Modeling Nuclear and Intracellular Calcium Dynamics in Rabbit Ventricular Cardiomyocytes

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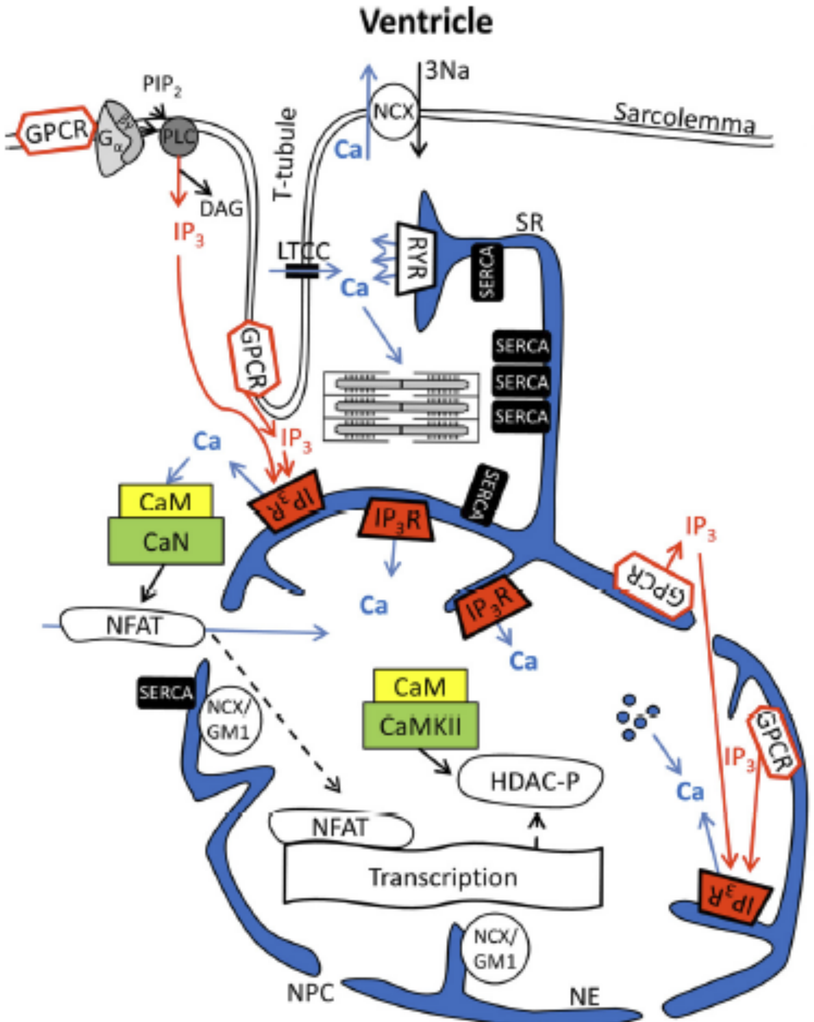
Research Proposal



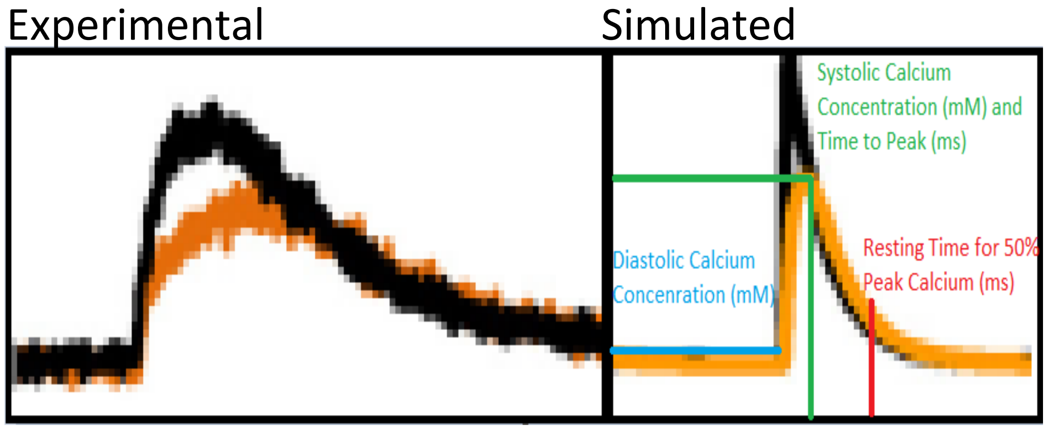
Hohendanner et al., 2014

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).

