Integration of an Electrophysiologically-Driven Heart Model into Three-Dimensional Haemodynamics Simulation using the CRIMSON Control Systems Framework

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Abstract We create a multiphysics cardiovascular model by integrating the electrical and active-tension generation properties of the cardiac myocyte into a lumped parameter network model of the left ventricle, which is then applied to create a boundary condition for three-dimensional haemodynamics simulation. The process demonstrates the power and flexibility of the CRIMSON Boundary Condition Toolbox and Control Systems Framework, our accessible tools for designing, implementing and testing novel physiological controlled boundary conditions for fluid flow.

Key words: Cardiovascular Modelling; Transitional Physiology; Haemodynamics; Physiological Control; Heart Model

1 Introduction

Lumped parameter network (LPN) models have been used extensively to simulate behaviour within the cardiovascular system, either exclusively [29, 3] or coupled with one-dimensional [12, 1, 13, 18] or three-dimensional [17, 25, 24, 30] vascular domains. Vascular regions which have been investigated using LPN models include the coronary arteries [7, 8], the heart [13, 5, 14, 9], the brain [1] and full closed-loop simulations [17]. With a few exceptions [1, 6], these LPNs have used static parameters. An awareness of the deficiencies of purely static or steady-state simulation in computational haemodynamics means that there is interest in models which can ad-just their own parameters in a physiologically-inspired manner. Recent examples in-clude using an autonomic nervous system reflex to control cardiac parameters [9], or ensuring that oxygen delivery to the myocardium closely matches cardiac metabolic demand [2]. Controlled models are important not only

because they reproduce key phenomena such as the change in heart rate when standing up [9], or the changes in coronary flow that occur during exercise [2], but also because the study of the highly-integrated networks that cardiovascular control systems form is challenging in vivo or in vitro, from both the technical and the conceptual perspective.

Despite the accepted need for control systems models, progress is hindered by the time-consuming nature of implementing and testing control systems within existing powerful simulation packages. In this work, we present the latest developments made to our cardiovascular geometry creation and incompressible Navier-Stokes hemodynamics simulation software, CRIMSON (CardiovasculaR Integrated Modelling and SimulatiON) [28], which we assert can accelerate progress by making the design of controlled physiological models faster, easier and more accessible, even to users without a strong background in software development. In order to demonstrate their flexibility, we use CRIMSON's boundary condition and control system design tools, the CRIMSON Boundary Condition Toolbox (BCT) and the CRIMSON Control Systems Framework (CSF), to create an electrophysiologically-driven heart model, and use it as an inflow boundary condition as part of a multidomain, multi-physics Navier-Stokes haemodynamics simulation in an example vascular geometry. The model makes use of an existing biophysical model of the cardiac myocyte and its active tension generation, which we obtain from the mathematical cell model repository cellML [10, 27]. The benefits of using an electrophysiologically-driven heart model is that it allows us to leverage decades of modelling work on the behaviour of the cardiac myocyte, with different desirable properties available depending on the particular choice of myocyte model. The primary purpose of this article is to demonstrate rapid model design and integration, so our heart model follows previous work [19].

Previous non-electrophysiological LPN heart models generally employ a time-varying elastance method [21, 3, 16], and include those that model flow-rate dependend pressure losses in the left ventricle [9]. These models successfully reproduce aortic pressure and flow waveforms. Electrophysiological LPN models have been shown to allow the effect of subcellular processes upon the haemodynamics to be investigated, for example aortic pressure can be seen to depend on L-type calcium channel conductance and upon on pacing frequency [19]. Similarly, appropriate electrophysiological heart models are capable of reproducing the Frank-Starling mechanism, the effects of dyssynchronous contraction and choice of pacing location [26]. In general, the use of the model means that the aortic valve inflow in the fluid domain is dependent upon subcellular processes and parameters, including transmembrane voltage difference, ion channel state and intracellular calcium concentration.

2 Methods

2.1 Overview of CRIMSON

We perform our simulations using CRIMSON, which provides a complete software pipeline for creating Navier-Stokes hemodynamics simulations from medical imaging stacks, with an emphasis on power and usability. It consists of two main components: the intuitive image analysis and segmentation interface, and the powerful flowsolver simulation package. The flowsolver is highly scalable, having been used previously to simulate pulsatile flow on 16,384 cores of an IBM Blue Gene/Q supercomputer. In the present work we discuss only two aspects of the pipeline: the boundary condition control tool: CRIMSON CSF, and the closely-related arbitrary LPN condition design and specification tool: CRIMSON BCT. We used CRIMSON to create a simple vessel geometry for our investigations, which can be seen in Figure 2.

