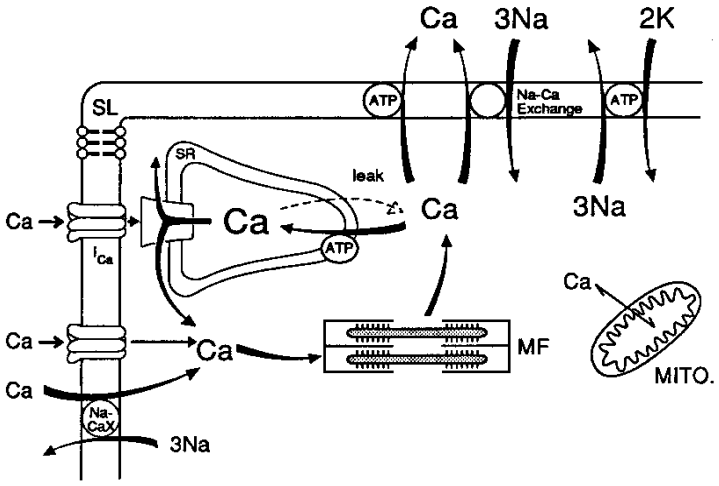
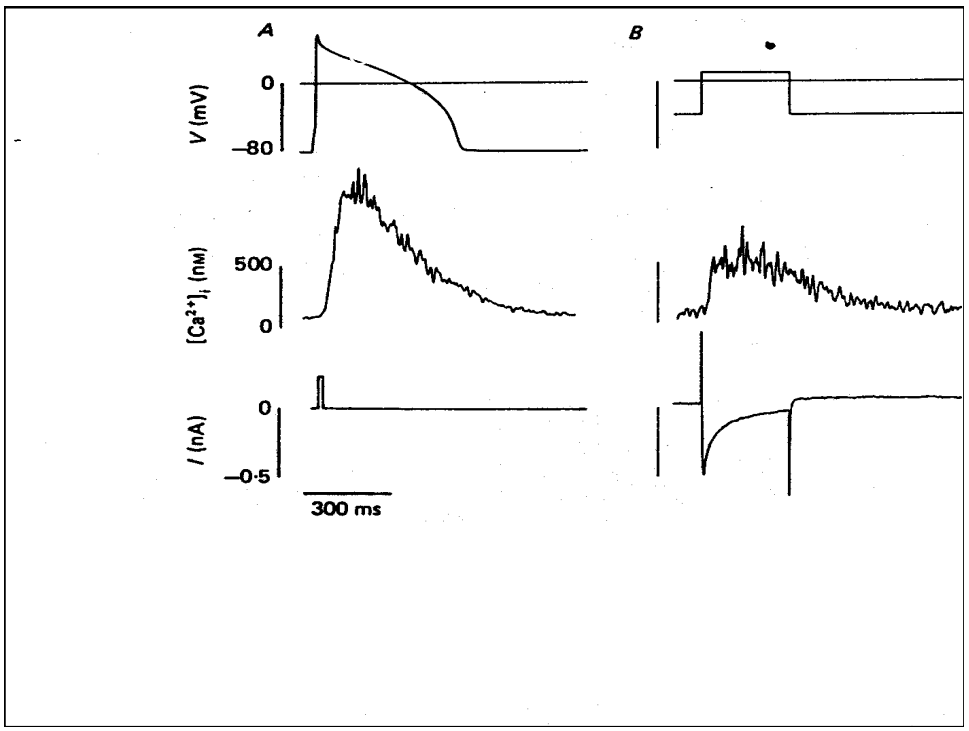
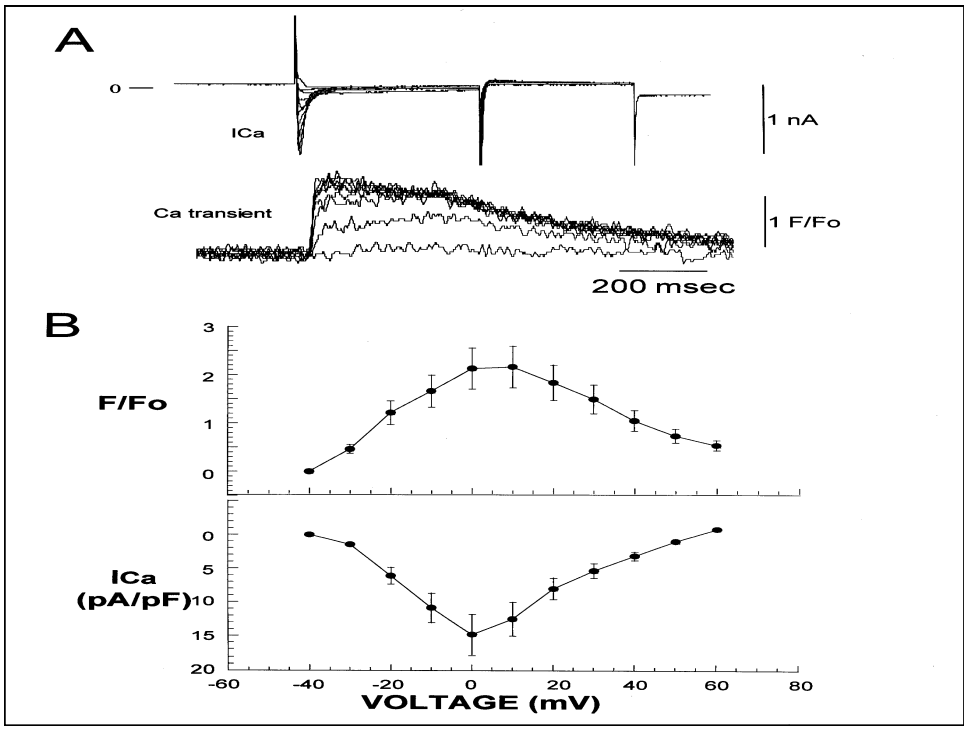
EC Coupling in Heart

