Statistical methods for understanding complex biophysical neural data

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Can we recover detailed biophysical properties?

- Active: membrane channel densities
- Passive: axial resistances, “leakiness” of membranes
- Dynamic: spatiotemporal synaptic input
Spatiotemporal voltage recordings

Djurisic et al, 2004
Conductance-based models

\[ C \frac{dV_i}{dt} = I_{i}^{\text{channels}} + I_{i}^{\text{synapses}} + I_{i}^{\text{intercompartmental}} \]

\[ I_{i}^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t)) \]

\[ I_{i}^{\text{synapses}} = \sum_s (\xi_s * k_s)(t)(E_s - V_i(t)) \]

\[ I_{i}^{\text{intercompartmental}} = \sum_a g_a \Delta V_a(t) \]

Key point: if we observe full \( V_i(t) + \) cell geometry, channel kinetics known + current noise is log-concave,

then loglikelihood of unknown parameters is concave.

Gaussian noise \( \Rightarrow \) standard nonnegative regression (albeit high-d).
Estimating channel densities from $V(t)$

(Huys et al., 2006)
Estimating channel densities from $V(t)$
Measuring uncertainty in channel densities

\[
\hat{a} = \arg \min_a \| \hat{V} - J a \|^2 \\
= \arg \min_a a^T H a - 2 a^T f \quad s.t. \quad a_i \geq 0 \forall i
\]
Estimating non-homogeneous channel densities and axial resistances from spatiotemporal voltage recordings

\[ I_{i,\text{channels}} = \sum_c g_c g_c(t) (E_C - V_i(t)) \]

True \( g_{Na} \)  
Estimated \( g_{Na} \)
A big cell
A big cell
Estimating synaptic inputs given $V(t)$
Estimating synaptic inputs given $V(t)$

A

without regularisation

B

with regularisation

<table>
<thead>
<tr>
<th>Inh spikes [mS/cm$^2$]</th>
<th>Voltage [mV]</th>
<th>Exc spikes [mS/cm$^2$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-57</td>
<td>0</td>
</tr>
<tr>
<td>-57</td>
<td>-52</td>
<td>0</td>
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<tr>
<td>-52</td>
<td>-47</td>
<td>0</td>
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<tr>
<td>-47</td>
<td>12</td>
<td>0</td>
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</tbody>
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Time [s]

0 0.05 0.1 0.15 0.2 0.25 0.3 0.35 0.4
Estimating synaptic inputs given $V(t)$

A. Synaptic conductances

B. Channel conductances

- True parameters (spikes and conductances)
- Data (voltage trace)
- Inferred (MAP) spikes
- Inferred (ML) channel densities

C. Channel conductances

Inh spikes | Voltage [mV] | Exc spikes

Time [ms]

max conductance [mS/cm$^2$]

HHNa, HHK, Leak, MNa, MK, SNa, SKA, SKDR
Estimating stimulus effects

\[ \frac{dV}{dt} = I_{channel} + \vec{k} \cdot \vec{x}(t) + \sigma N_t \]
Dealing with incomplete observations: Kalman filter

![Graph showing V(t) and estimated standard deviation]

- $V(t)$
- Estimated $V(t)$
- Estimated standard deviation $E[V(t) | Y(0:t)]$
- $E[V(t) | Y(1:T)]$

$t$ (sec)

0 0.02 0.04 0.06 0.08 0.1 0.12 0.14 0.16 0.18 0.2
Estimating parameters in the Kalman setting

Simulated data: five-compartment model $V(t)$, noisy observations
Estimating parameters in the Kalman setting

Leak

intercompartmental conductance

R

Observation noise

EM iteration

EM iteration
Smoothing given nonlinear dynamics

— via particle filtering (Huys and Paninski, 2006)
Subsampling and noise

<table>
<thead>
<tr>
<th>Observation noise</th>
<th>Temporal subsampling</th>
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<tbody>
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<td>$\sigma_0 = 5$</td>
<td>$\Delta_s = 10$</td>
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<td>$\Delta_s = 100$</td>
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<td>$\sigma_0 = 100$</td>
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</table>
EM estimation via particle filter

![Graphs showing EM iteration for Na, K, Leak, and R channels with Voltage and EM iteration on the x-axis.](image-url)
Particle filter to infer calcium from voltage observations
Inferring spike rates from calcium observations

\[ \lambda_t = \exp\{b + k'x_t + \omega'h_t\} \]

- **Firing Rate**

- **Spike Train**
  \[ n_t \sim e^{-\lambda_t dt} \frac{\lambda_t^{n_t}}{n_t!} \]

- **Calcium Concentration**
  \[ C_{t+1} = (1 - \alpha dt)C_t + \beta n_t + \sigma dB_t \]

- **Observations**
  \[ O_t = C_t + \varepsilon B_t \]

- **Inferred Calcium Distribution**

- **Inferred Firing Rate**
Collaborators

Theory and numerical methods
— J. Kulkarni, G. Szirtes, G. Fudenberg, K. Rahnama, Columbia
— J. Pillow, E. Simoncelli, NYU
— S. Shoham, Princeton
— A. Haith, C. Williams, Edinburgh
— M. Ahrens, Q. Huys, Gatsby
— J. Lewi, R. Butera, Georgia Tech

Motor cortex physiology
— M. Fellows, J. Donoghue, Brown
— N. Hatsopoulos, U. Chicago

Retinal physiology
— V. Uzzell, J. Shlens, E.J. Chichilnisky, UCSD

Cortical \textit{in vitro} physiology
— B. Lau and A. Reyes, NYU
References
