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INTEGRATE-AND-FIRE NEURONS MATCHED TO PHYSIOLOGICAL f-I CURVES YIELD HIGH INPUT SENSITIVITY AND WIDE DYNAMIC RANGE

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Abstract

Simple integrate-and-fire neurons that accurately reproduce *in vitro* data from cortical regular spiking cells can display surprisingly sophisticated behavior. To reproduce *in vitro* f-I plots, voltage after spikes was reset to 5 mV below threshold, and simple spike rate adaptation was added. Small reset results in input sensitivity (high gain) on short time scales; adaptation leads to wide dynamic range over longer time scales. The model displays physiological ISI variability using either delta function or temporally realistic synaptic conductances. Cross correlation between pre- and post-synaptic spikes suggests that cortical neurons may be capable of transmitting information on the millisecond time scale.

Introduction

One line of investigation into the issue of neural coding has been to explore the information processing abilities of simple model neurons. Is the classical notion of spike generation consistent with what we know about information transmission in cortical neurons? By "classical notion" we mean viewing neurons as integrating many synaptic inputs until some voltage threshold and then pro-

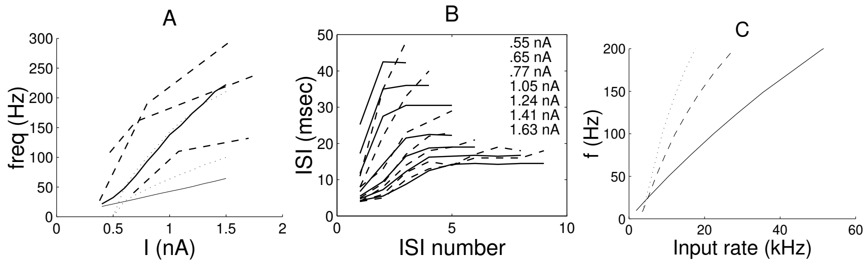

Figure 1: Model Parameters

Solid lines: model; dashed lines: experiment (A,B). RC parameters matched to slice recordings of regular spiking cells [3]: $V_{\mathrm{rest}} = -74\ mV$; $1/g_{\mathrm{leak}} = 40M\Omega; C = \tau g_{\mathrm{leak}}$, $\tau = 20\ msec$; spike width $t_{\mathrm{spike}} = 1.75\ msec$. $V_{\mathrm{thresh}} = -54\ mV$ was set 20 mV above V_{rest}. Adaptation was modeled as a spike-triggered K conductance ($E_K = -90$), $g_K = 15\ nS$ at spike conclusion, decaying with $\tau_K = 40\ msec$. V_{reset},τ_K, and g_K were fit to experimental f-I curves [3]. $V_{\mathrm{reset}} = -59\ mV = V_{\mathrm{thresh}} - 5\ mV$. Synaptic inputs initially were Poisson-distributed delta-function conductance changes. g_{syn} was taken from an exponential distribution with mean $\bar{g}_{\mathrm{syn}}$; values $> 4\bar{g}_{\mathrm{syn}}$ were then reset to this maximum value. For excitatory synapses, $V_{\mathrm{ex}} = 0mV$, and $\bar{g}_{\mathrm{ex}} = 3.4\ nS\ msec$, yielding mean EPSP size of .49 mV. For inhibitory synapses, $V_{\mathrm{in}} = -70mV$, and $\bar{g}_{\mathrm{in}} = 22.8\ nS\ msec$, yielding IPSPs twice as large as EPSPs (at V_{thresh}). Inhibition was quantified as the ratio R of the mean inhibitory current to the mean excitatory current at V_{thresh}. **A**. Firing frequency f (1/1st ISI) vs. current I for model (solid) and experiment (dashed, 3 cells). Lower line shows 1/7th ISI (after adaptation). Dotted lines show the model without adaptation for both high gain ($V_{\mathrm{reset}} = -60\ mV$) and low gain ($V_{\mathrm{reset}} = V_{\mathrm{rest}}$) cases. **B**. Adaptation: ISI length vs. ISI number for model (solid) and experiment (dashed) at different levels of current injection (shown at right). Note: to match physiological current ranges with adaptation, V_{rest} was changed to $-60\ mV$. This shifts the f-I plot to the left but does not affect the slope (gain). **C**. Steady state output rate vs. excitatory input rate for high gain nonadapting (dotted), low gain nonadapting (dashed), and high gain adapting (solid) models ($R = .75$).

ducing a spike. Such a neuron spikes at a rate dependent upon the net synaptic current reaching the soma and thus can embody the standard notion of “rate coding.” Are simple “integrate-and-fire” models also capable of more sophisticated “temporal coding” strategies? We have found that such simple model neurons exhibit surprisingly complex behavior when their parameters are fit to reproduce the input/output properties of cortical regular spiking cells.

