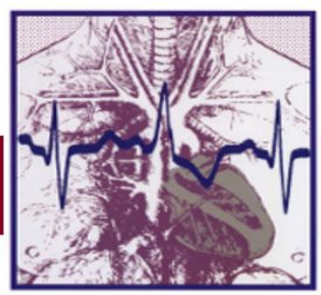


COMPUTING IN CARDIOLOGY

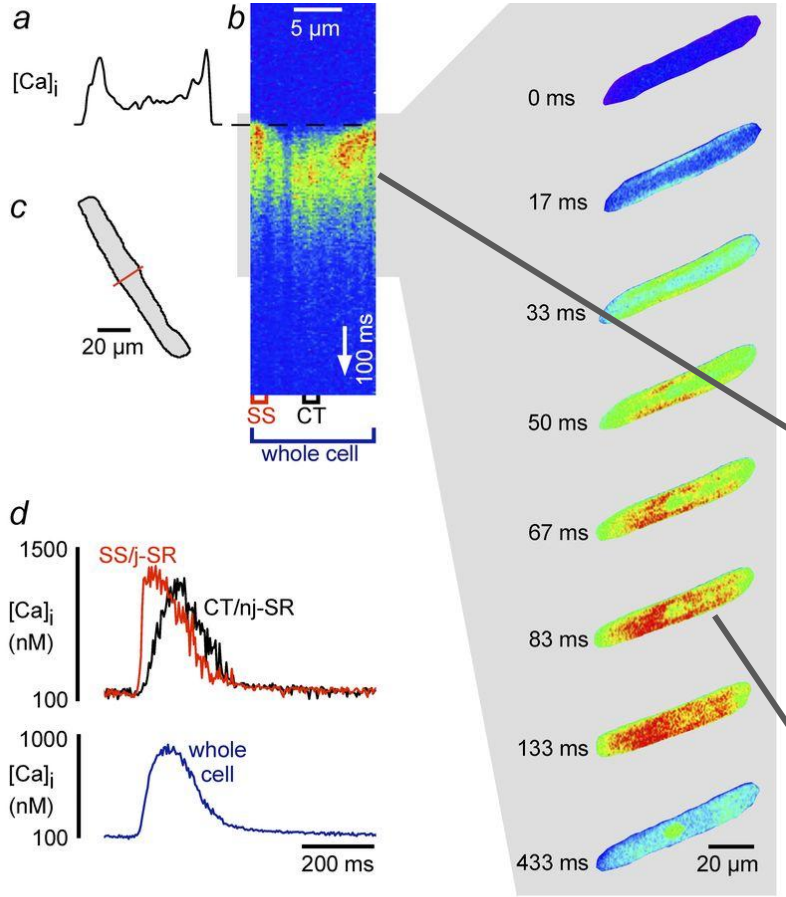
Insights Into the Mechanisms of Calcium Wave Propagation Failure From a Computational Model of the Rabbit Atrial Cardiomyocyte

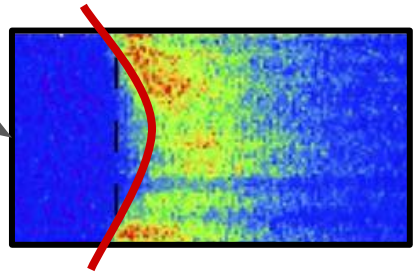
Márcia Vagos[1,2], Jordi Heijman[3], Hermenegild Arevalo[1], Ulrich Schotten[3], Joakim Sundnes[1,2]

[1] Simula Research Laboratory
[2] Department of Informatics, University of Oslo
[3] Maastricht University

Maastricht, 24 - 27th September 2018

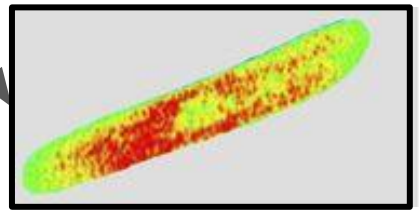
Intracellular calcium signals in atrial myocytes show a wide variation of amplitude and duration across time and spatial dimensions





Centripetal calcium wave propagation (U-shaped)

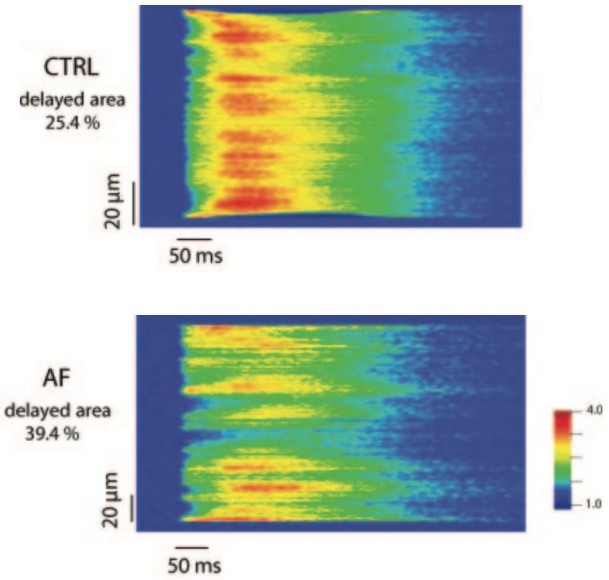
Calcium transient delay from subsarcolemmal (SS) space to cell center



