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IN-VIVO ASSESSMENT OF VALVULAR FUNCTION: AN INVERSE MODELING APPROACH

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Abstract. Heart valves control the blood flow and play an extremely important role in the functioning of heart. Either due to congenital defects or due to the changes with remodeling, the leaflets functionality is altered sometimes resulting in less efficient heart output. Such problems are difficult to diagnose at an early stage and may lead to heart failure if left untreated. In this work, we present a framework for determining the functional properties of heart valve leaflets from non-invasive imaging modules, with the main focus being on the inverse model development. As a first step, we use in-vitro experimental data from porcine bioprosthetic heart valve in a flow loop. We present the details of inverse model, its validation against experimental data and sensitivity to various input parameters and optimization constraints. In addition, we discuss other components of this in-vivo assessment tool - the average fiber architecture and the pre-strain in valve leaflets. This information when combined with the inverse model presented in this work will lead to an in-vivo assessment tool for heart valves and help diagnose problems in the mechanical functionality at an early stage. Additionally, this approach will have the potential to serve as a general-purpose in-vivo assessment tool for heart valves - for evaluating the performance of replaced prosthetic valves as well as monitoring the progression of valve diseases.

1 INTRODUCTION

Valves are critical components of heart because of their role in ensuring unidirection flow of blood, and opening and closing at the precise moments which should be synchro-

nized with the contraction of the myocardium. The valve leaflets are complex structural entities made from various layers with primary constituents being collagen, elastin, extracellular matrix and valve interstitial cells. Either due to congenital defects or due to the changes due to remodeling with age, the leaflets functionality is altered sometimes resulting in less efficient heart output. Such problems are difficult to diagnose at an early stage as they remain asymptomatic for the initial phases. However, they may lead to heart failure if left untreated. Therefore, a tool for determining the functional properties of heart valves from non-invasive imaging modalities will be of utmost clinical importance. So the long term overarching goal of the study presented here is to develop a tool, which uses in-vivo imaging, e.g. transesophaegal echocardiography, and calculates the stiffness properties of the heart valves and related mechanical stresses, and then relate them to the functional properties – the cellular function and remodeling potentials (Fig. 1). Such a tool will help diagnose the valve diseases at an early stage as well as provide tools for monitoring the performance of replaced prosthetic valves. The three components of such a tool are shown in Fig. 2. In order to define the correct reference configuration, we need the pre-strain information about leaflets. For defining the unknown fiber architecture, we need the population average architecture trends that can be used to constrain parameter optimization. And the main component is development of a numerical inverse-model which can be applied to in-vivo imaging data. In this paper, we discuss our progress in development of all these components.

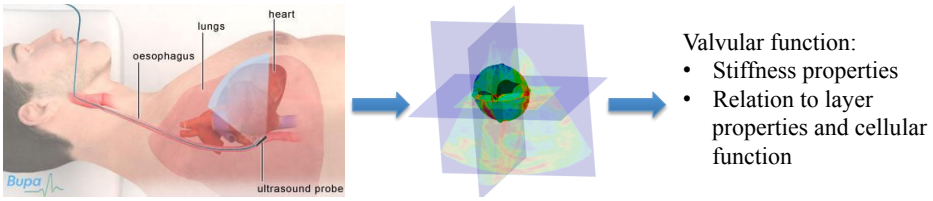

Figure 1: The overall aim of this study is to create an in-vivo assessment tool that can take echocardiographic data, and calculate the valvular function in terms of mechanical properties and cellular function.

2 INVERSE MODEL DEVELOPMENT

As a first step for the inverse model development, we use in-vitro experimental data from porcine bioprosthetic heart valve emulating an aortic valve put in a flow loop. The leaflet was imaged at three different static transvalvular pressures of 40, 80 and 120mm Hg using surface markers and dual-camera setup [1] (Fig. 3a). Leaflets were removed and their fiber architecture was determined using light scattering technique [2]. Then the leaflets were dissected and put under biaxial test to determine their stress-strain relationship. This highly comprehensive data set with high resolution, marker positions at multiple pressures, valve specific fiber architecture and biaxial data was ideal for this study to design the inverse model, validate it and calculate its sensitivity to various input

