Interaction between Cellular Voltage-Sensitive Conductance and Network Parameters in a Model of the Neocortex Can Generate Epileptiform Bursting

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Abstract—**We examined the effects of both intrinsic neuronal membrane properties and network parameters on oscillatory activity in a model of the neocortex. A scalable network model with six different cell types was built with the pGENESIS neural simulator. The neocortical network consisted of two types of pyramidal cells and four types of inhibitory interneurons. All cell types contained both fast sodium and delayed rectifier potassium channels for generation of action potentials. A subset of the pyramidal neurons contained an additional slow-inactivating (persistent) sodium current (NaP). The neurons with the NaP current showed spontaneous bursting activity in the absence of external stimulation. The model also included a routine to calculate a simulated electroencephalogram trace from the population activity. This revealed emergent network behavior, which ranged from desynchronized activity to different types of seizurelike bursting patterns. At settings with weaker excitatory network effects, the propensity to generate seizurelike behavior increased. Strong excitatory network connectivity destroyed oscillatory behavior, whereas weak connectivity enhanced the relative importance of the spontaneously bursting cells. Our findings contradict the general opinion that strong excitatory synaptic or insufficient inhibition effects are associated with seizure initiation, but our results agree with previously reported behavior in the neocortex.**

Keywords—**Epilepsy, neocortex, neural modeling**

I. Introduction

Surface recordings of brain electrical activity typically show oscillatory behavior, both during physiological states such as sleep and in pathological states such as epileptic seizures. When relating cellular behavior to a macromeasurement device such as the electroencephalogram (EEG), the scale associated with events at a single EEG electrode is astronomical: the number of neurons in the neocortex directly under an electrode surface of 1 cm^2 is estimated to be about 10,000,000. Oscillations generated in the neocortical structure and recorded at surface EEG electrodes can be attributed to intrinsic (voltage-gated) membrane conductances and behavior emerging from the network. In wide-band EEG recordings, the frequency components can range from near DC up to about 0.5 kHz. In terms of power contributions, the lower frequencies (0–15 Hz) typically dominate the EEG spectrum. At the cellular level, voltage-gated sodium and potassium currents are responsible for the fast component of membrane voltage fluctuations, the action potentials. The slower component of cell membrane potential fluctuation may arise from ion currents such as those associated with persistent sodium channels, different types of calcium channels, and slowly activating potassium channels [1]–[7]. At the network level, the balance between global excitation and inhibition determines the overall behavior of the cell population (see, e.g., [8]). In many seizure types, the EEG shows rhythmic bursting patterns that, because of the spatial summation of cellular activity under the electrode, necessarily imply some degree of synchrony in the underlying neural activity. Although this type of activity is one of the hallmarks of epilepsy, the occurrence of oscillatory components and synchrony in brain electrical activity is not restricted to epilepsy. Therefore it is critical to investigate neuronal bursting patterns in order to distinguish between normal and pathological oscillations.

In the present study we used a realistic model of the neocortex to evaluate the interplay between intrinsic and network parameters in the generation of slow oscillatory behavior frequently seen in EEGs associated with seizures. The network was built in a scalable fashion to allow for validation at cellular and different network scales. The results in this paper were obtained from medium-scale networks. A companion paper [9] details the efficiency with which larger networks based on this model can be implemented on parallel computing clusters.

II. Methodology

Neurons in the neocortex can be subdivided into excitatory and inhibitory types showing both horizontal and vertical organization [10]–[12]. The majority of excitatory cells are the pyramidal neurons concentrated in cortical layers 2–3 and 5–6. The scalable model of the neocortex used in this study, which includes pyramidal neurons and four types of inhibitory interneurons, has been described in detail in [8]. In short, the network consisted of 40% superficial pyramidal cells, 40% deep pyramidal cells, and

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TABLE I
OVERVIEW OF CELL TYPES, COMPARTMENTS, AND ION CHANNELS IN THE NEOCORTICAL MODEL.

Length and diameter of the cylindrical compartments in μm. For each compartment the voltage-sensitive sodium channels (**Na, NaP)**, potassium (**K**) channels, excitatory (**E**) channels, and inhibitory (**I**) synaptic channels are shown in the last two columns. The persistent sodium (**NaP**) channel is responsible for spontaneous bursting activity and is available only in the superficial pyramidal cells. The percentage of cells including the NaP channel is varied in different simulations. Inhibitory neurons are connected through gap junctions (**GJ**).