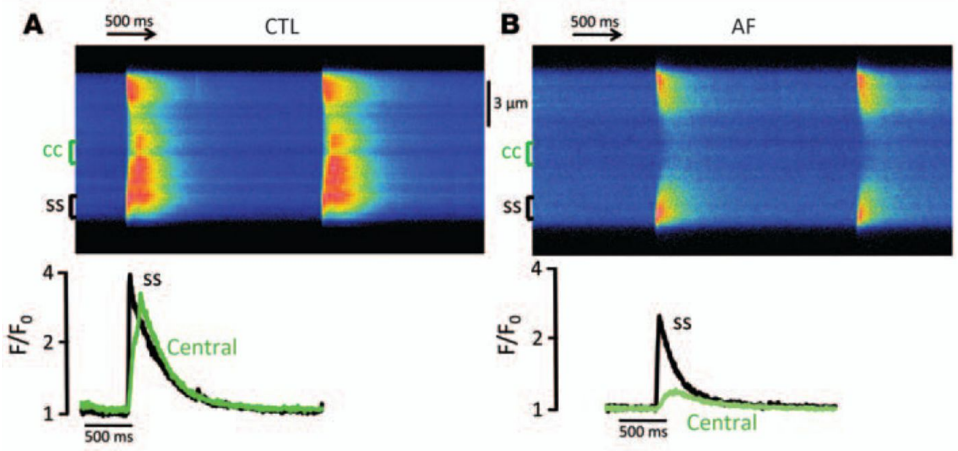
High spatial calcium heterogeneity

Adapted from Blatter et al.,J. Gen. Physiol. 2017, 149

Tachypacing-induced remodelling exacerbates incomplete regenerative calcium signaling in rabbit and human myocytes



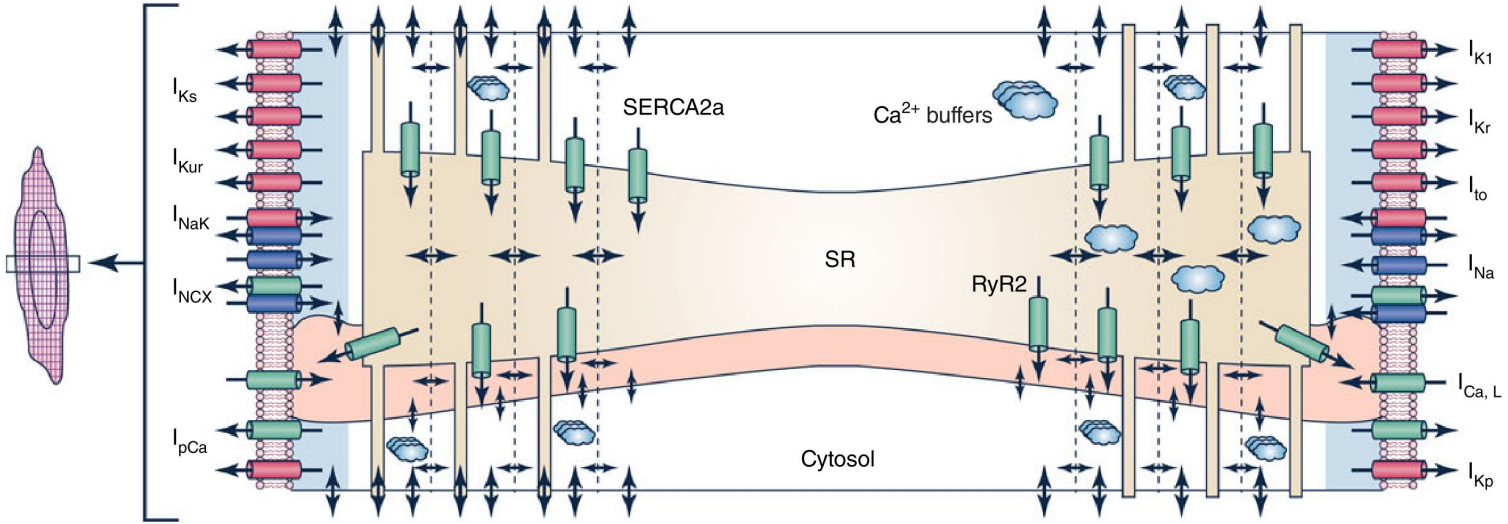
Adapted from Lenaerts et al., Circ Res. 2009



Adapted from Greiser et al., Circ Res. 2009

Calcium wave propagation failure;
Calcium silencing

The Voigt, Heijman (2014) spatial model contains adjacent domains with cytosolic, SR and subsarcolemmal compartments

