Optimal filtering methods for complex biophysical neural data

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w/ Q. Huys, J. Vogelstein, and M. Ahrens

The filtering problem

Spatiotemporal imaging data is very exciting, but we have to deal with noise and intermittent observations.

Goals:

- Noise filtering/interpolation of spatiotemporal voltage observations
- Inferring locations of synaptic input on the dendritic tree
- Learning biophysical parameters (membrane leakiness, channel density, etc.) given imaging data
- Inferring spike times from calcium traces
- Inferring synaptic input times from voltage traces

Basic paradigm: the Kalman filter

Variable of interest, $x(t)$, evolves according to a noisy differential equation:

$$dx/dt = f(x) + \epsilon_t.$$

Make noisy observations:

$$y(t) = g(x(t)) + \eta_t.$$

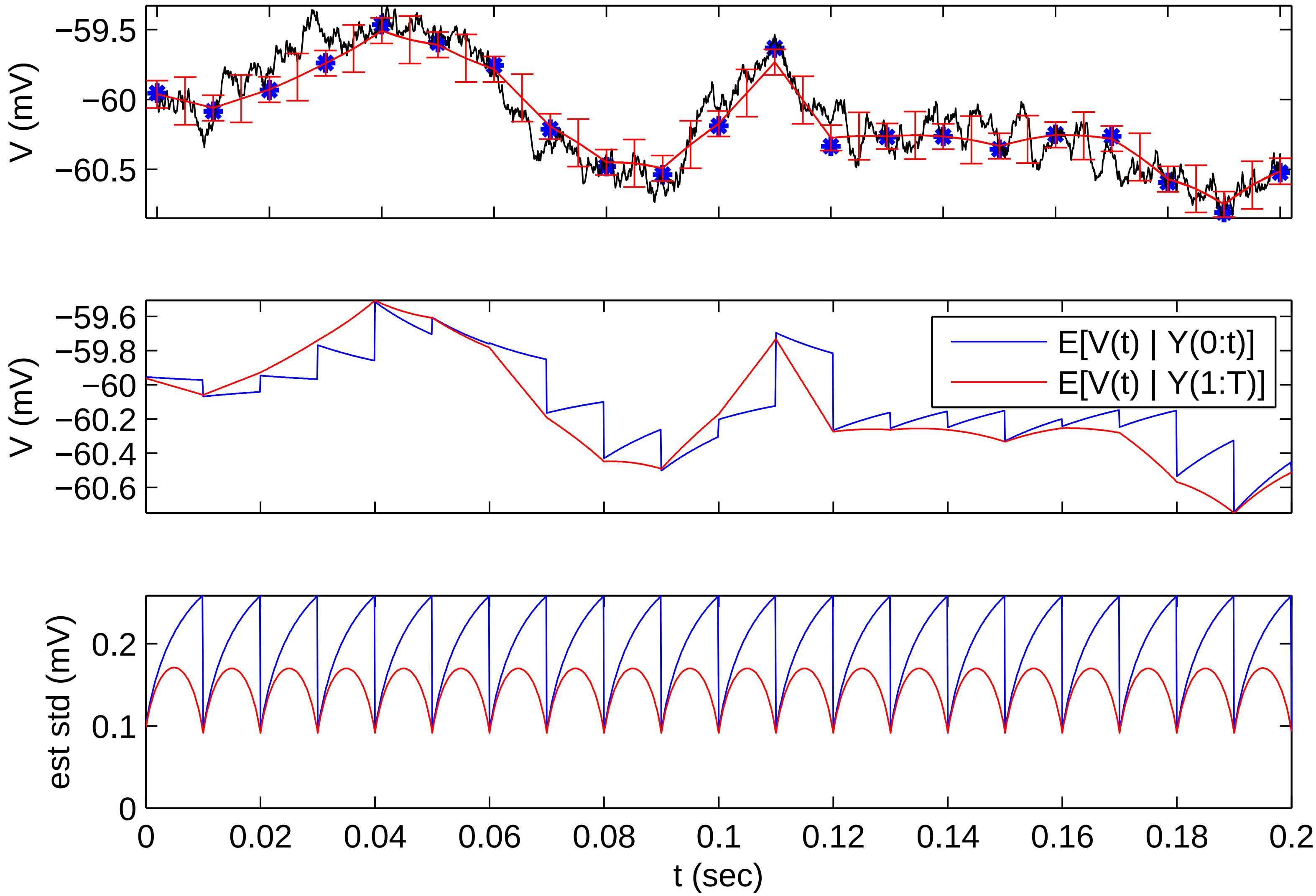
We want to infer $E(x(t)|Y)$: optimal estimate given observations. We also want errorbars: quantify how much we actually know about $x(t)$.

If $f(.)$ and $g(.)$ are linear, and ϵ_t and η_t are Gaussian, then solution is classical: Kalman filter.

Extensions to nonlinear dynamics, non-Gaussian observations: hidden Markov ("state-space") model, particle filtering

Application: incomplete observations of $V(t)$

— Leaky integrator model: $dV/dt = g_l[V_l - V(t)] + \epsilon_t$



Vector case

Easy extension of Kalman method:

$$d\vec{x}/dt = A\vec{x}(t) + \vec{\epsilon}_t$$

$$\vec{y}(t) = K\vec{x}(t) + \vec{\eta}_t$$

Example:

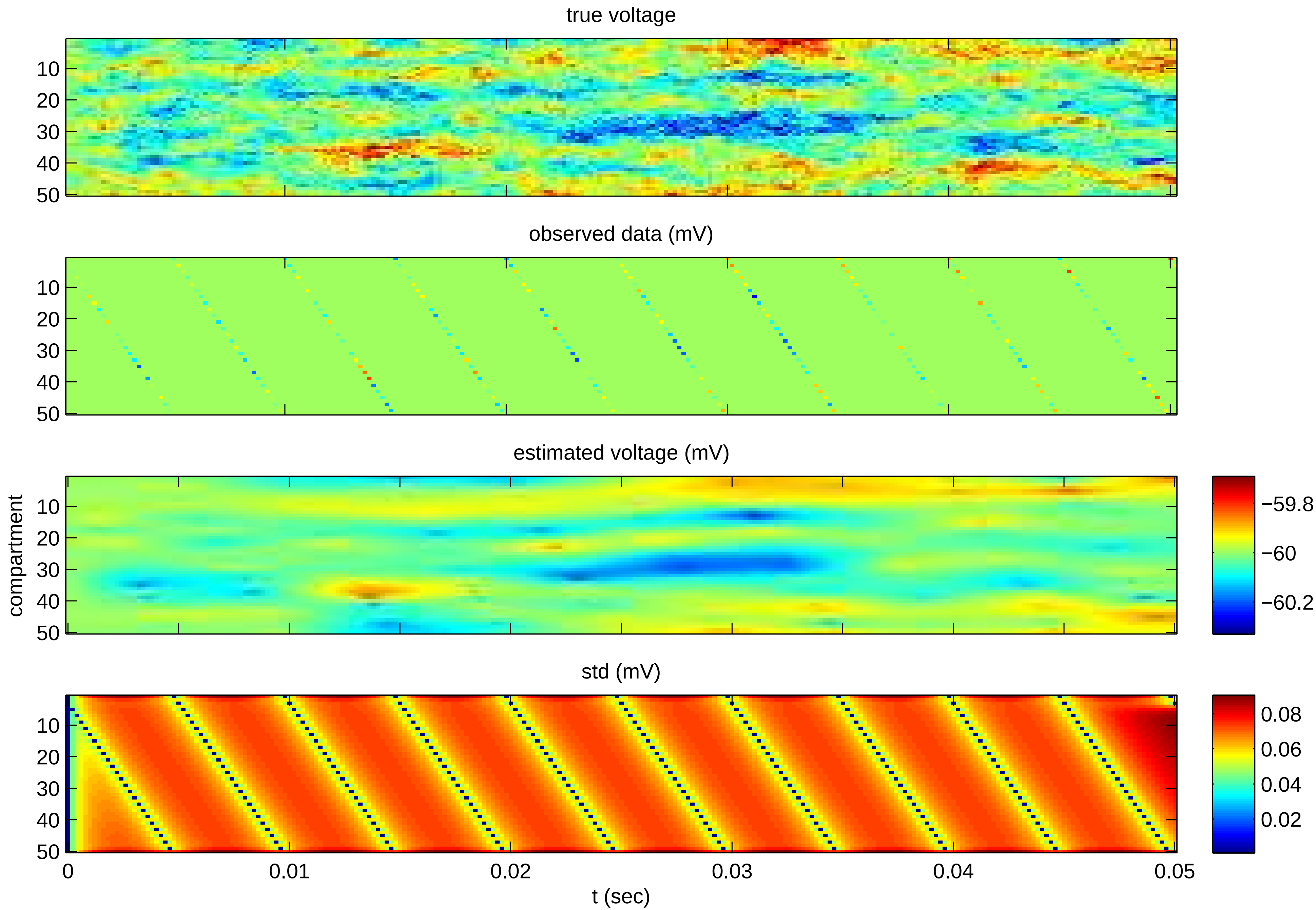
$x_i(t) =$ voltage at compartment i

$A =$ dynamics matrix: includes leak terms ($A_{ii} = -g_l$) and intercompartmental terms ($A_{ij} = 0$ unless compartments are adjacent)

$K =$ observation matrix: in laser-scanning setting, $K = K_t =$ single-node snapshot

(show movie...)

