Jose "Pepe" Puglisi, PhD
Department of Pharmacology
UC Davis

TEACHING ELECTROPHYSIOLOGY WITH THE AID OF MATHEMATICAL MODELS

Road Map

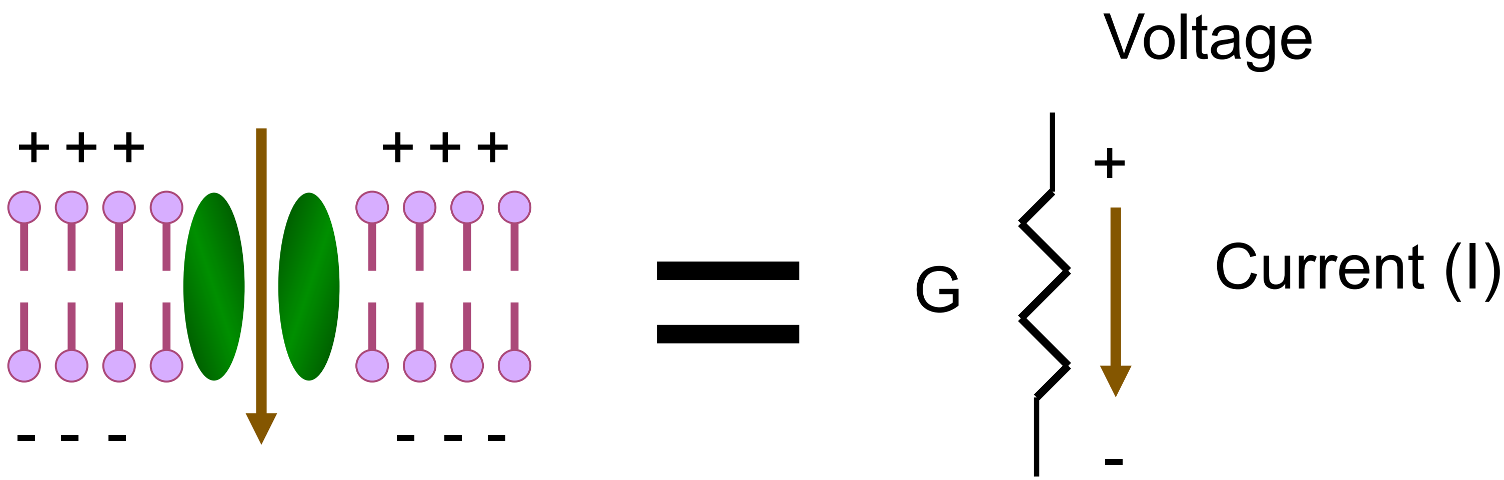
- Why do we need mathematical models?
- LabAXON (Hodgkin and Huxley)
- LabHEART (Ventricular Myocyte)
- MarkoLAB (Stochastic Simulation)
- Conclusions

Why do we need mathematical models?

- There are three stages in Science
- 1) Description
- 2) Quantification
- 3) Prediction

LabAXON

- Based on the Hodgkin & Huxley formalism (1952)



