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

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Abstract

We present a novel deterministic search technique for finding a set of maximal conductances in multi-compartmental models, and apply this to a model of a striatal medium spiny neuron. The search rapidly converges on a set of maximal conductances by fitting simulation output to current injection data. The search is robust, finding solutions in the presence of a multitude of inward and outward ionic currents, and is extendible to include a subset of the passive membrane parameters. After incorporating synaptic input, the resulting model of the medium spiny neuron provides a good fit to a range of experimental data.

keywords: parameter search, compartmental models, medium spiny neuron, neostriatum, basal ganglia

1 Introduction

One of the key difficulties in modelling neurons at the biophysical level of description is finding a consistent set of parameter values. In general, the modeller has access to only a limited number of parameters from published data. This is further compounded by the fact that a key subset of the parameters, the maximal channel conductances (G_{max}) can vary substantially from one cell to the next within 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 its past activity, so estimates of G_{max} based directly on experimental measurement may be of little use in a modelling context. One method of overcoming this problem is to handcraft the parameters to fit experimental

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data. However, even in models of intermediate complexity, the typical number of parameters that need to be fitted is sufficient to make this an extremely difficult and time consuming process. In practice the modeller will usually stop when the model is able to make a rough approximation of the target system.

A more efficient and principled method to determine the parameter values is to use a parameter optimisation technique. Typically these rely on stochastic search methods such as simulated annealing or genetic algorithms. While these methods offer a solution to the pitfalls of hand-fitting, they are also very computationally demanding, requiring many thousands of iterations to converge to a solution.

The power of these stochastic search methods is that they can be applied to almost any system of equations. However, by designing a search method limited to one particular problem, we can take advantage of the mathematics of the target system, and the natural constraints of its parameters, to design a more efficient method: this is the approach adopted here to optimise G_{max}. We have previously shown an early version of our technique successfully searching against limited biological data [10], and have validated the technique against 'data' generated by a simulation [11].

In order to develop the search it is necessary to choose an appropriate neuronal 'test-bed'. The rich membrane and range of physiological behaviors of the neostriatal medium spiny neuron (MSN) makes this cell an ideal candidate. We therefore applied the search to a model of the MSN constrained by experimental *in vitro* current injection data obtained in a study previously published by Nisenbaum and Wilson (1995).

While the search may be able to accurately fit a model to current clamp data, it remains to be discovered whether such constraints are sufficient to ensure a model that is physiologically plausible in other respects. We therefore added synaptic input to the model to test it against a range of physiological behaviours characteristic of MSNs.

2 Methods

2.1 Parameter Search

Consider a multi-compartment model with a soma (membrane potential V_s, leakage potential E_s, and membrane resistance and capacitance R_s, C_s) and some dendritic trunks (potential V_i, axial resistance of the soma R_a^i). In addition the soma has active channels with voltage dependent conductances G_k and reversal potentials E_k. We also suppose an injection current at the soma, I_{inj}. The dendrites may branch after the trunks and have their own active channels but we don't specify these here as the basis for the search technique is

contingent on the somatic potential only.

The membrane equation for the soma is then given by

$$C_s \frac{dV_s}{dt} = \frac{V_s - E_s}{R_s} + \sum_k^N G_k(V_s - E_k) + \sum_i \frac{V_i - V_s}{R_a^i} + I_{inj} \tag{1}$$

in which there are N active conductances. If G is a generic voltage-dependent conductance in the soma

$$G = G_{max} n(V_s, t, \boldsymbol{\zeta}) m(V_s, t, \boldsymbol{\eta})$$

Here n and m are normalised gating variables which are functions of V_s, t, and vectors of kinetic parameter $\boldsymbol{\zeta}$ and $\boldsymbol{\eta}$ (in general m, n will have associated exponents, but these have been omitted for ease of notation); G_{max} is the maximum conductance.