Spatiotemporal voltage filtering



Application: detecting synapses on a dendritic branch

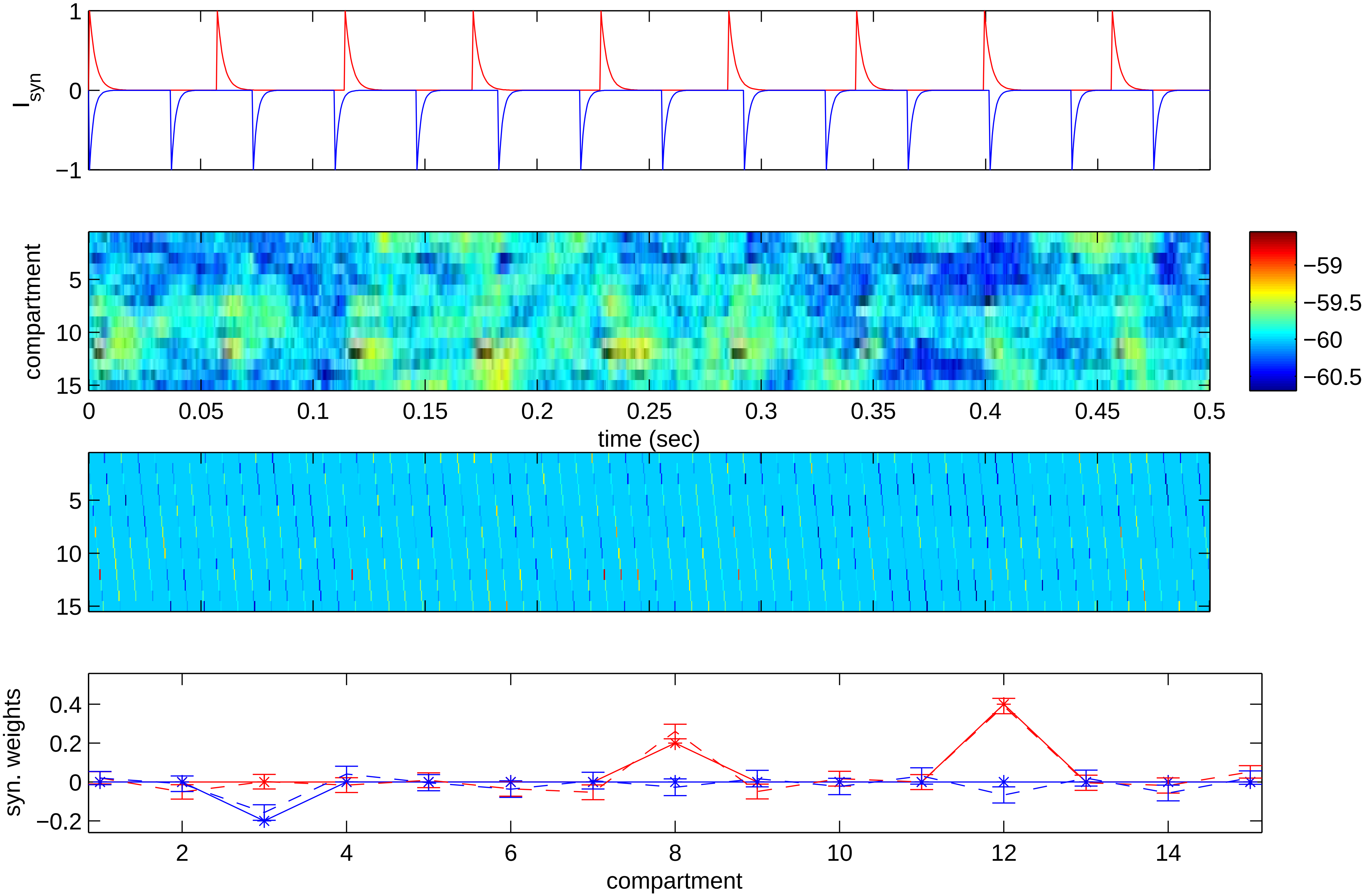
Including known terms:

$$d\vec{V}/dt = A\vec{V}(t) + W\vec{U}(t)$$

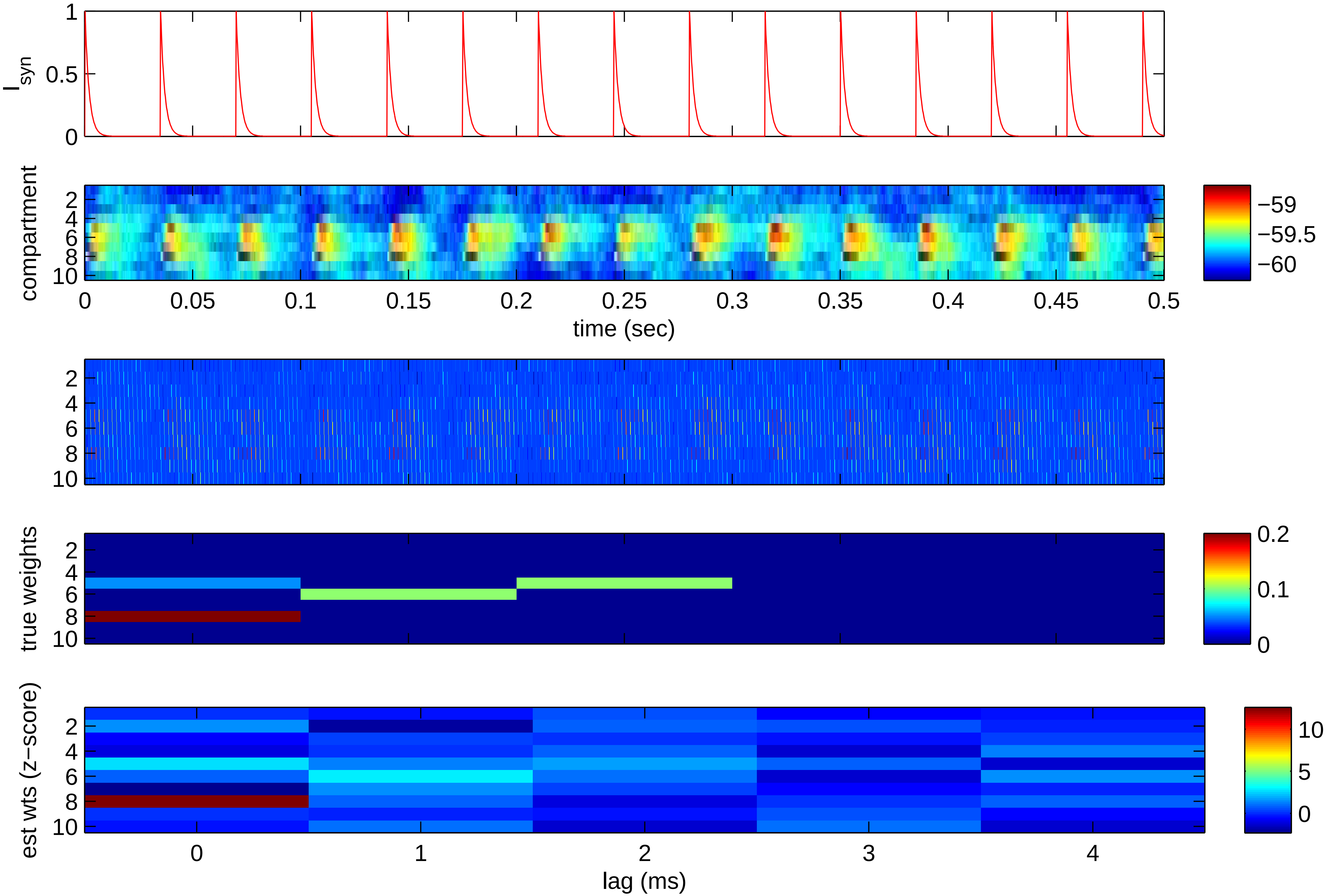
$U_j(t)$ = known input terms

Example: $U(t)$ are known presynaptic spike times, and we want to detect which compartments are connected (i.e., infer the weight matrix W).