$I_x = G_x * (V – V_x)$ $\quad\quad$ $I = G * V$

Ionic Channels **Basic Equation**

$$I_x = G_x * m * h * f\,(Ca) * (V - V_x)$$

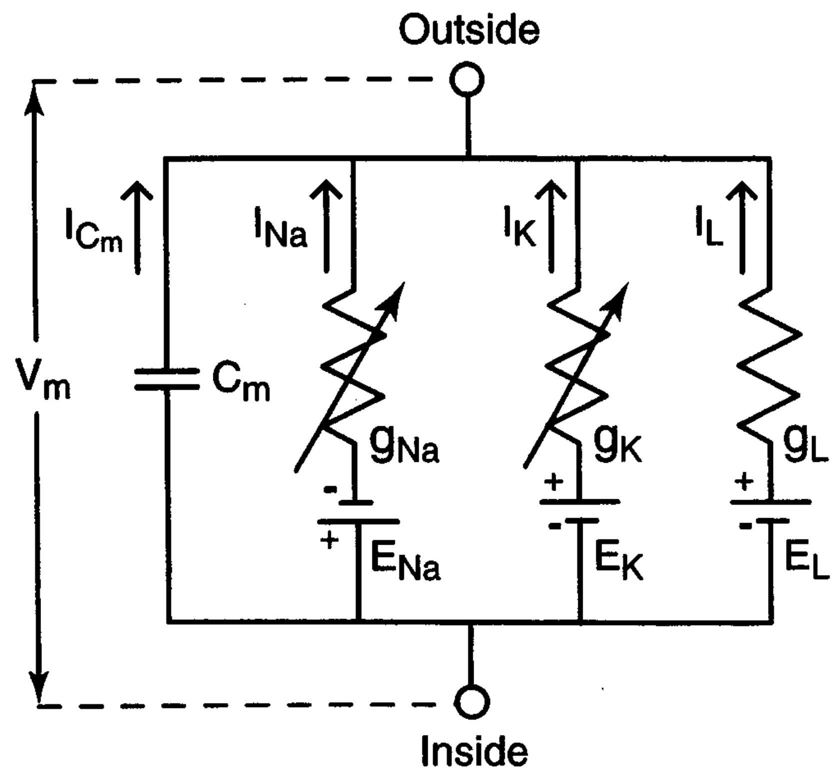
Voltage dependent activation

Ca -
Mg -
ATP - dependent

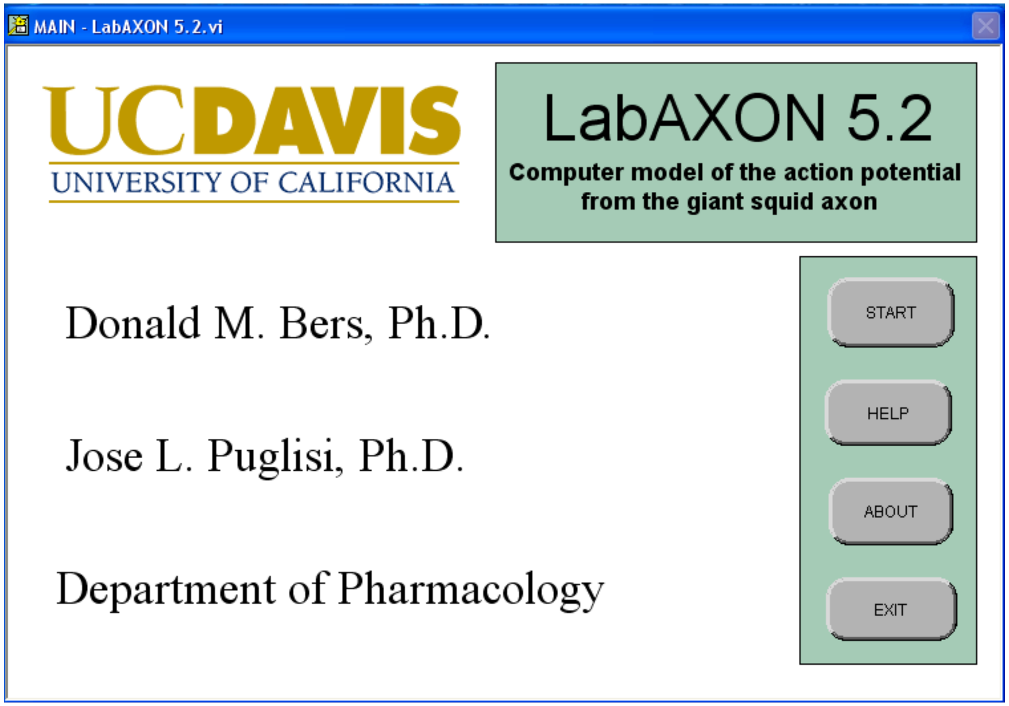
Voltage dependent inactivation

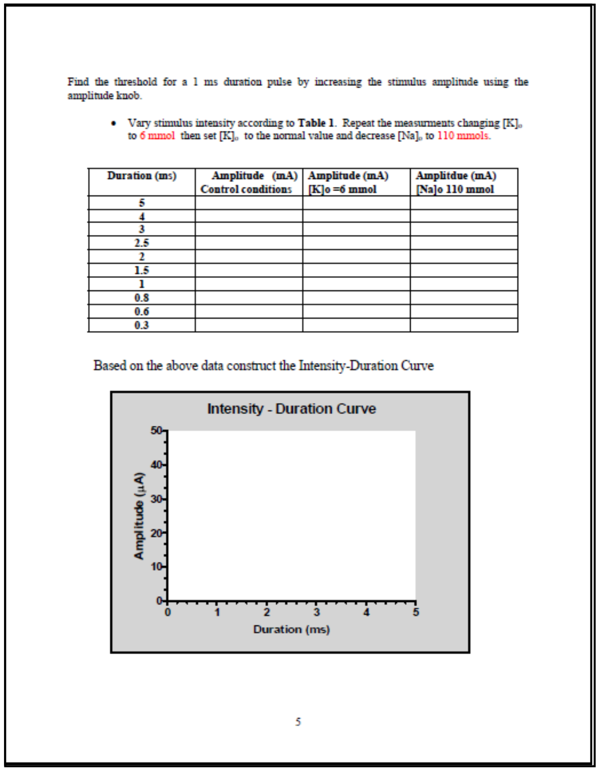
LabAXON

- Equivalent electrical circuit



LabAXON





Find the threshold for a 1 ms duration pulse by increasing the stimulus amplitude using the amplitude knob.

- Vary stimulus intensity according to **Table 1**. Repeat the measurments changing $[K]_o$ to 6 mmol then set $[K]_o$ to the normal value and decrease $[Na]_o$ to 110 mmols.

Duration (ms)	Amplitude (mA) Control conditions	Amplitude (mA) [K]o =6 mmol	Amplitdue (mA) [Na]o 110 mmol
5			
4			
3			
2.5			
2			
1.5			
1			
0.8			
0.6			
0.3			

Based on the above data construct the Intensity-Duration Curve

5

Demo

LabAXON

- Concepts
  - Cronaxia
  - Effects of ionic composition
  - The need of delay between I_K and I_{Na}
  - Temporal sumation

LabHEART

- Cardiac Action Potential
- Ca transient
- Force generation.

