Chapter 7
Computational Modeling of Aortic Heart Valves

Laura R. Croft and Mohammad R. Kaazempur Mofrad

Abstract Computational modeling is an excellent tool with which to investigate the mechanics of the aortic heart valve. The setting of the heart valve presents complex dynamics and mechanical behavior in which solid structures interact with a fluid domain. There currently exists no standard approach, a variety of strategies have been used to address the different aspects of modeling the heart valve. Differences in technique have included the imposition of the load, the portion of the cardiac cycle simulated, the inclusion of the fluid component of the problem, the complexity of anatomical parameters, and the definition of material characteristics. Simplifications reduce computational costs, but could compromise accuracy. As advancements in modeling techniques are made and utilized, more physiologically relevant models are possible. Computational studies of the aortic valve have contributed to an improved understanding of the mechanics of the normal valve, insights on the progression of diseased valves, and predictions of the durability and efficacy of surgical repairs and valve replacements.

Keywords Aortic valves · Calcific aortic stenosis · Mechanotransduction

1 Introduction

The aortic heart valve poses a complex mechanical problem both for the physicians repairing the valve and for the engineers seeking to design replacements for the living valve. Approximately 26,000 people die annually in the United States with an aortic valve disorder as a contributing cause [46], and it is predicted that by the year 2020, 800,000 people worldwide will require heart valve replacements annually [60]. Cardiovascular diseases, including those of the heart valves, will become increasingly prevalent as the average age of the world's population continues to increase.

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S. De et al. (eds.), *Computational Modeling in Biomechanics*,
DOI 10.1007/978-90-481-3575-2_7,

Many aspects of the mechanical environment of the heart valve have been studied in recent decades (see review by Sacks and Yoganathan [48]). In vitro studies have been performed investigating the mechanics of the valvular components on the cellular level [4] and the tissue level [50]. The dynamic function, including hemodynamic data, of physiological and replacement valves has been examined using in vitro methods such as laser Doppler anemometry [62] and using in vivo imaging such as magnetic resonance imaging [61]. All of those experimental methods have limitations in fully characterizing mechanical behavior of the assembled physiological valve, particularly data such as spatially and temporally detailed stresses.

Computational modeling of the valve provides an alternate means of investigation that can quantify many types of data and can simulate a variety of situations. As is the case when modeling any biological situation, simplifications and assumptions must be defined. A variety of strategies have been explored to assign the material properties of the tissue, and different approaches have been employed to model the loading onto the valve. These studies can analyze the valve in a static position, the dynamic opening and closing of the valve, and even the functioning relationship between the structures of the valve and the fluid flow of blood. Using computational simulations, many types of studies have been performed on the aortic valve. Mechanical analyses of the functioning physiological valves have provided insight on the native state, and studies on the altered conditions of a diseased valve have shown how disorders can influence the mechanical behavior of the valve. The efficacy and durability of surgical repairs have been examined, and simulations have also been used to test artificial heart valve designs and study how these valves may fail. This review will discuss the development and utility of these computational models primarily focusing on the native aortic valve with a lesser mention of the extension of these strategies to diseased models and artificial valves.

2 The Aortic Valve

The heart has four chambers and four corresponding valves which allow for unidirectional flow to exit these chambers, as seen in Fig. 1. The aortic valve is situated within the supporting aortic root and regulates blood flow exiting the left ventricle into the aorta, presenting the gateway for the oxygenated blood which is being pumped from the heart to the peripheral circulation. Like the pulmonary valve, which also controls blood flow exiting a ventricle, the aortic valve is a semilunar valve and has three cusps: the right coronary, left coronary, and noncoronary. The aortic valve is shown in Fig. 2. The cusps are attached to the wall of the aortic root at the crown-shaped annulus, circling the perimeter of the root. Each cusp is connected to its neighboring cusps at sites known as the commissures, which are the peaks of the crown-shaped annulus. Each leaflet also has a corresponding sinus, which is a bulbous portion of the root. The sinus is defined at one end by the leaflet attachment and by the sinotubular junction at the end nearest the aorta. The left and right coronary sinuses have coronary ostia which supply blood to the heart muscle itself. For more information on the valvular structure see [38, 55].

