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# Novel Integrate-and-fire-like Model of Repetitive Firing in Cortical Neurons

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## Abstract

Cortical neurons convert synaptic inputs arising from thousands of other neurons into a single output spike train. In order to better understand this basic computation, we have derived a simple repetitive firing model from the Hodgkin-Huxley equations. This novel model is related to the conventional integrate-and-fire model, but uses a time-varying time constant (whose value follows a stereotyped trajectory after each spike) in place of the usual fixed time constant. The model, whose parameters can be extracted from as few as two interspike intervals, provides an excellent fit to the responses of cortical neurons *in vitro* to both constant and time-varying inputs.

Neurons in the cortex convert the synaptic input generated by thousands of other neurons into an output spike train. Because this transformation is central for cortical computation, an understanding of the computation performed by cortical circuits requires an understanding of this basic input-output transformation.

Encoding is, at least in principle, well understood. The basic framework for our modern understanding was provided by Hodgkin and Huxley almost fifty years ago [Hodgkin and Huxley, 1952]. They showed that spike generation in the axon of the giant squid could be described in terms of just two distinct nonlinear conductance mechanisms: a sodium channel, and a potassium channel.

Since that time, hundreds of new channels have been identified. Dozens of channels coexist in single cortical neurons, distributed inhomogeneously throughout the dendritic tree. Thus while a description of the squid axon required measurement of the properties of only two channels, and the corresponding one or two dozen parameters, a comparably complete and accurate description of a cortical neuron—a description of each channel, along with its distribution throughout the dendritic tree—would require measurement of thousands of parameters. In practice, such a feat remains beyond the capacity of current experimental techniques. Moreover, even if it were possible, a complete description might be too complex to be of much use.

We have therefore pursued a different strategy. We have asked what the simplest model is that can account for the firing of cortical cells. Fig. 1 shows typical repetitive firing in a regular-firing layer 2/3 cortical neuron. Our goal, then, is to derive a simple model of such responses to a constant stimulation, and of the responses to more complex stimuli.

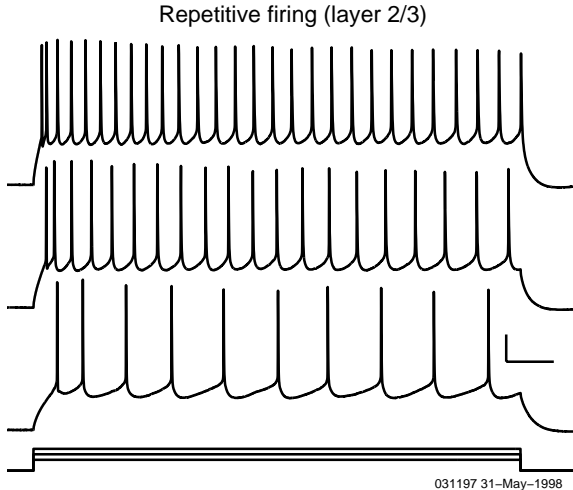


Figure 1: Repetitive firing in a layer 2/3 cortical neuron. The responses to injection of constant current at each of three stimulus intensities (*bottom to top*: 0.16, 0.24 and 0.32 nA) are shown. Standard slice recording methods were used (see [Stevens and Zador, 1998] for details). Calibration: *100 msec, 20 mV*

## 1 Conventional integrate-and-fire model

The conventional simple model of repetitive firing is the leaky integrate-and-fire mechanism [Tuckwell, 1988]. Let  $I(t)$  is the input to a leaky integrator with a time constant  $\tau$  and a threshold  $\theta$ . As long as the voltage is subthreshold,  $V(t) < \theta$ , the voltage is given by

$$C \dot{V} = -\frac{V(t) - V_{rest}}{R_n} + I(t), \quad (1)$$

where  $\dot{V}$  is the time derivative of  $V(t)$ ,  $R_n$  is the input resistance,  $C = \tau/R_n$  is the membrane capacitance, and  $V_{rest}$  is the resting potential. At the instant the voltage reaches the threshold  $\theta$ , the neuron emits a spike, and resets to some level  $V_{reset} < \theta$ . The five parameters of this model,  $\theta$ ,  $V_{reset}$ ,  $V_{rest}$ ,  $\tau$  and  $R_n$ , determine its response to a given input current.

This model might be expected to provide a good fit to data if (1) neurons have sharp spike threshold; and (2) the subthreshold behavior is well described as a simple passive circuit. Direct inspection of Fig. 1 confirms that this neuron does have a rather sharp spike threshold. In order to test whether the second condition is met, we injected a hyperpolarizing current step from the rest potential  $V_{rest} = -60$  mV. Fig. 2A shows that, indeed, the subthreshold behavior is well-described by a simple R-C circuit, with a time constant of  $\tau = 15$  msec and an input resistance of  $R_n = 150$  M $\Omega$ . Thus two basic conditions of the simple integrate-and-fire model are satisfied.

