Oscillation in a Network Model of Neocortex

Wim van Drongelen[1,2], Hyong Lee[1], Amber Martell[1], Jennifer Dwyer[1],
Rick Stevens[2,3], and Mark Hereld[2,3]

1- The University of Chicago, Department of Pediatrics, 5841 South Maryland Avenue, Chicago, IL, 60637, USA

2- The University of Chicago, Computation Institute, 5640 South Ellis Avenue, Chicago, IL, 60637, USA

3- Argonne National Laboratory, Mathematics and Computer Science Division, 9700 Cass Avenue, Argonne, IL, 60439, USA

Abstract. A basic understanding of the relationship between activity of individual neurons and macroscopic electrical activity of local field potentials or electroencephalogram (EEG) may provide guidance for experimental design in neuroscience, improve development of therapeutic approaches in neurology, and offer opportunities for computer aided design of brain-computer interfaces. We study the relationship between resonant properties of neurons and network oscillations in a computational model of neocortex. Our findings suggest that resonance is associated with subthreshold oscillation of neurons. This subthreshold behavior affects spike timing and plays a significant role in the generation of the network's extracellular currents reflected in the EEG.

1   Introduction

Brain activity can be studied at multiple levels, ranging from synapses, single neurons to networks of millions of nerve cells. Gaining understanding of the complex, opaque relationships between activities across the microscopic and macroscopic levels is a major goal in neuroscience, because it would be a tremendous help to unravel the underpinning of both normal and pathological function. For example one would be able to describe how individual neural components interact to generate the γ-rhythm of the electroencephalogram (EEG), how neurons go awry during an epileptic seizure, or how they generate a steering signal for a muscle group.

Current experimental techniques cannot capture compound signals of large networks and all their individual neural components simultaneously. Electrophysiology lacks the spatial resolution for measuring many individual cells in a network while imaging techniques lack temporal resolution. Data collected from computational models of neural networks are not thus limited, and therefore provide a tool to study both individual and aggregate neuronal activity at the same time (e.g. [1], [2], [3], [4], [5]).

Traditional network models usually contain neurons with integrate-and-fire properties. Recently it was recognized that neurons can also have inductor-like resonant characteristics (reviewed in [6]). Depending on the voltage-dependence of stabilizing ion channels, this can be simulated with models that include biophysically realistic channels (e.g. [7]). Since it is assumed that brain rhythms play a critical role in neural processing (e.g. [8]), it is important to establish how such resonant properties affect network dynamics.

The purpose of this study is to model and examine the relationship between cellular

and network oscillations. We examine cortical network activity in a previously developed neuronal model with biophysically realistic ion channels following the Hodgkin and Huxley formalism ([2], [3], [9], 10]). We determine resonant properties of single neocortical cells and study how these properties relate to onset and offset of network oscillations.
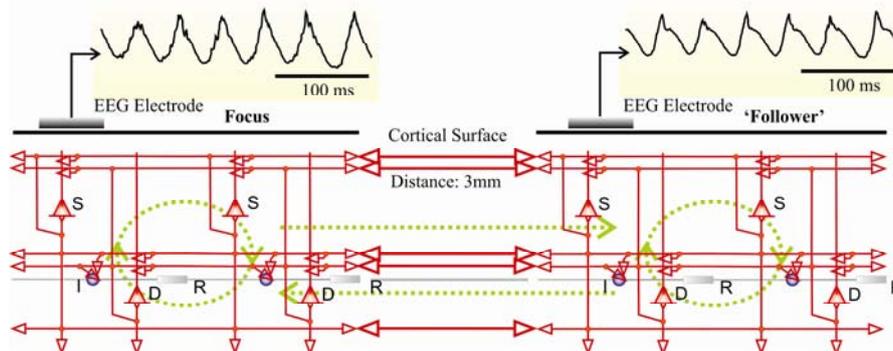

Fig. 1: Diagram of the neocortical model and the associated EEG electrodes. Both the Focus and the 'Follower' include superficial pyramidal neurons (S), deep pyramidal cells (D) and inhibitors (I). The pyramidal cells are the excitatory component with short range and long range connections (in steps of ~1mm), the inhibitors inhibit the pyramidal cells and each other and have only short range connections (not shown in the diagram). Each type of inhibitory neuron has interconnections via gap junctions, indicated by the resistor symbol (R). During oscillatory activity, symbolized with the stippled arrows, there is activity propagating between the superficial and deep layers and between the Focus and 'Follower'. These oscillations are reflected in the compound signals recorded from the EEG electrodes.

