VPH2
Virtual Pathological Heart of the Virtual Physiological Human
Grant Agreement Number 224635

– Deliverable –

D1.8 – Scientific manuscripts about FPT for peer reviewed biomedical engineering international journals and abstracts to international conferences

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D1.8 – Scientific manuscripts about FPT for peer reviewed biomedical engineering international journals and abstracts to international conferences

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## 1. Abbreviations

Here a table summarizing the abbreviations used in the next sections and in the publications:

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<thead>
<tr>
<th>Abbreviation</th>
<th>Stands for</th>
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<tr>
<td>FAT</td>
<td>Functional Assessment Tool</td>
</tr>
<tr>
<td>FPT</td>
<td>Functional Predictive Tool</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>LV</td>
<td>Left Ventricular</td>
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<tr>
<td>LVD</td>
<td>Left Ventricular Disfunction</td>
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<td>MV</td>
<td>Mitral Valve</td>
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<tr>
<td>MA</td>
<td>Mitral Annulus</td>
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<tr>
<td>PM</td>
<td>Papillary Muscle</td>
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<tr>
<td>APM</td>
<td>Anterolateral Papillary Muscle</td>
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<tr>
<td>PPM</td>
<td>Posteromedial Papillary Muscle</td>
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<tr>
<td>ED</td>
<td>End Diastole (or Diastolic)</td>
</tr>
<tr>
<td>ES</td>
<td>End Systole (or Systolic)</td>
</tr>
<tr>
<td>PS</td>
<td>Peak Systole</td>
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<tr>
<td>HF</td>
<td>Heart Frequency</td>
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<tr>
<td>SV</td>
<td>Stroke Volume</td>
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<tr>
<td>FE</td>
<td>Finite Element</td>
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<tr>
<td>FEM</td>
<td>Finite Element Model</td>
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<tr>
<td>ECG</td>
<td>ElectroCardioGram</td>
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<tr>
<td>LAD</td>
<td>Late Gadolinium Enhancement</td>
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<tr>
<td>GAD</td>
<td>Gadolinium</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>LAD (coronary)</td>
<td>Left Anterior Descending</td>
</tr>
<tr>
<td>RCA</td>
<td>Right Coronary Artery</td>
</tr>
<tr>
<td>LCX</td>
<td>Left Circumflex (coronary)</td>
</tr>
<tr>
<td>RFA</td>
<td>Regional Fractional Area</td>
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<tr>
<td>RFAC</td>
<td>Regional Fractional Area Change</td>
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<tr>
<td>REDA</td>
<td>Regional End Diastolic Area</td>
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<tr>
<td>SSFP</td>
<td>Steady-State Free Precession</td>
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<tr>
<td>RT3DE</td>
<td>Real-Time 3-Dimensional</td>
</tr>
<tr>
<td>ECG</td>
<td>Echocardiography</td>
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<tr>
<td>FCM</td>
<td>Fuzzy-C-Mean</td>
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<td>DE</td>
<td>Delayed-Enhancement</td>
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2. Executive Summary

D1.8 describes the publishing activity performed in the last fourteen months to disseminate the results related to the development, implementation and use of the Functional Predictive Tool (FPT).

The document briefly summarizes the full papers that were under review or in the process of being submitted to peer reviewed journal in September 2010 (see deliverable D1.7), and that were published since then. Those manuscripts dealt with the Functional Assessment Tool (FAT), but the results therein reported are still relevant to the FPT-related activities because they are the basis of the development of the FPT module.

The document includes two full papers dealing with the FPT module. Namely these regard the finite element modelling of the MV and the prediction of LV function following revascularization procedures, respectively. These will be shortly submitted to peer reviewed international journals covering the areas of cardiology and clinical image processing.

The document also includes the abstracts accepted at international Conferences on the topic.
3. Introduction
The Functional Predictive Tool (FPT) consists of two sub-modules. The first one is based on the patient-specific finite element simulation of MV systolic function, and is aimed at providing medical doctors with a database of simulations representing MV biomechanics in pathological conditions and following different annuloplasty procedures. The second sub-module is focused on LV function and is aimed at allowing cardiologists and, more in general, medical doctors with a user-friendly and fast simulator, capable of predicting ex ante the post-operative LV global function following the surgical procedures usually performed to treat severe LV ischemic dysfunction: cardiac resynchronization with pacemakers or implantable cardioverter defibrillators (ICD), myocardial revascularization performed by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), ventricular resection and reinforcement through a patch, and surgical restoration of the mitral valve.

The activity related to FPT development and validation is part of WP5 and under the coordination of POLIMI. Along with POLIMI, CNR, Niguarda and BED were involved in the activity. In particular, CNR and Niguarda provided the necessary feedbacks for the progressive refinement of the mathematical models that represent the core of the FPT module, as well as for the improvement of the user interface of the module. Moreover, SCS contributed by translating FPT modules in WP6.

4. FPT within the VPH2 Platform and its relation to FAT
The FPT module is the natural complement to the FAT module within the VPH2 platform. Through the FAT module, the final user can quantitatively analyze MV and LV function from CMR acquisitions, and assess detailed features of MV and LV pathologies, if present. Through the FPT module, the final user can infer about the outcome of the surgical procedures he/she hypothesizes to use in the correction of the identified pathologies. The link between the FAT and FPT modules is particularly tight when these are applied to the LV: in this case, the segmentation and the computation of regional wall strains performed through FAT are the input data for the FPT prediction of post-operative LV function. This is the reason why a reasonably sound validation of FAT was necessary prior to refining the FPT LV sub-module, and work done to refine the FAT module is strictly related to the development of FPT.

5. The role of this task within the VPH2 Project
The objective of this task is to provide a detailed overview of the activities performed in the last year of the project to disseminate the results about FPT and its use in VPH2.

6. The role of this deliverable within the VPH2 Project
The role of the D1.8 deliverable in the project is to track the activities related to dissemination. According to the FP7 guidelines, the success of a project is strictly related to the capability to make the community aware of the obtained results. On the same time dissemination activities allow to monitor the project and its activity success, as well as the interest of the community in the results.
7. Publications

7.1. Completion of previously ongoing dissemination activity

D1.7 included the content of two full papers related to FAT, which had been submitted to peer reviewed international journals. Both manuscripts have been accepted and published as:


7.2. New and ongoing dissemination activity

Two full papers dealing with the FPT module have been prepared and are in the process of being submitted to peer reviewed international journals covering the areas of cardiology and clinical image processing. The content of the corresponding refined drafts is herein reported.

7.3. Estimation of in vivo normal mitral annular forces via finite element modelling: implications on the design of annuloplasty rings

Emiliano Votta1, Marco Stevanella1, Carlo Conti1, Raffaele Cicerone2, Elisabetta Rusconi2, Paolo Ferrazzi3, Alberto Redaelli1, Eugenio Quaini2

7.3.1. ABSTRACT

Background — Mitral valve (MV) annuloplasty consists in reshaping the MV native annulus through an artificial ring. It is performed in the vast majority of the surgical repair procedures performed to treat MV regurgitation. Several rings are available to clinicians, based on different design concepts, but none of them is optimal, i.e. capable of reshaping the annulus while preserving its physiologic-like complex dynamics. The search for the optimal ring design may benefit from the detailed knowledge of the tensions experienced by the annulus in vivo, which are currently unknown.

Methods and Results — Cardiac magnetic resonance (CMR) was performed on five adult male healthy humans; 18 long-axis cut-planes, evenly rotated (10°) about the axis passing through the center of the MV orifice, were acquired in 55 time-frames per cardiac cycle. The patient-specific telediastolic 3-D geometry of
the MVs was reconstructed from CMR images, and used to perform the finite element simulation of MVs closure from end-diastole to peak systole, accounting for realistic tissues mechanical properties and in vivo boundary conditions. MVs biomechanics was analyzed, with particular focus on time-dependent annular tensions. At peak systole, these were equal to $104.34 \pm 19.88$ N/m and $56.27 \pm 11.04$ N/m on the anterior and posterior annulus, respectively, and were negligible at the commissures. The analysis of tensions components showed that tensions do not act on the annulus only radially, and that the contribution of their axial component, perpendicular to the valvular plane, is even more relevant.

**Conclusions** — Completely novel data were obtained regarding in vivo MV annular tensions. These data may be highly relevant in the design of new annuloplasty rings, and to identify an optimal trade-off between geometrical constrain to be imposed to the annulus and need for the preservation of its dynamics.

### 7.3.2. INTRODUCTION

Physiological mitral valve (MV) function requires the dynamic and synergic action of the substructures composing the MV apparatus: mitral annulus (MA), leaflets, chordae tendineae and papillary muscles (PMs). During ventricular systole, the MA shrinks and bends, thus reducing the extent of the valvular orifice; simultaneously, PMs contract, tightening the chordae tendineae and driving correct leaflets coaptation and valvular continence, thus preventing blood backflow from the ventricle into the atrium. During ventricular diastole, the MA dilates and becomes more circular and planar, thus providing a larger area for the blood to flow from the atrium to the ventricle, while PMs relax and elongate, chordae tendineae become slack and leaflets open. In this dynamic process, the sphincteric action of the MA is clearly pivotal.

Several dysfunctions can alter the above described mechanism and lead to mitral regurgitation (MR). Primary (or organic) disease is mainly characterized by tissue degeneration. Secondary (or functional) MR is instead the result of an altered ventricular geometry, due to ischemia or dilated cardiomyopathy, which affects the MA and PMs, and hence the entire MV. Namely, the MA flattens and becomes partly or completely akinetic, while PMs are dislocated towards the ventricular apex and away from each other and can lose their contractility [Enriquez-Sarano et al., 2009].

MR often requires surgical intervention and it is preferentially treated through MV repair, when the valve is suitable for repair and appropriate surgical skill and expertise are available. MV repair preserves the patient’s native valve without a prosthesis, and therefore avoids the risk of chronic anticoagulation (except in patients in atrial fibrillation) or prosthetic valve failure late after surgery. Improved postoperative function is expected with repair, because the mitral apparatus is an integral part of the left ventricle (LV) that is essential for maintenance of its normal shape, volume, and function.

The latter involves several techniques, which are applied depending on the specific etiology of MR and the specific morphological and functional alterations characterizing the pre-operative scenario. However, in the vast majority of these procedures, annuloplasty is adopted [Gammie et al., 2009], i.e. a prosthetic ring is inserted on the native MA to either reshape it or to reduce its dimensions, to overcome the alterations in annular dimensions, shape or dynamics associated to the pathology. In particular, in case of functional and
ischemic MR restrictive annuloplasty has been recently adopted; the orifice area is reduced so to allow for valve continence despite the leaflets tethering associated to PMs dislocation.

Currently a variety of different prosthetic rings are available to surgeons, based on different rationales [Bothe et al., Eur J Cardiothorac Surg 2010, J Thorac Cardiovasc Surg 2011, J Thorac Cardiovasc Surg 2010]. Differences mainly regard:

- shape, since rings can be flat or three-dimensional as seen in a long-axis view, D-shaped or with a more complex contour as seen in a short-axis view;
- profile, i.e. the thickness of the ring, which can be low or high;
- completeness of the contour, so that complete and partial rings exist;
- stiffness, which can be very high, as in rigid rings, or low, as in flexible rings. In the first case, control on MA reshaping is achieved, but annular dynamics is abolished; in the second case, annular dynamics is at least partially preserved, but a fixed shape cannot be imposed to the MA [Bothe et al., Eur J Cardiothorac Surg 2010]. Recently, devices with regionally varying stiffness have been introduced to the market, with the aim to achieve an efficient compromise between the two more classical options.

Moreover, disease-specific designs are available to treat functional and ischemic MR [Votta et al., 2007; McCarthy et al., 2009; Bothe et al., J Thorac Cardiovasc Surg 2011]. As a result, surgeons in principle can choose the prosthetic device that best suits their specific needs, although the criteria driving this choice are currently merely qualitative. At the same time, in other cases very different rings are made available by different companies to tackle the same issue, suggesting that the current abundance of different technical solutions is at least partly due to the lack of a clear and recognized design rationale. The lack of a real design rationale may be one of the reasons for the still unsatisfactory clinical results of restrictive annuloplasty in the treatment of functional and ischemic MR, associated to a high rate of MR recurrence [McGee 2004, Gillinov 2009], which contributes to further LV negative remodelling and increased tethering [Hung 2004, Gelsomino 2008], and to the appearance of functional mitral stenosis [Magne 2009, Magne 2008]. These factors may explain why MV repair procedures are performed only on a restricted minority of the numerous patients with heart failure and functional MR.

Also, studies performed on acute animal models of ischemic MR cast several doubts on the effectiveness of rings that are specifically designed to treat ischemic MR [Bothe et al., Eur J Cardiothorac Surg 2010, J Thorac Cardiovasc Surg 2011, J Thorac Cardiovasc Surg 2010], thus suggesting that, even in case of disease-specific prosthetic rings, current design criteria lead to suboptimal results.

In this scenario, a new and completely different annuloplasty ring was recently proposed to treat functional and ischemic MR. Its key feature consisted in the use of a garter spring as core element of the ring. This technical solution aimed at making the device capable of storing elastic energy during ventricular diastole and to shorten during systole, thus promoting physiologic-like MA dynamics and sphincteric contraction. In principle, in this way it would be possible to restore MV continence not by constraining the valvular orifice within an undersized and rigid ring, but by enhancing its natural tendency to shrink during systole and by compensating for the lack of contractility associated to LV dysfunction. This hypothesis was tested by
implanting a prototype of the device in 10 healthy sheep, concluding that the device fulfilled a *sine qua non* pre-requisite, i.e. preserving MA dynamics and allowing area and perimeter changes when inserted on a physiological MA. However, the elastic constant of the garter spring within the prototype ring was set through an empirical approach, without the quantitative knowledge of the annular forces experienced *in vivo* [Ferrazzi et al., 2009]. This limitation provides the motivation for the present study, which aims at using patient-specific MV finite element modelling to quantitatively estimate *in vivo* systolic MA forces in humans from cardiac magnetic resonance (CMR) imaging. These data are currently not available; up to now, only *in vitro* data have been obtained regarding the forces acting on the native MA [Bhattacharya et al., 2010; He et al., 2009] and on flat and saddle-shaped annuloplasty rings [Jensen 2008]. However, despite the very sophisticated experimental set-ups adopted in those studies, those data may not be exhaustive, since the *in vitro* approach *per se* cannot account for the forces associated to the complex in vivo annular motion associated to myocardial tissue contraction. If properly computed, in vivo forces would complete the already available in vitro data, and would help the optimal design not only of a spring-like annuloplasty ring, but also of flexible, or partially flexible, ones.

### 7.3.3. MATERIALS AND METHODS

**Cohort of Analyzed Subjects and CMR Acquisition** - Five male adult subjects (age 38±48 years, weight 77±96 kg, height 169±180 cm) with no myocardial infarction or ischemia, and with no other pathology of the mitral apparatus, were enrolled for the study.

For each subject, CMR imaging was acquired following an already adopted protocol [Stevanella et al., 2011]. 18 evenly rotated (one every 10°) long-axis planes were considered, the rotation axis passing approximately through the MA centre of mass and being aligned with the LV long-axis. Time resolution was equal to 55 frames/cardiac cycle, in-plane-spatial resolution to 0.78 mm, and slice thickness to 8 mm. For each of the selected five subjects, MV time-dependent geometry was characterized by processing the CMR images, and its biomechanics was analyzed via finite element modeling from end-diastole (ED), when the MV is generally assumed unloaded to peak systole (PS), when the MV experiences the maximal pressure load [Kunzelman et al., 2007].

**Mitral Valves Geometrical Characterization from CMR** – The morphology of MV annulus and PMs was quantitatively characterized throughout the entire cardiac cycle. By means of in home software implemented in MATLAB (The MathWorks Inc., Natick, MA, United States), for every CMR frame and in each cut-plane of the CMR sequences, two points at the leaflets insertions on the MA and a point for each visible PM tip were manually selected (figure 1).

As regards the MA, for every frame, the three-dimensional coordinates of the corresponding points on each cut-plane were reconstructed from the position of the cut-plane with respect to the rotation axis. Owing to the shape of the MA, its profile was reconstructed by approximating the selected points with two 13th order Fourier functions \(r(\theta)\) and \(z(\theta)\), defined in a cylindrical reference frame, whose \(z\)-axis was the rotation axis set in the CMR acquisition [Votta et al., Phil Trans 2008, Stevanella et al., CVET 2011].

MA geometry was characterized in terms of (figure 1.A-C):
perimeter extent;
- 3-D and 2-D orifice area, the latter being the projection of the former on the MA least square plane;
- commissure-commissure (CC) diameter, where the commissures were identified as the two minima of the MA profile;
- septo-lateral (SL) diameter, defined as the distance between the saddle-horn, i.e. the maximum of the anterior portion of the annulus, and P2, i.e. the mid-point of the posterior portion of the annulus;
- height, i.e. peak to valley extent of the MA profile.

The time-points characterized by maximal and minimal MA area, respectively, were identified and variations of the above listed features were computed to check for the normal MA dynamics of the selected subjects.

Concerning the PMs, as for the MA the three-dimensional coordinates of the corresponding points reconstructed. For each PM, a point-cloud was hence obtained and its center of mass was considered representative of the PM tip’s position. PMs configuration was characterized in terms of (figure 1.A):

- mutual distance;
- distance from the MA center;
- angle between the two lines connecting each PM tip to the MA center.

Among the data gathered through the above described analysis, those from the frames between end-diastole (ED) and peak systole (PS) were considered to provide input data to the subsequent biomechanical finite element analysis. ED and PS were identified in the CMR sequences as the frame immediately preceding leaflets separation and the mid-frame of the systolic phase, respectively. In the ED frame only, on each cut-plane multiple points were manually selected on each leaflet profile. Their three-dimensional position was then reconstructed, as already described for the MA, and used to define leaflets annulus-to-free margin extent and position.

Mitral Valves 3-D Geometrical Modelling – As in [Stevanella et al., 2011] The complete and discretized 3D geometrical model of the MVs was obtained with reference to the end-diastolic frame CMR datasets. The end-diastolic configuration was assumed as the unloaded one in the subsequent finite element analyses, since at ED the trans-valvular pressure drop is approximately zero.

The MA, reconstructed through the above described procedure, was sampled to obtain the nodes to be used as seeding for the subsequent discretization of the MV leaflets geometry.

Leaflets free margin was defined through four cubic spline functions, each one corresponding to a cusp. The shape and location of each function was based on the CMR measurement of leaflets annulus-to-free margin extent in eight regions: the two commissures, the two paracommissures, and the point of maximum extent of each cusp. Leaflets free margin was then sampled as the annulus. The leaflets surface limited by the annulus and the free margin was discretized into a mapped mesh of linear triangular shell elements (ABAQUS S3 shell element type), with a characteristic in-plane dimension of about 0.15 mm. A regionally varying thickness distribution was assigned to the leaflets, consistently with the one proposed in
[Kunzelman et al., 2007], with a maximum thickness around the fibrous trigones (1.69 mm), an average value of 1.32 mm and 1.26 mm on the anterior and posterior leaflets, respectively.

The tip of the PMs were modelled as two circumferences of 3 mm radius, oriented parallel to the valvular plane, i.e. the MA least square plane, and centred, respectively, in the centre of mass of the points selected in the CMR images for each PM.

Chordae tendineae of three orders including marginal, second-order and strut chordae, were modelled and discretized my means of linear truss elements (ABAQUS T3D2 elements). Thirteen chordae originated from each PM, i.e. from as many points of the circumference used to model the PM tip. Each chorda was split into branches, whose number, site of insertion on the leaflets free margin and cross-sectional area were set consistently with the literature [Lam et al., 1970].

Tissues Mechanical Properties - All tissues were modelled as homogeneous (density 10.4 g/cm³ [Votta et al., 2007]), non-linear elastic materials, by means of proper hyperelastic strain energy potentials.

The potential proposed by May-Newman was used for the leaflets, in order to account for their transversely isotropic stress-strain behaviour, associated to the presence of collagen fibres preferentially oriented parallel to the MA within the tissue [May-Newman 1998]:

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

where \(I_1 = \text{tr}(C)\) and \(I_4 = a_0^T C a_0 = \lambda^4\), in which \(C = F F^T\) is the right Cauchy-Green tensor, \(a_0\) is the unit vector that defines the preferential direction of the fibers in the material in the reference configuration, and \(\lambda\) is the stretch of the fibers in the \(a_0\) direction. \(F\) is the deformation gradient tensor, defined as \(F = \frac{\partial x}{\partial X}\) (i.e. the derivative of the current position as regards to the reference position). The constitutive parameters were to \(c_0 = 0.399\) kPa, \(c_1 = 4.325\), \(c_2 = 1446.5\) for the anterior leaflet and \(c_0 = 0.414\) kPa, \(c_1 = 4.848\), \(c_2 = 305.4\) for the posterior leaflet.

