GPUfit: A Tool for Real-Time Model Calibration and Prediction Testing

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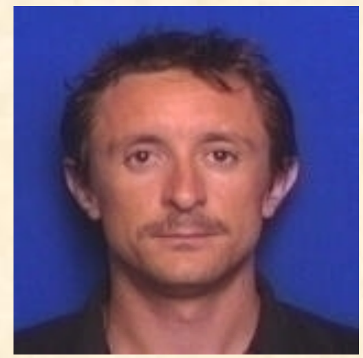


Maurizio Tomaiuolo
(High Performance
Computing Institute,
Frederick, MD)

Five types of anterior pituitary endocrine cells

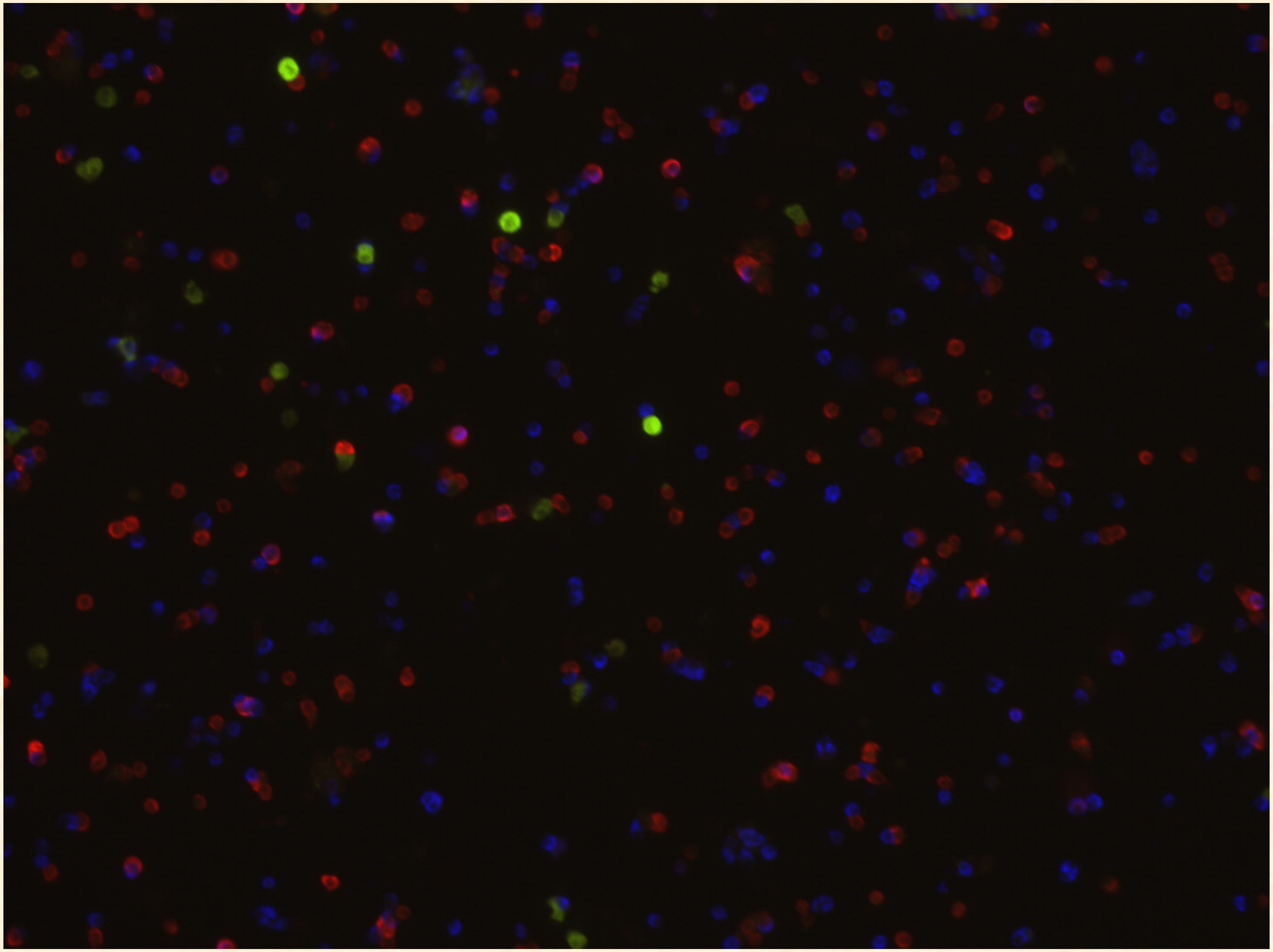
1. Lactotrophs: secrete prolactin

2. Somatotrophs: secrete growth hormone

3. Gonadotrophs: secrete luteinizing hormone and follicle stimulating hormone

4. Corticotrophs: secrete ACTH

5. Thyrotrophs: secrete thyroid stimulating hormone



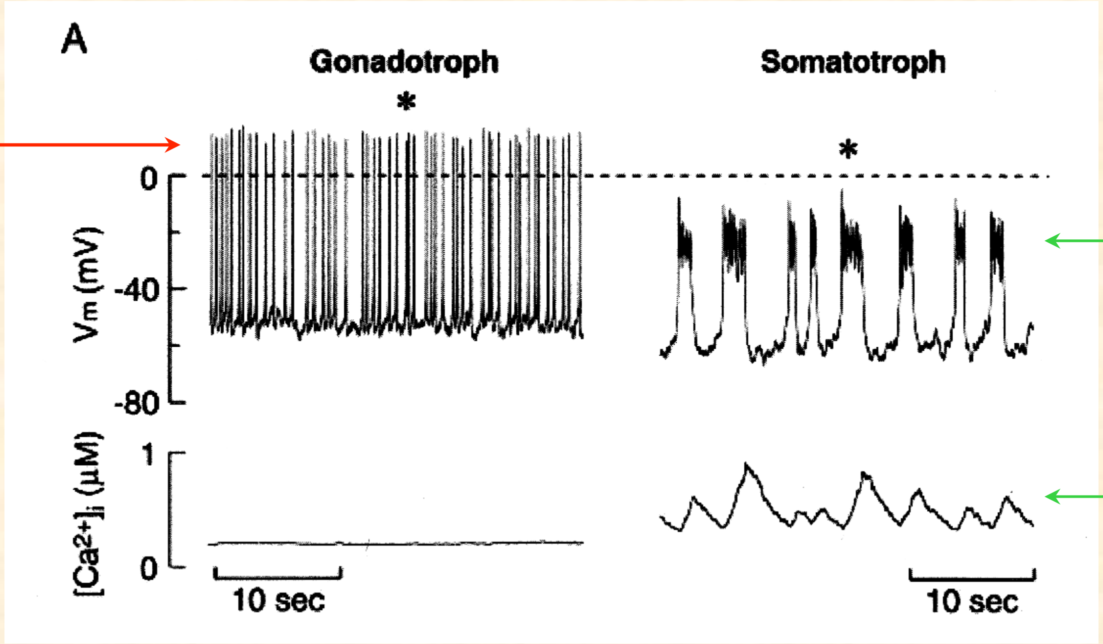
Thanks to Arturo Gonzalez-Iglesias, Jose Arias-Cristanch, and Ruth Cristancho-Gordo

Immunocytochemistry for prolactin, growth hormone, and leutinizing hormone.

Goal

Use mathematical modeling and analysis to help understand the electrical activity of the different types of endocrine pituitary cells

Spiking, little secretion

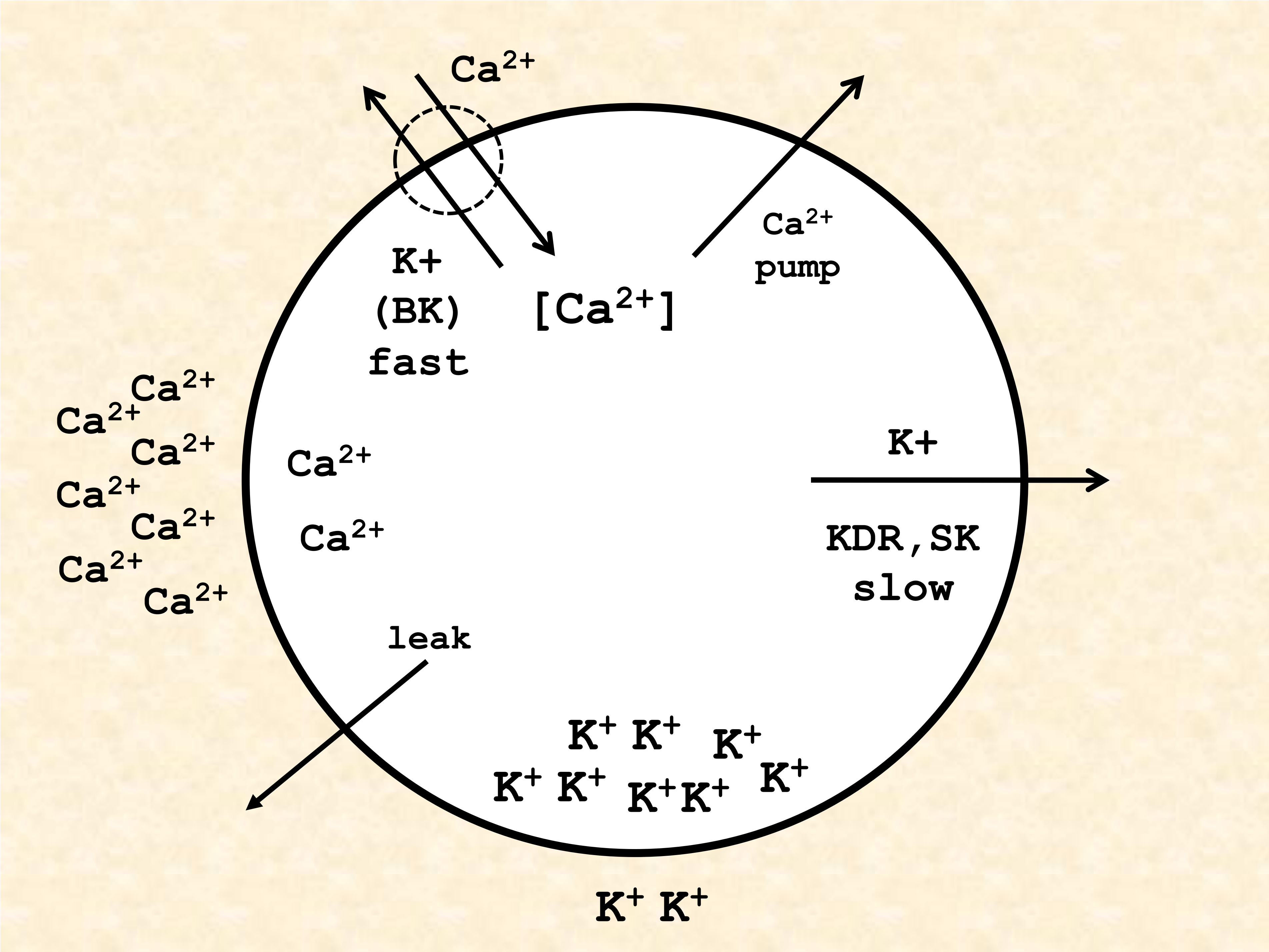


Bursting, much more secretion

Higher mean calcium

Van Goor et al., J. Neurosci., 2001:5902, 2001

What makes pituitary cells burst and secrete?