2   Methods

Modeling. Details of the model are described in van Drongelen et al. ([1], [2], [3]). Briefly, the network (Fig. 1) consists of superficial pyramidal cells from cortical layers 2/3 (S) and deep pyramidal cells from layers 5/6 (D). The inhibitory cells (I) receive input from both types of pyramidal neurons. Gap junctions (R) between inhibitory cells show nearest neighbor connectivity. Network inhibition is provided by three types of basket cells and the chandelier cell. The basket cell types inhibit the pyramidal cell soma, whereas the chandelier cell directly inhibits the initial segment. To study propagation of oscillatory activity we simulated two neuronal patches (described in [3], [10]) separated by 3 mm (depicted as Focus and 'Follower' in Fig. 1). The extracellular activity was obtained as a weighted sum of soma currents generated by the model neurons. The model neurons included fast sodium and delayed rectifier potassium currents; a fraction of the pyramidal cells included persistent sodium channels [2]. The computational model is implemented in the parallel GENESIS simulator [11].

The response of the model neurons and network to the frequency of external stimulation was evaluated by injecting sinusoidal currents. A 1 nA current (1-100 Hz)

applied to the soma of a single model cell elicited a response just below its spiking threshold. Network stimulation during bursting activity was modeled by injecting a 30 pA sinusoidal current into 25% of the superficial pyramidal cells in their distal dendrite compartments. We varied the frequency of this current between 1-300 Hz.

Experimental Procedures. Coronal slices (500 µm) were prepared from CD-1 mice ages P8-12 and transferred into artificial cerebral spinal fluid (ACSF) consisting of (in mM): 118 NaCl, 25 $NaHCO_2$, 30 glucose, 3 KCl, 1 NaH_2PO_4, 1 $CaCl_2$, 1 $MgCl_2$ (pH 7.4). Patch pipettes and electrodes for extracellular recordings were manufactured from glass capillaries and filled with intracellular solution containing (in mM): 140 D-gluconic acid, 10 EGTA, 10 HEPES, 2 $MgCl_2$, 1 $CaCl_2$, 4 Na_2ATP (pH 7.2). Layer 5 pyramidal neurons in the frontal cortex were patched via the blind-patching technique. The resonant properties of each neuron were measured by recording the cellular voltage response to intracellularly-injected sinusoidal current stimuli which ramped linearly in frequency from 0-15 Hz over 30 seconds (ZAP input). Extracellular recordings were performed in layer 5/6 frontal cortex using pipettes filled with bath ACSF solution. Network resonance was evaluated by delivering the ZAP current through a second stimulation electrode placed in layer 5/6. The measurement was repeated after blocking action potential generation (and synaptic transmission) via bath application of 1 μM Tetrodotoxin (TTX).

3 Results

Depending on the overall levels of synaptic excitation and inhibition, the model generated EEG with desynchronized activity, network bursts, or oscillations around 28 Hz [1]. As depicted by the (stippled) arrows in Fig. 1, the oscillatory network activity is associated with oscillations between the superficial and deep pyramidal cells, and between the Focal area and the 'Follower'. These cellular activity patterns generate extracellular currents detected by the EEG electrodes at the cortical surface. Details of this process are described in van Drongelen et al 2007.

Role of Neuronal Resonant Properties in Network Oscillation. A sample of the EEG generated by the focal neocortical patch is shown in Fig. 2A and the corresponding amplitude spectrum in Fig. 2B. Interestingly these oscillations are also observed in the membrane potentials of individual neurons in the focal patch (Fig. 2C, D). Although different cells show very different superthreshold (spiking) behavior during the network oscillation, their subthreshold oscillations are remarkably similar and synchronized (Fig. 2C). Frequency analysis of each neuron's activity shows a strong component around 28 Hz, the same frequency as the EEG oscillation. When isolated model neurons are stimulated with sinusoidal signals of varying frequencies, their response displays a resonant peak around 30 Hz (Fig. 2E, F): not identical, but very close, to the dominant frequency of the network oscillations.

