

Half neuron, half machine:

Neuronal excitability investigated with real-time computation

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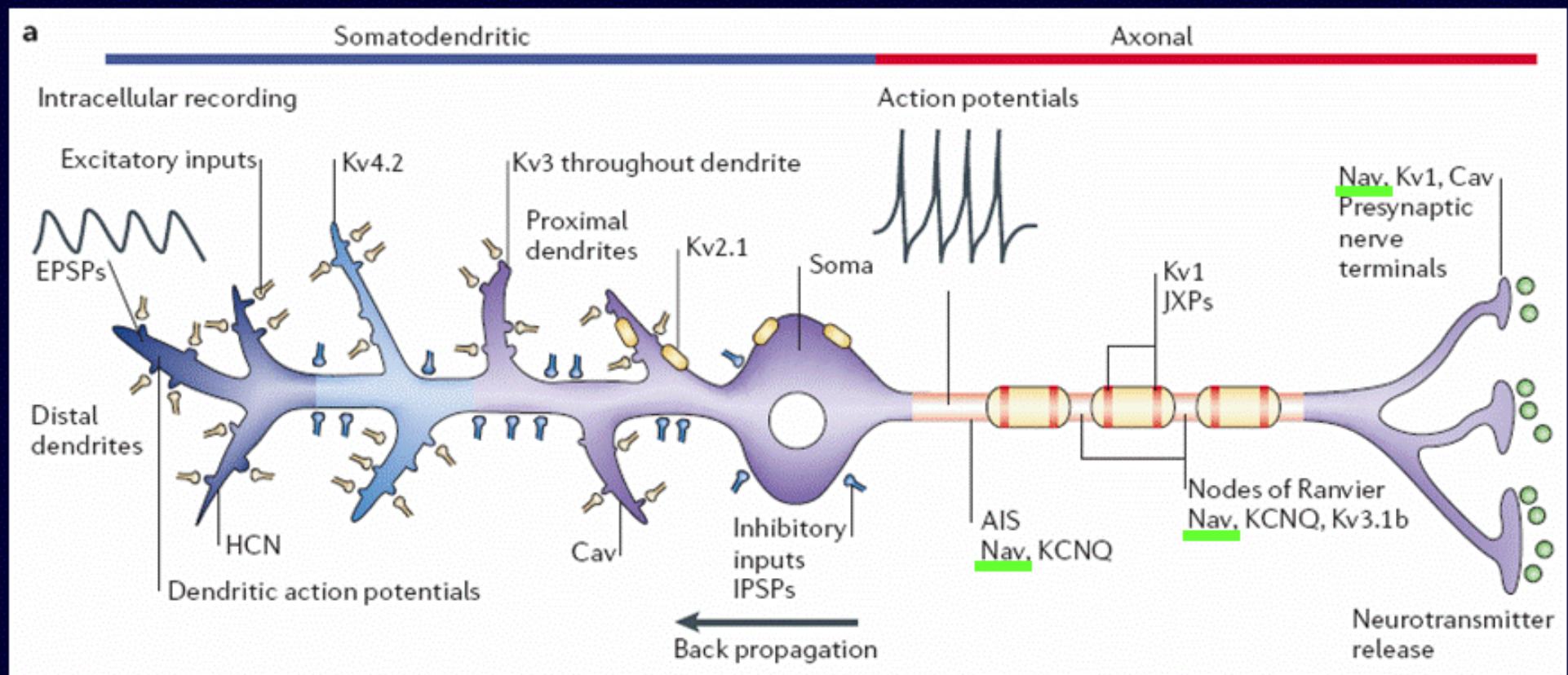
● Neuronal excitability

- Firing activity:

pacemaking, conditional spiking,
AP, spike trains

- Study:

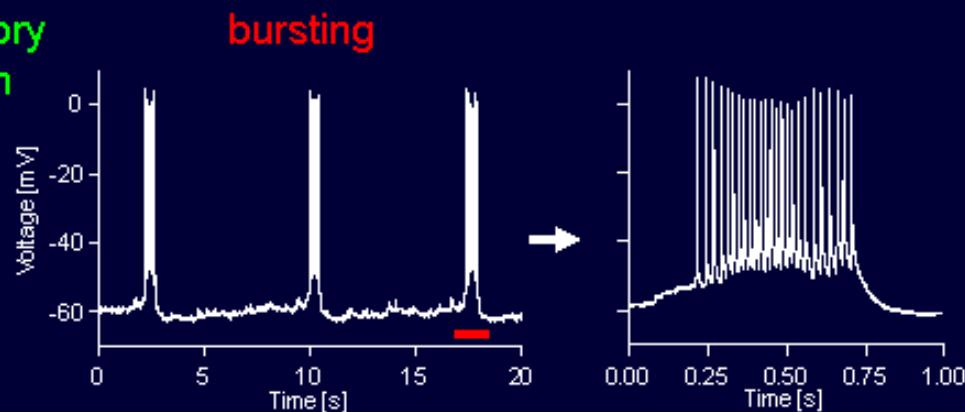
synapses, ion channels,
ionic currents



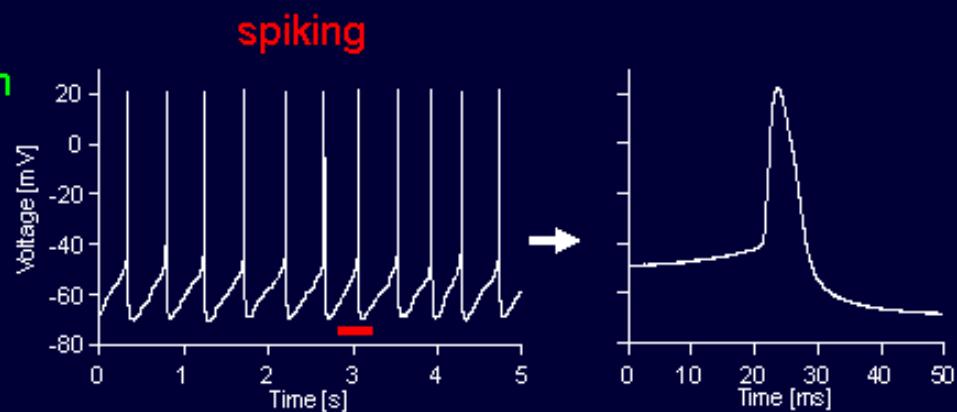
From: Lai and Jan, 2006

● Neuronal excitability: voltage-gated ion channels regulate firing patterns

respiratory
neuron



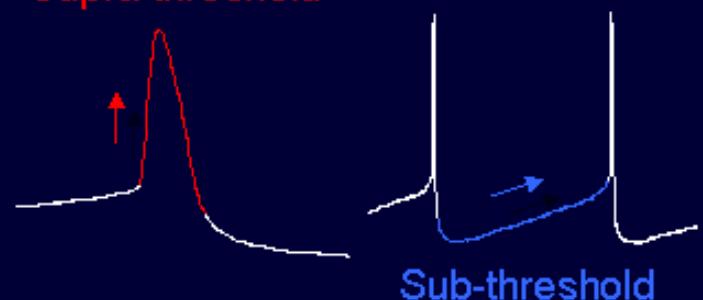
raphé
neuron



Na_v channels:

