Interfacing LabHEART with CellML

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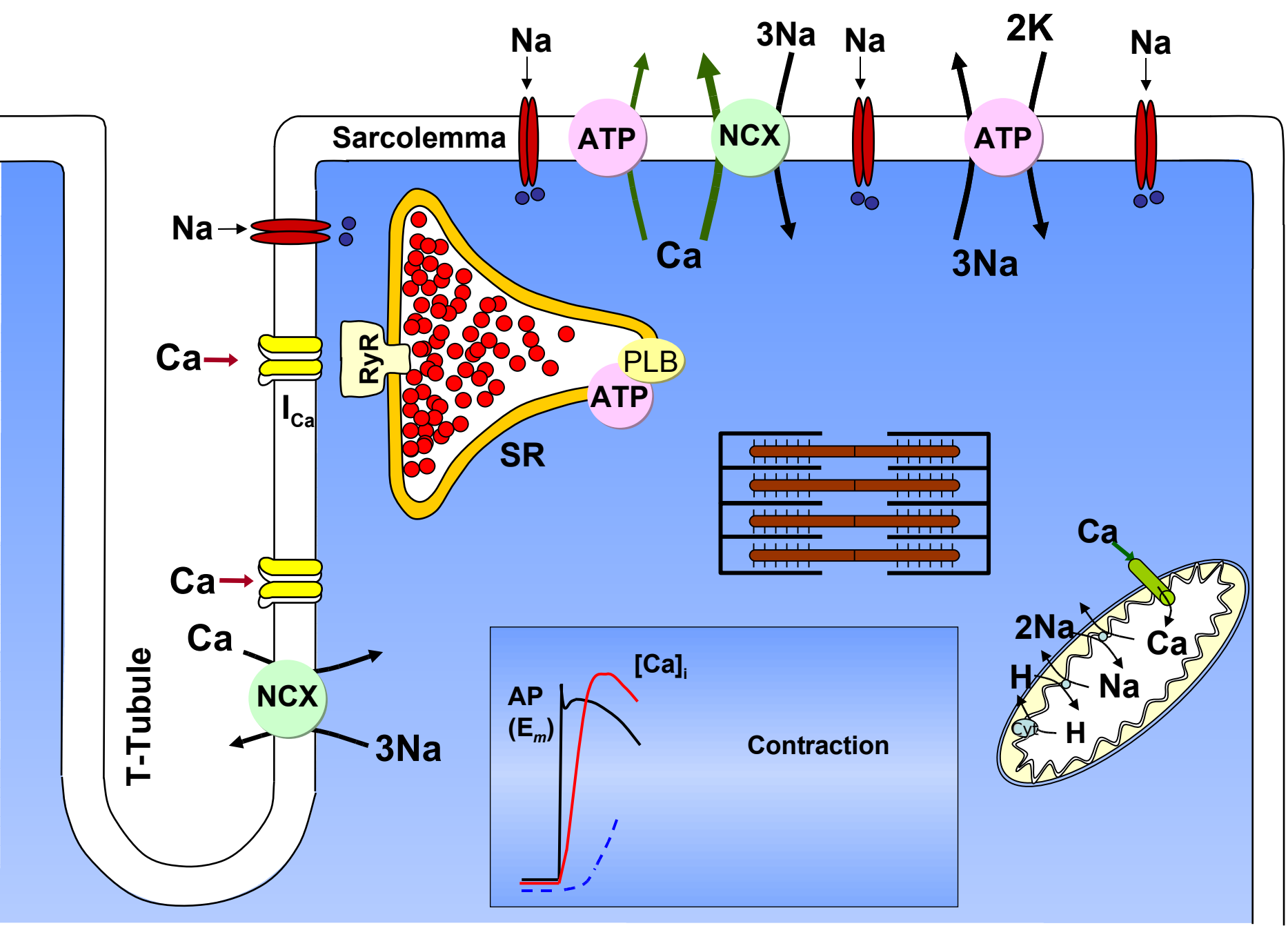
Introduction

- Biologists are the final users of our models
- They should be able to run and modify the model

Excitation-Contraction Coupling

- “The succession of events that take place since the moment the cardiac cell is excited until a contraction is generated”