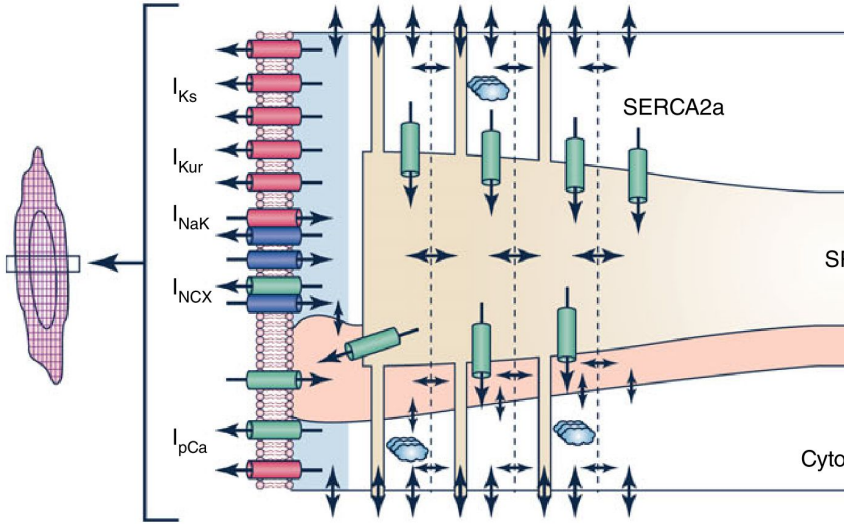


Voigt, Heijman et al 2014

SR: sarcoplasmic reticulum

SRS: SR Ca^{2+}-release space

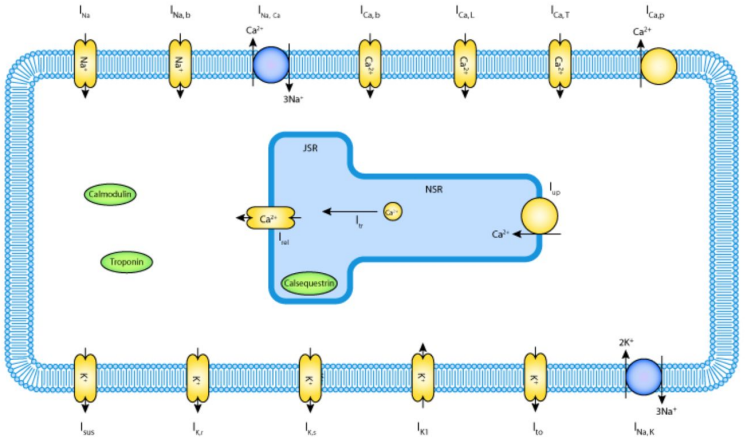
We developed a novel model of the rabbit atrial myocyte with rabbit specific electrophysiology and spatial calcium handling



Voigt, Heijman et al 2014

+

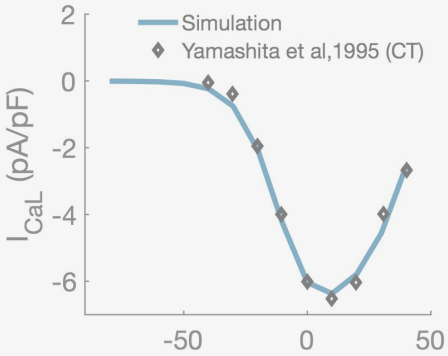
Rabbit electrophysiology from Aslanidi et al. (2009)

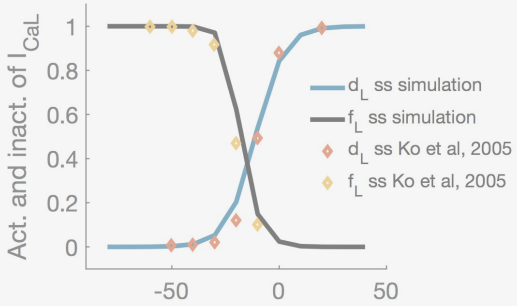


https://www.cellml.org

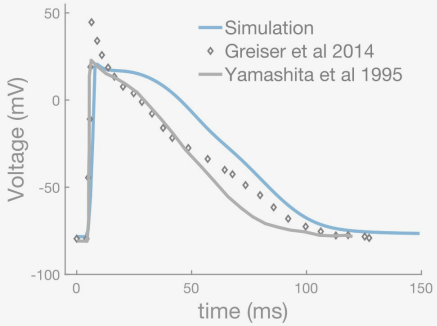
The model was extensively validated against experimental data

