Methods for Simulating High-Conductance States in Neural Microcircuits

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***Abstract*— A network simulation paradigm was developed to be consistent with observations of the high-conductance state of layer IV cortical neurons in an awake brain *in-vivo*. Two classes of integrate-and-fire based neurons, pyramidal (with adaptation) and inhibitory, were modeled. Synapses were conductance based. The high-conductance state was induced by synaptic bombardment with 1000 excitatory and 250 inhibitory Poisson process with firing rates (e,i) respectively. The rates (e,i) were chosen so that the respective neuron models, (pyramidal, inhibitory), reproduce these rates under this bombardment. Network synapses were then enabled, replacing a fraction of the Poisson process input. A 9x9x9 lattice of neurons with a cortical layer IV inspired network topology was simulated at 1/200th real-time. Coherent network bursting emerged at 5-7 Hz. The dependence of the burst period on the time constant of adaptation was demonstrated to be linear with a slope consistent with unity. The simulation uses event based communication and a scalable Linux cluster implementation is foreseen.**

I. Introduction

The field of neuroscience is in a state similar to that of the field of thermodynamics at the beginning of the 20th century prior to the introduction of the theory of statistical mechanics by L. Boltzmann. By connecting the properties and behavior of atoms and molecules with the large scale properties and behavior of the substances for which they are building blocks, Boltzmann brought clarity and new fundamental understanding to the field of physics and laid the foundation for much of present-day research.

In neuroscience, such a unification of the bottom-up and top-down approaches has yet to be achieved. Much is known about the anatomy and dynamics of single neurons, the building blocks of the central nervous system (CNS) [1]–[5]. Additionally, much is known about the holistic and dynamical properties of the developing and functioning brain [6]–[8]. However, unlike ensembles of indistinguishable atoms, the extent to which the unique contribution of each distinct neuron is important for network function remains a mystery. Networks of neurons are in detail analytically intractable and ensemble methods apply only in the simplest of cases and, in the end, seem to miss the point. Numerical investigations provide an ever more viable tool with continuing advancement in microprocessor speed and parallelization techniques. Still, simulations on the scale of a complete brain remain science fiction.

In what follows, a network simulation paradigm will be presented which, while working under computational limitations, still provides insight into emergence of global properties from local dynamical rules in a patch of a cortex-like neural network in an active awake state. Simulations on this modest scale will bring clarity to the dominant assumptions regarding the behavior of individual neurons in a network setting. Additionally, they could reveal semi-local principles for the function of small networks which are repeated throughout the brain [9], [10]. In the future, as network modeling matures, coupled simulations in a Linux cluster environment will allow a glimpse of the difficulties of larger scale experiments. This will provide critical information needed for the less configurable analog VLSI implementations which are likely the future of large scale network modeling [11].

II. Neuron Model

Two classes of integrate-and-fire (I&F) neurons, pyramidal and inhibitory, with conductance-based synapses, were modeled. The neuron parameters were determined by fitting to NEURON based Hodgkin-Huxley models under various conditions [12]. An additional phenomenological mechanism for spike-rate adaptation (SRA) was required, in the case of the pyramidal neuron class, to achieve satisfactory generality across all fit situations investigated. It consists of a action potential (AP) activated and exponentially decaying conductance,

$$g_{sra}(t_{AP} + dt) = g_{sra}(t_{AP}) + q_{sra},$$

$$\frac{dg_{sra}(t)}{dt} = \frac{-1}{\tau_{sra}} g_{sra}(t),$$

coupled to the neuron resting potential so that the standard membrane equation takes the form:

$$c_m \frac{dv(t)}{dt} = g_l(E_l - v(t)) + g_{sra}(t)(E_{sra} - v(t)) + \sum_j g_s^j(t)(E_s^j - v(t)),$$

where q_{sra} is the SRA quantal conductance increase, τ_{sra} is the time constant of adaptation and the sum j is over all input synapses. Recently, the use of a similar adaptation mechanism was reported in [13].

