An Integrated Framework for Finite-Element Modeling of Mitral Valve Biomechanics from Medical Images: Application to MitralClip Intervention Planning

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Abstract

Treatment of mitral valve (MV) diseases requires comprehensive clinical evaluation and therapy personalization to optimize outcomes. Finite-element models (FEM) of MV physiology have been proposed to study the biomechanical impact of MV repair, but their translation into the clinics remains challenging. As a step towards this goal, we present in this manuscript an integrated framework for finite-element modeling of the MV closure based on patient-specific anatomies and boundary conditions. Starting from temporal medical images, we estimate a comprehensive model of the MV apparatus dynamics, including papillary tips, using a machine-learning approach. A detailed model of the open MV at end-diastole is then computed, which is finally closed according to a FEM of MV biomechanics. Mitral annulus and papillary tips motions are constrained from the image data for increased accuracy. A sensitivity analysis of our system shows that chordae rest length and boundary conditions have a significant influence upon the simulation results. We quantitatively test the generalization of our framework on 25 consecutive patients. Comparisons between the simulated closed valve and the model estimated from the images at the same time point show encouraging results (average point-to-mesh distance: 1.49 ± 0.62 mm) but also the need for per-
sonalization of tissue properties, as illustrated in three patients. Finally, the predictive power of our model is tested on one case who underwent MitralClip by comparing the simulated intervention with the real outcome in terms of MV closure, yielding promising prediction. By providing an integrated way to perform MV simulation, our framework may constitute a surrogate tool for model validation and therapy planning.

**Keywords:** Mitral Valve Apparatus, Patient-Specific Anatomy, Machine-Learning, Biomechanics, Finite-Element Model, Therapy Planning

1. **Introduction**

1.1. **Clinical Rationale: Preoperative Planning of Mitral Valve Repair**

The mitral valve (MV), located between the left atrium (LA) and the left ventricle (LV), controls the unidirectional blood flow from the LA towards the LV. The MV is a complex cardiac structure comprising two leaflets, the mitral annulus and tendineae chordae. The leaflets are attached to the left heart through the fibrous mitral annulus, whereas the other extremity, called free edge, is tethered to the papillary muscles through the tendineae chordae (Fig. 1). During diastole, the leaflets open as the blood enters the LV. When the myocardium starts to contract, the leaflets close to prevent the blood from going back to the atrium. Tendineae chordae tighten to ensure perfect closure.

![Figure 1: Mitral valve anatomy as it is seen in a 3D+t transesophageal (TEE) ultrasound image.](image-url)
Mitral valve disease is one of the most common heart valve disease (Iung and Vahanian, 2011), with a prevalence sharply increasing with age, from < 2% before 30 to > 10% after 65 (Nkomo et al., 2006). Defects in leaflet morphology, chordae structure or ventricular asynchrony can result in incorrect MV closure. In this situation, the blood flows back towards the LA during systole, the so-called mitral regurgitation, which decreases cardiac efficiency. In severe cases, a surgical intervention may be necessary to repair, or even replace the incompetent valve. The edge-to-edge technique, which consists in suturing the two mitral leaflets at the regurgitant hole, has demonstrated good clinical outcomes in patients with severe mitral insufficiency due to leaflet prolapse or calcified annulus (Maisano et al., 1998). Recently, a percutaneous device, called MitralClip, has been designed to attach the two leaflets through catheter (Herrmann and Feldman, 2006). A careful preoperative planning is necessary to select patients and to determine the clipping sites. Strict guidelines have been defined based on the first results of the clinical trial Everest I (Feldman et al., 2009). However, current selection criteria still lack prediction power with respect to complications and effectiveness of the therapy in specific patients. It is not uncommon to perform several trials during the intervention and, in some cases, decide to place two clips (≈ 30% of the patients) or even to abort the procedure due to complications (≈ 10% of the patients) (Feldman et al., 2009). There is thus a need for an efficient and predictive framework that can assist the surgeon in planning the MitralClip procedure and guide him during the intervention.

1.2. Technical Background: Computational Models of the Mitral Valve

1.2.1. Geometrical Models of MV Anatomy

Comprehensive assessment of MV physiology requires detailed modeling of patient MV anatomy and dynamics from images. However, the complexity of MV anatomy and its fast dynamics make its accurate delineation from medical images difficult. Ultrasound images, and 3D+t transesophageal (TEE) in particular, are the images of choice to evaluate MV function in patients. They not only show the dynamics of the structure but also enable the clinicians to compute diagnostics parameters through tedious and time-consuming delineation, with little computational assistance (Chandra et al., 2011; Jassar et al., 2011).

More automatic methods have been proposed to make MV assessment more efficient. Burlina et al. (2010) proposed an interactive algorithm based on thin-tissue detection and level-set deformable models to identify the MV
and the LV endocardium in 3D TEE images. Detailed geometrical models were obtained but several user interactions were still necessary to guide the algorithm. Moreover, the temporal sequences would have to be handled frame by frame, which may result in inconsistent annotations. Schneider et al. proposed a complex pipeline to automatically delineate the MV from 3D+t TEE images, obtaining results with promising accuracy. The method relied on mitral annulus detection and tracking (Schneider et al., 2011b), leaflet segmentation of the open valve (Schneider et al., 2011a) and leaflet tracking using a deformable model that handled contacts and chordae stresses (Schneider et al., 2011d). Temporal resampling of 3D+t TEE images acquired on multiple heartbeats was proposed to improve temporal consistency (Schneider et al., 2011c). However, it is not clear how the authors’ approach generalizes on large populations, with wider spectrum of MV disease, because of the numerous parameters to set.

In (Ionasec et al., 2010), we provided a fast and accurate method based on machine learning to detect the MV on 3D+t TEE or CT images. The method has been recently extended to all heart valves (Grbić et al., 2010) and papillary tips (Voigt et al., 2011b). Biomechanical constraints have been added to improve the robustness of MV tracking in presence of noise and signal drop-off in TEE images (Voigt et al., 2011a). The algorithm has been validated on hundreds of patients with various heart valve diseases, showing very good robustness and accuracy in any imaging modality.

1.2.2. Biomechanical Models of MV Physiology

Quantifying the current function of the MV might not be sufficient to plan the optimal treatment for a specific patient. Mechanical insights are necessary to assess how the pathological MV dynamics will be modified after intervention. Furthermore, a comprehensive understanding of MV physiology is crucial in order to design treatments that last in the long term and do not alter normal LV function. To address these questions, computational models of MV physiology have been proposed. Since the pioneering work of Kunzelman et al. (1993), several models have been proposed and new insights on the MV function have been obtained. Three categories of computational MV models can be distinguished: structural models, fluid-structure interaction (FSI) models and deformable models.

