A Novel Parameter Optimisation Technique for Compartmental Models Applied to a Model of a Striatal Medium Spiny Neuron

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Introduction

The neostriatum accounts for over 95% of the neurons in the dorsal division of the rat basal ganglia - a set of sub-cortical structures which is critical in initiating and shaping movement. The neostriatum is, in turn, comprised overwhelmingly of a single type of neuron, the medium spiny projection (MSP) cell. An understanding of these cells is, therefore, crucial for an understanding of dorsal basal ganglia function.

MSP neurons receive a variety of local input including GABAergic and cholinergic synapses from other striatal neurons, and dopaminergic input from the substantia nigra. In addition to the local afferents the medium spiny neurons are also the major target of cortical afferents projecting to the basal ganglia, and express both AMPA and NMDA glutamertergic synapses. The membrane of medium spiny neurons expresses a rich variety of voltage dependent ionic currents mediated by potassium, sodium and calcium.. These include an inward (or anomalous) rectifier (Mermelstein et al, 1998), a persistent potassium current (Gabel & Nisenbaum, 1999), fast and slow A currents (Gabel & Nisenbaum, 1998; Surmeier, 1989), a persistent and a slowly inactivating sodium current (Chao & Alzheimer, 1995; Hoehn et al, 1993), and L-type and N-type calcium currents (Bargas et al, 1994). In the presence of these channels it is not surprising that these neurons also display a range of interesting physiological behaviours, including ramp depolarisation, a dual-state behaviour (Nisenbaum & Wilson, 1995), hysteresis and dendritic calcium spikes

The structural and behavioural complexity of MSP neurons therefore make them an interesting and challenging target for computational modelling. One of the key difficulties in modelling neurons that display such a rich membrane behaviour, is finding a consistent set of parameters. While it is possible to obtain some parameter values from published observations, the modeller is usually left with a number of 'blank spaces' to fill in. This is further compounded by the fact that a key subset of the parameters – the maximal channel conductances (*Gmaxs*) - can vary substantially from one cell to the next in the same population. In particular, Golowasch et al (1999) observed that these parameters will vary adaptively to ensure a target behaviour for the neuron. Thus, their values depend critically on the morphology of an individual cell, and experimental measurements may be of little use for a particular model neuron. The modeller may hand-craft the parameters to fit experimental data but this approach can be extremely time consuming with models of only moderate complexity. A more efficient method is to use a parameter optimisation technique. In many cases, however, these rely on stochastic search methods and can be very computationally demanding, requiring many thousands of iterations to converge to a solution. We therefore sought to develop a deterministic parameter search technique specifically targeted at finding the maximal conductances by taking advantage of their linear occurrence in the membrane equation.

Method

We used a two compartment model to simulate the medium spiny neuron, which included four potassium channels (IKir, IKrp, IKAs, IKAf), two sodium channels (INaP and INaS), an L-type calcium channel (ICa-L), and 'Hodgkin-Huxley' action potential currents (IKdr, INa). The passive parameters were estimated by fitting an analytic solution of the model with no active currents to experimental data from a neuron treated with TTX, Cadmium, 4-AP and TEA (Nisenbaum & Wilson, 1995). The gating kinetics of all channels apart from IKdr, IKAf and INa were obtained from published data for MSP neurons, while kinetics for IKAf were taken from a model of a cerebellar purkinje cell (De Schutter & Bower, 1994), and the 'Hodgkin-Huxley' channels from a hippocampal model neuron (Traub, 1991). We then optimised the maximal ionic conductances with our search technique by matching simulation output to current injection data.

The search is based on the observation that the maximal conductances, *Gmaxs*, occur linearly within the membrane equation. We then construct a set of such equations, with one equation for each experimental voltage-current data point. If the gating variables were known, we could then proceed to solve (using least squares techniques) these equations for the *Gmaxs*. In fact, of course, the gating variables are not known and so are estimated by running the simulation using the current value of the *Gmaxs*. The search then iterates by repeatedly solving the linear equations for

the *Gmaxs,* and then using these values in the model simulation to obtain new estimates for the gating variables which are then, in turn, substituted back into the original equation set. For complex membranes where instability threatens to take hold if the conductances are poorly conditioned, the search may be controlled by projecting the *Gmaxs* vector incrementally in the direction suggested by the search, rather than taking the newly solved values themselves.

Results

- The search converges rapidly and deterministically on a solution. Depending on the number of currents in the model it may take from between ~15 to ~100 iterations to find a good fit to the data
- The search can accommodate both inward and outward currents, the leakage current, and passive parameters.
- Searching on data sets generated by the model itself has demonstrated the robustness of the search in being independent of initial parameter values and its ability find exact solutions if they exist.
- For experiments with experimental MSP neuron data, we obtained parameter sets that enabled good fits to experimental current clamp data for neurons poisoned with a variety of toxins (including TTX, cadmium, TEA and 4-AP) as well as untreated neurons.
- For untreated neurons we were able to demonstrate one of the characteristic features of MSP neurons: slow ramp depolarisation to first spike initiation

Discussion

A similar technique has been proposed independently by Hines et al (2001) but which relies on clamping the gating variables to the experimentally determined membrane voltage. While this appears to be more efficient (it doesn't require iteratively searching for the gating variable time series) there are two drawback with this technique. First, it is only applicable to single compartment models since we do not, in general, have access to voltage clamp data for the dendrites. Second, it assumes that the set of channels in the model can, indeed, follow the experimental voltage time course; in general an exact fit is not possible and so the gates are driven into states that are not internally consistent with each other. In our search technique, there is no limitation to the number of compartments, although we are, of course, limited to searching on Gmaxes in each compartment that are fixed multiples of those in the soma. Second, the parameters obtained always represent a consistent solution to the model.

We are currently conducting experiments using glutamatergic input applied to the models obtained using our search. The preliminary results are suggestive of our being able to replicate further characteristic features of MSP neurons including dual-state behaviour and non-synaptic dopaminergic modulation of this behaviour.

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