Synchronization of stochastic calcium waves in atrial cells

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Outline

1. Calcium waves and cardiac arrythmias

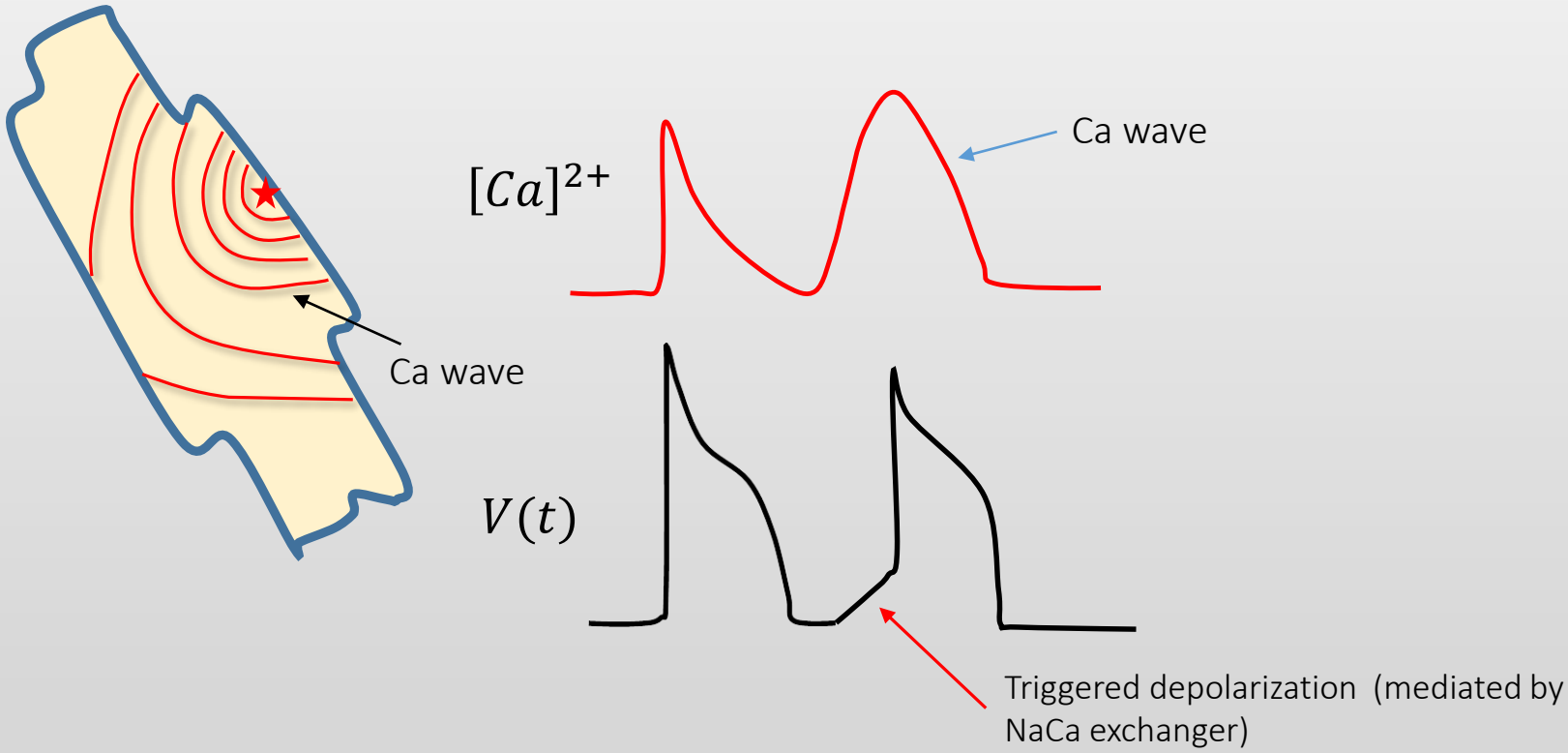
2. The problem of synchronization

3. Detailed and phenomenological modeling of Ca cycling in atrial myocytes

4. Mechanisms of Ca wave synchronization in cardiac tissue

Ca waves and triggered activity

Ca waves can induce triggered excitations

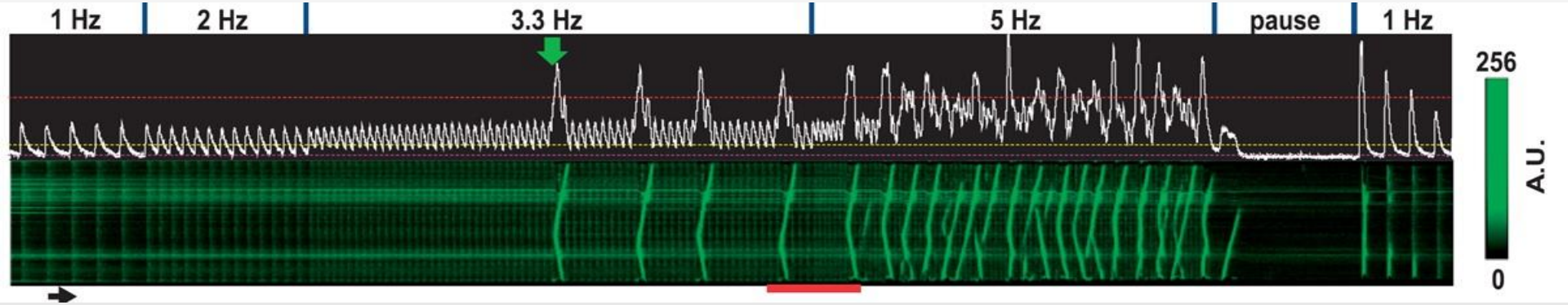


It is generally believed that triggered depolarization can propagate in tissue and initiate Arrythmia.

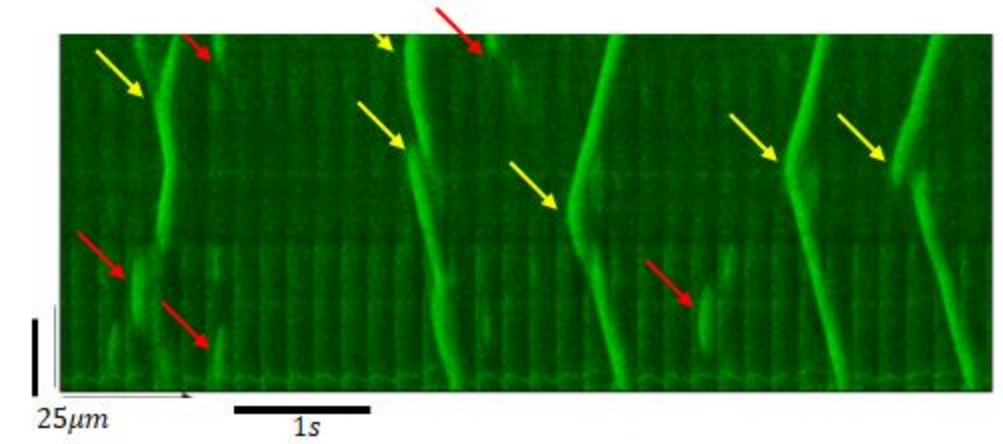
A wide range of arrhythmias have been attributed to a distruption in Ca cycling.

Ca waves are stochastic events

Dog atrial myocyte



Aistrup et al, Cardivascular Research 2017



Stochasticity is due to fluctuations at the ion channel level which determine wave nucleation.

Can these stochastic events induce electrical excitations at the tissue scale?

Electrical coupling averages voltage over a length scale

$$\xi \sim \sqrt{D_V CL} \approx 5mm$$

This corresponds to roughly 100 cells (in 1D) and over a million in 3D.
Therefore, stochastic triggered waves effect on voltage averaged out over many cells.

Therefore, in cardiac tissue stochastic Ca activity must be synchronized over hundreds of thousands of cells.

How can stochastic Ca waves, which originates at the subcellular scale, be Synchronized between large populations of cells??

A computational challenge

A multiscale approach to model stochastic Ca waves at the subcellular scale, and their effects in populations of millions of cells

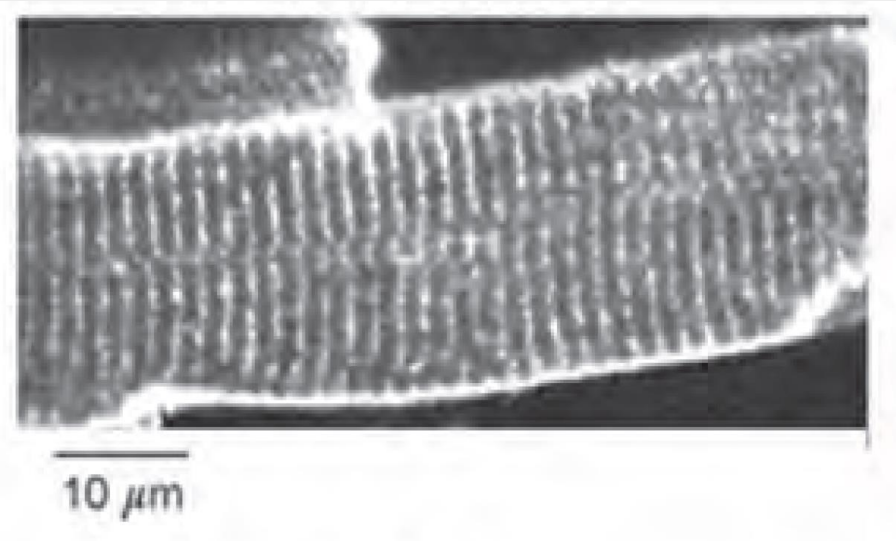
Length and time scales

Signaling between ion channels: $\text{space} \sim 1 - 10\ nm$ $time \sim 0.01 - 0.1\ ms$

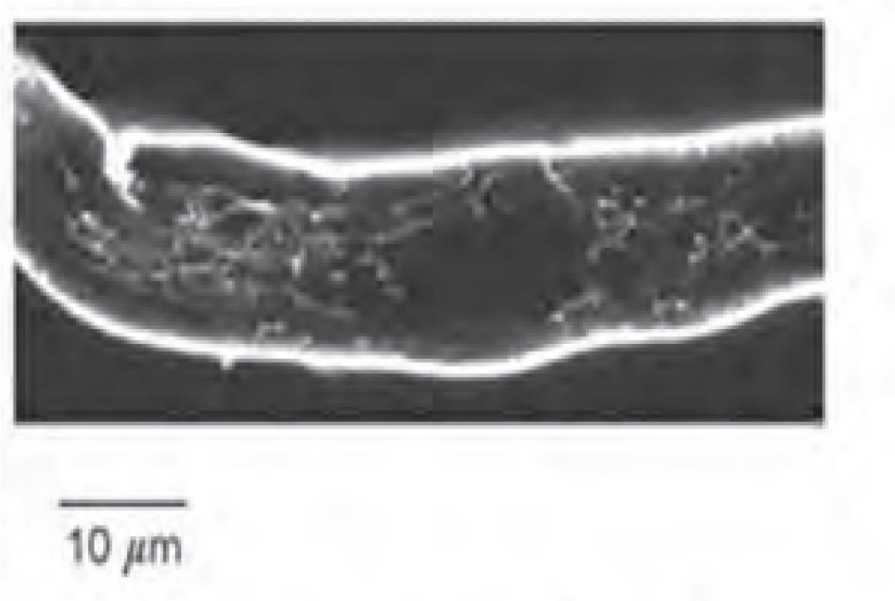
Tissue excitations: $\text{space} \sim mm$ $time \sim 1 - 1000 ms$

