A NOVEL COMPUTATIONAL MODEL OF THE RABBIT ATRIAL MYOCYTE OFFERS INSIGHT INTO CALCIUM WAVE PROPAGATION FAILURE

Márcia R. Vagos [1,2], Jordi Heijman [3], Hermenegild Arevalo [1,4], Molly Maleckar [5], Bernardo de Oliveira [1], Ulrich Schotten [6], Joakim Sundnes [1,2]

[1] Simula Research Laboratory, Norway [2] Department of Informatics, University of Oslo, [3] Department of Cardiology, Maastricht University, [4] Center for Cardiological Innovation, Norway [5] Allen Institute for Cell Science, Seattle [6] Fac. Health, Medicine and Life Sciences, Maastricht University

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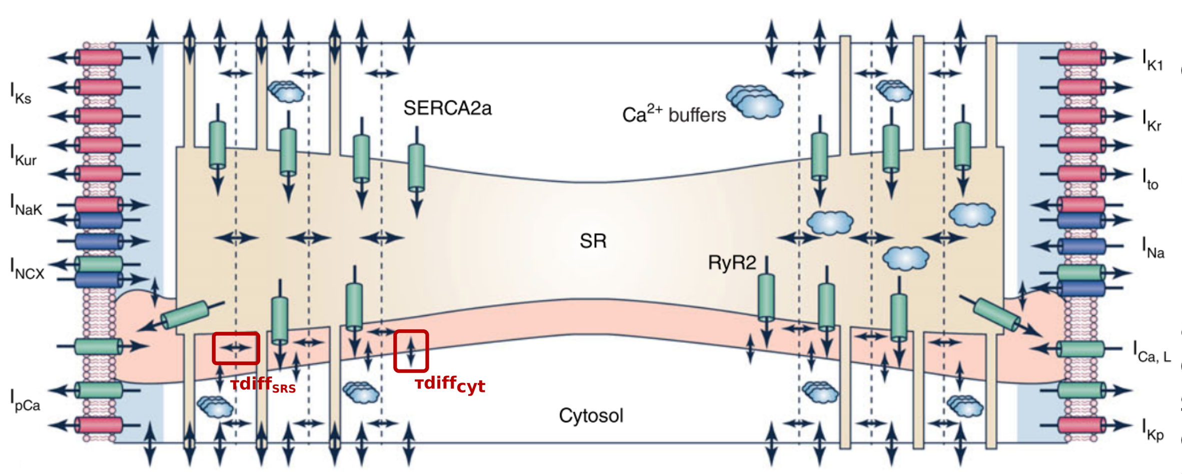
INTRODUCTION

The lack of a well-developed T-tubular system in rabbit atrial myocytes results in calcium waves propagating from the membrane towards the center of the cell. Experiments in rabbit cells and human patients with AF have shown that failure of calcium wave propagation can occur under rapid atrial pacing conditions. This phonomenon is known as calcium silencing, but the underlying mechanisms are not yet fully understood.

In this study we developed a novel model of the rabbit atrial cardiomyocyte under control conditions, and assessed the effect of calcium diffusion parameters on calcium wave propagation properties. The model was based on the human atrial cell model by Voigt, Heijman et al (2014), and on the rabbit atrial cell model by Lindblad et al (1996), and Aslanidi et al (2009). The main goal was to identify potential mechanisms and specific conditions that could lead to calcium propagation failure.