Bers, 2001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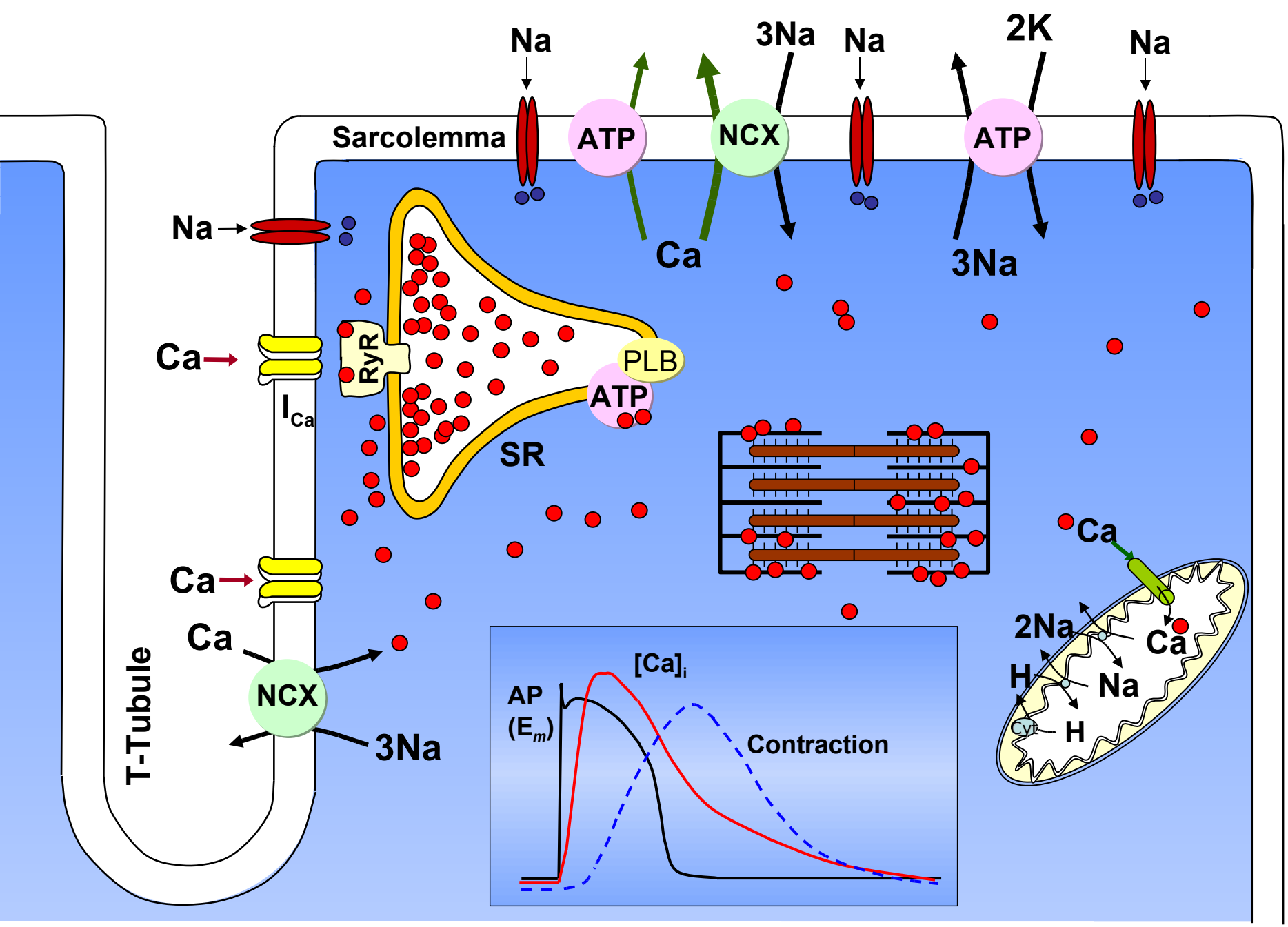
2K
Na
Sarcolemma
ATP
NCX
ATP
Ca
3Na
Na
Ca
RyR
PLB
ATP
SR
I_{Ca}
Ca
Ca
T-Tubule
NCX
3Na
[Ca]$_i$
AP
(E_m)
Contraction
Ca
2Na
Ca
H
Na
Cyt
H

