Chapter 10
Modelling of the Cardiovascular System

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Learning outcomes

1. Describe the purpose of a cardiovascular computational model.
2. Understand the complexity of such a model.
3. Understand the difference between zero, one, three and multi-dimensional models.
4. Understand the role of rigid and compliant-wall models of the cardiovascular system.
5. Understand how to apply a computational model to represent a specific region of the cardiovascular system.

This chapter introduces the process of modelling of the cardiovascular system. Modelling incorporates the representation of the fundamental mechanics of the cardiovascular system, as well as the determination of important features needed to ensure that the model captures the essential information relevant to the problem.

10.1 Introduction to Cardiovascular Modelling

10.1.1 Model Definition

A model is a simplified version of reality designed to answer a specific question. In the cardiovascular system, typical questions are:

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- What are the overall distributions of pressure and flow in the arterial system, and how would they change under different states of physical activity, or in the presence of pathology?
- What is the load on the heart in a particular physiological state?
- Is there a risk that this artery (e.g. aneurysm) will rupture?
- What is the prognosis for this individual? Will the pathology get worse, and what will be the consequences?
- How will things change, both in the short and the long-term, if there is an intervention?

The aim of a model can often be categorised as diagnostic or prognostic. Diagnostic models seek to quantify a characteristic of a system that determines the current health or disease. Prognostic models seek to predict how health or disease might evolve in the future. In the case of the cardiovascular system, a comprehensive model might determine the diagnosis of a specific disease, predict the prognosis after a specific treatment and enable a range of different treatments to be compared.

10.1.2 Model Complexity

The complexity of the model depends on the needs of the problem to be solved. A complex model will be computationally large with many parameters and require long run-times. If used in a patient-specific sense the model may require physiological input data which is not readily available or requires invasive tests or data from medical imaging at a resolution which is not available from modern medical imaging systems (see Chap. 11). If the model is too simple then it may not adequately describe key features which are relevant to the specific question that the model has been designed to address. In general a model should be sufficiently complex to address the question, and no more complex than that. It is the responsibility of the analyst to identify the purpose of the model and the level of complexity needed to determine relevant data.

An example of a specific question is the determination of the distribution of pressure and flow in the arterial system. The model must be capable of determining the relationship between flow and pressure in branching vessels. This requires information on the diameter of each vessel (which may be available from medical images), information as to where and how the vessels branch (which also may be available from imaging), information on the compliance of the vessel wall, and information on the characteristics of the blood itself. These data constitute the minimum that would be needed to build a model for this purpose. Other features of the system that it might not be necessary to model in the context of this specific question might be, for example, details at a microscopic level such as the interaction between individual red cells (which would be taken into account using a viscosity

term) or the detailed cellular and matrix composition of the artery wall (which would be taken into account using a stress–strain function).

When localised features such as wall shear stress are not required, a lower dimensional model (one which does not account for variations in space, or does so only in fewer dimensions) may be sufficient. On the other hand, when concerned with the interaction between blood forces and the endothelium in a highly irregular geometry, a 3D model that accounts for blood–wall interaction may be better suited.

10.1.3 Modelling

Generally, the process of modelling takes a series of inputs and transforms them through a series of operations into a series of outputs. For the applications that are the focus of this chapter the model describes relationships between the parameters in a quantitative sense, usually by equations, based on an understanding of the underlying physical processes. Other types of model represent associations between parameters based on multiple observations together with machine learning and/or statistical operations. An overview of the operation of a model of heart valve physiology, based on a Computational Fluid Dynamics (CFD) work flow developed by EurValve (Horizon 2020, Project Number 689617), is presented in Fig. 10.1. The modelling elements are illustrated in green. An analysis protocol is chosen based on the specific question and then a model is constructed using input parameters from a range of possible sources. The work flow element is discussed more extensively in Chap. 11. Most models compute the variation of parameters in a local domain, which is bounded by other domains and other structures. One of the most challenging parts of the modelling process is to set the correct boundary conditions on the domain of interest. The combination of the domain inputs, which generally include a representation of the geometry and of the rheological properties, together with the boundary conditions and the description of the operations to be performed specifies the model. The operation produces outputs which are the result of the model. Sometimes the outputs will be very large, for example full descriptions of pressure and velocity fields varying in time and space, and it is not unusual for these data to run to tens or even hundreds of GB of storage. Almost always some data reduction operation is performed to evaluate characteristics that are easy to understand and to compare.