- Action potential generation
- Spontaneous firing (pacemaking)
- Frequency control
- Complex spiking patterns

Supra-threshold



- Neuronal excitability investigated with real-time computation

Ion channel
gating mechanism



Neuronal
excitability

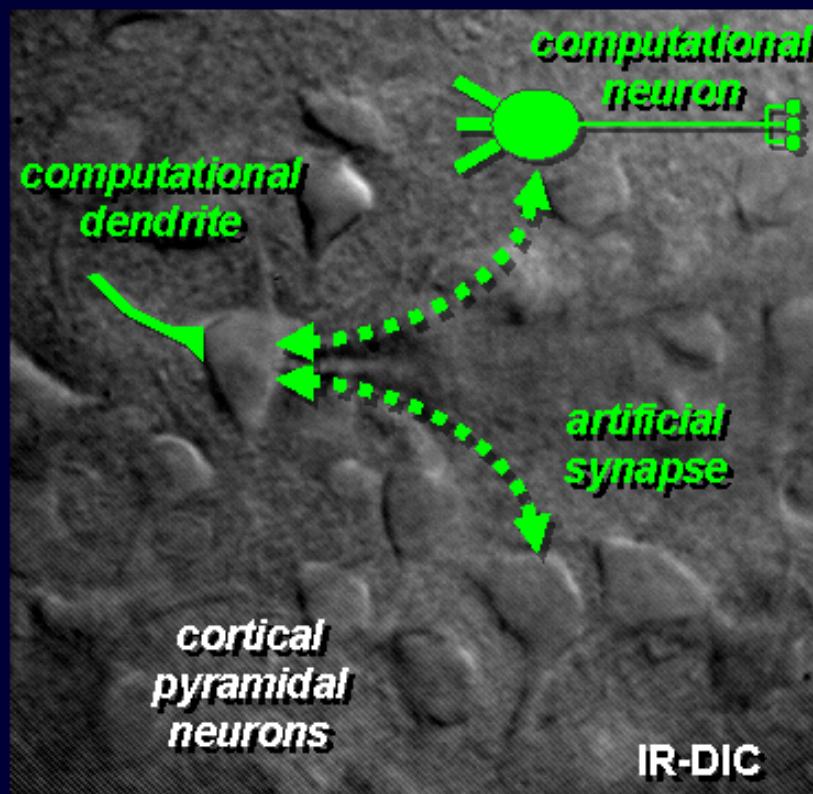
- Pharmacology
- Genetics
- Computer simulation
- Hybrid models: half neuron, half computational model

Dynamic clamp

Sharp et al, 1993

● Hybrid models: half neuron, half computational model

- Real neuron
- + artificial synapses
 - + computational neuron
 - + computational compartment
 - + virtual ion channels