Structural Models. Structural models aim to simulate the biomechanics of MV apparatus without directly considering the blood that flows across it.
The standard approach is to use finite-element models (FEM) to solve the dynamics equation of MV leaflets, under chordae tension, surface pressure and boundary conditions (Kunzelman et al., 1993). Several constitutive laws of leaflets and chordae have been proposed. Chordae were identified as non-linear tensile tissues very early (Kunzelman and Cochran, 1990). Biaxial stress-stretch experiments revealed that leaflets are non-linear tissues, owing to crimped collagen fibers that unfold when the leaflet are under stress, and anisotropic, as these fibers are mostly oriented parallel to the mitral annulus (May-Newman and Yin, 1995; Grashow et al., 2006; Sacks et al., 2009).

Thus, although some studies relied on anisotropic linear elasticity (Kunzelman et al., 1993; Schievano et al., 2009; Krishnamurthy et al., 2009), leaflets biomechanics are mostly modeled using hyperelasticity theory (May-Newman and Yin, 1998; Prot et al., 2007). These studies enabled to analyze leaflet stress distribution during valve closure (Prot et al., 2007; Votta et al., 2008) and to quantify the effects of material properties on valve closure (Prot et al., 2010). They also highlighted the key role of MV annulus motion and papillary tips position for optimal valve closure (Prot et al., 2009). Considered as passive tissues until recently, leaflets may actually be active as revealed by recent studies (Krishnamurthy et al., 2009; Stevanella et al., 2011a), responding to atrial contraction. Computational models simulating this property (Skallerud et al., 2011; Swanson et al., 2011) suggested that MV shape at systole may be driven by the active stiffening of the leaflets during this phase of the cardiac cycle.

Fluid-Structure Interaction Models. While structural models focus on MV biomechanics, FSI models aim to study the interactions between the MV and the blood flow by coupling FEM MV models with computational fluid dynamics (CFD) of blood flow (Einstein et al., 2010). Common FSI models rely on Lagrangian frameworks (Kunzelman et al., 2007; Lau et al., 2010) or immersed boundaries approaches (Watton et al., 2008). While FSI models are necessary for comprehensive analysis of MV physiology, such models are significantly more complex to solve. Additionally, FSI models require blood flow boundary conditions that may be difficult to measure from standard clinical data. The standard approach is to immerse the MV into an idealized fluid domain (tubes (Watton et al., 2008), boxes (Einstein et al., 2010) or idealized ventricular geometries (Lau et al., 2010)), which may not reflect the actual condition of the patient. Recently, TEE ultrasound data have been used to solve CFD of blood flow according to patient-specific LV geometry.
Deformable Models. Finally, deformable models have been proposed to simulate MV mechanics. These approaches usually require less computational power and can therefore be used for surgery training and therapy planning. In (Hammer et al., 2011), the authors proposed an anisotropic mass-spring model to simulate MV closure. This is achieved by modeling the edges between vertices with springs, whose stiffness is fitted to a typical leaflet stress-strain energy. The authors tested their approach on ex-vivo pig data with success. Burlina et al. (2010) developed a stationary analysis framework for MV closure simulation based on shape-finding finite elements (Arcaro, 2006). Given a triangulated mesh, the algorithm finds the equilibrium position of its vertices by minimising a total energy that comprises external forces, contact forces, tethering forces and linear elastic energy. The approach was applied on in-vivo geometries, resulting in prediction errors of $4 - 5 \text{mm}$. However, in both works, model parameters are not directly related to physical quantities, making them difficult to estimate from clinical or experimental data.

1.2.3. Computational Analysis of MV Repair

As MV modeling reaches maturity, researchers are beginning to investigate the effects of therapies on MV function. Mitral annuloplasty was simulated on a patient-specific anatomy (Votta et al., 2007; Stevanella et al., 2011b), showing that FEM models can be used to determine ring size. But reported simulations were not compared with actual outcomes. Schievano et al. (2009) investigated two different techniques for percutaneous valve dilatation using a linear elastic model and idealized geometries, based on the original model proposed by (Kunzelman et al., 1993). Structural changes due to edge-to-edge repair were also simulated (Votta et al., 2002; Avanzini, 2008). In (Avanzini et al., 2011), the authors concluded that MitralClip intervention yields leaflet stresses similar to those resulting after the surgical edge-to-edge procedure. Finally, FSI modeling of the edge-to-edge procedure on idealized valve geometry identified an increased fluid jet velocity due to the double orifice (Lau et al., 2011). However, all these studies could not be evaluated against clinical data on large populations due to their idealized framework or the tedious process to get patient-specific anatomical models.
1.3. **Aim of the Study**

Translating computational models of MV physiology to clinical practice remains a tremendous challenge. One of the major difficulties is the lack of integrated and efficient framework for MV modeling based on patient data. Studies based on in-vivo patient images are being reported but time-consuming manual delineations are still required, with no (Stevanella et al., 2011b; Conti et al., 2010) or partial automation (Votta et al., 2008; Burlina et al., 2010). Because of the user interactions, validation is still limited to few subjects (usually ≤ 5). For this same reason, current approaches can hardly scale up and may yield inconsistent results due to user variability.

![Diagram of MV closure simulation process](image.png)

**Figure 2:** Main steps of the proposed framework for MV closure simulation based on image data.

As a first step towards patient-specific MV FEM, we propose in this manuscript an integrated framework that combines efficient machine-learning methods with a biomechanical model of the valve apparatus to simulate MV function and therapies in patients. As illustrated in Fig. 2, and detailed in Sec. 2, our approach first estimates a comprehensive anatomical model of MV apparatus, including papillary tips, from the images. We then automatically build a detailed volumetric model comprising leaflet fibers, and simulate MV closure based on a biomechanical model. After parameter sensitivity analysis, we evaluated the generalization of our biomechanical model with respect to tissue properties, i.e. how accurately MV closure can be simulated by using patient geometry and boundary conditions but standard tissue parameters. To that end, MV closure was simulated on 25 consecutive patients and compared with the anatomical model estimated from the images at the same time.
point, showing that good results can be achieved (mean point to mesh error: 1.49 ± 0.62 mm) but also highlighting the importance of personalizing tissue biomechanics. Finally, we applied our framework to MitralClip planning by simulating the intervention on the preoperative data of one retrospective patient. Comparison with the real outcome in terms of MV closure suggested a promising prediction power.

