Modeling Ca cycling in cardiac cells: from ion channels to whole cell dynamics

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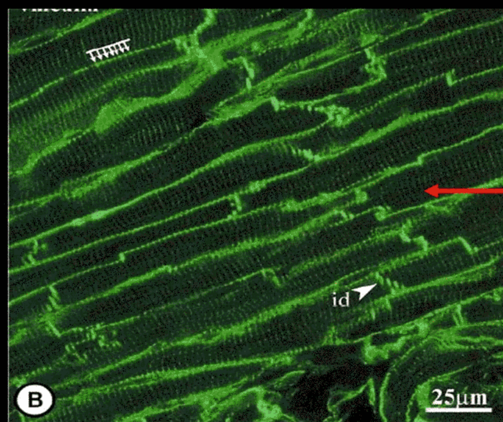
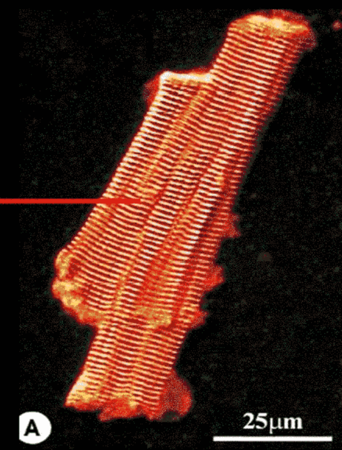
Outline

- Overview of some important features of Ca cycling in cardiac cells.
- Developing a phenomenological model of Ca cycling
- Some features of the nonlinear dynamics of paced cells.
- Relating whole cell properties to Ca signalling at the ion channel level.
- Summary

Cardiac tissue and cells



Cardiac tissue



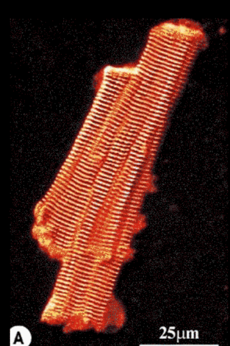
(Guinea-pig ventricular cell)

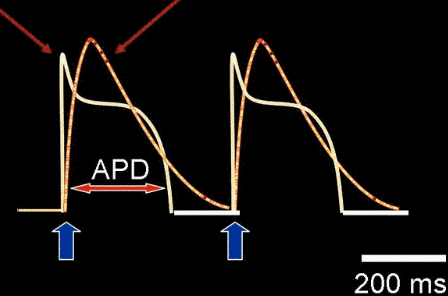
Function

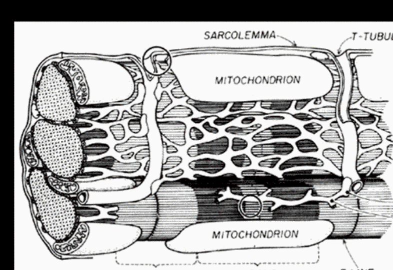
- Conduct electrical waves
- Contract in response to an electrical stimulus

Basic Cell physiology

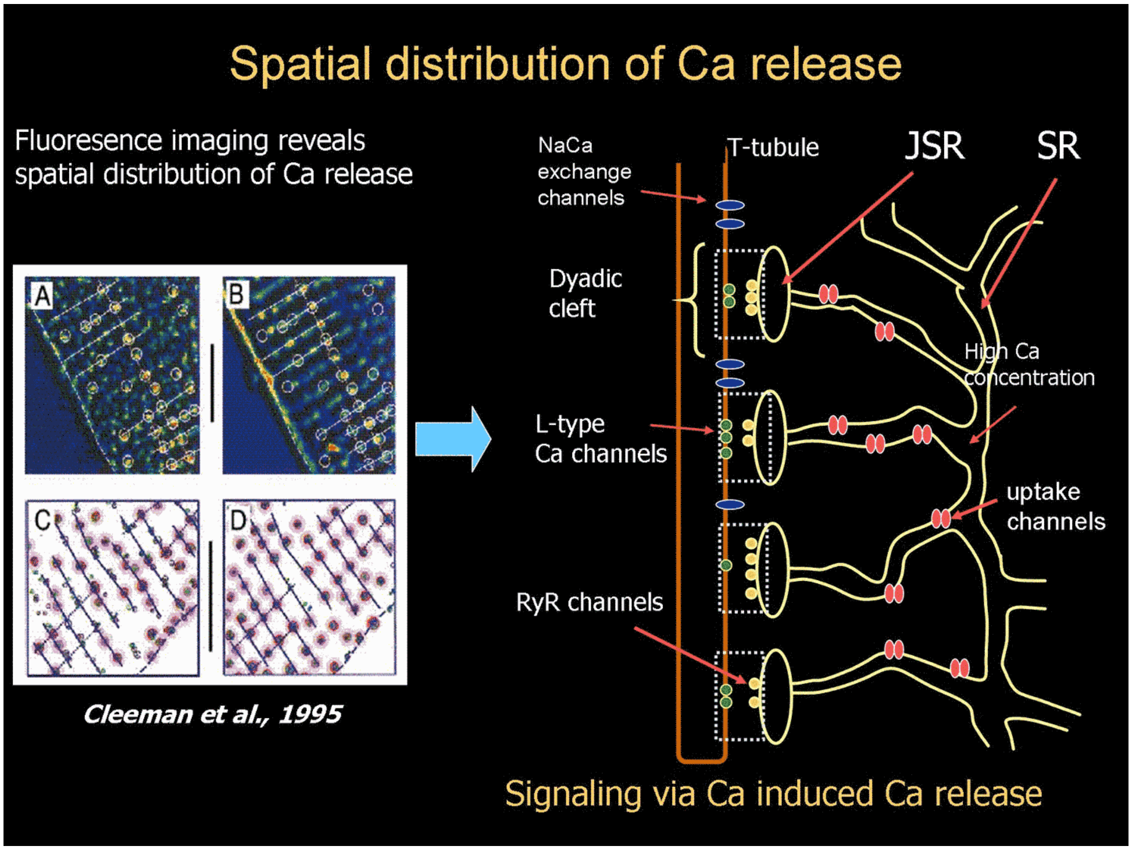
Action potential regulates intracellular calcium

