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Influence of atrial contraction dynamics on cardiac function

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Abstract

In recent years, there has been a move from mono- or biventricular models of the heart, to more complex models that incorporate the electromechanical function in all four chambers. However, the biophysical foundation is still under-developed, with most work in atrial cellular models having focused on electrophysiological properties. Here we present a biophysical model of human atrial contraction at body temperature, and use it to study the effects of atrial contraction on whole organ function, and a study of the effects of remodelling due to atrial fibrillation on atrial and ventricular function.

Keywords: Cardiac modelling, Atrial mechanics, Atrial fibrillation

1 Introduction

Models of cardiac ventricular mechanics are increasingly used to study the physiology of the heart with a range of mature software packages having been developed [23]. At the same time, atrial models of electrophysiology are moving towards clinical applications, particularly in the study of atrial ablation sites [43]. However, the study of the mechanical function of the atria, and integration with ventricular models, is far less common. Some four chamber models of contraction have been developed [38, 10, 1], but the biophysical basis of these models at the cellular scale is still under-developed. Four chamber heart models also extend the range of physiological and pathophysiological simulations, but at the cost of additional complexity.

The atria influence ventricular filling in three different ways: functioning as a reservoir during systole, passive filling during early diastole, and a phase with active contraction during late diastole [37]. In particular in situations where the physiological hypothesis under investigation is related to diastolic filling due to increased ventricular stiffness, such as in heart failure with preserved ejection fraction, or in cases where atrial function is decreased such as in patients with a history of atrial fibrillation, the increased predictive power of models that include atria could be especially useful. However, many fundamental questions remain on the influence of atrial mechanics on ventricular function, differences in predictive power between biventricular and whole heart models, and the physiological importance of atrioventricular interactions. In particular, atrial fibrillation is an increasingly common condition in which re-entrant waves in the atria interfere with normal heart rhythm [32, 30, 36]. Although contractile function during fibrillation is almost completely absent, the condition also causes long-term remodelling of the atria which persists even after normal heart rhythm is restored.

The goals of this paper is to provide a numerical framework with a new biophysical model of human atrial contraction, based on our previous work in ventricular mechanics [24]. We use this framework to study the influence of changes in atrial contraction on whole heart function. We test the impact of reusing a ventricular contraction model in the atria or tuning a contraction model to measurements of atrial contraction. Having developed a four chamber model we investigate the impact of an altered atrial calcium transient due to atrial fibrillation, following cardioversion back to sinus rhythm. We study the effects of these changes to the calcium transient and calcium sensitivity caused by atrial fibrillation on whole organ function. In addition, we test appropriate boundary conditions to apply and their influence on simulation results.

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2 Methods

2.1 Model definition

To model the heart, we use a framework based on large deformation mechanics theory and finite element methods. We model the myocardial tissue as fully incompressible, resulting in the governing equations:

$$\nabla \cdot \left(\sum_M F_{iM} T_{MN} \right) = 0 \quad \text{for } i = 1, 2, 3 \quad (1)$$

$$J = 1 \quad (2)$$

Where coordinates in the undeformed and deformed configuration are denoted by $\mathbf{X}$ and $\mathbf{x}$, $\mathbf{F} = \frac{d\mathbf{x}}{d\mathbf{X}}$ is the deformation gradient, $J = \det \mathbf{F}$ is the local change in volume, $\mathbf{E} = \frac{1}{2}(\mathbf{C} - \mathbf{I})$ is the Green-Lagrange strain tensor and $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the right Cauchy-Green strain tensor. The second Piola-Kirchhoff stress is given by

$$\mathbf{T} = \frac{dW}{d\mathbf{E}} + (\kappa(J - 1) - pJ)\mathbf{C}^{-1} + T_a \mathbf{f} \mathbf{f}^T \quad (3)$$

Where p is hydrostatic pressure, $\kappa = 5 \text{ kPa} + p_{1V}$ a compressibility penalty for improved stability [25], $\mathbf{f}$ is a column vector indicating the fibre direction, with $\|\mathbf{f}\| = 1$, and T_a indicates active contraction. We use a general exponential strain energy function W based on work by Guccione et al. [12]:

$$W(\mathbf{E}) = \frac{C_1}{2}(e^Q - 1) \quad \text{where} \quad (4)$$

$$Q = C_2 E_{ff}^2 + C_3 (E_{ss}^2 + E_{nn}^2 + 2E_{sn}^2) + 2C_4 (E_{fs}^2 + E_{fn}^2)$$

Where f refers to the fibre direction, and s, n refer the two other orthogonal components of the local coordinate system. With parameters $C_1 = 1, C_2 = 8, C_3 = 3, C_4 = 4$ based on previous work [24].

