Statistical methods for understanding neural codes

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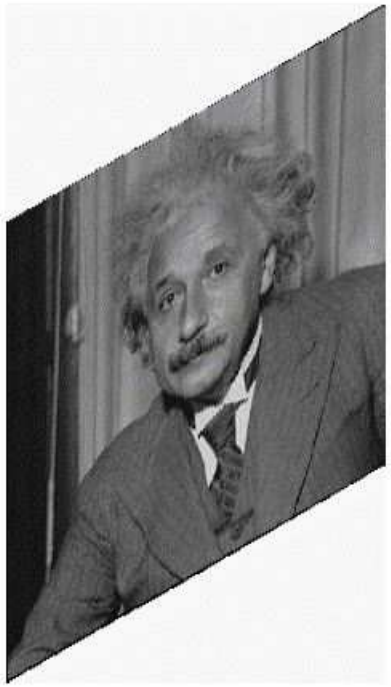
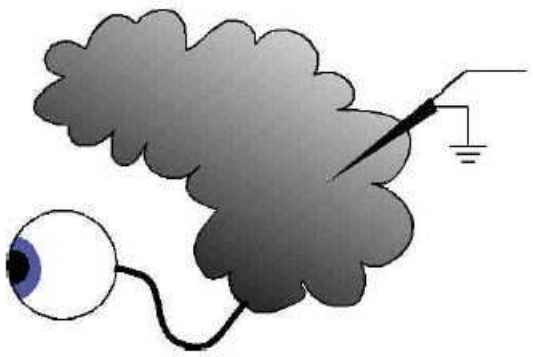
The neural code





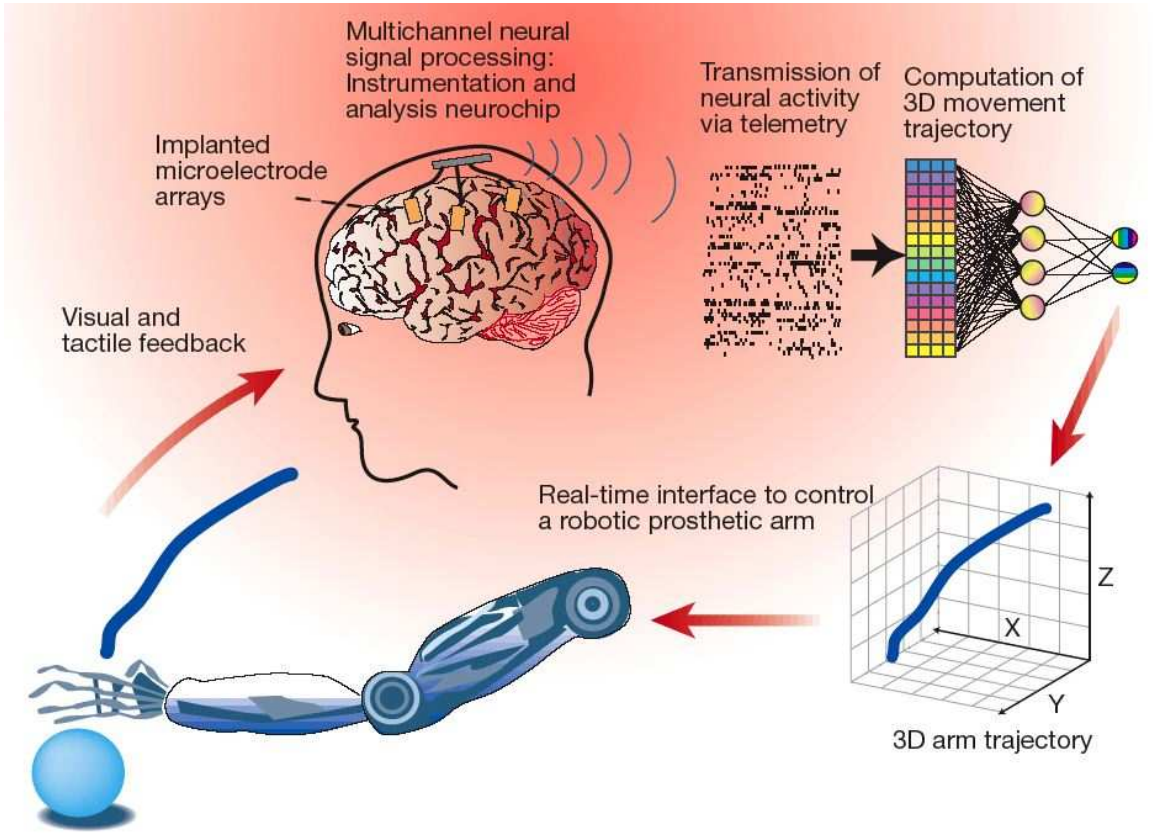
Spike Responses

Input-output relationship between

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

Probabilistic formulation: stimulus-response map is *stochastic*

Example: neural prosthetic design



Nicolelis, Nature '01

Donoghue; Cyberkinetics, Inc. '04

(Paninski et al., 1999; Serruya et al., 2002; Shoham et al., 2005)

Basic goal

...learning the neural code.

Fundamental question: how to estimate $p(response|stimulus)$ from experimental data?

General problem is too hard — not enough data, too many possible stimuli and spike trains

Avoiding the curse of insufficient data

Many approaches to make problem tractable:

1: Estimate some function of p instead

e.g., information-theoretic quantities (Nemenman et al., 2002; Paninski, 2003b)

2: Select stimuli as efficiently as possible

e.g., (Foldiak, 2001; Machens, 2002; Paninski, 2003a)

3: Fit a model with small number of parameters

Part 1: Neural encoding models

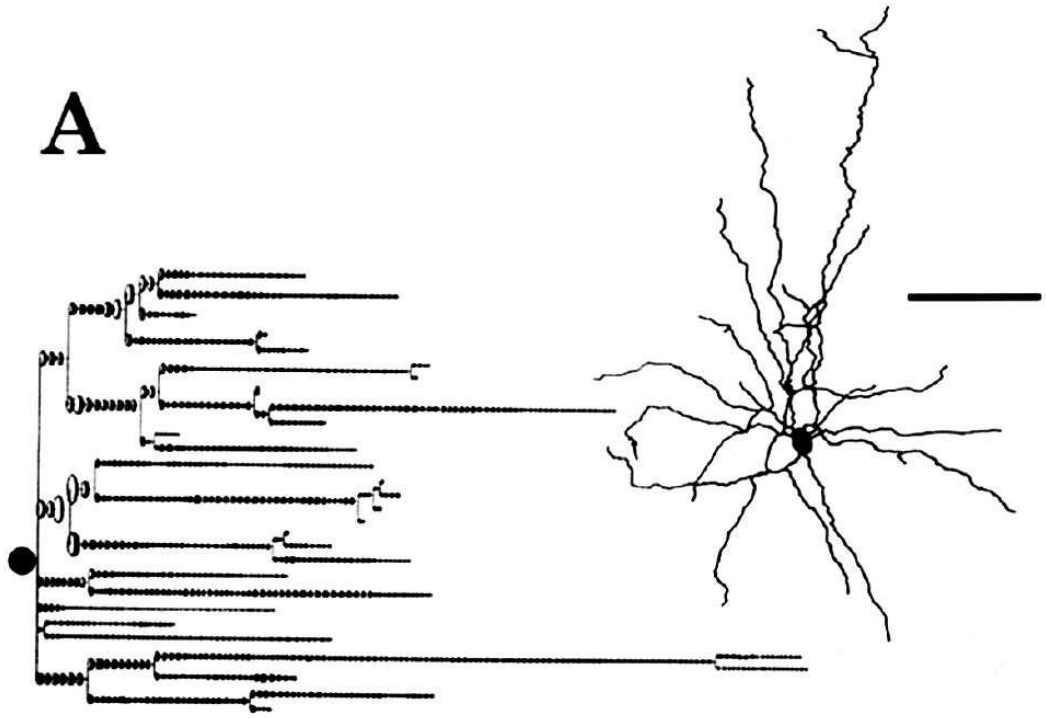
"Encoding model": $p_{model}(response|stimulus)$.

