Mitral valve finite-element modelling from ultrasound data: a pilot study for a new approach to understand mitral function and clinical scenarios

BY EMILIANO VOTTA 1,*, ENRICO CAIANI 1, FEDERICO VERONESI 1, MONICA SONCINI 1, FRANCO MARIA MONTEVECCHI 2 AND ALBERTO REDAELLI 1

1 Bioengineering Department, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy
2 Mechanics Department, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy

In the current scientific literature, particular attention is dedicated to the study of the mitral valve and to comprehension of the mechanisms that lead to its normal function, as well as those that trigger possible pathological conditions. One of the adopted approaches consists of computational modelling, which allows quantitative analysis of the mechanical behaviour of the valve by means of continuum mechanics theory and numerical techniques. However, none of the currently available models realistically accounts for all of the aspects that characterize the function of the mitral valve. Here, a new computational model of the mitral valve has been developed from in vivo data, as a first step towards the development of patient-specific models for the evaluation of annuloplasty procedures. A structural finite-element model of the mitral valve has been developed to account for all of the main valvular substructures. In particular, it includes the real geometry and the movement of the annulus and papillary muscles, reconstructed from four-dimensional ultrasound data from a healthy human subject, and a realistic description of the complex mechanical properties of mitral tissues. Preliminary simulations allowed mitral valve closure to be realistically mimicked and the role of annulus and papillary muscle dynamics to be quantified.

Keywords: mitral valve; finite-element modelling; three-dimensional real-time echocardiography

1. Introduction

The mitral valve separates the left atrium from the left ventricle and guarantees unidirectional blood flow from the first to the second chamber. The correct closure and reopening of the valve, as well as its normal interaction with the surrounding ventricular chamber, are driven by several factors: the action of the transvalvular pressure drop, the dynamic contraction of the annulus and the papillary muscles (PMs), and the effect of ventricular haemodynamics.

* Author for correspondence (emiliano.votta@biomed.polimi.it).

One contribution of 11 to a Theme Issue ‘The virtual physiological human: building a framework for computational biomedicine II’.
The mitral valve is an object of particular interest to clinicians, owing to the high prevalence of its pathologies, which usually have to be surgically treated. In the last two decades, clinicians have been searching for increasingly more effective surgical techniques and devices. These, however, need to be carefully designed, tested and optimized prior to being used in clinical practice. To this end, different tools and approaches are available, including computer models based on the finite-element (FE) method, which allows the numerical solution of the equations of continuum mechanics applied to complex systems. FE modelling is naturally appealing, since it allows the flexible, repeatable and quantitative analysis of multifactorial scenarios, such as those that characterize mitral function in pathological and post-operative conditions. Moreover, FE models, and structural ones in particular, are becoming more and more widely adopted, thanks to the continual increase in computing performance. However, the implementation of a fully realistic FE model of the mitral valve still represents a challenging task, owing to the high complexity of the four aspects to be modelled at once: valvular morphology, the valvular tissues’ mechanical response, dynamic loading and boundary conditions during the cardiac cycle, and the interaction between the mitral valve and surrounding blood.

Only five groups have developed effective three-dimensional structural FE models of the human mitral valve. Kunzelman and co-workers were the first to use this approach and have adopted it to the widest extent, either to mimic normal mitral function (Kunzelman et al. 1993a; Einstein et al. 2005a) or to understand the biomechanics underlying valvular diseases (Kunzelman et al. 1997, 1998a; Einstein et al. 2005b) and surgical corrections (Reimink et al. 1995, 1996; Cochran & Kunzelman 1998; Kunzelman et al. 1998b). More recently, two other research groups have focused their attention on normal mitral function (Lim et al. 2005; Prot et al. 2007). Finally, the group at Politecnico di Milano have used FE models to analyse the effects of annuloplasty procedures (Maisano et al. 2005; Votta et al. 2007) and to simulate the biomechanical response of the valve to the Alfieri stitch technique (Votta et al. 2002). This second clinical issue was also the subject of the study of Dal Pan et al. (2005). Very recently, a sixth research group has used fluid–structure interaction modelling as a tool to predict the performance of bioprosthetic mitral valves (Watton et al. 2007, 2008). Although the focus of their studies is on prostheses with different morphological and mechanical properties when compared with the natural human valve, their modelling strategy could be adopted in analysis of the mitral valve.

Every model was based on simplifying assumptions, whose nature, number and impact varied from model to model, depending on the degree of complexity of the latter and on its particular application. As a result, the four above-mentioned aspects were differently accounted for; an overview of the solutions adopted for this purpose is provided in §2.

2. Literature review

(a) Modelling of time-dependent mitral morphology

The mitral valve is an apparatus consisting of different substructures, whose correct interaction is necessary for proper valvular function: the annulus, the two valvular leaflets, the chordae tendineae and the two PMs (figure 1).
A realistic geometrical model of the valve should include all of these substructures and should account for their time-dependent shape, proportions and reciprocal positions.

Currently, none of the published FE models of the mitral valve has these features. The first general limitation shared by nearly all of the available models consists in assuming reflection symmetry for the entire valve; valve asymmetries were partially accounted for only by Lim et al. (2005), who modelled the annulus and the PMs using in vivo data. The second general limitation shared by the mentioned models consists in the limited time-frame of the simulated phenomenon; the focus is usually on valve closure from end diastole to the systolic peak. Two exceptions are the work of Lim and colleagues, who simulated valve function during the whole cardiac cycle, and that by Watton et al. (2007, 2008).