2.2 Graphical Design of Arbitrary Lumped Parameter Boundary Conditions

Lumped parameter components are assembled into a network using a drag-n-drop interface. The available components include resistances, compliances, valves, inductances and volume-tracking compliance chambers, and they can be arbitrarily arranged, and attached at a point to a boundary of the 3D simulation domain, as shown in Figure 1. One circuit is created for each boundary, connected, for example, as shown in Figure 2, and if desired, a circuit to represent the venous system can be created and attached to some or all of the boundary circuits, in order to create a full closed-loop network. We used the BCT to create the heart model (Figure 4) and two downstream Windkessel models.

We use a standard component layout for the heart model LPN; similar designs have been used previously to simulate aortic inflow [9, 6]. However, because we want to control pressure generation using an electrophysiological model, we abandon the usual feature that the pressure within the ventricle is computed using a time-varying elastance approach, and instead model the left ventricle by a component which simply keeps track of the volume of blood that it contains. The construction of the model in CRIMSON BCT is shown in Figure 4.

2.3 Powerful, Rapid and Accessible Control Systems Design

CRIMSON CSF has access to, and is able to adjust, any of the component parameters or nodal pressures within any of the CRIMSON BCT boundary condition mod-

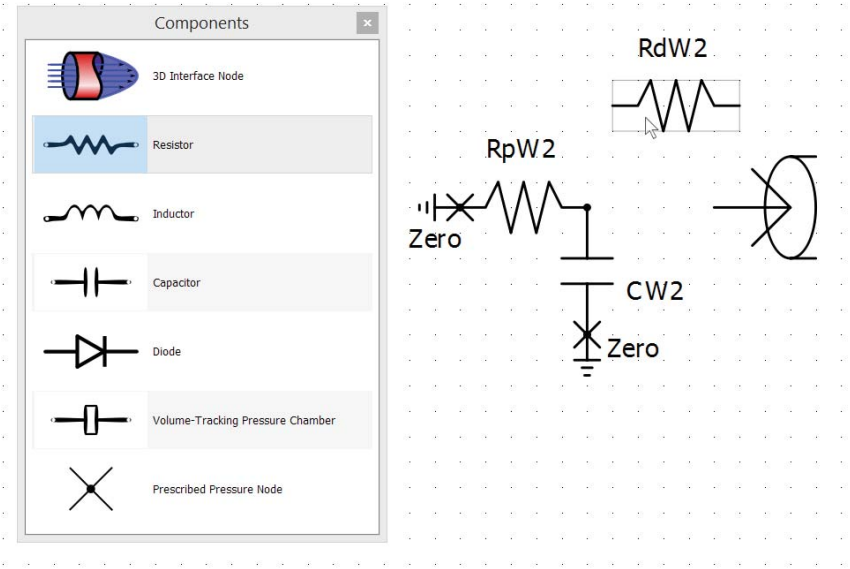

Fig. 1 The creation of a three-element Windkessel model using the drag-n-drop CRIMSON boundary condition toolbox.

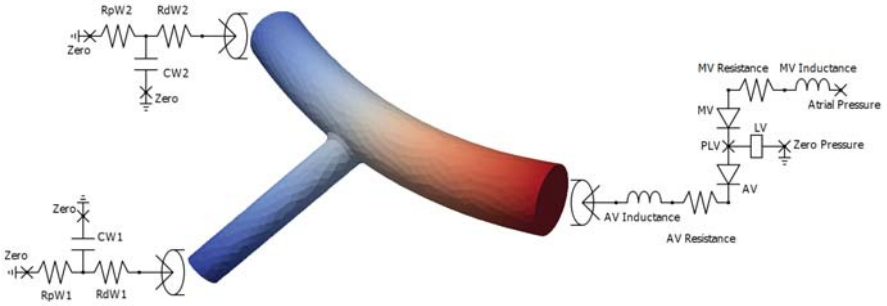

Fig. 2 A complete set of boundary conditions, designed in the arbitrary boundary condition toolbox and attached to a 3D domain. A heart model is shown on the right, and the three-element Windkessel models on the left represent downstream vascular beds.

