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Modeling Cardiac Structure-Function Relations *In Silico*

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Abstract. Three-dimensional (3-D) ventricular geometry and muscle fiber architecture are fundamental determinants of regional myocardial mechanics and electrophysiology and their mutual interactions in the intact heart. I describe how we develop anatomically and biophysically detailed 3-D models of myocardial mechanics, electrophysiology and electromechanical interactions in the normal and diseased heart, and test them using experimental methods for simultaneously mapping regional strain and impulse propagation in isolated or intact heart preparations. The computational and experimental models are used together to investigate hypotheses regarding the structural and molecular determinants of ventricular electromechanical function.

Keywords:*Ventricular myofiber architecture, mechanics, electrophysiology, finite element methods*

Introduction

The heart is a complex 3-D structure in which the biophysics of myocyte excitation and the mechanics of crossbridge interaction are coordinated to produce ventricular pumping. Although much is known about the cellular basis of the cardiac action potential and the uniaxial mechanics of cardiac muscle contraction, relating these properties to the pattern of activation and regional mechanics in the whole heart is greatly complicated by its 3-D anatomy and architecture [1,2]. While some variables such as regional strain and epicardial activation patterns have been measured in the intact heart-both in animals and humans-practical methods for mapping the 3-D distributions of other important variables such as stress, strain energy, or transmembrane potential are still not available.

Therefore, there is a fundamental need for computational models that integrate the biophysics of ventricular myocytes into realistic 3-D representations of the anatomy and morphology of the heart wall, on the basis of the underlying physics and biology.

To date, cardiac models have included: detailed 3-D cardiac geometry, myofiber architecture [3,4] and coronary anatomy [5]; 3-D ventricular and atrial fluid mechanics and flow around

elastic valves [6]; mechanical and electrical properties that are transversely isotropic with respect to mean myofiber axes [4,7,8], and a considerable degree of detail for some cellular processes such as oxygen transport and metabolism [9], transmembrane ion currents [10], intracellular calcium cycling [11], and crossbridge kinetics [12, 13], but not others such as signal transduction. There have also been some models of functional coupling such as solid-fluid interactions [14], coronary-myocardial [15], and electromechanical [16]. The largest of these models require high-performance computing [6, 7, 17].

We have developed accurate, efficient 3-D finite element (FE) models of the left and right ventricles for computing regional distributions of stress and strain, electrical excitation and recovery in the myocardium. To validate these models, accurate measurements in carefully controlled experimental preparations are essential.

Methods

Anatomic Modeling

Since the rabbit heart is a well established experimental model both for ventricular mechano-energetics and electrophysiology, we developed a 3-D model of rabbit ventricular anatomy [18]. A compact, finite element model was fitted to detailed anatomic measurements of left and right ventricular geometry and muscle fiber distributions in a New Zealand white rabbit. The heart was arrested, perfusion-fixed at zero transmural pressure, embedded in polyvinylsiloxane, and sliced into 12 short-axis sections 1-2 mm thick. After each cut, the exposed tissue was digitally imaged and contoured, and each slice was cut radially into 8-11 blocks and frozen-sectioned. The sections were imaged and fiber angles measured in each.

8,351 boundary contour points were fitted to a prolate spheroidal geometric model interpolated with bicubic-linear Hermite FE basis functions using a constrained least-squares method. The 36-element 3-D mesh (552 total DOF) fitted the measurements with a RMSE of ±0.55 mm. Over 14,300 local fiber angle were measured from 3,592 serial sections and mapped to the ventricular geometry, correcting for differences between the orientation of the sections and the local reference axis in the model. Fiber angles were fitted in the model (184 degrees of freedom) using 3-D bilinear-cubic basis functions with a RMSE of ±19°. The fitted 3-D model of ventricular geometry and fiber angles is shown in **Figure 1**. Parametric models of the rabbit and canine hearts as well as dense structured grids for finite difference modeling are available to download from our web site.