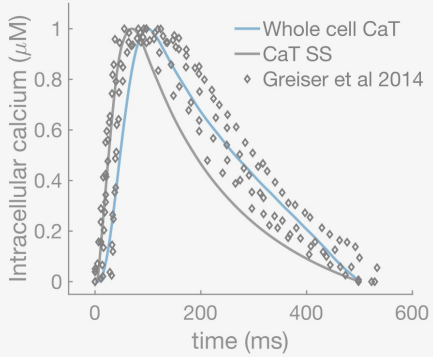
Voltage clamp data



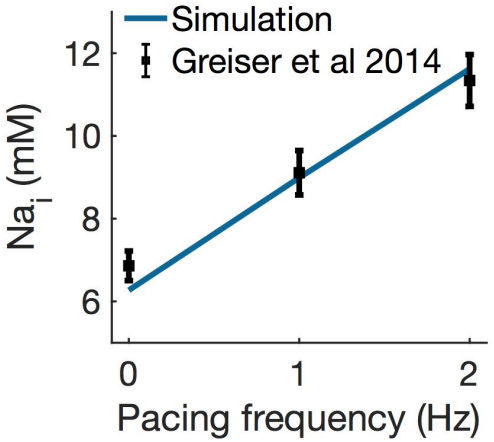


AP and CaT traces

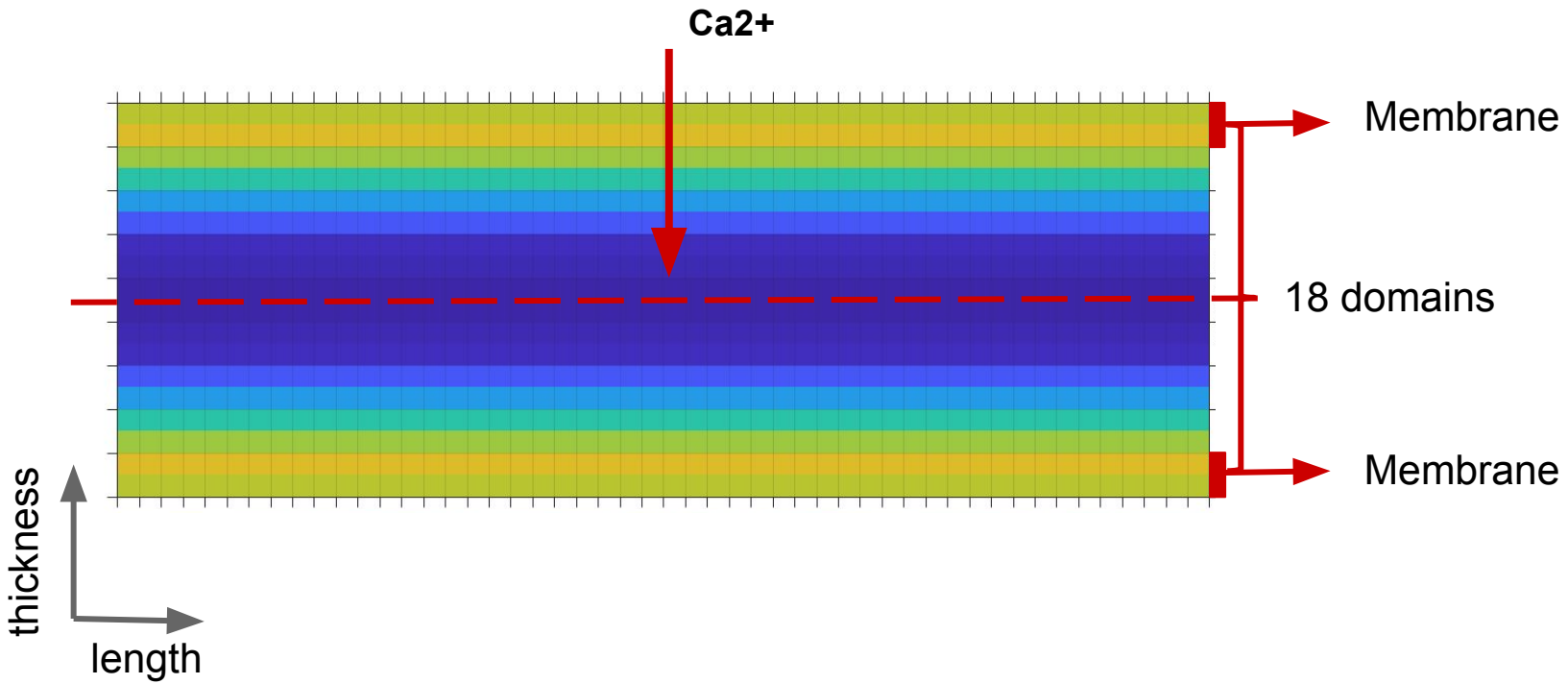




Rate dependent intracellular Na+ concentration



The spatial model replicates properties of calcium wave propagation



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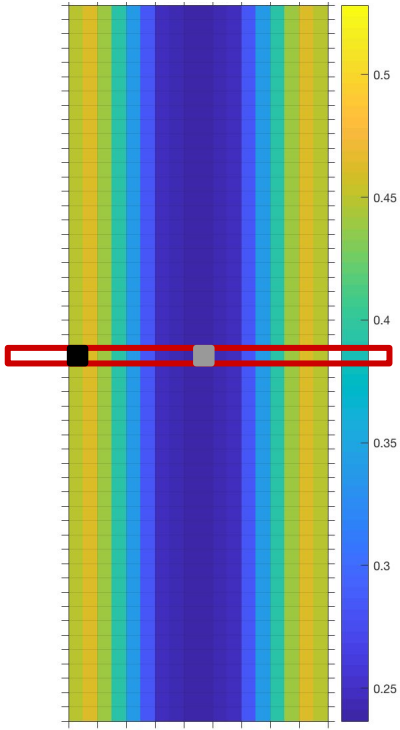
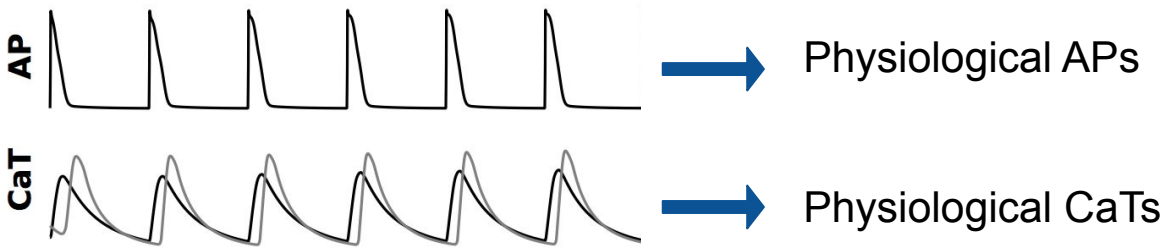