S_PYR and **D_PYR** are the superficial and deep pyramidal cells, **BAS1-3** represent three types of basket cells, and **CHAND** is the chandelier cell. The abbreviations **sd1-2, dd1-4, bd**, and **is** denote the superficial cell's dendrite, the deep cell's dendrite, the basal dendrite, and the initial segment, respectively. The dendritic compartment of inhibitory neurons is indicated as **d**.

Cell - Compartment	Size (μm)	V-Channels	Synapse
S_PYR – soma	22, 16.1	Na, K, NaP	I
- **sd1**	140, 2	-	-
- **sd2**	190, 3.3	-	E
- **bd**	200, 2.4	-	-
- **is**	15, 2.5	Na, K	I
D_PYR – soma	22, 16.1	Na, K	I
- **dd1**	250, 2	-	-
- **dd2**	400, 2.9	-	-
- **dd3**	400, 4.4	-	E
- **dd4**	400, 4.7	-	-
- **bd**	200, 6.3	-	-
- **is**	15, 2.5	Na, K	I
BAS1-3 – soma	5.5-22, 4-16.1	Na, K	E, I
- **d**	300-900, 2	-	GJ
CHAND – soma	5.5, 4	Na, K	E, I
- **d**	150, 2	-	GJ

cells, 40% deep pyramidal cells, and 20% interneurons. The interneurons were equally divided into wide-, medium-, and local-arbor basket cells and chandelier cells [13]. Each type of inhibitory cell was interconnected with gap junctions at a probability of 80%. The cells were represented by multicompartmental models with voltage-sensitive and synaptic ion channels (Table I). Diagrams of the excitatory and inhibitory connections are shown in Fig. 1.

Each compartment was modeled as an electrical circuit in which the membrane potential V, the membrane capacitance C, and the currents of the individual ion species I_k (including the voltage-gated, leakage and ligand sensitive currents) were related to the intercompartmental current I by

$$C\frac{dV}{dt} + \sum I_k = I \quad . \qquad (1)$$

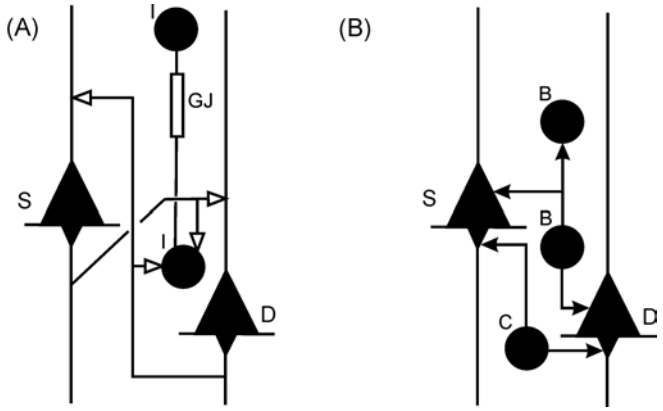

Fig. 1. Diagrams of the synaptic connections.
(A) Excitatory synaptic contacts between the deep (D), superficial (S) pyramidal cells, and the inhibitory cell types (I). Gap junctions (GJ).
(B) The inhibitory synapses between the basket cell types, B, the chandelier cells, C, and the pyramidal neurons.

The current I_k of the kth ion species is determined from its conductance across the membrane G_k and its equilibrium potential E_k by

$$I_k = G_k\left(V - E_k\right) . \qquad (2)$$

The value of G_k in (2) was voltage dependent for the fast sodium, persistent sodium, and delayed rectifier potassium currents. The persistent sodium channel NaP [14] was implemented in a fraction of the superficial pyramidal cells only. The synaptic conductances are ligand sensitive and were modeled with a dual exponential function. The EEG generated by the cell model was calculated as the weighted sum of the extracellular currents [15]. To allow scalability to network sizes of 10^5 neurons and above, we implemented the neocortical model in the pGENESIS neurosimulator [16]. Network parameter searches for medium-sized models (160–640 cells) were performed on the Jazz 350-node computing cluster at Argonne National Laboratory.