We can take advantage of the linear occurrence of G_{max} in the membrane equation by rewriting (1) as

$$\sum_k A_k G_{max}^k = b \tag{2}$$

where for the k^{th} channel

$$A_k = n_k(V_s) m_k(V_s)(V_s - E_k) \tag{3}$$

$$b = C_s \frac{dV_s}{dt} - \frac{(V_s - E_s)}{R_s} - \sum_i \frac{V_s - V_i}{R_a^i} - I_{inj} \tag{4}$$

and, in (3), the dependence on t and on the kinetic parameters $\boldsymbol{\zeta}$ and $\boldsymbol{\eta}$ has been suppressed.

We now constrain the coefficients A_k using experimental data and solve a set of linear equations of the form (2). If we assume that the model was capable of perfectly following the voltage trajectory of the experimental data we could use a dynamic voltage-clamp in the model, allowing us to substitute V_s in (3) with values from the biological recordings. However, if there is no solution of the model that can fit the data exactly, the dynamic clamp will exercise the channel kinetics over a trajectory that does not represent a best fit available to the model. This will result, in turn, in any G_{max} values being suboptimal. To avoid this, we 'clamp' the membrane voltage in a less rigid fashion by introducing it only in the driving force, and the derivatives dV_s/dt. It then remains to get estimates of the gating variables $m(V_s), n(V_s)$. This is done by running the model in simulation with an initial estimate $\boldsymbol{g}_0$ of $\boldsymbol{g}_{max}$, the vector of maximal conductance values $(G_{max}^1, G_{max}^2 .... G_{max}^N)$. Thus, if $V_s^*[t_i]$ and $V_s[t_i]$ are the experimental and model-derived somatic membrane potentials at time t_i, respectively

$$A_k = n_k(V_s[t_i])m_k(V_s[t_i])(V_s^*[t_i] - E_k) \tag{5}$$

$$b = C_s \left.\frac{dV_s^*}{dt}\right|_{t_i} - \frac{(V_s^*[t_i] - E_s)}{R_s} - \sum_i \frac{V_s^*[t_i] - V_i[t_i]}{R_a^i} - I_{inj}$$

where $V_i[t_i]$ is the membrane potential of the ith dendritic trunk adjoining the soma. Notice that this is necessarily a model-derived quantity since, in general, we only have access to somatic recordings. This also implies that, in obtaining model solutions in the dendrites, the G_{max} values there cannot be obtained by a process of fitting to data. However, it is possible to proceed by setting the specific maximal conductances of each current in the dendritic compartments to be in a fixed ratio with its somatic counterpart. Without firm data to direct us otherwise, these ratios were set to 1.

Replicating this process over time samples and current injections gives a set of equations of the form given in (2), in which the coefficients A_k of the G_{max} and the constant b are given by expressions of the form in (5). These equations may be conveniently expressed in matrix form

$$\mathbf{A}(\boldsymbol{g}_0)\boldsymbol{g}_{max} = \boldsymbol{b}(\boldsymbol{g}_0) \tag{6}$$

where the model dependence of $\mathbf{A}$ and $\boldsymbol{b}$ on the initial estimate $\boldsymbol{g}_0$ of maximal conductances has been made explicit. We now solve (6) using a least squares technique to get a new *target* $\tilde{\boldsymbol{g}}_1$ of the maximal conductances. However, empirically, moving to the new target immediately results in instability. The new estimate $\boldsymbol{g}_1$ is therefore based on a more conservative change according to $\boldsymbol{g}_1 = \lambda(\tilde{\boldsymbol{g}}_1 - \boldsymbol{g}_0)$ where λ is a 'search rate'. This process proceeds iteratively until the error between V_s^* and the corresponding simulation output, V_s, is not decreasing appreciably.