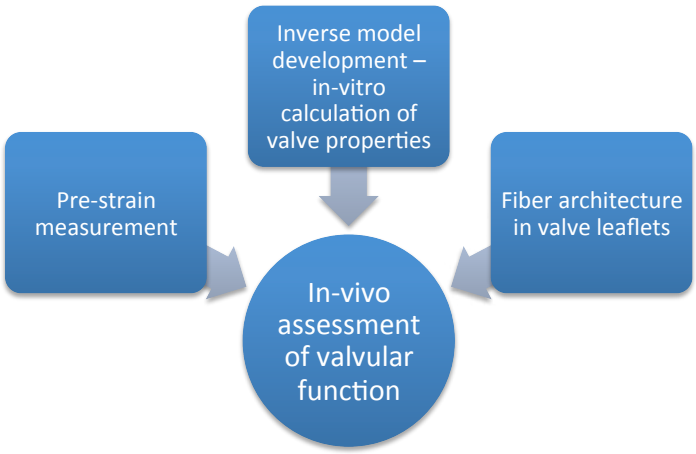

Figure 2: Three components required to build the in-vivo assessment tool for valvular function.

parameters and optimization constraints. There is no existing method for inverse modeling of heart valves as per authors' knowledge. This is due to the difficulty in modeling them as well as their small size and thickness and fast movement in-vivo leading to poor quality of imaging. The in-vitro experimental data provides us with a platform for solving these challenges (Fig. 3a). The framework for current inverse model is shown as a flowchart in Fig. 3b.

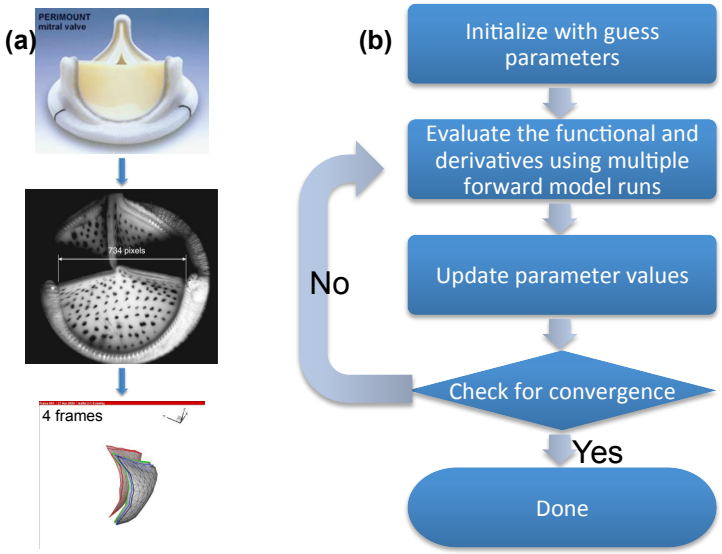

Figure 3: (a) The experimental setup using a bioprosthetic heart valve put in a quasi-static pressure head and imaged using optical technique at four different pressures. (b) The flowchart of inverse modeling approach for parameter estimation of valve leaflets' material properties.

2.1 Forward model

In our work, the valve leaflet was modeled as a thin-shell membrane. The geometry was meshed using ∼8400 quadrilateral elements with reduced integration. The basal attachment was fixed as in the experiments and a linearly increasing pressure was applied for 0.2 seconds with another 0.2 seconds at steady pressure for achieving equilibrium. Contact between leaflets was treated using a hard constraint Lagrange multiplier method. Each forward dynamic problem was solved using explicit scheme with a time step of 5×10^{-5} seconds and some damping introduced for stabilization. 4 processors were employed with loop level parallelization.

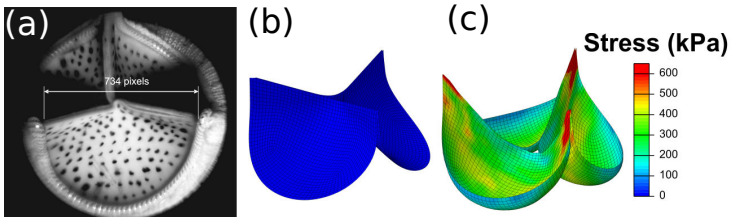

Figure 4: Experimental setup (a), the thin shell model (b) and the stresses calculated using forward model (c).