To model atrial cells we have to account for their unique architecture

Ventricular myocyte



Atrial myocyte

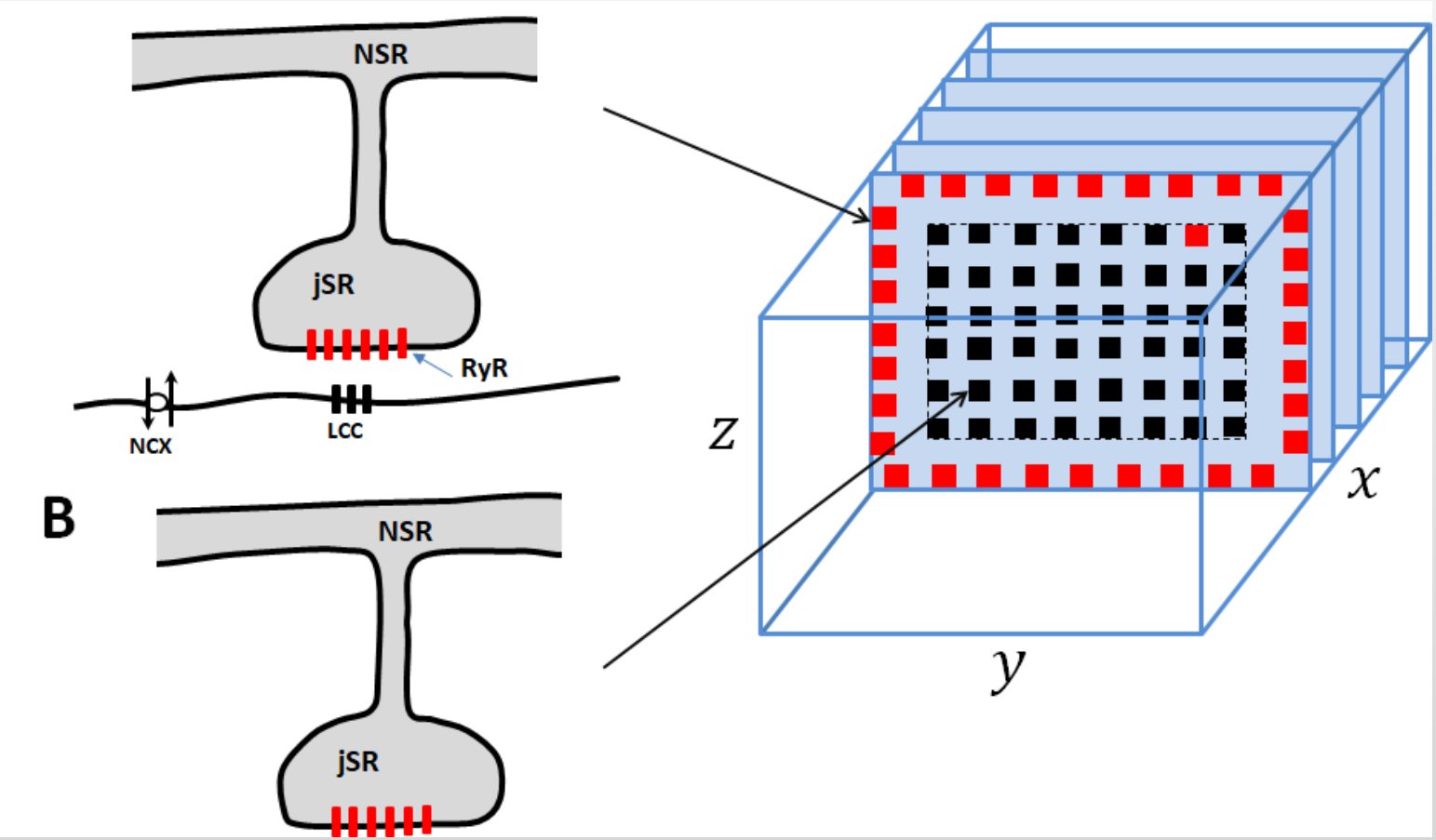


Di-8-ANEPS membrane staining of rat myocyte

Kirk et al. J. Physiol, 2004

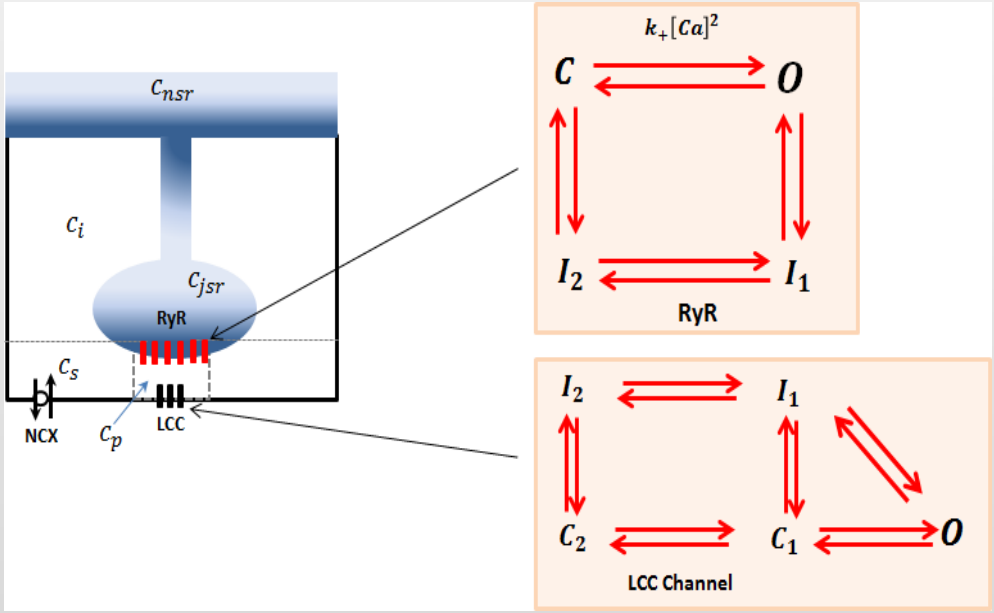
Atrial myocytes lack a well developed t-tubule system
Signaling occurs mostly at the cell boundary.

Detailed computational model of subcellular Ca in atrial cells



Stochastic simulations of $60 \times 20 \times 20$ lattice of compartments

Model structure



$$\frac{dc_p}{dt} = \beta_p \left(I_{RyR} + I_{ca} - \frac{c_p - c_s}{\tau_{ds}} \right)$$

$$\frac{dc_s}{dt} = \beta_s \left(\frac{c_p - c_s}{\tau_{ds}} \left(\frac{v_p}{v_s} \right) - \frac{c_s - c_i}{\tau_{cs}} + I_{NCX} \right)$$

$$\frac{dc_i}{dt} = \beta_i \left(\frac{c_s - c_i}{\tau_{cs}} \left(\frac{v_s}{v_i} \right) - I_{up} \right)$$

$$\frac{dc_{jsr}}{dt} = \beta_{jsr} \left(\frac{c_{nsr} - c_{jsr}}{\tau_{csr}} - I_{RyR} \left(\frac{v_p}{v_{jsr}} \right) \right)$$

$$\frac{dc_{nsr}}{dt} = I_{up} \left(\frac{v_i}{v_{nsr}} \right) - \left(\frac{v_{jsr}}{v_{nsr}} \right) \frac{c_{nsr} - c_{jsr}}{\tau_{csr}}$$

$$I_{RyR} = g_{RyR} n_o (c_{jsr} - c_d)$$

$$I_{ca} = g_{ca} m_o (c_o - c_d)$$

Stochastic variables

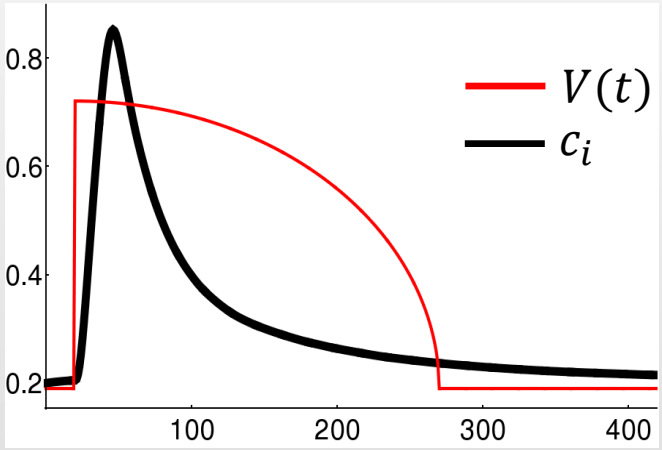
$n_o = \#\ of\ \ RyR\ channels\ in\ state\ O$

$m_o = \#\ of\ \ LCC\ channels\ in\ state\ O$

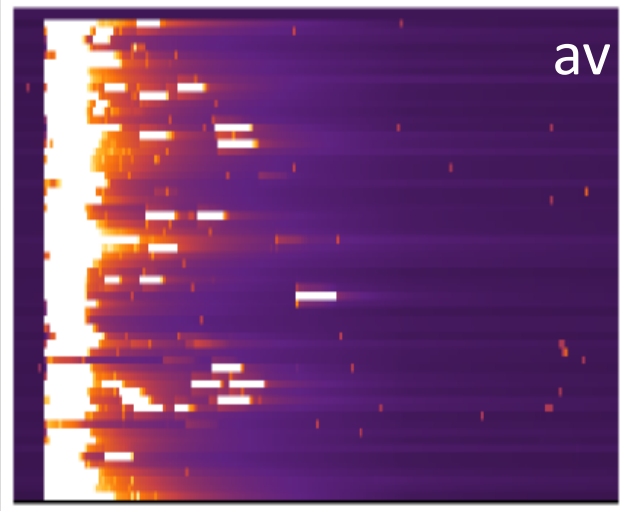
Restrepo et al. 2008

Simulation of normal Ca release in response to AP clamp

$c_{sr} = 1100\mu M$



c_i (μM)

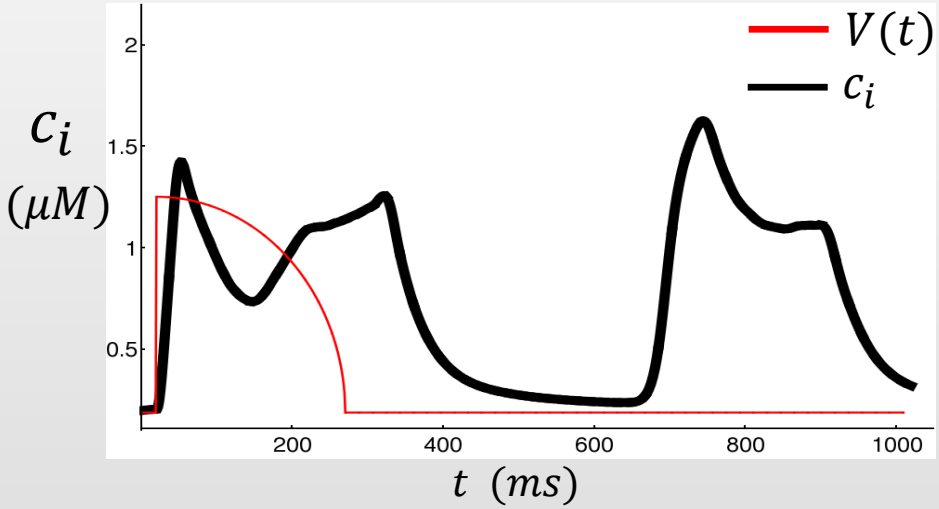


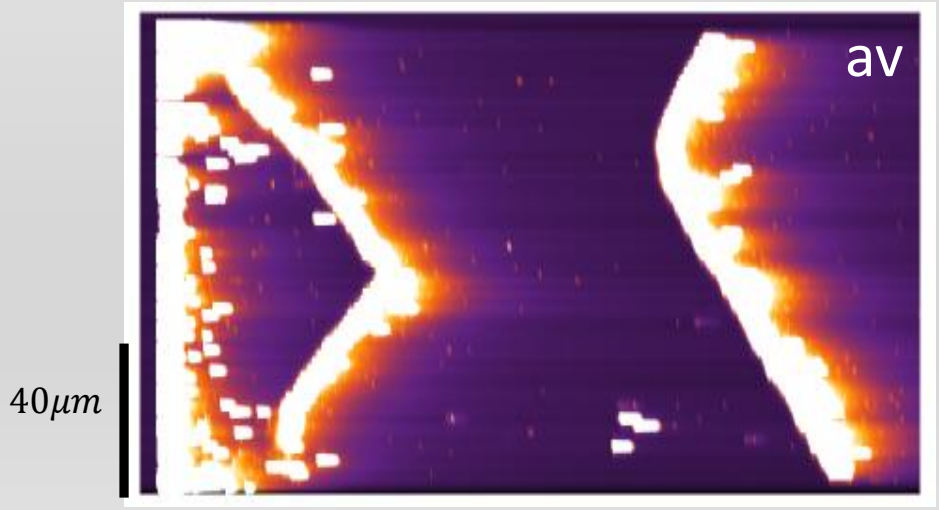
t (ms)