This study extends our previous work (Mansi et al., 2011) as follows:

i The anatomical model used to simulate MV closure is closer to experimental data reported in the literature, more especially leaflet thickness (Kunzelman et al., 2007; Conti et al., 2010).

ii The biomechanical model is improved to consider tissue anisotropy due to collagen fibers. MV fiber orientation is modeled as in (Prot et al., 2009).

iii A sensitivity analysis of the main biomechanical parameters is carried on to identify the parameters to adjust first when calibrating the model.

iv The generalization of the biomechanical model with respect to tissue properties is tested on 25 cases.

v A first personalization of chordae biomechanics is reported on three cases.

2. Methods

2.1. Estimation of Mitral Valve Apparatus from 3D+t TEE Images

In this study, MV anatomy is estimated from 3D+t TEE images, although the approach can be extended to other modalities (Grbić et al., 2010). The model that is estimated from the images comprises (Fig. 3): the mitral annulus, the anterior and posterior leaflets (henceforth denoted AL and PL respectively), and the anterior and posterior papillary tips. To capture a broad spectrum of morphological variations, the model is parameterized by three coarse-to-fine components: i) Three transformations $B$ for global location, orientation and scale over the cardiac cycle; ii) The trajectories of ten anatomical landmarks $L(B) = (l_1 \ldots l_{10}) \in \mathbb{R}^{3 \times 10}$ (two trigones, one posterior annulus mid-point, two commissures, two leaflet tips and two papillary tips, see Fig. 3); and iii) a triangulated surface mesh $S_{LA}(B, L)$ to represent the left atrial (LA) surface of both anterior and posterior leaflets. The position of the vertices of the LA surface is constrained by the anatomical landmarks, resulting in an anatomically consistent parameterization $(\Omega, u, v)$ that ensures intra- and inter-patient point correspondence (Ionasec et al., 2010). $\Omega$
is the vertex of the mitral annulus that is directly perpendicular to the anterior commissure, \( u \) (resp.) is the curvilinear coordinate tangent (radial resp.) to the annulus (Fig. 3). \( u_{res} \) and \( v_{res} \) are the resolutions along the \( u \)– and \( v \)– coordinates respectively.

Figure 3: **Anatomical model of the MV and sub-valvular apparatus that is estimated from clinical images.** Leaflets are uniquely parametrized through the curvilinear coordinates \( (\Omega, u, v) \) calculated from detected landmarks.

\( B, L(B) \) and \( S_{LA}(L, B) \) are estimated from the images using a hierarchical discriminative learning algorithm, as illustrated in Fig. 4. The probability \( p(B, L, S|I) \) knowing the image data \( I \) is incrementally modeled within the Marginal Space Learning (MSL) framework, based on the Probabilistic Boosting Tree (PBT). Intuitively, given a test image, MLS framework first finds position candidates around the MV based on Haar- and steerable features. The position candidates are then successively refined by rotation and scaling candidates (see Zheng et al., 2008). This defines a region of interest inside which the position of ten landmarks is estimated using the same strategy. Next, a point-distribution model of the MV surface is mapped according to the landmarks and deformed, within the learned space of shapes, according to boundary detectors estimated through PBT. Finally, the complete MV anatomy is tracked over the cardiac sequence using a manifold-based motion model. The reader is referred to (Zheng et al., 2008; Ionasec et al., 2010) for further details.

2.2. **Volumetric Anatomical Model of the MV Apparatus**

The anatomical model used to simulate MV closure comprises *i)* a thick, tetrahedral representation of MV leaflets, *ii)* MV leaflet fiber orientation to
Figure 4: **Main steps of the automatic estimation pipeline.** From 3D+t TEE images, we first estimate the global position of the MV. Landmarks are then detected inside this region of interest. Triangulated surfaces are mapped to these landmarks and deformed to segment the MV leaflets. See text for details.

capture tissue anisotropy and \(iii\) MV chordae.

**Tetrahedral Representation of MV Leaflets.** In this study, MV biomechanics are computed using tetrahedral FEM (Sec. 2.3). The thick geometry of MV leaflets must therefore be modeled but due to the inconsistent quality of ultrasound images, accurate measurement of leaflet thickness from the images is still challenging. Instead, we compute the LV surface of the leaflets, \(S_{LV}\), by extruding the previously estimated atrial surface \(S_{LA}\) towards the ventricle. The surfaces \(S_{LA}\) and \(S_{LV}\) are merged at the free edge and annulus to obtain the thick geometry. Leaflet thickness is directly controlled through the extrusion depth, here 1.32 \(mm\) and 1.26 \(mm\) for the AL and PL respectively, as in (Votta et al., 2008; Kunzelman et al., 2007). Tetrahedral elements are created between \(S_{LA}\) and \(S_{LV}\) by connecting the surface vertices. As a result, the number of elements is directly controlled by the resolution of the surfaces, \(u_{res}\) and \(v_{res}\), and point correspondence is ensured across time frames and patients. For regional personalization, each element is automatically tagged according to the leaflet it belongs to (Fig. 5, left panel).

**MV Fibers Modeling.** Current in-vivo imaging technology cannot quantify the orientation of leaflet collagen fibers. We thus modeled their direction like in (Prot et al., 2009), following the experimental observations reported in (May-Newman and Yin, 1995). Fibers are mainly parallel to the annulus (circumferential direction). For the anterior leaflet, the fibers close to the
commissures gradually rotate to become perpendicular to the annulus (radial direction), as illustrated in Fig. 5, right panel.

**Figure 5:** *Left panel:* Tetrahedral mesh of MV leaflets. Colors encode element tag for regional personalization. *Right panel:* Computational model of MV fiber orientation. Fibers are oriented mainly parallel to the annulus. On the anterior leaflet, fibers become radial close to the commissures. Colors encode fiber direction.

**MV Chordae Modeling.** Chordae being not visible in 3D+t TEE images, we followed a strategy similar to (Hammer et al., 2008; Votta et al., 2008) by defining 28 marginal chordae evenly attached between papillary tips and leaflet free edges. Four basal chordae are attached to each leaflet, two for each papillary tip (Fig. 6). To avoid any bias in the evaluation, insertion points are identical across subjects owing to the point correspondence. More precisely, the insertion points of the marginal chordae are defined by \((u, v) = (ku_{res}/28, v_{res} - 1)\), where \(k \in [0 : 27]\). Basal insertion points are defined by \((u, v) = ((2i + 1)u_{res}/8, (v_{res} - 1)/2)\) and \((u, v) = ((2i + 1)u_{res}/8 + 1, (v_{res} - 1))/2\), \(i \in [0 : 3]\).