(i) The annulus

The first valvular substructure is the annulus, which is the boundary of the valve orifice and is continuous with the surrounding myocardium of the atrium. Its profile is saddle shaped and changes dynamically during the cardiac cycle (Flachskampf et al. 2000). When observed from an atrial view, the annulus appears almost elliptical; for this reason, its extent is often described in terms of its two main diameters, the septolateral and commissure–commissure (CC) ones, whose extent changes from diastole to systole (Ormiston et al. 1981; Fyrenius et al. 2001). In the majority of the models available in the literature, the annular profile is defined as an idealized line with a simplified shape, according to geometrical rationales.

The different idealized annular shapes are sketched in the centre column of figure 2. In particular, Kunzelman and co-workers in their first-generation model of a physiological mitral valve assumed a planar annulus, which from an atrial view appeared D-shaped and smoothed; the straight part of the D represented the anterior portion of the annulus and the curved tract represented the posterior one (Kunzelman et al. 1993a). Even though the initial state of the valve was supposed to be the end-diastole one, the proportions of the D profile were defined according to the typical annular dimensions in systole and were kept constant.
throughout the entire simulation, as if the annulus was akinetic. This annular shape was maintained in successive versions of the model, which were applied to the structural analysis of clinical scenarios (Reimink et al. 1995, 1996; Kunzelman et al. 1997, 1998a,b; Cochran & Kunzelman 1998), as well as in the new-generation fluid–structure interaction model recently developed by the same research group (Einstein et al. 2005a,b). The annulus was still assumed to be flat and akinetic. A similar annular profile was adopted by Dal Pan et al. (2005), who also hypothesized a straight anterior tract of the annulus smoothly connected to an elliptical posterior tract. Annular planarity and the absence of contraction also characterize the model proposed by Prot et al. (2007) and our first-generation model (Votta et al. 2002), where a circular annulus is adopted. A different shape was used in a computational study that has recently been proposed by our research group (Votta et al. 2007). In this case, the physiological profile of the annulus was idealized as the union of two semi-ellipses, which represented the anterior and posterior annuli, with a shared major axis, which represented the valve CC dimension. The overall profile was still planar and fixed in time.

The only study that proposed a totally different approach to the modelling of the annulus is the one proposed by Lim et al. (2005). In their study, the authors tracked through time the position of 12 ultrasound crystals implanted

<table>
<thead>
<tr>
<th>model</th>
<th>annular profile</th>
<th>leaflet profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kunzelman and Einstein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lim</td>
<td>real profile</td>
<td></td>
</tr>
<tr>
<td>Dal Pan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Votta</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Qualitative sketches of the profiles of the annulus (centre) and the free margin of the leaflets (right) adopted in the computational studies from the literature. The leaflet free margin appears as if the leaflets were excised and positioned on a planar surface.
on the annulus of a single sheep. Interpolating the positions of the markers at different time points, they were able to define a realistic saddle-shaped, non-symmetric annular profile, accounting also for its contraction through the cardiac cycle.

(ii) The leaflets

The second fundamental valvular substructure consists of the two leaflets, named anterior and posterior, which are distinct from a functional point of view although they form a single membranous structure inserted onto the annulus (figure 1). The first one, consisting of a single wide cusp, is inserted on a shorter tract of the annulus but is more extended in the annulus-to-free edge direction. The second one, having three cusps, is inserted on a longer tract of the annulus but is shorter in the annulus-to-free edge direction. Both leaflets have a non-constant thickness, being thicker in the annular and commissural regions and thinner in the belly region. The extent and morphology of the leaflets were quantitatively characterized by experimental measurements on fresh human and porcine valves, the two populations having been proved to be not statistically different (Kunzelman et al. 1994). Despite the availability of precise morphological data, the leaflet profile has been reproduced in very different ways in the various computational models, as sketched on the r.h.s. of figure 2. The simplest approach to the geometrical modelling of mitral leaflets was adopted by Lim et al. (2005), who described them as a single membrane, with a constant 1.26 mm thickness, which, in the open valve configuration, lies on a nearly conical surface that originates from the annulus profile and whose free margin does not have any cusps. Thus, the local morphological details that characterize the leaflets are neglected. In all of the other models the anterior and posterior leaflets are described as two different entities, each one with its own geometrical features. In the model proposed by Prot et al. (2007), as well as in those developed by Dal Pan and colleagues and by Kunzelman’s research group (Kunzelman et al. 1993a; Einstein et al. 2005a), each leaflet is defined as a single cusp. However, these models differ in some details: the initial position of the leaflets, their thickness and the description of their commissural region. In Prot’s model, the valve in its initial condition is totally open, the leaflets, whose thickness is assumed to be uniform and equal to 1 mm, are inserted on completely opposite sides of the annulus, so that the commissural region is not modelled. In Dal Pan’s model, the valve in its unloaded configuration is assumed to be almost closed, the leaflets being separated by a small gap. The commissures are modelled as a pair of hinges, where the free edges of the leaflets converge, rather than as an actual part of the leaflets. In Kunzelman’s model, the valve in its initial condition is not totally open and the leaflets form an entire membranous structure, which includes the two commissural regions. Moreover, thickness in the model varies depending on the region of the leaflets. A different solution was adopted in the models that we developed in the past, where the valve was assumed to be initially totally open, i.e. the leaflets were assumed to be laying on a cylindrical surface whose generatrix was the annulus. Moreover, the three cusps usually observable in the posterior leaflet were explicitly accounted for and a constant thickness of 0.8 mm was assumed.
(iii) **Chordae tendineae and PMs**

The last mitral structures to be considered are the chordae tendineae and PMs, which are often referred to as the subvalvular apparatus. The chordae tendineae are branched fibrous strings that connect the leaflets to two PMs, which protrude from the left ventricular wall and are named anterolateral and posteromedial (figure 1). The chordae tendineae are commonly classified as marginal, basal and strut, according to the respective insertion zone on the leaflets; these are, respectively, the free margin of the leaflets, the annular region of the posterior leaflet and the belly of the anterior one. As demonstrated by published experimental studies, different chordae types have different functions. Marginal chordae, which are stiffer and thinner, bear the main part of the pressure loads acting on the valve, while basal and strut chordae regulate the dynamics of valve closure (Obadia *et al.*, 1997; Timek *et al.*, 2001; Goetz *et al.*, 2003). The PMs consist of one or more conical tips, from where chordae depart, which originate from a main almost globular core. These two muscles move and contract synergically with the ventricular myocardium during the systolic phase, in order to stretch the chordae tendineae and thus prevent mitral leaflets from prolapsing into the atrium.

