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'Balancing' of conductances may explain irregularity of cortical spiking.

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Abstract

How may synaptic and voltage-dependent conductances be adjusted in models to achieve spiking as noisy as that seen in cortical neurons? We identify five factors contributing to inter-spike-interval (ISI) irregularity: the mean and variance of the input current, the instananeous membrane resistance, the degree of repolarisation after spiking and bistabilities in the membrane dynamics. Crucially, by balancing excitation and inhibition so the cell is typically around threshold, we are able to achieve ISI coefficients of variation of around 1 in single compartment models. Our simulations suggest that the currents entering a neuron are 'balanced' to achieve maximum sensitivity to inputs.[1]

Factors causing irregular firing.

In a modeling study, Softky and Koch [5] attempted to account for the high irregularity of firing of cortical neurons. They subjected a biophysically realistic compartmental model neuron to random synaptic input. With reasonable parameters, the model was unable to reproduce the high irregularity found in cortical cells. Instead, temporal integration over many synaptic inputs caused regular spiking in the model neurons.

They concluded that irregular spiking could only come about if the synaptic inputs were strongly synchronised on a millisecond scale, or if there were fast and strong dendritic nonlinearities which could amplify weak correlations in the inputs and counter the effects of an integrative membrane.

In this contribution, we identify five factors which contribute to irregular firing in biophysically realistic model neurons. Only one of these (the variance in input currents) has been considered in detail in the model of Softky & Koch. Using all five together, we show that it is possible to achieve, in model neurons, a coefficient of variation (CV) of up to and greater than 1.0 using plausible biophysical parameters, and completely unstructured input (independent Poisson processes).

1. Mean input current.

Figure 1 shows the striking effect of adjusting excitatory and inhibitory poissonian synaptic conductances by small amounts so that the cell's potential, on average, hovers around the

threshold for firing. In 1(b), the ridge in the 'CV-surface' (a function of the maximum strength of the conductances 'glu' and 'gaba') is seen to be exactly aligned along the area of greatest slope in the corresponding 'frequency-surface', 1(a). This is the area where the mean input current holds the neuron around threshold: a regime we call the 'balance point'. In this regime, spurious correlations between the random synaptic inputs can cause a spike. This contrasts with a neuron far from threshold which has to integrate many EPSPs to reach threshold, and therefore requires coherent (or amplified) input.

2. Variance in input current.

The input current's variance around this mean is the primary source of irregularity. Softky & Koch used voltage-dependent conductances to amplify this variance, but if the neuron is not at the balance point, such variations in the input current will be less effective in producing variation in the output inter-spike intervals.

3. Instantaneous membrane resistance.

When changing synaptic conductance levels and input rates, it is important remember that increasing the overall synaptic activity reduces the instantaneous membrane resistance and time constant (Bernander et al 1991). At a certain point this has the paradoxical effect of reducing the variance in the input current even though more input is being received. For highest irregularity, therefore, there is an optimal level of overall synaptic input.

4. Weak repolarisation.

In vivo recordings from cortical pyramidal cells differ from *in vitro* ones in that they lack a strong after-hyperpolarisation [3], attributable to the global action of acetylcholine in blocking potassium currents, particularly I_{AHP} and I_M [4]. Weakening the repolarisation that occurs after a spike reduces the amount of integration required between spikes, since the neuron is not 'reset' to a lower potential. This raises the irregularity of firing, since the neuron spends more time at the balance point. We have simulated this effect by reducing the strength of the potassium delayed rectifier current in our models, and observing a corresponding increase in the irregularity of firing. Figure shows one such spike train.

5. Hysteretic effects.

Further reduction of the potassium conductance leads to hysteretic effects. Such effects occur when the net current delivered to the cell during the course of a spike becomes great enough that there is an increase in the probability of an another spike immediately following. In this parameter regime, spiking is an *attracting state*, and the neuron requires correlated inhibition to turn it off. If, in the non-spiking state, the neuron also requires correlated excitation to turn spiking on, then the system is bistable. It has a non-unique threshold, describable by an f-I curve with a 'hysteretic' S-bend. Figure shows an example of severely bistable firing, a phenomenon we call 'stochastic bursting'. This behaviour can occur when there is a subcritical Hopf bifurcation in the membrane equations. With such dynamics, it is possible to achieve very high CVs (over 3 or 4) from stationary uncorrelated input. This may be regarded as 'cheating', but it does raise the possibility that some of the irregularity in real cells is due to weak membrane bistability amplifying spurious correlations. This idea is not new: Wilbur &

Rinzel [6] proposed a variable-threshold integrate-and-fire model to explain irregularity. Here we propose a biophysical basis for this variable threshold idea.

Balancing conductances.

