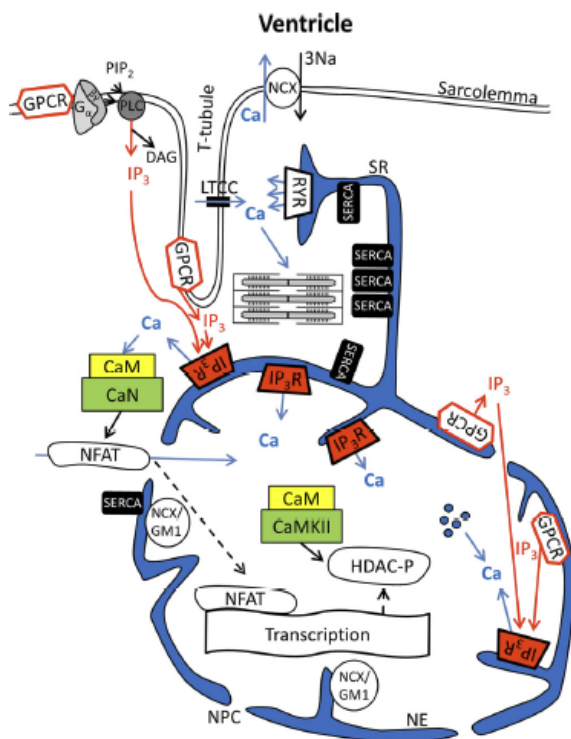# Modeling Nuclear and Intracellular Calcium Dynamics in Rabbit Ventricular Cardiomyocytes.

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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).

Experimental Data   Simulated Data
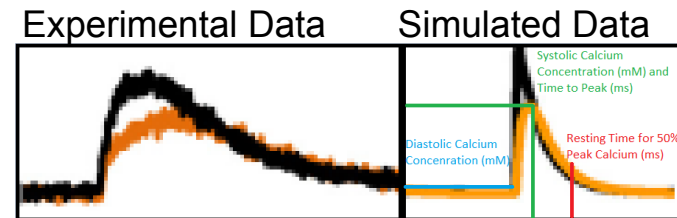
Progress

- Identified 6 key parameters most significantly influencing the kinetic values by perturbing the system with 10% and 30% increase in parameter values.

Estimated change diastolic calcium concentration in the cytosol after a 30% increase in parameter values
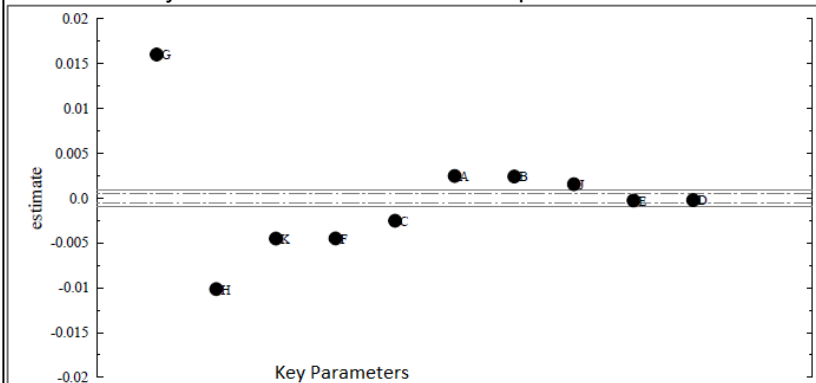

- Wrote planning file (.pln) for NIMROD O to search for optimal parameters values that result in the least difference in experimental and theoretical data.

```
1   parameter x1 float range from 0.0002 to 2
2   parameter x2 float range from 0.0006 to 6
3   parameter x3 float range from 0.0002 to 2
4   parameter x4 float range from 0.000000002 to 0.00002
5   parameter x5 float range from 0.00001 to 0.1
6   parameter x6 float range from 0.00001 to 0.1
7
8   results 1
9
10  task main
11      copy rabbit.sk node:.
12      copy extract.m node:.
13      substitute rabbit.sk rabbit.m
14      node:execute /bin/touch out %creates a file called out
15      node:execute ${HOME}/bin/runmatlab "rabbit()" >> matlab.output
16      node:execute /bin/echo "${x1}, ${x2}, ${x3}, ${x4}, ${x5}, ${x6}"  >> params
17      node:execute ${HOME}/bin/runmatlab "extract()"
18      copy node:params OUTPUTS/params.${jobname}
19      copy node:quantities.text output.${jobname}
20  endtask
21
22  method simplex
23    starts 2
24      starting points random
25      tolerance 0.000
26      on error ignore
27    endstarts
28  endmethod
29
```

Future Plans

- Re-run NIMROD G/E/O for the Shannon-Bers-Michailova Model.
- Obtain optimized parameter values for model control condition (without IP3R present in model).
- Conduct sensitivity analysis using fitted parameters.

Lamington National Park, Queensland
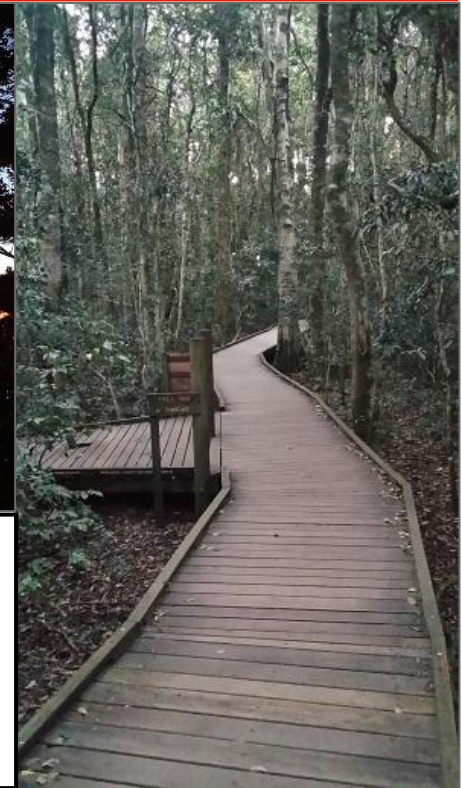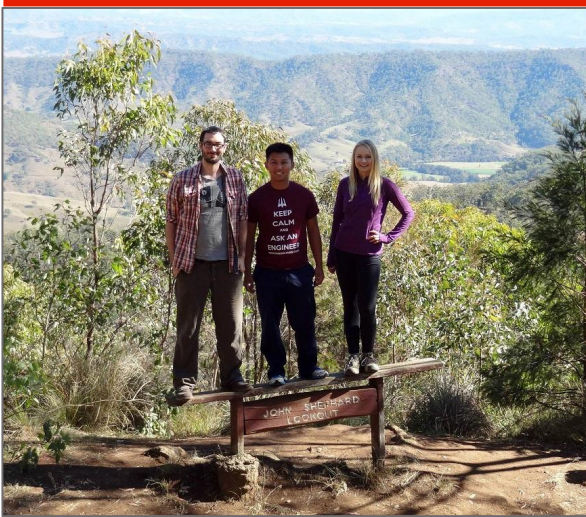
Left: Group photo after a 4WD expedition to the park.

Middle: Just barely caught the sunset atop the treetop lookout.

Right: The treetop entrance from the Box Forest Circuit

Acknowledgements

R.I.P. Dr. Anushka Michailova

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