To test whether this simple integrate-and-fire model could account for the this repetitive firing, the two remaining parameters (the threshold  $\theta$  and the reset voltage  $V_{reset}$ ) were determined by inspection of Fig. 1. Fig. 2B shows that the model provides a very poor fit to the data. The model overestimates by almost three-fold the actual spike rate.

Why has the standard integrate-and-fire model failed so dramatically? A more detailed view of a single experimentally recorded interspike interval (Fig. 2C) shows that the voltage follows a smooth concave trajectory. By contrast, the model shows an convex exponential approach to threshold, as required by Eq. 1. This suggests that a third basic assumption implicit in the standard integrate-and-fire model—that the subthreshold behavior during repetitive spiking is the same as that near rest—is not satisfied. The voltage trajectory during the interval between spikes suggests a fundamental way in which the standard integrate-and-fire model fails.

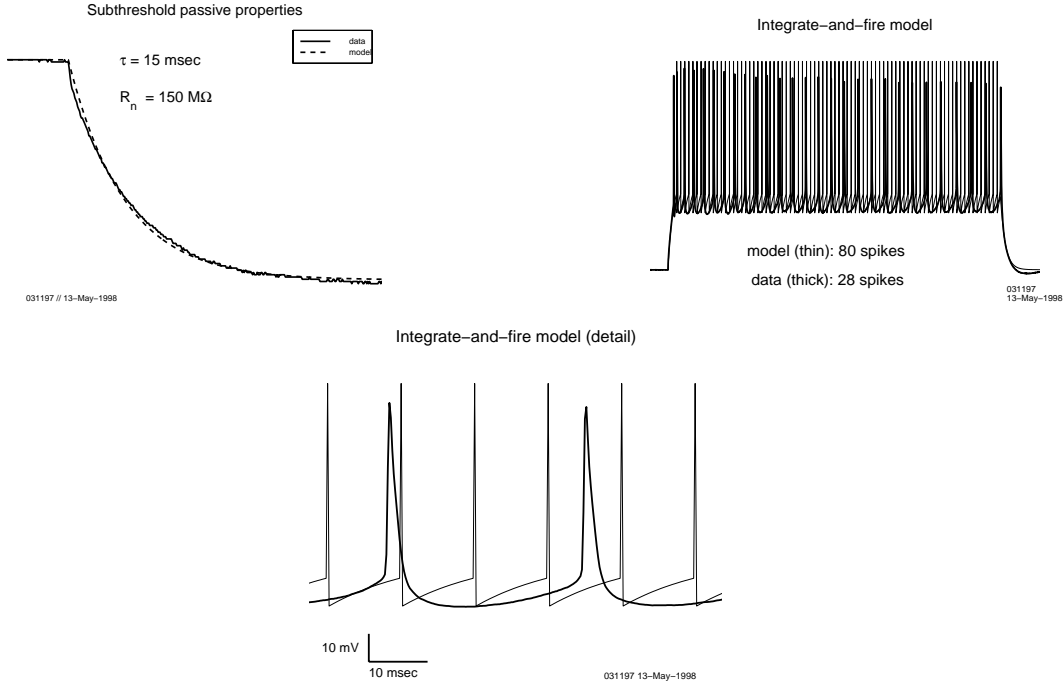


Figure 2: Conventional integrate-and-fire model fails to account for repetitive firing. **A, top left** The subthreshold response to a  $-0.04$  nA hyperpolarizing current step is well described as a simple passive circuit, with a time constant of 15 msec and an input resistance of  $150$  M $\Omega$ . The data are taken from the same layer 2/3 cortical neuron shown in the previous figure. **B, top right** The passive properties measured from the subthreshold response, along with the measured spike threshold and reset, lead to an integrate-and-fire model that dramatically overestimates the spike rate. **C, bottom** A close-up of a single experimentally recorded interspike interval is compared to the 2 or 3 corresponding model intervals. The model shows an exponential convex approach to threshold, while the experimental record shows a much smoother concave approach.

## 2 Time-varying integrate-and-fire model

Why did the conventional integrate-and-fire model fail? In order to understand the problem, let us return to the underlying Hodgkin-Huxley equations for a single compartment Hodgkin-Huxley model,

$$C \dot{V} = - \sum_i^N g_i [V(t) - E_i] + I(t), \quad (2)$$

where  $V(t)$  is the membrane voltage,  $C$  is the cell capacitance,  $g_i(t, V(t))$  are the  $N$  time- and voltage-dependent conductances (such the fast sodium conductance underlying an action potential, as well as the passive membrane conductance),  $E_i$  are the associated batteries, and  $I(t)$  is an externally injected current. We can rewrite Eq. (2) as

$$C \dot{V} = - \frac{V(t) - E(t)}{R(t)} + I(t), \quad (3)$$

where we have defined  $R(t) = \sum_i 1/g_i$  and  $E(t) = R(t) \cdot \sum_i E_i g_i$ .  $R(t)$  is a time-varying resistance corresponding to the trajectory of the inverse of the total conductance following an action potential, while  $E(t)$  is the associated driving force. Eqs. (2) and (3) are formally equivalent.