2.2 Algorithm

The above forward model was put in an optimization loop where the parameters were initialized with a guess and solution was iterated until convergence was achieved. For the optimization, cost function was defined as

$$\mathcal{F} = \sqrt{\sum_{i,\alpha} \left(x_i^\alpha - \tilde{x}_i^\alpha \left(\boldsymbol{c}_m\right)\right)^2} \tag{1}$$

where, x_i^α are the input points from experiment and $\tilde{x}_i^\alpha \left(\boldsymbol{c}_m\right)$ are their projection on deformed valve surface obtained from the forward model with material parameters $\boldsymbol{c}$ at iteration m. To minimize the cost function, Levenberg Marquardt algorithm is used, so that

$$\left(\mathbf{J}^T\mathbf{J} + \lambda \text{diag}\left(\mathbf{J}^T\mathbf{J}\right)\right) \Delta \boldsymbol{c}_m = \mathbf{J}^T \left[\boldsymbol{x} - \tilde{\boldsymbol{x}}\left(\boldsymbol{c}_m\right)\right] \tag{2}$$

where, $\mathbf{J} = \partial\tilde{\boldsymbol{x}}/\partial\boldsymbol{c}$ is the gradient vector, which is calculated using numerical differentiation.

2.3 Preliminary Results

The first example presented is of the case with homogenous properties with Fung's hyperelastic constitutive model

$$\mathcal{W} = \frac{c}{2}\left(e^{Q} - 1\right) + \frac{1}{D}\left(\frac{J_{\text{el}}^2 - 1}{2} - \ln J_{\text{el}}\right), \tag{3}$$

where $Q = \bar{\epsilon}_{ij}^{G} b_{ijkl} \bar{\epsilon}_{kl}^{G}$. When only one parameter c is varied, the resulting landscape is shown in Fig. 5 with the iteration results of optimization shown in inset. The problem is well behaved with converged solution obtained in about 15 iterations. The computational time for this optimization was about 6 hours using 4×3 processors. When we vary four parameters c, b_{1111}, b_{2222} and b_{1122}, the computation becomes much more expensive and it takes longer to converge. The preliminary results are shown in Fig. 6, which took approximately 50 hours using 4×5 processors. As we can see the optimization algorithm needs further improvement and we are working on that now. Also, Fung's orthotropic constitutive model is known to cause problems in terms of convergence because of the lack of convexity everywhere. Therefore, we plan to use a new constitutive law developed by Lee and Sacks (unpublished results),

$$\mathcal{W} = C_{10}(I_1 - 3) + \frac{c_0}{2}\left\{(1-\beta)\exp\left[c_1(I_1-3)^2\right] + \beta\exp\left[c_2(I_4-1)^2\right] - 1\right\} \tag{4}$$

where β defines the degree of anisotropy and can be related to the splay in fiber architecture measured from light scattering [2]. This model will be used in the future and convergence properties will be compared to the Fung's model.

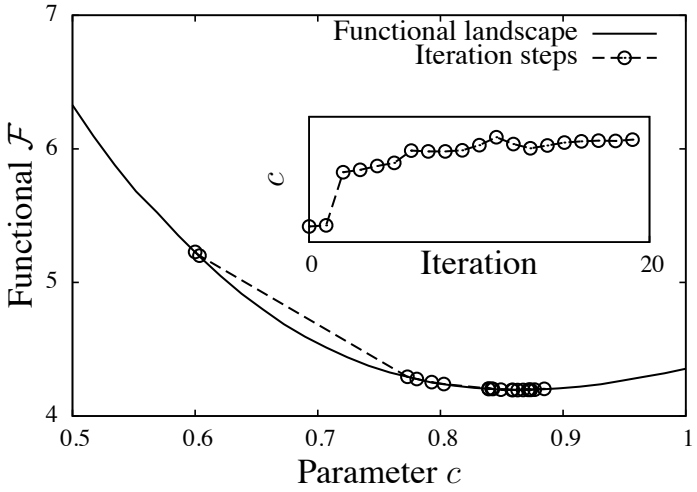

Figure 5: Functional landscape and the optimization result for one parameter using current framework.

