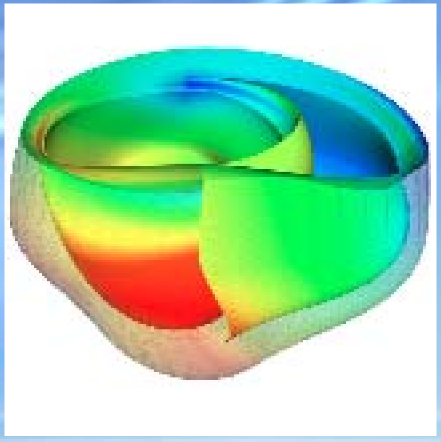
Computational Modeling of Cardiac Resynchronization Therapy

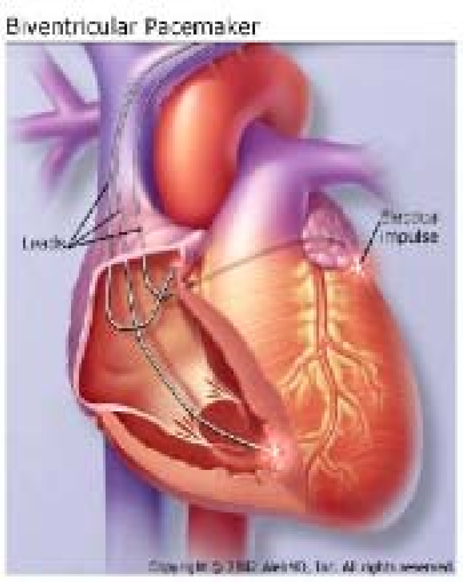


Britta Baynes

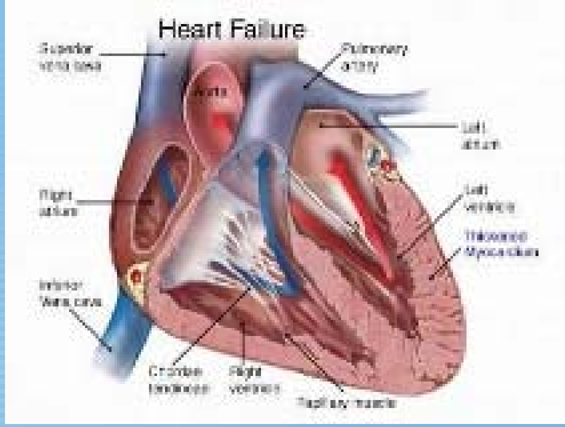
UC San Diego- Cardiac Mechanics Research Group

Background

- Cardiac Resynchronization Therapy (CRT) is a widely used and proven treatment for a select group of patients experiencing heart failure due to ventricular dyssynchrony.
- Cardiac dyssnchrony results in decreased stroke volume, increased wall stress and delayed relaxation.
- CRT is achieved by simultaneously pacing both left and right ventricles by resynchronizing the timing of the global left ventricle depolarization and overall improvement of mechanical contractility and mitral regulation.
- CRT improves cardiac output, systolic pressure, magnitude of wall contraction, LA pressure and mitral regulation.



My PRIME project



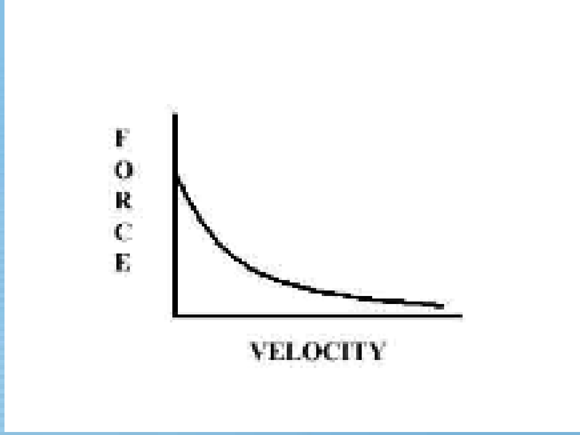
- My project uses Computational modelling of a rabbit heart to investigate why CRT is only effective in restoring cardiac synchrony in 70% of congestive heart failure (CHF) patients.

