

ES240 Project

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Introduction

Heart disease is the most prevalent cause of death in the United States. Two common forms of heart failure are cardiac (concentric) hypertrophy and dilated cardiomyopathy (eccentric hypertrophy). Each of these is associated with pathological structural remodelling of the myocardium. Under normal physiological conditions, the ventricles are, to a first order, spherical cavities with a natural radius and wall thickness. However, under disease conditions, the radius can enlarge (as in eccentric hypertrophy) or the wall thickness can increase (as in concentric hypertrophy). These two structural changes are accomplished by either series addition or parallel addition of sarcomeres respectively. The sarcomere is the fundamental molecular contractile ensemble of the myocardial cell.

Physicians have noted for years that the efficiency (frequently assessed as the ejection fraction, or volume of blood pumped per beat) of the ventricles is deteriorated in cardiomyopathies. This traditional metric of ejection fraction is a macroscale measure. However, it may also be possible that microscale inefficiencies also exist. For instance, the dynamics of a single cell may be altered so as to dissipate more or less energy into internal friction. The energetics in cardiomyopathies on the length scale of the sarcomere to the myocyte are not well understood. This requires knowledge of the contraction or displacement of the cell in time. The models described below seek to quantify the maximum displacement under peak systolic loading of the cell, a first step in understanding the wasted energy of contraction. Modeling was performed with the geometries of the cell observed in a physiological and pathological (dilated cardiomyopathy) case.

Another model described below sought to understand the effects of transverse tubules in the contraction of the myocyte. The transverse tubules constitute a network of sarcolemmal invaginations ameliorating diffusion of ions, oxygen and other solutes to the myofibrils within the myocyte. The effect of these on deformation is particularly interesting from an experimental perspective. Since these transverse tubules develop several days to weeks postpartum, they are absent in the neonatal (2-day old) rat ventricular myocytes commonly employed in *in vitro* research.

While these models do provide quantitative values as results, such values may not be reliable. There is an attempt at a comprehensive itemization of the challenges of finite element modeling of biological structures within the discussion section.

Models

There were two pairs of models which were simulated and compared. The first pair was designed to simulate physiological and dilated cardiomyopathic geometries. The myocyte was simply modelled as an axisymmetric cylindrical shell to represent the sarcolemma with dimensions: radius = $10\mu\text{m}$, length = $80\mu\text{m}$ and thickness = 50nm . The shell was subjected to

uniform normal inward traction at the circular ends of 27kPa corresponding to the force generated by contraction of the myofibrils. Additionally, hydrostatic pressure of varying magnitude was applied transversely along the length of the shell mimicking ventricular pressure. This pressure was varied from 10.6kPa (80mmHg) to 32kPa (240mmHg). The sarcolemma under cardiac dilated myopathy was modelled with the same parameters, except the length was increased to $110\mu m$. Also, the traction on the circular ends was increased to 32kPa as the cross sectional area is nearly that of the physiological case and the fact that the myocyte achieves longitudinal growth by series addition of sarcomeres implies a greater contractile force. The magnitude of contraction was found by simply scaling the estimate of myofibril force in normal conditions by the added length. The material actually being modelled in both physiological and pathological cases was the sarcolemma, a heterogenous protein-phospholipid bilayer. This was given an elastic modulus of 30kPa and a Poisson's ratio of 0.49. The maximum longitudinal displacement was recorded at several hydrostatic pressure gradations.

The other pair of models was to simulate the effects of transverse tubules on the contraction of the myocyte. The case of absent t-tubules was simulated by a cylindrical solid with dimensions: radius = $10\mu m$, length = $80\mu m$, $E = 70kPa$, $\nu = 0.5$. These material properties are taken from those of the myocardium at a larger length scale. The case with transverse tubules was simulated by addition of 112 (7 radially by 16 longitudinally) cylindrical invaginations of the myocyte with dimensions: radius = $1\mu m$, length = $8\mu m$. In each case the circular ends were loaded with normal inward traction of 27kPa and varying hydrostatic pressure applied transversely as before. Again, the maximum longitudinal displacement was recorded at several hydrostatic pressure gradations.

