Whole Heart Computational Modeling

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I. Abstract

In biomedical research today, simulation is a powerful tool in helping scientists solve complex cardiac problems. The University of California, San Diego (UCSD) and Oak Ridge National Laboratory (ORNL) are doing collaborative research in computational, multi-scale heart modeling using ***Continuity***, finite-element software developed by UCSD. When problem solving of this nature is extended to ORNL's high performance computing (HPC) resources, advanced simulations can be used to study detailed heart function over extended time periods, including such conditions as arrhythmia, the details of connections between the electrophysiology and biomechanics of the heart, and ischemia or restriction in blood supply to a portion of the heart. To conduct these studies, ***Continuity*** implements interconnected, multi-scale models including biomechanics, electrophysiology, and the underlying cellular mechanisms of cardiac myocytes. Problem solving is conducted on an iMac using Linux, a Linux workstation and on the ORNL Institutional Cluster (OIC). Rendering of these results is done at the desktop. The accuracy of the electrophysiology and biomechanical data results prove to be heavily dependent on the orientation of the mesh, how fine or course the mesh is, and changes in other variables. Finer meshes and extensive data require more random access memory (RAM) and computing power. Implementing ***Continuity*** on HPC resources provides faster and more efficient solution of the underlying equations than standard computing resources. Results from this research will help to develop tools for implementation and analysis of some of today's most challenging cardiac problems.

II. Introduction

Continuity 6, developed by the University of California San Diego (UCSD) applies finite elements using the theory of finite elements to the specific discipline bioengineering and biomedical research. In the efforts to computationally simulate, analyze, and then solve common problems using finite elements require vast amounts of computing power, time, and accuracy. The requirements in computing finite element problems is the understanding of the models used, what properties of each model can be changed, and the compatibility of the models and changes to the finite element mesh application. Finite elements problem solving entails partial differential equations or PDE being solved over complex domains such as plates or pipes. Scientists and engineers today commonly use finite elements to solve common problems such as heat transfer problems, basic mechanics problems such as stress and strain, and electrical problems such as current, resistance, and voltage. However, *Continuity 6* uses finite element problems such as mechanical, involving stress and strain analysis on the heart, electrical, concerning stimulus current pathology, and cell, the foundation for both the electrical and mechanical problems containing cellular properties of the critical parts of the model.

The unique characteristic of this software is the way these problems are compiled for solving within the heart FE model. Most finite element codes have preset universal equations that work well with many meshes applied. Continuity has this but allows you to create your own model and compile using either a g95 or Intel FORTRAN compiler. The electrophysiological i.e. the electrical models of study that are assembled are the Beeler-Reuter ventricular myocyte model, Modified Fitz-Hugh Nagumo model, and the Luo-Rudy cell model. The effective biomechanical model of study that is compiled is the transversely isotropic exponential function of Langrangian strains model. These models contain various cellular, mechanical, and electrical components critical for heart function.

III. Methodologies/Theory

The computational resources used for whole heart computational modeling are a Macintosh laptop computer equipped with four gigabytes (GB) of RAM and two gigahertz (GHz) processing speed, a desktop Linux workstation equipped with two gigabytes of RAM and 2.4 gigahertz processing speed, and the ORNL institutional clusters have sixteen GB of RAM and 3 GHz processing speed. Each of these resources has a specific purpose in the modeling and simulation of the heart. The goal of the Macintosh workstation is to utilize its graphical display as well as the RAM it uses to render and record the results of the biomechanics models or the electrophysiology models. The collaborative goal of the Linux workstation and the OIC is for the OIC to use its processing power and it's RAM for extensive calculations, such as biomechanical stress and strain calculations of the heart over an extended period of time or the electrophysiology of the heart using a refined finite element mesh that is refined from a number of elements close to 50 to a number close to1000. This can be done interactively via the graphical user interface (GUI) of continuity via a python script file on the Linux workstation with a fast, hard-wired connection to the institutional cluster.

