STATIC AND DYNAMIC CARDIAC MODELLING: INITIAL STRIDES AND RESULTS TOWARDS A QUANTITATIVELY ACCURATE MECHANICAL HEART MODEL

C. Constantinides¹, N. Aristokleous¹, G. A. Johnson², D. Perperides¹
¹Laboratory of Physiology & Biomedical Imaging, Mechanical and Manufacturing Engineering, University of Cyprus, Nicosia, Cyprus, ²Center for In Vivo Microscopy, Duke University, Durham, NC, USA

ABSTRACT

Magnetic Resonance Imaging (MRI) has exhibited significant potential for quantifying cardiac function and dysfunction in the mouse. Recent advances in high-resolution cardiac MR imaging techniques have contributed to the development of acquisition approaches that allow fast and accurate description of anatomic structures, and accurate surface and finite element (FE) mesh model constructions for study of global mechanical function in normal and transgenic mice. This study presents work in progress for construction of quantitatively accurate three-dimensional (3D) and 4D dynamic surface and FE models of murine left ventricular (LV) muscle in C57BL/6J (n=10) mice. Constructed models are subsequently imported into commercial software packages for the solution of the constitutive equations that characterize mechanical function, including computation of the stress and strain fields. They are further used with solid-free form fabrication processes to construct model-based material renditions of the human and mouse hearts.

Index Terms— Magnetic Resonance Imaging, cardiovascular system, image processing, finite element methods, rapid prototyping.

1. INTRODUCTION

The emergence of embryonic stem cells and their pluripotent nature, in addition to recent advents in imaging techniques that have allowed cell-targeting and tracking, have led to a resurgence in interest for the engineering of tissue grafts, scaffolds, artificial organs, and for invasive regenerative procedures. Stem cell implantation, in particular, has proven to be an invasive, yet a most powerful technique, that allows the regeneration of cardiomyocytes as a way to improve global and local cardiac function. Prior evidence [1] for the somewhat limited ability of cardiomyocytes to regenerate [2] has led to a plethora of recent attempts to repair myocardial injuries by injecting myogenic cells into the scarred myocardium [3], or to endeavors of direct entire scar tissue replacement with engineered grafts [4, 5]. Polymeric or elastomeric materials utilized for such applications have been found to be ideally injectable and possess biocompatibility and bioactivity properties that facilitate good adhesion with the surrounding environment, ensuring mechanical stability that withstands active and static dynamic loading [6]. Myocardial tissue characterization, pre- and post-implantation or following therapy, has thus become an elusive and active research area in clinical and basic science practice. Prior efforts, including advances in Magnetic Resonance Imaging (MRI) have focused on the invasive [7] and non-invasive characterization [8, 9] of the left ventricular muscle material properties to document energetic status, and rates and extent of filling and relaxation. The quantitative description of heart ventricular strain and stress as important determinants of cardiac muscle physiology, and pathophysiology, thus become significant for the evaluation of cardiac mechanical performance as diagnostic indices for heart disease. Knowledge of the stress distributions in the intact myocardium can lead to useful insights into normal and abnormal ventricular function, since regional coronary blood flow, myocardial oxygen consumption, hypertrophy, and remodeling are all influenced by ventricular wall stress [10].

This study presents work in progress that aims towards the: (a) construction of quantitatively accurate three-dimensional (3D) static and 4D dynamic surface, and finite element models of murine left ventricular (LV) muscle in C57BL mice; (b) quantification of cardiac mechanical indices from MRI; (c) solution of the constitutive equations that characterize mechanical status, including computation of the stress and strain fields; (d) construction of model-based material renditions of the human and mouse hearts with the aid of solid-free form fabrication processes.

2. METHODS

Physiology: Ten male C57BL/6J (weight 23.56±5.4g) mice were anesthetized using isoflurane (ISO) and imaged using Magnetic Resonance Imaging. The mice were allowed to breathe freely throughout the study. ECG and breathing rate were monitored using an SA Instruments Inc. system (Edison, NJ, USA). Heart rate was maintained between 450-550 beats per minute by adjusting the mixture of ISO and oxygen. A rectal probe was monitored and maintained stable body temperature in the magnet (37±0.5°C).