III. Results

A. EEG and Underlying Cellular Synchrony

Simulations were routinely started with a 0.5 s current injection of 1 nA in the somatic compartment of the superficial pyramidal cell situated in the corner of the patch. Two typical examples of the EEG generated by the model are shown in the top traces of Fig. 2. These traces reveal two distinct bursting patterns in association with the underlying activity of superficial pyramidal cells shown in the raster plot below. The top trace in Fig. 2A shows EEG oscillations grouped in short bursts (SB), whereas Fig. 2B is a repetitive (R) busting pattern. Although both types of activity in Fig. 2 can be classified as bursting patterns, the

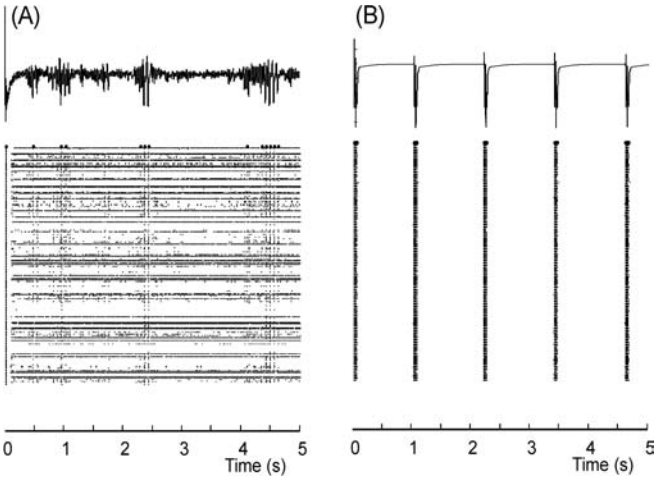

Fig. 2. Examples of the relationship between the EEG (top traces) and the activity patterns of the superficial pyramidal neurons (raster plots) in a 640-cell model. A fraction of 20% of the superficial pyramidal neurons contained NaP, a voltage-sensitive slowly inactivating sodium channel. (A) shows slow bursting activity at a high level of synaptic excitation. (B) shows repetitive discharges at a low level of synaptic excitation.

Gestalt of the two traces, as well as the underlying distributions of cellular activity, is distinct. The SB pattern (Fig. 2A) resembles EEG recordings from subjects, with some synchrony between the firing patterns of the pyramidal neurons. The R type behavior (Fig. 2B), however, is qualitatively similar to EEG traces from patients with neurological disorders and is associated with the highest level of synchrony.

B. Synaptic Strength and Intrinsic Properties

Network activity (represented by the EEG) for the global synaptic excitation-inhibition parameter space was explored for a model in which all superficial pyramidal cells contain NaP conductances (Fig. 3A); the variety of EEG patterns observed are shown in Fig. 3B. When synaptic excitation was weak, the R type behavior described above was observed. With increasing levels of excitation and inhibition, the emerging activity of the network included fast bursting and short bursts (FB and SB, respectively, in Fig. 3). Desynchronized activity (D) appeared at relatively high levels of both excitation and inhibition. Networks similar to those used in this study, but without NaP conductances, did not display R or FB [8].

IV. Discussion

Our results demonstrate how neural networks may generate behavior with varying degrees of population synchrony and how this synchrony may be reflected in global measurements like EEG. In some areas of the excitation-inhibition parameter space (such as those indicated with D and SB in Fig. 3) the network displays EEG behavior that has a ``normal'' look. The S, FB, and R in Fig. 3 areas, on the other hand, are associated with ``abnormal''-looking behavior, some of which resembles rhythmic bursting seen in seizure activity, *status epilepticus*, or EEG burst suppression. Since global synaptic strength may vary over time in a functioning neural network, a route to seizure onset can be postulated as a path through the excitation-inhibition parameter space such as the one indicated with the arrow in Fig. 3. It is interesting to note that this path represents a reduction in excitatory synaptic efficacy, whereas seizures are commonly thought to be associated with high levels of synaptic excitation or low levels of synaptic inhibition (*, Fig. 3). Although such a