During the brief millisecond or two of an action potential, the underlying conductances typically follow a rather stereotyped trajectory. Do the conductances and batteries between action potentials show similarly stereotyped behavior? To answer this, we must estimate  $R(t)$  and  $E(t)$  for a single interspike interval.

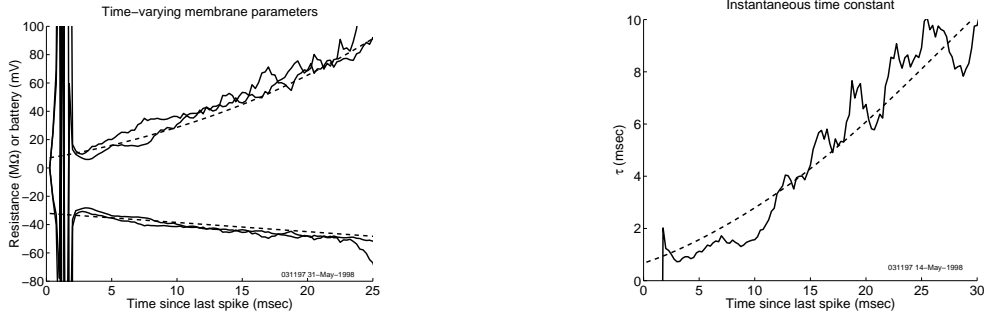


Figure 3: Resistance and driving forces following an action potential show stereotyped behavior. **A, left** The time-varying resistor  $R(t)$  (*upper curve*) and driving force  $E(t)$  (*lower curves*), computed from Eq. (4), are plotted as a function of the time since the last action potential. Each data curve was computed from ISIs representing responses to a different pair of stimuli (0.16 & 0.24 or 0.24 & 0.32 nA), which together span the entire range of stimuli tested. The fact that the derived curves are nearly superimposed upon each other over this wide range of stimuli indicates the  $R(t)$  and  $E(t)$  behave in a stereotyped fashion that is essentially independent of the firing rate. The smooth fits, used to generate the model responses in subsequent figures, were given by  $R(t) = 14/(0.05 + e^{-t/3} + e^{-t/12})$  M $\Omega$  and  $E(t) = -32 - 0.65t$  mV. **B, right** The time-varying resistance can also be thought of as a time-varying time constant. Here the time-varying resistance from (A) has been replotted following multiplication by the membrane capacitance  $C$ .

## 2.1 Estimating $R(t)$ and $E(t)$

In order to compute the trajectories from data, it is convenient to rewrite Eq. (3) as

$$R(t) \left[ I(t) - C\dot{V}(t) \right] + E(t) = V(t). \quad (4)$$

This form emphasizes that at each time point  $t$ , the unknown quantities  $R(t)$  and  $E(t)$  can be estimated from the known quantities  $I(t)$ ,  $C$  (estimated from the passive membrane time constant),  $V(t)$ , and  $\dot{V}$  (computed from  $V(t)$ ). In matrix form, this means we have to solve the following matrix equation *at each point  $t$  in time*,

$$\underbrace{\begin{bmatrix} (I_1(t) - C\dot{V}_1(t)) & 1 \\ \vdots & \vdots \\ (I_i(t) - C\dot{V}_i(t)) & 1 \\ \vdots & \vdots \\ (I_N(t) - C\dot{V}_N(t)) & 1 \end{bmatrix}}_{A(t)} \underbrace{\begin{bmatrix} R(t) \\ E(t) \end{bmatrix}}_{x(t)} = \underbrace{\begin{bmatrix} V_1(t) \\ \vdots \\ V_i(t) \\ \vdots \\ V_N(t) \end{bmatrix}}_{b(t)} \quad (5)$$

where the subscripts index over the  $N$  trials. The least squares solution for  $x(t)$  is given by

$$x(t) = A^+(t) b(t) \quad (6)$$

where  $A^+(t)$  is the pseudoinverse of  $A(t)$ . For the computed quantities to be meaningful, at least two measurements at different current stimulus intensities. That is, there are two unknowns at each time point, so responses to at least two distinct stimuli  $I(t)$  must be available. If  $N = 2$  the pseudoinverse corresponds to the standard inverse. Of course there can be more:  $N \geq 2$ .