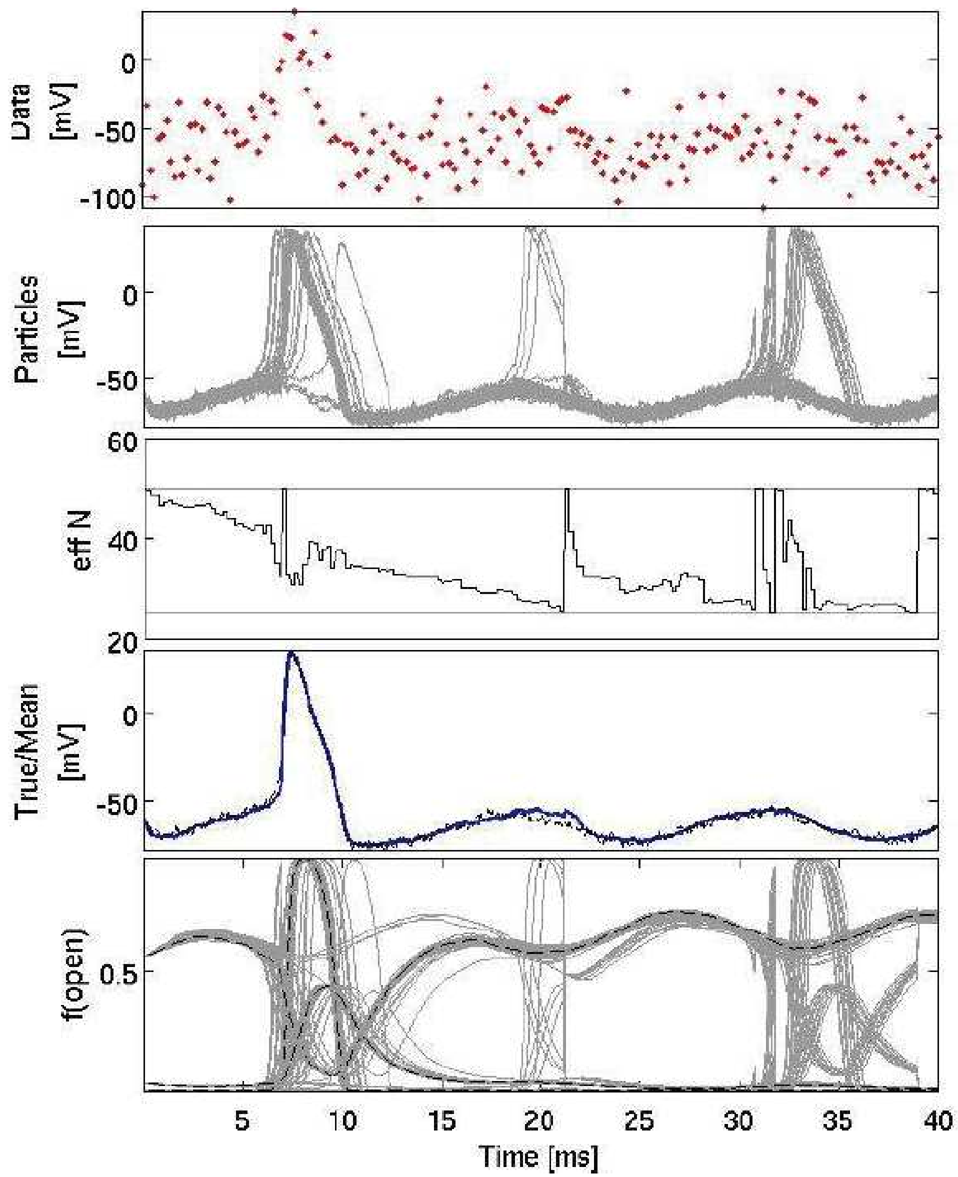
Detecting synapses



Detecting synapses: spatiotemporal example

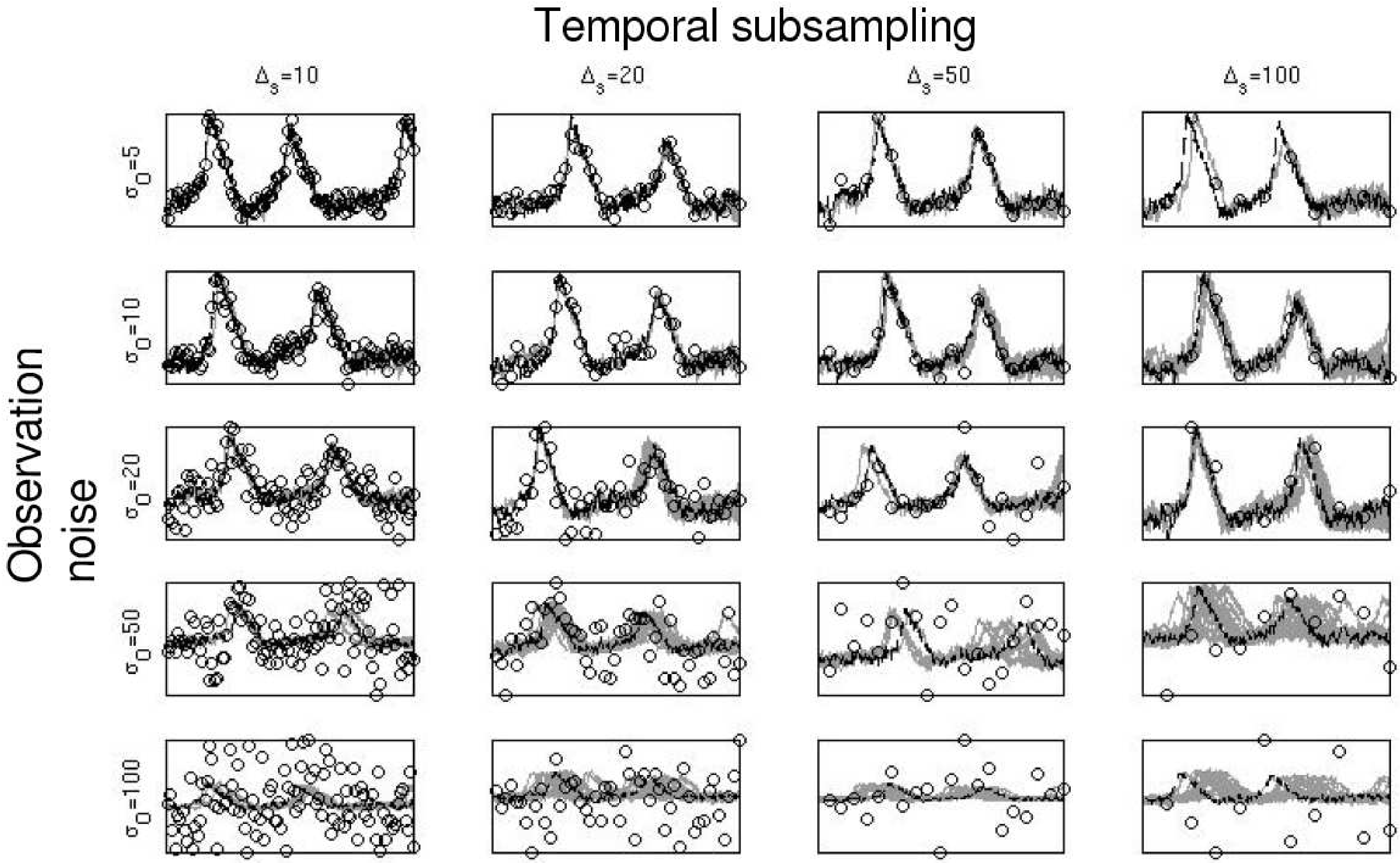


Smoothing given nonlinear dynamics



— via particle filtering (Huys and Paninski, 2006)

Subsampling and noise



Estimating model parameters

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

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

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

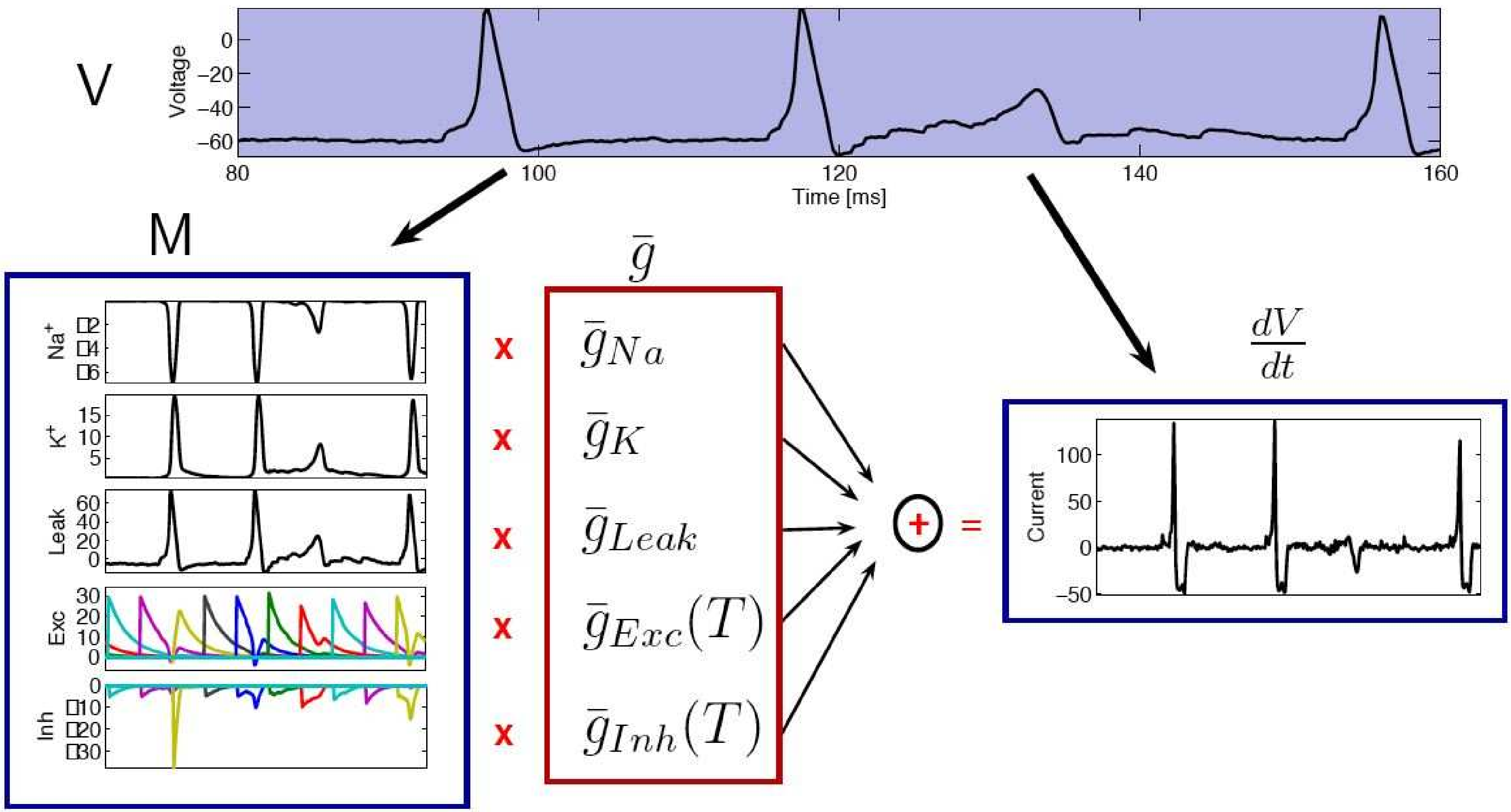
$$I_i^{\text{intercompartmental}} = \sum_a g_a \Delta V_a(t)$$

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.

