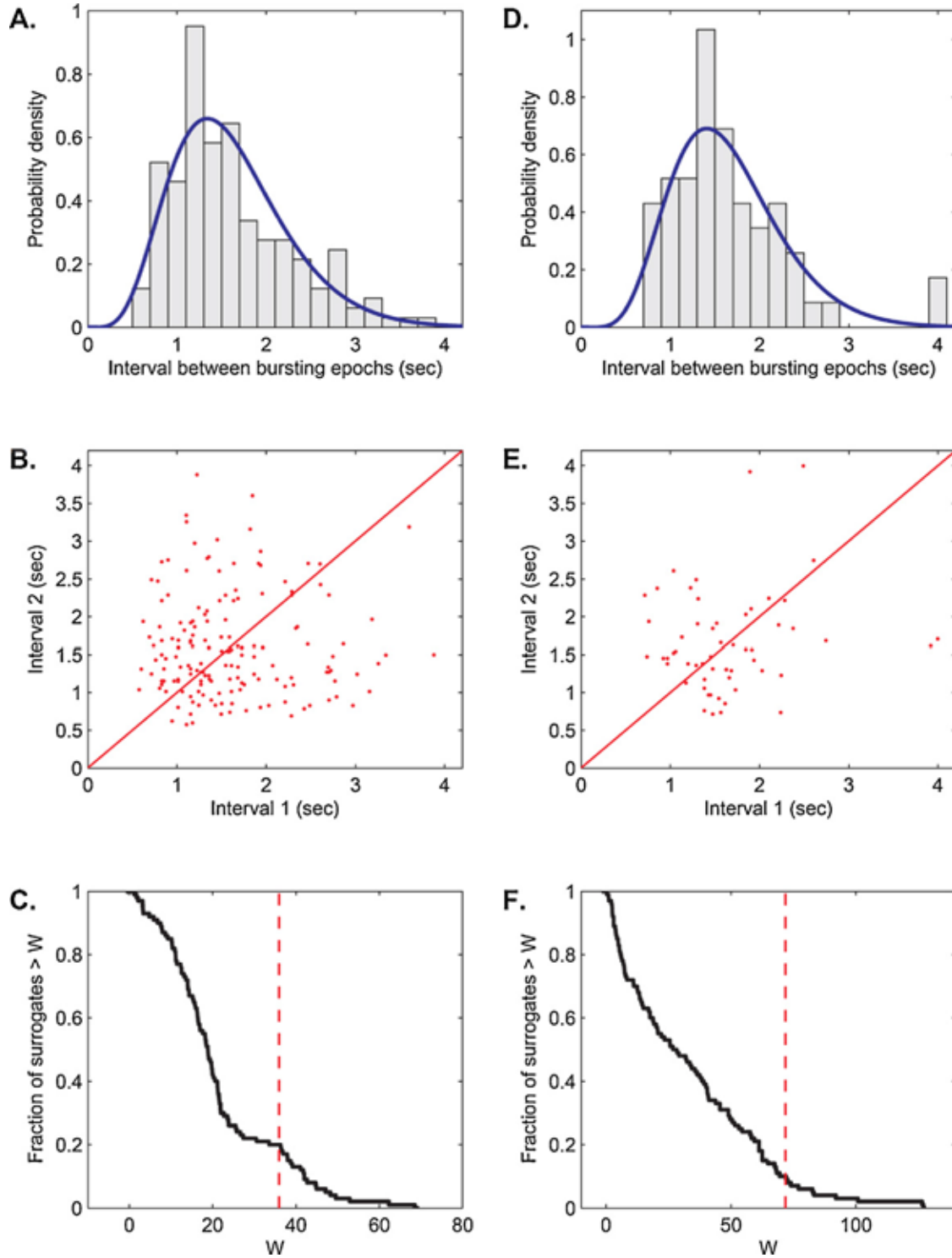


Figure 5 Statistical analysis of the interbursting phase intervals. (A and D) Interval histograms are fit with gamma distributions revealing shape parameters $\alpha > 1$ in the case of Continuous Run 1 (A) and Continuous Run 4 (D). (B and E) Two dimensional delay embedding of sequential intervals (Spearman correlation coefficients are not significantly different from zero) for Continuous Runs 1 and 4, respectively. (C and F) Testing the significance of potential period-1 orbits detected through a dynamical analysis of the sequence of points displayed in (B) and (E), respectively. The y-axis represents the fraction of surrogate (shuffled, see "Materials and methods" section) sequences with a maximal deviation from the mean surrogate result of greater than W (So et al., 1996, 1997) (10^4 random matrices and 10^2 surrogates were used). The horizontal dotted (red) line displays the maximal deviation for the simulation data. Since there exists a significant fraction of surrogates with deviation greater than that for the simulation data (for both C – 20% and F – 10%), neither plot displays convincing evidence of the existence of a period-1 orbit. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

work has been performed on changes in connectivity with resultant epileptic effects in hippocampus (Morgan and Soltesz, 2008; Dyhrfeld-Johnsen et al., 2007). In our results, local increases or decreases in connectivity in the model may alter the network in a similar manner (a tempting comparison which must be tempered by our lack of understanding of the functional significance of new or absent connections, see Sallin et al., 1995; Dinocourt et al., 2003; Marco et al., 1997; Dudek and Sutula, 2007; Maglósky, 2010). In the model above, the external background activity can be held constant or changed in a variety of time-frequency manipulations. Various simulations can be created where seizures occur rarely or very frequently.

Similarly, human epileptic seizures are episodic, transient events. Whether epileptic seizures are random events is not clear, but times of ictal onset can behave as a random process (Suffczynski et al., 2006). In some patients there are no identifiable contributing factors, in other patients such conditions such as sleep deprivation may increase the chance of seizure occurrence and in still other patients seizures can be provoked by specific stimuli (e.g. hyperventilation, intermittent photic stimulation; Lu et al., 2008; Vinogradova et al., 2009; Kaplan et al., 2009). In these examples there may be resulting alterations of background activity within and outside the epileptogenic zone (not evident from the EEG) that make it more likely that a seizure may arise from the existing focal epileptogenic network. While these influences might create a state where seizures are more likely to occur, this facilitatory state should be distinguished from the presence (or absence) of a preictal state in unprovoked seizures.