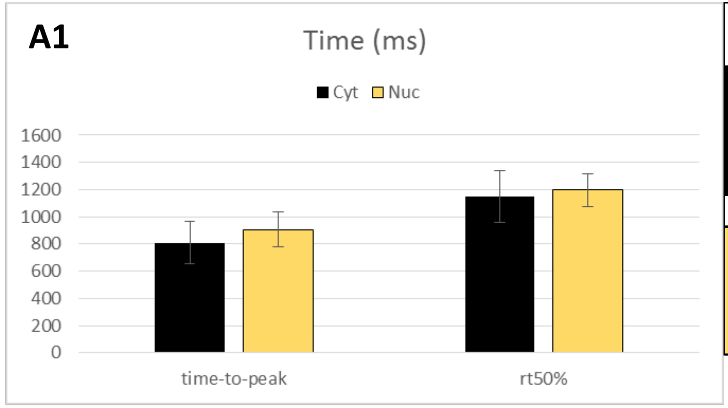


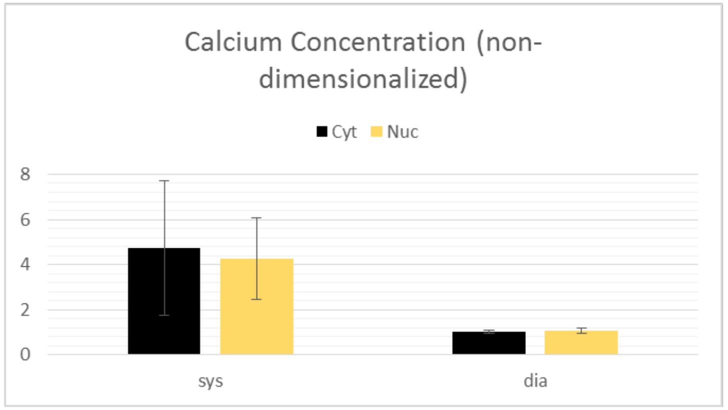
Progress: Experimental Data from 6 Single-Cell Ventricular Cardiomyocytes

Figure A
A1: Graphical representation of these kinetic parameter values including their standard deviations (SD).
A2: Table of experimental kinetic parameter values extracted from cells being paced at 0.5 Hz.

Figure B(a-d): Summary of simulated kinetic parameter values at various stimuli (0.5, 1, and 2 Hz).

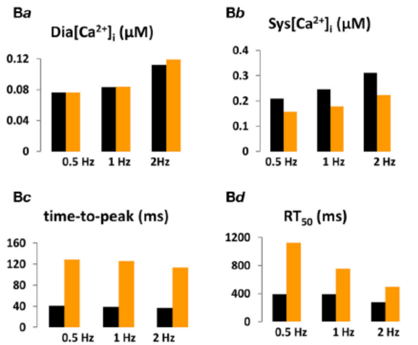
Figure A





A2		Average	Std. Dev (SD)	SEM	Coefficient of Variation (CV)
(n=6) Cyt (38)	time-to-peak	809.57085	155.9849908	63.680606	0.192676145
	rt50%	1150.071367	187.7314391	76.641039	0.1632346
	sys	4.7482	2.984686168	1.218493	0.628593186
	dia	1.020216667	0.065839538	0.0268789	0.064534858
(n=6) Nuc (41)	time-to-peak	905.9146	127.9804683	52.247807	0.141272111
	rt50%	1196.6	123.3905048	50.373963	0.103117587
	sys	4.27145	1.82478365	0.7449648	0.427204731
	dia	1.08485	0.11425089	0.0466427	0.105314919

Figure B



Hohendanner et al., 2014

- Consolidated data from the 6 cells paced at 0.5 Hz without uncaging of IP3R (see Figure A):
  - Found the trends are the same as with our simulated data for 0.5 Hz and no intervention (see Figure B).
  - Planning on plugging these kinetic parameter values in the MATLAB script and running NIMROD O in order to test the developed objective function.