els, and it has access to all of the pressures, volumes and flows within each boundary condition. This provides sufficient functionality for modelling many physiological control mechanisms. Control systems themselves are described using Python, a popular high-level language which is suitable for both beginners and advanced users. While the CRIMSON flowsolver itself is written in Fortran and C++, both of which require considerable expertise to work with, Python is similar to MATLAB in terms of being much easier to learn and to use. The Python interface with the CRIMSON

```python
from math import pi, cos

# Each controller is a class
class sinusoidalResistanceController:

    # This function is called once, at the start of the simulation.
    # We can use it to set up any constant values we might need
    def __init__(self):
        self.m_periodicTime = 0.0;
        self.m_heartPeriod = 0.86;


    # updateControl is the method that the CRIMSON flowsolver looks for. It calls it
    # on each timestep, and passes all the pressures, flows and stored volumes in
    # the attached boundary condition. The flowsolver it knows what to do with the
    # return value; in this case, it will use it to set a resistance, causing
    # it to vary in time.
    def updateControl(self, currentResistance, timestep, pressuresInBoundaryCondition, \
                            flowsInBoundaryCondition, volumesInBoundaryCondition):
        # Call the function defined below to update the current time
        self.updatePeriodicTime(timestep)
        # Cause the resistance of the target resistor to oscillate in time, and to depend
        # on the pressure at the node with index 1 within the boundary condition
        resistance = cos(self.m_periodicTime * 2.0 * pi) + 5.0 + pressuresInBoundaryCondition[1]
        # Return the resistance
        return resistance


    # We can write additional functions to call from updateControl
    def updatePeriodicTime(self, timestep):
        self.m_periodicTime = self.m_periodicTime + timestep
        # Keep m_periodicTime in the range [0,m_heartPeriod):
        if self.m_periodicTime >= self.m_heartPeriod:
            self.m_periodicTime = self.m_periodicTime - self.m_heartPeriod

```

Fig. 3 A simple example Python script that could be used to control a resistance in one of the boundary conditions, dependent here on time and on a pressure within the boundary condition.

flowsolver is simple, and works as follows. To design a control system for a particular node or component, we annotate it with the name of the Python controller script within the arbitrary boundary condition toolbox. We then take the CRIMSON Python script template which contains all of the necessary boilerplate code, including the automatically passed-in data on the state of the system, and the return value (the new value of the controlled parameter that we wish to set), and we write the code for the custom control system we wish to design into the template. A simple example control script for controlling a resistor is shown in Figure 3.

2.4 The Cardiac Myocyte Model

The use of the electrophysiological model follows a previous approach used for zero-dimensional simulation due to Bo Shim et al. [19], in which the authors took an existing electrophysiological model of a cardiac myocyte, the ten Tusscher 2004 model [23] which, upon the application of an electrical stimulus, generates an action potential caused by the flow of ions across the cell membrane. The model simulates the concomitant calcium release within the cell, which is the internal signal which causes the cell to generate active tension. This model was modified to be suitable for

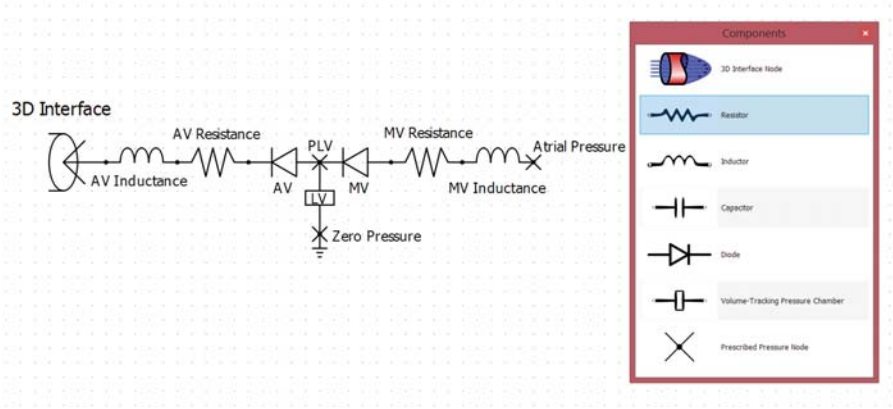

Fig. 4 The CRIMSON Boundary Condition Toolbox, used here to design a heart model. Nodes with prescribed pressure are tagged with the X symbol. The pressure prescription at the left-ventricular pressure node (PLV) here will be set on each time-step by the electrophysiological cell model, within the Python control script, using the volume stored in the LV component as input.