by D.M. Bers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Contraction

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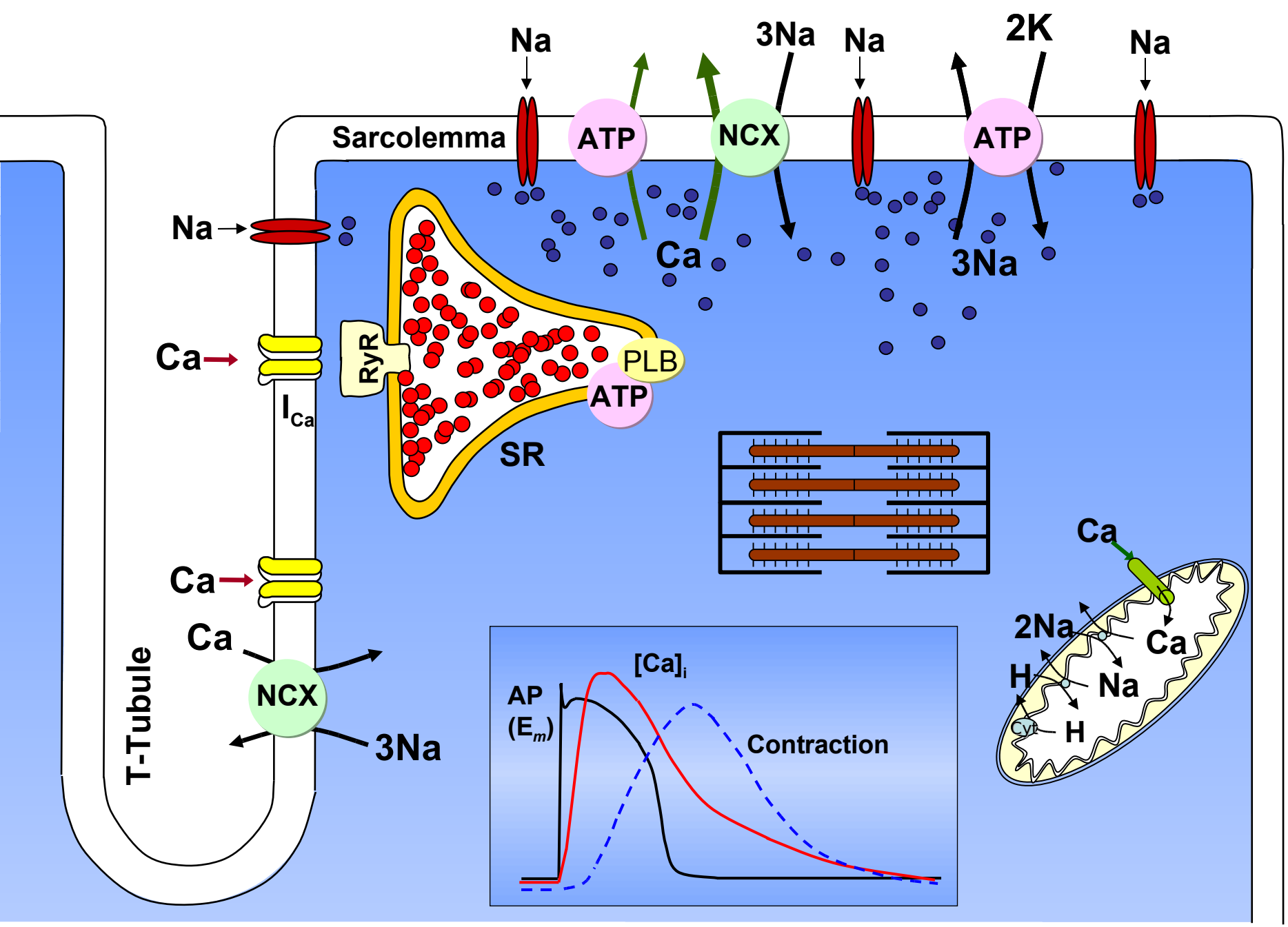