MODEL DEVELOPMENT

Model structure

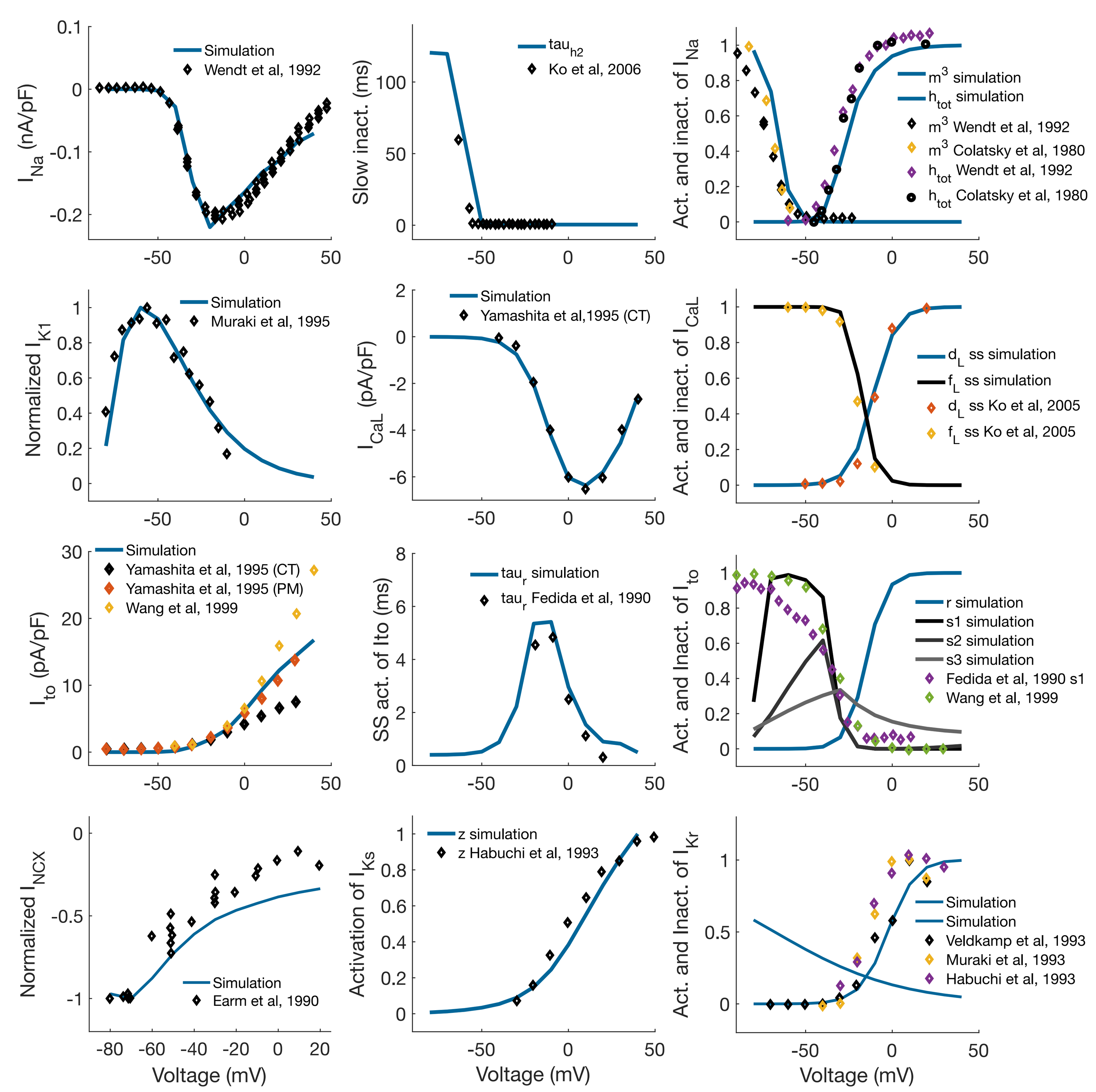


Voigt, Heijman et al 2014

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

Fig. 1 Original model of the human atrial myocyte by Voigt, Heijman et al (2014), upon which the present rabbit atrial myocyte model was based. The model has a spatial discretization of the intracellular space divided into cytosolic, SR, and SRS compartments and is able to reproduce calcium waves.

