

# Statistical methods for understanding neural codes

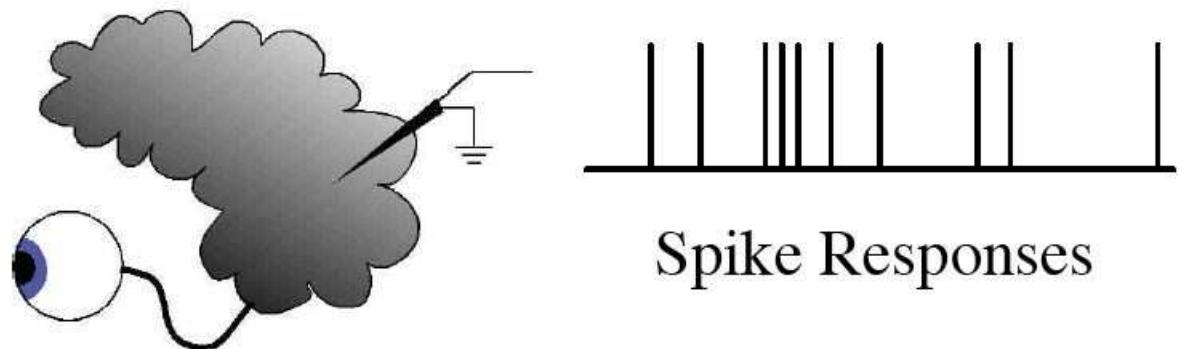
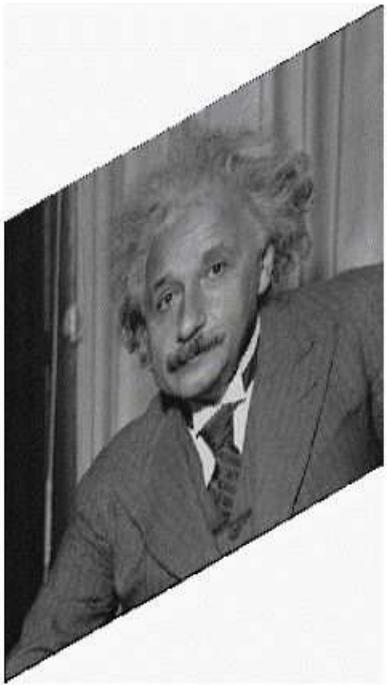
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# The neural code



Input-output relationship between

- External observables  $x$  (sensory stimuli, motor responses...)
- Neural variables  $y$  (spike trains, population activity...)

Probabilistic formulation:  $p(y|x)$

# Basic goal

...learning the neural code.

Fundamental question: how to estimate  $p(y|x)$  from experimental data?

General problem is too hard — not enough data, too many inputs  $x$  and spike trains  $y$

# Avoiding the curse of insufficient data

Many approaches to make problem tractable:

- 1:** Estimate some functional  $f(p)$  instead  
e.g., information-theoretic quantities (Paninski, 2003)
  
- 2:** Select stimuli as efficiently as possible (Machens, 2002;  
Paninski, 2005; Lewi et al., 2006)
  
- 3:** Fit a model with small number of parameters

# Neural encoding models

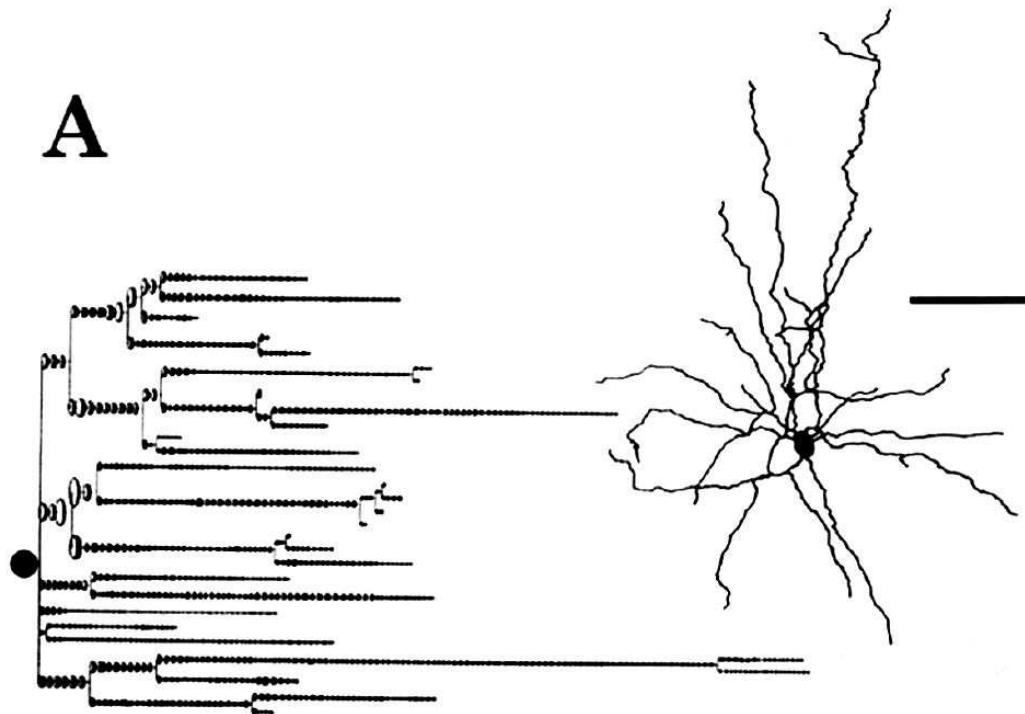
“Encoding model”:  $p_\theta(y|x)$ .

- Fit parameter  $\theta$  instead of full  $p(y|x)$

Main theme: want model to be flexible but not overly so

Flexibility vs. “fittability”

# Multiparameter HH-type model



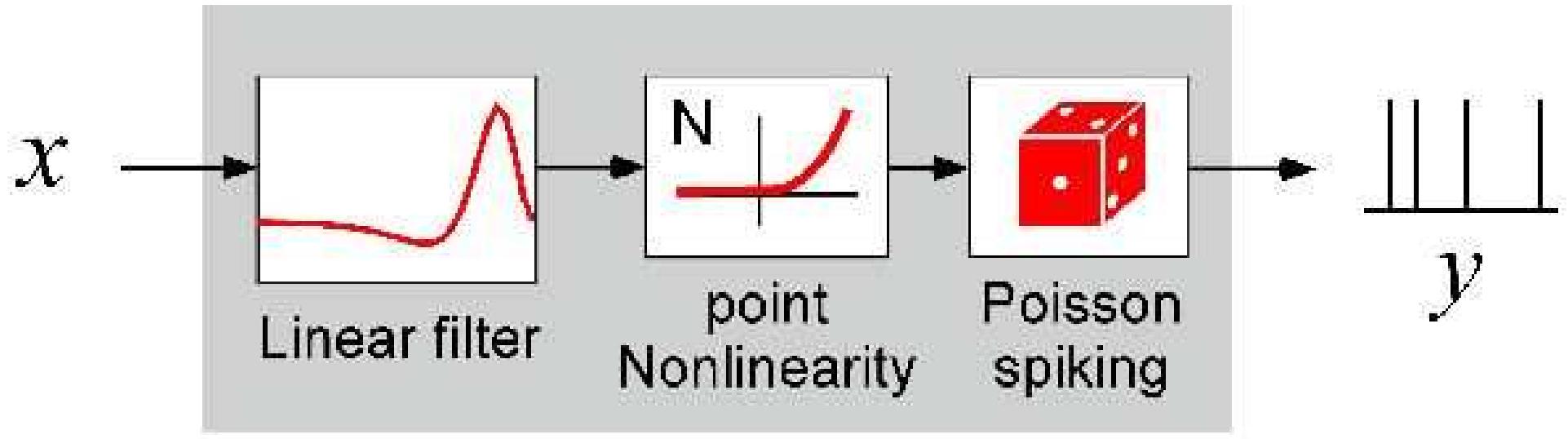
Regional Conductances ( $\text{mS/cm}^2$ )

Model	Current	Dendrites	Soma	AH	NR	Axon
EC2.5 REAL	$I_{\text{Ca}}$	2.0	1.5	1.5	—	—
$j = 1$	$I_{\text{K,Ca}}$	0.001	0.065	0.065	0.065	0.065
$\text{SD}^* (\text{real}) = 21.9 \mu\text{m}$	$I_{\text{Na}}$	25	80	100–150†	100	40–70‡
$\text{SD} (\text{EC2.5}) = 20 \mu\text{m}$	$I_{\text{K}}$	12	18	18	18	12–18‡
$\tau_{\text{Ca}} = 1.5$	$I_{\text{A}}$	36	54	54	54	—
$E_{\text{L}} = -60 \text{ mV}$	Leak (Real)	0.008	0.008	0.008	0.008	0.008
$E_{\text{Na}} = 35 \text{ mV}$	(EC2.5)	0.005	0.005	0.005	0.005	0.005

- highly biophysically plausible, flexible
- **but** very difficult to estimate parameters given spike times alone

(figure adapted from (Fohlmeister and Miller, 1997))

# Cascade (“LNP”) model



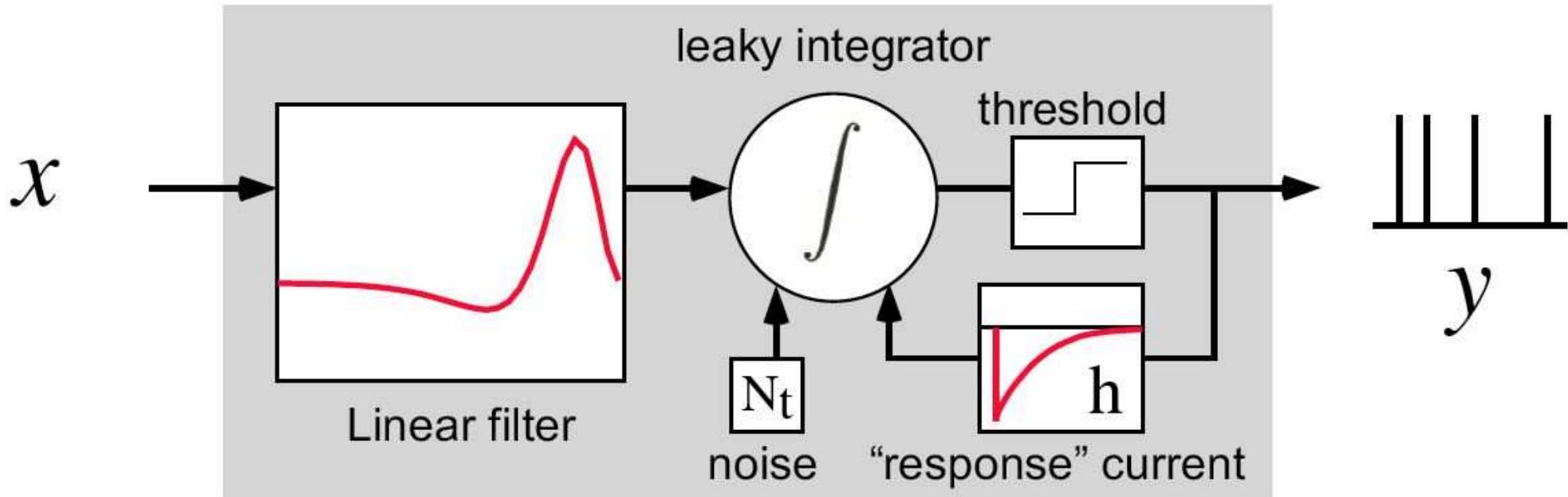
- easy to estimate via correlation-based methods  
(Simoncelli et al., 2004)
- **but** not biophysically plausible (fails to capture spike timing details: refractoriness, burstiness, adaptation, etc.)

# Two key ideas

1. Use likelihood-based methods for fitting.
  - well-justified statistically
  - easy to incorporate prior knowledge, explicit noise models, etc.
2. Use models that are easy to fit via maximum likelihood
  - **concave** (downward-curving) functions have no non-global local maxima  $\implies$  concave functions are easy to maximize by gradient ascent.

Recurring theme: find flexible models whose loglikelihoods are guaranteed to be concave.