We have studied single compartment models in order to simplify our search for the right parameter regimes. We have systematically varied four parameters: the strength of excitatory and inhibitory synapses, and the strengths of the sodium and potassium conductances involved in spiking. The synaptic conductances control factors 1-3 in our list, and the spiking conductances, factors 4 and 5. With the spiking conductances adjusted so that repolarisation was weak and, for very low input variance, bistable, we were able to record the CV-surface in Figure , showing high variation when synaptic conducatnces were balanced. A typical voltage trace in this regime is shown in Figure .

The notion of 'balancing' conductances will have to be defined more rigorously if we are to apply these notions to multi-compartment neurons with a full spectrum of voltage-dependent currents. It does seem, however, that if the 'goal' of the neuron is to produce a highly informative spike-train (the Poisson process being the most informative in terms of information theory), then it has many mechanisms to fine-tune, both in the soma and the dendrites, in order to achieve this. This begs the question of whether or not there is a self-organisational mechanism (see for example [1]) which performs activity-dependent fine-tuning of these parameters in order to satify some maximum-sensitivity criterion.

Finally, our simulations support the hypothesis that cortical neurons *in vivo* may operate around a *balance* potential, in contrast with the impression gained from generations of *in vitro* studies, for which the natural reference was the *resting* potential.

References

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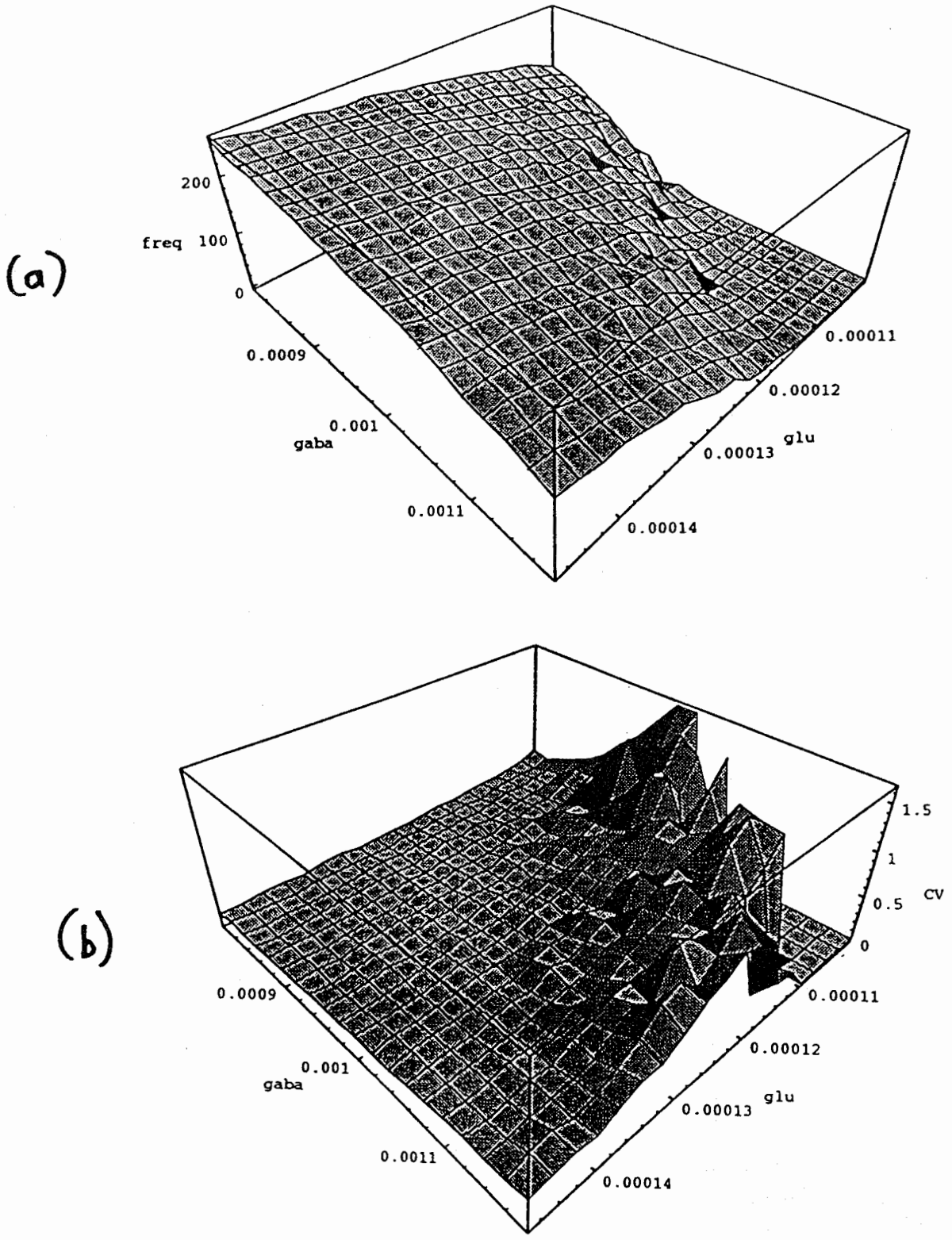

Figure 1: (a) Average firing frequency as a function of the maximum strengths of excitatory (glu) and inhibitory (gaba) synaptic input. (b) On the same axes: the coefficient of variation of the inter-spike interval (ISI). This shows peak variability of firing when excitation and inhibition are 'balanced' so that the system is constantly near threshold.