LabHEART

- Cardiac Action Potential
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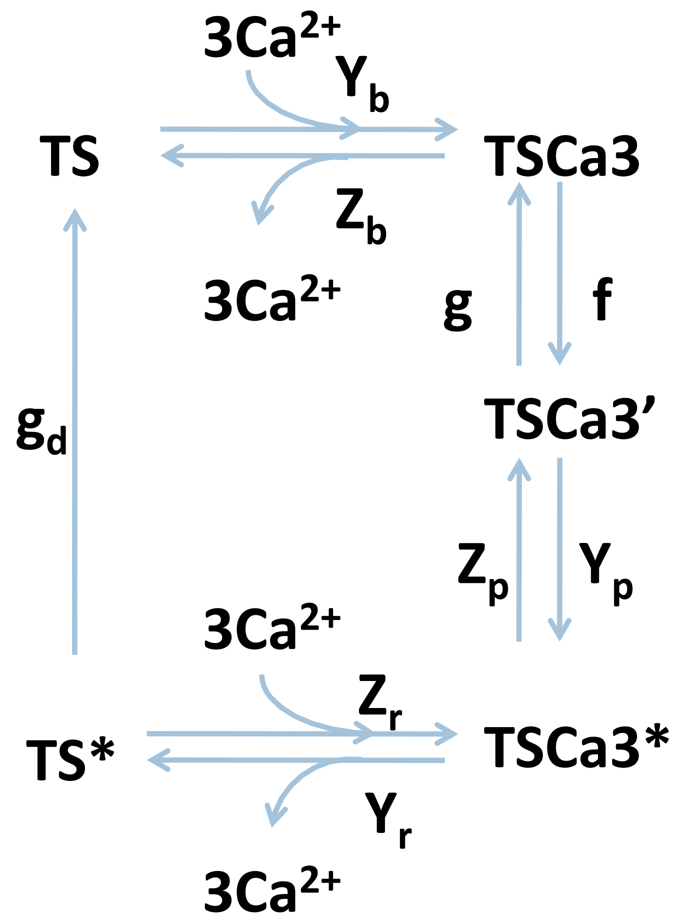
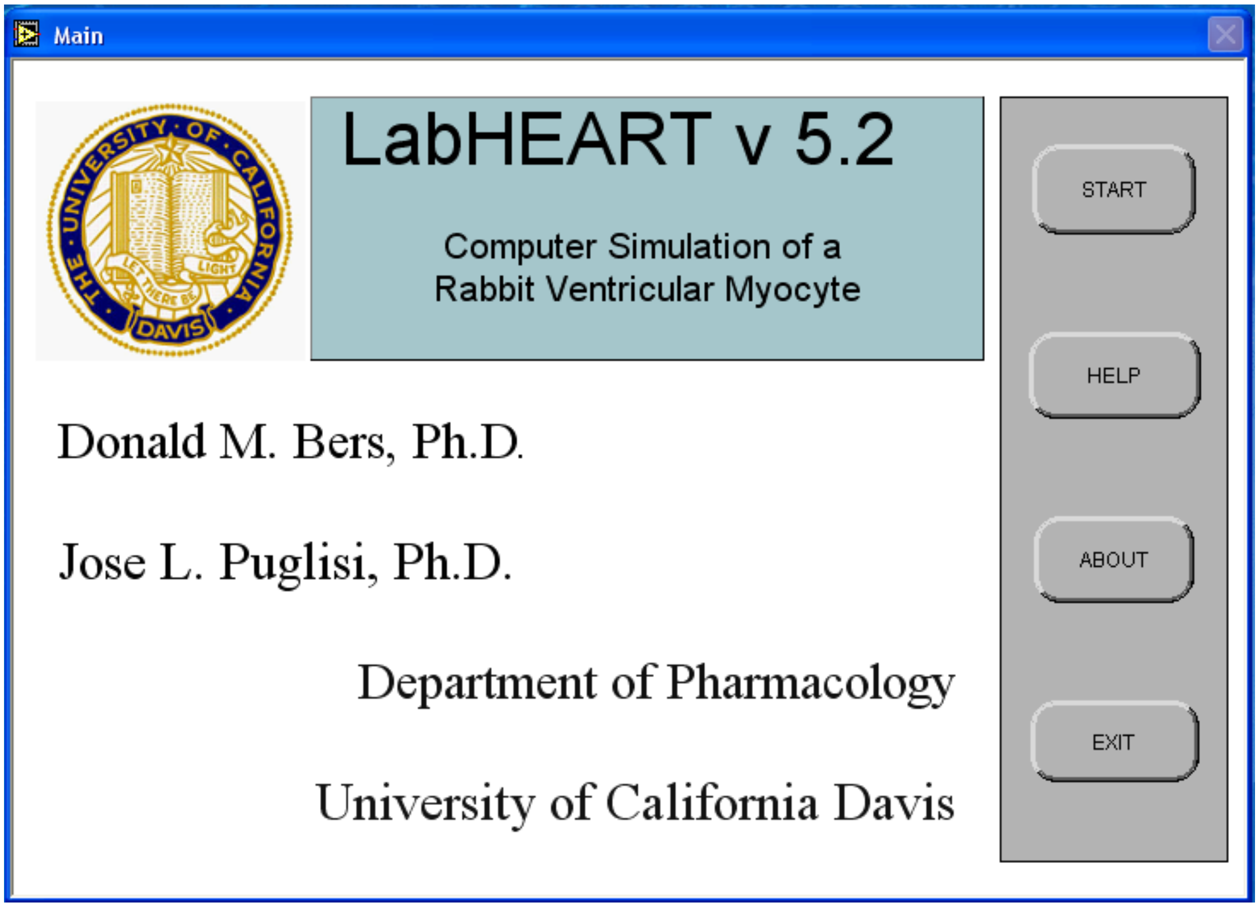


