Estimation of Single-Neuron Parameters from Spike Data

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Estimating parameters for models of neurons requires a quantitative comparison between the model output and empirical data. The present study compares three error functions: **voltage-time-series (VTS)**, **cumulative-voltage-integrals (CVI)**, and **phase-histograms (PH)**. In two test cases, predefined models were used to produce target data and to compare the efficacy of the three error functions. In a third example, empirical data were used to parameterize a model. VTS was found to be inferior, whereas as CVI and PH were similar and effective. Reliable parameters were derived from analyzing as few as two datasets.

Error Functions

An error function compares the output of a model to a target dataset. One of the main problems for optimization algorithms is the presence of local minima in the error function, which can force the algorithm to terminate on less than optimal parameter values. Stochastic optimization algorithms surmount this problem by occasionally randomly changing parameter values, allowing the algorithm to escape local minima. One of our goals in trying different error functions was to eliminate the occurrences of local minima, because the optimization program used here is not stochastic. **Fig. 1** illustrates the three error functions that were used in the present study.

Voltage time-series (VTS). The VTS error function simply subtracts one trace from another at each time point and squares the differences so that they will always be positive (Fig. 1A).

$$E_{VST} = \int_0^T \left\| v_{\text{model}} - v_{\text{data}} \right\|^2 dt \qquad \text{Eq. 1}$$

VTS works well for fitting smoothly varying processes such as hyperpolarizing current injections, single postsynaptic potentials or single action potentials recorded at high time resolution. However, when fitting narrow peaks, such as trains of action potentials, the voltage time-series is vulnerable to phase-shift errors. (Note the double peaks in squared error in **Fig. 1A4**.) An optimization scheme using this function is prone to settling into local minima in silent (non-spiking) regions of parameter space.

Cumulative Voltage Integral (CVI). One way to deal with the phase-shift problem is to smooth the data somewhat by summing the individual traces over time. This procedure has the effect of broadening the peaks in the error function (**Fig. 1C**).

$$E_{\text{CVI}} = \int_0^T \left\| \int_0^t v_{\text{model}} - \int_0^t v_{\text{data}} \right\|^2 dt \qquad \text{Eq. 2}$$

Phase Histogram (PH). A different way to deal with the phase-shift problem is to ignore the time dimension entirely, and instead plotting the membrane voltage vs. its time-derivative in the phase plane. Summing the plotted points at each combination of voltage magnitude and voltage slope produces a phase histogram (also called a trajectory density function) (**Fig. 1B**). Subtracting the two phase histograms and squaring the differences produces an error function that is sensitive to spike shape and spike frequency and that is robust to differences in spike phase.

$$E_{PH} = \sum_{v} \sum_{v'} \left[\delta_{data}(v,v') - \delta_{model}(v,v') \right]^2 \qquad \text{Eq. 3}$$

where δ is the normalized trajectory density as defined in Eq.1.26 of LeMasson and Maex (2001). The PH error function has been used previously in neural models, in optimization of single parameters such as maximum conductances. Here we extend its use to searching for up to 11 parameters at the same time.

Software

The present study used two software packages: the neurosimulator SNNAP and the parameter estimation program PEST.

SNNAP (Simulator for Neural Networks and Action Potentials). SNNAP was designed as a tool for the rapid development and simulation of realistic models of single neurons and neural networks. The electrical properties of individual neurons are described with Hodgkin-Huxley type voltage- and time-dependent ionic currents.

PEST (Parameter ESTimation). PEST is a Windows-executable program that acts as a shell around a simulator, such as SNNAP. The simulator is called through a line command that in this case consists of three elements: the invocation of java, the name of a java archive (*.jar) file such as SNNAP, and the pathname of the simulation input files. PEST interacts with the simulator through ASCII input and output files, a feature that makes it particularly convenient to use with SNNAP. PEST uses a *Gauss-Levenberg-Marquardt* method of parameter estimation. For nonlinear problems parameter estimation is iterative. During each iteration, the relationship between model parameters and model output is linearized by formulating it as a Taylor expansion about the currently best parameter set. PEST then increments each parameter and runs the model *n* times to fill a *m* × *n* Jacobean matrix of partial derivatives, where *m* is the number of state variables and *n* is the number of parameters. This linearized problem is then solved for a better parameter set, and the new parameters are tested by running the model again.