2.3. Biomechanical Model of Mitral Valve Apparatus

Valve closure is simulated by solving the dynamics system:

\[
M \ddot{U} + C \dot{U} + K U = F_c + F_p
\]

\(U\) is the displacement vector of the free vertices of the MV mesh, \(\dot{U}\) the velocity vector and \(\ddot{U}\) the acceleration vector. \(M\) is the lumped mass matrix (a uniform mass density \(\rho = 1.04 \text{g/mL}\) is used, Table 1). \(K\) is the stiffness matrix of the internal elastic forces. \(C\) is a Rayleigh damping matrix defined by \(C = 0.1M + 0.1K\). \(F_c\) and \(F_p\) are the forces developed by the chordae and heart pressure respectively.
2.3.1. Leaflet Passive Properties

MV leaflets are modeled as linear, transverse isotropic elastic tissues (Hammer et al., 2008; Schievano et al., 2009; Krishnamurthy et al., 2009) as we are not directly interested in leaflet stresses during the entire cardiac cycle but we rather seek to predict how well they close during systole to assess possible residual regurgitant holes after intervention. Besides, recent works based on inverse-problem methods suggested that the leaflets may behave as linear materials in the range of physiological pressures (Krishnamurthy et al., 2009). Finally, linear elasticity models are computationally efficient, thus enabling fast simulations and real-time intervention planning. In our experiments, different tissue properties are assigned to the AL and PL. Parameters are reported in Table 1.

2.3.2. Chordae Passive Properties

Chordae are modeled by piecewise tensile springs between papillary tips, modeled as spatial points, and leaflet insertion points (Fig. 6). Between an insertion point $v_i$, $i \in \{\text{marginal, basal}\}$ and its corresponding papillary tip $p_i$, we apply the force:

$$f_c(v_i; p_i, t) = -k_{c,i}(\epsilon_{c,i}, t) \times (L_i(t) - L_{i,0}), \quad (2)$$

where $L_i$ is the current elongation $\|v_i(t) - p_i(t)\|$ and $L_{i,0}$ is the chordae rest length, defined as the distance between the papillary tips and the insertion
points estimated at the end diastole time frame. The stiffness $k_{c,i}(\epsilon_{c,i}, t)$
depends on the strain $\epsilon_{c,i} = (L_i(t) - L_i,0)/L_i,0$ to model the non-linear
response of the chordae (Kunzelman and Cochran, 1990). At compression,
$\epsilon < 0$, $k_{c,i} = 0 \text{ g/mm}$ (free compression). At low tension, chordae exhibit low
stress-strain behavior, which then increases dramatically and almost linearly
(Fig. 7, left panel). Spring tensile stiffnesses $k_{c,i}$ are calculated from the
chordae Young moduli according to $k_{c,i} = A_{0,i}E_{c,i}/L_{0,i}$ where $A_{0,i}$ is the
chordae cross-section at rest. Parameters are reported in Table 1.

2.3.3. External Loads, Boundary Conditions and Contacts

We simulated valve dynamics between end of diastole and beginning of
iso-volumetric contraction (when the valve just closes) by applying a generic
profile that increases from 0 mmHg to 120 mmHg (Prot et al., 2009) (Fig. 7,
right panel). The motions of the papillary tips and of the mitral annulus are
prescribed from the automatic detection (Fig. 6). In practice the displace-
ment and velocity of the prescribed vertices are projected at every time step
of the simulation such that they correspond to the motion observed in the
images. This contribution is of fundamental importance as correct valve clo-
sure highly depends on the papillary positions and the shape of the annulus
during systole (Prot et al., 2009). Finally, self-collisions are detected using a
ray-casting approach. Leaflet-leaflet interactions in the normal direction are
handled using a penalty constraint. Tangential interaction is modeled with
a friction coefficient of 0.1.

Figure 7: Left panel: Stress-strain behavior of chordae. Linear approximation in dashed
lines. Data from (Kunzelman and Cochran, 1990)). Right panel: Pressure profile applied
to the leaflets to simulate closure. The time is adjusted for each patient to match valve
closure duration.
Table 1: Parameters of the biomechanical model

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<tr>
<td>Mass density</td>
<td>( \rho = 1.04 \text{ g/mL} )</td>
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<tr>
<td>Poisson ratio</td>
<td>( \nu = 0.488 )</td>
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<tr>
<td>AL Young’s modulus</td>
<td>( E_{AL_f} = 6.233 \text{ MPa} ), ( E_{AL_{f+}} = 2.350 \text{ MPa} )</td>
<td>( E_{c} = 312 \text{ g/mm}^2 ) (( \epsilon &lt; 2.5% ))</td>
<td>( E_{c} = 66 \text{ g/mm}^2 ) (( \epsilon &lt; 5% ))</td>
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<td>AL shear modulus</td>
<td>( G_{f+} = 1.369 \text{ MPa} )</td>
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<tr>
<td>PL Young’s modulus</td>
<td>( E_{PL_f} = 2.087 \text{ MPa} ), ( E_{PL_{f+}} = 1.887 \text{ MPa} )</td>
<td>( E_{c} = 3406 \text{ g/mm}^2 ) (( \epsilon \geq 2.5% ))</td>
<td>( E_{c} = 2120 \text{ g/mm}^2 ) (( \epsilon \geq 5% ))</td>
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<tr>
<td>PL shear modulus</td>
<td>( G_{f+} = 0.694 \text{ MPa} )</td>
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<td>Marginal Chordae</td>
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<td>Basal Chordae</td>
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<td>General</td>
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<td>Time step</td>
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<td>Mesh resolution</td>
<td>( u_{res} = v_{res} = 30 )</td>
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<tr>
<td>Number of marginal chordae</td>
<td>28</td>
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<tr>
<td>Number of basal chordae</td>
<td>4</td>
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<td>( k_{clip} )</td>
<td>1000 g/mm</td>
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2.4. MitralClip Simulation

Virtual mitral clipping is performed interactively, in real-time, on the preoperative anatomical model as pictured in Fig. 8. On the open anatomy, the user successively picks a vertex on each leaflet. A stiff spring (\( k_{clip} = 1000 \text{ g/mm} \)) is then created between the two vertices to hold the leaflets together and model the clip. Leaflet deformations are computed according to Eq. (1). Tissue properties stay unchanged (Table 1) but pressures are disabled and mitral annulus and papillary tips are fixed to facilitate the virtual mitral clipping.