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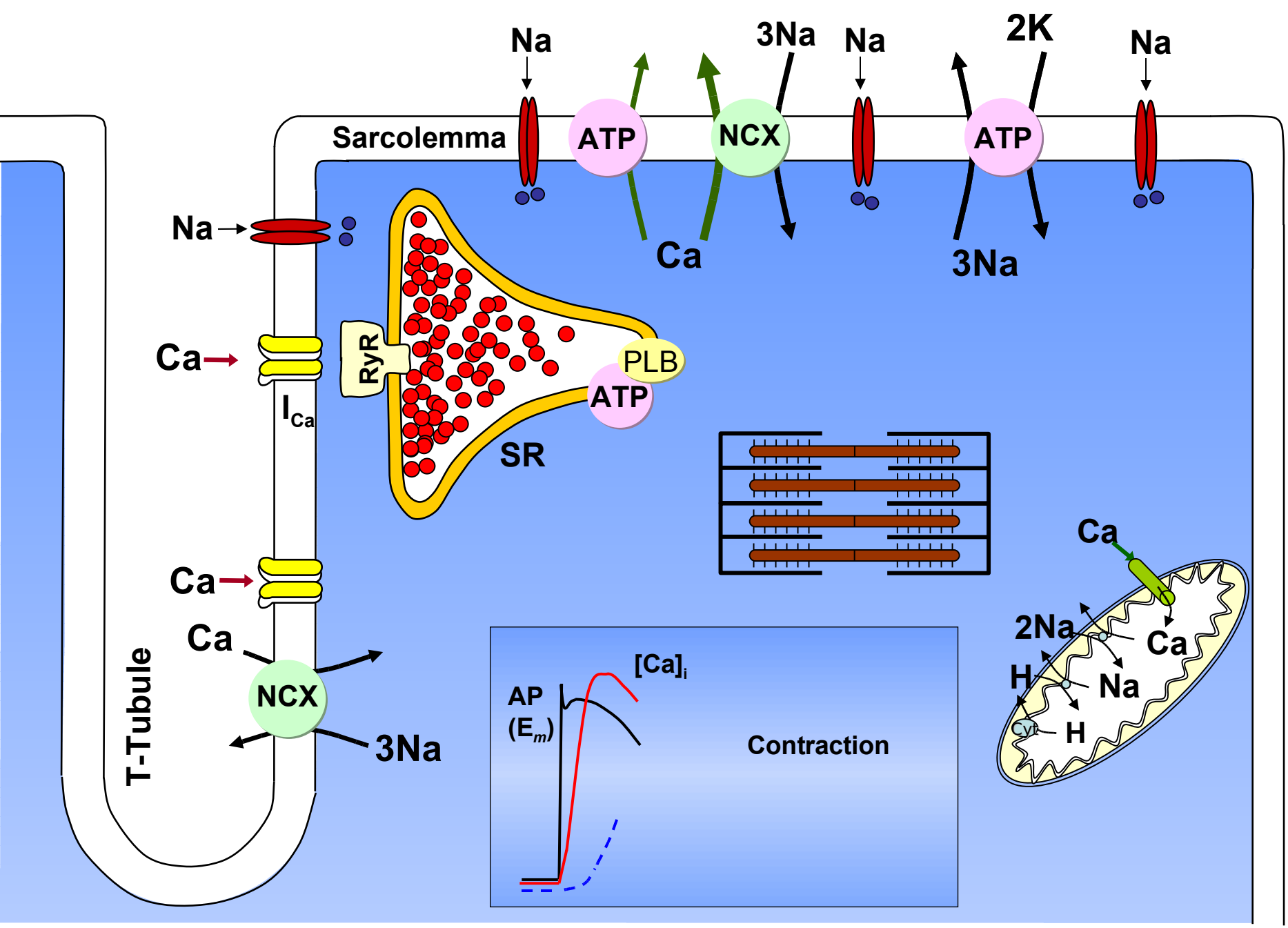
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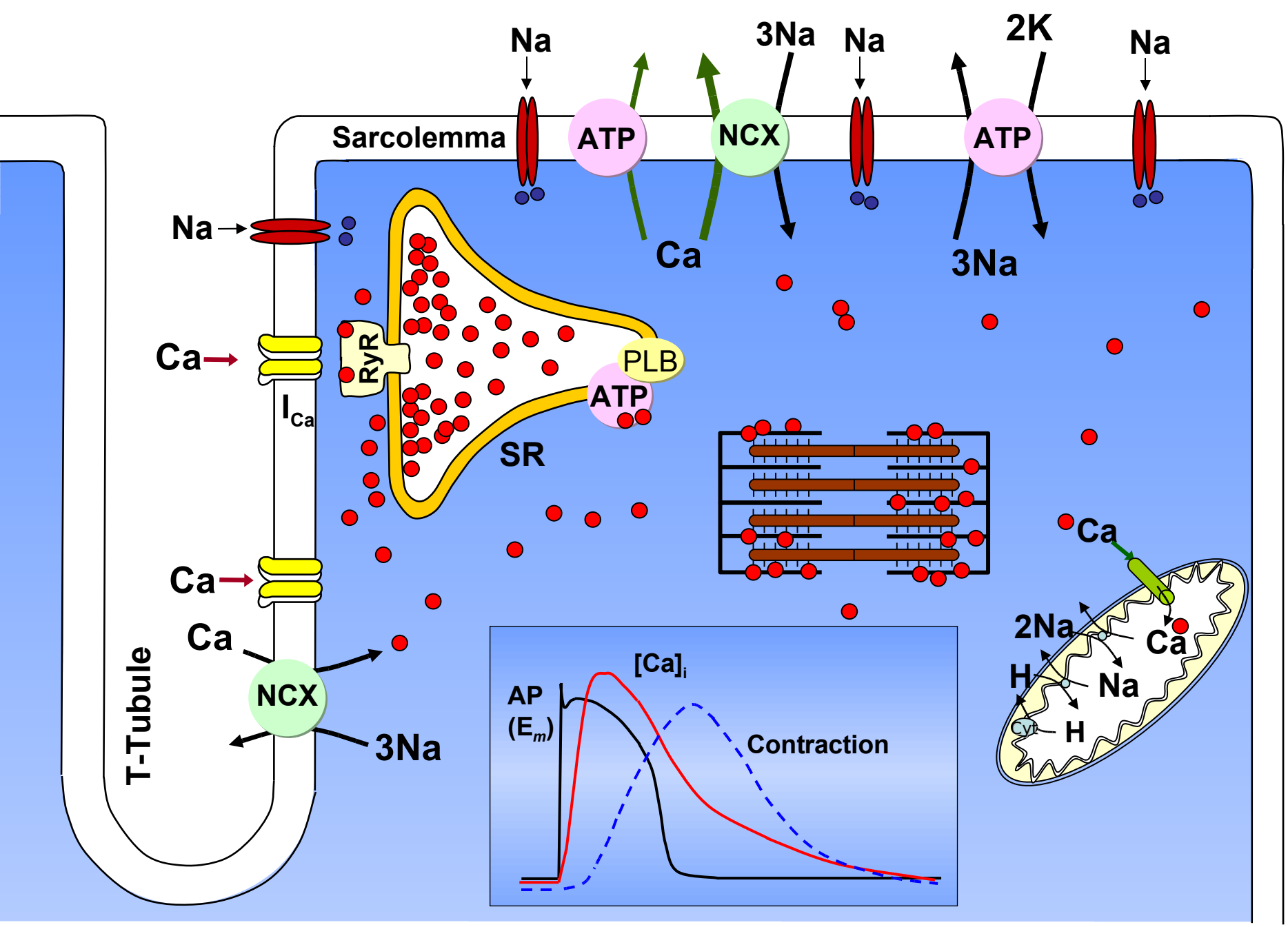
by