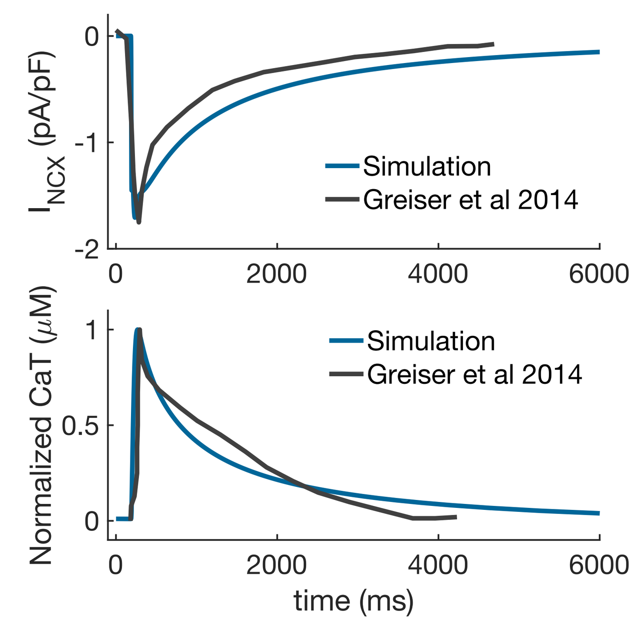
Voltage clamp simulations



VALIDATION

SR calcium content and intracellular sodium level

Caffeine-induced calcium release



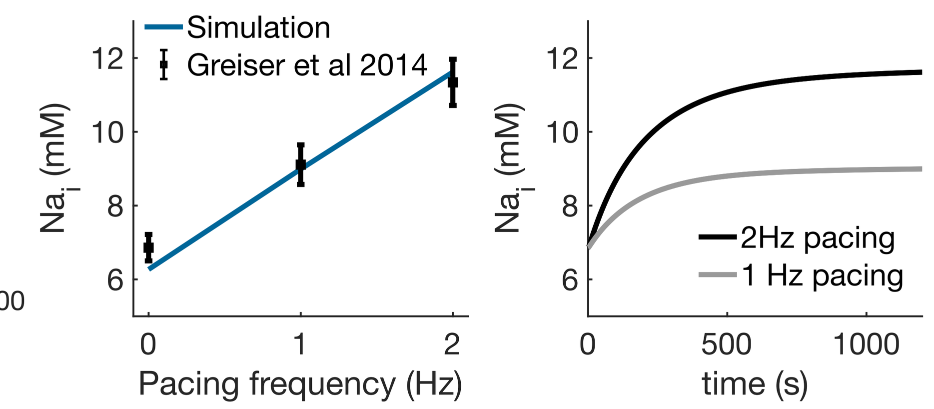


Fig. 4 A) Rate dependece of intracellular sodium in control model, and comparison with experimental by Greiser et al. 2014. **B)** Steady-state intracellular sodium level in model after 20 min pacing at 1 and 2 Hz.

Fig. 3 Simulation of caffeine-induced calcium release from the SR, and comparison with experimental data by Greiser et al. 2014.

Action potential and calcium transient morphology

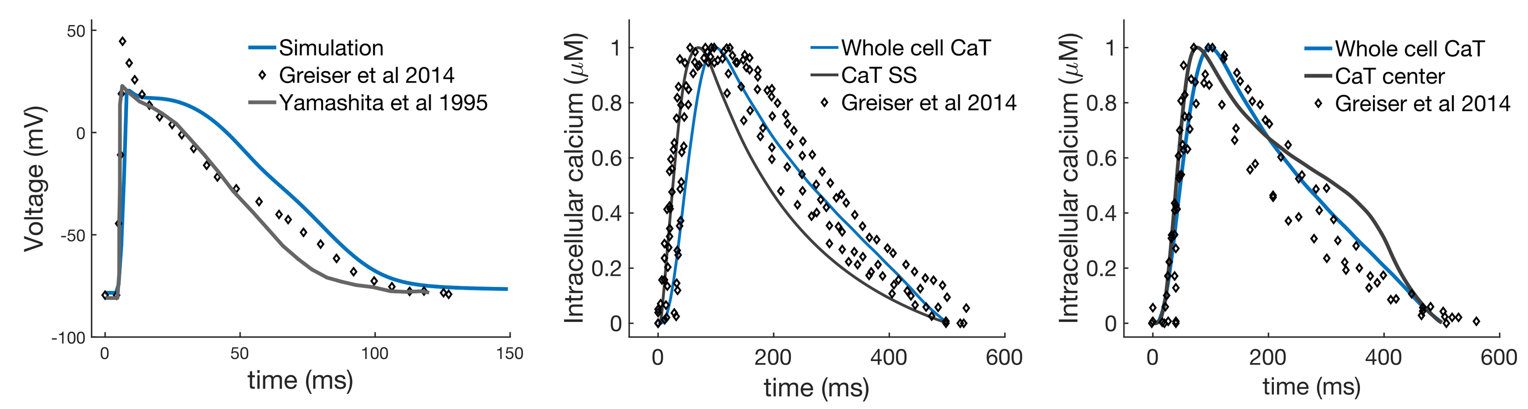


Fig. 5 A) Simulated and experimental action potentials of rabbit atrial cells. Data by Greiser et al 2014 and Yamashita et al 1995. **B)** and **C)** Calcium transients (CaT) at the subsarcolemmal space and center of the cell, respectively, from simulations and linescan data. Plots show whole cell (blue) and domain-level (grey) CaT.