Calcium Cycle in Cardiac Muscle

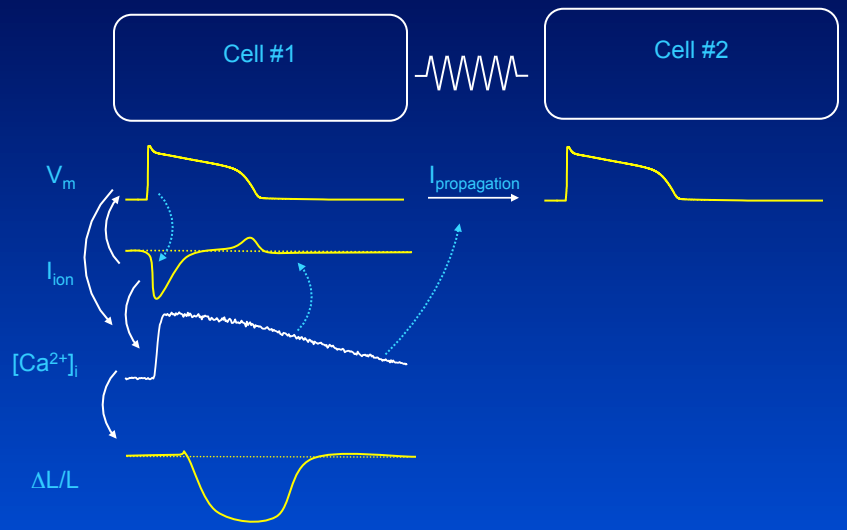


General scheme of Ca cycle in a cardiac myocyte. Ca can enter via Ca channels and Na/Ca exchange. Ca current may also control the SR Ca release by the SR Ca release channel/ ryanodine receptor/ foot protein. Ca is removed from the myofilaments (MF) and cytoplasm by the SR Ca-ATPase pump and the sarcolemmal Ca-ATPase pump and Na/Ca exchange.


A
B
V (mV)
0
–80
[Ca2+]i (nM)
500
0
I (nA)
0
–0·5
300 ms


A
0
ICa
1 nA
Ca transient
1 F/Fo
200 msec
B
F/Fo
3
2
1
0
ICa
(pA/pF)
0
5
10
15
20
-60
-40
-20
0
20
40
60
80
VOLTAGE (mV)