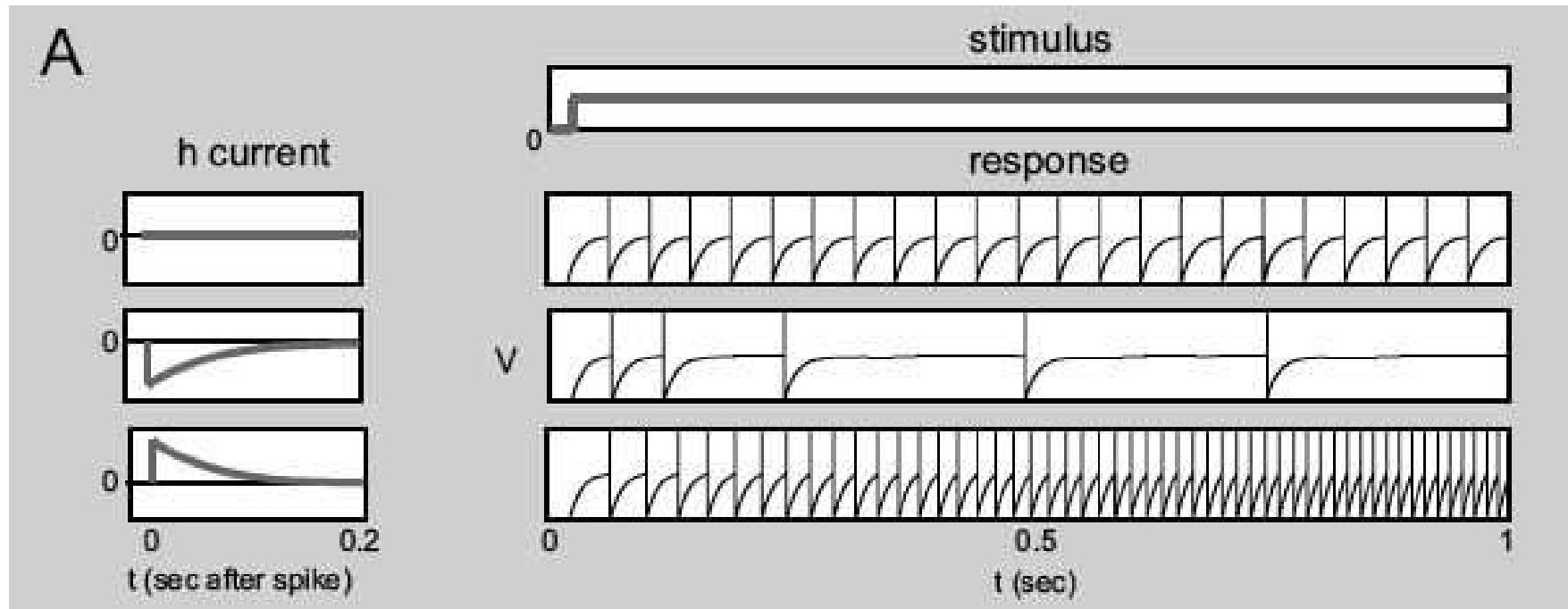
# Filtered integrate-and-fire model



$$dV(t) = \left( -g(t)V(t) + I_{DC} + \vec{k} \cdot \vec{x}(t) + \sum_{j=-\infty}^0 h(t - t_j) \right) dt + \sigma dN_t;$$

(Paninski et al., 2004b)

# Model flexibility: Adaptation



# The estimation problem

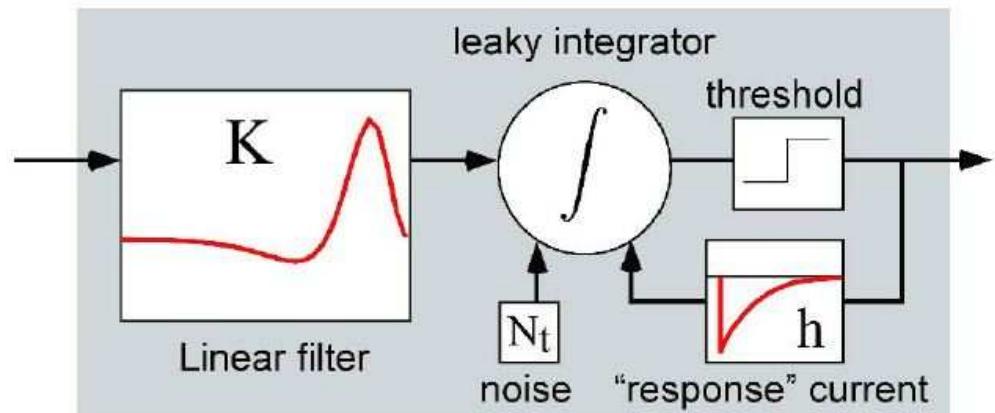
Learn the model parameters:

$\vec{K}$  = stimulus filter

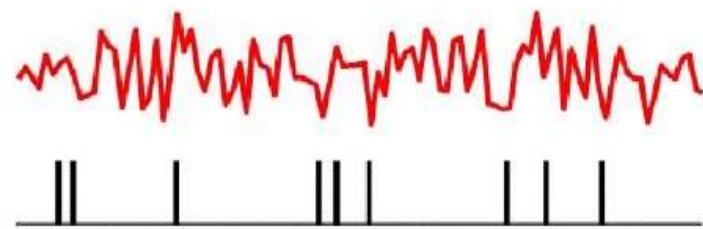
$g$  = leak conductance

$\sigma^2$  = noise variance

$\vec{h}$  = response current

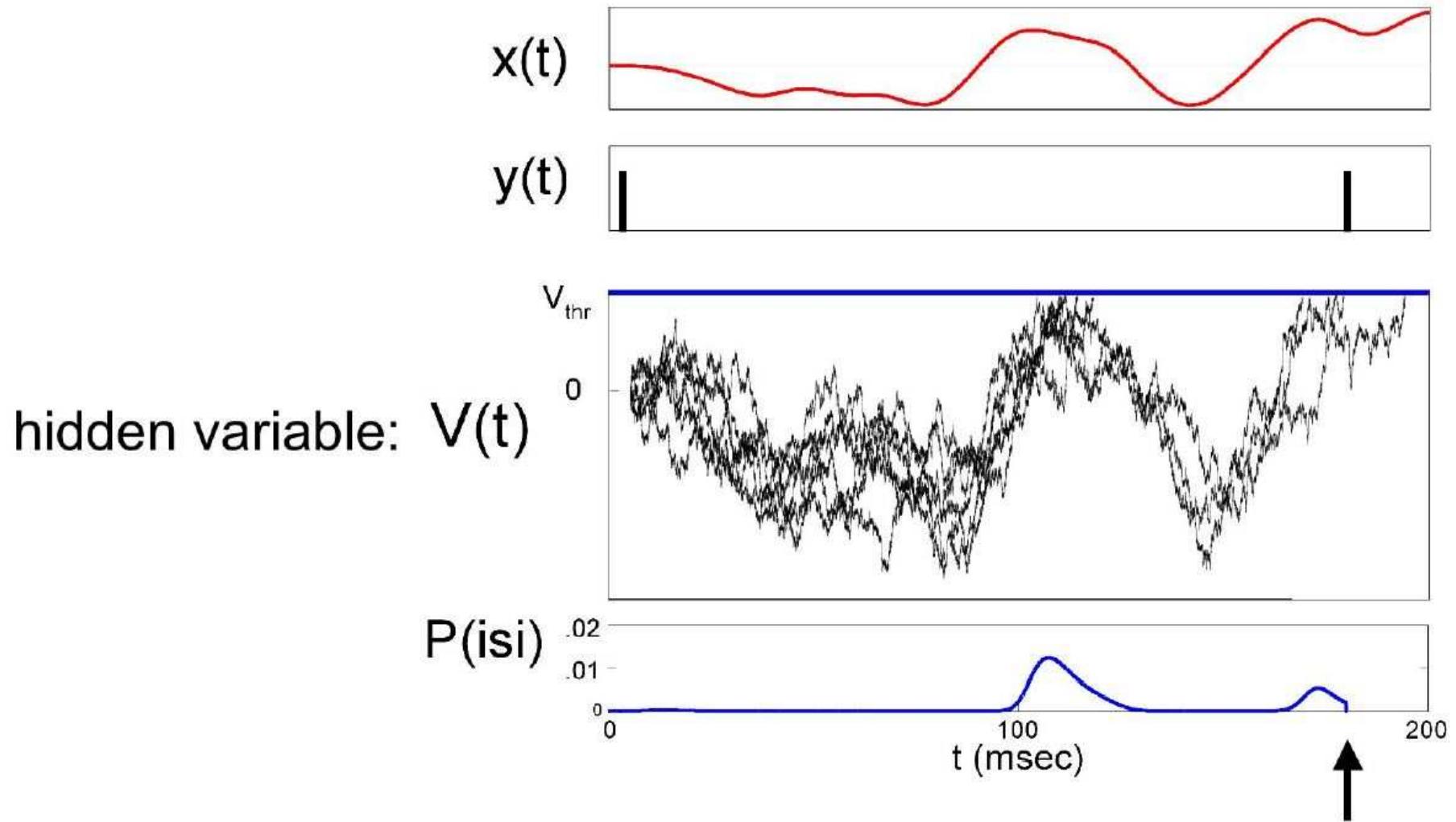


From: stimulus train  $x(t)$   
spike times  $t_i$



(Paninski et al., 2004b)

# First passage time likelihood



$P(\text{spike at } t_i) = \text{fraction of paths crossing threshold for first time at } t_i$

(computed numerically via Fokker-Planck or integral equation methods)

# Maximizing likelihood

Maximization seems difficult, even intractable:

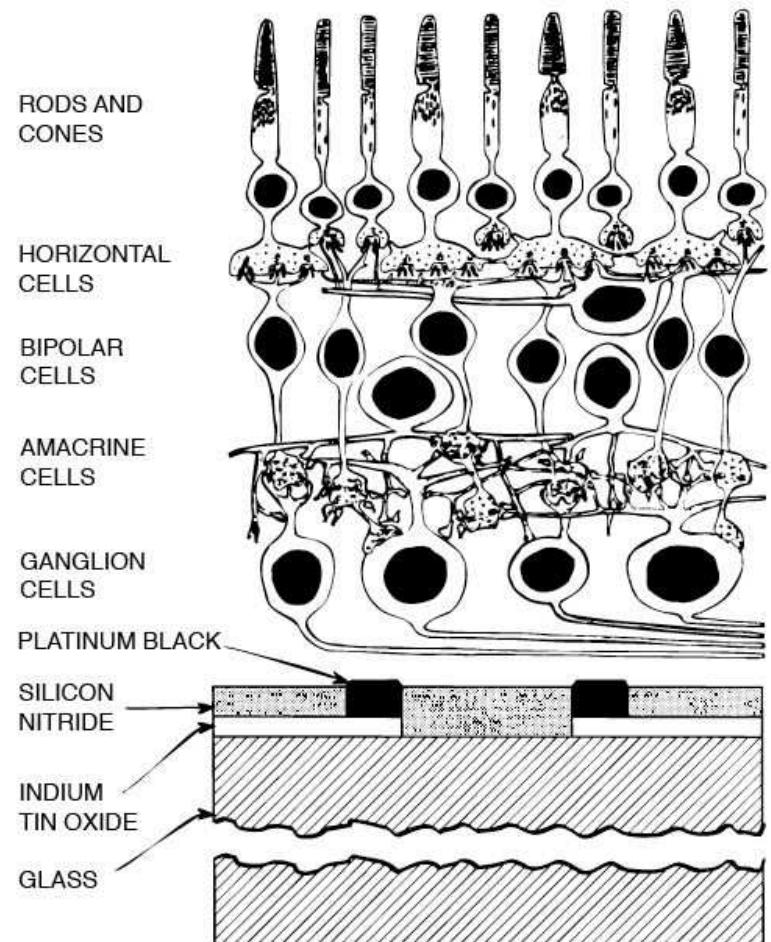
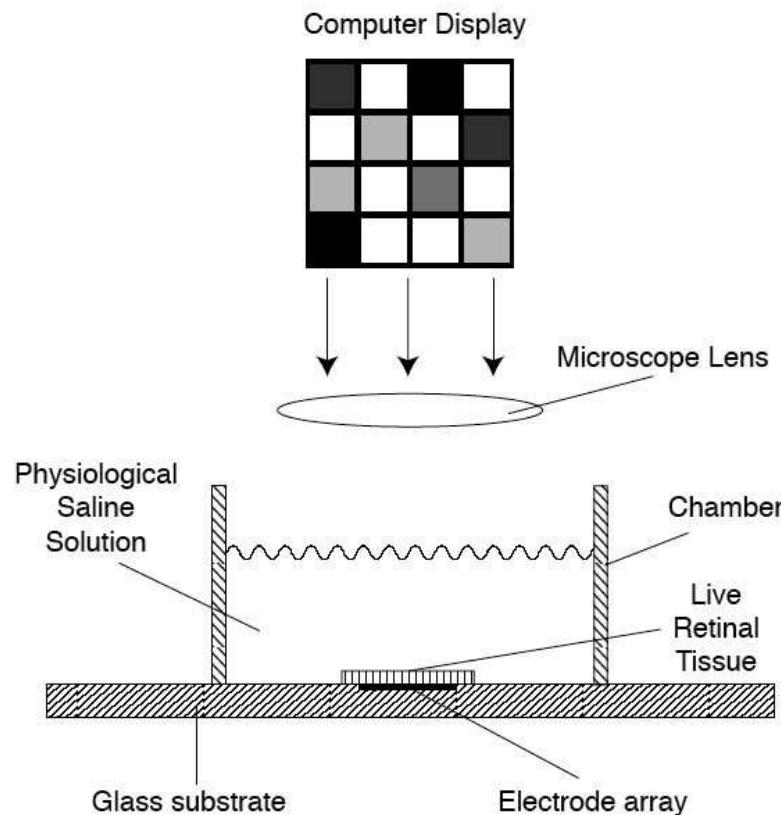
- high-dimensional parameter space
- likelihood is a complex nonlinear function of parameters

**Main result:** The loglikelihood is concave in the parameters, no matter what data  $\{\vec{x}(t), t_i\}$  are observed.