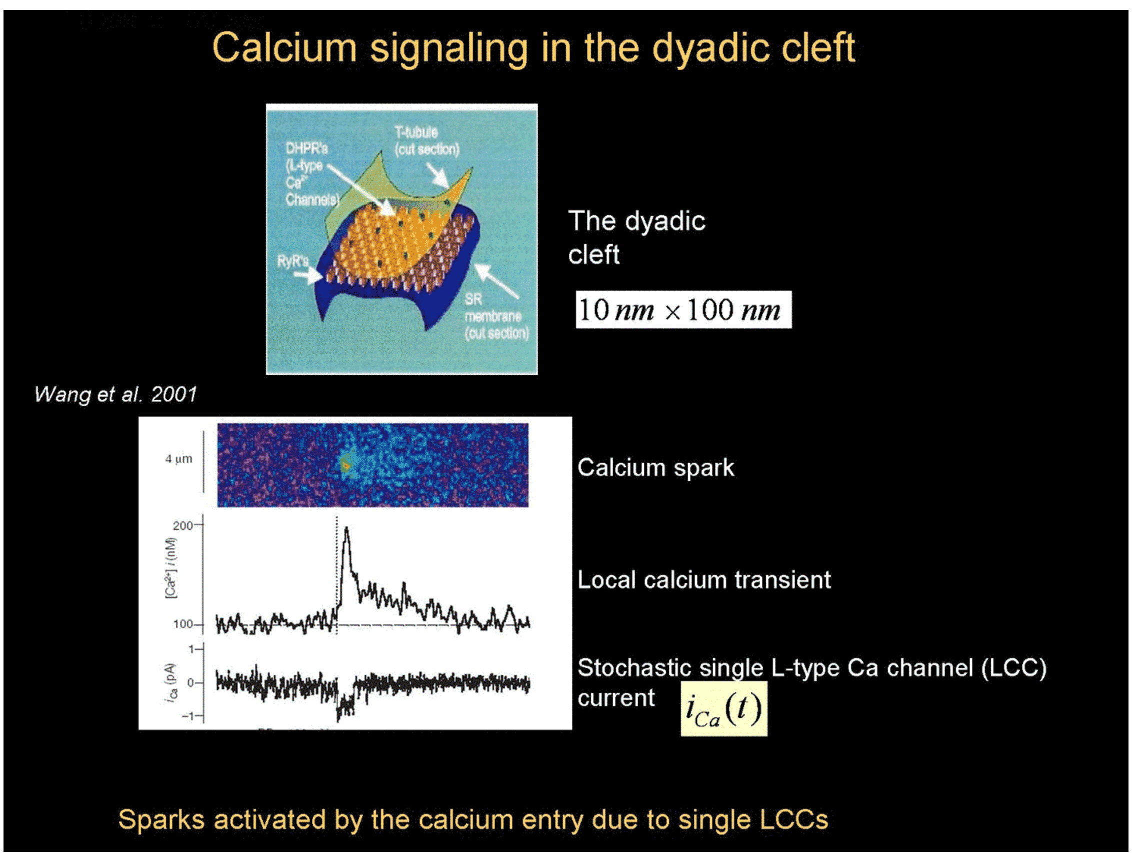


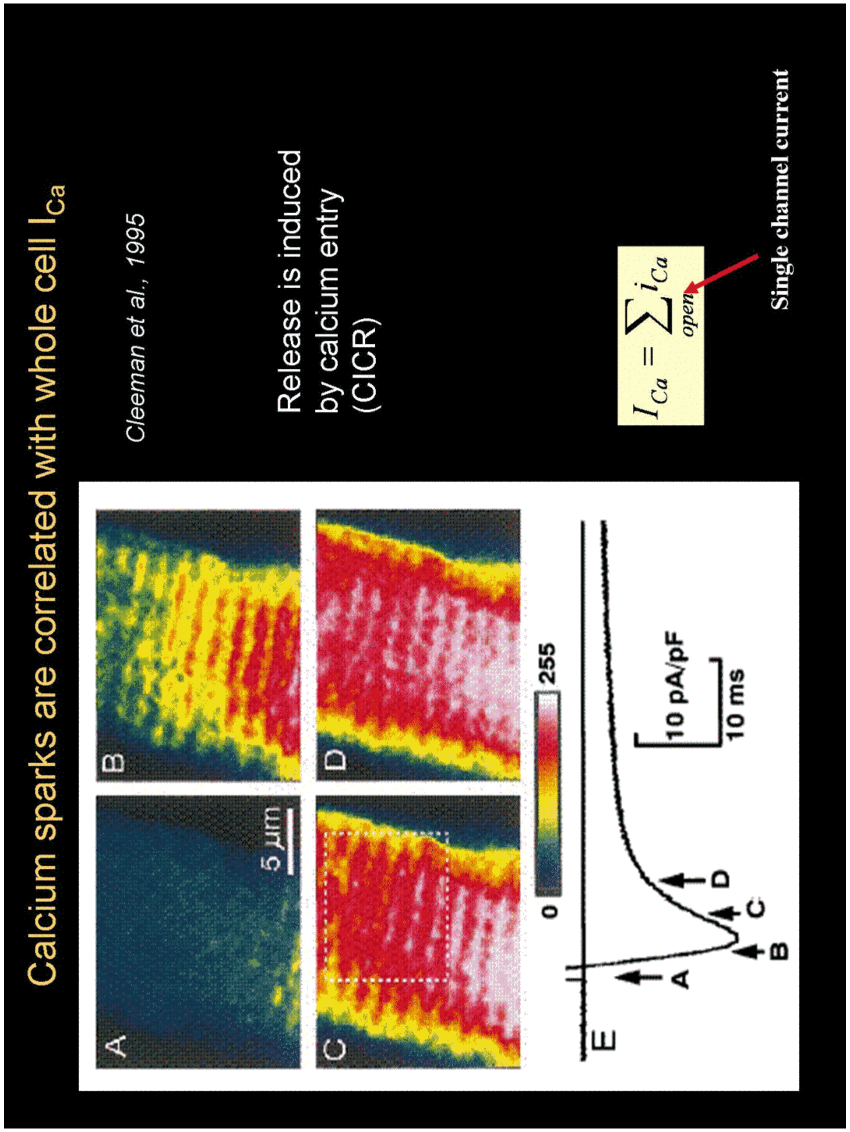


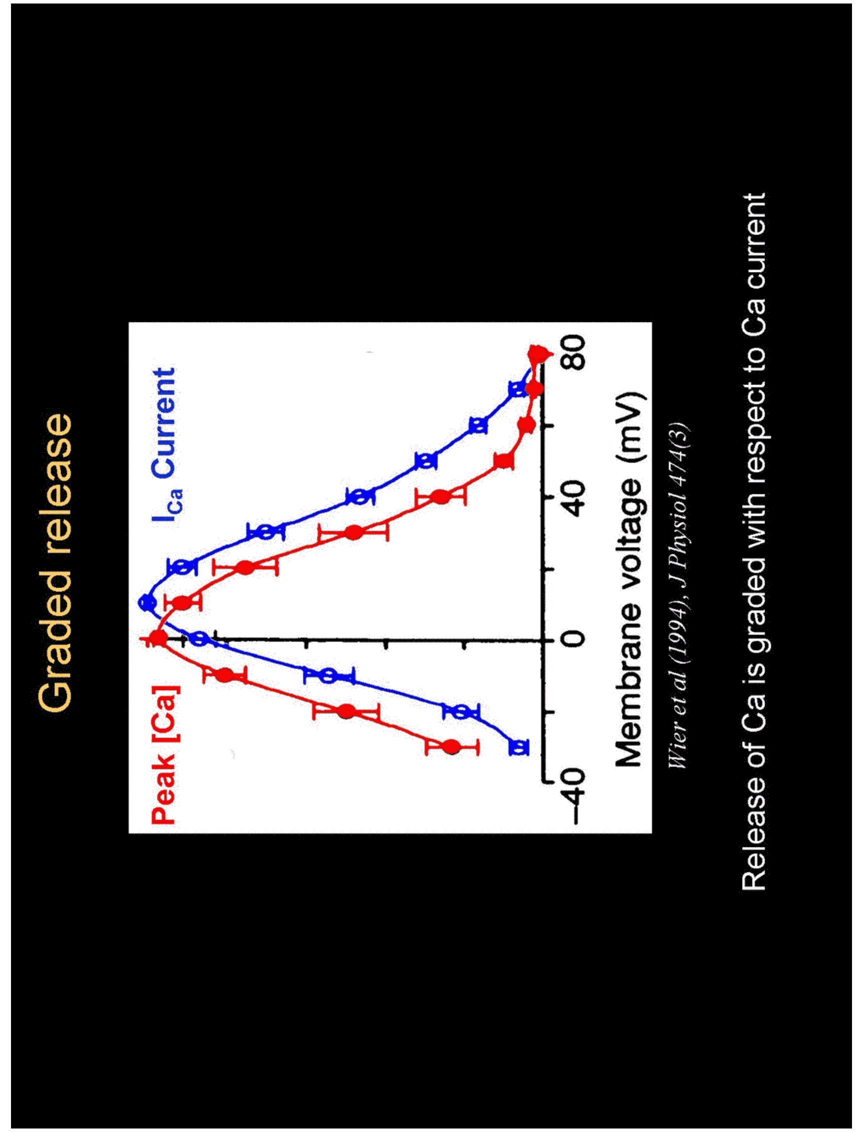


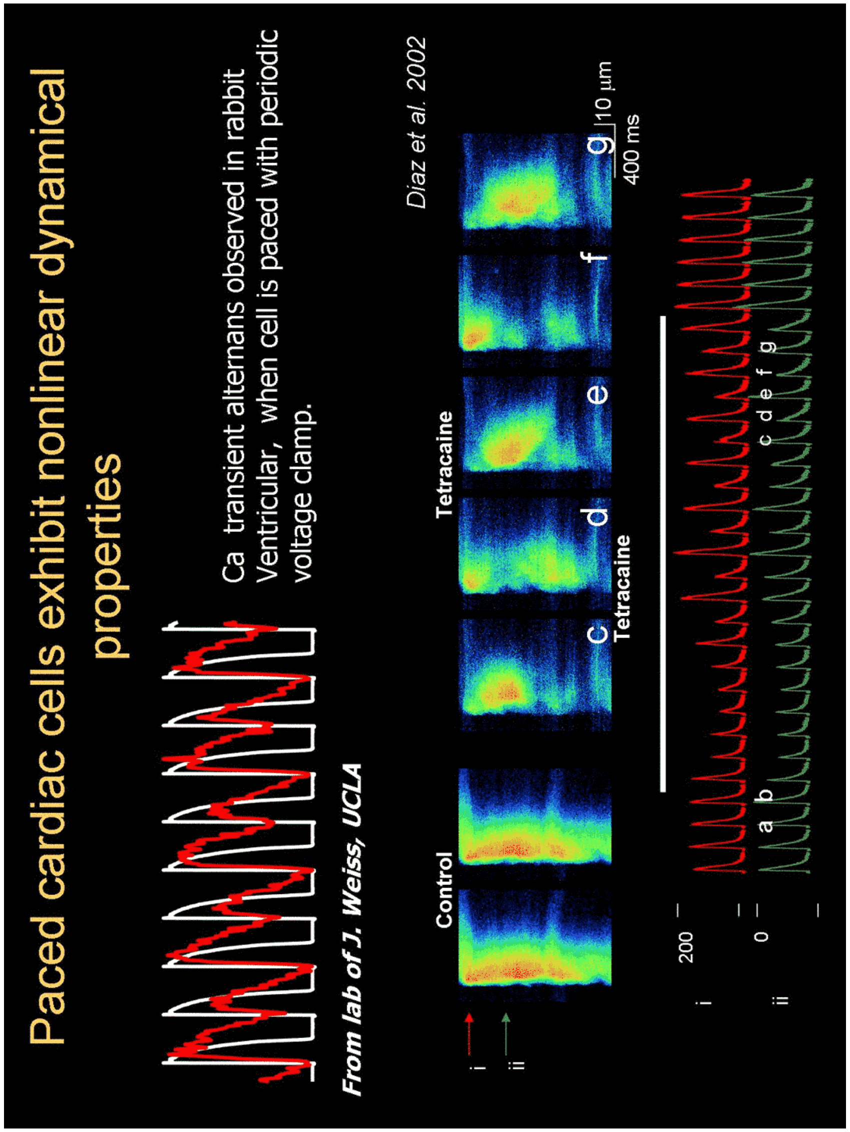
Calcium → Contraction

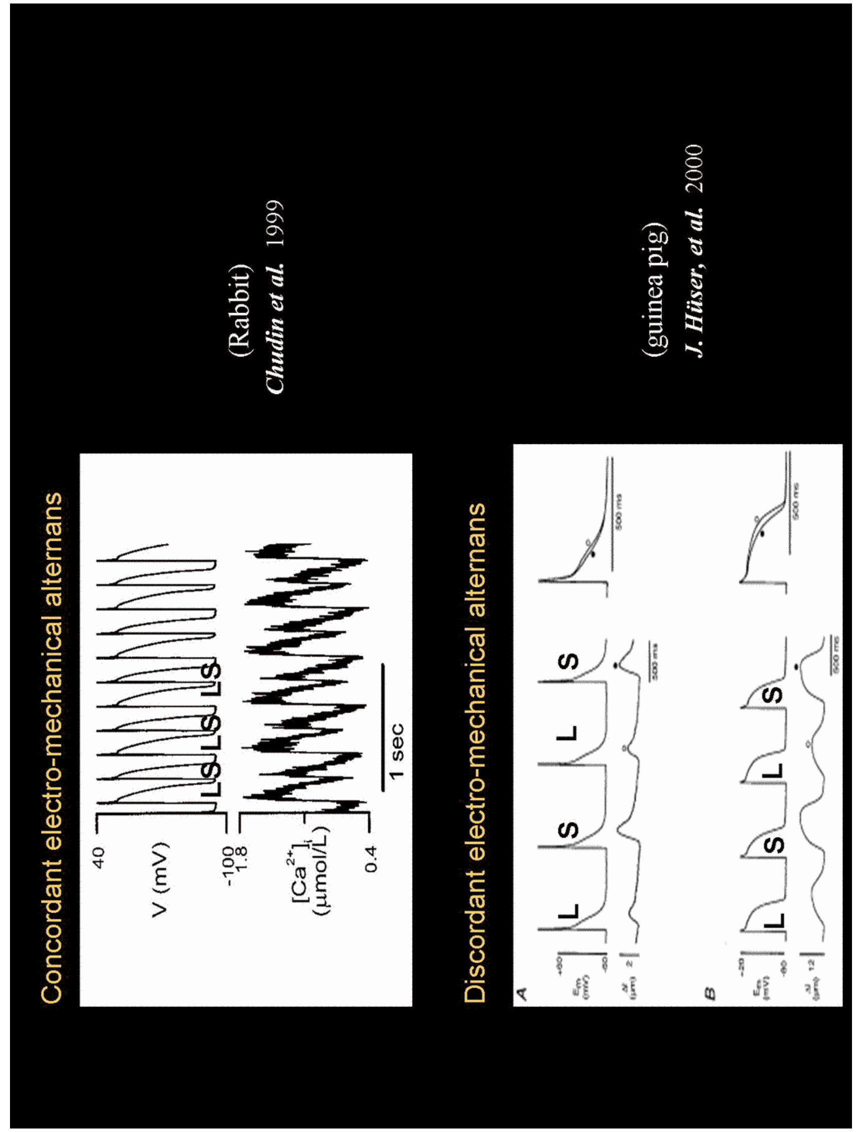

Spatial distribution of Ca release
Fluoresence imaging reveals spatial distribution of Ca release
A
B
C
D
Cleeman et al., 1995
NaCa exchange channels
T-tubule
JSR
SR
Dyadic cleft
High Ca concentration
L-type Ca channels
uptake channels
RyR channels
Signaling via Ca induced Ca release