D.M. Bers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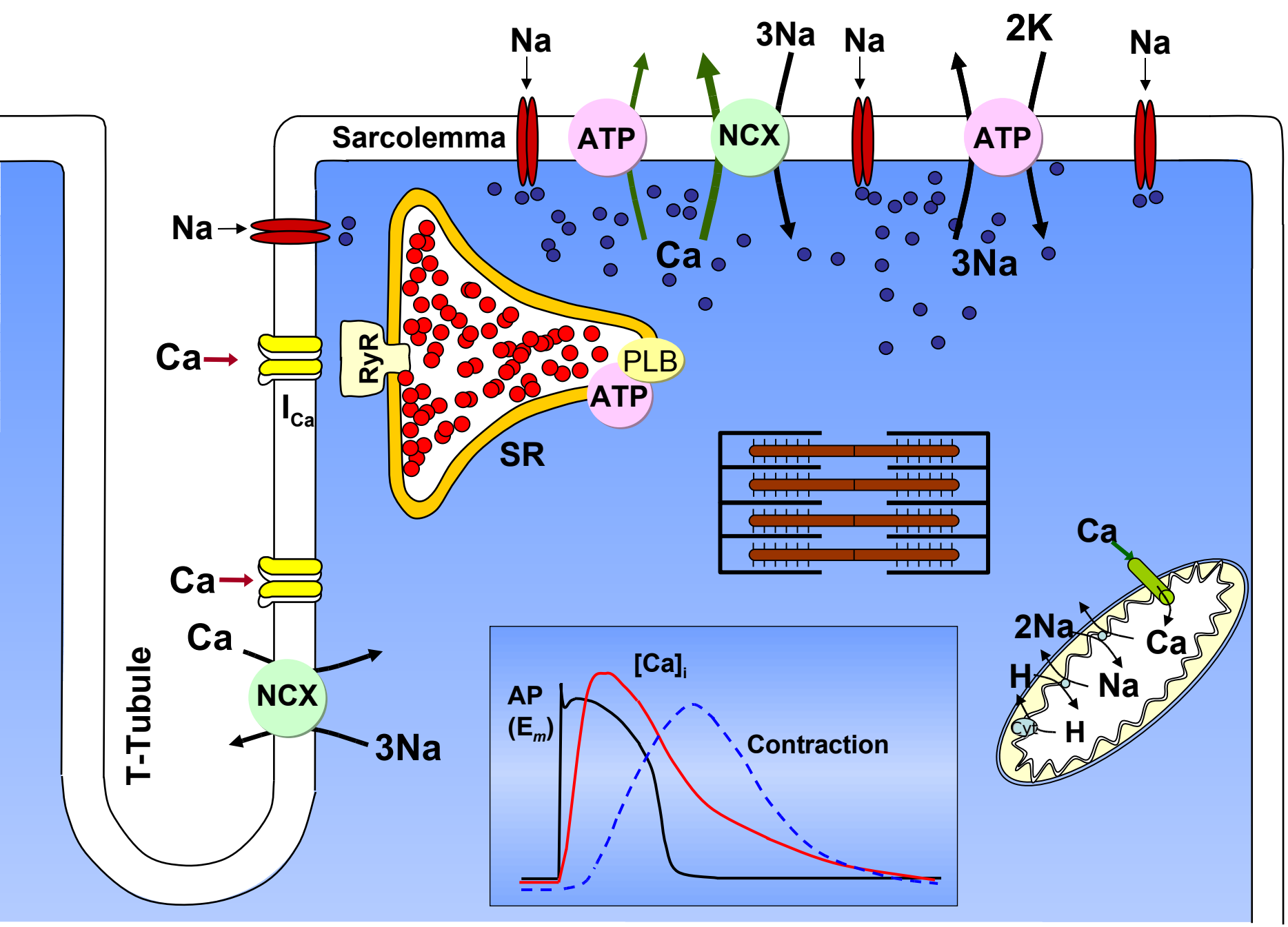
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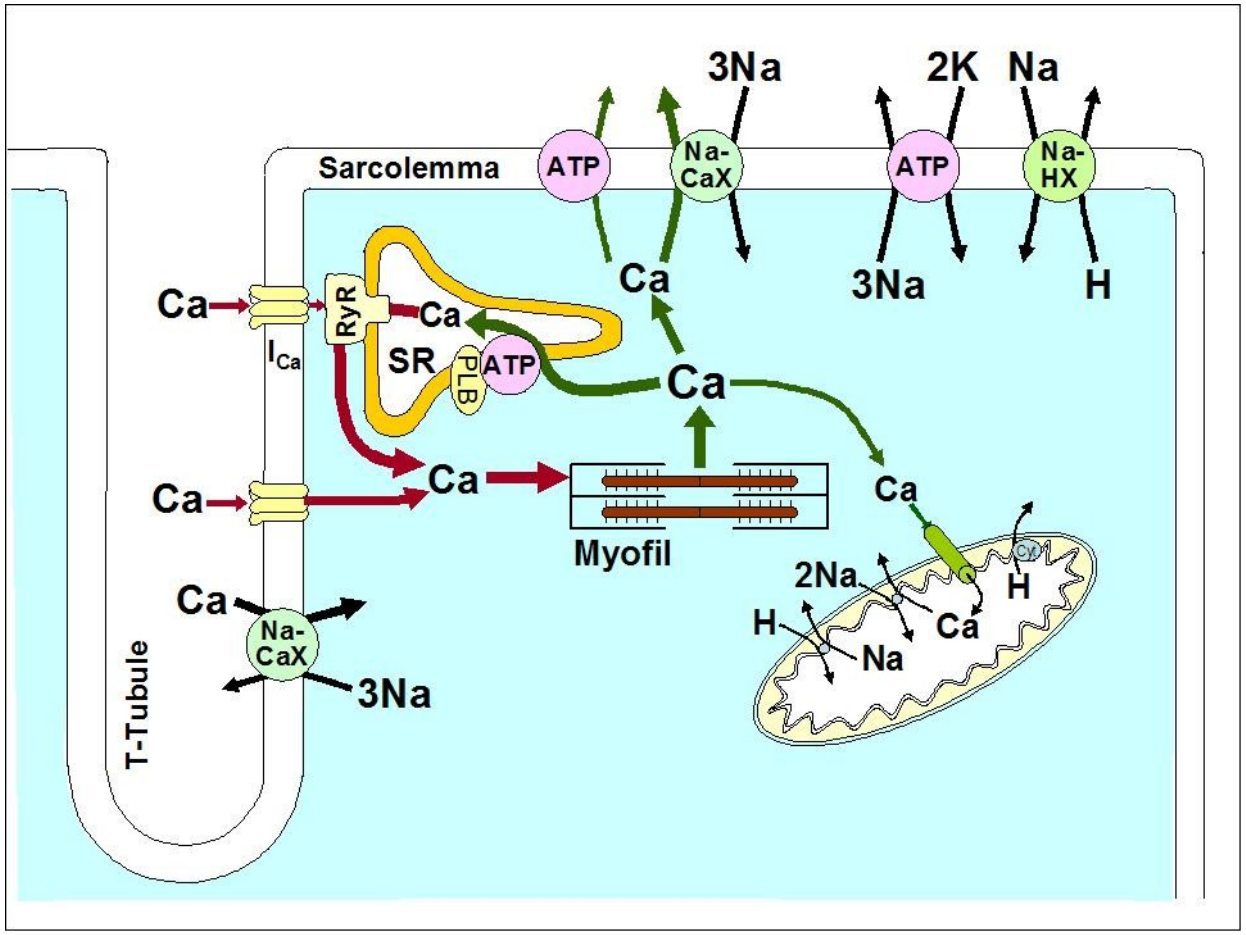
(E_m)
$[Ca]_i$
Contraction