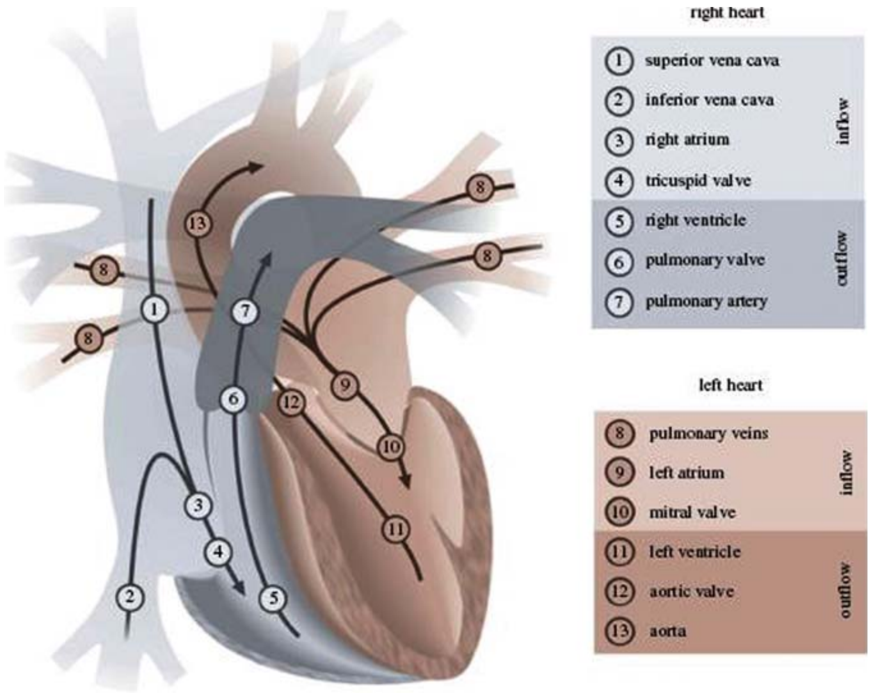
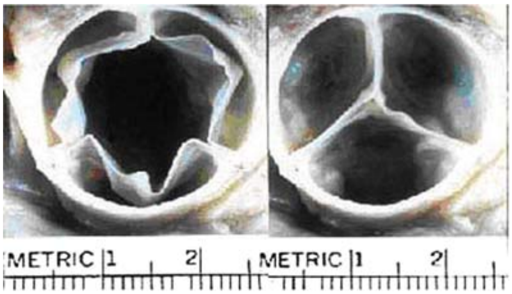


Fig. 1 Blood flow through the heart, red represents oxygenated blood and blue represents deoxygenated blood [61]

Fig. 2 The aortic valve in the open (*left*) and closed (*right*) configurations [36]



The leaflet tissue is outwardly covered by a layer of endothelial cells, and beyond that is composed of fibrous extracellular matrix. Valvular interstitial cells, which have characteristics of both smooth muscle cells and fibroblasts, exist throughout the matrix. There are three main fibrous layers of the leaflet: the ventricularis, the spongiosa, and the fibrosa, in order of inflow surface to outflow surface (Fig. 3). The ventricularis is the thinnest layer and contains collagen and elastin fibers, the elastin being mainly radially oriented. This arrangement permits large radial strains of the leaflet tissue. The spongiosa is gel-like, comprised primarily of glycosoaminoglycans, and likely acts as a shock and shear absorber. The layer nearest the outflow, the

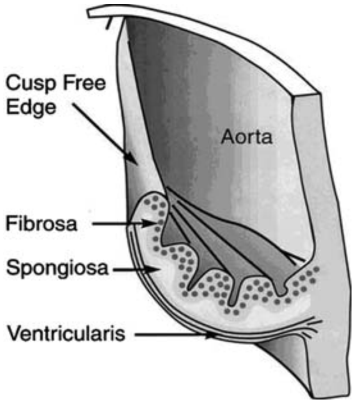


Fig. 3 A cutaway view of the three layers of the aortic valve leaflet [56]

fibrosa, is predominantly composed of collagen fibers oriented circumferentially and strongly contributes to enduring the heavy loads experienced by the closed leaflets [36]. The fibrosa has corrugations in the unstressed state which unfold as the valve opens, aiding the leaflet in its ability to undergo considerable stretch. The differing constituents and characteristics of these layers integrate to compose leaflets that are capable of withstanding the heavy and varied mechanical demands of the valve function.

The aortic valve is mainly a passive structure, where the leaflets open and close based on the pressure difference across the valve, which varies with the cardiac cycle. This cycle has two main periods, systole and diastole. During the beginning of systole, pressure is high in the contracting left ventricle, forcing the valve open and propelling blood from the ventricle. As the pressure in the ventricle is relieved and the aortic pressure rises, the valve closes. During diastole, the left ventricle relaxes and is refilled via the mitral valve and left atrium, and the closed leaflets of the aortic valve experience a mounting pressure load as the cycle approaches the start of systole once more. The valve and its surrounding structures of the sinuses and aortic root undergo dynamic local contractions and relaxations throughout the cardiac cycle (see review by Cheng et al. [10]).

3 Anatomical and Material Properties

In order to create a computational model of a complicated biological system like the aortic valve, simplifications and assumptions must be imposed on the geometrical and material properties. As improvements are made in the numerical methods and software packages that execute these simulations, more realistic properties can be implemented. However, complexities are added at the cost of increased computation time and resources. Depending on the specific aim of the study, certain simplifications may be reasonable as they will not greatly influence the results of that study.