The model is a set of mathematical equations. These equations are relevant to the question the model has been designed to answer. They describe the governing dynamics (e.g. stress–strain behaviour of the wall, shear–shear-rate behaviour of the blood). In the real-world things exist in four dimensions; x, y, z and t. The model may also exist in four dimensions but lower dimensional models might be able to represent the system with sufficient accuracy, and might even produce additional insight that is obscured in a more complex model. There is some inconsistency in

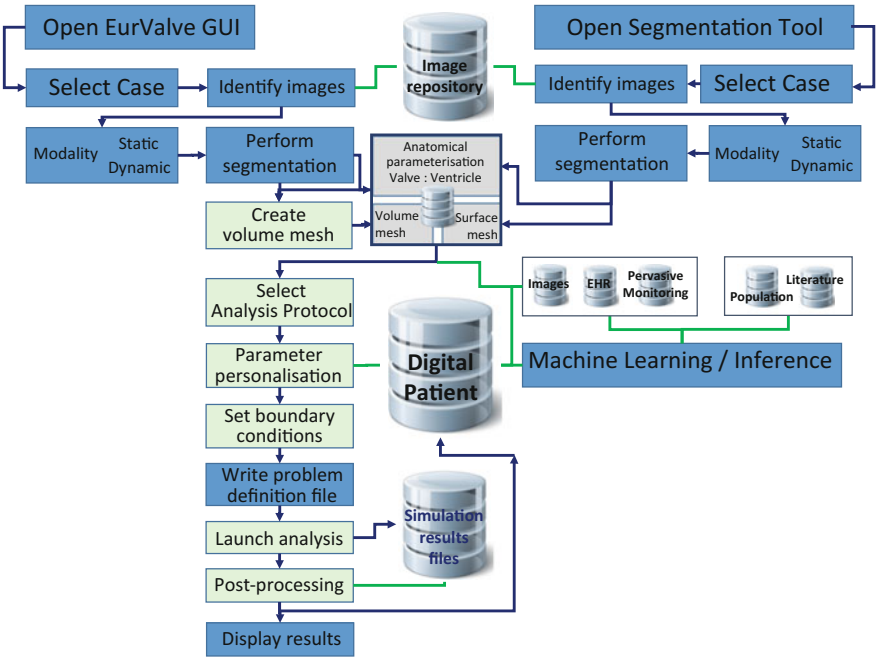

Fig. 10.1 Overview of the operation of a model of heart valve physiology, based on a Computational Fluid Dynamics (CFD) work flow developed by EurValve (Horizon 2020, Project Number 689617)

the description of the dimensionality of models. Generally 0D, 1D, 2D and 3D indicate the number of spatial dimensions in the model. For 0D models variation in time is implicit, for the higher dimensions, transient analyses are sometimes described for example as 3D + t and sometimes as 4D. There are even references, particularly in the medical imaging community, to higher dimensions such as '7D'. This refers to the three-dimensional field of the three components of velocity, changing in time.

Additional constraints relevant to the problem being solved are needed which are applied to the model in order that a solution can be obtained from the equations which make up the model. It is useful to separate these additional constraints into 'boundary conditions' and 'input data'. For example, in a 3D flow model one might be interested in the variation in wall shear stress for different input flow waveforms. In this case the boundary conditions would be the 3D geometry and the pressure which would be set the same for all simulations. The input data would be the flow-time waveform which would vary from one simulation to the next.

The output data is the data which arises from the simulation. For the example above this would be a 3D time-varying dataset of blood velocity from which wall shear stress could be calculated.

10.2 Zero Dimensional Models

Zero dimensional (0D) models are a reduced order abstraction of reality. In these models it is assumed that there is no spatial variation of a quantity within any individual compartment of the model. The system within any compartment is described by a series of ordinary differential equations, with only time derivatives. Zero-D models can be powerful tools to describe system-level interactions between components. Characteristics such as ventricular pressure-volume loops, systolic-diastolic pressure ratios, temporal pressure gradients, cardiac output, ejection fractions, ventricular work, etc., can all be computed using 0D models. The most commonly used 0D model of a chamber of the heart is the *variable elastance model*. In this model, a relationship is described between elastance, which is specified as a function of time, chamber volume and chamber pressure. The elastance terms describe the active contraction of the heart. The 0D vascular components lump all of the inertia, resistance and compliance of a portion of the vasculature into simple electrical analogue representations. A very simple model of the left side of the heart and the systemic circulation, including a snapshot of the model representation from the CellML repository (www.cellml.org), is presented in Fig. 10.2. Despite its simplicity, a typical implementation of this model actually has 23 input parameters. It is a real challenge to select appropriate parameters and parameter ranges for the study of the mechanics of the system, and an even greater challenge to personalise them to represent an individual.