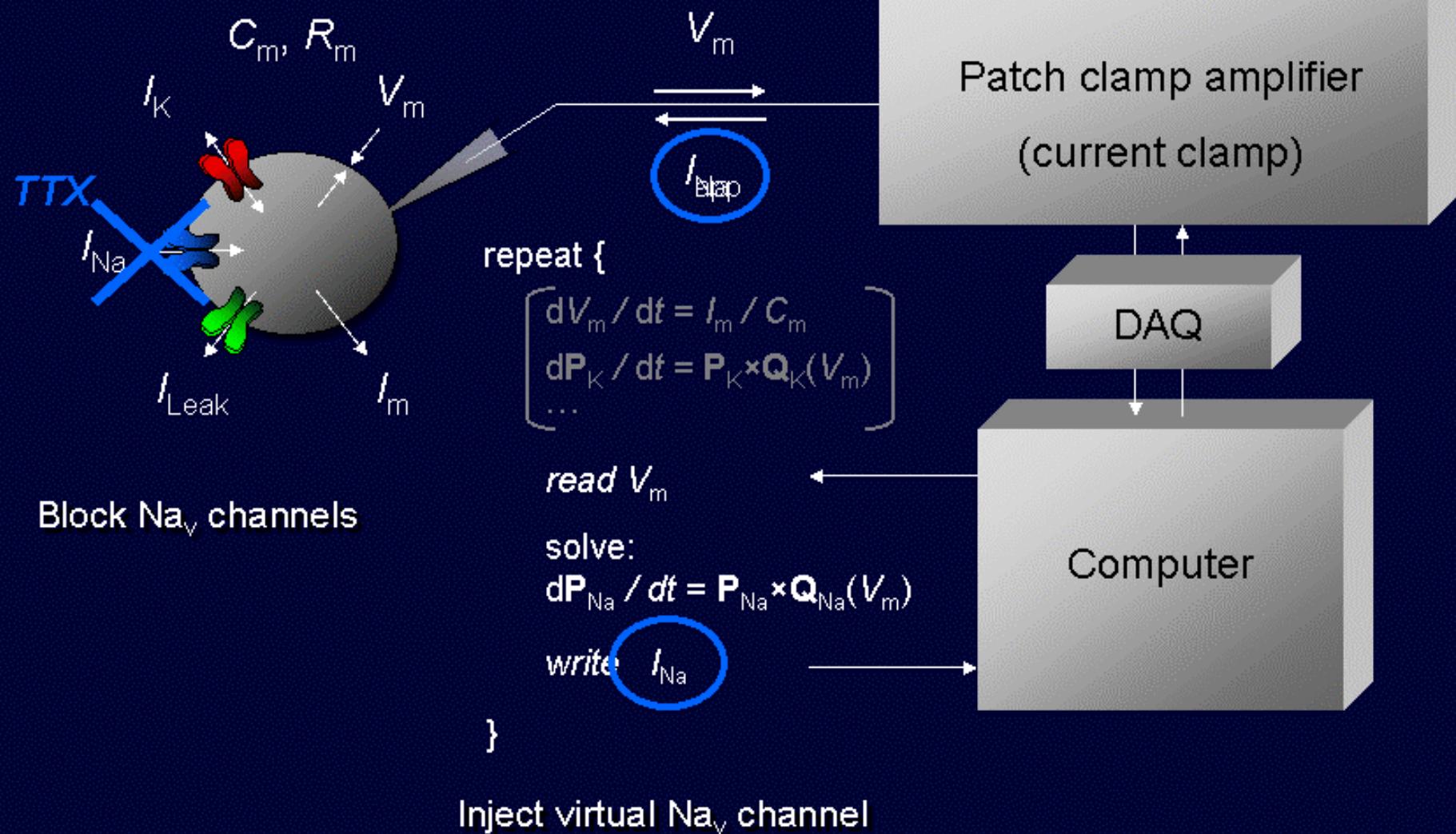


Combine patch clamp experiment with real-time simulation

Functionally replace ion channels with computational models

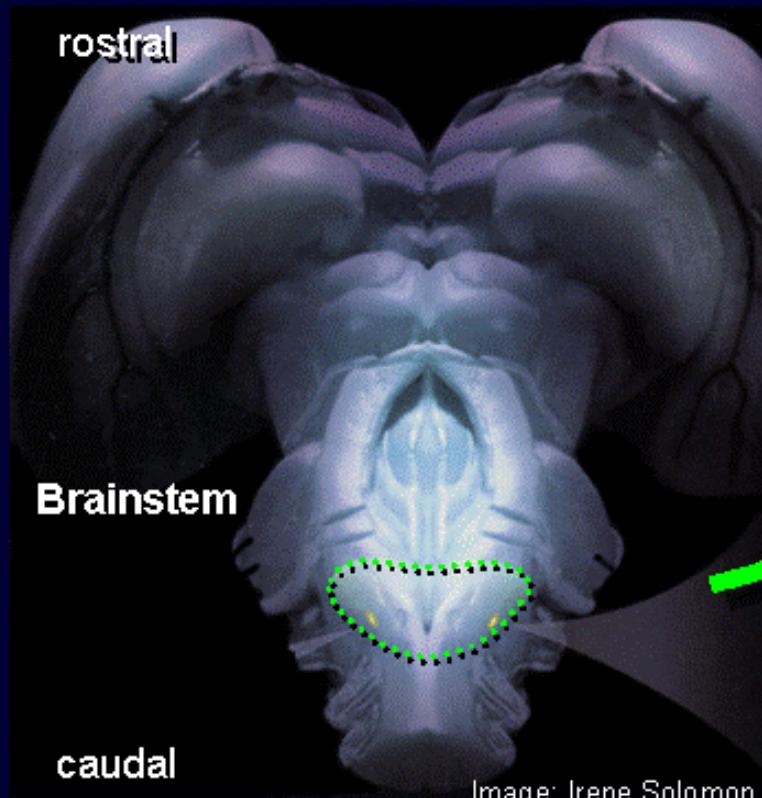
- Accurate simulation of one channel type
- Change gating properties of the model and manipulate the current during the spiking cycle

Hybrid models: neuron + computer

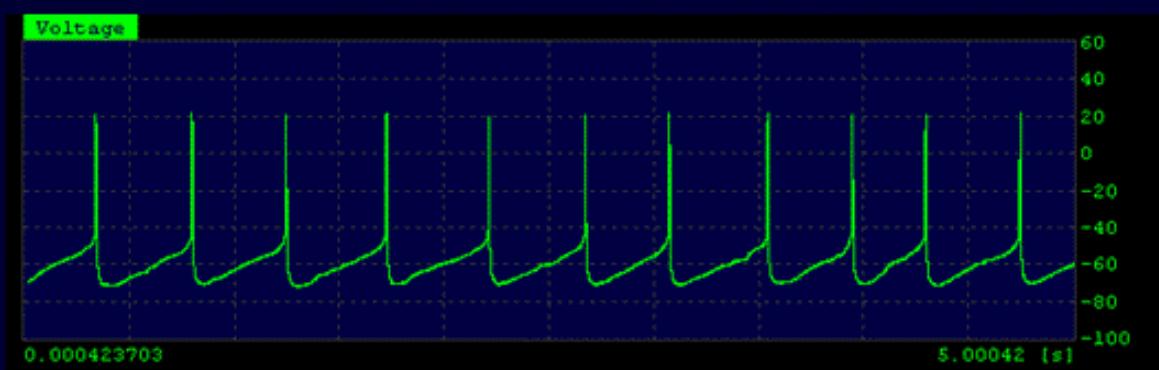
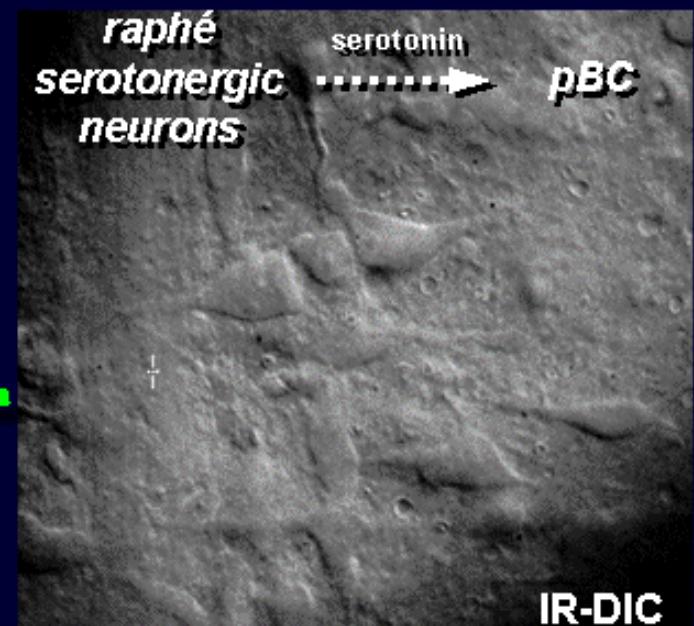
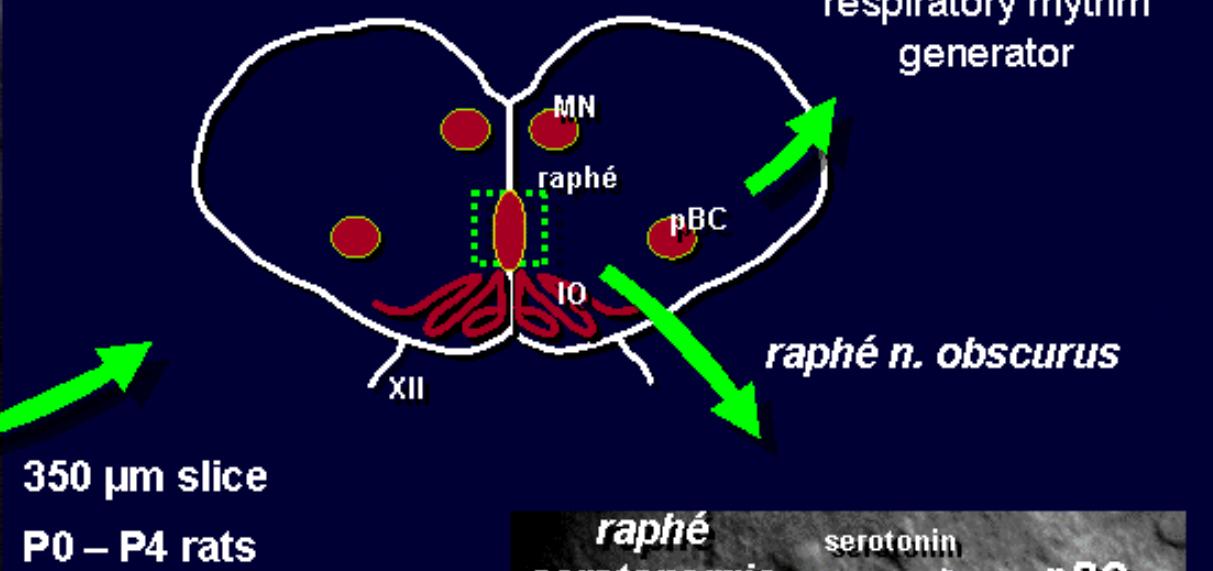