- ⇒ no non-global local maxima
- ⇒ maximization easy by ascent techniques.

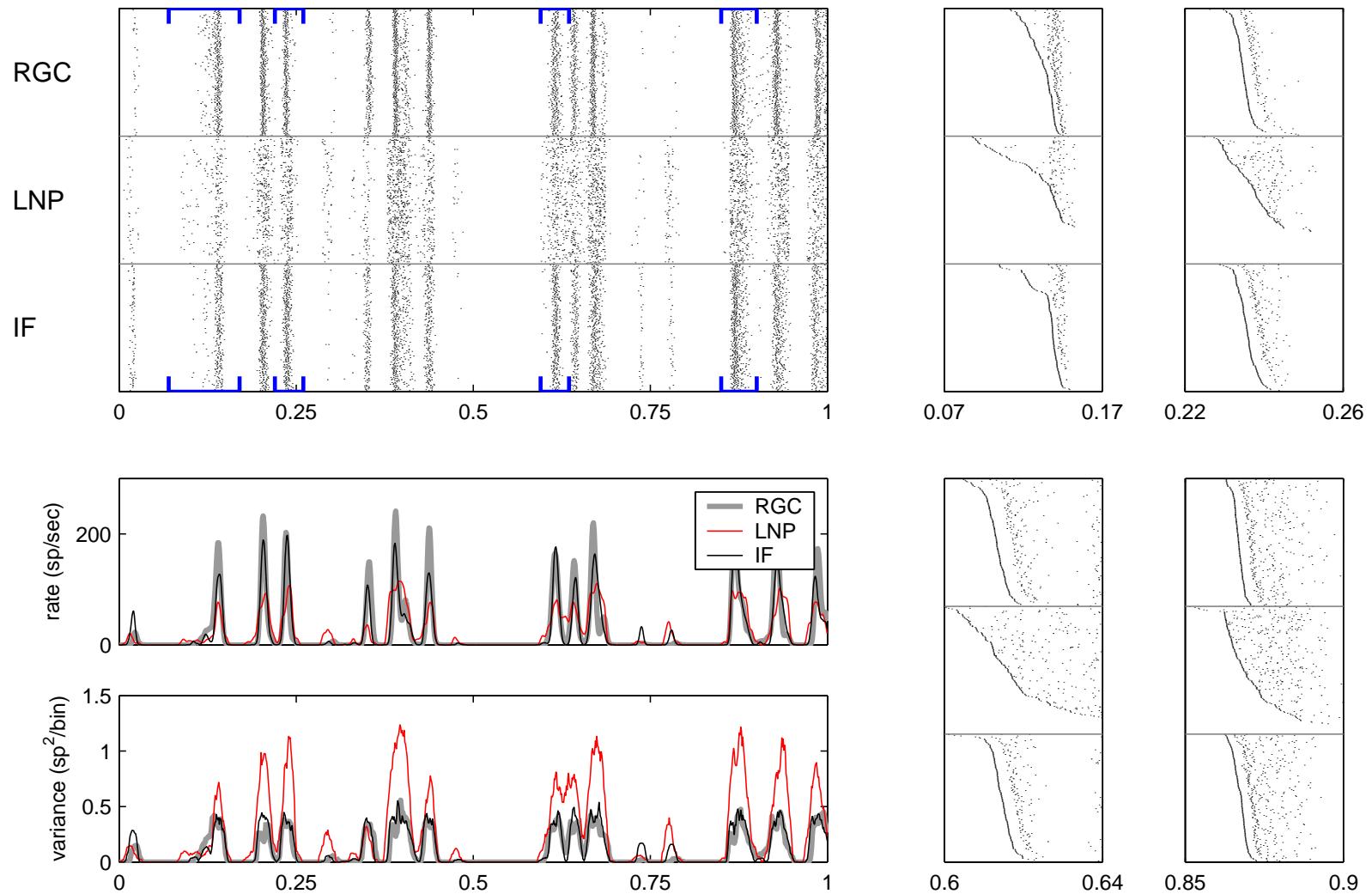
# Application: retinal ganglion cells

Preparation: dissociated salamander and macaque retina  
— extracellularly-recorded responses of populations of RGCs



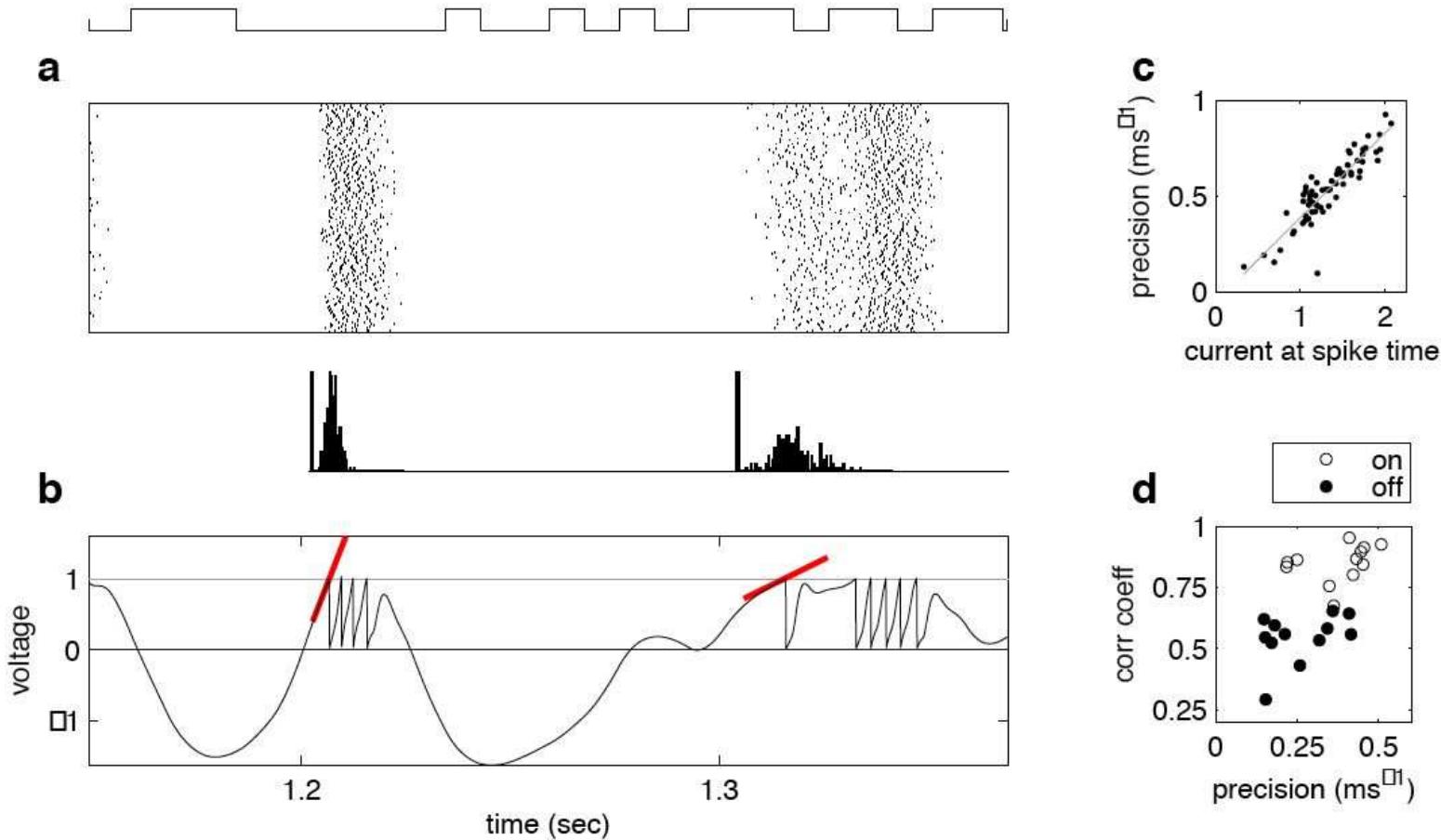
Stimulus: random “flicker” visual stimuli

# Spike timing precision in retina



(Pillow et al., 2005b)

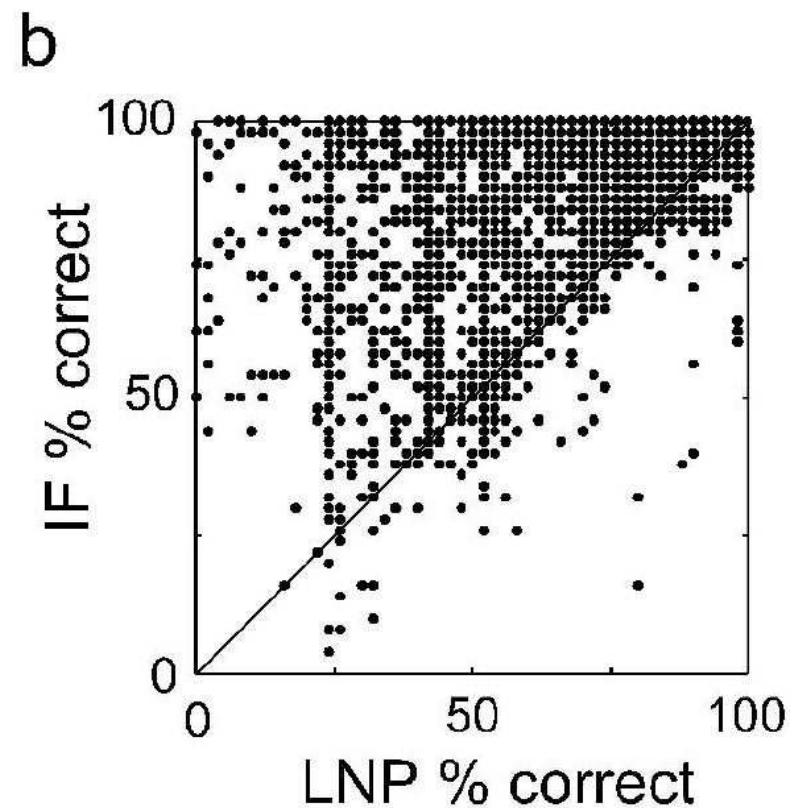
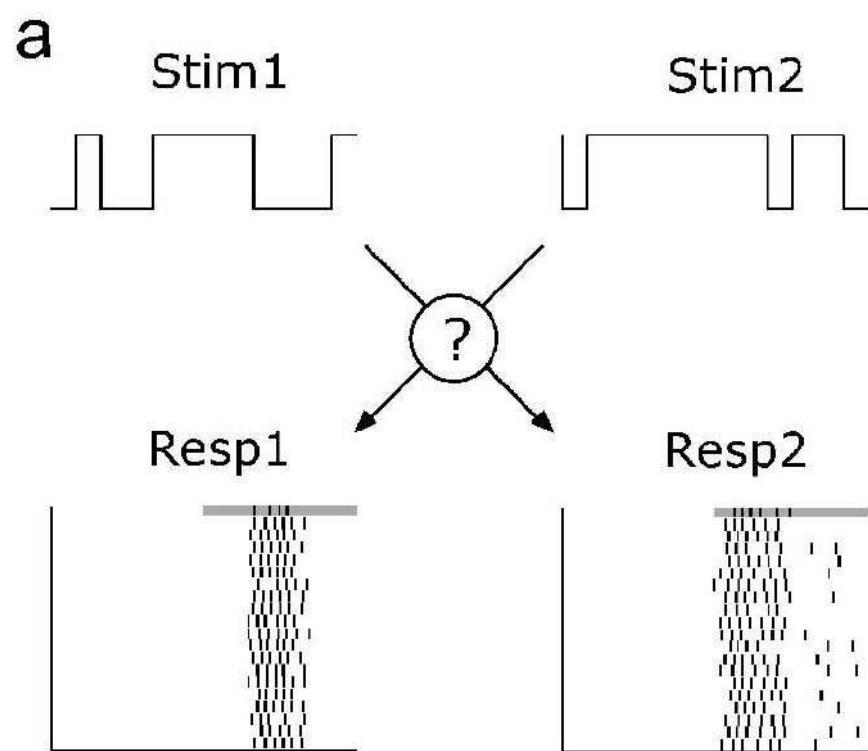
# Linking spike reliability and subthreshold noise