One important class of applications of 0D models includes the representation of changes under prospective interventions. As the human system is not passive, but is actively regulated by both central and local control systems, it is necessary to model

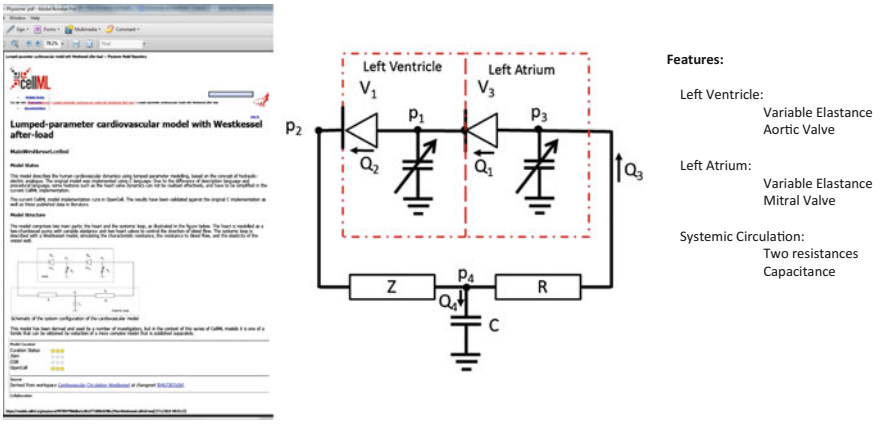

Fig. 10.2 Simple model of the *left side* of the heart and the systemic circulation ('Westkessel'), including a *snapshot* of the model representation from the CellML repository (www.cellml.org)

control mechanisms if the model is to accurately represent the effects of interventions (pharmacological or surgical), or changes of physiological state (e.g. exercise). Such control models can describe regulation, neural signals to control pressure, volume and flow fluctuations, physiological and interventional changes, as well as haemorrhage. The CellML repository contains a wealth of curated models that are freely available for download. For further reading on all the above aspects of 0D models of the cardiovascular system, please see Shi et al. (2011).

10.3 One Dimensional Models

One dimensional (1D) models are useful to capture gross features of the circulation and are particularly useful downstream of the heart. They are described by partial differential equations that relate pressure and the axial component of velocity and their spatial and temporal derivatives. The 1D equations can be derived directly from the full 3D Navier-Stokes equations (see for example Landau and Lifshitz 1959), represented in polar co-ordinates, by making the assumption of axisymmetry. The characteristics of these equations are studied in detail by Canic and Kim (2003), who show for example that, if the radius of the vessel is small relative to a characteristic length, the pressure is constant over the radius of the vessel. This is an important practical result for flow in arteries. A radial distribution of the axial velocity is assumed, the form of which depends on the flow regime that is to be represented. One-D models are particularly useful to capture wave transmission in the cardiovascular system without the computational expense of a 3D model. Wave transmission arises from the elasticity of the vessels and their capacity to store fluid as they are pressurised.

A 1D representation of the circulation can be important in the use of system models that characterise, for example, cardiac load under a range of physiological conditions, or the impact of disease on the elevation of cardiac and vascular pressures. An example of the application of state-of-the-art branching tree models to the physiology of the pulmonary circulation is presented by Qureshi et al. (2014). In some applications, particularly in the context of coronary and pulmonary physiology, 1D models are used to describe and to characterise the relationship between forward and backward travelling waves in the circulation. Analysis might be conducted in the frequency domain or in the time domain: for the latter the concept of wave intensity analysis, reviewed by Hughes et al. (2008) is a useful device. The healthy system maximises the efficiency of blood transmission and minimises the load on the heart by matching the impedance of different branching vessels. In disease, this impedance matching can be diminished, with measureable differences in power of the forward and backward travelling waves. For a comprehensive review of 1D models including theoretical considerations, see van de Vosse and Stergiopulos (2011).