- The Hill relation, examining sarcomere shortening velocity and resultant stress created on the heart poses a possible answer to this clinical question.

My PRIME project cont…

- During this project, I have been using the Rice Model, examining the Hill (force-velocity) relation, showing that when this relation changes in Heart Failure (HF) patients, both regional and global effects can be seen.
- Regionally, fiber shortening and strains are effected
- Globally, ejection fraction and overall cardiac function is greatly affected especially when in combination with a variation of dyssynchronous electrical activation sequences.

Hill Relation basics



- The hill relationship is essentially a force-velocity curve specific for muscle contractions
- The hill equation can be represented various ways including

$$(P + a)(V + b) = (P_o + a)\,b$$

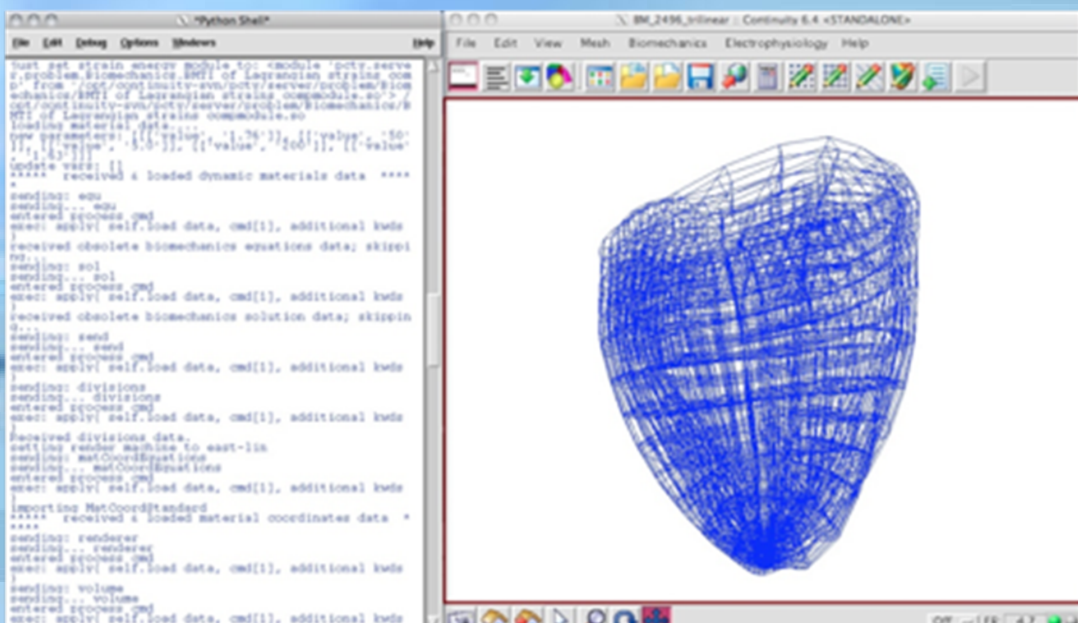
- P is the force during shortening velocity (V)
- P_o is the isometric force
- a & b are constants with dimensions of force and velocity

•Force generated is increasing when rate of detachment is low (muscle is highly contracted and there is increased overlap between thick and thin filaments)

•When rate of detachment of myosin filaments is increased, overlap decreases, and muscle force generated decreases.