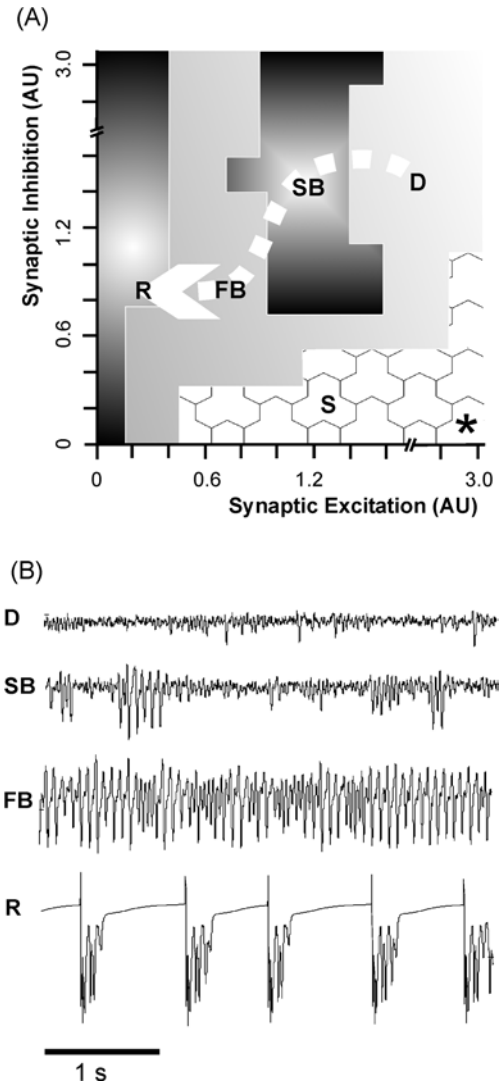

Fig. 3. Activity patterns in a 640-cell model as a function of global strength of excitatory and inhibitory connections. All superficial pyramidal cells include NaP conductance. The plot in (A) shows the different areas in the excitation-inhibition parameterspace; both axes are in arbitrary units (AU). (A) shows a potential path to seizure onset (white arrow). The traces in (B) show associated EEG activity: D – Desynchronized activity; SB – Short bursts; FB – Fast bursting activity; R – Repetitive discharges; S - Saturated neuronal activity; * - M indicates the area of strong excitatory and weak inhibitory coupling, commonly viewed as the area where seizures could occur.

hyperexcitatory state may be expected to produce short bursting effects, as a result of sudden saturation of cellular activity, the path indicated in Fig. 3 presents an alternative or additional hypothesis for the mechanism of seizure onset.

Seizure activity associated with impaired synaptic function has also been described in vivo, both in the hippocampus and in the neocortex. Pumain et al. [17] studied epileptic ``seizures in neocortex of a baboon and reported that seizures were accompanied by abnormal large decreases in concentration of extracellular calcium ions, reaching values at which chemical synaptic transmission was certainly very reduced or blocked." These authors also reported that low extracellular Ca^{++} concentration frequently preceded seizure onset. This later observation is especially important in light of a recent study in hippocampal pyramidal neurons showing that reduced [Ca^{++}] not only reduces synaptic transmission but also increases the effects of NaP, that is, it strengthens cellular bursting and increases the number of intrinsically bursting cells [18]. Such a state of increased intrinsic bursting with low levels of synaptic transmission creates a circumstance where our model predicts epileptiform discharges associated with either moderate or high levels of synchrony in the network. In addition, recent observations show that riluzole reduces the effects of NaP and can also stop rhythmic spontaneous network bursting in mouse neocortical slices [19]. We note that reduced [Ca^{++}] or increased bursting effects are only examples of mechanisms that create a favorable circumstance for seizurelike behavior in neural networks. Multiple causes may have a similar effect on synaptic transmission, and we certainly do not exclude other paths that may lead to seizures. In our opinion, it would be premature to draw firm conclusions, but our findings provide circumstantial evidence to support our hypothesis.

V. Conclusion

We showed that spontaneously active neurons can drive network oscillations. This effect occurs at low excitatory synaptic strength, whereas strong excitatory synapses destroy such rhythmic activity in the neuronal population. These results indicate that dynamic changes in network coupling strength involving a decrease in excitatory drive may cause onset of seizurelike activity. This mechanism can be considered the first hypothesis of seizure onset that opposes the prevailing opinion that seizures are associated with strong excitatory or weak inhibitory synaptic coupling in the underlying neural network.