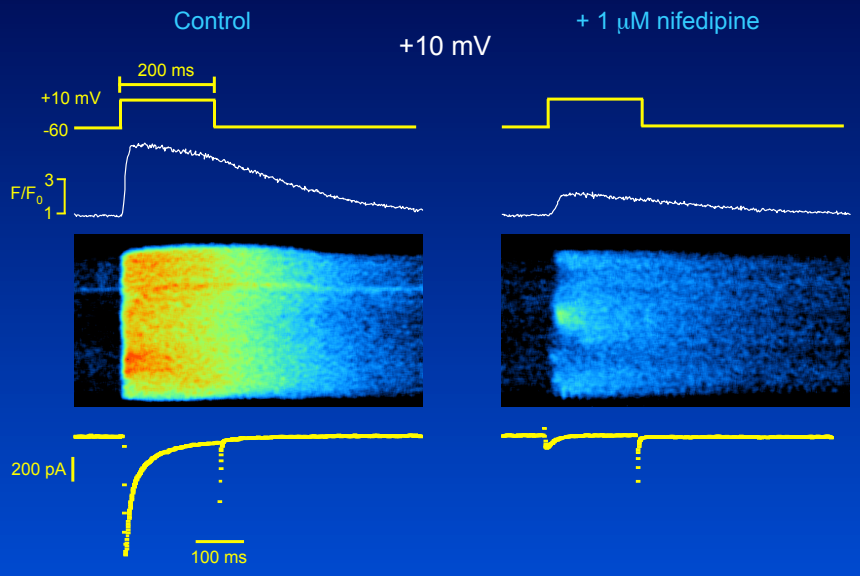
Cardiac signaling

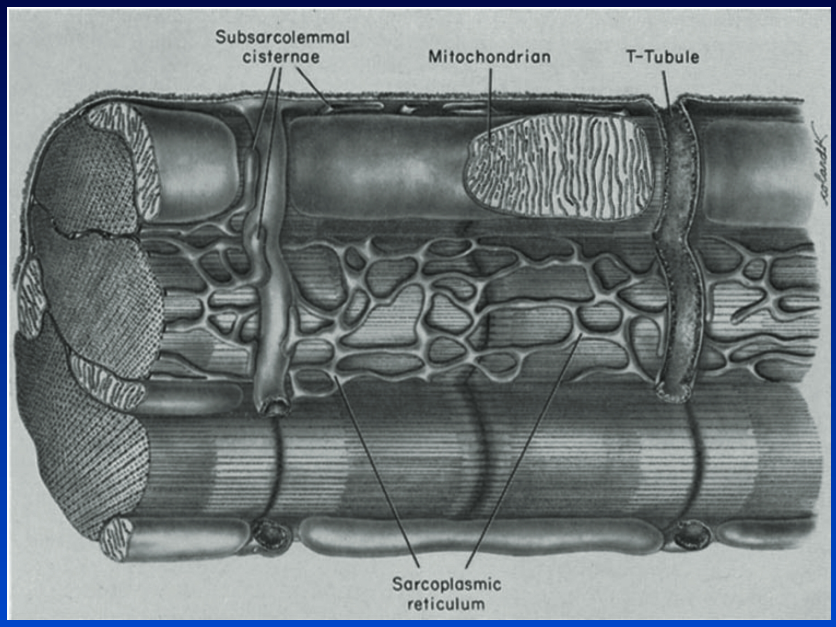


Some Characersistics of EC Coupling

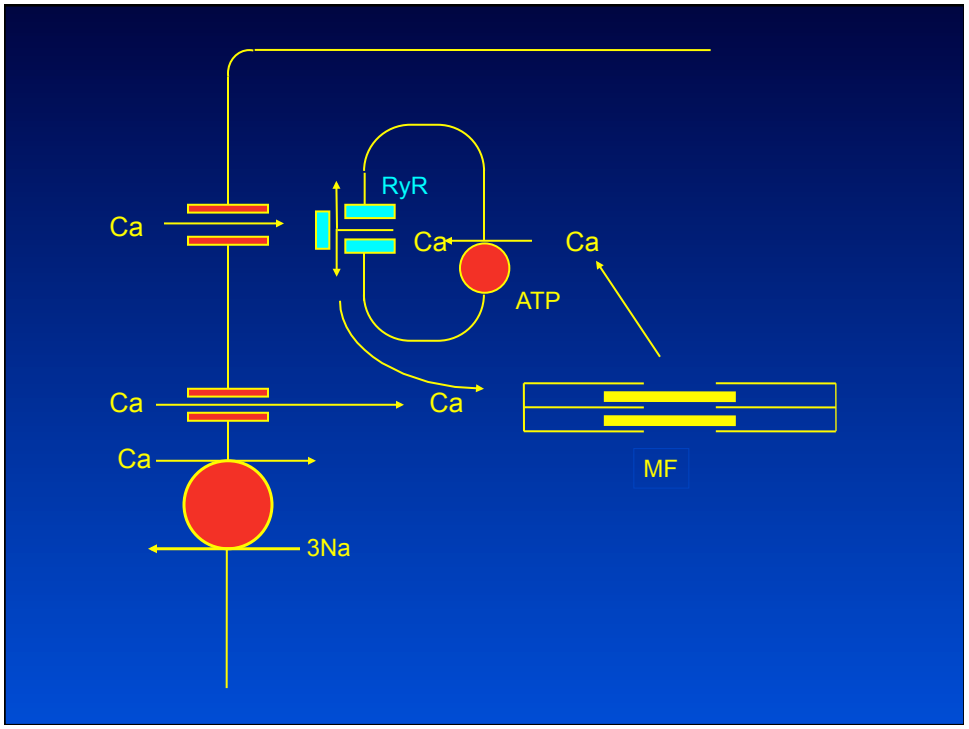
- Sidney Ringer clearly recognized that extra cellular Ca is required for contraction in heart.
- In heart cells contraction can be graded rather than all or none.
- To produce graded contractions EC coupling in heart must possess mechanisms that eliminate positive feedback
- Mechanisms and theories of EC coupling must accommodate these facts.

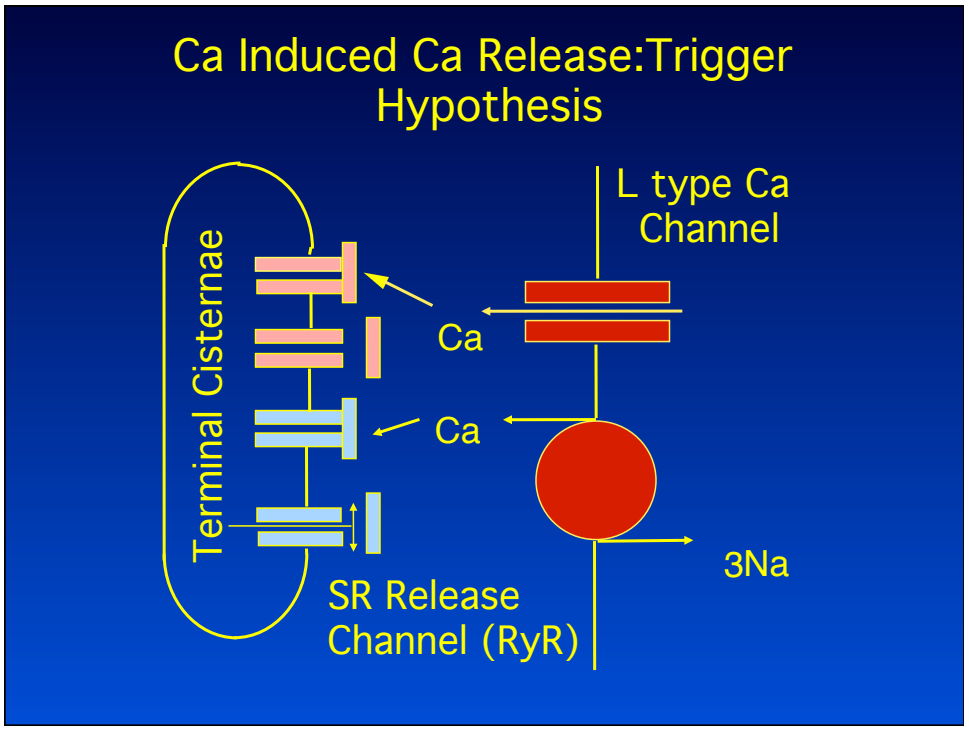
Ca^{2+} sparks and the Ca^{2+} transient