— Fit model parameters instead of full $p(response|stimulus)$

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

Flexibility vs. "fittability"

Multiparameter HH-type model



		Regional Conductances (mS/cm²)				
Model	Current	Dendrites	Soma	AH	NR	Axon
EC2.5 REAL	I_{Ca}	2.0	1.5	1.5	—	—
$j = 1$	$I_{K,Ca}$	0.001	0.065	0.065	0.065	0.065
SD* (real) = 21.9 μm	I_{Na}	25	80	100–150†	100	40–70‡
SD (EC2.5) = 20 μm	I_K	12	18	18	18	12–18‡
$\tau_{Ca} = 1.5$	I_A	36	54	54	54	—
$E_L = -60$ mV	Leak (Real)	0.008	0.008	0.008	0.008	0.008
$E_{Na} = 35$ 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))

Integrate-and-fire-based model

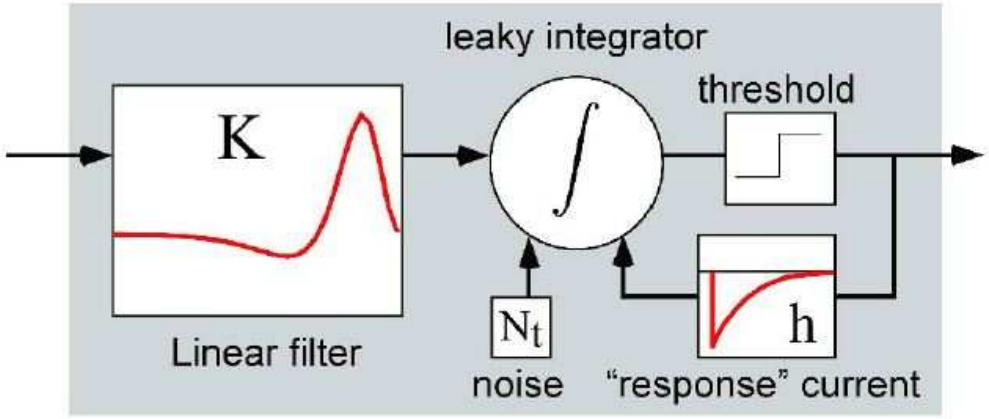
Learn the model parameters:

$\vec{K}$ = stimulus filter

g = leak conductance

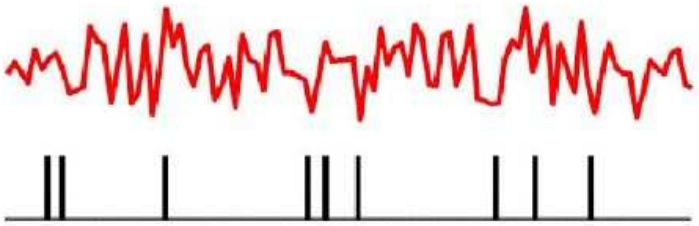
σ^2 = noise variance

$\vec{h}$ = response current



From: stimulus train $x(t)$

spike times t_i

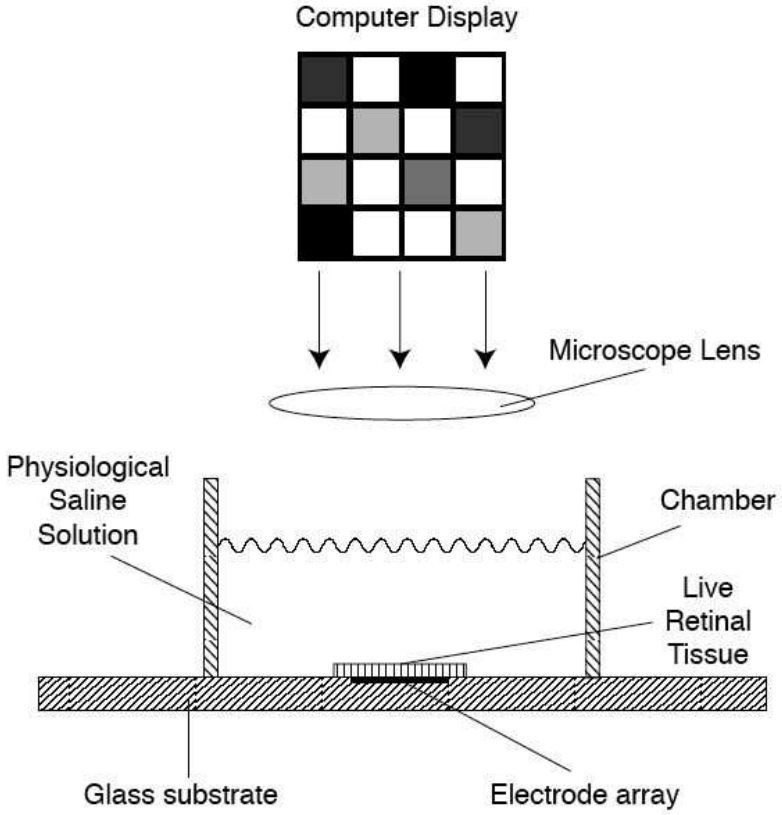


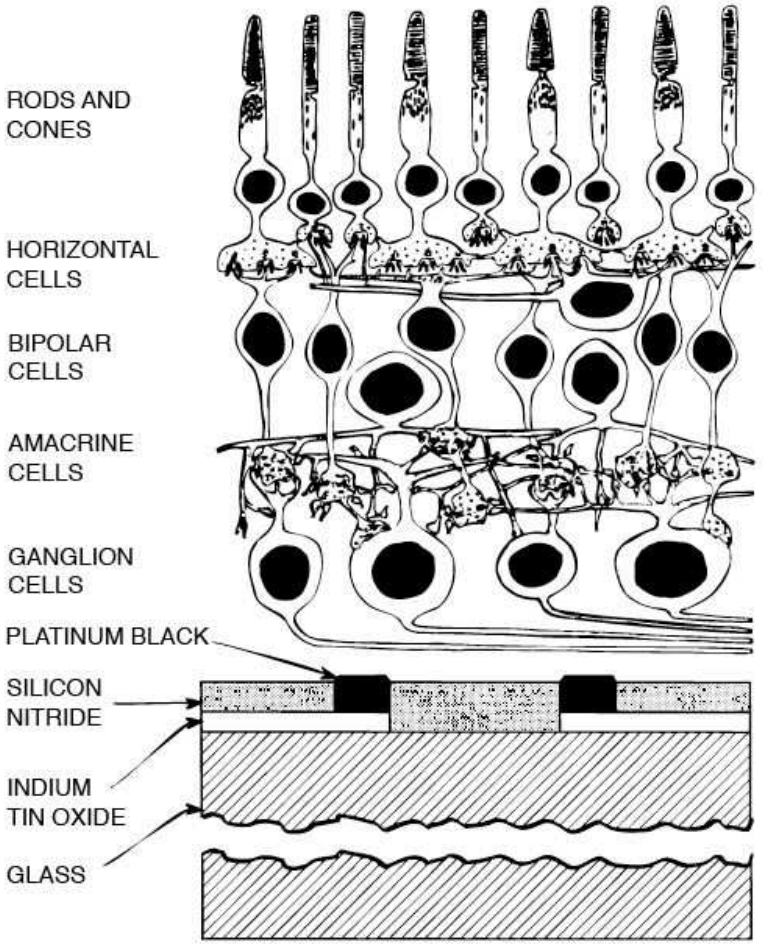
Fit parameters by *maximum likelihood* (Paninski et al., 2004b)

Application: retinal ganglion cells

Preparation: dissociated salamander and macaque retina

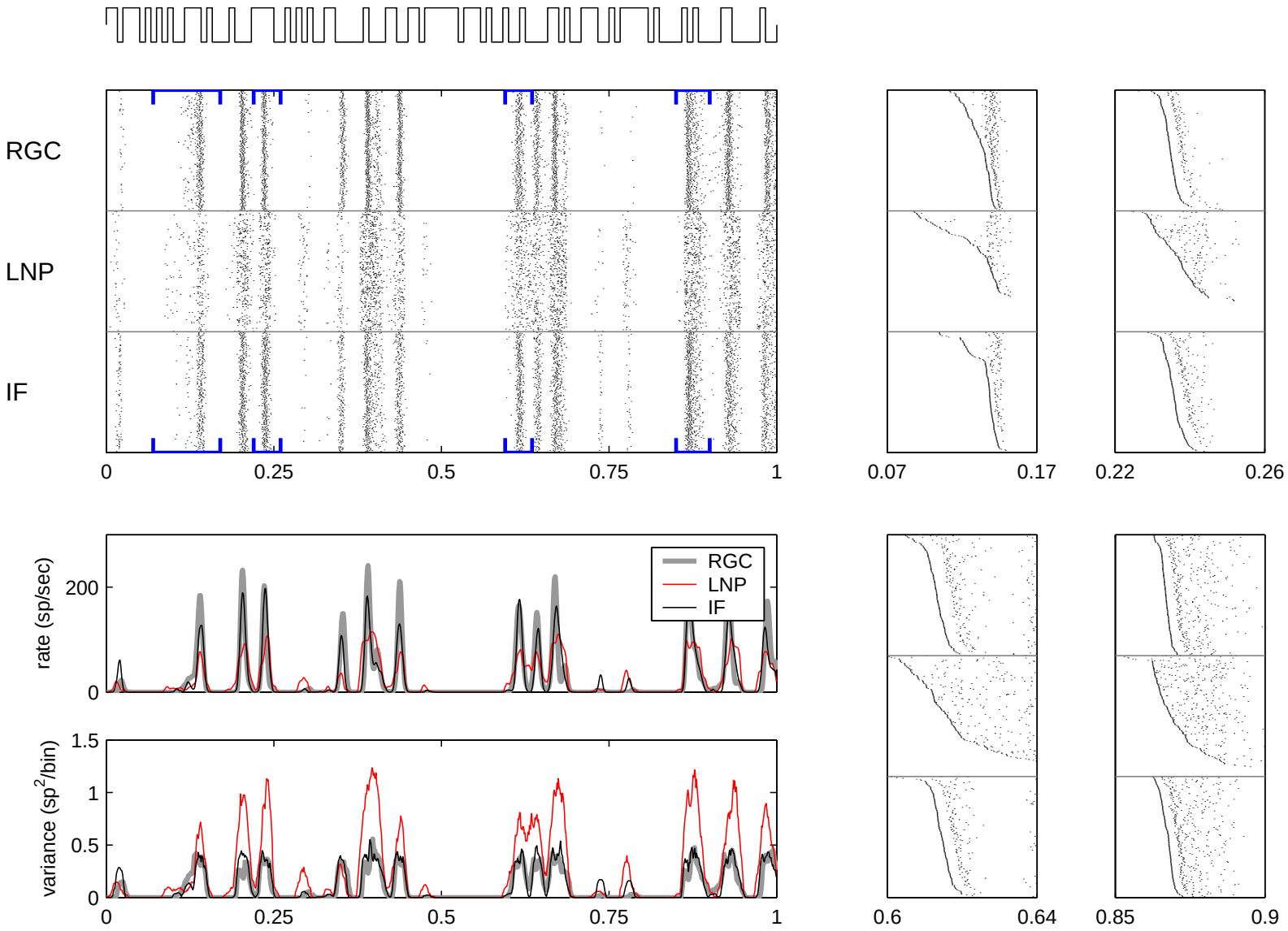
— extracellularly-recorded responses of populations of RGCs





Stimulus: random "flicker" visual stimuli (Chander and Chichilnisky, 2001)