Chordae tendineae response was described through hyperelastic models available in ABAQUS/Explicit. For second order chordae, a fifth order Ogden strain energy function was used, while for all the other chordal types a second order polynomial strain energy function was adopted. For each chordae type, constitutive parameters were defined by ABAQUS/CAE via interpolation of nominal stress and strain data from uniaxial tensile tests [Kunzelman et al., 1990], provided to ABAQUS/CAE as lookup tables. Constant cross-sectional area values of 0.40, 1.15 and 0.79 mm² were assigned to marginal, strut and basal chordae, respectively.

Boundary Conditions – The motion of MA and PMs was accounted for by means of time-dependent nodal displacement boundary conditions. These were set after ruling out the rigid motions of the MV, since rigid motions do not contribute to MV strains and stresses.

MA nodal displacements were computed as following: for every frame of the CMR datasets, the commissures were identified on the MA as its two minima, and then the anterior and posterior portions of the MA were sampled in the same number of uniformly distributed nodes, so that their time-dependent positions were known and used to compute the corresponding nodal displacements. Similarly, PMs
displacements were computed from the time-dependent position of the centre of mass of the point-cloud detected on the CMR datasets for every PM.

It might be worth noticing that when nodal displacement boundary conditions are applied the corresponding nodal reaction forces are computed by the solver in the numerical simulation.

Concomitantly, a uniform time-dependent pressure load, obtained from a standard Wigger's diagram, was applied to MV leaflets ventricular surface, so to model the effect of blood pressure. The pressure load was assumed equal to 0 mmHg at end-diastole and 120 mmHg at peak systole.

**Biomechanical Analysis** – based on simulations’ results, MVs biomechanics from ED to PS was characterized in terms of:

- leaflets closure dynamics, testing whether MV continence was achieved at proper trans-valvular pressure values;
- leaflets maximum principal stresses, i.e. the maximal normal stresses experienced by leaflets’ tissue at each point, at PS, when the maximum pressure loads the leaflets;
- time-dependent PMs forces, i.e. the reaction forces experienced by the nodes representing PMs’ tips as a consequence of the pressure load and of the boundary conditions;
- time-dependent MA forces, i.e. the reaction forces experienced by the nodes on the MA profile as a consequence of the pressure load and of the boundary conditions. Forces were further processed to compute MA linear tensions, i.e. forces per unit length. Owing to the geometry of the MA, its linear tensions were decomposed in three mutually perpendicular components in the same cylindrical reference frame used to describe the annular profile: radial, tangential and axial (figure 1, A-C).

### 7.3.4. RESULTS

**CMR Analysis: MA Morphology and Dynamics** – Over the five analyzed subjects, MA area normalized by the body surface area ranged from 5.1 to 6.8, consistently with the ranges of normality identified in [Sonne et al., 2009]. All of the five MVs shared a common MA dynamic behavior. MA 2-D area and length changed by about 18.7% and 8.6%, respectively, from diastole to systole (figure 1.D-E), consistently with in vivo findings on healthy humans and sheep [Flachskampf et al., 2000; Rausch et al., 2011]. Contextually, the MA underwent bending in all of the studied patients, as highlighted by the 55.6% increase in annular height (figure 1.G).

**Numerical Analyses: MVs closure Dynamics and Continence** – According to numerical simulations, the analysed MVs all closed with a similar dynamics, despite the morphological differences between them. They were all continent at PS, and reached a completely closed configuration already at low ventricular pressure values, respectively equal to 15, 18, 22, 28, and 22 mmHg, and consistent with previous in vivo measurements on ovine MVs [Timek, T., et al. 2000].

**Numerical Analyses: Leaflets Stresses** – All of the simulated MVs shared a common leaflets stress pattern. The analysis of maximum principal stresses showed higher values (≈600 kPa) in the annular region, next to
the fibrous trigones, and at the insertion of the two strut chordae. These features confirm previous numerical findings reported in [Stevanella 2011; Prot 2009].

**Numerical Analyses: PMs forces** – as in previous numerical and in vitro studies [Votta et al., 2008; Stevanella et al., 2011; Askov et al., 2011], PMs forces increased from ED to PS, reaching tension values equal to 5.32÷7.9 N and 5.68÷8.79 N for the antero-lateral and postero-medial PM, respectively. In all of the simulated MVs, the time-dependency of PMs forces resembled the one of the pressure load.

**Numerical Analyses: MA forces** – the regional distribution of the magnitude of MA forces at peak systole is depicted in figure 4 for the five simulated MVs. Despite the inter-subject variability, a common pattern was observed: greater values were computed on the anterior annulus, where peak values (0.05÷0.11N) were detected at the trigones. On the posterior annulus, the highest forces (0.03÷0.05N) were computed at the insertion of P2, i.e. the mid scallop of the posterior leaflet. At the commissures, annular forces were negligible.

As previously mentioned, MA linear tensions, i.e. forces/unit length, were computed by dividing the nodal reaction force values by the distance separating their points of application. These were decomposed in their radial, tangential and axial (i.e. perpendicular to the annular plane) components (figure 1.A-C). The value of these components, averaged over space, was calculated for the anterior and posterior annulus of every simulated MV (table 2). In general, for every component computed values were higher in the anterior annulus than in the posterior annulus; with only two exceptions, such difference was always greater than 50% and up to 220%. As a results, for every simulated MV the average magnitude of the computed tensions was greater by 76÷93% in the anterior annulus than in the posterior annulus.

Moreover, in the anterior annulus the main role was played by the axial component of MA tensions (76.68 ± 11.28 N/m, average ± standard deviation over the five simulated MVs), while the radial and tangential components, which were mutually comparable, were equal to 48.94 ± 22.24 N/m and 35.62 ± 14.95 N/m, respectively. Differently, in the posterior annulus the tangential component of MA tensions was by far the smallest one (13.12 ± 2.89 N/m), while the radial and axial component were mutually comparable and equal to 36.10 ± 15.38 N/m and 34.96 ± 9.40 N/m, respectively.

Furthermore, the time-evolution of these three components was assessed for each simulated MV in four regions: the intertrigonal tract, the two short tracts running from each trigone to the adjacent commissure, and the posterior annulus (figure 5). Differently from PMs tensions, MA forces did not always resemble the monotonically increasing time-course of the pressure load acting on the leaflets; in at least two subjects (mitrale3 and mitrale5), differences with respect to that trend were notable, in particular in the MA intertrigonal tract, i.e. where the highest loads were computed.

**7.3.5. DISCUSSION**

**Simulations reliability** - For the numerical simulations to be reasonably reliable, two minimum requirements had to be fulfilled: i) simulated systolic MVs dynamics and continence had to be consistent with previous experimental findings obtained for healthy MVs; ii) the computed biomechanical variables had to be in accordance with values reported in the literature for healthy MVs. The computed closure dynamics of all of
the five modeled MVs was fully consistent with the one previously obtained through numerical modeling [Stevanella et al., 2011; Votta et al., 2008; Prot et al., 2009] and observed experimentally [Timek et al., 2000]. Similarly, computed mechanical variables, namely leaflets stresses and PMs forces, were consistent with previous numerical and experimental findings [Stevanella et al., 2011; Votta et al., 2008; Askov et al., 2011]. Furthermore, an overall repeatability of the results was observed over the five modelled valves. Simulations were hence considered reliable.

**Novelty of the computed results** – As already mentioned, the current scientific literature includes several studies focused on MA dynamics, which provide insight into its complex *in vivo* changes in shape and dimensions from diastole to systole [Flachskampf et al., 2000], as well as into its regional strains throughout the cardiac cycle [Raush et al., 2011]. However, no studies report *in vivo* values of MA tensions; the only available experimental data on MA tensions are those obtained *in vitro* by He and Bhattacharia, who developed an elegant set-up to measure MA tensions acting in the radial direction on the anterior and posterior annulus, which were both fixed on a planar surface, by means of a system of strings and ad hoc force transducers [Bhattacharya et al., 2008]. By testing fourteen excised porcine MVs, they measured tensions of $53.86 \pm 14.98$ N/m and $36.29 \pm 8.89$ N/m on the anterior and posterior annulus, respectively. However, as highlighted by the authors, due to the inherent limitations of the *in vitro* approach, those values are due to the equilibrium between the pressure acting on the MV leaflets and the reaction forces at the annulus, and do not account for the effect of MA dynamics associated to the contraction of the surrounding myocardial tissue.

To our knowledge, this is the first study reporting *in vivo* MA regional forces and analyzing them in detail. With respect to the abovementioned *in vitro* findings, our computational results lead to very similar values of radial tension on the anterior and posterior annulus ($48.94 \pm 22.24$ N/m and $36.10 \pm 15.38$ N/m, respectively). However, the actual magnitude of MA tension in the two tracts is about twice as high ($104.34 \pm 19.88$ N/m and $56.27 \pm 11.04$ N/m, respectively), due to the presence of relevant tangential and axial components of the tension. Actually, the latter is the main component acting on the anterior annulus.

**Implications on the design of annuloplasty rings** – Reported MA tension values may provide a basis for the identification of a sound rationale in the design of new annuloplasty rings, possibly leading to prostheses capable of constraining the extent of the valvular orifice and of limiting the alterations to MA dynamics. Current technologies allow for the tuning of local tensile and bending stiffness of annuloplasty rings; such tuning could benefit from the availability of detailed regional MA tensions. Moreover, the local features of the ring may be further refined based on the information regarding the single components of MA tensions.

**ACKNOWLEDGEMENTS**

The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) under Grant agreement no. 224635, and was also supported by Regione Lombardia and CILEA consortium through a LISA Initiative (Laboratory for Interdisciplinary Advanced Simulation) 2010 Grant (http://lisa.cilea.it).
7.3.6. REFERENCES


Figure 1

A

\[ \text{SH} \] \[ \text{C2} \] \[ \text{C1} \] \[ \alpha \] \[ \text{PPM} \] \[ \text{APM} \]

B

C

\text{Area 2D}

\text{Area 3D}

D

E

\text{Perimetro}

\text{Altezza}
Figure 2

End Diastole

Closing Phase
\( p = 6 \text{ mmHg} \)

Closing Phase
\( p = 28 \text{ mmHg} \)

Peak Systole
\( p = 120 \text{ mmHg} \)
Figure 3

Max. stress [kPa]

MITRALE 1

MITRALE 2

MITRALE 3

MITRALE 5

MITRALE 6
Figure 4
Figure 5

$F_{rad} (N)$ vs $F_{tang} (N)$ for different mitral leaflets.
7.3.7. CAPTIONS

**Figure 1** – Characterization of MA and PMs configuration throughout the cardiac cycle. **A)** Sketch of a mitral annulus, depicting the main measurements evaluated from CMR imaging. The anterior and posterior portions of the annulus are represented in red and blue, respectively. The saddle horn (SH) and the mid-point of the posterior annulus (P2) identify the SL diameter; the commissures (C1, C2) identify the CC diameter; the antero-lateral and postero-medial PMs (APM, PPM) and the centre of the valvular orifice (O) identify the angle $\alpha$. **B) to E)** With reference to a representative subject, the time course of MA perimeter, area, CC and SL diameters and height is depicted for a full heartbeat.

**Figure 2** – Closure dynamics of the modeled MVs.

**Figure 3** – Contours of leaflets maximum principal stresses at peak systole, as seen in an atrial view. Stresses are referred to the mid-section of the shell elements used to discretize leaflets’ geometry.

**Figure 4** – **Left:** atrial view of a MV, in which the annulus is visible and some notable annular points are highlighted. SH=saddle horn; $T_1, T_2=trigomes; C_1, C_2=commissures; P=mid-point of the posterior portion of the annulus. **Right:** spatial distribution of the magnitude of annular forces; the notable points defined in the left panel are used to identify the different annular portions on the horizontal axis of the diagram.

**Figure 5** – Time course of the radial and tangential components of the annular forces ($F_{rad}$ and $F_{tang}$, respectively) averaged over space in four regions of the annulus, whose location and extent is exemplified in the top panel together with the indication of the cylindrical reference frame. ED=end diastole and PS=peak systole in the time axes.
Table 1 – Main characteristics of the enrolled subjects and of their annular geometry.

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<td>77</td>
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**Annulus Geometry at End-Diastole**

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**Annulus Geometry at Peak Systole**

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<tr>
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<tr>
<td>D(_{SL}) (mm)</td>
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<tr>
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<td>0.11</td>
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Table 2 – Annular tensions at peak systole in the anterior and posterior annulus. Tension magnitude is reported along with its radial, tangential, and axial (i.e. perpendicular to the valvular plane) component.

<table>
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<tr>
<th>Tension (N/m)</th>
<th>mitrale1</th>
<th>mitrale2</th>
<th>mitrale3</th>
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<th>mitrale6</th>
<th>average</th>
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<td>83.50</td>
<td>62.09</td>
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<td>11.28</td>
</tr>
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<td>Magnitude</td>
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<td>13.80</td>
<td>8.48</td>
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<td>Magnitude</td>
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<td>74.36</td>
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<td>56.27</td>
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7.4. From CMR-based quantitative assessment of left ventricular function to the quantitative prediction of the effects of revascularization procedures through a simple mathematical model

Marco Stevanella¹, Emiliano Votta¹, Carlo Conti¹, Francesco Maffessanti¹, Enrico G. Caiani¹, Alberto Roghi², Renata De Maria³, Oberdan Parodi³, Alberto Redaelli¹

7.4.1. INTRODUCTION

Post-ischemic left ventricular dysfunction (LVD) has become in recent decades the most common form of myocardial damage leading to heart failure, a condition where the heart is unable to pump enough blood into the circulation to support tissue needs [Hertz et al., 2008].

Post-ischemic LVD may result from acute myocardial infarction where non-contracting scar tissue substitutes viable cardiomyocytes and leads to the complex of changes in chamber size and function known as ventricular remodeling. LVD is also the final pathway of chronic flow reduction due to narrowing of the coronary arteries that may determine severe contractile dysfunction of viable myocardium [Sutton et al., 2000].

The appropriate choice of treatment to relieve ischemia and restore effective pump function in the individual patient is challenging to the clinician [St John Sutton et al., 2003; Fattouch et al., 2009; Goland et al., 2009; Zhong et al., 2009]. Improved accuracy in the definition of the extent and severity of myocardial damage, mitral regurgitation (MR) and associated contractile dysfunction is relevant to planning and performance of therapeutic procedures.

Within the framework of the virtual pathological heart of the virtual physiological human (VPH2) project, we aim at developing a decision support tool for cardiologists and cardiac surgeons, based on LV patient-specific modelling, that comprises a functional assessment tool (FAT) and a functional predictive tool (FPT). FAT allows to quantitatively analyze global and regional LV function through the semi-automated detection of endocardial and epicardial contours from short-axis CMR images, and to integrate these results with information on myocardial viability derived from late hyperenhancement in gadolinium-enhanced magnetic resonance imaging, thus helping in defining the severity and extent of disease in patients with LV dysfunction.

FPT is designed to allow for an easy and fast simulation of post-operative scenarios subsequent to different surgical procedures, such as such as cardiac resynchronization therapy with including single chamber or biventricular pacemakers or implantable cardioverter defibrillators (ICD), myocardial revascularization performed by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), or surgical restoration of the left ventricle.

The implementation of FAT was reported in a previous work [Conti et al., 2011], in which its features were preliminarily tested on a virtual phantom model and on three paradigmatic subjects: a normal healthy subject, a patient with antero-lateral infarction and diffused ventricular hypokinesia (EF=44%), and a
patient with anterior and inferior-lateral infarction, severe LV dilation and highly impaired ventricular function (EF=16%).

In the present paper our goal is three-fold: i) to extend the use of FAT to a wider cohort of patients, enrolled at Niguarda Hospital (Milan); ii) to evaluate the possible benefit from integrating on a single computational tool different clinical information describing the left ventricular function, such as the intracavitary volume throughout the cardiac cycle, wall motion scores, local contractility, and transmural extent of late hyperenhancement; iii) to describe a simple mechanicistic mathematical model that accounts for all of these quantitative parameters and predicts the reverse remodeling effects of myocardial revascularization therapy in terms of long-term post-operative LV volumes.

7.4.2. MATERIALS AND METHODS

The design of the study is schematized by the flow chart in Figure 1. Twenty-five patients with ischemic disease underwent the standard clinical procedures, consisting in pre-operative CMR acquisition and LV function evaluation, surgical procedure, and 6-months post-operative follow-up, inclusive of post-operative CMR (or echocardiographic) acquisition and LV function evaluation. Pre-operative CMR acquisitions were also processed using FAT; for a subclass of patients (N=8) treated with myocardial revascularization only, an ex ante prediction of the post-operative LV global function was performed through FPT, based on FAT computations.

FAT was validated by comparing its computations on the pre-operative CMR datasets to the results of the corresponding standard analysis. FPT was validated by comparing its predictions to the results of the corresponding post-operative standard analysis.

Patients cohort

Enrollment Criteria - In this prospective observational single-center investigation (Niguarda Hospital, Milan), 25 patients were enrolled. Clinical and functional capacity assessment, echocardiography and cardiac magnetic resonance (CMR) were performed at baseline. Inclusion criteria were history of AMI, LVSD as expressed by echo LVEF ≤40% and current or prior HF symptoms. Exclusion criteria were previous coronary artery bypass grafting (CABG), previous aneurysmectomy or surgical ventricular restoration (SVR) and previous valve surgery, prior device therapy including single chamber or biventricular pacemakers (CRT) or implantable cardioverter defibrillators (ICD) and being on heart transplant waiting list. This study was approved by the Local Ethical Committee (Niguarda Hospital, Milan).

Cohort demographic characteristics, risk factors and comorbidity conditions - Subjects were from 48 to 77 years old (mean 64 ± 10 standard deviation), and the proportion of female subjects was 12%, in line with the observation from Niguarda chronic CAD retrospective dataset. Cardiovascular risk factors were present in all patients, diabetes in particular was found in half of the study population. Comorbidities typical of ischemic heart disease, such as chronic kidney dysfunction (CKD), chronic obstructive pulmonary disease (COPD), peripheral (PVD) and cerebrovascular vessel disease (CVD) were highly prevalent (Table 2).
Cohort cardiac history - Seventeen patients had a clinical history of previous myocardial infarction, with involvement of the anterior wall in 10 and of the inferior wall in 7. In the remaining 8 patients, that presented with symptoms of heart failure and ventricular dysfunction, the ischemic etiology was ascertained after diagnostic work up. Four patients had single vessel disease, 9 had 2-vessel and 12 had 3-vessel disease. Moderate to severe mitral regurgitation was found in 4 patients (Table 3).

Patients were followed up at an average of 6 months to assess clinical status and reverse remodeling by means of CMR and 3D Echocardiography when CMR was not feasible.

Cardiac magnetic resonance imaging

CMR acquisitions were performed using a Siemens Avanto (Siemens Medical System, Germany) 1.5 Tesla wholebody scanner, equipped with a commercial cardiac coil. ECG-gated breath-hold cine images of the left ventricle were acquired in multiple short axes using steady-state free procession sequences (20 time-frames/cardiac cycle, reconstruction matrix 256 x 256 pixels, spatial resolution 1.719 mm x 1.719 mm). Full ventricular coverage was achieved with 8-mm thick slices separated by a gap of 1.6 mm, obtaining a stack (from 8 to 12) of cine short-axis slices from the atrio-ventricular ring to the apex (Figure 2, top panel).

Delayed enhancement (DE) CMR was performed 15 minutes after intravenous administration of gadolinium diethylenetriamine penta-acetic acid 0.2 mmol/Kg (Magnevist; Schering AG, Germany), with a breath-hold segmented inversion-recovery sequence (inversion time 240 to 300 ms), acquired in the same orientation as the cine images (single time-frame, reconstruction matrix 256 x 256 pixels, spatial resolution 1.563 mm x 1.563 mm). LV volume, mass, ejection fraction were analyzed by commercial software.

Global LV function was assessed off-line through standard commercial software, in terms of intracavitary end-diastolic and end-systolic volume (EDV, ESV), stroke volume (SV), and ejection fraction (EF).

Analysis of pre-operative LV function through FAT

FAT Algorithms for contours detection - LV endocardial and epicardial surfaces segmentation was performed using semi-automated detection algorithm based on region-based image noise distribution (for LV endocardial detection) and on edge-based image gradient (for LV epicardial detection), as previously described in [Conti et al, 2011].