As far as the chordae tendineae are concerned, the most common simplifications consist in neglecting their branched structures and in accounting only for the presence of marginal chordae, which, according to experimental findings, bear the major portion of the pressure load that closes the valve during ventricular systole. These assumptions are present in the first-generation structural model by Kunzelman’s research group (*Kunzelman et al.* 1993a), in the studies we have performed (*Votta et al.* 2002, 2007; Maisano *et al.* 2005), in the one by Prot *et al.* (2007) and in the model adopted by Dal Pan *et al.* (2005), who also verified that the action of marginal chordae can be implicitly accounted for by imposing proper kinematical boundary conditions on the leaflets’ free margin. As for other modelling aspects, the most sophisticated approach was adopted by Einstein *et al.* (2005a, b), who accounted for the presence of all types of chordae, marginal, basal and strut, as well as for their branched insertions into the leaflets.

As far as the PMs are concerned, they are never modelled as anatomical entities with finite dimensions and physical properties. Instead, their tips are usually included into the model as the origins of the chordae tendineae; their movement can be imposed to simulate the effect of PM contraction during the cardiac cycle. The only study that accurately defined the position and the movement of the PM tips is the one by Lim and colleagues (*Lim et al.* 2005), who used animal *in vivo* data also to implement this aspect of the model. PM contraction was also modelled by Kunzelman and colleagues in their second-generation structural model, but in a more idealized fashion; their pulling action was simulated by displacing them 1 mm away from the valve orifice, towards the ventricular apex. In all of the other models herein discussed, the initial position of the PMs is set following geometrical criteria that, although rational and consistent, provide an idealized description. Moreover, their time-dependent movement is neglected.

(b) **Modelling of mechanical response of tissues**

The tissues of the mitral valve substructures are soft and hydrated. Their stress–strain response is the macroscopic result of their microscopic structure. Usually the annulus and the PMs, although being proper anatomical entities with
their own mechanical properties, are treated simply as the boundary between the mitral valve and the surrounding ventricular wall and are subject to boundary conditions. For this reason, the physical properties of these substructures are normally neglected. On the other hand, the description of the physical properties of the mitral leaflets and chordae tendineae has always been considered a key aspect in mitral valve FE modelling.

(i) The leaflets

The tissue of the mitral leaflets might be described as a multilayer, fibre-reinforced material, whose main constituents are water, collagen, elastin and glycosaminoglycans (Kunzelman et al. 1993a). Among them, collagen and elastin play a pivotal role and determine the biomechanical behaviour of the leaflets’ tissue; collagen fibres, crimped when the tissue is unloaded, are preferentially oriented parallel to the annulus when the belly of the leaflets is considered, independently from the examined tissue layer (Kunzelman et al. 1993b; May-Newman & Yin 1995). Thus, the leaflets’ mechanical response is nonlinear, owing to the progressive uncoiling of collagen fibres during tissue tensile loading, and transversely isotropic, owing to the preferential orientation of the fibres. Moreover, the arrangement of collagen fibres embedded in the tissue is different in the anterior and posterior leaflets, resulting in a more extensible behaviour of the latter.

Currently, only two models include a realistic description of the leaflets’ stress–strain behaviour: the structural model by Prot et al. (2007) and the fluid–structure interaction model by Einstein et al. (2005a). In both cases, the stress–strain relationship is modelled by means of a strain energy function $\psi$, in accordance with the theory of hyperelasticity. In general, $\psi$ is a function of the components of the strain tensor, and its derivatives allow the calculation of the corresponding component of the stress tensor.

Prot et al. (2007) adopted two functional forms of $\psi$. The first one was initially proposed by May-Newman & Yin (1995) and is written as

$$\psi(I_1, I_4) = c_0 \left[ \exp \left( c_1 (I_1 - 3)^2 + c_2 (\sqrt{I_4} - 1)^4 \right) - 1 \right],$$

where $c_i$, $i=0,1,2$, are the material constitutive parameters; $I_1$ is the first invariant of the right Cauchy–Green strain tensor $\mathbf{C}$; and $I_4$ is its fourth invariant, defined as $I_4 = \mathbf{a}_0 \cdot \mathbf{C} \mathbf{a}_0$, $\mathbf{a}_0$ being the unit vector that identifies the collagen fibres’ direction within the leaflet tissue in its reference configuration. The quantity $(\sqrt{I_4} - 1)^4$ accounts for the collagen fibres’ response to traction and is considered only when $I_4 \geq 1$, i.e. when the collagen fibres are stretched. The second and alternative functional form is

$$\psi(I_1, I_4) = c_0 \left[ \exp (c_1 (I_1 - 3)^2 + c_2 (I_4 - 1)^2) - 1 \right],$$

where the parameters have the same meaning as in the previous strain energy function. Both functional forms allow one to realistically reproduce the stress–strain behaviour exhibited by mitral leaflets in experimental traction tests, and with the indicated set of constitutive parameters both of them guarantee, from a theoretical point of view, the mechanical stability of the modelled material, i.e. they guarantee that the tangent stiffness matrix of the material is...
positive definite. However, according to the authors, the computation of the second form was more cost effective once it had been implemented by means of a UMAT user-defined material subroutine to be included into their model developed by means of the ABAQUS/STANDARD software.