by D.M. Bers

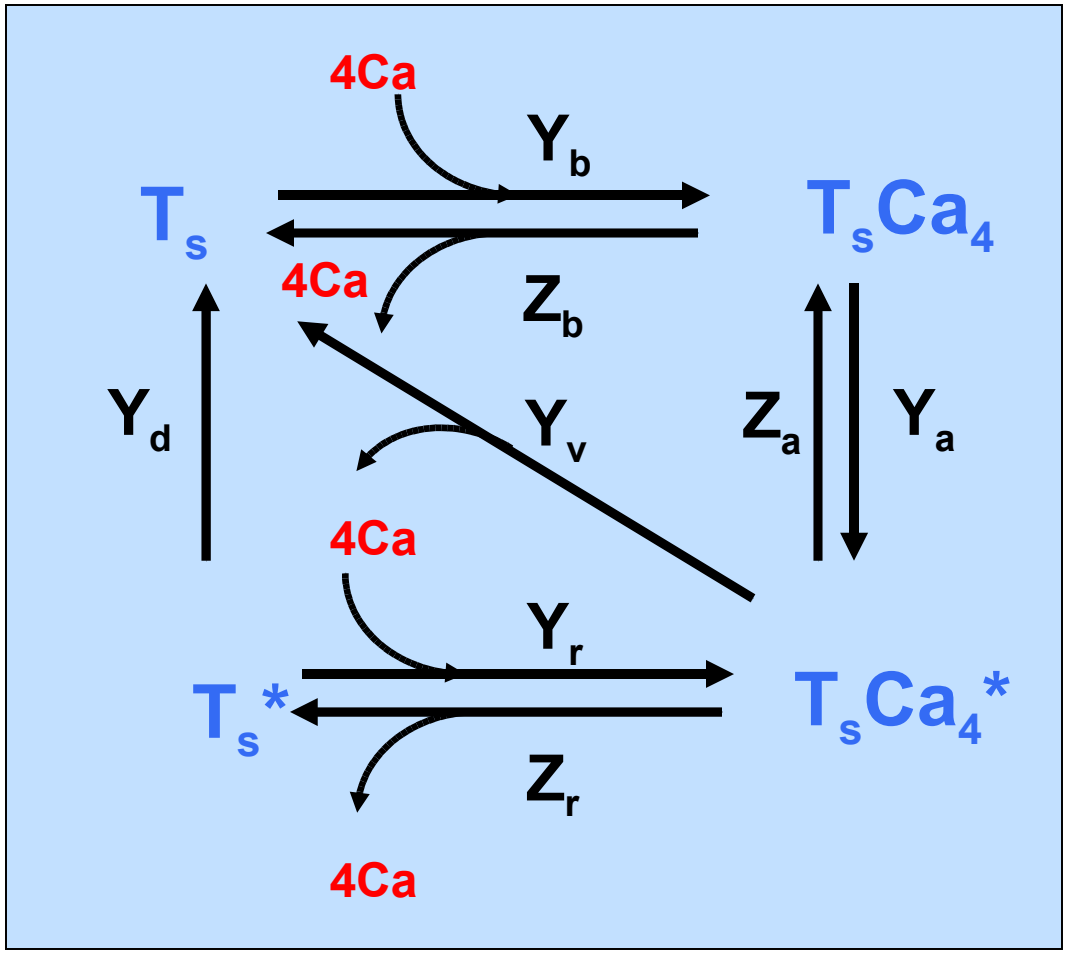
Modeling Excitation-Contraction Coupling

- We need a model that links the three main players:
  - Action Potential
  - Force/Shortening
  - Calcium Transient