LV endocardial boundary was detected using the approach proposed in [Chan & Vese, 2001] and on embedding in the segmentation model the a priori knowledge of the statistical distribution of grey levels in medical images [Bovik, 1988]. In particular, concerning CMR, we note that the videointensity of the image pixels is modelled as Gaussian distributed random variables. Then the proposed method drives the curve evolution to achieve a maximum-likelihood segmentation of the target, with respect to the statistical distribution law of image pixels. Following this step, the boundary regularization was achieved using a curvature-based motion not allowing curvature above the mean Euclidean curvature value of the detected
contour and designed to automatically include the papillary muscles in the LV cavity. This region-based approach was applied from basal to apical slices for each frame. In the basal slice, after initialization of the algorithm parameters (radius of the initial circle, and per cent of radius decrement from one slice to the next one), the operator selected one point inside the LV cavity. Then, automatically, the applied algorithm expanded the initial circle according to the videointensity probability distribution followed by the regularizing expansion to include the papillary muscles, when present. Then, the algorithm processed the other slices, using the detected contour on the current slice (s) as initialization for the next (s+1) slice, after reducing it by the per cent set by the operator (Figure 2, mid panel).

LV epicardial boundary was detected through the Malladi–Sethian algorithm for active contour evolution, which drives the evolution of an initial contour by iteratively searching for the balance between an expansion term and an advection term [Sarti et al., 2005], once adequate boundary conditions are provided [Perona et al., 1990]. The contour evolution will have a steady-state solution when the geometry dependent and expansion terms balance the advection term. At the end of this step, the epicardial boundary was also regularized applying a modified curvature motion. For epicardial detection, this approach required a robust initialization on the first frame f. Then, for the next frame f + 1, the initialization was obtained by applying the ‘erode’ morphological operation applied to the resulting epicardial contour on the frame f.

For each slice and frames, the detected contours were then superimposed to the original image, to allow for possible manual corrections, if needed (Figure 2, bottom panel).

In the gadolinium DE-CMR images, endocardial and epicardial contours were detected using the procedure described above. Scarred myocardium was then identified by manually tracing the transmural extent of hyperenhanced tissue.

**Parameters quantifying LV function** – Global LV function was quantified in terms of time-dependent intracavitary volume. The LV volume was automatically computed by summing the LV area in each slice (measured as pixel count within the endocardial contour) multiplied by the pixel spatial resolution and by the distance between two consecutive short-axis planes, i.e. slice thickness plus interslice gap, except for the most apical and most basal slices, whose areas were multiplied by slice thickness plus half of the interslice gap (Figure 2, top panel).

Regional LV function was quantified in terms of local wall motion and local wall strains. For the automated computation of regional wall motion, the ED frame was used to define the standard segmentation scheme for the LV short-axis view in each slice. In the slice at the mid-ventricular position, the ED centroid of the LV cavity was calculated as centre of mass of the binary image representing the detected LV cavity, and used as the origin of segmentation. An additional point was then manually placed at the junction between the right ventricular free wall and the interventricular septum. Starting from that point, the LV cavity was divided into six wedge-shaped segments, corresponding to those used for visual assessment and grading of WM. For each segment, regional fractional area (RFA) in per cent of regional ED area was automatically calculated throughout the cardiac cycle using a fixed-coordinate reference system. From these six curves in each slice, RFA change (RFAC) was computed as the difference between the maximum and minimum value of RFA, expressed in per cent of the regional ED area. For each segment, these values were used to
automatically interpret WM as normal (RFAC ≥50%), hypokinetic (50%>RFAC ≥25%), severely hypokinetic (25%>RFAC≥10%), akinetic (10%>RFAC≥-10%) and dyskinetic (RFAC<-10%) [Mor-Avi et al., 2000].

Local wall strains were calculated through four steps. First, at each time-frame smooth endocardial and epicardial surfaces were obtained by biplanar cubic spline approximation of previously detected contours (Figure 3.A). These surfaces were then discretized into three-node triangular elements.

Second, in the ED frame, endocardial and epicardial surfaces were divided into six longitudinal sections and three circumferential sections, thus using a 18-segment model that resembles the one recommended by the American Heart Association [Cerqueira et al., 2002]. For each sector, its eight vertices were identified and the corresponding local principal curvatures calculated as in Vieira & Shimada [21] (Figure 3.B-C).

Third, the eight vertices of each sector were tracked throughout the subsequent time-points by means of a nearest neighbour search, assuming that the position of a given point P on the LV surface and the surface local shape in P change continuously throughout the cardiac cycle, and thus undergo small changes in a the short time-frame separating two consecutive time-points of CMR acquisitions. This nearest neighbour search, described in details in [Conti et al., 2011], minimizes the frame-by-frame variations in spatial position and local curvature and provides the time-dependent position of the eight vertices of each of the 18 sectors of the LV myocardium and, thus, the corresponding time-dependent displacements.

Finally, the displacement field was reconstructed within each sector by treating the latter as an eight-node isoparametric hexahedral finite element. For each sector, Lagrangian strains in radial, tangential and axial directions were calculated in the center of the element through the finite strain theory (Figure 3.D).

**FPT prediction of post-revascularization LV global function: mathematical model**

FPT is based on in home software for the prediction of LV remodeling after myocardial revascularization through percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) takes as inputs all the data computed using the functional assessment tools described above, and returns the post-operative LV volume time-course. This software, implemented in MATLAB (The Mathworks, Natick, MA) combines a graphical user interface (GUI) with a simple mathematical model of the LV remodeling phenomena. In this study, the software was applied to predict the post-operative outcome for those patients (N=9) within the enrolled cohort that underwent only revascularization procedures.

Through the GUI, the operator can:

i) import and visualize local wall strains data previously computed by FAT. The contractility of each sector, represented by the circumferential strain time-course throughout the cardiac cycle, is visualized both as line plots and in a bull’s eye representation of the end-systolic values (Figure 4A);

ii) simultaneously import gadolinium uptake information, if available, and visualize it in a grey-scale bull’s eye diagram, black representing necrotic tissue with high gadolinium uptake (Figure 4B);

iii) simulating the desired surgical intervention. Namely, when simulating revascularization procedures, the operator can select on which coronary artery perform the PCI or CABG, on the basis of coronary
angiographic information. Any combination of left anterior ascending (LAD), left circumflex (LCX) and right coronary artery (RCA) is possible. On each of these branches, the procedure can be simulated at a proximal level (LV base), a medial level (LV midline) or a distal level (LV apex). In this way, the operator implicitly indicates the wall sectors potentially affected by the procedure, accordingly with the coronary segment-LV sector correspondence described in [Cerqueira et al., 2002].

The algorithm for the prediction of post-operative LV volume throughout the cardiac cycle after myocardial revascularization is schematized in Figure 5. For each segment i, the potential increase in local contractility $\Delta C_i(t)$ was calculated as:

$$\Delta C_i(t) = (C_{\text{max}}(t) - C_i(t)) \cdot p_i \cdot \delta_i$$

$(C_{\text{max}}(t) - C_i(t))$ is the difference between the circumferential strain curve with the global highest strain values $(C_{\text{max}}(t))$ and the local circumferential strain curve $C_i(t)$. This potential strain increase is then weighted by two factors: $p_i$ and $\delta_i$. $p_i$ accounts for the likelihood of improved contractility after revascularization; it depends on the transmural extent of gadolinium hyperenhancement and on the wall motion score (Table 3) [Kim et al., 2000]. $\delta_i$ is equal to one if the LV segment is affected by the revascularization procedure, i.e. if it corresponds to one of the coronary branches selected by the operator, and to zero otherwise.

The pre-operative end-diastolic volume of each segment was then multiplied by the estimated post-operative contractility curve $C_i(t)+\Delta C_i(t)$ to obtain the post-operative segmental volume time-course. From the summation of all 18 contributions, the estimated post-operative LV volume time-course was calculated.

At this point, newly estimated stroke volume $SV_n$ and pre-operative stroke volume $SV_0$ were compared, and, whether they differed by more than 5%, the algorithm was iterated by scaling the pre-operative end-diastolic segmental volumes by a factor $k = 1 + (SV - SV_0)/SV_0$, until $(SV - SV_0)/SV_0 < 5\%$, consistently with the findings of the STICH trial [Jones et al., 2009], that showed a negligible variation in SV after revascularization alone.

**FAT and FPT validation**

The validation of the assessment module was focused on the LV dimension and function indices usually computed from the cardiac MRI images, such as end-diastolic (ED) and end-systolic (ES) volumes, stroke volume (SV), ejection fraction (EF). For these measurements, the gold standard was represented by the result of the manual tracing of endo- and epicardial LV contours on CMR images by an expert cardiologist. Results for each parameter were compared to the “gold standard” by linear regression and Bland-Altman analysis. The goodness of the linear fitting of the two measurements was evaluated the $R^2$ coefficient of the regression. Bias (in absolute and % values) and 95% limits of agreement were computed for each parameter.

For the validation of the revascularization model, predictive post-operative volumes were compared with the manual tracing of endocardial and epicardial LV contours by an expert cardiologist on follow-up CMR datasets, when available, or with 3D echocardiographic findings. As for the assessment module, Bland-Altman analysis was performed on each parameters to evaluate bias and limits of agreement.
7.4.3. RESULTS

One patient (NIG-005) had inadequate short-axis CMR pre-operative acquisition and was excluded from the study. The resulting population at the pre-operative stage showed range of LV dimensions equal to 104-380 ml for EDV, 46-295 ml for ESV, 39-119 ml for SV, and 18-62% for EF, as measured by the gold standard approach.

**FAT validation**

Results of FAT analysis and of the standard analysis performed by an expert cardiologist are reported in Table 4. Linear regression analysis showed very good correlation between the two approaches in the estimation of EDV ($r^2 = 0.975$) and ESV ($r^2 = 0.947$), while good agreement was found for SV ($r^2 = 0.816$) and EF ($r^2 = 0.760$).

Bland-Altman analysis resulted in minimal non-significant bias and narrow limits of agreement, as shown in Figure 6. In terms of percentage of the mean parameter value, these limits of agreement represented 10.1%, 20.1%, 29.9%, and 35.1%, respectively, for EDV, ESV, SV and EF.

**FPT validation**

Of the 25 patients enrolled, only 11 underwent myocardial revascularization therapy alone and thus included into the FPT validation. Three of them were further excluded as the follow-up evaluation was performed by echocardiography and not by CMR for clinical counter-indications. This subset presented pre-operatively the following LV mean parameters: EDV= 189 ± 56 ml, ESV= 119 ± 43 ml, SV= 70 ± 24 ml, EF= 38 ± 11%. The analyzed subset presented post-operatively the following LV mean parameters, calculated by the gold standard analysis: EDV= 165 ± 42 ml, ESV= 100 ± 33 ml, SV= 65 ± 20 ml, EF= 40 ± 11%. Paired t-test showed a significant effect of the performed procedure on the reduction of EDV and ESV; on the other hand, SV and EF did not change significantly after the revascularization.

Results of FPT, in terms of LV EDV, ESV, SV and EF, predicted on the basis of the pre-operative CMR datasets, were compared with the standard analysis of an expert cardiologist performed on the follow-up CMR datasets, as reported in Table 5.

Bland-Altman analysis showed a good agreement between predicted and measured parameters, with a small but statistically significant (p<0.05) underestimation of post-operative ESV, and narrow limits of agreement. In terms of percentage of the mean parameter value, these limits of agreement were the 16.7%, 21.3%, 44.6%, 30.6%, respectively, of EDV, ESV, SV and EF.

FPT limits of agreement proved to be comparable to those obtained in the FAT validation, both in absolute value and as a percentage of the mean parameters’ value.
7.4.4. DISCUSSION

In the present paper, we presented an integrated computational platform for the LV function analysis from CMR imaging and the prediction of LV performances after myocardial revascularization therapy, based on a simple mathematical model of the LV reverse modeling.

With respect to phenomenological predictive models as the one proposed by Yoon and colleagues [Yoon et al., 2010], in which patient survival over time is predicted from several risk factors on the basis of a large database of previous interventions, we tried to identify and validate a mechanistic model for the quantitative prediction of post-operative LV performance starting from several LV functional parameters derived from CMR imaging.

FAT module, whose results were preliminary tested on 3 patients in [Conti et al., 2011], was validated on a cohort of 24 ischemic patients. The results of the comparison of volumetric quantitative indices computed using FAT with the standard analysis performed by an expert cardiologist confirmed the good performance of the applied methodology for the detection of endocardial borders.

The results of FPT prediction showed a good agreement with the gold standard analysis performed on the follow-up CMR datasets, with a very small increase in the width of the limits of agreement with respect to FAT, due to the fact that FPT values were based only on the pre-operative CMR data and on the rules implemented in the model. FPT limits of agreement were satisfactory also when compared to the performance of previously published algorithms for LV quantification from CMR images [Corsi et al., 2005], that reported similar limits of agreement.

From the t-test between the pre-operative and post-operative gold standard measurement on the patients that underwent myocardial revascularization, it emerged that after six months there was a morphological reverse remodeling (significant decrease in EDV and ESV) but not a functional improvement, since EF did not vary significantly (40±11% vs. 38±11%, p=0.22). On the contrary, FPT predicted a significant improvement also in the ejection fraction (44±9% vs. 38±11%, p<0.05).

From this point of view, a further follow-up acquisition at 1 year could probably clarify if the reverse remodeling after 6 months is still incomplete due to complications in the post-operative short term, or if some of the patients are not responsive to the revascularization therapy because of aspects we are not taking into account in our mathematical model, such as comorbidities and genetic factors.

7.4.5. CONCLUSIONS

Treatment of patients with LV dysfunction caused by ischemic heart disease needs to be assisted by real-time clinical decision-making tools. In the present paper, we presented a computational platform for the assessment of LV function from CMR imaging and the prediction of post-operative LV performance after myocardial revascularization therapy. FAT proved accurate in assessing LV volumetric parameters and in its capability of capturing regional functional features. FPT prediction were in good agreement with gold standard measurements of 6-months follow-up patients parameters. With further refinement of the algorithm, that would take into account for additional factors influencing the reverse remodeling process of
the left ventricle, our platform will provide a valuable predictive tool in the patient-specific decision making process for the treatment of ischemic patients with LVD.

ACKNOWLEDGMENTS

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7.4.6. REFERENCES


7.4.7. FIGURES

Figure 1. Flow chart of the study.
Figure 2. A) Sketch of the characteristics of CMR acquisitions (left) and of the volumes assigned to each short-axis cut-plane when computing LV volume (right). B) Endocardial contour detection; from left to right: initialization, contour evolution and steady-state solution of the detection algorithm. C) Epicardial contour detection; from left to right: initialization, contour evolution and steady-state solution of the detection algorithm.
Figure 3. A) Stack of CMR short-axis cut-planes acquired for one time-point of the cardiac cycle. B) Endocardial (red) and epicardial (blue) contours detected on the cut-planes. C) 3D smoothed endocardial (red) and epicardial (blue) surfaces reconstructed by cubic spline approximation of the contours. D) Paradigm adopted to define 18 sectors (3 levels from base to apex, 6 sectors for each level) in the LV wall. E) Single sector treated as a isoparametric hexahedral finite element, where the axial, circumferential and radial directions used to compute myocardial strains are indicated.
Figure 4. A) Graphical user interface (GUI) of FPT. On the left-hand side, time-course of the circumferential strains throughout the cardiac cycle for the 18 ventricular segments. On the right-hand side, in the top panel the bull’s eye representation of segmental circumferential strains at end-systole, in the bottom panel the time-course of the LV intracavitary volume throughout the cardiac cycle and the values (in ml) of ED volume, ES volume, stroke volume and ejection fraction (EF). B) The same widget is shown, in which the distribution of the gadolinium uptake is represented in the bull’s eye diagram (right-hand sized top panel).
Figure 5. Schematic of the algorithm for the prediction of post-operative LV volume throughout the cardiac cycle after myocardial revascularization.

Pre-operative volume
\[ V_0(t) = \sum_{i=1}^{18} V_{0i}(t) \]

Revascularization

Definition of likelihood of improved contractility \( \rho_i \)

Calculation of post-operative increment in contractility
\[ \Delta C_i(t) = p_i \delta_i \left( \max_i(C_i(t)) - C_i(t) \right) \]

Calculation of post-op segmental volume
\[ V_{0i}(t) = V_0(t) \cdot \left( C_i(t) + \Delta C_i(t) \right) \]

\( i \)-th segment

Updated post-op volume
\[ V_{n+i}(t) = \left( 1 + \frac{SV_n - SV_0}{SV_0} \right) V_i(t) \]

Calculation of post-op volume
\[ V_n(t) = \sum_{i=1}^{18} V_{n+i}(t) \]

\[ \frac{SV_n - SV_0}{SV_0} < 0.05 \] ?

Post-operative volume
\[ V_{post}(t) \]
Figure 6. Bland-Altman plots of EDV, ESV, SV and EF, as assessed by FAT with respect to the gold standard method. Blue continuous line represents the bias, while blue dashed lines represent the limits of agreement.
### 7.4.8. TABLES

Table 1. General characteristics of prospectively enrolled patients.

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<td>I</td>
</tr>
<tr>
<td>8</td>
<td>no</td>
<td>STEMI</td>
<td>Anterior</td>
<td>2</td>
<td>LAD, RCA</td>
<td>yes, stent</td>
<td>no</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>no</td>
<td>STEMI</td>
<td>Inferolateral</td>
<td>3</td>
<td>LM, LAD, RCA</td>
<td>yes, stent</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
<td>10</td>
<td>persistent</td>
<td>STEMI</td>
<td>Anteroseptal, apical</td>
<td>3</td>
<td>LAD, LCx, RCA</td>
<td>no</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>11</td>
<td>no</td>
<td>no</td>
<td></td>
<td>3</td>
<td>LAD, LCx, RCA</td>
<td>no</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>12</td>
<td>no</td>
<td>no</td>
<td></td>
<td>3</td>
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<td>no</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>13</td>
<td>no</td>
<td>STEMI</td>
<td>Anterior</td>
<td>3</td>
<td>LAD, OM1, RCA</td>
<td>no</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>14</td>
<td>no</td>
<td>STEMI</td>
<td>Anterior</td>
<td>2</td>
<td>LAD, RCA</td>
<td>yes, stent</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
<td>15</td>
<td>no</td>
<td>no</td>
<td></td>
<td>2</td>
<td>Stent on LAD, OM1</td>
<td>yes, stent</td>
<td>yes</td>
<td>II</td>
</tr>
<tr>
<td>16</td>
<td>no</td>
<td>STEMI</td>
<td>Anteroseptal</td>
<td>3</td>
<td>LAD, LCx, RCA</td>
<td>no</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
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<td>no</td>
<td>no</td>
<td></td>
<td>2</td>
<td>LCx, RCA</td>
<td>yes</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>18</td>
<td>chronic</td>
<td>no</td>
<td></td>
<td>3</td>
<td>LAD, LCx, RCA</td>
<td>no</td>
<td>yes</td>
<td>II</td>
</tr>
<tr>
<td>19</td>
<td>no</td>
<td>undefined</td>
<td>Lateral and apical</td>
<td>1</td>
<td>RCA</td>
<td>no</td>
<td>no</td>
<td>I</td>
</tr>
<tr>
<td>20</td>
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<td>STEMI</td>
<td>Inferior</td>
<td>3</td>
<td>LM, LAD, LCx, RCA</td>
<td>no</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
<td>21</td>
<td>no</td>
<td>NSTEMI</td>
<td>Anterior</td>
<td>1</td>
<td>Stent on LAD</td>
<td>yes, stent</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
<td>22</td>
<td>no</td>
<td>STEMI</td>
<td>Anterolateral</td>
<td>1</td>
<td>Stent on LAD, stenotic distal LAD, D1,</td>
<td>yes, stent</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>23</td>
<td>no</td>
<td>STEMI</td>
<td>Anterolateral</td>
<td>1</td>
<td>Stent on LAD</td>
<td>yes</td>
<td>yes</td>
<td>III</td>
</tr>
<tr>
<td>24</td>
<td>no</td>
<td>STEMI</td>
<td>Inferior and apical</td>
<td>2</td>
<td>Stent on LAD, RCA</td>
<td>no</td>
<td>no</td>
<td>II</td>
</tr>
<tr>
<td>25</td>
<td>no</td>
<td>no</td>
<td></td>
<td>3</td>
<td>LAD, LCx, RCA</td>
<td>no</td>
<td>no</td>
<td>II</td>
</tr>
</tbody>
</table>

HF=heart failure, LM=left main, LAD=left anterior descending; LCx=Left circumflex, D1=first diagonal, OM=obtuse marginal, PL=posterolateral
Table 3. Values of $p_i$, that represents the likelihood of improved contractility after revascularization, as a function of the transmural extent of gadolinium hyperenhancement and of the wall motion score [Kim et al., 2000].