Random behavior of network

One interesting aspect of this model is its ability to demonstrate both spontaneous periods of bursting activity as well as self-termination of the bursting. As illustrated in Figs. 2–5, these periods of bursting can be quite variable in their length. Throughout the bursting and quiescent phases, the distributed background activity is constantly active, affecting approximately 1% of the total cells. We believe this model may represent the type of network behavior described by Lopes da Silva et al. (2003), in which epileptic activity within the network cannot be predicted from the interictal state. The non-parametric and nonlinear dynamical analyses described in the “Results” section support this, however inference from this is somewhat limited given the finite size of the data set, the small region of modeled area, and the gamma distribution fits described earlier.

This obviously may not be true of all types of clinical and model epileptiform behavior. For example Osorio et al. (2009, 2010) show that pharmacoresistant seizures tend to cluster, and may have an inherent self-triggering capacity. This might make a prediction algorithm possible to implement in a useful fashion. Others (Suffczynski et al., 2005, 2006), however demonstrate that seizure onset can be described in both experimental and model data as a random walk process, with possibly a deterministic mechanism ascribed to seizure termination. The random onset nature would (in a bistable network with Poisson transitions) be difficult to predict.

In the case of our model the underlying fluctuations leading to seizure onset are the random background activity we have imposed on the network. The properties of the network connectivity then support the bursting frequency observed (Anderson et al., 2007). These types of grossly synchronized bursting states in the context of a neural network have been studied extensively by Kowalski et al. (1992). They are truly pathological in the sense that they would block or confound any information flow through this network. It is also a network-generated state, and can be stopped by eliminating synaptic transmission (Kowalski et al., 1992; Keefer et al., 2001; Rhoades and Gross, 1994).

