Determining the Optimal Site for BiVentricular Pacing on Rabbit Heart With LBBB and Scar Tissue

Name: **Venkatakaushik Voleti, PRIME 2010**
Mentors: **Dr. Roy C. P. Kerckhoffs, Cardiac Mechanics Research Group, UCSD**
Dr. Andrew McCulloch, Cardiac Mechanics Research Group, UCSD
Dr. David Abramson, MeSsAGE Lab, University of Monash

Abstract

This study uses an anatomically detailed mesh of the rabbit heart with a coupled electromechanical model in order to determine optimal left ventricular lead placement in Cardiac Resynchronization Therapy. The mesh and models were created in Continuity 6, developed by the Cardiac Mechanics Research Group in the University of California, San Diego. Continuity 6 is a finite-element modeling software packaged designed specifically for the multi-scale modeling of cardiac tissue. Pacing at various sites will be modeled through Nimrod/G. Nimrod/G is a parameter-variational toolkit developed by the MesSAGE Lab at the University of Monash, Melbourne. Parameter variation by Nimrod will make possible a multi-objective analysis on the influence of pacing site and scar properties on ejection fraction and regional shortening. The model simulates Left Bundle Branch Block, with varying levels of ischemic tissue, in an attempt to better understand the relationship between the biomechanical, electrophysiological and clinical implications of these conditions and proposed therapies.

Introduction

In Left Bundle Branch Block, electrical signals normally transmitted to the left ventricle (LV) via the Purkinje Fiber Network are blocked, forcing signals to spread from the right ventricle (RV) through the inter-ventricular septum (IVS) in order to reach their final destination,

the lateral LV wall [**Figure 1**].This heterogeneous activation of intraventricular regions results in asynchronous contractions and leads to adverse structural remodeling of cardiac tissue. Chronic LBBB displays a redistribution of external work and blood flow from the IVS to the posterior-lateral LV wall, as well as severe cellular hypertrophy and ventricular dilation (Ref. 7, 11). If left untreated, such cardiomyopathiesdegrade cardiac function to the point of failure.

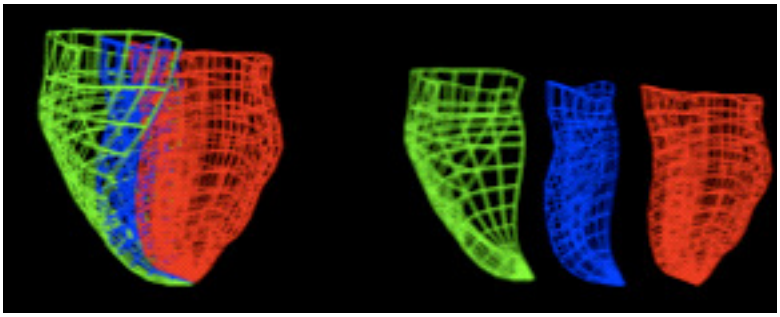


Figure 1: The mesh on the left represents a rabbit heart with LBBB. Signals propagate from the RV (green) to the IVS (blue) and finally reach the LV (red)

BiVentricular Pacing (BiV) has been shown to improve cardiac function in approximately 70% of patients with LBBB by artificially simulating healthy activation patterns via electrodes placed in the right atrium, RV apex and LV wall (Ref. 1). As LBBB normally manifests in tandem with other problems, itsetiologyis still insufficiently characterized. Thus, the resistance of the remaining 30% of patients to BiV may be attributed to several factors such as the preexistence of mitral regurgitation, Purkinje Branch ablations and congenital defects.Multiple

studies also have shown that the presence, size and pervasiveness of ischemic tissue severely compromises patient responsiveness to BiV (Ref. 2, 3, 4), however contractility of non-infacted tissue may be independent of scar size (Ref. 8).