Once the clip is implanted on the preoperative anatomy, postoperative MV closure is simulated to assess the efficacy of the intervention in terms of MV regurgitation, just after clip release. To that end, we assume the ventricle motion to be fairly similar to the preoperative motion, as only the morphology of the leaflets changed. Preoperative boundary conditions and ventricular pressures are applied on the clipped geometry to simulate closure.
2.5. Implementation

The biomechanical model is implemented using SOFA framework\textsuperscript{1}, an open-source soft-tissue intervention platform (Allard et al., 2007). The dynamics system Eq. (1) is solved using co-rotational linear tetrahedral finite elements to cope with large deformations and rotations (Nesme et al., 2005). The simulation time is scaled such that the simulated MV closure is ten times longer than what is observed in the images (from 70 $ms$ to 150 $ms$) to handle the strong and discontinuous contact forces, as in (Votta et al., 2008). An implicit Euler solver is used to update mesh positions (Baraff and Witkin, 1998). We finally stress that the pipeline is completely integrated, from model estimation to simulation, although the user can manually adjust the models if necessary.

3. Experiments and Results

Three experiments were carried out. We first evaluated on a large database of patients the accuracy of the model estimation from the images. We then assessed the performance and the generalization with respect to tissue properties of our biomechanical model on 25 consecutive subjects. We finally applied our framework to preoperative planning of MitralClip intervention by simulating the intervention in one case and comparing the simulated, postoperative closed valve with the real outcome.

\textsuperscript{1}http://www.sofa-framework.org
3.1. Validation of the MV Anatomical Model

In a first stage, we quantitatively evaluated the performances of the automatic estimation of the MV and its sub-valvular apparatus. To that end, the anatomical model was estimated on 200 3D+t TEE images from 120 patients with a wide range of diseases (MV prolapse, calcified mitral annulus, stenosis, ventricular dysfunction, ...). Images were acquired with different angulation, field of view and resolution (spatial and temporal). Three-fold cross-validation against manual delineation yielded a point-to-mesh error of 2.75±0.86 mm. Qualitative evaluation showed that the algorithm was able to faithfully track the MV throughout the cardiac sequence, even during valve closure and opening when the dynamics are fast (Fig. 9). Computation time was 4.8 s per 3D volume on a standard desktop machine (Intel Core2Duo, 2.66GHz quad core, 2GB RAM). A thorough evaluation of model estimation is beyond the scope of this study. We refer the reader to (Ionasec et al., 2010; Grbić et al., 2010; Voigt et al., 2011b) for more comprehensive evaluations.

Figure 9: Automatic detection of the MV apparatus on 3D TEE time sequences of four patients with different diseases. As one can see, the model accurately fits patients’ MV in the images.
3.2. Evaluation of MV Closure Simulation

3.2.1. FEM Convergence Analysis

We first determined the spatial resolution and temporal time step that is required for computationally efficient but accurate simulations. Accuracy was measured as the difference between the simulation at a given spatial / temporal resolution and the result obtained at the finest discretization. Sub-millimetric errors were considered as satisfactory in comparison with image resolution (typically $\approx 0.75 - 1.58 \text{ mm}$). The analyses were performed using the MV anatomy and boundary conditions of one patient selected from our database (Fig. 10), but with the tissue parameters reported in Table 1. MV closure was simulated from the anatomical model computed from the last frame where the valve was fully open (end-diastole). Simulation time was synchronized with patient data as described in Sec. 2.3.

![Figure 10: Anatomical model of the patient used for the parameter sensitivity analysis.](image)

Spatial Convergence Analysis. Spatial convergence was analyzed as follows. We first fixed $v_{res} = 30$ and simulated MV closure with $u_{res} = 30, 40, 50$, corresponding respectively to 9408, 12768, 16128 elements with 1.67 mm, 1.24 mm and 0.98 mm average edge-length. Results are illustrated in Fig. 11. As one can see, $u_{res}$ had fairly little effect on the simulation result. This observation was confirmed quantitatively by measuring the point-to-mesh error with respect to the result obtained with $u_{res} = 50$ ($e_{u_{res}=30} = 0.43 \pm 0.22 \text{ mm}$, $e_{u_{res}=40} = 0.43 \pm 0.19$). We thus chose to use $u_{res} = 30$ in our simulations to maximize computational efficiency.

We then fixed $u_{res} = 30$ and used $v_{res} = 10, 20, 30$, corresponding respectively to 2688, 6048 and 9408 elements with 4.89 mm, 2.49 mm and 1.67 mm average edge-length. Results are illustrated in Fig 12. Here, significant differences between the simulation at $v_{res} = 10$ and the others were found (point to mesh error with the result obtained with $v_{res} = 30$:...
$u_{res} = 30, v_{res} = 30$ | $u_{res} = 40, v_{res} = 30$ | $u_{res} = 50, v_{res} = 30$

Point to mesh error (in mm)

Figure 11: **Effect of the resolution along the $u$-coordinate on the simulation.** Only millimetric differences were visible. Colors encode point to mesh error with respect to the solution obtained at $u_{res} = 50, v_{res} = 30$

$e_{v_{res}=10} = 0.51 \pm 0.51 \text{mm}$). In particular, the posterior leaflet ended in a totally different position. Results at $v_{res} = 20$ and $v_{res} = 30$ were significantly closer to each other ($e_{v_{res}=20} = 0.30 \pm 0.18 \text{mm}$), suggesting convergence at $v_{res} = 30$. Those results also hold for non-reported simulations at higher $v_{res}$ and $u_{res} > 30$. We therefore decided to use meshes generated with $u_{res} = v_{res} = 30$ (9408 elements, 1.67 mm average edge-length) for our subsequent simulations.

**Temporal Convergence Analysis.** Although Euler implicit scheme theoretically allows large time steps $dt$, collision detection can be hampered if $dt$ is too large. We investigated the effects of time discretization on the simulation results by computing MV closure with $dt = 10^{-1} \text{s}, 10^{-2} \text{s}, 10^{-3} \text{s}$ and $10^{-4} \text{s}$. $u_{res}$ and $v_{res}$ were set to 30 as mentioned earlier. Fig. 13 reports the point-to-point distances at the end of the simulations between the closed MV computed with $dt = 10^{-1} \text{s}, 10^{-2} \text{s}$ and $10^{-3} \text{s}$ and the closed MV computed with $dt = 10^{-4} \text{s}$. Convergence was clearly reached at $dt = 10^{-3} \text{s}$ (mean error: $0.02 \pm 0.02 \text{mm}$, maximum: $0.11 \text{mm}$). $dt = 10^{-2} \text{s}$ yielded already sub-voxel accuracy (mean error: $0.18 \pm 0.12 \text{mm}$, maximum: $0.64 \text{mm}$) but $dt = 0.1 \text{s}$ was too large to reach convergence (mean error: $1.17 \pm 1.25 \text{mm}$, maximum: $5.72 \text{mm}$). The leaflets did not have time to close. In light of
these results, we chose $dt = 10^{-2}$ s for our simulations.