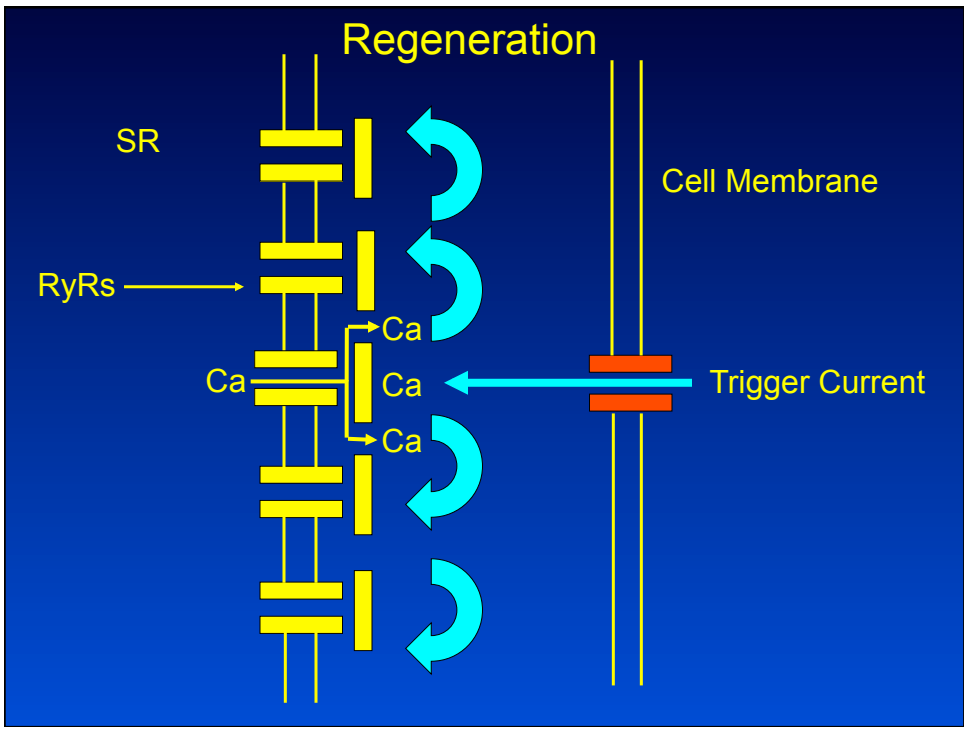


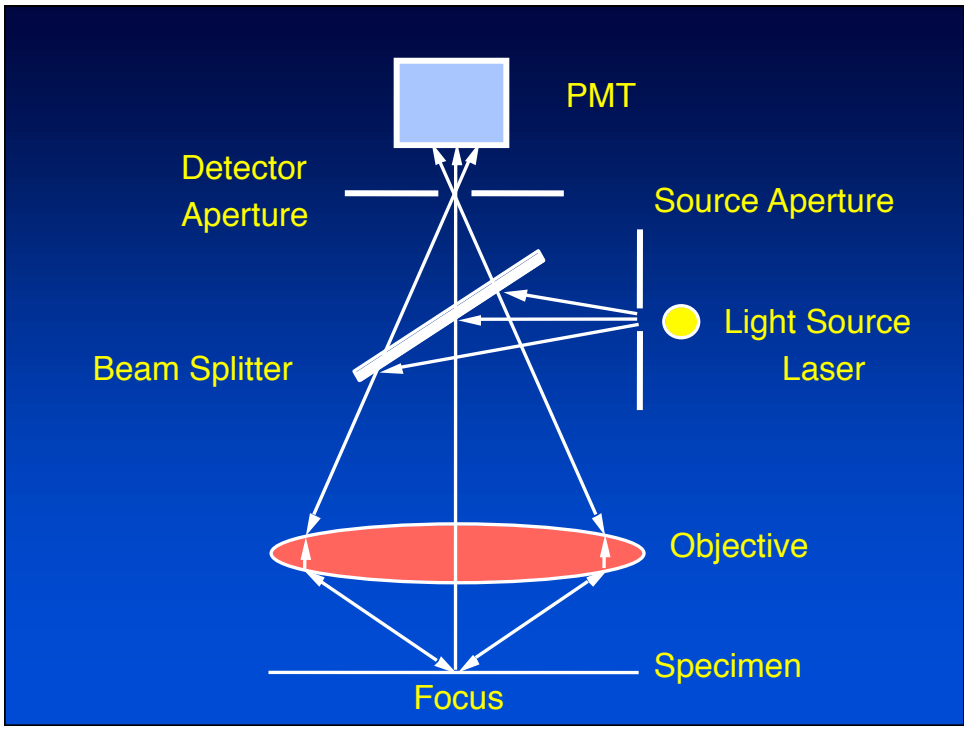


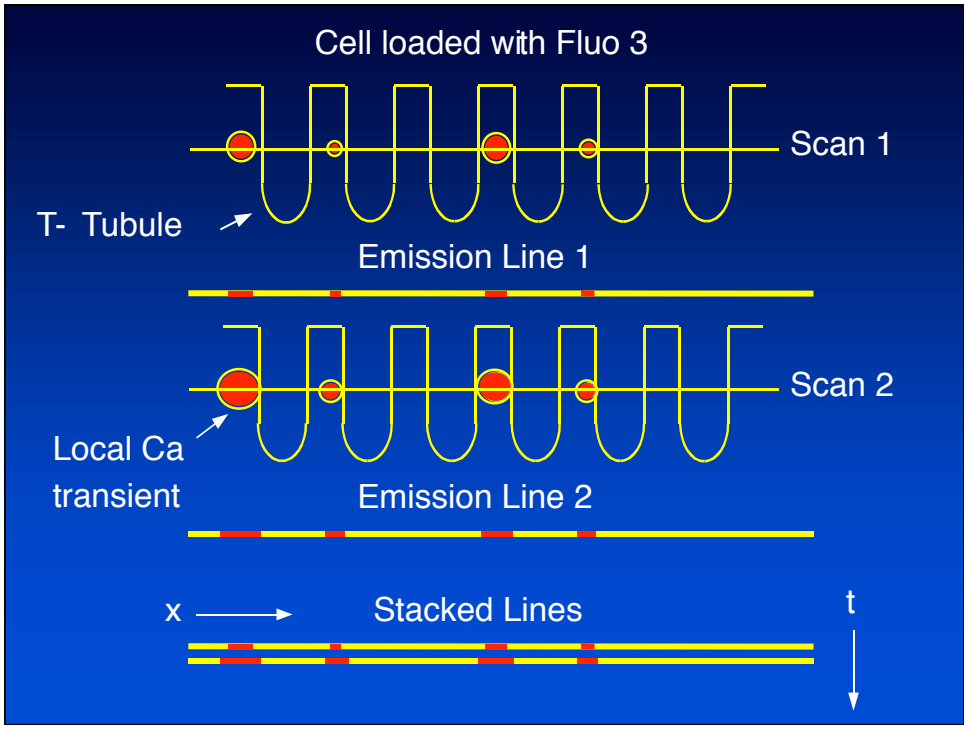
From Fawcett and Mc Nutt , 1969