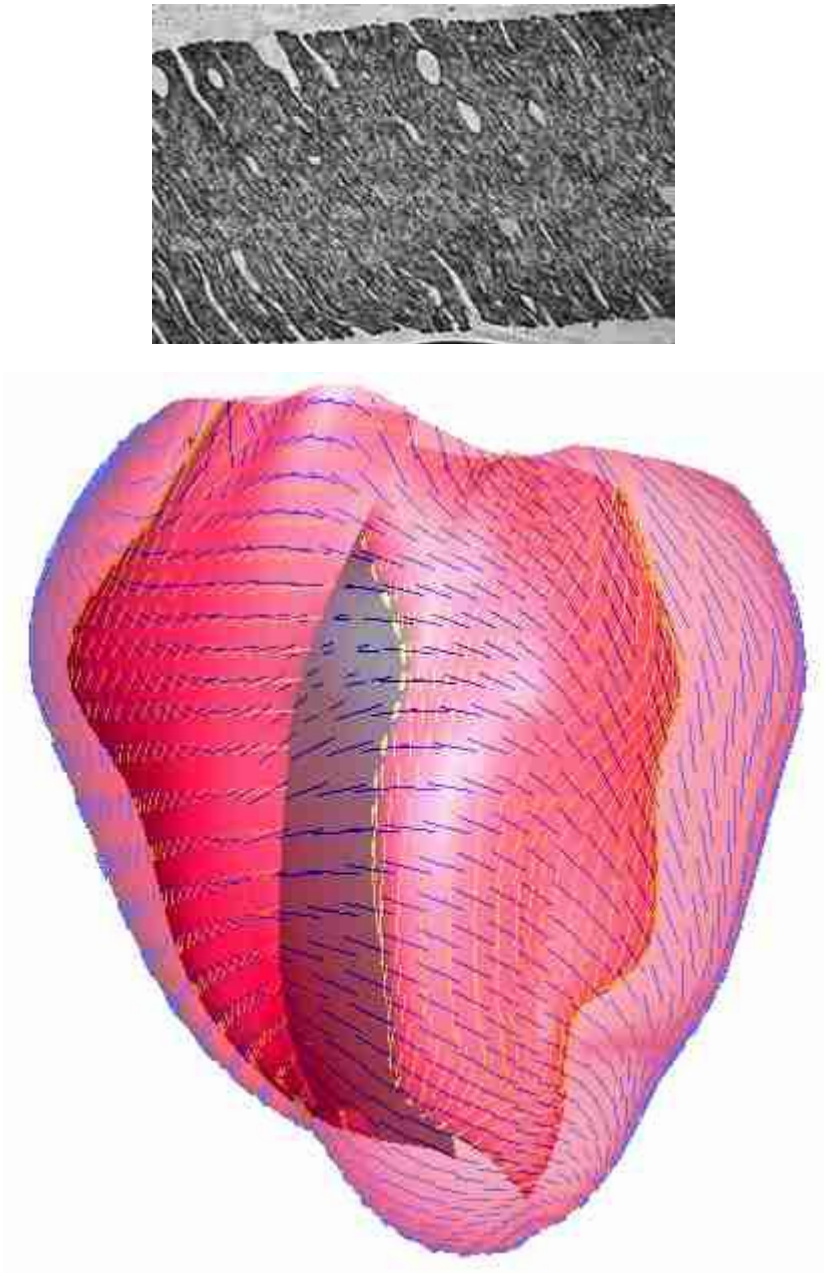


Figure 1. Cross-section of fixed embedded rabbit heart and micrograph showing fibers . 3-D model showing interpolated fiber vectors on inner and outer surfaces. From Vetter and McCulloch [18].

We have also mapped regional atrial geometry and myofiber orientations in the pig heart after fixing the heart *in situ* at physiological pressures with the pericardium intact. These data were used to construct a 3-D parametric model of the left and right atria including portions of the cavae and pulmonary veins as described in the paper at this meeting by Steingötter *et al*. 36,000 fiber angles have also been measured and are now being incorporated into the model.