2.2 Medium Spiny Neuron Model

We used a 64 compartment model to simulate a MSN, with the morphology of the model based on summaries published in Wilson (1999), and Bennett and Wilson (2000). The passive parameters were set to biologically realistic values. The membrane of MSNs expresses a rich variety of voltage dependent potassium (K^+), sodium (Na^+) and calcium (Ca^{2+}), mediated ionic currents. The model MSN included an inward rectifier (Kir), a persistent K^+ current (Krp), fast and slow A-type K^+ currents (KAf and KAs respectively), a persistent and a slowly inactivating Na^+ current (NaP and NaS respectively), an L-type Ca^{2+} current (Ca-L), and 'Hodgkin-

Huxley action potential currents (Kdr, Naf). The gating kinetics for Krp, Kir, KAs, NaP, NaS and Ca-L were based on published data for MSNs, the kinetics for KAf, Kdr and Naf were taken from other models. The search technique was applied to a model that included all the subthreshold currents (Krp, Kir, KAf, KAs, NaP, and NaS). The G_{max} values for the suprathreshold channels (Kdr, Naf, and Ca-L), were fitted by hand after the search.

3 Results

3.1 Fitting to current injection data

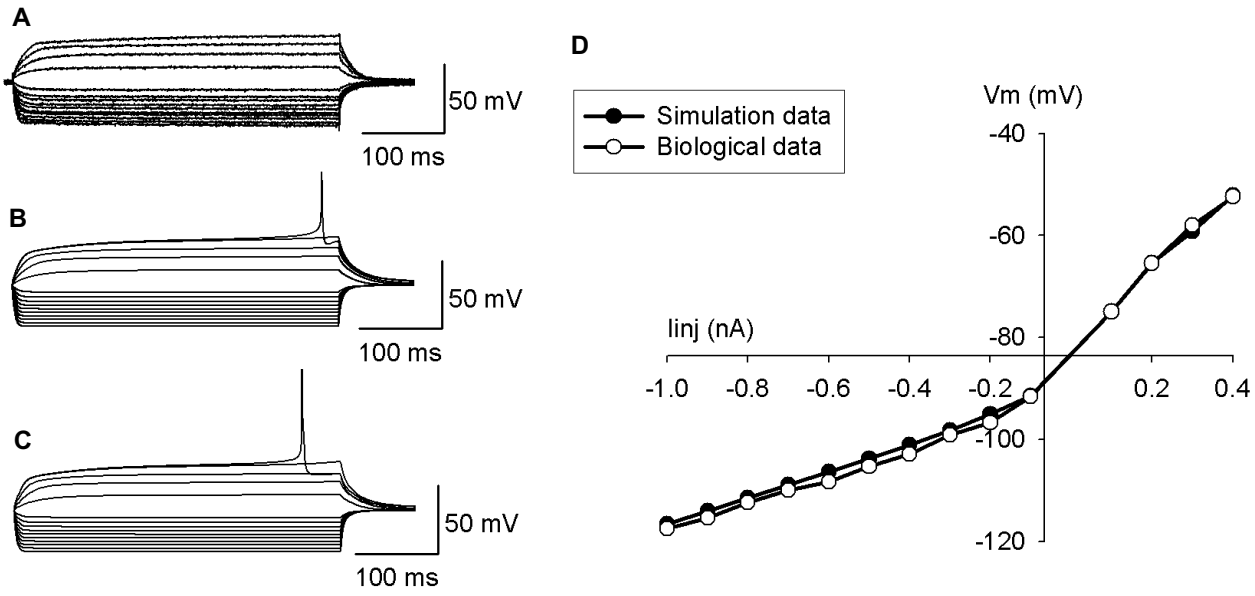

Figure 1: A, The response of a medium spiny neuron, to hyperpolarising (-1.0 to -0.1nA) and depolarising (0.1 to 0.4nA) constant current pulses of 400ms duration (from data used in [8]). B, the results from the simulation under the same conditions as A, and C, with an additional current injection pulse of 0.41nA. D, current-voltage plot of biological and simulation data.

The response of medium spiny neurons to current injection pulses (Figure 1) is characterised by a marked rectification of the membrane potential in response to hyperpolarising current pulses, a slowly developing ramp depolarisation, and long latency to spike discharge using a threshold current pulse [8].