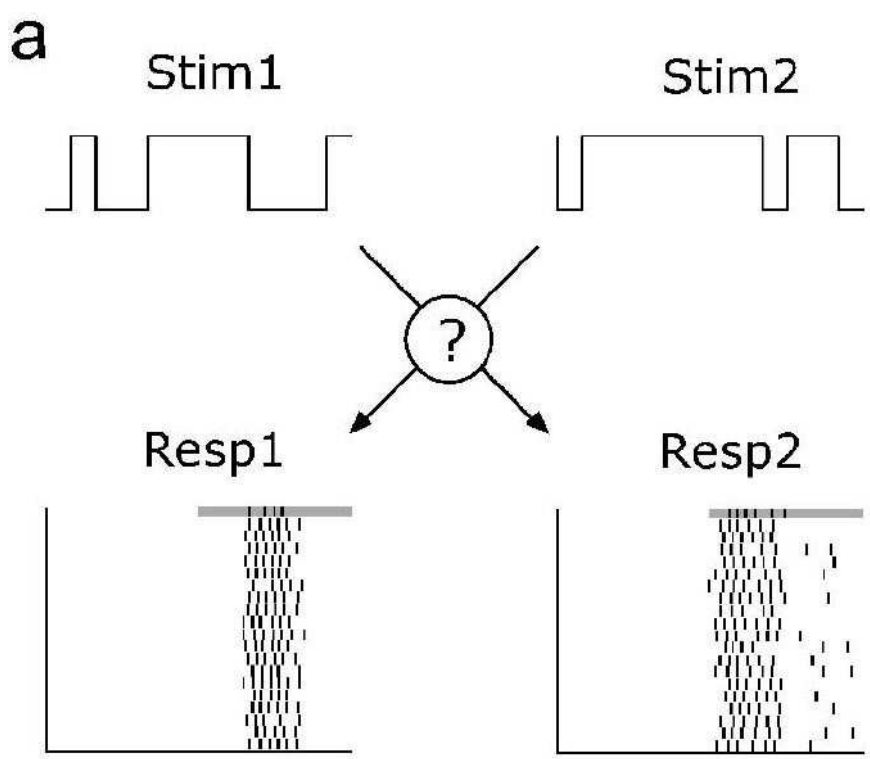
Spike timing precision in retina

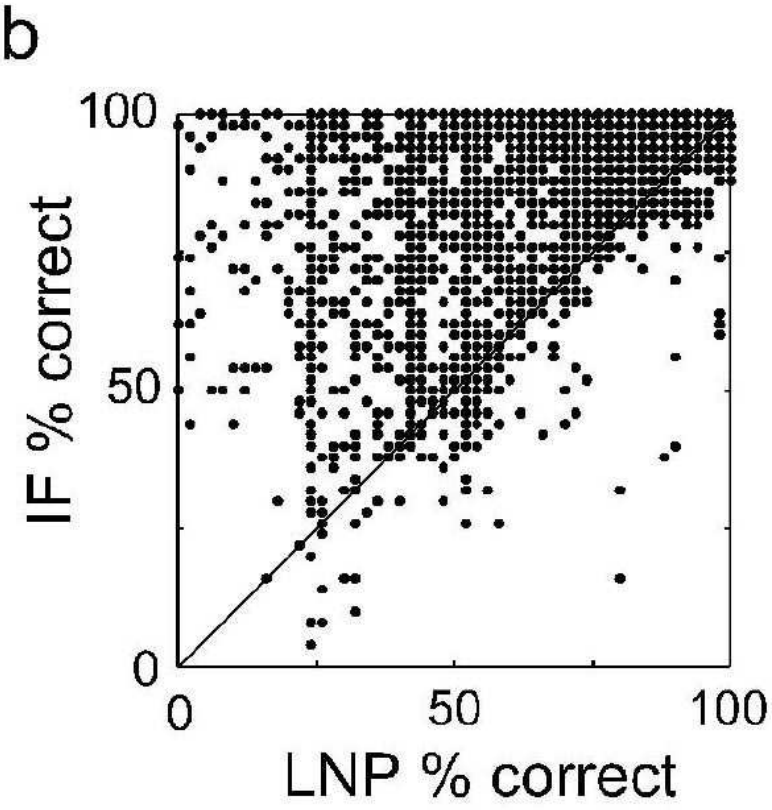


(Pillow et al., 2005)

Likelihood-based discrimination

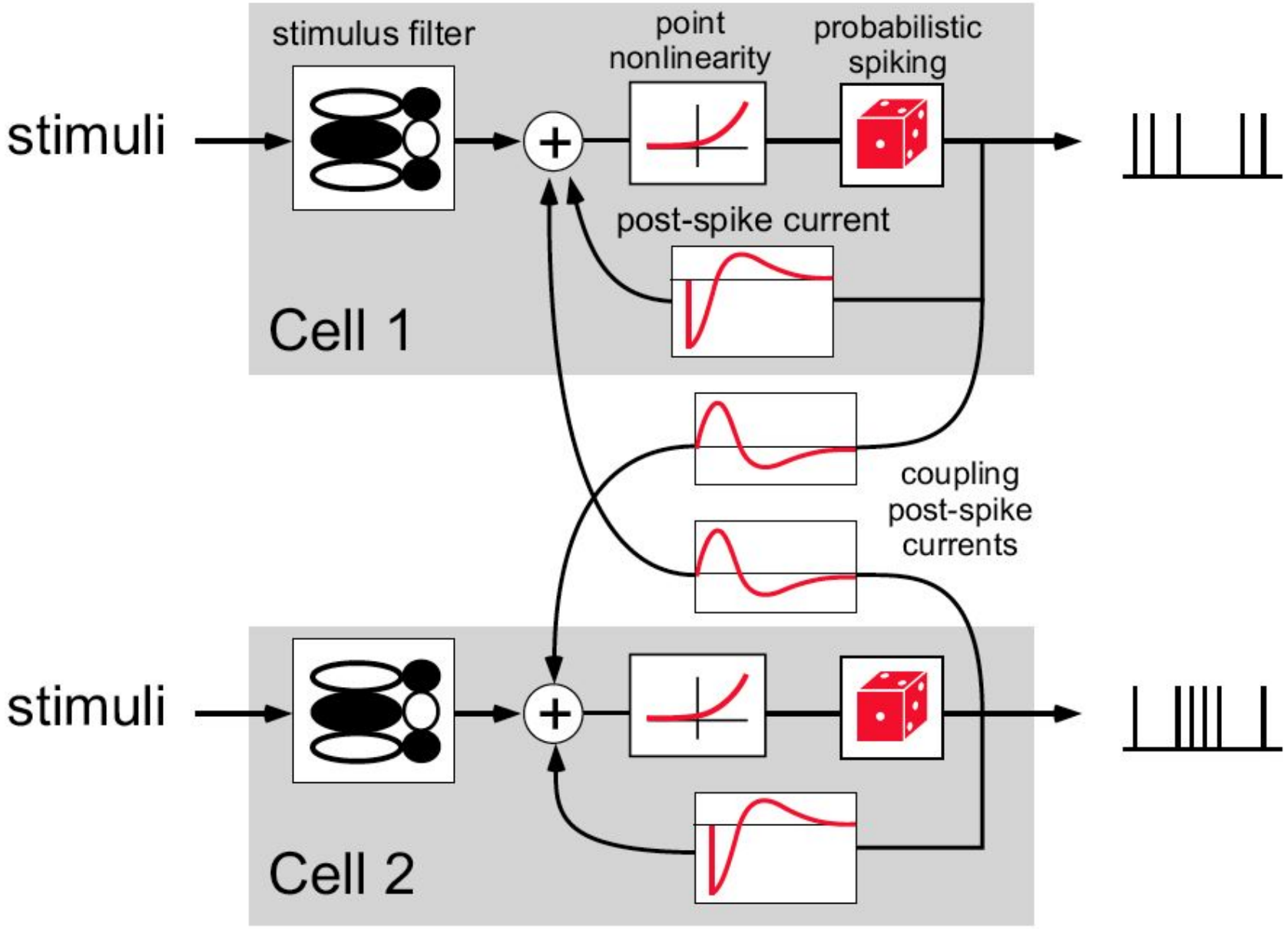
Given spike data, optimal decoder chooses stimulus $\vec{x}$ according to likelihood: $p(spikes|stim\ 1)$ vs. $p(spikes|stim\ 2)$.

