Inverse Problems in Neuronal Calcium

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1. Introduction

A. Abstract

Neuronal calcium handling machinery both sculpts and is sculpted by synaptic input. This interplay is known to take place in a highly nonuniform fashion, with distinct types of voltage-gated calcium channels found in distinct regions of the dendritic tree and distinct types of Ca sensitive receptors likewise partitioned along the ER. To date, this Ca channel/receptor map has been too crude to contribute to predictive models of synaptic integration and neuromodulation. The recent development of novel fluorescent microscopy techniques enable high resolution spatial-temporal measurement of buffered intracellular calcium to be made in single cells of rodent hippocampal slices. We exploit this imaging capability and, utilizing two experimental protocols of differing time-scales, implement methods to infer from the dye-buffered data

- Intracellular calcium concentrations and associated currents
- Density of membrane-bound voltage-gated calcium channels and density of ER bound Ca sensitive receptors

2. Single-Cell Model

A. Overall assumptions

- We account for intracellular calcium, Ca, fluorescent-dye-bound calcium, CaB, and protein-buffered calcium CaE.
- Ca, CaB, and CaE are diffusible within the cell.
- Extracellular and ER calcium levels are constant.
- Through experiment, we can measure CaB.

B. Simplified calcium dynamics

$$\mathrm{Ca}^{2+} + \mathrm{B} \overset{k_b^{\pm}}{\leftrightarrow} \mathrm{CaB}$$

$$\mathrm{Ca}^{2+} + \mathrm{E} \overset{k_e^{\pm}}{\leftrightarrow} \mathrm{CaE}$$

- We denote the total concentration of fluorescent dye, B_{tot}, and native buffers, E_{tot}.

$$B_{tot} = B_{unb} + b$$

$$E_{tot} = E_{unb} + e$$

- From the law of mass action, we derive a system of reaction-diffusion equations for [Ca]: (*c*), [CaB]: (*b*), and [CaE]: (*e*):

$$b_t = D_b b_{xx} + k_b^+ c(B_{tot} - b) - k_b^- b$$

$$e_t = D_e e_{xx} + k_e^+ c(E_{tot} - e) - k_e^- e$$

$$c_t = D_c c_{xx} + k_b^- b + k_e^- e - k_b^+(B_{tot} - b) - k_e^+(E_{tot} - e)$$

$$b_x(0,t) = b_x(L,t) = 0$$

$$e_x(0,t) = e_x(L,t) = 0$$

$$c_x(0,t) = c_x(L,t) = 0$$

- To denote no-flux conditions at the dendrite terminals, we impose homogeneous Neumann boundary conditions.

3. c from b following uncaging

Objective: Recover *c* from measurements of *b*

A. Define the error function

$$\min_c \Phi(c) = \min_c \left\{ \frac{1}{2} \sum_{j=1}^{N} \int_0^T (b^\sharp(x_j,t) - b(x_j,t;c))^2 dt \right\}$$

- Data, $b^\sharp$, are time series from N measurement sites on the cell.
- Minimize error function over all possible calcium profiles *c(x,t)*.
- *b* must satisfy the aforementioned reaction-diffusion equation.

B. Define Lagrangian with adjoint variable, *B*

$$L(c,b,B) = \frac{1}{2} \sum_{j=1}^{N} \int_0^T \left(b^\sharp(x_j,t) - b(x_j,t;c)\right)^2 dt + \int_0^T \int_0^\ell \left(b_t - D_b b_{xx} - k_b^+ c(B_{tot} - b) + k_b^- b \right) B dx dt$$

C. Derive the gradient of the error function

- Write the error function in terms of the Lagrangian:

$$\Phi(c) = \min_b \max_B L(c,b,B)$$

- Derive the directional gradient of the error function, assuming that L is at a critical point:

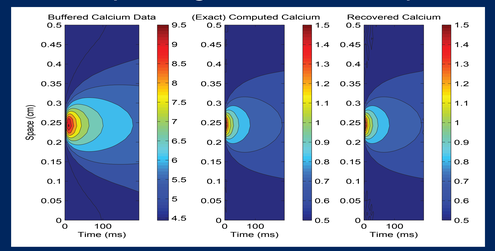
$$\langle \partial\Phi(c), \tilde{c} \rangle = \langle \partial_c L(c,b,B), \tilde{c} \rangle = -\int_0^T \int_0^\ell k_b^+(B_{tot} - b) B \tilde{c} dx dt$$

- For *L* to be at this critical point, the following must hold:

$$0 = \left\langle \partial_b L(c,b,B), \tilde{b} \right\rangle = \int_0^T -D_b \tilde{b}(0,t) B_x(0,t) dt + \int_0^T D_b \tilde{b}(\ell,t) B_x(\ell,t) dt + \int_0^\ell \tilde{b}(x,T) B(x,T) dx + \int_0^T \int_0^\ell \left(-B_t - D_b B_{xx} + k_b^+ cB + k_b^- B + \sum_{j=1}^{N} \delta(x - x_j)(b - b^\sharp) \right) \tilde{b} dx dt$$

- Thus, *B* must satisfy an 'adjoint' reaction-diffusion equation.