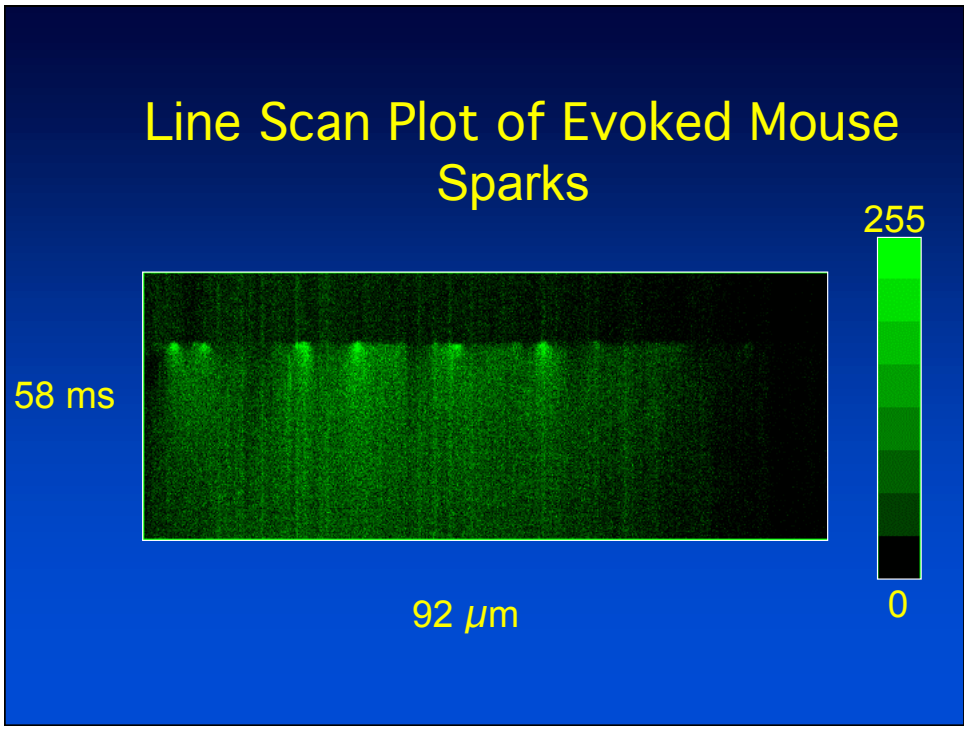

RyR
Ca
Ca
Ca
ATP
Ca
Ca
Ca
MF
3Na


Ca Induced Ca Release:Trigger Hypothesis
L type Ca Channel
Terminal Cisternae
Ca
Ca
3Na
SR Release Channel (RyR)