Sarcolemmal currents

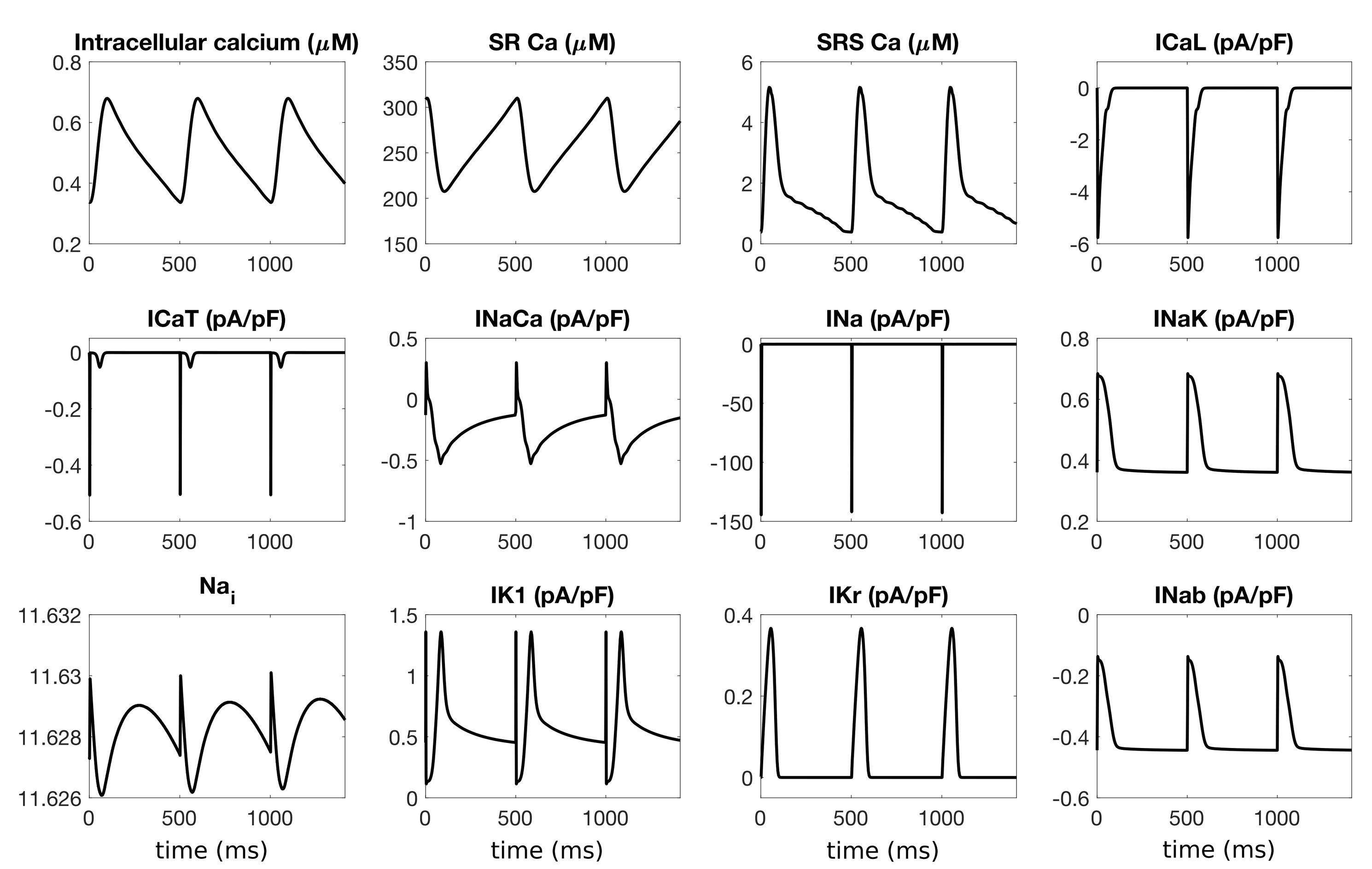