This project requires the use of Continuity's mesh module which creates and manipulates a finite-element mesh representative of observed tissue geometry; a biomechanics module which defines equations governing the stresses, strains and blood flow across the mesh; and an electrophysiology module which defines the equations governing the creation and propagation of electrical signals across the same. While only the mesh and electrophysiology components of Continuity were used over the summer of 2010, Revelli extensively utilized the biomechanics module during his work in 2009. Revellirefined a 48-element rabbit mesh (Ref. 12) governed by tri-cubic basis functions into a 2496-element mesh governed by tri-linear basis functions. The passive material properties of the mesh were based on values by Vetter et al. 2000 and active tension was based on a model by Rice et al. in 2008 (Ref. 9, 12). The model was passively inflated at the University of Monash using theEnterpriseGrid's south cluster,and validated against data from Vetter et al. 2000 (Ref. 12). Scarson the mesh were defined element-wise,possessed stiffer passive mechanical properties and lacked active tension. Values from Walker et al. 2005 were used to calculate the passive material constants required for scar tissue (Ref. 13). A 3-element windkessel model was also implemented to blood flow.

This biomechanical model is to be coupled with a mechanistic electrophysiology model, each using the same mesh structure. The meshes will implement various scar sizes and locations, and are to be paced at each of their 3496 nodes with varying scar densities. The outputs in consideration are regional strains, which may predict ventricular remodeling, and ejection fraction, a clinical indicator of global cardiac function. An understanding of how ischemic tissue

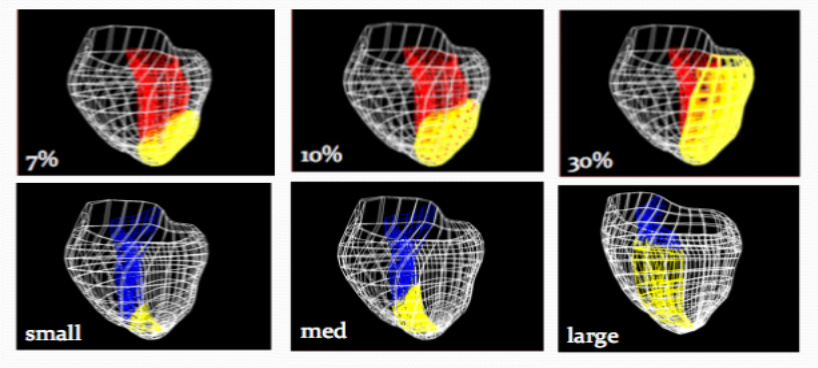
properties and pacing site affect cardiac efficiency can help improve the quality of Cardiac Resynchronization Therapy for patients with LBBB.

Figure 3: **Endocardial (blue), midmyocardial (red) and epicardial (green) cells each have distinct electrical signatures stemming from differences factors such as ion channel conductance. Ischemic cells (dashed line) and non-ischemic cells (solid line) also behave differently. Note how ischemia alters the action potential duration of midmyocardial cells to a greater extent than endocardial cells.**

Methods:

1. Expansion of Models with Scar

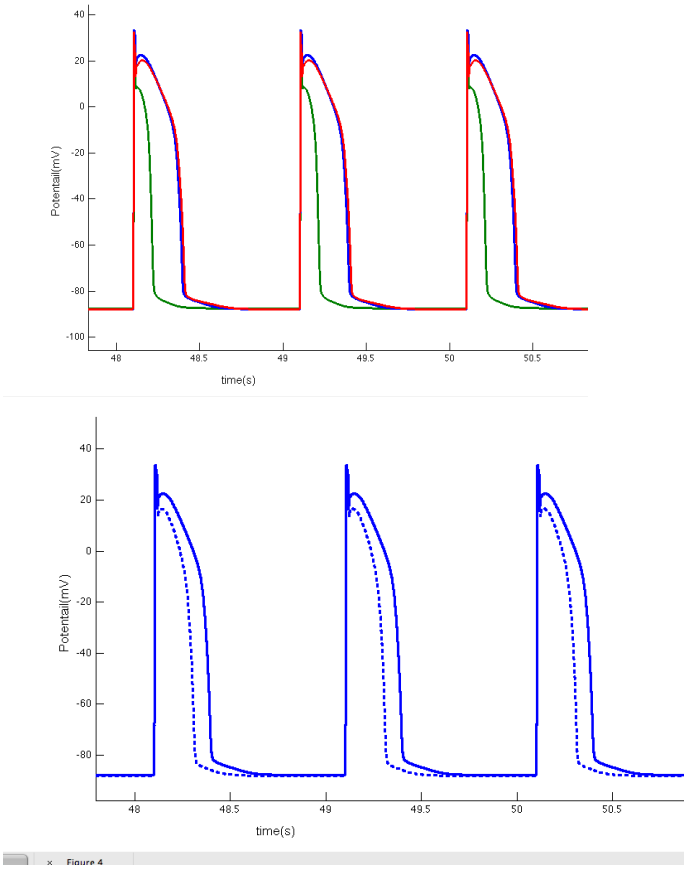
At the beginning of Summer 2010, the four preexisting models with scar tissue could be separated by location: LV scar and Septal scar. It was suggested, however, that the differences in scar size within the groups themselves wouldbe sufficient to observe legitimate differences in cardiac function. An additional two meshes were created with a 30% LV and large septal scar to serve as a better comparison **[Figure 2]**.

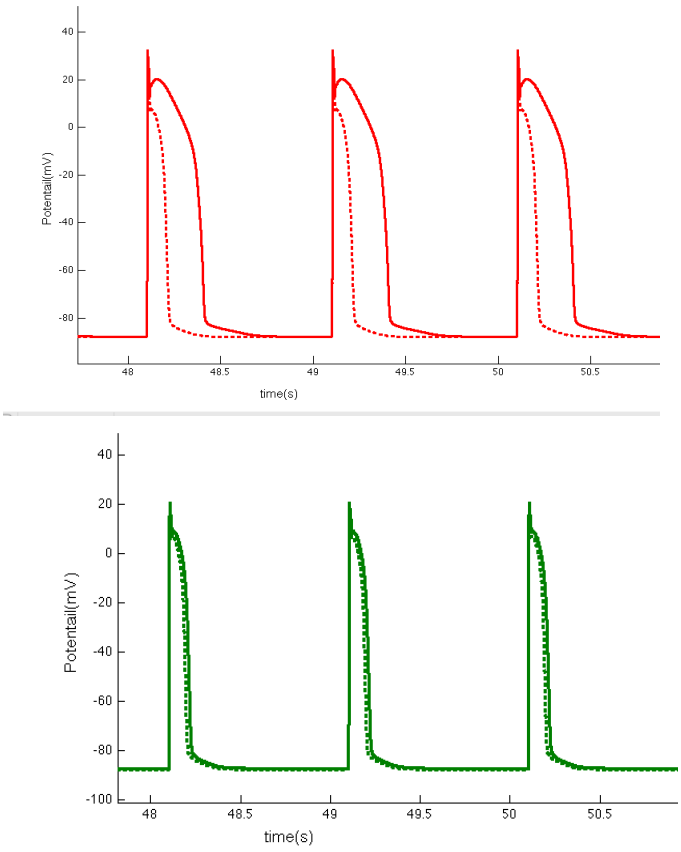


2. Creation of Electrophysiology Model

An ionic model based on Shannon et al. 2004 and Michailova et al. 2007 was created by Dr. Aguado Sierra using Matlab (Ref. 5, 10). This model implemented 39 interrelated differential equations, as well as seven scaling factors, in order to mechanistically represent the differences between various cell types; for example, the fact that epicardial cells have alower action potential duration than endocardial and midmyocardial cells. Four additional scaling factors were added to the script in order to represent the differences between healthy and

ischemic tissue in each cell type **[Figure 3]**.Solving the Shannon-Bers/Michailova(SBM) model is computationally expensive but necessary in order to represent the transmural heterogeneity of activation times displayed by various cells. Without it, the electromechanical model would exhibit unphysiological regional strains (Ref. 6). The Matlab model was ported into Continuity and initial conditions were assigned to the ODE's based on element groups. Similarly, the scaling factors were also dependent on element groups and were implemented using Heaviside and Durac Delta functions.