### 3.2.2. Sensitivity Analysis of Biomechanical Model Parameter

We analyzed the sensitivity of our framework with respect to boundary conditions and chordae configuration since these parameters were reported to influence significantly the simulations on membrane models (Prot et al., 2009) and with mass-spring models (Hammer et al., 2011). In the following, simulation parameters were set according to (Table 1), if not stated otherwise. Spatial resolution was $u_{res} = v_{res} = 30$ and time discretization $dt = 0.01$ s.

**Sensitivity to Boundary Conditions.** We first verified the importance of boundary conditions on the computed MV closure. To that end, we ran the simulation with fixed mitral annulus and papillary tips. As it can be seen from Fig. 14, the MV did not close anymore and was significantly different from the results obtained so far. The result was also wrong when compared to the model estimated from the images at the same time point. As suggested in previous studies (Prot et al., 2009), mitral annulus deformation helps the leaflets to close and papillary tips must be synchronized with the annulus to ensure perfect closure. Being able to estimate patient-specific boundary conditions efficiently is therefore a key feature of our framework.
Sensitivity to Marginal Chordae Properties. Our MV model comprises 28 marginal chordae evenly attached to the free edges, at the same spatial location for all subjects. Yet, chordae distribution can change from patient to patient (Kunzelman and Cochran, 1990). We thus investigated the impact of the number of marginal insertions points on the simulation by computing MV closure with 56, 28, 20, 16 and 12 marginal chordae evenly attached to the free edges. All other parameters were kept constant (Table 1). Not surprisingly, the number of marginal chordae modified the dynamics of the leaflets. In particular, MV free edges came closer to the mitral annulus as the number of chordae decreased, as quantified by the distance of the leaflet tips to the annulus plane defined by the trigones and the posterior mid-point (Fig. 15, left panels). Leaflet speed was also higher with fewer chordae as the leaflets were less tighten and more flexible under pressure.

Marginal chordae rest length $L_{i,0}$ (Sec. 2.3.2) was also reported to have a significant influence on the MV dynamics (Hammer et al., 2011). In our framework, $L_{i,0}$ is the distance between papillary tips and insertion points at end diastole but this approach may under-estimate $L_{i,0}$ if chordae folds. We quantified the impact of that parameter by computing MV closure with $L_{i,0} \pm 10\%, 20\%$ and $30\%$ (Fig. 15, mid panels). We obtained variations of the same order of magnitude as those obtained by varying the number.
Simulation without prescribed annulus and papillary motion

Model estimated from the images at the same time point

Figure 14: **Effect of boundary conditions on the simulation.** Simulation with fixed mitral annulus and papillary tips was less accurate than simulations with prescribed motions (Fig. 12, left panels), compared to what is observed in the images (left).

The longer was the rest length, the higher the leaflets went towards the annulus plane. A change of 30% in rest length resulted in \( \approx 38\% \) and \( \approx 1.1\% \) change in the position of the anterior and posterior tips respectively, almost 8 mm difference for the AL. Moreover, the abrupt change in the dynamics observed with a rest length of 110%, and not elsewhere, illustrates that modifying the rest length can bring new collisions between the AL and PL, thus significantly modifying the end result. It is therefore crucial to set up this parameter accordingly for each patient for accurate predictions.

Finally, we evaluated the sensitivity of the simulation with respect to chordae stiffness by computing MV closure with stiffnesses spanning from \( \pm 30\% \) of the standard values, the anisotropy ratio being kept constant. The variations were much lower compared to the two previous experiments (\( \approx 11\% \) and \( \approx 2.1\% \) in leaflet tip positions, less than 2 mm overall).

As a direct consequence of these results, we can derive a personalization strategy for chordae tissue properties. In our experiments, we noticed that both number of chordae and rest length parameters had similar effects on the simulated MV dynamics. This may suggest that one can fix the number of chordae for all patients, and then set the rest length such that the position of the free edges match what is observed in the images. Chordae stiffnesses can then be adjusted to further refine the simulation.
Anterior tip to mitral annulus distance (in mm)

Number of Chordae | Chordae Rest Length | Chordae Stiffness

<table>
<thead>
<tr>
<th>Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Posterior tip to mitral annulus distance (in mm)

Number of Chordae | Chordae Rest Length | Chordae Stiffness

<table>
<thead>
<tr>
<th>Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>10.5</td>
</tr>
</tbody>
</table>

Figure 15: **Effect of chordae parameters on the simulation.** The number of chordae and their rest length had a significant influence on the dynamics of the computed MV closure, compared to chordae stiffness, as quantified by the distance between the tips and the mitral annulus plane. Chordae rest length can also alter MV dynamics by creating conditions for new collisions (pink curve in mid panels).

3.2.3. Evaluation of Biomechanical Model Generalization with Respect to Tissue Properties

Our integrated framework enabled us to evaluate the generalization of the biomechanical model in terms of tissue parameters on 25 consecutive patients. The objective was to assess how well MV closure can be captured using patient-specific anatomy and boundary conditions only, tissue properties being set according to Table 1.

**Patient Selection and Experimental Protocol.** 25 patients were randomly selected from five hospitals, representing a large spectrum of heart diseases (MV diseases, aortic valve diseases, myocardium infarction, etc.). For these patients, standard 3D+t TEE images of the MV were acquired (image resolution: 0.75 – 1.58 mm isotropic, 7 – 28 (median: 14) time frames). The
dynamic models of MV anatomy were automatically estimated on all time frames of the sequences. To minimize bias in the evaluation of the simulation due to model estimation errors, an expert (M.H.) carefully verified the models and corrected them manually whenever it was necessary. In particular, papillary tips were carefully verified using all temporal information.