Figure 1 illustrates the transverse tubules with the contractile traction (on circular end faces) and hydrostatic pressure (on all other surfaces).

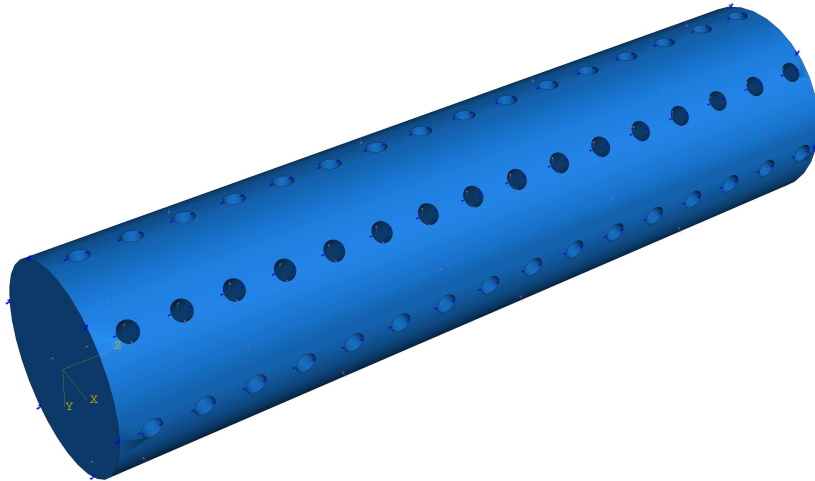


Figure 1: Modelled Myocyte with Transverse Tubules

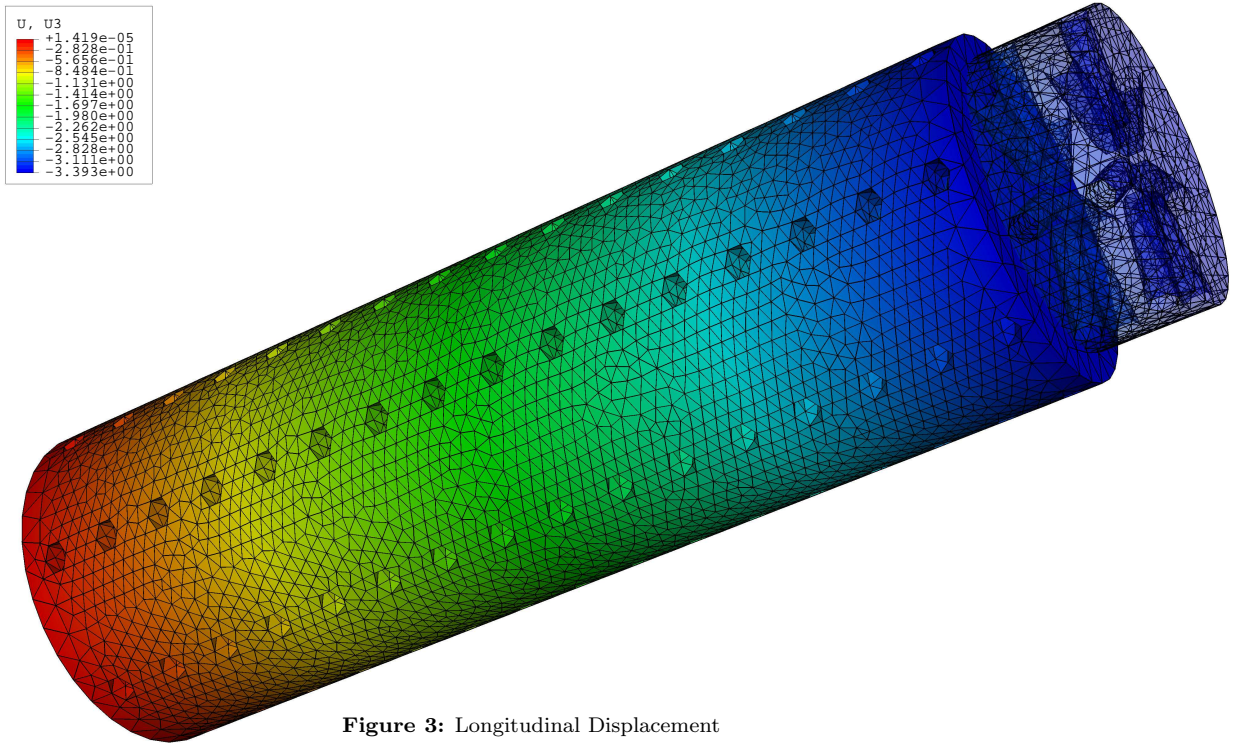


Figure 3: Longitudinal Displacement

The second pair of experiments sought to understand the role of the transverse tubules in allowing contraction of the myocyte. It was found that the addition of the transverse tubules did not alter the quantitative behavior of the displacement at various applied hydrostatic pressures. The presence of transverse tubules provided slight mitigation: a smaller change in displacement per increment of pressure noted by the lesser slope of the transverse tubule curve in Figure 5. It is also likely that the transverse tubules are able to serve as a lipid pool for the very plastic sarcolemma. This phenomenology was completely omitted from the model due to an absence of parameter values in the literature.