$t = 20ms$

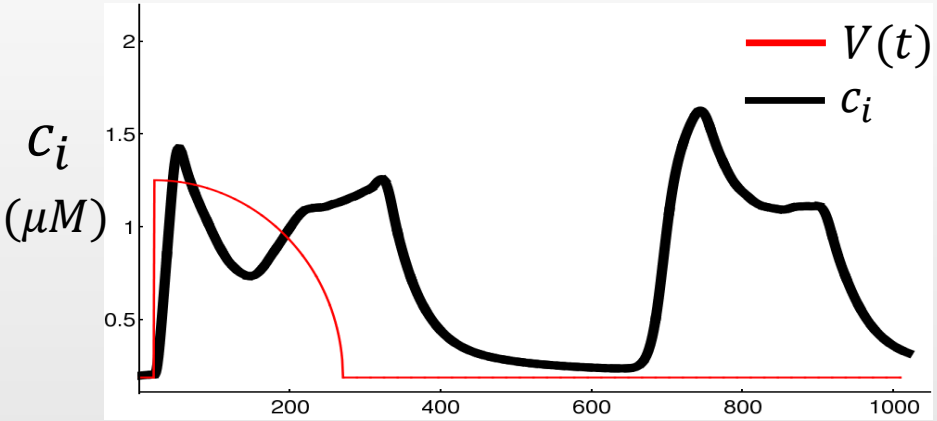
Response at higher SR load

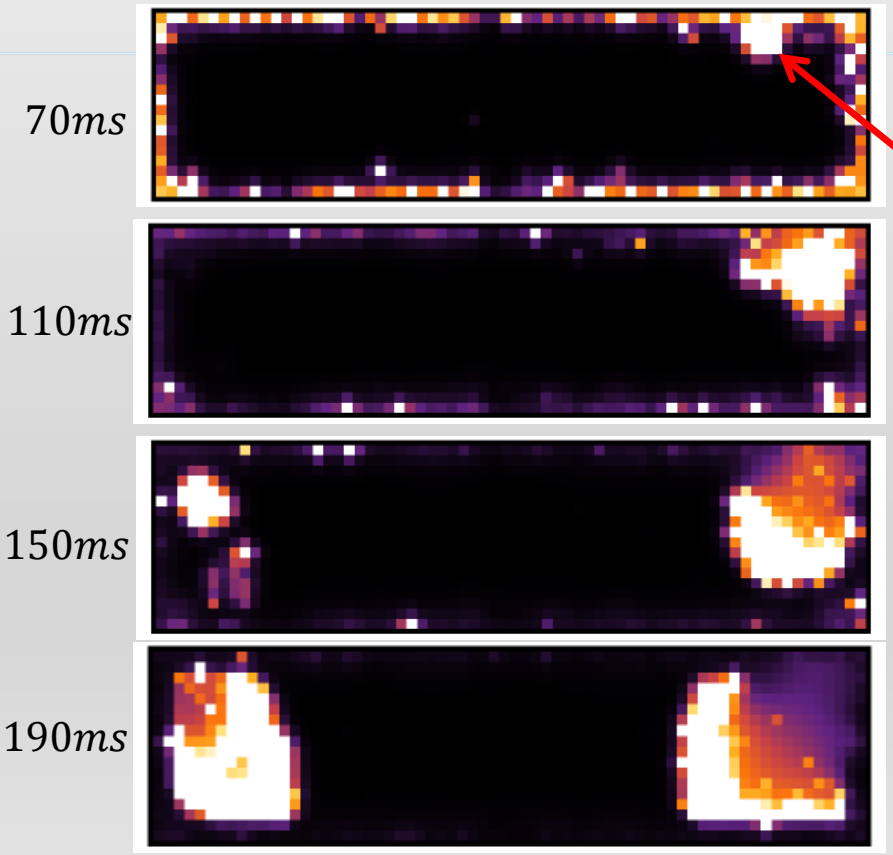
$$c_{sr} = 1230\mu M$$





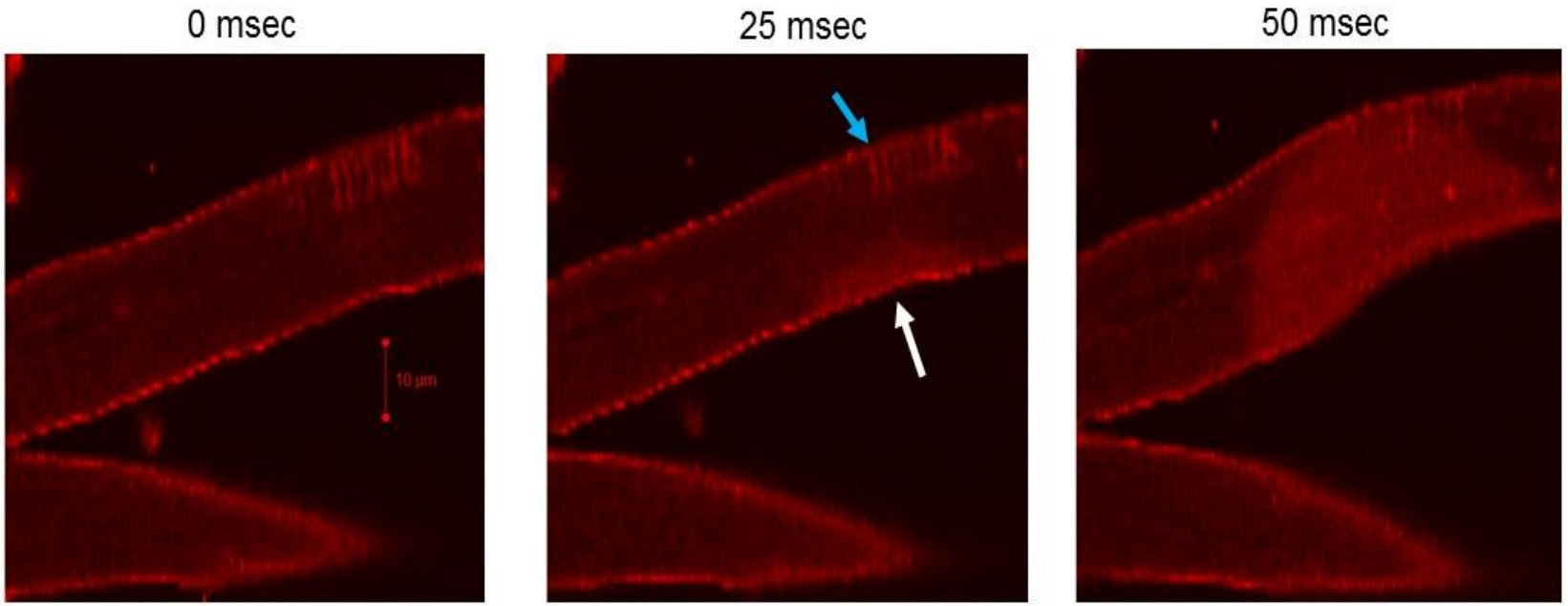
Ca waves are excited from the cell boundary





Release at boundary can *Trigger Ca waves* in the cell Interior.

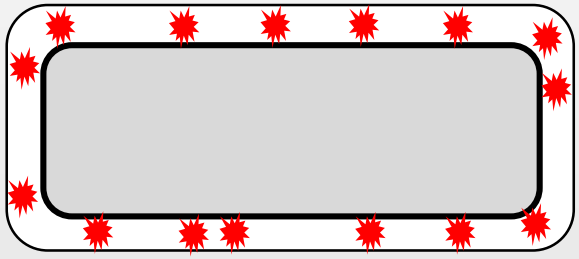
2D Imaging confirms mechanism



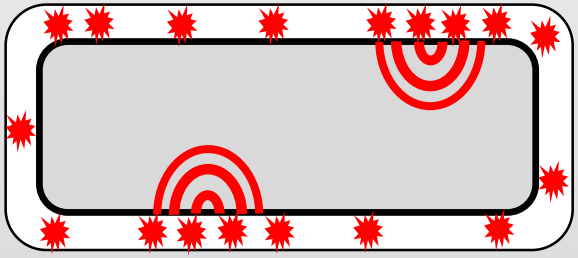
From Wasserstrom lab

Mechanism for Ca waves (dog atria)

normal

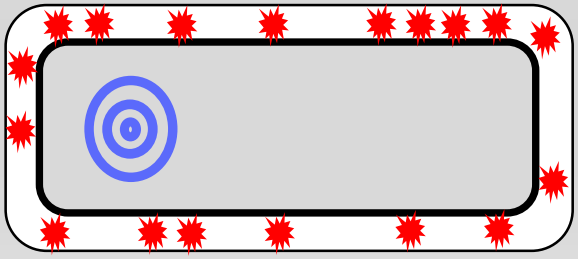


Triggered wave



Wave nucleation at cell boundary due to L-type Ca current triggered Ca sparks

Spontaneous wave



Wave nucleation in interior due to stochastic fluctuations. Typically longer waiting times.

Tissue modeling problematic

Detailed model is intractable in tissue since it requires stochastic simulation of several million Ion channels within hundreds of thousands of cells in 3D cardiac tissue.

Need a phenomenological model that captures the stochastic and nonlinear dynamics and can be implemented in cardiac tissue.

Phenomenological modeling of Ca cycling

We will apply a population dynamics approach and keep track only of the number of sparks in a population of RyR clusters. Avoid keeping track of Individual channel states.

The number of sparks will obey a simple rate process:

$$NS \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} S$$

NS: no spark
S: spark

α → Rate of spark recruitment from population of available RyR clusters
β → Rate of spark extinction

Stochastic simulation of spark number

Let N be the number of clusters and $n(t)$ is the number of sparks at time t:

$$n(t + \Delta t) = n(t) - \Delta n^{-} + \Delta n^{+} .$$

Change in channel numbers is taken to have a binomial distribution.

Number of sparks that extinguish: $\Delta n^{-} \rightarrow B(\beta \Delta t, n).$

Number of new sparks: $\Delta n^{+} \rightarrow B(\alpha \Delta t, N - n).$

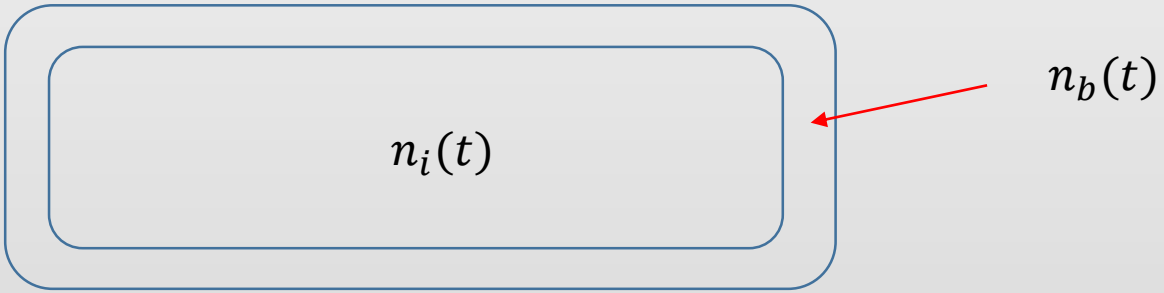
$B(p, n)$ is the number of successes from n trials with probability of success p

This approach should capture the correct statistics of spark number fluctuations.