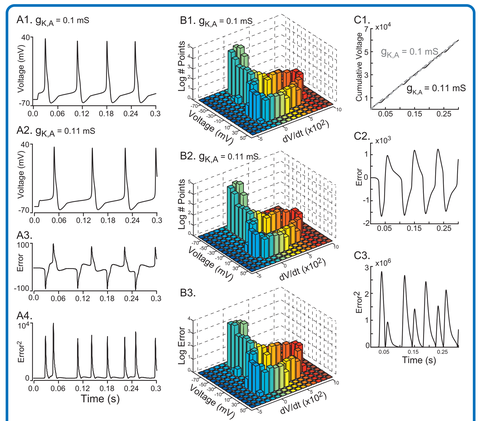

Fig. 1. Three error functions generated by a 10% change in A-type K^+ conductance ($g_{K,A}$). Spike activity was elicited in the model of cell B34 before (**A1**) and after (**A2**) a 10% increase in the value of $g_{K,A}$. **A)** Voltage time-series. A point-by-point subtraction of the voltage traces in **Panels A1** and **A2** produce the error function in **Panel A3**. This error function is squared to produce the function in **Panel A4**, which provides the numerical input to the optimization program. **B)** Phase histogram. The data in **Panels A1** and **A2** were projected into the V:dV/dt phase plane and phase histograms were generated (**Panels B1** and **B2**, respectively). An error function (**Panel B3**) was generated using **Eq. 3**. **C)** Taking the cumulative integral of the two voltage traces before subtraction broadens and smoothes the resulting error function, which provided numerical input to the optimization program.

Models

Three models were examined. The first was the conventional Hodgkin and Huxley mode of a spaced-clamped squid axon. The second was an unpublished model that was developed to replicate the firing properties of identified neuron B34 in the buccal ganglia of *Aplysia*. The third was model developed in the present study to test the ability of the SNNAP/PEST interactions to fit empirical data and parameterize a model. The empirical data were unpublished intracellular recordings of spike trains from identified cell CBI-2 in the cerebral ganglia of *Aplysia*.

Hodgkin-Huxley model (HH model). The HH model included a fast Na^+ (g_{Na}) and delayed K^+ (g_K) conductances. The target dataset were the standard parameters for an action potential at 6.3ºC and 1 cm^2 of membrane.

***Aplysia* cell B34**. There were two fundamental differences between the HH model and the B34. First, in addition to including fast Na^+ and delayed K^+ conductances, the B34 model also included a transient, A-type K^+ conductance ($g_{K,A}$). Second, that activation and inactivation variables for these conductances were modeled with time-constant expressions that utilize Boltzman functions rather that rate-constant functions.

***Aplysia* cell CBI-2**. To test the optimization procedures on empirical data, we created a third model cell. This cell was constructed in two steps. First, capacitance and g_L, the leak conductance, were set by matching the response of model to hyperpolarizing currents (-1 to -5 nA) to those recorded from a CBI-2 neuron in a reduced preparation of the isolated cerebral ganglia. In a second step, maximum conductance and activation/inactivation parameters for the voltage-dependent conductances, which included g_{Na} and g_K, were fit by PEST.

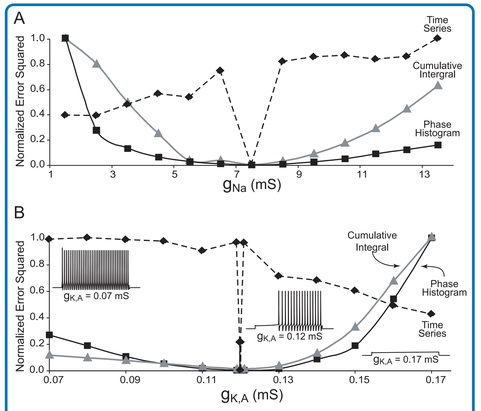

Fig. 2. Systematic manipulation of individual maximum conductances in the B34 model. Summed squared error for each function, normalized by each function's maximum, is plotted vs. maximum conductance. **A)** Sodium conductance. **B)** A-type potassium conductance. In both cases, the VTS shows local minima in regions of silence, where the cell does not spike. Both the CVI and the PH vary smoothly towards a single minimum.

Results

Fig. 2 illustrates the various error functions for current injection into the B34 model. For these simulations, a single parameter was varied systematically. In both cases, the VTS showed a narrow well around the true conductance value, meaning that only close matches to the true value reduced the value of the error function substantially. The gradient of the error function was nearly flat along one side of the VTS function, rendering optimization difficult. In addition, the VTS showed local minima, which can force a non-stochastic optimization program such as PEST to terminate on non-optimal parameter values. In contrast, both the PH and the CVI functions showed a single minimum at the true values of the maximum conductances. Both functions varied smoothly and gradually, which would be expected to improve optimization efficiency.