In order for *Continuity 6* to perform multi-core batch jobs on the cluster, the cluster has been equipped with an MPI that is compatible with the cluster's operating system. For modifying some of the models that are put to use in the simulations, there is compiling that has to take place. The G95 FORTRAN compiler has been implemented into the Macintosh laptop computer and the Linux computer for fast modifications. For compiling major problems on the clusters, the Intel FORTRAN compiler is implemented because this particular compiler is the most compatible and efficient on the cluster for the Continuity code on the cluster.

Modification of the FORTRAN code is performed in the model editor of the biomechanics as well as the electrophysiology. The finite element model of the heart is meshed from point data taken from a canine heart from researchers at the University of Oxford. The canine heart is used because of its similarities to humans in the functioning systems and its similarities in size. The nodal data and elemental data is plotted into an excel spreadsheet. From that point, *Continuity* takes this data and creates the mesh. In the finite element heart model the optimal basis functions for solving PDEs are 3D cubic Hermite and 3D linear functions with three integration and collocation points.

In the electrophysiology module of *Continuity*, equation modifications that were made to the Fitz-Hugh Nagumo model include the stimulus time, transmembrane potential, conductivity tensors, and membrane capacitance. The Fitz-Hugh Nagumo model is a simplification of the Hodgkin-Huxley Model where the number of equations in the MFHN model is two, one being a cubic equation that represents the fast variable u and a linear equation that represents the slow variable w. In *Continuity,* this equation has been modified in order to conform to the three-dimensional mesh of the model hence the reason it's called "Modified Fitz-Hugh Nagumo" (MFHN) model.

The first modification made to the FHN model is the conductivity tensor, the conductivity tensor in mathematical terms is a tensor when multiplied by the electric field, give the current density vector. This particular parameter is 100% mathematical in this model and has much to do with the susceptibility of current flow throughout the heart. The conductivity tensor was adjusted to "field 1" for all tensors which signifies a positive change in the *Continuity* electrophysiology ionic model editor. The next modification made in the conductivity tensor was setting this to the "field 9" a lower setting. With the MFHN model in *Continuity* reset, the next modification made

to this model was the stimulus time. The stimulus time was initially set for start time at 1 millisecond and the duration of the stimulus was set for 3 milliseconds. Three seconds is a setting for quick analysis, however the heart has a stimulus time of 220 milliseconds and the simulation of the stimulus is needed to start at the time of 0 for a correct representation of the stimulus throughout the heart. With all other tests this was the set time henceforth for a good basis of comparison. Rendering these results frame by frame takes 1000 frames derived from the time steps and samples taken in solving the PDE. The third test for comparison was the modification to the transmembrane potential. The transmembrane potential is the electrical potential across the cell membranes in the heart's cells. The transmembrane potential modification entailed an adjustment to field one (positive) and an adjustment to field nine (negative). The last modification was the membrane capacitance, a measure of the electrical capacitance of the cell membranes of the heart's cells, which included and increase into 10 microfarads.

The next model of study is the Beeler-Reuter Ventricular Myocyte (BR) model. The BR model formulates ionic current gating in terms of Hodgkin-Huxley type equations (Beeler 177). This model describes four ionic currents, fast inward sodium current, slow (calcium-carried) inward current, time-dependent outward potassium current, and time-independent (predominantly potassium) outward current (Beeler 177). The same four parameters as stated in the MFHN model remain the same in *Continuity* as well as how they are modified. What differentiate models concerning parameters in BR model from the MFHN model are the parameters of intracellular calcium concentration and sodium potential. Intracellular calcium concentration and sodium potential are both reflections of how much of these elements the mammalian body contains. The final model, the Luo-Rudy Mammalian Ventricular model is the model that is under assembly in the ionic model editor in *Continuity.* The model was originally designed to measure guinea pig cardiac action potentials. It formulates ionic current gating in terms of Hodgkin-Huxley type equations. This model contains description of fourteen ionic currents and pumps (Rudy 74). Once this model is compiled correctly there will be modifications and tests of the model.