All simulations to follow were custom written in C++ and analyzed off-line in MATLAB (The MathWorks, Inc., Natick, MA). Single neuron experiments were compared to their equivalents in NEURON for quality assurance [14]. The exponential Euler method with a time step of $0.1\mathrm{ms}$ was used for all temporal integration [15].

III. Model-Consistent Background Rates

Cortical neurons under awake conditions *in-vivo* are found to be characterized by low input resistance, depolarization, continuous membrane potential fluctuations and spontaneous firing, all features due mostly to opposing excitatory and inhibitory spontaneous synaptic activity [6]. This mode of operation is known as the *high-conductance state* of cortical neurons.

There are many approaches to induce a high-conductance state in simulation. Synaptic bombardment with Poisson process events was the method chosen here. Synaptic activity is generated by 1000 excitatory and 250 inhibitory Poisson processes with Poisson release rates of e and i respectively. For rates, (e,i), above a few Hz, the synaptically activated contribution to the membrane conductance becomes appreciable and the transition to the high-conductance state occurs.

The synaptic events used to establish the high-conductance state for a single neuron could just as well come from another neuron in a high-conductance state so long as the neuron firing rates are equal to the synaptic bombardment (background) rates. The model-consistent background (MCB) rates are defined here as those background rates (e,i) under which the pyramidal and inhibitory models together fire again at the rates (e,i) respectively. The MCB rates can be determined by finding the (e,i) for which the functions

$$f(e,i) = f_{PY}(e,i) - e,$$
$$g(e,i) = f_{IN}(e,i) - i,$$

have simultaneous zeros, where $f_{PY}(e,i)$ and $f_{IN}(e,i)$ are the firing rates of the respective neuron classes as a function of (e,i) shown in fig. 1. To determine the MCB rates, first find $i^*(e)$, the zero of $f(e,i)$, as a function of e. Then find e^{**}, the zero of $g(e, i = i^*(e))$.

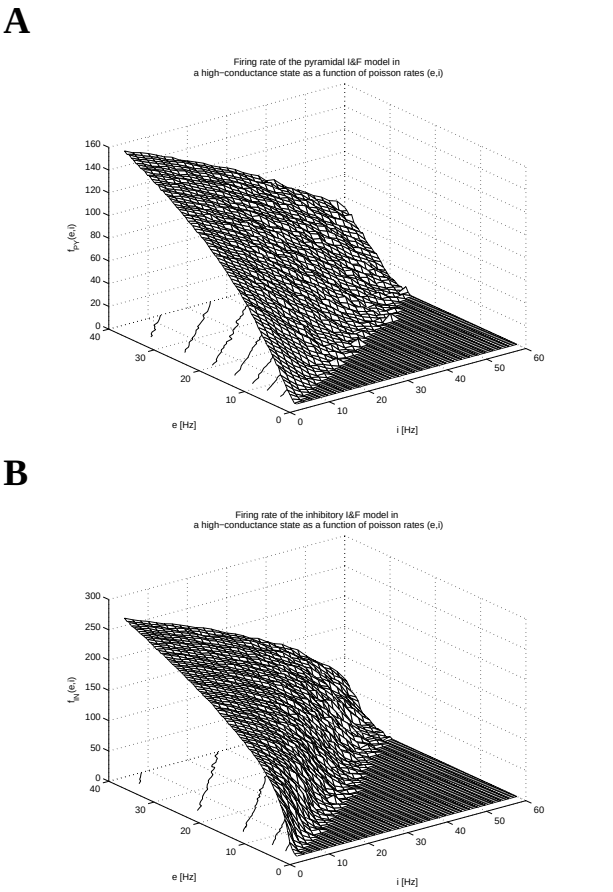

Fig. 1. **A**: Reciprocal mean ISI as a function of synaptic bombardment background rates for the pyramidal I&F neuron model. **B**: As in A, but for the inhibitory I&F neuron model.

Then $(e^{**}, i^*(e^{**}))$ are the MCB rates. A graphical representation of the procedure is shown in fig. 2.