LabHEART


Main
LabHEART v 5.2
Computer Simulation of a
Rabbit Ventricular Myocyte
START
HELP
ABOUT
EXIT
Donald M. Bers, Ph.D.
Jose L. Puglisi, Ph.D.
Department of Pharmacology
University of California Davis

Testing the model

- β-adrenergic Stimulation:

  Does it increase the cross-bridge cycling?

Protein Kinase A does not alter unloaded velocity of sarcomere shortening
In skinned rat cardiac trabeculae

Janssen & De Tombe, 1977. *Am. J. Physiol.*

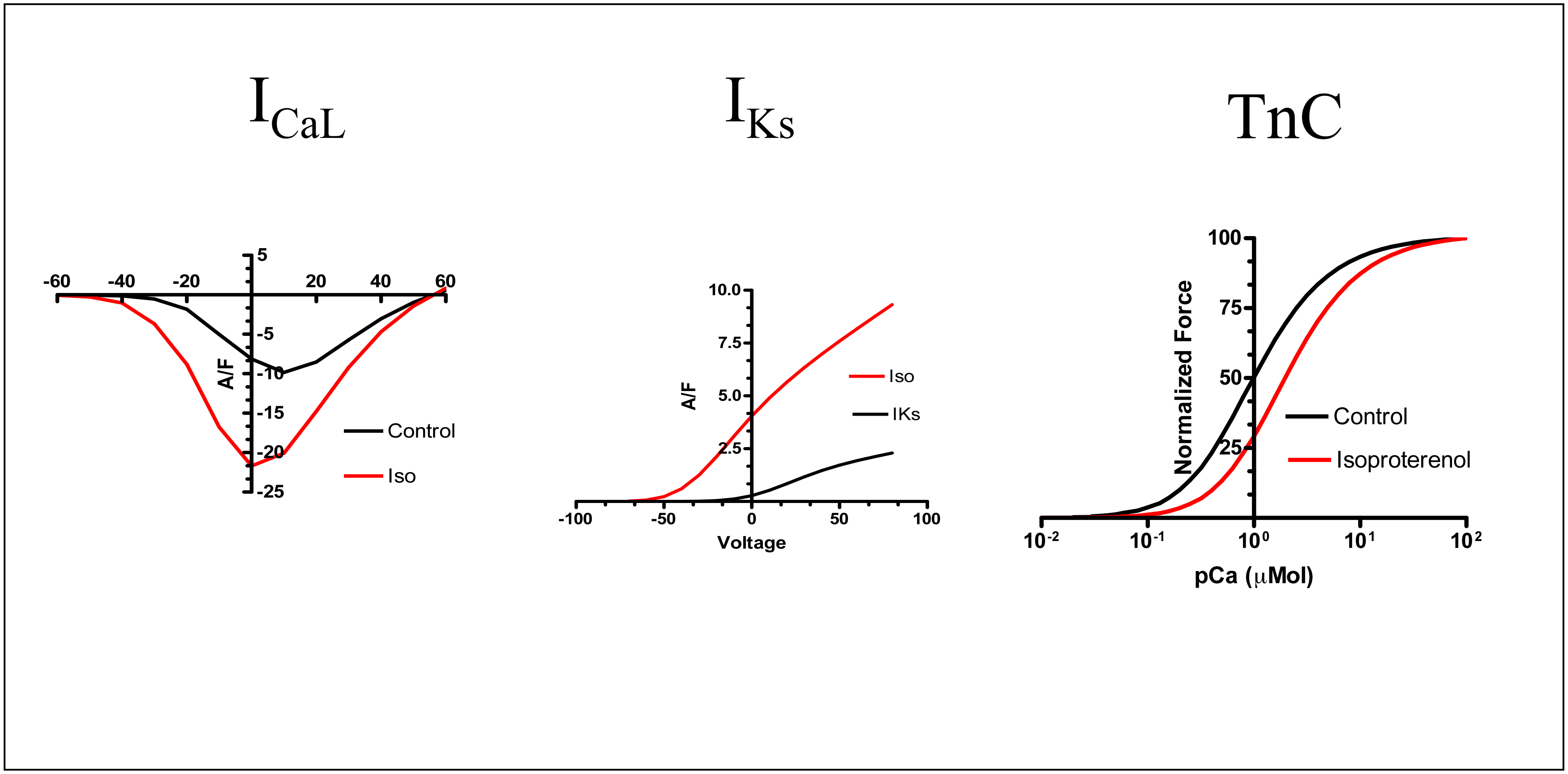
Phosphorilation of troponin I by PKA increases relaxation rate and
Cross-bridge cycling kinetics in mouse ventricular muscle.