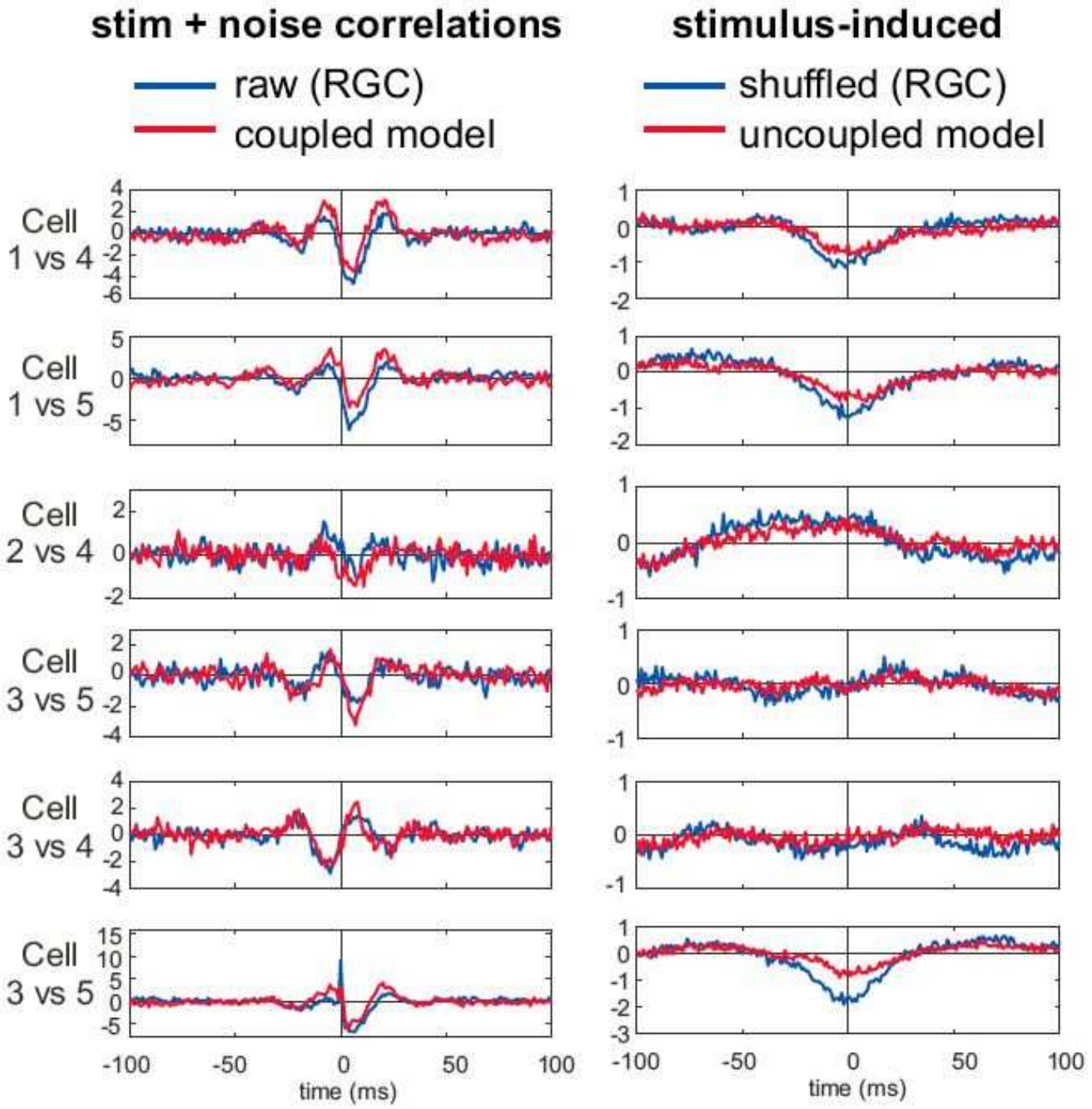




Using accurate model is essential (Pillow et al., 2005)

Generalization: population responses

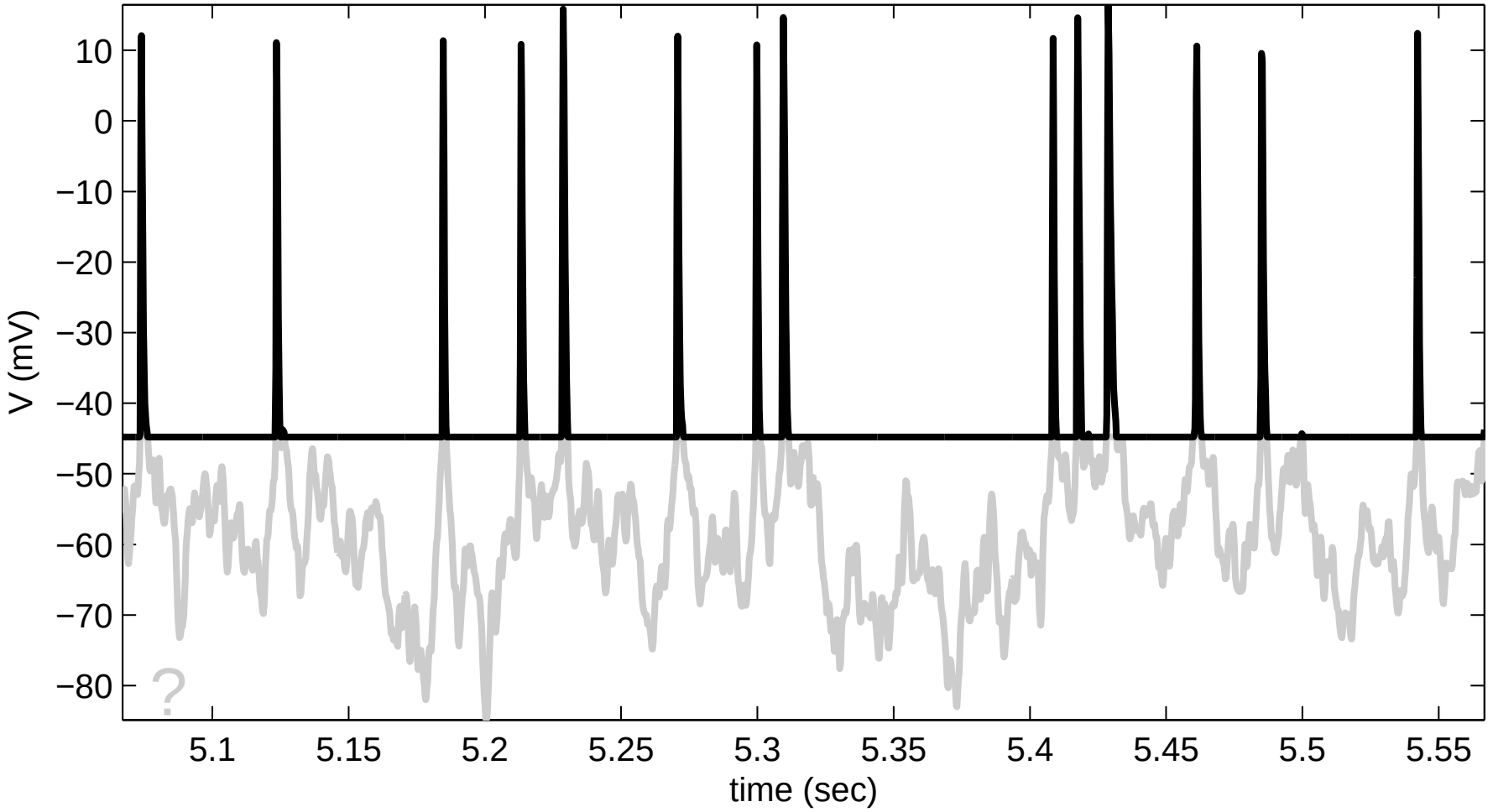




Pillow et al., COSYNE '05

Part 2: Decoding subthreshold activity

Given extracellular spikes, can we decode subthreshold $V(t)$?