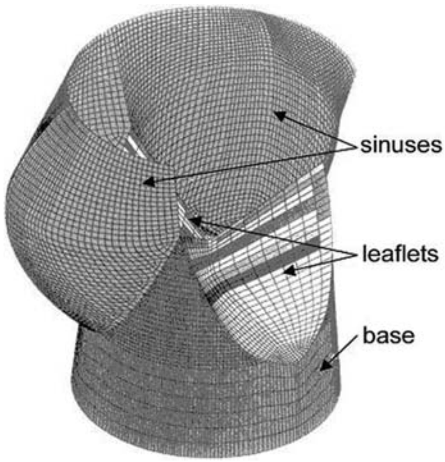


Fig. 4 Example of the computational mesh of the valve using geometry based on idealized parameters [28]

When attempting to reconstruct the aortic valve, the first decision to be addressed is from what source to base the geometry. A basic protocol to create an aortic valve model based on experimentally measured parameters for each dimension is described in detail by Thubrikar [55]. This approach assumes that each of the leaflets and their associated sinuses are identical. This type of method using reported values from Thubrikar and/or other publications of experimentally measured data has been implemented in many computational studies of the natural valve [7, 21, 28, 43, 44, 49, 58]. Recent computational studies have expanded this approach to include the coronary ostia [44] or variations in leaflet thickness within a single leaflet [28, 58]. See Fig. 4 for an example of this type of geometry.

Other computational models have used magnetic resonance imaging data, generally obtained from ex vivo specimens, to construct a realistic valvular geometry [23, 25, 26, 39]. These models account for the differences between the left coronary, right coronary, and noncoronary leaflets and sinuses such as areas, perimeters, thicknesses, and the presence of the coronary ostia in the left and right coronary sinuses. Additionally, variations in thickness within each leaflet and within the root in the axial direction are included in the geometry. This type of geometry characterizes local differences in structure, and therefore the results of these studies may differ significantly depending on region.

Native heart valve tissue is most accurately described as a nonlinear, pseudoelastic, and anisotropic multilayered material. In computational studies valve tissue is typically assumed to be incompressible to ease computational demands, an acceptable approximation due to the high water content of the tissue. The aortic leaflet contains collagen fibers oriented mainly in the circumferential direction and elastin fibers oriented mainly in the radial direction. This arrangement causes the elastic modulus to be significantly greater in the circumferential direction than in the radial direction, producing strong anisotropic behavior. A low elastic modulus is associated with systole when fiber crimping is present, which reduces flexion stresses on the leaflets. When the leaflets are closed during diastole, the tissue transitions to a much greater elastic modulus as the waviness of the fibers straighten, enabling the tissue to withstand the great pressure load without bulging or prolapse [54]. This fiber crimping and two elastic modulus transition phases contribute to the nonlinear property of the leaflet tissue. Bioprosthetic heart valves, which are constructed from porcine or bovine pericardium or intact aortic roots, also possess nonlinear and anisotropic characteristics. Although the native human and BHV tissue exhibit these complex properties, many computational models make the simplifications of isotropy [2, 7, 28, 31, 41], linear elastic behavior [23, 25, 26, 39], or both [21, 49]. In some cases, the commercial finite element modeling software used was at that time not capable of assigning both nonlinear and anisotropic material properties to the same structure.

Research has been conducted to investigate the influence these material simplifications may have on the results of a computational model. Patterson et al. [41] compared two identical isotropic models of a BHV, one of which was given linear elastic properties and the other was assigned nonlinear elastic properties. A pressure differential was imposed on the leaflets as it varies throughout the cardiac cycle. The nonlinear model was more responsive to this applied pressure load and experienced more complex deformations during the opening and closing phases. This difference in deformation resulted in higher tensile and lower compressive stresses in the leaflets. The importance of the nonlinear properties of the aortic root was also examined in a study by Ranga et al. [43] using an isotropic model of the natural valve. Displacement, strain, and stress results for the nonlinear model most closely matched experimental results. Different elastic modulus values were investigated for the linear model, and the value of 2,000 kPa was the most comparable to the nonlinear model and experimental results. The nonlinear model had more uniformly distributed strain values and had lower stress values than that of the linear models (Fig. 5), demonstrating how the nonlinear property aids in alleviating and distributing the mechanical load on the structures of the valve. The results of these studies support the importance of the inclusion of nonlinear properties in computational models of the aortic valve.