Many limiting cases of the gamma distribution have physical interpretations that might make it easier to understand spiking data from cortex when used for fitting (Papoulis, 1984; Suffczynski et al., 2005). When the shape parameter, α , in the gamma distribution is an integer, the distribution is known as an Erlang distribution and represents the probability distribution of the waiting time until the α th event from a sampled Poisson process with characteristic time β . This might be comparable to the distribution of the number of spiking or underlying synaptic events required to trigger the network bursting behavior. One could envision trying to extract the integer value of α from either computational or experimental data. Similarly, the Maxwell–Boltzmann distribution can be related to the gamma distribution under certain restrictions on the gamma scale and shape parameters, implying the possibility of extracting almost thermal-like or statistical mechanical interpretations of the network activity (Hegyi, 1996).

Limitations of the model

Our plots demonstrate gross summed numbers of time-binned action potentials in the model for given neuron classes. The interictal activity is a random Poisson input to 1% of the cells in the model and is demonstrated in the plots, particularly in Fig. 2, Panel 1, inset. We chose to impose this random interictal behavior on the model to demonstrate that these fluctuations can produce very coherent synchronous oscillations in an unpredictable fashion. However, the surrounding input might not have to be completely random to bring about the same effect. Epilepsies involving specific stimuli might require a coherent surrounding input to give rise to the seizure (Lu et al., 2008; Vinogradova et al., 2009; Kaplan et al., 2009). A more realistic technique would be to treat the interictal background as a log-normal process which does have some support in the literature (see Farkhooi et al., 2009; Waters and Helmchen, 2006). Newer recording methods from invasively monitored epilepsy patients might help determine what patterns of background activity are causative (Truccolo et al., 2011; van Gompel et al., 2008). Our intent was to represent the resting interictal cellular activity as fundamentally sparse with a random component. This was most easily implemented as a low frequency Poisson process.

It is possible to view the single synaptic input (driven by the background source) as representing several weaker but synchronized inputs. This represents a limitation to this modeling approach, a limitation that in large degree could be corrected with more elaborate multicompartment and

synaptic representations of the cells to make the multiple weaker inputs more independent. Additionally in this limited data set, we are unable to say much about time epochs larger than several hundreds of seconds (our largest continuous simulation being 320s). This is clearly a limitation in this technique and future computational work, including efforts in our laboratory will explore longer time intervals of ictal and interictal behavior, and possibly push the detection limit for predictable activity lower (or detect it more accurately). Models such as this particular rigid crystalline arrangement of neurons with many fixed cellular properties in some sense have less inherent “randomness” than real neocortex. This work was primarily meant to spark interest in a possible mechanism for the difficulties inherent in seizure prediction, but by no means should it be interpreted too literally.

Implications for seizure prediction

The purpose of the model presented here is not to judge the effectiveness of seizure prediction, but rather to present a plausible, alternative hypothesis for partial seizure occurrence that could explain situations where seizure prediction may not be possible. Indeed, it is conceptually attractive to consider that, just as partial seizures may result from various pathologies and mechanisms, that some partial seizures may not be reliably predicted. It is beyond the scope of this discussion to address the various methods being used in attempts to predict epileptic seizures. It is always important to differentiate true seizure prediction from improved seizure detection. Other commentaries and reviews address these methods and include discussions of the challenges and frustrations to date in routine seizure prediction even with intracranial electrodes (Estellar et al., 2001; Litt and Echauz, 2002; Sackellares et al., 2006; Haas et al., 2007; Osorio et al., 2001).