10.4 Three-Dimensional Models

Three-dimensional (3D) models aim to incorporate 3D geometry. A 3D model requires geometry, which can either be created using computer aided design (CAD) software, or can be obtained from medical images (described in Chap. 11). For the heart and the larger arteries and veins, blood is usually assumed to be a fluid continuum, ignoring its microscopic make-up, and incompressible. Under these conditions there are:

- Two fundamental variables of interest, pressure (p) and velocity (v), and, since velocity is a vector with three direction components (u, v, w), there are four degrees of freedom (p, u, v, w) that together describe the physical state at each point within the fluid domain.
- Two governing equations accurately describe the variation of the fundamental variables (p, u, v, w) throughout the domain, given material properties and boundary conditions. The first is based on the conservation of mass and the second is based on the conservation of momentum. Since the velocity has three component directions, there are three momentum equations. The equation of conservation of mass is often called the continuity equation and the equations of conservation of momentum are called the Navier–Stokes equations.

10.4.1 Rigid Wall Models

A rigid wall model is one in which the vessel walls do not move during the cardiac cycle. This is opposed to the reality in vivo where the vessel wall in an artery typically changes in diameter by 5–10 % during the cardiac cycle. Rigid wall analysis is suited to applications where the purpose of the model is to evaluate flow characteristics that are not strongly influenced by shape changes. It is a necessary, but not sufficient, condition that the fractional volume change of the domain of interest over the cardiac cycle is small. Examples in which the rigid wall assumption might be adequate include the modelling of flow separation and of vortical structures, wall shear stress distributions in the region of bifurcations, aneurysms, stenoses or anastomoses. In particular, wall shear stress in arteries is relatively insensitive to the motion of the vessel wall, and therefore, it is often adequate to assume a rigid wall model.

The boundary conditions for a rigid walled arterial flow model are typically described by the wall itself together with one proximal (upstream) boundary where the blood enters and multiple distal (downstream) boundaries through which the blood leaves. The fundamental variables are pressure and velocity. It is usually assumed that the velocity at all points on the wall of the vessel is equal to zero (as the wall is stationary). This is called the ‘no slip boundary condition’. If the pressure at the outlets, or the pressure gradient across the domain, is known, a pressure boundary

condition will often be assigned to an outlet. This information might be measured invasively via a catheter. Care is needed when the outlet of the domain cuts through an area in which complex flow features, such as recirculation, are expected. It is often advised to extend the domain so that flow is in only one direction at the boundary.

The boundary condition at the inlet of a vascular domain might be velocity, flow (an integral measure of velocity) or pressure. As discussed above, the outlet boundary condition is often pressure, and generally then it is preferred, for reasons of computational stability, to define the inlet as a velocity or flow condition. On a plane the inlet flow field data is defined by a 2D velocity profile with 3 velocity components. For patient-specific models inlet flow data may be obtained using MRI or ultrasound as described in Chap. 11. In the absence of explicit data on velocity distribution, the following are the most commonly used assumptions.

- *Plug flow or parabolic flow.* In this approach it is assumed that the velocity profile remains unchanged through the cardiac cycle. In plug flow the velocity is the same at all points of the cross-section. As noted in Chap. 1 plug flow is a feature of inertial flow where viscous effects are minimal. Plug flow is found in large arteries where flow is pulsatile, especially at the beginning of the cardiac cycle. Parabolic flow is a feature of steady flow where the velocity profile is dominated by viscous effects, with maximum velocity in the centre of the vessel. In arteries which supply organs with high-flow demand there is a large baseline component of flow; for example in the carotid arteries supplying the brain, the renal arteries supplying the kidneys and in the uterine and arcuate arteries supplying the placenta. In this case flow is mainly viscous in nature and flow profiles will be more parabolic than plug. However, all arteries have some form of pulsatile flow, and some component of viscous flow, so that the use of purely plug flow or parabolic flow is too simplistic to be used directly at the inlet. In practice one of these simple inlet flows may be applied in combination with a short development length of typically one to five times the inlet diameter.
- *Womersley flow.* In Chap. 1 Womersley flow was introduced. It was noted that this is the flow which is pulsatile and fully developed. The velocity profile changes during the cardiac cycle. When overall flow changes direction, the flow close to the wall is in the opposite direction to the flow in the centreline. These equations allow estimation of the 2D time-varying velocity profile from the flow-time waveform. The flow-time waveform may be estimated in the person or patient from ultrasound or MRI, so that the Womersley method provides an easy way for obtaining inlet flow data useful for modelling. This may be applied directly at the inlet or, more commonly, in combination with a short length of one to five times the inlet diameter.
- *Measured 2D velocity profile.* While the above methods provide 2D time-varying inlet data, they do not easily account for flow which is non-axial (helical), asymmetric or not fully developed. As noted in Chap. 4 arteries may exhibit all of these features. If it is necessary to model these features then the full 2D 3-component time-varying velocity field is required, which may be measured using MRI (see Chap. 11).

