

Comparing integrate-and-fire-like models estimated using intracellular and extracellular data¹

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Abstract

We have recently (Pillow et al., 2003) developed a method for estimating integrate-and-fire-like stimulus encoding models that can be used even when only extracellular spike train data (no intracellular voltage record) is available. Here we apply this method to responses recorded *in vitro*, allowing a direct comparison of model fits given extracellular versus intracellular data. Both models are able to capture the behavior of these cells under dynamic stimulus conditions to a high degree of temporal precision, although we observe significant differences in the stochastic behavior of the two models.

Key words: Integrate-and-fire, stimulus-response encoding, noise

A central issue in systems neuroscience is the characterization of the functional relationship between sensory stimuli and neural spike trains. A common model for this relationship consists of linear filtering of the stimulus, followed by a nonlinear, probabilistic spike generation process. The linear filter is typically interpreted as the neuron’s “receptive field,” while the spiking mechanism accounts for simple nonlinearities like rectification and response saturation. Given a set of stimuli and observed spike times, the characterization problem consists of estimating both the linear filter and the parameters governing the spiking mechanism.

¹ JP was partially supported by an NYU Dean’s Dissertation fellowship. The data analyzed here were collected jointly with B. Lau in the lab of A. Reyes. We thank T. Lewis for an advance copy of a long draft of (Jolivet et al., 2003).

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We have recently developed methods for estimating a model of this type (given only extracellular spike train data), in which the nonlinear spike generation step is implemented by a noisy integrate-and-fire mechanism; see e.g. (Gerstner and Kistler, 2002; Pillow et al., 2003; Keat et al., 2001) for detailed arguments on why models of this type are of interest. On the other hand, the problem of estimating this class of model given the full intracellular voltage trace can be solved somewhat more straightforwardly and has been extensively studied (Stevens and Zador, 1998; Jolivet et al., 2003). Here we examine the performance of the two methods on *in vitro* data (Paninski et al., 2003), allowing a detailed comparison of the methods. Our results serve both to validate our method, in a sense, but more importantly to illuminate the statistical differences in the models obtained.

Methods

See (Paninski et al., 2003) for (fairly standard) physiological details of the rat cortical slice dual-electrode whole-cell recordings analyzed here.

Intracellular model

We use a slightly different method than either (Stevens and Zador, 1998) or (Jolivet et al., 2003), which is worth describing here. Perhaps the most important difference is that we pose the problem in an explicitly probabilistic setting, allowing us to examine the noise properties of the model (i.e., the variability of response to a fixed stimulus) systematically.

We develop the maximum likelihood estimator (MLE) for the following form of the “spike-response” (Gerstner and Kistler, 2002) integrate-and-fire-like model (in discrete time, for simplicity):

$$V(1) = V(0) + dt \left(- \sum_{i=-m}^0 g_i(-t_0) V(i) + \sum_l a_l f_l(V(0)) + \vec{k} \cdot \vec{x}(0) + \sum_{j=-\infty}^0 h(-t_j) \right) + \sigma \sqrt{dt} N.$$

The tap weights g_i implement an I.I.R. filter whose coefficients can vary as a function of the time t_0 since the last spike (if $m = 0$, g is simply the membrane conductance); the functions f_l , which can be chosen arbitrarily, allow us to model nonlinear sub-threshold dynamics (Brunel and Latham, 2003); \vec{k} summarizes the linear filtering properties of the cell given the input \vec{x} . On short time scales, h gives the spike shape; on longer time scales, h can induce burstiness, refractoriness, or adaptation effects, depending on its form and magnitude (Pillow et al., 2003). The cell spikes whenever V reaches a threshold potential V_{th} . Finally, we took the noise term N to be Gaussian and i.i.d.; this means that the MLE for the model parameters has the usual mean-square formulation, which we now describe.

Assume the spikes $\{t_j\}$ have been detected (typically via automatic thresholding, assuming sufficiently well-isolated recordings). Then the model parameters $\{g_i, a_l, \vec{k}, h\}$ act linearly on $\{V(i), f_l(V(0)), \vec{x}(0), \sum \delta(t_j)\}$ in the spike-response model equation to produce the voltage differences $(V(1) - V(0)) / dt$, and as such can be fit (along with the noise scale σ) using standard least-squares linear regression techniques. Finally, V_{th} is chosen as a maximizer of the loglikelihood