LabHEART 4.9.6



Negroni's Formulation



Demo

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.*

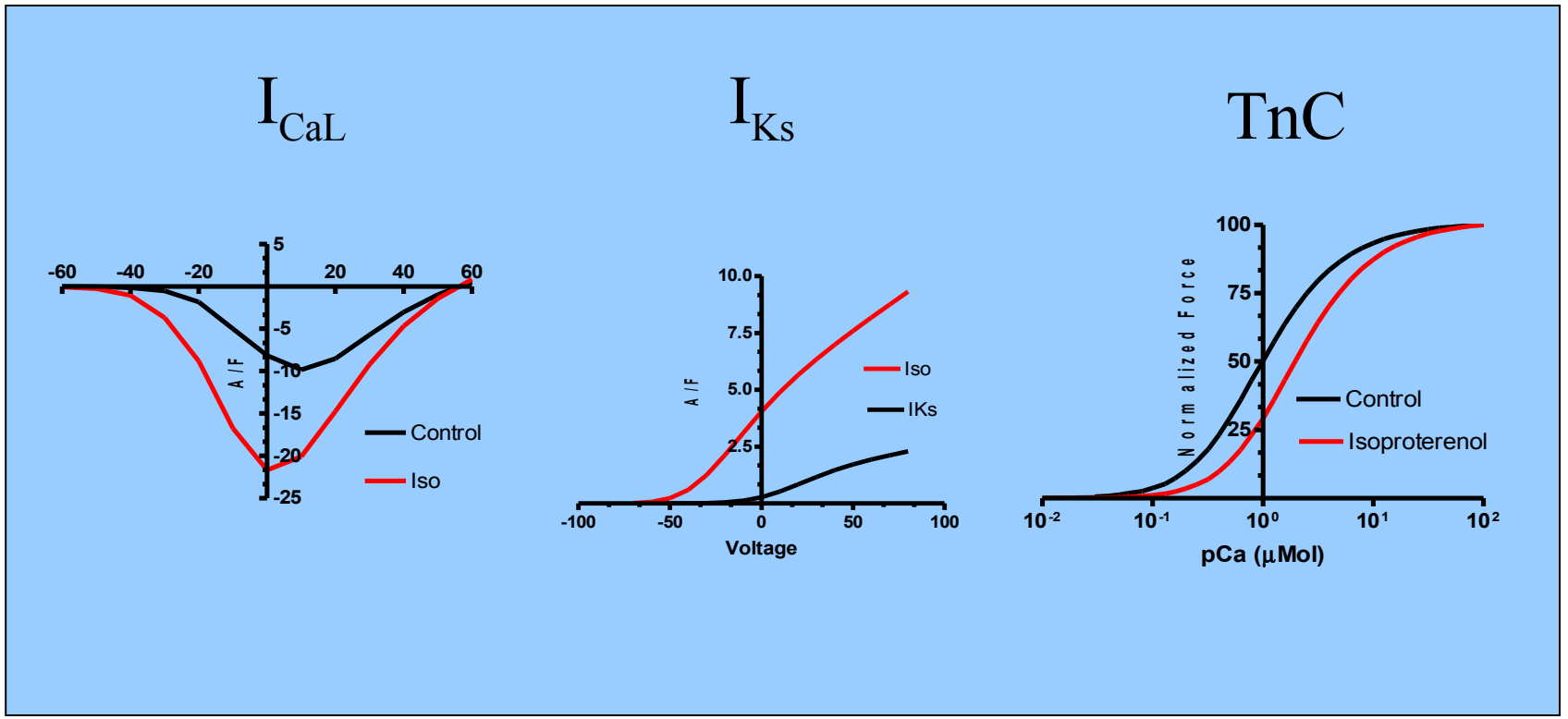
Phosphorilation of troponin I by PKA increases relaxation rate and
Cross-bridge cycling kinetics in mouse ventricular muscle.

Kentish et al. 2001. *Circulation Research*

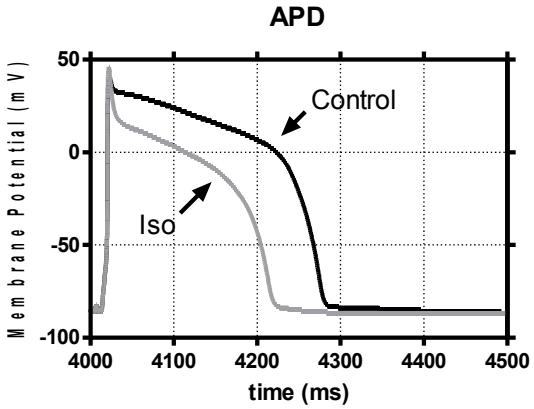
Effects of Isoproterenol

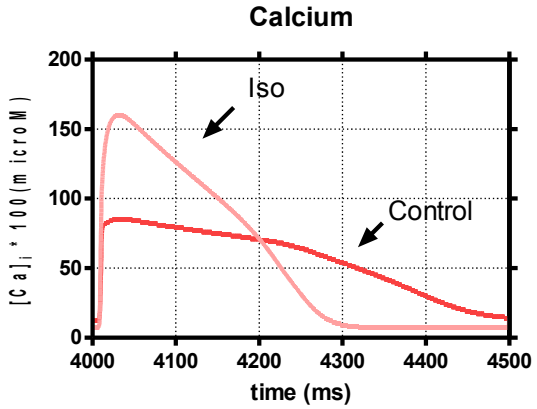
- L-type Ca Channel ↑
- I_{Ks} channel ↑
- SR Ca pump ↑
- Myofilament Ca sensitivity ↓