In the biomechanics module experimentation of *Continuity,* the type of model that works very well with the finite element model of the heart is the Transversely Isotropic Exponential Function of Langrangian Strains Model: slightly compressible. This is a model designed for the analysis of ventricular stress and strain of the heart. The coefficients in this model that can be modified are the fiber and transverse strain coefficients as well as the stress scaling coefficients. All of these models when modified had a value increase of 20. The circulation models in the biomechanics model editor are models separated from the strains model containing virtual models of the valves, chambers, and ventricular walls that regulate blood flow throughout the body. The particular model of our study in the circulation model editor is the Closed Loop Left and Right Ventricular model. This model is best used for its modeling of the left and right ventricles and the virtual simulation of the various outer heart components. The modified parameters for the circulation model are the arterial impedance, mitral valve resistance, tricuspid valve resistance, and ventricular pressure. The arterial impedance concerns the resistance of blood flow throughout the body and to the heart. In order for the heart to function it requires oxygen rich blood because the heart muscles have similar characteristics of any other muscle in the body. If there are high amounts of arterial impedance these muscles may become weak or die; this condition is known as ischemia. Depending on the levels of arterial blockage or impedance this condtion could have various negative effects on the heart. The arterial impedance

value of 7.0dyne · s · cm^{-5} in *Continuity* is the setting where there is instantaneous change in heart behavior; this is also the impedance used in the heart model testing. By simulating the first few heartbeats it should be a significant change in stress and strain during heartbeat. A setting in the range between 0.5 and 4.0dyne · s · cm^{-5} require testing of hundreds to thousands of heartbeats. Testing of this magnitude should be ported only on a parallel cluster because the effects of a modification such as this may cause a standard workstation to crash. In mitral valve resistance, the resistance of this valve that regulates non-oxygenized blood into the left ventricle can be critical, leading to ischemic conditions not only to the cardiac muscles, but every other muscle of the body. Simulation of mitral valve resistance in *Continuity* is involved changing to a value of 10.0dyne · s · cm^{-5} compared to the original value of 0.5dyne · s · cm^{-5}.

Another method used in the study of the *Continuity* model with ischemic conditions is tricuspid valve resistance. For symmetry the tricuspid valve resistance value is set to 10.0. The tricuspid valve controls the flow of oxygenized blood into the heart, bringing ischemic conditions if there is blood flow restriction to the right ventricle. The last parameter in the circulation model testing is the ventricular pressure. The value for this originally is 1.5KPa to the left ventricle and 1.2KPa to the right ventricle. In the modification to the pressure is three times the amount of the original pressure. This specific modification is strictly for stress and strain analysis and muscle fiber strength. In addition to muscle fiber strength the active stress model in the biomechanics model, Guccione, contains properties of underlying cellular mechanisms that relate to muscular integrity of the heart. The parameters of the model are intracellular calcium concentration in *milli*moles and the sarcomere length in μ*m*. The sarcomeres are the basic units of the heart muscles cross-striated myofibrils, the basic structures of the heart contracting muscles. In the Guccione model in *Continuity,* the modified length is ten times longer than that of the original length of 1.5μ*m* and the modified calcium concentration has an additional 10 μmoles more than the original concentration.

IV. Results/Discussion

Primarily, when rendering of the results in the electrophysiology and biomechanics modules, the mesh orientation of the models is key. In the case of the MFHN electrophysiology model, figure 1.1 and 1.2 shows the heart mesh in a fine mesh presentation with a linear nodal and elemental orientation. Figure 1.3 and 1.4 shows heart mesh in a fine mesh presentation with a curvilinear, rounded, nodal and elemental orientation with a course mesh presentation.