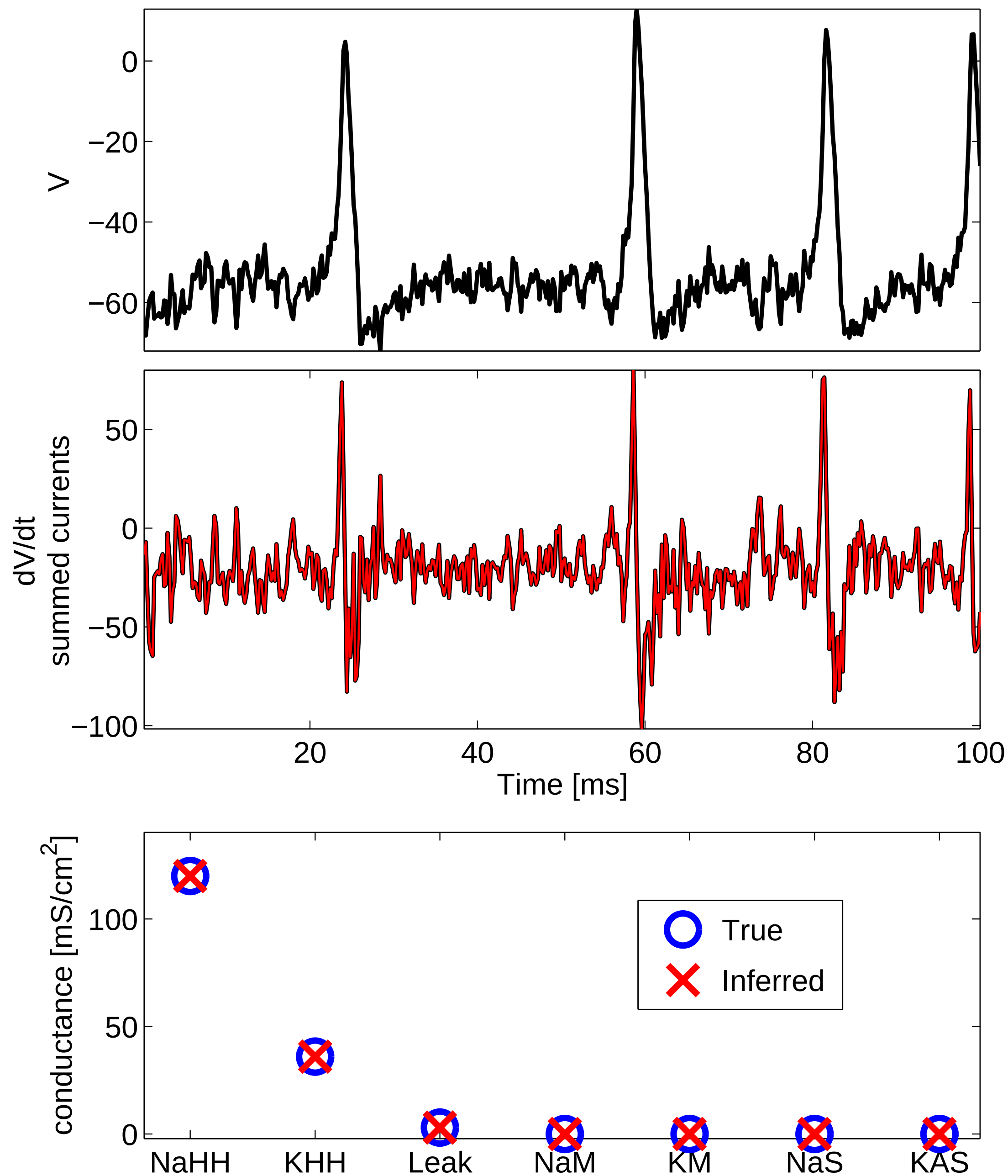
Gaussian noise $\implies$ standard nonnegative regression (albeit high-d).

Estimating channel densities from $V(t)$



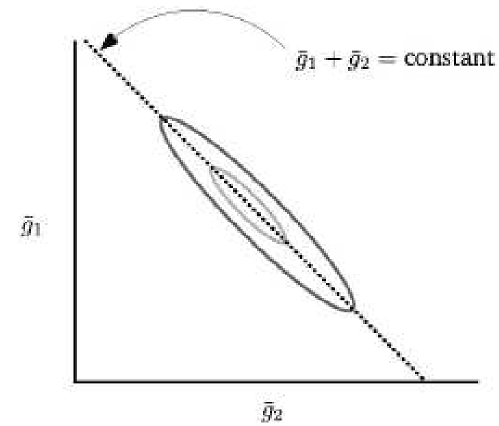
(Huys et al., 2006)

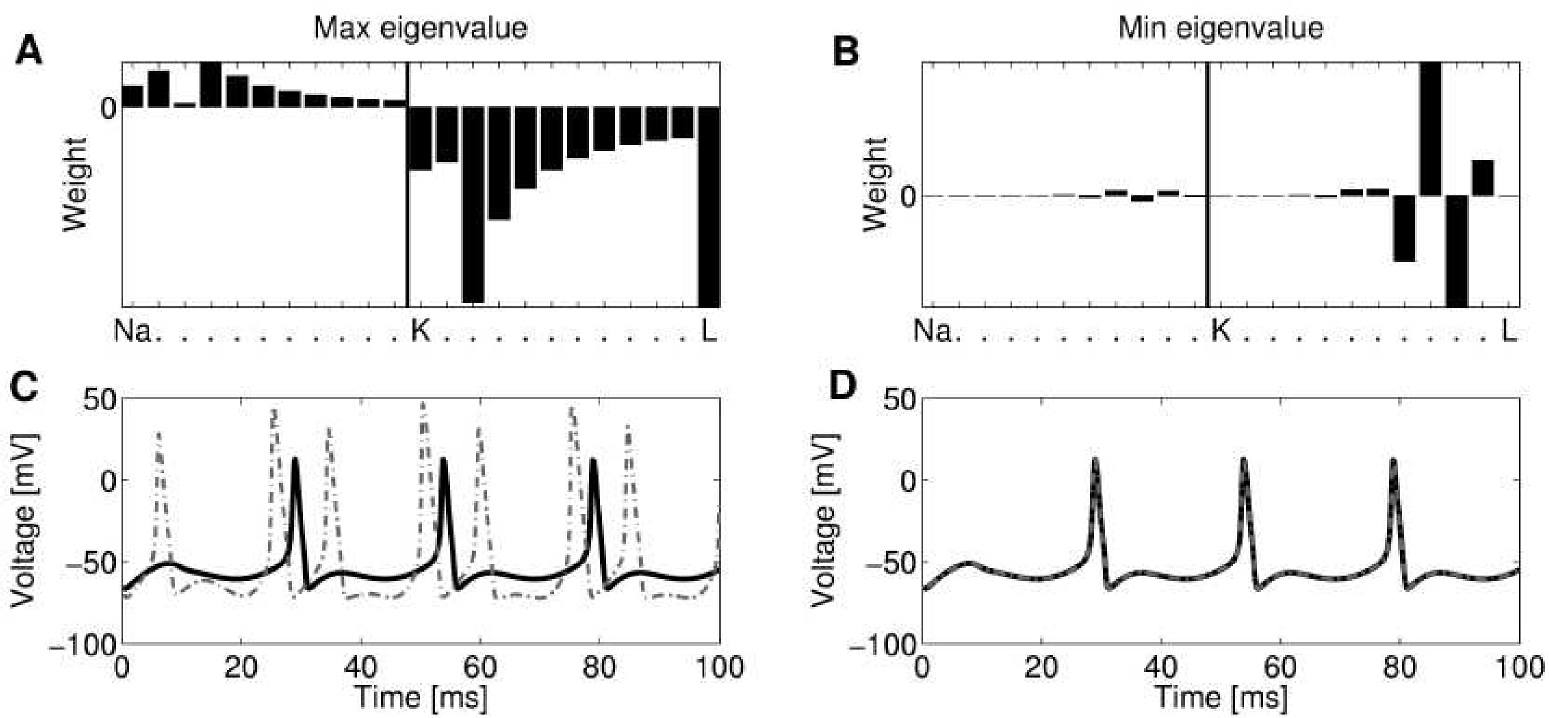
Estimating channel densities from $V(t)$



