Estimating non-homogeneous channel densities and synaptic activity from spatiotemporal dendritic voltage recordings

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Introduction

In estimation methods for neuronal properties, there is a tradeoff between biophysical realism and computational tractability [3].
If we have

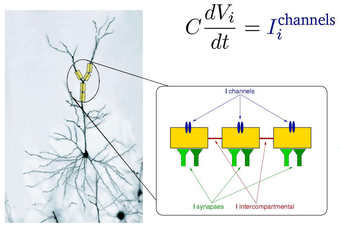
i) the spatiotemporal voltage signal (from voltage sensitive dyes)
ii) the exact branching structure of the neuron or piece of dendrite
iii) a description of channel kinetics

we can simultaneously infer

a) channel distribution
b) intracellular conductance
c) time-varying synaptic conductance distribution

This is possible because these parameters are coefficients in the voltage evolution equation and can be estimated by linear regression [see also 1, 2].

Method



$$C\frac{dV_i}{dt} = I_i^{\text{channels}} + I_i^{\text{synapses}} + I_i^{\text{intercompartmental}}$$

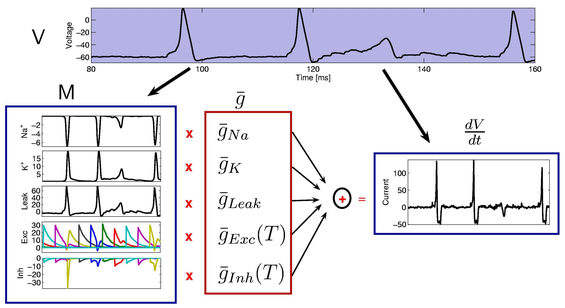
$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$

$$I_i^{\text{synapses}} = \sum_s (\xi_s * k_s)(t)(E_s - V_i(t))$$

$$I_i^{\text{intercompartmental}} = \sum_a g_a \Delta V_a(t)$$

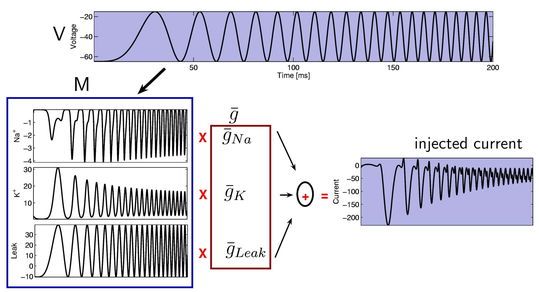
Voltage-dye or current clamp setting

From the (known) voltage trace in each compartment, we can deduce the transmembrane current dV/dt and the "current shapes", which consist of the product of open probabilities o(t) and driving forces. We can now infer the parameters g



Voltage clamp setting

Unlike above, the current is known and does not need to be inferred



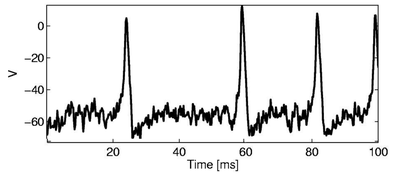
Channel densities

Solving the voltage evolution equation we perform a linear regression for all parameters, e.g. for the channel densities:

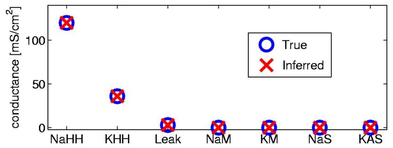
$$\hat{\bar{\mathbf{g}}} = \arg\min_{\bar{\mathbf{g}}} (\dot{\mathbf{V}} - \bar{\mathbf{g}}\mathbf{M})^2 \qquad M_{ct} = g_c(t)(E_c - V(t))$$

NB: this is the ML solution under white Gaussian current noise.

Data: 100ms, single compartment, Hodgkin-Huxley channels only.

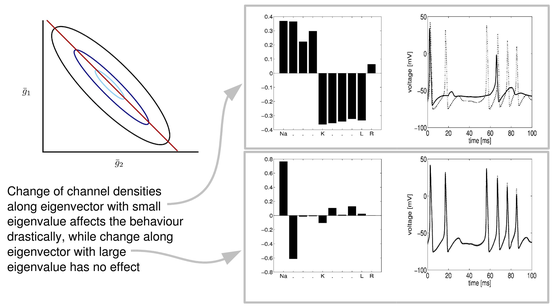


True and inferred channel densities



Uncertainty / Channel combinations

If two equal channels are fitted, there is irreducible uncertainty, only the sum $g_1 + g_2$ is relevant. More generally the eigenstructure of Hessian tell us which channel combinations the data are informative about.

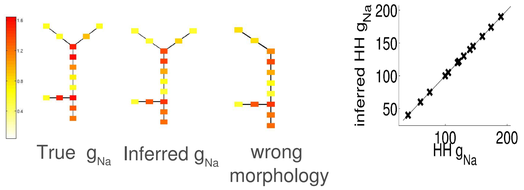


Change of channel densities along eigenvector with small eigenvalue affects the behaviour drastically, while change along eigenvector with large eigenvalue has no effect

Multicompartmental model

14 compartment model fitted with Hodgkin Huxley type channels.