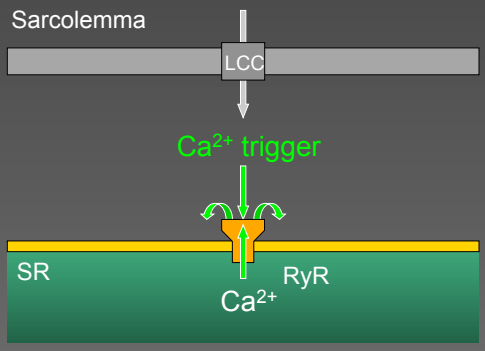

Regeneration
SR
RyRs
Ca
Ca
Ca
Ca
Cell Membrane
Trigger Current

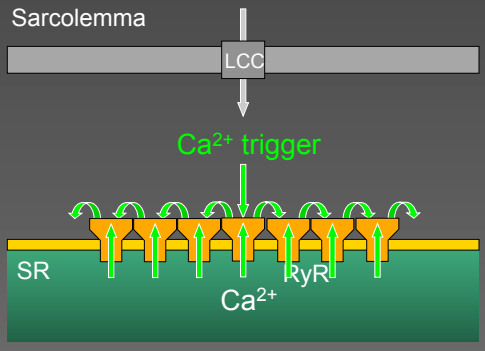

PMT
Detector
Aperture
Source Aperture
Light Source
Laser
Beam Splitter
Objective
Specimen
Focus

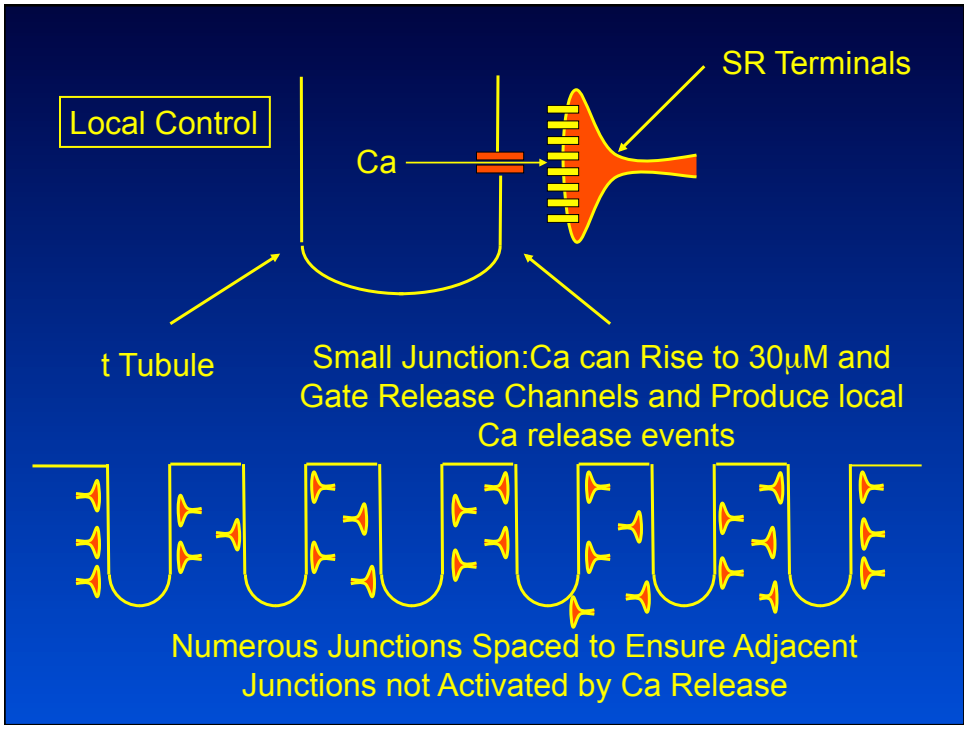

Cell loaded with Fluo 3
Scan 1
T- Tubule
Emission Line 1
Scan 2
Local Ca
transient
Emission Line 2
x
Stacked Lines
t