This study focused on the interval to the time of the next “seizure” or bursting phase in the model. Our interest was in the occurrences of the transitions from the quiescent or background state into the pathologic state, since that is what most seizure prediction algorithms are optimized for. There is fairly strong evidence, certainly in the case of complex partial seizures in temporal lobe epilepsy, that the length of clinical seizures can be fairly uniform in a given patient (see for instance Afra et al., 2008). The time interval durations of the seizures themselves may also prove to have to predictive guidance as well and should be explored in the future in modeling efforts. This may be more useful in the case of neocortical epilepsy with its rapid spread and possible involvement of larger regions of tissue.

Additionally, this model can incorporate incremental changes in connectivity in the epileptogenic zone, changes that could be a model for progressive epileptogenesis (e.g. sprouting). This type of model also provides data that is comparable to clinical data from epilepsy patients. The simulated network activity is taken from a small region of modeled cortex comparable in size to the surface area under a typical subdural grid electrode, and makes comparisons between modeling efforts and clinical data easy to perform (Anderson et al., 2007, 2009; Kudela et al., 1997, 2003a,b; Franaszczuk et al., 2005). Indeed the major advantage of

neural network modeling is the ability to simultaneously monitor activity in all of the network neurons under given experimental conditions, something not possible with biological systems, even with sophisticated recording arrays.

Conflict of interest

None of the authors has any conflict of interest to disclose.

Acknowledgements

WSA is supported by NIH-NINDS K08 (K08NS066099-01A1).

The model described in this manuscript has been posted to the Yale SenseLab ModelDB database of computational neuroscience models, web address: <http://senselab.med.yale.edu/modeldb/default.asp>.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eplepsyres.2011.11.006.

References

- Afra, P., Jouny, C.C., Bergey, G.K., 2008. Duration of complex partial seizures: an intracranial EEG study. *Epilepsia* 49 (4), 677–684.
- Anderson, W.S., Kudela, P., Cho, R.J., Bergey, G.K., Franaszczuk, P., 2007. Studies of stimulus parameters for seizure disruption using neural network simulations. *Biol. Cybern.* 97, 173–194.
- Anderson, W.S., Weinberg, S., Kudela, P., Bergey, G.K., Franaszczuk, P., 2009. Phase dependent stimulation effects on bursting activity in a neural network cortical simulation. *Epilepsy Res.* 84, 42–55.
- Andrzejak, R.G., Chicharro, D., Elger, C.E., Mormann, F., 2009. Seizure prediction: any better than chance? *Clin. Neurophysiol.* 120 (8), 1465–1478.
- Arellano, J.I., Muñoz, A., Ballesteros-Yáñez, I., Sola, R.G., DeFelipe, J., 2004. Histopathology and reorganization of chandelier cells in the human epileptic sclerotic hippocampus. *Brain* 127, 45–64.
- Av-Ron, E., 1994. The role of a transient potassium current in a bursting neuron model. *J. Math. Biol.* 33, 71–87.
- Berg, A.T., Shinnar, S., 1991. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 41, 965–972.
- Bragin, A., Engel, J., Staba, R.J., 2010. High-frequency oscillations in epileptic brain. *Curr. Opin. Neurol.* 23 (2), 151–156.
- Braitenberg, V., Schüz, A., 1998. *Cortex: Statistics and Geometry of Neuronal Connectivity*, 2nd edition. Springer, Berlin.
- Dinocourt, C., Petanjek, Z., Freund, T.F., Ben-Ari, Y., Esclapez, M., 2003. Loss of interneurons innervating pyramidal cell dendrites and axon initial segments in the CA1 region of the hippocampus following pilocarpine-induced seizures. *J. Comp. Neurol.* 459, 407–425.
- Douglas, R.J., Martin, K.A.C., 2004. Neuronal circuits of the neocortex. *Annu. Rev. Neurosci.* 27, 419–451.
- Dudek, F.E., Sutula, T.P., 2007. Epileptogenesis in the dentate gyrus: a critical perspective. *Prog. Brain Res.* 163, 755–753.
- Dyhrfjeld-Johnsen, J., Santhakumar, V., Morgan, R.J., Huerta, R., Tsimring, L., Soltesz, I., 2007. Topological determinants of epileptogenesis in large-scale structural and functional models