Results

Matching physiological f-I curves

A rate encoding neuron is characterized by its input/output function, i.e. the

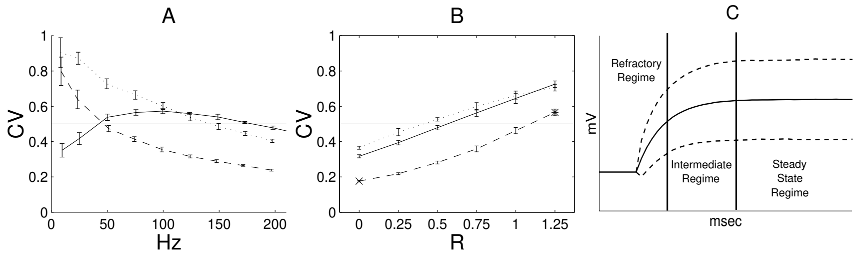

Figure 2: ISI Variability and Dynamic Range

A,B: Solid lines: full model; dashed lines: low gain nonadapting model ($V_{\text{reset}} = V_{\text{rest}}$); dotted lines: high gain nonadapting model. Variability assessed as CV of the ISI distribution (mean CV $\pm$ standard deviation for 10 simulations of 10 sec each). Thin line shows CV$=$.5 (rough lower bound for data in [6]). **A**. CV vs. firing rate ($R=.75$). **B**. CV vs. inhibition ratio R. Output firing rate $= 100(\pm 5)\ Hz$. Approximations to an EPSP integrator [6] and balanced inhibition [4] models marked by 'x' and '*' respectively. **C**. Schematic showing three regimes of spike behavior (see text). Shown are the mean (solid) and $\pm$ 2 standard deviations of membrane voltage following a spike ($V = V_{\text{reset}}$ for initial $t_{\text{spike}} = 1.75$ msec; spiking thereafter turned off).

transformation from presynaptic input rates to postsynaptic firing rate. While experimental estimates of synaptic input *in vivo* provide only weak constraints [4], the input/output behavior *in vitro* of a neuron can be characterized by an f-I curve: a plot of instantaneous spike frequency (f) vs. intracellularly injected current (I). By matching the *in vitro* data from McCormick et al. [3], we have constructed an integrate-and-fire model of a cortical "regular spiking" cell (fig. 2A,B; [8, 9]). After matching RC parameters and setting spike threshold, *the only free parameter in our basic model is the after-spike reset voltage* V_{reset}. Traditionally, $V_{\text{reset}} = V_{\text{rest}}$. However, the fast spiking conductances and those contributing to the resting potential are unrelated. Therefore, *we set* V_{reset} *to match physiologically observed f-I curves*. We also incorporated spike rate adaptation by adding a spike-triggered potassium conductance. Parameters for this conductance were also set by fitting experimental f-I curves.

Sensitivity and dynamic range

The neuron's sensitivity to changes in input current *in vitro*, the *neuronal gain*, is simply the slope of the f-I curve. By definition, a cell with high gain is sensitive to small changes in input current. However, input sensitivity implies narrow dynamic range: beyond a small range of superthreshold input currents, the output rate saturates. This problem is greatly reduced by incorporating spike rate adaptation into the model. Adaptation provides negative feedback that reduces the gain to slowly varying inputs. In our model, spike repolarization determines the neuronal gain on the time scale of single interspike intervals (ISIs), whereas adaptation determines neuronal gain to slowly varying input currents. This "gain control" feature of adaptation applies both to current injection *in vitro* (lower line in fig. 1A) and synaptic input (fig. 1C).

While there is no direct way to quantify *in vivo* "sensitivity", an indirect measure is found in the variability in the distribution of interspike intervals. Softky and Koch [6] have shown that spike trains from cortical neurons display high variability, reporting values of the coefficient of variation (CV – the standard deviation divided by the mean) of the ISI distribution in the range .5 to 1. For an integrate-and-fire neuron needing N randomly occurring excitatory postsynaptic potentials (EPSPs) to reach threshold, one expects the CV to be approximately $1/\sqrt{N}$. For reasonable values of N (≈ 30), CV $\approx .18$, i.e. *an EPSP integrator yields low variability*. Shadlen and Newsome [4] pointed out that if large numbers of excitatory inputs are tightly balanced by inhibition, the membrane voltage follows a "random walk" and ISIs are quite variable. However, neither of these groups considered models that accurately reproduce *in vitro* f-I curves. Recently, we showed that a simple integrate-and-fire model matched to physiological f-I curves displays high ISI variability for a wide range of firing rates and levels of inhibition (Fig. 2A,B; [8, 9]).