2.2 Mesh generation

In previous work we have used mesh generation tools to generate meshes with cubic order elements for the biventricular geometry [20, 21]. Due to the more complex topology in the four chamber heart, creating a mesh based on cubic hexahedral elements is challenging, and our existing tools do not support this topology. Instead, we use tetrahedral finite elements, with a second order (ten node) element for deformation, and a first order (four node) element for hydrostatic pressure (T2P1 elements). The heart anatomy comes from high-resolution MR (magnetic resonance) images, acquired using a 1.5T Philips Achieva system, of a heart failure patient. The model is generated from a four chamber segmentation of the steady-state free precession images acquired of the 3D whole heart at the end diastolic phase of the cardiac cycle with image resolution $0.8 \times 0.8 \times 1 \text{ mm}$. The mesh is generated using Seg3D to segment the cardiac tissue. Next, we use the Computational Geometry Algorithms Library (CGAL [8]) to generate a linear tetrahedral mesh. In generating the mesh we ensure cavities are closed as in the work by Fritz et al. [10], with atrioventricular valves present, and with pressure applied on both sides of these valves, throughout the simulations. This both leads to ease of automatic cavity detection, and stops unbalanced forces causing significant unphysiological movement of the heart, as happens during ejection if there is no force applied to the atrioventricular valve on the ventricular side. Figure 1C shows the interior of the cavities.

The mesh is deflated to a reference configuration using a deflation algorithm based around fixed-point iterations [5], assuming the patient's geometry corresponds to a ventricular end-diastolic pressure of 1 kPa, with atrial contractile and pressure forces balancing out to not require significant deflation in the atria.

2.3 Fibre definitions

The direction of the long, cylindrical muscle cells of the heart has long been an important aspect of cardiac physiology. In the ventricles of the heart, these fibres are highly regular, twisting from approximately -60 at the epicardium to +80 degrees at the endocardium from the circumferential direction. The change

in fibre angle across the wall leads to a twisting motion during ejection. Due to the highly structured nature of these fibres, and increasing numbers of measurements from histology and diffusion tensor MRI imaging (DTMRI), fully automated rule-based algorithms exist for accurately reproducing these fibre fields in the ventricles [26, 15, 3].

Defining fibre definitions is significantly more challenging on a tetrahedral four chamber heart. Our general pipeline for defining fibre directions is based on establishing a consistent transmural direction and apex-to-base directions. We do this by solving the heat equation $\Delta U = 0$ on our computational mesh similar to methods described by Bayer et al [3] for ventricular models. The transmural direction is established as $\mathbf{T} = \nabla U$ after solving the heat equation with Dirichlet boundary conditions $U(\text{left heart endocardium}) = 1, U(\text{epicardium}) = 0, U(\text{right heart endocardium}) = 0.5$. The difference in values for the right and left endocardium ensures the septal regions are similar to the left ventricular free wall. The relevant regions for the Dirichlet boundary conditions for the heat equations are already required for defining pressure boundary conditions, making this step in fibre generation require no additional user input. The apex-to-base direction is established as the direction of maximal change in the ‘heat’ U , i.e. $\mathbf{A} = \nabla U$ after solving the heat equation with Dirichlet boundary conditions $U(\text{apical node}) = 1, U(\text{selected basal node}) = 0$, which requires manually selecting an apical and basal point. The conventional circumferential direction, or zero angle fibre direction for the ventricles is given by $\mathbf{Z} = \mathbf{A} \times \mathbf{T}$, and the apical-basal (90° angle) direction by $\mathbf{T} - (\mathbf{A}^T \mathbf{T}) \mathbf{A}$. Suitable interpolation of these two directions gives intermediary fibre direction:

$$\mathbf{f} = \cos(\alpha) \mathbf{Z} / \|\mathbf{Z}\| + \sin(\alpha) \mathbf{N} / \|\mathbf{N}\|$$

This method provides a local coordinate frame for definitions of cardiac ventricular fibres, and guarantees that fibres are orthogonal to the transmural direction, ensuring effective contraction. In the atria, fibre directions are more complex, and do not appear to follow a simple rule. Furthermore, due to the thin walls, less experimental data is available on changes in fibre angle throughout the wall. Current state of the art algorithms include, semi-automatic algorithms for fibre generation, requiring the user to select approximately 20 seed points [18], or division of atria in 42 areas [39]. Simpler solutions include cylindrical components around the veins [19].

Most current research into the importance of the fibre orientation focuses on the effect on atrial arrhythmias and ablation procedures. Not much is known about the importance of these for mechanical function, atrial output, and the effects on the pressure-volume relationship. As atrial fibres are more complex, and not the focus of our study, we simply extend the ventricular fibres to the atria. Figure 1A shows the fibre vectors used throughout the cardiac geometry.

2.4 Hemodynamic modelling

For the hemodynamic model we use a closed loop circulation. In line with the valves in a healthy circulation, our compartments and connections are left ventricle $\rightarrow$ systemic arteries $\leftrightarrow$ systemic veins $\leftrightarrow$ vena cava $\leftrightarrow$ right atrium $\rightarrow$ right ventricle $\rightarrow$ pulmonary arteries $\leftrightarrow$ pulmonary veins $\leftrightarrow$ left atrium $\rightarrow$ left ventricle, where $a \rightarrow b$ indicates flow from a to b if there a higher pressure in compartment a ($P_a > P_b$), i.e. a valve, and $a \leftrightarrow b$ indicates bidirectional flow between compartments a and b . Compartments are either cardiac chambers of areas of the vasculature, and flow between these compartments is modelled as $\frac{1}{R_{ab}} (P_a - P_b)$, i.e. the same as is used in standard windkessel models.