10.4.2 Compliant-Walled Models

If a cardiac model is used to determine the flow into the arterial system, then clearly the representation of the change of chamber volume is critical. For larger arteries the issues are more subtle. The aorta changes volume by approximately 10 % over the cardiac cycle. One important consequence of the distensibility of the aorta is that the flow out of the domain is not equal to the flow in at each instant in time. Some of the blood mass is stored in the aorta during systole and gradually released during diastole, therefore acting like a reservoir and secondary pump, smoothing out the flow distribution to the organs and distal circulation. A corollary is that there is a finite pressure (and flow) wave-speed in the aorta. The rise of pressure at the inlet, in the region of the aortic valve, is not immediately transmitted to more distal locations. Typically, the wave-speed in the human aorta is in the region of 5–10 m s^{-1}. The pressure pulse in the abdominal aorta will typically lag behind the pressure pulse at the valve by approximately 100 ms, which is a significant portion of the cardiac cycle and particularly of systole. In a rigid walled domain, any change in velocity at the inlet is immediately manifested at the outlet and the pressure per unit of acceleration is concurrently high. In a non-rigid walled domain, the temporal gradients of pressure are much lower. However, the computational cost of a rigid model might be an order of magnitude, or more, lower than that of a model with elastic walls. These issues are discussed in more depth by Brown et al. (2012).

Many clinically meaningful questions can be answered by rigid walled models, especially if the primary interest concerns local haemodynamics and/or average measures. However, if wall motion is important, for example, because the change of volume of the system is significant, then it is necessary to include its representation in the model.

There are fundamentally two approaches to the determination of wall motion: (a) measure it and impose this motion directly as a boundary condition, or (b) compute it using another model.

Depending on the application, wall motion can be measured using medical imaging such as ultrasound, MRI or cardiac-gated CT. However, small measurement errors in the displacement of the wall can lead to very large local pressure fluctuations in an incompressible fluid. The more desirable approach is to incorporate vessel elasticity into the model. This requires coupling of a flow model (CFD) and a solid model (FEA) into a single modelling regime. This is called ‘fluid structure interaction’ (FSI). Modelling regimes are considered further in Chap. 11.

10.4.3 Material Properties

An important limitation facing the solid mechanics component of the model is the lack of knowledge of material properties. In vivo material properties are difficult to

obtain non-invasively. While tissue stiffness may be measured in vivo using elastography (Chaps. 9 and 11), measurements in the cardiovascular system, especially in arteries and veins are not well developed at the time or writing. It is therefore common to assume that every person has the same mechanical properties for the region under investigation.

In almost all cardiovascular applications it is reasonable to assume that blood is incompressible with a fixed density of approximately 1056 kg m^{-3}. However, as described in Chap. 3, blood is a non-Newtonian fluid. It is more viscous at low shear rates than it is at high shear rates. As the shear rate increases the viscosity approaches asymptotically a value of approximately 0.004 Pa s, or four times that of water. For most analyses of the larger vessels, down to 0.5 mm diameter and even lower, it is reasonable to take this asymptotic limit and to treat blood as a Newtonian fluid. For smaller vessels it is more appropriate to use one of the empirically fitted shear–stress/shear-rate curves, perhaps a power law approximation. Blood is primarily a suspension of disc-shaped red cells, approximately 7 μm in diameter, in plasma. In the very small vessels, <100 μm, down to the capillaries, a more comprehensive model would explicitly represent the multi-phase nature of the fluid, including the deformable bodies of the red cells (Krüger et al. 2013).