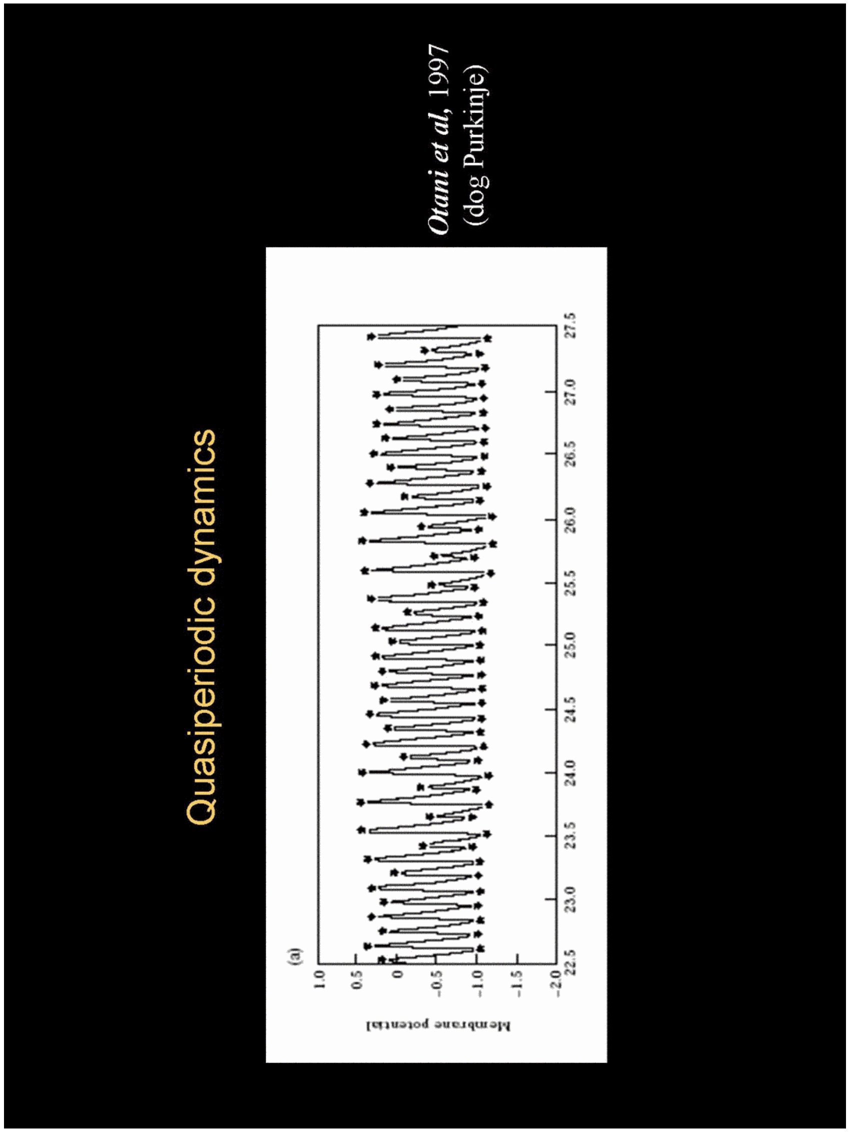

Calcium signaling in the dyadic cleft
DHPR's (L-type Ca2+ Channels)
T-tubule (cut section)
RyR's
SR membrane (cut section)
The dyadic cleft
$10\,nm \times 100\,nm$
Wang et al. 2001
4 µm
Calcium spark
Local calcium transient
Stochastic single L-type Ca channel (LCC) current $i_{Ca}(t)$
Sparks activated by the calcium entry due to single LCCs

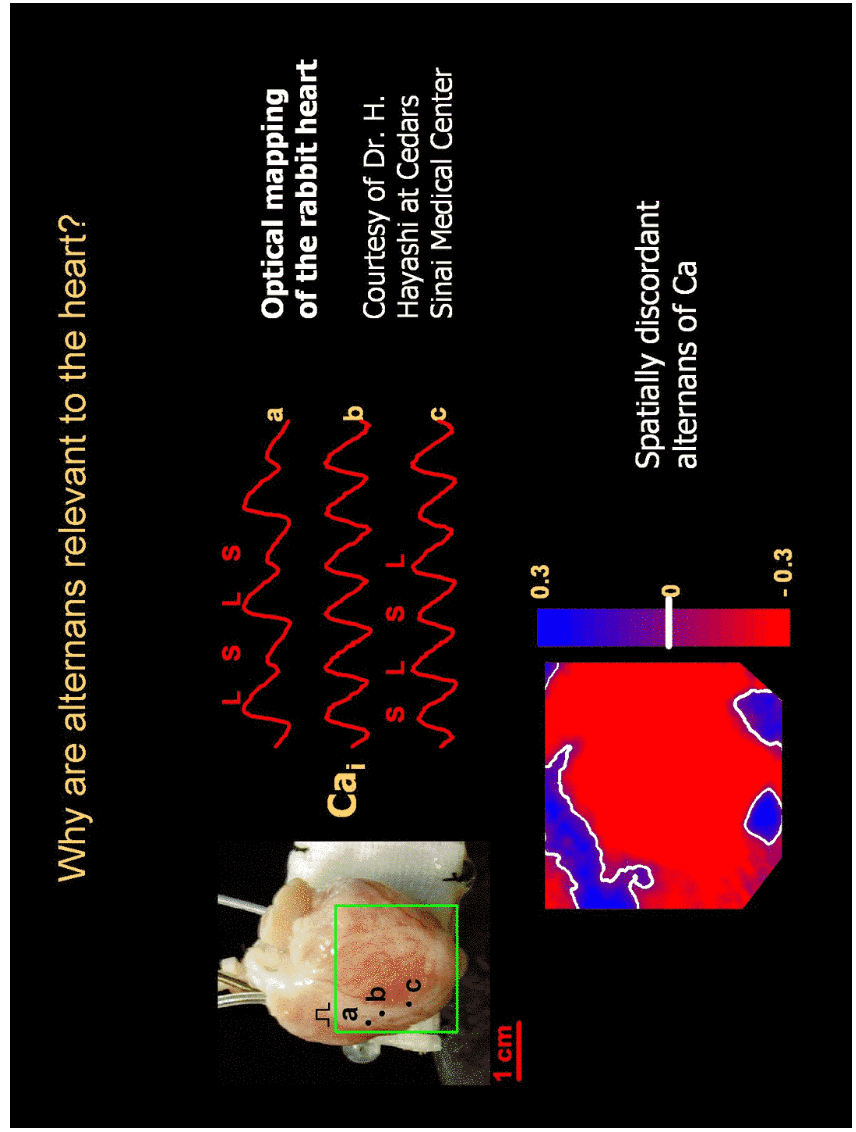

Calcium sparks are correlated with whole cell I_{Ca}
Cleeman et al., 1995
Release is induced by calcium entry (CICR)
$I_{Ca} = \sum_{open} i_{Ca}$
Single channel current
A
B
C
D
E
5 µm
0
255
10 pA/pF
10 ms


Graded release
Peak [Ca]
I_{Ca} Current
−40
0
40
80
Membrane voltage (mV)
Wier et al (1994), J Physiol 474(3)
Release of Ca is graded with respect to Ca current


Paced cardiac cells exhibit nonlinear dynamical properties
Ca transient alternans observed in rabbit Ventricular, when cell is paced with periodic voltage clamp.
From lab of J. Weiss, UCLA
Diaz et al. 2002
Control
Tetracaine
Tetracaine
a b
c d e f g
10 µm
400 ms
200
0
i
ii


Concordant electro-mechanical alternans
(Rabbit)
Chudin et al. 1999
40
V (mV)
-100
1.8
[Ca2+]i (µmol/L)
0.4
1 sec
L S L S L S L S
Discordant electro-mechanical alternans
(guinea pig)
J. Hüser, et al. 2000
A
B
L S L S


Quasiperiodic dynamics
Otani et al, 1997
(dog Purkinje)
(a)
Membrane potential
1.0
0.5
0
−0.5
−1.0
−1.5
−2.0
22.5
23.0
23.5
24.0
24.5
25.0
25.5
26.0
26.5
27.0
27.5


Why are alternans relevant to the heart?
Optical mapping of the rabbit heart
Courtesy of Dr. H. Hayashi at Cedars Sinai Medical Center
Ca_i
L S L S L S
S L S L
a
b
c
0.3
0
- 0.3
1 cm
Spatially discordant alternans of Ca

Can we construct a model of Ca cycling where:

1. Release is triggered by Ca entry via a CICR mechanism operative within ~10^4 dyadic cleft.
2. Release occurs via discrete release events called Ca sparks.
3. Release mirrors the whole cell Ca entry (graded release).
4. Can be used to understand the rich dynamical behavior of Ca cycling.

A Phenomenological approach:

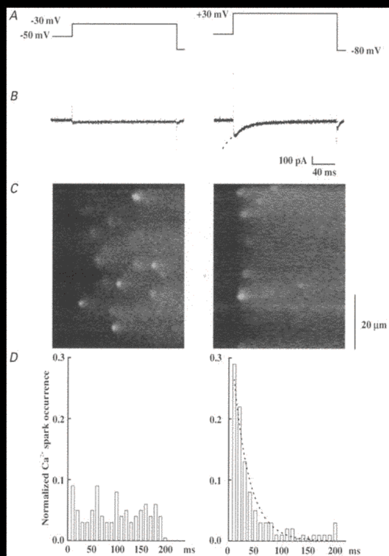
Phenomenological model of Ca release at the dyadic cleft (spark):

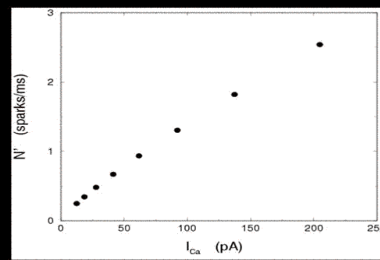
$$I_{spark}(t) = J(c_j')e^{-(t-t')/\tau_s}$$

Concentration of JSR

Duration of spark $\approx 10-20\ ms$

Spark recruitment rate





Sparks are recruited at a rate roughly Proportional to the Ca entry:

$$\frac{dN_s(t)}{dt} = gI_{Ca}(t)A(c_j'(t))$$

Summing discrete release events

Whole cell current due to summation of discrete Ca fluxes:

$$I_r(t) = \int_{t_0}^{t} \frac{dN(t')}{dt'} J(c_j'(t'))\, e^{-(t-t')/\tau_s}\, dt'$$

Satisfies

$$\frac{dI_r(t)}{dt} = gI_{Ca}(t)Q(c_j'(t)) - \frac{I_r(t)}{\tau_s}$$

$$Q(c_j'(t)) = A(c_j'(t))J(c_j'(t))$$

Full Model Equations for Ca cycling

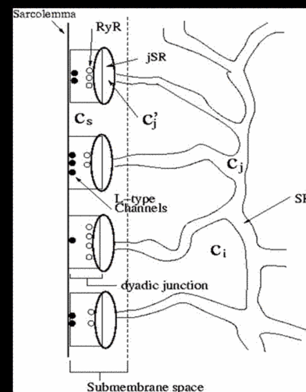
$$\frac{dc_s}{dt} = \frac{\alpha_i}{\alpha_s}\left(I_r(t) - \frac{c_s - c_i}{\tau_d} - I_{Ca}(c_s, V(t)) + I_{NaCa}(c_s, V(t))\right)$$

$$\frac{dc_i}{dt} = \frac{c_s - c_i}{\tau_d} - I_{up}(c_i)$$

$$\frac{dc_j}{dt} = \frac{\alpha_i}{\alpha_j}\left(-I_r(t) + I_{up}(c_i)\right)$$

$$\frac{dI_r(t)}{dt} = gI_{Ca}(t)Q(c_j'(t)) - \frac{I_r(t)}{\tau_s}$$

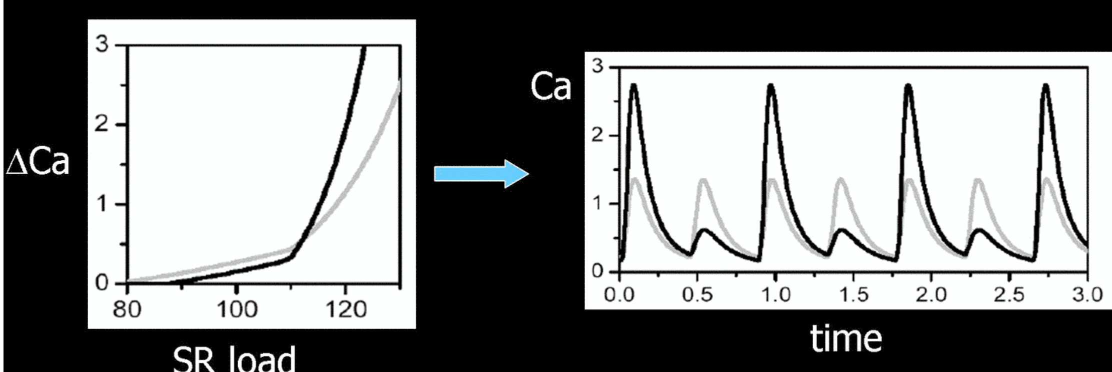
$$\frac{dc_j'(t)}{dt} = \frac{c_j(t) - c_j'(t)}{\tau_j}$$