Line Scan Plot of Evoked Mouse Sparks
255
58 ms
0
92 μm

Preliminary Ideas on Couplons





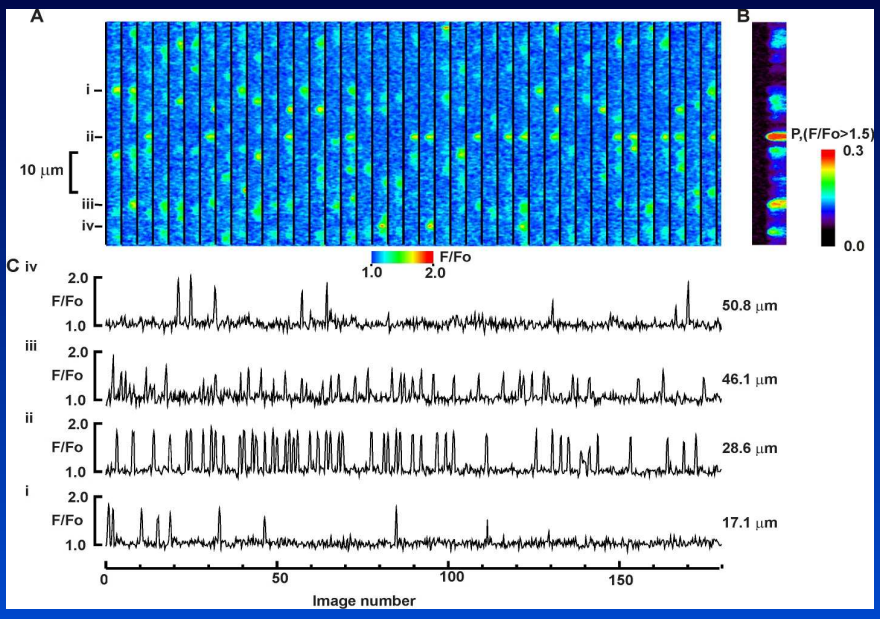


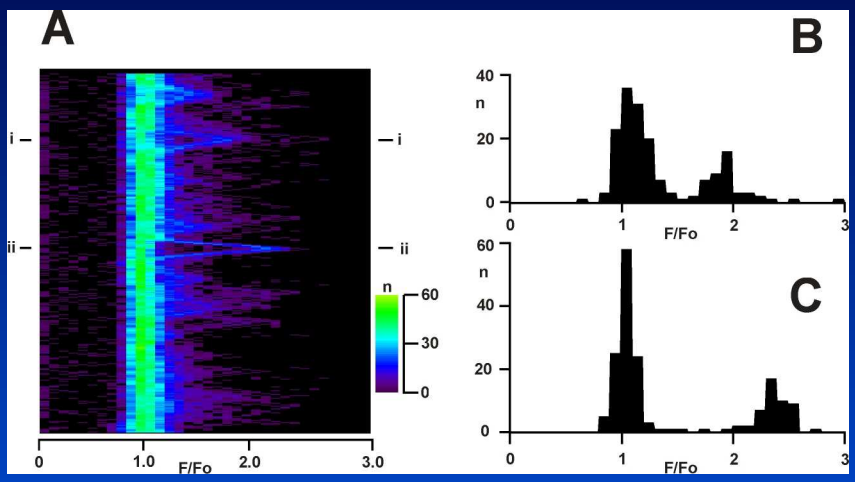
Is a Single RyR Responsible for Producing a Spark

- It is important to understand two aspect of the structure of junctional regions
- The first is the number of RyRs responsible for generating a spark
- The second is the number of L-type Ca channels required to trigger a spark

Single Channel Sparks

- Open time frequency histogram exhibits an exponential distribution
- Spark amplitude $\propto \int Ca\ flux_{ryr}.dt$
- Therefore we expect spark amplitudes to distribute exponentially if they are produced by a single channel