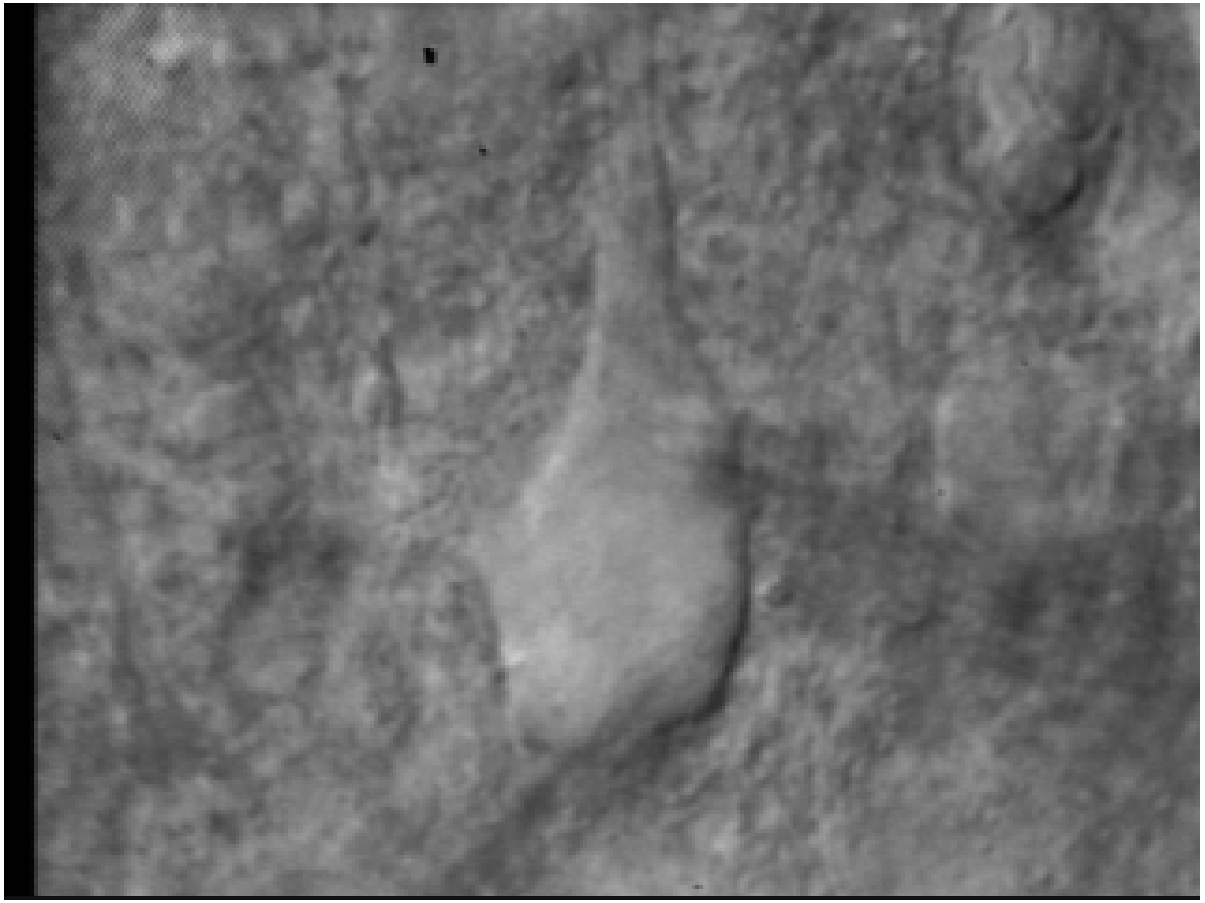


Idea: use maximum likelihood again (Paninski, 2005a).

Also, interesting connections to spike-triggered averaging (Paninski, 2005b).

Application: *in vitro* data

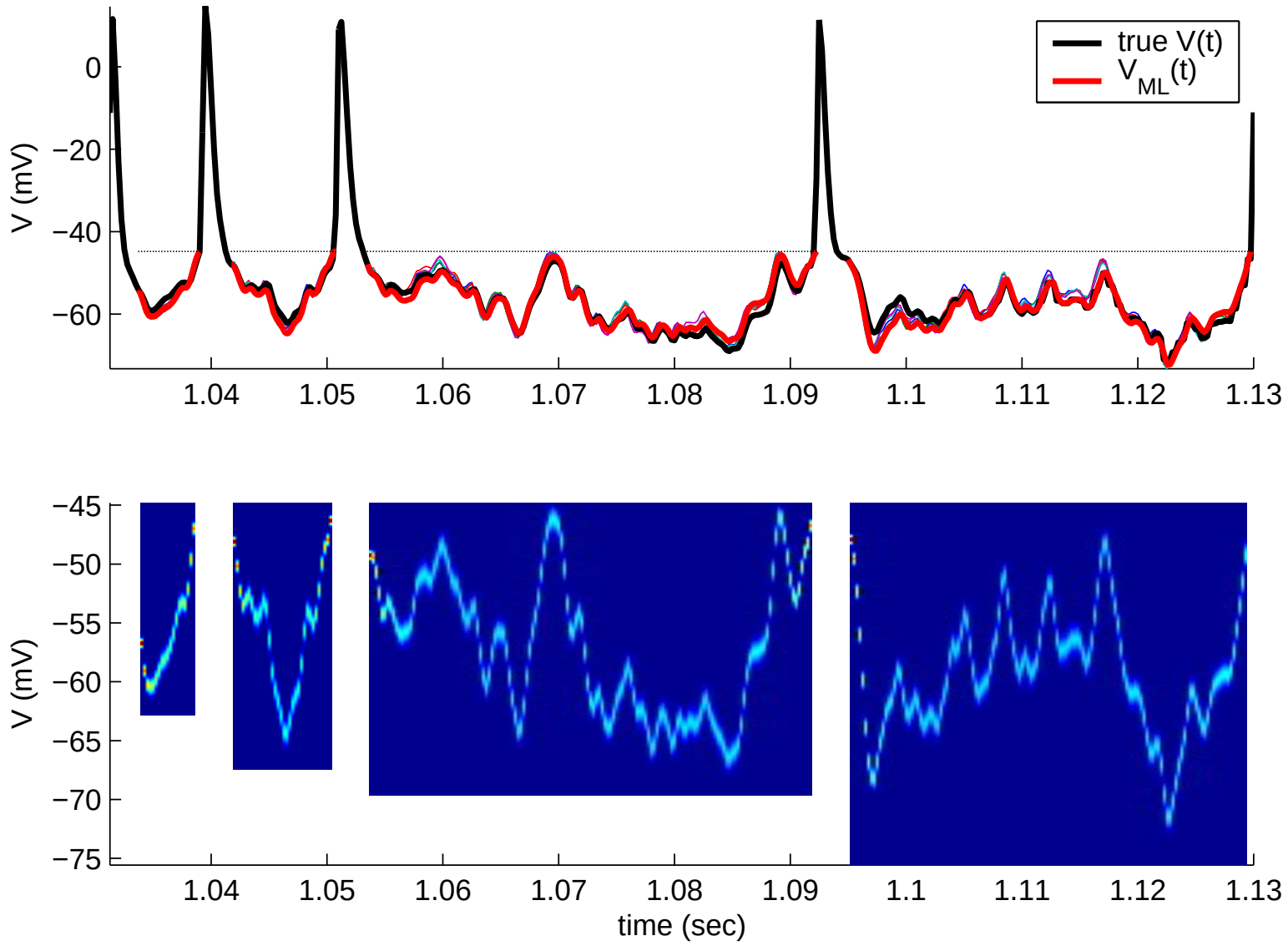
Recordings: rat sensorimotor cortical slice; dual-electrode whole-cell



