

WORKSHOP
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Inverse problems in neuronal calcium signaling

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Abstract

Calcium, the most important of the second messengers, sculpts and records synaptic input and modulates the excitability of both nerve and muscle. Calcium enters the cytoplasm through voltage-gated channels in the plasma membrane as well as through calcium and/or IP₃ sensitive receptors on the ER membrane. We exploit the recent ability to dynamically monitor cytosolic calcium, throughout rat hippocampal pyramidal cells in slice, with sub-millisecond temporal resolution and sub-micron spatial resolution in the construction of a map of receptor and channel density. In the process we pose and solve a number of inverse problems associated with dye recordings under two stimulus protocols:

1. Focal uncaging of intracellular calcium
 - (i) Infer from the change in cytosolic dye-buffered calcium fluorescence the affinities and diffusivities of all relevant exogenous and endogenous calcium buffering proteins.
 - (ii) Infer from (1.i) the concentration of free calcium and so determine the distribution of ER-bound ryanodine and IP₃ receptors as well as plasma membrane and ER-bound calcium extrusion pumps.
2. Suprathreshold somatic current injection
 - (i) Infer from the change in cytosolic dye-buffered calcium fluorescence the local concentration of free cytosolic calcium.
 - (ii) Infer from this estimate of buffered and free calcium the associated membrane calcium current in space and time.

- (iii) Infer from this calcium current the conductance density of calcium channels.
- (iv) Infer the full membrane potential from this knowledge of current and conductance.
- (v) Infer from the membrane potential the remaining gating variables and their associated conductances.

The requisite imaging tools are drawn from

V. Iyer, T. Hoogland, and P. Saggau (2006), *Fast functional imaging of single neurons using random-access multiphoton (RAMP) microscopy*, J. Neurophysiological **95**, 535–545.

The modeling framework is drawn from

A.C. Ventura, L. Bruno, A. Demuro, I. Parker, and S.P. Dawson (2005) *A model-independent algorithm to derive Ca^{2+} fluxes underlying local cytosolic Ca^{2+} transients*, Biophysical J. **88**, 2403–2421.

The mathematical and computational tools are drawn from S. Cox (2006) *An adjoint method for channel localization*, Math. Medicine and Biology **23**, 139–152.