Phenomenological Ca cycling equations

We can now write ODE models of Ca cycling coupled to stochastic evolution of Ca spark number:

Keep track of spark number in the interior and boundary regions:



Interior

$$NS \underset{\beta_i}{\overset{\alpha_i}{\rightleftharpoons}} S$$

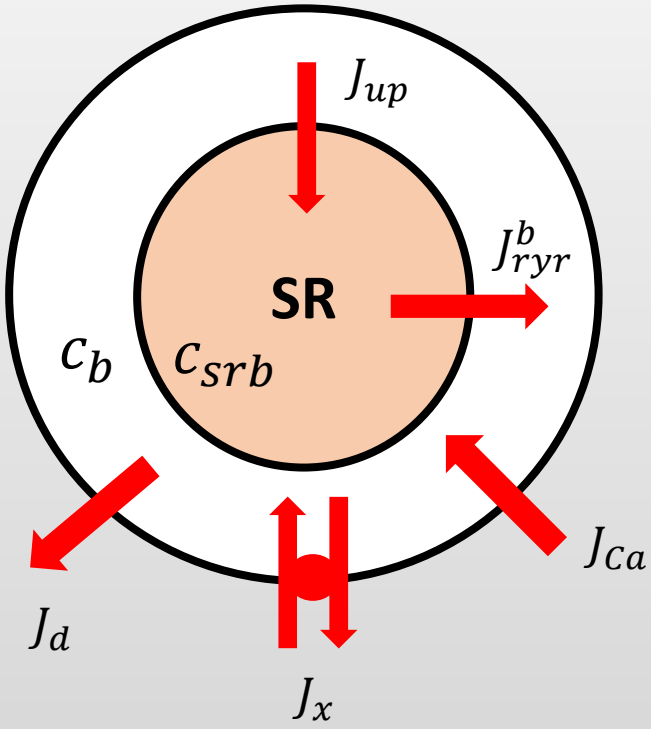
Boundary

$$NS \underset{\beta_s}{\overset{\alpha_b}{\rightleftharpoons}} S$$

NS: no spark
S: spark

Phenomenological Ca cycling equations

Boundary region



c_{srb} & c_b: Average Ca concentration in SR and cytosol of boundary region.

Ca fluxes

J_{Ca}: L-type Ca current

J_x: NaCa exchanger

J_{up}: SERCA pump

J_d: diffusion into the cell interior

J^b_{ryr}: RyR flux

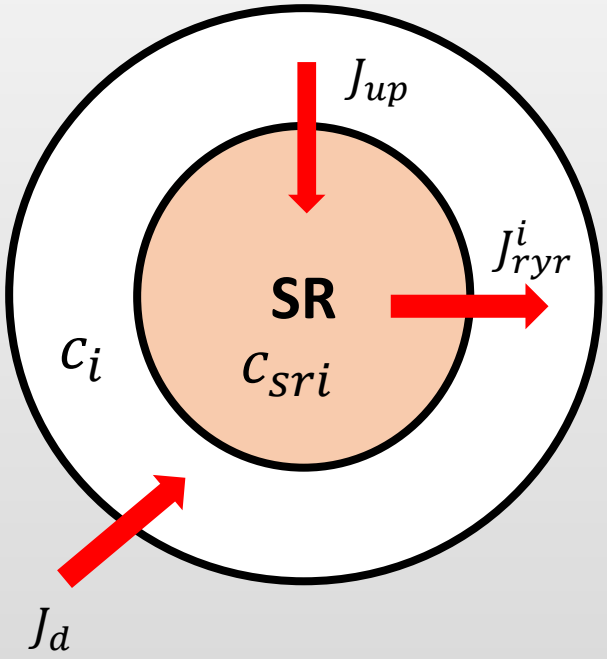
$$J^b_{ryr} = g \cdot n_b \cdot (c_{srb} - c_b)$$

$$\frac{dc_b}{dt} = \beta(c_b)\left(J^b_{ryr} - J_{up}(c_b) + J_x + J_{ica} - J_d\right)$$

$$v^b_{sr}\frac{dc_{srb}}{dt} = \beta(c^b_{sr})(-J^b_{ryr} + J_{up} - (c_{srb} - c_{sri})/\tau_{sr})$$

Phenomenological Ca cycling equations

Interior region



c_{sri} & c_i: Average Ca concentration in SR and cytosol.

Ca fluxes

J_{up}: SERCA pump

J_d: diffusion into the cell interior

J^i_{ryr}: RyR flux

$$J^i_{ryr} = g \cdot n_i \cdot (c_{sr} - c_i)$$

$$\frac{dc_i}{dt} = \beta(c_i)\left(\frac{v_b}{v_i}\right)\left(\left(J^i_{ryr} - J_{up} + J_d\right)\right)$$

$$v^i_{sr}\frac{dc_{sri}}{dt} = \beta(c_{sri})(-J^i_{ryr} + J_{up} + (c_{srb} - c_{sri})/\tau_{sr})\Big)$$

Phenomenological modeling of spark rates

Rate of spark recruitment at boundary sites

$$\alpha_b = A\,|I_{Ca}|\,\phi(c_{srb})$$

I_{Ca}: Ca entry due to L-type Ca current (graded release)

$$\phi(c_{srb}) = \frac{1}{1 + \left(c^*_{srb}/c_{srb}\right)^{\gamma_{sr}}}$$

Sensitivity to SR load

$\gamma_{sr} = 4$

$c_{srb} = 800\mu M$

Sparks extinguish at a rate:

$$\beta_b = \frac{1}{\tau}$$

$\tau = 10 - 40ms$: Average spark lifetime

Phenomenological modeling of spark rates

Recruitment of sparks at internal sites modeled phenomenologically

$$\alpha_i = \left(a\, f_b(p_b) + \; b\, f_i(p_i)\right)\phi(c_{sri})$$

$p_b = n_b/N$: fraction of internal sites with sparks

f_b: sensitivity to fraction of interior sparks

p_b^*: *threshold for boundary-interior interaction*

$$f_b(p_b) = \frac{1}{1 + \left(p_b^*/p_b\right)^{\gamma_b}}$$

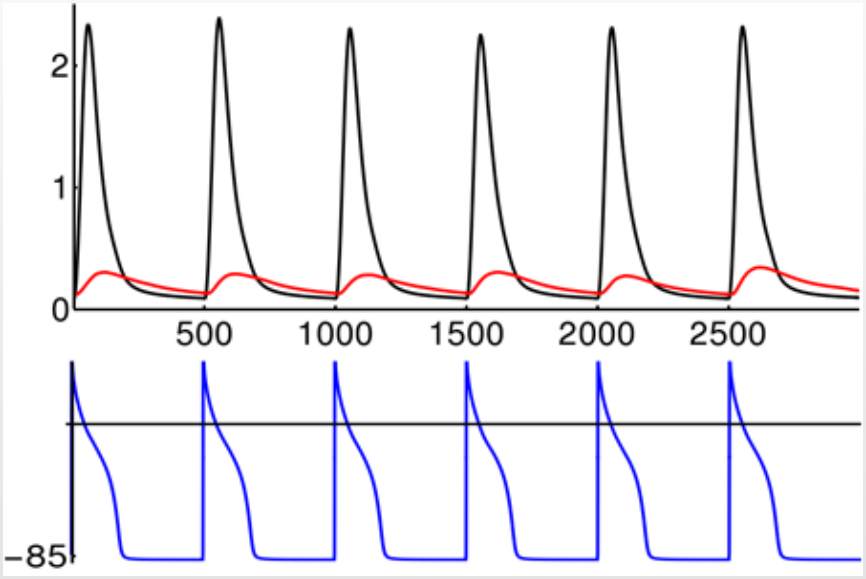
$p_i = n_i/N$: fraction of internal sites with sparks

f_i: sensitivity to fraction of interior sparks

p_i^*: *threshold for Ca wave onset*

$$f_b(p_i) = \frac{1}{1 + \left(p_i^*/p_i\right)^{\gamma_i}}$$

Results



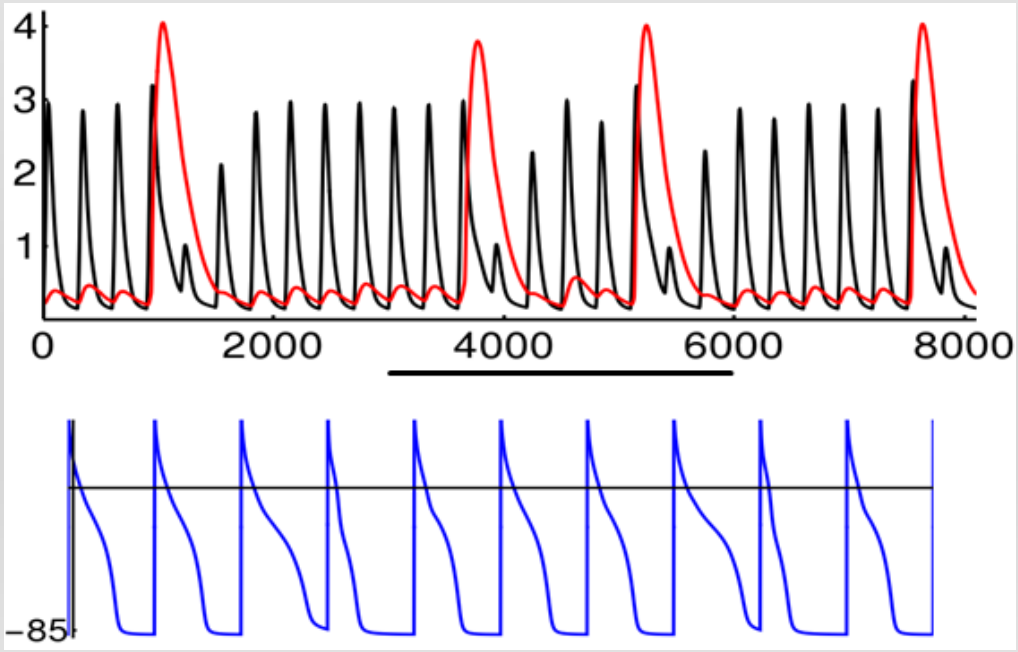
$CL = 500ms$

$\gamma_b = 5, \gamma_i = 8.$

c_i

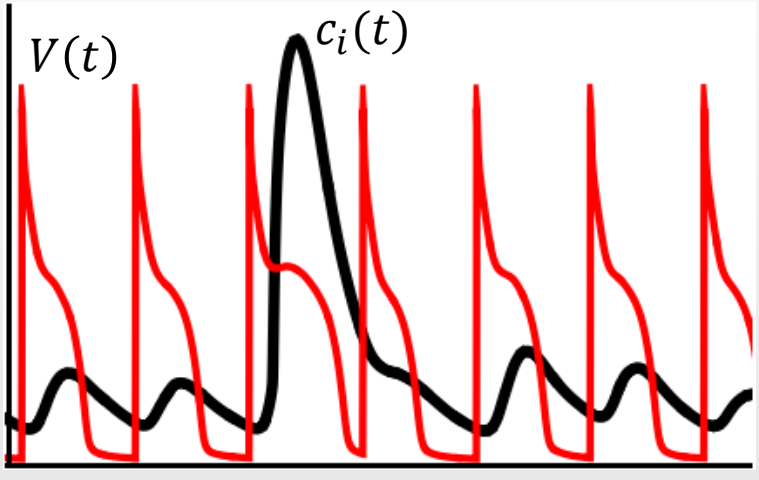
c_b

Coupled to Grandi Human Atrial cell model (2011).