An intuitive picture

After each spike, there is a transient period in which the cell is less likely to fire, the so-called "relative refractory period". Spike rates *in vitro* are determined by the rate at which the injected current overcomes this refractory tendency not to spike. When considering the input the cell receives *in vivo*, however, refractoriness only tells half the story. After the effects of the previous spike become negligible, the cell spikes when *fluctuations* in the synaptic input are sufficient to push the membrane voltage above threshold. Thus, in a simple intuitive picture for *in vivo* spiking, ISIs are divided into three regimes (fig. 2C; [1, 9]). In the initial *refractory regime*, the state of the neuron is dominated by the recovery from the previous spike. In this regime, $1/\sqrt{N}$ arguments are valid and spiking is regular. In the final, *steady state regime*, synaptic variation causes the cell to fluctuate about some steady state mean voltage (necessarily subthreshold). Since threshold crossings in this regime result from random voltage fluctuations, spike statistics in this regime are Poisson – threshold crossings are equally likely to occur in any small interval. In the *intermediate regime*, the mean voltage is still significantly rising, yet typical voltage fluctuations can be sufficient to cross threshold. For neurons with high gain and hence weak refractoriness, steady state behavior predominates. Thus, in contrast to the common intuition, *we should expect cortical neurons to display high ISI variability.*

Neuronal processing on multiple time scales

To ensure robustness of these mechanisms, we varied the time course of synaptic transmission. Short synaptic time constants give results similar to delta function conductances. If there is only a single synaptic time constant, and it

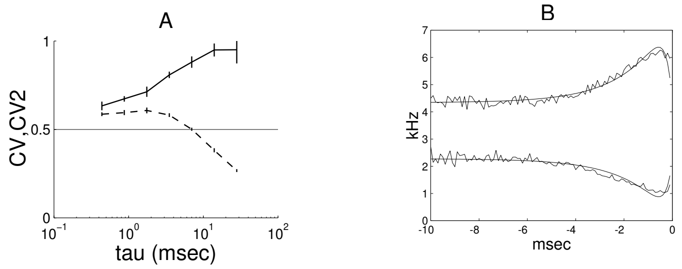

Figure 3: Effects of Finite Synaptic Time Course
A. *Solid lines: CV. Dashed lines: CV2.* Two variability measures vs. synaptic decay constant τ. The area under the conductance curve was fixed at 5 $nS\ msec$ for excitatory and 33.6 $nS\ msec$ for inhibitory synapses. To quantify "burstiness", we plot τ vs. both CV (solid) and an alternate measure of variability, CV2 (dashed) [2]. CV2 is the CV of consecutive pairs of ISIs, averaged over the whole ISI distribution. Since CV2 depends only on consecutive intervals, it is much less sensitive than CV to changes in short term firing rate (e.g. alternating low and high firing rates), while closely approximating CV for Poisson distributed spikes with constant rate. Total input was adjusted to ensure final firing rate of 100 ($\pm$5) Hz. Inhibition/excitation ratio $R = .75$. **B.** Average rate of presynaptic input before a spike (occurring at t=0). Upper trace: excitatory input. Lower trace: inhibitory input. Smooth line is fit with scaled and inverted trace of the postsynaptic conductance (rise time $= .25\ msec$; decay $= 1.75\ msec$). Mean output rate $\approx 25\ Hz$; $\approx$ 5000 spikes collected.

becomes long relative to the mean ISI, then spike trains come to display an unrealistic burstiness: correlations induced in the somatic input current yield long periods of subthreshold current (long ISIs) alternating with periods of suprathreshold current (bursts of spikes with short ISIs) (fig. 3A). However, we do not see this burstiness with physiologically realistic mixtures of fast and slow synapses: with at least one fast synaptic time constant, e.g. AMPA and/or $\mathrm{GABA_A}$, physiologically realistic CVs and distributions are robustly obtained.

In the steady state regime, the *timing* of individual spikes depends on the *fluctuations* in the synaptic input current, whereas the *probability* of spiking depends on the mean current. This can be seen from the cross-correlation between an output spike train and its presynaptic inputs (fig. 3B). As expected, before each spike a cell receives more excitatory and fewer inhibitory inputs [5, 7]. Surprisingly, the time course of this effect closely follows the postsynaptic conductance (1-2 msec), and is largely independent of the membrane time constant.

Summary and Conclusions

By fitting the parameters of a very simple neural model to available *in vitro* data [3], we see that classical notions of neuronal integration are consistent with sophisticated information processing abilities. With parameters set to reproduce the high gain of cortical regular spiking cells, the neuron mainly operates in the steady state regime and is sensitive to the fluctuations in input current. Cells operating in this regime may be capable of spiking with precision on the millisecond time scale (fig. 3B), and could process information using a scheme radically different from the usual "rate code" ([1, 7], but see [5]). However, our simulations show that such cells can also function as "noisy rate encoders", with neuronal gain modulated in time to increase dynamic range. This work suggests that the different temporal filtering properties of (fast) AMPA and (slow) NMDA receptors in combination with differing neuronal gain on fast and slow time scales may enable networks of simple integrate-and-fire neurons to *simultaneously* process information on *multiple* time scales.

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