Kentish et al. 2001. *Circulation Research*

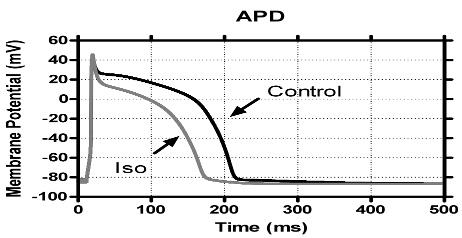
Effects of Isoproterenol

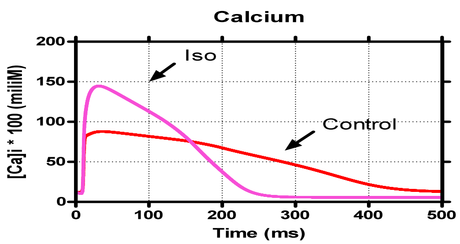
- L-type Ca Channel ↑
- I_{Ks} channel ↑
- SR Ca pump ↑
- Myofilament Ca sensitivity ↓

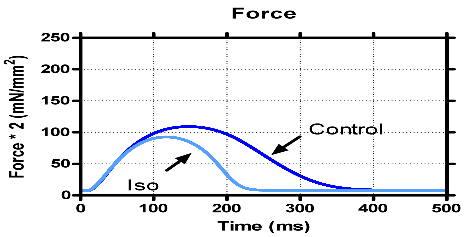
Effects of Isoproterenol

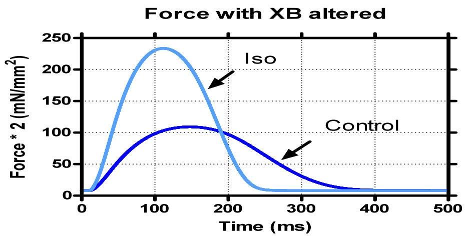


Force with/out altering XB cycling









Demo

LabHEART - Discussion

- Our simulations agree with the hypothesis that the cross bridge cycling is increased by isoproterenol

  "..the amount of calcium entering overcomes the decrease in myofilament Ca-sensitivity"

- Force-Frequency Relationship have to be revisited.