3. Compilation of Electrophysiology Model

In June 2010, a software update for Continuity-6.3 necessitated a conversation of all electrophysiology and biomechanical models from FORTRAN to Sympy. The newer version, Continuity-6.4, ran into numerous incompatibilities with the local operating system, OS X 10.5. It persistently reported an inability to compile the Sympy model, necessitating the reinstallation of numerous software packages. These packages included g95, f2py, numpy, MGLTools and XCode, as well as numerous installations of Continuity-6.4 downloaded from the Continuity repository. Continuity-6.4 was eventually built from source on two separate operating systems: Mac OS X 10.5 running Darwin 9.8 and Linux running CentOS 5.3. Successful compilation of the SBM model was achieved on CentOS 5.3.

4. Validation of the Electrophysiology Model

Validation of the SBM model was supposed to be carried out on a single element cube. This cube was refined into four prisms of equal volume to represent the different cell types. The first integration of the SBM model led to NaN answers for all state variables. Modifying the initial conditions and meshes did little toamelioratethis problem. It was discovered that the rapidly equilibriating nature of certain sarcoplasmic calcium buffering variables necessitated the usage of algebraic variables, which were not ready for full use in Continuity-6.4 at the time of this discovery. However, once functionality was restored to these variables, the SBM model still gave NaN answers.

It was then decided that the phenomenological Modified Fitzhugh-Nagumo(MFHN) model would be used to collect preliminary data on each mesh. The MFHN model has the advantage of being pre-validated and computationally less expensive than the SBM, but cannot differentiate between different cell types. As a result, an electromechanical coupling using the MFHN would provide unreliable stress-strain data. Regardless, it could provide information regarding the spatial propagation of electrical signalsacross various meshes and could narrow the proposed 3496 pacing sites down to a select subset.Implementation of the MFHN on the meshes revealed multiple mesh concavities and nodal irregularities, which were eventually fixed by Dr. Aguado-Sierra.

Future Work:

The SBM model must still be validated. Once validated, the electrophysiology model will be coupled to the biomechanical and revalidated. A parameter sweep using Nimrod/G will be

conducted, varying the pacing site in order to determine its effects on ejection fraction and regional strain. The scaling factors implemented to distinguish scar tissue in the biomechanical and electrophysiological modules can also be varied using Nimrod/G in order to represent the effects of different scar densities. Different scar sizes and locations will depend on the mesh upon which the parameter sweep is being conducted. Furthermore, holding all scar properties constant during a sweep of possible pacing sites, it would be possible to conduct a multi-objective analysis of ejection fraction and regional strains.

References

1) Abraham, W.T., Fisher, W.G., Smith, A.L., Delurgio, D.B., Leon, A.R., Loh, E., Kocovic, D.Z., Packer, M., Clavell, A.L., Hayes, D.L., Ellestad, M., Messenger, J., Trupp, R.J., Underwood, J., Pickering, F., Truex, C., McAtee, P., 2002. Cardiac resynchronization in chronic heart failure. New Engl. J. Med. 346, 1845–1853.

2) Adelstein, E.C., Saba, S., 2007. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. Am. Heart J. 153, 105–112.

3) Arzola-Castaner, D., Taub, C., Heist, E.K., Fan, D., Haelewyn, K., Mela, T., Picard, M.H., Ruskin, J.N., Singh, J.P., 2006. Left ventricular lead proximity to an akinetic segment and impact on outcome of cardiac resynchronization therapy. J. Cardiovasc. Electrophysiol. 17, 623–627.

