'Balancing' of Conductances May Explain Irregular Cortical Spiking

**Anthony J. Bell, Zachary F. Mainen,
Misha Tsodyks and Terrence J. Sejnowski**

February 23, 1995

Technical Report INC-9502

Institute for Neural Computation
University of California, San Diego
9500 Gilman Drive, DEPT 0523
La Jolla, CA 92093-0523

Anthony J. Bell, Zachary F. Mainen, and Misha Tsodyks are with The Salk Institute and Terrence J. Sejnowski is with The Salk Institute and the Institute for Neural Computation at the University of California, San Diego. Correspondence concerning this article may be addressed to: Anthony J. Bell, Computational Neurobiology Laboratory, The Salk Institute, 10010 North Torrey Pines Road, La Jolla, CA 92037 (email: tony@salk.edu).

'Balancing' of conductances may explain irregular cortical spiking.

Anthony J. Bell, Zachary F. Mainen,
Misha Tsodyks & Terrence J. Sejnowski

Computational Neurobiology Laboratory
The Salk Institute
10010 N. Torrey Pines Road
La Jolla, California 92037*

Abstract

Five related factors are identified which enable single compartment Hodgkin-Huxley model neurons to convert random synaptic input into irregular spike trains similar to those seen in *in vivo* cortical recordings. We suggest that cortical neurons may operate in a narrow parameter regime where synaptic and intrinsic conductances are balanced to reflect, through spike timing, detailed correlations in the inputs.

*Please send comments to tony@salk.edu. The reference for this paper is: Technical Report no. INC-9502, February 1995, Institute for Neural Computation, UCSD, San Diego, CA 92093-0523.

1 Introduction

Cortical cells *in vivo* normally fire irregularly, both in response to sensory stimuli (Softky and Koch 1993) and during so-called spontaneous firing (Burns and Webb 1976). Two questions immediately arise: what is the cause of such irregularity, and what role does it play in information processing? Assuming that synaptic input is the underlying source of neuronal variability (Calvin and Stevens 1968), one approach to answering the first question is to use models to search for parameter regimes where such input 'noise' (or, in fact, 'signal') is transduced into maximal variability in the output spike train. This was attempted by Softky and Koch (1993). They concluded that high output variability could only be obtained if the irregular inputs were strongly synchronised, or if there were strong dendritic non-linearities which could amplify weak correlations in the inputs. Implicit in their study was the assumption that the primary determinant of irregularity is high variance in the current delivered to the soma.

In this contribution, we look beyond the variance of the current. In the spirit of the work of Geisler & Goldberg (1966) on integrate-and-fire models, we identify it as one of five main factors contributing to irregularity. By calibrating all five, we show that it is possible to achieve, in model neurons, a coefficient of variation (CV; see Fig. 1) of greater than 1.0 using plausible biophysical parameters and completely unstructured input (independent Poisson processes). The five factors are: (1) the mean values of excitatory and inhibitory input, (2) the variance of these inputs, (3) the strength of repolarisation after a spike, (3) the (fluctuating) time constant of the the neuron, and (5) hysteretic effects due to intrinsic conductances. When these factors are correctly combined, we say the neuron is in a balanced or 'sensitive' state.

2 Balanced excitation and inhibition.

The effect of varying the rates of random excitatory and inhibitory input can be seen in Fig. 1. High values for the CV are only obtained in a narrow parameter regime where the mean excitatory and inhibitory inputs have a certain linear relation to each other (Fig. 1B). This creates a *high CV ridge.* By comparing the positioning of the ridge with the corresponding average

frequency of firing in Fig. 1A, it can be seen that the ridge occurs where the cell is hovering around the threshold for firing. It is in this region that fluctuations due to the stochastic nature of the inputs can make a difference to the timing of the output spikes. This contrasts with a neuron far from threshold which has to integrate many synaptic events to reach threshold, and therefore requires coherent (or amplified) input. This simulation shows the conditions under which it is possible to put 'noise in' and get 'noise out'. In order to achieve this, it was necessary to stop the cell from integrating for too long between spikes.[1]