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

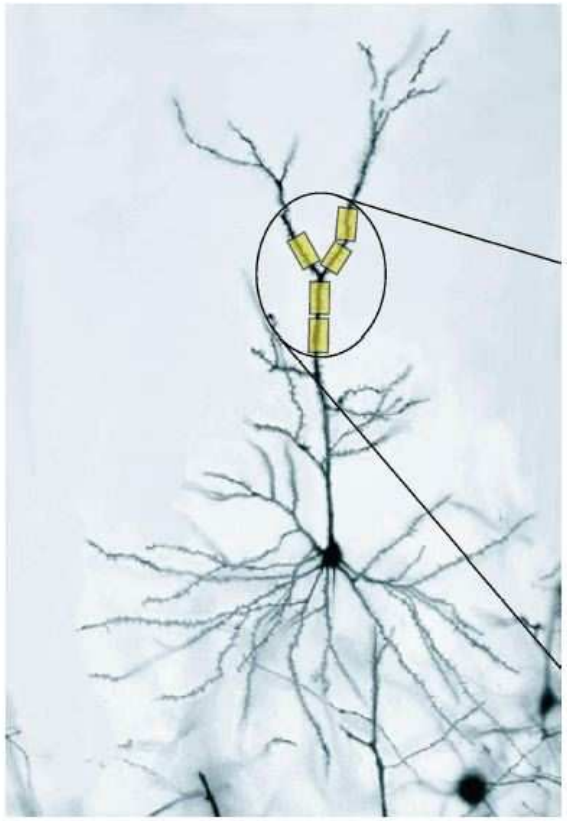
Analysis: fit IF model parameters $\{g, \vec{k}, h(.), V_{th}, \sigma\}$ by maximum likelihood (Paninski et al., 2003; Paninski et al., 2004a), then compute $V_{ML}(t)$

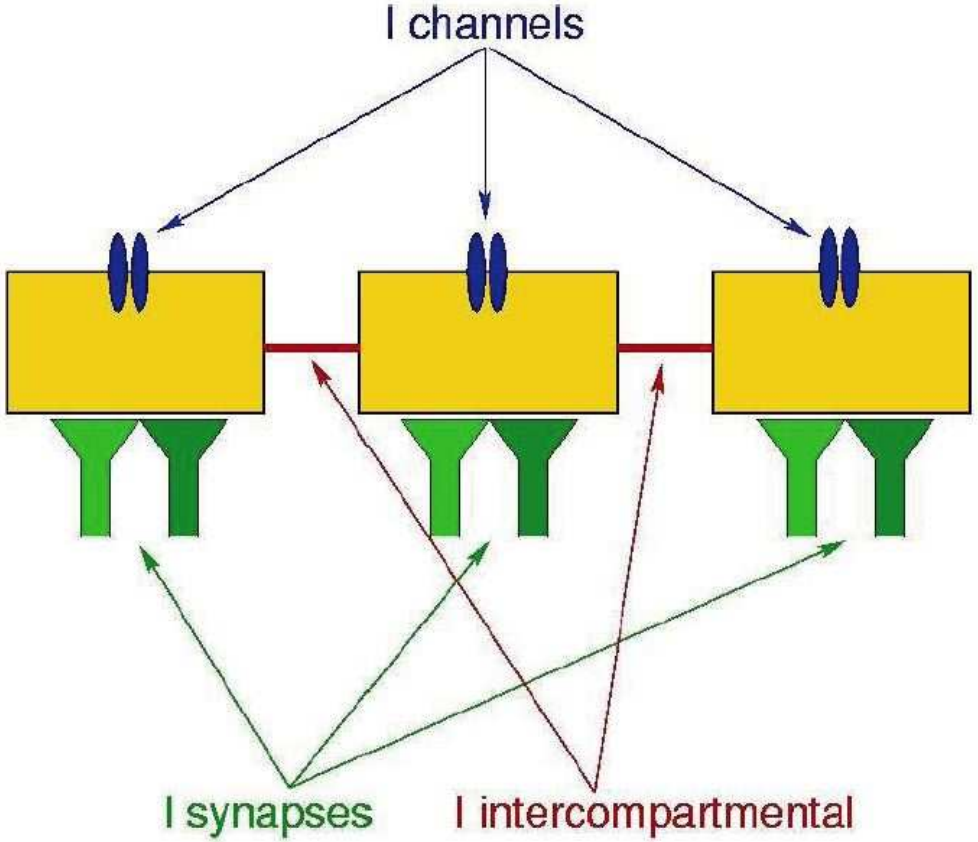
Application: *in vitro* data



ML decoding is quite accurate (Paninski, 2005a)

Part 3: Back to detailed models





Can we recover detailed biophysical properties?