Einstein et al. (2005a) adopted a different strain energy function, based on the actual microstructure of the leaflet tissue, following the approach previously proposed by Billiar & Sacks (2000) to characterize the mechanical properties of aortic valve cusps. In this case, the second Piola–Kirchhoff stress tensor $S$ is calculated according to the following mathematical relationships:

$$S = pJC^{-1} + 2J^{-2/3} \text{DEV} \left[ \frac{\partial \tilde{W}}{\partial C} \right],$$

$$\frac{\partial \tilde{W}}{\partial C} = aI + \int_{-\pi/2}^{\pi/2} S_t R(\theta) A \otimes A d\theta,$$

$$S_t = \alpha \left\{ \exp \left[ \frac{\beta}{2} A(\vartheta) CA(\vartheta) - 1 \right] - 1 \right\},$$

$$R(\vartheta) = \frac{1}{\sigma \sqrt{2\pi}} \exp \left[ - \frac{(\vartheta - \mu)^2}{2\sigma^2} \right],$$

where $C$ is the right Cauchy–Green strain tensor; $J$ is its Jacobian; $p$ is the hydrostatic pressure; $S_t$ is a function that describes collagen stress–strain behaviour; $I$ is the identity matrix; $A$ is the orientation tensor; $\alpha$ and $\beta$ are the material’s constitutive parameters; and $R(\theta)$ accounts for the statistical normal distribution of fibres, which are rotated, as an average, by an angle $\mu$ with respect to a fixed direction in space, $\sigma$ being the standard deviation of their orientation.

All of the other models available in the literature adopt simpler approaches, neglecting different aspects of the leaflets’ mechanical properties depending on the particular model. Dal Pan and colleagues neglected leaflet anisotropy and differences between the two mitral leaflets. However, in order to assess the impact of neglecting nonlinearities also, they compared two different constitutive models: a linear one, characterized by a Young’s modulus of 4 MPa and a Poisson’s ratio of 0.45 to model the leaflets’ nearly uncompressible behaviour, and a hyperelastic one, consisting of a fifth-order reduced polynomial form whose constitutive parameters were set in accordance with experimental results (Dal Pan et al. 2005). The comparison pointed out that accounting for the nonlinear response of the leaflets leads to much lower values in the estimation of the stresses in the leaflets. On the other hand, in the structural models developed by Kunzelman’s research group (Kunzelman et al. 1993a and following) and by our research group (Votta et al. 2002, 2007; Maisano et al. 2005) the leaflets’ nonlinear response was neglected and their anisotropy was accounted for. In both cases, a Poisson’s ratio of 0.488 was assumed to model the nearly incompressible behaviour of the tissue, the Young’s modulus of the anterior leaflet was assumed to be equal to 6.23 and 2.08 MPa in the directions parallel and perpendicular to the annulus, respectively, and the corresponding values set for the posterior leaflet were 2.35 and 1.88 MPa. All values resembled the tangent elastic modulus exhibited by mitral leaflets for large strains, when all the collagen fibres within
the tissue are recruited. The simplest modelling of the leaflets’ mechanical response was used by Lim et al. (2005), who neglected differences between the two leaflets and assumed them to be of linear and isotropic material, with a Young’s modulus of 0.8 MPa, this value being particularly low with respect to the others adopted in the literature, and a Poisson’s ratio of 0.45.

(ii) Chordae tendineae

The essential framework of the chordae tendineae is constituted by a central core of crimped collagen fibres covered by elastic fibres and both are enveloped by endothelium (Millington-Sanders et al. 1998). This microstructure provides the mechanical response that is typical of collagenous tissues. This response is nonlinear and is characterized by a relatively low Young’s modulus at small strains and by a high Young’s modulus at large strains, with a transition region at intermediate strain values. From a mathematical point of view, hyperelasticity is a suitable theory to describe this behaviour and was adopted by Einstein, Prot and us (Einstein et al. 2005a; Prot et al. 2007; Votta et al. 2007). In the first-generation structural model by Kunzelman’s research group (Kunzelman et al. 1993a), as well as in the one by Lim et al. (2005), a simpler linear elastic stress–strain response was modelled. However, while in the first case a Young’s modulus of 40 and 22 MPa was adopted for marginal and basal or strut chordae, in the second case a stiffer behaviour was hypothesized, with a Young’s modulus of 132 MPa. The simplest modelling solution was adopted by Dal Pan et al. (2005), who described the chordae tendineae as inextensible, i.e. rigid.

Moreover, since the chordae are structured as strings, they resist only traction loads and yield to compressive ones. To account for this feature, Einstein (Einstein et al. 2005a) and Lim (Lim et al. 2005) used traction-only elements available in the code that they adopted to implement their respective models. A different solution has been adopted in our most recent model (Votta et al. 2007), where each chorda was discretized into several elements, thus resulting in a structure that immediately yields to compressive loads.

(c) Loading conditions

Lim et al. (2005) simulated mitral function throughout the entire cardiac cycle. Thus, in order to account for the effects of the transvalvular pressure drop acting on the leaflets, they applied the real atrial and ventricular time-dependent pressures on the corresponding sides of the leaflets. All of the other models cited so far focused their analysis on mitral valve closure from end diastole to the systolic peak. In the structural models, leaflets are loaded directly by a time-dependent pressure load, usually according to idealized pressure curves, while in the case of Einstein’s fluid–structure interaction model pressure on the leaflets is a consequence of the fluid dynamics within the fluid domain, thus being more realistically modelled.

