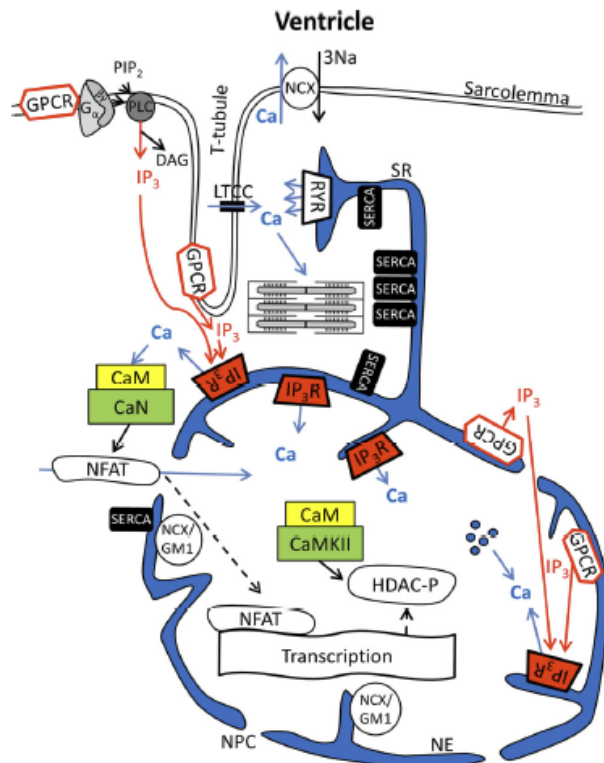# Modeling Nuclear and Intracellular Calcium Dynamics in Rabbit Ventricular Cardiomyocytes

Kyle-David Lim Suico
University of Queensland
July 23 2014
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).

Experimental   Simulated
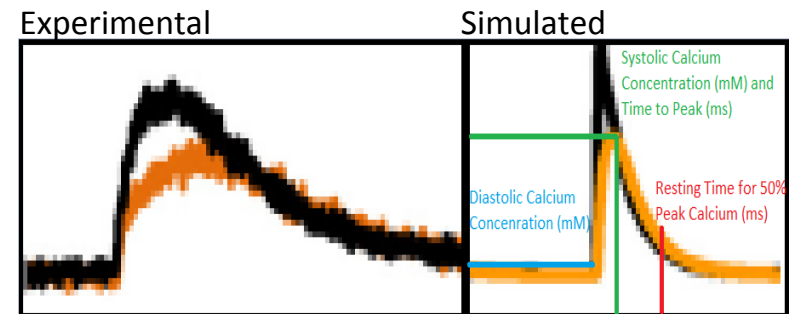
Progress: Optimization Results

Parameter Space:

	Default Values	Optimal Values	Change in Values
B_tot_nuc	50	74.993	50%
kon_nuc	0.125	0.187451	50%
koff_nuc	0.114375	0.057188	-50%
S_ca_myonuc	0.8	0.930169	16%
ds_NPC	1	0.512325	-49%
Vmax_SERCAnuc	0.0053114	0.00266824	-50%
Kmf_SERCAnuc	0.000246	0.000123033	-50%
Kmr_SERCAnuc	1.7	1.84555	9%
hill_SERCAnuc	1.787	1.99318	12%
ds_SERCAnuc	0.005	0.0046987	-6%

Difference before and after optimization:

		Difference between Simulated vs. Experimental (%)		
Compartment	Kinetic Parameter	Afer Opimization	Default Parameters	Change after Optimization
Cytosol	Time to Peak	71.32965772	78.55266628	(7.22)
	Resting Time to 50% Calcium Concentration	64.7835492	72.8080288	(8.02)
	Systolic	53.47153588	35.35545349	18.12
	Diastolic	3.830743267	14.4271067	(10.60)
Nucleus	Time to Peak	1.156548442	7.796345393	(6.64)
	Resting Time to 50% Calcium Concentration	3.267959571	0.192459704	3.08
	Systolic	74.06308702	68.2505361	5.81
	Diastolic	3.574926618	23.75509564	(20.18)
	Total Difference (%)	275.4780077	301.1376921	(25.66)

Results from Nimrod/O after fitting model to parameter values within a 50% difference of suggested default values.

Systolic nuclear calcium concentration is quite large, above 30% threshold criteria for optimizing the model.

May have to refine optimization methods. This is likely due to large standard deviation taken into account when performing optimization.

Before continuing onto further sensitivity analysis more optimization must be done.

Future Plans

- Investigate other optimization methods and build a work flow to test model
- Will continue fitting various ranges of parameter values after investigating a feasible range of parameters.
  - Conduct sensitivity analysis by perturbing parameters in the nucleus by ±10, 30, 50, and 100%.
- Run additional sensitivity analysis in order to identify mechanisms that regulate nuclear Ca2+

Byron Bay, New South Wales

Left: Cape Byron Bay Lighthouse.
Middle left: View from a lookout of Byron Bay.
Middle right: Tour bus of eager internationals going into the countryside.
Bottom left: View of a majestic lake in the country.
Bottom right: First kangaroo burger! Don't worry it's eco-friendly to eat these guys!

Acknowledgements

R.I.P. Dr. Anushka Michailova

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