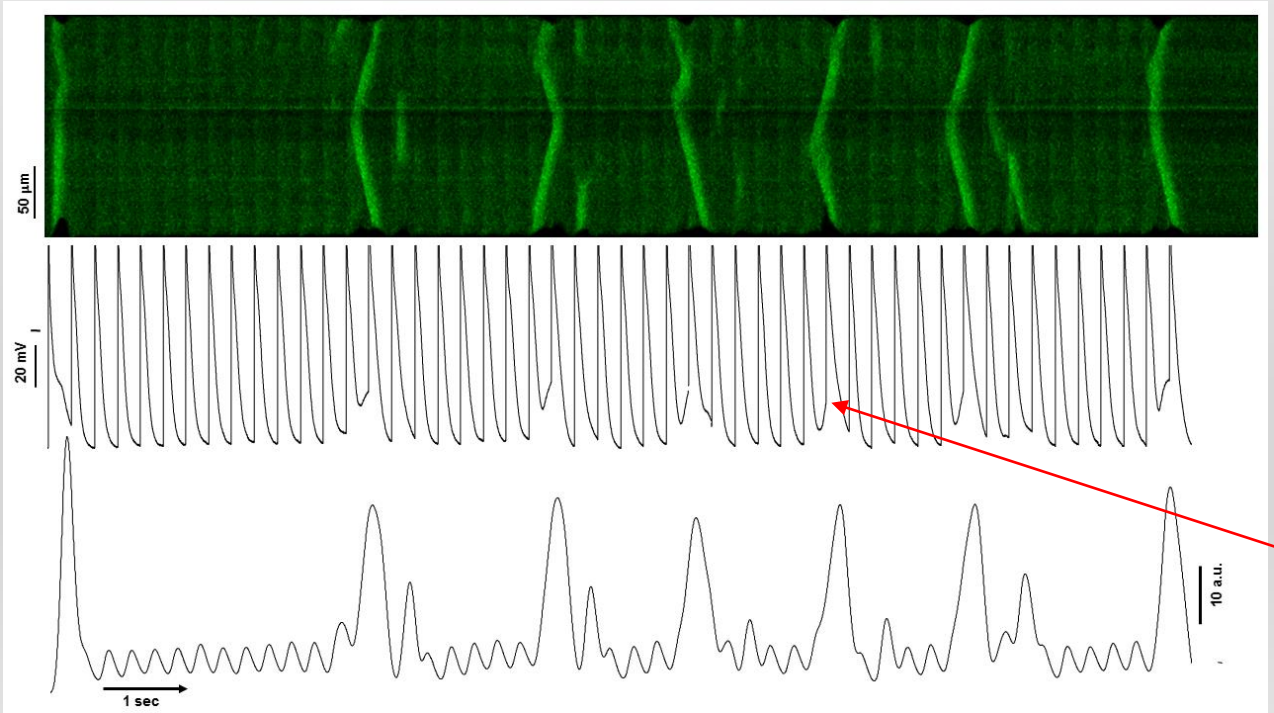
$CL = 300ms$

Triggered waves cause intermittent APD perturbations



$CL = 300ms$

Experiments from Andy's lab



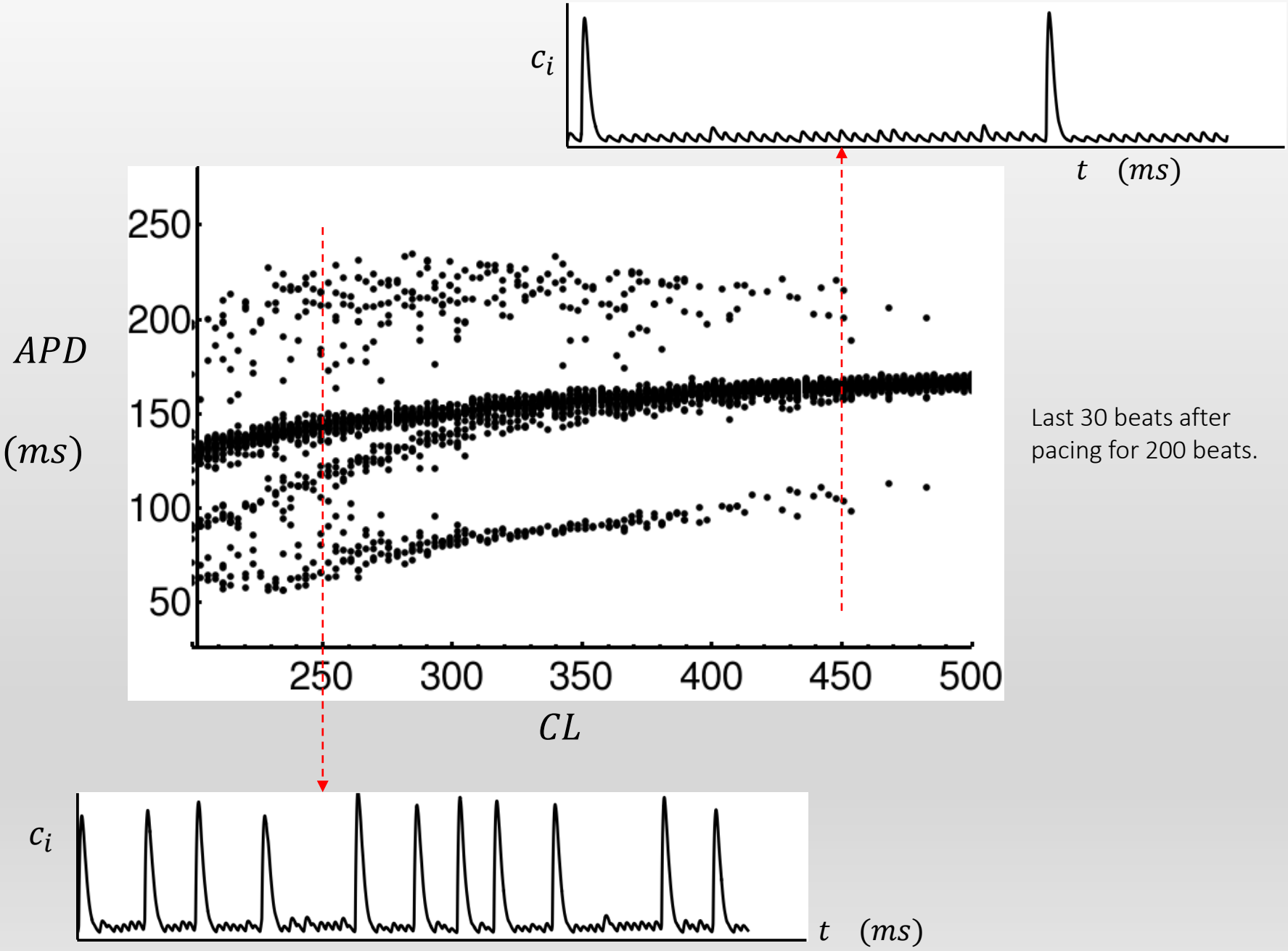
$V(t)$

$c_i(t)$

Isolated dog Atrial myocytes Paced at 3.3Hz Gusak et al. (AHA poster, 2017).

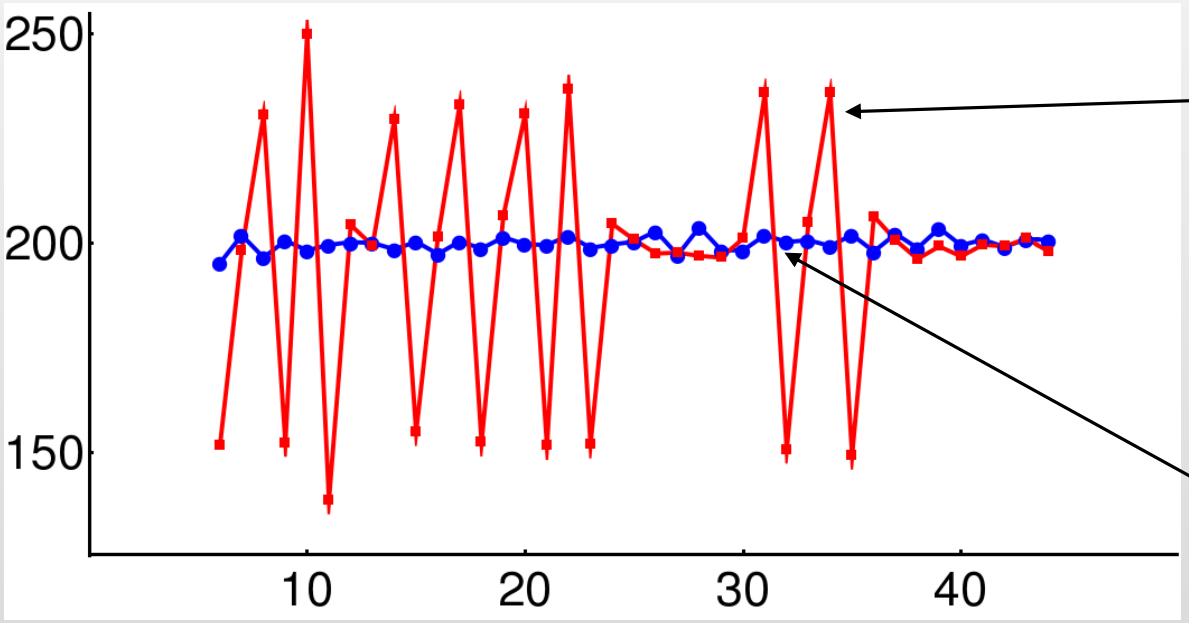
Prolonged AP

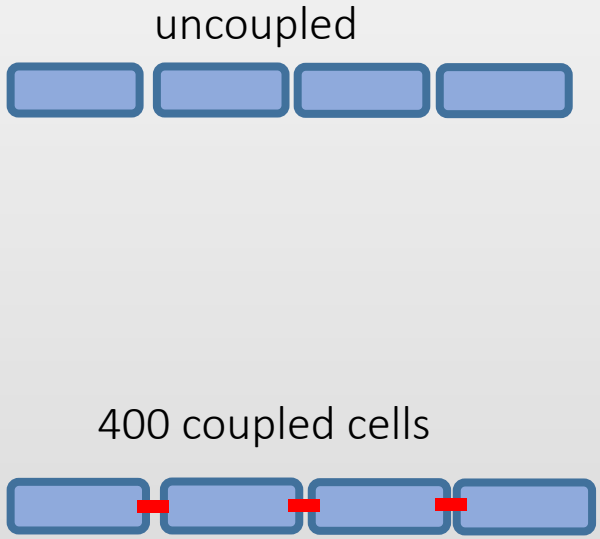
APD perturbations are stochastic and rate dependent



Last 30 beats after pacing for 200 beats.

The problem problem: Electrical couping in tissue eliminates beat-to-beat APD fluctuations



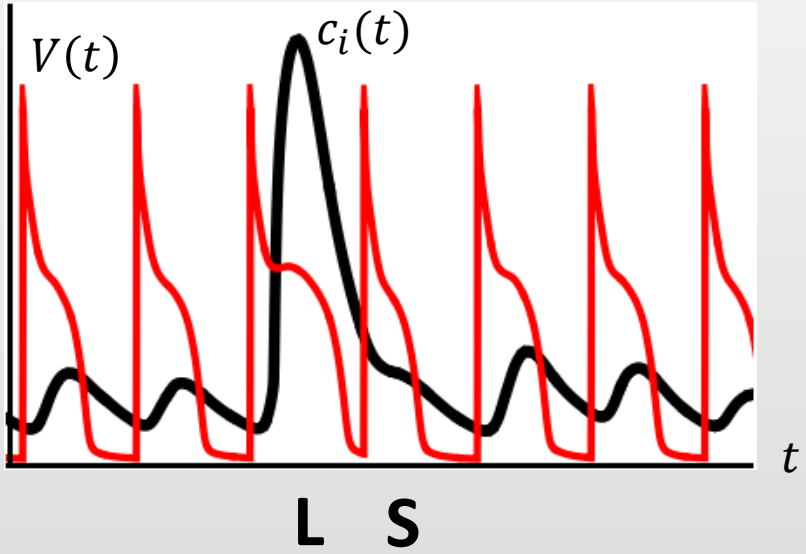


$D_V = 10^{-3} cm^2/ms$

Why?