Regional Ventricular Mechanics

We have developed and rigorously validated novel nonlinear FE methods for the 3-D analysis of ventricular wall stress [8, 19]. The Galerkin FE formulation includes important characteristics of ventricular mechanics including large deformations, nonlinear constitutive laws, curvilinear coordinates, 3-D anisotropy with respect to continuously varying myofiber axes, muscle contraction, and pressure and displacement boundary conditions [20]. Stress and strain solutions converged to within 0.2% were be obtained for a model of the left

ventricle with 32 tricubic elements. Compared with 3-D strains that we measured in the dog heart [21, 22], the models agreed well with the observed mechanics except for transverse shear and radial strains, especially during systole. More recent models of the dog LV [23] showed that agreement between predicted and observed strains was improved over transverse isotropy when orthotropic material parameters were adjusted so that transverse normal and shear stiffnesses were reduced in the cross-sheet plane relative to those parallel to the sheet plane.

These FE methods are scalable because the specialized high-order elements are comparatively large and few in number, and the computation of the local element equations is "data parallel". The stress analysis algorithms were parallelized using the message passing interface (MPI) on the Cray T3E parallel supercomputer at the San Diego Supercomputer Center. Each processor maintains its own copies of the global solution and residual vectors, but element stiffness matrices are not assembled into a global matrix. Instead they reside on each processor: an "element-by-element" formulation. The nonlinear system of global equations is solved using Newton iteration. At each iteration, the linear system is solved using a Generalized Minimum Residual iterative method, requiring one global matrix-vector multiplication.

The parallel code was tested using the 3-D rabbit heart model. Solutions were converged to within 1% using 90 elements. **Figure 2** shows near linear speed-ups for a 16-element model of the canine LV. Solutions taking 60 min on an SGI R10000 workstation were obtained in 5.2 min using 16 processors on the T3E.

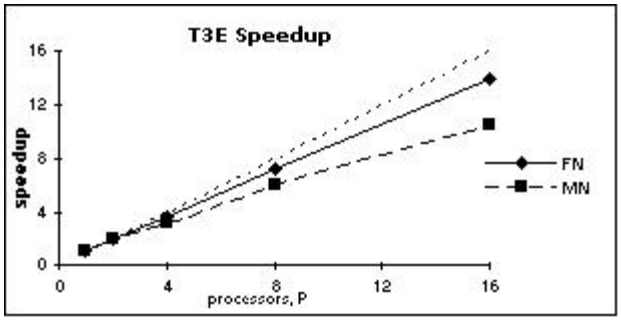


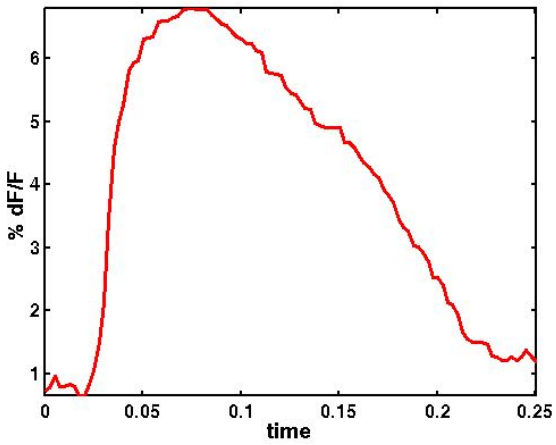
Figure 2. Speedups for 3-D left ventricular finite element model on Cray T3E parallel supercomputer. FN = full Newton iteration; MN = modified Newton.