(d) Valve–blood interaction

The fluid–structure interaction between mitral leaflets and the surrounding blood was taken into account by Einstein et al. (2005a) and Watton et al. (2007, 2008). The two groups modelled the fluid–structure coupling through different algorithms:
an arbitrary Lagrangian–Eulerian formulation in the first case, and a properly modified immersed boundary method in the second one. Both groups immersed the modelled valve, a native and a bioprosthetic one, into a regular fluid domain: hexahedral in the first case and cylindrical in the second one. Besides, Watton and colleagues adopted the mentioned geometry in order to reproduce in vitro conditions to be used as an experimental counterpart of the study.

3. A possible new modelling strategy

The overview of the approaches adopted to model the mitral valve shows that none of the cited research groups has been able to realistically model all of the key aspects of mitral function, not even in the most sophisticated study (Einstein et al. 2005a, b). The latter describes accurately the morphology of the leaflets and chordae tendineae, accounts for the nonlinear and anisotropic mechanical response of tissues and includes the fluid–structure interaction between the valve and the surrounding blood. However, it accounts neither for the real annular profile nor for its natural dynamics during the simulated period of the cardiac cycle, i.e. in the time-frame from end diastole to the systolic peak. Moreover, it does not simulate the movement of the PM tips. Owing to these limitations, the model is a feasible tool to gain insight into several aspects of normal mitral function and into the effects of abnormal tissue alterations, but it would be difficult to use it to assess the effects of some important surgical repair techniques, such as annuloplasty procedures.

In the present work, we present a pilot study, in which we tested a novel modelling approach. We developed a new structural FE model that takes into account all of the main valvular substructures, describes the mechanical properties of tissues by means of sophisticated constitutive formulations and comprises an accurate description of the time-dependent annular profile and PM positions, based on four-dimensional (three-dimensional volume during time) ultrasound data from human subjects. Thus, when compared with the fluid–structure interaction model developed by Kunzelman’s research group (Einstein et al. 2005a, b), the model herein proposed neglects a key aspect, i.e. fluid–structure interaction, but merges for the first time a realistic description of two important features: the mechanical response of tissues and the dynamics of the annulus and PMs, based on non-invasively acquired in vivo data. This choice was driven by the long-term goal of using the developed approach, after mandatory validation and improvements, for the analysis of the effects of annuloplasty procedures.

As a first preliminary benchmark to test the modelling strategy, the closure of a healthy mitral valve, from end diastole to the systolic peak, was simulated. Moreover, an auxiliary simulation was performed with the same model, but with fixed annulus and PMs. The aim of this second simulation was to have a comparison for the first one, in order to understand if and how dynamic boundary conditions affect the mechanical response of the valve. FE simulations were run using the ABAQUS/EXPLICIT commercial software v. 6.7-1 (SIMULIA).

(a) Reconstruction of the initial valve geometry from ultrasound data

The end-diastole valve configuration was chosen as the initial unloaded one, since, at this point in time, the transvalvular pressure drop acting on the leaflets is almost zero. The reconstruction of the valve geometry, depicted in figure 3a,
was performed through a semi-automatic procedure consisting of three consecutive steps. These correspond to the reconstruction of (i) the annulus and PMs, (ii) the leaflets, and (iii) the chordae tendineae.

(i) **Annulus and PMs**

Transthoracic real-time three-dimensional echocardiography (RT3DE, Philips) was performed on a healthy subject. The acquired data, characterized by a 31 Hz time frequency, were processed using new in-house custom software for frame-by-frame tracking of the mitral annulus on three-dimensional ultrasound datasets (Veronesi et al. 2008). In the end-diastole frame, which corresponded to the beginning of the QRS complex in the subject’s ECG, 36 points were manually selected on the annulus and a further point was selected on each visible tip of the two PMs, as exemplified in figure 3b,c. The 36 points on the annulus were interpolated three dimensionally with sixth-order Fourier functions to obtain a continuous annular profile. On the latter, the following reference points were identified: the commissures, defined as the line’s minima; the saddle horn,
identified as its maximum; the midpoint of the posterior annulus, identified as the point that divides the latter into two equal tracts; and the trigones, identified as the limits of the intertrigonal tract, whose length was calculated by assuming its proportions with the orifice area as in Timek et al. (2003). These points were identified since they are functional to the criterion adopted to identify the time-dependent position of PMs, described later. Finally, the continuous annular line was sampled into 404 uniformly distributed nodes, which represented the seeding for the leaflets’ discretized geometry. Given the end-diastolic annular perimeter (111.18 mm), the annular portion between two adjacent nodes was approximately 0.28 mm long.

As far as PMs are concerned, a single point was defined as the centre of mass of the corresponding selected tips, thus obtaining a single tip for each muscle.

(ii) Leaflets

The geometrical model for the leaflets was generated according to anatomical measurements reported by Kunzelman et al. (1994); it includes both leaflets, the posterior one having three cusps and the commissural regions. As in our previous models (Votta et al. 2002, 2007; Maisano et al. 2005), a sinusoidal function was used to describe the annulus-to-free margin extent of the leaflets. The function, whose coefficients were originally chosen to suit a valve with an 88 mm long annulus, was scaled consistently with the length of the reconstructed annulus.

Leaflets were originally generated by extruding the annulus along the z-axis, i.e. perpendicularly to the annular plane, and then tilting at their insertion on the annulus in order to reproduce their end-diastole position as provided by echocardiographic data (figure 3d); for the particular simulated subject, the anterior leaflet was tilted by 8.3° with respect to a plane parallel to the z-axis, while the posterior one was tilted by 5.3°. The anterior and posterior leaflets were assumed to be 1.32 mm and 1.26 mm thick, respectively, and were discretized by means of 48 480 three-node shell elements with reduced integration.

(iii) Chordae

Fifty-eight marginal and two strut chordae were included in the model, while basal chordae were neglected. Chordae were modelled as straight strings without branches, originating from the two PMs. For this reason, the amount of modelled chordae resembled that of chordae insertions into the leaflets. A cross-section of 0.4 and 2.05 mm² was assumed for marginal and strut chordae, respectively.