(Pillow et al., 2005b)

# Likelihood-based discrimination

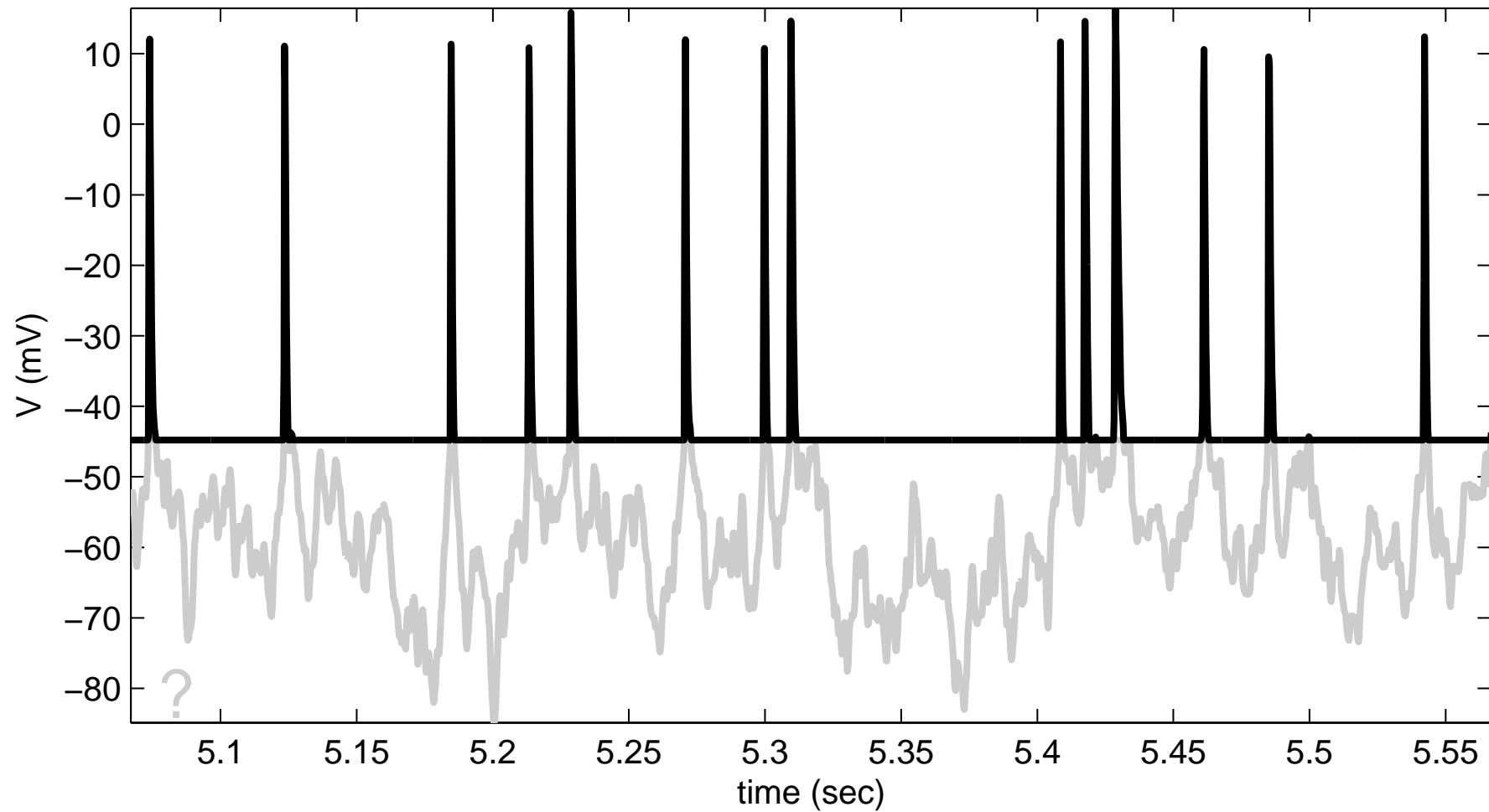
Given spike data, optimal decoder chooses stimulus  $\vec{x}$  according to likelihood:  $p(\text{spikes}|\vec{x}_1)$  vs.  $p(\text{spikes}|\vec{x}_2)$ .



Using accurate model is essential (Pillow et al., 2005b)

## Example 2: decoding subthreshold activity

Given extracellular spikes, what is most likely intracellular  $V(t)$ ?



# Computing $V_{ML}(t)$

Loglikelihood of  $V(t)$  (given LIF parameters, white noise  $N_t$ ):

$$L(\{V(t)\}_{0 \leq t \leq T}) = -\frac{1}{2\sigma^2} \int_0^T \left[ \dot{V}(t) - \left( -gV(t) + I(t) \right) \right]^2 dt$$

Constraints:

- Reset at  $t = 0$ :

$$V(0) = V_{reset}$$

- Spike at  $t = T$ :

$$V(T) = V_{th}$$

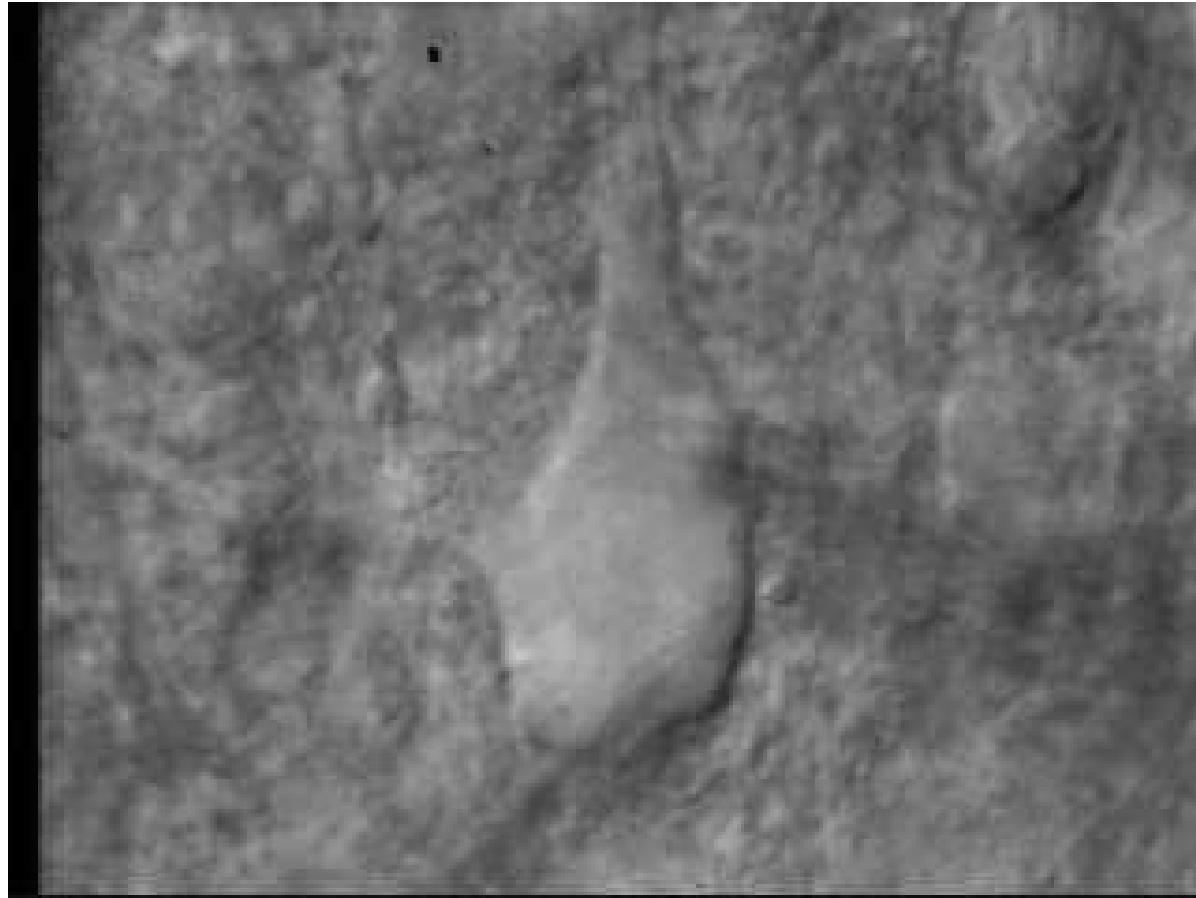
- No spike for  $0 < t < T$ :

$$V(t) < V_{th}$$

Quadratic programming problem: optimize quadratic function under linear constraints. **Concave**: unique global optimum.

# Application: *in vitro* data

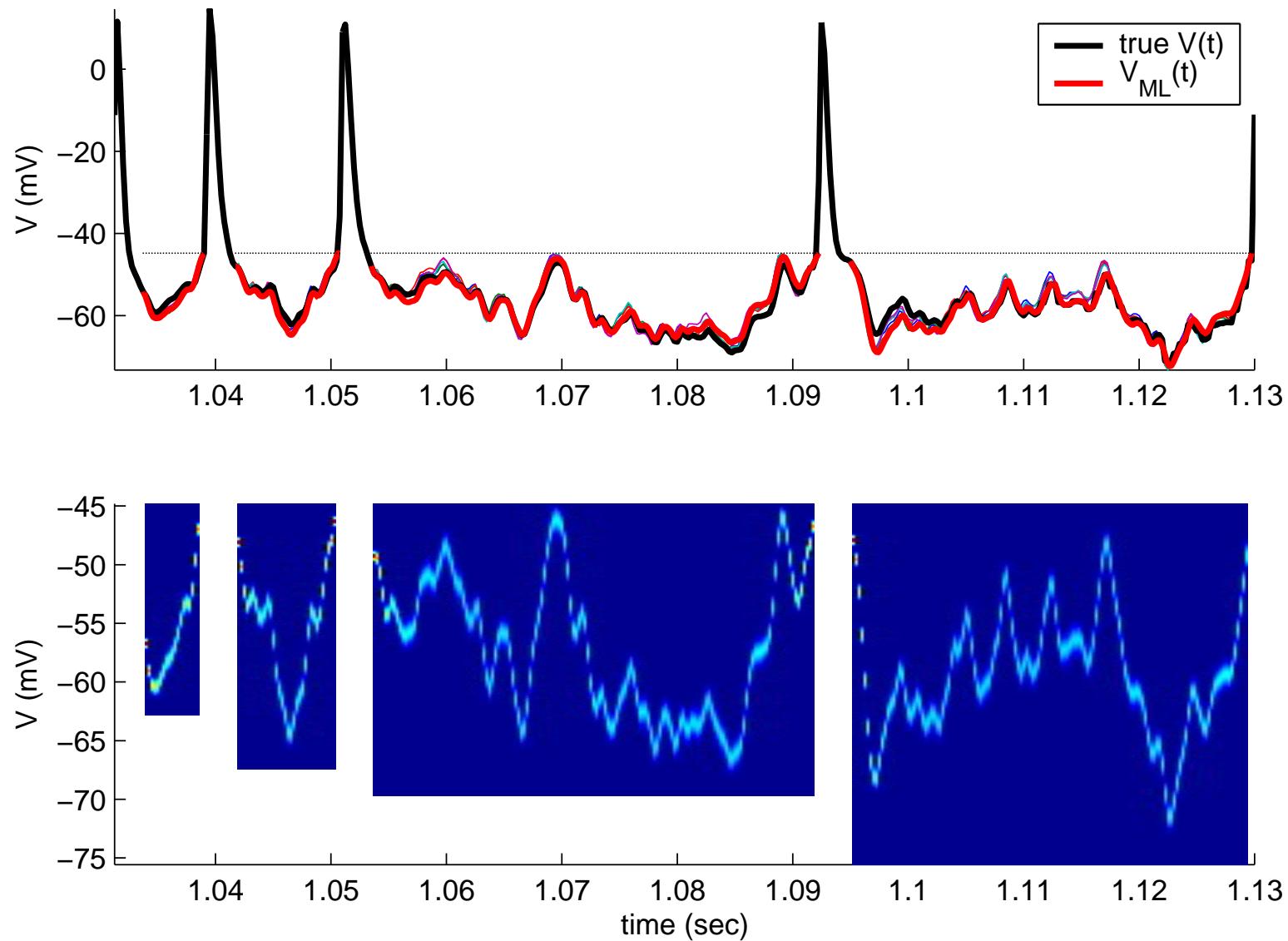
Recordings: rat sensorimotor cortical slice; dual-electrode whole-cell