3 Strength of repolarisation.

In the preceding simulation, $\overline{g}_K$ was substantially lower than $\overline{g}_{Na}$. This causes the voltage reset after a spike to be small: the cell is almost ready to spike again if stimulated further by correlated fluctuations. In contrast, when the reset is high, many synaptic events must be integrated to reach threshold again, leading (because of the central limit theorem) to greater regularity of spiking. This can be seen in Fig. 2, which shows spike trains from a strongly (Fig. 2A) and weakly (Fig. 2B) repolarising neuron. The greater irregularity of the weakly repolarising spike train is reflected in its inter-spike interval histogram, which contains a long, exponentially-decaying tail. ISI histograms of *in vivo* cortical recordings share this feature.

4 The time constant.

Strong after-hyperpolarisation does not reduce the irregularity of the neuron so markedly when the time constant of the system is very small. This is because at low time constants the voltage can change very abruptly, making refractory periods brief whether the voltage reset is strong or weak. As emphasised by the studies of Bernander et. al. (1991), the *overall* level of synaptic input is the major determinant of the time constant of the neuron.

[1] Our study is to be contrasted with that of Shadlen & Newsome 1994, who also explored the consequences of balancing excitation and inhibition. In their model, however, the 'balance-point' is not near the threshold for firing a spike, so the cell must integrate in order to fire. This leads to an interpretation of cortical neurons as rate-coding devices, rather than coincidence-detectors (Abeles 1982, Softky 1995).

With strong input, the neuron 'acts faster', enabling it to respond quickly to fluctuations instead of temporally integrating them. This is illustrated in Fig. 3. In Fig. 3A, strong input induces a much more irregular spike train than weak input, even though the mean and variance of the net synaptic currents are similar Fig. 3C. The corresponding net synaptic conductances (inversely proportional to the time constant) are shown in Fig. 3B, identifying the difference in the net conductance as the root of the irregularity.

5 Hysteretic effects due to membrane conductances.

Finally, the intrinsic membrane currents themselves can influence the irregularity of the spike trains. This has already been touched on when we considered the membrane reset given by a strong delayed rectifier. If we weaken this potassium current even more than in the Fig. 2B simulation, then the system can become bistable, alternating randomly between stretches of spiking and quiescent behaviour. This is because the repolarisation after a spike is so weak that the neuron will spike again unless it happens to receive strong inhibitory synaptic input. Any spiking system with two such phases will spike with a very high CV, so it is not unreasonable to suppose that some mild form of this bistability may contribute to the irregularity of *in vivo* cortical spike trains. Such bistabilities can arise with many membrane currents, not only the delayed rectifier. The bifurcation-theoretic landscape of such dynamical effects has been charted for the Hodgkin-Huxley equations by Guckenheimer & Labouriau (1993), amongst others. The bistability caused by varying $\overline{g}_{Kdr}$ is an instance of a degenerate Hopf bifurcation. It occurs when the f-I curves of the system become non-unique; in other words, when *hysteresis* (Fig. 4) sets in. The influence of bistability in an integrate-and-fire model has also been investigated by Wilbur & Rinzel (1983).

6 Conclusion.

The parameter regime that enables poisson synaptic inputs to be converted into irregular output spike trains is a narrow one. It suggests that excitation and inhibition are finely balanced when cortical networks are operating in

their natural state. It also suggests that repolarisation may be weak so that cells do not have to integrate much between spikes. If cortical cells and networks do self-calibrate to maintain themselves in this 'sensitive' state, then the implication is that detailed spike timings could carry information about synaptic inputs, but this remains to be explored.

References

[1] Abeles M. 1982. Role of the cortical neuron: integrator or coincidence detector? *Israel Journal of Medical Sciences*, 18, 83-92

[2] Bernander Ö., Douglas R.J., Martin K. & Koch C. 1991. Synaptic background activity determines spatio-temporal integration in single cortical pyramidal cells. *Proc. Natl. Acad. Sci. USA* 8, 1569-1573.