Ca2+
K+
(BK)
fast
[Ca2+]
Ca2+
pump
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
K+
KDR,SK
slow
leak
K+ K+ K+
K+ K+ K+ K+ K+ K+
K+ K+

Equations

voltage $$C\frac{dV}{dt} = -(I_{Ca} + I_K + I_{SK} + I_{BK} + I_{leak} + I_{noise}),$$ $I_{noise=0}$

I_K activation $$\tau_n \frac{dn}{dt} = n_\infty(V) - n,$$

I_{BK} activation $$\tau_{BK} \frac{df}{dt} = f_\infty(V) - f,$$

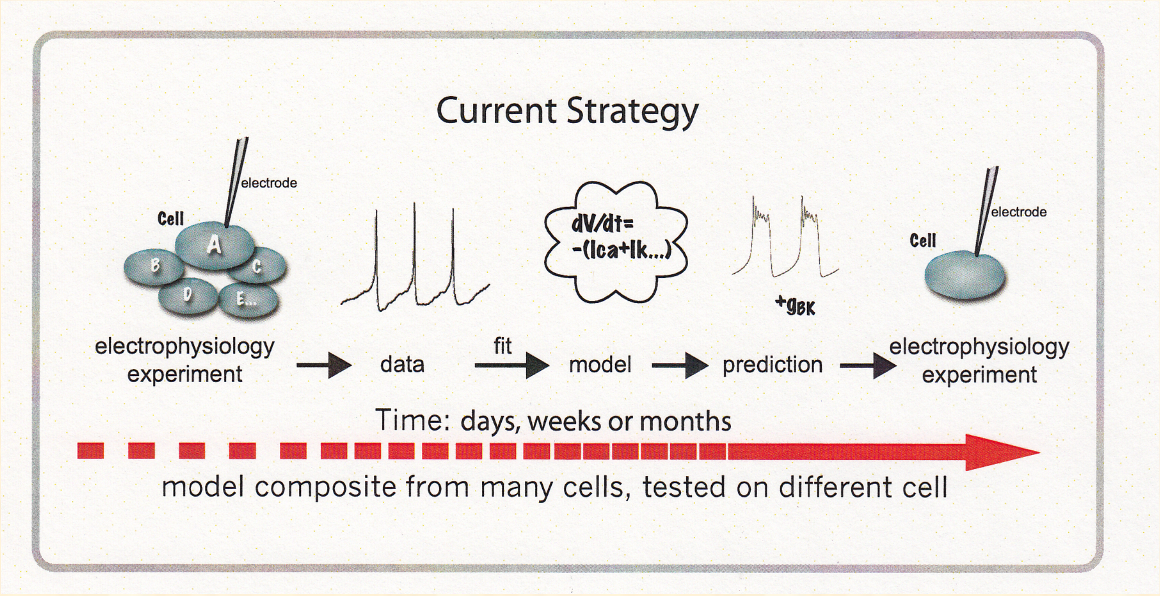
cytosolic calcium $$\frac{d[Ca]}{dt} = -f_c(\alpha I_{Ca} + k_c[Ca]),$$

Ionic current have an Ohmic form, e.g., $I_k = g_k n(V - V_K)$

Conductance and time constants are all parameters.
There are more parameters in the equilibrium functions.

Picking parameter values

If your model has many parameters, how do you find values for them all?



Heterogeneity…a big problem

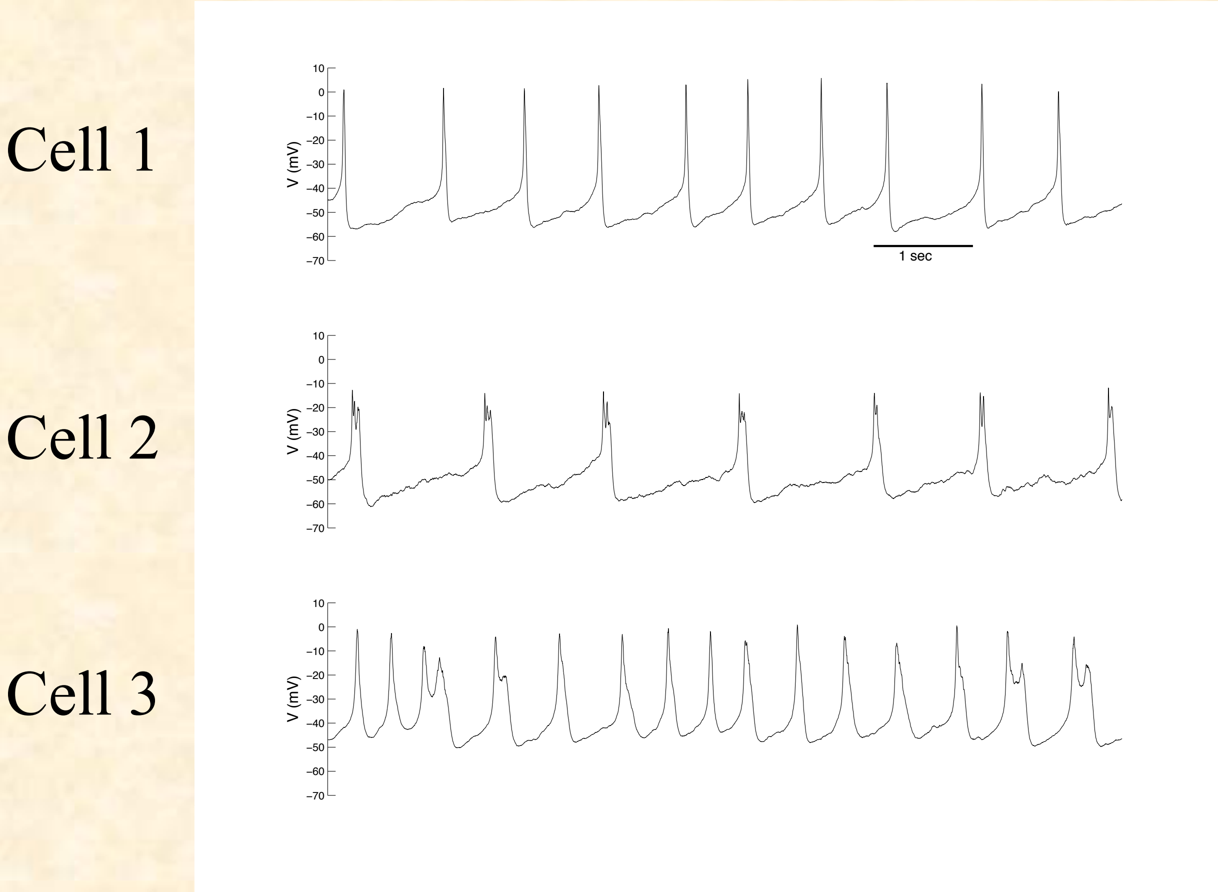
The mix of ionic currents within a single cell type is highly variable

➡ Electrical activity is highly variable, and

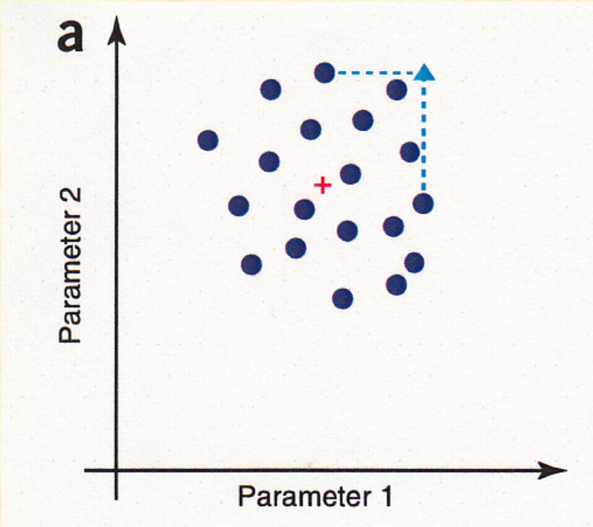
➡ The “true” parameter values vary from cell to cell

Pituitary cells are very heterogeneous

The mix of ionic currents within a single cell type is highly variable, as shown with the GH4C1 cell line