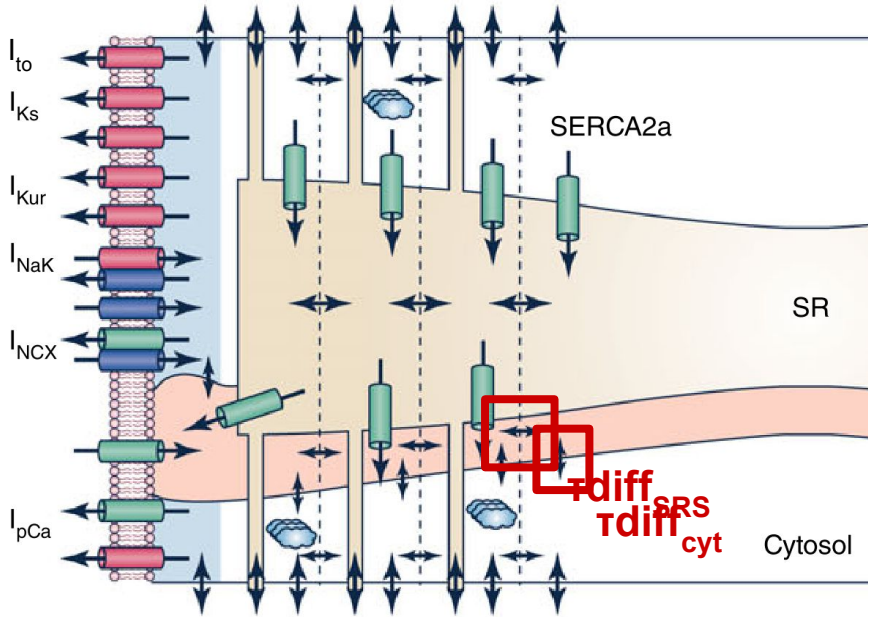


Modulators of calcium wave propagation?

Potential mechanisms of calcium propagation failure

1. Time constants of Ca^{2+} diffusion (modulate CICR kinetics)
1. Serca2a pump constants (modulate SR Ca^{2+} uptake kinetics)
1. Intracellular [Na^{+}]

Diffusion time constant of calcium in the cytosol and SRS compartments modulate calcium transient dynamics



Voigt, Heijman et al 2014

$\tau diff_{cyt}$: time constant of calcium diffusion between SRS space and cytosol

→ Stationary buffers (SR, myo-filaments, mitochondrias, phospholipids); Mobile buffers (calmodulin, ATP)

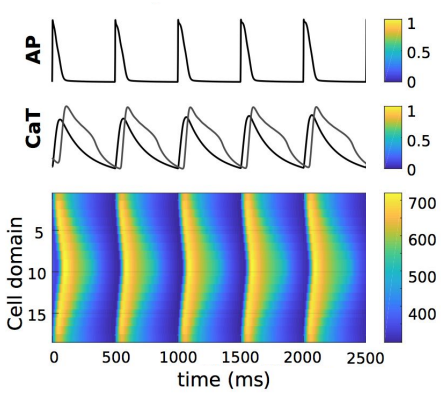
$\tau diff_{SRS}$: time constant of calcium diffusion in SRS space along radial direction

→ Ca2+ uptake/release from SR

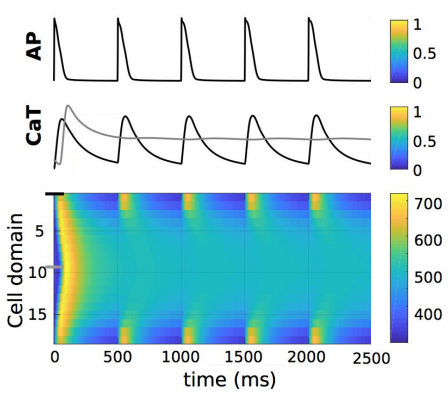
Varying $\tau diff_{cyt}$ reproduces a range of calcium propagation scenarios