Studies have also examined the assumption of isotropy. Burriesci et al. [3] modeled a bicuspid BHV, comparing the assignment of isotropy, orthotropy with

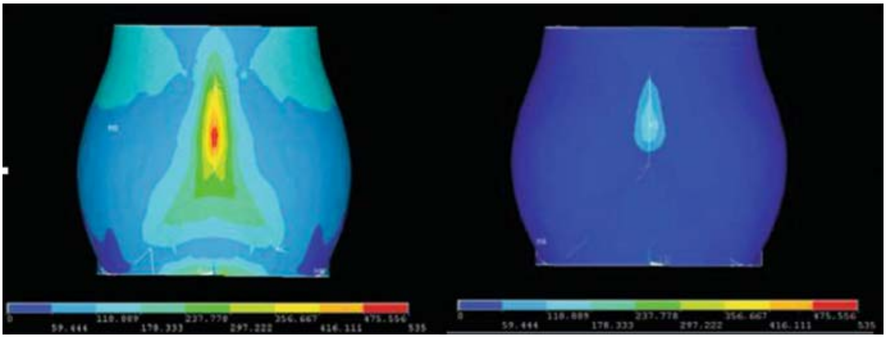


Fig. 5 Comparison of the stress distributions present in the aortic root in diastole for a linear (2,000 kPa) model (*left*) and a nonlinear model (*right*) (From [43])

an axial primary direction, and orthotropy with a circumferential primary direction (nonlinear elastic material properties were used). Burriesci concluded that even a relatively low presence of orthotropy will significantly alter the stress distributions of the valve. Li et al. [33] also compared isotropic and anisotropic models of the aortic valve, in this case a static trileaflet model of porcine aortic leaflets, assumed to be attached to a rigid stent. Li found differing results in leaflet deformations and stress magnitudes and distributions between isotropic and anisotropic models; the maximum longitudinal normal stress was increased and the maximum transversal normal stress and in-plane shear stress were decreased with the inclusion of anisotropy. De Hart extended his implementation of anisotropy to defining two fiber layers to comprise the leaflets, with distinctly different fiber orientations assigned. This approach more accurately recreates the multilayered anisotropic leaflet as compared to the simple isotropic model. This fiber-reinforced model greatly reduced peak systolic stresses in the leaflets, compressive and tensile. The fiber-reinforcement also stabilized the leaflets during opening and closing, eliminating leaflet fluttering and high bending deformations seen with the isotropic model [16, 18]. As demonstrated in these studies, the anisotropic nature of the aortic valve affects the mechanical behavior of the valve, particularly the stress distributions and values.

Implementing anisotropy into a numerical model requires translating the anisotropic tendencies of the tissue into mathematical models which can be assigned to structures within the model. There have been various approaches to this problem within the literature. Since the dominant characteristic of the material is the uniaxially aligned collagen fibers in the circumferential direction, several models have been developed using a transversely isotropic approach. Li et al. [33] developed an anisotropic model for porcine aortic leaflet tissue by extending the linear transversely isotropic model, defining the stiffness matrix as a function of two Young's moduli, two Poisson's ratio, and a shear modulus. Equations for the two Young's moduli and an effective strain were defined so as to append nonlinearity to this model. Most studies, however, impose anisotropic characteristics in the definition of the hyperelastic strain energy function. A transverse isotropic exponential stain energy function strategy has been shown to agree well with experimental data on mitral valve leaflets [35], and this approach has been employed in heart valve simulations [57]. Studies on BHV tissue have used a mixed constitutive model strategy in which the in plane and bending behaviors are characterized separately and uncoupled [29, 30]. For the planar material model, a generalized Fung-type elastic strain energy function was used to define the anisotropic properties, and was found to have comparable strain responses to experimental data [51]. Another method to mimic the oriented fibers within the leaflet tissue is to integrate one-dimensional cable elements which run in two perpendicular directions framing the top and bottom faces of the three-dimensional isotropic solid elements. This technique was used to model the aortic valve leaflet tissue and will be discussed in more detail in Section 6 [58]. A similar concept was used to model mitral valve leaflets as a network of embedded fibers in an isotropic solid [19]. These varied strategies have shown to be effective techniques to approximate the mechanical response of this complex tissue.

Simplifications of the aortic valve setting are selected depending on the scope and aim of the study. For example for studies which only simulate diastole, authors reason that the use of the higher elastic modulus associated with diastole is acceptable; the addition of nonlinear elastic properties may be unnecessary in this case [23]. Geometrical simplifications and assumptions of symmetry are also reasonable if the researchers are not concerned with local variability and aim to characterize general patterns or to isolate the effects of one globally applied variable. For a dynamic study of the full cardiac cycle, the nonlinear elastic and anisotropic properties of the valve should be considered to obtain realistic results. The geometrical and material properties should be defined to most accurately model the valve for the purpose of the study, while still maintaining computational costs at an acceptable level.

4 Simulation of the Cardiac Cycle

The valve undergoes varied dynamic and mechanical changes throughout the cardiac cycle. Computational studies have focused on either specific portions of the cycle or the entire cycle. Static models have focused on the stresses and strains imposed by the high pressure load experienced by the valve during valve closure. The deformations and stresses that occur as the valve opens and closes have also been investigated using incremental static or dynamic models. The advent of fluid-structure interaction (FSI) capabilities has expanded the field of study to include the fluid mechanics associated with the problem. In all of these scenarios a load is applied to structures of the model, and as modeling techniques have improved, more aspects of valve function have been investigated.