(b) Reconstruction of kinematical boundary conditions from ultrasound data

The 36 points selected on the annulus at end diastole were automatically tracked throughout the cardiac cycle, so that their positions in time were available. As done for the coordinates obtained at end diastole, the coordinates referred to every point in time were translated and rotated in order to be expressed in a proper cylindrical coordinate system. They were then interpolated and sampled in 404 uniformly distributed nodes, whose time-dependent positions were used to calculate the corresponding time-dependent displacements to be used as kinematical boundary conditions within the simulation. The displacement...
calculation was carried out removing those contributions whose only consequence consisted in rigid motions of the entire valvular apparatus. The reconstructed continuous annular profile throughout the cardiac cycle is depicted in figure 4a.

The PM positions through time, and consequently their displacement through time, were not available; owing to the four chambers view adopted in the echocardiographic acquisition, it was not possible to track them automatically. Thus, once their position at end diastole was known, a geometrical criterion was adopted to estimate their position at the following time points. On the basis of the experimental observations of Dagum et al. (2000), at end diastole their distances from the trigones, the commissures and the midpoint of the posterior annulus were calculated. At every point in time the position of the PMs was looked for as the one that preserved the calculated distances. As a result of this procedure, the time-dependent positions depicted in figure 4b were obtained.

(c) Mechanical properties of tissues

The stress–strain response of the leaflets was modelled as elastic, nonlinear, transversely isotropic and isochoric. To this end, we adopted the strain energy function suggested by Prot et al. (2007), whose polyconvexity and thermodynamic stability are guaranteed. The strain energy as a function of the strain tensor is hence defined as

$$\psi(I_1, I_4) = c_0[\exp(c_1(I_1 - 3)^2 + c_2(I_4 - 1)^2) - 1],$$

where $c_i$, $i=0,1,2$, are the material constitutive parameters and are equal to 0.052, 4.63 and 22.6 kPa and 0.171, 5.28 and 6.46 kPa for the anterior and posterior leaflets, respectively; $I_1$ is the first invariant of the right Cauchy–Green strain tensor; and $I_4$ is its fourth invariant, defined as $I_4 = a_0 \cdot C a_0$, $a_0$ being the unit vector that identifies the collagen fibres’ direction within the leaflet tissue in its unloaded configuration. The quantity $(I_4 - 1)^2$ accounts for the collagen fibres’ response to traction and is considered only when $I_4 \geq 1$, i.e. when the collagen fibres are stretched.

The reported strain energy function was included into the FE model via a VUMAT subroutine implemented in FORTRAN 90 and interfaced with the explicit solver used in the simulation.

Chordae tendineae mechanical response was described as elastic, nonlinear and isotropic by means of a second-order polynomial strain energy function, which is available in the hyperelastic materials library within the ABAQUS software. The constitutive coefficients to be used in the characterization of marginal and strut chordae response were calculated by interpolating experimental data from the literature (Kunzelman & Cochran 1990).

(d) External loads

The pressure drop acting on mitral leaflets was modelled as a pressure load applied to the leaflets’ ventricular surface. The load increased up to a systolic peak value of 120 mm Hg, with a time dependence already adopted by other authors (Prot et al. 2007). The time-scale of the simulated event was scaled: in vivo it lasts for approximately 0.15 s, while in the simulation the systolic peak was reached in 1 s. This choice allowed extremely abrupt contact phenomena to be avoided and convergence to be obtained more easily.
Contact interactions

Contact between the leaflets was accounted for by means of the general contact algorithm available in ABAQUS. As in our most recent FE study (Votta et al. 2007), a friction coefficient equal to 0.05 was assumed to describe the leaflets’ interaction tangentially to their contact surface. Penalty contact was used to describe the leaflets’ mechanical interaction in the direction normal to their contact surface.

Figure 4. (a) Time-dependent continuous annular profile, as reconstructed by interpolation from ultrasound data. The end-diastolic profile is depicted in light grey and the subsequent configurations are depicted in dark grey; (b) time-dependent position of PMs. SH, saddle horn; P, papillary muscle. The numbers on the axes represent distances in mm.

(e) Contact interactions

Contact between the leaflets was accounted for by means of the general contact algorithm available in ABAQUS. As in our most recent FE study (Votta et al. 2007), a friction coefficient equal to 0.05 was assumed to describe the leaflets’ interaction tangentially to their contact surface. Penalty contact was used to describe the leaflets’ mechanical interaction in the direction normal to their contact surface.

Phil. Trans. R. Soc. A (2008)
Preliminary simulation results

(i) Valve closure dynamics

Deformation and coaptation of the leaflets during valve closure for the model with dynamic annulus and PMs are depicted in figure 5, where the atrial view of the valve is depicted in six sequential frames from end diastole to the systolic peak. Even from these qualitative pictures, three outcomes are evident. The first one consists in the change in annular profile from frame to frame, which is visible even in an atrial view. The second one regards the asymmetry of the deformed configurations of the valve; the two lateral cusps of the posterior leaflet (normally called P1 and P3 in clinical practice) are differently deformed. The third outcome relies on the fact that coaptation occurs at very low values of transvalvular pressure drop (when a 16 mm Hg value is reached, the valve orifice is already occluded) and that after the transvalvular pressure drop reaches 68 mm Hg the valve undergoes only minor further deformations, which are mostly associated with the motion of the annulus and PMs and the development of deeper wrinkles at the commissures and paracommissures. This outcome is consistent with the leaflets’ mechanical response; owing to their nonlinear behaviour they undergo large deformations and thus coapt even for a small pressure applied to the leaflets. Once a threshold strain value is reached (approx. 0.20), which corresponds to the complete recruitment of the collagen fibres embedded in their tissue, the leaflets stiffen and a further increase in the applied pressure does not cause major further deformations.