Ventricular Electrophysiology

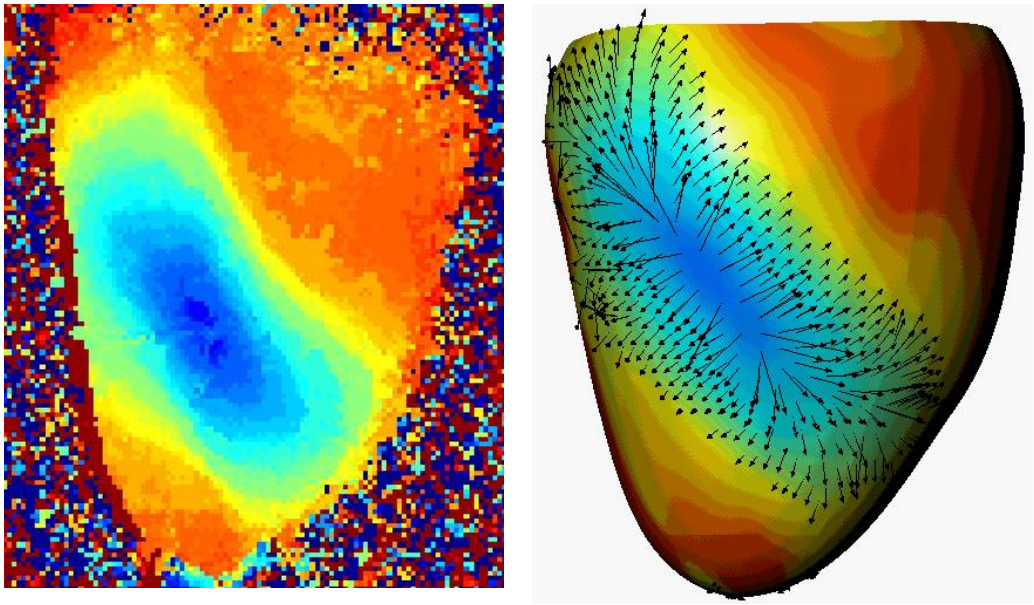
We developed an efficient and novel collocation-Galerkin FE method [24, 25] for modeling 3-D action potential propagation in nonuniformly anisotropic myocardium [26]. The technique is implemented in the same software as the anatomic and mechanical models facilitating model integration. Since the original implementation using the FitzHugh-Nagumo kinetic model, the methods have been extended to incorporate more realistic ionic models including the Beeler-Reuter [27] model of the ventricular action potential and the Luo-Rudy model of the guinea pig ventricular myocyte [28]. This is necessary to allow the cellular mechanisms of excitation-contraction coupling and mechanoelectric feedback to be included in new analyses.

We use optical mapping to image epicardial activation and recovery in the isolated heart with the voltage-sensitive dye, DI-4-ANEPPS, which is fast enough to measure millisecond changes in membrane potential [29]. The fluorescence emission closely mimics the action potential measured using an intracellular microelectrode [30]. It has been calculated that the fluorescence signal recorded from the epicardium represents a layer of cells 300 μm thick [31].

We image the epicardium using a high-speed digital CCD camera (399 frames per sec, 128×128 pixels) in the isolated perfused rabbit heart, paced at 240 bpm in the presence of 2,3 butanedione monoxime (BDM), an electromechanical decoupler. Action potentials (**Figure 3a**) are derived from the image time series by a filter that first uses an FFT of the time series to adjust for phase differences between neighboring pixels. Activation times (**Figure 3b**) are mapped on to a FE model of the epicardial surface reconstructed from a pair of perpendicular biplane video images (**Figure 3c**). The gradient of this activation time map is a wave vector field whose inverse is the velocity of the propagating wavefront [32]. Using the parametric model to incorporate anatomic information on regional fiber anatomy in the rabbit (**Figure 1**), mean conduction velocities were 39.5 cm/s in the fiber direction and 17.6 cm/s in the cross-fiber direction. These correspond well with published results in similar preparations [33]. Biplane video images of an array of optical markers on the LV epicardium are now being used to compute epicardial fiber and cross-fiber strain distributions in the same hearts using least squares methods.



(a)



(b) **(c)**

Figure 3. (a) optical action potential from a pixel of the rabbit epicardial image. (b) activation time image derived from time of maximal derivative of action potentials. (c) activation time field variable mapped onto 3-D model of epicardial surface and used to compute conduction velocity vectors. From Sung et al. [34].