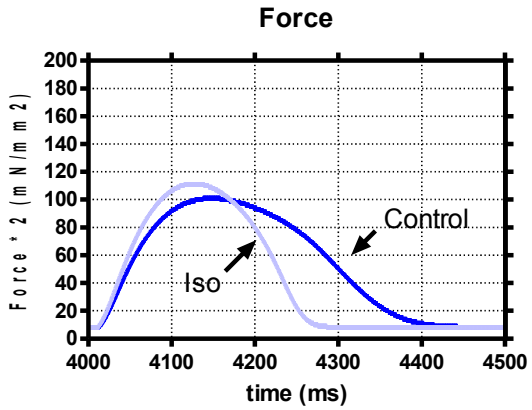
Effects of Isoproterenol

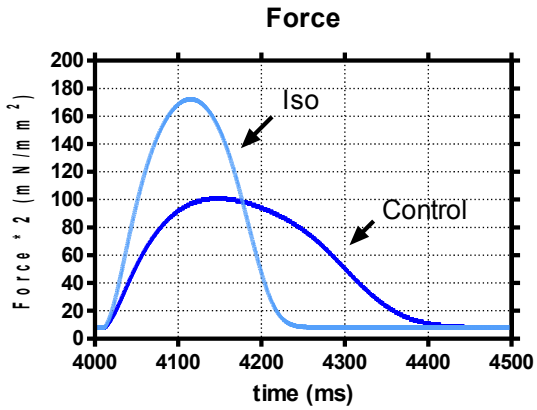


Force simulation with/out altering Xb cycling





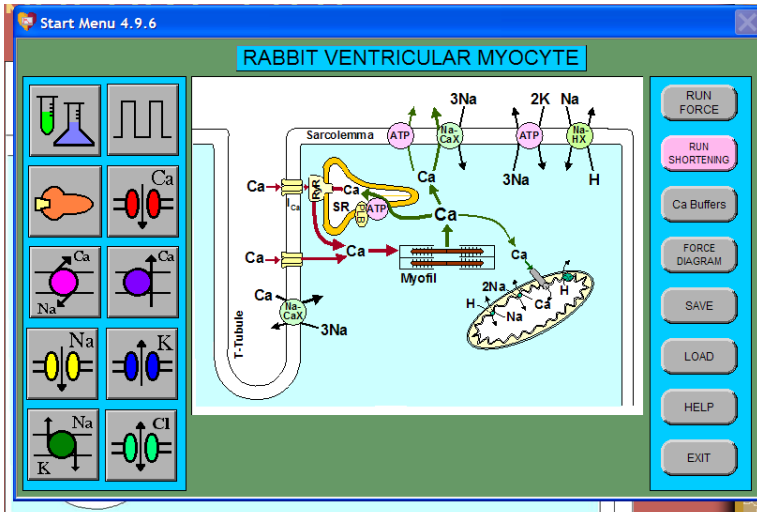


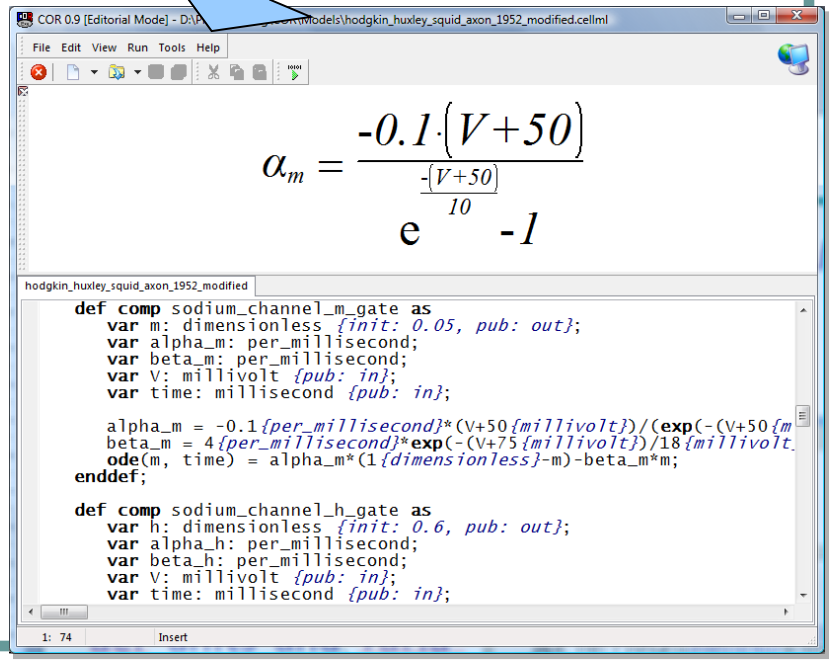


Discussion

- Our simulations agree with the hypothesis that the cross bridge cycling is increased by isoproterenol
- Force-Frequency Relationship have to be revisited.

Future work


Start Menu 4.9.6
RABBIT VENTRICULAR MYOCYTE
RUN FORCE
RUN SHORTENING
Ca Buffers
FORCE DIAGRAM
SAVE
LOAD
HELP
EXIT
Sarcolemma
T-Tubule
Myofil
SR
RyR
ATP
3Na
2K
Na
H
Ca
2Na


COR 0.9 [Editorial Mode] - D:\P...\Models\hodgkin_huxley_squid_axon_1952_modified.cellml
File Edit View Run Tools Help
$\alpha_m = \frac{-0.1\cdot(V+50)}{e^{\frac{-(V+50)}{10}} - 1}$
hodgkin_huxley_squid_axon_1952_modified
def comp sodium_channel_m_gate as
var m: dimensionless {init: 0.05, pub: out};
var alpha_m: per_millisecond;
var beta_m: per_millisecond;
var V: millivolt {pub: in};
var time: millisecond {pub: in};
alpha_m = -0.1{per_millisecond}*(V+50{millivolt})/(exp(-(V+50{m
beta_m = 4{per_millisecond}*exp(-(V+75{millivolt})/18{millivolt
ode(m, time) = alpha_m*(1{dimensionless}-m)-beta_m*m;
enddef;
def comp sodium_channel_h_gate as
var h: dimensionless {init: 0.6, pub: out};
var alpha_h: per_millisecond;
var beta_h: per_millisecond;
var V: millivolt {pub: in};
var time: millisecond {pub: in};
1: 74
Insert

Thanks for your attention