The anatomical model at the time frame just before closure, which corresponds to the end-diastole time point, was used to simulate MV closure. The motions of the mitral annulus and papillary tips estimated from the images were used as boundary conditions. The pressure profile described in Sec. 2.3.3 was applied to simulate MV closure. The simulated closed valve was compared to the MV geometrical model estimated at the first time frame at which the MV is closed, which corresponds to the beginning of the isovolumetric contraction. That reference is henceforth termed ground truth.

MV Closure Simulation. Table 2 reports the average point-to-mesh distances from the simulations to the ground truth for every patient. Population-wise, the average error was $1.49 \pm 0.62 \text{mm}$, which was of the same order of magnitude of the automated detection and in the range of values reported in the literature (Hammer et al., 2011; Burlina et al., 2010). We qualitatively evaluated the results by ranking them as satisfactory if closure was captured (Fig. 16), passable if closure was partial (Fig. 17), or unsatisfactory if the valve was still open (Fig. 18). With those criteria, simulations were qualified as satisfactory in 7 patients (28%, average point-to-mesh error: $e_{\text{mean}} = 1.07 \pm 0.36 \text{mm}$, $e_{\text{max}} = 1.66 \text{mm}$), passable in 9 patients (36%, $e_{\text{mean}} = 1.38 \pm 0.31 \text{mm}$, $e_{\text{max}} = 2.01 \text{mm}$) and unsatisfactory in 9 patients (36%, $e_{\text{mean}} = 1.91 \pm 0.77 \text{mm}$, $e_{\text{max}} = 3.13 \text{mm}$).

The biomechanical model was able to capture MV closure in 7 patients with an accuracy equivalent to the image resolution. In the other cases, our experiment confirmed that tissue properties required further personalization, in particular in a population of patients where leaflet properties and chordae tendineae configurations can vary significantly among individuals. Large errors were often due to non-optimal chordae rest length, as observed in patient 1 and 17 for instance (Fig. 18, black arrows). In these two cases, the anterior leaflet remained open, pulled down by tensed chordae. Although a complete inverse problem analysis of our population is out of the scope of this manuscript, we evaluated the ability of our model to capture valve closure for those two patients and for one case rated as satisfactory (Patient 10). To that end, we manually estimated chordae rest length based on the full
dynamic data by minimizing the differences between the simulation results and the models estimated from the images. Fig 18 shows the results obtained before and after personalization for Patient 1 and 17. Fig 18, top row, shows the results for Patient 10. Point-to-mesh errors after personalization are reported in Table 3. As it can be seen from the figures, adjusting chordae rest length enabled us to improve the accuracy of MV closure prediction. Further improvement could be reached by adjusting all biomechanical parameters at once through inverse problem algorithms (Powell, 2008).

Table 3: **Point-to-mesh distance between simulation and ground truth after chordae rest length adjustment in three cases.** Personalizing MV chordae rest length enabled us to capture MV closure, which was not possible with standard rest length (Table 2).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Point-to-Mesh Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>1.67 ± 1.08 mm</td>
</tr>
<tr>
<td>02</td>
<td>1.46 ± 1.51 mm</td>
</tr>
<tr>
<td>03</td>
<td>3.04 ± 1.84 mm</td>
</tr>
<tr>
<td>04</td>
<td>3.14 ± 2.10 mm</td>
</tr>
<tr>
<td>05</td>
<td>1.34 ± 1.03 mm</td>
</tr>
<tr>
<td>06</td>
<td>1.21 ± 0.82 mm</td>
</tr>
<tr>
<td>07</td>
<td>0.61 ± 0.38 mm</td>
</tr>
<tr>
<td>08</td>
<td>0.99 ± 0.51 mm</td>
</tr>
<tr>
<td>09</td>
<td>1.19 ± 0.72 mm</td>
</tr>
<tr>
<td>10</td>
<td>1.43 ± 0.96 mm</td>
</tr>
<tr>
<td>11</td>
<td>1.83 ± 2.13 mm</td>
</tr>
<tr>
<td>12</td>
<td>1.07 ± 0.60 mm</td>
</tr>
<tr>
<td>13</td>
<td>1.66 ± 1.21 mm</td>
</tr>
<tr>
<td>14</td>
<td>2.01 ± 1.30 mm</td>
</tr>
<tr>
<td>15</td>
<td>1.41 ± 0.78 mm</td>
</tr>
<tr>
<td>16</td>
<td>1.38 ± 0.75 mm</td>
</tr>
<tr>
<td>17</td>
<td>1.70 ± 1.18 mm</td>
</tr>
<tr>
<td>18</td>
<td>1.28 ± 0.82 mm</td>
</tr>
<tr>
<td>19</td>
<td>1.07 ± 0.65 mm</td>
</tr>
<tr>
<td>20</td>
<td>0.90 ± 0.52 mm</td>
</tr>
<tr>
<td>21</td>
<td>1.44 ± 1.13 mm</td>
</tr>
<tr>
<td>22</td>
<td>2.43 ± 1.47 mm</td>
</tr>
<tr>
<td>23</td>
<td>0.94 ± 0.63 mm</td>
</tr>
<tr>
<td>24</td>
<td>0.79 ± 0.61 mm</td>
</tr>
<tr>
<td>25</td>
<td>1.14 ± 0.94 mm</td>
</tr>
</tbody>
</table>
Figure 16: Simulated MV closure in three patients compared to observed MV shape. These cases were visually ranked as satisfactory.
Figure 17: Simulated MV closure in two patients compared to observed MV shape. Partial MV closure was achieved in these cases, mainly because of incomplete closure of posterior leaflet.
Figure 18: **Simulated MV closure in two patients compared to observed MV shape.** Simulation with generic tissue parameters was not able to capture MV closure in these patients. Too short chordae prevented the anterior leaflet to close *(black arrow).* Adjusting chordae rest length significantly improved the results.
Computation Time. Simulation was performed in $\approx 0.3$ frames per second ($fps$) on a desktop machine (Intel Xeon, 2.40GHz octo-core, 4GB RAM), which amounts to $\approx 10\ min$ of computation time on a single core. No particular optimizations were implemented. The entire process, from the 3D+t TEE images to the simulation, took about 12 min.