IV. Network Simulation

A network of 729 neurons arranged on a 9x9x9 lattice with approximately 80% pyramidal and 20% inhibitory neurons was simulated. The number of output synapses per neuron is parameterized by the connection factor, r_{con} which, based on biological measurements [8], is between 20%-40%. Connections are random without spatial preference over the lattice, as the volume of cortical tissue the network represents, $(200\mu\mathrm{m})^3$, is smaller than the axonal extent of typical cortical cells. Synaptic strengths are uniform. Transmission delays are the Euclidean distance times the delay factor, f_{delay} ($\approx 0.5\mathrm{ms}$ per unit distance) [16]. A schematic of the network is show in fig. 3. A simulation run consists of two phases:

Initiation phase: synapses between network neurons are disabled and each neuron is synaptically bombarded for $100\mathrm{ms}$ by 1000 excitatory and 250 inhibitory Pois-

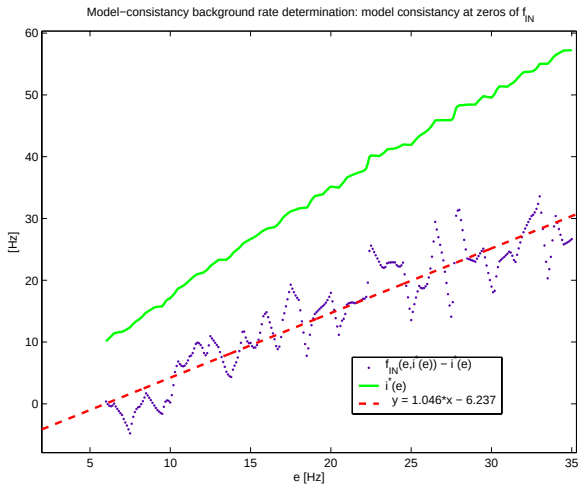

Fig. 2. Determining the model-consistent background rates by zeros of $g(e, i = i^*(e))$ by linear fit ($e = 6 \pm 1$Hz, $i = 10.1 \pm 1.5$Hz).

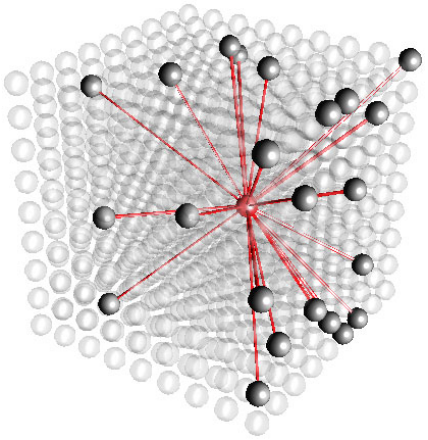

Fig. 3. A schematic of the synaptic connections made by a representative neuron (center,red) in the lattice.

son processes firing at the model-consistent background rates. This establishes the high-conductance state for each individual neuron.

Run phase: The neurons are now firing at exactly the same average rates as the background activity. At each neuron the network synaptic inputs are enabled and the number of background synaptic inputs is reduced by the number of enabled network inputs.

We now have a coupled network of neurons, each in a high-conductance state. Is the configuration stable? Do novel dynamics emerge?

V. Observations

Run times of 5 second lengths were simulated. A raster plot of the typical spiking activity of the network as a function of time is shown in fig. 4. Periodic coherent network bursting on the order of $5 - 7$Hz

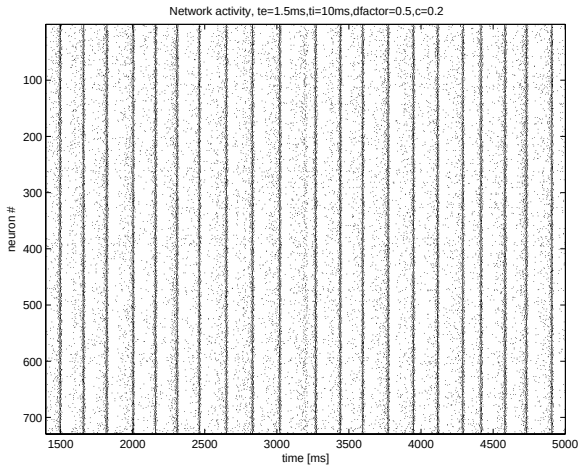

Fig. 4. A spiking activity raster plot for 5 seconds of simulation with $r_{con} = 0.2$ and $f_{delay} = 0.5$ms. Periodic coherent bursting of the network emerges with a period $\tau = 170 \pm 20$ms.

was observed. The dependence of bursting character on network parameters that leave the MCB rates unchanged was investigated, see [12]. Bursting was observed in all such cases. The bursting period was found to be linearly dependent on the time constant of adaptation with a slope of unity.