Stimulus: Gaussian white noise current  $I(t)$

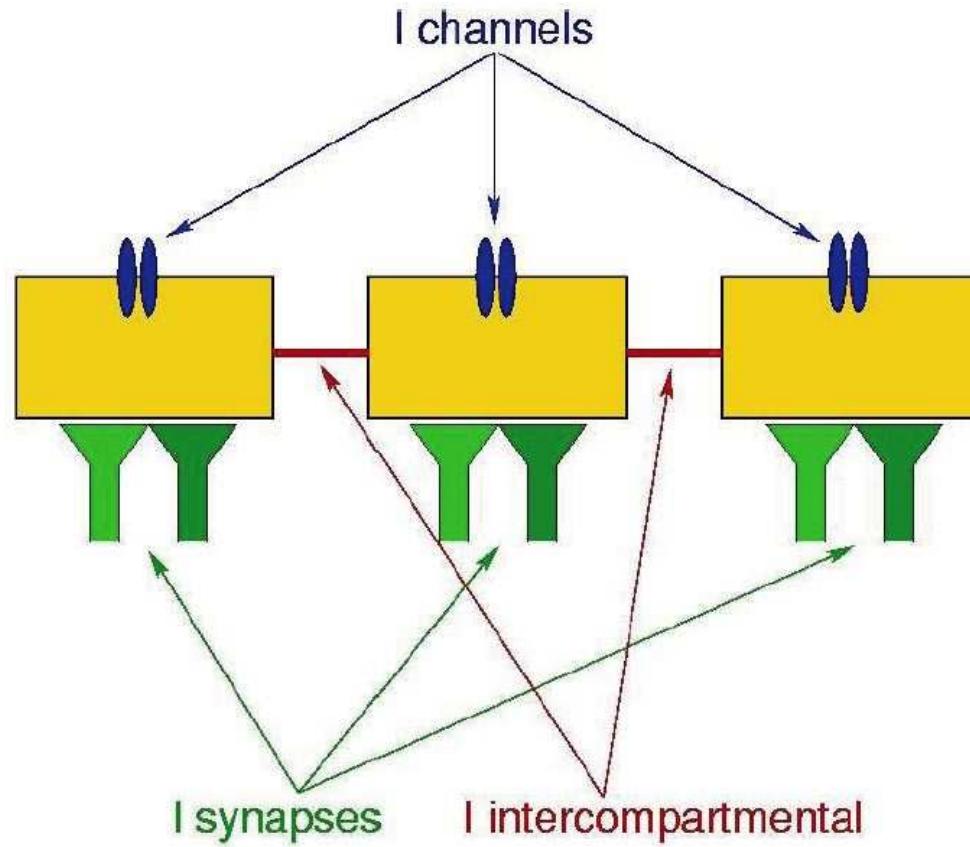
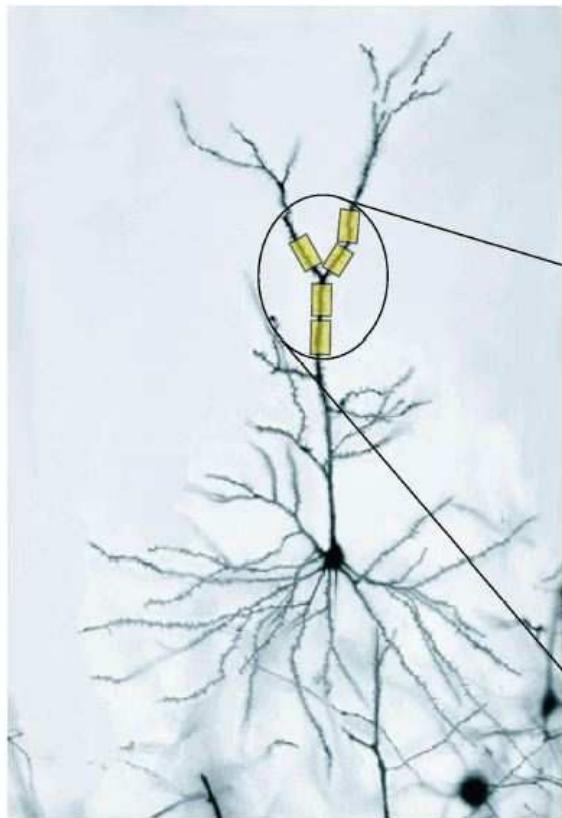
Analysis: fit IF model parameters  $\{g, \vec{k}, h(\cdot), V_{th}, \sigma\}$  by maximum likelihood  
(Paninski et al., 2003; Paninski et al., 2004a), then compute  $V_{ML}(t)$

# Application: *in vitro* data



(Applications to spike-triggered average (Paninski, 2006a; Paninski, 2006b).)

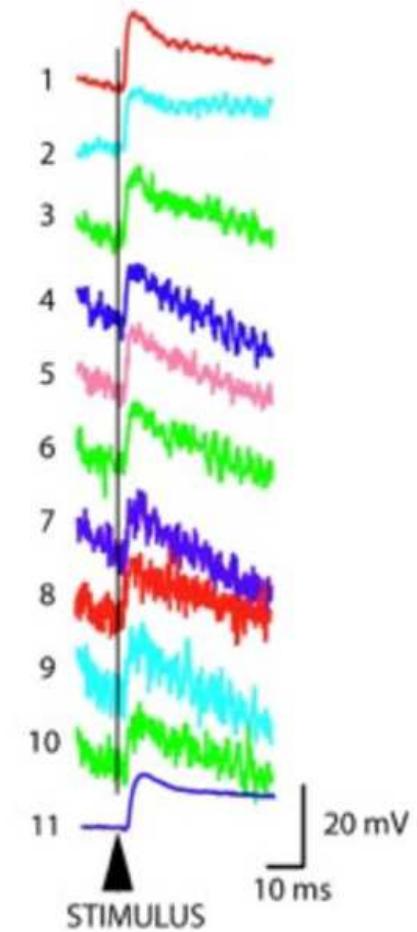
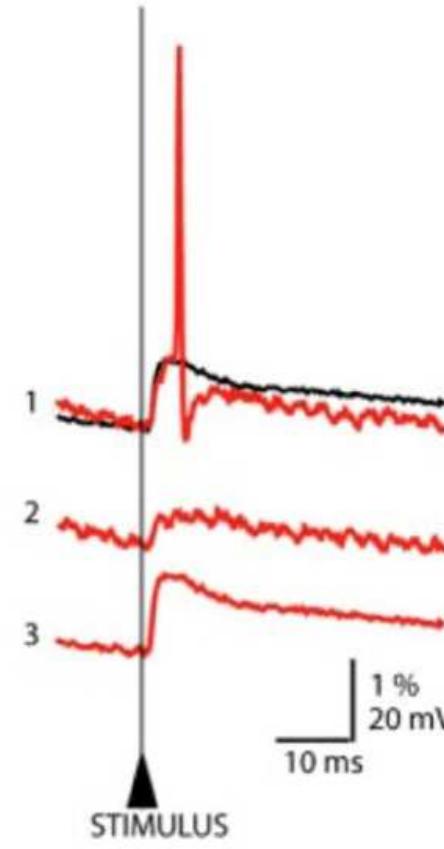
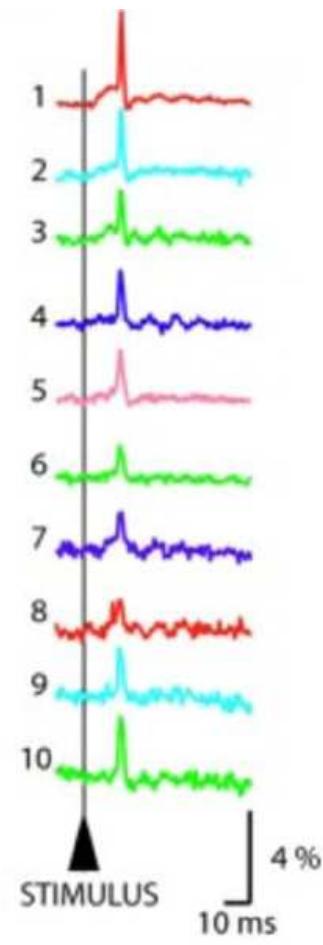
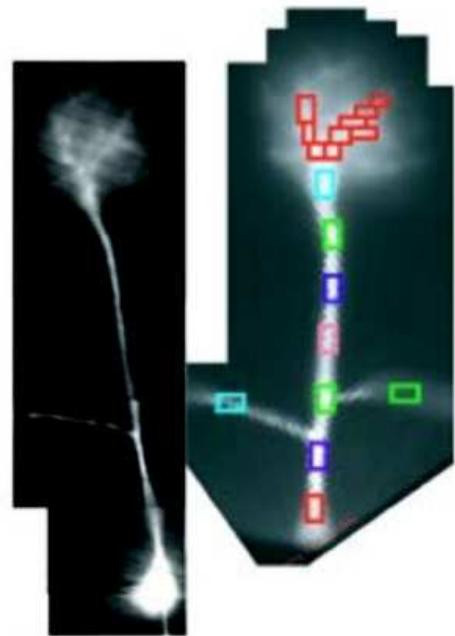
# Back to detailed models



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

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

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

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

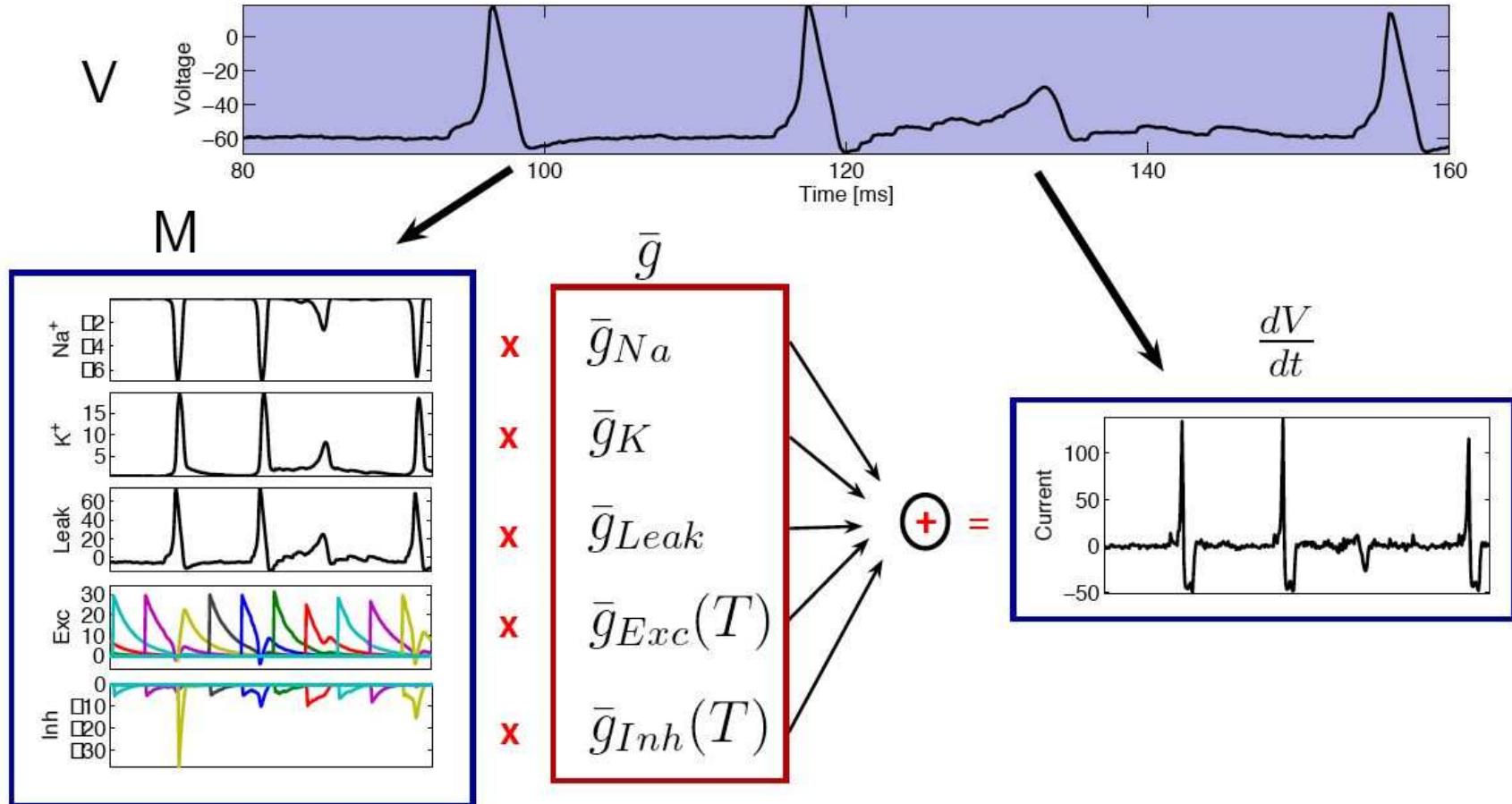
$$I_i^{\text{intercompartmental}} = \sum_a g_a \Delta V_a(t)$$

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.