The pressure-volume relationship of cardiac chambers is governed by the finite element solution, determining the appropriate pressure corresponding to the volume changes, while in other compartments the pressure-volume relationship follows $dV = C dP$ where C is the compliance of the compartment. The ordinary differential equations generated by the flow constraints between compartments are added to the matrix and solved along with the mechanics equations. Table 1 shows hemodynamic parameters, which are based on rescaling parameters used in a dog model [16] by a factor 1.5 to account for differences in volume between dog and human, and the addition of a vena cava compartment for proper filling of the right atrium. We use this scaling as the cardiac geometry is derived from a human patient, but detailed optimization of the hemodynamic parameters was beyond the scope of this study, both due to the computational cost, and the unavailability of invasive hemodynamic measurements in this patient. Instead, we aimed for a simple scaling of parameters to a ventricular stroke volume of approximately 70mL and a peak pressure of approximately 15 kPa.

Figure 1: **Model setup** Panels A and B show the epicardial fibre directions corresponding to -60 degrees from the apical-basal direction vector field. The fibres vary throughout the cardiac wall, reaching +80 degrees on the epicardium. Panel C shows the locations of the applied boundary conditions. Nodes indicated in gold show the nodes where spring boundary conditions are applied. Panel D shows the activation time in ms throughout the ventricle, based on a set atrioventricular delay.

Name	Parameter	Value	
Mitral valve resistance	$R_{la,lv}$	0.00033	ms kPa/ μ L
Aortic valve resistance	$R_{lv,sa}$	0.0046	ms kPa/ μ L
Bulk arterial-venous resistance	$R_{sa,sv}$	0.1389	ms kPa/ μ L
Bulk venous-vena cava resistance	$R_{sv,vc}$	0.0167	ms kPa/ μ L
Vena cava-right atrium resistance	$R_{vc,ra}$	0.0034	ms kPa/ μ L
Tricuspid valve resistance	$R_{ra,rv}$	0.00033	ms kPa/ μ L
Pulmonary valve resistance	$R_{rv,pa}$	0.0026	ms kPa/ μ L
Pulmonary resistance	$R_{pa,pv}$	0.0034	ms kPa/ μ L
Pulmonary veins-left atrium resistance	$R_{pv,la}$	0.0034	ms kPa/ μ L
Systemic arterial compliance	C_{sa}	12000	μ L/kPa
Systemic venous compliance	C_{sv}	575000	μ L/kPa
Vena cava compliance	C_{vc}	75000	μ L/kPa
Pulmonary arterial compliance	C_{pa}	62550	μ L/kPa
Pulmonary venous compliance	C_{pv}	75000	μ L/kPa
Initial conditions			
Left ventricular pressure	$p_{lv}(0)$	0.6	kPa
Left atrial pressure	$p_{la}(0)$	0.6	kPa
Right ventricular pressure	$p_{rv}(0)$	0.3	kPa
Right atrial pressure	$p_{ra}(0)$	0.3	kPa
Systemic arterial pressure	$p_{sa}(0)$	12	kPa
Systemic venous pressure	$p_{sv}(0)$	2	kPa
Vena cava pressure	$p_{vc}(0)$	0.5	kPa
Pulmonary arterial pressure	$p_{pa}(0)$	1.75	kPa
Pulmonary venous pressure	$p_{pv}(0)$	0.75	kPa

Table 1: Hemodynamic parameters

2.5 Numerical methods

The larger number of elements and different matrix structure means the problem is less suitable for a direct LU factorization used in our previous work [22, 25]. Therefore, alternative methods based on iterative solvers were developed. We use an approach similar to the one proposed by Gurev et al. [13].

The nonlinear system to be solved with each time step is $\mathbf{r}(\mathbf{v}) = 0$, where the unknowns $\mathbf{v} = (\mathbf{x}, \mathbf{p}_h, \mathbf{p}_c)$ are nodal positions $\mathbf{x}$, hydrostatic pressure $\mathbf{p}_h$ and cavity pressures $\mathbf{p}_c$. The residual $\mathbf{r} = (\mathbf{r}_x, \mathbf{r}_p, \mathbf{r}_w)$ consists of the residual for the stress balance equation $\mathbf{r}_x(\mathbf{x}, \mathbf{p}_h, \mathbf{p}_c)$, the incompressibility equation $\mathbf{r}_p(\mathbf{x})$ and the hemodynamic constraints for each cavity $\mathbf{r}_w(\mathbf{x}, \mathbf{p}_c)$. We solve this system using Newton's method. The overall linear system that requires solving with each Newton iteration includes unknowns for the update of the nodal positions $\Delta_{\mathbf{x}}$, hydrostatic pressure $\Delta_{\mathbf{p}}$ and cavity pressures $\Delta_{\mathbf{p}_c}$. The right hand side consists of the residual for the stress balance equation $\mathbf{r}_x$, the incompressibility equation $\mathbf{r}_p$ and the hemodynamic constraints for each cavity $\mathbf{r}_w$. In our derivation, we initially combine the vector of unknown nodal positions and the vector of unknown hydrostatic pressures in a single vector $\Delta_{\mathbf{x}\mathbf{p}} = (\mathbf{x}, \mathbf{p}_h)$ and the corresponding residuals in the vector $\mathbf{r}_{\mathbf{x}\mathbf{p}} = (\mathbf{r}_x, \mathbf{r}_p)$, resulting in the system:

$$M \begin{pmatrix} \Delta_{\mathbf{x}\mathbf{p}} \\ \Delta_{\mathbf{p}_c} \end{pmatrix} = \begin{pmatrix} \mathcal{J} & \mathcal{B} \\ \mathcal{C} & V_p \end{pmatrix} \begin{pmatrix} \Delta_{\mathbf{x}\mathbf{p}} \\ \Delta_{\mathbf{p}_c} \end{pmatrix} = - \begin{pmatrix} \mathbf{r}_{\mathbf{x}\mathbf{p}} \\ \mathbf{r}_w \end{pmatrix}$$

As the matrix V_p is small, this can be efficiently decoupled as:

$$\mathbf{S}_w \Delta_{\mathbf{p}_c} = \mathbf{r}_w - \mathcal{C} \mathcal{J}^{-1} \mathbf{r}_{\mathbf{x}\mathbf{p}} \quad (5)$$

$$\Delta_{\mathbf{x}\mathbf{p}} = \mathcal{J}^{-1} \mathbf{B} \Delta_{\mathbf{p}_c} - \mathcal{J}^{-1} \mathbf{r}_{\mathbf{x}\mathbf{p}} \quad (6)$$

$$(7)$$

Where the Schur complement matrix is $\mathbf{S}_w = \mathcal{C} \mathcal{J}^{-1} \mathcal{B} - V_p$. We pre-calculate $\mathcal{J}^{-1} \mathcal{B}$ and use a direct solve for the small system involving $\mathbf{S}_w$. This procedure requires $k+1$ applications of $\mathcal{J}^{-1}$, where $k \approx 10$ is the number of columns in $\mathcal{B}$, which corresponds to the number of hemodynamic compartments. After

solving the system, the equation for $\Delta_{\mathbf{x}\mathbf{p}}$ uses the same precalculated expressions, and thus requires no significant additional computations. Solving $\Delta_{\mathbf{x}\mathbf{p}} = \mathcal{J}^{-1}\mathbf{r}_{\mathbf{x}\mathbf{p}}$ is equivalent to solving the system

$$\mathcal{J} = \begin{pmatrix} A & B \\ C & 0 \end{pmatrix} = \begin{pmatrix} \frac{d\mathbf{r}_{\mathbf{x}}}{d\Delta_{\mathbf{x}}} & \frac{d\mathbf{r}_{\mathbf{x}}}{d\Delta_{\mathbf{p}}} \\ \frac{d\mathbf{r}_{\mathbf{p}}}{d\Delta_{\mathbf{x}}} & \frac{d\mathbf{r}_{\mathbf{p}}}{d\Delta_{\mathbf{p}}} \end{pmatrix}$$

As the hydrostatic pressure does not appear in the incompressibility constraint, the bottom right block is zero.

To solve this system, we apply flexible GMRES with the preconditioner:

$$\begin{pmatrix} A_{pc}^{-1} & 0 \\ 0 & I \end{pmatrix} \begin{pmatrix} I & -B \\ 0 & I \end{pmatrix} \begin{pmatrix} I & 0 \\ 0 & -\gamma S_{pc}^{-1} \end{pmatrix} \quad (8)$$

Where S_{pc}^{-1} is an approximation of the inverse of the Schur complement matrix $S = CA^{-1}B$, and A_{pc}^{-1} is an approximation of the inverse of A . Application of this preconditioner results in expected convergence in at most two GMRES iterations if $A_{pc}^{-1} = A^{-1}$ and $S_{pc}^{-1} = S^{-1}$, and requires one application of A_{pc}^{-1} and S_{pc}^{-1} [13].

To approximate $A_{pc}^{-1}x$ we apply an algebraic multigrid preconditioner for A , specifically the Boomer-AMG implementation available in PETSc [2, 14], with options `-apc_hypre_boomeramg_relax_type_all` `SOR/Jacobi` `-apc_hypre_boomeramg_coarsen_type` `CLJP` `-apc_hypre_boomeramg_strong_threshold` `0.3` `-apc_hypre_boomeramg_max_row_sum` `1.0` `-apc_hypre_boomeramg_interp_type` `FF1`. For approximating the application of the Schur complement, we use $S_{pc}^{-1} = C\text{diag}(A)^{-1}B$, which is a simple and memory efficient approximation.