<table>
<thead>
<tr>
<th>Transmural Extent of Hyperenhancement (%)</th>
<th>All Dysfunctional Segments</th>
<th>Segments with Severe Hypokinesia, Akinesia, or Dyskinesia</th>
<th>Segments with Akinesia or Dyskinesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>77.8%</td>
<td>86.5%</td>
<td>100.0%</td>
</tr>
<tr>
<td>1% - 25%</td>
<td>59.6%</td>
<td>65.1%</td>
<td>82.1%</td>
</tr>
<tr>
<td>26% - 50%</td>
<td>41.8%</td>
<td>42.6%</td>
<td>45.0%</td>
</tr>
<tr>
<td>51% - 75%</td>
<td>10.5%</td>
<td>9.7%</td>
<td>7.4%</td>
</tr>
<tr>
<td>76% - 100%</td>
<td>1.7%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Table 4. Results of FAT analysis and of standard analysis performed by an expert cardiologist on the pre-operative CMR datasets, in terms of end-diastolic and end-systolic volumes (EDV, ESV), stroke volume (SV), ejection fraction (EF).

<table>
<thead>
<tr>
<th>Patient</th>
<th>FAT analysis</th>
<th>Standard analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDV</td>
<td>ESV</td>
</tr>
<tr>
<td>NIG-001</td>
<td>263</td>
<td>149</td>
</tr>
<tr>
<td>NIG-002</td>
<td>207</td>
<td>131</td>
</tr>
<tr>
<td>NIG-003</td>
<td>177</td>
<td>94</td>
</tr>
<tr>
<td>NIG-004</td>
<td>140</td>
<td>103</td>
</tr>
<tr>
<td>NIG-006</td>
<td>178</td>
<td>140</td>
</tr>
<tr>
<td>NIG-007</td>
<td>152</td>
<td>70</td>
</tr>
<tr>
<td>NIG-008</td>
<td>102</td>
<td>60</td>
</tr>
<tr>
<td>NIG-009</td>
<td>145</td>
<td>96</td>
</tr>
<tr>
<td>NIG-010</td>
<td>264</td>
<td>221</td>
</tr>
<tr>
<td>NIG-011</td>
<td>168</td>
<td>96</td>
</tr>
<tr>
<td>NIG-012</td>
<td>266</td>
<td>153</td>
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<td>NIG-013</td>
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<td>NIG-014</td>
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<tr>
<td>NIG-015</td>
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<td>66</td>
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<tr>
<td>NIG-016</td>
<td>152</td>
<td>98</td>
</tr>
<tr>
<td>NIG-017</td>
<td>382</td>
<td>296</td>
</tr>
<tr>
<td>NIG-018</td>
<td>210</td>
<td>147</td>
</tr>
<tr>
<td>NIG-019</td>
<td>145</td>
<td>70</td>
</tr>
<tr>
<td>NIG-020</td>
<td>209</td>
<td>125</td>
</tr>
<tr>
<td>NIG-021</td>
<td>158</td>
<td>71</td>
</tr>
<tr>
<td>NIG-022</td>
<td>179</td>
<td>140</td>
</tr>
<tr>
<td>NIG-023</td>
<td>225</td>
<td>180</td>
</tr>
<tr>
<td>NIG-024</td>
<td>231</td>
<td>115</td>
</tr>
<tr>
<td>NIG-025</td>
<td>290</td>
<td>235</td>
</tr>
</tbody>
</table>
Table 5. Results of FPT simulations and of standard analysis performed by an expert cardiologist on the post-operative 6-months follow-up CMR datasets, in terms of end-diastolic and end-systolic volumes (EDV, ESV), stroke volume (SV), ejection fraction (EF).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Surgical intervention</th>
<th>FPT simulation</th>
<th>Follow-up at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EDV</td>
<td>ESV</td>
</tr>
<tr>
<td>NIG-002</td>
<td>revascularization RCA + LAD</td>
<td>163</td>
<td>85</td>
</tr>
<tr>
<td>NIG-008</td>
<td>revascularization LAD + LCX</td>
<td>85</td>
<td>41</td>
</tr>
<tr>
<td>NIG-009</td>
<td>revascularization LAD</td>
<td>133</td>
<td>85</td>
</tr>
<tr>
<td>NIG-011</td>
<td>revascularization LAD</td>
<td>141</td>
<td>69</td>
</tr>
<tr>
<td>NIG-012</td>
<td>revascularization LAD, RCA, LCX</td>
<td>216</td>
<td>98</td>
</tr>
<tr>
<td>NIG-013</td>
<td>revascularization LAD + LCX</td>
<td>192</td>
<td>131</td>
</tr>
<tr>
<td>NIG-016</td>
<td>revascularization LAD + LCX</td>
<td>137</td>
<td>82</td>
</tr>
<tr>
<td>NIG-018</td>
<td>revascularization LAD + LCX basal + RCA distal</td>
<td>176</td>
<td>114</td>
</tr>
</tbody>
</table>
7.5. Visualisation and simulated surgery of the left ventricle in VPH2

NJB McFarlane¹, X Lin¹, Y Zhao¹, GJ Clapworthy¹, F Dong¹, A Redaelli², O Parodi³, D Testi⁴

Key words

Heart, Heart failure, Left ventricle, Left ventricular dysfunction, Surgical planning, Virtual surgery, Visualisation, Computer graphics

7.5.1. ABSTRACT

Ischemic heart failure remains a significant health and economic problem worldwide. This paper presents a user-friendly software system that will form a part of the Virtual Pathological Heart environment which is currently being developed under the FP7 VPH2 project. VPH2 is an integrated medicine project which will create a suite of modelling, simulation and visualisation tools for patient-specific prediction and planning in cases of post-ischemic LVD. The work presented here describes a 3D interactive visualisation for simulating left ventricle restoration surgery, comprising the operations of cutting, stitching and patching, and for simulating the elastic deformation of the ventricle to its post-operative shape. This will supply the quantitative measurements required for the post-operative prediction tools being developed in parallel in the same project.

7.5.2. INTRODUCTION

Heart failure (HF) is a serious problem worldwide in terms of mortality and economic cost. In the US, the lifetime risk of developing HF above the age of 40 is 20%, and approximately half of patients die within 5 years of diagnosis. In 2010, the cost of HF to the US in direct healthcare alone was estimated to be $35 billion [1]. In the UK, HF was estimated to cost 4% of all healthcare expenditure in 2000 [2].

The most common cause of HF is ischemic heart disease [3], in which part of the heart muscle, or myocardium, has ceased to function because of a lack of oxygen. This is most serious when it affects the left ventricle (LV) and causes left ventricular dysfunction (LVD), in which the ability of the left ventricle to pump blood to the body is impaired. The dysfunction is a result of several factors: the loss of muscle action in the affected part of the myocardium; changes in the size and shape of the ventricle; and, in some cases, backward flow (regurgitation) through the mitral valve.

Surgical treatment of LVD consists of removing those parts of the myocardium that are entirely necrotic. The dysfunctional ventricle is typically enlarged, and often a bulge associated with an aneurysm will be found in the necrotic area. Its form also tends to change from an ellipsoid to a less efficient spherical shape. The enlargement is undesirable because it increases the muscle tension required to achieve a given
blood pressure, forcing the heart to work harder to eject blood from the LV. The distortion can also make valve closure less complete, which makes regurgitation more likely.

Thus, the aim of surgery is not only to remove the diseased tissue, but also to return the LV to its correct volume and shape – this is known as LV restoration. Other procedures that might be performed in combination with the LV restoration surgery include revascularisation, in which the blood flow is rerouted in an attempt to restore some function to regions that are failing but not necrotic, correction of mitral valve regurgitation, and resynchronisation, in which one or more pacemakers are fitted. A description of LV restoration procedures is given in [4].

Currently, few tools are available to assist the cardiac surgeon with treatment and surgical planning, though the right ventricle (RV) has received some attention in the literature, mainly because of its role in congenital defects. Two studies have shown that valid models can be constructed and predictions made from MRI sequences: Tang et al. [5] developed patient-specific models of the mechanics and fluid flow in RV’s with tetralogy of Fallot, and were able to predict the post-operative shape and performance of the RV after removal of scar tissue; and Sorensen et al. [6] simulated a range of RV surgical procedures on a highly realistic virtual reality model, and reported good agreement in appearance between the real surgery and the simulation. Hartyanszky et al. [7] developed a system called CAVE (Computer Assisted Ventricle Engineering) for pre-operative planning of the cutting lines, based on CT slices; CAVE predicts post-operative LV volume and has been used to predict a successful outcome in a patient who would otherwise not have been treated. Ionasec et al. [8] developed a 4D patient-specific model of the whole heart, including its chambers, valves and haemodynamics, and demonstrated its application for planning the placement of stent-mounted implants.

Treatment planning is made more difficult by the different responses of patients to the same treatment. Several studies, for example, [9,10,11] have reported that almost a third of cardiac resynchronisation therapy patients were “non-responders” in that their hearts did not show significant improvement in function. If no distinction is made between responders and non-responders, it can be possible to conclude, as in [4] that there is no evidence of any long-term benefit from LV restoration, despite the short-term relief of symptoms. To distinguish responders from non-responders, a range of patient-specific risk factors, including genetics, should be taken into account. A review of current progress in patient-specific modelling can be found in [12].

VPH2 is an integrated medicine project which will create a suite of modelling, simulation and visualisation tools for patient-specific prediction and planning in cases of post-ischemic LVD, with or without mitral valve regurgitation. The project employs MRI imaging and models of the LV, the mitral valve, the fluid flow and the blood circulation, together with surgical simulation and genetics to assess the patient’s current condition, to perform virtual surgery and to predict the post-operative result and the long-term response to the treatment. While endocardial and epicardial segmentation, regional function and tissue viability are characteristics that are present in the majority of the currently available software products, the VPH2 platform will be unique in including quantitative analysis of the mitral valve and the simulation of surgical procedures, and in having export capabilities for further FEM design and processing.

1 www.vph2.eu. VPH2 is “The Virtual Pathological Heart of the Virtual Physiological Human”; it should not be confused with the VPH programme, of which it forms a part.
Highly detailed simulations of cardiac surgery exist, but they are not primarily intended for surgical planning as they tend to be designed for training purposes [13], or to require a virtual reality environment and haptic feedback [14]. A multiscale, integrated model of the heart called euHeart\(^2\) is currently being developed within the VPH programme; this can be registered to patient-specific data, but it is still at a development stage and has not yet been used in clinical practice.

This paper describes the tool being developed in VPH2 for simulated LV reconstruction surgery. This provides an interactive 3D visualisation of the LV which enables the user to view the epicardium and endocardium and the extent of the necrotic damage, to carry out the operations of cutting, stitching and patching, and to view the deformation of the ventricle into its post-operative shape. An earlier stage of this work has been described in [15]. The tool is novel in being designed for rapid use in a clinical setting, being entirely based on patient data, and requiring a minimum amount of modelling to produce a post-operative prediction. Clinical outcomes will be improved because the user will be able to include different surgical options in a highly integrated prediction of risk.

It is not claimed that the system described will be the final output from the project, but it is felt that sufficient has been achieved so far to make a description of the concept behind the system and its initial realisation worthwhile. We have indicated in the text additional components that will be available in the near future as a result of work in progress at the time of writing.

### 7.5.3. INPUT DATA

The input data for this work consists of two sets of MRI images: a time-varying “short-axis” MRI, and a static gadolinium (Gd) MRI. VPH2 has aimed for simplicity of use and minimal discomfort to the patient in the clinical setting; hence the minimum of imaging modalities have been used to satisfy the data requirements of high resolution images, motion capture and accurate location of the necrotic region.

Short-axis MRI was chosen as the main imaging modality because its high spatial and temporal resolution make it the best technique for capturing the wall motion of the ventricle: it is widely available, non-invasive and requires no radiation or contrast agent. Echocardiography provides similar resolution, but the transthoracic mode is prone to attenuation and artefacts caused by air and fat, and the transesophageal mode is particularly invasive. A further disadvantage of echocardiography is the difficulty in producing a single image of the whole ventricle.

For quantifying the necrotic region, Gd MRI is a well-validated technique. Additional modalities such as fMRI or tagged MRI would have been interesting, but are not as widely available, and such extra imaging would have placed unacceptable demands on the patients.

In the short-axis MRI, the scanner is positioned to collect slice images of the heart with the image planes normal to the long axis of the LV. This sequence is time-varying, with 30 frames captured at each slice position, starting with the first frame at end-systole, the end of the contraction part of the cardiac cycle. A small number of slices, approximately 10, are captured, each starting at the same nominal point in the

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\(^2\) www.euHeart.eu
heart cycle. The inter-slice resolution is approximately 8mm, which is the minimum slice-to-slice step size of the MRI scanner, and is not untypical of MRI machines in general. Hence, the slices comprise a 3D image with very good pixel resolution within the slice planes, but poor inter-slice resolution. The top and bottom (apex) of the ventricle are not captured. The time sequence is used in related parts of the VPH2 suite to map the contractility of the ventricle wall, but all the work described in this paper is non-time-varying, and based on the end-diastole frame; the end-diastole is used because the volume at this point is needed in the calculation of the ejection fraction, which is one of the most important measures of the functioning of the ventricle.

In the Gd MRI imaging modality, the MRI is configured to detect a Gd compound that is preferentially absorbed by necrotic tissue. A 3D data volume is captured in the same manner as the short-axis MRI, but without the time variation; only the mid-diastole frame is captured. This particular point in the cardiac cycle is used because the heart is relatively still during diastole, so the image contains fewer motion artefacts. The capture of the Gd MRI at a different point in the cardiac cycle from that of the short-axis MRI surfaces is not ideal for the purposes of registration but is unavoidable due to the different demands on the images. The Gd injection is highly toxic, and the number of slices tends to be limited by the short time during which it remains active. The result is a 3D image of the heart revealing the location of the necrotic region. Fig. 1 shows approximately-corresponding slices through the same heart, in short-axis and Gd MRI respectively.

![Figure 1. (a) Short-axis MRI image of heart, indicating the left ventricle; (b) Gd MRI image of heart, indicating the brighter necrotic area in the septal region of the myocardium](image-url)
7.5.4. PREPROCESSING

The MRI images are pre-processed to extract the endocardium and epicardium (the inner and outer surfaces of the ventricle wall) in the form of triangular mesh surfaces which can be visualised and manipulated in 3D. The pre-processing stages are:

- **segmentation**, in which the endocardium and epicardium are located in the images;
- **reconstruction**, in which the mesh surfaces are built from the segmented points in the images;
- **registration**, in which the positions of the Gd surfaces are registered with the short-axis MRI, and the Gd data copied on to the mesh surfaces for visualisation.

**Segmentation**

The purpose of segmentation is to identify contours in the MRI image slices that correspond to the endocardium and epicardium of the LV. The ventricle wall is segmented by a novel combination of two methods: the segmentation method for extracting the endocardium is a region-based level set method [16]; and the segmentation method for the epicardium is an edge-based level set method [17]. The segmentation is applied to the short-axis MRI images, and the result is a pair of contours in each image slice, corresponding to the endocardium and epicardium, respectively. The segmentation requires one point per slice to be selected in the ventricle cavity, otherwise it is fully automatic.

Segmentation of the necrotic areas from the Gd MRI images is performed by the method developed for this specific application as described in [18]. This has previously been described and validated in [19]. Each point in the contour of the ventricle wall is labelled with the “transmurality” value, which is the percentage thickness of the wall that is necrotic at that point.

The segmentation produces four separate point clouds marking the endocardium and epicardium in the short-axis MRI and Gd MRI images, respectively. The points are labelled with their respective slice numbers; the Gd points are also labelled with the transmurality.

**Surface reconstruction from 3D contour points**

The reconstruction step creates the LV surface models from the point clouds output from the segmentation. The data consists of sets of contour points; they are sparse in the axial direction, rarely consisting of more than 10 contours, approximately 8mm apart. Fig. 2 shows one such set.

The contours are not captured simultaneously; rather they are captured at different times but nominally all at the same point in the cardiac cycle. The low resolution and errors due to mistiming or the patient’s breathing make it difficult to create a good mesh for later processing.
The novel surface reconstruction method developed in this work is a hybrid algorithm and has been reported in detail in [15]. It combines features of point-based algorithms [20,21,22] and slice-based algorithms [23,24,25]. Fig. 3 shows a point cloud with its corresponding reconstructed surface.

One problem to note is that movement of the patient during the scanning can result in some slices being translated parallel to the slices. This should be corrected without removing any genuine bulges caused by aneurysms. In VPH2, the contours are corrected by aligning the centres of mass of the contour points along a linear regression line. Slices containing aneurysms have to be manually excluded from the correction.

**Gadolinium heart ventricle registration**

Registration is necessary because the Gd MRI is taken in an independent pass, so a correspondence has to be established between the Gd data and the short-axis MRI surface. This is achieved using the iterative
closest point (ICP) algorithm [26]; ICP is a fast, classical and well-tested registration algorithm which does not rely on sensitive surface information.

ICP is used to minimise the difference between two point clouds. It iteratively updates the transformation (translation and rotation) needed to minimise the distance between two input point sets, and always converges monotonically to a local minimum with respect to the distance objective function. Its output is the refined transformation matrix.

The input data is low-resolution in the axial direction and noisy. There are no surface landmarks apart from bumps, which are as likely to be noise as real features. In addition, the top and bottom of the ventricle are absent from the data, the up-and-down motion of the heart making them too difficult to capture; if the input datasets have different lengths missing, or parts were captured at different points in the cardiac cycle, registration in the axial direction becomes very difficult. Details on these problems, and approaches to solve them have been previously reported in [15]. Work currently taking place to facilitate the process will allow the inclusion of the position of the septum (the wall between the right and left ventricles) in the segmented input data, thus providing a reliable constraint for the relative rotation of the surfaces, and the identification of landmarks to constrain the vertical translation component.

After the transformation matrix is calculated from the registration of the two models, the transmurality values on the Gd data are mapped to the short-axis surface in the following manner. The gadolinium points and the short-axis surface are both mapped to a parameterised surface – in this case, a cylinder. Although the individual points in both cases represent the same physical surface, there is no correspondence between the two sets of points. Interpolation is then performed on the parameterised surface to map the transmurality associated with the gadolinium vertices. In the final step, the interpolated transmurality is mapped back from the cylinder to the vertices on the short-axis surface. The process is illustrated in Fig. 4.

![Figure 4. Mapping of transmurality from Gd MRI points to short-axis MRI surface](image)

7.5.5. SURGICAL SIMULATION

This section describes an interactive tool for the simulation of LV restoration surgery, consisting of cutting, stitching and patching. When these operations have been completed, the stitches are pulled tight, and the LV deforms elastically to predict the final post-operative shape. The tool is implemented on the Multimod Application Framework (MAF) platform for medical visualisation [27], and makes extensive use of the Visualization Toolkit (VTK) library [28].
The purpose of the tool is the rapid prototyping of surgical options, indicating to the surgeon which options are likely to give good or bad results. The timescale for surgical planning is quite short: in this study, the MRI data are available 3-7 days before the surgical decision. The pre-processing of the images is performed by the MRI personnel, and the surgeon is expected to spend no longer than 30 minutes on simulation and planning, so the tool should be easy to use and quick to return quantitative predictions of the post-operative ventricle and its functionality.

Initial Visualisation

Fig. 5 shows the epicardium and endocardium, displayed as mesh surfaces. The user can interactively view the ventricle from any angle, with translation and zooming controlled via the mouse. The resolution needs to be high, partly so that the user does not see shape artefacts arising from discretisation, and partly because the mesh-cutting algorithm in VTK produces better results when the triangles are small; the endocardium and epicardium surfaces in Fig. 5 contain approximately 27,000 and 38,000 triangles respectively. If the user wishes to view the endocardium through the epicardium, a pseudo transparency is available by switching to a wireframe view; true transparency would be desirable, but would be too computationally expensive to implement with so many triangles.

![Initial Visualisation](image)

**Figure 5.** The left ventricle, showing the endocardium and epicardium surfaces and the necrotic area, shaded dark.

The colour scale for transmurality is the same as that used throughout the VPH2 project: a linear mapping of the percentage onto a 10-point scale from red to black, with 0% (completely healthy) mapped to pure red, and 100% (completely necrotic) mapped to pure black. The relationship between transmurality and...
the probability of recovering myocardial function [29,30] is itself sufficiently linear that the scale can be considered a good representation of the clinical severity.

In its current form, the visualisation lacks location features, and the positions of the coronary arteries, which constrain where sections can be cut, are not marked. As noted, this is being addressed currently by the inclusion of the position of the septum. Further, ongoing work to support revascularisation will provide a map of the coronary arteries, which will be registered and displayed on the surface.