Imaging: Work was performed at a 7T MRI scanner with a GE EXCITE console (EPIC 12.4). A custom-made 2.5x3cm² transmit/receive coil maximized SNR. A 4D radial MRI pulse sequence was implemented and optimized to reduce TE and TR to 300µs and 2.4ms respectively, as published in [11]. Eight phases of the heart cycle were acquired at temporal resolution of 9.6ms and a spatial resolution of 87x110µm² in 31 minutes, with BW=±125kHz, and flip angle=45°. The first acquired phase represents end-diastolic phase. A non-uniform fast Fourier transformation performed regridding-reconstruction using a least squares optimized kernel for interpolation. Raw data were reconstructed offline.

Image Processing and Surface Model Development: Mouse cardiac images were segmented by seed-point spline contour...
segmentation of the left ventricular myocardium, and left ventricular blood cavity (Analyze 7.0, USA) from short axis cardiac MRI spanning the entire heart over eight phases throughout the entire cardiac cycle. Binary masks were generated, intensity normalized, and converted to the Analyze (.imp) format using ImageJ (ImageJ, NIH, USA). Alignment of all mouse models to a common coordinate system was achieved using a multipoint-landmark affine registration (ITK software for IXICO) algorithm [12]. Uncertainties in the apical regions were corrected with the RView program (IXICO, UK) and saved in the standard Analyze (.img) format [13]. Surface models were constructed using the commercial packages Analyze (Analyze Inc, Mayo Clinic, USA) or MIMICS (Materialize, Belgium).

Fig. 1: (Top) Seed-point segmentation and binary mask construction in short axis mouse MRI; (Mid) RView 3D binary mask correction; and (Bot) ventricular surface model construction using the software package MIMICS.

Quantification of Global Cardiac Function: Three-dimensional volume renditions of the left ventricular cavity were generated using Analyze and the volume estimated. Estimated volumes were converted to absolute volume units by multiplication with the image voxel volume (110x110x110μm³). Stroke volume (SV) and Ejection Fractions (EF) were calculated according to:

\[
SV = EDV - ESV \\
EF = \frac{SV}{EDV}
\]

where EDV and ESV represent the end-diastolic, and end-systolic left ventricular blood volumes, respectively.

Finite Element Model Development: Finite element meshes were created with tetrahedral elements for each of the eight reconstructed phases of the cardiac cycle using the surface extractor tool in Analyze (image-space to mesh-space transformation). The constructed models were converted and saved in standard stereolithographic formats (.stl).

![Finite Element Model Development](image)

Fig. 2: Left ventricular volume variation (mean±-sd) over eight phases of the cardiac cycle for 5 male C57BL mice.

![Cardiac Cycle Phases](image)

Fig. 3: Typical representation of the dynamic surface and finite element model of C57BL/6J mice through eight cardiac phases over the entire cardiac cycle.

Empirical Optimization of Constructed Finite Element Model: The generic surface extraction algorithm was empirically optimized to yield accurate mesh models. Accuracy was assessed based on computed volumes for each of the constructed mesh.
models of LV blood cavities through an inverse transformation from the mesh-space to the image-space and repetition of the process until the error ε between the original (V₁) and final (V₂) computed volumes ε = |V₁ - V₂| ≤ 10%. The empirical optimization utilized the gradient method of the marching cubes algorithm and allowed changes of the number of surface extraction iterations between 5-11, changing cube edge sizes between 3-7, and selections of varying kernel sizes between 3x3x3 to 7x7x7 elements.

Fig. 4: Schematic flow diagram representation of the empirical optimization process for generation of quantitatively accurate finite element models.

Fig. 5: Typical mesh constructions of the LV blood cavity using the generic Analyze algorithm. (Left to right) Mesh generated with 5 iterations, a cubic edge size 3 (1592 polygons and 4776 vertices); mesh with cubic size 5 (644 polygons and 1932 vertices); mesh with cubic size 7 (372 polygons and 1116 vertices); mesh with 5 iterations, cube edge size 3 and a kernel size 7x7x7 (3048 polygons and 9144 vertices).

Model Based Manufacturing using Rapid Prototyping Processes: Critical to the construction of tissue-equivalent materials and organs using solid-free form manufacturing (rapid prototyping) is the selection of the appropriate material with properties that ensure (a) proper mechanical function, (b) biocompatibility, and (c) cost. Since the ultimate goal is the construction of tissue mimicking materials or organs, such properties must match published [14, 15] mechanical properties of myocardial tissue (Table 1). Additional complexity factors of the manufacturing process include the cardiac morphology, its size, and structure. This initial model construction was based on PC-ISO, a hard, solid material. The construction adhered to modern rapid prototyping specifications set a priori and adhered to by the manufacturing company (Redeye RPM, Materialize, Belgium). Two separate left ventricular cardiac models were constructed, one of the murine heart, and a scaled-up model to emulate the human heart.