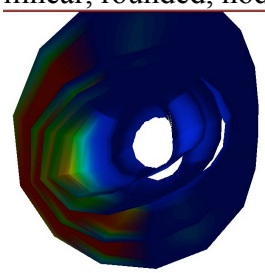

Figure 1.1

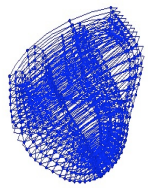

Figure 1.2

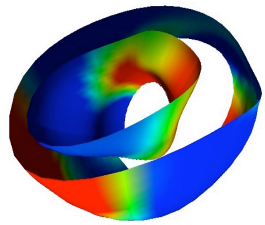

Figure 1.3

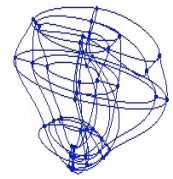

Figure 1.4

When the same EP model that is solved different results come about. In figures 1.1and 1.2 the stimulus current follows the lines in the mesh downward but doesn't propagate throughout the whole heart. This nodal and elemental orientation does not work very well for accurately representing action potential throughout the cardiac muscles. In contrast to the previous figures, figures 1.3 and 1.4 demonstrate stimulus current propagation throughout more parts of the heart. This particular orientation of nodes and elements is good for this type of model. The MFHN

model in figure 1.3 and 1.4 is more effective in current propagation when the stimulus time in the ionic model editor is set in real time of approximately 220.0*m*s. The colors represent levels of current in *m*A from red being the highest and blue being the lowest in an RGB fashion.

In the modification of the transmembrane potential, it is evident that this is very sensitive to any modification. In a positive and or negative modification the coverage of stimulus current changes, some areas will be highly covered while the others lose signal. Modification of the conductivity tensor in the MFHN heart model once adjusted to (field 1) increased total current density and it is proven by the propagation of the signal throughout the cardiac muscles. In this simulation, orange and red are the only two colors representing the current intensity meaning this modification has a dramatic effect on overall current. A drop in the conductivity tensor to (field 9) created scattered areas of stimulus current. Positive modifications to the membrane capacitance were made in parts of the equation editor, requiring some recompiling of the MFHN *Continuity* code. After the recompilation of the code, the model was run and the direction of the current was positive, however, the stimulated parts of the heart were scattered, similar to that of the transmembrane potential results.

The next EP test new to *Continuity* is the Luo-Rudy model, most of this modeling involves long term compiling of the equations from scratch involving the ionic channels. In the compiling process of this model, there are many ongoing compilation errors due to some missing parameters. The goal is to find the missing parameters and find the correct value for a complete test model. The last test involved in electrophysiology is the testing of the Beeler Reuter Ventricular Myocyte model; the rendered results in this model were not correct and had no visual evidence of stimulus current propagation. At this point is where the mesh is particularly important. In order for the Beeler Reuter model to be most effective requires a finer mesh.

In the modification of the biomechanics modules the constitutive model is the model critical in the analysis in stresses and strains. The model of study is the Transversely Isotropic Exponential Function of Lagrangian Strains, *slightly compressible* model. It only entails compiling of mostly equations and not parameters. However, the parameters used for this model showed no effect to the model in either stress or strain. In the circulatory model portion of the biomechanics module the model of study is the simple closed loop for the left and right ventricle. The ventricular pressure is subject to change, however when there was any significant change in ventricular pressure the problem solving seemed to fail. When there was a very small change in ventricular pressure the problem completed with no failure. This alone was a very controversial problem that was later understood as a mesh problem. The problem was the modification made was a change to the initial conditions, which has a very dramatic effect on how the problem works with the mesh. Changing this in a very small increment had little to no effect on the solving of the problem but of course had some significance on the stress and strain data. What was observed on the python shell was an increase in pressure of the ventricles as more time steps were added on. The heart reaches it's highest of pressures in the 150*m*s to 300*m*s range since the full heartbeat is 600 milliseconds. When making adjustments to the mitral and tricuspid valve resistance there was no change at all. The reason for this phenomenon was the amount of time the heart calculations were set for. The heart calculations should have been set for more than six hundred milliseconds to actually see a noticeable change. Calculations such as these are best done on a cluster because calculations of 1200 milliseconds or more in time steps stable enough to solve without computational errors take an average of 12 hours to solve on a workstation using one of its processors. Due to MPI complications with the clusters there was no way to run the *Continuity* code in parallel so all of these calculations biomechanics and electrophysiology alike