Possible parameter distribution scenarios

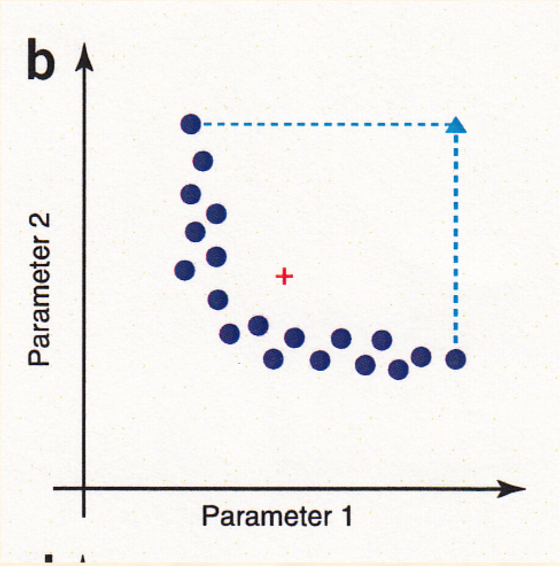


+ = mean of distribution

Marder and Taylor, Nature Neurosci., 14:133, 2011

Averaging over distribution should be fine

Possible parameter distribution scenarios

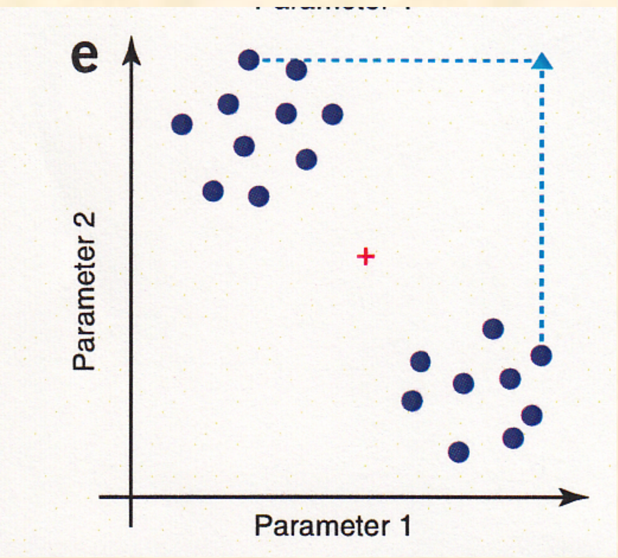


+ = mean of distribution

Marder and Taylor, Nature Neurosci., 14:133, 2011

Averaging puts you out of the distribution

Possible parameter distribution scenarios



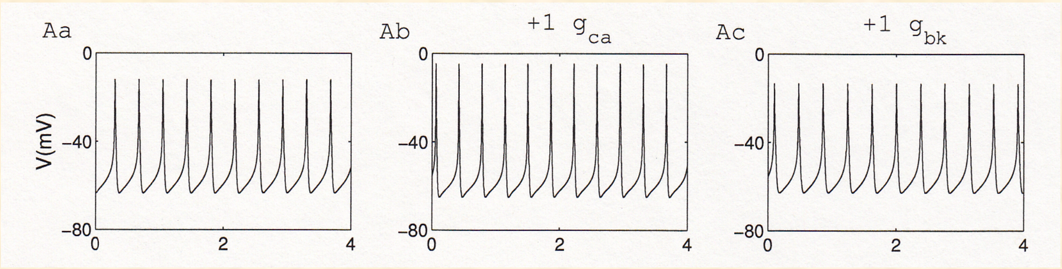
+ = mean of distribution

Marder and Taylor, Nature Neurosci., 14:133, 2011

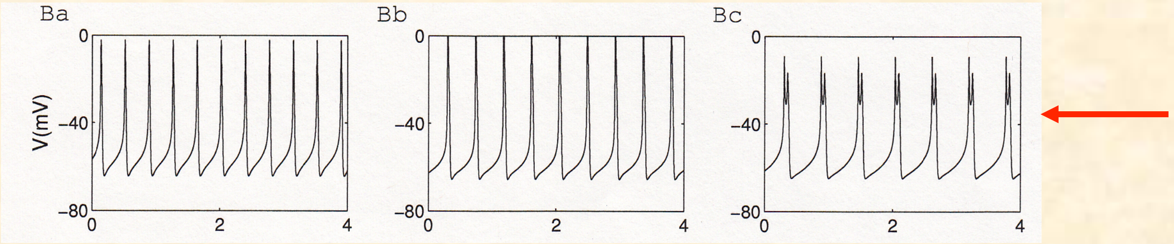
Averaging puts you out of the distribution

Does heterogeneity matter for us?

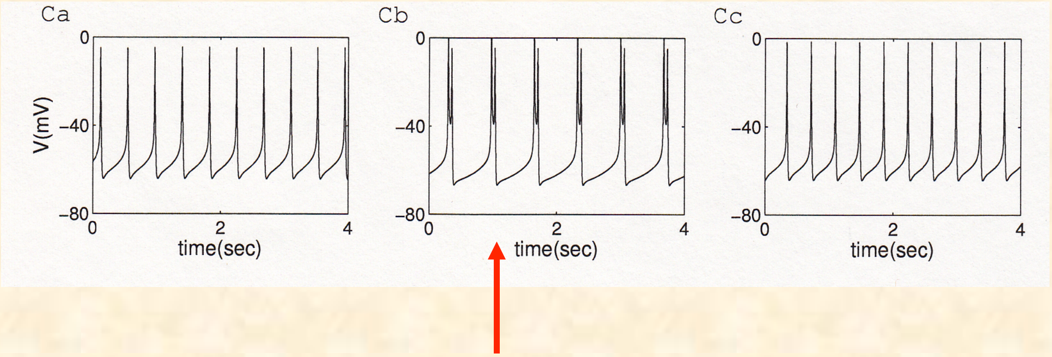
One spiking model cell



Another spiking model cell



A third spiking model cell



Tomaiuolo et al., Biophys. J., 103:2021, 2012

Main approach: Parameterize the model to an individual cell

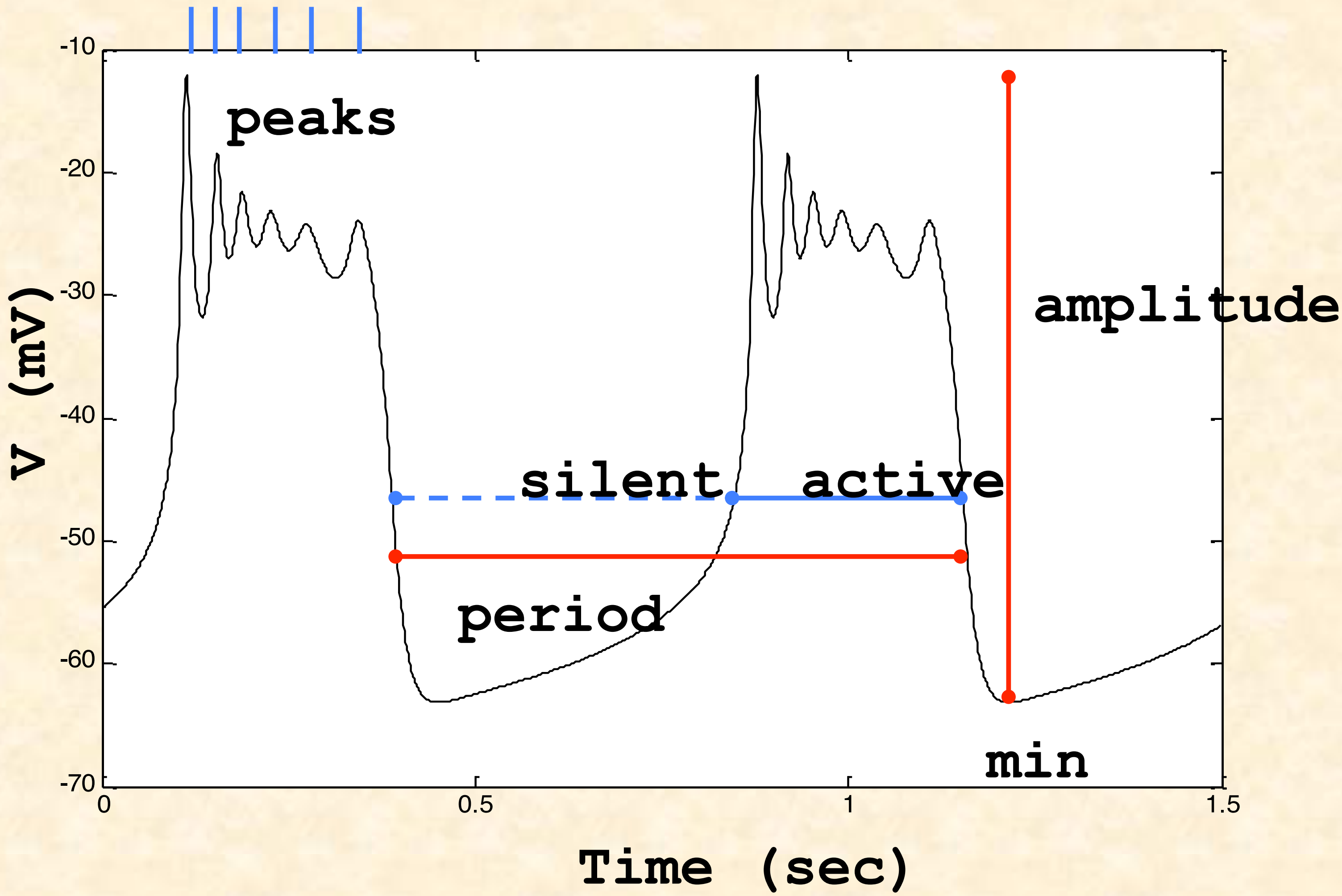
$\overrightarrow{p_1}$

$\overrightarrow{p_2}$

$\overrightarrow{p_3}$

Parameterize the model to an individual cell, while still patched onto that cell. Then different cells will have different parameter vectors.

Set parameters to fit **features** of the voltage trace, rather than the voltage trace itself



Feature fitness function

$$F_{features} = \sum_j c_j \exp\left(-\frac{(m_j - d_j)^2}{\sigma_j}\right) \Bigg/ \sum_j c_j$$