(ii) Leaflet stresses

The distribution of maximum principal stresses acting on the leaflets for increasing values of the transvalvular pressure drop is reported in figure 6 for the simulation with dynamic annulus and PMs and for the one with fixed boundaries.
Figure 6. Maximum principal stresses acting on the leaflets during valve closure for increasing values of the transmitral pressure drop. (a) Simulation with dynamic annulus and PMs and (b) simulation with fixed annulus and PMs. (i) $p = 3$ mm Hg, (ii) $p = 15$ mm Hg, (iii) $p = 98$ mm Hg, (iv) $p = 110$ mm Hg, (v) $p = 120$ mm Hg.
As far as the first model is concerned, the comparison of the contour plots at different pressure values provides two main indications. First, as reasonably expected, the most stressed regions are those close to chordae insertions, either marginal or strut ones. This general pattern is observed in both the anterolateral and the posteromedial halves of the leaflet; however, in the latter, peak stress areas are more extended. Second, while the valve geometrical configuration does not change greatly after the leaflets’ coapation, the peak stress values follow a different trend. Consistent with stiffening of the leaflets at large strains, stresses increase more and more rapidly as the pressure load on the leaflets increases. In particular, for a transvalvular pressure drop of 80 mm Hg ($t=0.025$ s), the stress peak value is approximately 800 kPa and occurred at the insertion of strut chordae. The belly of the anterior leaflet undergoes stresses that range from 60 to 400 kPa. The posterior leaflet experiences a lower stress value, of the order of 60 kPa, the central cusp being the most stressed one. When the systolic peak pressure (120 mm Hg) is applied to the leaflet, the peak stress reaches 1200 kPa. Stresses acting on the belly of the anterior leaflet range from 130 to 540 kPa, while those acting on the posterior one are, again, lower (60–270 kPa).

Stress contour maps computed by the simulation with fixed boundaries are not significantly different from those obtained with dynamic annulus and PMs when the leaflets experience low pressure loads. However, after the leaflets’ coapation, the stress peak values close to strut chordae insertions are lower (equal to 1000 kPa at the systolic peak) and do not act in the region between strut chordae insertions. The stresses acting on the belly of the anterior leaflet are in the same range as those calculated with dynamic boundaries, but have a slightly different pattern. The stresses acting on the posterior leaflets resemble those calculated with dynamic boundaries.

The time course of the leaflets’ maximum principal stresses averaged on six longitudinal sections of interest of the leaflets is plotted in figure 7 for the two simulations performed. In both cases, comparison of the stresses referred to the sections T1 and T2, which are next to the trigones, highlights the asymmetry of the stress distribution acting on the anterior leaflet. Moreover, consistent with the above-mentioned results reported in figure 6, when the simulation with dynamic annulus and PMs is considered, stresses in the midsection of the anterior leaflet are equal to 313 kPa at the systolic peak, 67 per cent higher when compared with ones obtained with fixed boundaries.

(iii) Chordae tensions

Chordae tensions at the systolic peak were calculated for both simulations. Marginal chordae experience tensions ranging from 0.11 to 0.28 N when motion of annulus and PMs is simulated and from 0.08 to 0.25 N when annulus and PMs are kept fixed. However, a peak value of 0.41 N was detected in the chordae inserted in the paraacommissures in both cases. Strut chordae response reflected the model’s asymmetry; when dynamic annulus and PMs are simulated, the chord originating from the anterolateral PM bears a 1.31 N load, while the one originating from the posteromedial PM bears a 2.26 N tension. On the other hand, when motion of the annulus and PMs is prevented, such asymmetry becomes much less evident, the two tensions becoming 1.14 and 1.42 N, respectively.
Figure 7. Time course of average stresses on six sections of the valve leaflets. (a) Sections of interest: MA, mid-anterior section; P1, P2 and P3, midsections of the posterior cusps; T1 and T2, sections close to the trigones. Plots for (b) dynamic annulus and PMs and (c) fixed annulus and PMs: diamonds, MA; filled circles, P1; squares, P2; open circles, P3; open triangles, T1; filled triangles, T2.

Phil. Trans. R. Soc. A (2008)
(iv) **PM reaction forces**

Reaction forces at the two nodes representing the PMs were calculated for both simulations (figure 8). Their evolution through time resembles one of the pressures applied to the leaflets; a rather steep increase occurs in the early part of valve closure, while in its final part a plateau is reached. At the systolic peak, the final and maximum force values for the anterolateral PM and the posteromedial PM are 5.49 and 6.59 N, respectively, when dynamic annulus and PMs are considered, while these are 5.30 and 6.32 N when annulus and PMs are kept fixed. After 260 ms from end diastole, when an 80 mm Hg pressure is applied to the leaflets, these values are 4.03 and 3.45 N for the first simulation and 3.46 and 3.68 N for the second one.

(g) **Comments**

We presented here a structural FE model of the mitral valve that combines a detailed description of valvular geometry and the tissues' mechanical response with the modelling of real annular contraction and PM movement on the basis of in vivo data acquired from a healthy human subject. To the authors' knowledge, despite the preliminary character of the study, this is the first time that these features have been included in a single FE model and that real annular dynamics based on in vivo data acquired non-invasively have been reproduced. Moreover, we tried to assess the effect of simulating annulus and PM dynamics by comparison with an auxiliary simulation, performed on the same model but with fixed annulus and PM.

Even though the model may undergo future refinements, as discussed in more detail in §3h, and even if it needs further testing, some of the indications it provided may be discussed.