were done in the workstation environment. In modifying the arterial impedance, simulating ischemic conditions, which was a controversial subject in the heart modeling research process, so the modeling of that on the workstation was a must. Making small changes to arterial impedance was not going to be enough for running two heartbeats so there had to be a large change so that immediate change could happen within the heart model. When the increase was made the heart made changes but not very dramatic changes as expected. Reasons for that may have been because more than two heartbeats should have been run for those types of results but there was a slight increase in strain in the outtake stage of the left and right ventricle and a decrease in the strain of the right ventricle on the intake stage. The possible reason for the decrease in strain on intake is the loss of elasticity of the muscle fiber from lack of blood or the lack of blood making it back to the heart due to reduced blood flow caused by an arterial impedance increase.

In the cellular model modifications made to the intracellular calcium concentration were various positive and negative changes these changes resulted in no change at all visible to the naked eye. Two major factors may have affected the outcome of this test is the refinement level of the mesh or the number of heartbeats simulated. The sarcomere length modification resulted in a big change in stress and strain 400 milliseconds before the heart could complete a full cycle. In figure 2.1 shows a heart with increased sarcomere length and there is no sign of deformation within the left ventricle as compared to the normal heartbeat in the same stage. This here can be useful in the findings of sarcomere defects in someone with abnormally low blood pressure throughout the body since the LV is responsible for such actions. The right ventricle had little change in strain but the way it deformed in the time steps was significantly different.

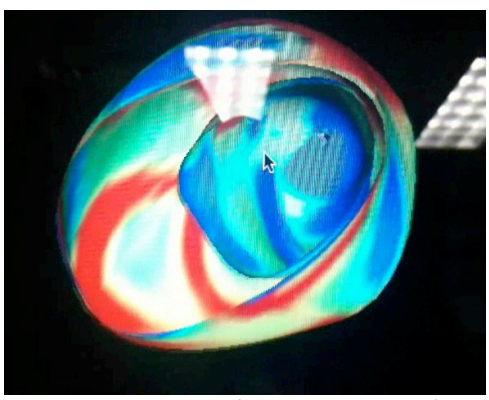

Figure 2.1: Increased Sarcomere Length

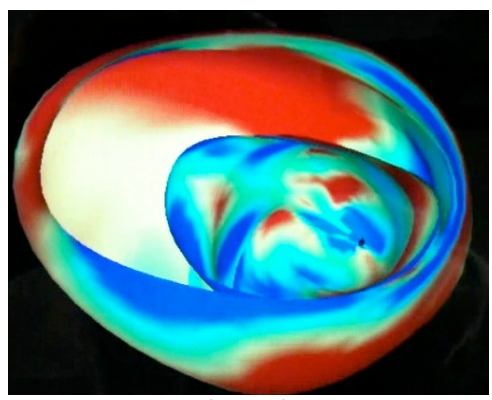

Figure 2.2: Normal Heartbeat

V. Conclusion

Whole heart computational modeling is a system of cardiac problem solving that will lead to breakthroughs in biomedical and bioengineering research. By having the ability to compute more heartbeats in a single run, increased use of Continuity on parallel machines will help to solve some problems concerning any arterial, valve, or tissue fiber related problems with the heart in the theory of biomechanics. In electrophysiology this would be beneficial for solving more models other than the MFHN model because many other models require a finer mesh in order to calculate and render the solution. Mesh orientation is highly important in any problem that is solved in *Continuity* because the data rendered through that mesh could be corrupt without notice. Cellular models and properties do play a large role of behavior of the heart and can one day be subject to analysis in the world most common cardiac problems.

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