$$L(V_{th}) \equiv \sum_j \log \left(\int_{V_{th}}^{\infty} \mathcal{N}(\mu_j, \sigma^2 dt) \right) + \sum_{j'} \log \left(\int_{-\infty}^{V_{th}} \mathcal{N}(\mu_{j'}, \sigma^2 dt) \right),$$

where $\mathcal{N}(\mu, \sigma^2)$ is the Gaussian of mean μ and variance σ^2 , and μ_j denotes the mean of V at the spike times $\{t_j\}$ under the spike-response model, $\mu_j \equiv$

$$V(s) + dt \left(- \sum_{i=-m}^0 g_i(s - t_{j-1})V(s + i) + \sum_l a_l f_l(V(s)) + \vec{k} \cdot \vec{x}(s) + \sum_{j_*=-\infty}^{j-1} h(s - t_{j_*}) \right),$$

with $s \equiv t_j - 1$; $\mu_{j'}$ is the mean computed at all other times (at which no spike was observed). One can show that $L(V_{th})$ is concave (Rinott, 1976), and hence quite easy to maximize using ascent algorithms (note also that the derivatives $L^{(i)}$ are easily computed once one has computed L). Note that this approach does not require us to generate a new voltage trace for each setting of the model parameters, to numerically optimize the mean-square difference between the model and true voltages (in general, this latter optimization problem is non-concave and is therefore more challenging, due to the possible presence of local minima, than the solution of $L(V_{th})$); thus our approach is faster and somewhat more easily interpretable than the method described in (Jolivet et al., 2003).

A brief technical note: we have just described the MLE given both the voltage $V(t)$ and the spike times $\{t_j\}$. It is also possible — indeed, somewhat more straightforward — to write down the MLE given only the voltage $V(t)$ (in which case the solution is completely given by least-squares regression). However, our experiments with the latter approach (details not shown) indicate that this method is less robust; the MLE given only $V(t)$ tends to set V_{th} far too high, basically because missing the first part of the spike (due to improperly high V_{th}) costs less in mean square error than does adding a few false threshold crossings (as is inevitable with V_{th} near the true optimal value, if the cell's threshold is not perfectly sharp).

Extracellular model

The model for extracellular data introduced in (Pillow et al., 2003) is a greatly reduced version of the above spike-response model:

$$V(1) = V(0) + dt \left(-gV(0) + I_{DC} + \vec{k} \cdot \vec{x}(0) + \sum_{j=-\infty}^0 h(-t_j) \right) + \sigma \sqrt{dt} N;$$

thus we have effectively set $m = 0$, $g(t) \equiv g$, and $f_l = 1$. We lack the space necessary to describe the MLE for this model, given only the spike train $\{t_j\}$; see (Pillow et al., 2003) for full details. For fair comparison, this is the model we examine in the intracellular model figures below.

Note that, despite the fact that the full $V(t)$ provides a much richer data set than just the spike times $\{t_j\}$, the extracellular model is in some senses easier to estimate, because we don't have to worry about getting V right, just the spike times. This means, e.g., that we only have to deal with voltage up to a scale and offset that we don't need to estimate (another way of saying this is that the V in the extracellular model is dimensionless). More importantly, if threshold doesn't depend linearly on just V , but also, say, $\frac{\partial V}{\partial t}$ (Koch, 1999; Gerstner and Kistler, 2002), the intracellular model will do poorly, whereas the extracellular model (because it doesn't have to match V) will perform well (since $\frac{\partial V}{\partial t}$ is a linear functional of the $V(t)$ signal). A possible improvement for the intracellular model, not pursued here, would be to generalize the simple voltage condition to allow linear combinations of $\vec{V} \equiv \{V(i)\}_{m \leq i \leq 0}$, for example allowing a spike to occur when $\vec{V} \cdot \vec{V}_{th} > 1$ for some vector \vec{V}_{th} . This more powerful model remains easily solvable by the global convexity of the corresponding loglikelihood $L(\vec{V}_{th})$ (as can be shown, again, by the results in (Rinott, 1976)).

Results

We compare the responses of the fit models to two different types of injected current stimulus. The first (Fig. 1) is a series of DC pulses of randomly chosen magnitudes, each lasting 500 milliseconds (10 seconds of data; 34 spikes); the second (Fig. 2) is a white noise current (100 s long; ≈ 300 spikes). The models performed much better on the latter, dynamic stimulus, as expected given previous results on the predictability of cortical cellular responses to fixed current stimuli (Mainen and Sejnowski, 1995; Tiesinga et al., 2003).