![Fig. 6: Solid ventricular heart models constructed with the material PC-ISO using rapid prototyping of the (left) human and (right) mouse hearts.](image)

### Stress and Strain Computations using Finite Element Analysis (FEA):
Constitutive law characterization necessitates importing the geometric model, definition of adequate material properties, definition of boundary conditions and pressure fields and model solutions, similar to previously published results in canine [16]. Correspondingly, the developed .stl files were first imported in the commercial package Patran (Version 5.0, MSC Software, CA, USA). In this model 9476 tetrahedral elements were used to represent the left ventricular (LV) myocardium. The heart muscle was assumed to be a non-linear elastic, isotropic, incompressible, and homogeneous material, in accordance to prior published findings [14, 15]. The quantitative tissue mechanical values of the Young’s modulus, Poisson’s ratio and end-diastolic LV cavity pressure used in the model match those listed in Table 1 [14, 15]:

<table>
<thead>
<tr>
<th>Properties</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young’s Modulus (E)</td>
<td>0.001 MPa</td>
</tr>
<tr>
<td>Poisson’s ratio (v)</td>
<td>0.495</td>
</tr>
<tr>
<td>Intra LV cavity Pressure (Pₑ₀)</td>
<td>16 kPa</td>
</tr>
</tbody>
</table>

Table 1: Published myocardial mechanical properties used in the model construction for stress-strain field computation.

While such work constitutes work-in-progress, this first computational attempt assumed a boundary condition with zero degrees of freedom on the apical area of the epicardium. The type of solution of the governing equations was set to linear static, and the structural analysis code for pre-processing analysis was MSC.Nastran. The computed stress-strain results for stress-strain fields were exported in text files containing nodal stress-strain values. For 4D dynamic analyses for all cardiac frames throughout the cardiac cycle, the spatiotemporal pressure field within the chamber needs to be determined. Such field can often be obtained from experimental cardiac catheterization studies or other non-invasive modalities [17].

3. RESULTS AND DISCUSSION

Figure 1 represents the end-diastolic surface model of C57BL/6J mice constructed using binary masks, employing seed-point segmentation (Analyze) and boundary edge corrections (RView). Figure 2 graphically represents the variation in mean left ventricular chamber volume with cardiac phase, over the entire cardiac cycle for 5 male C57BL mice (body weight, 26.3±2.7g). The estimated stroke volume was 23.6±5.4μl (mean±sd, n=10) and
the ejection fractions 51.9±7.5% (n=10), in agreement with prior published results using non-invasive techniques [18, 19]. Constructed four-dimensional (4D) surface renditions and finite element mesh models are depicted in Figure 3. Figure 4 depicts diagrammatical representation of the flow diagram outlining the empirical optimization process for the generation of quantitatively accurate finite element models. Typical examples of left ventricular blood cavity models, a direct result of the iterative process, are shown in Figure 5. Prominent is over-smoothing effect of the cavity boundaries due to the increasing cube edge size and the inner hollow effect noted for increasing kernel sizes (7x7x7). Figure 6 shows the human and mouse heart models constructed using the material PC-ISO with rapid prototyping. Figure 7 shows imported geometric models in Patran, set operating pressure fields and boundary conditions imported for the strain and stress field calculations.

4. ACKNOWLEDGEMENTS

Work was performed at the Duke Center for In Vivo Microscopy (CIVM), an NIH-NRCR National Biomedical Technology Research Center funded under the research program P41 RR005959 and the Small Animal Imaging Research Program (U24 CA092656). Work was also performed at the Laboratory of Physiology and Biomedical Imaging (LBI) “Hippocrates” and was supported in part by the Hellenic Bank grant “HEART” and by the Physiology and Biomedical Imaging (LBI) “Hippocrates” and was supported in part by the Hellenic Bank grant “HEART” and by the Research Promotion Foundation grant on International collaboration between CIVM and LBI 0308/02. We thank MSC Software for their support and Materialize Inc. for granting permission to use MIMICS.

5. REFERENCES