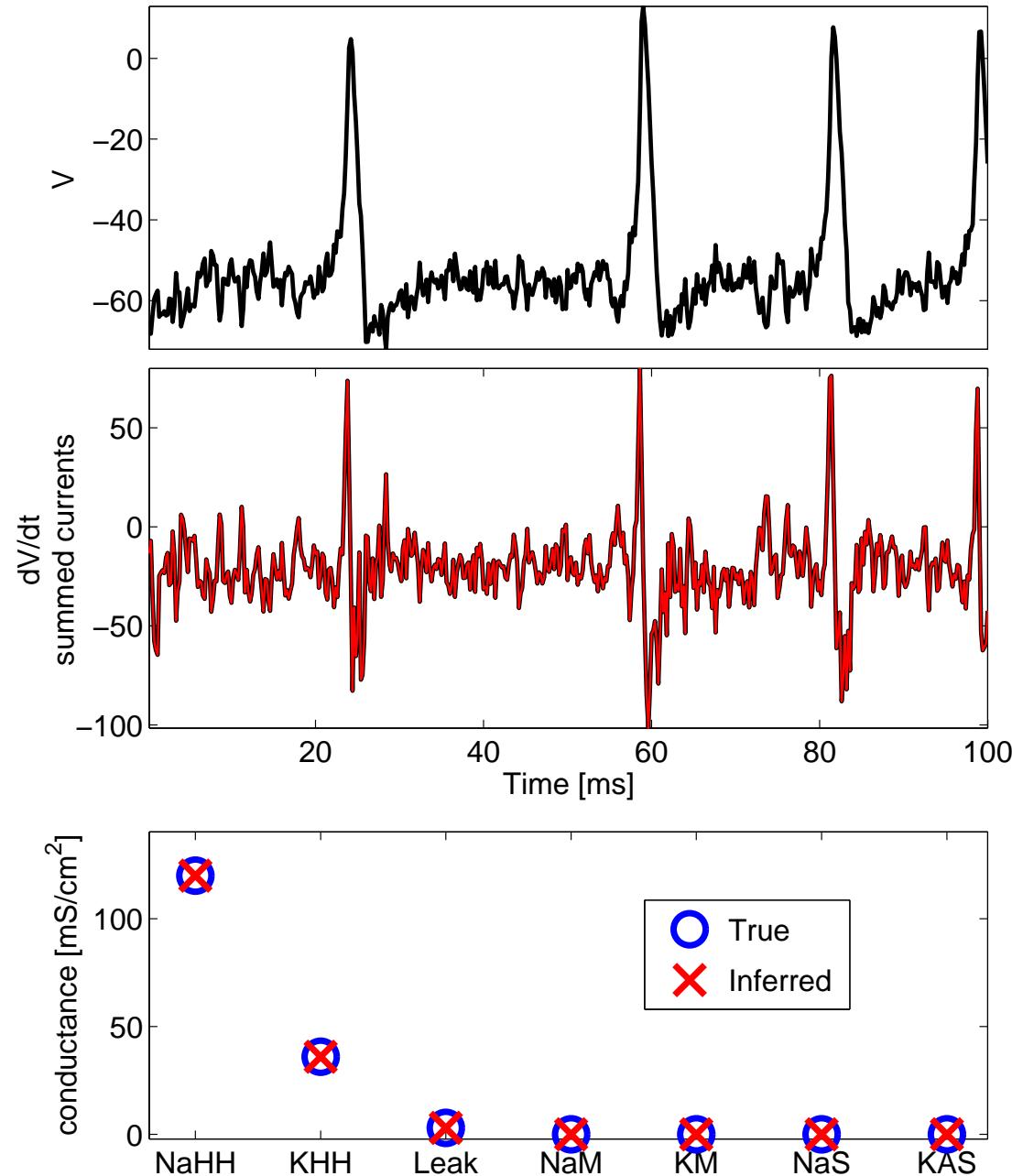
Gaussian noise  $\implies$  standard nonnegative regression (albeit high-d).

# Estimating channel densities from $V(t)$



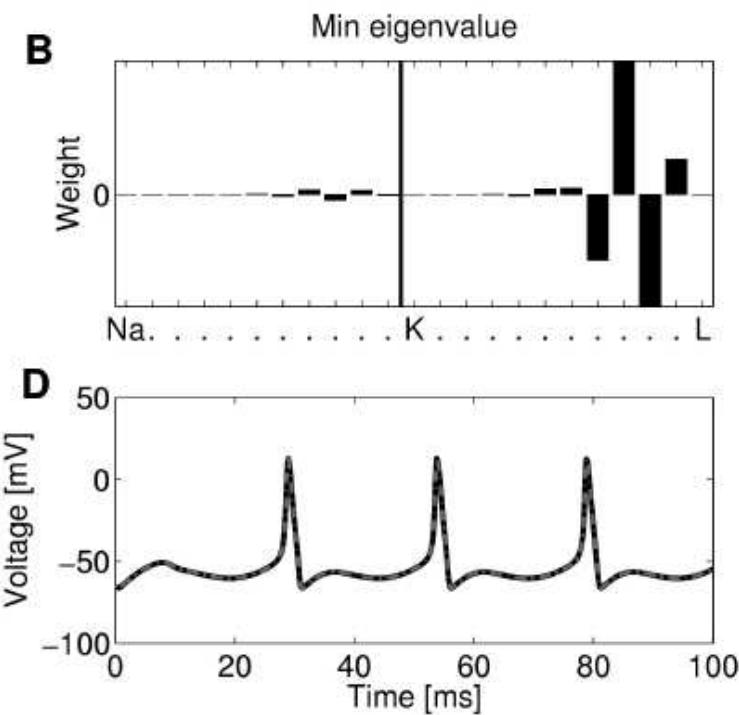
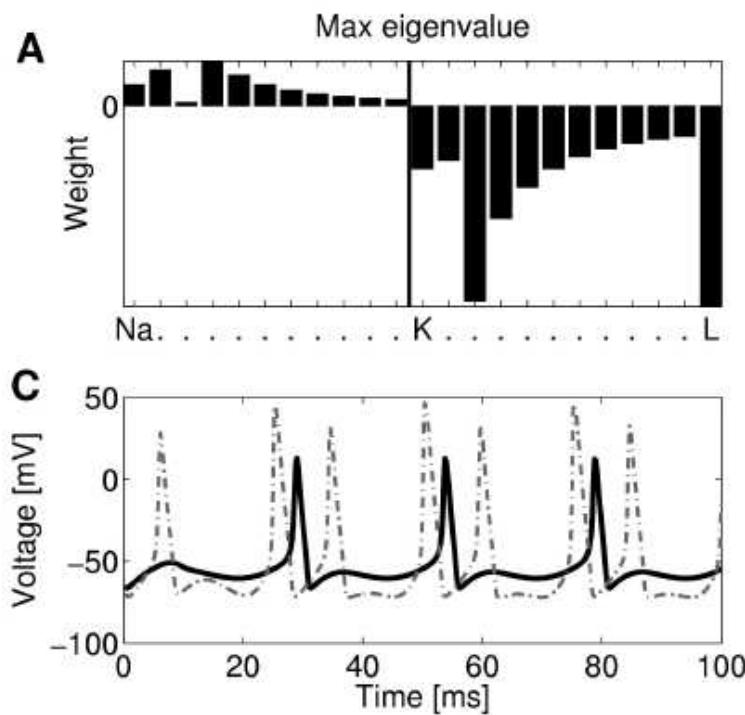
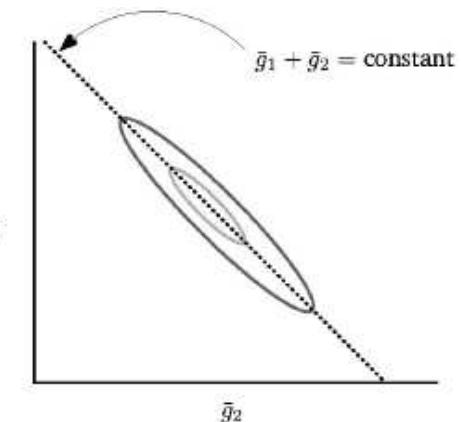
(Huys et al., 2006)

# Estimating channel densities from $V(t)$



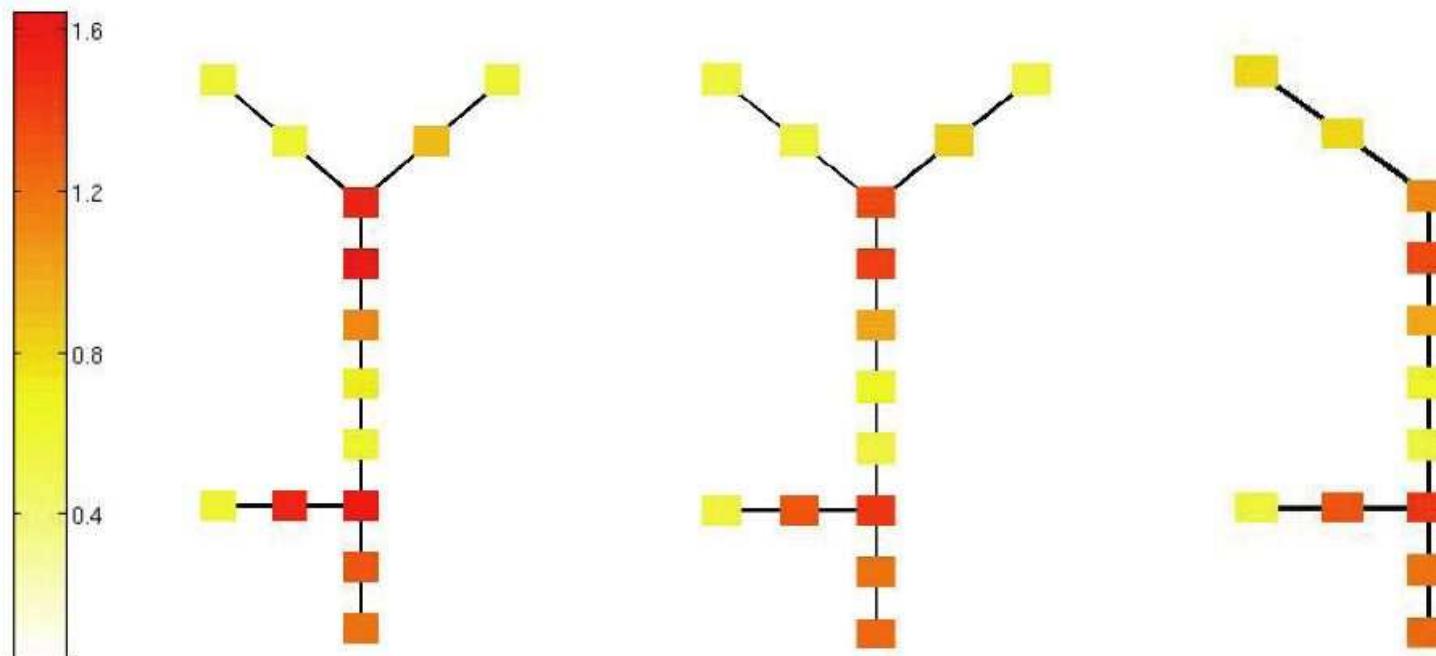
# Measuring uncertainty in channel densities