Fig. 5 shows the various conductances of a single neuron during a burst event. Characteristic is the rapid increase in excitatory synaptic conductance of network origin, followed by a rapid increase in inhibitory synaptic conductance. Adaptation current can be seen to accumulate over multiple AP events during the burst. Whether it is inhibition or adaptation which extinguishes the explosion of excitation during a burst remains unclear. However, bursting, periodic or otherwise, was decidedly less frequent for simulations where the adaptation mechanism was disabled. This suggests it is the periodic application and release of a resrictive force which brings about the cascades of excitatory activity, rather than an inherently present mechanism.

VI. Conclusions & Outlook

A neural network simulation was designed and implemented which focused on replicating the high-conductance states of the individual neurons as observed during awake measurements *in-vivo*, while conforming to computational restrictions. A modest network of 729 neurons with a cortical layer IV inspired connectivity was simulated. Periodic coherent network bursting emerged with a period of $5 - 7$Hz. Bursting was preserved under mild variation of network parameters and was shown to be dependant on the time constant of adaptation present in the pyramidal neuron model.

The interspike interval (ISI) statistics of single neurons in the coupled network exhibited an excess of

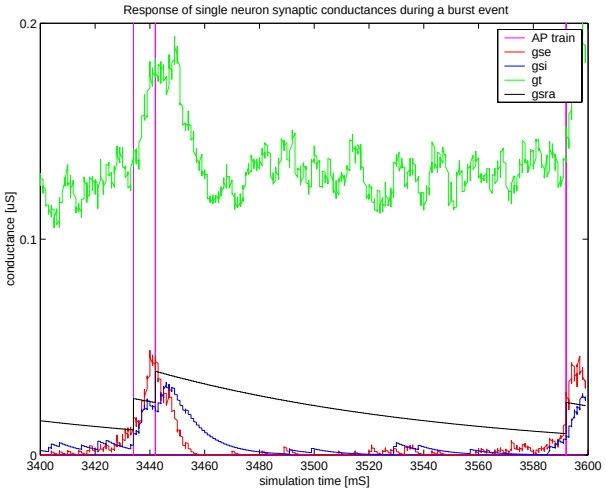

Fig. 5. Conductances of single neuron during a coherent network burst event. (red) gse - excitatory synaptic activity originating from network neurons, (blue) gsi - same as gse but inhibitory, (black) gsra - spike-rate-adaptation conductance, (green) gt - total conductance including background activity but not gsra, (magenta) AP train - vertical lines indicate those times an action potential was generated by the neuron.

short ISI events compared to uncoupled neurons due to coherent network bursting. This seems to contradict present *in-vivo* observations [17]. The emergence of bursting is thus to be taken as a bug rather than a feature. It suggests inadequacy of the underlying neuron model or network setup. Immediately suspect are uniform network weights and neuron parameters, and the absence of STDP rules and structured input. Moreover, this raises doubts that simulations at this limited scale have the potential for the complexity of dynamical behavior sufficient to reproduce, even in a vague sense, *in-vivo* firing patterns.

The possibility of running many interacting simulation nodes, such as those described here, in parallel in a Linux cluster environment is a topic currently under investigation. The highly parallelized computational paradigm of the CNS has aspects which make this pursuit attractive. First, with biological firing rates of $\approx$ 10Hz and each node simulating $\approx 10^3$ neurons at 1/200th real-time, roughly 50 events per second will be generated by each node. The network bandwidth requirements are therefore low. Second, inherent transmission delays between neurons on the order of milliseconds translate into seconds of simulation time during which processing nodes can operate independently. A discrete-event based implementation is therefore possible. Third, cortical areas separated by millimeters are largely uncoupled except through sparse connections through the white matter. The number of nodes to which a single node must send its events is therefore limited making the paradigm scalable. Such a pursuit to model the CNS on a large scale would require us to confront details regarding its configuration. What it would reveal concerning the design behind such a configuration is of unquestionable value.