Estimation of conductance parameters

Having confirmed that the PH function was superior to the VTS and equal to the CVI, we used the PH for the rest of these experiments. Previous studies earlier demonstrated the utility of the PH in recovering single model parameters (LeMasson and Maex 2001). Here we extend its use, first to three parameters, then to 11 parameters. **Table 1** indicates the performance of the PH in recovering the values of three maximum conductance parameters (g_{Na}, g_K, and $g_{K,A}$) from a simulated B34 spike train.

Estimation of half-activation voltages

We next subjected the PH to a more stringent test, asking it to simultaneously recover the values of 3 maximum conductances and 8 activation/inactivation parameters from the two spike train datasets from B34. The responses to 3 and 8 nA of injected current were used for the analysis (see **Fig. 3B**). This is a more difficult condition for the optimization algorithm because when more parameters are fitted, multiple parameter combinations may be able to satisfy the data. The initial values of the parameters, the estimated parameters, and the target data that generated the spike train data are listed in **Table 1**.

Finally, we used the PH to estimate the same 11 parameters from experimental data for cell CBI-2. The values of the initial and estimated parameters are listed in **Table 1** (see **Fig. 3C**).

Input-Output Curves

We tested the robustness of the optimized parameters by injecting a series of constant currents (1-10 nA) into the HH and B34 models. The results of this experiment are illustrated in **Fig. 3**. For the HH and B34 models, the recovered current-frequency curves were quite similar to the target data, even at currents that were not used in the PEST fit. However, as illustrated in **Table 1**, the recovered parameter values for the HH and B34 models were similar to but not identical to the target parameters. Indeed, some cases the target data and recovered parameters differed as much as 50%. This result suggests that there may be no unique solution to the current-frequency relationship for these cells. In addition to re-parameterizing predefined models, PH and parameter estimation algorithm were able to parameterize the CBI-2 model in such a way as to accurately recapitulate the empirical data over a wide range of spiking behaviors (**Fig. 3C**).

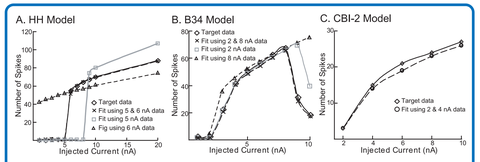

Fig. 3. Predicted current-frequency curves. **A)** HH model. Parameters extracted from either a single experimental dataset (5 nA or 6 nA) failed to predict the firing rate of HH model across the entire range of injected currents. However, simultaneously fitting parameters to both the 5 nA and 6 nA datasets constrained the model that correctly reproduced the firing rates. **B)** B34 model. Parameters estimated from a single simulated dataset (2 nA injected current) correctly predicted the firing rate of the B34 model to several, but not all, of the injected currents. Similarly, parameters estimated from only the 8 nA dataset correctly predicted the firing rate over limited range of injected currents. However, simultaneously fitting the 2 and 8 nA data sets substantially improved the behavior of model. **C)** Cell CBI-2. A pair of experimental datasets (2 nA and 4 nA) was sufficient to constrain the model parameters in such a way that the model could reproduce experimental firing rates over the range tested.

Table 1

B34 Model

	Initial Value	Final Value	Target Data	Relative Sensitivity
$\bar{g}_{Na}$ (µS)	10.5	7.13	7.5	56.23
$\bar{g}_K$ (µS)	35	27.2	25	4.07
$\bar{g}_{K,A}$ (µS)	0.07	0.138	0.1	38

HH Model

	Initial Value	Final Value	Target Data	Relative Sensitivity
g_{Na}				
$\bar{g}_{Na}$ (mScm^{-2})	108	104.37	120	147.97
$V_{1/2}$ of α_m (mV)	38.51	39.18	35.01	189.45
$V_{1/2}$ of β_m (mV)	-54	-56.76	-60	190.4
$V_{1/2}$ of α_h (mV)	-54	-57.58	-60	121.91
$V_{1/2}$ of β_h (mV)	-27	-27.69	-30	121.42
g_K				
$\bar{g}_K$ (mScm^{-2})	40	43.85	36	172.63
$V_{1/2}$ of α_n (mV)	55.01	49.62	50.01	74.34
$V_{1/2}$ of β_n (mV)	-66	-62.68	-60	169.38