Electrical coupling averages voltage over a length scale $\xi \sim \sqrt{D_V CL} \approx 5mm$

In the absence of synchronization APD variations tend to cancel



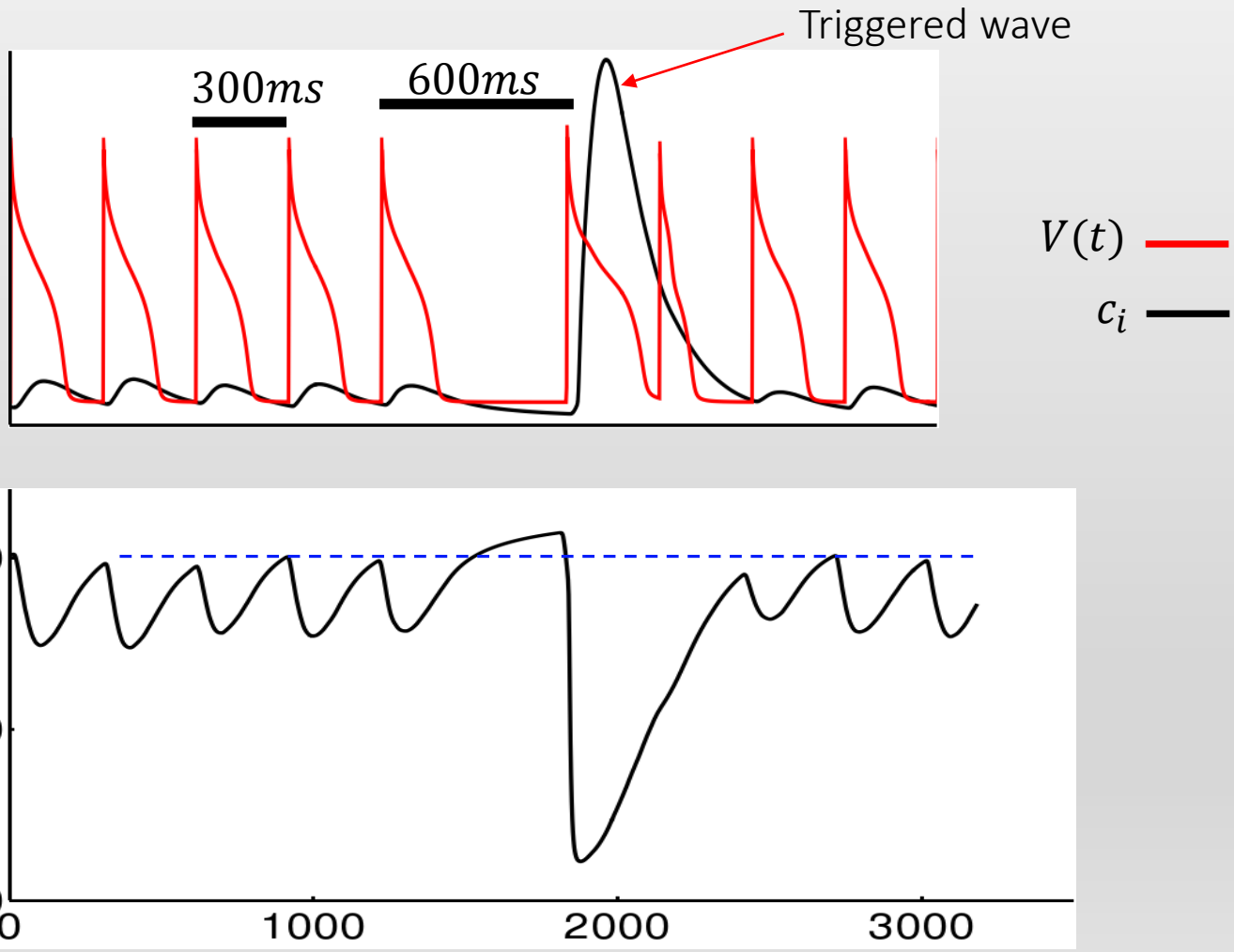
Long (L) and short (S) APD will tend to cancel in a population of cells.

Effectively, random Ca waves in cardiac tissue will lead to minimal beat-to-beat Voltage fluctuations.

Can Ca waves be synchronized in tissue?

Answer: YES! Voltage can be used to synchronize release events over large populations of cells. There are 2 distinct mechanisms:

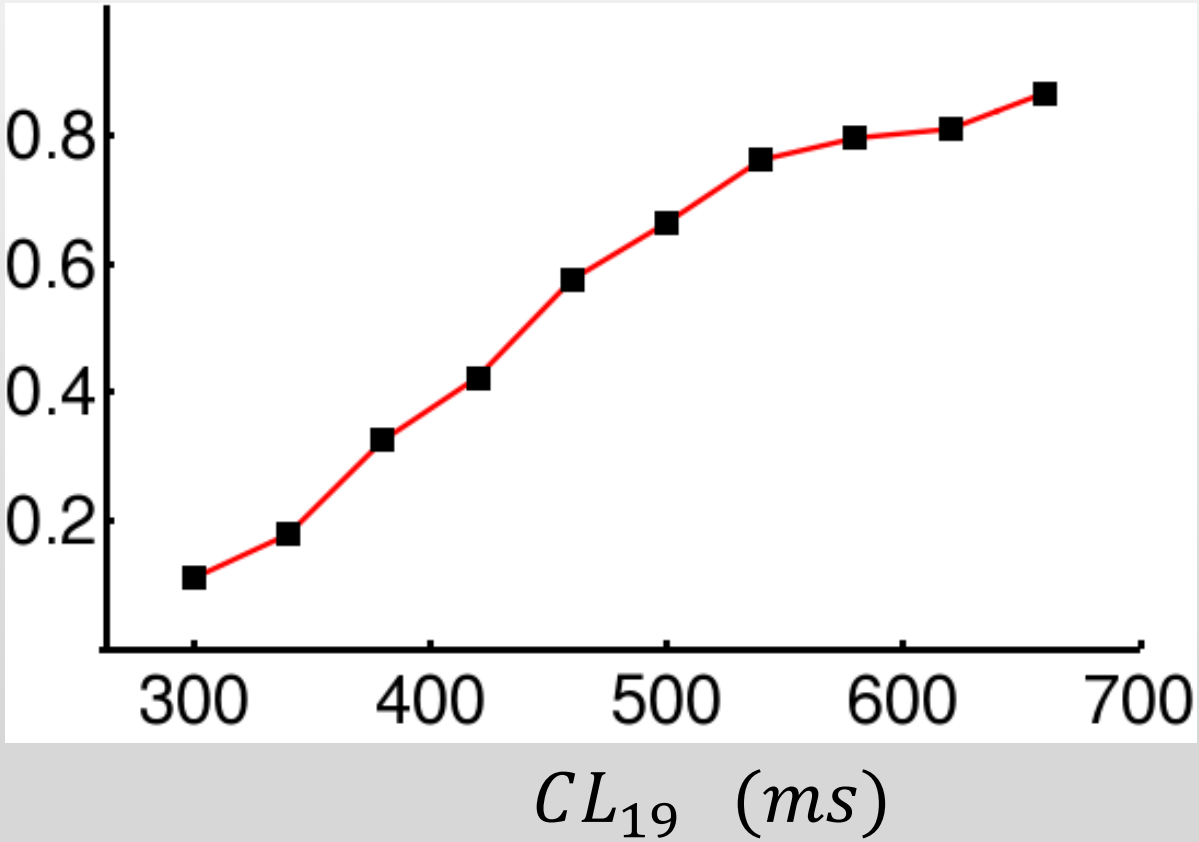
Mechanism 1: Cycle length variability



Synchronization at beat $n+1$ due to prolonged CL at beat n

(on 20th beat)

Probability of triggered wave on 20^{th} beat



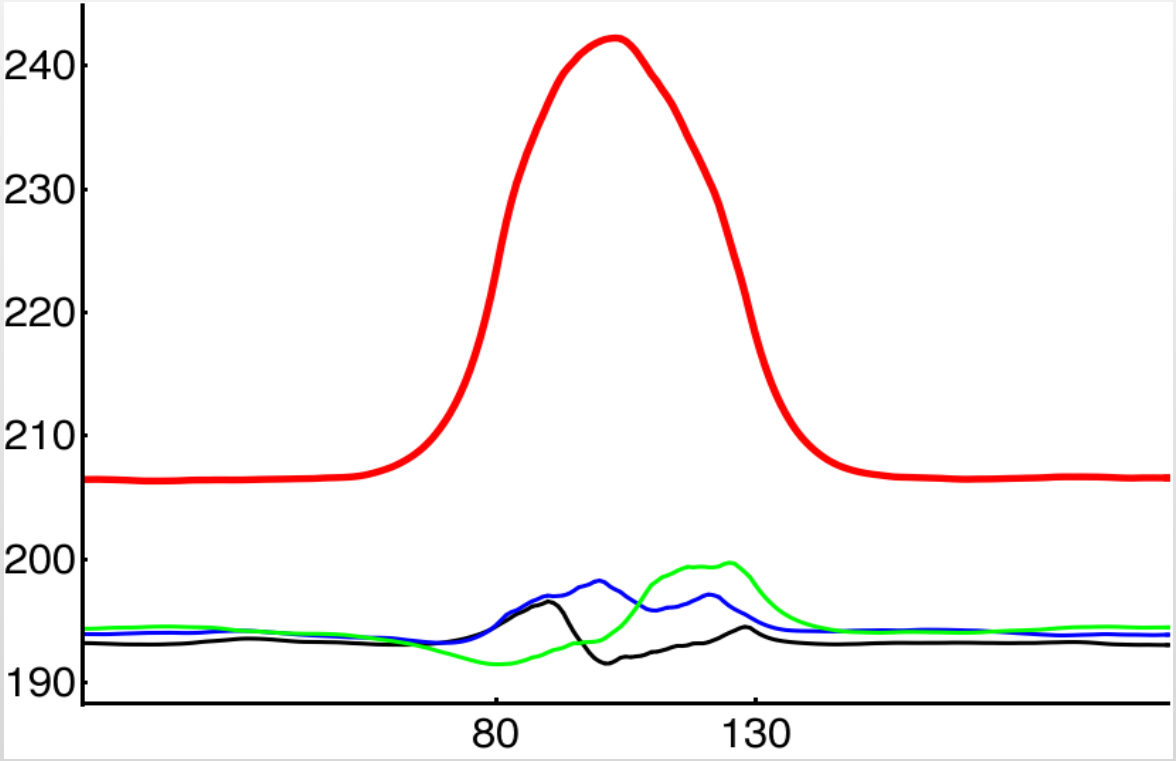
CL of 19th beat increased from basic $CL = 300ms$

Computed using 500 samples.

Heterogeneous 1D cable

210 coupled cells. Only cells 80-130 have triggered waves.