Real-time hybrid biological / computational simulation of a neuron

● Neuronal control of respiration



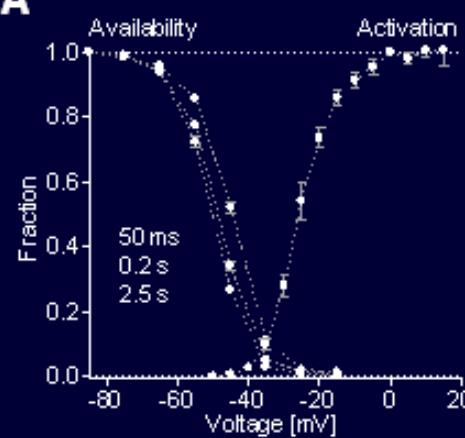
Jeff Smith Lab
NINDS/NIH



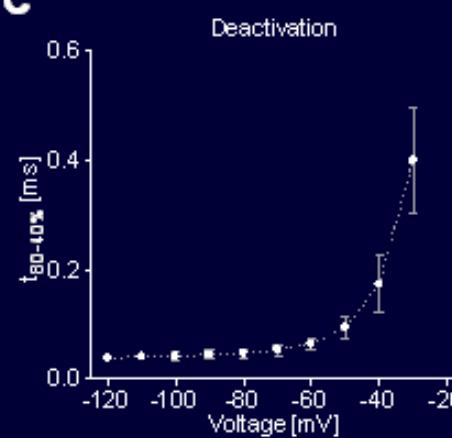
Spontaneous spiking (1-3 Hz)

Voltage clamp data for kinetic modeling

A



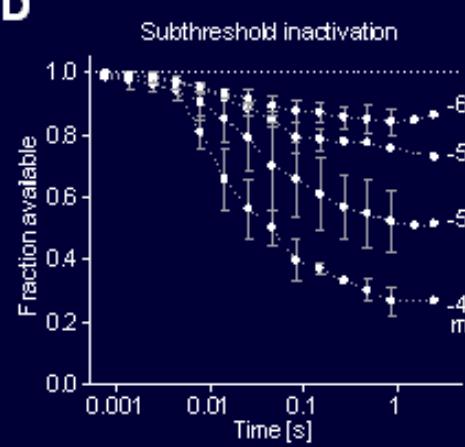
C



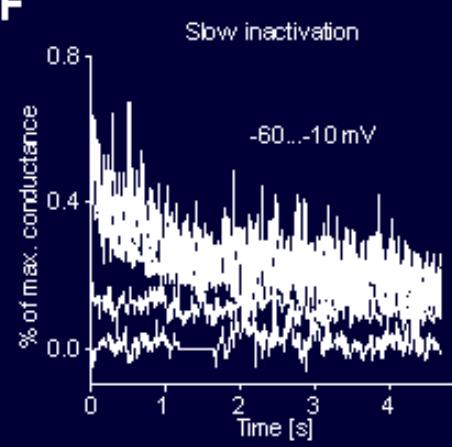
Information about:

- activation / deactivation
- opening / closing
- s.s. activation / inactivation
- inactivation time course
- entry slow inactivation
- inter-spike availability
- activity-dependent inact.

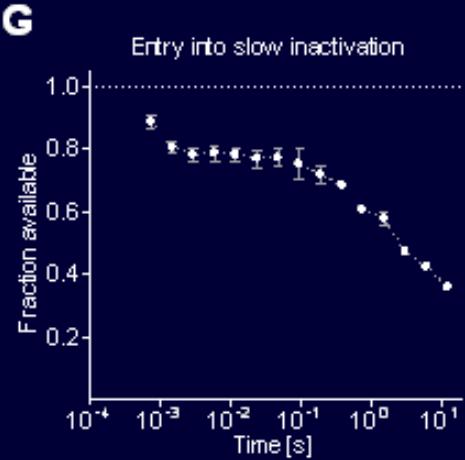
D



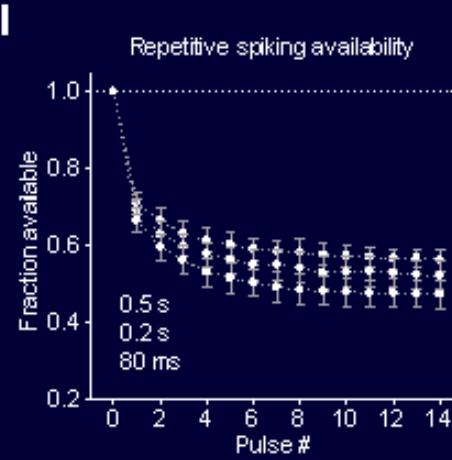
F



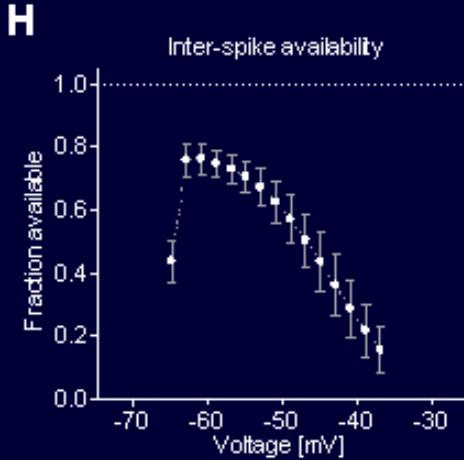
G



I



H

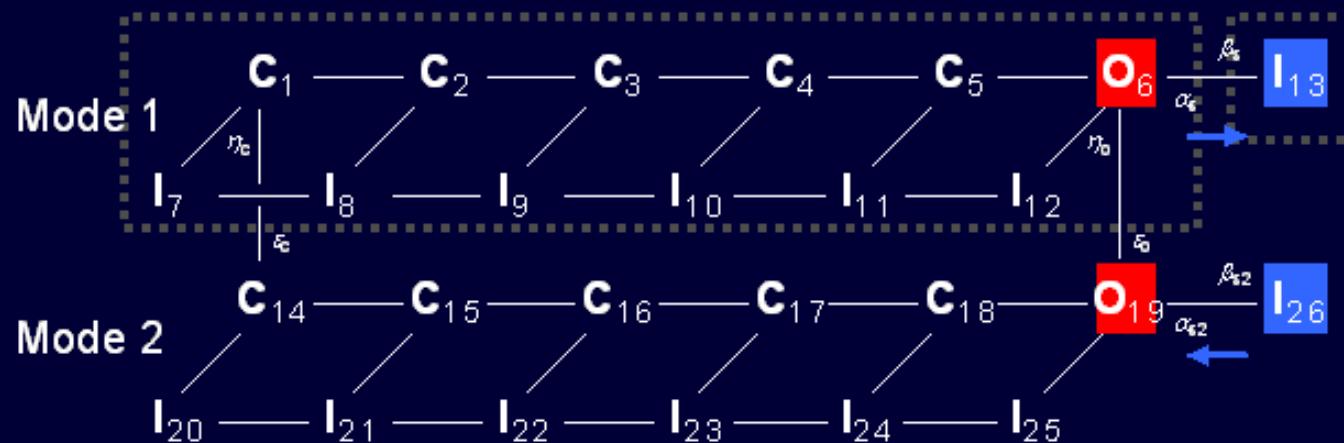


● Na_v channel kinetic model

Explains basic properties (four voltage sensors, etc)