Whether static or dynamic, the load imposed on the components of the valve is generally pressure. An exception is the study by Carmody et al. [7]. This dynamic study implemented fluid-structure interaction to investigate the role of blood flow in interface with the structures of the aortic valve. To supply an inlet boundary condition for the model of the valve, inflow data were obtained from a second three-dimensional model of the left ventricle. Wall displacements were applied to the ventricular model to simulate ventricular contraction and relaxation, and the outflow velocity profiles through the aortic outlet reservoir were acquired. This data varied spatially as well as temporally throughout the cardiac cycle. These velocity profiles, exiting the left ventricle through the orifice representing the location of the aortic valve, were used as the inlet condition of the model of the aortic valve. The circulatory flow observed in the ventricular model produced a primarily axial flow through the aortic orifice. The pressure difference thus created across the valve leaflets was approximately uniform and showed, to a large extent, three-fold rotational symmetry. This study concluded that the use of spatially uniform pressure conditions is justifiable as the input to aortic valve models. Each of the remaining studies to be discussed utilized spatially uniform pressure loads for both static and time-varying cases.

An inherent difficulty associated with modeling the valve is that of defining the stress-free state of the structure. Physiologically, a stress-free state does not exist as there are residual stresses present due to the anatomical environment and growth as well as tissue layering of the valve. Static studies, in which the valve leaflets remain closed, define the stress-free state as the pressure free state, with the leaflets in the closed position which they will retain throughout the simulation [23, 25, 26]. Some dynamic studies, in which the leaflets will undergo the cycle of opening and closing, define the zero stress state as that when the leaflets are in the open position, also before pressure waveforms have been applied [21, 49]. Other dynamic studies have applied a baseline pressure to the model for its initial state [28, 58]. Bioprosthetic valves (BHVs), which are artificially constructed, are fixed so that they generally adapt a closed configuration in the absence of forces, unlike the natural valve which will collapse. For studies concerning BHVs, the zero stress state is typically assumed to be the pressure-free state when the leaflets are closed [29].

Static analyses of the natural valve focus on specific portions of the cardiac cycle. Studies by Grande-Allen simulated end-systole to end of isovolumetric relaxation, focusing on the peak stresses generated during diastole when the valve is closed. The aortic root was pressurized to the end-systolic condition, and then calculated physiological pressures were applied to the aortic root and valve. Although these studies are static in the sense that the leaflets and valve components stay relatively stationary, time-varying pressures are used to mimic the increasing pressure load experienced after valve closure [23, 25, 26]. Ranga et al. [43] also performed static simulations of the valve, in both the open and closed configurations. Eighty mmHg of pressure was applied to the valve for the closed configuration of diastole, and 120 mmHg was imposed for the open configuration of systole. The commissural expansion of the aortic root was calculated by comparing the commissural displacements of the two configurations, and the stresses and strains of the aortic root were investigated for the two major points in the cardiac cycle. This static approach was sufficient as the aim of the study was to compare the use of linear and nonlinear material properties for the aortic root. A study on stented porcine leaflet tissue also investigated varying leaflet material properties for computational studies, and therefore elected a static method. Results were obtained at a constant outflow leaflet surface pressure of 120 mmHg, which was incrementally loaded to achieve convergence [33].

To elicit the opening and closing function of the valve, dynamic studies employ time-varying pressure loads, which are generally experimentally derived. Since the finite element method solves at discrete intervals, the continuous physiological pressure curves must be idealized somewhat to discretize into time steps. Time-stepping methods may be explicit, e.g., the forward-Euler method, or implicit, e.g., the backward-Euler method. While the explicit method may not provide as accurate results as those of the implicit, it does not require the inversion of the stiffness matrix as the implicit approach does, reducing computational demands. An explicit dynamic study by Howard et al. [28] simulated the opening phase of the valve (Fig. 6). Different pressure patterns were imposed on the sinus, base, and leaflets of the valve; increases were made linearly while still reasonably resembling the physiological curves. Gnyaneshwar et al. [21] and Sripathi et al. [49] applied pressure waveforms to the leaflet surface, and waveforms were applied to the aortic and left ventricular regions. The pressure on the leaflet surface was the transvalvular pressure, the difference between the ventricular and aortic pressures. A pressure of 100 mmHg