Increasing $\tau diff_{cyt}$

+ 20%

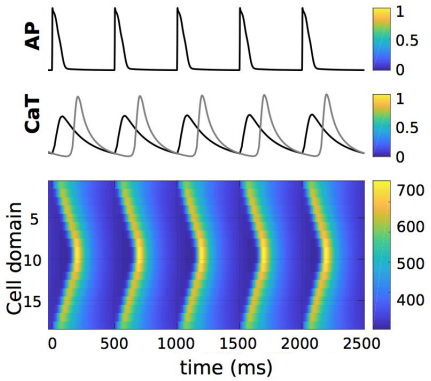


+ 27%

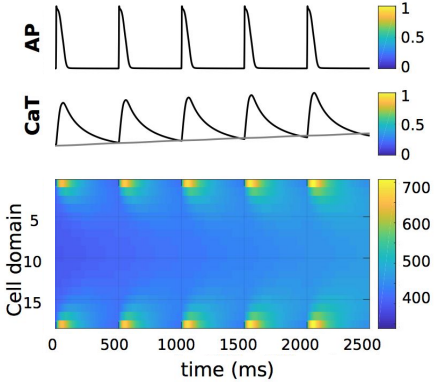


Decreasing $\tau diff_{cyt}$

- 30%



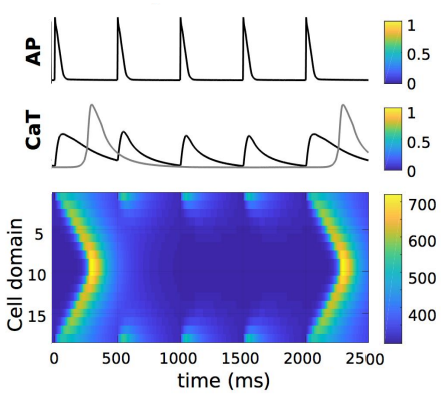
- 40%



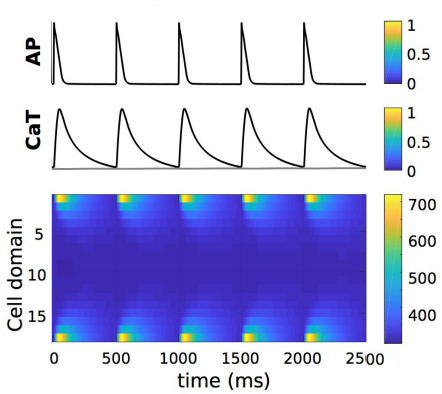
Varying $\tau diff_{SRS}$ reproduces a range of calcium propagation scenarios