	B34 Model				CBI-2 Model		
	Initial Value	Final Value	Target Data	Relative Sensitivity	Initial Value	Final Value	Relative Sensitivity
g_{Na}							
$\bar{g}_{Na}$ (µS)	5.5	12.62	7.5	9.58	14.5	15.76	4.29
$V_{1/2}$ of A_{∞}(mV)	-35.1	-38.46	-39	305.45	-43.1	-42.84	113.70
$V_{1/2}$ of τ_A (mV)	-36	-37.46	-40	133.97	-42	-38.67	3.80
$V_{1/2}$ of B_{∞}(mV)	-54	-54.16	-36	190.42	-67	-66.12	30.25
$V_{1/2}$ of τ_B (mV)	-32	-36.67	-36	2.44	-67.5	-69.62	0.78
g_K							
$\bar{g}_K$ (µS)	20	22.14	25	6.1	25	27.71	1.33
$V_{1/2}$ of A_{∞}(mV)	-21.3	-21.93	-23	234.66	-31.3	-28.75	2.69
$V_{1/2}$ of τ_A (mV)	-8	-15.11	-10	1.39	-23	-21.68	1.57
$V_{1/2}$ of B_{∞}(mV)	-17.2	-22.52	-14.4	1.75	-26.2	-25.08	0.43
$V_{1/2}$ of τ_B (mV)	-17	-15.86	-21	1.34	-33	-26.24	0.69
g_l							
$\bar{g}_l$ (µS)	0.88	0.1	0.1	7.66			

The PH error function was used to recover parameter values from the B34 and HH models and to parameterize a model of CBI-2. **Fig. 2** illustrates recovery of a single parameter. The top Panel of Table 1 illustrates simultaneous recovery of three parameters. The lower Panels illustrate the simultaneous recovery of 8 parameters in the HH model and 11 parameters in the B34 model. Target dataset for the HH and B34 models are listed in the column labeled 'Target Data'. In addition, parameters for a model of CBI-2 were predicted from empirical data that was recorded from CBI-2. Since values for CBI-2 were estimated from experimental data, there are no target values. Initial values were perturbed from the target values by +/-20%. Final values are those estimated after 20-40 PEST iterations. PEST also analyzes the relative sensitivity of each parameter, and these values are reported for the final PEST iteration.

Discussion

Models of neurons and neural circuits are important tools for synthesizing large amounts of disparate empirical data within a dynamical framework that allows for quantitative evaluation of hypotheses of neural function. The value of a model, however, is related to its ability to accurately recapitulate biological function.

Often building models requires estimation of parameters from limited, less than ideal data sets. It would be particularly useful if it was possible to adequately parameterize models using commonly available current-clamp data, such as recordings of spike trains. However, spike trains have properties that are difficult to fit with existing methods. For example, empirical recordings of spike trains often have irregular interspike intervals, and these relatively minor irregularities can make a disproportionate contribution to the error function, which in turn can cause parameter search algorithms to recover less than optimal values for parameters. Such current-clamp data require error functions that are robust to variations in interspike intervals.

The present study compared three methods for generating error functions and examines which method is best suited for analyzing spike train recordings. Two methods, CVI and PH, were found to be insensitive to the problem of local minima and to be very robust. Moreover, these two methods were amenable to deterministic optimization algorithms. To surmount the problem of local minima, most studies use stochastic optimization algorithms, which are less sensitive to local minima, but which require many thousands of model runs to correctly estimate model parameters. Use of error functions without local minima allowed PEST to estimate a modest number of model parameters. For the cases used for the present study, solutions were achieved with usually <30 PEST iterations, which invoked <1000 SNNAP simulations.

PEST was successful in estimating parameter subsets in model-generated data with as little as two datasets. We were unable to uniquely determine all of the parameters of CBI-2 from a single dataset, which is not necessarily surprising. Many complex systems do not have unique solutions, often because increases in one parameter can be offset by decreases in another. When working with limited data, it may not be possible uniquely determine every parameter. However, for functional studies of neural circuits, it may not be necessary to do so. Matching the input-output characteristics of neurons may be adequate for some purposes, such as simulated lesion experiments when one neuron is simply removed from a circuit to determine its contribution to a motor output.

The most commonly used methods for parameterizing models are still trial-and-error and fit-by-eye, a strategy that can be quite successful for relatively simple models. As models and datasets continue to grow in size and complexity, however, automated parameter search methods will become common through sheer necessity. This transition will be eased by simple, robust methods that work with traditional experimental data such as those derived from current injection.

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