We used the search to fit our model MSN to the data shown in figure 1A. The search typically took 200 iterations to converge to a good fit to the data. The model was then able to capture the dynamic

subthreshold behaviour, as well as the current-voltage relationship of the cell (Figure 1D). Adding Kdr and Naf to the model, and applying an additional current injection of 0.41nA, resulted in the characteristic ramp depolarisation and latency to spike discharge (Figure 1B). The amplitude of action potentials in MSNs are typically quite large, ranging from 50 to 76mV [4]; adding Ca-L to the model increased the spike amplitude from roughly 45mV to 65mV (Figure 1C).

3.2 Driving the model with synaptic input

In order to show the model working under more natural physiological conditions, synapses using NMDA and non-NMDA glutamatergic receptors were added to the model (the model of the NMDA receptors included a magnesium block). The synapses were located in eight of the models compartments, distributed randomly over the dendritic trees. The cortical input was simulated by Poisson distributed spike trains, governed by a probability parameter that varied in time with a rectangular waveform. This was designed to mimic the slow-wave (1Hz) oscillatory activity of the cortex seen in figure 2A, typical of slow wave sleep and anesthesia in the rat [3]. Driving the model with a similar pattern of synaptic input resulted in a low firing frequency, fast up-state transitions, and a slower return to the down-state, characteristic behaviour of MSNs (figure 2D). In addition there is synchrony in the model between the MSN membrane potential and the cortical input as observed *in vivo* [5, 3].

3.3 Short term facilitation

In a series of *in vivo* experiments in the MSN, Mahon et al have shown that current pulses strong enough to elicit ramp depolarisation, cause a time dependent increase in the excitability of these cells that is dependent on their intrinsic membrane properties (i.e. not synaptic-based). We used a stimulus paradigm in our model, similar to that used by Mahon et al, to examine this phenomenon. The results show a time dependent increase in excitability in line with the *in vivo* data (Figure 3)

4 Discussion

The search was able to fit the model to experimental biological current clamp data in a computationally efficient way. The resulting model was able to generalise to capture a range of current injection driven, and synaptically driven, behaviours. This suggests that there is enough information in the original current clamp