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



# Estimating non-homogeneous channel densities and axial resistances from spatiotemporal voltage recordings

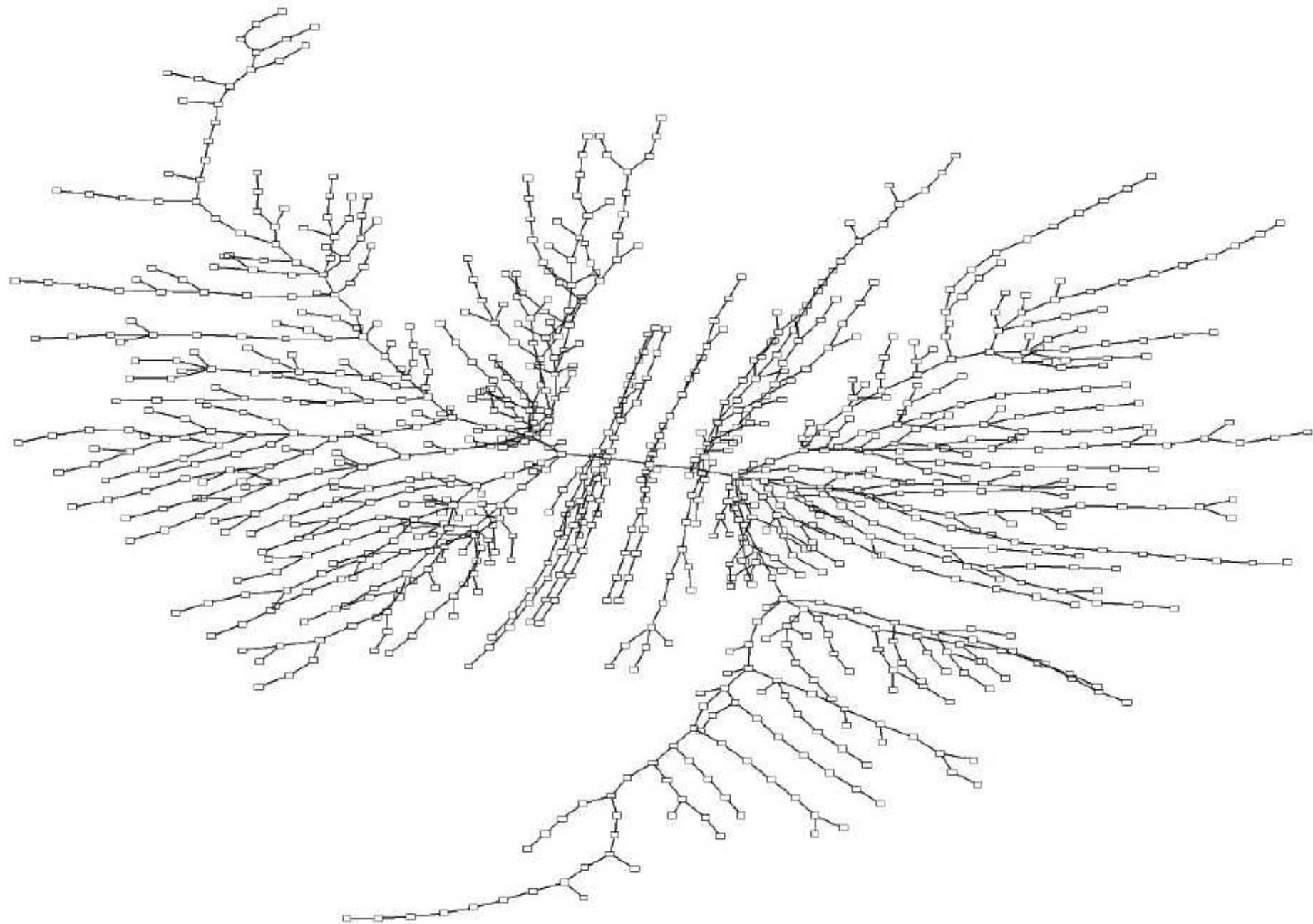
$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$