Progress: Parameter Fitting (Pilot) using Nimrod/O

start	Unfinished bests:	cost
s1	(0.000268804, 1.86541, 0.9, 54.9542, 0.1375, 0.102938)	132.968
s2	(0.000259828, 1.86554, 0.9, 55, 0.1375, 0.102938)	132.936

- Ran a "pilot" experiment looking for several global/local minima. Results from Nimrod/O (above)
  - Unfinished bests = combinations of the parameter values that are being varied (see table below for the constraints of the parameter space)
    $K_{-f\text{-}SERCAnuc}$(SERCAnuc forward mode),
    $K_{r\text{-}SERCAnuc}$(SERCAnuc reverse mode),
    $ds_{SERCAnuc}$ (density of SERCA in the nuc),
    $[B_{tot}]_{nuc}$(Total nuclei Ca(2+) buffer),
    k_{on_nuc}(Ca2+ on-rate const. for nuclei), and
    k_{off_nuc}(Ca2+ on-rate const. for nuclei).
  - Cost – using several iterations (of different parameter combinations) Nimrod/O tries to reduce the cost. See equations to the right in this scenario cost = total difference.

```
parameter Kmf_SERCAnuc float range from 0.2214e-03 to 0.2706e-03 points 2;
parameter Kmr_SERCAnuc float range from 1.53 to 1.87 points 2;
parameter ds_NPC float range from 0.9 to 1.1 points 2;
parameter B_tot_nuc float range from 45 to 55 points 2;
parameter kon_nuc float range from 0.1125 to 0.1375 points 2;
parameter koff_nuc float range from 0.1029375 to 0.1258125 points 2;
```

RT50=Resting time to 50% calcium relaxation (ms)

ttp=time-to-peak (ms)

Sys=Systolic Calcium Concentration

Dia=Diastolic Calcium Concentration

Exp=Experimental

Sim=Simulated

σ=standard deviation

$$total_{nuc} = \frac{1}{\sigma^2_{Sys_{exp}}}\left(Sys_{Exp} - Sys_{Sim}\right)^2 + \frac{1}{\sigma^2_{Dia_{exp}}}\left(Dia_{Exp} - Dia_{Sim}\right)^2 + \frac{1}{\sigma^2_{RT50_{exp}}}\left(RT50_{Exp} - RT50_{Sim}\right)^2 + \frac{1}{\sigma^2_{ttp_{exp}}}\left(ttp_{Exp} - ttp_{Sim}\right)^2$$

$$total_{cyt} = \frac{1}{\sigma^2_{Sys_{exp}}}\left(Sys_{Exp} - Sys_{Sim}\right)^2 + \frac{1}{\sigma^2_{Dia_{exp}}}\left(Dia_{Exp} - Dia_{Sim}\right)^2 + \frac{1}{\sigma^2_{RT50_{exp}}}\left(RT50_{Exp} - RT50_{Sim}\right)^2 + \frac{1}{\sigma^2_{ttp_{exp}}}\left(ttp_{Exp} - ttp_{Sim}\right)^2$$

$$total\ difference = total_{nuc} + total_{cyt}$$

Future Plans

- Will continue fitting various ranges of parameter values after investigating a feasible range of parameters.
- Consider the addition of a sodium buffering equation in the nucleus in order to correct drift within the model.
- Conduct sensitivity analysis after fitting parameters by perturbing the model with a ±10, 30, 50, and 100% in key parameters.

Stradbrooke Island and South Bank

Right: Typical sign on the island warning drivers of local wildlife in the area.
Middle: View of the beach atop by the Manta Lodge
Left (top): View of the South Bank from the Cultural Center.
Left (bottom): Dinner with fellow UCSD students at Torba, an Eastern European restaurant in South Bank.

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