Both methods miss the resonance displayed by the cell in the DC step experiment (this is again quite predictable, since we set $m = 0$ for these figures and the filter \vec{k} is of length 10 ms, too short to capture the relatively slow resonance seen here); moreover, the models partially scramble the observed spike timing and do a poor job matching DC voltages (especially for high V , where active currents start to turn on), and as a result miss some periods of activity completely. Much of this can be fixed by adding a resonance term ($m = 1$) and a nonlinear V term (data not shown). On the positive side, the models choose h properly; no spike-rate adaptation is displayed by this cell or by either of the models.

The most striking feature of Fig. 1 is displayed by the extracellular model: the model actually adds noise by increasing σ beyond the value obtained by the intracellular method. This has the effect of increasing the model's simulated firing rate and decreasing its selectivity (although note that the noiseless predictions — center rasters — are comparable in accuracy to those of the intracellular method, both

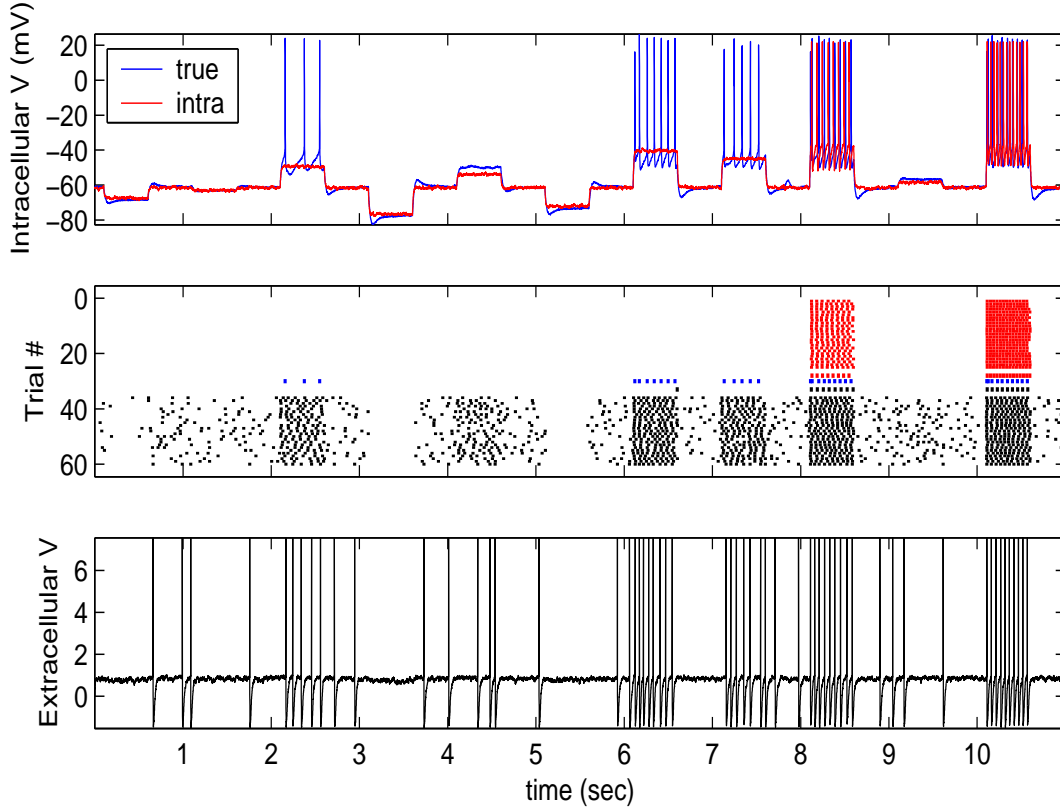


Fig. 1. Responses to step current input. **Top:** Comparison of sample from fit intracellular model (red) to true observed voltage (blue). Trace corresponds to trial #1 in middle panel. **Middle:** Comparison of rasters. Trials 1-25 (red) are random samples from the intracellular model; the last 25 (black) are from the extracellular model. Middle three rasters (red, blue, black) are noiseless responses (intracellular, true, and extracellular, respectively), i.e., σ set to zero. **Bottom:** Random sample from extracellular model (corresponding to trial #60 in middle panel).

here and in the dynamic noise case, Fig. 2). This noise increase is formally identical to a shrinkage of \tilde{k} , I_{DC} , and h and is a kind of model selection phenomenon (James and Stein, 1960; Rasmussen and Ghahramani, 2001; Sahani and Linden, 2003): roughly stated, for robust fitting of this model — especially when the model error is relatively large, as is the case here — it is better to be uncertain than certain and wrong.