[3] Burns B. & Webb A.C. 1976. The spontaneous activity of neurons in the cat's cerebral cortex. *Proc. R. Soc. London B* 194, 211-223.

[4] Calvin W. & Stevens C. 1968. Synaptic noise and other sources of randomness in motoneuron interspike intervals. *J. Neurophysiol.* 31, 574-587.

[5] Destexhe A., Mainen, Z.F., & Sejnowski, T.J. 1994. Synthesis of models for excitable membranes, synaptic transmission, and neuromodulation using a common kinetic framework. *J. Comput. Neurosci.*, 1, 195-230

[6] Geisler C.D. & Goldberg J.M. 1966. A stochastic model of the repetitive activity of neurons. *Biophys. J.* 6, 53.

[7] Guckenheimer J. & Labouriau I.S. 1993. Bifurcation of the Hodgkin & Huxley equations: a new twist. *Bull. Math. Biol.* 55, 5, 937-952.

[8] Hines M. 1989. A program for simulation of nerve equations with branching geometries. *Int. J. Biomed. Comput.*, 24, 55-68.

[9] Shadlen M.N. & Newsome W.T. 1994. Noise, neural codes and cortical organisation, *Curr. Opin. Neurobiol.*, 4, 569.

[10] Softky W.R. 1995. Simple codes vs. efficient codes, *Current Opinion in Neurobiology*, in press, April 1995

[11] Softky W.R. & Koch C. 1993. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J. Neurosci.* 13, 1, 334-350.

[12] Wilbur W.J. & Rinzel J. 1983. A theoretical basis for large coefficient of variation and bimodality in neuronal interspike interval distributions. *J. Theor. Biol.*, 105, 345-368.

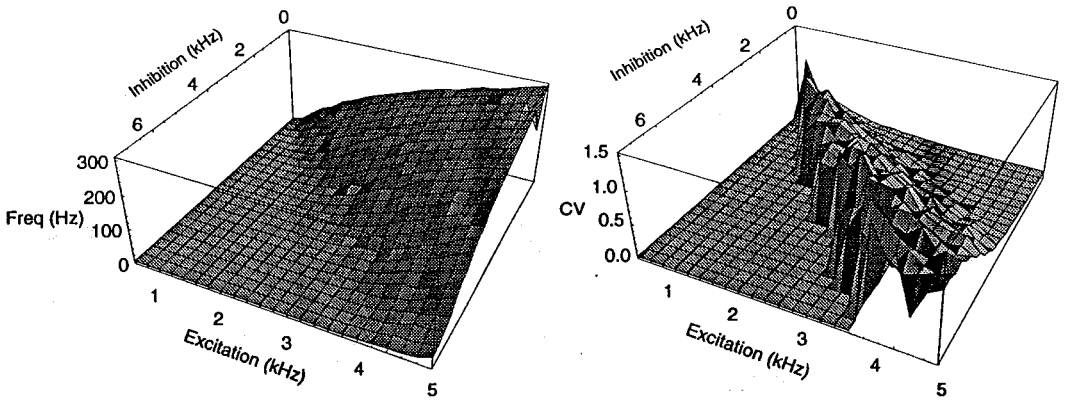

Figure 1: Hodgkin-Huxley simulations of a model neuron with one compartment. Surfaces showing (A) mean firing rate and (B) CV as functions of mean number of excitatory and inhibitory events per second. The prominent ridge in (B) shows the narrow parameter ranges in which inputs are 'balanced' to achieve high irregularity.