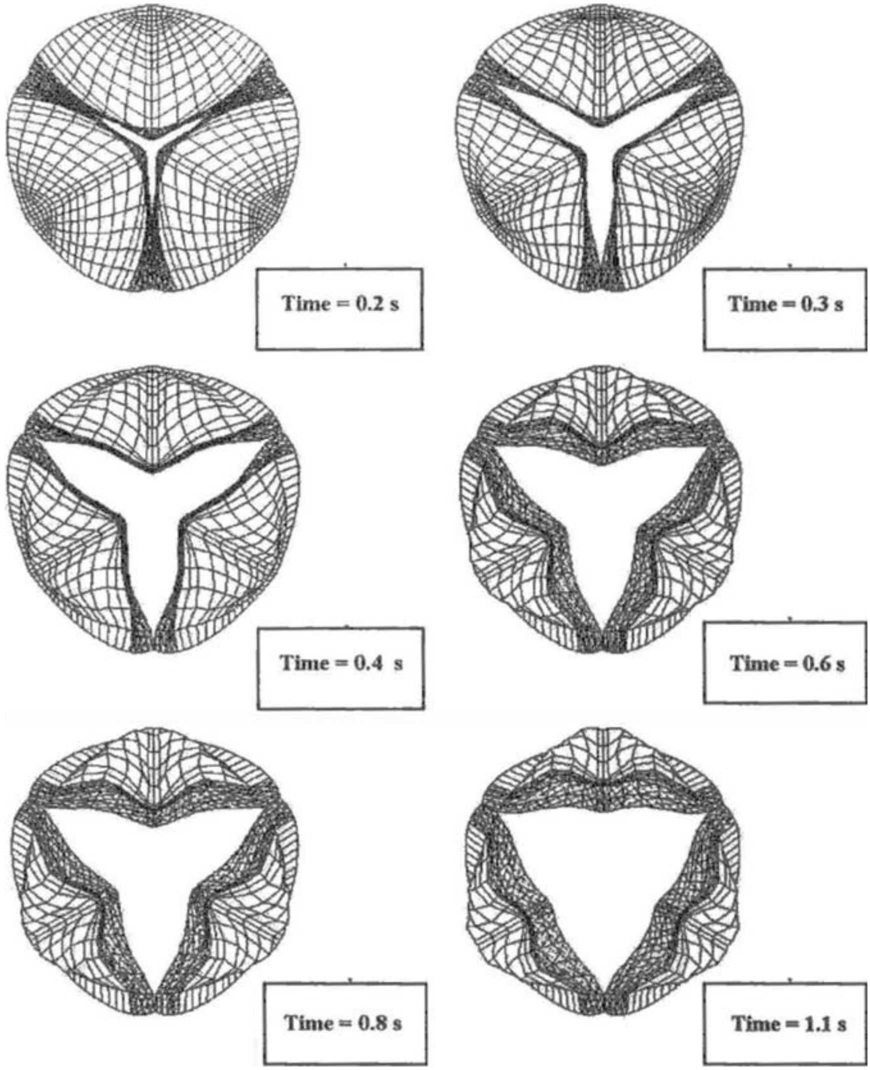


Fig. 6 Example by Howard et al. [28] of time-varying leaflet deformation, as seen from the outlet of the model

was applied to the aortic region to close the valve before the curves representing the cardiac cycle were imposed. The waveforms used by Gnyaneshwar resembled relatively simple linear ramps, whereas the waveforms used by Sripathi were closer to the physiological curves. Studies on artificial heart valves have also applied adapted physiological pressure curves to the leaflet surfaces to predict the stresses and strains which develop during portions of the cycle [11, 14, 29, 31]. The development of dynamic computational studies has allowed study of valve motion and how mechanical behavior evolves throughout the cardiac cycle.

Fluid-structure interaction has enhanced the abilities of the dynamic valve study by incorporating the movement of both the solid and fluid. As mentioned earlier, Carmody et al. [7] used velocity profiles obtained from a left ventricular model as the input into the aortic valve model to create and sustain the movement of the fluid and solid structures throughout the cardiac cycle. FSI studies by Nicosia et al. [39] and Ranga et al. [44] applied the transvalvular pressure differential, the difference between the left ventricle and the ascending aorta pressures, to the inlets of their valve models, as the differential varies through systole and diastole. Nicosia noted that the pressure difference across the aortic root would be a necessary improvement to the model to obtain more accurate aortic root stress data and to more accurately characterize valve-root interactions. Weinberg and Mofrad utilized the pressure history for the aorta and left ventricle regions as boundary conditions to their appropriate fluid sources. Additionally, experimentally-derived radial displacements were imposed on the base of the valve to include the movement associated with ventricular contraction [58, 59]. FSI studies implement their pressure loads onto the fluid components of their study, as opposed to directly onto the leaflets or other valvular structures, which is the custom for the purely structural models. These studies which administer the load via the fluid medium more closely recreate the physiological setting of the valve and how this environment transforms at each point in the cardiac cycle.