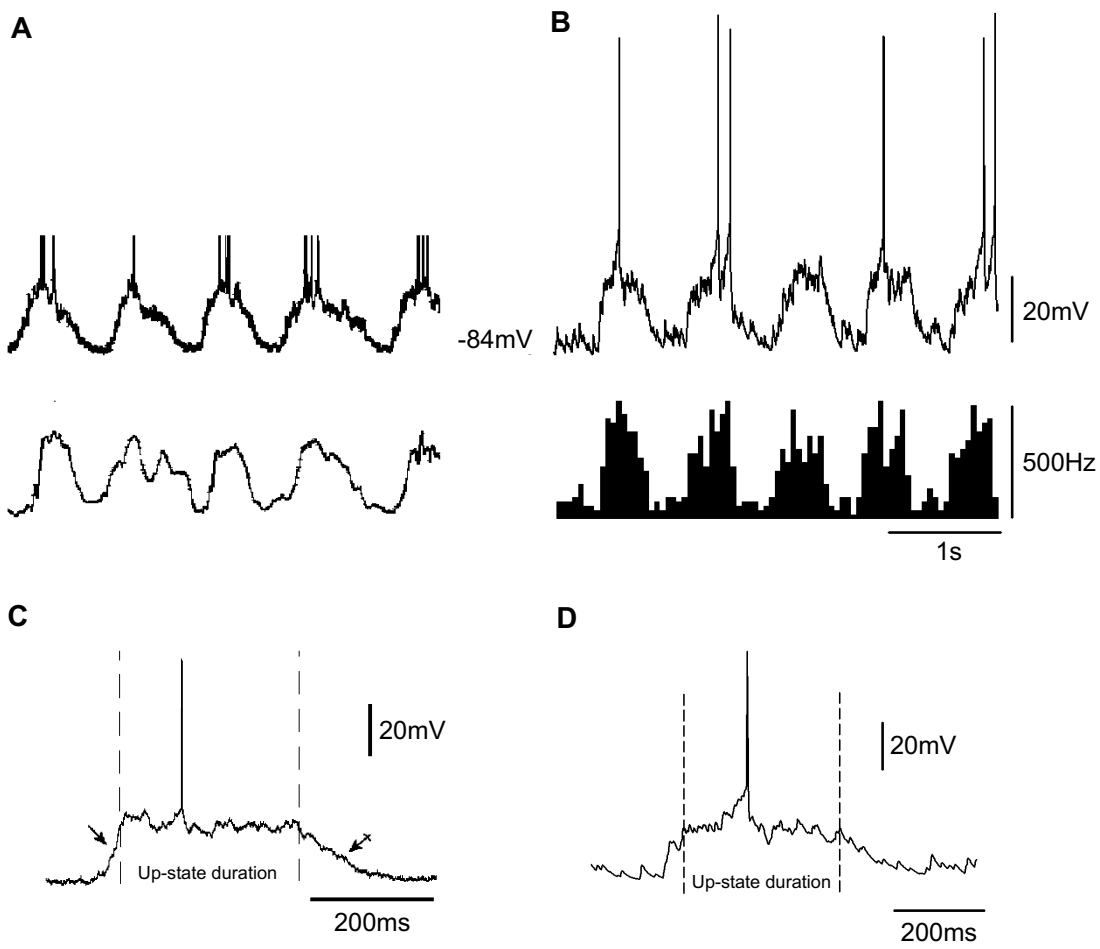

Figure 2: A, intracellular recording from a medium spiny neuron (top) and a simultaneous electrocorticogram (ECoG) recording (bottom) [3], spikes are truncated at -20mV. The slow 1Hz oscillation of the ECoG recording and the state transitions of the MSN occur in synchrony [5, 3]. B, plot of the model V_m (top), and histogram of the spike rate of the simulated cortical input (bottom). C, intracellular recording from a MSN showing the fast transition to the up-state (arrow), and the slower return to the down-state (crossed arrow) [5]. D, the model shows similar behaviour in making the transitions between the two states.

data to constrain the search in order to find a set of G_{max} values that is representative of the real cell.

Hines et al [7] has independently developed a similar search technique based on the membrane equation linearity with respect to G_{max}. However, their algorithm uses a dynamic voltage clamp whose shortcomings have already been noted in the Methods. In addition, an iterative technique (such as the one presented here) is necessary in order to deal with multi-compartmental models in which clamp data for all compartments is unknown.

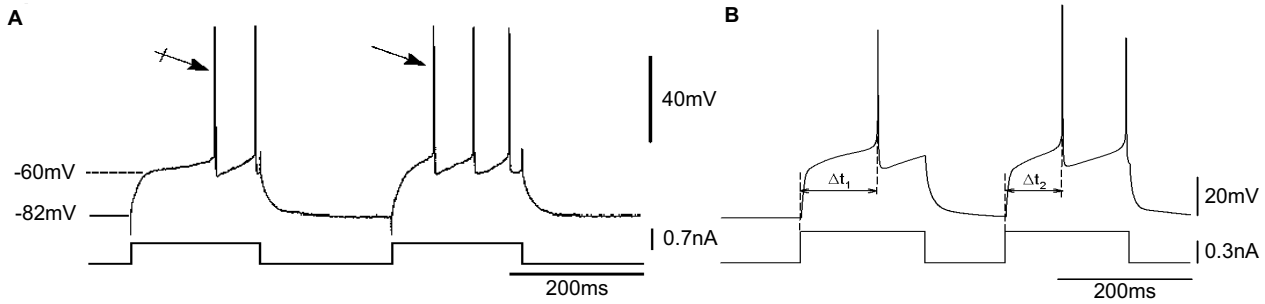

Figure 3: A, the response of a MSN to two consecutive current pulses. An initial current pulse leads to an increase in the excitability of the membrane [6]. This is seen during the second pulse as, 1) an increase in the slope of the ramp depolarisation, 2) a reduced time to first spike, and 3) an increase in the number of spikes. B, following a similar experimental protocol in the model we see all three features associated with facilitation in the MSN.

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