Both models are seen to predict the responses to dynamic input quite well (Fig. 2). A large proportion of spikes are predicted with submillisecond accuracy; “mistaken” spikes — that is, spikes which occur in the model but not in the data — typically appear at plausible times (i.e., near peaks in the true voltage). The intracellular model also captures the subthreshold responses quite well (as emphasized in (Stevens and Zador, 1998; Jolivet et al., 2003)). Similar results were seen in experiments with higher firing rates and less data (800 spikes in 50 seconds; data not shown). Further quantification of the models’ accuracy (dependence of fits on observed number of spikes, etc.) will appear elsewhere.

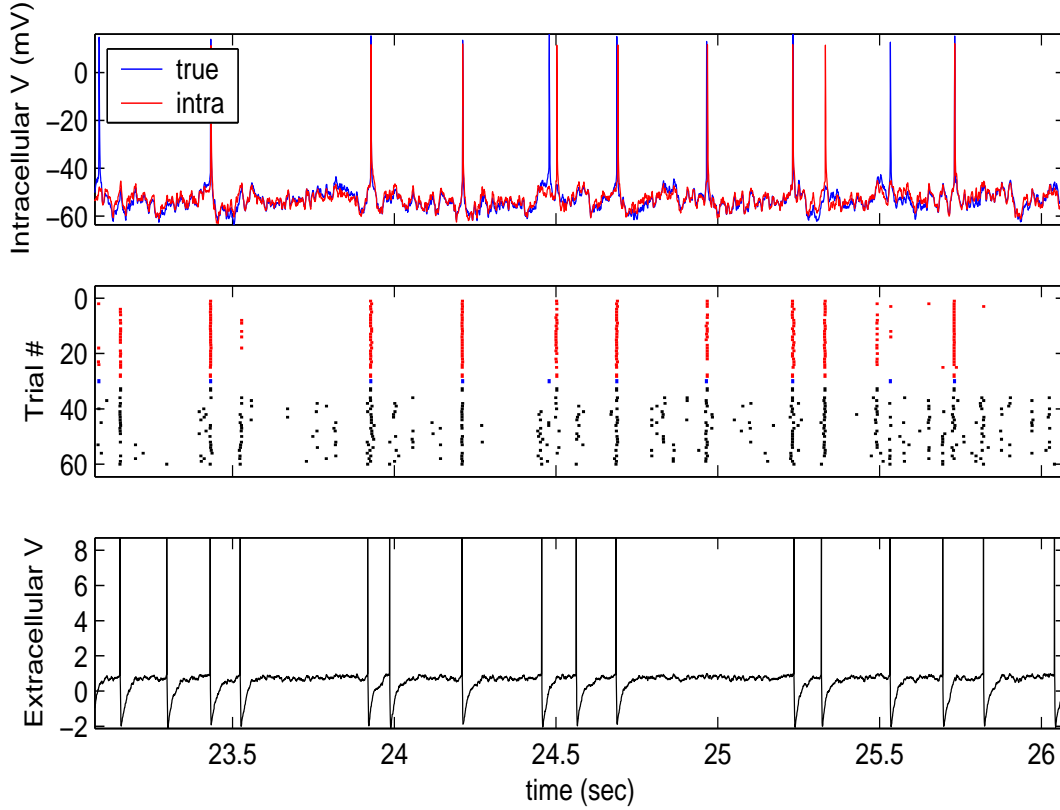


Fig. 2. Responses to white noise current input. Conventions as in Fig. 1, though note difference in time scales. Display is a randomly-chosen segment of a 100-second long white noise experiment.

In short, we have found that the extracellular model and estimation procedure performs well in predicting the responses of neurons to dynamic stimuli, at least in the setting of a highly simplified *in vitro* preparation. Future research will examine the performance of the model *in vivo*. We close by mentioning one additional interesting direction for future work: we found that the model fits are stable over different input variance (i.e., firing rate) regimes (data not shown), but that the estimated g consistently increases with firing rate (see (Pillow and Simoncelli, 2003) for another example of this). To model, e.g., variance adaptation (Paninski et al., 2003) accurately, it may be necessary to capture this effect. One way to do this is to allow g to vary with time, as mentioned above and discussed in more detail in (Stevens and Zador, 1998; Jolivet et al., 2003); since $g(t)$ is typically found to be largest just after a spike, increasing the spike rate increases the average g . It is unclear at the moment whether the results in (Pillow et al., 2003) on the estimation of the extracellular model extend to this time-varying g case.

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