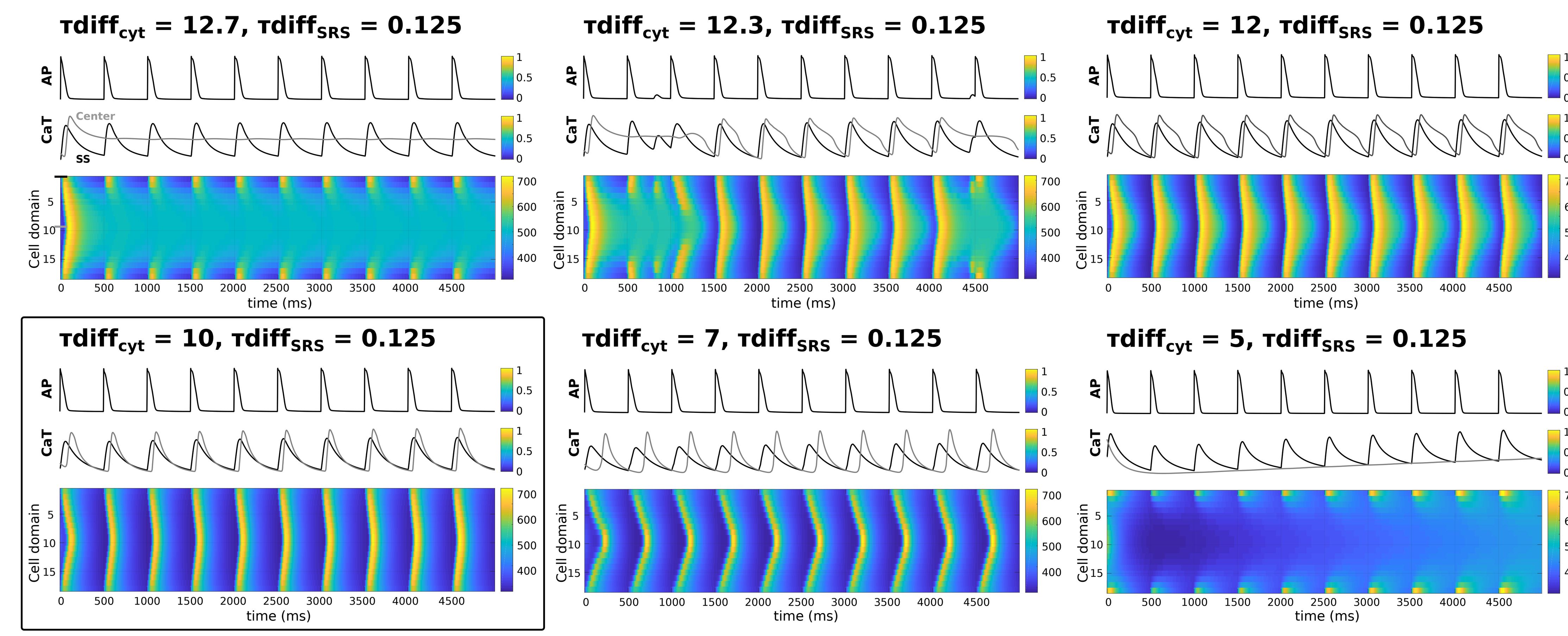