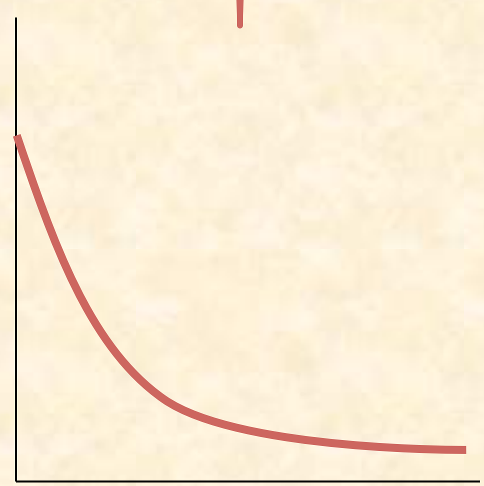
F=fitness function

m_j=model feature

d_j=data feature

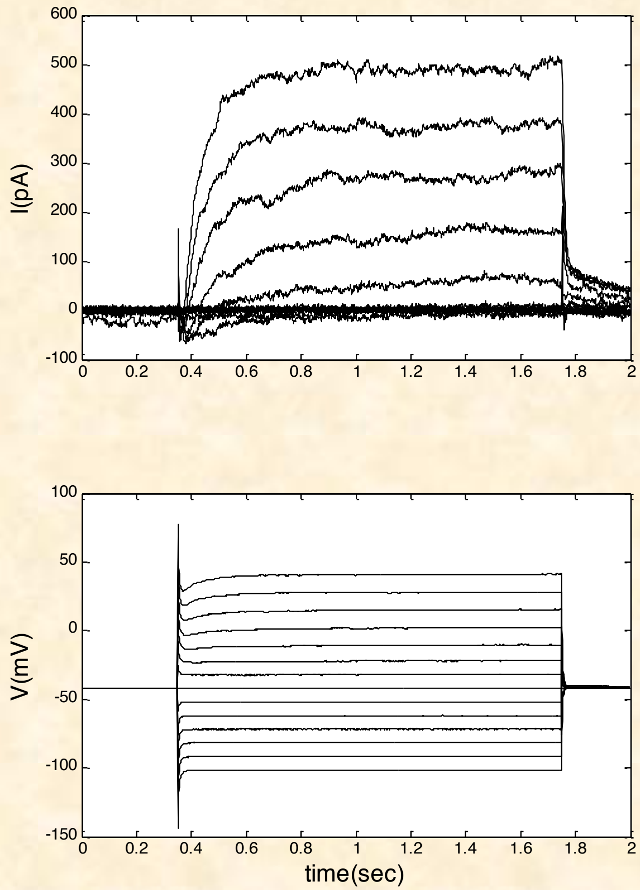
c_j=feature weight

σ_j=feature scaling



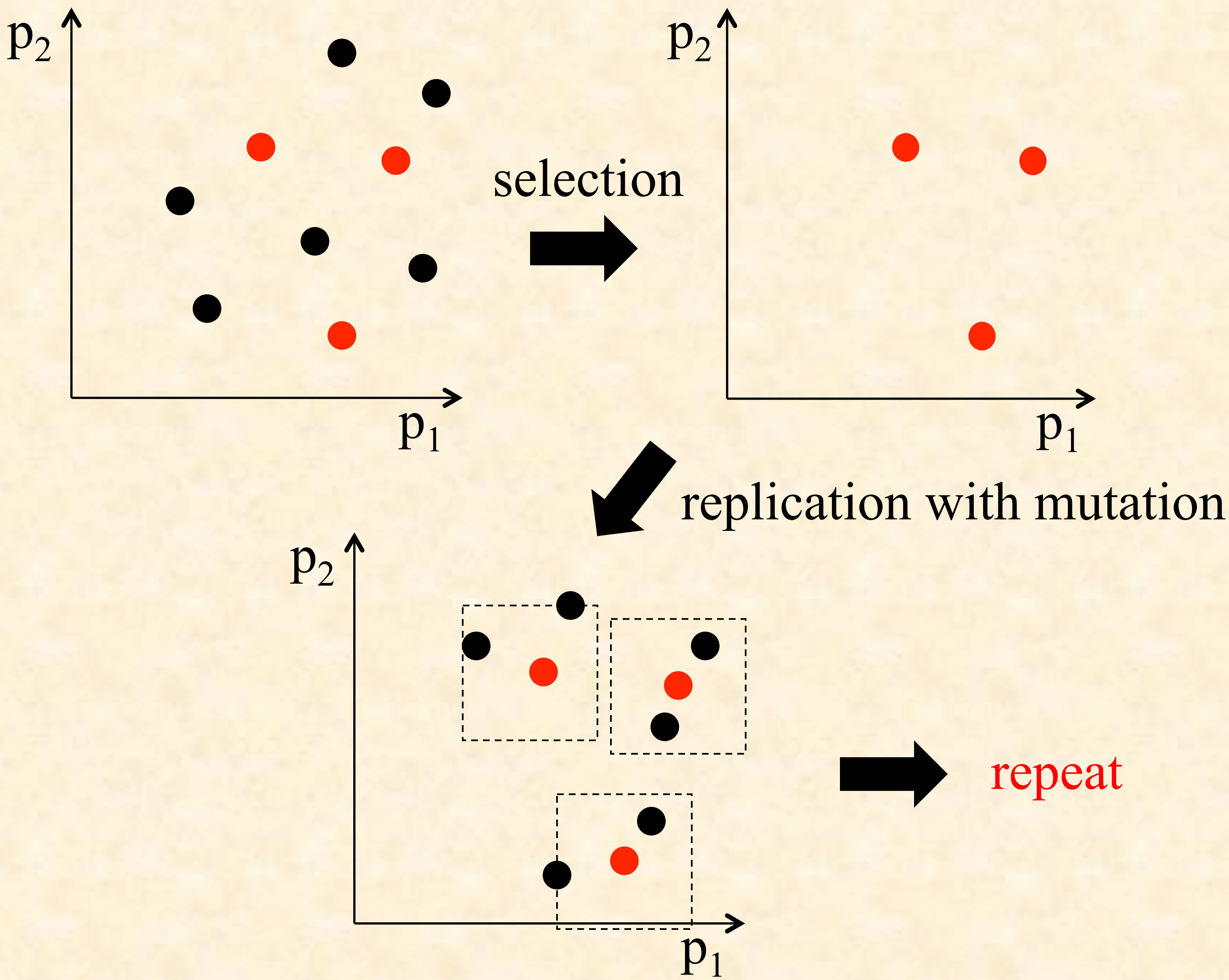
$|m_j - d_j|$

Also fit voltage clamp data



Maximize $F = \beta F_{features} + (1-\beta)F_{clamp}$ where $\beta \in [0,1]$

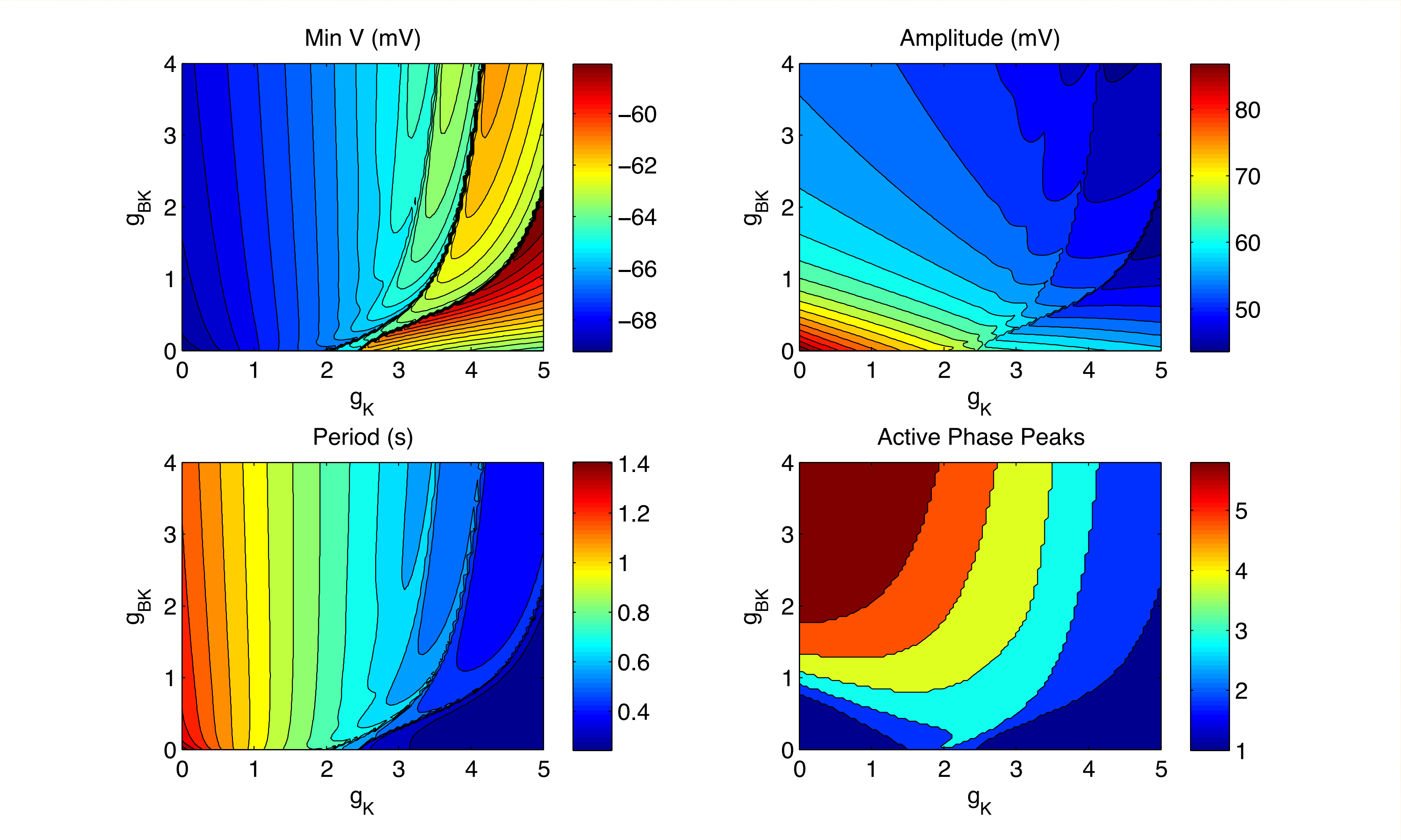
Optimization using a genetic algorithm



We need rapid calibration, so use a Programmable Graphics Processing Unit (GPU)