True  $g_{\text{Na}}$

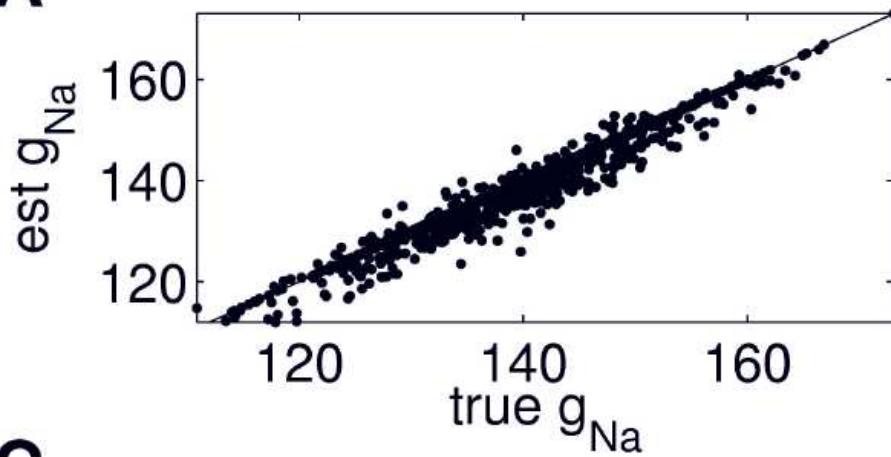
Estimated  $g_{\text{Na}}$

# A big cell

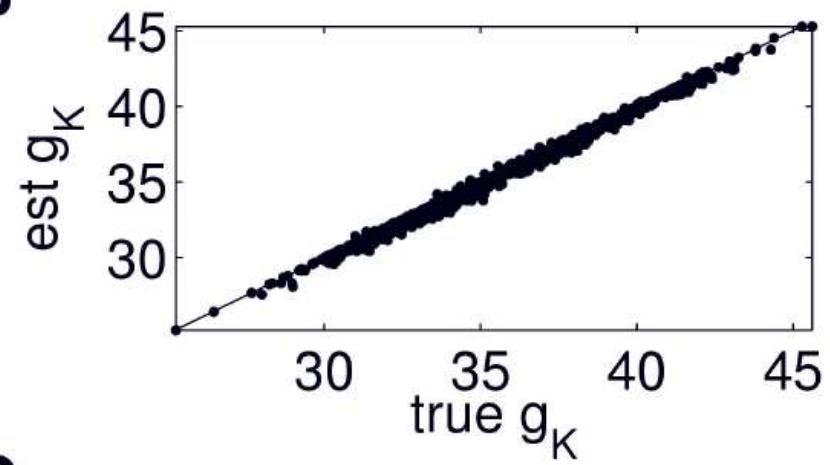


# A big cell

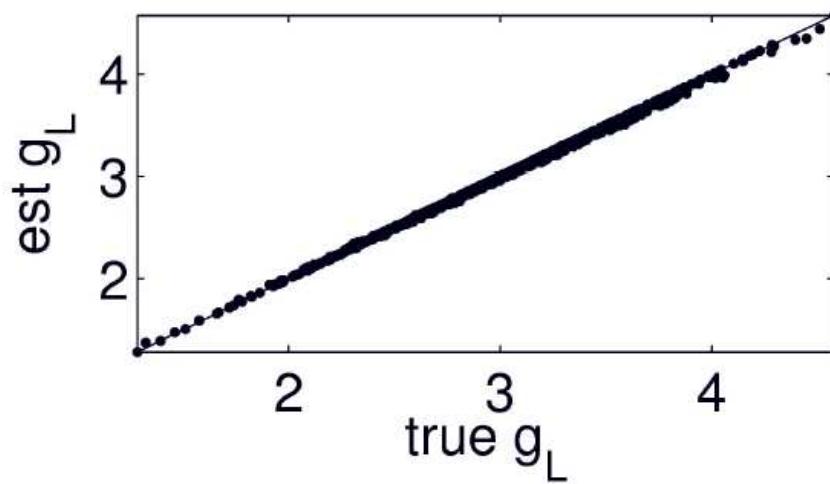
**A**



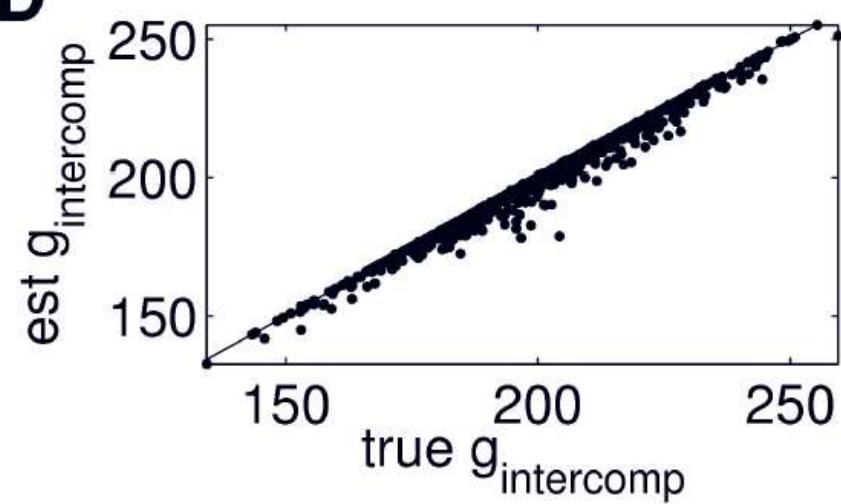
**B**



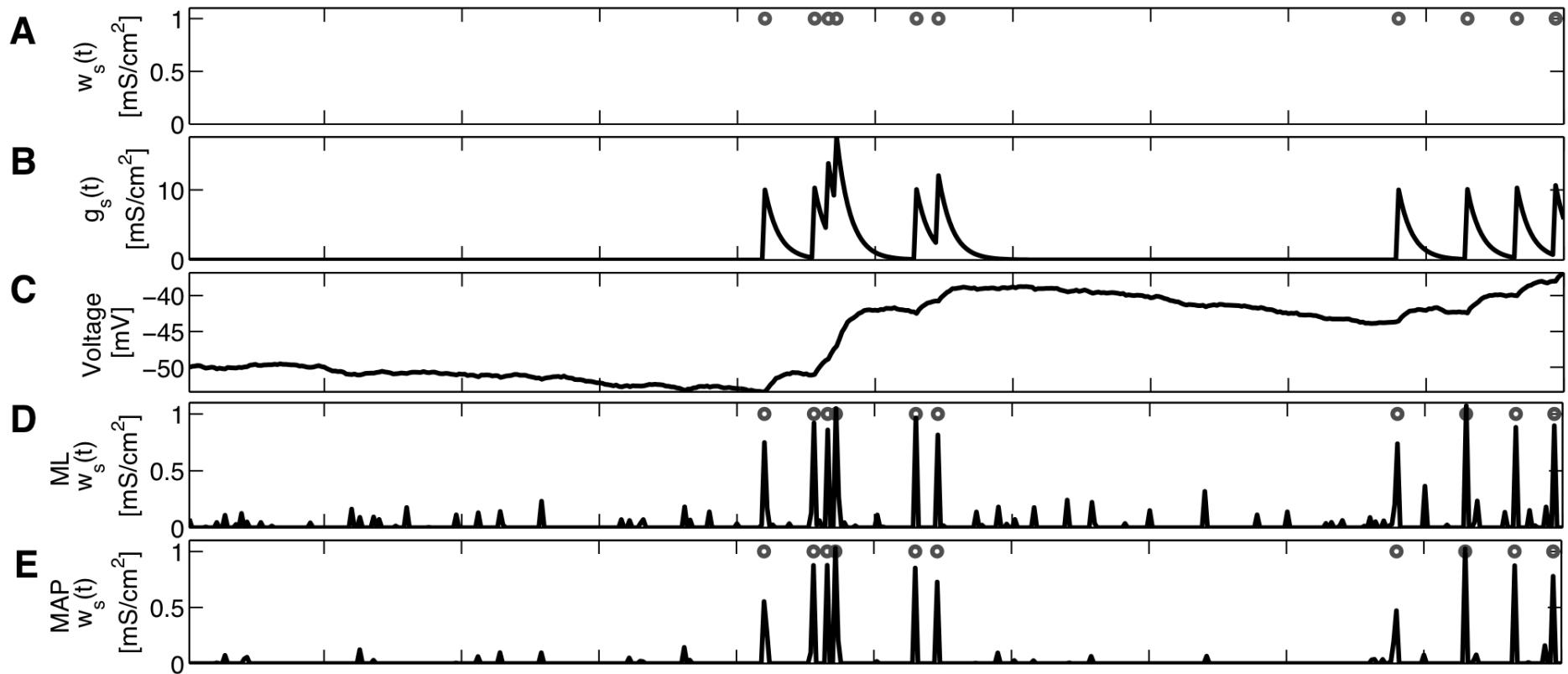
**C**



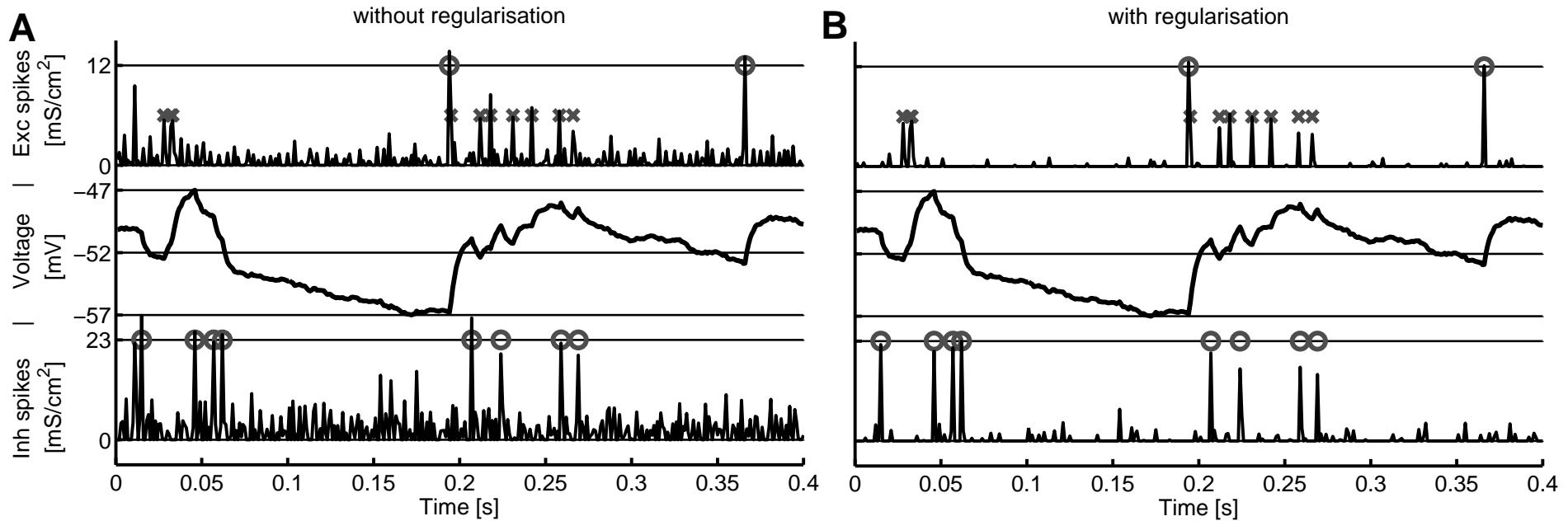
**D**



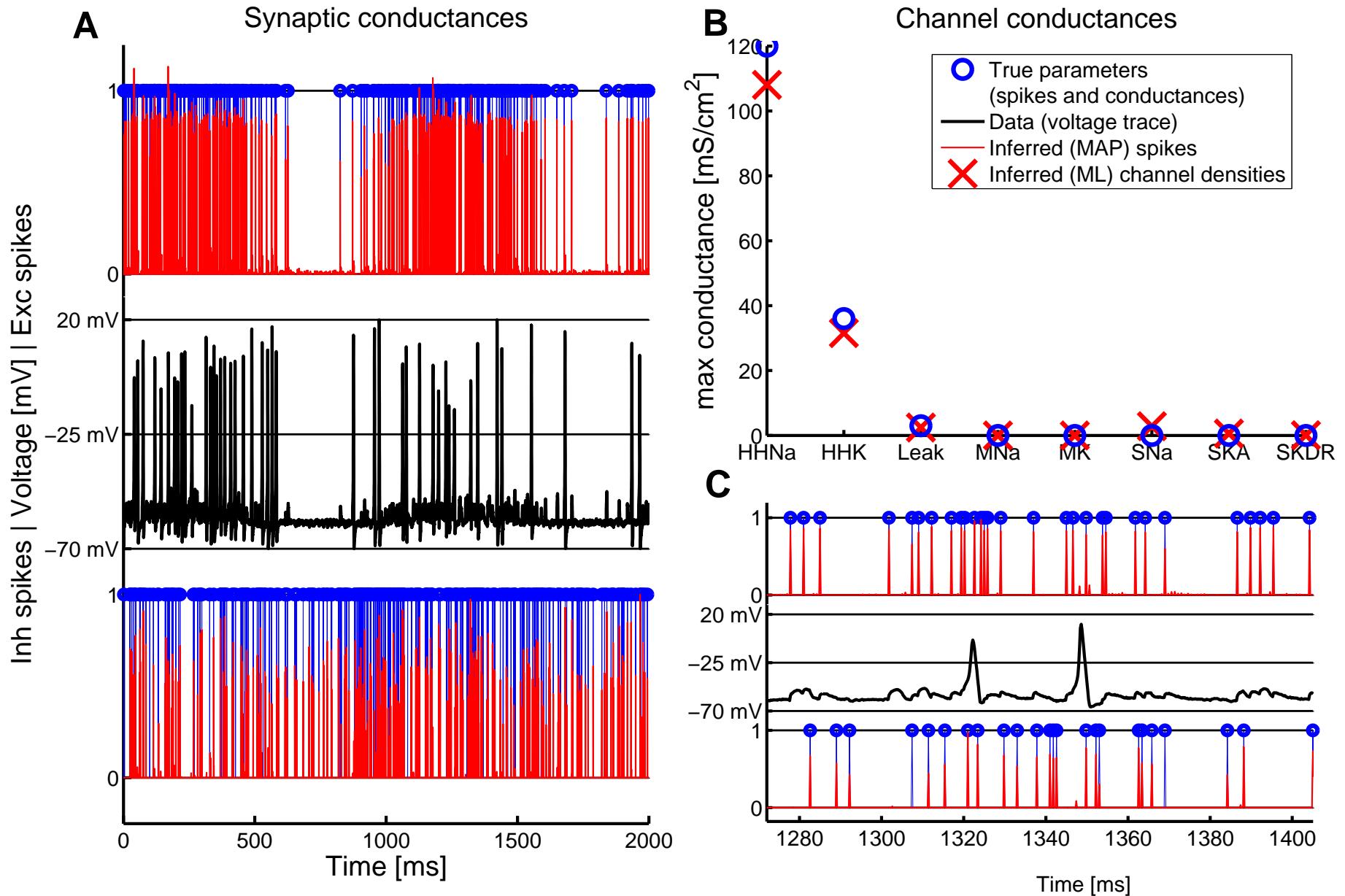
# Estimating synaptic inputs given $V(t)$



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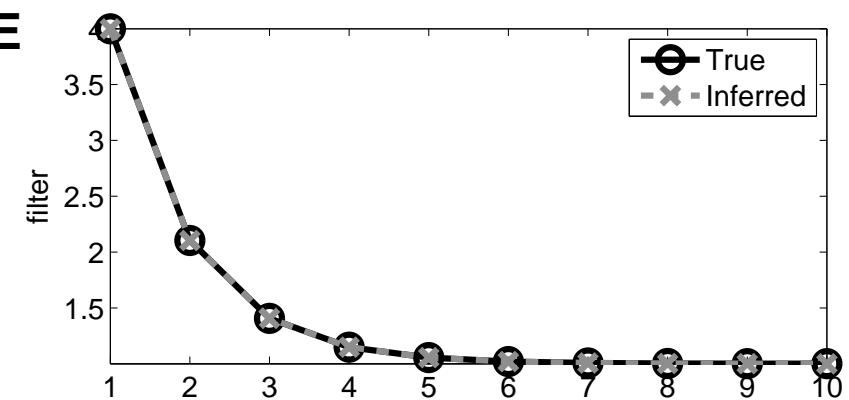
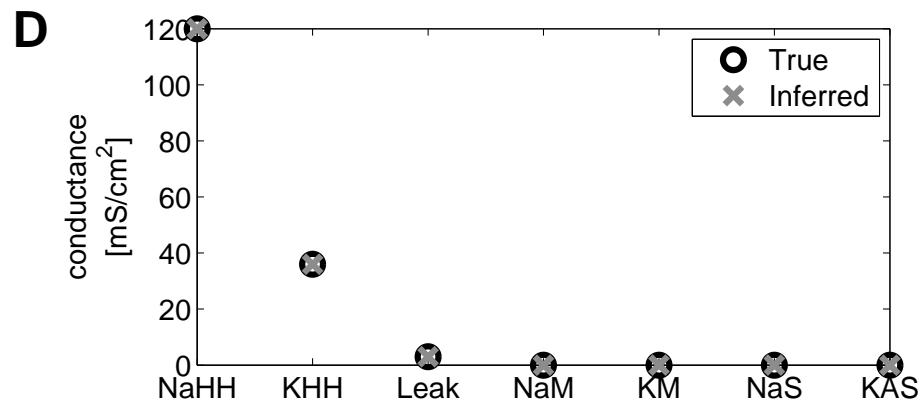
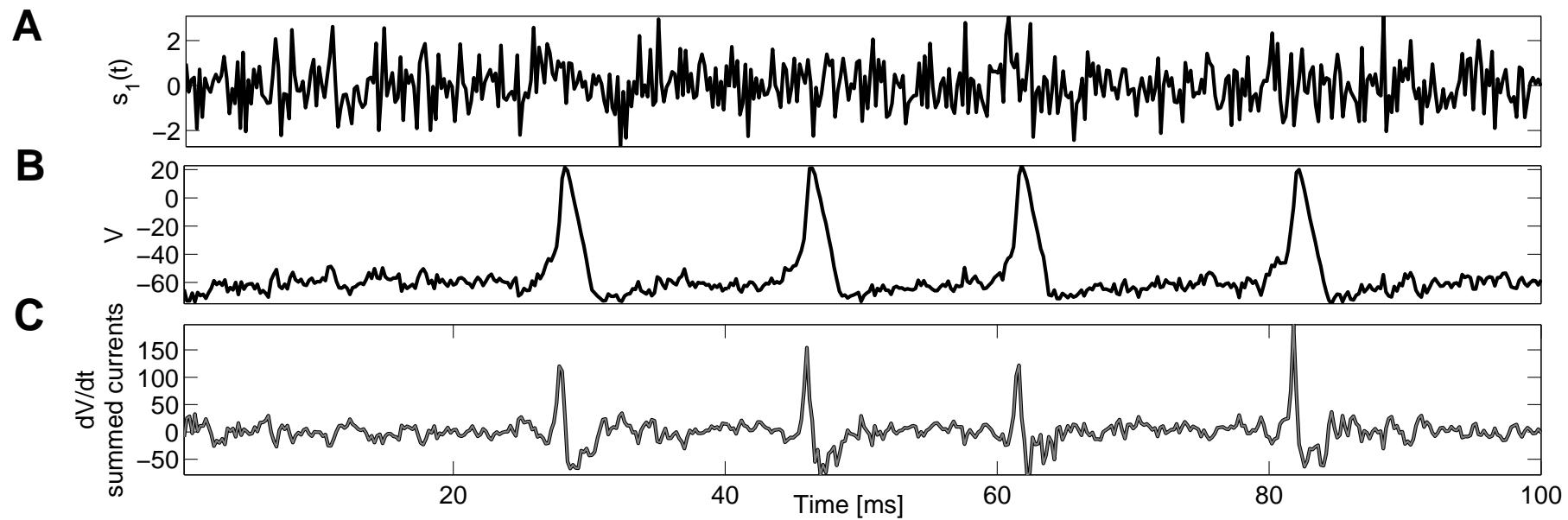


# Estimating synaptic inputs given $V(t)$



# Estimating stimulus effects

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



# References

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