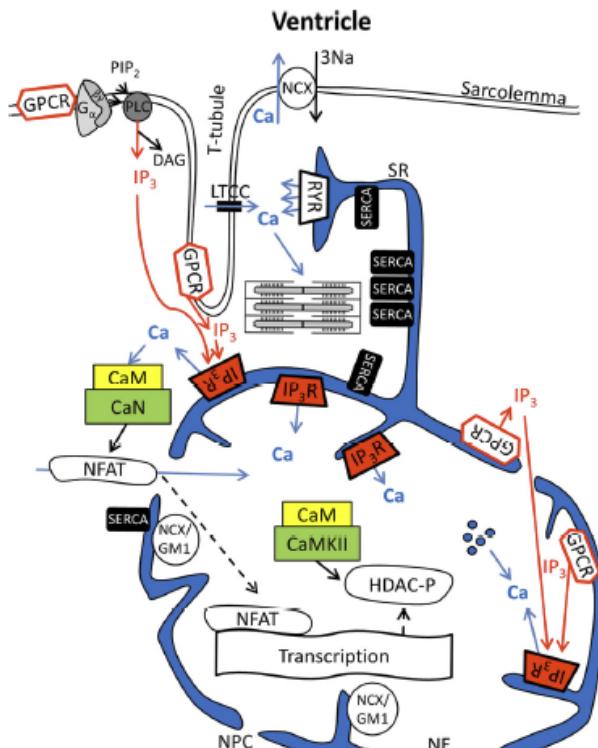


Modeling Nuclear and Intracellular Calcium Dynamics in Rabbit Ventricular Cardiomyocytes

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UCSD PRIME



Research Proposal



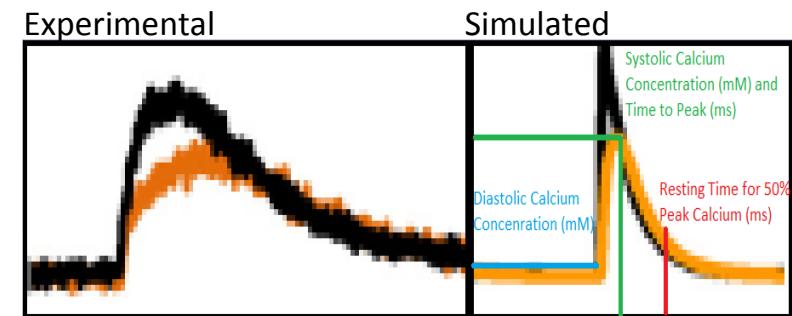
Hohendanner et al., 2014

Using the Nimrod toolkit, a set of tools that allows for investigating highly complicated parametric systems, my goal is to optimize Excitation-Contraction-Transcription-Coupling Model (Shannon-Bers-Michailova Model) for a ventricular cardiomyocyte in rabbits and run sensitivity analysis in order to elucidate how the model behaves under various stimuli.

The model will be optimized and fitted for 4 kinetic measurements of calcium:

- Systolic (mM)
- Diastolic (mM)
- Time-to-peak (ms)
- Resting time to 50% peak calcium concentration (ms)

Left: Schematic for a ventricular cardiomyocyte.
Right: Experimental calcium vs. simulated data from MATLAB,
Both plots show calcium vs. time
(non-dimensionalized).



Progress: Kinetic Parameter Data from Exp. Data

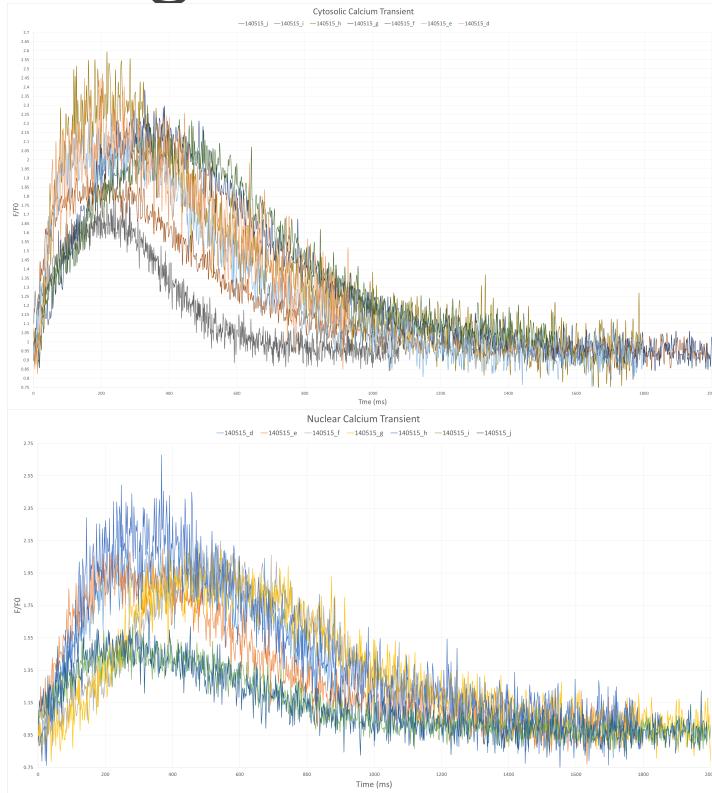


Figure: Cytosolic calcium transient (top) and nuclear calcium transient (bottom) of ventricular cardiomyocytes paced at 0.5 Hz