Measuring uncertainty in channel densities

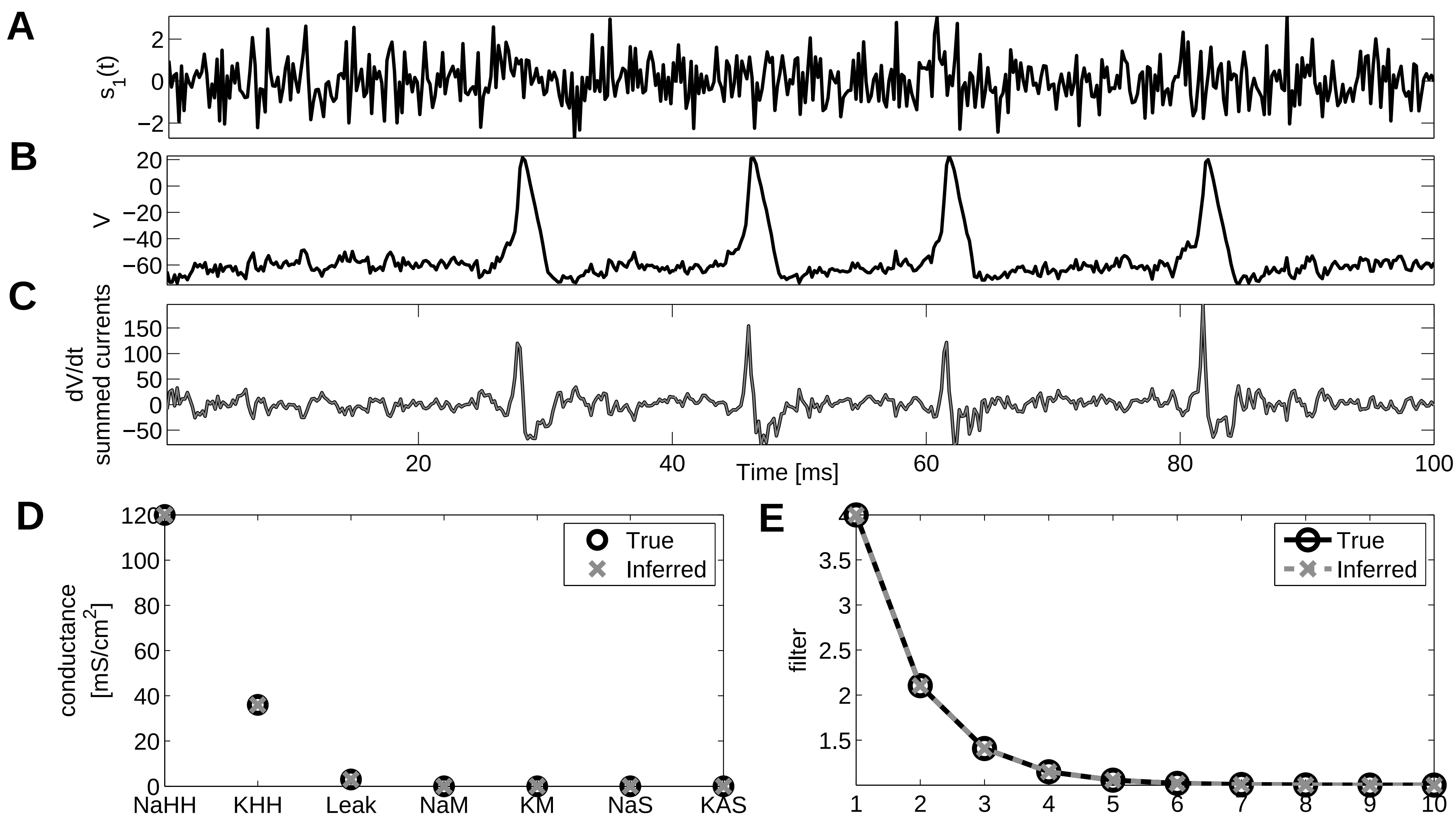
$$\hat{\mathbf{a}} = \arg\min_{\mathbf{a}} ||\dot{\mathbf{V}} - \mathbf{J}\mathbf{a}||^2$$
$$= \arg\min_{\mathbf{a}} \mathbf{a}^T\mathbf{H}\mathbf{a} - 2\mathbf{a}^T\mathbf{f} \quad s.t. \quad a_i \geq 0 \forall i$$





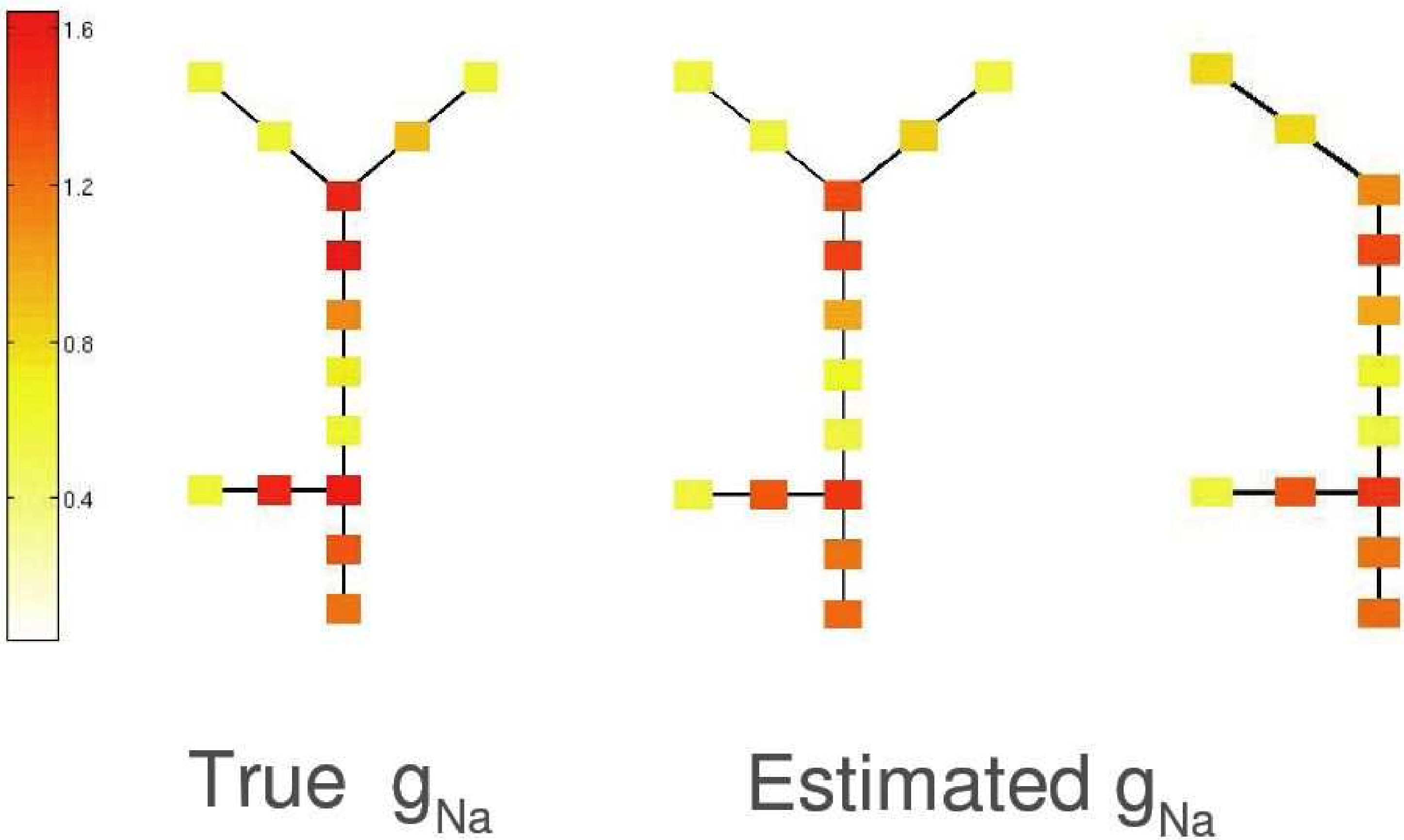
Estimating stimulus effects

$$dV/dt = I_{channel} + \vec{k} \cdot \vec{x}(t) + \sigma N_t$$



Estimating non-homogeneous channel densities

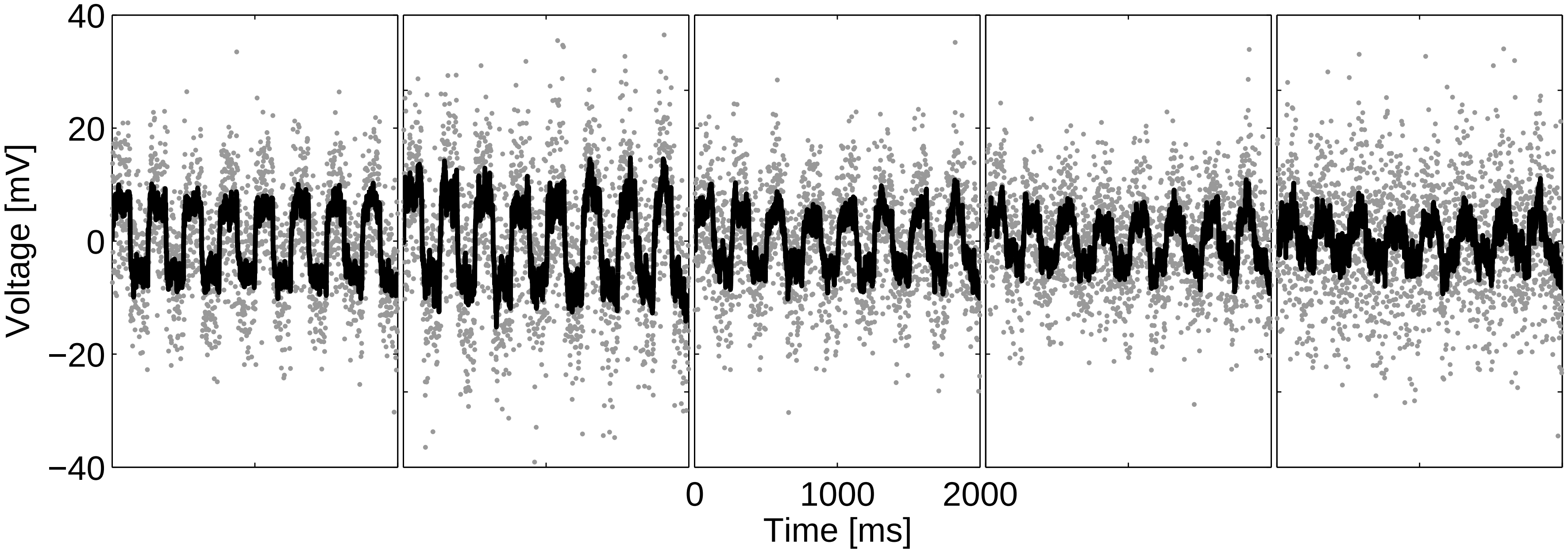
$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$