Fig. 3A shows  $R(t)$  and  $E(t)$  extracted from two distinct pairs of ISIs ( $N = 2$ ). The *top* curves show that  $R(t)$  is essentially identical for the two pairs, indicating that  $R(t)$  does indeed show a stereotyped trajectory that is largely independent of the applied stimulus  $I(t)$ . Immediately after the action potential  $R(t)$  is very small, reflecting the large sodium and potassium conductances

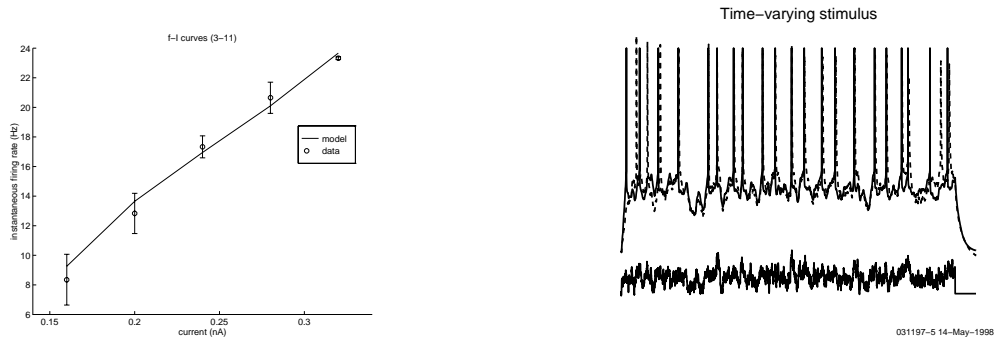


Figure 4: The model matches the data. **A, left** The model matches the f-I curve. The measured (*open circles*) and predicted (*solid line*) firing rates are plotted as a function of input current. The predicted firing frequency was computed using the measured values of  $R(t)$  and  $E(t)$ ; the only remaining free parameter, the firing threshold, was determined by inspection. Error bars indicate standard deviation. **B, right** The model predicts the response to a fluctuating current. (*Top*) The actual (*dotted*) voltage trace is compared with that predicted (*solid*) from the measured  $E(t)$  and  $R(t)$  function. The two curves agree best in the middle, but diverge a bit at the edges because of spike frequency adaptation. Spikes to 40 mV were pasted on the predicted curve when the voltage crossed threshold. (*Bottom*) The injected current.)

still open. The resistance then increases nearly linearly throughout the entire interspike interval. We have fit the resistance with the empirical function  $R(t) = 14/(0.05 + e^{-t/3} + e^{-t/12})$ ; while this function was motivated by the considering the exponential decay of two conductances, its real justification is just that it fits the data.

The *bottom* curves in Fig. 3A show that the time-varying driving force  $E(t)$  also exhibits a stereotyped trajectory during the interspike interval. Immediately following the action potential  $E(t)$  is only somewhat more negative than threshold (which in this cell is -22 mV). It then decreases very linearly over the next 30 msec or so to rest (-60 mV).

## 2.2 Time-varying time constant

The time-varying resistance can also be thought of as producing a time-varying time constant. Fig. 3B shows the result of multiplying the time-varying resistance shown in Fig. 3A by the membrane capacitance. The result is an “instantaneous” time constant whose value follows the same stereotyped trajectory as  $R(t)$ . It is interesting to note that this time constant starts a very short value—only about 1 msec—and then increases to only 10 msec. The fact that this instantaneous time constant is so short implies that cortical neurons integrate their inputs over only a relatively short time.

## 2.3 Fit to data

How well does this revised integrate-and-fire model fit the data? We used the empirical spike threshold  $\theta$ , along with the calculated  $R(t)$  and  $E(t)$  shown in Fig. 3, to generate model spike trains. We first tested its response to constant inputs of the sort illustrated in Fig. 1A. Fig. 4A shows that, using the measured values of  $R(t)$  and  $E(t)$ , the time-varying model matches the f-I curve quite well. Recall that, by contrast, the standard integrate-and-fire model does not (Fig. 2).

As a further test, we compared the predicted and actual responses to time-varying input. The time-varying input used here can be thought of as the synaptic current that would be expected at the soma if there neuron were driven by many independent synaptic inputs [Stevens and Zador, 1998]. Fig. 4B shows that the model matches the data very closely here as well. (The failure of the model to match the first and last few spikes is due to spike-frequency adaptation, which we have not considered here).

### 3 Conclusions

We have presented a simple model of repetitive firing that can account for the responses of cortical neurons to both constant and time-varying inputs. The model was derived from the Hodgkin-Huxley equations, and so is well grounded in the basic biophysics of repetitive firing. The model is closely related to the standard integrate-and-fire model, but instead of assuming time-invariant behavior the present model assumes that the membrane properties follow a stereotyped trajectory following each spike. The parameters of this novel model can be extracted from measurement of two pairs of interspike intervals.

### References

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