Biophys J., 2003

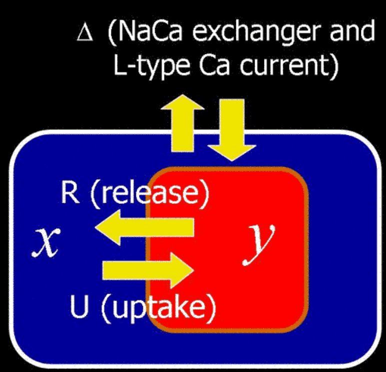
Instability Mechanism

Steep SR-release vs. SR-load relationship induces alternans



$$u = \frac{dQ(c_j')}{dc_j'}$$ Load dependence of release

Nonlinear map reduction



$$x_{n+1} = x_n + R_n - U_n + \Delta_n$$
$$y_{n+1} = y_n - R_n + U_n$$

Calcium cycling dynamics

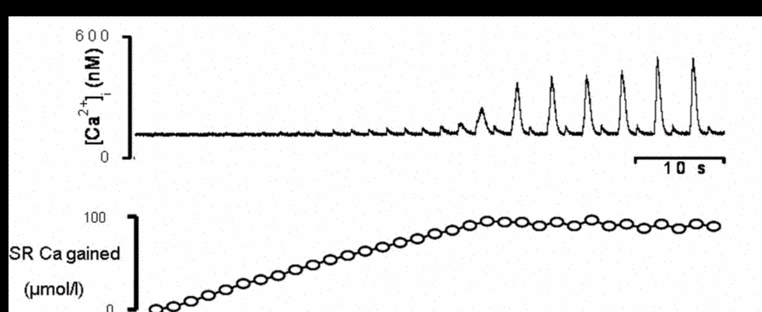
Shiferaw et al., 2005

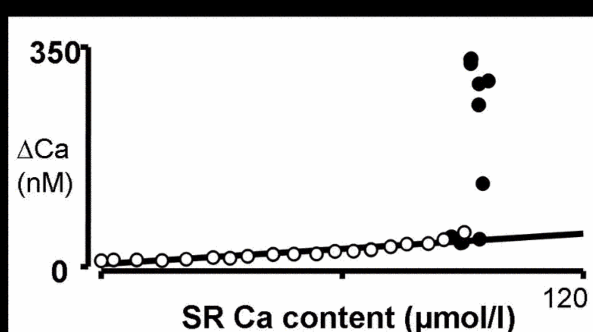
Alternans occurs when:

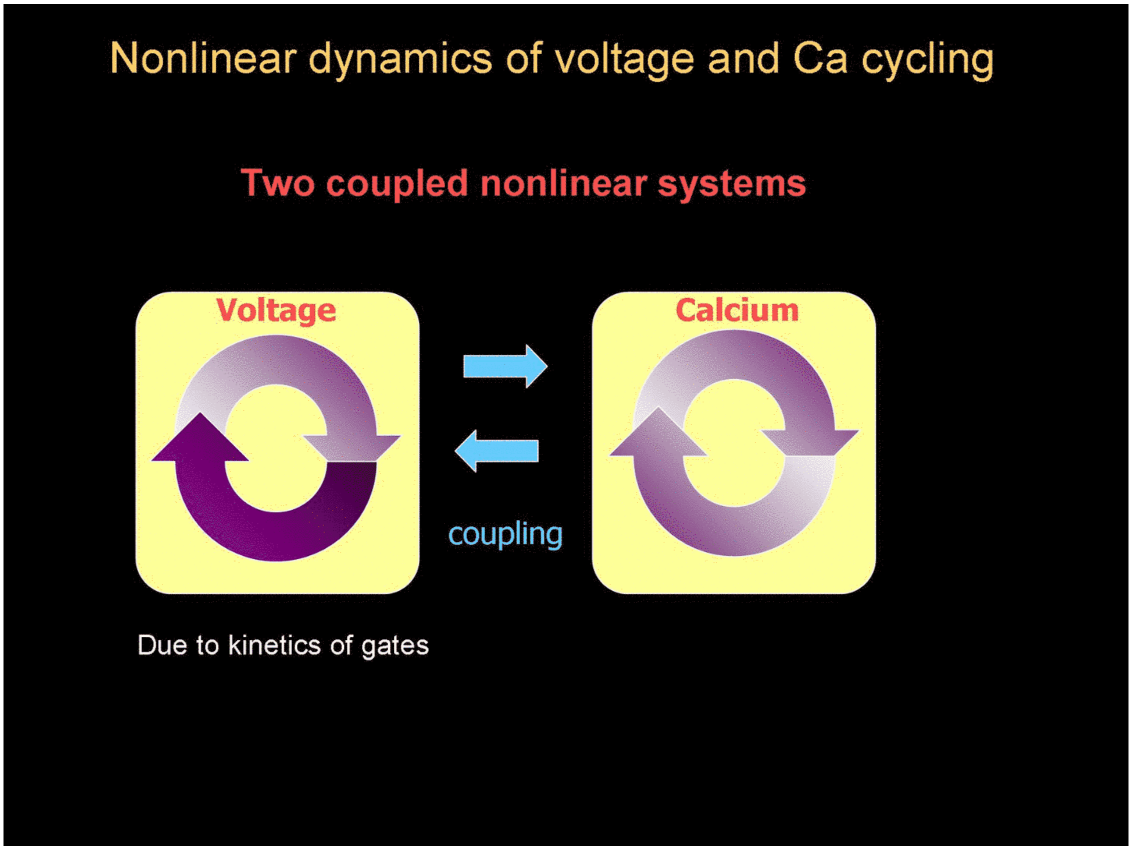
$$(1-w)\left(-1-\frac{\partial R}{\partial x_n}+\frac{\partial R}{\partial y_n}\right) > 1$$