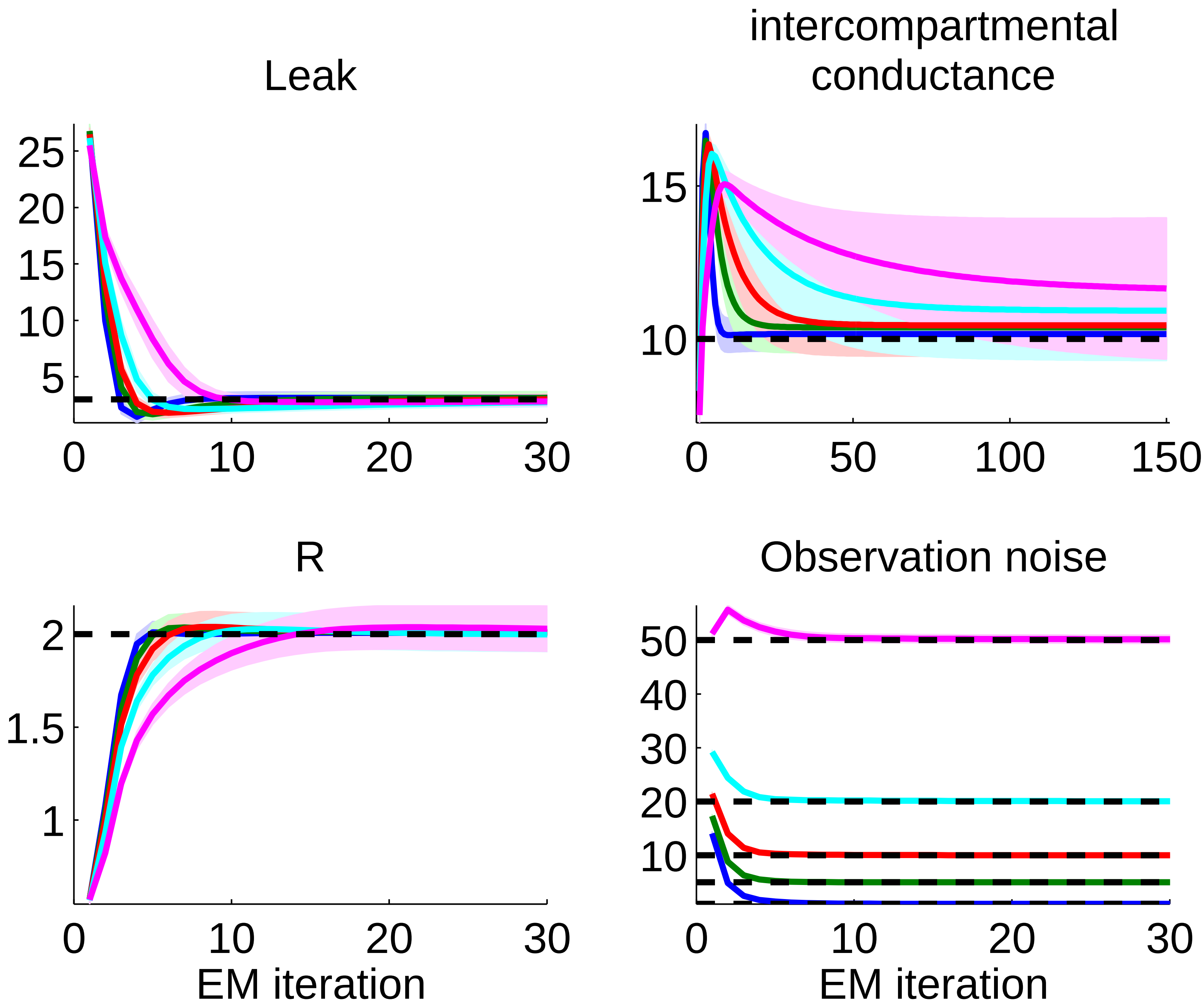
Estimating parameters given intermittent, noisy observations

"EM" algorithm: iterate between estimation of $E(V(t)|Y, \theta)$, then fitting model parameters given estimated $V(t)$.

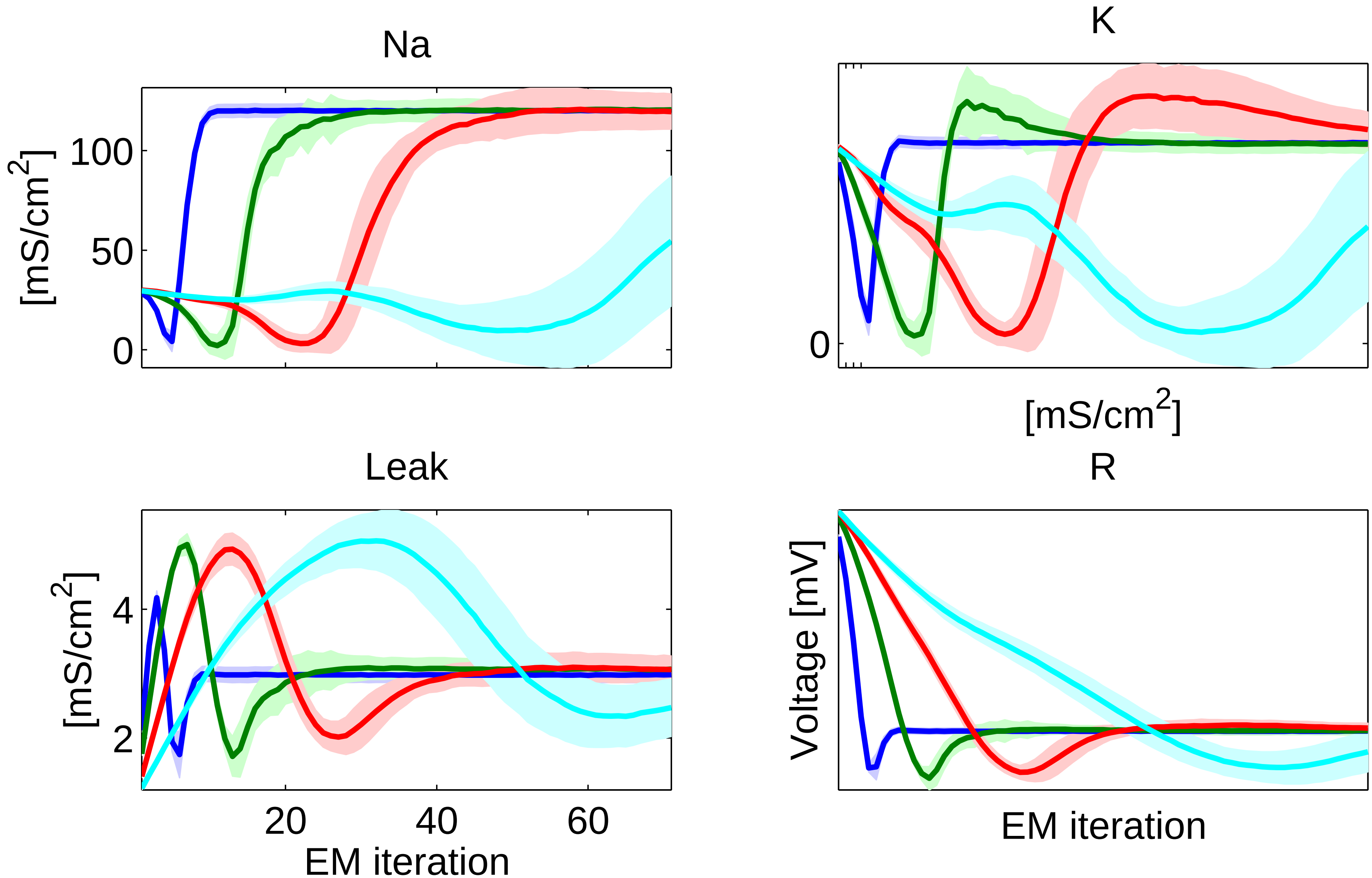
Example: Simulated data: five-compartment $V(t)$, noisy observations



Estimating parameters in the Kalman setting



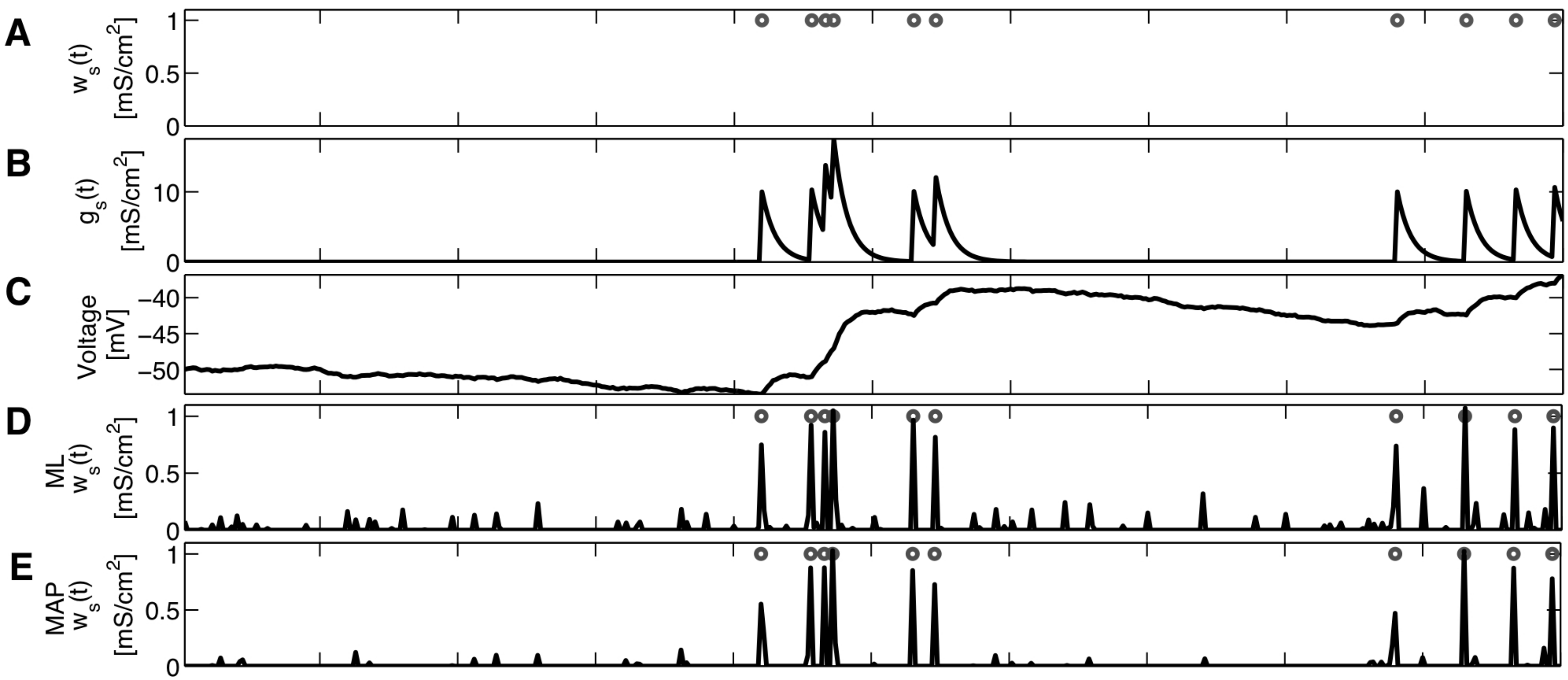
Estimating parameters for nonlinear dynamics