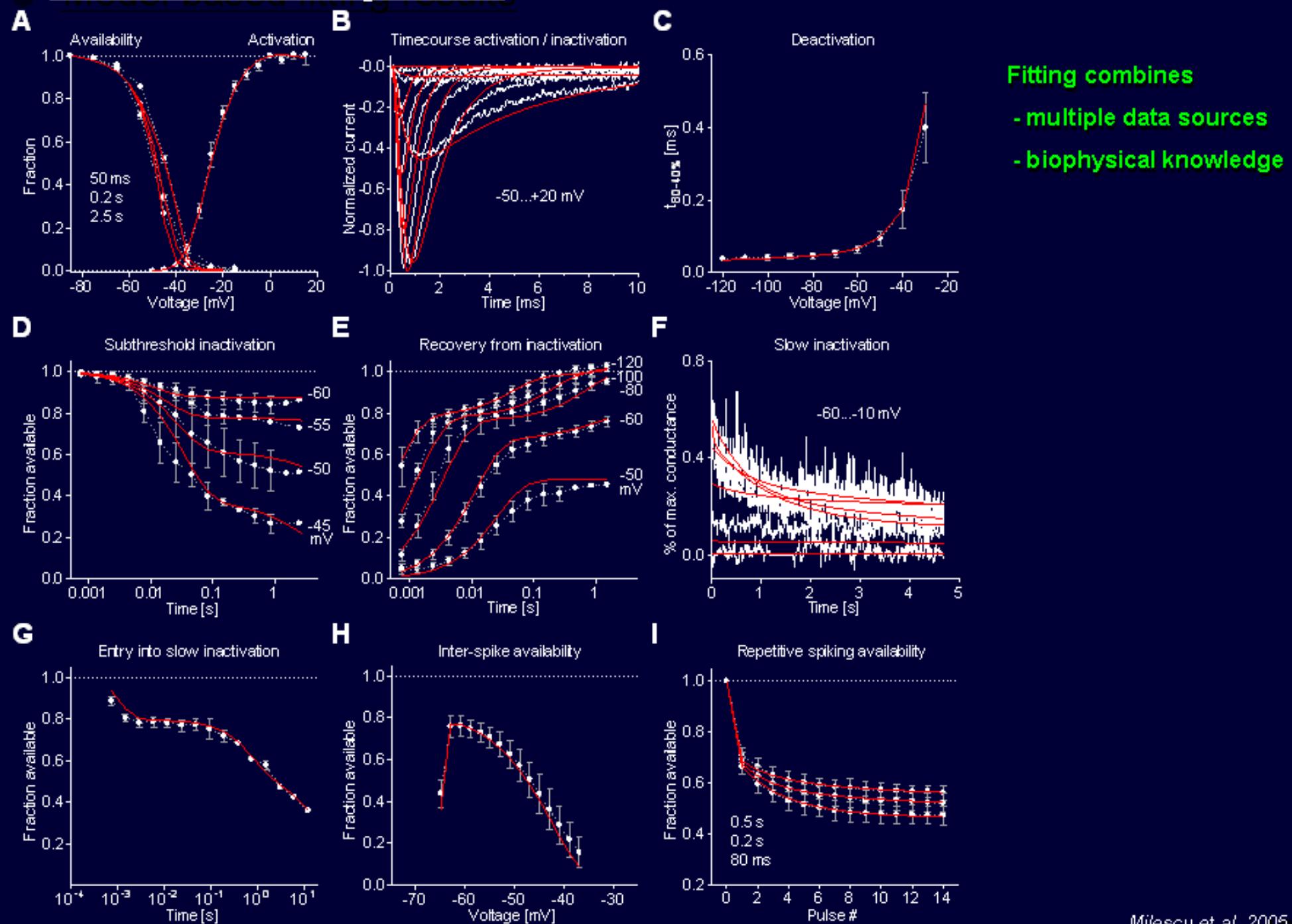
(Kuo and Bean)

Explains slow inactivation



Modal gating explains inactivation
during repetitive spiking

● Model-based fitting results



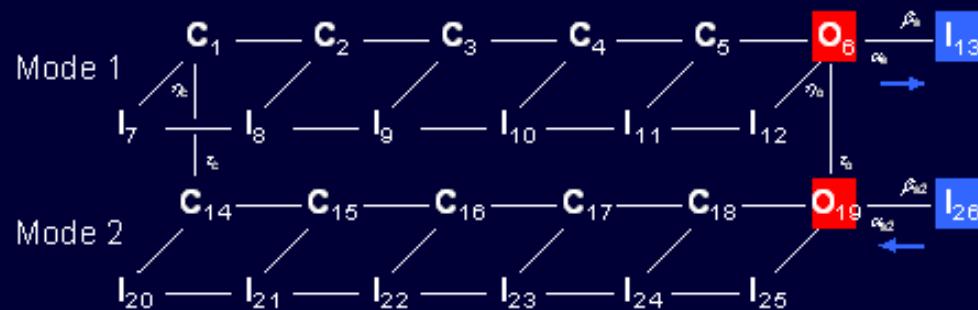
Fitting combines

- multiple data sources
- biophysical knowledge

Dynamic clamp: Na_v channels are difficult to model

- Fast rates: I/O and model computation
- Complex models, many (stiff) equations to solve

$N = 26 \text{ states} \rightarrow 25 \text{ O. D. Equations}$



Simulations:

~~Runge-Kutta~~

~~Exeter~~

$$\left\{ \begin{array}{l} \frac{dP_1}{dt} = \sum_{i>1} (P_i \times k_{i1}) - P_1 \times \sum_{j<1} k_{j1} \\ \frac{dP_2}{dt} = \dots \\ \frac{dP_3}{dt} = \dots \\ \frac{dP_4}{dt} = \dots \\ \frac{dP_5}{dt} = \dots \\ \frac{dP_6}{dt} = \dots \\ \frac{dP_7}{dt} = \dots \\ \frac{dP_8}{dt} = \dots \\ \frac{dP_9}{dt} = \dots \\ \frac{dP_{10}}{dt} = \dots \\ \frac{dP_{11}}{dt} = \dots \\ \frac{dP_{12}}{dt} = \dots \\ \frac{dP_{13}}{dt} = \dots \\ \frac{dP_{14}}{dt} = \dots \\ \frac{dP_{15}}{dt} = \dots \\ \frac{dP_{16}}{dt} = \dots \\ \frac{dP_{17}}{dt} = \dots \\ \frac{dP_{18}}{dt} = \dots \\ \frac{dP_{19}}{dt} = \dots \\ \frac{dP_{20}}{dt} = \dots \\ \frac{dP_{21}}{dt} = \dots \\ \frac{dP_{22}}{dt} = \dots \\ \frac{dP_{23}}{dt} = \dots \\ \frac{dP_{24}}{dt} = \dots \\ \frac{dP_{25}}{dt} = \dots \end{array} \right.$$

Dynamic clamp: technical improvements

- Integrate ODEs using “exact” solution

- Large models (30 states)
- Accurate integration

Differential equation:

$$d\mathbf{P}_t / dt = \mathbf{P}_t \times \mathbf{Q}(V_t)$$

Solution:

$$\mathbf{P}_{t+dt} = \mathbf{P}_t \times \exp(\mathbf{Q}(V_t) \times dt) = \mathbf{P}_t \times \mathbf{A}(V_t)$$