Results

Mechanics of Ischemic Ventricular Myocardium

The parametric models also provide a framework for analyzing experimental measurements. Arrays of radiopaque markers on the LV epicardium in anesthetized dogs were imaged by biplane radiography. By reconstructing their 3-D coordinates and mapping them on to FE models, non-homogeneous strain distributions were obtained and registered with measurements of regional ventricular geometry, fiber architecture and blood flow (fluorescent microspheres) [35]. Combining these measurements with predictive computational models of ventricular mechanics, we investigated the structural basis of regional dysfunction in acute myocardial ischemia. In 10 dogs, abnormal systolic strain extended further into the normally perfused adjacent myocardium for fiber strain than for cross-fiber strain, and for left anterior descending coronary artery occlusion than for left circumflex occlusion [36].

A model stress analysis (**Figure 4**) explained the structural mechanisms of these observations. The model reliably reproduced observed regional variations in fiber and cross-fiber strain across the perfusion boundary including the experimental observation that the functional border zone of normally perfused but dysfunctional myocardium adjacent to the perfusion boundary is wider for occlusions of the left anterior descending (LAD) coronary artery than the left circumflex (LCx) artery. By adjusting model variables we found that this regional difference is associated with differences in systolic blood pressure during LCx and LAD ischemia, rather than due to differences in the orientation of the perfusion boundary relative to the muscle fiber direction.

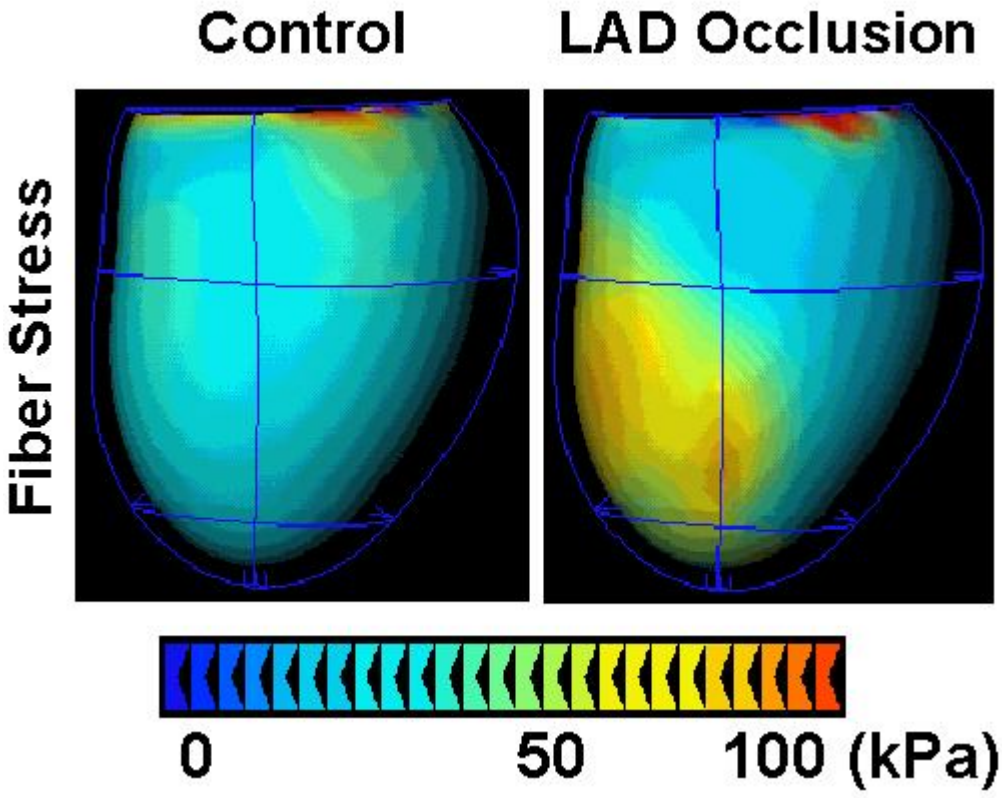


Figure 4. Regional distributions of midwall fiber stress in finite element models of the canine left ventricle during normal perfusion (LEFT) and acute left anterior descending coronary artery occlusion (RIGHT). From Mazhari et al. [36].