Project progress

- Research on Continuity, the Hill Relation, cardiac forces/pressures/velocities, sarcomere shortening mechanics
- Became acquainted with Nimrod/G
- Literature reviews on Rice Model, Campbell Model, myosin heavy chain isoforms
- Nimrod/G test work/experiments
- Rice Model figure replication and Matlab script writing work
- Conversion of various cont6 models from ForTran to SymPy
- troubleshooting with Continuity and version/revision requirements and subsequent effects on models and running inflations
- Parameter variations with x_0 and xPsi in Rice Model examining Hill relation
- Ran start of passive and active inflation with linear increase in pressure for LV/RV and 3-element windkessel model. (was not completed due to large amount of elements in the biomechanic model and time required to complete computational work)

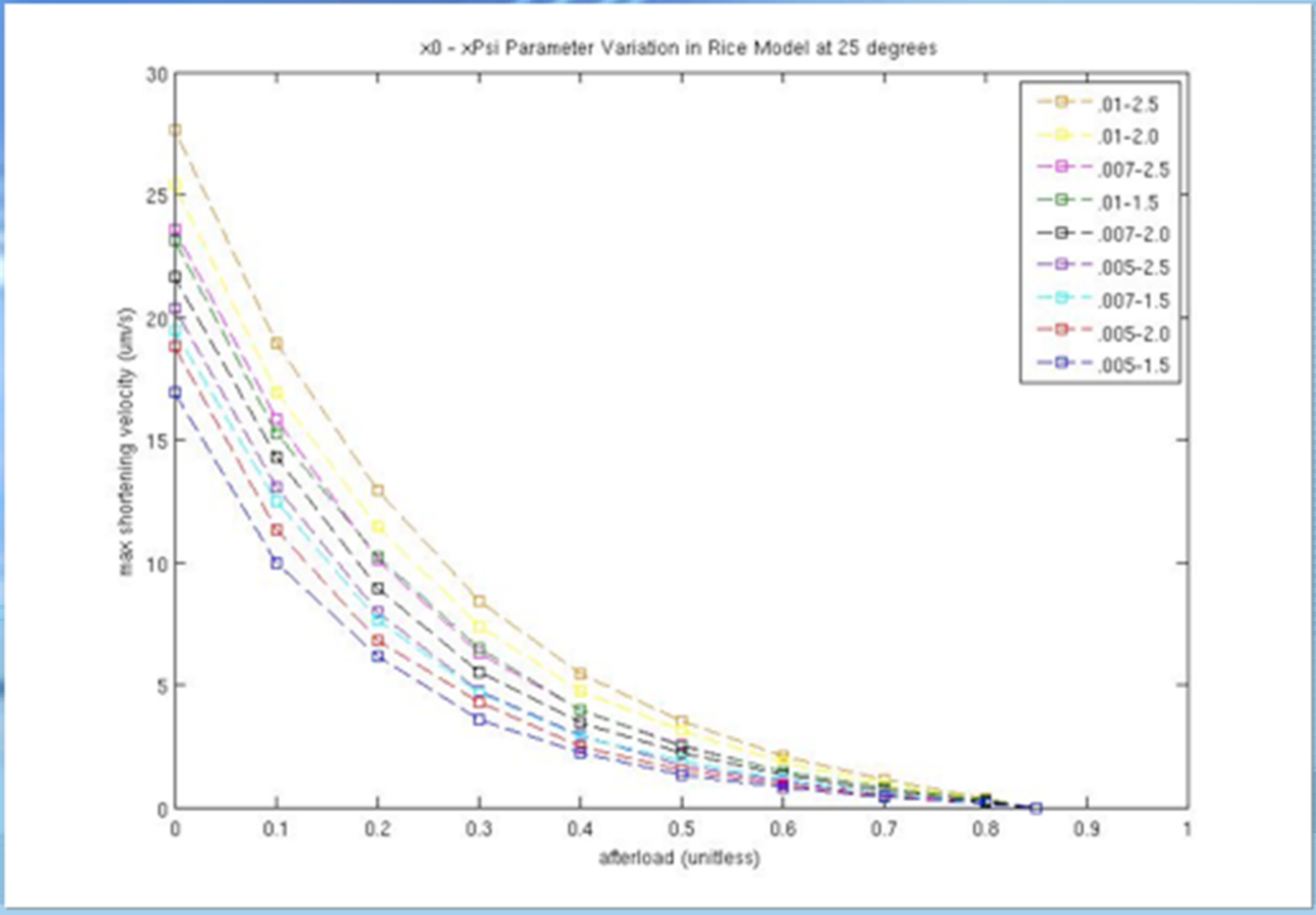


Methods

The project is being executed with the use of NIMROD/G, NIMROD/O (David Abramson) and Continuity (Andrew McCulloch). With these resources, parameter variations are conducted to quantify and analyze the effects of each of the parameters in question.