connection to an intracellular cross-bridge dynamics model [15], which generates the active tension in response to the calcium release. From this, Bo Shim et al. created a pressure generation model by assuming the ventricle to be a thin-walled hemispherical shell, and applying Laplaces law to convert a known volume and wall tension into ventricular pressure. Our approach uses the electrophysiological model of Shirokov et al. [20] coupled with the Negroni and Lascano model for active tension generation, as this combination was available in the cellML [10, 27] repository, as the work of Matsuoka et al. [11]. We modified the model to include the thin-shell-based ventricular pressure generation approach of Bo Shim et al.

2.5 Inserting the Cardiac Cell Model into the CRIMSON Flowsolver using the Control Systems Framework

We downloaded the Matsuoka model from the cellML model repository as Python code [4], and inserted it into our CRIMSON Python interface template script, modifying it so that it would advance a single time-step each time it was called to update the control. We did not adjust the parameters from the CellML exposure of the model [4]. We introduced the shell-based pressure computation, using the left ventricular volume data automatically passed to the controller by the flowsolver, and including the change of half-sarcomere length as the myocytes are stretched by the volume within the ventricle. We further modified the model so that during diastole, the filling is controlled by a constant diastolic elastance. The computed pressure is returned to the flowsolver at the end of each update, and is used to set the left-

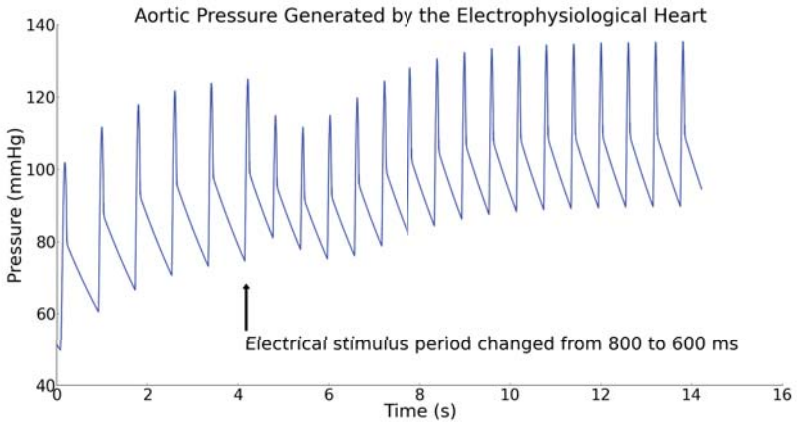

Fig. 5 Aortic pressure generated by the heart model. Note that changes in heart rate are handled automatically and naturally by the cardiac cell model.

ventricular pressure within the heart model. When this prescribed pressure exceeds the aortic pressure, the aortic valve opens and blood flows into the aorta, and the volume in the left ventricle seen by the control system is reduced. The converse is true during diastolic filling.

We relate active tension to left ventricular pressure using the left-ventricular volume, a spherical approximation of the ventricle, and Laplace's law, and the parameters of the Windkessel models at the two other boundaries of the domain, seen in Figure 2, were tuned to adjust the aortic pressure waveform and ventricular ejection fraction.

3 Results

We were able to achieve our primary objective of creating a complex boundary condition, an electrophysiological heart model, by making use of the CRIMSON Boundary Condition Toolbox and Control Systems Framework. This demonstrates the power of the tools, which enabled us to create the heart model from initial design to full functionality in the space of two days.

Figures 5 and 6 show that the heart model successfully reproduces an aortic pressure pattern and left-ventricular pressure-volume loop. Each beat is the result of an electrical stimulus applied to the myocyte within the control script, and so we can change the heart rate by changing the frequency of the electrical stimulus; we do this four seconds into the simulation shown in Figure 5.