APD_{20}

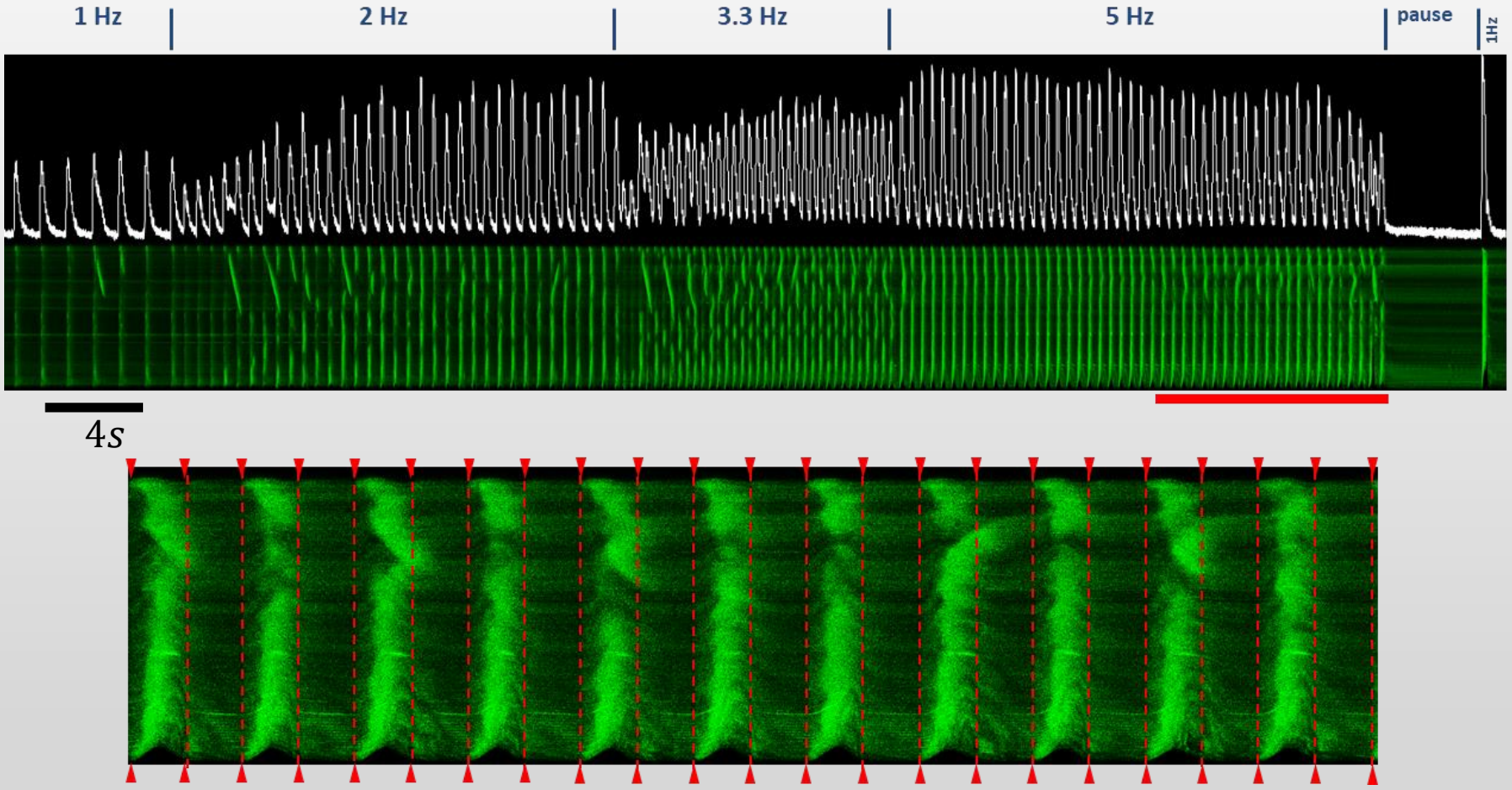


Cell paced at $CL = 300ms$. 19^{th} beat has $CL = 450ms$.

Cycle length variations in atrial tissue amplify the effect of triggered waves in tissue: highly arrhythmogenic. Note: effect in 3D will be even more dramatic given that there are $\sim 10^6$ coupled cells.

Synchronization due to triggered wave alternans

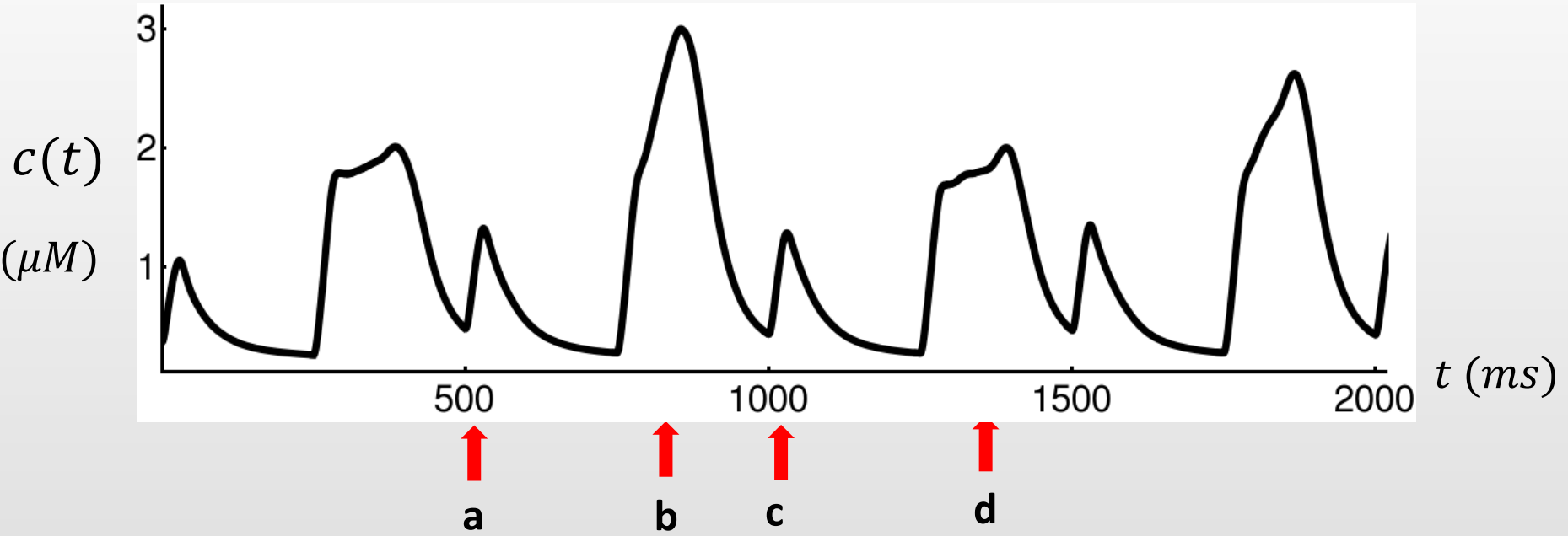
Failing dog hearts

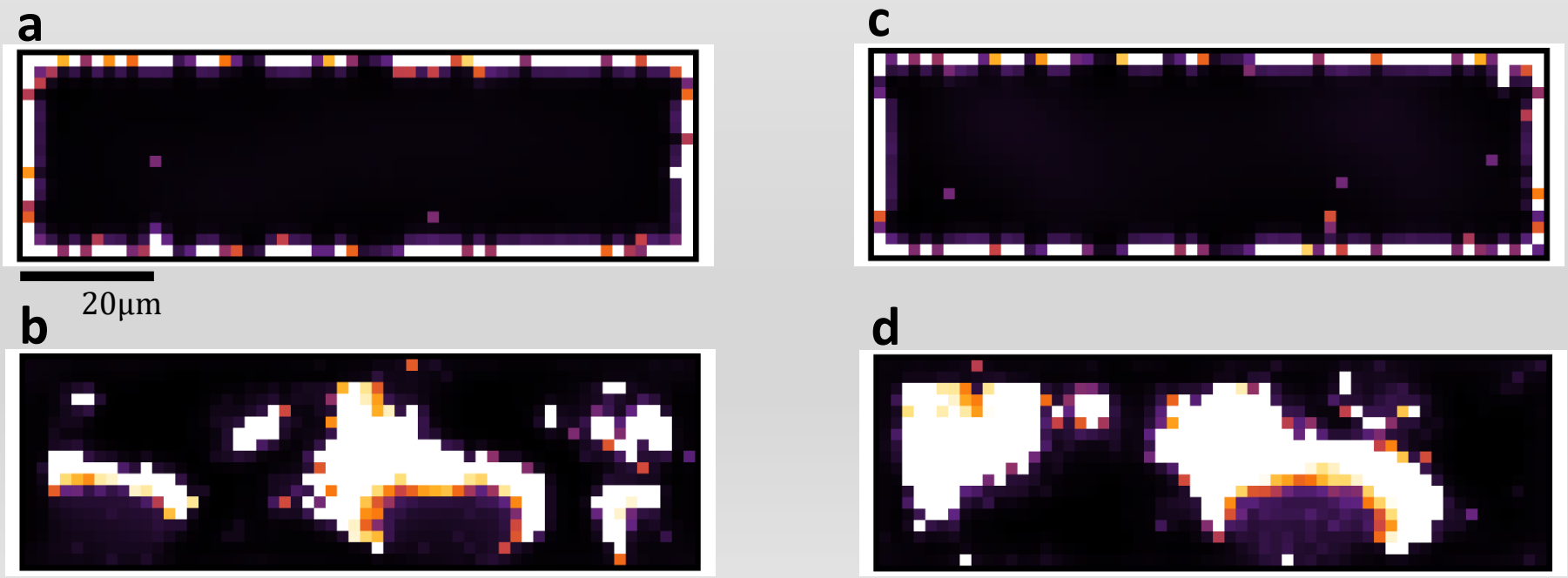


Wasserstrom lab.

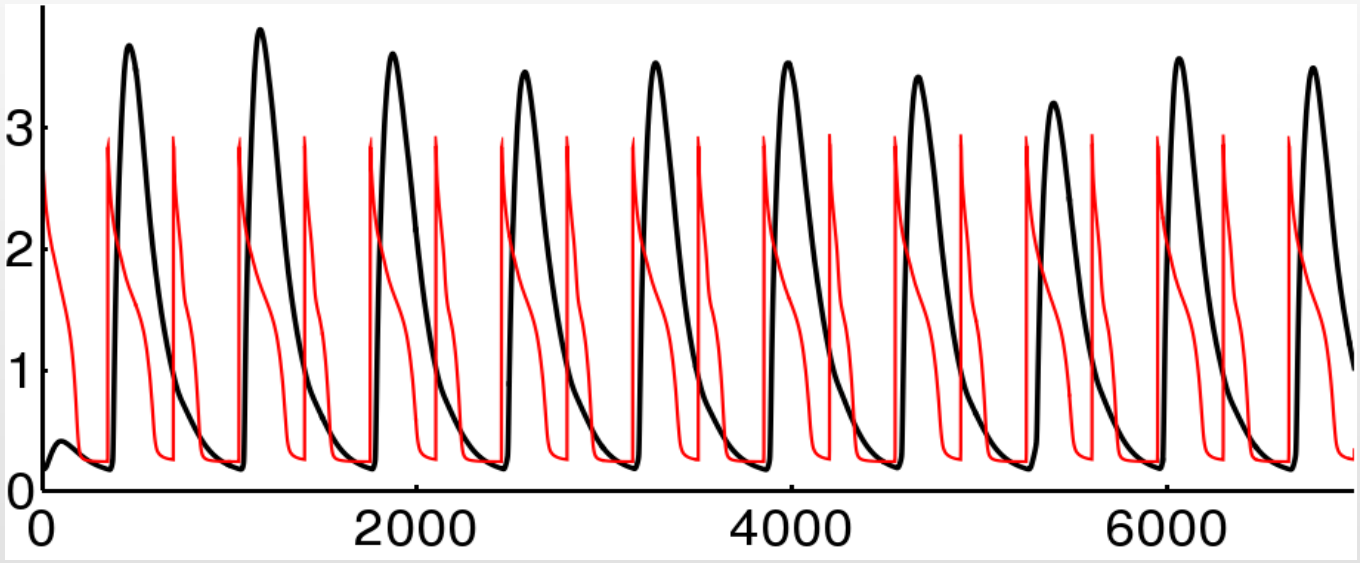
At rapid rates triggered waves can occur on alternate beats only

Triggered wave alternans





Phenomenological model reproduces robust alternans response



$V(t)$

c_i

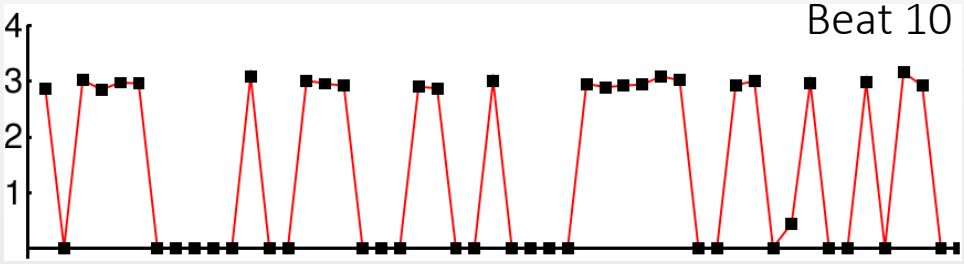
Good model for iso and Caffeine data.

Internal sites release large Ca on alternate beats

Effectively, APD restitution tends to synchronize stochastic Ca waves by providing a global signal that favors wave nucleation on alternate beats.

