Automated Parameter Fitting for Compartmental Models

Workshop chair: Erik De Schutter (Okinawa Institute of Science and Technology, Japan)

Duration 1 day

Abstract: Several factors have caused an increase in the demand for methods that are able to automatically fit the parameters of neuron models. More and more computing power becomes available to neuroscientists so is less difficult to extensively explore the fitness landscape created by, for example, varying the densities or kinetics of the ion channels in a neuron model. Because of the detail used in some compartmental neuron models, it is becoming difficult to hand-tune these parameters. Also the advent of massive modeling efforts like the Blue Brain project has increased the number of cell types that need to be modeled, and the effort that is put into the field. This workshop brings together neuroscientists that have proposed different techniques to search the fitness landscape for optimal parameters that generate neuron model output reproducing experimental data well. But while a lot of progress has been made we are clearly not (yet) as good at parameter fitting as the integrate-and-fire modelers and a wide variety of approaches are being pursued. The workshop will focus on methodological issues: speakers have been invited to give talks that not only point to success, but also to failures or problems encountered.

Program July 22, 2009

Morning Session
9:00
Erik De Schutter (Okinawa Institute of Science and Technology, Japan): Introduction: what should be the goal of automated parameter fitting?

9:20
Naomi Keren and Alon Korngreen (Bar-Ilan University, Israel): Designing your data to fit the fitting routine
10.00
Nathan Lepora, Paul Overton, and Kevin Gurney (University of Sheffield, UK): Current-based optimization techniques for neuronal parameter estimation

10.40
Coffee break

11.00
Werner Van Geit (Okinawa Institute of Science and Technology, Japan): Fitting models to specific experimental data traces using the phase-plane method

11.40
Shaul Druckmann and Idan Segev (Hebrew University Jerusalem, Israel): The predictive power of conductance-based models

12:20
Lunch
Afternoon Session

14:00
Tomasz Smolinski, Amber Hudson and Astrid Prinz (Emory University, USA): Conductance correlations in pacemaking model neurons revealed by parameter exploration using brute-force and evolutionary algorithms

14:40
Erik Sherwood and Joe Tien (Boston University, USA): Parameter estimation for bursting neural models

15:20
Coffee break

15:40
Cengiz Günay, Jeremy R. Edgerton and Dieter Jaeger (Emory University): Channel density distributions explain spiking variability in the globus pallidus

16:20
General discussion: Automated parameter fitting: where are we now and what is in the future?

17:30:
Closure

Abstracts

Introduction: what should be the goal of automated parameter fitting?
Erik De Schutter (Okinawa Institute of Science and Technology, Japan)
Several factors have caused an increase in the demand for methods to automatically fit the parameters of neuron models. As more and more computing power becomes available to neuroscientists, it is less difficult to extensively explore the fitness landscape created by, for example, varying the densities or kinetics of the ion channels in a neuron model. Because of the

detail used in some compartmental neuron models, it is becoming difficult to hand-tune these parameters. Also the advent of massive modeling efforts like the Blue Brain project has increased the number of cell types that need to be modeled, and the effort that is put into the field.
This workshop brings together neuroscientists that have proposed different techniques to search the fitness landscape for optimal parameters that generate neuron model output similar to experimental data. But while a lot of progress has been made, perfect parameter fitting has rarely been achieved and a wide variety of approaches are being pursued. Some lessons have been learned. For example, success at fitting surrogate data (output from a computer model) does not guarantee success at fitting real experimental data and this makes it difficult to evaluate fitting methods. One can also distinguish differences in the criteria used to judge the qualify of the fits. Feature-based fitting methods build canonical models that are statistically matched to the data. Trace-fitting methods try to find models that faithfully replicate specific voltage recordings. The difficulties faced and the outcomes generated by these two approaches can be very different and the choice of fitting method should match the scientific question being investigated.

Designing your data to fit the fitting routine
Naomi Keren and Alon Korngreen (Bar-Ilan University, Israel)
Compartmental models with many non-linearly dependent parameters are routinely used to investigate the physiology of complex neurons. However, the number of loosely constrained parameters makes manually constructing the desired model a daunting if not an impossible task. Recently, progress has been made using automated parameter search methods, such as genetic algorithms. However, these methods have been applied to somatically recorded action potentials using relatively simple target functions. Can dendritic recordings help constrain the compartmental model better? Using a genetic minimization algorithm and a reduced compartmental model based on a previously published model of layer 5 (L5) neocortical pyramidal neurons we compared the efficacy of five cost functions to constrain the model. When the model was constrained using somatic recordings only, the combined cost function was found to be the most effective. The combined cost function was then applied to investigate the contribution of dendritic and axonal recordings to the ability of the genetic algorithm to constrain the model. The more recording locations from the dendrite and the axon were added to the data set the better was the genetic minimization algorithm able to constrain the compartmental model. Based on these simulations we propose an experimental scheme that, in combination with a genetic minimization algorithm, may be used to constrain compartmental models of neurons. However, practical recordings from L5 pyramidal neurons are routinely performed from only two locations simultaneously. We show that a data set recorded from the soma and apical dendrite in combination with a parameter pealing procedure is sufficient to constrain a compartmental model for the apical dendrite of L5 pyramidal neurons. The pealing procedure was tested extensively on several compartmental models showing that it is able to avoid local minima in parameter space. The results support the hypothesis that conductance density gradients, within one sub type of neurons, vary in a small parameter space and not over large parameter manifolds.