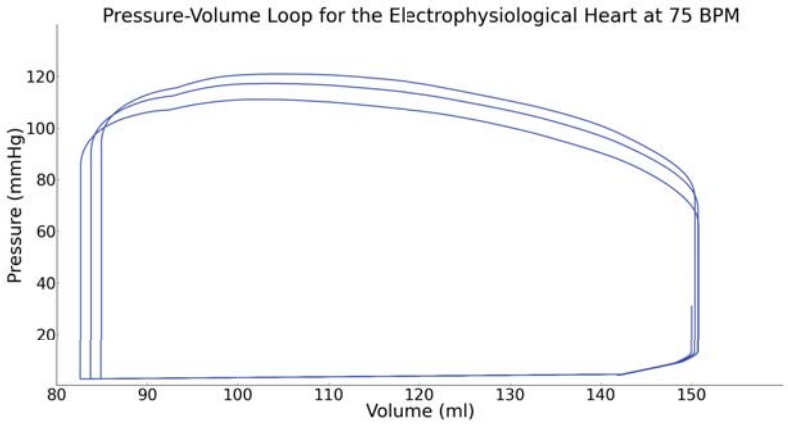

Fig. 6 The pressure-volume loop produced within the left ventricle by the electrophysiological heart model, implemented using the control systems framework. Several beats are displayed.

4 Discussion

We successfully used the model to generate inflow pressure and flow in a Navier-Stokes simulation domain, and to generate pressure-volume loops for the left ventricle. The use of the cell model allows us to initiate each pressure pulse by simulating the application of an electrical stimulus. The development of the model was rapid, due to the novel tools which we have created.

4.1 The Cardiac Cell Model

Using a cardiac electrophysiology myocyte model means that the effects of changing the electrical pacing cycle length on the cell's internal state variables are naturally propagated to the generation of ventricular pressure. Cell models have differing levels of realism in their ability to reproduce physiologically-observed pheonmena. The model of Shirokov et al. [20], as modified by Matsuoka et al. [11], is only one such possiblity. One reason to investigate other modes is that the duration of systole is too short. This is a limitation of the cell model used; it is likely casued by the Matsuoka model using data from guinea pig myocytes. This is something that we could improve upon by replacing the electrophysiological component of the Matsuoka model with one for a human myocyte [23, 22].

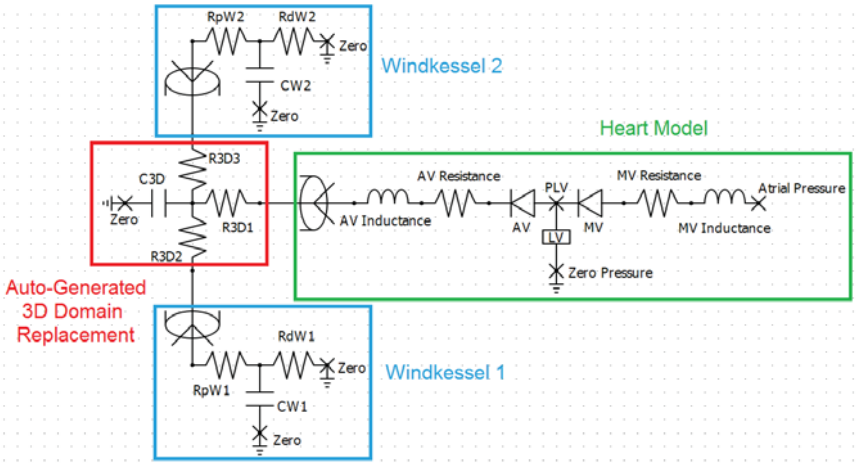

Fig. 7 A schematic of circuit in pure zero-dimensional mode. In this mode, CRIMSON flowsolver automatically generates a replacement for the 3D domain (red) with the same topology (compare Figure 2), and connects it to the boundary conditions, as prescribed for the 3D interface. This allows very rapid prototyping simulations to be run.

4.2 Scope of Arbitrary Cardiovascular Control Mechanism Design

CRIMSON CSF aims to provide a complete set of tools for controlling the parameters within boundary condition models. For example, its access to the parameters which determine physiologically-important factors such as tissue perfusion and oxygen delivery means that control systems which monitor and adjust to varying tissue perfusion requirements can be created. Additionally, control systems which do not rely on any such monitoring, such as the cardiovascular response to psychological stress, could be simulated by creating a control system which does not use any of these variables as input. We believe that the facility to in this manner adjust any of the nodal pressures and any of the component parameters within the boundary conditions should allow most physiological control systems to be modelled.