| | | Mean | Standard Deviation | SEM |
|-----|--------------------------|----------|--------------------|----------|
| Cyt | Time to Peak | 245.0284 | 130.9490863 | 41.40974 |
| | Resting Time to 50% [Ca] | 500 | 98.21925776 | 31.05966 |
| | Systolic | 2.503755 | 0.481356373 | 0.152218 |
| | Diastolic | 0.971645 | 0.076088642 | 0.024061 |
| | Time to Peak | 317.8267 | 111.8179481 | 35.35994 |
| | Resting Time to 50% [Ca] | 551.1364 | 141.9841842 | 44.89934 |
| Nuc | Systolic | 2.476945 | 0.733112057 | 0.23183 |
| | Diastolic | 0.966802 | 0.048188723 | 0.015239 |

Table: Summary of kinetic parameter values from trial #1 and #2.

Kinetic parameters were extracted after cleaning up data from a new trial (#2) of ventricular cardiomyocytes being paced a 0.5 Hz. The data from the trials were combined and averaged together.

Optimization is underway and results will be received by next week.

Criteria for parameter selection is explained on the next slide.

Progress: Nimrod/E Results for Shannon-Bers Parameters

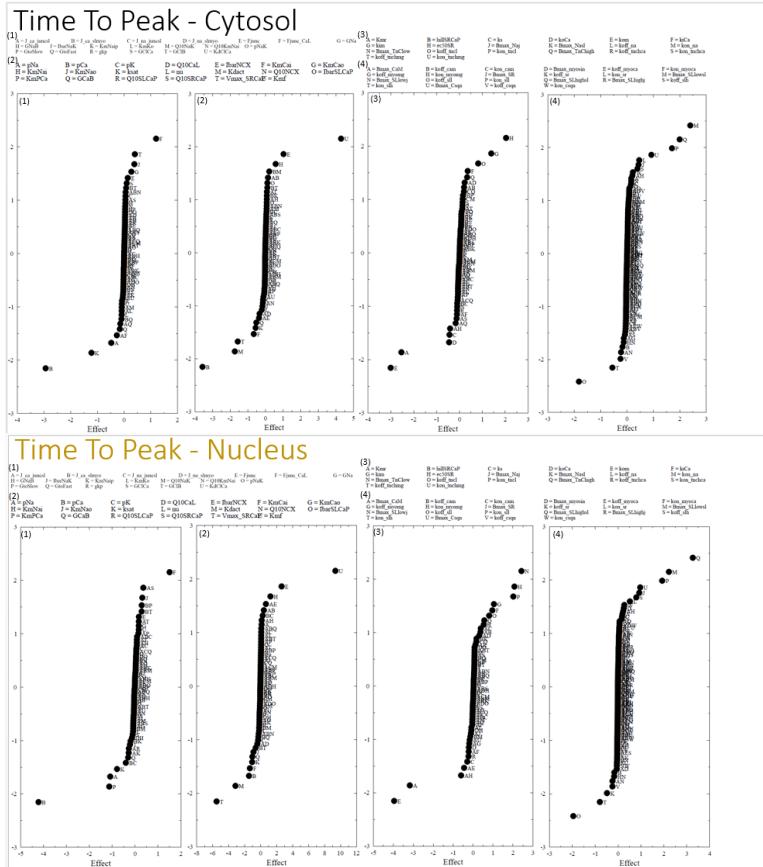


Figure: Results from a $\pm 10\%$ perturbation in cytosol parameter values. Four sets of parameters for a total of 82 parameters were selected for perturbation. The plots generated by Nimrod/E are called Daniel Plots. On the y-axis is the z-score and on the x-axis is the effect of the perturbation and it's influence on the Time to Peak. These plots were generated for RT50, Systolic and Diastolic calcium concentration.

From these plots parameters with a z-score with an absolute value of 2 or more were selected for optimization.

Future Plans

- Extract more kinetic parameter data from experimental data and calculate population statistics.
- Carry out parameter estimation using experimental data.
- Conduct sensitivity analysis by perturbing parameters in the nucleus by ± 10 , 30, 50, and 100%.
- Identify mechanisms that contribute to nuclear Ca^{2+} transport.

Melbourne, Victoria

Going from Left to right and top to bottom:

- (1) Me standing next to a little penguin replica for scale.
- (2) Australian Football League (AFL) match. Collingwood vs. Port Adelaide!
- (3) Manchester Press, a “must” for your daily brunch needs. Beware for lines though.
- (4) Matt having a staring contest with the local birds.
- (5) The view from the Space Hotel of beautiful Melbourne.
- (6) A koala, cute ball of fluff, resting in the Wildlife Park.
- (7) View of the Woolamai Cape.
- (8) Entering the Moonlit Sanctuary Wildlife Park.



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In memory of Dr. Michailova...
a mother, mentor, and scientist.