  (Frequency is NOT an independent variable)

MarkoLAB

- The Hodgkin & Huxley representation has slowly been replaced by state diagrams
- These diagrams are not restricted to the idea of independent gates (activation and inactivation)
- Those states can be closely related to the underlying channel structure and conformational changes

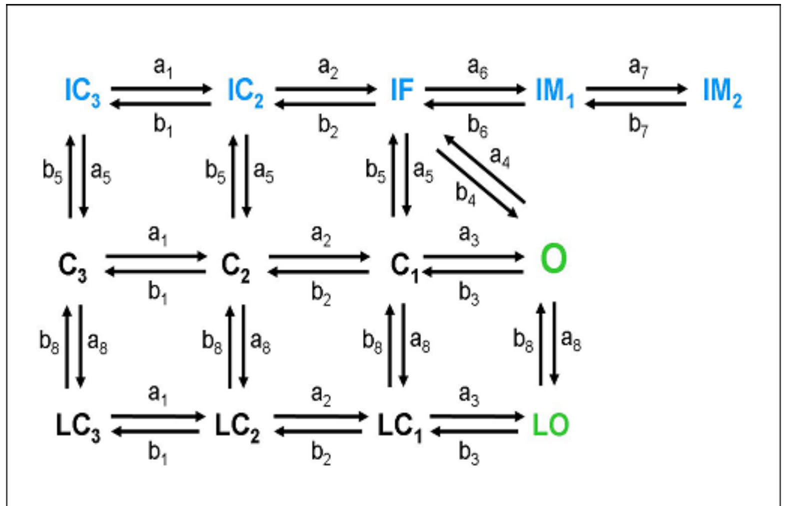
MarkoLAB

$$I_{Na} = G_{Na} * m^3 * h * j * (V - V_{Na})$$

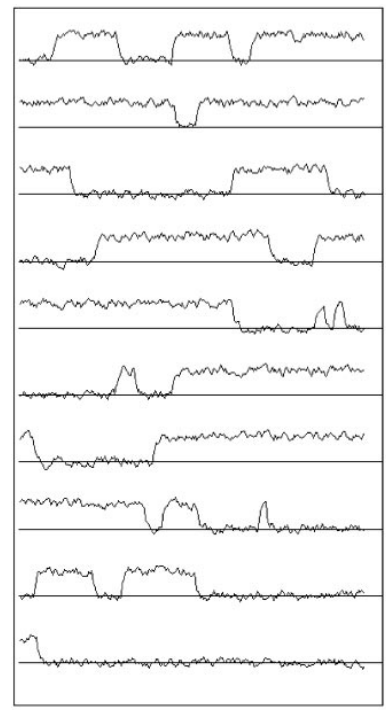
$$m, h, j = f(V, t)$$

$$\frac{dm}{dt} = \alpha_m * (1 - m) - \beta_m * m$$