**Cutting operation**

For the cutting operation, the user selects a shape for the cut from a dialog menu. Currently the shapes available are triangle, spindle or ellipse; these were agreed with cardiologists and the cardiac surgeons in the project consortium. Mathematical precision is not necessary in defining the cut, as the shape cannot be reproduced exactly in the operating theatre; it is sufficient that the tool allows a reasonable approximation to the common surgical options.

On first thoughts, a freehand drawing tool might appear to be an attractive way of defining the position of the incisions, but in practice the cutting tool widget is much quicker and less clumsy to use than such a drawing tool would be. It also stands repeated use without becoming tiresome. While the user is not free to draw every possible shape, the system includes the shapes that are commonly used in practice, and more could easily be added if users required them.

A further advantage of providing a set menu of shapes is that the corresponding stitching patterns can be determined in advance, allowing stitching to be simulated automatically; this would be difficult to achieve with an unconstrained shape.

![Figure 6. Cutting tool widgets: (a) triangle; (b) spindle; (c) ellipse](image)
When the shape of the cut is selected from the menu, an interactive widget appears on the epicardium surface, as shown in Fig. 6. The widget can be positioned and manipulated by using the spherical handles supplied. It is initially positioned on the surface facing the virtual camera, and an automatic correction is applied at each interaction to ensure that the widget remains as close as possible to the surface, whilst keeping the handles visible. When the user is satisfied with the widget position, the “cut” button is selected and the widget shape is punched through the surfaces.

Fig. 7 shows the result of the ellipse cut; the epicardium diametrically opposite the cut is visible through resulting hole. The cut itself is executed by the standard VTK cutting function, but the widgets and the implicit functions controlling the cut are novel VTK extensions created specifically for this work.

![Figure 7. Result of cutting using an ellipse widget](image)

**Stitching**

When the user has cut the required hole in the LV, an option is provided to place a patch (see Section 4.4), or to stitch without a patch. For the latter, the stitches are placed automatically across the hole with no user input. In the case of the spindle and ellipse, the stitches are placed normal to the central axis, which is defined as the longest chord between pairs of points around the hole. Pairs of points opposite each other across the central axis are identified, and each pair is joined by a stitch. Fig. 8a shows the stitching pattern for a spindle-shaped hole. In the case of the triangle, the longest chord is simply the longest side, and is not the correct axis for the stitching direction; instead, the correct way to stitch a triangle is to place the stitches parallel to the shortest side. To avoid buckling, the mid-point of the shortest side is pulled outwards, deforming the triangle into a kite shape. This is shown in Fig. 8b.
Patching

As stated in the Introduction, one of the aims of LV restoration surgery is to reduce the volume of the LV to a normal size. However, if the amount of necrotic tissue that must be removed is so large that the post-operative LV would become too small to function suitably, the surgeon may decide to insert a patch.

The patch is a piece of dacron material which is placed across the surgical hole, beneath the endocardium. The edge of the hole is then stitched to the patch, rather than to the opposite edge of the hole. This enables the surgeon to close the hole but leave a LV with an optimal volume. It also gives the surgeon some extra control over the final shape.

In this work, when the patch option is selected, a patch is placed automatically in the hole. The precise shape and size are not important, so the patch is created with the same shape as the hole (triangle, spindle or ellipse) and slightly larger, so that the hole will be sealed. Unlike the automatic stitching in the previous section, the procedure of stitching to the patch requires manual input from the user, since the placement of stitches on the patch depends on how much closure is required to achieve the desired reduction in the ventricle volume.

In the case of the spindle and ellipse, it would be possible to change the dimensions of the stitching line with two parameters corresponding to the percentage closure in the axial and normal-to-axis directions; however, it is extremely difficult to generalise this to the triangle case, or indeed, to any other shape that might implemented. A convenient and general solution to this is to re-use the cutting tool widget (see Section 4.2) as a stitch-to-patch tool. The tool is constrained to “stick” to the patch and to remain within the hole. The stitches join the points on the edge of the endocardium hole to points on the patch, controlled by the widget. Each point on the hole is stitched to the patch point which is nearest to the nearest widget point. Fig. 9 shows a patch and its associated stitching tool in a spindle-shaped hole.

It can be seen in Fig. 9 that the patch mesh is composed of quad cells, rather than triangles; this anticipates the elastic deformation in the following section, in which the low shear strength of the quads should be a closer match to properties of the dacron material than triangles.
Deformation

The final stage of the surgical simulation is to predict the final shape of the LV after the stitches have been pulled tight and the ventricle has deformed to its new shape. This requires an elastic model of the LV. A review of deformable modelling in surgical simulation can be found in [31]. Most elastic models used in surgical simulation are of two types: finite element and spring-mass. Finite element models divide the tissue into volumetric cells and are the model-of-choice when highly accurate simulation of mechanical properties is required; however, they have not proved popular because of the difficulty in creating a well-formed volumetric mesh and in simulating surgical cutting in real time. Spring-mass models represent a surface, or sometimes a volume, by a set of point masses joined by springs. As such, they are simpler and faster to solve than finite elements, and are the most common type of model used in surgical simulation. The disadvantages of spring-mass models are that they cannot simulate physical properties as accurately as finite elements (it is difficult to decouple the tension and shear constants), and additional components are required to simulate bending forces.

In this work, a spring-mass model of the LV is being developed. The components included in the model are the meshes corresponding to the endocardium and the patch, and the stitches. The epicardium is omitted, because it is no longer of any quantitative interest; all of the subsequent post-operative functional analysis is based on the endocardium alone. The model corresponds to the mesh in that the nodes of the mesh become point masses, and the edges of the cells become springs. However, the number of triangles in the endocardium mesh is too large for the deformation equations to be solved in a reasonable time, so the mesh is first decimated to produce a low-resolution version composed of approximately 6000 triangles. The springs are Hookian, so the force $F_{ij}$ on each point $i$ due to spring $j$ is given by

Figure 9. A spindle-shaped hole with a patch and the associated stitching tool.
\[ F_{ij} = K_{ij} (L_{ij} - L_{0ij}) \frac{x_j - x_i}{|x_j - x_i|} \]  

...(1)

where \( K_{ij} \) is the spring constant, \( L_{ij} \) is the length, \( L_{0ij} \) is the rest length, and \( x_j \) and \( x_i \) are the positions of the end points. With a mass \( m_i \) and a damping factor \( \gamma_i \) associated with each point, the equation of motion of point \( i \) is

\[ m_i \ddot{x}_i = \sum F_{ij} - \gamma_i \dot{x}_i \]  

...(2)

In the simulation shown here, all the masses \( m_i \) were set to 1.0, and all the damping factors \( \gamma_i \) were set to 1.4, corresponding to a critical damping ratio of 0.7. All of the spring constants \( K_{ij} \) were set to 1.0. These were example values to demonstrate the deformation, but the model will ultimately include correct elastic constants, with bending and pressure forces. The rest lengths were set to the lengths of the springs in the starting configuration. The stitches were pulled tight by setting the rest lengths of the stitches to a small value, and the system was deformed to its new equilibrium state by symplectic Euler integration. The maximum stable timestep is limited by the highest frequency mode of the mesh, or approximately by the frequency of the stiffest spring. A detailed analysis of the stability of numerical integration methods has been given by [32]. Fig. 10 shows an endocardium before closure, and the post-operative shape after 1,000 Euler iterations. The simulation required 50 seconds on a 2.3 GHz AMD processor.

![Figure 10. Deformation of the endocardium: (a) pre-operative shape, showing spindle-shaped cut with stitches; (b) predicted post-operative shape after 1,000 Euler iterations of mass-spring model](image)
cycle, and a smaller external pleural pressure, which varies with the respiratory cycle. It is not possible to directly measure the patient-specific intraventricular pressure without invasive catheterisation; therefore the end-diastole value will be predicted from the known properties of the patient-specific heart, using the suite of functional assessment tools currently being developed in parallel within VPH2 (see Section 4.6).

As stated previously, a problem with Euler integration is that the maximum timestep is limited by the highest natural frequency in the mesh, so that a small number of “stiff” springs can force the whole integration to run slowly. One solution to this is to balance the dynamics of the mesh by adjusting the masses of the points so that every spring has the same natural frequency. Thus, stiff springs will be attached to larger masses, so that they move more slowly. This is possible in this application because the distribution of masses affects only the dynamics of the mesh, not the final equilibrium position – the dynamics of the deformation are of interest only to the extent that the animation should remain stable from start to finish. This will allow the tissue, stitches and patch to be assigned different spring constants without having to reduce the speed of the integration.

Finally, it is noted that the simulated LV is under pressure, and therefore that the act of cutting should itself cause some elastic deformation, prior to stitching. This means that the equilibrium position of the mass-spring model is that of the mesh before the cut, not after. Further investigation is taking place to see if the effect is significant and, if so, to take the additional deformation into account.

**Outputs and integration with VPH2**

This work described lies within the larger framework of VPH2, and forms a link between the pre-operative functional assessment of the patient and the post-operative functional predictive tools.

When the user has completed the simulated surgery, various quantitative measurements must be made on the predicted post-operative LV to integrate with the post-operative assessment tools. These measurements are to be added to the workflow in the immediate future.

The most important measurement is the volume between the top and bottom slices, which is used to calculate the total end-systolic volume of the ventricle. Another important shape parameter with an effect on the efficiency of the LV is sphericity, which is the ratio of the length to the radius.

The functional assessment tools in VPH2 are based on a standard 18 or 16-sector model of the LV, the conventional display for which is the “bullseye diagram”. This shows the ventricle viewed from above and flattened, with the sectors from the top of the LV at the centre and the sectors from the bottom of the LV towards the periphery, as shown in Fig. 11.
Figure 11. Bullseye diagram of a left ventricle divided into 16 sectors, showing the distribution of necrotic areas (dark). The top sectors are at the centre and the bottom sectors are around the outside.

The input epicardium or endocardium are labelled at each point with the sector number. By this means, it is possible to calculate the fraction of each sector that was removed during surgery. This is essential for the post-operative tools that predict the motility of each sector of the ventricle. These tools are the subject of a separate paper currently in preparation.

Validation

The validation phase of the project will start shortly. MRI images of the pre-operative and post-operative states will be available against which to test the predicted outcome. VPH2 is currently running a study with 24 patients, from whom follow-up MRI images will be captured 2 or 6 months after the surgery. The delay between the operation and the follow-up MRI is not ideal for validation, as the shape of the heart could again change in the intervening period, but it does have the advantage of allowing the VPH2 predictions to be compared with the medium-term outcome, which is clinically more important than the immediate post-operative result.

The greatest difficulty in validating the system is not the availability of the before and after images, but in ensuring a true correspondence between the actual surgery and the virtual surgery performed in the simulation. It is not possible to require that a simulation should be exactly replicated in the operating
theatre, nor that the surgeon should replay the operation immediately afterwards on the computer. While the cardiac surgeons involved will provide as accurate a record of the actual surgery performed to support this process, the project also intends to film the surgery, to record as faithfully as possible the location, shape and size of the cut. This will allow a comparison between the predicted and actual shape of the post-operative LV, and the validation of the VPH2 functional predictive tools which are currently being developed in parallel (see Section 4.6).

7.5.6. FURTHER WORK

As mentioned in the earlier sections, now that the main features of the system are in place, further work continues to enhance the available facilities and to improve the running of the system. In addition to the integration with the VPH2 assessment tools mentioned previously in Section 4.6, and the validation discussed in Section 4.7, further work will complete the surgical simulation tool described in Section 4, including the visualisation of the septum and the vasculature on the epicardium and the pressurisation of the mass-spring model.

7.5.7. CONCLUSIONS

Ischemic heart failure remains a significant health and economic problem worldwide despite continued progress in treatment. The VPH2 project is currently developing an integrated system for patient-specific treatment planning in the case of left ventricle dysfunction. In this paper, we have presented a user-friendly visualisation system for surgical planning and simulation, which forms part of this.

The proposed system allows the user to visualise the dysfunctional left ventricle and the degree of ischemic damage interactively, and to simulate the surgical procedures of cutting, patching and stitching. A spring-mass model predicts how the ventricle will deform to its post-operative shape and further work will make available quantitative predictions of the post-operative shape and volume to other parts of the treatment planning pipeline in VPH2.

ACKNOWLEDGEMENTS

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7.5.8. REFERENCES


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7.5.9. FIGURE CAPTIONS

Figure 1. (a) Short-axis MRI image of heart, indicating the left ventricle; (b) Gd MRI image of heart, indicating the brighter necrotic area in the septal region of the myocardium.

Figure 2. Example of a point cloud corresponding to the segmentation of the epicardium.

Figure 3. Point cloud with reconstructed surface.

Figure 4. Mapping of transmurality from Gd MRI points to short-axis MRI surface.

Figure 5. The left ventricle, showing the endocardium and epicardium surfaces and the necrotic area, shaded dark.

Figure 6. Cutting tool widgets: (a) triangle; (b) spindle; (c) ellipse.

Figure 7. Result of cutting using an ellipse widget.

Figure 8. Stitching patterns: (a) spindle; (b) triangle.

Figure 9. A spindle-shaped hole with a patch and the associated stitching tool.

Figure 10. Deformation of the endocardium: (a) pre-operative shape, showing spindle-shaped cut with stitches; (b) predicted post-operative shape after 1,000 Euler iterations of mass-spring model.

Figure 11. Bullseye diagram of a left ventricle divided into 16 sectors, showing the distribution of necrotic areas (dark). The top sectors are at the centre and the bottom sectors are around the outside.


**Purpose.** Ischemic mitral regurgitation (IMR) is usually treated through restrictive annuloplasty via rigid rings, which constrain the annular shape, or flexible rings, which preserve annular dynamics. The choice between these two options is still debated and several methodologies have been adopted to identify the best solution. Among those, finite element (FE) models have provided useful insight, but past models suffered of simplifications that could have limited and biased the conclusions. We aimed at analyzing the effects of ring’s flexibility in restrictive annuloplasty through mitral valve (MV) patient-specific realistic FE models based on cardiac magnetic resonance (CMR) imaging, thus overcoming previous limitations.

**Methods.** CMR imaging of 18 evenly rotated long-axis planes (one every 10°) along the left ventricular long-axis was performed in 7 ischemic patients (55 time-frames/cardiac cycle). In each plane and for each systolic frame, MV annulus, leaflets, and papillary muscles were manually identified using custom software. These structures were then automatically reconstructed in the 3-D space, and used as input to the MV FE models. MV tissue response was modeled as non-linear elastic and anisotropic. A physiological transvalvular pressure load was applied to the leaflets to simulate valve closure up to peak systole. For each patient, three conditions were simulated: (i) pre-operative, (ii) after insertion of a ring with closed profile and regionally varying bending stiffness (CV ring), and (iii) after implanting a rigid ring with partially open profile at saddle-horn (RO ring).

**Results.** The RO ring restored MV competence in 7/7 patients resulting in higher coaptation length, while CV ring succeeded only in 5/7. Conversely, annular dynamics was lost with the RO ring, while CV ring partially preserved it. Both rings significantly reduced leaflets stresses and tensions on chordae tendineae and papillary muscles.

**Conclusions.** While RO rings seem resulting in a good performance, flexible CV rings could not always guarantee to counterbalance the effect of leaflets tethering associated to IMR. Moreover, despite their flexibility, annular dynamics was not completely preserved. Our patient-specific FE approach could provide new insight in optimizing tuning of local stiffness, thus potentially improving the performance of new ring design, as well as help in surgery planning.

C.A. Conti¹, E. Votta¹, C. Corsi², D. De Marchi³, M. Stevanella¹, F. Maffesanti¹, M. Lombardi³, O. Parodi³, E. Caiani¹, A. Redaelli¹

7.7.1. Introduction

Dilated cardiomyopathy following ischemic disease increases the degree of heart failure and its surgical management remains controversial. The most challenging objective in the clinical decision making for the management of patients with myocardial dysfunction or overt heart failure (HF) is to choose the best option for improving myocardial function and the clinical outcome. Medical versus surgical and, among surgical options, coronary revascularization, myocardial restoration, mitral valve repair, are the proposed solutions for avoiding progression of cardiac dysfunction toward HF. Magnetic resonance imaging (MRI) can provide patient-specific identification of dysfunctioning left ventricular (LV) segments and recognition of not viable myocardium by gadolinium (GAD) late hyperenhancement pattern.

Within EU project VPH2 we aimed at developing two software tools for the quantitatively prediction the post-operative mechanical performance of the complex left ventricle: a functional assessment tool (FAT) and a functional predictive tool (FTP). In particular, the former is aimed to the automatic extraction of contours from 4D MRI images and automatic calculation of global and regional parameters (e.g. EF, synchronicity) while the latter is aimed to the prediction of postoperative LV function through mechanical modeling.

7.7.2. Methods

FAT

FAT is a software tool for MRI semi-automatic segmentation of endo- and epicardium. Two segmentation strategies were included in the tool. For endocardial detection (Figure 1.a), the region-based approach was chosen. Briefly, after initialization of some algorithm’s parameters and after the selection of one point inside the LV cavity, the applied algorithm expands the initial circle according to the initial videointensity probability distribution. The algorithm uses the detected contour as initialization for the next slice. For epicardial detection, the algorithm to be used is the based on the edge-based level-set that requires an initialized contour in the neighbor of the contour to be detected to correctly operate. The contour initialization can be provided manually or the previously detected (if present) endocardial contour can be used. After the endo- and epicardial contours have been detected from base to apex, the software automatically computes the LV volume and the LV mass.

Once all the contours were detected, the ED centroid of the LV cavity was calculated and used as the origin of segmentation. An additional point was then manually placed at the junction between the right ventricular free wall and the interventricular septum on the ED frame. Starting from that point, the LV cavity was divided into six 60° wedge-shaped segments. For each segment, regional fractional area (RFA) in
% of regional end-diastolic area (REDA) was calculated automatically throughout the cardiac cycle using a fixed-coordinate reference system. From these 6 curves in each slice, regional fractional area change (RFAC) was computed as the difference between max and min RFA, expressed in % of the regional end-diastolic area (REDA). These values for each segment were used to automatically interpret wall motion as normal (RFAC>=50%) or abnormal (RFAC<50%).

**FAT Validation**

The validation was focused on the LV dimension and function indices usually computed from the cardiac MRI images, such as end-diastolic (ED) and end-systolic (ES) LV volumes, stroke volume (SV), ejection fraction (EF), LV mass computed both at ED and ES. For these measurements, the “gold standard” is represented by the result of the manual tracing of endo- and epicardial LV contours that an expert cardiologist performed on a subset of patients.

A subset of 15 patients with previous myocardial infarction, manifesting regional wall motion abnormalities, was selected. All cardiac MRI studies were performed using a 1.5 Tesla scanner (Signa Hdx, GE Healthcare, Milwaukee, Wisconsin). An eight-element cardiac phased-array receiver surface coil with breath-holding in expiration and ECG-gating was used for signal reception. Three standard cine long-axis slices and a stack of contiguous cine short-axis slices from the atrio-ventricular ring to the apex were acquired using a steady-state free-precession pulse sequence with the following parameters: 30 phases, slice thickness 8 mm, with no overlap and no gap, views per segment 8, number of excitation 1, field of view 40 cm, matrix 224x224, reconstruction matrix 256 x 256, repetition time 3.5 ms, echo time 1.5 ms, flip angle 45°, bandwidth 125 KHz.

The MRI data were analyzed using commercial software (MASS 6.1, Medis, Leiden, the Netherlands). The expert cardiologist proceeded into the conventional analysis of these images, by manual tracing endo- and epicardial LV contours. Biventricular volumes, function and LV mass were measured using standard volumetric techniques with that dedicated software. Results for each parameter were compared to the “gold standard” by linear regression and Bland-Altman analysis. The goodness of the linear fitting of the two measurements was evaluated the $r^2$ coefficient of the regression. Bias (in absolute and % values) and 95% limits of agreement were computed for each parameter. Also, to test the performance of the developed procedure in order to automatically detect possible wall motion abnormalities, a “gold standard” for wall motion interpretation was decided as the visual interpretation of the dynamic images from the same expert cardiologist who performed the contour tracings.
FPT

FPT is a software tool for MRI modelling of post-operative mechanical performance of the complex left ventricle. The left ventricle is divided into 6 longitudinal sections and 3 circumferential sections, for a total of 18 segments (Figure 1.b). For each segment we applied a nearest neighbour correction algorithm to compute segmental time-variant strains both in longitudinal and circumferential direction from 4-D short-axis cardiac magnetic resonance imaging data. The software tool allows to calculate independently or in combination: 1. the simulation of the restoration procedure so to provide the new ventricular shape, dimension and performance; 2. the simulation of the resynchronization of selected regional segments; 3. the simulation of the effects of a revascularisation procedure on regions of hibernated myocardium; 4. the calculation of the myocardial contractility enhancement due to left ventricular end-diastolic volume reduction following the mitral regurgitation correction.