4.3 Rapid Prototyping

One of the features which we found to be the most useful during this work was the facility for rapid boundary condition design, testing and approximate parameterization provided by the CRIMSON flowsolvers pure zero-dimensional prototyping mode. Enabled using a single input flag, this mode automatically replaces the 3D simulation domain with an additional, simplified zero-dimensional domain (Figure 7), allowing many hundreds of cardiac cycles to be simulated in a short period of time on a laptop, as opposed to achieving a few beats per hour on powerful comput-

ing hardware. This is particularly useful for approximately parametrizing a control system in order to study some state transition, as we generally require the system to reach an equilibrium state before testing a control perturbation, and then we require a further extended period of simulation to observe the transitional behavior. We note that because this mode neglects all 3D effects, the resulting parameterization should only be seen as an approximate value, which must be fine-tuned in full 3D simulation mode.

5 Conclusions

We performed multiphysics simulation of the cardiovascular system by using an electrophysiological heart model to generate flow within a three-dimensional Navier-Stokes haemodynamics simulation. The model allows an electrical stimulus applied to the myocyte to trigger a blood pressure pulse. Creating this model required the merging of models from different subfields of cardiovascular modelling; due to the available tools we were able to do this with a minimum of effort, with the model design and integration taking two days of work.

In particular, this work demonstrates that our boundary condition design tools and control systems framework enable rapid development of remarkably complex enhancements of the CRIMSON flowsolver. While pressure generation in the heart model is not typically considered to be a control system, using the control framework allowed us to show that it is useful for more than just control systems, and also, because fusing two models in this manner would otherwise be a time-consuming task, it demonstrated the ease with which potentially difficult tasks can be achieved. A key purpose of these new tools is that it gives researchers the space to explore, so we do not expect to predict all possible uses, but to list a few, potential applications include simulating hemorrhage, both by creating the bleed in the first place, and by simulating the response of the peripheral resistance and venous compliance, modelling the exercise response in the peripheral vasculature and in the heart, as coordinated by the neural central command, or implementing autoregulation systems within individual tissue beds. Many potential control system models will have a lower level of complexity than the electrophysiological heart, so we believe that our framework will be of great use to workers as they design the next generation of transitional physiological models in hemodynamics.

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References

1. Alastruey J, Moore SM, Parker KH, David T, Peirò J, Sherwin SJ (2008) Reduced modelling of blood flow in the cerebral circulation: coupling 1-d, 0-d and cerebral auto-regulation models. Int J Numer Meth Fluids 56:1061–1067
2. Arthurs CJ, Lau KD, Asrress KN, Redwood S, Figueroa CA (2015) A mathematical model of coronary blood flow control: patient-specific three-dimensional haemodynamics during exercise. Submitted to Am J Physiol Heart Circ Physiol
3. Barnea O (1994) Mathematical analysis of coronary autoregulation and vascular reserve in closed-loop circulation. Comput Biomed Res 27:263–275
4. Garny A (2009) CellML Model Exposure: Role of individual ionic current systems in the SA node hypothesized by a model study, Matsuoka, Sarai, Kuratomi, Ono, Noma, 2003. https://models.cellml.org/exposure/398d5dc7db9f2b9809abc29f440bd456/, Accessed 2015/05/20 at 18:42 BST
5. Kim HJ, Vignon-Clementel IE, Figueroa CA, LaDisa JF, Jansen KE, Feinstein JA, Taylor CA (2009) On coupling a lumped parameter heart model and a three-dimensional finite element aorta model. Annals of Biomedical Engineering 37:2153–2169
6. Kim HJ, Jansen KE, Taylor CA (2010) Incorporating autoregulatory mechanisms of the cardiovascular system in three-dimensional finite element models of arterial blood flow. Annals of biomedical engineering 38:2314–2330
7. Kim HJ, Vignon-Clementel IE, Coogan JS, Figueroa CA, Jansen KE, Taylor CA (2010) Patient-specific modeling of blood flow and pressure in human coronary arteries. Annals of biomedical engineering 38:3195–3209
8. Kim HJ, Vignon-Clementel IE, Figueroa CA, Jansen KE, Taylor CA (2010) Developing computational methods for three-dimensional finite element simulations of coronary blood flow. Finite elements in analysis and design 46:514–525
9. Lau KD, Figueroa CA (2015) Simulation of short-term pressure regulation during the tilt test in a coupled 3d0d closed-loop model of the circulation. Biomech Model Mechan 14:915–929
10. Lloyd CM, Lawson JL, Hunter PJ, Nielsen PF (2008) The cellml model repository. Bioinformatics 24:2122–2123
11. Matsuoka S, Sarai N, Kuratomi S, Ono K, Noma A (2003) Role of individual ionic current systems in ventricular cells hypothesized by a model study. Japanese J Physiol 53:105–123
12. Matthys KS, Alastruey J, Peiró J, Khir AW, Segers P, Verdonck PR, Parker KH, Sherwin SJ (2007) Pulse wave propagation in a model of human arterial network: assessment of 1-d numerical simulations against in vitro measurements. J Biomech 40:3476–3486
13. Mynard J, Nithiarasu P (2008) A 1d arterial model incorporating ventricular pressure, aortic valve and regional coronary flow using the locally conservative galerkin (lcg) method. Commun Numer Meth Engng 24:367–417