4) Díaz-Infante, E., Mont, L., Leal, J., García-Bolao, I., Fernández-Lozano, I., Sitges, M., Pavón-Jiménez, R., Barba, J., Cavero, M.A., Moya, J.L., Pérez-Isla, L., Brugada, J., 2005. Predictors of lack of response to resynchronization therapy. Am. J. Cardiol. 95, 1436–1440.

5) Michailova AP, Lorentz W, McCulloch AD (2007) Modeling transmural heterogeneity of K_{ATP} current in rabbit ventricular myocytes. *Am J Physiol Cell Physiol*, Feb 2007;293:542-557 doi:10.1152/ajpcell.00148.2006

6) RCP Kerckhoffs, PHM Bovendeerd, JCS Kotte, FW Prinzen, K Smits, T Arts. Homogeneity of cardiac contraction despite physiological asynchrony of depolarization: a model study. Ann. Biomed. Eng. 31(5): 536-547, 2003

7) RCP Kerckhoffs, J Lumens, K Vernooy, JH Omens, LJ Mulligan, T Delhaas, T Arts, AD McCulloch, FW Prinzen. Cardiac Resynchronization: insight from experimental and computational models. Progress in Biophysics and Molecular Biology 97: 543–561, 2008. Invited review.

8) RCP Kerckhoffs, AD McCulloch, JH Omens, and LJ Mulligan. Effects of biventricular pacing and scar size in a computational model of the failing heart with left bundle branch block. Medical Image Analysis 13: 362-369, 2009.

9) Rice, J.J., Wang, F., Bers, D,M., Tombe, P.P., 2008. Approximate Model of Cooperative Activation and Crossbridge Cycling in Cardiac Muscle Using Ordinary Differential Equations. Biophysical Journal. 95, 2368-2390.

10) Shannon T, Wang F, Puglisi J, Weber Ch, Bers DB. A mathematical treatment of integrated Ca dynamic within the ventricular myocyte.Biophys J 87: 3351-3371, 2004

11) Vernooy K, Verbeek XAAM, Peschar M, Crijns HJGM, Arts T, Cornelussen RNM, Prinzen FW. Left bundle branch block induces ventricular remodeling and functional septalhypoperfusion. Eur. Heart J. 2005;26:91–98.

12) Vetter FJ, McCulloch AD (2000) Three-dimensional stress and strain in passive rabbit left ventricle: A model study. *Annals of Biomed Eng* 28:781-792

13) Walker, J.C., Ratcliffe, M.B., Zhang, P., Wallace, A.W., Fata, B., Hsu, E.W., Saloner, D., Guccione, J.M., 2005. MRI-based finite-element analysis of left ventricular aneurysm. Am. J. Physiol. – Heart Circ. Physiol. 289, H692–H700.

Acknowledgements

UCSD PRIME

Dr. Gabriele Wienhausen, Principal Investigator, PRIME
Dr. Peter Arzberger, Co-Principal Investigator, PRAGMA
Teri Simas, UC San Diego PRIME
Tricia Taylor, AIP

UCSD Cardiac Mechanics Laboratory

Dr. Andrew D. McCulloch, Principal Investigator, UCSD Dept of Bioengineering/Medicine
Dr. Roy Kerckhoffs, Project Scientist, Dept of Bioengineering
Dr. JazminAguado-Sierra, Postdoctoral Researcher, Dept of Bioengineering
Jeff Van Dorn, Programmer/Analyst, Dept of Bioengineering
Scott Revelli, Undergraduate Researcher for Project, 2009

University of Monash, MeSsAGE Laboratory

Dr. David Abramson, Principal Investigator
Rob Gray, Lab Manager
Blair Bethwaite, Programmer/Analyst/Admin

A special thanks to the National Science Foundation, IOSE-0710726