7.7.3. Results

FAT validation

Of the 15 patients, two were excluded for the presence of artifacts. Good correlations were found with the “gold standard” measurements of LV ED and ES volumes, as well as with the derived parameters of SV and EF% (Table 1).

Table 1. Regression analysis results.

<table>
<thead>
<tr>
<th></th>
<th>EDV</th>
<th>ESV</th>
<th>SV</th>
<th>EF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression line</td>
<td>y=0.9859x+5.0906</td>
<td>y=0.9989x+4.3418</td>
<td>y=0.9819x−0.2435</td>
<td>y=1.0006x−1.5555</td>
</tr>
<tr>
<td>r²</td>
<td>0.9879</td>
<td>0.9943</td>
<td>0.968</td>
<td>0.9796</td>
</tr>
</tbody>
</table>

Also for LV mass, correlation was acceptable: ED, y = 1.0722x + 5.4149, r²=0.8091; ES, y = 0.9726x + 12.86, r²=0.7353. Bland-Altman analysis resulted in minimal bias and narrow limits of agreement in LV ED and ES volumes, and derived parameters. On the contrary, a significant bias and wider limits of agreement was found for LV mass (Table 2).

In particular, the bias expressed as error%/mean of the gold standard values resulted less than 10% in all the parameters except ED LV mass. As regards the automated detection of LV wall motion, the gold standard resulted in 135 segments interpreted as normal, and 99 as abnormal.

Of the 234 segments, 77 were classified as True Positive, 115 as True Negative, 20 as False Positive and 22 as False Negative. These counts resulted in a sensitivity of 77.8%, specificity of 85.1% and accuracy of 82%.
Table 2. Bland-Altman analysis results.

<table>
<thead>
<tr>
<th></th>
<th>Bias</th>
<th>Bias as error%/mean</th>
<th>95% limits of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV</td>
<td>-2.5 ml</td>
<td>-1.4%</td>
<td>-17.7 ÷ 12.7 ml</td>
</tr>
<tr>
<td>ESV</td>
<td>-4.2 ml</td>
<td>-4.1%</td>
<td>-15.3 ÷ 6.8 ml</td>
</tr>
<tr>
<td>SV</td>
<td>1.7 ml</td>
<td>2.1%</td>
<td>-7.6 ÷ 11.0 ml</td>
</tr>
<tr>
<td>EF%</td>
<td>1.5 %</td>
<td>3.2%</td>
<td>-3.2 ÷ 6.2 %</td>
</tr>
<tr>
<td>ED LV mass</td>
<td>-15.2 g</td>
<td>-11.2%</td>
<td>-44.9 ÷ 14.6 g</td>
</tr>
<tr>
<td>ES LV mass</td>
<td>-8.7 g</td>
<td>-5.8%</td>
<td>-41.3 ÷ 23.8 g</td>
</tr>
</tbody>
</table>

**FPT**

The software tool allows for the estimation of the postoperative performance of the repaired ventricle (EDV, volume time-course, SF, EF).

1. **Restoration.** Myocardial segments to be partially or totally resected can be identified on the basis of their reduced peak contractility associated to Gadolinium uptake information. Once the segments have been selected from the FPT interface, the user can set the fractional circumferential and longitudinal extent of the tissue to be removed within the segment. The volume reduction induces a wall tension decrease and an associated muscle contractility increase [1].

2. **Resynchronization.** The software shifts the contractility curves and calculates the new ventricular performance. Due to the increased stroke volume, it is also hypothesised that the end diastolic volume can be reduced. The decrease extent will correspond to a fraction of the difference between the pre-operative and post-operative stroke volumes [2].

3. **Revascularization.** Myocardial segments that can be revascularised can be identified on the basis of their reduced peak contractility in absence of Gadolinium uptake. In order to account for an incomplete recover of the contractile function, the user has to set the degree of recovery. Since the post-operative stroke volume increases, it is also hypothesised that the end diastolic volume can be reduced [3,4,5]. The decrease extent will correspond to a fraction of the difference between the pre-operative and post-operative stroke volumes. LV size reduction will then cause the reduction in wall tension and an associated increase in muscle contractility whose magnitude is determined by the inotropic gain parameter.

4. **Mitral regurgitation correction.** The prediction relies on the hypothesis that the left ventricular volume decreases after mitral valve surgical repair. The decrease extent will correspond to a fraction of the preoperative regurgitant volume [3, 4]. Once the volume reduction is calculated, the software esteems the LV reduction, the reduction in wall tension and the associated increase in muscle contractility.

Preliminary tests have been carried out concerning synthetic data and clinical data.
7.7.4. Conclusions

In this study, we present two semi-automated softwares for the assessment of the LV function and for the prediction of the effects of surgical treatments on LV performance, accounting for different scenarios. Although further tests to optimize and validate the algorithms are mandatory, these tools could constitute a reliable aid for the planning of surgical procedures.

In the next step the FTP simulation parameters used in the present version will be refined accordingly with the feedback of the clinicians and an accurate literature review. Also, further parameters will be included, such as the effects of changes in the peripheral resistance and in the heart rate, typically associated to the postoperative scenario.

Acknowledgements

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7.7.5. References


Geometrical multiscale model of an idealized left ventricle with fluid-structure interaction effects coupled to a one-dimensional viscoelastic arterial network

Toni Lassila,1, Cristiano L. Malossi,2 Matteo Astorino,2 and Simone Deparis*

1 MATHEON-CMC, École Polytechnique Fédérale de Lausanne
EPFL, Station 8, CH-1015 Lausanne, Switzerland,
{toni.lassila, cristiano.malossi, matteo.astorino, simone.deparis}@epfl.ch

Abstract

A geometrical multiscale model for blood flow through an idealized left ventricle and the main arteries is presented. The blood flow in the three-dimensional idealized left ventricle is solved through a monolithic fluid-structure interaction solver. To account for the interaction between the heart and the circulatory system, the heart flow is coupled through an ideal valve with a network of viscoelastic one-dimensional models representing the arterial network. The geometrical multiscale approach used in this work is based on the exchange of averaged/integrated quantities between the fluid problems. The peripheral circulation is modelled by zero-dimensional windkessel terminals. We demonstrate that the geometrical multiscale model is (i) highly modular in that component models can be easily replaced with higher-fidelity ones whenever the user has a specific interest in modelling a particular part of the system, (ii) precise in that it reaches a stable limit cycle of flow rate and pressure in a few heartbeat cycles when driven by a periodic force acting on the epicardium, and (iii) capable of operating at physiological regimes.

Keywords: left ventricle; fluid-structure interaction; hemodynamics; geometrical multiscale modelling; heterogeneous models.

Introduction

The accurate prediction of localized effects of therapeutic procedures on patients suffering from cardiovascular and arterial disease requires the simulation of the entire closed-loop system: the heart, the aorta, the arteries, the peripheral circulation, the veins, the lungs, and the pulmonary circulation. For this purpose many one-dimensional (1D) and zero-dimensional (0D) lumped parameter models for blood flow have been proposed in literature—see, for example, [24] for a recent review. While the 0D models do well in capturing the essential phenomena of the flow, the lumped parameters therein are often uncritically physiological meaning and need to be calibrated based on patient-specific measurements before the models can produce physiological results. Therefore, when using such models it may be difficult to predict changes in a patient’s physiology after a hypothetical surgery, since no measurements are at present available for calibration.

With the advent of highly scalable parallel CFD codes, full-fidelity three-dimensional (3D) fluid-structure interaction (FSI) simulations of localized compartments of the cardiovascular system have become feasible. In this framework, we recall for example the works [1, 12, 15], where 3D FSI simulations of important parts, namely the heart and the ascending aorta, have been reported. With respect to the reduced models, these high-fidelity models are characterized by more realistic physical laws and they can potentially provide very accurate information on the complex physical phenomena that occur in the various compartments. From a practical point of view, however, a 3D FSI simulation of the whole cardiovascular system is characterized by excessive computational costs that would make such a simulation feasible even with the use of the most modern supercomputer.

From this perspective, the geometrical multiscale model proposed in [8, 9], coupling together dimensionally heterogeneous models (3D, 1D, and 0D), offers a compromise between the two previous approaches (reduced models and 3D FSI). The use of 3D FSI models is therefore limited to specific regions of interest, where the 3D description of the domain plays an important role (e.g. in the heart and/or in the aortic arch), in order to provide accurate information on the local physics. The remaining regions (i.e. the other major branches of the arterial tree) still rely on very cheap 1D models, which are perfectly suited for describing the waveform propagation along the arterial network. Finally, the model is completed by introducing lumped parameter models at the end of the arterial segments (representing the peripheral circulation) and for some other interface conditions (e.g. heart valves).

In this work the geometrical multiscale approach is adopted with a twofold objective: on the one hand to provide information on the global blood dynamics of the arterial system; on the other hand to accurately describe the...
cal FSI phenomena in the left ventricle. As a consequence, in our framework we describe the arterial tree and the left ventricle. From a mathematical and numerical point of view these heterogeneous computational models are coupled together by matching averaged/averaged quantities, namely the flow rate and the normal component of the traction vector, and the implicit coupling at each time step is achieved through nonlinear quasi-Newton iterations [14]. The geometrical multiscale framework has been implemented with the state-of-the-art parallel CFD code LifeV [5], and is highly modular and easily extensible to include more fine-scale consistent models.

Possible clinical applications involve pre- and post-surgical simulations of a pathological left ventricle, prediction of critical quantities such as cardiac output after the ventricle remodeling, and investigation of the influence of peripheral modifications of the arterial tree to the heart dynamics.

**Physical models**

Three-dimensional models. The 3D FSI model proposed here is adopted for simulation of the blood flow in the left ventricle. Despite the complexity of the blood rheology, a Newtonian incompressible fluid represents a suitable model for blood when we are not interested in the inner details of the flow [9]. The blood dynamics are therefore modeled by formulating the incompressible Navier-Stokes equations in the case of a moving fluid domain, resulting in the so-called Arbitrary Lagrangian Eulerian (ALE) formulation [17].

In order to describe the evolution of the fluid domain, the placement of the endocardium (the inner surface of the left ventricle) has to be recovered. Within this perspective two main approaches can be identified. A first possibility consists in reconstructing the displacement field from a suitable interpolation in space and time from a set of data points $h(x, t)$, $i = 1, \ldots, I$, $j = 1, \ldots, J$ obtained from medical images (see e.g. [10, 30]), followed by simulating only the fluid inside a moving ventricle. The second approach relies on an accurate mechanical simulation of the myocardium and on the corresponding numerical resolution of the coupled fluid-structure interaction problem, including possibly the electrical activation of the heart. Both approaches have their own challenges. The former is computationally less expensive, but the straightforward prescription of time-dependent computational geometries reconstructed from medical images, which are often characterized by noisy input data, may induce strong boundary singularities in the fluid solution (especially in the pressure field). The latter approach provides a smooth (and potentially very accurate) interface solution, but the mathematical model that characterizes an aortic tissue is often very complex and involves the description of important biological characteristics such as the fiber directions, the active and passive deformation, and the electric impulse [16, 18, 23].

In this work, we propose a different strategy, aiming at being a compromise between the two previous approaches. Rather than using the medical data to recover the displacement field of the endocardium, we focus on the reconstruction of the displacements of the epicardium, the outer surface $\Gamma_{\text{epi}}$. The resulting field is then adopted as a boundary condition of a (simplified) structural model (the linear elasticity model), which is eventually coupled with the fluid through the endocardium, now the fluid-structure interface $\Gamma_{\text{FSI}}$.

**Remark.** Note that in this approach the structural model adopted is a poor approximation of the real mechanical model. It main purpose is to smooth the noisy data and transfer them onto $\Gamma_{\text{FSI}}$. It should therefore be understood that within this strategy we can not expect to recover any physiologically relevant information on the biological tissue, such as internal stresses. Ongoing work consists in extending this strategy to more complex mechanical models [22].

Let $\Omega = \Omega_t \cup \Omega_s$ be a reference configuration of the fluid-structure system, with $\Omega_t$ and $\Omega_s$ the reference domains for the fluid and the solid, respectively. We denote by $\Gamma_{\text{FSI}} = \partial \Omega_t \cap \partial \Omega_s$ the fluid-solid interface. The current configuration of the fluid domain, $\Omega(t)$, is parameterized by the ALE map

$$A_t : \Omega_t \rightarrow \Omega(t)$$

$$x \mapsto A_t(x) = x + d_t(x), \quad (1)$$

as $\Omega(t) = A_t(\Omega_t)$, where $d_t : \Omega_t \times \mathbb{R}^+ \rightarrow \mathbb{R}^3$ are the displacement of the fluid domain. We denote by $\Gamma_{\text{FSI}}(t) = \partial \Omega_t(\Omega_t) \cap \partial \Omega_s(\Omega_s)$ the current position of the fluid-solid interface. In practice, $d_t = \text{Ext}(d_{\text{Ext}})$, where $d : \Omega_t \times \mathbb{R}^+ \rightarrow \mathbb{R}^3$ stands for the solid displacement and $\text{Ext}()$ denotes a harmonic lifting operator from $\Gamma_{\text{FSI}}$ to $\Omega_t$.

The nonlinear fluid-structure problem under consideration reads as follows (see e.g. [9, Chapter 3]):

Find the fluid velocity $u = u(x, t) : \Omega_t \times \mathbb{R}^+ \rightarrow \mathbb{R}^3$, the pressure $p = p(x, t) : \Omega_t \times \mathbb{R}^+ \rightarrow \mathbb{R}$, and the solid displacement $d = d(x, t) : \Omega_t \times \mathbb{R}^+ \rightarrow \mathbb{R}^3$ such that

$$\rho \partial_t u_{\mid A} + \rho (u - w) \cdot \nabla u - \nabla \cdot \sigma_t = 0 \quad \text{in} \ \Omega(t),$$

$$\nabla \cdot u = 0 \quad \text{in} \ \Omega(t),$$

$$\nabla \cdot d = 0 \quad \text{on} \ \Gamma_{\text{FSI}}, \quad (2)$$

with the interface coupling conditions

$$d_t = \text{Ext}(d_{\text{Ext}}), \quad w = \partial_t d_t \quad \text{in} \ \Omega_t,$$

$$u = \partial_t d \quad \text{on} \ \Gamma_{\text{FSI}},$$

$$\Pi_{\text{FSI}} = -\partial_t \sigma_t(F_\text{FSI}) \cdot \n_t \quad \text{on} \ \Gamma_{\text{FSI}}.$$
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$\sigma_f(u, p) \equiv -pI + 2\mu\epsilon(u)$ the fluid Cauchy stress tensor, 
$\mu$ the fluid dynamic viscosity, $\epsilon(u) \equiv 1/2 \left( \nabla u + \nabla u^T \right)$ the strain rate tensor, $II = ID$ the first Piola-Kirchhoff stress tensor of the structure, $F_I \equiv \nabla A$, the fluid domain gradient of deformation and $J_f \equiv \det F_I$ the Jacobian. $n_g$ and $n_e$ are, respectively, the outward unit normals to the fluid and solid domains. The displacement field $u$ is reconstructed from a suitable interpolation in space and time of some registration point on the outer surface $\Gamma_\text{fas}$ (cf. [20]).

In the linearized $St$ Vonov–Kirchhoff model the Piola tensor is approximated as:

$\Pi = \kappa \epsilon(u) + 2\mu \epsilon_u$,

with $\kappa = 1/2 \left( \frac{\nu}{1+\nu} \right)$ and $\lambda$ and $\mu$ are the Lamé coefficients. Finally, the harmonic extension problem associated to the operator $\text{Ext}()$ reads: Find $d_f \in D_0(\Omega, \mathbb{R})$ such that

$$\begin{cases}
-\Delta d_f = 0 & \text{in } \Omega_f, \\
\partial d_f = d_l & \text{on } \Gamma_f.
\end{cases}$$

One-dimensional models. The entire arterial system can be modeled as a network of 1D models, each characterized by a circular cross-section (eventually narrowed along the axial direction) and a viscoelastic arterial wall (e.g. [6, 7, 21]). Such models have proven to be able to provide useful information under physiological and pathological conditions, and therefore give insight about the main characteristics that lead to the interplay among physical phenomena taking place in the systemic arteries.

For each cross-section $S(t, z)$, let us define the state variables

$$\begin{align*}
A(t, z) &= \int_{S(t, z)} \text{d}S, \quad \text{(cross-sectional area)} \\
Q(t, z) &= \int_{S(t, z)} u(z, t) \text{d}S, \quad \text{(flow rate)} \\
P(t, z) &= \frac{1}{A(t, z)} \int_{S(t, z)} p(x, t) \text{d}S. \quad \text{(merged pressure)}
\end{align*}$$

Their evolution is governed by the following system of hyperbolic equations derived in [8]

$$\begin{align*}
\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} &= 0, \\
\frac{\partial Q}{\partial t} + \frac{\partial (Q^2/A)}{\partial z} + A \frac{\partial P}{\partial z} + K_c \frac{\partial Q}{\partial A} &= 0.
\end{align*}$$

Here $K_c$ is a resistance parameter accounting for fluid viscosity and $\alpha$ is the Coriolis coefficient. In order to close the system, an additional equation relating the averaged pressure with the other unknowns $Q$ and $A$ is needed. Considering only the elastic and viscoelastic contributions (as all the other terms are negligible in a cardiovascular setting) the following expression for the pressure–area relation can be derived [13]:

$$P - P\text{fas} = \beta \left( \frac{A}{A^0} - 1 \right) + \gamma \frac{\partial A}{A^0}$$

with

$$\beta = \frac{\pi}{4} \lambda \frac{hE}{A^0(1 - \nu^2)}, \quad \gamma = \frac{\pi}{4} \frac{hE}{A^0(1 - \nu^2)}.$$

$P\text{fas}$ and $A^0$ being the external pressure of the tissues on the vessel walls and the area of the cross-section of the vessel in the pre-stressed configuration, respectively. The vessel wall is characterized by a thickness $h$, an elastic Young modulus $E$ and a Poisson coefficient $\nu$. Finally the parameters $\beta$ and $\gamma$ are the characteristic time (usually taken equal to the systolic period) and the so-called viscoelastic angle, respectively.

In this work we use the data of the arterial network provided in [21] (Figure 2 and Table 2), the model includes 103 elements – 4 coronary, 24 aortic, 51 cerebral, 10 in the arms, and 14 in the legs.

Lumped parameter models. In order to complete our geometrical multiscale model it is necessary to include two additional elements: the peripheral circulation and the venous circuitry. Both of the $m$ are here described by means of lumped parameter models.

The peripheral circulation is taken into account by connecting the terminal nodes of the 1D network to windkessel models. In particular, here we use the three element RCR windkessel model described in Figure 1 which leads to the following equation (see [21])

$$\frac{dP}{dt} = -\frac{P}{CR_c} - \frac{R_1 + R_2}{CR_c} Q - \frac{R_1}{CR_c} \frac{dQ}{dt} + \frac{P}{CR_c},$$

where $P$ and $Q$ are the pressure and the flow rate at the terminal node, respectively, $P_c = 666 \text{ Pa}$ [5 mm Hg] is the venous pressure, while $R_1$, $R_2$, and $C$ model the resistances and the compliance of the peripheral circulation.

For the venous valves, different lumped parameter models have been proposed in literature (see [1, Chapter 7] for a review). Similarity to [1, 7], the valves are here defined as ideal diodes that allow the blood to flow in only
one direction, preventing its backflow. In order to present the model, let us consider the sake of simplicity the aortic valve surface (AV) and define on its two sides (ventricular and aortic) the mean normal stress $\mathbf{S}$ and the flow rate $Q$. On the ventricular side ($SV$), these quantities are computed as:

$$
\Sigma_{SV}(t) := \frac{1}{A_{AV}} \int_{A_{AV}} (\sigma_{1}(t) \cdot \mathbf{n}) \, d\mathbf{A},
$$

$$
Q_{SV}(t) := \int_{A_{AV}} u(t) \cdot \mathbf{n} \, d\mathbf{A},
$$

while for aortic side ($SA$) they are defined by:

$$
\Sigma_{SA}(t) := p_{a}(t) \mathbf{e}_r + \rho \mathbf{v}, \quad Q_{SA}(t) := Q(t) \mathbf{e}_r,
$$

where $p_{a} = 10$ kPa (75 mmHg) is the reference pressure. The state of the valve (open or closed) is defined according to the values of these scalar quantities and the resulting lumped parameter models is based on the following two physiological considerations:

1. If the valve is closed and $\Sigma_{SV} > \Sigma_{SA}$, then it opens.
2. If the valve is open or $Q_{SV} < 0$ (i.e., when backflow from the aorta is observed), then it closes.