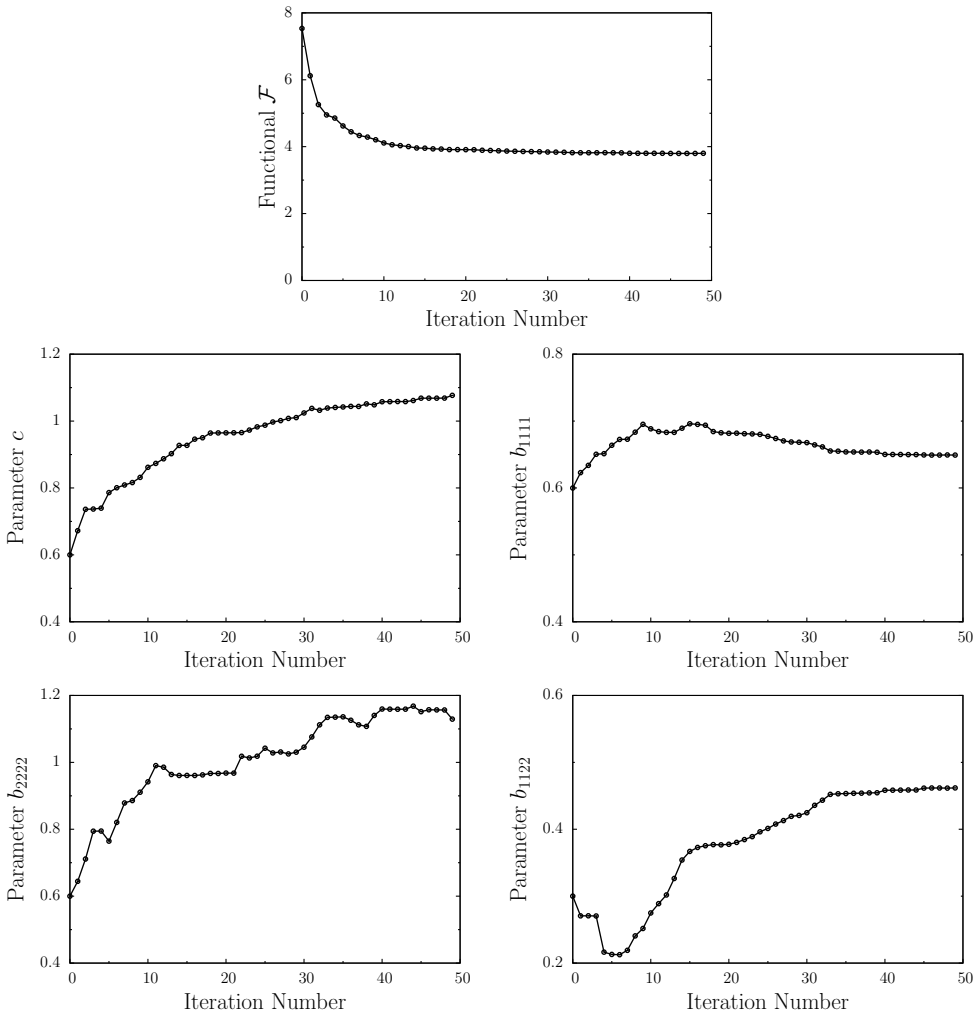

Figure 6: Optimization result for five parameter using current framework.

3 FIBER ARCHITECTURE

In the in-vitro model, fiber architecture was determined using light scattering experiment on dissected leaflets. This information is critical in obtaining the correct results because of two results. The fiber direction significantly affects the parameter estimation and stress calculation. Also, once the parameters are obtained, they need to be used to estimate stresses at the fiber level and connect cellular behavior to the leaflet deformations.

For in-vivo models, it is not possible to obtain the fiber architecture on a patient-specific basis. Therefore, we previously measured fiber architecture on human aortic valves – both in healthy and diseased state, and calculated the average fiber architecture using an novel spline based mapping technique [3]. The results are shown in Fig. 7, where we can see

significant difference in the healthy and bicuspid valves. Such differences suggest that the material parameters estimated from in-vivo imaging might be correlated to the disease development, and can be used to patient stratification. Moreover, the spline mapping technique also provides the benefit that the fiber architecture can be mapped from any valve to any other geometry, thus giving the capability of creating patient specific models [4].