- of the dentate gyrus derived from experimental data. *J. Neurophysiol.* 97 (2), 1566–1587.
- Estellar, R., Echaz, J., Tchong, T., Litt, B., Pless, B., 2001. Line length: an efficient feature of seizure onset detection. In: *Proc 23rd Annu Int Conf IEEE Eng Med Biol Soc, Istanbul*, pp. 1707–1710.
- Farkhooi, F., Strube-Bloss, M.F., Nawrot, M.P., 2009. Serial correlation in neural spike trains, experimental evidence, stochastic modeling, and single neuron variability. *Phys. Rev. E: Stat. Nonlin. Soft Matter Phys.* 79, 021905.
- Franaszczuk, P.J., Kudela, P., Bergey, G.K., 2003. External excitatory stimuli can terminate bursting in neural network models. *Epilepsy Res.* 53, 65–80.
- Guckenheimer, J., Holmes, P., 1983. *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. Springer-Verlag, New York.
- Haas, S.M., Frei, M.G., Osorio, I., 2007. Strategies for adapting automated seizure detection algorithms. *Med. Eng. Phys.* 29 (8), 895–909.
- Hauser, W.A., Annegers, J.F., Kurland, L.T., 1993. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 34, 453–468.
- Hegy, S., 1996. Multiplicity distributions in strong interactions: a generalized negative binomial model. *Phys. Lett. B* 387, 642–650.
- Jacobs, K.M., Graber, K.D., Kharazia, V.N., Parada, I., Prince, D.A., 2000. Postlesional epilepsy: the ultimate brain plasticity. *Epilepsia* 41 (Suppl. 6), S153–S161.
- Kaplan, Y., Kurt, S.G., Karaer, H., Sarikaya, B., Bebek, N., 2009. Intra-familial incidence and characteristics of hot water epilepsy. *Can. J. Neurol. Sci.* 36 (5), 575–581.
- Keefer, E.W., Gramowski, A., Gross, G.W., 2001. NMDA receptor-dependent periodic oscillations in cultured spinal cord networks. *J. Neurophysiol.* 86, 3030–3042.
- Kowalski, J.M., Albert, G.L., Rhoades, B.K., Gross, G.W., 1992. Neuronal networks with spontaneous, correlated bursting activity: theory and simulations. *Neural Netw.* 5, 805–822.
- Krumholz, A., Wiebe, S., Gronseth, G., Shinnar, S., Levisohn, P., Ting, T., Hopp, J., Shafer, P., Morris, H., Seiden, L., Barkley, G., French, J., 2007. Practice parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 69, 1996–2007.
- Kudela, P., Franaszczuk, P.J., Bergey, G.K., 1997. A simple computer model of excitable synaptically connected neurons. *Biol. Cybern.* 77, 71–77.
- Kudela, P., Franaszczuk, P.J., Bergey, G.K., 2003a. Changing excitation and inhibition in simulated neural networks: effects on induced bursting behavior. *Biol. Cybern.* 88, 276–285.
- Kudela, P., Franaszczuk, P., Bergey, G.K., 2003b. Reduction of intracellular calcium removal rate can explain changes in seizure dynamics: studies in neuronal network models. *Epilepsy Res.* 57, 95–109.
- Kudela, P., Franaszczuk, P.J., Bergey, G.K., 2005. Synaptic and cellular influences on the composite EEG signal during seizures. In: *Proc 2nd Inter IEEE EMBS Conf Neural Eng. IEEE, Arlington, VA*, pp. 245–247.
- Kumar, S.S., Jin, X., Buckmaster, P.S., Huguenard, J.R., 2007. Recurrent circuits in layer II of medial entorhinal cortex in a model of temporal lobe epilepsy. *J. Neurosci.* 27, 1239–1246.
- Lehnertz, K., Mormann, F., Osterhage, H., Müller, A., Prusseit, J., Chernihovskiy, A., Staniek, M., Krug, D., Bialonski, S., Elger, C.E., 2007. State-of-the-art of seizure prediction. *J. Clin. Neurophysiol.* 24 (2), 147–153.
- Leussis, M.P., Heinrichs, S.C., 2007. Temporal ontogeny of circuit activation prior to the onset of seizure susceptibility in EL/Suz mice. *Neuroscience* 145, 33–41.
- Le Van Quyen, M., Martinerie, J., Adam, C., Varela, F.J., 1997. Unstable periodic orbits in human epileptic activity. *Phys. Rev. E* 56 (3), 3401–3411.