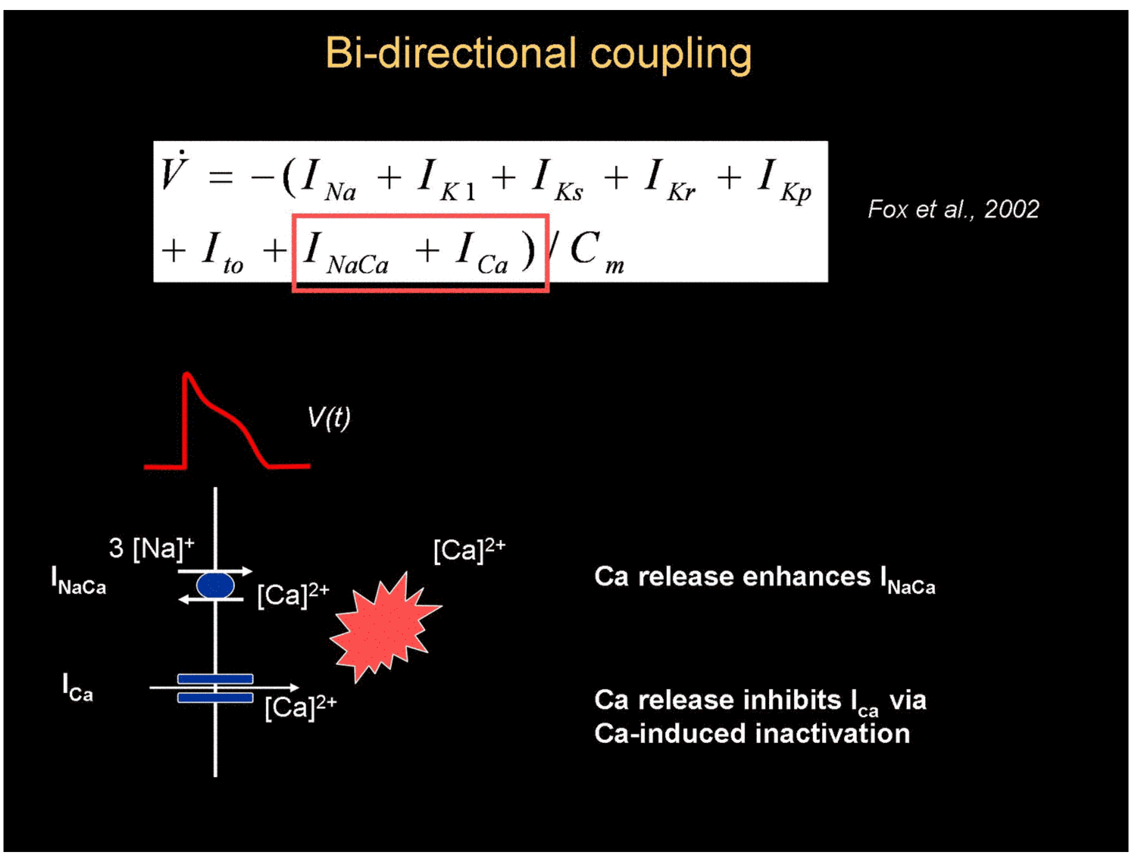
Experimental Validation

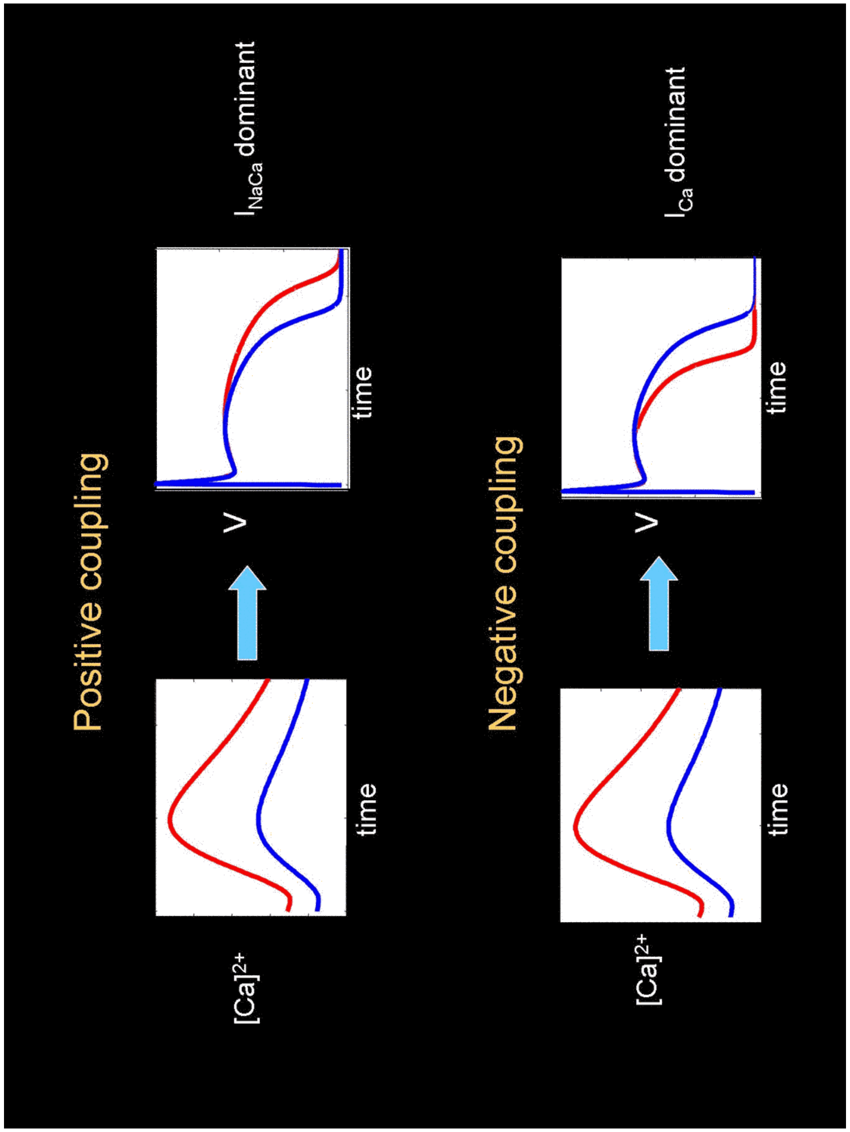
Diaz et al., 2004

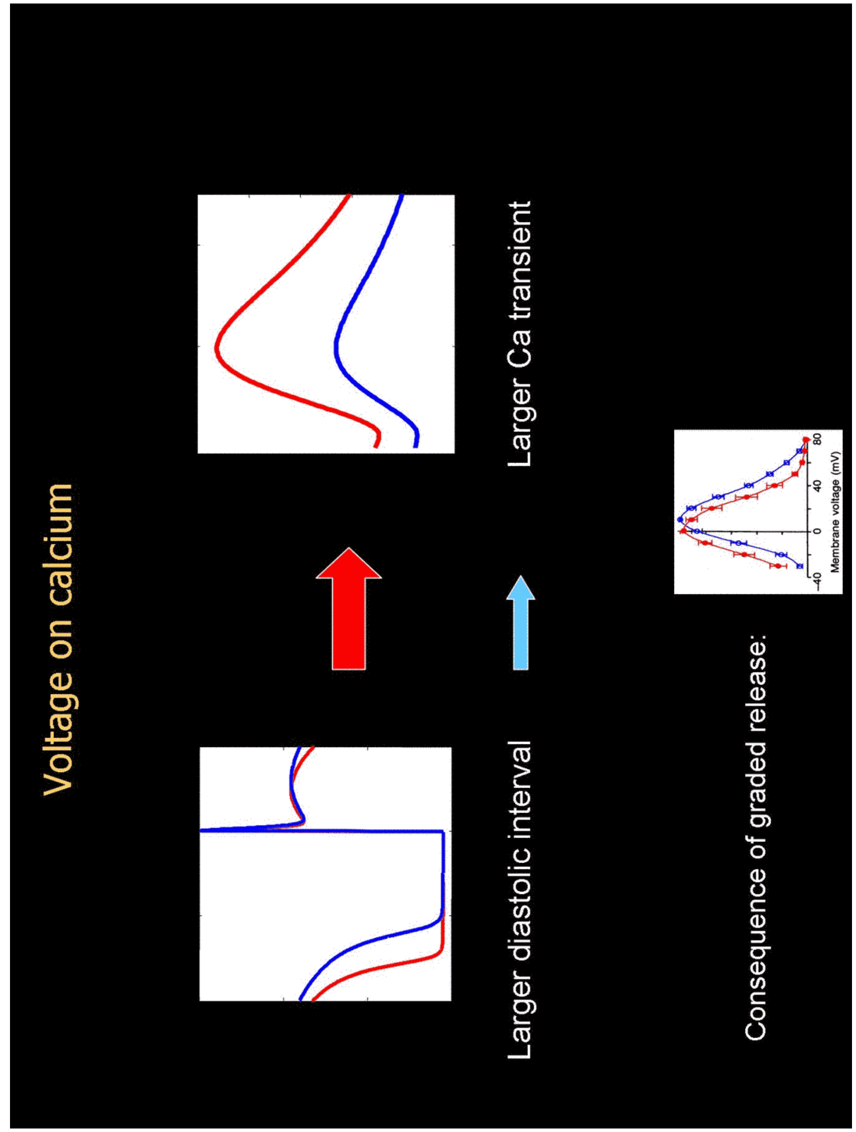


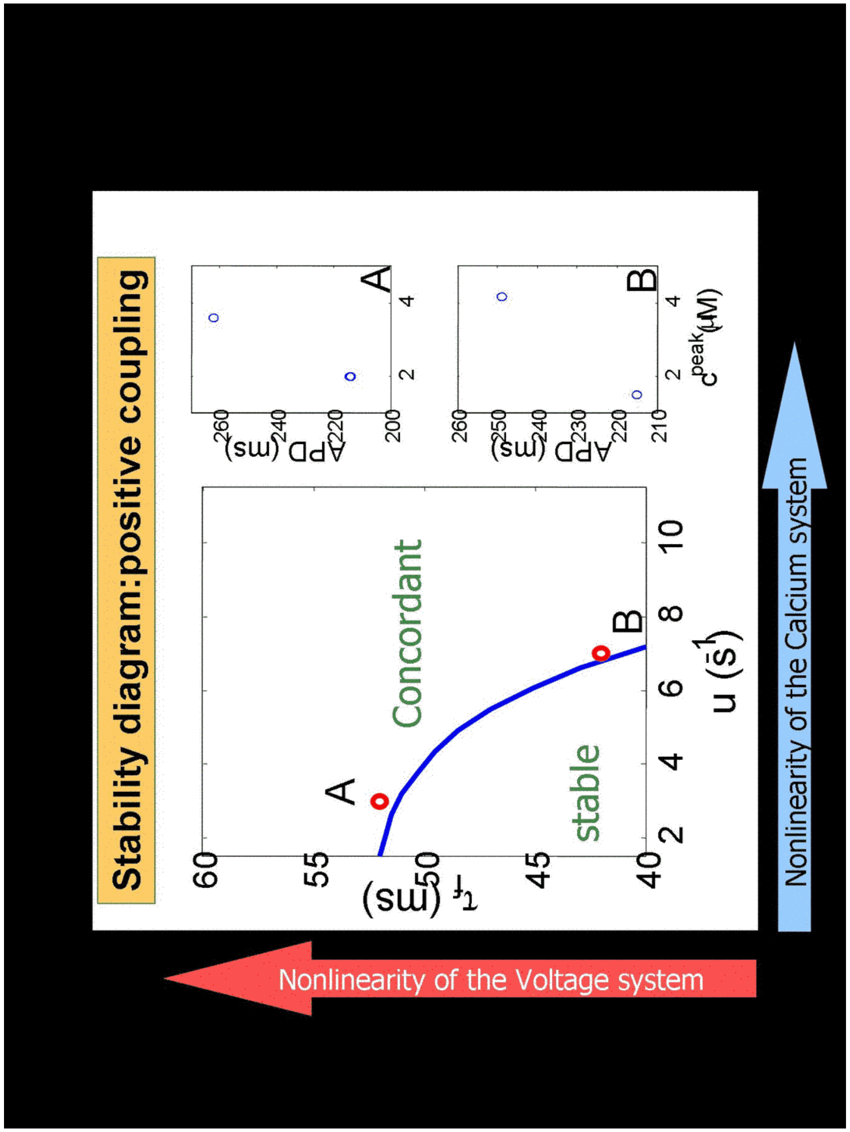


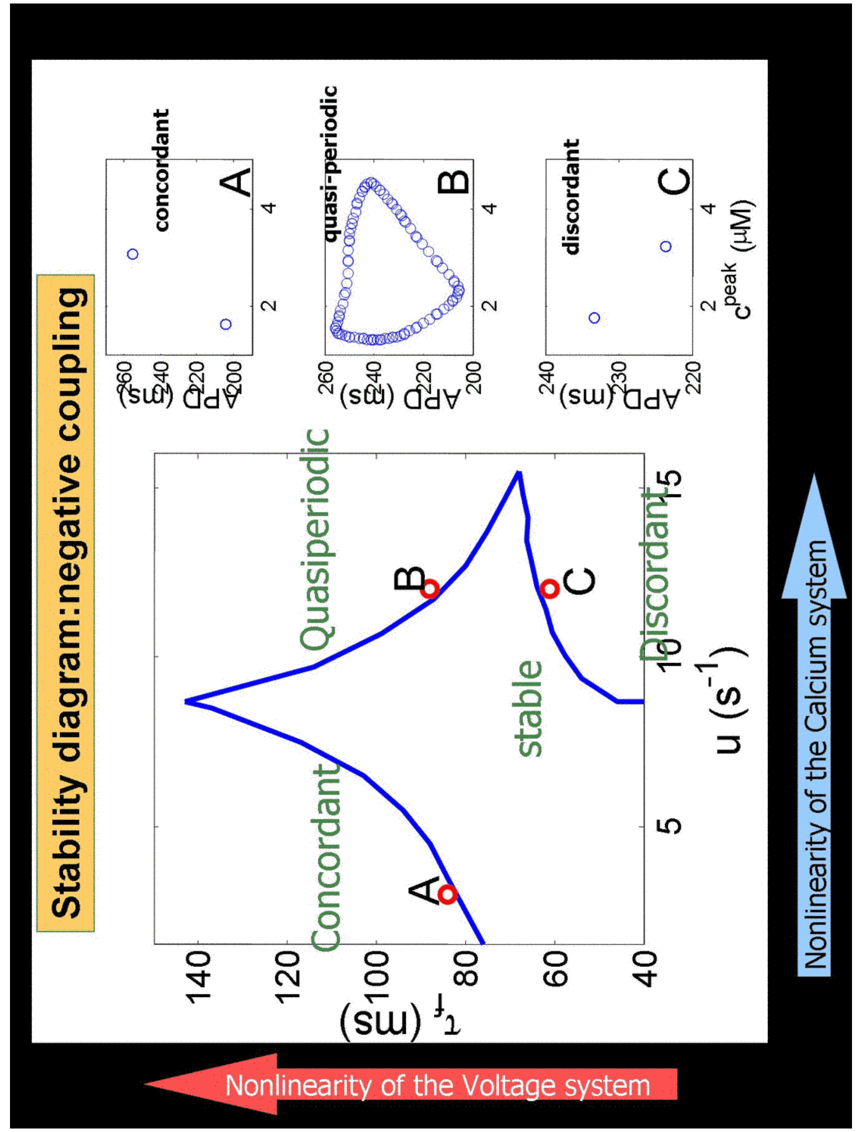

Nonlinear dynamics of voltage and Ca cycling
Two coupled nonlinear systems
Voltage
Calcium
coupling
Due to kinetics of gates


Bi-directional coupling
$\dot{V} = -(I_{Na} + I_{K1} + I_{Ks} + I_{Kr} + I_{Kp} + I_{to} + \boxed{I_{NaCa} + I_{Ca}}) / C_m$
Fox et al., 2002
V(t)
3 [Na]+
I_{NaCa}
[Ca]2+
[Ca]2+
I_{Ca}
[Ca]2+
Ca release enhances I_{NaCa}
Ca release inhibits I_{ca} via
Ca-induced inactivation


Positive coupling
[Ca]$^{2+}$
time
V
time
I_{NaCa} dominant
Negative coupling
[Ca]$^{2+}$
time
V
time
I_{Ca} dominant


Voltage on calcium
Larger diastolic interval
Larger Ca transient
Consequence of graded release:
Membrane voltage (mV)
-40
0
40
80