	Rate matrix					
-4α	4α	0	0	0	0	0
β	-(β+3α)	3α	0	0	0	0
0	2β	-(2β+2α)	2α	0	0	0
0	0	3β	-(3β+α)	α	0	0
0	0	0	4β	-(4β+γ)	γ	
0	0	0	0	δ	δ	-δ

Simple matrix multiplication:

→ $\mathbf{P}_0 \times \mathbf{A}(V_1) \times \mathbf{A}(V_2) \times \mathbf{A}(V_3) \times \mathbf{A}(V_4) \times \mathbf{A}(V_5) \times \dots$

Pre-compute $\mathbf{A}(V = -100 \dots 50 \text{ mV, every } 0.1 \text{-} 1 \text{ mV})$

Spectral decomposition:

$$\mathbf{A} = \exp(\mathbf{Q} \times dt) = \sum_i [\mathbf{A}_i \times \exp(\lambda_i \times dt)]$$

λ_i = i^{th} eigenvalue of \mathbf{Q}

$\lambda_0 = 0$

\mathbf{A}_i = i^{th} spectral matrix of \mathbf{Q}

0.9114	0.0855	0.0030	4.707e-5	2.758e-7	2.783e-10
0.0041	0.9290	0.0654	0.0015	1.198e-5	1.510e-8
1.835e-5	0.0083	0.9467	0.0444	0.0005	8.742e-7
8.232e-8	5.609e-5	0.0127	0.9646	0.0226	5.691e-5
3.690e-10	3.351e-7	1.141e-4	0.0173	0.9777	0.0049
2.234e-13	2.536e-10	1.151e-7	2.612e-5	0.0030	0.9970

State transition probabilities (a numerical example)

Colquhoun and Sigworth

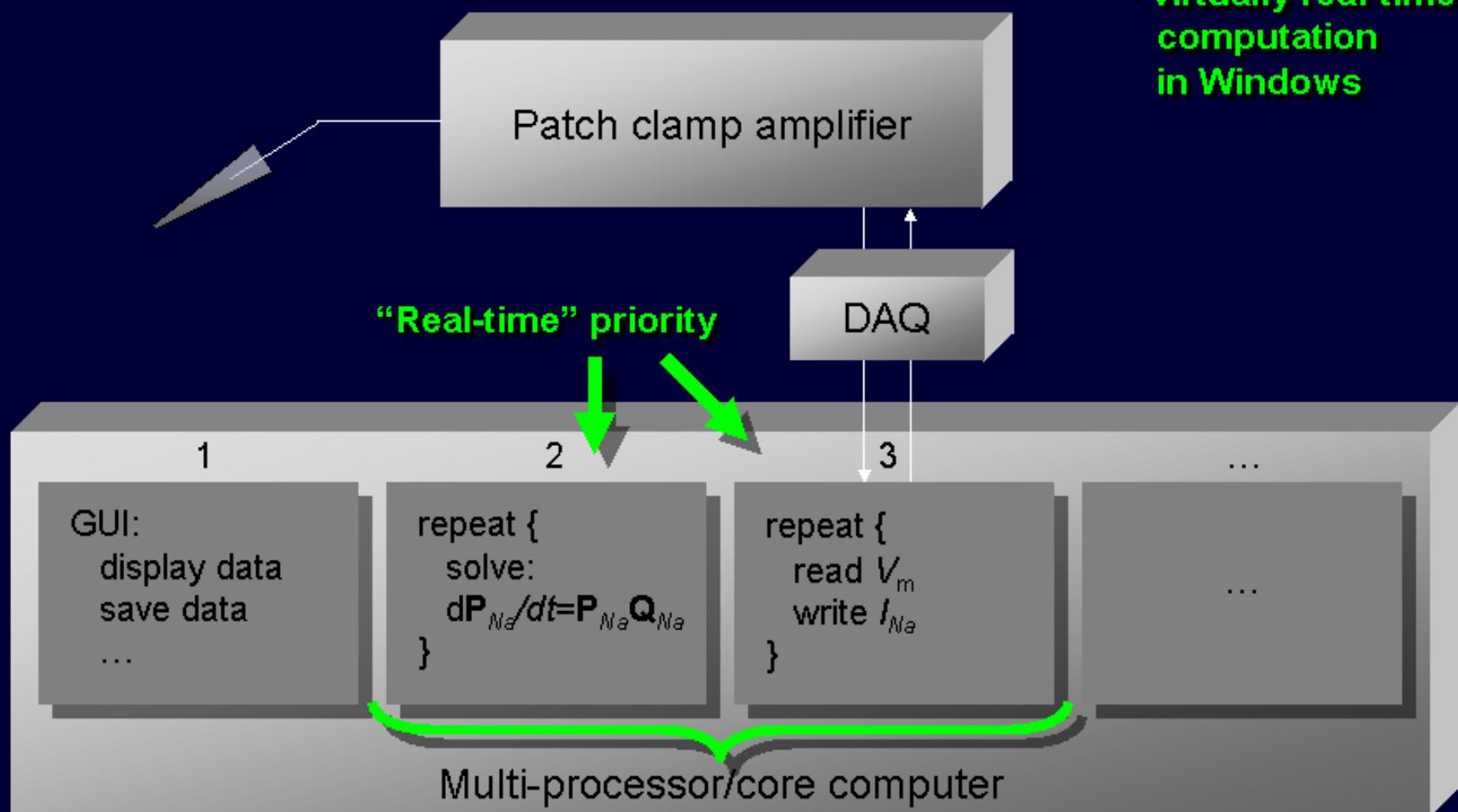
Milescu et al, 2008

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● Dynamic clamp: technical improvements

- Integrate ODEs using “exact” solution
- Parallelize the software

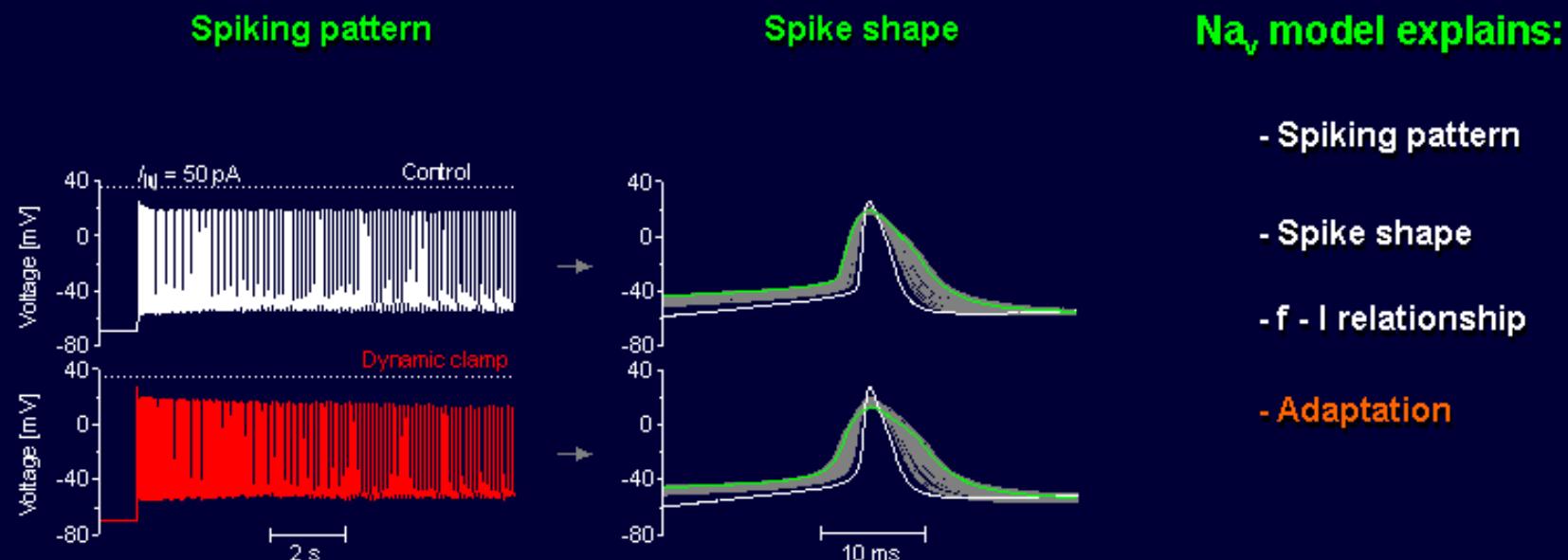
- Fast (50÷100 kHz)
- virtually real-time computation in Windows