10.5 Heart Models in 3D

The representation of the heart and its interactions with the cardiovascular system is one of the most complex challenges in physiological modelling. Major interdisciplinary research efforts aim to better understand and model the system in multi-dimensional (0D, 1D, 3D), multi-scale (molecular, cellular, organ, system), multi-physics (electrical, structural, fluid) and multi-science (physics, chemistry, biology) analysis processes. Smith et al. (2011) describes the current state-of-the-art and the major euHeart initiative (www.euHeart.eu) aimed at developing a 'full' heart model that integrates:

- *The propagation of an electrical wave through the myocardium.* This is partly an active process, with the cells responding to the electrical stimulus to generate an action potential, and partly a passive process representing the diffusion of the voltage through the myocardium. The active part requires a description of the electrochemical cellular processes, which ultimately are described by systems of ordinary differential equations. These are zero dimensional models that are embedded locally into 3D tissue models.
- *The structural contraction of the myocardium induced by the electrical wave, combined with the stresses generated within the myocardium by the pressures in the heart chambers.* This is the least numerically stable and most difficult part of the model. The tissue is anisotropic (both electrically and structurally), as well as nonlinear in its constitutive equations.

- *The ejection of fluid from the heart chambers, caused by the contraction and resulting pressure elevation, working against the impedance of the cardiovascular system.*

There are generally three reasons for modelling the heart in 3D:

- Representation of 3D vortex structures within the ventricles to evaluate the haemodynamic efficiency of the ejection processes, viscous losses, acceleration profiles and energy consumption.
- Representation of local jets through normal, diseased and prosthetic valves (usually aortic and/or mitral, but there are studies of tricuspid valves) to evaluate pressure gradients and sometimes leakage characteristics. If the motion of the valve is important (i.e. the details of the opening and closing phases) then the model has to include either fluid–solid interaction and/or an imposed valve motion.
- Identification of regions of slow flow potentially associated with a propensity for the formation of thrombus. These are typically quantified by evaluation of residence times for blood elements (including activated platelets). This type of analysis can be very valuable, for example, in the study of the connection of a ventricular assist device into the apex of the left ventricle.

10.6 Multi-dimensional Models

In the context of cardiovascular biomechanics, the term multi-dimensional model typically refers to a computational model that spans more than one spatial dimension. So in this case, the region of interest is modelled in 3D, but the rest of the system is modelled with a lower dimensional model. A key challenge is the coupling of a 3D model with a lower dimensional model as the former contains more information at the boundary than the latter, e.g. information about the distribution of velocity. This can be especially challenging for FSI models in which the boundary domain itself might be changing size. Information and advice on multi-dimensional coupling can be found in Formaggia et al. (2011).

A typical stylised cartoon, illustrating a multi-dimensional cardiovascular model from EurValve is illustrated in Fig. 10.3. A simplified version of this model was used in the euHeart project to estimate pressure gradients in sixteen cases with aortic coarctation. The aorta was modelled in 3D based on CT image data, the heart model was removed and in its place a proximal boundary condition of transient flow in the ascending aorta was prescribed, based on measured phase-contrast MRI data. The distal boundary condition on each outlet was a 0D RCR Windkessel model (resistor, R; capacitor, C). Windkessel parameters were tuned to produce measured flow in the descending aorta and a distribution of mean flow in the

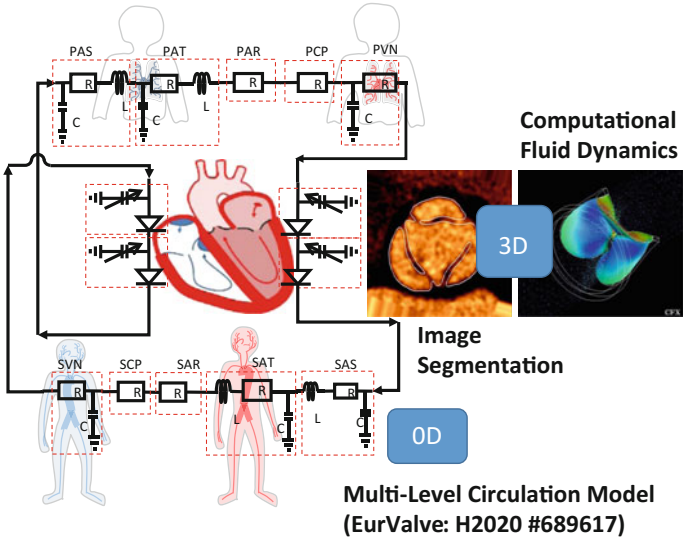

Fig. 10.3 Example of a multi-dimensional model of aortic coarctation (www.euheart.eu)

supra-aortic vessels based on Murray's Law using the measured vessel diameters. The results are sensitive to the values of these parameters and they must be chosen to reflect as closely as possible the measured conditions.

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