Estimating synaptic inputs given $V(t)$

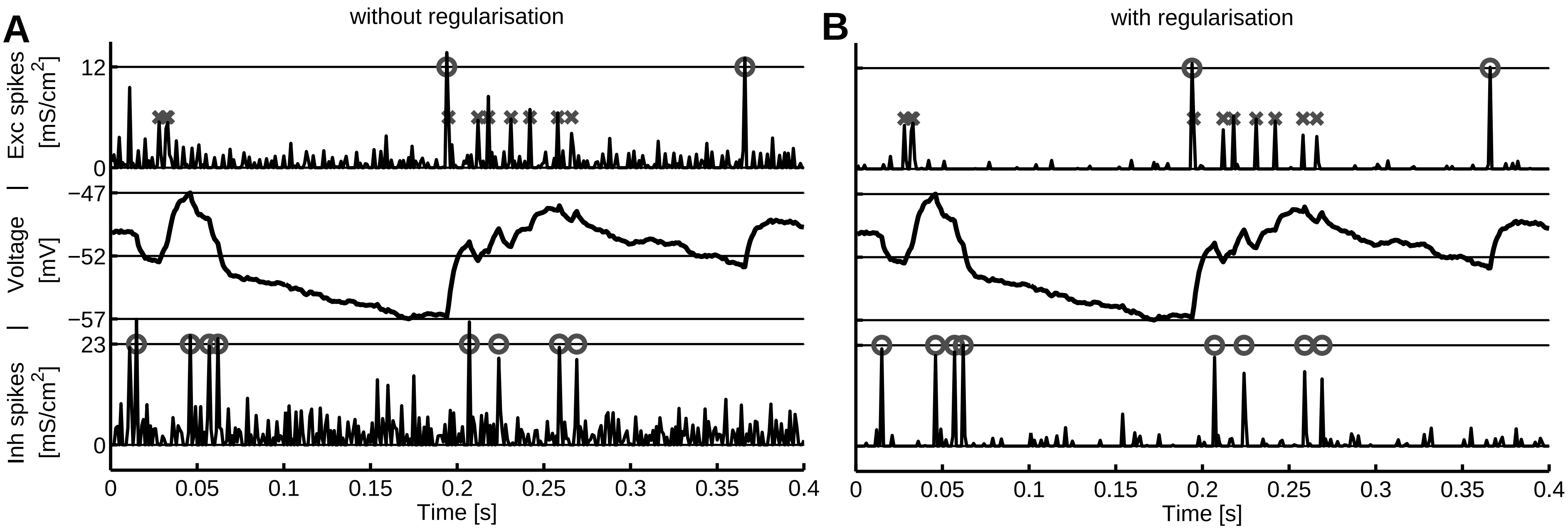
$$V(t+dt) = V(t) + dt\left[g_l(V_l - V(t)) + g_I(t)(V_I - V(t)) + g_E(t)(V_E - V(t))\right] + \epsilon_t$$

$$g_I(t+dt) = g_I(t) - dt\frac{g_I(t)}{\tau_I} + N_I(t)$$

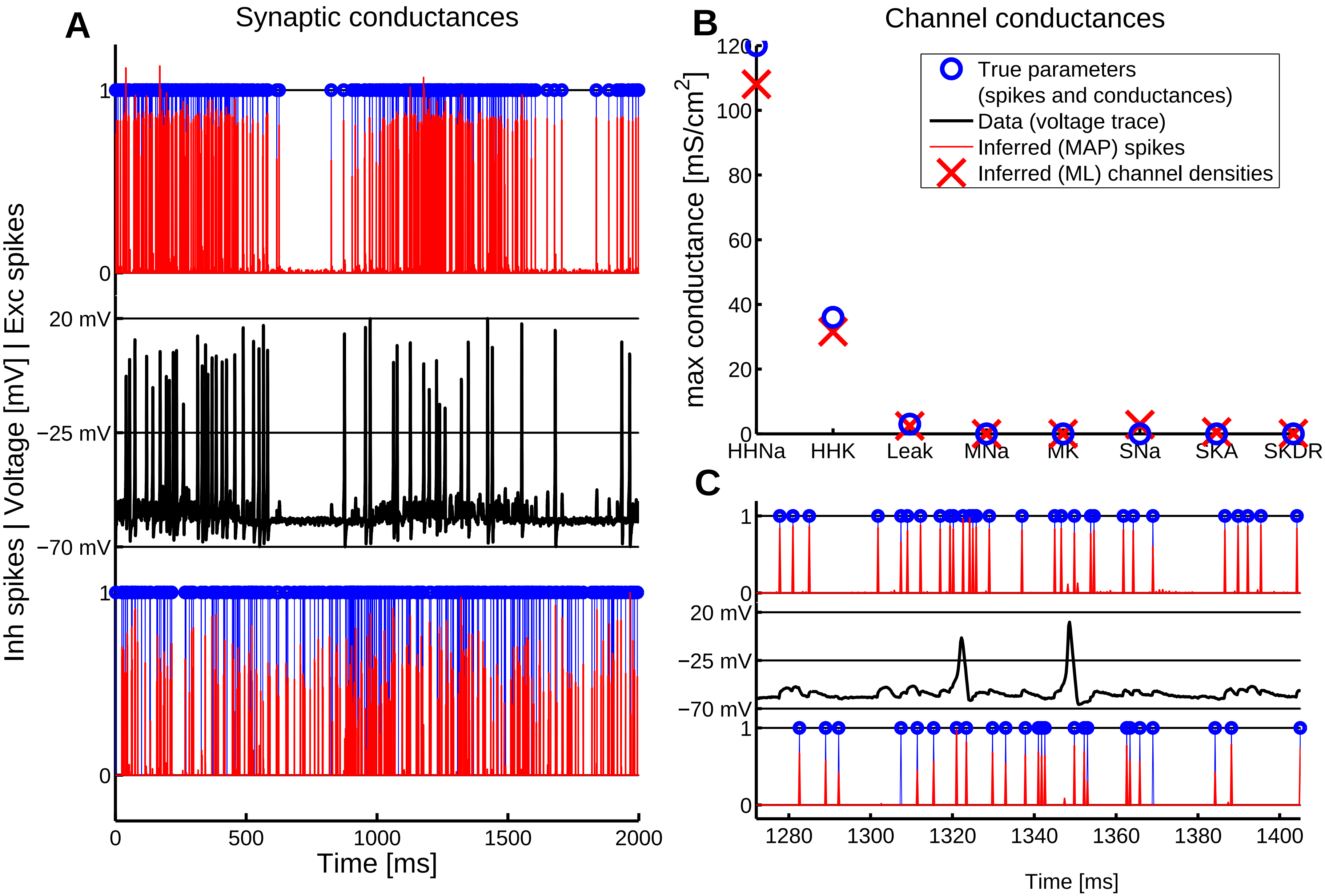


(Huys et al., 2006; Paninski, 2007)