By continuing with the methods described here, numerically mapping the perturbation of single neuron models to the emergence of global properties in simulations of ever increasing complexity and scale, we may hope to gain much insight into the void between the bottom-up and top-down approaches in the field of neuroscience. By unifying the macroscopic and microscopic worlds, Boltzmann made an undeniable contribution to the field of physics. The mechanisms of discovery at play then in the field of physics will play out once again in the field of neuroscience, but undoubtedly in a new and unique way. They will bring about clarity and understanding where it is presently absent. Certainly there will be a revolutionary idea, and a lack of universal acceptance, but some will listen, and a fundamentally different world will emerge where we are equipped with new conceptual tools to understand our own minds.

VII. Acknowledgments

Thanks to A. Destexhe for providing the Hodgkin-Huxley neuron models as NEURON scripts and for the encouraging discussion.

This work is supported in part by the European Union under the grant no. IST-2001-34712 (Sensemaker).

References

[1] P. D. and L.F. Abbott. *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*. The MIT Press, Cambridge, Massachusetts, 2001.

[2] W. Gerstner and W. Kistler. *Spiking Neuron Models: Single Neurons, Populations, Plasticity*. Cambridge University Press, 2002.

[3] H. Markram, Y. Wand, and M. Tsodyks. Differentieal signaling via the same axon of neocortical pyramidal neurons. *Proceedings of the national academy of science USA*, 95:5323–5328, April 1998.

[4] G. Bi and M. Poo. Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type. *Neural Computation*, 9:503–514, 1997.

[5] A. Destexhe. Conductance-based integrate and fire models. *Neural Computation*, 9:503–514, 1997.

[6] A. Destexhe, M. Rudolph, and D. Paré. The high-conductance state of neocortical neurons in vivo. *Nature Reviews Neuroscience*, 4:739–751, 2003.

[7] M. Sur and C. A. Leamey. Development and plasticity of cortical areas and networks. *Nature Reviews Neuroscience*, 2:251–262, 2001.

[8] V. Braitenberg and A. Schüz. Cortex: hohe ordnung oder größtmögliches durcheinander. *Spektrum der Wissenschaft*, 1989.

[9] W. Maass, T. Natschläger, and H. Markram. Real-time computing without stable states: A new framework for neural computation based on perturbations. *Neural Computation*, 14(11):2531–2560, 2002.

[10] V. B. Mountcastle. The columnar organization of the neocortex. *Brain*, 120:701–722, 1997.

[11] J. Schemmel, K. Meier, and E. Müller. A new VLSI model of neural microcircuits including spike time dependent plasticity. *submitted*, 2004.

[12] E. Mueller. Simulation of high-conductance states in cortical neural networks. In *MSc Thesis*. Kirchhoff-Institut for Physics, University of Heidelberg, Germany, 2003.

[13] G. Fuhrmann, H. Markram, and M. Tsodyks. Spike frequency adaptaion and neocortical rhythms. *Journal of Neurophysiology*, 88:761–770, 2002.

[14] M. L. Hines and N. T. Carnevale. The neuron simulation environment. *Neural Computation*, 9:1179–1209, 1997.

[15] A. D. Protopapas, M. Vanier, and J. M. Bower. Simulating large networks of neurons. In Christof Koch and Idan Segev, editors, *Methods in Neuronal Modeling: From Ions to Networks*, chapter 12. The MIT Press, Cambridge, Massachusetts, second edition, 2001.

[16] D. Schubert, R. Kötter, K. Zilles, H. J. Luhmann, and J. F. Staiger. Cell type-specfic circuits of cortical layer iv spiny neurons. *The Journal of Neuroscience*, 23:2961–2970, 2003.

[17] M. Rudolph and A. Destexhe. The discharge variability of neocortical neurons during high-conductance states. *Neuroscience*, 2003.