Regional Ventricular Mechanoelectric Feedback

We incorporated mechanoelectric feedback into a 3-D model of the rabbit ventricles by adding a non-specific stretch-activated cation current in the Beeler-Reuter ionic model . However stretch is not one-dimensional. Therefore, we compared three coupled computational models based on the ventricular mechanics models. The models showed a significant effect of stretch on regional activation times (not shown) and transmural distributions of action potential amplitude (**Figure 5**). Much better agreement with experimental observations [37] was achieved when stretch-activated current was a function of both fiber and cross-fiber strain (c) than either fiber strain (a) or cross-fiber strain (b), alone.

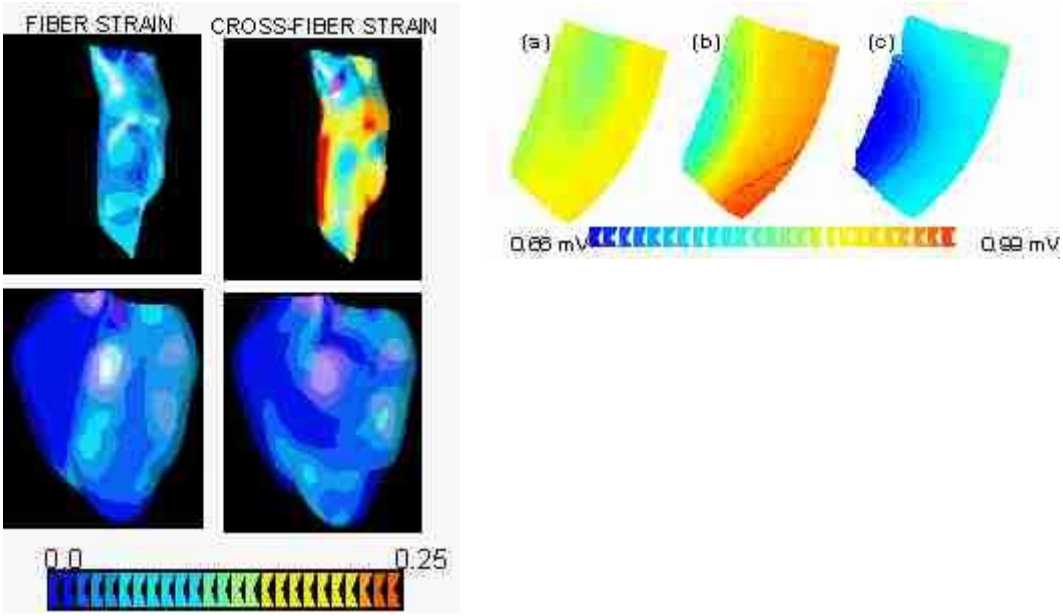


Figure 5. Regional action potential amplitudes (ABOVE) in three models of stretch-activated current derived from regional strains in a model of the rabbit ventricles (LEFT). From Vetter [38].

Conclusions

Anatomically detailed continuum models provide a parametric framework for integrating biophysical processes into simulations of the regional mechanics and electrophysiology of the intact heart. By comparing model results with experimental studies, the structural basis of regional cardiac electromechanical function, in health and disease, can be elucidated.

Acknowledgements

This work was conducted by several of the author's past and present students, especially Frederick Vetter (ventricular anatomy and mechanoelectric feedback), Reza Mazhari (mechanics of acute myocardial ischemia), and Derrick Sung (optical mapping). We also acknowledge the support of NIH grant RR08605, the National Biomedical Computation Resource, and grant BES-9634974 from the National Science Foundation.

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