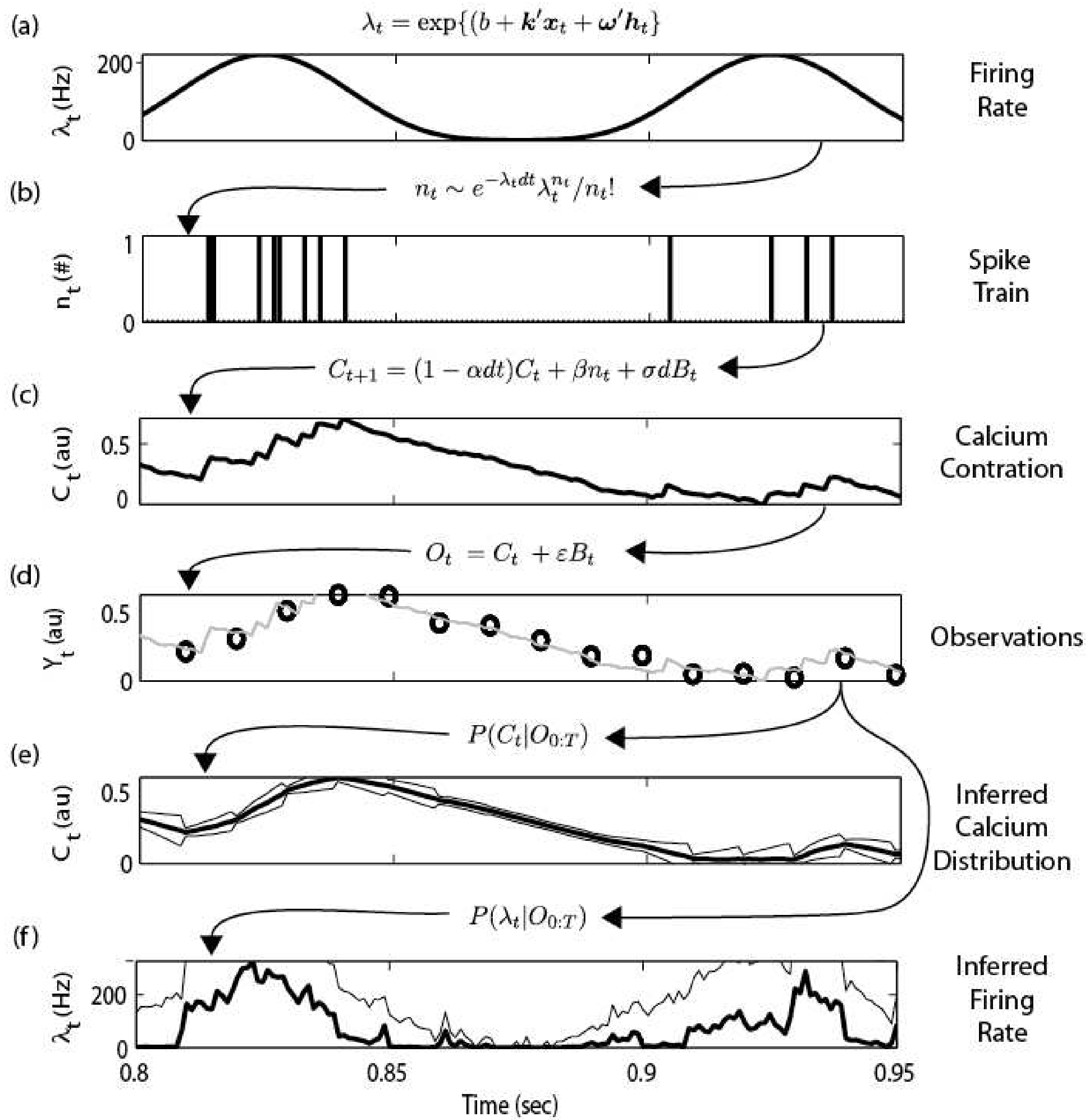
Estimating synaptic inputs given $V(t)$



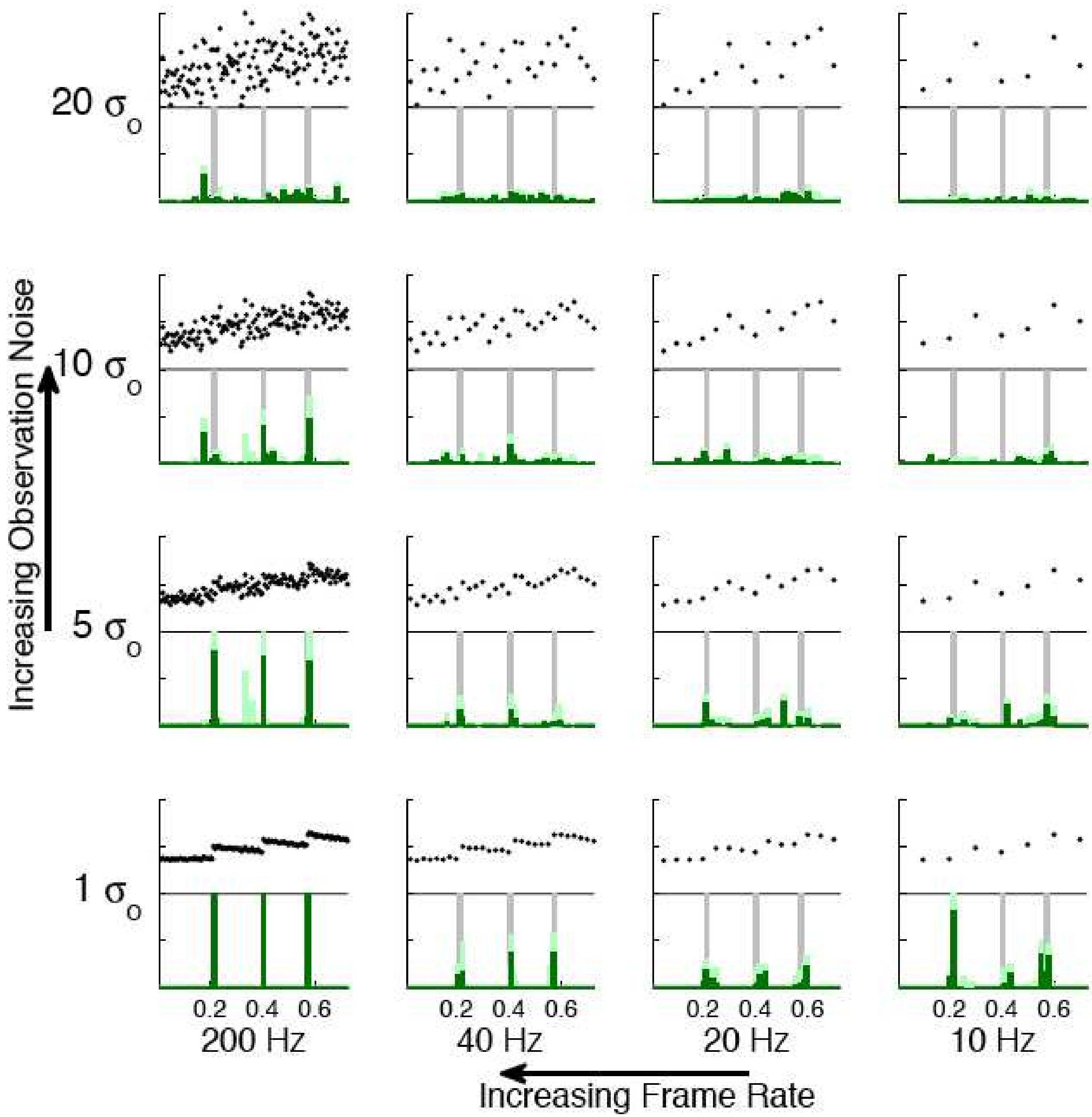
Estimating synaptic inputs given $V(t)$



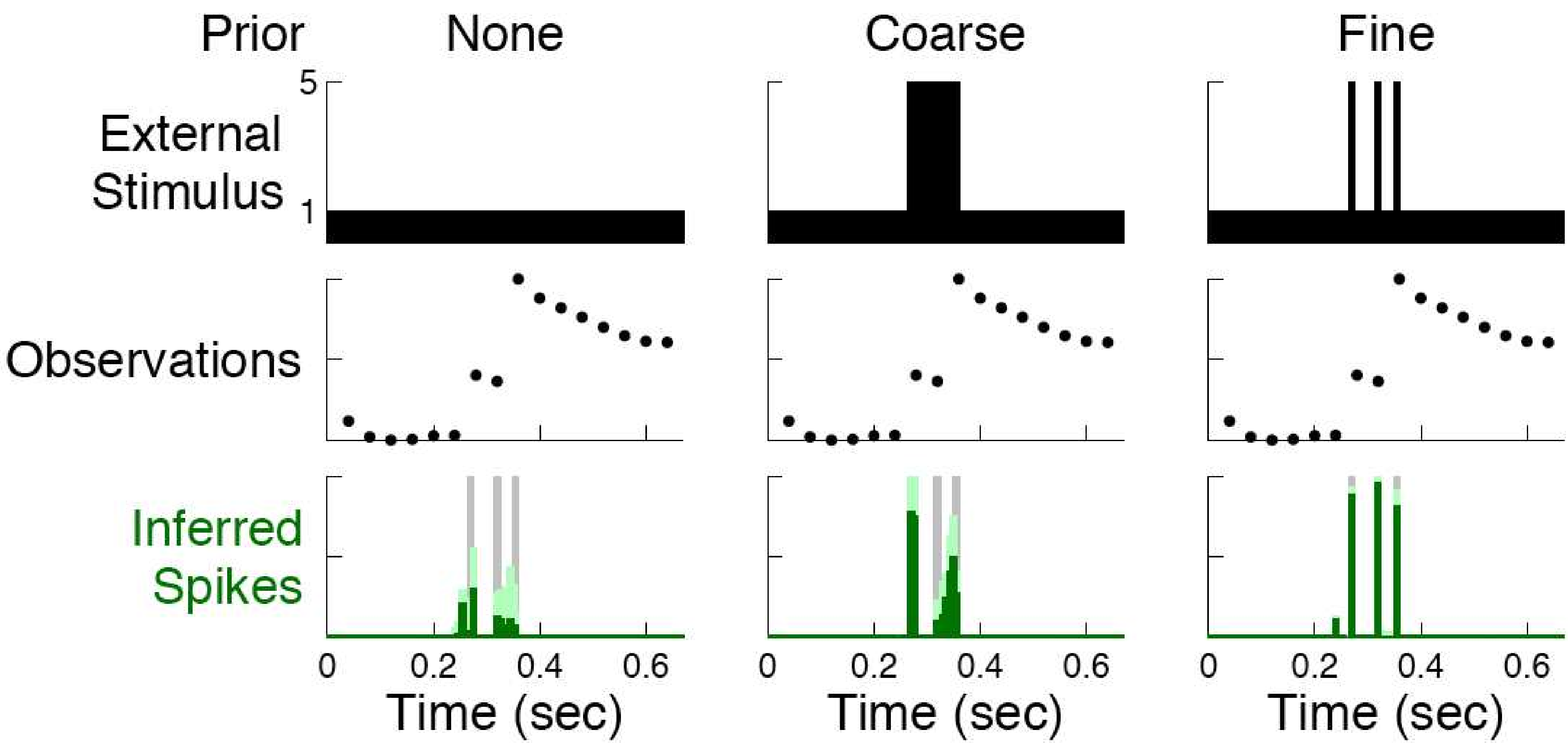
Inferring spike rates from calcium observations



Inferring spike rates from calcium observations



Including stimulus information improves estimates



(Vogelstein et al., 2007)

Conclusions

Advantages of model-based approach:

- Flexibility (can fit optimal filters directly to noisy data; no need to rely on a single deconvolution filter)
- Direct biophysical interpretability of estimated parameters
- Connections to models of stimulus encoding, decoding (Paninski et al., 2008)
- Direct quantification of uncertainty

Next steps:

- Application to data
- Further relaxation of assumptions

References

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