- Active: membrane channel densities
- Passive: axial resistances, "leakiness" of membranes
- Dynamic: spatiotemporal synaptic input

Conductance-based models

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

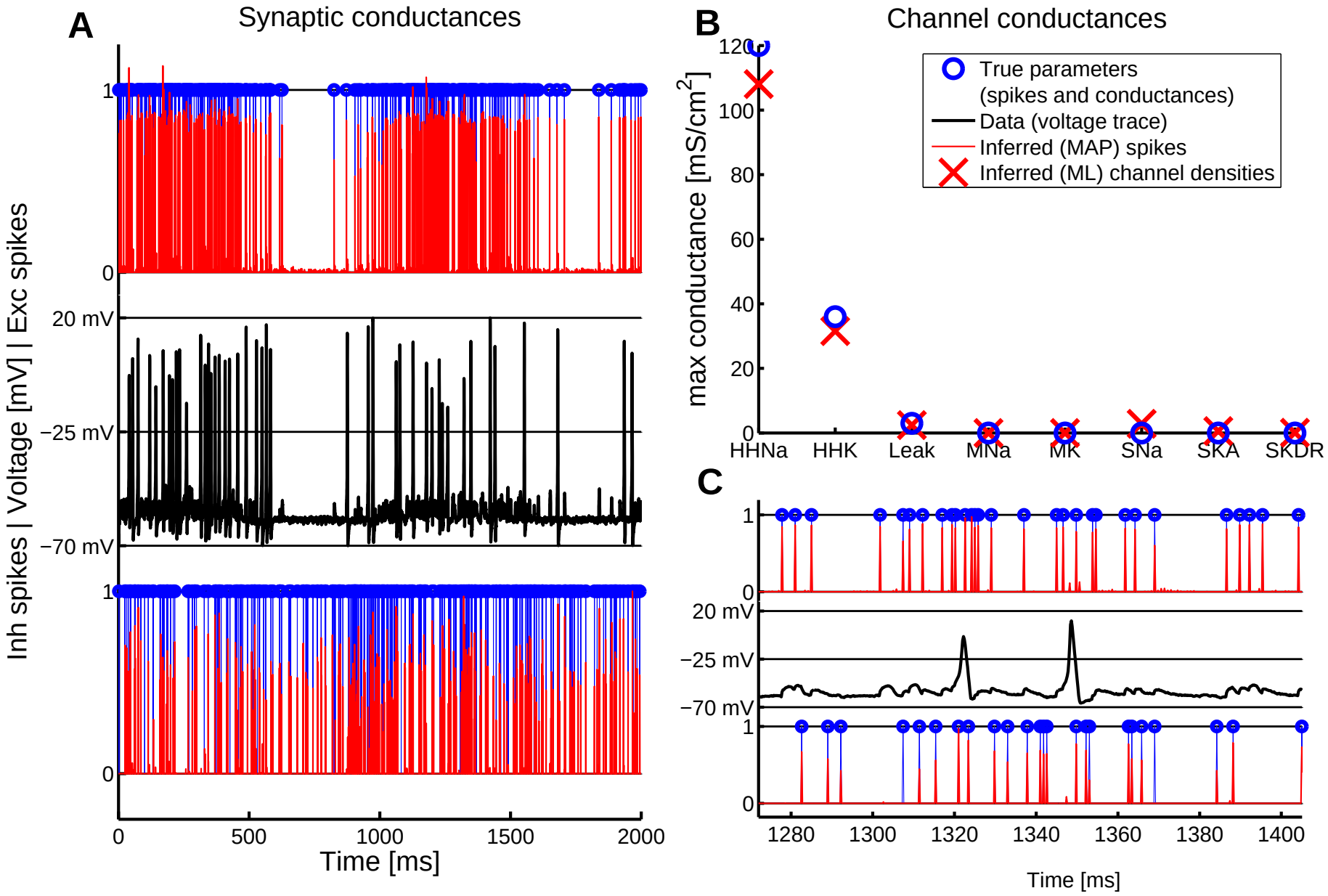
$$I_i^{\text{channels}} = \sum_c \bar{g}_c g_c(t)(E_c - V_i(t))$$

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

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

Key point: **if** we observe full $V_i(t)$ + cell geometry, channel kinetics known, **then** maximum likelihood is easy to perform.

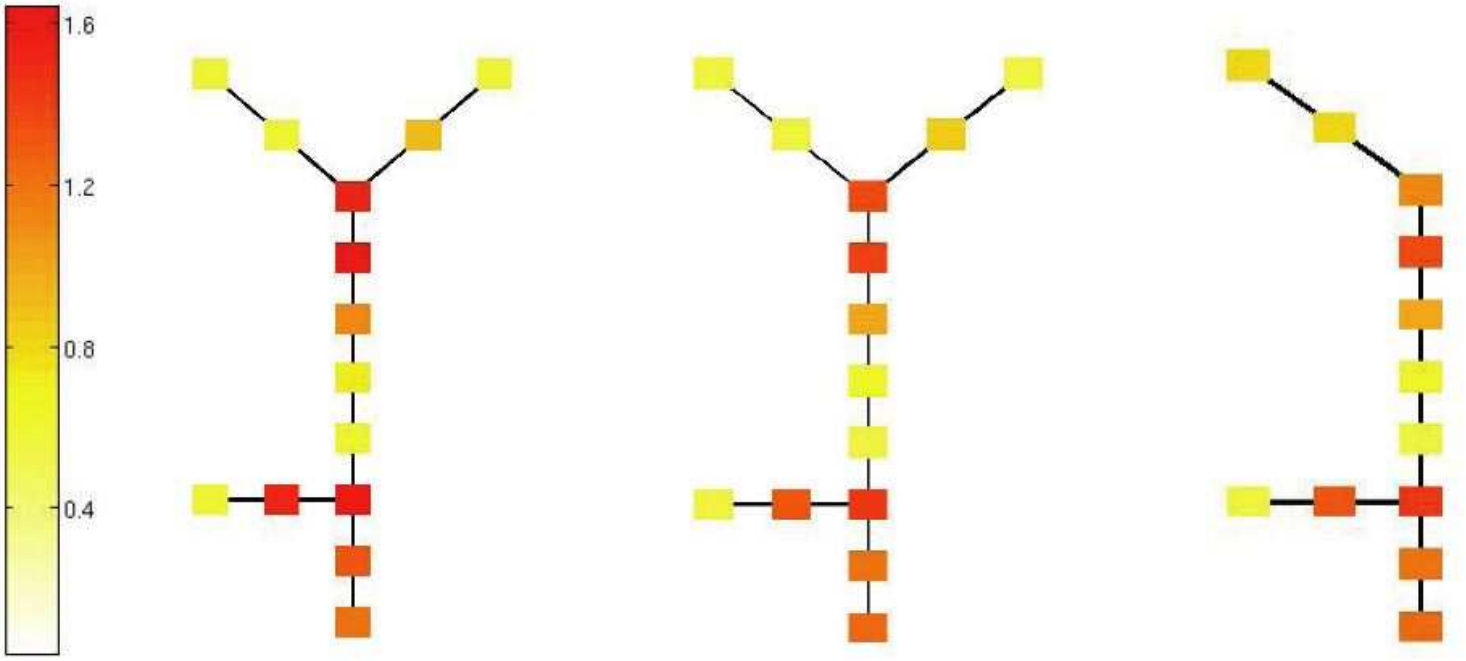
Estimating channel densities + synaptic inputs



Ahrens, Huys, Paninski, NIPS '05

Estimating spatially-varying channel densities

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



Ahrens, Huys, Paninski, COSYNE '05

Collaborators

Theory and numerical methods

— J. Pillow, E. Simoncelli, NYU

— S. Shoham, Princeton

— A. Haith, C. Williams, Edinburgh

— M. Ahrens, Q. Huys, Gatsby

Motor cortex physiology

— M. Fellows, J. Donoghue, Brown

— N. Hatsopoulos, U. Chicago

— B. Townsend, R. Lemon, U.C. London

Retinal physiology

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

Cortical *in vitro* physiology

— B. Lau and A. Reyes, NYU

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