We further speed up the solution process by using techniques described in our previous work [22]. Firstly, we use modified Newton iterations, i.e. we only update $\mathbf{M}$ (and thus $\mathcal{J}^{-1}\mathbf{B}$ and other operations that only rely on $\mathbf{M}$) when convergence is slow. Secondly, we calculate the residual for the previous solution, linear extrapolation, and quadratic extrapolation from previous solutions, and initialize the solver with the choice that gives the lowest residual norm.

2.6 Activation pattern

Activation is determined using a shortest distance algorithm, searching breadth-first from the activation points. For atrial activation, we start at the selected atrial node we use in the fibre generation algorithm, near the sinoatrial node. For ventricular activation, we use the endocardial nodes in both ventricles which are closest to the selected apical node used in fibre generation. Ventricular activation is started after a set delay of 160 ms from the start of atrial activation, accounting for the delay in the atrioventricular node and conduction to and from this node [34]. Conduction proceeds homogeneously with a velocity of 0.75 mm/ms, except for the bottom 50% of the ventricles which have a conduction velocity of 3 mm/ms to account for the fast conduction system. This results in a realistic overall activation time 263 ms. Figure 1D shows the resulting activation pattern.

2.7 Atrial contraction model

There is currently a wide range of available atrial electrophysiology models [7, 33, 28, 11, 17]. However, these models have typically been developed to study atrial fibrillation, and not optimized for studies of atrial contraction. In particular, the calcium transients seen in these models show a wide range of behaviours [42], which would be expected to result in a wide range of contractile behaviour. To circumvent this uncertainty and variability surrounding the atrial calcium transient in computational models, we use experimentally measured calcium transient data from Brixius et al. [6], offset by the local activation time described in the previous section. As this data has not been calibrated, we assume peak and diastolic calcium levels of 0.6 μM and 0.1 μM respectively, based on the ranges seen in computational models [42] and ventricular myocytes [24]. The resulting calcium transient based on calibrating, smoothing and extrapolating the experimental data can be seen in Figure 2A, compared to several recent computational models.

We base the atrial contraction model on our previously published ventricular model [24], which models calcium binding to troponin C, tropomyosin cooperativity, and a three-state crossbridge model

Figure 2: **Calcium and tension transients** Panel (A) shows the calcium transients from available atrial electrophysiological models compared with our baseline calcium transient based on experimental data by Brixius et al. [6], Panel (B) shows the ventricular, atrial, and atrial fibrillation transients used in modelling, and Panel (C) shows isometric twitch tension at resting length for the ventricles and the six different conditions of the atria. All results are paced at 1 Hz and represent cardiac function at body temperature.

with length- and velocity dependencies in tension generation. The model equations are given in Appendix A.

There is only limited data available for contraction in human atrial myocytes. Thus, in creating a computational model of human atrial cellular contraction, we assume atrial myocytes are broadly similar to ventricular myocytes. The only two parameters we consider changing are (1) a scaling factor ξ for all crossbridge cycling rates ($k_{ws}^{atr} = \xi k_{ws}$, $k_{su}^{atr} = \xi k_{su}$), as contraction kinetics are highly dependent on these parameters, and crossbridge cycling rates are known to vary between species and between atria and ventricles [31], (2) calcium sensitivity $[Ca^{2+}]_{T50}^{ref,atr}$, as this parameter is highly dependent on the calcium transient used, and tightly regulated by phosphorylation [29].

With respect to available data on atrial contractile dynamics in human cells at body temperature, Flesch et al. [9] report time to peak (TPT) measurements as 85.0 ± 5.5 and 88.3 ± 2.5 ms and time to 50% relaxation (RT_{50}) as 66.1 ± 5.9 , 73.3 ± 1.7 ms for two separate experimental batches. However, Brixius et al. [6] report equal TPT=110 ms and RT_{50} =110 ms, considerably different from Flesch et al.

Our previously published ventricular model [24], when driven by an atrial calcium transient, produces a TPT = 113 ms, $RT_{50} = 96$ ms, compatible with the measurements by Brixius et al. Note that due to the differences in calcium kinetics, peak tension in the atria is marginally lower than in the ventricles. We consider this difference of 15-20% to be physiologically plausible, due to lower pressures in the atria (See Figure 2C). Matching the Flesch et al. measurements while maintaining the same peak tension requires adjusting $\xi = 3$, $[Ca^{2+}]_{T50}^{ref,atr} = 0.86$ μ M, resulting in TPT = 82 ms, $RT_{50} = 75$ ms. This change is consistent with measurements of myosin ATPase being 4 times higher in atrial tissue [31]. We test both parameterizations of the contraction model, to investigate the physiological consequences of higher crossbridge cycling rates in the atria.