Current-based optimization techniques for neuronal parameter estimation
Nathan Lepora, Paul Overton, and Kevin Gurney (University of Sheffield, UK)

Most existing methods for fitting conductance-based models to somatic current clamp data rely on constructing an error between the measured and modeled voltage traces, and then using a sophisticated search algorithm to find the optimal model parameters that minimize this voltage error. Our laboratory has been exploring a search strategy in which inferred channel currents in the soma are fitted to an inferred total current flow through the channels; the somatic voltage traces are then found indirectly from the current fits. The reason for our interest in this technique is that the maximal conductance (Gmax) parameters linearly scale the channel currents, which suggests the optimization problem can be solved more easily than if the voltage traces are used directly. In contrast with many other techniques, ours can utilize deterministic search methods and is and therefore computationally very efficient. In the first stage of this work, we tested this current-based search technique on single compartment model neurons found by [Popischill et al 2009] to fit a range of neuronal types, including bursters and other types of non-uniform firing rate. If the channels and passive membrane parameters are assumed known, then we could accurately find the target Gmaxs in just a few seconds of simulation time for all model neurons. These fits deteriorated rapidly for sampling rates <100kHz because the data became too sparse to capture the fast currents. Fortunately, we were able to successfully apply the method to physiological sampling rates ~20kHz by interpolating the test data to higher sampling frequencies. Varying the channels kinetics away from their targets gave a graceful deterioration of the Gmax estimates, and the error in the currents was a smooth U-shaped function of e.g. the half-way activation/inactivation voltages. Meanwhile, the corresponding voltage traces deviated from their targets in a complex way—for example, the phase plane voltage error had many local minima superimposed on a global minimum at the target kinetic parameters. These results are being applied to current clamp data from medium spiny neurons. Because of the smooth U-shaped error function with channel kinetics, a deterministic (simplex) search was sufficient to find the kinetics that minimize the inferred current error within each spike. Several methods are being compared to find the Gmaxs for the other channels, which determine the spiking timing features of the voltage traces, including using additional information from sub-threshold voltage traces and post-hoc tuning of the neuronal parameters to the voltage trace. Once this part of the work is complete, we will examine the effect of active dendrites within the model neuron by including the axial current and optimizing over dendritic channel parameters. Initial work suggests that an iterative (yet still deterministic) method will extend the technique to such cases. In addition the iterative approach has a good analytic foundation in the theory of root-finding, thereby promising insights into the specific effects of different kinds of error on the solution.

Fitting models to specific experimental data traces using the phase-plane method

Werner Van Geit (Okinawa Institute of Science and Technology, Japan)

Neurofitter is a tool that allows scientists to automatically tune free parameters of a neuron model to experimental data. It thereby uses phase plane trajectory density plots of the recorded traces, to score the ability of sets of model parameter values to reproduce the experimental data in a neuron simulator. Relying on these density plots for the fitness measure has as advantage that the method is less sensitive to small time shifts between different traces. To find the best parameter values in the solution space Neurofitter applies general global optimization algorithms. A previous study has demonstrated that the method is able to fit a cerebellar Purkinje cell model to data consisting of voltage recordings that were produced by the model itself with the ion channel maximal conductances set to values unknown to the method. In this study we

show results of fitting a compartmental model containing Na, K, Ca and Ih currents to data that consists of 13 voltage traces recorded from Purkinje cells experimentally using a current clamp setup with different current injection steps. Using real experimental data as target of the optimization introduces new challenges, not only because of the existence of noise in the recorded traces, but also because, unlike in the case of surrogate data, the underlying activation/inactivation kinetics of the ion channels are not necessarily fully known. If the only parameters that Neurofitter can tune are the maximal conductances, it will in most cases not be able to fit the traces if the fixed parameters are too different from the actual values in the recorded cell. Therefore we included the ion channel kinetics as parameters in the search, thereby largely increasing the total number of dimensions of the optimization problem. Introducing a multi-objective genetic optimization algorithm increased the performance of the search in this complicated parameter space.

The predictive power of conductance-based models
Shaul Druckmann and Idan Segev (Hebrew University Jerusalem, Israel)

Conductance correlations in pacemaking model neurons revealed by parameter exploration using brute-force and evolutionary algorithms
Tomasz Smolinski, Amber Hudson and Astrid Prinz (Emory University, USA)

Parameter estimation for bursting neural models
Erik Sherwood and Joe Tien (Boston University, USA)

Channel density distributions explain spiking variability in the globus pallidus
Cengiz Günay, Jeremy R. Edgerton and Dieter Jaeger (Emory University)
Globus pallidus (GP) neurons recorded in brain slices show significant variability in intrinsic electrophysiological properties. To investigate how this variability arises, we manipulated the biophysical properties of GP neurons using computer simulations. Specifically, we created a GP neuron model database with 100,602 models that had varying densities of nine membrane conductances centered on a hand-tuned model that replicated typical physiological data. To test the hypothesis that the experimentally observed variability can be attributed to variations in conductance densities, we compared our model database results to a physiology database of 146 slice recordings. The electrophysiological properties of generated models and recordings were assessed with identical current injection protocols and analyzed with a uniform set of measures, allowing a systematic analysis of the effects of varying voltage-gated and calcium-gated conductance densities on the measured properties and a detailed comparison between models and recordings. Our results indicated that most of the experimental variability could be matched by varying conductance densities, which we confirmed with additional partial block experiments. Further analysis resulted in two key observations: (1) each voltage-gated conductance had effects on multiple measures such as action potential waveform and spontaneous or stimulated spike rates; and (2) the effect of each conductance was highly dependent on the background context of other conductances present. In some cases, such interactions could reverse the effect of the density of one conductance on important excitability measures. This context dependence of conductance density effects is important to understand drug and neuromodulator effects that work by affecting ion channels.

Bibliography

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