We tested for the presence of resonance in mouse *in vitro* neocortical networks by injecting a so-called ZAP current in individual cells and also extracellularly to
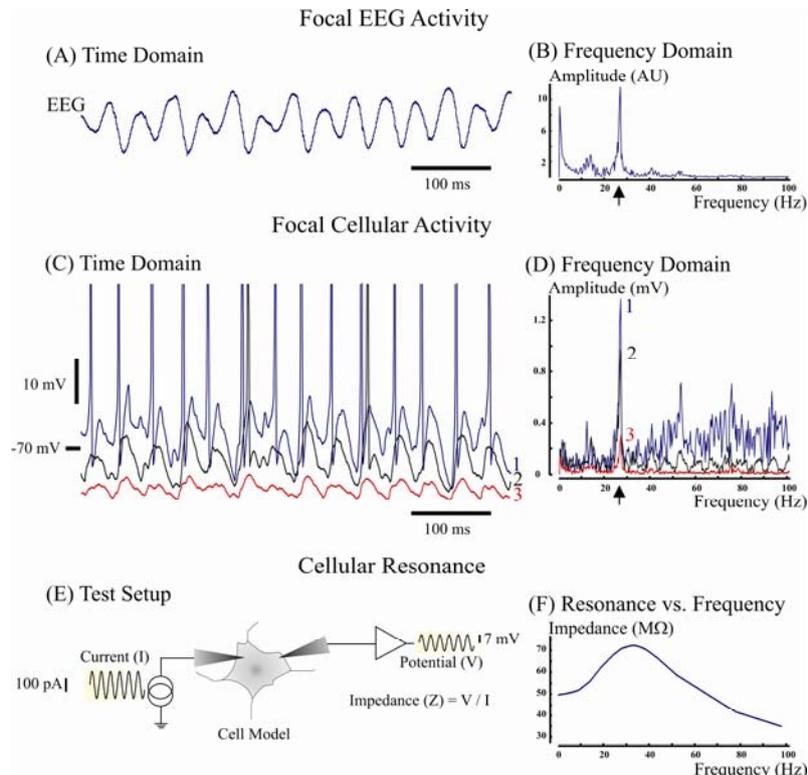
Fig. 2: Resonance and oscillatory activity across different levels in the model. Panels (A) and (B) show the time and frequency domain representations of the compound activity from the EEG electrode. The dominant oscillation of ~28 Hz is indicated by the arrow in panel (B). Panels (C) and (D) show oscillations in individual superficial pyramidal cells during the same EEG epoch (spikes in (C) are truncated). These cells have different levels of activity varying from non-spiking (cell 3), occasional firing (cell 2), to continuous spiking (cell 1). Interestingly the subthreshold signal component shows somewhat synchronized oscillations in all neurons and the associated amplitude spectrum (D) shows that these oscillatory components are located at ~28 Hz (arrow), the same frequency as the EEG in panel (B). Single cell resonance can be recorded by injecting currents at a range of frequencies and recording the response in the membrane potential (E). The neuronal resonance can be expressed as the ratio of membrane potential amplitude and injected current amplitude, i.e. the impedance (F). The peak of the cellular resonance is in the same area as the subthreshold oscillations of the neurons and the network oscillations.

stimulate the network (Fig. 3). Although an order of magnitude below the resonant peak in our model (~2 Hz versus ~30 Hz in the model), we did observe similar principles at work: the network resonates in the same range as the individual nodes. We showed that communication between the cells in the network is critically important for this observation, because addition of TTX abolished the network activity (Fig. 3B, bottom trace).
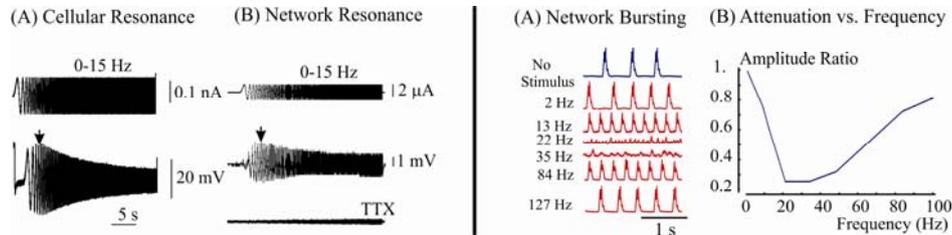
Fig. 3: **(Left)** Cellular (A) and network resonance (B) in mouse neocortical tissue *in vitro*. The resonance properties of real neural structures were examined by injection of a ZAP current (a signal for which the frequency increases from 0 – 15 Hz over time, top traces in panels (A) and (B)). Both in the cell and network we see resonance occurring at 1.6 Hz and 1.9 Hz respectively (arrows, panel (A) and (B)). To show the biological origin of the network response, we show that the response disappears after adding tetrodotoxin (TTX) to the bath (bottom trace in panel (B)).