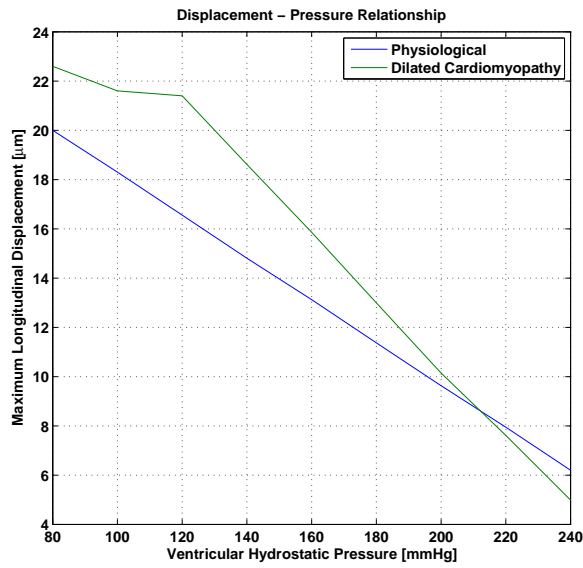


Figure 4: Displacement — Hydrostatic Pressure Relationship

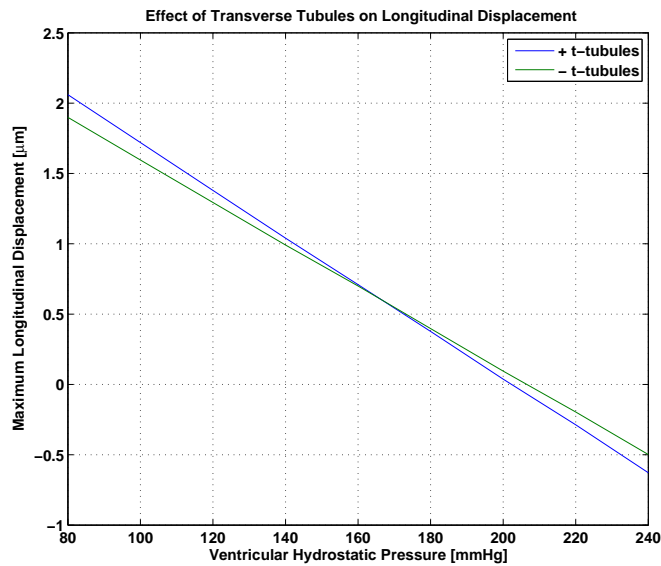


Figure 5: Effect of Transverse Tubules

Discussion

The utility of models such as this in contemporary biomechanics is uncertain. The strengths of finite element modeling lie in the arbitrary complexity, with respect to geometry or material properties, which can be numerically simulated. It is certainly true that biological structures exhibit complexity of several types: high degree of heterogeneity, material anisotropy, nontrivial geometries, nonlinear material properties, etc. It would seem as if the capabilities of finite element modeling are well-suited for biological structures; however, several nontrivial impediments exist which call into question the applicability of this line of finite numerical mechanics

in analysis of biological problems.

Firstly, the length scales involved in the study of cell-sized biological structures approach those of the molecular length scale. Though I personally am not familiar with molecular dynamics at this mesoscale, I am inclined to believe the definitions of the elastic modulus and Poisson's ratio and of similar mechanical parameters break down at this scale. Besides the potential non-applicability of elastic modulus etc at this length scale, there exists the difficulty of ascertaining values for these material parameters. Traditional mechanical tests are often not possible with microscale living samples and so the biomechanician is left with experiments providing indirect evidence for material parameters. Such experimentation can only be implemented on particular length scales and only through perturbing the biological system in a not-fully-understood fashion. Additionally, experiments from different research groups can yield different effective values.

There are other striking divergences from traditional mechanical testing. The material properties of biological structures can be much more sensitive to temperature fluctuations than traditional materials. In addition to temperature, intracellular ionic concentrations and other solutes are able to dramatically change mechanical properties by encouraging or discouraging protein-protein interactions or by stabilizing or destabilizing protein conformations. One must now recognize that the elastic modulus is a tensor dependent upon space, time, temperature, ion concentrations and many other factors in a nontrivial manner. While these effects can normally be separated from each other in traditional experiments, inherently cell function is strongly dependent upon their simultaneity.