Cost < $ 1000

Feature planes can be rapidly computed



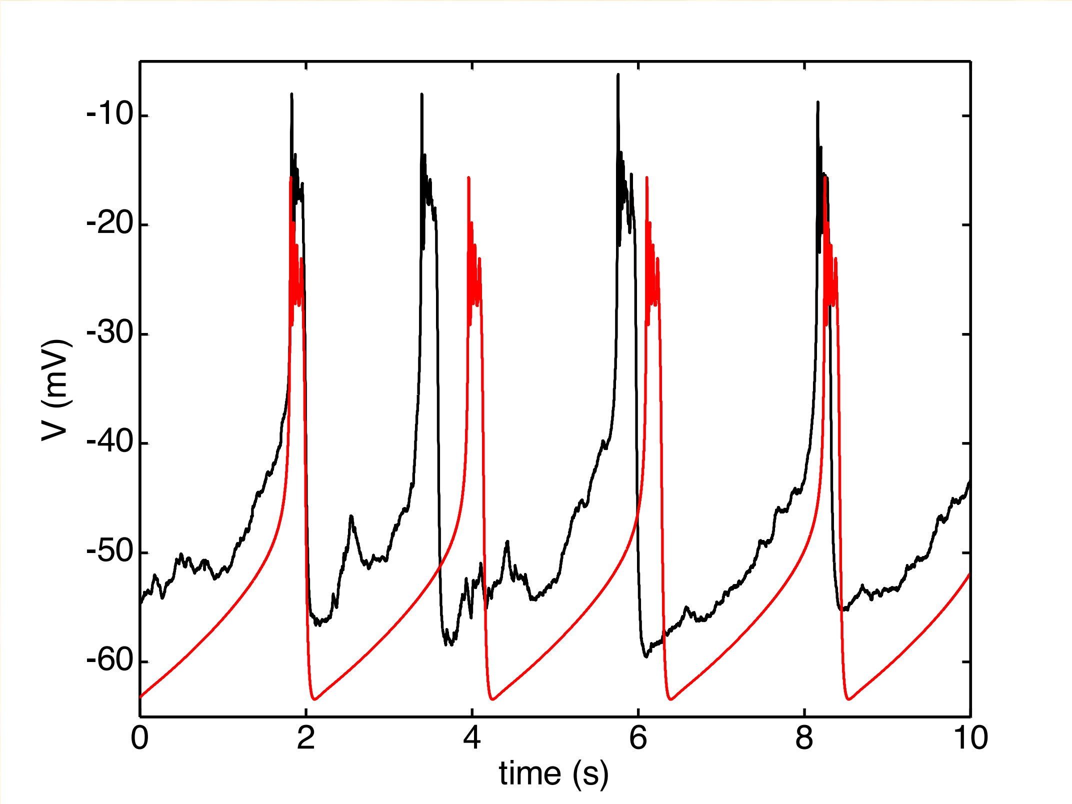
100x100 grid

10,000 simulations

Simulation time=70 sec each

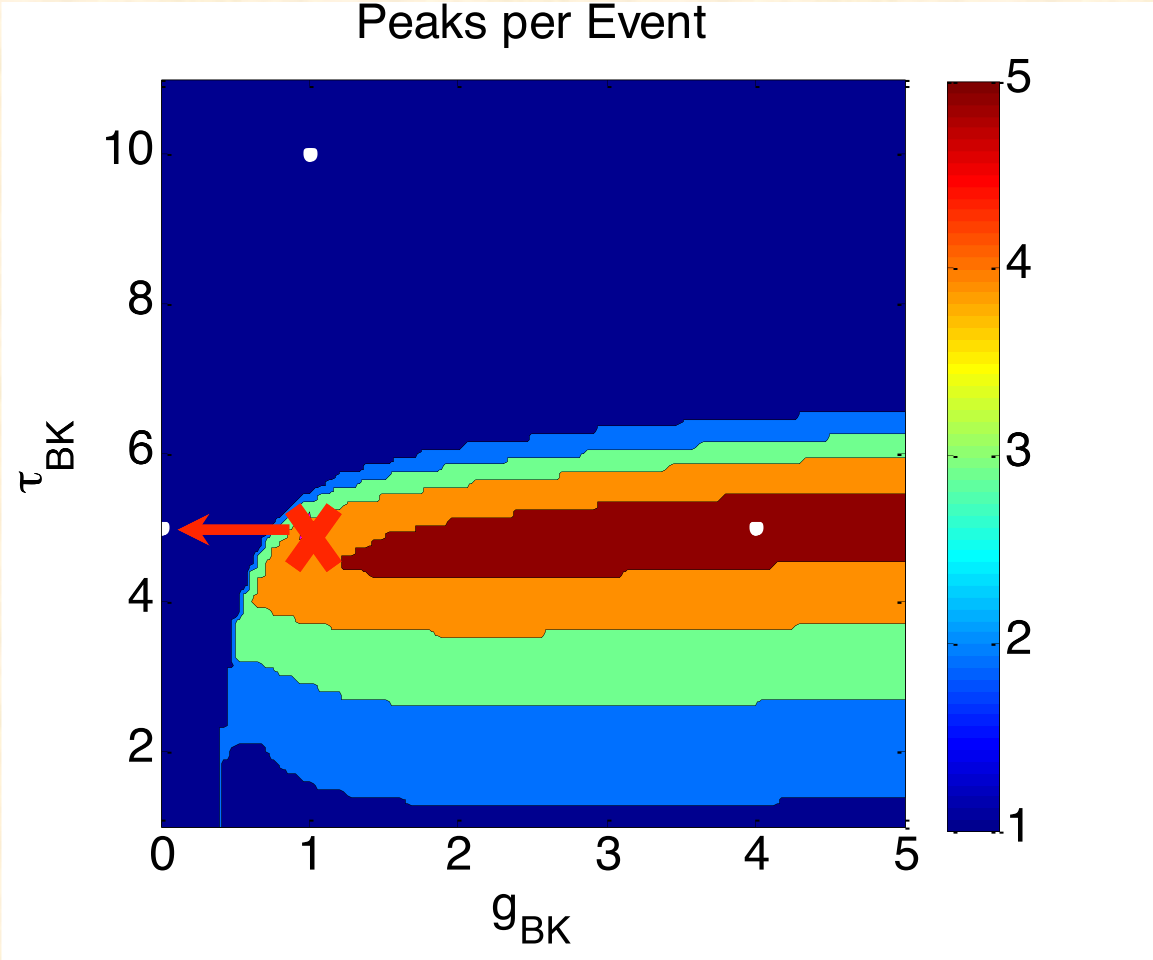
Total computation time=20 sec

Example: Calibrate, predict, and test



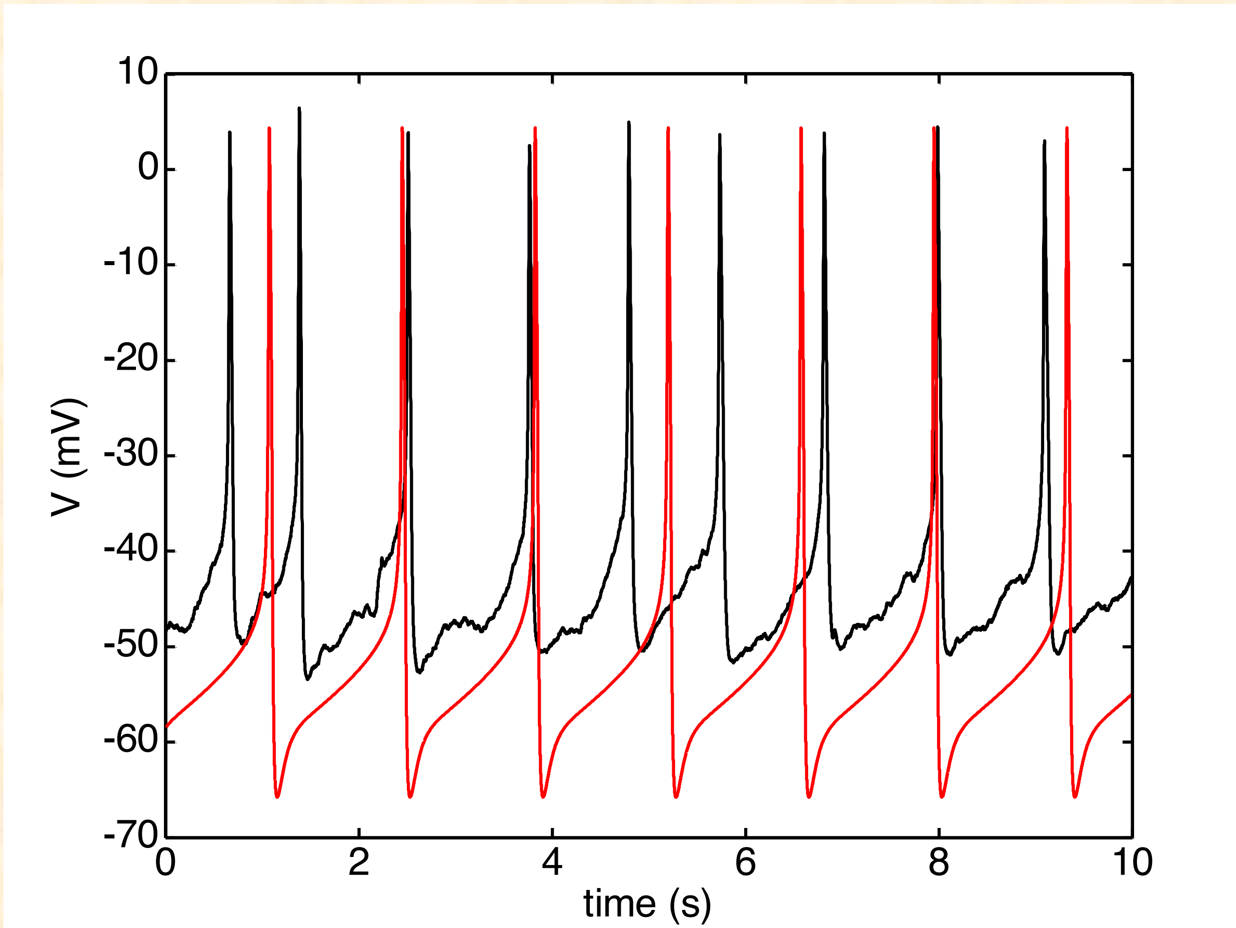
The model (red) is fit to a bursting Gh4 cell (black)