5 Fluid-Structure Interaction

The fluid mechanics of blood flow determine the speed and efficiency of valve opening and closure. During systole, blood flow accelerates through the valve, achieves a peak velocity, and then decelerates due to the transvalvular pressure gradient. During deceleration, recirculation develops in the sinus regions of the valve and the vortices formed facilitate rapid closure of the valve. The dilation (diastole) and contraction (systole) of the annulus of the valve is also influenced by pressure conditions of the regions of fluid. Just as the dynamics of the blood affect the behavior of the solid components of the valve, the valve structures alter fluid dynamics as well. Stenosis is the development of a reduced effective orifice, for example due to calcified leaflets which are hindered from opening fully and occlude the orifice during systole. This event increases the pressure drop of the valve and resistance to the ejection of blood. Another common condition is regurgitation, in which case backwards blood flow occurs due to incompetent leaflet closure. Valve hemodynamics can be indicative of disease as well as a measure by which to evaluate valve replacements. Parameters such as the pressure drop across the valve, regurgitation, regions of high shear stress, and adverse flow patterns and phenomena such as stagnation or turbulence can be used to assess the efficacy of a valve and to predict its future viability. A thorough review of the fluid mechanics of the valve and related computational studies can be found in Yoganathan et al. [63].

Many models have been used to study the strictly structural aspects of aortic valve mechanics [21, 23, 28], whereas other models have focused on the fluid mechanics associated with left ventricular ejection [52, 53]. Modeling the valvular structures along with a moving fluid volume is not a trivial task. The thin-walled leaflet structures experience large degrees of deformation within the fluid flow. Fluid domains are typically modeled using an Eulerian reference frame, in which case the mesh grid is stationary regardless of fluid motion. On the other hand, solid structures such as the leaflets or root of the valve are modeled using a Lagrangian reference frame, in which the mesh moves and deforms along with the structure. Movement of the solid structure through the fluid introduces a challenge to the techniques used for computational modeling. Methods such as the arbitrary Lagrange-Euler (ALE) method allow for a deformable fluid mesh, whereas methods such as the operator splitting approach or fictitious domain technique retain the stationary fluid mesh approach. Although the ALE method is the most commonly used in FSI studies in general, it has not been as successfully implemented in valve models. The large movement of the leaflet structure through the fluid mesh is better accomplished by the strategies which use a static fluid mesh. Another difficulty associated with modeling valvular biomechanics, particularly in the FSI setting, is the ability of the model to provide for contact between the solid elements, which is critical to capturing leaflet coaptation. The marriage of the solid and fluid constituents of the aortic valve setting is a challenging task in the computational setting.

Early attempts at coupling the fluid and solid aspects of the valve problem were accomplished by using an immersed boundary technique [42] and by using an "influence coefficient" technique [34]. To better capture the systolic phase, De Hart implemented a fictitious domain approach in which the fluid and solid grids are solved independently so that the mesh of the fluid domain is not distorted by the leaflet structures moving within its domain. This method is based on Lagrange multipliers which couple the two domains on the fictitious boundary. This technique was first utilized in a two-dimensional model of the valve [15] and then extended to the three-dimensional case [16–18]. The compliancy of the aortic root was investigated in the study by De Hart et al. [16], and the ALE method was used to address the coupling of the root structure to the fluid domain, while the fictitious domain method was still used for that of the leaflets. The ALE method allows for the continuous alteration of the fluid domain without significantly changing the mesh scheme. Whereas the large deformations caused by the leaflets could compromise mesh quality if using this coupling strategy, the motion of the aortic root moves in reference to the fluid domain in a manner that is conducive to the implementation of the ALE method. Results from these studies depicted the movement of the leaflet structures in response to the fluid motion and were qualitatively comparable to past numerical and experimental studies on valve mechanics and hemodynamics; however, contact between leaflets was not achieved and the fluid data near the leaflets may have had questionable accuracy due to the nature of the fictitious domain method at the fluid-structure interface.

Commercial FEM software has also been implemented by researchers to employ numerical methods robust enough to be capable of fluid-structure interaction [7, 39, 44, 58, 59]. The most commonly used software for this purpose is LS-DYNA (LSTC, Livermore, CA, USA), an explicit code which immerses the structural

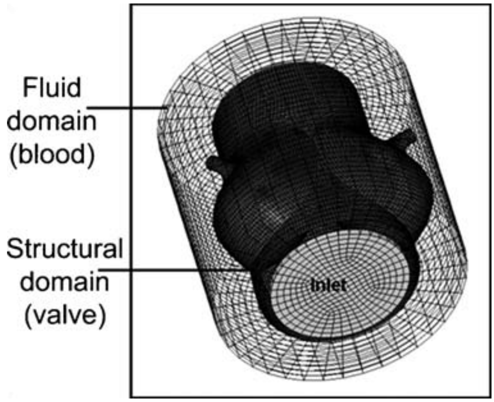


Fig. 7 The structural domain of the valve immersed within the fluid domain used to execute the FSI simulation by Ranga et al. [44]