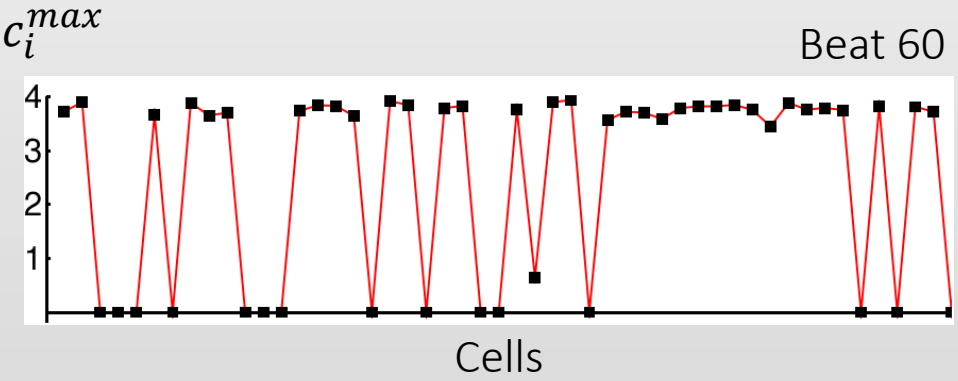
Mechanism 2: Phase synchronization of alternating triggered waves

c_i^{max}

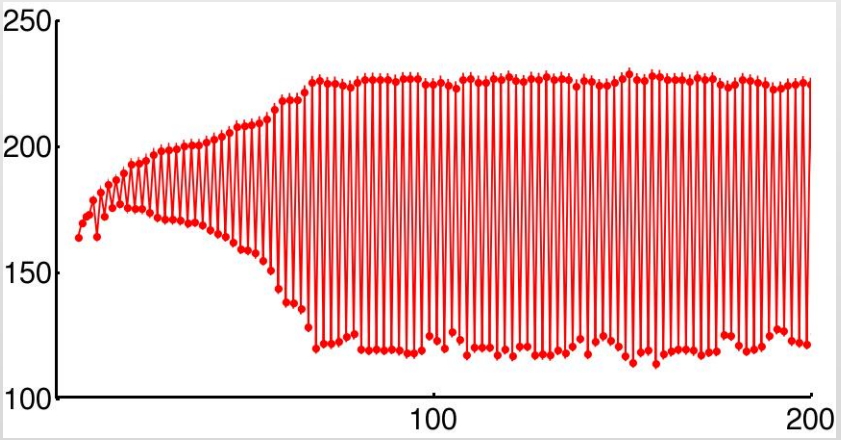


Model with alternans parameters.
50 cells.

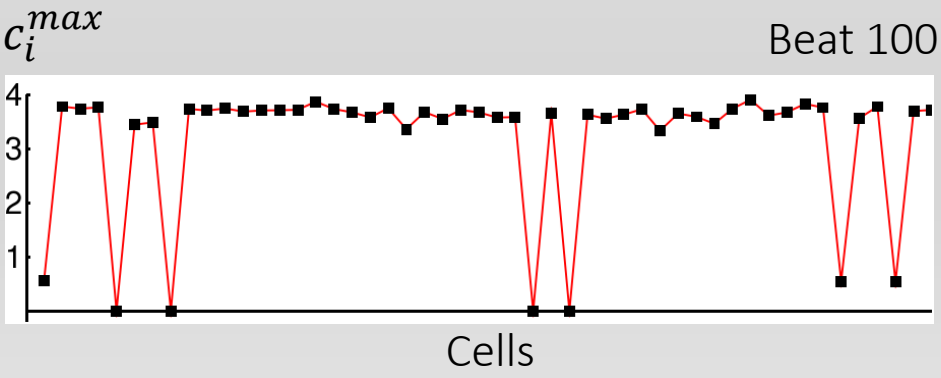
c_i^{max}



APD of 10th cell in cable of 50 cells

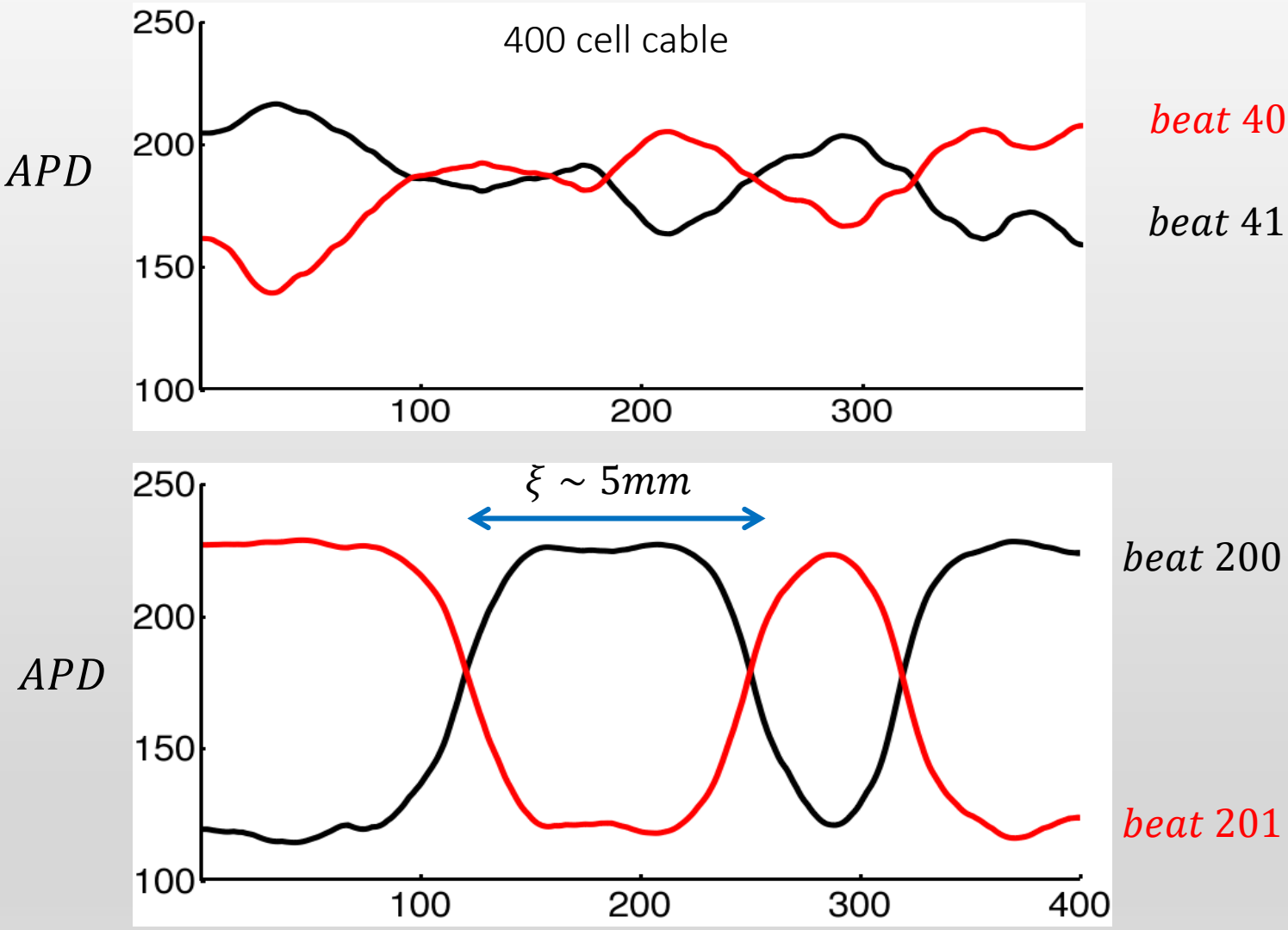


c_i^{max}



APD variations synchronize triggered Waves on cable on alternate beats.

Phase synchronization of triggered waves in a 1D cable of cells



Gradual formation of discordant alternans due to phase synchronization of triggered waves. Similar mechanism in different context proposed in Daisuke et al. 2013.

Summary

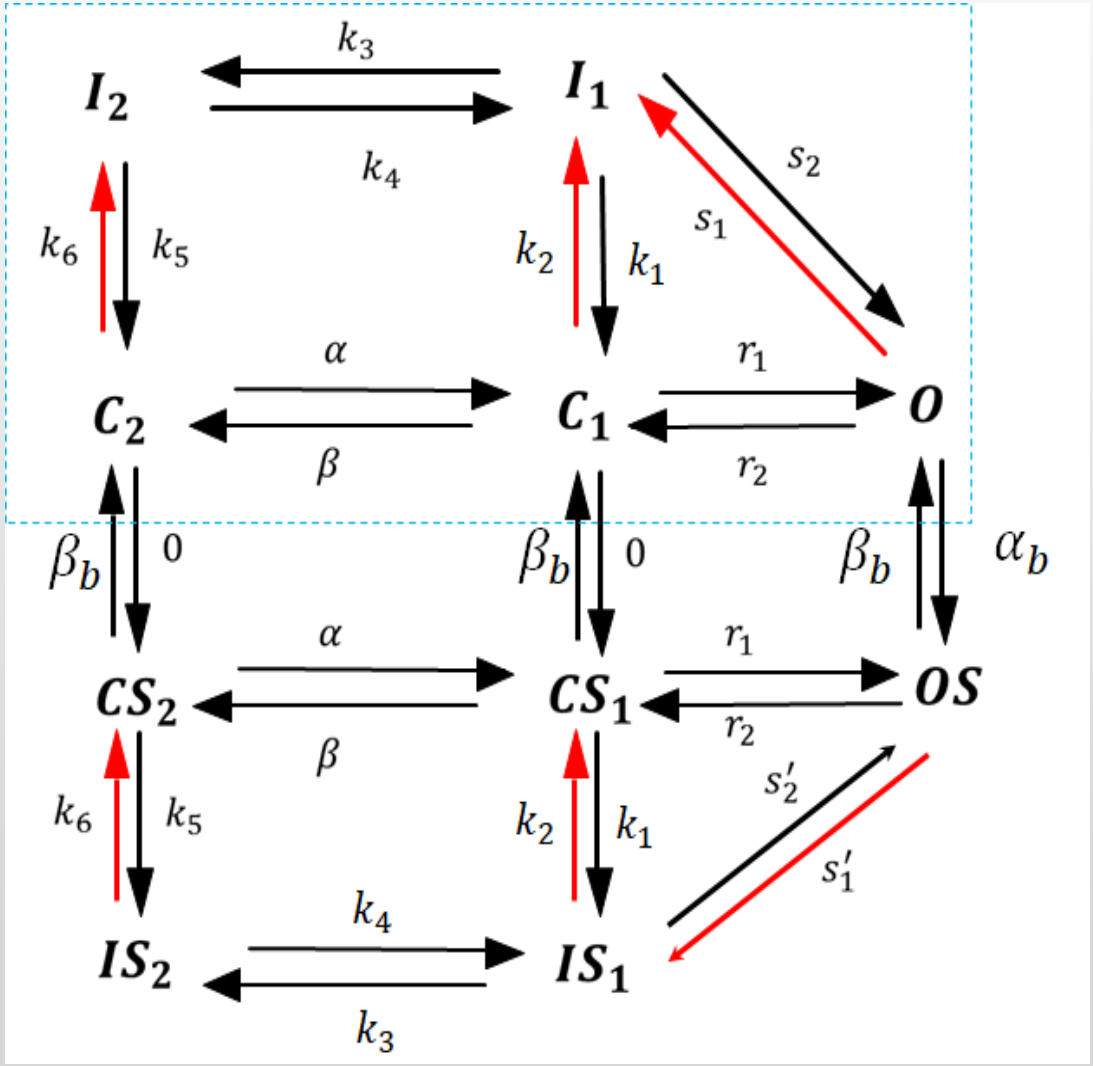
1. Stochastic Ca waves can synchronize in tissue due to interactions between voltage and Ca. At the end it is precisely the voltage that drives synchronization!

2. Alternating triggered waves occur at rapid rates and are especially arrythmogenic since they naturally synchronize over large length scales (electrotonic length).

3. Regions of synchronized triggered Ca waves may underlie the initiation and maintenance of atrial fibrillation.

THE END

L-type Ca current Markov model can be integrated into population approach



Population of channels facing sparks

$[Ca] \sim 100\mu M$

Population of channels With no sparks

$[Ca] \sim 0.1\mu M$

Accounts for the different kinetics of Ca channels facing high and low Ca concentrations