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References

[1] F. Lopez da Silva, "Neural mechanisms underlying brainwaves: from neural membranes to networks," *Electroencephalogr. Clin. Neurophysiol.* vol. 79, pp. 81–93, 1991.

[2] D. A. McCormick, and J. R. Huguenard, "A model of the electrophysiological properties of thalamocortical relay neurons," *J. Neurophysiol*. vol. 68, no 4, pp. 1384-1400, Oct 1992.

[3] R. D. Traub, J. G. R. Jefferys, R. Miles, M. A. Whittington, and K. Toth, "A branching dendritic model of a rodent CA3 pyramidal neurone," *J. Physiol.* (London) vol. 481, no. 1, pp. 79–95, 1994.

[4] X.-J. Wang, "Fast burst firing and short-term synaptic plasticity: a model of neocortical chattering neurons," *Neuroscience* vol. 89, no. 2, pp. 347-362, 1999.

[5] R. J. Butera, J. Rinzel, and J. C. Smith, "Models of respiratory rhythm generation in the pre-Botzinger complex: I. Bursting pacemaker neurons," *J. Neurophysiol.* Vol. 82, pp. 382–397, 1999.

[6] R. J. Butera, J. Rinzel, and J. C. Smith, "Models of respiratory rhythm generation in the pre-Botzinger complex: II. Populations of coupled pacemaker neurons," *J. Neurophysiol*. Vol. 82, pp. 398–415, 1999.

[7] A. Kepecs, X.-J. Wang, and J. Lisman, "Bursting neurons signal input slope," *J. Neurosci.* vol. 20, no. 22, pp. 9053–9062, Oct. 2002.

[8] W. van Drongelen, H. C. Lee, M. Hereld, D. Jones, M. Cohoon, F. Elsen, M. E. Papka, and R. L. Stevens, "Simulation of neocortical epileptiform activity using parallel computing," *Neurocomputing*, in press.

[9] M. Hereld, R.L. Stevens, W. van Drongelen, and H. C. Lee, "Developing a petascale neural simulation," presented at the 26th Annual International Conference IEEE Engineering in Medicine and Biology Society, San Francisco, 2004.

[10] R. Nieuwenhuys, "The neocortex: An overview of its evolutionary development, structural organization and synaptology," *Anat. Embryol*. vol. 190, pp. 307–337, 1994.

[11] V. B. Mountcastle, "The columnar organization of the neocortex," *Brain* vol .120, pp. 701–722, 1997.

[12] J. DeFelipe, L. Alonso-Nanclares, and J. I. Arellano, "Microstructure of the neocortex: Comparative aspects," *Journal of Neurocytology* vol. 31, pp. 299–316, 2002.

[13] L. S. Krimer, and P. S. Goldman-Rakic, "Prefrontal microcircuits: membrane properties and excitatory input of local, medium and wide arbor interneurons," *J. Neurosci*. vol. 21, pp. 3788–3796, 2001.

[14] C. R. French, P. Sah, K. J. Buckett, and P. W. Gage, "A voltage-dependent persistent sodium current in mammalian hippocampal neurons," *J. Gen. Physiol*. vol. 95, pp. 1139–1157, 1990.

[15] P. L. Nunez, *Electric fields of the brain: the neurophysics of EEG*. Oxford: Oxford University Press, 1981.

[16] J. M. Bower, and D. Beeman, *The Book of Genesis*. New York: Springer, 1998.

[17] R. Pumain, C. Menini, U. Heinemann, J. Louvel, and C. Silva-Barrat, "Chemical synaptic transmission is not necessary for epileptic seizures to persist in the baboon *Papio papio*," Exp. Neurol. Vol. 89, pp. 250–258, 1985.

[18] H. Su, G. Alroy, E. D. Kirson, and Y. Yaari, "Extracellular calcium modulates persistent sodium current-dependent burst-firing in hippocampal pyramidal neurons," *J. Neurosci.* vol. 21, no. 12, pp. 4173–4182, June 2001.

[19] H. Koch, W. van Drongelen, C. J. Marcuccilli, and J.-M. Ramirez, "Are slow oscillations in somatosensory cortex of mice *in vitro* dependent on the persistent sodium current," in Abstract Viewer/Itinerary Planner, Society for Neuroscience, Washington, D.C., No. 411.18, 2003.