14. Mynard J, Davidson MR, Penny DJ, Smolich JJ (2012) A simple, versatile valve model for use in lumped parameter and one-dimensional cardiovascular models. Int J Num Method Biomed Engng 28:626–641
15. Negroni J, Lascano EC (1996) A cardiac muscle model relating sarcomere dynamics to calcium kinetics. J Mol Cell Cardiol 28:915–929
16. Pope SR, Ellweian LM, Zapata CL, Novak V, Kelley CT, Olufsen MS (2009) Estimation and identification of parameters in a lumped cerebrovascular model. Math Biosci Eng 6:93–115
17. Quarteroni A, Ragni S, Veneziani A (2001) Coupling between lumped and distributed models for blood flow problems. Comput Visual Sci 4:111–124
18. Raymond P, Merenda F, Perren F, Rüfenacht D, Stergiopulos N (2009) Validation of a one-dimensional model of the systemic arterial tree. Am J Physiol Heart Circ Physiol 297:H208–H222
19. Shim EB, Leem CH, Abe Y, Noma A (2006) A new multi-scale simulation model of the circulation: from cells to system. Phil Trans R Soc A 364:1483–1500
20. Shirokov R, Levis R, Shirokova N, Riós E (1993) Ca2+-dependent inactivation of l-type ca2+ channels does not affect their voltage sensor. J Gen Physiol 102:1005–1030
21. Suga H, Sagawa K (1974) Instantaneous pressure-volume relationships and their ratio in excised, supported canine left ventricle. Circ Res 35:117–126
22. ten Tusscher KHWJ, Panfilov AV (2006) Alternans and spiral breakup in a human ventricular tissue model. Am J Physiol Heart Circ Physiol 291:H1088–H1100
23. ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV (2004) A model for human ventricular tissue. Am J Physiol Heart Circ Physiol 286:H1573–H1589
24. Vignon-Clementel IE (2006) A coupled multidomain method for computational modeling of blood flow. PhD thesis, Stanford University
25. Vignon-Clementel IE, Figueroa CA, Jansen KE, Taylor CA (2006) Outflow boundary conditions for the three-dimensional finite element model of blood flow and pressure in arteries. Computer methods in applied mechanics and engineering 195:3776–3796
26. Walmsley J, Arts T, Derval N, Bordachar P, Cochet H, Ploux S, Prinzen FW, Delhaas T, Lumens J (2015) Fast simulation of mechanical heterogeneity in the electrically asynchronous heart using the multipatch module. PLoS Comp Bio DOI 10.1371/journal.pcbi.1004284
27. Website (2015) CellML Model Repository, Auckland Bioengineering Institute, University of Auckland. https://www.cellml.org/, Accessed 22 July 2015
28. Website (2015) CRIMSON (CardiovasculaR Integrated Modelling and SimulatiON). http://www.crimson.software, Accessed 22 July 2015
29. Westerhof N, Bosman F, de Vries CJ, Noordergraaf A (1969) Analog studies of the human systemic arterial tree. J Biomech 2:121–143
30. Xiao N, Humphrey J, Figueroa C (2013) Multi-scale computational model of three-dimensional hemodynamics with a deformable full-body arterial network. Journal of Computational Physics 224:22–40