Simulation details: The CV is calculated as the standard deviation of the inter-spike interval (ISI) divided by its mean. Simulations were executed using NEURON (Hines 1989). Synaptic inputs were poisson distributed. Given an event frequency, ν, successive inter-spike interval times were generated according to the formula, $-(\log \mathcal{R})/\nu$, where $\mathcal{R}$ was a uniform random variable in the [0,1] interval. From these event trains, excitatory and inhibitory synaptic conductance waveforms were generated. The waveforms were modelled by a superposition of alpha functions of time constant τ. Na and K spiking conductances were modelled with 2 and 3-state kinetic models, respectively (Destexhe et. al. 1994). Parameters values used were (with $\overline{g}$ denoting maximum conductance and E denoting reversal potential): *excitatory input:* $\overline{g}$=1.5nS, E=0 mV, τ= 3 ms; *inhibitory input:* $\overline{g}$=1.5nS, E=85 mV, τ= 3 ms; *Na conductance:* $\overline{g}$=1200 pS/μm^2, E=50 mV; *K conductance:* $\overline{g}$=25 pS/μm^2, E=-85 mV; *Leak conductance:* $\overline{g}$=30 kΩ-cm^2, E=-75 mV. The capacitance of the modelled cell was 1μF/cm^2 with a membrane area of 10000 μm^2.

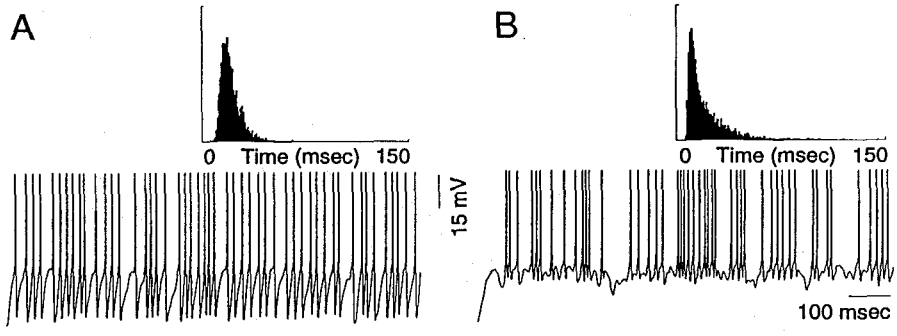

Figure 2: Spike trains from strongly and weakly repolarising models. In (A) the system was driven by excitatory input alone, but $\overline{g}_{Kdr}$ was high. In (B) the system received both excitation and inhibition and $\overline{g}_{Kdr}$ was low, causing minimal after-hyperpolarisation. Both systems spiked at similar frequencies, but the weakly repolarising system spiked much more irregularly: a CV of 0.71 in (B), compared to 0.35 in (A). Above: inter-spike interval histograms for the spike trains.