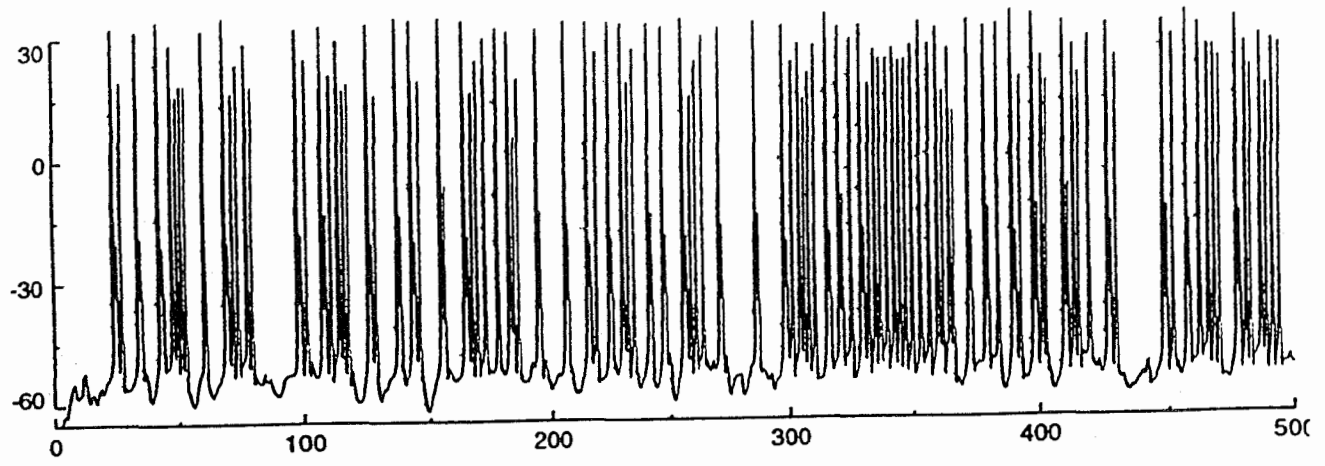

Figure 2: (a) Spike train in which weak repolarisation allows synaptic noise to cause irregular inter-spike intervals. The model cell does not have to integrate between spikes.

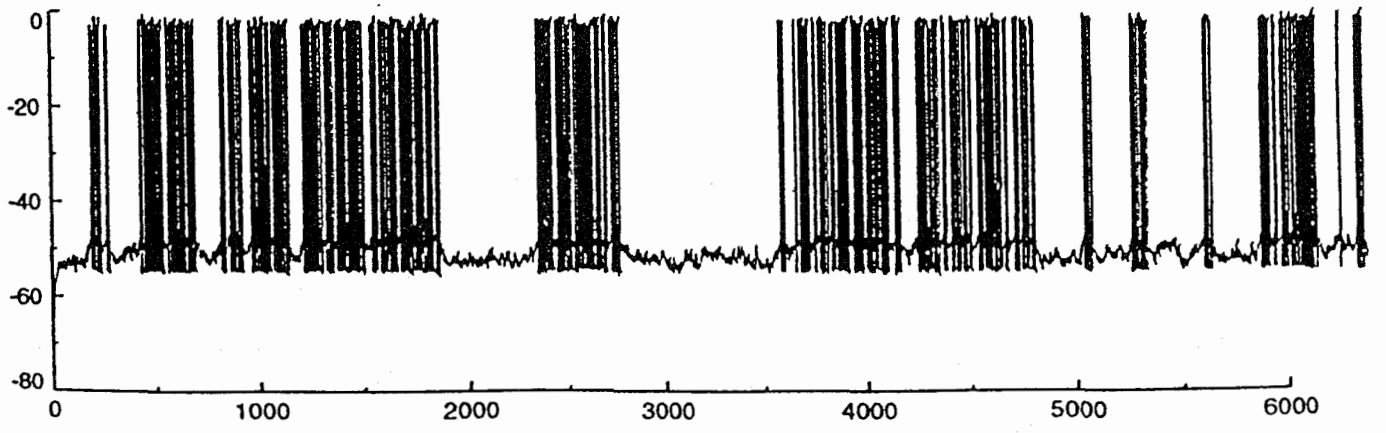

Figure 3: (a) Bistability caused by further weakening of the delayed rectifier conductance. The model neuron switches stochastically between high-frequency irregular firing and quiescence, while receiving only stationary random input.