For the majority of this project, the Rice Model (by J.J. Rice) has been used to examine the Hill (force-velocity) relation. The Rice Model simulates cardiac myofilaments in a variety of muscle relations including, force, calcium, and velocity under multiple muscle conditions such as isometric, isotonic, and isovolumetric contraction.

Hill Relation
(force-velocity)



Rice Model

Parameters:

x0- strain induced by head rotation

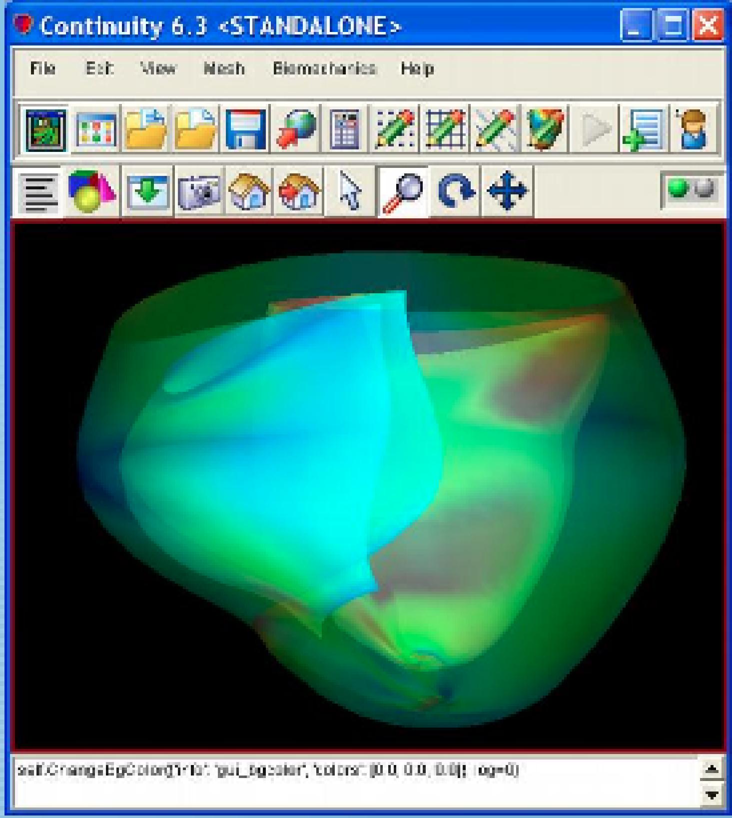
xPsi- scaling factor balancing SL motion and XB cycling

(par.sim = 4; figure 7)

This shows that the unloaded shortening velocity (y-axis) is affected. However, the overall curvature is generally unaffected.

Continuity

- For application projects in bioengineering and physiology
- It is a problem-solving environment specializing in solving problems in the biomechanics, electrophysiology, and biotransport fields.
- Allows symbolic modeling creation and compilation based on simple processing, fitting and refinements.
- Continuity as a whole is made up of two different parts, the Server and the Client.



Project specifics in Continuity

- For this project, the Rice Model was first run in MATLAB with parameter variations on x_0 (strain induced by head rotation) and xPsi (the scaling factor balancing SL motion and cross bridge cycling).