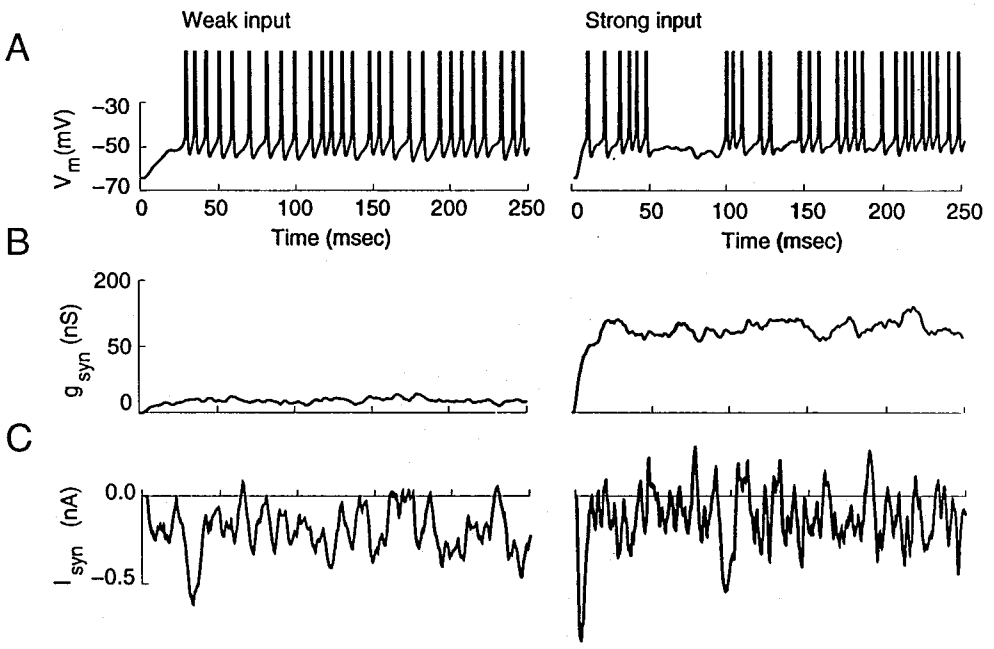

Figure 3: (A) Inhibitory and excitatory psps were balanced at either low levels (ν_e=1.0 kHz, ν_i=0.5 kHz, left panel) or high levels (ν_e=5.7 kHz, ν_i=4.5 kHz, right panel) to give approximately the same output frequencies (weak, F=118 Hz; strong, F=110 Hz). Stronger input results in much higher CV at similar frequency (weak, CV=0.22; strong, CV=1.06) (B) Total synaptic conductance is much higher for strong input. (C) Net synaptic current shows similar mean and variance of net current but significantly faster current fluctuations during strong input. (The sodium and potassium conductances were set to zero in B and C in order to eliminate currents from spiking which would disturb g_{syn} and I_{syn}).

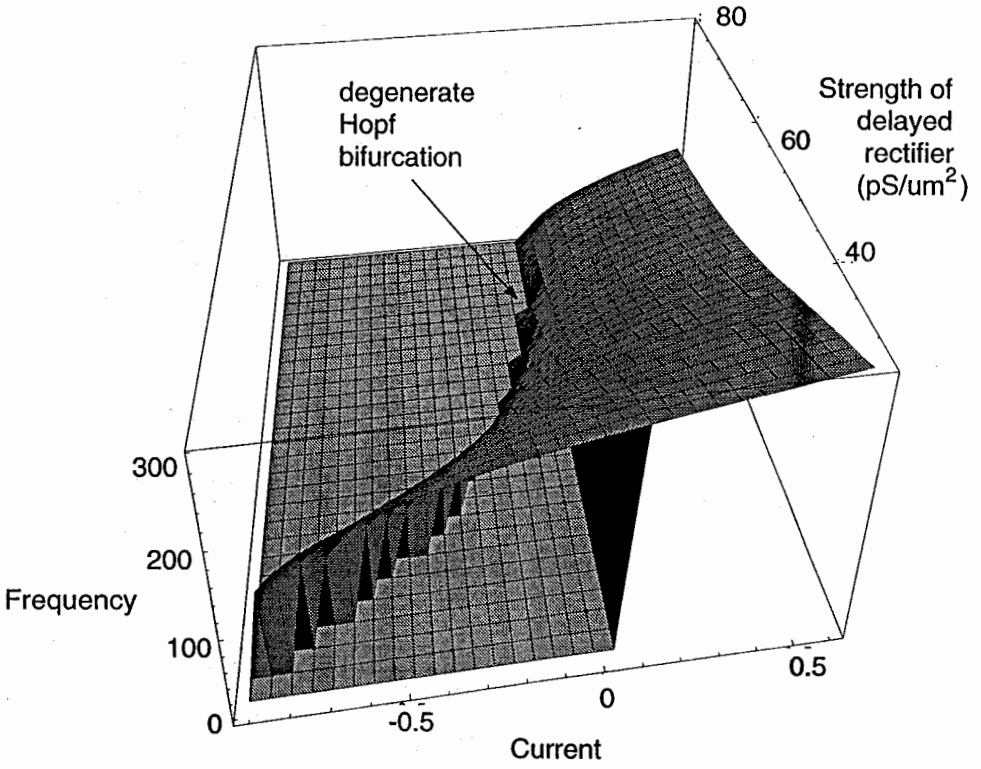

Figure 4: The onset of bistability as a function of $\overline{g}_{Kdr}$. The surface displays a set of f-I (frequency-current) curves which become non-unique functions of the input current when the Hopf bifurcation causing the spiking becomes sub-critical.