Despite the fact that the valve operates only on the average/integrated quantities of the flow field, we have observed little unphysiological residual flow through it during the simulation of the diastolic phase. In any case, the modularity of our geometrical multiscale model allows for a very simple incorporation of more advanced models, e.g., for the mitral valve, since all models, be they 0D, 1D, 3D, or 3D FSI, are implemented as sub-systems that are coupled together with the same methodology.

In order to prescribe the displacement of the ventricle, while still obtaining physiological pressure values for the blood inside it, we need to model both the mitral valve and the pressure inside the left atrium. As a first approximation, the latter can be taken as constant. The mitral valve is simulated with the same diode model as the aortic valve. The mitral inflow during the diastolic phase is prescribed as an integrated flux $Q_{MV}$ related to the pressure difference between the left atrial pressure and the left atrium according to the linear law

$$
Q_{MV} = \begin{cases} 
\frac{P_{LM} - P_{LV}}{R_{MV}} & \text{if } P_{LM} > P_{LV} \\
0 & \text{otherwise}
\end{cases},
$$

where $R_{MV} = 1$ Pa/s/m$^2$ is the flow resistance of the mitral valve that we tuned empirically to fit our model parameters. Thus we make no assumption of the flow profile at the mitral valve relying on unbounded assumptions of fully-developed flow. This correctly captures the E-wave of the diastolic phase, as the mitral inflow during the early diastolic phase is believed to be mainly driven by the suction created by the expansion of the left ventricle [26]. In order to model the A-wave, i.e., the secondary flow peak caused by the contraction of the left atrium that occurs at the latter part of the diastolic phase, it is necessary to incorporate a further model with nonconstant atrial pressure and the contraction of the left atrium. We will address this aspect in a future work.

**Numerical approximation**

Three-dimensional models. The 3D FSI problem is discretized in time with a geometry-convergent explicit scheme (GCE) [3], i.e., the fluid computational domain and the corrective field are extrapolated from the previous time iteration. The Navier–Stokes equations therefore reduce to the linear Oseen equations, and the 3D FSI problem at each time level is linear. The Oseen equations are discretized in space by $\mathbf{F}_1/\mathbf{r}$, finite elements that are stabilized with the interior penalty (IP) method [2]. In this work we do not consider any turbulence model, even if in the physiological case a transition to turbulence takes place during the diastolic. In our experience the IP stabilization is sufficient to avoid stability problems related to the onset of turbulence.

The structural equations are also linear and require no special treatment. Since the geometry is treated explicitly, the fluid computational domain $\Omega(t^{k+1})$ is computed by using $\mathbf{e}_r$ as boundary condition in (4). Thus the coupled 3D FSI model after discretization gives at each timestep $t^{k+1}$ a monolithic linear system to solve for

$$
\begin{bmatrix}
F_{TT} & F_{TT} \\
F_{TT} & F_{TT}
\end{bmatrix}
\begin{bmatrix}
\rho_{LM} \\
\rho_{LV}
\end{bmatrix}
+ \begin{bmatrix}
\mathbf{B}_u & \mathbf{B}_u \\
\mathbf{B}_u & \mathbf{B}_u
\end{bmatrix}
\begin{bmatrix}
\dot{u}^{k+1} \\
\dot{u}^{k+1}
\end{bmatrix}
= \begin{bmatrix}
\mathbf{F}_1(t^{k+1}) \\
\mathbf{F}_1(t^{k+1})
\end{bmatrix}
$$

where $\dot{y} := (u^a, p^a)$ denotes the fluid variables, vectors with subindices $\Gamma$ represent all the variables on the fluid-structure interface $\Gamma_{FS}$, $\lambda$ is a Lagrange multiplier that corresponds to the force transferred from fluid to structure, and the blocks $F_{TT}$ and $S_{TT}$ correspond to the sub-blocks of the finite element matrices of the fluid and structure problems respectively. The 3D FSI system (13) is solved by a GMBLS method preconditioned by overlapping diagonals Schwarz preconditioners based on an exact block factorization of the system in the block-composed form.

The solution strategy of the monolithic 3D FSI system (13) is detailed in [3].

**One-dimensional models.** By inserting (7) into (6), after some manipulations, we reach a system of differential equations that can be written in a classical conservative form as follows

$$
\frac{\partial U}{\partial t} + \frac{\partial F(U)}{\partial x} + S(U) = 0,
$$

where $U$ are the conservative variables, $F$ the corresponding fluxes, and $S$ represents the source terms. Following
[5] we solve problem (4) by using an operator splitting technique that takes a fully explicit second-order Taylor-Galerkin type for the elastic part of the operator, followed by a viscoelastic correction step. A full description of the solution method is given in [13].

Geometrical multiscale algorithms
The coupling between all the elements in the network (including all the 3D arterial segments and the 3DFSI heart) is provided by imposing at each interface the conservation of the flow rate \( \dot{Q}_{v,m} \) and the equilibrium of the normal stresses \( \Sigma_{n,m} \):

\[
\forall e = 1, \ldots, C : \begin{cases}
\sum_{m=1}^{M_e} \dot{Q}_{v,m} = 0, \\
\Sigma_{n,1} = \Sigma_{n,m}, \quad \forall m = 2, \ldots, M_e
\end{cases}
\]

(15)

where \( C \) is the total number of coupling interfaces, and \( M_e \) is the number of models coupled by the \( e \)-th coupling interface (see Figure 2). To satisfy the set of equations (15),

\[ \text{Figure 2 General configuration for the } e\text{-th coupling between } M_e\text{ models.} \]

we can use different coupling strategies corresponding to the imposition of different quantities on the boundaries. In other words, we can set up each subproblem with different combinations of boundary data over the coupling interfaces. Some examples are provided in [14].

The global coupled system is then solved by using a classical nonlinear Richardson strategy until convergence to a sufficient tolerance has been achieved. In particular, we use a quasi-Newton iterative technique where we compute the approximate Jacobian matrix of the coupled problem and then proceed to correct each iteration using a Broyden update strategy. This approach leads to a convergent coupling algorithm even when more than one hundred constituent models are coupled together. In particular, we reach the convergence in few iterations (around 5, with a tolerance of \( 1e-6 \) and without topological changes) after an initial buildup phase. In case of topological changes of the system between two time steps (such as the opening or closing of the aortic valve), we are forced to discard the previous Broyden approximant for the Jacobian of the coupled problem and then proceed with a reinitialization of the Jacobian matrix by performing one inexact Newton step. This causes an increase of the average number of iterations required by the Broyden method, due to the fact that all the previous updates of the Jacobian are lost, even those unrelated to the change of the topology. Therefore a better approach would be to reinitialize just the lines/columns directly affected by the topological change. This and other improvements will be discussed in future works. More details about the coupling algorithms are provided in [14].

Results
The idealized heart is modeled as an ellipsoid with two valves on the top, the larger one being the mitral valve and the smaller one the aortic valve. The ellipsoid is discretized using two tetrahedral meshes. The meshes are matching at the interfaces. The mesh for the fluid consists of 41,250 tetrahedral elements (structured) with 7,943 vertices, and the mesh for the structure consists of 25,080 tetrahedral elements (structured) with 6,256 vertices. In Figure 3 we display a baseline mesh for the fluid and structure parts respectively. These meshes are refined in order to obtain the meshes used in the actual simulations. At the top of the fluid mesh the two circular valve surfaces can be seen.

As a first test of our proposed multiscale model, we prescribe idealized inputs for the left ventricle, mainly the atrial pressure \( p_{aa}(t) \) and a time-varying normal force \( g_{nf}(t) \) acting on the epicardium to simulate a heart undergoing electromechanical activation and deformation. The applied force is shown Figure 4 and it can be identified using the time-varying elastance method of Suga et al [2].

The goal is to demonstrate that our multiscale model is stable and that its accuracy is sufficient to be a good model for the heart. In a future work we aim to consider an applied displacement of the structure obtained from a set of medical images that could be used to obtain more realistic patient-specific behavior.

Model parameters and inputs are described in Table 1 for reference. The numerical simulation of the left ventricle is initialized with \( u = 0, p = 0 \) and with both valves closed at the end-of-diastole. A reference pressure of \( 10 \text{ kPa} \) [76 mmHg] is imposed at the aortic valve, which means that the pressure rises until it reaches a physiological level at around \( t = 0.04 \text{ s} \) and the aortic valve opens. The simulation is allowed to proceed until \( t = 4.8 \text{ s} \), i.e., six heartbeats, in order to reach the physiological pressure level. The time step for the 3DFSI simulation is \( \Delta t = 0.001 \text{ s} \).
\[ \omega := | \nabla \times \mathbf{u} | \] inside the ventricle during the early diastole are shown in Figure 5 and Figure 6. The velocity profile is strongly nonparabolic in the early diastole and only develops into parabolic inflow during the middle part of the diastole. With the model used we did not capture the A-wave effect of the atrial contractions. Despite the lack of valve leaflets in our 3D FSI model, two vortices are created on both sides of the mitral valve that travel across the length of the ventricular cavity and slowly dissipate in the base of the ventricle during the late diastole. Thus even with such a relatively idealized model it may be possible in the future to make qualitative evaluations of vortex patterns between healthy and pathological left ventricles along the lines presented in [10].

All simulations were performed on four nodes with eight cores each of the IBM Intel Nehalem cluster Amanor at the EPFL. The simulation of one heartbeat takes approximately 25 hours of wall-clock time. The number of nonlinear iterations taken by the Broyden/Newton schemes for coupling all the models together at each time step is shown in Figure 7. The coupling tolerance was fixed at 1e-6. We observe that, after an initial transient phase where the model starts from rest and tries to reach the physiological conditions, the Broyden method takes consistently 5-15 iterations per time step except whenever the aortic valve opens and a fallback to the Newton scheme is necessitated. In order for the multiscale coupling algorithm to be practical it is vital that the number of nonlinear it-
The upper part of the Wiggens diagram in Figure 8 displays the simulated blood pressure inside the left ventricle, base of the ascending aorta, and left atrium (prescribed input to the model). Due to the idealized one-valve we use here there is no backflow through the mitral valve during the end-diastole. This could be rectified by incorporating a more detailed 3D model for the mitral valve a.g. along the lines presented in [1, 11]. Isovolumetric contraction and relaxation phases can be observed from the volume diagram. Volumetric quantities of the left ventricle obtained during the 3rd heartbeat are EDV = 165.4 mL, ESV = 89.7 mL, and the cardiac output CO = 5.68 l/min. The low ejection fraction (45.8%) is due to the physiological deformation applied to the ventricle that does not account for tension and axial contraction.

In Figure 9 we show the simulated flow rate and pressure at various aortic branches of the 1D network. The results are in close agreement to the ones obtained using [21] with a prescribed cardiac output. Some features of note include the diastolic notch visible in the pressure function of the ascending aorta at t = 0.2 s, which corresponds to the closure of the aortic valve, and the backflow in the abdominal aorta during the early diastole. In order to achieve smooth non-oscillatory profiles it is necessary to incorporate in the models both the viscous term for the 1D arterial walls as well as the RCR windkessel elements for the terminals, modelling the peripheral circulation. In our experience neglecting either of these two aspects from the multiscale model leads to excessively oscillating profiles in both the flow rate and blood pressure. Our multiscale model reaches a nearly-periodic pressure level in as few as three heartbeats.

A visualization of the arterial tree as a 1D network is represented Figure 10. The thickness of the 1D sections is not in scale to their length (in order to enhance the visualization), and their positioning is purely visual.

Conclusions

We have presented a multiscale model of an idealized left ventricle coupled to a 1D viscoelastic arterial tree for sim-
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Figure 10 Arterial tree, propagation of the pressure wave during late systole. Positioning of 1D network purely visual.

| Parameter | Value
<table>
<thead>
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<tbody>
<tr>
<td>$\rho_{pe}$</td>
<td>Force on the epidermis (peak) 4.7 N</td>
</tr>
<tr>
<td>$E_c$</td>
<td>Young modulus of pseudo-structure 0.7 MPa</td>
</tr>
<tr>
<td>$\nu_s$</td>
<td>Poisson ratio of pseudo-structure 0.4</td>
</tr>
<tr>
<td>$\rho_s$</td>
<td>Density of elastic pseudo-structure 1.2 g/cm³</td>
</tr>
<tr>
<td>$p_{sa}$</td>
<td>Left atrial pressure 1.2 MPa</td>
</tr>
<tr>
<td>$p_{ve}$</td>
<td>Venous pressure 0.061 kPa</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Viscosity of blood 2.4 mPa·s</td>
</tr>
<tr>
<td>$\rho_b$</td>
<td>Density of blood 1.045 g/cm³</td>
</tr>
<tr>
<td>$v$</td>
<td>Dynamic viscosity of blood 0.035 g cm⁻² s⁻¹</td>
</tr>
<tr>
<td>$p_{ad}$</td>
<td>Reference pressure at mitral valve 0.95 kPa</td>
</tr>
<tr>
<td>$H_0$</td>
<td>Heart rate 75 bpm</td>
</tr>
<tr>
<td>$t_s$</td>
<td>Simulation time 4.8 s</td>
</tr>
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Algorithms for the coupling of one-dimensional arterial networks with three-dimensional fluid-structure interaction problems

A. Cristiano I. Malosi\(^1\), Simone Deparis\(^2\), and Pablo J. Blanco\(^2\)

1 CMC5, Chair of Modelling and Scientific Computing, MATHEON, Mathematics Institute of Computational Science and Engineering, EFPL, École Polytechnique Fédérale de Lausanne, Station 8, CH-1015, Lausanne, Switzerland, e-mail: cristiano.malosi@epfl.ch, simone.deparis@epfl.ch

2 LNCC, Laboratório Nacional de Computação Científica, Av. Getúlio Vargas 333, Quitandinha, 25651-075, Petrópolis, Brazil, e-mail: pablo@lncc.br.

Abstract
This work is focused on the development of a geometrical multiscale framework for modeling the human cardiovascular system. This approach is designed to deal with different geometrical and mathematical models at the same time, without any preliminary hypothesis on the layout of the general multiscale problem. This flexibility allows to set up a complete arterial tree model of the circulatory system, assembling first a network of one-dimensional models, described by non-linear hyperbolic equations, and then replacing some elements with more detailed (and expensive) three-dimensional models, where the Navier–Stokes equations are coupled with structural models through fluid–structure interaction algorithms. The coupling between models of different scale and type is achieved imposing the conservation equations in terms of averaged/integrated quantities (i.e., the flow rate and the normal component of the traction vector); in particular, three coupling strategies have been explored for the fluid problem. In all the cases, these strategies lead to small non-linear interface problems, which are solved using classical iterative algorithms.

Keywords: Geometrical multiscale, Fluid-structure interaction algorithms, Cardiovascular networks, Hemodynamics.

Introduction
The simulation of blood flow in the human body is a challenging task. A very accurate model should account for the arterial and venous networks, the heart, and the capillaries, keeping into account also the non-Newtonian blood behavior and complex wall constitutive laws. Even with nowadays powerful supercomputers, it is not possible to solve such a problem and several approximations must be employed.

A first approximation is to consider reduced models for the fluid-structure interaction (FSI) dynamics\(^4\) and glue them together by the imposition of integrated quantity: in an explicit hierarchical fashion\(^1\),\(^2\),\(^3\),\(^4\),\(^5\) or implicitly\(^6\). The resulting model is a network of one-dimensional (1-D) models for the arterial system, which can be closed with zero-dimensional (0-D) models to account for the left heart valve and the capillaries (and therefore neglecting the venous system).

Another possible approximation is to restrict the region of interest and consider a three-dimensional (3-D) fluid-structure simulation. As pointed out in e.g.,\(^7\), in these cases it is important to select appropriate boundary conditions. These can be found either by direct measurement of integral quantities, like flow rates\(^8\),\(^9\), or by using a separate 3-D network to provide the correct boundary data\(^10\). It is also possible to couple the 3-D network with the 3-D model: in\(^11\),\(^12\) the authors propose an explicit coupling between such models.

In this work we use the methodology described in\(^13\) and we couple these single models in an implicit fashion, then we solve the coupled problem by implicit Newton iterations on the coupling variables. Each model used in the network has its own optimal time discretization step and often this also has an upper bound limitation derived from the CFL condition\(^1\) in the case of explicit algorithms. When discretizing in time the coupling of many models of equal or different scales we shall therefore use the most stringent condition, which may lead to unnecessary comparation. Here we propose to use two time step scales, one for the global arterial tree and one for the local 3-D model, the former typically having a smaller time step due to its explicit nature.
Models
In the following paragraphs, we briefly introduce the geometrically-heterogeneous models which are the main ingredients of our geometrical multiscale framework.

3-D FSI model
In a geometrical multiscale setting, 3-D FSI models are used for modeling components where the geometrical description play a fundamental role, e.g., in vessels with aneurysms, stenoses, or other complex pathologies. In those cases, a 3-D description of the flow field is mandatory in order to capture the true physics of the phenomenon.

Equations
The blood dynamics of the 3-D FSI model is described by formulating the incompressible Navier–Stokes equations for Newtonian fluids in moving domains. We choose to use an Arbitrary Lagrangian Eulerian (ALE) frame of reference [14].

Let \( \Omega = \Omega_t \cup \Omega_s \) be a configuration of the fluid-structure system, with \( \Omega_t \) and \( \Omega_s \) the reference domains for the fluid and the solid, respectively. We denote by \( \Gamma_{FSI} = \partial \Omega_t \cap \partial \Omega_s \), the fluid-solid interface. The current configuration of the fluid domain, \( \Omega_t(t) \), is parameterized by the ALE map

\[
A_t : \Omega_t \to \Omega_t(t) \quad \quad x \mapsto A_t(x) = x + d_t(x),
\]

\( \Omega_t(t) = A_t(\Omega_t(0)), \)

\( d_t \) denotes the displacement of the fluid domain. We denote by \( \Gamma_{FSI}(t) = \partial A_t(t) \cap \partial A_s(t) \) the current position of the fluid-solid interface. In practice, \( d_t = \text{Ext}(d_s) \)\( |\Gamma_{FSI}| \),

where \( d_s : \Omega_s \times \mathbb{R}^+ \to \mathbb{R}^3 \) stands for the solid displacement and \( \text{Ext}(\cdot) \) is an harmonic lifting operator from \( \Gamma_{FSI} \) to \( \Omega_s \).

The nonlinear Cauchy–stress problem under consideration reads as follows (see, e.g., Chapter 11): Find the fluid velocity \( u = u(x,t) : \Omega_t \times \mathbb{R}^+ \to \mathbb{R}^3 \), the pressure \( p = p(x,t) : \Omega_t \times \mathbb{R}^+ \to \mathbb{R} \), and the solid displacement \( d_s = d_s(x,t) : \Omega_s \times \mathbb{R}^+ \to \mathbb{R}^3 \) such that

\[
\rho \frac{\partial u}{\partial t} + (u \cdot \nabla)u - \nabla p + \sigma_f = 0 \quad \text{in} \quad \Omega_t(t),
\]

\[
\nabla \cdot u = 0 \quad \text{in} \quad \Omega_t(t),
\]

\[
\rho \frac{\partial d_s}{\partial t} + (d_s \cdot \nabla) \sigma_f - \nabla \Pi = 0 \quad \text{in} \quad \Omega_s(t),
\]

with the following fluid-structure interface coupling conditions:

\[
d_t = \text{Ext}(d_s)|\Gamma_{FSI}|, \quad w = \partial_v d_t \quad \text{in} \quad \Omega_t(t),
\]

\[
u = \partial_v d_s \quad \text{on} \quad \Gamma_{FSI}(t),
\]

\[
\Pi_{\text{ns}} = -JF \sigma_f^{-1} \Pi_{\text{ns}} |\Gamma_{FSI}|.
\]

The initial conditions are: \( u(0) = u_0, d_s(0) = 0 \) and \( \partial_t d_s(0) = 0 \). \( \rho \) and \( \rho_f \) represent the fluid and solid densities, respectively, \( d_t \) the ALE time derivative, \( \sigma_f = \sigma_f(u,p) \) the Cauchy stress tensor, and \( \mu \) the fluid dynamic viscosity, \( c(u) \) denoting the strain rate tensor, \( \Pi = \Pi(d_s) \) the first Piola–Kirchhoff stress tensor of the structure, \( F_f = \nabla \Pi \) the fluid domain gradient of deformation and \( J_f \) its Jacobian; \( \rho_f \) and \( \rho_s \) are, respectively, the external unit normals to the fluid and solid domains.

In the linearized St. Venant–Kirchhoff model, the Piola tensor is approximated as

\[
\Pi = \lambda I + 2 \mu \Pi_{\text{ns}},
\]

with \( \Pi_{\text{ns}} = 1/2 (\nabla u + \nabla u^T) \) and \( \lambda \) and \( \mu \) the two Lamé coefficients.