$$\alpha_m = 0.1 \frac{25 - V}{\exp\left(\frac{25 - V}{10}\right) - 1}$$

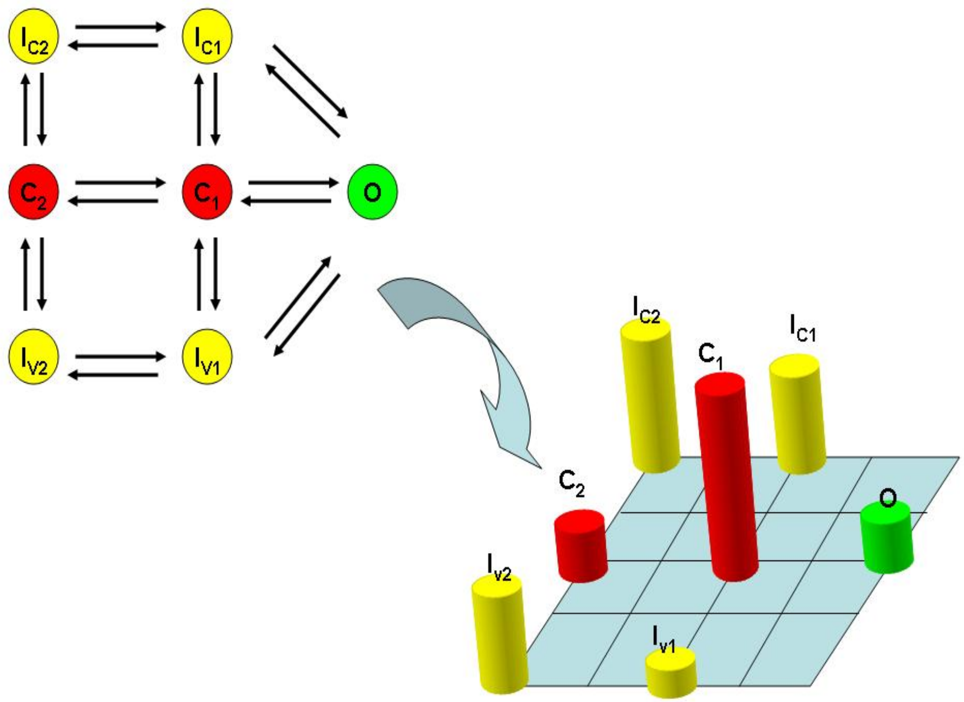


Clancy Model



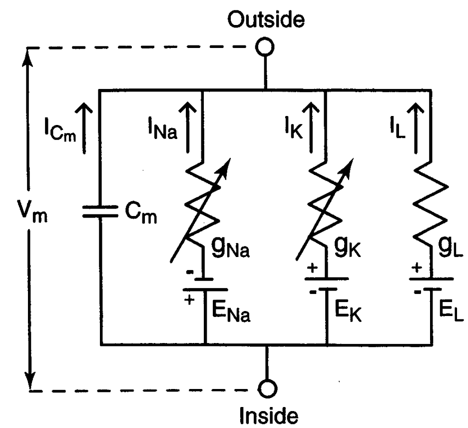
45 mV

MarkoLAB

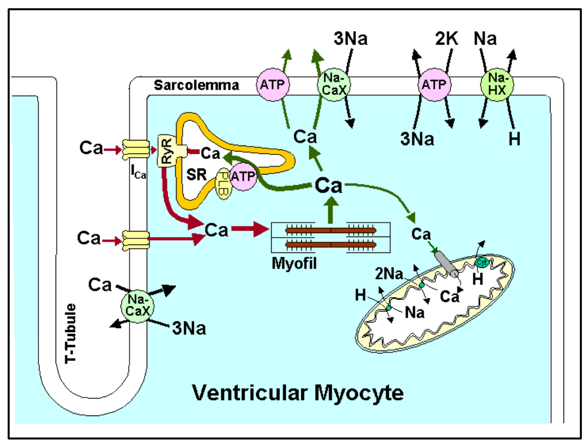


Demo

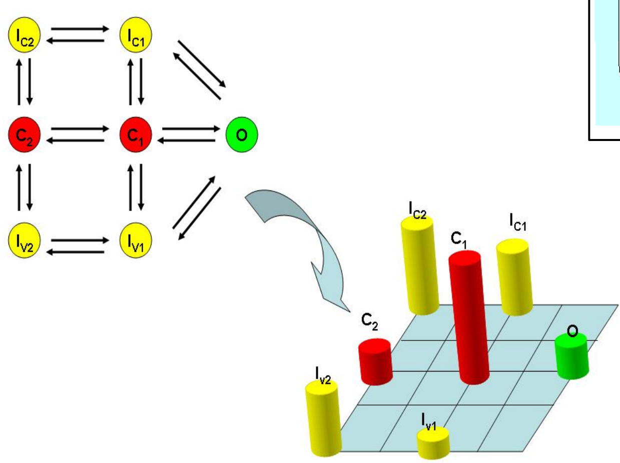
Conclusions



Classical Hodgkin & Huxley



Transporters and Pumps



Markovian Models

Conclusions

- Mathematical models are tools to study Biology
- But also tools to teach Biology
- They are freely available at www.labheart.org