Feature plane for BK conductance and time constant



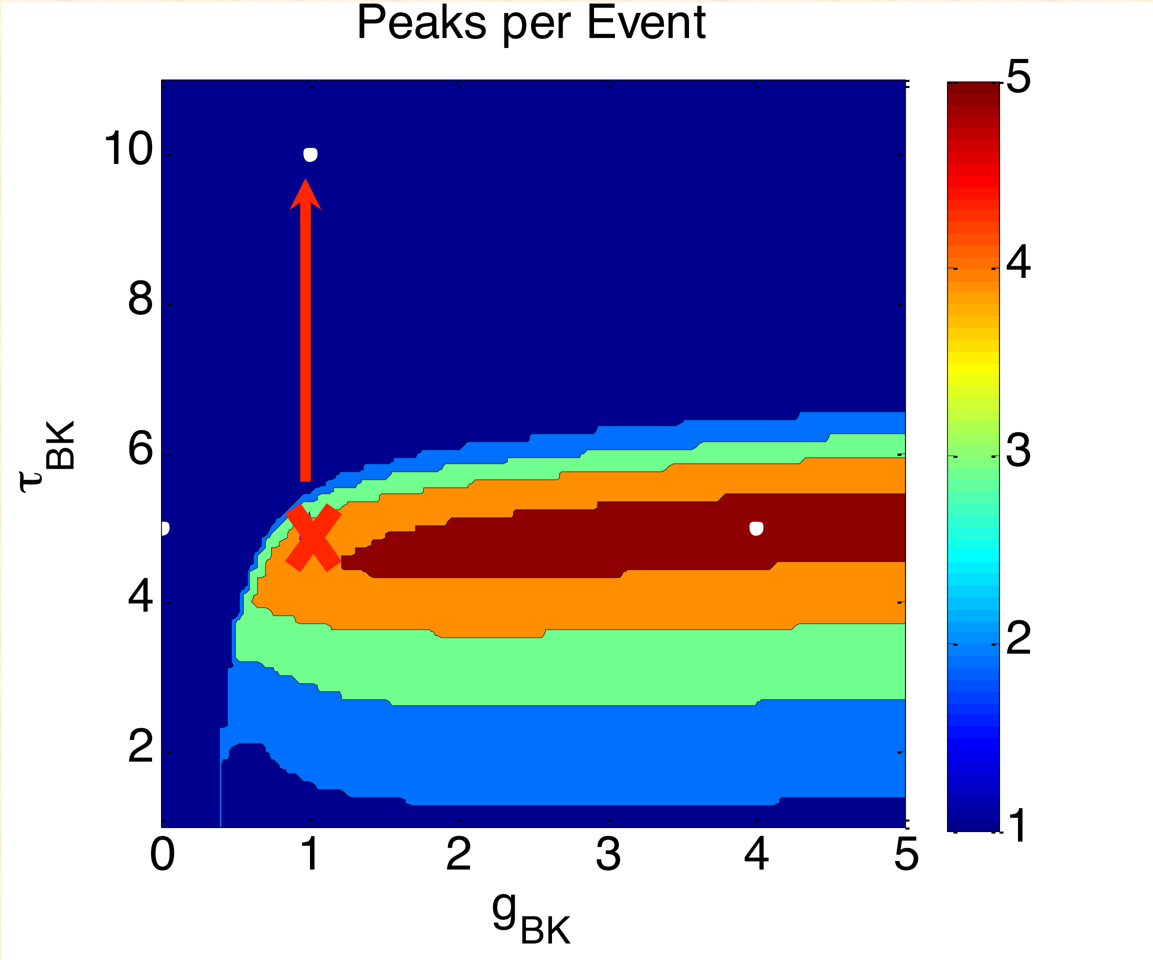
 Best fit to bursting data → Block BK current

Model prediction tested by blocking BK current with paxillin



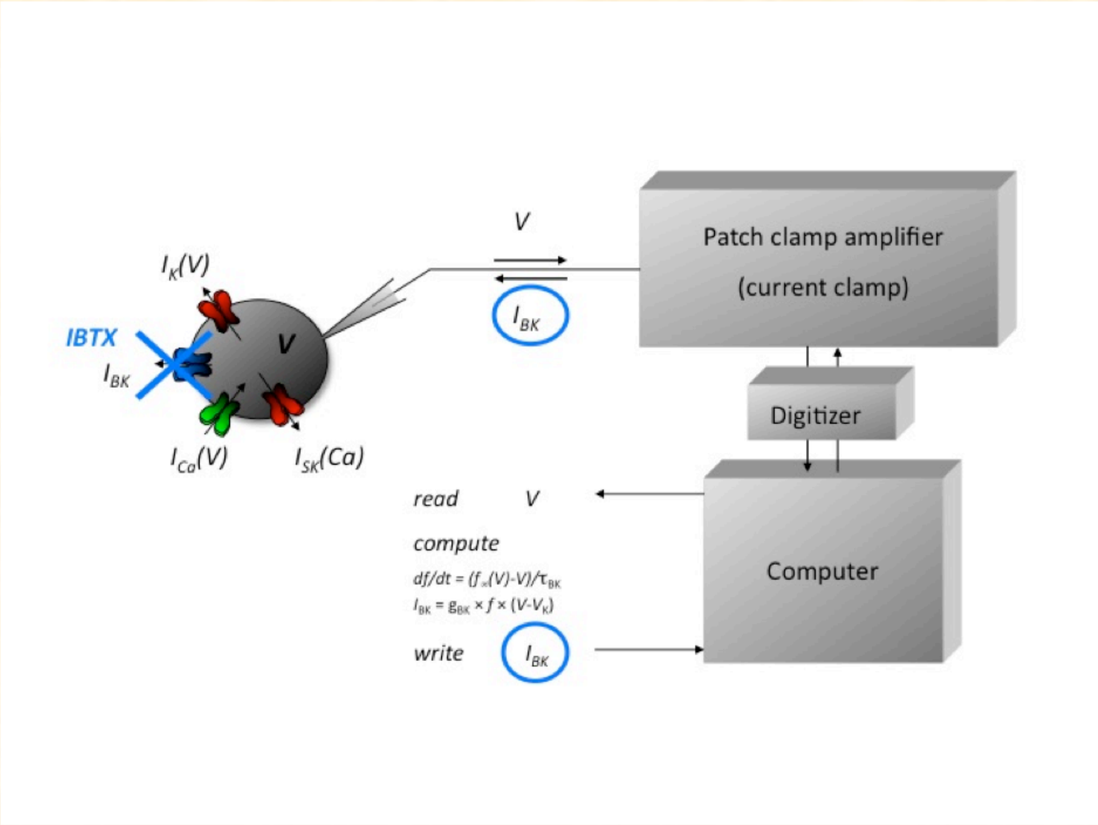
Actual cell (black) and model (red) convert from bursting to spiking

Feature plane for BK conductance and time constant



Best fit to bursting data → Double BK time constant

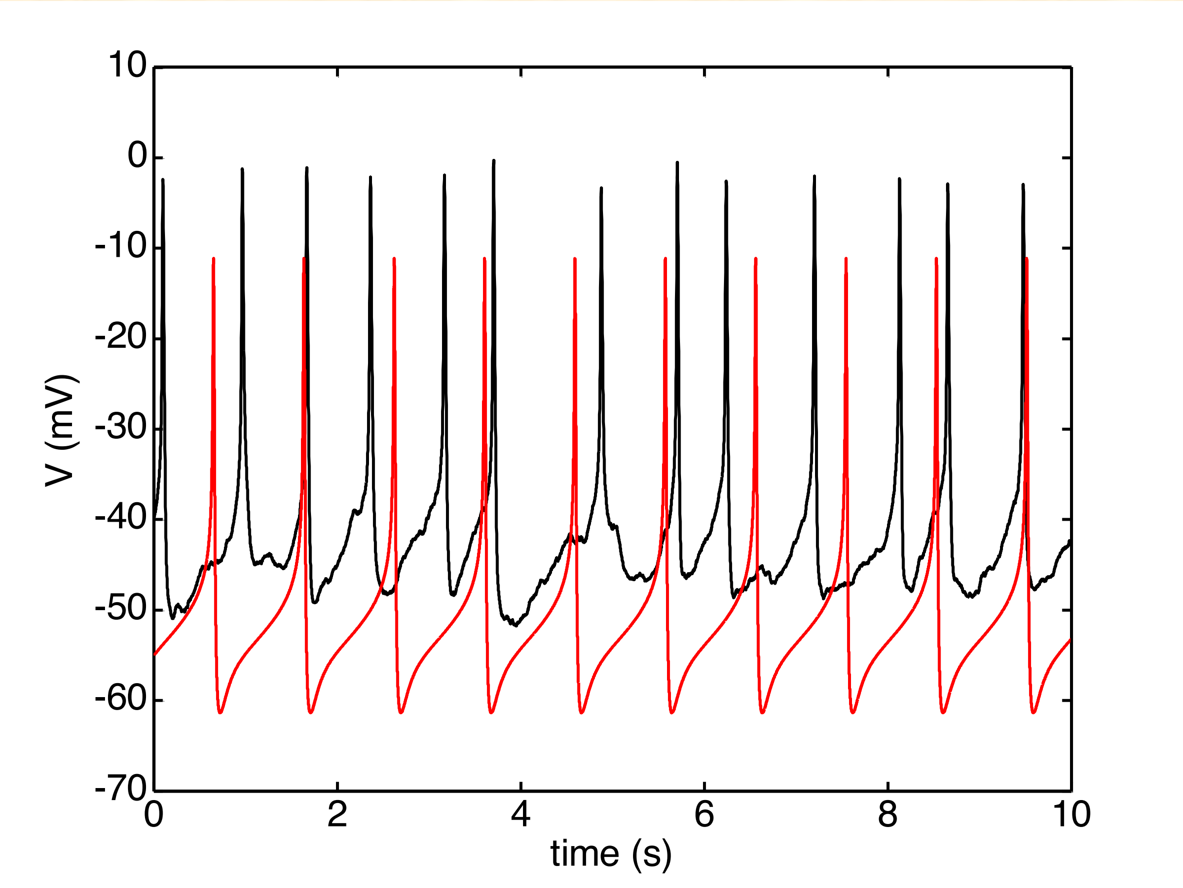
The Dynamic Clamp: a tool for adding a model current to a real cell