Increasing $\tau diff_{SRS}$

+ 500%



+ 1000%

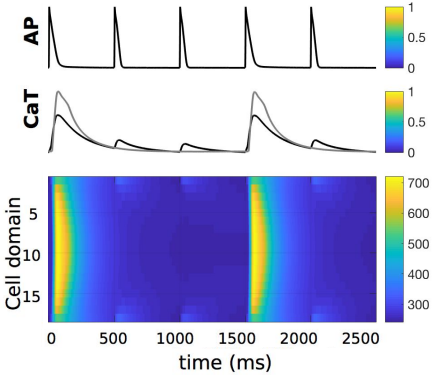


SRS space

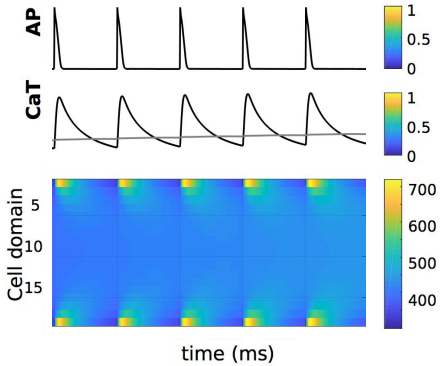
Cell center

Decreasing $\tau diff_{SRS}$

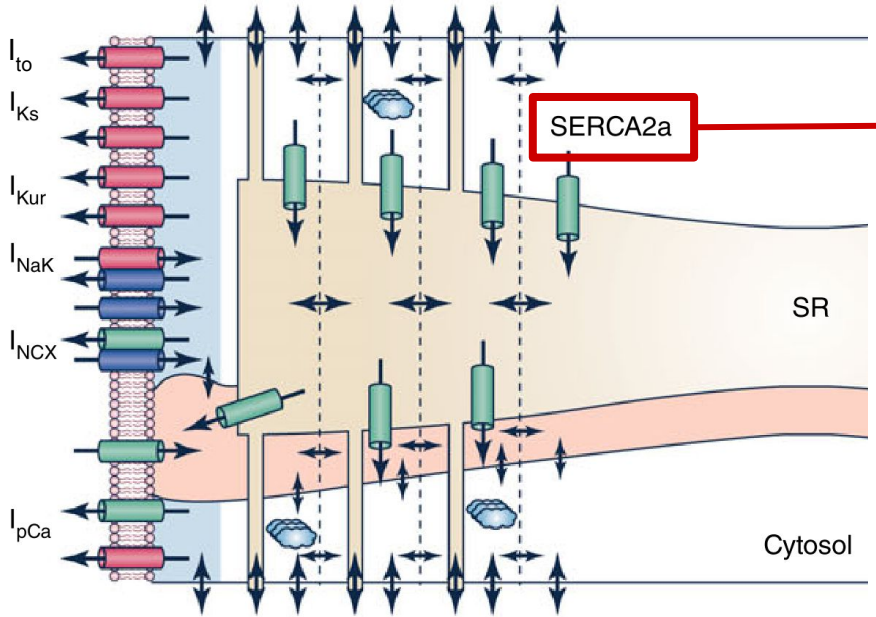
- 90%



- 99%



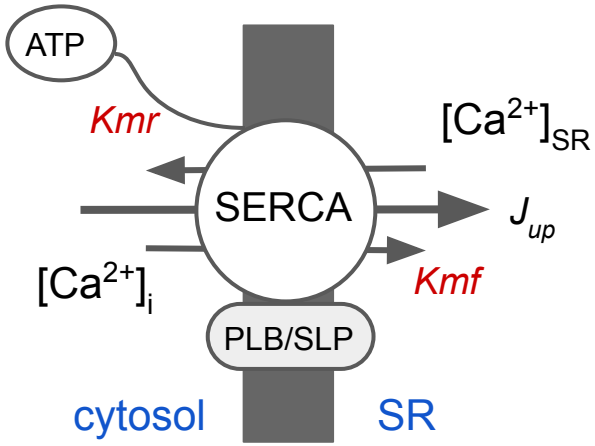
Calcium diffusion rate in the cytosol and SRS spaces depend on buffering strength and concurrent SR Ca2+ release/uptake



Pump Ca^{2+} uptake/leak constants

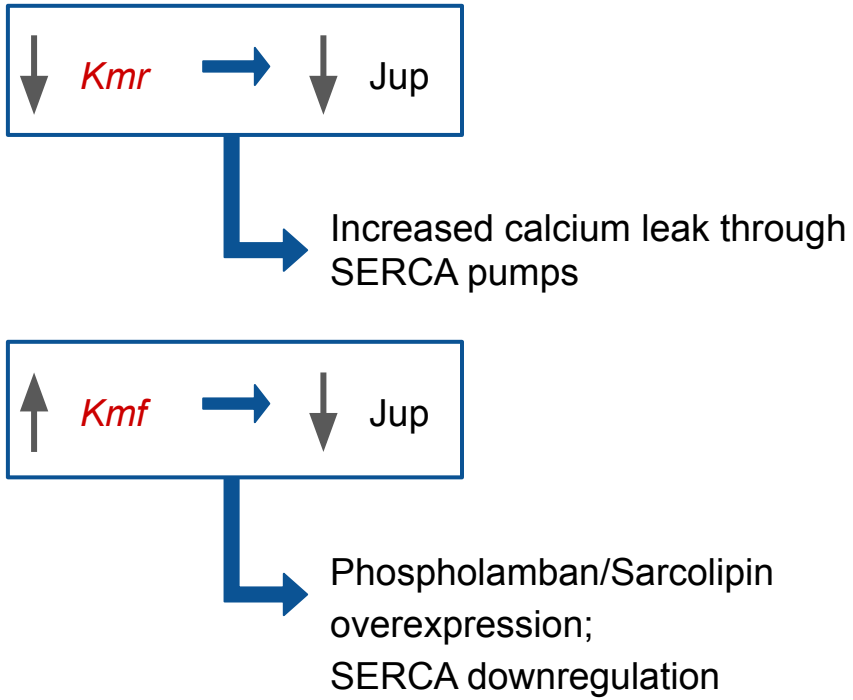
Voigt, Heijman et al 2014

SERCA pump constants modulate calcium uptake



***Kmf*: Forward mode pump constant**

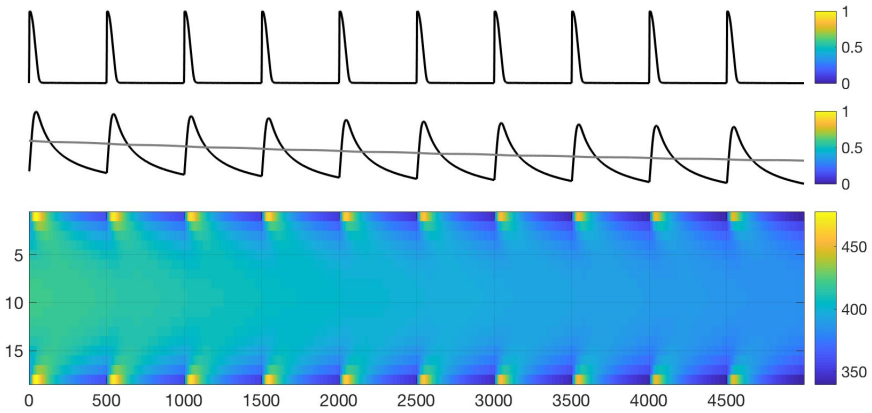
***Kmr*: Reverse mode pump constant**



Decreased calcium uptake by SERCA results in calcium alternans and calcium silencing