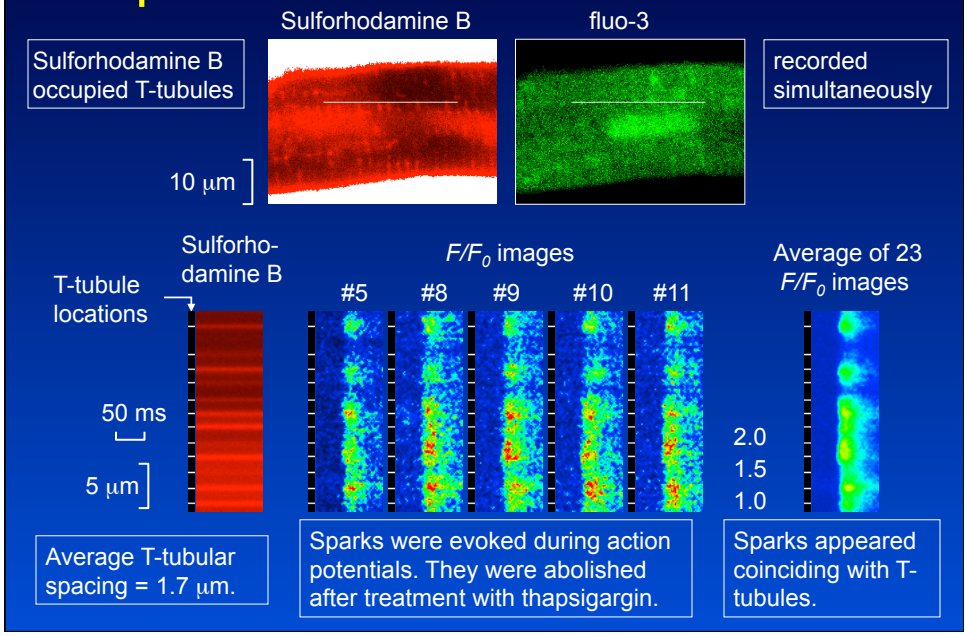




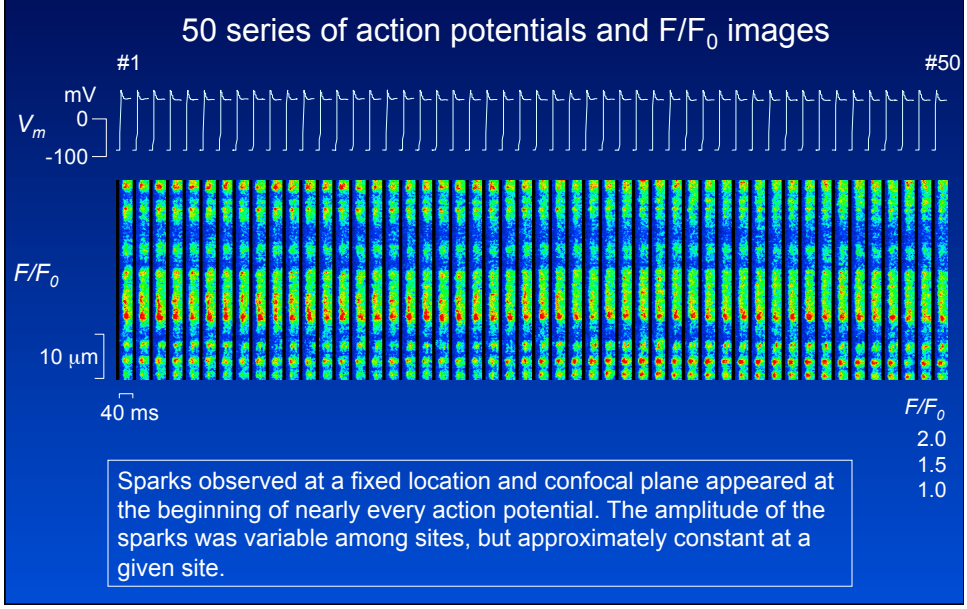
The Structure of the Junction

Although is appears that a cluster of RyRs contribute to the formation of a spark, it is not clear how many L-type Ca^{2+} channels are required to ensure that a spark is triggered. We investigated this by examining both the properties of Ca^{2+} sparks evoked by action potentials and single channel activity in rabbit ventricular myocytes.

Sparks and T-tubule locations

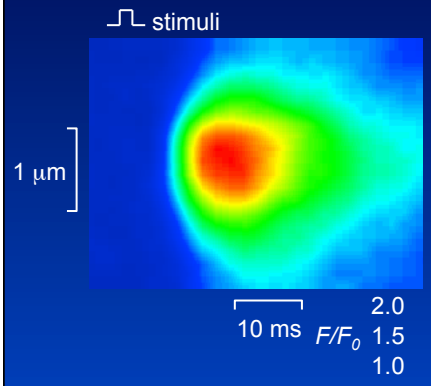


Sparks produced by sequential stimuli

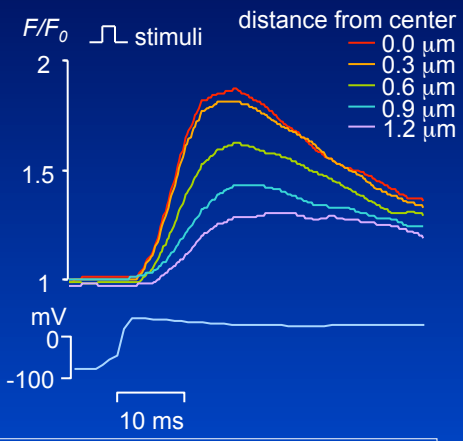


Properties of signal-averaged spark

Averaged single spark



Spark profiles and action potential

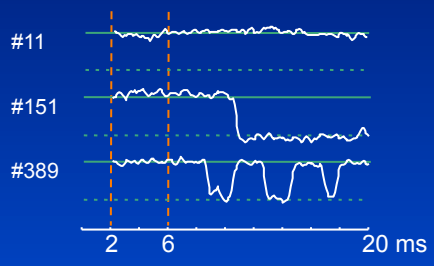


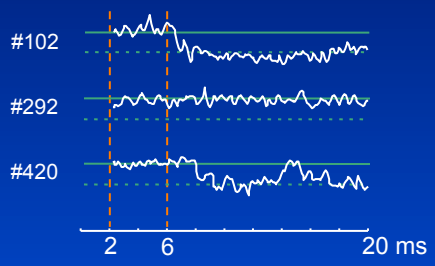
Spark size = 1.8 μm (at half maximum width)

10% of the peak of every spark occurred with latency of 2 - 6 ms from the peak of every action potential.

Probability of null sweeps

- We detected all open events in 1000 sweeps during the period 2 - 6 ms after the clamp pulses.
- Open events are detected at half-amplitude threshold.
- From this, we calculated the probability of null sweeps at +10 mV and +50 mV.





$P_{null+10mV} = 0.58$

$P_{null+50mV} = 0.17$

Summary - Ca^{2+} sparks

- The properties of sparks in rabbit ventricular myocytes are similar to those in other species.
- Sparks at fixed sites during a series of action potentials occurred at the beginning of nearly every action potential, i.e., they appeared with a probability ~ 100%. Close examination of spark probability revealed a small proportion of spark failures, i.e., 0.3%.
- Sparks occur in a limited interval 2 - 6 ms after the action potential peak.