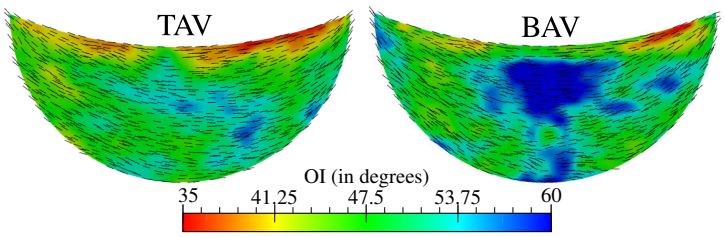

Figure 7: Average collagen architecture in human normal tricuspid leaflets (left) and bicuspid leaflets (right).

4 PRE-STRAIN CALCULATION

The bioprosthetic valve leaflets used in the in-vitro study are chemically fixed, and thus the reference configuration for mechanical studies is well known. However, this is not true for native heart valves. They are known to shrink when explanted [5], as well as its different layers are pre-strained. These pre-strains have been shown to significantly affect the mechanical properties of mitral valve [6]. In general the idea of pre-strain has been shown to change the phase diagram of elastic shells in a fundamental way [7], and should be accounted for carefully while analyzing structures. As per authors' knowledge, pre-strain has not been measured in human aortic valves. We previously calculated the pre-strain in an ovine aortic valve using our spline mapping technique [4]. The advantage of this technique is that it gives the pre-strain tensor as an in-homogenous and anisotropic field (Fig. 8). We are currently working on improving this mapping technique and applying it on a sample of ovine valves to calculate the averages and variations among population.

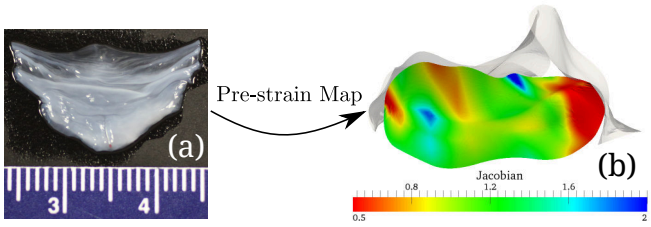

Figure 8: Pre-strain calculated on a ovine aortic valve using spline technique.

5 DISCUSSION

The framework presented here is directed towards solving a clinically relevant problem of monitoring the functional properties of heart valves from in-vivo imaging. The steps needed to make such a tool were discussed. The main component is the inverse model which includes many computational challenges. The forward problem of leaflet deformation, in general, is highly non-linear because of the contact between leaflets. One has to be careful while putting such a forward model in an inverse modeling loop, since the optimization problem may not be convex. However, we show that for our in-vitro experimental data, the chosen cost function is well behaved. The results presented for the Fung's material model are the first such attempt. In the future, the model will be extended much further to assess the maximum amount of information possible to obtain from in-vivo imaging. For the constitutive law, Fung's elastic model and a new adjustable anisotropic hyperelastic model will be used to evaluate the sensitivity of estimated mechanical behavior on specific forms of stress-strain relation. Here each leaflets is considered to have homogenous elastic parameters. In future, the method will be extended for the parameters to vary spatially. The results thus obtained will be homogenized to obtain the coarse scale material properties and compared to the biaxial data for validation.

The other components discussed here are the fiber architecture and pre-strain, which were not an issue for the in-vitro study but become critical when we apply it to in-vivo situations. The average fiber architecture has been calculated in our earlier work and will be used in combination with the inverse model. We presented some preliminary result for the pre-strain in ovine aortic valve leaflets. Currently, we are working on extending that study, and calculating the averages and variations in pre-strain among population. Finally the material parameters obtained from the leaflets will used to assess the stress states at cellular level and connected to their functional properties.

These represent small yet important steps towards developing a clinically acceptable tool, which can be used for in-vivo assessment of the heart valves and help diagnose problems in the mechanical functionality at an early stage. Additionally, this approach will have the potential to serve as a general-purpose in-vivo assessment tool for heart valves – for evaluating the performance of replaced prosthetic valves as well as monitoring the progression of valve diseases. The information thus produced over time will help us understand the mechanical behavior of valve leaflets and design better surgical tools to repair and replace them.

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