Prediction tested by adding BK current via D-clamp, with τ_{BK}=10 ms

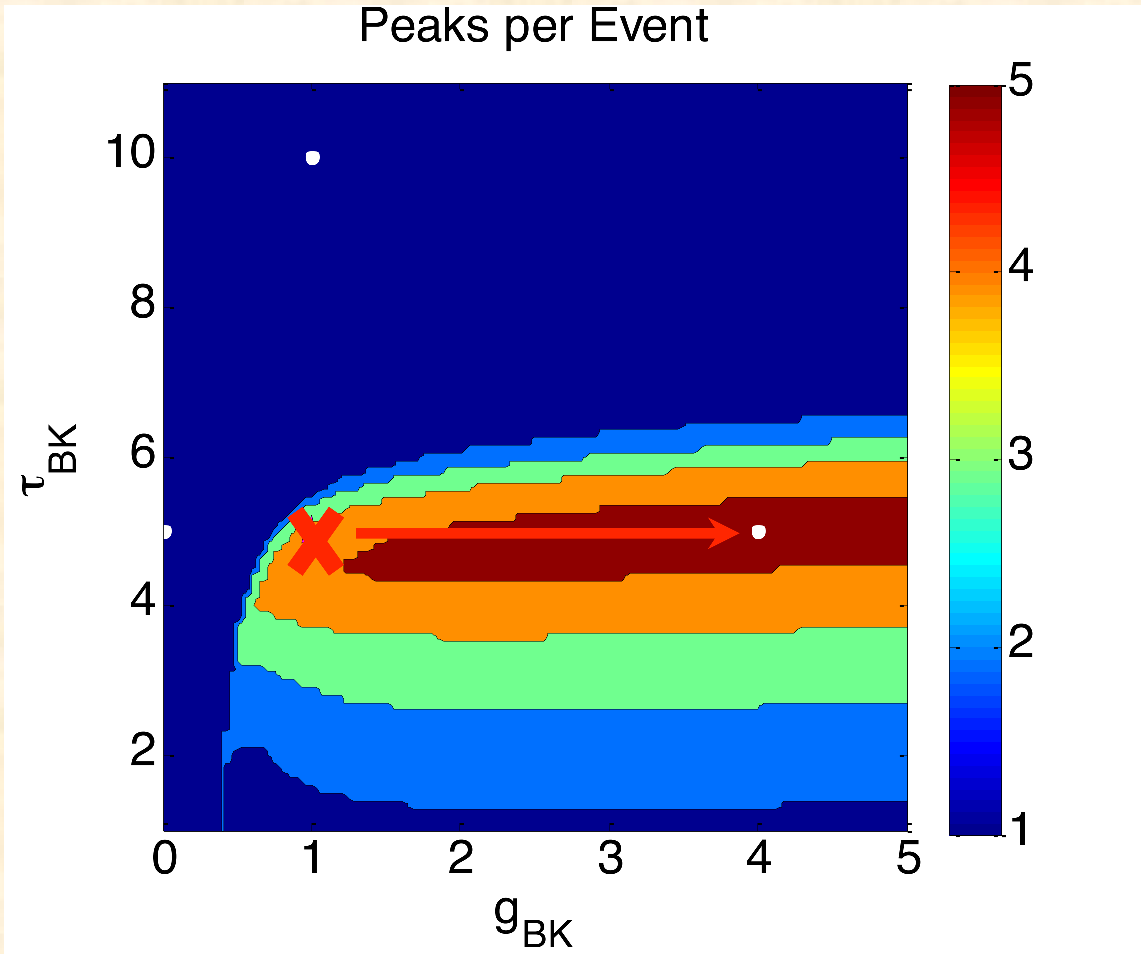
Black=cell

Red=model



Adding BK current with slow activation converts bursting to spiking

Feature plane for BK conductance and time constant

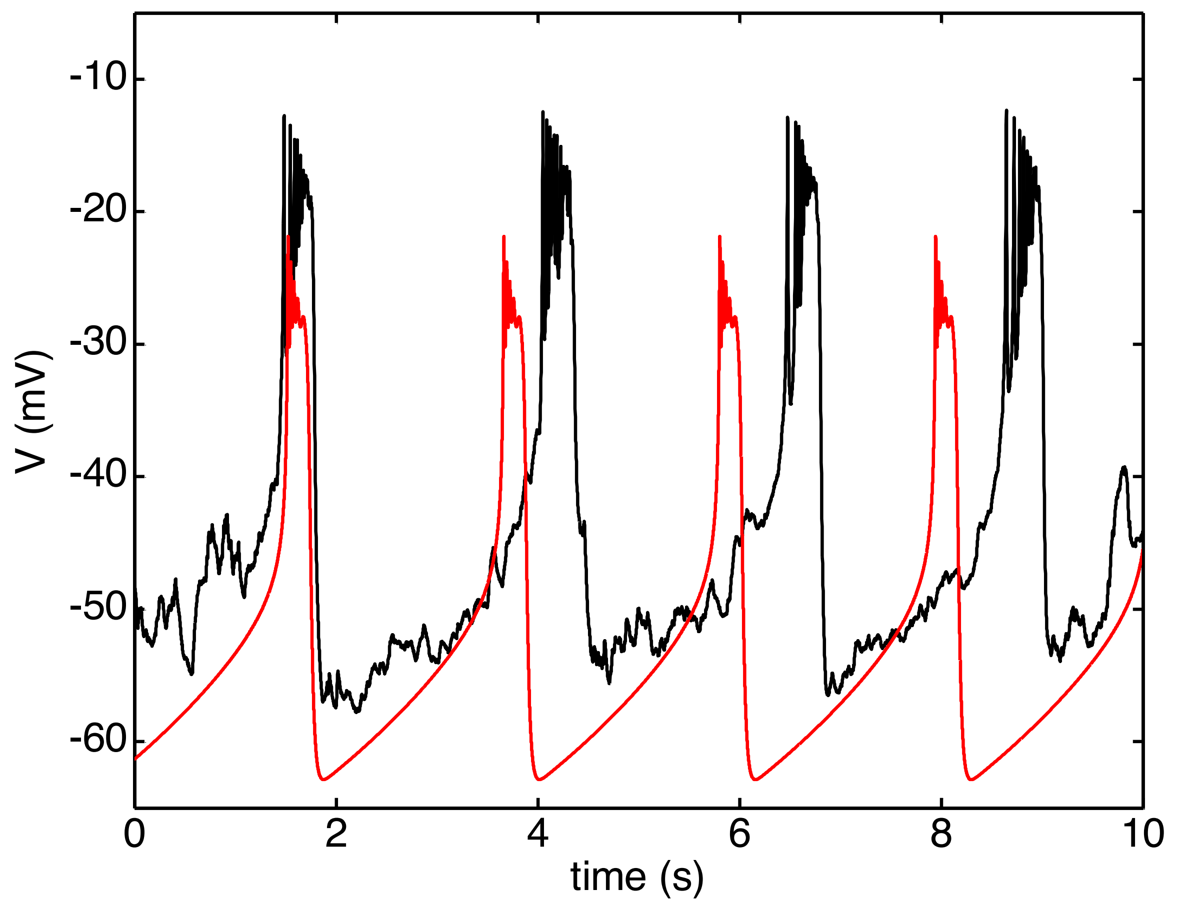


Best fit to bursting data → Increase BK conductance

Prediction tested by adding BK conductance to a bursting cell with D-clamp

Black=cell

Red=model



Bursting persists, with more spikes per burst

Understand bursting using geometric singular perturbation analysis

$$\varepsilon \dot{V} = f_1(V, n, f, Ca)$$

$$\dot{n} = f_2(V, n)$$

$$\dot{f} = f_3(V, f)$$

$$\dot{Ca} = f_4(V, Ca)$$

Analyze the reduced system obtained in the limit $\varepsilon \to 0$

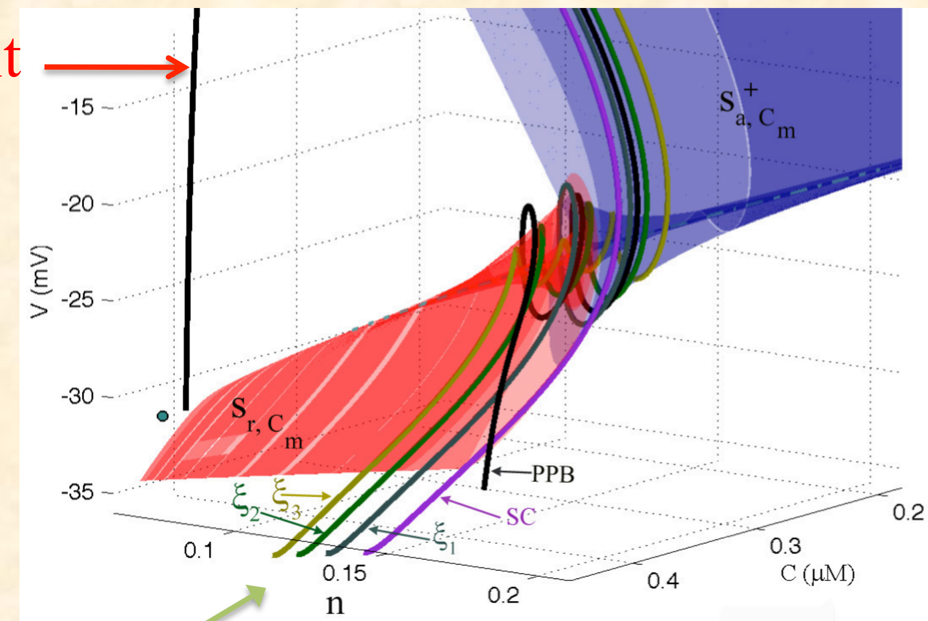
Voltage V is in a state of quasi-equilibrium with the other variables

(Work done with Martin Wechselberger, Joël Tabak, Theo Vo, and Wondimu Teka)

Geometric singular perturbation theory tells us about the origin of bursts

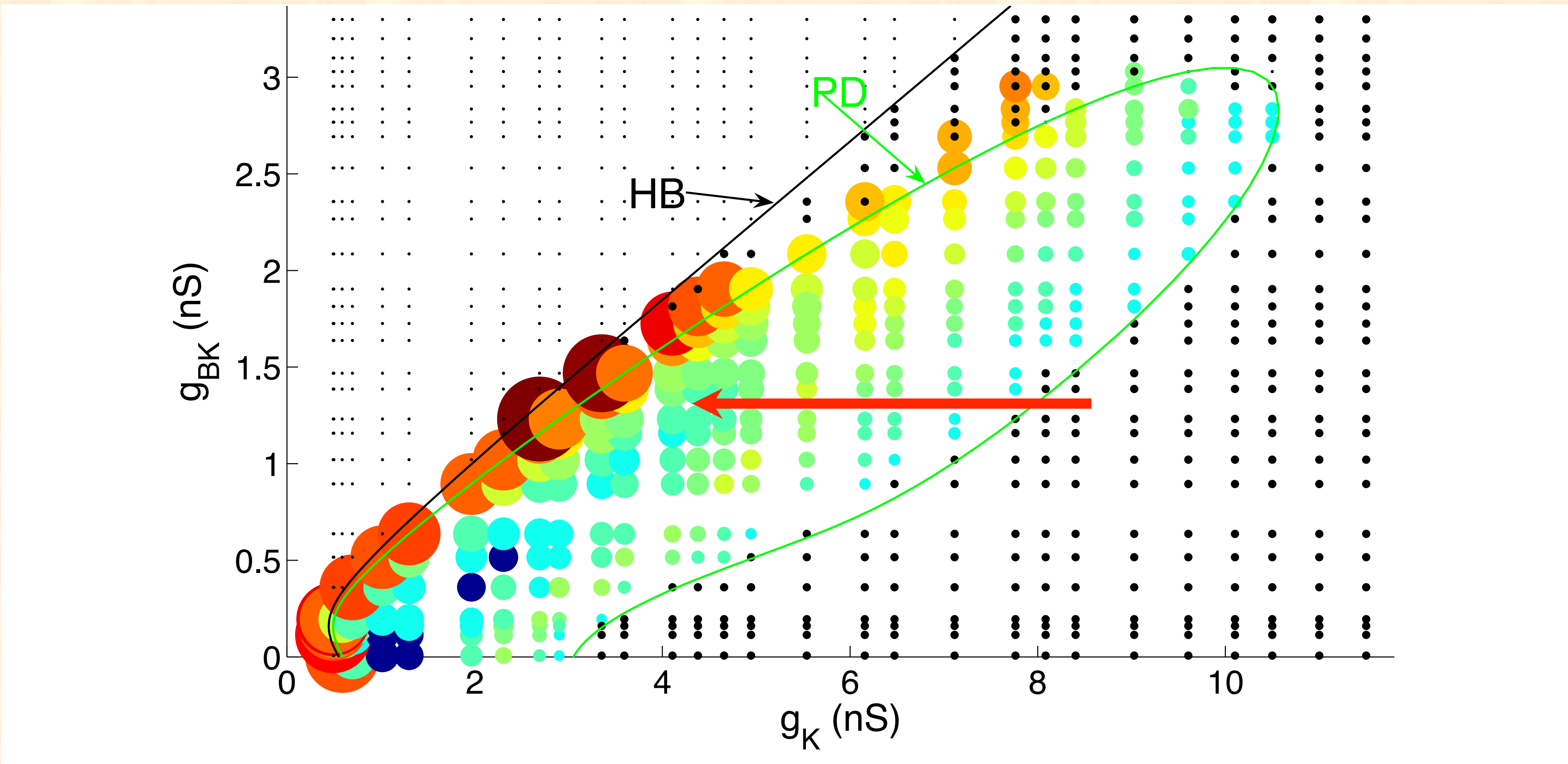
The "spikes" of the bursts are small rotations of the burst trajectory that occur due to the presence of a **folded node singularity** in the slow subsystem.