Fig. 5 Intracellular, SR and SRS calcium transients, and major sarcolemmal currents at 2 Hz pacing.

Fig. 2 (Left) Voltage clamp simulations of major ionic currents (I_{Na}, I_{CaL}, I_{K1}, I_{to}, I_{Kr}, I_{Ks} and I_{NCX}), and comparison with experimental data measured in rabbit atrial myocytes. Pacing protocol: 200 ms stimulus every 2 s from -80 mV to +40 mV.

CALCIUM WAVE PROPAGATION

Time constant of calcium diffusion between SRS space and cytosol ($\tau diff_{cyt}$, ms)



Time constant of calcium diffusion in SRS space along radial direction ($\tau diff_{SRS}$, ms)

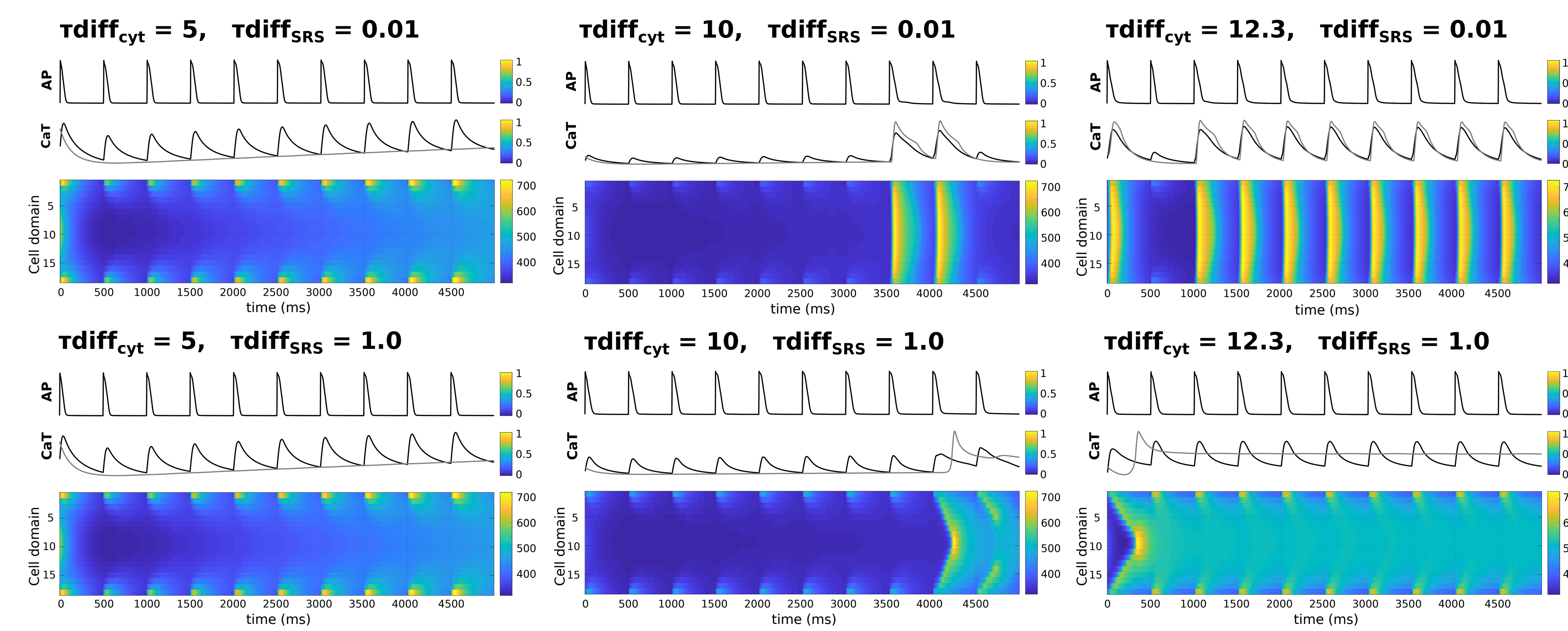


Fig. 6 *Upper* Effect of varying $\tau diff_{cyt}$ on calcium wave propagation properties: calcium silencing, CaT alternans, prolonged CaT at center, delayed centripetal wave and calcium silencing (decreasing $\tau diff_{cyt}$). *Lower* Effect of varying $\tau diff_{SRS}$ on calcium wave propagation: CaT alternans, and delayed centripetal wave propagation combined with calcium silencing (increasing $\tau diff_{SRS}$). AP and CaT traces are normalized to maximum values, and calcium wave plots show intracellular calcium concentration in nM.

CONCLUSIONS & FUTURE WORK

- A novel model of the rabbit atrial cardiomyocyte has been developed from a previously published model of the human atrial cell (Voigt, Heijman et al 2014). The model has been validated with published experimental data, and parameters have been fine-tuned to match physiological behavior.
- Simulations of intracellular calcium wave with varying values of the calcium diffusion time constants ($\tau diff_{cyt}$ and $\tau diff_{SRS}$) have shown that the model is able to reproduce fully functional calcium wave propagation, as well as propagation abnormalities, such as alternans and propagation failure.
- This novel model is a useful tool for investigating the cellular mechanisms underlying calcium wave propagation failure ('calcium silencing') under rapid atrial pacing conditions. Future work will also include the implementation of a rapid atrial pacing-remodeled version of the model.

References

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