In particular, the calculated stress pattern, when compared with the one reported by Einstein et al. (2005a), is somewhat similar when similar pressure loads are considered. However, the stress values are higher here, the main difference being noted in the case of the peak values. These differences may be due to several factors. Possibly, one of them is the different initial valve geometry. In the present study, the two leaflets are more distant from each other; in order to coapt, they undergo larger deformations and, thus, larger stresses. Also, this difference may be due to the inclusion of annulus and PM motion into the model, as suggested by the fact that when these are kept fixed (auxiliary simulation) the mentioned peak stresses are noticeably lower. A further reason is probably the different modelling of the chordal apparatus: Einstein and colleagues also included basal chordae in their model, and this morphological detail may have allowed a different load transfer from chordae tendineae to mitral leaflets to be obtained.

As far as chordae tendineae tension is concerned, the calculated values are comparable with the ones gathered in vitro, on six human mitral valves, by Jimenez et al. (2005), who measured 1.11 ± 0.57, 0.18 ± 0.16 and 0.08 ± 0.11 N loads on the strut, anterior marginal and posterior marginal chordae, respectively.

With reference to the PM reaction forces, the values of 4.03 and 3.45 N for the anterolateral and posteromedial PMs, calculated for an 80 mm Hg pressure drop across the valve, are greater than the 2.5 N calculated by Einstein’s model and observed in previous in vitro studies (Hashim et al. 1997; Jensen et al. 2001). This discrepancy is not due to the simulated annulus and PM motion, because when these are prevented similar values (3.46 and 3.68 N) are obtained. A possible reason may be the different leaflet morphology, as modelled in the present study, with
The work presented herein is a pilot study aimed at testing a new modelling approach. Given its preliminary character, the study still suffers from some limitations. These demand attention in the interpretation of obtained data and highlight that the current version of the model has to be improved prior to being used for its long-term goal, i.e. the simulation of annuloplasty procedures.

(h) Current limitations and future developments

The work presented herein is a pilot study aimed at testing a new modelling approach. Given its preliminary character, the study still suffers from some limitations. These demand attention in the interpretation of obtained data and highlight that the current version of the model has to be improved prior to being used for its long-term goal, i.e. the simulation of annuloplasty procedures.
First, four aspects of the reconstruction of annular and PM dynamics need to be pointed out. The first one concerns the fact that the reported results were obtained by simulating the valve closure of a single healthy subject, whose annular motion did not fully resemble the experimental observations reported in the literature concerning annular motion. For instance, saddle-horn elevation during this time-frame was evident, consistent with the literature (Dagum et al. 2001; Gorman et al. 2004), but no significant reduction in septolateral dimension was observed, although it is well accepted that this occurs during annular contraction from diastole to systole (Ormiston et al. 1981; Fyrenius et al. 2001). Hence, before any conclusion of general validity can be drawn, the analysis has to be extended to datasets of more subjects in order to test the robustness of the modelling strategy and to gather data with an acceptable statistical significance. The second aspect concerns the use of kinematical boundary conditions to simulate annular contraction and motion of the tips of the PMs. This strategy allows assessment of their effect on valve leaflets and chordae, but does not provide any information about strains and stresses in the tissues and muscles surrounding the annulus and in the PMs, because the respective mechanical responses are not accounted for. The third aspect concerns the possible future use of the model in the simulation of annuloplasty procedures. The strategy adopted to simulate annular contraction displacement would allow only the effects of annuloplasty procedures performed with rigid devices to be predicted. In fact, in this case, the deformations of the device would be negligible and its profile could be imposed on the native annulus by means of a set of nodal displacements, as in Votta et al. (2007). On the contrary, in the case of annuloplasty procedures performed with flexible devices, it would not be possible to know a priori the time-dependent annular profile in the post-operative scenario. Hence, the model could be used only to analyse a posteriori the effects of the device’s implantation, including the motion of the corrected annulus on the basis of ultrasound data acquired after the surgical correction. Besides, as far as the modelling of annular contraction is concerned, an interesting improvement of the developed method would consist of replacing the current uniform sampling of the annular profile with the local discretization of the annular tracts between adjacent points selected on the ultrasound images. This possible solution would allow a better estimation of local stretches and shortenings of the annulus. The fourth and last aspect concerns the reconstruction of the time-dependent position of the PMs through a geometrical criterion, based on data from an animal model (Dagum et al. 2000). At the preliminary stage this strategy was considered satisfactory, owing to the availability of ultrasound data only for the end-diastolic configuration. However, a change in the image-acquisition protocol may be taken into consideration to extract PM movement directly from ultrasound data.

Second, the modelling of the chordae tendineae needs to be improved by adding basal chordae to the model and by accounting for the more realistic, branched structure of the single chorda. In the authors’ opinion, this future improvement may modify the calculated stress pattern of the leaflets, since chordae tension would be transmitted to the leaflets in different areas and, overall, in a more distributed fashion.

Third, constant thickness within each leaflet was assumed. This limitation could be overcome by using, for instance, the thickness pattern reported by Kunzelman in a recent publication concerning her research group’s FSI model (Kunzelman et al. 2007).
Fourth, the real time-scale of the simulated phenomenon was dilated. A better realism could be achieved by using a realistic timing and preserving the robustness of the simulation in alternative ways, such as reducing the time increment in the numerical solution of the problem.

Fifth, the model currently simulates only valve closure from end diastole to the systolic peak, hence suffering the same limitation that characterizes the majority of the models from the literature. The extension of the simulation to the entire cardiac cycle represents a mandatory and interesting future development of the model.

Sixth, the interaction between the valvular substructures, leaflets in particular, and the surrounding blood is not accounted for in the model, which is purely structural. This limitation prevents us from modelling the formation of vortices in the ventricle and quantifying their impact on valve closure and opening (Kheradvar & Gharib 2007).

References


Phil. Trans. R. Soc. A (2008)