The harmonic extension problem associated to the operator \( \text{Ext} \) reads: find \( d_t = d_t(x,t) : \Omega_t \times \mathbb{R}^+ \to \mathbb{R}^3 \) such that

\[
-\Delta d_t = 0 \quad \text{in} \quad \Omega_t,
\]

\[
d_t = d_s \quad \text{on} \quad \Gamma_{FSI}.
\]

The problem is finally closed by imposing a suitable set of boundary conditions on the external wall of the solid \( \Gamma_{ext} \) and all the other fluid and solid external interfaces. The latter are automatically provided by the adjacent 1-D models within the geometrical multiscale problem (see in the forthcoming section), while for the former we postpone the discussion to the section of results.

Numerical approximation
For the time discretization of the 3-D FSI problem we use a geometry-convective explicit scheme [15], i.e., the convective field and the fluid computational domain are extraplated from the previous time step. The other terms are treated with a first-order backward Euler scheme. The Navier–Stokes equations therefore reduce to the linear systems of equations, leading to a linearized 3-D FSI problem at each time step. The linear equations are then discretized in space by a P1-P1 finite element method, stabilized through interior penalty (see [16]), which shows a convergence of order one in \( h \) (the spatial discretization of the whole domain \( \Omega_t \)) and \( h \) (the velocity and pressure).

The structural equations are also linear and require no special treatment. Since the geometry is treated explicitly, the fluid computational domain \( \Omega_t(t^{n+1}) \) is computed by using \( \Pi_{\text{ns}} \) as boundary condition in (1). Thus, the coupled 3-D FSI model after discretization gives at each time step \( n+1 \) a monolithic linear system to solve for

\[
\begin{bmatrix}
F_f & F_f & I
\end{bmatrix}
\begin{bmatrix}
\mathbf{y}^n
\mathbf{y}^{n+1}
\mathbf{y}^{n+1}
\end{bmatrix}
= \begin{bmatrix}
0
0
1/\Delta t
\end{bmatrix}
\begin{bmatrix}
\lambda_{n+1}^n
\lambda_{n+1}^n
\lambda_{n+1}^n
\end{bmatrix},
\]

where \( \mathbf{y}^n := (u^n, p^n) \) denotes the fluid variables, vectors with sub-indices \( f \) represent all the variables on the fluid-structure interface \( \Gamma_{FSI} \), \( \lambda_{n+1}^n \) is a Lagrange multiplier that...
corresponds to the force transferred from fluid to structure, and the blocks \( P_j \) and \( S_j \), \( j = f, o \), or \( T \) correspond to the sub-blocks of the finite element matrices of the fluid and structure problems respectively. The 1-D FSI system (3) is solved by a GMRES method preconditioned by overlapping algebraic Schwarz preconditioners based on an implicit block factorization of the system in the block-composed form. The solution strategy of the monolithic 3-D FSI system (2) is detailed in [13].

1-D model
The global arterial circulation can be modeled by a network of 1-D elements, each characterized by a circular cross-section (eventually narrowed along the axial direction) and a viscoelastic arterial wall (see, for instance, [1, 3, 5]). Even if the 1-D model is very simple and does not account for the 3-D geometrical description of the vessel, it has been proven to be able to accurately capture the behaviour of the principal physiological quantities, like the volumetric flow rate and the mean pressure. For this reason, in a geometrical multiscale setting, the 1-D model is used to describe the entire arterial system.

Equations: A straightforward derivation of the 1-D model can be found in [17]. The resulting governing equations for continuity of mass and momentum are

\[
\begin{align*}
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) &= 0, \\
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{Q^2}{A} \right) &= \frac{A}{\rho} \frac{\partial P}{\partial t} + K_n \frac{Q}{A} = 0,
\end{align*}
\]

where \( A \) is the area of the vessel, \( P \) is the mean pressure, \( Q \) is the volumetric flow rate, \( \rho \) is the Coriolis coefficient, and \( K_n \) is the friction coefficient accounting for fluid viscosity.

In order to close the problem an additional equation relating the averaged pressure with the other unknowns \( Q \) and \( A \) is needed. A complete mechanical model for the structure of the vessel wall is described in [1]. Here we consider only the elastic and viscoelastic contributions, as all the other terms are negligible in a cardiovascular setting, leading to the following pressure-area relation (see [18]):

\[
P - P_{eq} = \beta \left( \sqrt{\frac{A}{A_0} - 1} \right) + \frac{\gamma}{A\sqrt{A}} \frac{\partial A}{\partial x},
\]

with

\[
\beta := \frac{\pi}{4 \sqrt{1 - \nu^2}}, \quad \gamma := \tan \phi \frac{E}{\sqrt{1 - \nu^2}}.
\]

where \( P_{eq} \) is the external pressure (i.e. the pressure of the tissues or the external wall), \( A_0 \) is the area of the cross-section of the vessel before the pre-stressed configuration, \( A \) is the wall thickness, \( E \) is the elastic Young modulus, \( \nu \) is the Poisson coefficient, \( T \) is a characteristic time (usually taken equal to the systolic period), and \( \phi \) is the so-called viscoelastic angle. Note that the viscoelastic term in (4) leads to an algebraic-differential equation which requires a special treatment when plugged into (3), as we show in the following paragraph.

Numerical approximation By inverting (4) into (3), after some manipulations, we get a system of differential equations that can be written in a classical conservative form as follows:

\[
\begin{align*}
\frac{\partial U}{\partial t} + \frac{\partial F(U)}{\partial x} + S(U) &= 0,
\end{align*}
\]

where \( U \) are the conservative variables, \( F \) the corresponding fluxes, and \( S \) represents the source terms.

Following [1] we solve problem (5) by using an operator splitting technique, where the flow rate is split into two components such that \( Q = \dot{Q} + \bar{Q} \), where \( \bar{Q} \) is the solution of the pure elastic problem and \( \dot{Q} \) is the viscoelastic correction. Let us consider the time interval \([n, n+1] \), for \( n = 0, 1, 2, \ldots, \) and \( \Delta t = n \Delta t \), \( \Delta t \) being the time step:

1st step, elastic response given \( U^n \) and \( \dot{U}^{n+1} \) is such that:

\[
(F_{\alpha}^n, \dot{\phi}_n) = (U^n, \dot{\phi}_n) + \Delta t \left[ \left( F(U^n), \frac{\partial \phi_n}{\partial x} \right) - (S(U^n), \dot{\phi}_n) \right] - \left( \frac{\Delta t}{2} \frac{\partial F(U^n)}{\partial U} \frac{\partial S(U^n)}{\partial U} \right) \dot{U}^{n+1} \end{align*}
\]

\[
\frac{\partial \mu}{\partial x} H(U^n) \frac{\partial \mu}{\partial x} + \frac{\Delta t}{2} \frac{\partial S(U^n)}{\partial U} H(U^n) \frac{\partial S(U^n)}{\partial U}, \quad \mu \in V_h
\]

where \( U_h \) is the discrete counterpart of \( U \), \( V \) is the space of piecewise linear Finite Element (FE) functions, and:

\[
H(U^n) := \frac{\partial F(U^n)}{\partial U} + S(U^n).
\]

2nd step, viscoelastic correction given \( \dot{U}^{n+1} \). find \( \dot{Q}_{\alpha}^{n+1} \) such that:

\[
\begin{align*}
\left( \frac{\partial \mu^0}{\partial x} \frac{\partial \mu^0}{\partial x}, \dot{\phi}_n \right) + \Delta t \left( \frac{\gamma}{\rho} \frac{\partial \mu^0}{\partial x} \frac{\partial \mu^0}{\partial x}, \dot{\phi}_n \right) &= \Delta t \left( \frac{\gamma}{\rho} \frac{\partial \mu^0}{\partial x} \frac{\partial \mu^0}{\partial x}, \dot{\phi}_n \right) + \frac{\partial F(U^n)}{\partial U} \frac{\partial S(U^n)}{\partial U} \dot{U}^{n+1} \end{align*}
\]

\[
\frac{\partial \mu^0}{\partial x} \frac{\partial \mu^0}{\partial x} + \frac{\Delta t}{2} \frac{\partial S(U^n)}{\partial U} \frac{\partial S(U^n)}{\partial U}, \quad \mu^0 \in V_h.
\]

The first step corresponds to an explicit second-order Taylor-Galerkin (TG) scheme, where we neglect the viscoelastic component of the wall. The problem is closed by imposing a suitable set of boundary and compatibility conditions on both sides of the 1-D segment. For the second step, we impose either homogeneous Dirichlet or homogeneous Neumann boundary conditions, depending from the
Coupling the fluid

In a geometrical multiscale setting, where the models are defined in different geometric spaces (e.g., 0-D, 1-D, 3-D, etc.), the problem at the coupling interfaces can be formulated in a general way only by writing the conservation equations in terms of averaged/integrated quantities. In particular, for a generic fluid coupling interface $\Gamma$, we select

$$ Q = \int_{\Gamma} \mathbf{u} \cdot n \, d\Gamma,$$

and

$$ \Sigma = \frac{1}{|\Gamma|} \int_{\Gamma} (\mathbf{\sigma} \cdot n) \cdot n \, d\Gamma,$$

where $Q$ is the volumetric flow rate and $\Sigma$ is the average of the normal component of the traction vector, hereafter referred to as the coupling stress. Specifcally, we choose to consider that $(\mathbf{\sigma} \cdot n) \cdot n$ is constant over $\Gamma$, in order to close the problem. This choice leads to the following conservation equations for the problem at the coupling interfaces:

$$ \forall e = 1, \ldots, E : \begin{cases} \sum_{m=1}^{M_e} Q_{en} = 0, \\ \Sigma_{n1} = \Sigma_{nm}, \quad \forall m = 2, \ldots, M_e, \end{cases} \quad (7)$$

where $E$ is the total number of coupling interfaces of the network of model and $M_e$ is the number of models coupled by the $e$-th coupling interface (see Figure 2). To sat-

![Figure 2 General configuration for the $e$-th coupling between Mathematical models.](image)

ify the set of equations (7), different coupling strategies can be used, corresponding to the imposition of different quantities on the boundaries. In other words, we can set up each subproblem with different combinations of boundary data over the coupling interfaces. Some examples are provided in [13].
Coupling the solid

The coupling between the solid parts of the model can be achieved with a similar approach, i.e., by imposing the continuity of the area over the coupling interfaces. However, from the practical viewpoint, the imposition of the area on the 1-D model is equivalent to impose a pressure, and this is already done by coupling the fluid problem. Moreover, due to the sub-critical nature of the flow field (see [1]), the 1-D model can receive just one physical quantity on each side of the 1-D segment, that is already a fluid quantity. Nevertheless, it is possible to impose on the 3-D solid the value of a given area, for example, by a 1-D model. Investigations in this direction are subject of future works. The results presented in this paper are obtained by clamping the solid interface of the 3-D FSI model. Even if this condition is not physical, it is necessary for the well-posedness of the problem, which can be solved only by removing the rigid modes from the 3-D FSI model.

Numerical approach

Let $\lambda$ be the global vector of coupling variables. The problem at the coupling interfaces is solved by using a classical non-linear Richardson strategy

$$\lambda_{k+1} = \lambda_k + \delta\lambda,$$

until convergence to a suitable tolerance has been achieved. In order to devise a convergent methodology, we make use of the Newton method

$$J(\lambda)(\delta\lambda) = -R(\lambda),$$

which requires the computation of the exact Jacobian matrix $J(\lambda)$ at each iteration. Each coefficient of the Jacobian matrix corresponds to the variation of a boundary value due to the variation of a coupling quantity on the same model. Therefore, from the computational point of view, each coefficient requires the solution of the target problem associated to the corresponding model (see [11] for more details on the computation and assembling of the Jacobian matrix). This approach is very expensive, especially when dealing with many 3-D FSI boundary interfaces. Moreover, the Jacobian matrix should be updated at each iteration. In view of these considerations, we use the Newton method only at the very first iteration, to initialize the Jacobian matrix. Then we update the matrix at each iteration through the Bryden method

$$J(\lambda) = \left( J(\lambda^{k-1}) + \left( R(\lambda^{k}) - R(\lambda^{k-1}) \right) \left( \delta\lambda^{k-1} \right)^T \left( \delta\lambda^{k-1} \right) \right)^{-1} \left( \delta\lambda^{k-1} \right)^T,$$

which does not require the solution of any tangent problem.

A two-level time step technique for coupling 1-D and 3-D FSI models

As anticipated before, the explicit second order TG scheme entails a strong time step limitation due to the low value of the Courant–Friedrichs–Lewy (CFL) condition, equal to $\sqrt{3}/\beta$. In particular, under physiological conditions this leads to a maximum time step of about $1\times10^{-5}$ s, that is around one hundred times smaller than the one typically used for 3-D FSI simulations. Indeed, 3-D FSI models are very expensive from the computational viewpoint and for this reason we aim to solve them as few times as possible, i.e., using a very large time step.

In order to satisfy the 1-D CFL condition without reducing the 3-D FSI time step, we devise a two-level time step technique (see Figure 5) where

- the inner time step meets the 1-D CFL requirements and it is used just by the 1-D models;
- the outer time step is used for the 3-D FSI model and for the strong coupling between the models, i.e., (7) is satisfied just at this level.

Note that in order to perform the inner time steps, we need to interpolate the values of the coupling conditions between $t^n$ and $t^{n+1}$.

The resulting scheme is robust from the computational point of view, however two problems may arise. First of all, we need to find a different strategy for the computation of the Jacobian coefficients, since the analytical formulation of the tangent problem is too complex due to the recursion of the problem. To address this issue we use two different techniques: a finite difference approximation and an approximated formulation of the tangent problem. In both cases we end up with convergent exact–Newton schemes.

Another issue regards the possible presence of numerical reflections at the coupling interfaces, due to the fact that (7) are satisfied just at the outer time step. Nevertheless, investigations in this direction show that these reflections are strongly related to the size of the wavelength. In particular under physiological conditions the wavelengths are long and the numerical reflections are negligible.

More details and investigations about the two-level time step technique and these issues are given in [18].

Figure 1 Two-level time step technique scheme between the global time step $\Delta t = t^{n+1} - t^n$, some local time steps (in blue) are performed in the 1-D model.
Results
In this section we show some numerical results and applications of the methodology discussed in the previous section.

1-D modeling of the human arterial network
First of all, we validate our methodology by using the arterial network provided in [5, Figure 2 and Table 2]. This model is composed by 163 elements: 4 coronary, 24 aortic, 51 cerebral, 10 in the legs, and 14 in the body. It includes all the parameters required to describe the true physiological flow, such as the narrowing of the area, the viscoelastic response of the arterial wall, and the terminals, which are modeled as 3-D simplified elements. The resulting coupled problem is composed of 555 interface variables. Even if the number is relatively small, it represents the implicit coupling of 150 (101 1-D plus 49 0-D) non-linear problems, in a complex network topology (that includes bifurcations and closed loops), hence the solution is not trivial.

In Figure 2 we present the result of the last of six cardiac cycles, when the periodic regime has been reached. We can observe that our results follow the ones given in [5, Figure 4], even if some differences are present, due to the different model for the viscoelastic part of the arterial wall and to the different flow rate time profile. Regarding the number of iterations of the coupling algorithm we tested different methods in presence of the two-level time-step technique (in view of the coupling with 3-D FSI models), using an outer time step of 0.001 s, which is the typical one for 3-D FSI simulations. The results are shown in Figure 3, where we observe that the Erodeny strategy leads to a reduction factor of five with respect to the Newton method. Note that there are no significant differences between the cases with and without the viscoelastic term, even if it adds some additional non-linearities to the problem.

1-D arterial network with 3-D FSI aorta
In this paragraph we present some preliminary results about the coupling of the full 1-D network with a 3-D FSI aorta. The layout of the model is shown in Figure 4. To set up the model, first of all we identify the position of the 7 coupling interfaces of the 1-D aorta in the 1-D arterial network. Then, we perform a cut of the 1-D segments at these positions, such that we match the original length of the 1-D arterial network. Finally, we also change the proximal diameter in those segments in order to match the one of the corresponding 3-D FSI interfaces. On the one hand, this procedure may seem somehow arbitrary, in the sense that there is not a unique technique to identify the cutting positions, nor the correct length of the 1-D segment. However, on the other hand, this arbitrariness should not affect the results, as the values of the averaged internalized quantities (vascular flow rate and stress area) is not affected by small geometrical changes.

The mesh of the fluid part of the aorta consists of 271,970 tetrahedral elements with 54,131 vertices, while the solid part is made of 108,770 tetrahedral elements with 35,044 vertices. All simulations were performed on computational nodes with eight cores each of the Intel Nehalem cluster Anubis at the EPFL. The simulation of one heartbeat takes approximately 52 hours of wall-clock time. In Figure 7 we show a detailed view of the velocity field inside the 3-D FSI aorta, while comparing the number of iterations in Figure 8 we can observe that there is no significant difference between the full 1-D arterial network case and the coupled 1-D plus 3-D FSI aorta one. Now that the two green peaks correspond to a restart of the simulation where, at the present time, we lose the information about the previous Jacobian matrix; in the future we plan to store the last Jacobian matrix for the next restart, in order to solve this small issue. For the full 1-D network a restart is not needed due to the small computational cost.

Sensitivity analysis of the external wall Robin boundary condition for the 3-D FSI model
From the modeling point of view, one critical aspect to get physiological results in the 3-D FSI aorta is the tuning of the boundary condition on the solid external wall. The influence of external tissues and organs tightening and constraining the movement of blood vessels is of critical importance when simulating 3-D FSI problems in the arterial system. Obviously, it is currently unfeasible to model the detailed multi-contact relations between the aortic system and the other tissues. In [19] the authors propose to handle the external tissues support on the outer arterial wall by enforcing a Robin boundary condition which models the elastic and viscoelastic response of the tissue. For the sake of simplicity, we base our analysis by neglecting the viscoelastic contribution. Therefore on the solid wall of the 3-D FSI problem we impose

\[
\Pi \cdot n_u + h_n \cdot \mathbf{d}_n + F_{wall} \cdot n_u = 0, \quad \text{on } \Gamma_{wall}
\]

where \( h_n \) is an empirical elastic coefficient. Then we set up different test cases of the same problem. In particular, we identify three main cases in the aortic arch and we select different sets of values for the elastic coefficient \( h_n \) (see Table 1). The results at the ascending and thoracic aorta coupling interfaces are shown in Figures 9 and 10, respectively. As we can see from the images, the first three sets of coefficients (the smallest ones, including also a Neumann case) lead to unphysiological results. Removing those cases from the graphs we end up with very similar results (see the second row in Figures 9 and 10), where strong variations of the elastic coefficient do not produce sensible variations of the main quantities. Moreover, these latest results are in a physiological range and comparable to the ones obtained with the full 1-D arterial network. Further tests including the viscoelastic term in the Robin boundary condition are subject of future works.
Figure 4 Periodic flow rate (solid line) and pressure (dashed line) results in six different arterial segments. Positioning of 1-D network elements is purely visual.

Figure 5 Comparisons, in terms of number of iterations, of different algorithms for the coupling of the full 1-D network. The first three heart beats are shown. Note that in the Broyden method $J^{-1}(X)$ is the Jacobian matrix of the previous time step, while in the reinitialized version, it is recomputed using the inexact-Newton method.

Conclusions

In the present work, a geometrical multiscale framework for modeling the human cardiovascular system has been presented. The main ingredients of the framework are (i) a complete set of models for describing each component of the arterial network with a proper level of detail (0-D, 1-D, and 3-D), and (ii) a general and robust coupling algorithm to assemble the heterogeneous models into one large geometrical multiscale problem.

We show that our geometrical multiscale framework is able to assemble and solve complex problems, including networks of more than 100 elements, with a reasonable computational cost. Moreover, we also demonstrate that the resulting geometrical multiscale model provides physiological results, comparable to the ones of the full 1-D arterial network. Further test and investigations on this field are subject of future works.
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Figure 6: A global view of the 1-D arterial network coupled with the 2-D FSI setup at the beginning of the 3rd systole. Positioning of 1-D network elements is purely visual.

Figure 7: A view of the 3-D aortic arch velocity field during the systolic peak of the 3rd heart beat. The color of the 1-D segments refers to the pressure field (blue: 65000 dyn/cm², red: 115000 dyn/cm²). Positioning of 1-D network elements is purely visual.

Figure 8: Comparison, in terms of number of Eddy-dissipation terms, between the full 1-D arterial network and the coupled 3-D FSI setup plus 1-D network. The first three heart beats are shown.
Table 1. Set of values for the elastic coefficient \( k_e \) of the 3-D FSI aorta external wall Robin boundary condition. See the figure below to identify the three regions (Top, Center, and Bottom).

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<th>Center</th>
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References