3 Results

3.1 Boundary conditions

In simulations of ventricular mechanics in isolation, boundary conditions are typically applied to the base of the ventricles, using Dirichlet or Robin boundary conditions [23]. However, in four chamber simulations, the situation is more complex. Applying the equivalent Dirichlet boundary condition by fixing the valve plane would decouple ventricular and atrial mechanics, preventing study of the mechanical interactions between these chambers. Physiologically, the mechanical interactions of the heart with the rest of the body include contact mechanics with the chest cavity, changes in the forces of these interactions with breathing (lungs, diaphragm), interaction with the pericardium, and forces due to the blood vessels leading to and from the heart. Including contact forces with the pericardium and chest cavity requires a geometric model of these as well as computationally demanding contact mechanics. Veins and arteries can be more easily included in a mechanical model of the heart, although accurately doing so requires a separate model of their mechanics, and introduces the question of where to put their boundary. The insertion points of blood vessels into the heart do however, introduce a point where boundary conditions can be more naturally applied to a four chamber heart model.

For the purpose of this study, we only consider boundary conditions related to the blood vessels attached to the heart. To take into account the fact that these connections are not completely static, we tested both Dirichlet boundary conditions as well as spring-like boundary conditions on the nodes, using simple linear springs to the nodes.

The use of Dirichlet boundary conditions was found to lead to unacceptable results as the atria inflate 'into' these boundary conditions. Thus, we test (1) Spring boundary conditions on the locations of the atrial veins, and (2) Spring boundary conditions on the locations of the atrial veins and ventricular arteries. (3) Varying the stiffness of the springs.

Figure 1C shows the position of the atrial veins and ventricular arteries. Results for the different boundary conditions show the influence on the ventricular pressure-volume curves is minor, as shown in Figure 3, which shows results for cases (1) and (2) with stiffness $k = 10$ kPa/mm. In general, ejection and valve plane movement is maintained, and for stronger or extra boundary conditions, there is more extreme deformation near the boundary. For stiffer springs ($k > 50$ kPa/mm), simulations can become unstable and fail to converge. Given the minor differences, we choose to use only boundary conditions on the atrial side (i.e. case 1), as this limits the use of unnecessary boundary conditions and unnatural

Figure 3: Results for boundary conditions. Pressure-volume loops for left ventricle and atrium (5th beat).

deformations near them.

3.2 Atrial contraction model

To study the importance of atrial-specific contraction modelling and its effect on the timing of atrial contraction and relaxation, we run the model for atrial cells with three different configurations: (1) the unmodified human ventricular model and human ventricular calcium transient, (2) with the human ventricular model, but atrial calcium transient, and (3) the adjusted atrial model ($\xi = 3$, $[\text{Ca}^{2+}]_{\text{T50}}^{\text{ref, atr}} = 0.86 \mu\text{M}$) and atrial calcium transient. Results are shown in Figure 4. These show significant differences in atrial function depending on the contractile model parameters and calcium transient. However, we can see that atrial contraction dynamics have surprisingly little influence on ventricular contraction. For the model with increased crossbridge cycling rates, left-ventricular volume is slightly higher, pointing to more effective ventricular filling. The main difference between the models is seen at the end of atrial contraction. Whereas the model with increased crossbridge cycling rates shows a smooth transition from contraction into relaxation, the model with only an atrial calcium transient shows a tension spike. The ventricular model with ventricular calcium transient shows an even greater spike. Further investigation of this phenomenon revealed it to be due to an increase in atrial contractile force after the atrioventricular valve had closed, due to the ventricles stretching the atria, and the length-dependence of tension generation causing extended prolongation of contraction. Thus, faster atrial contraction and calcium cycling are key in preventing this phenomenon both in modelling and physiologically. In light of these results, we denote the model which uses an atrial calcium transient and increased crossbridge cycling rates as the ‘baseline’ healthy model condition for comparison in the next section. The results of this case are shown in more detail in Figure 5.

3.3 Changes to calcium transients in atrial fibrillation

Atrial fibrillation is known to cause electrophysiological remodelling of the atria, increasing the risk for maintaining and re-inducing atrial fibrillation in the future [41]. For the purposes of this study we consider only the effect of changes to calcium dynamics after restoration of sinus rhythm.

Data from Voigt et al. [40] shows changes to the atrial calcium transient as a result of atrial fibrillation. These include a 30% increase in the time constant of calcium transient decay, and a 10% decrease in peak calcium. To reproduce this effect, we decrease peak calcium transient, and slow early relaxation rate of the

Figure 4: **Results** for atrial contraction models. Pressure-volume loops for all four chambers (5th beat). Highlighted in green is the pressure spike in the atria after the atrioventricular valves have closed.