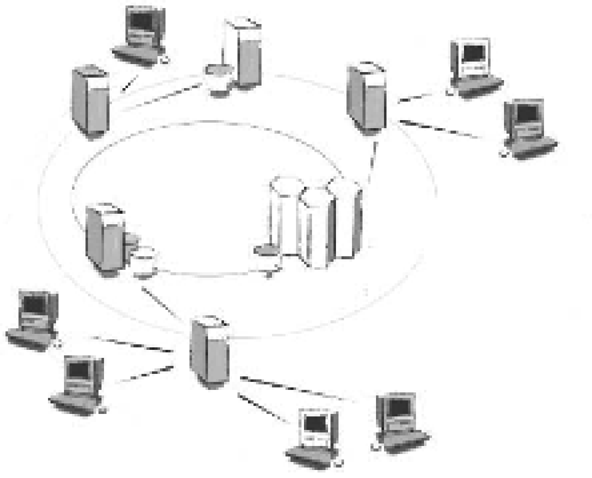
- Next, the Rice Model was implemented and run in Continuity, a software platform used for general computational biology, but specifically designed for cardiac modeling.

- For this project, an inflation starting from an end-diastole needed to be performed. This was executed with a finite element model with passive and active inflation properties containing 3072 elements in the mesh.

- The constitutive and active tension models used for inflation were the Rice Model in sympy, with 1.5/0.05 (30) steps resulting in 1.5 kPa pressure at end-diastole. Once that inflation model was saved, the circulation model was changed from, linear increase in pressure in LV and RV to a 3-element Windkessel model to allow for active contraction rather than just a passive inflation.

Nimrod/G

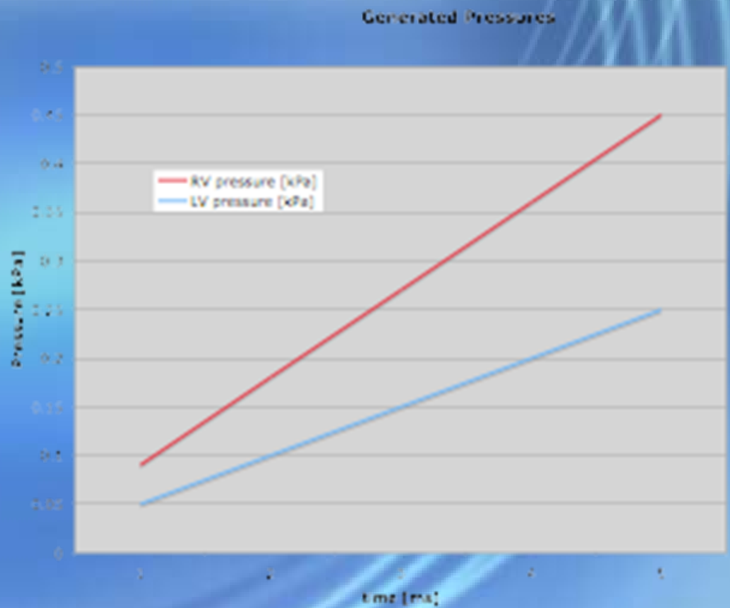
- In this project, Nimrod/G has allowed for a means of obtaining vast amounts of data through computational parameter experiments with the use of grid computing. Nimrod/G utilizes scheduling jobs among various compute resources while performing parameter sweeps as a method for exploring the effects of the Rice Model in cardiac mechanics within Continuity.