$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$



True g_{Na} Inferred g_{Na} wrong morphology

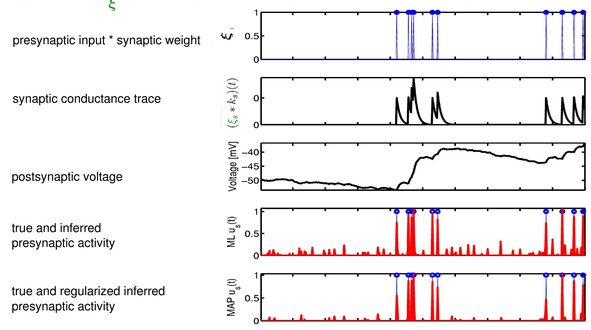
Synaptic input

Single passive compartment with inhibitory and excitatory synaptic inputs

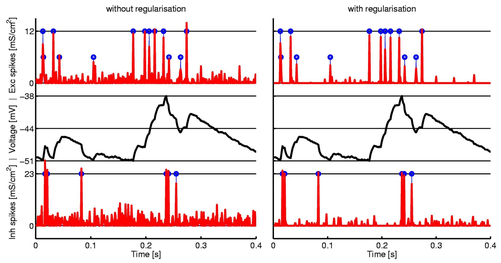
$$I_i^{\text{synapses}} = \sum_s (\xi_s * k_s)(t)(E_s - V_i(t))$$

Each timepoint independent parameter for each synapse.
Synaptic input really is sparse, so use an exponential regularizer, ie minimize:

$$\hat{\boldsymbol{\xi}} = \arg\min_{\boldsymbol{\xi}} (\dot{\mathbf{V}} - \boldsymbol{\xi}\mathbf{M})^2 + \lambda\boldsymbol{\xi} \qquad M_{st} = \mathbf{K}_s(E_s - V(t))$$



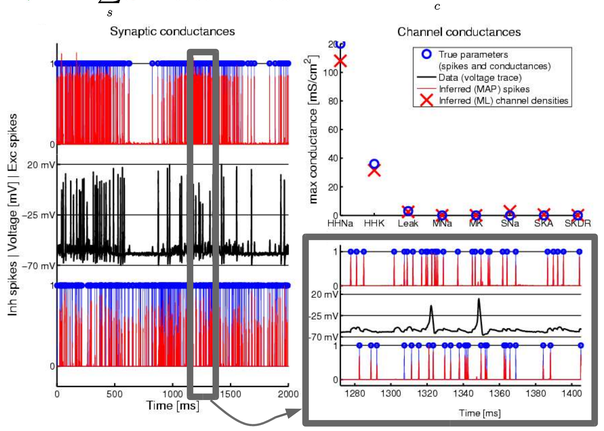
Regularization is more important when there are both excitatory and inhibitory synapses on the compartment.



Joint estimation

Here we jointly estimate both presynaptic input and channel conductances. Presynaptic spikes are usually correctly identified, apart from when they occur during an action potential. The right panel shows that the conductances of channels not present during the generation of the voltage trace were mostly set to zero.

$$I_i^{\text{synapses}} = \sum_s (\xi_s * k_s)(t)(E_s - V_i(t)) \qquad I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$



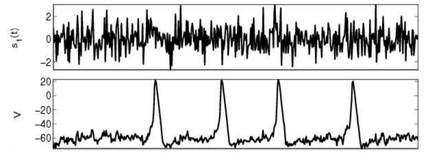
Linear filter

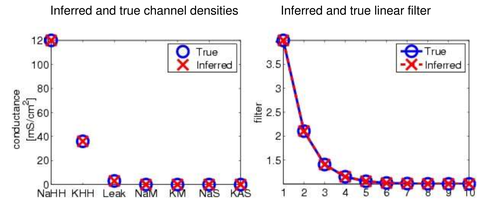
Write synaptic input as linearly filtered stimulus

$$C\frac{dV_x}{dt} = \sum_{c=1}^{\mathcal{C}} \bar{g}_c g_c(V,t)(V_c - V(t)) + \langle \mathbf{s}(t), \mathbf{k} \rangle + \sigma dN(t)$$

First dimension of white noise stimulus

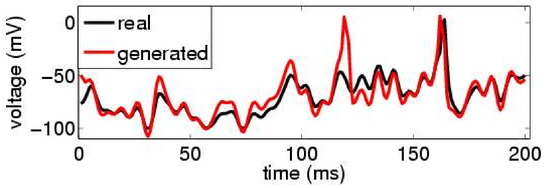
Data: 100 ms Voltage trace





Application to real data

Current clamp recordings from magnocellular neurons, which are electrotonically compact and well modelled by single compartment. Data courtesy Sean Slee.



Discussion

- Calcium channels are ignored so far.
- Mistaken channel kinetics?
- Synaptic kinetics? Kinetics of synapses interact nonlinearly in spines.
- Voltage sensitive dyes may require a hidden variable formulation:
  - high voltage noise,
  - missing data due to partial sampling and missed dendrites.

References

[1] Wood, Gurney and Wilson (2004): Neurocomputing, 58-60: 1109-1116
[2] Morse, Davison and Hines (2001): Soc. Neurosci. Abstract
[3] Vanier and Bower (1999): J. Comp. Neurosci., 7(2): 149-171