There are more impediments to the success of finite element modeling of biological structures. These following challenges seem innately biological. Firstly, biological materials are active. The implication from a mechanics perspective is that material parameters, geometries, mass, volume, charge, etc can be variable in time. The scale at which this occurs is problem dependent, ranging from less than nanoseconds to days. The experimenter must be cautious about such active-ness when designing experiments. Some studies attempt to quantify only the passive material properties (though these may not have any biological significance) by extracting components from a cell or by killing the sample then performing experiments. It is not clear what bearing these obtained values may have on the sample in its natural state. Secondly, the precise constituents, as well as their arrangements and interconnectedness, of many subcellular structures have not all been identified or is disputed within the literature. For instance, a given structure within the cell may have N components which are proteins, though only several of these have been identified and the total, N , is unknown. One must also experimentally determine which of these are load-bearing. This is usually done through genetic mutation, an experimental process inherently lacking true rigorous controls. It is also known that mechanical energy can be dissipated not only to heat through internal viscosity, but also to biochemical events. Such facts greatly complicate arguments regarding energy conservation. In general, the active-ness of live biological structures is a difficulty without a clear answer.

Lastly, finite element modeling requires precise statements in definition of the model. However, biological diversity is seen at any length scale from subcellular component to organism. Hence, when considering biological samples such as individual cells, while there is high conservation of subcellular structures between cells there are also differences in precise geometry, subcellular arrangements and the like. Cells of the same type can exhibit functional robustness despite some variability in structure and composition. This suggests that if biologically-valuable information can be obtained from mechanics modeling, then the modeling results should not

be dominated by details which are variable from sample to sample. It is most likely acceptable that some structure can be ignored during modeling; however, there is no systematic method of identification of these less-relevant details.

While the list of difficulties to mechanical modeling of biological structures is formidable, the field is not without hope. Great care must be taken when constructing or assessing the validity of a particular modeling scheme. This field will require an approach both innately biological and mechanical.