Bursting orbit



Secondary canards

Prediction: Reducing K(dr) conductance increases the burstiness



Diameter: active phase duration
Color: number of spikes per active phase

Teka et al., J. Math. Neurosci., 1:12, 2011

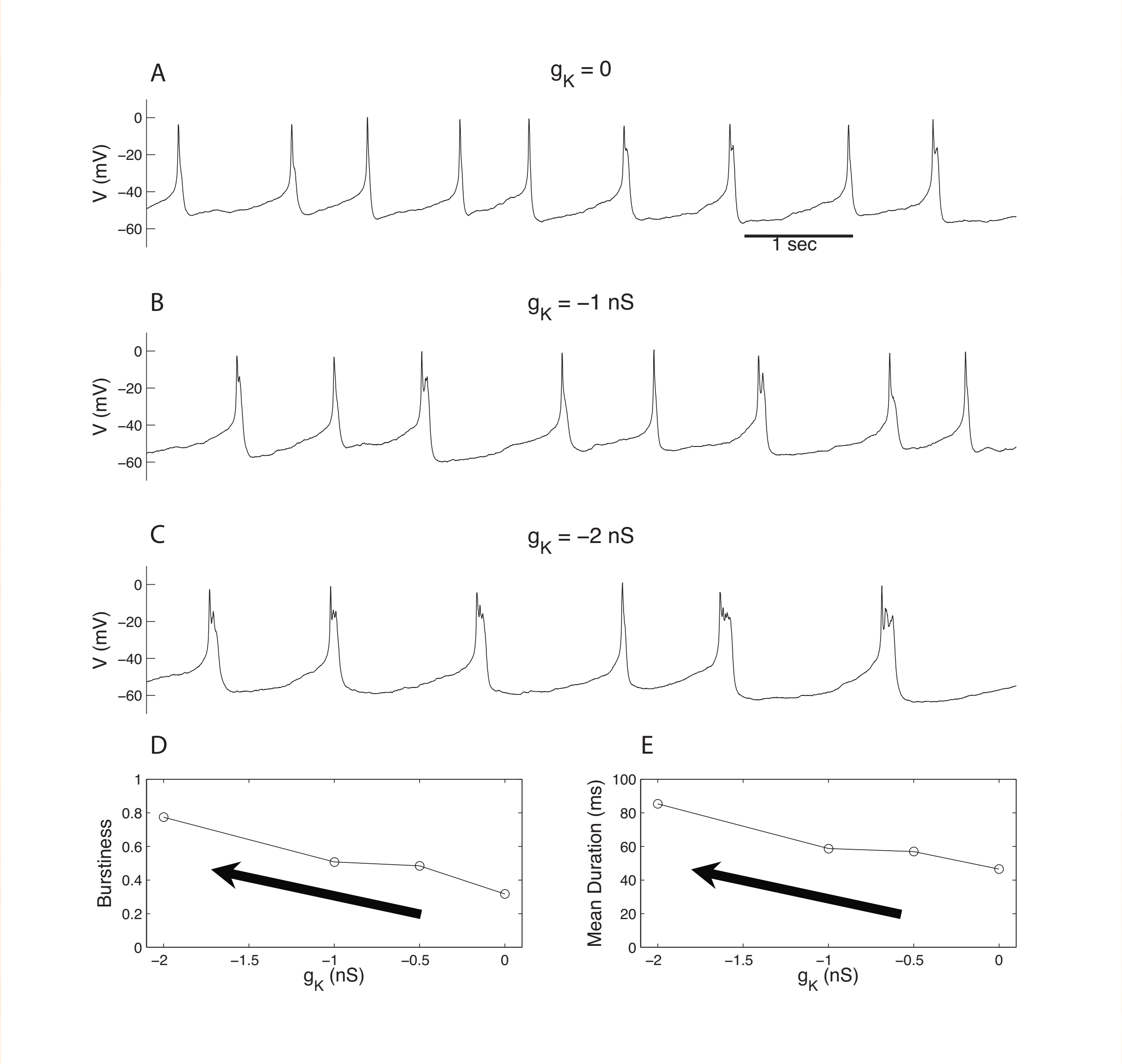
Prediction tested using D-clamp

Control cell

Subtract some K(dr) current

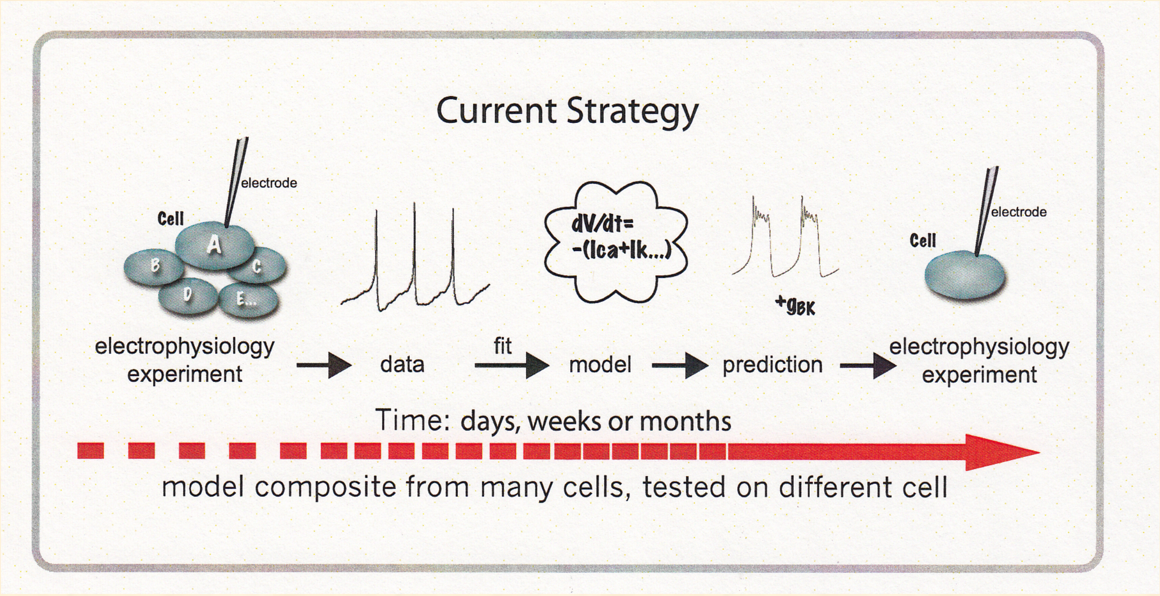
Subtract more K(dr) current

Summary

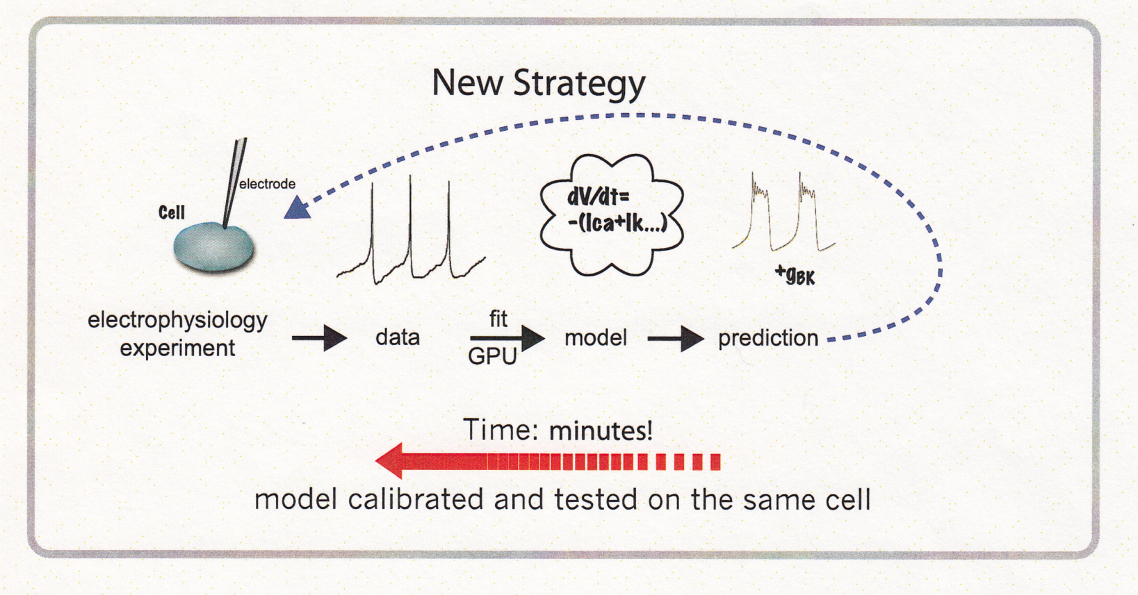


Bertram et al., in press

The "traditional" approach



Our new approach



Thank you