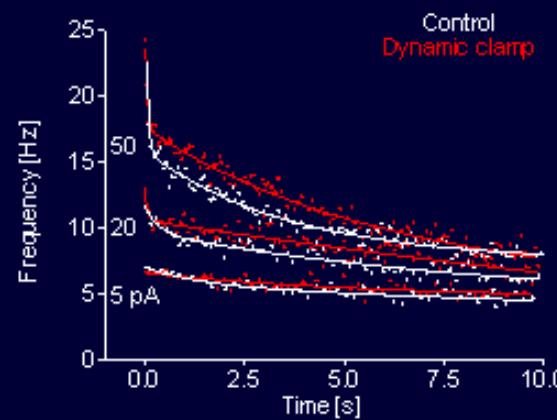
● Functional model verification with dynamic clamp

Control exp.

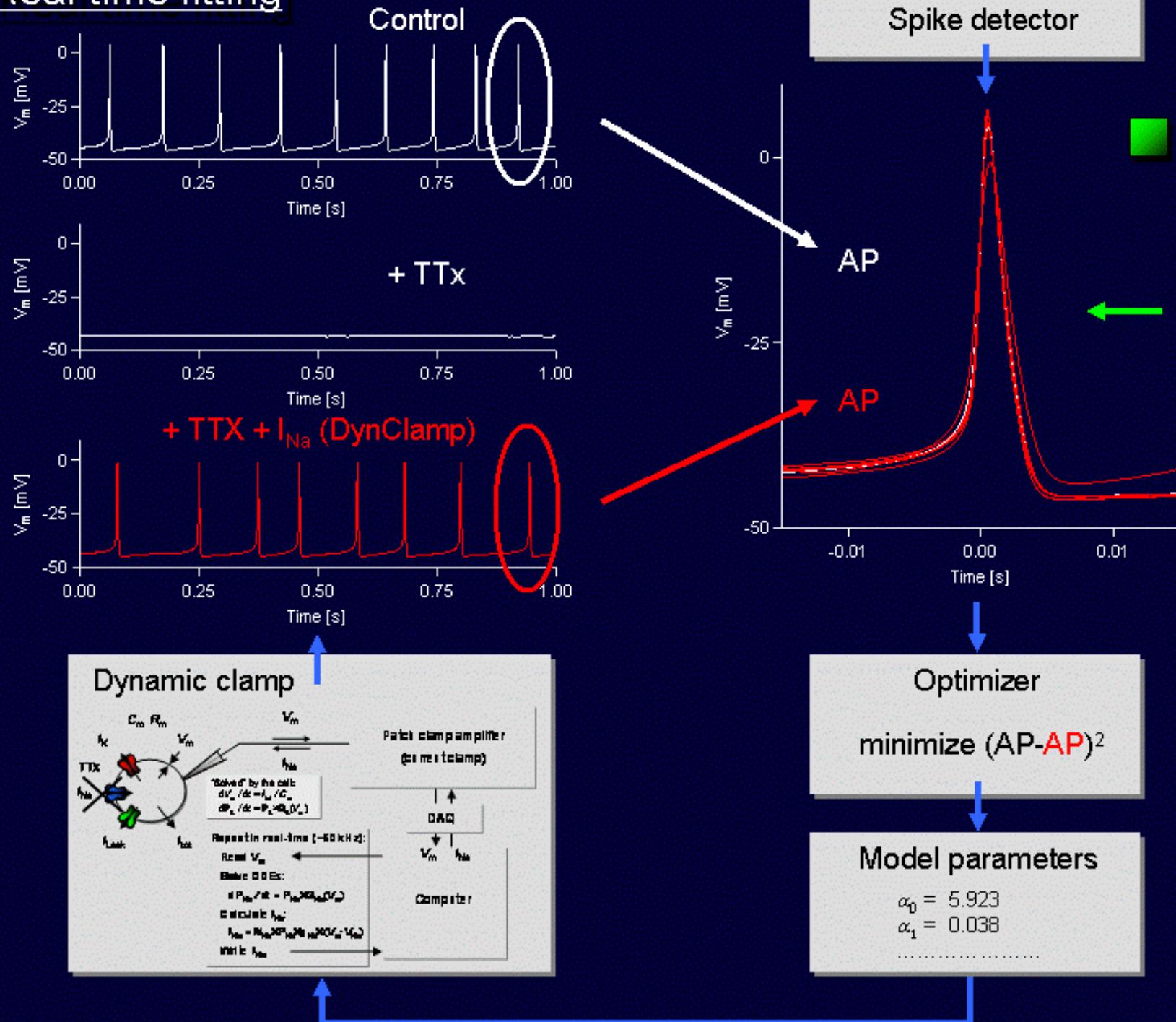
+ TTX + DynC



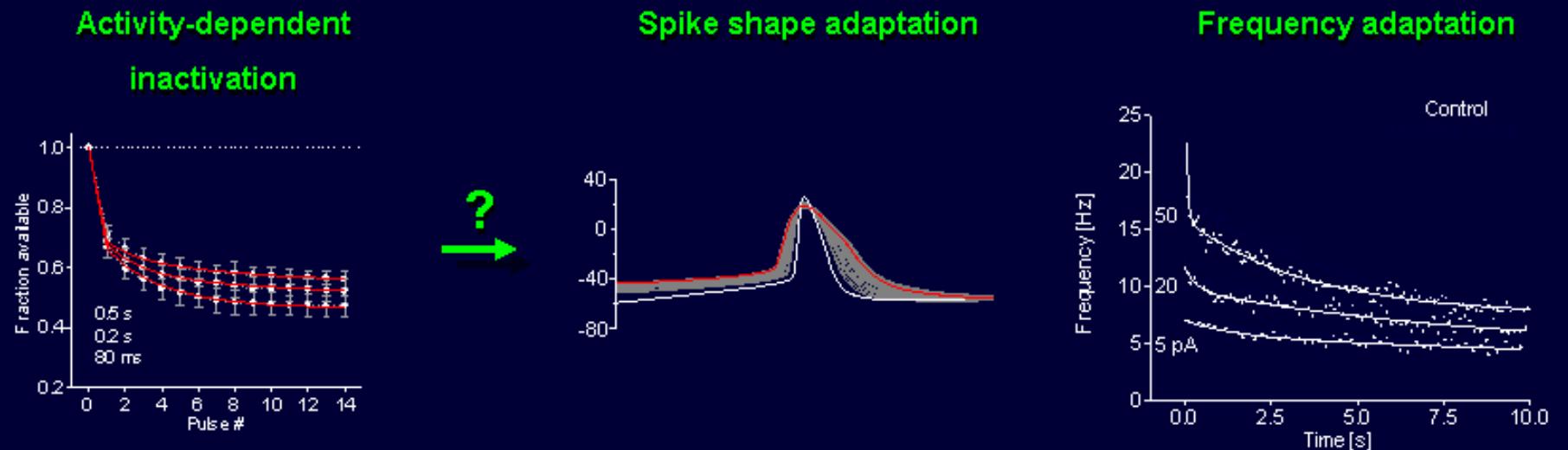
f - I relationship



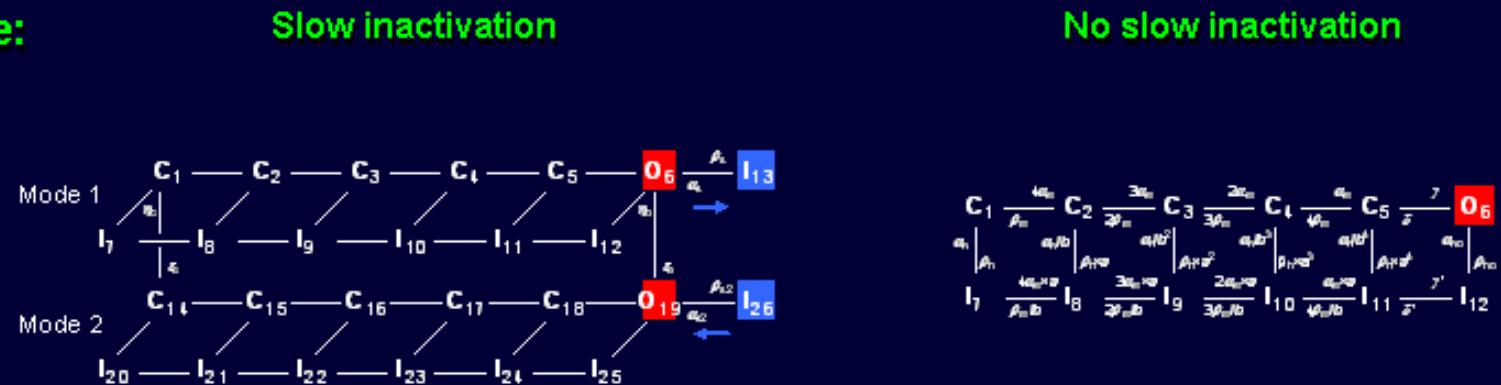
Real-time fitting



● Na_v channel slow inactivation

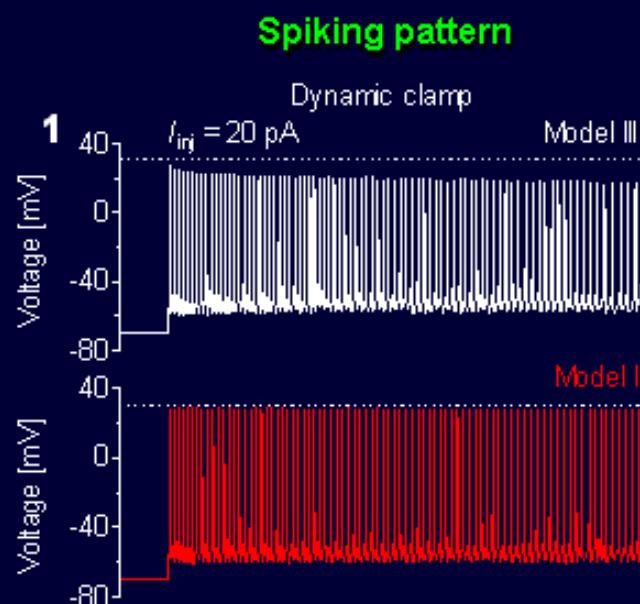


Compare:

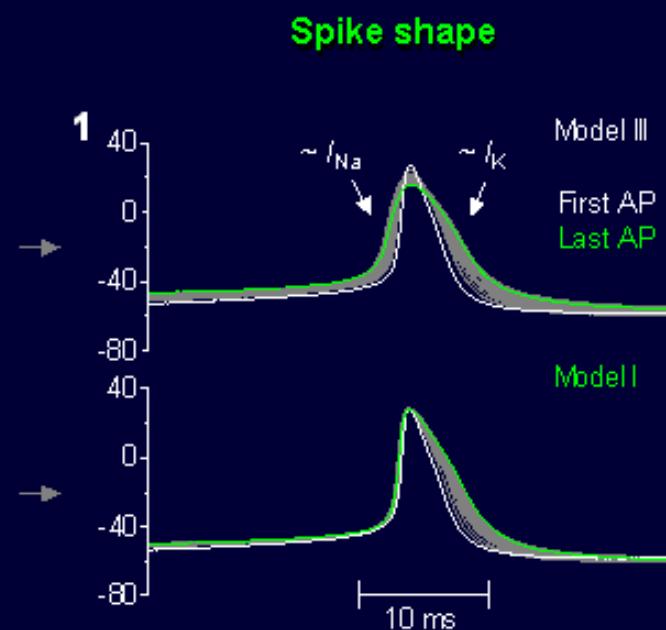


● Na_v channel slow inactivation

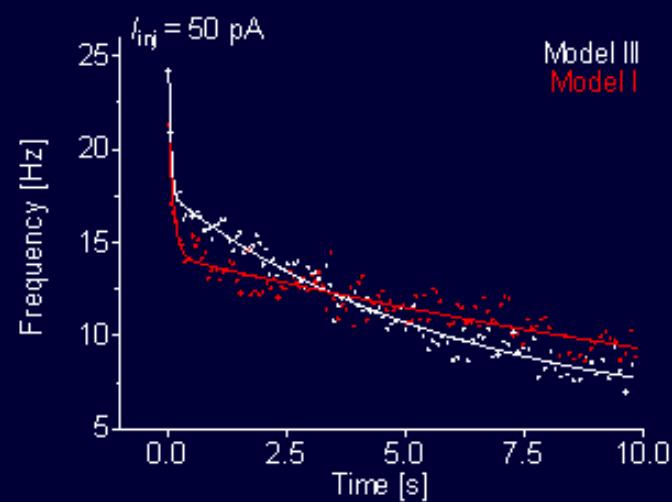
With slow inactivation



No slow inactivation



f - I relationship



Slow inactivation modulates:

- Adaptation
- Spiking pattern
- Spike shape

● Summary

Real-time computation:

- A powerful paradigm for studying the neuronal function of one ion channel type on a background of native conductances
- Very fast computation allows us to model Na_v channel function using biophysically realistic gating models
- Can solve many channel types simultaneously, simulate compartments (axon, dendrites), create synapses