- Litt, B., Echaz, J., 2002. Prediction of epileptic seizures. *Lancet Neurol.* 1, 22–30.
- Lopes da Silva, F., Blanes, W., Kalitzin, S.N., Parra, J., Suffczynski, P., Velis, D.N., 2003. Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. *Epilepsia* 44 (Suppl. 12), 72–83.
- Lu, Y., Waltz, S., Stenzel, K., Muhle, H., Stephani, U., 2008. Photosensitivity in epileptic syndromes of childhood and adolescence. *Epileptic Disord.* 10 (2), 144–145.
- Maglócsky, Z., 2010. Sprouting in human temporal lobe epilepsy: excitatory pathways and axons of interneurons. *Epilepsy Res.* 89, 52–59.
- Marco, P., Sola, R.G., Ramón y Cajal, S., DeFelipe, J., 1997. Loss of inhibitory synapses on the soma and axon initial segment of pyramidal cells in human epileptic peritumoural neocortex: implications for epilepsy. *Brain Res. Bull.* 44, 47–66.
- Morgan, R.J., Soltesz, I., 2008. Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *Proc. Natl. Acad. Sci. U.S.A.* 105 (16), 6179–6184.
- Mormann, F., Andrzejak, R.G., Elger, C.E., Lehnertz, K., 2007. Seizure prediction: the long and winding road. *Brain* 130, 314–333.
- Niedermeyer, E., 2005. Epileptic seizure disorders. In: *Niedermeyer, E., Lopes da Silva, F. (Eds.), Electroencephalography*, 5th edition. Lippincott Williams & Wilkins, Philadelphia, pp. 505–619.
- Osorio, I., Frei, M.G., Manly, B.F.J., Sunderam, S., Bhavaraju, N.C., Wilkinson, S.B., 2001. An introduction to contingent (closed-loop) brain electrical stimulation for seizure blockage, ultra-short-term clinical trials, and to multidimensional statistical analysis of therapeutic efficacy. *J. Clin. Neurophysiol.* 18 (6), 533–544.
- Osorio, I., Frei, M.G., Sornette, D., Milton, J., 2009. Pharmacoresistant seizures: self-triggering capacity, scale-free properties and predictability? *Eur. J. Neurosci.* 30, 1554–1558.
- Osorio, I., Frei, M.G., Sornette, D., Milton, J., Lai, Y.-C., 2010. Epileptic seizures: quakes of the brain? *Phys. Rev. E* 82, 021919.
- Papoulis, A., 1984. *Probability, Random Variables, and Stochastic Processes*, 2nd edition. McGraw-Hill, New York.
- Rhoades, B.K., Gross, G.W., 1994. Potassium and calcium channel dependence of bursting in cultured neuronal networks. *Brain Res.* 643, 310–318.
- Sackellares, J.C., Shiao, D.S., Principe, J.C., Yang, M.C., Dance, L.K., Suharitdamrong, W., Chaovaitwongse, W., Pardalos, P.M., Iasemidis, L.D., 2006. Predictability analysis for an automated seizure prediction algorithm. *J. Clin. Neurophysiol.* 23, 509–520.
- Sackellares, J.C., 2008. Seizure prediction. *Epilepsy Curr.* 8 (3), 55–59.
- Sallin, P., Tseng, G.-F., Hoffman, S., Parada, I., Prince, D.A., 1995. Axonal sprouting in layer V pyramidal neurons of chronically injured cerebral cortex. *J. Neurosci.* 15 (12), 8234–8245.
- So, P., Ott, E., Schiff, S.J., Kaplan, D.T., Sauer, T., Grebogi, C., 1996. Detecting unstable periodic orbits in chaotic experimental data. *Phys. Rev. Lett.* 76 (25), 4705–4708.
- So, P., Ott, E., Sauer, T., Gluckman, B.J., Grebogi, C., Schiff, S.J., 1997. Extracting unstable periodic orbits from chaotic time series data. *Phys. Rev. E* 55 (5), 5398–5417.
- Suffczynski, P., Lopes da Silva, F., Parra, J., Velis, D., Kalitzin, S., 2005. Epileptic transitions: model predictions and experimental validation. *J. Clin. Neurophysiol.* 22 (5), 288–299.
- Suffczynski, P., Lopes da Silva, F.H., Parra, J., Velis, D.N., Bouwman, B.M., van Rijn, C.M., van Hese, P., Boon, P., Khosravani, H., Derchansky, M., Carlen, P., Kalitzin, S., 2006. Dynamics of epileptic phenomena determined from statistics of ictal transitions. *IEEE Trans. Biomed. Eng.* 53 (3), 524–532.