Figure 5: **Results** the baseline model. Shown on the top left is the time into the simulation (all in the 5th beat, 4s to 5s simulation time, as in other results) for the ‘baseline’ model, with atrial calcium transient and re-parameterized contraction model.

calcium transient by 30%, speeding up later relaxation to reach appropriate diastolic calcium levels. Work by Schotten et al. shows a 75% decrease in twitch tension, mainly due to decreased calcium sensitivity, with only a 15% reduction in maximal force. We test the effect of such decreased calcium sensitivity by changing $[Ca^{2+}]_{T50}^{ref}$ to reproduce the decrease in force. Figure 2 shows the calcium transients used and resulting tension transients (panels B,C). Figure 6 shows the result of our simulation compared to the healthy heart. This shows major effects on atrial contraction of the changes in the calcium transient, with lower peak atrial pressure and reduced atrial relaxation, and a small but noticeable decrease in ventricular filling. Adding changes in calcium sensitivity causes an additional, but smaller decrease in atrial function.

4 Discussion

Mechanical models of the heart which include all four chambers are increasingly becoming more popular. However, many fundamental questions remain.

This manuscript extended our model of ventricular dynamics, including the recently published model of a human ventricular myocyte, to include atrial dynamics. We also addressed some of these fundamental questions relating to the development of four-chamber mechanical models of the heart.

Firstly, four chamber heart models require a representation of atrial contraction. In this manuscript we have tested several ways of addressing this problem. Using measurements of atrial instead of ventricular calcium transients, and increased crossbridge cycling rates consistent with experimental measurements of ATPase, result in better timing of atrial contraction and relaxation. Slow relaxation of the atria can lead to substantial contraction of the atria after the atrioventricular valves are closed, as they are stretched by the ventricles. This unnecessary re-activation of the atria leads to a minor decrease in atrial filling and ventricular contraction, and would also lead to unnecessary stress on the atria, increased energy consumption, and decreased myocardial efficiency. Due to remodelling after atrial fibrillation, contractile function of the atria is significantly decreased. Our model confirms this decrease in function. However, the effects on ventricular filling are relatively minor in the absence of other cardiac defects, and ventricular function is largely maintained, with ejection fraction decreasing by less than 5%.

Secondly, hemodynamic modelling is significantly different from the approach typically used in biventricular models. Instead of using a lumped three-element windkessel model for each ventricle, in our four chamber heart model we model the entire circulation in a flexible way, allowing for investigation of different chamber layouts such as monoventricle hearts, septal defects, and other cardiomyopathies. In addition, we described an effective numerical method for including these constraints in the nonlinear solver without requiring nested iterations. In four chamber models, a model of ventricular diastolic filling comes naturally, in contrast to previous work in biventricular models, which use an imposed boundary condition with a simple diastolic filling or time-varying atrial elastance model. This will be particularly important in the increasing interest in cardiomyopathies in which ventricular filling is impaired, such as heart failure with preserved ejection fraction (HFpEF).

Furthermore, while in ventricular simulations, the geometry is typically inflated to end-diastolic pressure before the simulation is started, as the state of the tension development can be reasonably approximated as low and homogeneous at this point. However, in atrioventricular simulations this assumption is no longer true as the atria are not in a relaxed state at end-diastole, and as a result it is more difficult to determine a suitable starting point for simulations. We have chosen to inflate the chambers to equal pressure in left ventricle and left atrium, and equal pressure in the right atrium and right ventricle, representing the end of passive filling (diastasis). To reduce the influence of this initial condition, we run all simulations to a minimum of 5 beats, despite the increased computational cost.

The purpose of this work was primarily to develop a numerical framework and a suitable model of human atrial contraction. As a result of this focus, the model in its current form still has a number of limitations.

Optimization of hemodynamic parameters is more challenging when coupled to large 3D cardiac biomechanics models. Steady-state runs are computationally unfeasible, and detailed data for hemodynamic parameters are often unavailable. In the absence of physiological mechanisms related to blood pressure regulation, a long-term simulation is more likely to diverge. As a result of using adjusted animal data, the main limitation of the current work is that the left-atrial and left-ventricular diastolic pressures are higher than expected, most likely as a result of the parameterization of the pulmonary

Figure 6: Results for atrial fibrillation changes. Pressure-volume loops for all four chambers (5th beat).

compartments. In addition, in the atrial pressure-volume loop, the phase plot produces the typical figure of eight morphology with the left loop corresponding to the atrial contraction and the right loop to ventricular contraction. In healthy individuals the two loops should be closer in size [4], and the model predicts a short period of atrial filling prior in the early stages of atrial contraction. This is likely due to these limitations in the parametrization of the hemodynamic model, and lack of dynamic regulation of cardiovascular system resistance. Potentially a model of blood pressure regulation such as CircAdapt [27] could be coupled, but at the cost of additional complexity and computational cost.

Secondly, the implementation of boundary conditions could be improved, for example by including a mesh of parts of the connected veins and atria. However, it appears from our simulations that the effect of boundary conditions is relatively minor, and such additions are not expected to have a major impact on the models predictive power.

Thirdly, the atrial contraction model inherits most of its parameters from work in human ventricular myocytes. The current reparametrization appears effective, but additional measurements from human atrial myocardium would improve the accuracy of this model component.

Finally, generating accurate myocardial fibre directions is particularly challenging on these more complex geometries. However, recent advances in atrial electrophysiological modelling and DTMRI measurements of the atria are likely to improve this aspect [35]. The impact of the choice of atrial fibre on atrioventricular function is as of yet unknown, and this would be a particularly interesting avenue of future research.