3.3. Simulation of MitralClip

As it has been shown in the previous section, it is possible to find a set of parameters that would enable one to simulate the MV closure of a specific patient. Yet, the computational model may still not be able to predict changes in MV physiology after modifications of cardiovascular parameters or therapies. As this feature is of high importance for clinical applicability of such methods, we tested the ability of our framework to predict the outcome of MV intervention based on preoperative data only. Among our patients, Patient 10 underwent MitralClip intervention. Intra-operative 3D+t TEE images of the MV before, during and after clip release were available. Simulation of MV closure based on the images before clip release yielded satisfactory accuracy after slight personalization of chord rest length (10% higher than the distance between papillary tips and leaflet free edges measured at end diastole). Point to mesh error between the simulation and the ground truth decreased from $1.43 \pm 0.96\ mm$ to $1.12 \pm 0.80\ mm$ after personalization. We then simulated the MitralClip intervention on the pre-clip anatomy as described in Sec 2.4. The virtual intervention was performed in real-time (2 frames per second). We finally applied the pressure profile on the ventricular surface and the preoperative boundary conditions (mitral annulus and papillary tips motion) to predict MV closure just after release of the device. Biomechanical parameters were kept constant. Fig 19 reports the results for each step. As it can be seen, the model was able to simulate MV closure after the intervention with results similar to what was observed in the post-clip images, suggesting promising prediction power. One should remark that the difference in mitral annulus shape between the simulated clipped valve and the real outcome is due to the different boundary conditions. In that experiment we applied preoperative annulus and papillary tips motion to reproduce a real-case scenario where the postoperative outcome is unknown.
4. Discussion and Conclusions

We have presented in this article an integrated framework that combines efficient machine learning techniques and MV FEM to simulate MV closure in patients. Patient-specific models of MV anatomy and boundary conditions are estimated from 3D+t TEE images, although our approach could be applied to other imaging modalities (Grbić et al., 2010). The anatomical model was then used to simulate MV closure based on an FEM biomechanical model of MV apparatus. The level of integration reached by our framework enabled us i) to perform a sensitivity analysis of MV FEM on patient-specific geometry; ii) to test the generalization of a biomechanical model in terms of tissue properties in 25 patients, which, to the best of our knowledge, constitutes
the largest in-vivo FEM study reported so far; and iii) simulate MitralClip intervention and predict its outcome in terms of valve closure in one patient.

Our sensitivity analysis was in agreement with the results reported in the literature realized on membrane (Prot et al., 2009) or mass-spring models (Hammer et al., 2011). Mitral annulus and papillary tips motions were found crucial for correct MV closure. Being able to estimate them from the images in an efficient way is therefore a desirable feature of our framework. Chordae rest length were also found to have significant effect on MV closure. Unfortunately, this parameter is not directly measurable from images. In this article, the rest length was defined as the distance between papillary tips and leaflet free edges at end diastole. However, the evaluation on 25 patients showed that using one time frame only may not be sufficient, information from MV dynamics being necessary for more accurate estimation.

The automation provided by our machine learning algorithms significantly reduced the amount of user interactions necessary to get an accurate anatomical MV model. As a result, we could assess the generalization of the biomechanical model in terms of tissue properties in 25 patients. To the best of our knowledge, this is the first time that such an analysis is performed on a large number of cases. Overall, the average accuracy was of the same order of magnitude as the one of the automatic detection. Despite the generic parameters and the model simplifications, we could simulate MV closure in seven cases. More importantly, this experiment provided evidence that using patient geometries and boundary conditions only, although necessary, is not sufficient to simulate MV closure in all patients. Tissue properties need to be estimated. In particular, we showed in three patients that adjusting chordae rest length can significantly improve the results. As our framework estimates MV model from dynamic images, a next step of our study will be to use inverse problem methods (Powell, 2008) to estimate the tissue properties from MV dynamics.

Simulating the current MV dynamics may not be enough to have a predictive model. A set of parameters can be found that reproduces the observed MV function, but cannot predict changes in MV physiology due to disease or therapies. To evaluate the predictive power of our system, we simulated MitralClip intervention in one patient based on preoperative data solely and compared the results with the real outcome in terms of MV closure. Obtained results were promising despite the use of preoperative boundary conditions, encouraging further works towards FEM-based therapy planning. Future works include validation on larger population and other therapies.
The effect of some modeling simplifications still need to be consolidated. First, we relied on transverse isotropic linear elasticity to model leaflet biomechanics, whereas biaxial studies showed a highly non-linear constitute law (May-Newman and Yin, 1995). Co-rotational tetrahedra were used to cope with large rotations and deformations but tissue linearity may introduce errors in the simulation, in particular in terms of tissue stress distribution. Yet, differences between linear and non-linear models in terms of MV closure prediction still remain to be quantified in in-vivo set-ups. Furthermore, recent studies based on inverse problem suggested that leaflets may have linear behavior in the range of physiological values (Krishnamurthy et al., 2009). Further investigations would be necessary to confirm this finding. Relying on a modular platform (Allard et al., 2007) enables us to easily extend our framework with more detailed biomechanical models to quantify the added value of such detailed models in terms of MV closure prediction.

Second, we modeled the leaflets as purely passive and homogeneous tissue. Recent studies showed that this may not be the case. On the one hand, leaflet stiffness varies throughout the cardiac cycle (Krishnamurthy et al., 2009; Stevanella et al., 2011a; Swanson et al., 2011), which contributes to the funnel shape of the anterior leaflet at systole. Integrating this feature in our model may improve the accuracy of the predictions in that region (Skallerud et al., 2011). On the other hand, tissue properties are spatially heterogeneous, and more especially in patients. It has been shown that the leaflet are made up of three different layers, with different material behaviors (Prot and Skallerud, 2009). Furthermore, patients may suffer from tissue calcification, which alters the biomechanical properties locally. Including these features in our model could improve the results. Calcification could be quantified from CT imaging for instance, or estimated indirectly from the MV dynamics using inverse problems.

Third, our simulation of MitralClip intervention relied on preoperative data exclusively. However, it is acknowledged that ventricular pressure can change after mitral regurgitation repair. Myocardium force can increase, and thus the ventricular pressure, to preserve stroke volume. As a result, mitral annulus motion may change although only leaflet morphology are affected by the intervention. An integrated LV / MV model like in (Wenk et al., 2010) may increase prediction accuracy at the price of additional parameters to adjust related to ventricular biomechanics.

Finally, only MV closure was considered in this study to predict residual regurgitation after therapy. Full cycle simulation may provide insights on
the entire MV dynamics and tissue stresses for long-term therapy prognosis. This aspect of MV function will be investigated in future works.

In conclusion, we have presented in this article an integrated framework for FEM modeling of MV closure in patients, with a first evaluation on 25 patients and prediction of MitralClip intervention. The level of integration provided by our framework paves the way to the large-scale studies necessary to validate advanced FEM models in clinical settings. Our results suggest that FEM models may constitute surrogate tools for mitral valve repair planning.

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