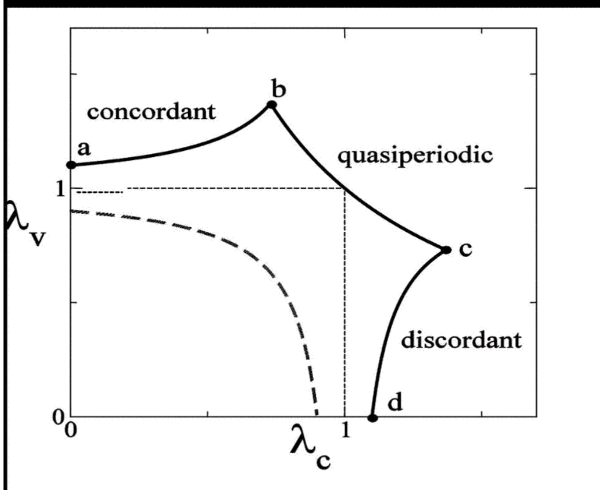

Stability diagram:positive coupling
Concordant
stable
A
B
τ_f (ms)
u (s^{-1})
APD (ms)
c^{peak} (μM)
Nonlinearity of the Calcium system
Nonlinearity of the Voltage system


Stability diagram:negative coupling
concordant
quasi-periodic
discordant
Quasiperiodic
Concordant
Discordant
stable
A
B
C
τ_f (ms)
u (s^{-1})
APD (ms)
c^{peak} (μM)
Nonlinearity of the Calcium system
Nonlinearity of the Voltage system

Discrete maps

$$x_{n+1} = x_n + R_n - U_n + \Delta_n$$
$$y_{n+1} = y_n - R_n + U_n$$

$$\Leftrightarrow \quad A_{n+1} = F(D_n, x_n, y_n)$$



$$\lambda_v = \frac{\partial F}{\partial D_n}$$ The restitution slope.

$$\lambda_c = -1 - \frac{\partial (R_n - U_n)}{\partial x_n} + \frac{\partial (R_n - U_n)}{\partial y_n}$$

Degree of instability of Ca cycling.

$$C = \frac{\partial (R_n - U_n)}{\partial D_n}\left(\frac{\partial F}{\partial y_n} - \frac{\partial F}{\partial x_n}\right)$$

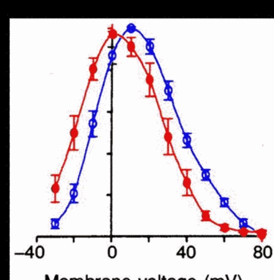
Degree of coupling between voltage and Ca systems.

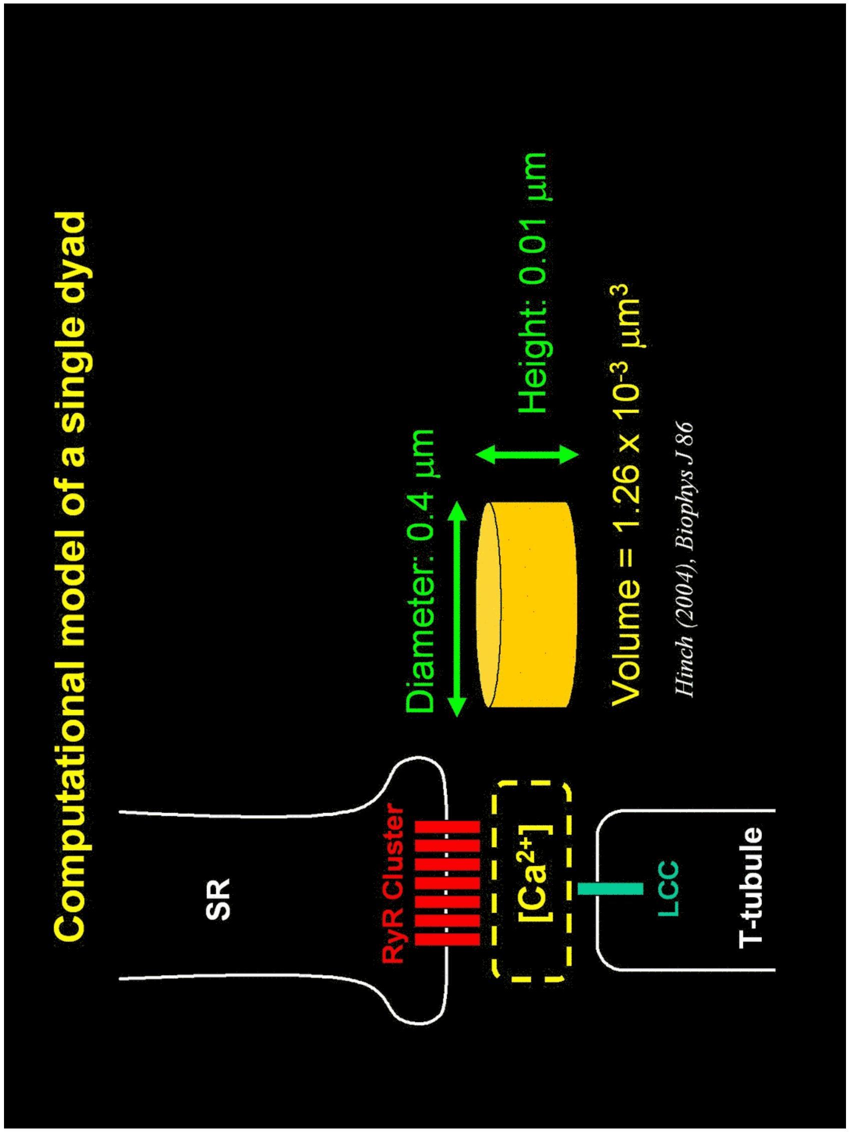
Limitations

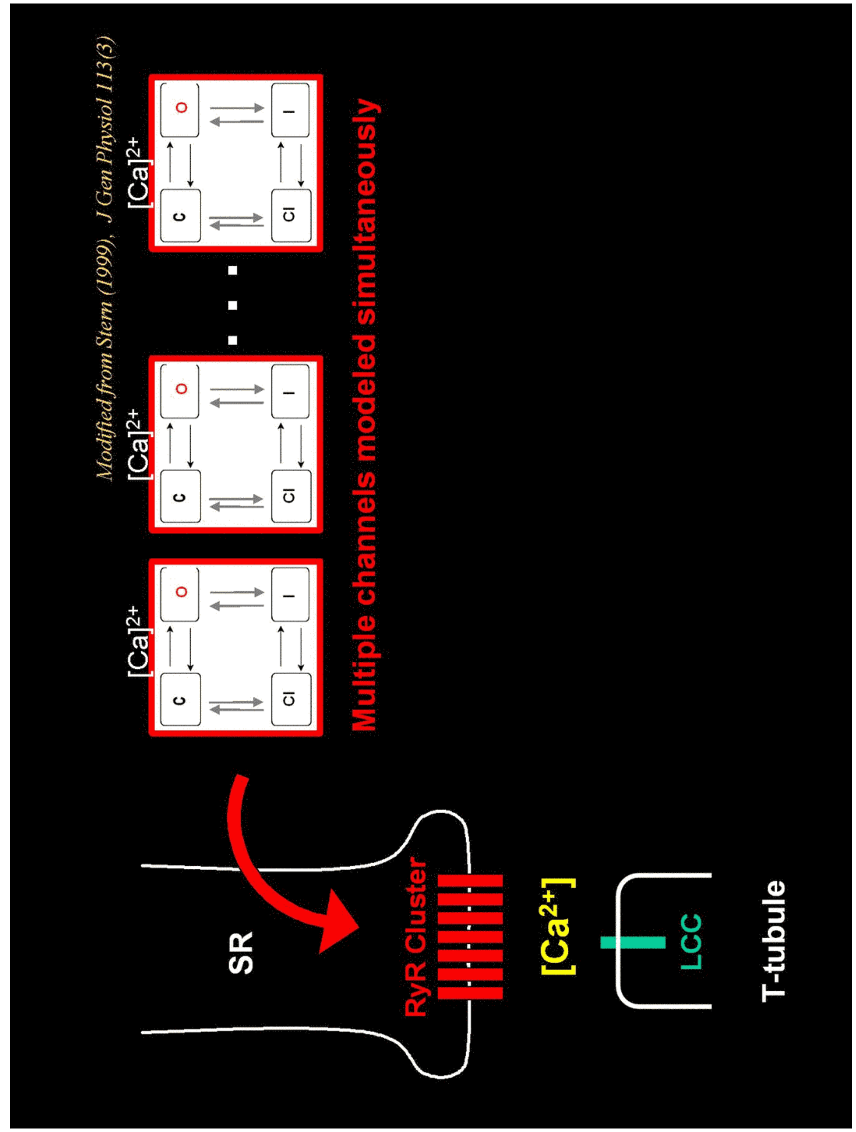
Model does not yield insight on the role of ion channels.

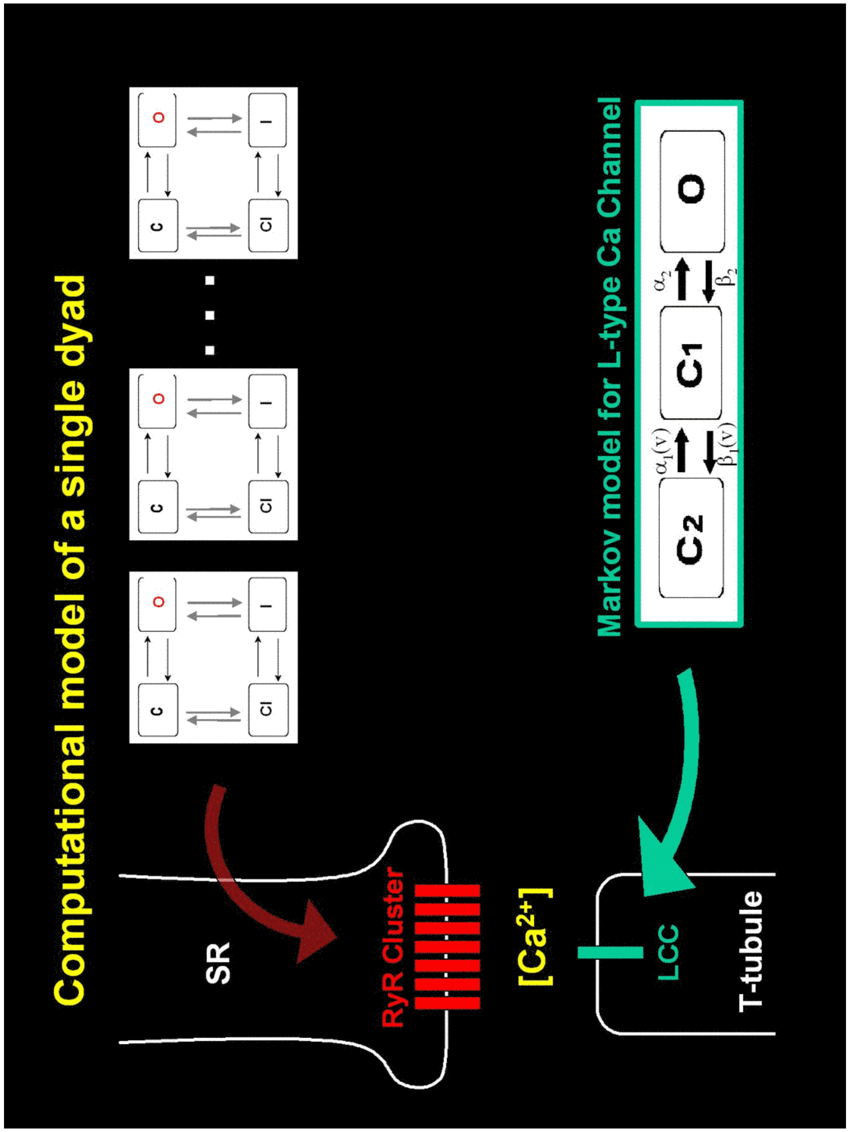
Can we understand the basic whole cell properties in terms of the kinetics and interaction of ion channels?