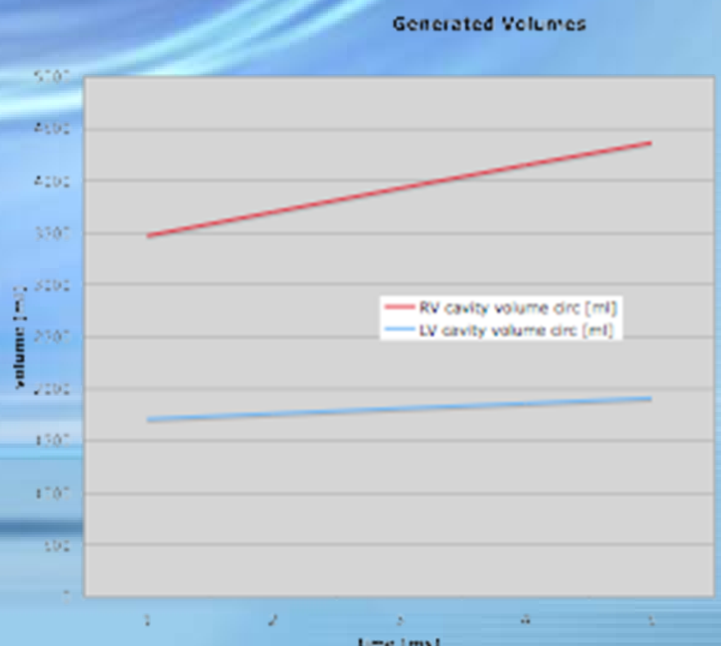


Results

- The experiemnts in Matlab and Continuity/Nimrod show the force-velocity relationship could be an important factor in CRT responders/non-responders.
- This is due to the fact that a more elastic heart, with no major Hill-relation effect (as shown in the graph) overall ejection fraction is not significantly increased during synchronization in CRT by .
- In Heart Failure patients vs. normal patients as seen with Rice Model or without, regionally, fiber shortening and strains are affected and more globally, ejection fraction and overall cardiac function is greatly affected.
- From the MATLAB experiments specifically it is clear that the unloaded shortening velocity (as shown on the y-axis) is greatly affected in the parameter variations of x_0 and xPsi but that the overall curvature of the relationship is generally unaffected and remains fairly consistent throughout the contraction.
- This provides information confirming that variations in induced strains and cross bridge cycling seen in cardiac tissue of various levels in HF patients,

Numerical data representation





Time step	Time [ms]	LV pressure [kPa]	LV cavity volume FE [ml]
0	1	0.05	1759.894165
1	2	0.1	1810.319214
2	3	0.15	1860.372314
3	4	0.2	1909.175537
4	5	0.25	1909.175537
5	1	0.3	2055.343262
6	2	0.35	2113.859131
7	3	0.4	2168.815186

LV cavity vol circ [ml]	RV pressure [kPa]	RV cavity vol FE [ml]	RV cavity vol circ [ml]
1710.0271	0.04	1938.050537	1760.515747
1759.894165	0.08	2116.366455	1938.050537
1810.319214	0.12	2290.051514	2116.366455
1860.372314	0.16	2454.405273	2290.051514
1909.175537	0.2	2454.405273	2454.405273
1909.175537	0.24	2804.652588	2454.405273
2055.343262	0.28	2942.519775	2804.652588
2113.859131	0.32	3066.075928	2942.519775

Project Significance

- This project could be of great use to society such that if successful, the information learned could have incredible clinical use and increase the effectiveness of a widely used therapy that improves survival, heart function, and overall quality of life for many CHF patients

- Although this project is at the very preliminary steps that precede clinical work, its clinical relevance could be immense. Congestive Heart Failure is a very large problem world wide and the effectiveness of such therapy could be increased through this research. Which also could have a large impact on the acceptance, clinical use and successful treatment by CRT.

Future Work

- Perform the remainder of the parameter sweeps with the Rice Model in Continuity need to be completed on Nimrod to finish up the first set of results obtained for this project, especially examining the x_0 and xPsi effects.

- A parameter variation examining the effects of temperature would provide insight into an alternate interior important hill relation altering conditions.

- I also would like to obtain the Campbell Model, which has a much greater emphasis of myosin (heavy chain) filaments within cardiac muscle, allowing for an alternate, more specific look at muscle contraction and internal parameters.

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