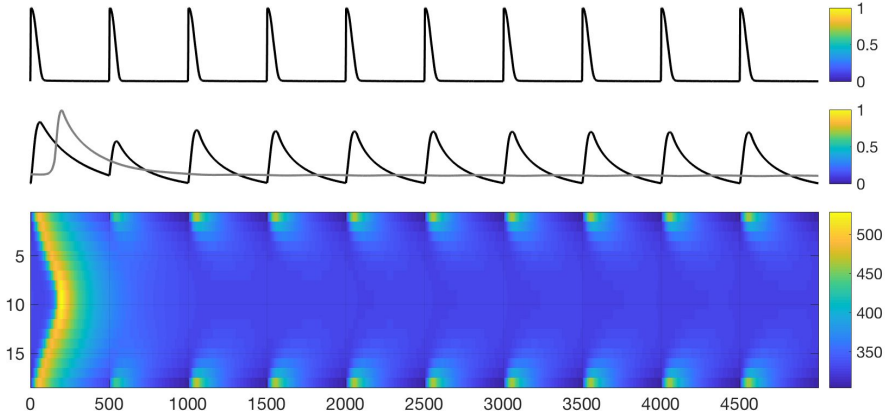
Backward pump constant (Kmr)

75% reduction (97% less Jup)



Forward pump constant (Kmf)

500% increase of Kmf (83% less Jup)



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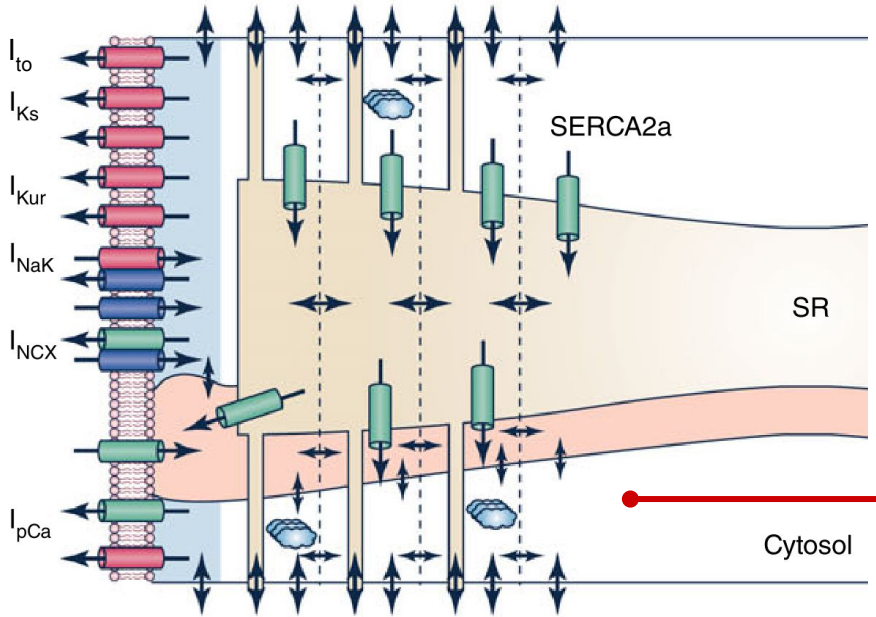
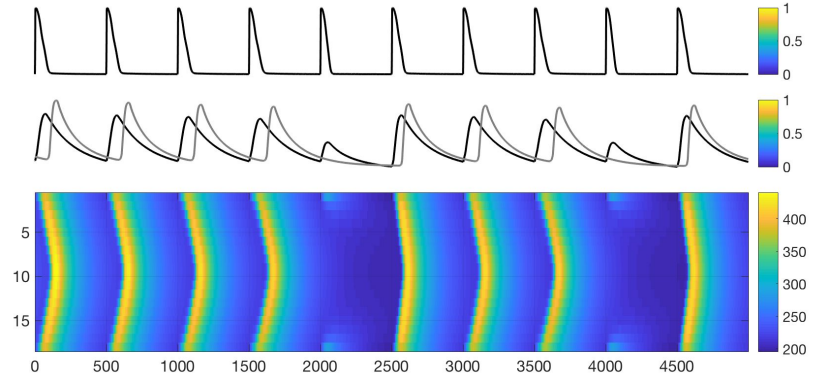


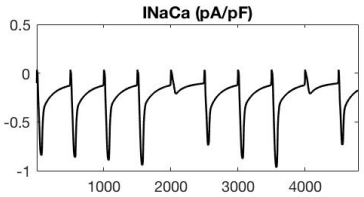
Cytosolic **Na^+** concentration

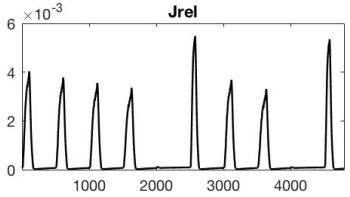
Voigt, Heijman et al 2014

Decreased intracellular Na^+ results in calcium alternans and silencing

Na_i = 6.86 mM







Concluding insights

> A novel model of the rabbit atrial cardiomyocyte has been developed and validated with published experimental data; parameters were fine-tuned to match physiological behavior.

simula

UiO : University of Oslo

Maastricht University

MARIE CURIE ACTIONS

Joakim Sundnes

Hermenegild Arevalo

Jordi Heijman

Ulrich Schotten

AFib TrainNet

Thank you