Fig. 4: **(Right)** Effect of electrical stimulation in a bursting model network. The top trace in panel (A) shows the EEG of a bursting network. When stimulating the network with sinusoidal currents at different frequencies, both the amplitude and frequency of the network bursting is affected (panel (A), six bottom traces with stimulus frequencies ranging from 2-127 Hz). The ratio between the amplitude of the network bursts with and without electrical stimulation is plotted versus the stimulus frequency in panel (B).

Offset of Network Bursting. In a second set of simulations we evaluated how effectively one might stop network bursting patterns with electrical stimulation. The upper trace in Fig. 4A depicts the EEG of a bursting network and the six bottom traces show examples of how the EEG is altered by electrical stimulation with a sinusoidal current of different frequencies (ranging between 2 and 127 Hz). The graph in Fig. 4B shows how well different frequencies attenuate the network bursts. The stimulus is most effective ~30 Hz, in the range of the cellular resonance (~30 Hz).

4   Discussion

Although one would expect that the superthreshold behavior of neurons is most important for the network's activity and the generated local field potentials and EEG, we show that subthreshold resonant behavior may determine spike timing and that synchronized subthreshold oscillation significantly contribute to the compound electrical activity generated by the population of neurons in the network. Although it would be difficult to unravel cause and effect, it is possible to relate the different functional neuronal properties to the end result: the network oscillation. The population of cells in the network creates sufficient activity to sustain oscillations in the neuron's membrane potential and the likelihood of sustained oscillations is highest near the peak of the single-cell resonance curve. These subthreshold oscillations affect the probability of action potential generation, thereby influencing overall spike

timing in the network. At reasonable levels of spiking activity, the subthreshold oscillations in individual neurons become synchronized, and together generate an oscillating extracellular current observable in the EEG signal. From the perspective of the network function, the oscillatory activity propagates back and forth between the superficial and deep layers and between focus and follower (van Drongelen et al, 2007).

The ultimate goal of our computational modeling effort is to create a virtual nervous system. In such a virtual environment one can study spontaneous and perturbed activity patterns, thereby generating insight into neural function across scales. This insight helps to understand brain function and malfunction, but can also be used for computer aided design (CAD) of brain-computer interfaces (BCI). This approach may help to decide what signals are most effective as steering input to an interface (e.g. for a robotic arm), or it may provide a strategy for developing algorithms to decompose compound signals into more effective individual steering components.

Acknowledgements

References

[1] Van Drongelen W, Lee HC, Koch H, Hereld M, H, Elsen F, Chen Z, Stevens RL (2005) – Emergent epileptiform activity in neural networks with weak excitatory synapses. *IEEE Trans. Neur. Sys. & Rehab*. 13: 236-241.

[2] Van Drongelen W, Koch H, Elsen FP, Lee HC, Mrejeru A, Doren E, Marcuccilli CJ, Hereld M, Stevens RL, Ramirez JM. (2006) - The role of persistent sodium current in bursting activity of mouse neocortical networks in vitro. *J. Neurophysiol*. 96:2564-77.

[3] Van Drongelen W, Lee HC, Stevens RL and Hereld M (2007) – Propagation of seizure-like activity in a model of neocortex. *J. Clin. Neurophysiol*. 24:182-188.

[4] Lytton WW (2008) - Computer modelling of epilepsy. *Nat Rev Neurosci*. 9:626-637.

[5] Traub RD, Contreras D, Cunningham MO, Murray H, LeBeau FE, Roopun A, Bibbig A, Wilent WB, Higley MJ, and Whittington MA (2005) - Single-column thalamocortical network model exhibiting gamma oscillations, sleep spindles, and epileptogenic bursts. *J Neurophysiol* 93:2194-2232.

[6] Hutcheon B, Yarom Y (2000) - Resonance, oscillation and the intrinsic frequency preferences of neurons.*Trends Neurosci*. 23:216-22.

[7] Izhikevich EM (2006) - *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*, MIT Press, Cambridge, MA.

[8] Buzsáki, G (2006) – *Rhythms of the brain*, Oxford University Press, New York, NY.

[9] Hodgkin AL and Huxley AF (1952) - A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 117: 500-544.

[10] Lee HC, Hereld M, Stevens R, Van Drongelen W (2005) – Epileptiform activity patterns in coupled neural networks. 5th International Conference BEM&NFSI, Minneapolis, MN.

[11] Bower JM and Beeman D (1998) - *The Book of Genesis*. Springer Verlag, New York, NY.