- Swann, J.W., Le, J.T., Lee, C.L., 2007. Recurrent seizures and the molecular maturation of hippocampal and neocortical glutamatergic synapses. *Dev. Neurosci.* 29, 168–178.
- Telfeian, A.E., Connors, B.W., 1998. Layer-specific pathways for the horizontal propagation of epileptiform discharges in neocortex. *Epilepsia* 39, 700–708.
- Theiler, J., Eubank, S., Longtin, A., Galdrikian, B., Farmer, J.D., 1992. Testing for nonlinearity in time series: the method of surrogate data. *Physica D* 58, 77–94.
- Truccolo, W., Donoghue, J., Hochberg, L., Eskandar, E., Madsen, J.R., Anderson, W.S., Halgren, E., Cash, S.S., 2011. Single neuron dynamics during human focal seizures. *Nat. Neurosci.* 14 (5), 635–641.
- van Gompel, J.J., Stead, S.M., Giannini, C., Meyer, F.B., Marsh, W.R., Fountain, T., So, E., Cohen-Gadol, A., Lee, K.H., Worrell, G.A., 2008. Phase I trial: safety and feasibility of intracranial electroencephalography using hybrid subdural electrodes containing macro- and microelectrode arrays. *Neurosurg. Focus* 25 (3), E23.
- Vinogradova, L.V., Kuznetsova, G.D., Coenen, A.M., 2009. Unilateral cortical spreading depression induced by sound in rats. *Brain Res.* 1286, 201–207.
- Wald, A., Wolfowitz, J., 1943. An exact test for randomness in the non-parametric case based on serial correlation. *Ann. Math. Stat.* 14 (4), 378–388.
- Waters, J., Helmchen, F., 2006. Background synaptic activity is sparse in neocortex. *J. Neurosci.* 26 (32), 8267–8277.
- Worrell, G.A., Gardner, A.B., Stead, S.M., Hu, S., Goerss, S., Cascino, G.J., Meyer, F.B., Marsh, R., Litt, B., 2008. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain* 131 (Pt 4), 928–937.
- Worrell, G.A., Parish, L., Cranstoun, S.D., Jonas, R., Baltuch, G., Litt, B., 2004. High-frequency oscillations and seizure generation in neocortical epilepsy. *Brain* 127 (Pt 7), 1496–1506.