Overall, these newer computational models are complex and introduce both new opportunities and challenges in computational modelling of the heart. Although the resulting images are visually impressive, more transparency about predictions of pressure-volume curves in all chambers and acknowledging limitations is a key step in moving forward and improving their predictive power.

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A Contraction Model Equations

The model of passive and viscoelastic tension development consists of a single ordinary differential equation:

$$\frac{dC}{dt} = \frac{d\lambda}{dt} - 1 \quad (9)$$

$$F_1 = a(e^{bC} - 1) \quad (\text{parallel elastic element}) \quad (10)$$

$$F_2 = akC_s \quad (\text{series elastic element}) \quad (11)$$

$$F_d = \begin{cases} a\eta_l \frac{dC_d}{dt} & \frac{dC_d}{dt} > 0 \\ a\eta_s \frac{dC_d}{dt} & \frac{dC_d}{dt} < 0 \end{cases} \quad (\text{viscous dashpot element}) \quad (12)$$

$$C_s + C_d = C \quad (\text{series constraint}) \quad (13)$$

$$F_2 = F_d \quad (\text{series constraint}) \quad (14)$$

$$F_{\text{tot}} = F_1 + F_2 = F_1 + F_d \quad (\text{total tension}) \quad (15)$$

The model of active tension development consists of six ordinary differential equations. Four differential equations model the binding of calcium to troponin C (CaTRPN), the subsequent conformational change in tropomyosin which unblock the myosin crossbridge binding sites on actin (B), and cycling of crossbridges through a pre-powerstroke (W), post-powerstroke (W), and (implicitly defined) unbound state. Two additional equations for ζ_w, ζ_s model the mean distortion of crossbridges due to movements of the myofilaments, and their effect on force generation and crossbridge cycling.

$$\frac{d\text{CaTRPN}}{dt} = k_{\text{TRPN}} \left(\left(\frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_{\text{T50}}} \right)^{n_{\text{TRPN}}} (1 - \text{CaTRPN}) - \text{CaTRPN} \right) \quad (16)$$

$$\frac{dB}{dt} = k_b \cdot \text{CaTRPN}^{-n_{\text{Tm}}/2} \cdot U - k_u \cdot \text{CaTRPN}^{n_{\text{Tm}}/2} \cdot B \quad (17)$$

$$\frac{dW}{dt} = k_{\text{uw}}U - k_{\text{wu}}W - k_{\text{ws}}W - \gamma_{\text{wu}}W \quad (18)$$

$$\frac{dS}{dt} = k_{\text{ws}}W - k_{\text{su}}S - \gamma_{\text{su}}S \quad (19)$$

$$\frac{d\zeta_w}{dt} = A_w \frac{d\lambda}{dt} - c_w \zeta_w \quad (20)$$

$$\frac{d\zeta_s}{dt} = A_s \frac{d\lambda}{dt} - c_s \zeta_s \quad (21)$$

$$T_a = \frac{T_{\text{ref}}}{r_s} (S(\zeta_s + 1) + W\zeta_w) \quad (22)$$

Where:

$$\lambda = \text{SL}/\text{SL}_0 = \|\mathbf{F}\mathbf{f}\| \quad (\text{in multiscale simulations}) \quad (23)$$

$$U = (1 - B) - S - W \quad (24)$$

$$\gamma_{\text{wu}} = \gamma_w |\zeta_w| \quad (25)$$

$$\gamma_{\text{su}} = \begin{cases} \gamma_s(-\zeta_s - 1) & \text{if } \zeta_s + 1 < 0 \\ \gamma_s \zeta_s & \text{if } \zeta_s + 1 > 1 \\ 0 & \text{otherwise (if } \zeta_s + 1 \in [0, 1]) \end{cases} \quad (26)$$

$$A_s = A_w = A_{\text{eff}} \cdot r_s / ((1 - r_s)r_w + r_s) \quad (27)$$

$$k_{\text{wu}} = k_{\text{uw}}(1/r_w - 1) - k_{\text{ws}} \quad (28)$$

$$k_{\text{su}} = k_{\text{ws}}r_w(1/r_s - 1) \quad (29)$$

$$k_b = k_u \text{CaTRPN}^{n_{\text{Tm}}} / (1 - r_s - (1 - r_s)r_w) \quad (30)$$

$$c_w = \phi \cdot k_{\text{uw}} \cdot U/W = \phi \cdot k_{\text{uw}} \cdot ((1 - r_s)(1 - r_w)) / ((1 - r_s)r_w) \quad (31)$$

$$c_s = \phi \cdot k_{\text{ws}} \cdot W/S = \phi \cdot k_{\text{ws}} \cdot ((1 - r_s)r_w) / r_s \quad (32)$$

In a multi-scale modelling application, only part of the viscoelastic force in the model should be included, resulting in:

$$T_a + F_d \quad (33)$$