D. Use computed gradient to find optimal *c*



Our intial guess was a constant concentration across space and time based on our measurement data. Our relative 2-norm and inf-norm errors were 0.0029 and 0.0174, respectively. Using the adjoint gradient gives over a hundred-fold speed increase when compared to using Matlab's *fminunc* without a user-inputed gradient.

4. g_{Ca} from b during AP volley

Objective: Recover g_{Ca} from measurements of *b*

A. Define calcium flux from calcium channels

$$J_{in} = I_{Ca}/\gamma$$

$$c_t = D_c c_{xx} + k_b^- b + k_e^- e - k_b^+(B_{tot} - b) - k_e^+(E_{tot} - e) + J_{in}$$

- Add calcium channel-flux to calcium reaction-diffusion equation
- Inward flux is defined by a scaled calcium channel current

B. Invert and differentiate twice to find I_{Ca}

$$I_{Ca} = [c_t - (k_b^- + k_b^+)b - (k_e^- + k_e^+)e + k_b^+ B_{tot} + k_e^+ E_{tot}]\gamma$$

$$c = \frac{b_t + k_b^- b}{k_b^+(B_{tot} - b)}$$

- Due to the relative slowness of diffusion in the context of the brief data-collection intervals, the diffusion terms can be ignored.
- The measurements are de-noised with smoothing splines.

C. Solve for membrane potentials

- Using the computed I_{Ca} as a driving term in the active cable model, obtain the membrane potential profile, *v(x,t)*.
- Duplicate the initiating stimulus *I(t)* applied in the experimental setup (current injection at the cell-body).
- We assume prior knowledge of the other membrane currents, I_{Ca}, I_{Na}, and I_K.

$$\frac{1}{R_a r}(r^2 v_x)_x = C_m v_t + I_L + I_{Na} + I_K + I_{Ca}$$

$$v_x(0,t) = \frac{R_a}{\pi r^2} I(t), \quad v_x(\ell_i,t) = 0, \quad i = 1, \ldots, N_{leaf}$$

- R_a : axial resistivity
- C_m : membrane capacitance
- *r* : dendritic radius

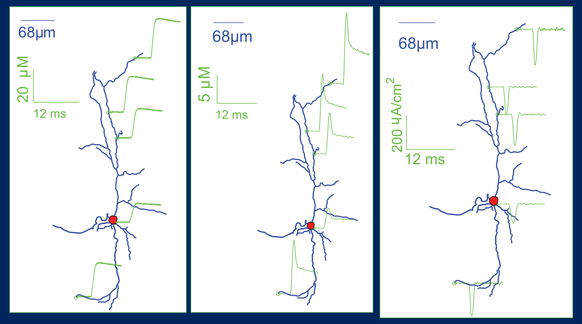
D. Compute g_{Ca} for arbitary channel types

$$I_{Ca} = g_{Ca} m^a n^b (V - V_{Ca})$$

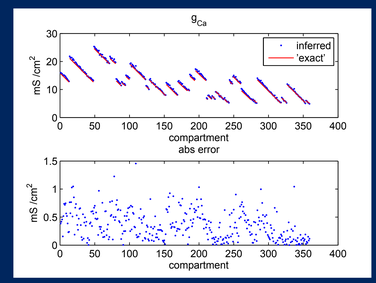
$$m_t = (m_\infty(V) - m)/\tau(V)$$

$$n = k/(k + c)$$

- The gating variables *m* and *n* have explicit dependence upon *v* and *c*.
- Directly compute *m* and *n*.
- Directly compute g_{Ca}.



We injected a constant current pulse of 2 ms to elicit a single action potential. Left to right: synthetic buffered calcium data (*b*), calcium (*c*), and recovered calcium current (I_{Ca}) at five sites.



'Exact' maximal calcium channel conductances (a linear function of distance from the cell body) from synthetic hippocampal pyramidal neuron compared with recovered conductances. The indirect method reproduces the increase in calcium channel conductance as distance increases from cell body.

5. Discussion

A. Adjoint method for intracellular calcium

We have shown that the adjoint method significantly accelerates the gradient computation required of steepest descent algorithms for calcium identification. These descent algorithms however choose their steps by applying the inverse of the Hessian of the misfit to its gradient. We are in the process of constructing and coding the relevant Hessian and expect a further significant speedup. Although published values exist for the (un)binding rate and diffusivities appearing in (2B) these were culled from multiple experiments at disparate temperatures in multiple cell types and as such we are working to infer these along with the inference of calcium. We are also pursuing the natural extension of provoking CICR via uncaging and the subsequent inference of RyR density.

B. Indirect method for channel densities

This method allows inference of membrane potentials, and thus calcium channel densities, from sufficiently fine measurements of fluorescent-dye-buffered-calcium. The main advantage of this method is that the step for inferring the calcium channel density is independent of the choice of the theoretical model used to describe the calcium channel, as well as the number of different types of calcium channels that are present in the actual cell. The rub is that we require measurements with high temporal and spatial resolution, and due to the inherent limitations of the experimental setup, one must be traded for the other. Future work involves altering the method to only require local information about membrane potentials so that only local measurements of buffered calcium are required (high temporal resolution at fewer recording sites).

6. Acknowledgements and References

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