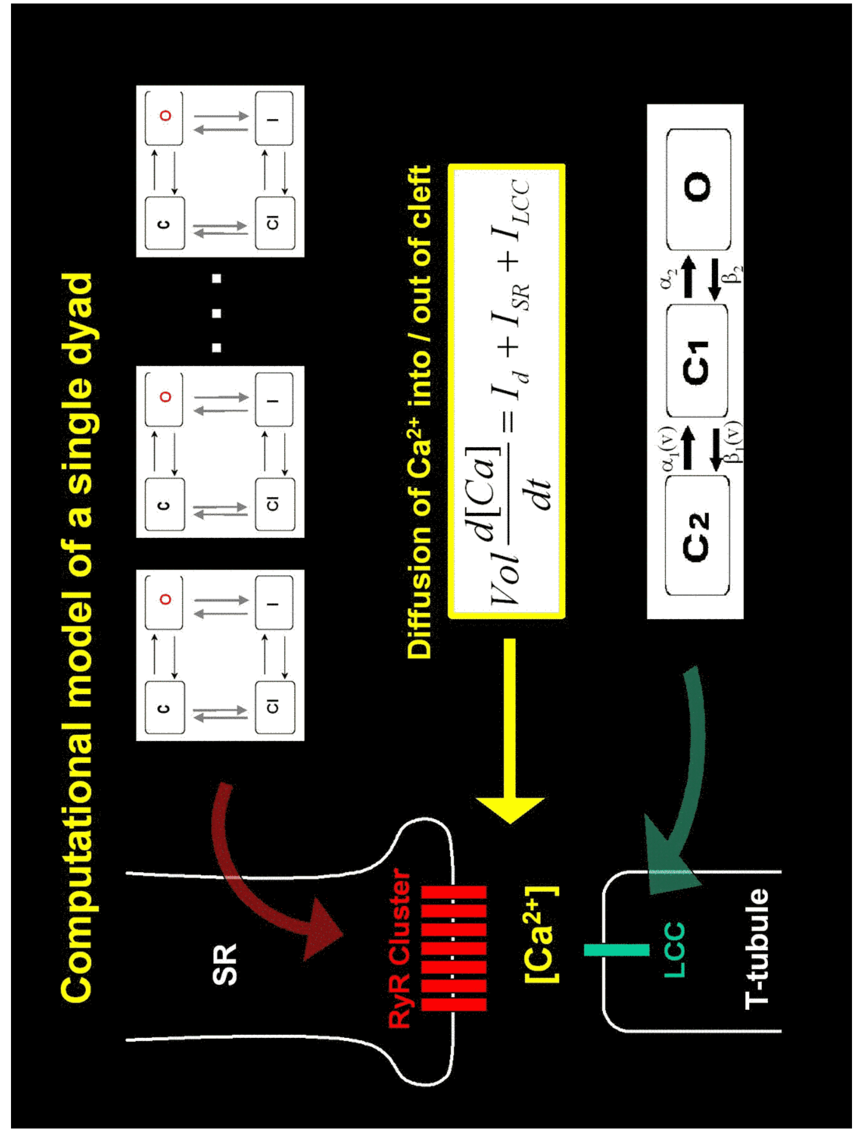
For example, can we explain graded release in terms of Ca signaling between Ion channels in the dyadic cleft??



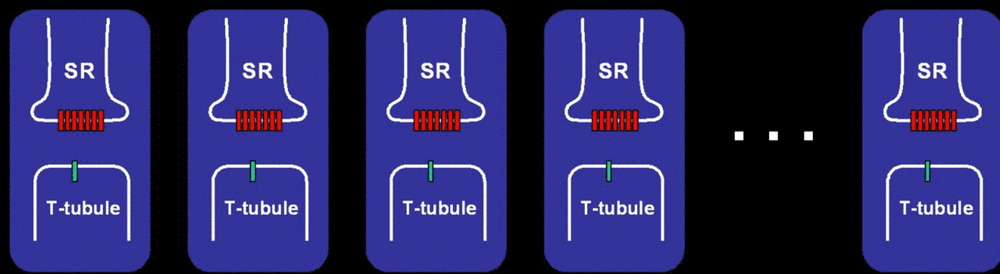

Computational model of a single dyad
SR
RyR Cluster
[Ca2+]
LCC
T-tubule
Diameter: 0.4 µm
Height: 0.01 µm
Volume = 1.26 x 10-3 µm3
Hinch (2004), Biophys J 86


Modified from Stern (1999), J Gen Physiol 113(3)
[Ca]2+
c
o
ci
i
Multiple channels modeled simultaneously
SR
RyR Cluster
[Ca2+]
LCC
T-tubule


Computational model of a single dyad
SR
RyR Cluster
[Ca2+]
LCC
T-tubule
Markov model for L-type Ca Channel
C2
C1
O
$\alpha_1(v)$
$\beta_1(v)$
α_2
β_2
c
o
ci
i


Computational model of a single dyad
SR
RyR Cluster
[Ca2+]
LCC
T-tubule
Diffusion of Ca2+ into / out of cleft
$Vol\frac{d[Ca]}{dt} = I_d + I_{SR} + I_{LCC}$
C2
C1
O
$\alpha_1(v)$
$\beta_1(v)$
α_2
β_2
c
o
ci
i

Whole-cell data is composed of multiple independent simulations

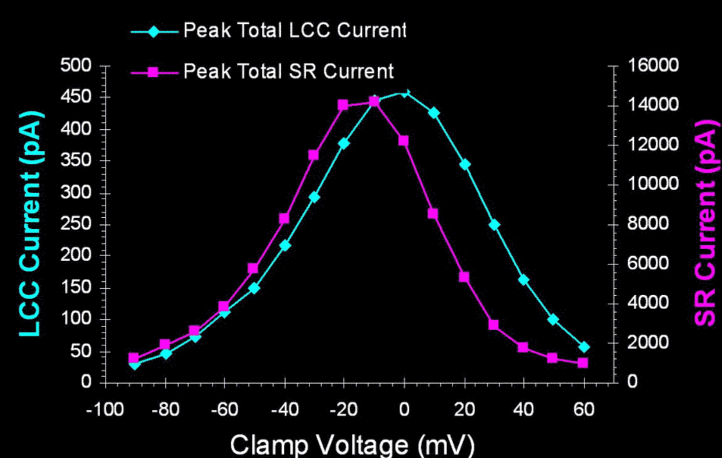


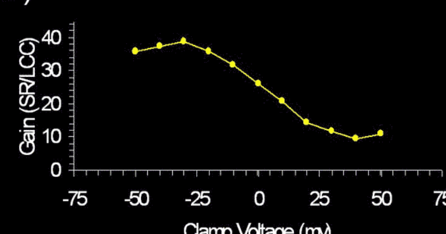
~ 100 RyR channels per dyadic junction
~ 50,000 independent dyadic junctions per cell

About 5 million computations are done at each time step (1 μs)

Whole-cell data is computed after summing up currents from each individual dyadic junction:

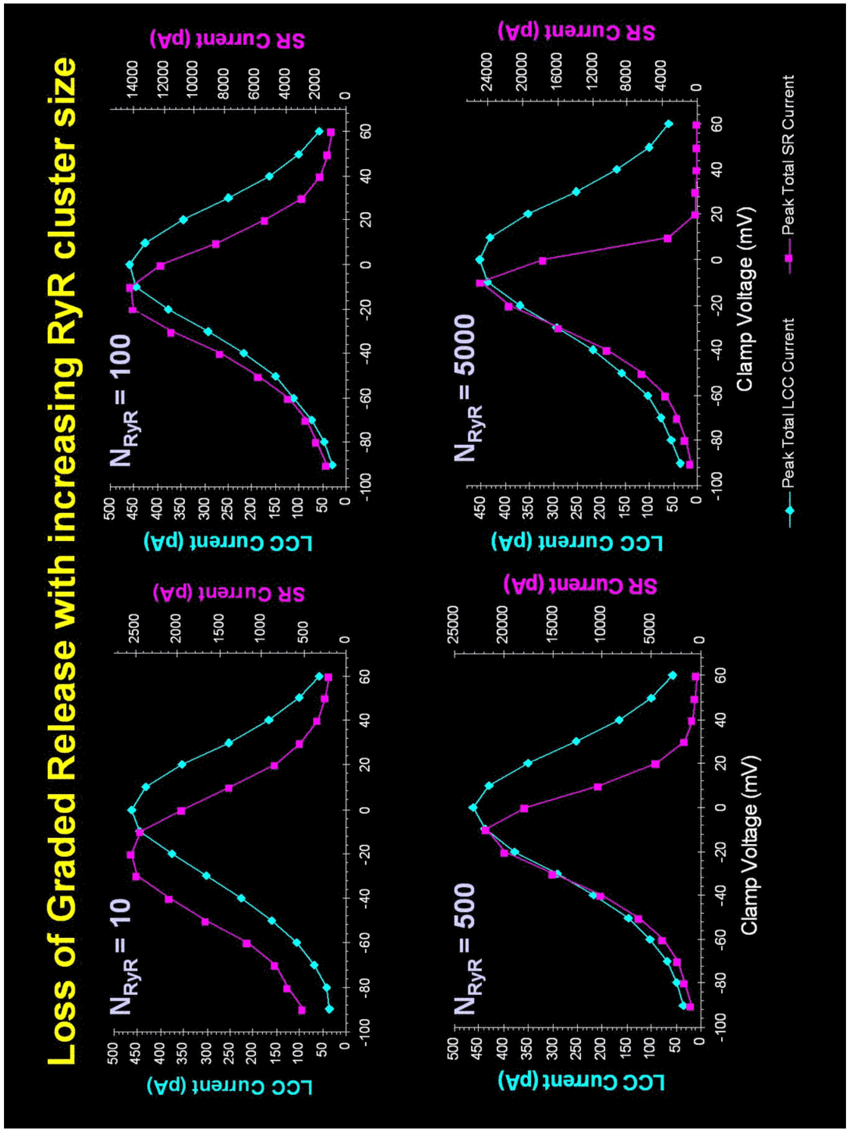
Peak LCC current   Peak SR release

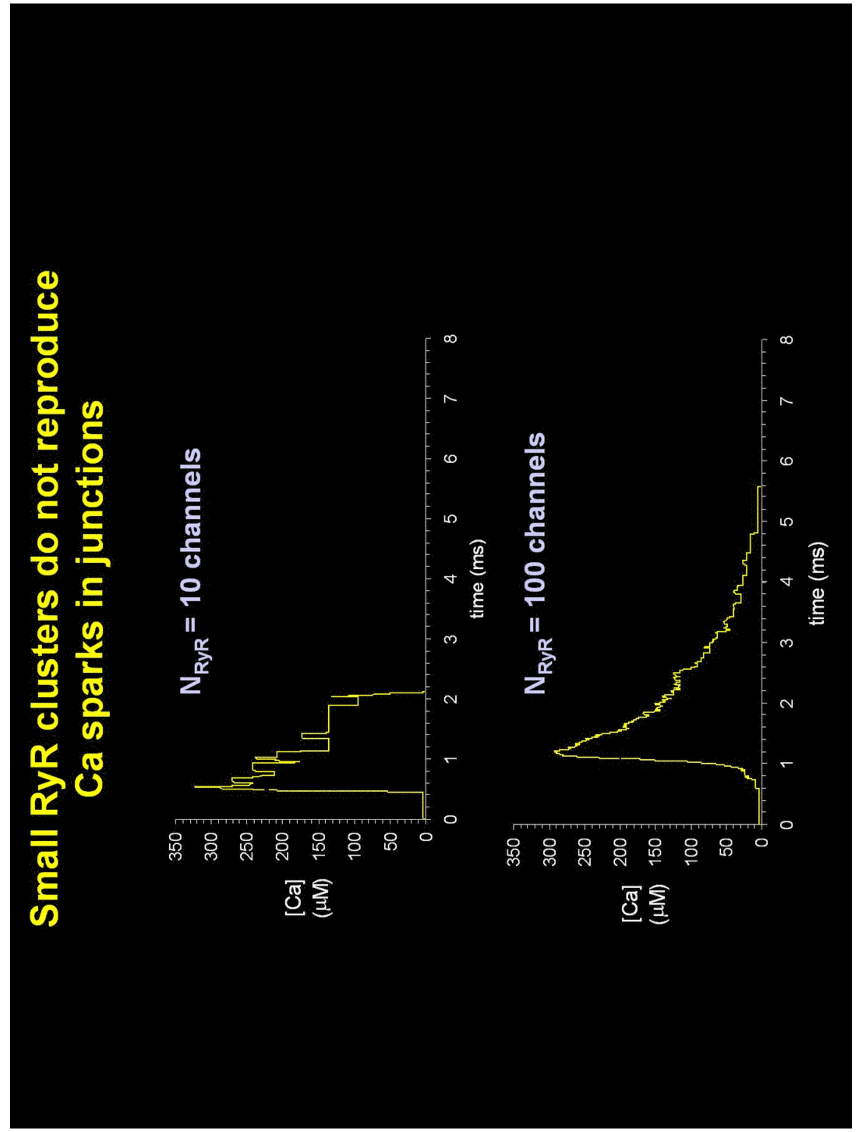


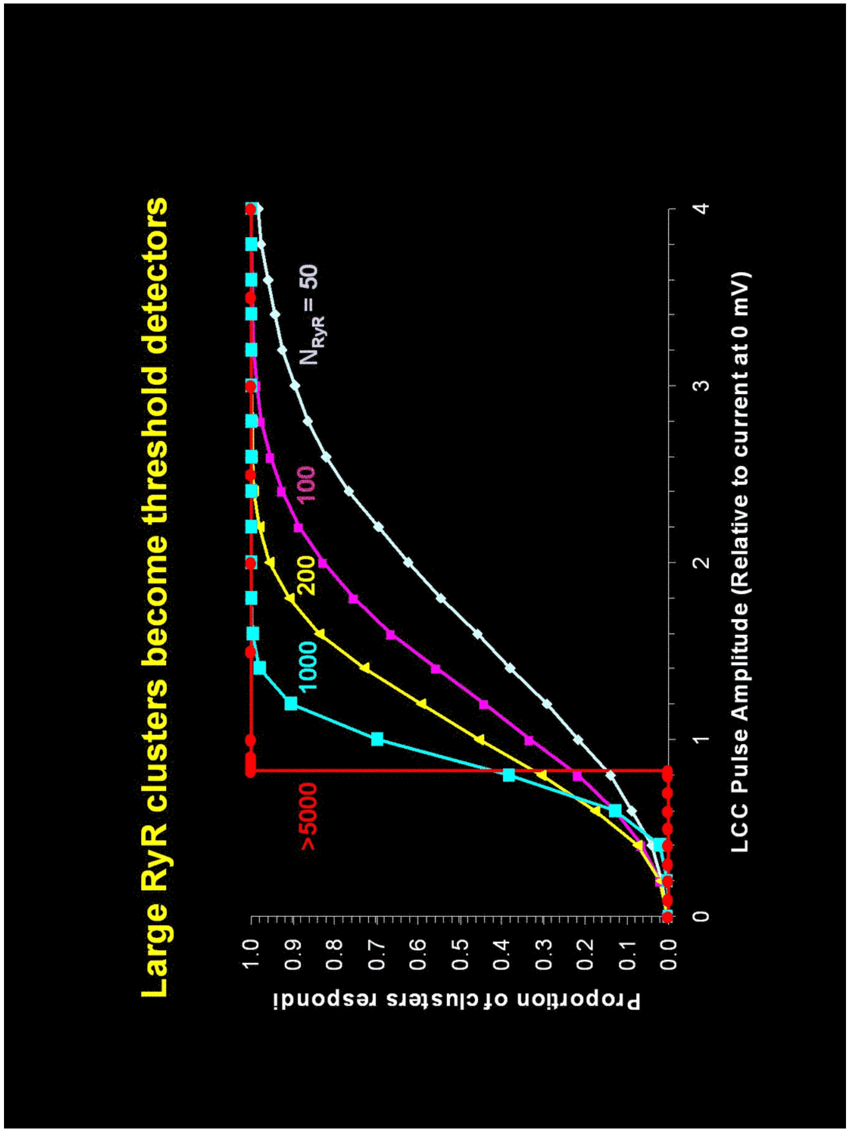


Peak currents are computed for a range of test voltages

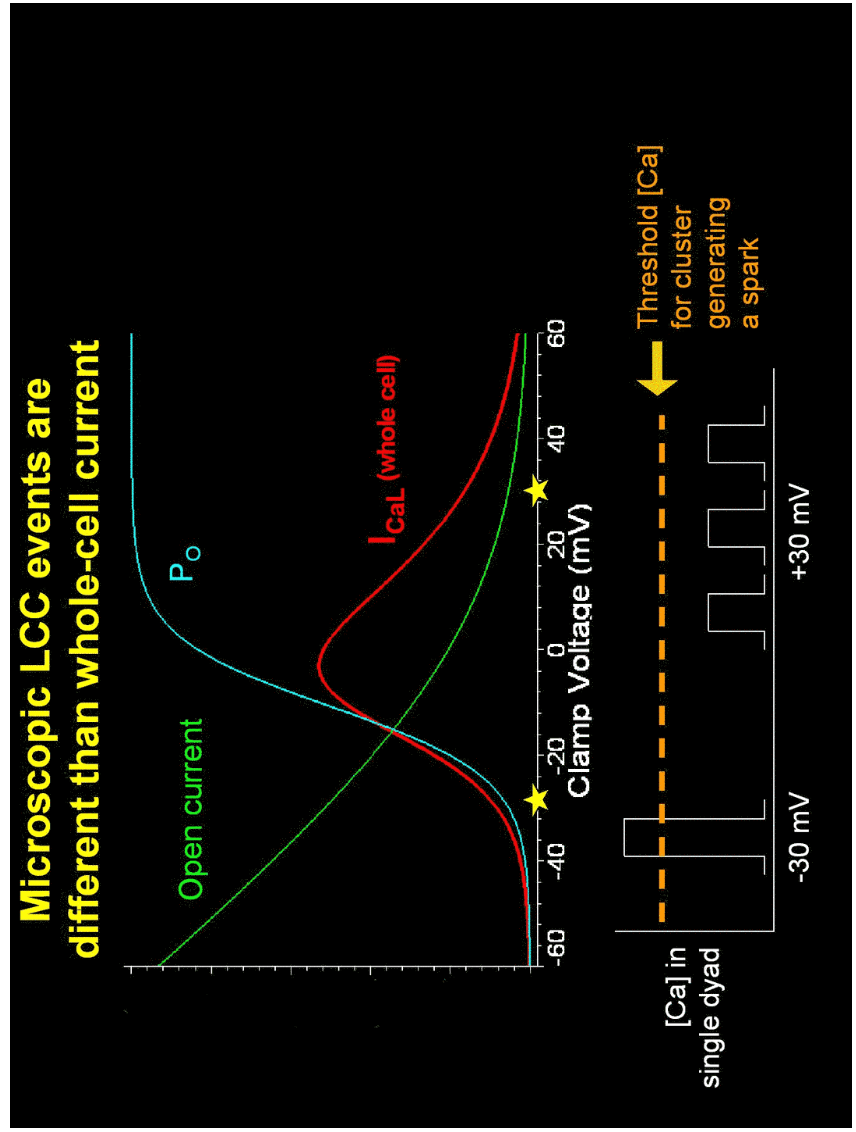
Each dyad contains a cluster of 100 RyR channels and 1 L-type Ca Channel


Loss of Graded Release with increasing RyR cluster size
N_{RyR} = 10
N_{RyR} = 100
N_{RyR} = 500
N_{RyR} = 5000
LCC Current (pA)
SR Current (pA)
Clamp Voltage (mV)
Peak Total LCC Current
Peak Total SR Current


Small RyR clusters do not reproduce
Ca sparks in junctions
N_{RyR} = 10 channels
N_{RyR} = 100 channels
[Ca] (μM)
time (ms)

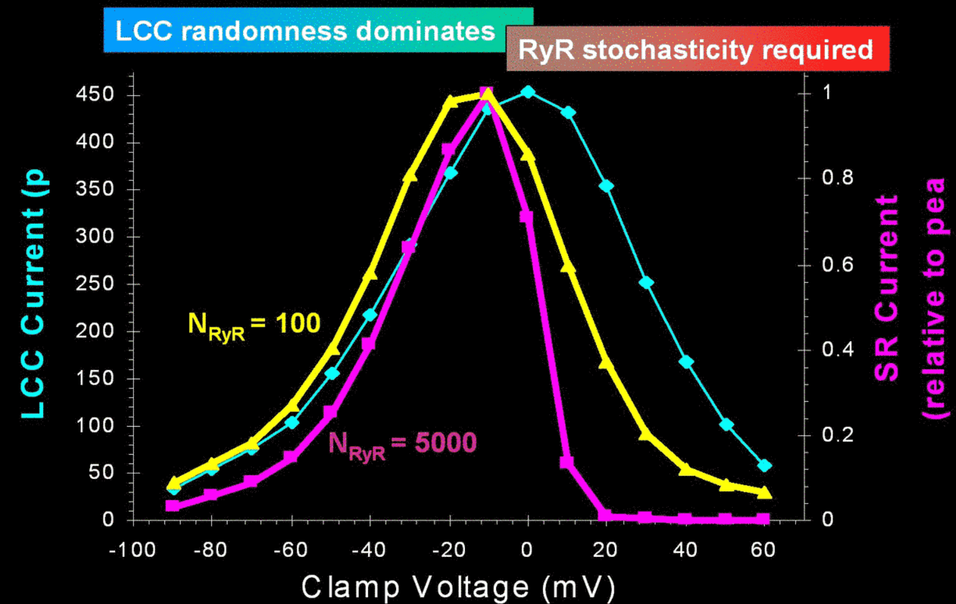


Large RyR clusters become threshold detectors
Proportion of clusters respondi
LCC Pulse Amplitude (Relative to current at 0 mV)
N_{RyR} = 50
100
200
1000
>5000



Microscopic LCC events are different than whole-cell current
Open current
P_O
I_{CaL} (whole cell)
Clamp Voltage (mV)
Threshold [Ca] for cluster generating a spark
[Ca] in single dyad
-30 mV
+30 mV

Graded Release requires stochasticity of both LCC and RyR



As number of channels increases, RyR cluster becomes a deterministic system which will not respond to low driving force (at high voltages) through LCC.

Main points

1. Rich nonlinear dynamics of voltage-calcium of cardiac cells. Dynamics can be understood in terms of basic features of Ca release, and bi-directional coupling.

2. Whole cell properties dependent on local ion channel signaling in the dyadic cleft.

3. Stochasticity at the ion channel level is critical to understanding whole cell properties.