components in a fluid control volume so that the two domains are allowed to coexist in the same space, as illustrated in Fig. 7. An "operator split" technique is used to solve the fluid domain, and the ALE method is used to couple the two domains with remeshing being allowed for the Lagrangian structural elements as their movements distort the mesh topology. These software packages are able to support more complicated geometries such as those created from MRI data [39] and have even included visualization of the flow to the coronary ostia [39,44]. Another advancement in FSI that has been achieved using commercial software simulations is the inclusion of the progressive coaptation of the leaflets, sealing against flow. Both hemodynamic data and mechanical behavior results have been compared to experimental and past numerical results, validating these models. Regardless of the method or technique used to accomplish FSI, the properties of the fluid phase are generally assumed to be isothermal, incompressible, homogeneous, Newtonian, and laminar. Although blood is non-Newtonian, it can be approximated as Newtonian in regions of high shear rate where the diameter of the vessel is relatively large. In the region of the aortic valve, turbulent flow does occur, however, this is very difficult to recreate computationally. Therefore until techniques improve, models are limited to laminar flow.

The information which becomes available to study using aortic valve models with fluid-structure interaction is quite substantial. Like the purely structural models, the orifice area, opening and closing times, deformation, stress, and strain distributions and magnitudes can be predicted, but in this case, realistically including the effects which the fluid flow has on the structures. In addition to measures of the solid deformations, hemodynamic data becomes available such as peak velocity magnitudes, pressure values and distributions throughout the fluid domain, and the visualization of velocity vectors, circulation patterns, and vortex development (Fig. 8). FSI studies have demonstrated how blood flow through the valve is altered by the anatomical structures present, and how correspondingly the movement of blood instigates and participates in the opening and closing of the valve leaflets. These models which include the coupling of fluid and solid have already succeeded in examining the effects of root compliancy [16], assessing the importance of fiber-reinforcement in leaflet tissue [18], comparing different repair techniques [44], and investigating the

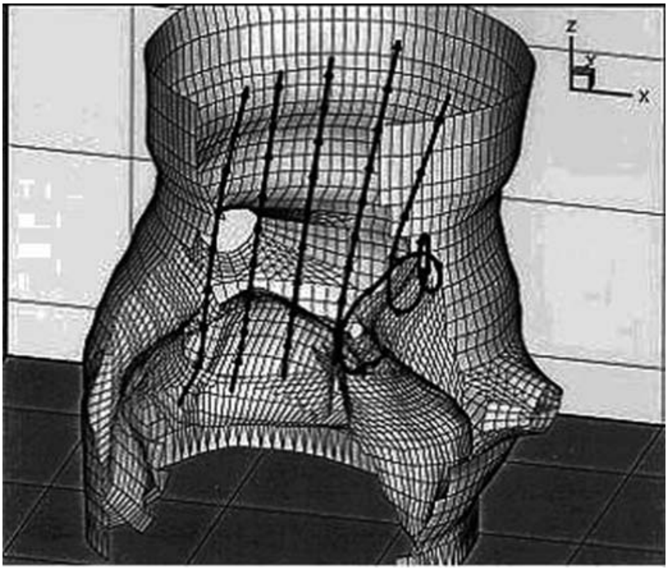


Fig. 8 An example of the results which can be obtained using FSI techniques: Streamlines present during an instant of the deceleration phase (Note the depiction of a region of recirculation [39])

congenital bicuspid valve [59]. Compared to solid-only models, fluid-structure interaction provides a more realistic and physiologically relevant simulation of valve function.

6 Multiscale Approach

While models have been developed with excellent constitutive material models which portray the nonlinear elastic and anisotropic characteristics of valve tissue [29, 30], few define the distinct layers of the leaflet tissue. These three layers, the ventricularis, spongiosa, and fibrosa, each possess different material characteristics. Few of these models, which possess more accurate material definitions, incorporate fluid-structure interaction to better recreate the physiological setting. In a model recently developed by Weinberg and Mofrad [58], not only are the individual layers of the valvular tissue described using nonlinear anisotropic designations and simulated within a fluid domain, but the model is capable of simulations at the organ, tissue, and cell levels of the system as well. This multiscale approach makes it possible to analyze a problem from the organ level which includes the complex multi-structure and fluid interplay to the cellular level where cellular deformation could indicate a biological response. In vitro experiments have demonstrated that the behavior of valvular cells, such as gene expression, is strongly influenced by mechanical stimuli [5]. Multiscale methods have also been employed in other areas of research [9, 37].

In Weinberg and Mofrad [58], a set of reference configurations were defined to describe the state of the tissue from the individual layers to a loaded assembled valve and are derived from those created by Stella and Sacks [50]. In the first configuration Ω_0, the fibrosa and ventricularis are separate and free from stress; the layers are then combined with the appropriate corrugations and arrangement to construct configuration Ω_1. Next the tissue is assembled into the valve structure, pressure-free Ω_2. For the next configuration Ω_3, a pressure is applied to the valve to create a physiological initial state. Finally Ω_t represents the functioning valve as it varies with time. Radial and circumferential extensibilities were assigned to the tissue in each configuration, and in the cases of Ω_0 and Ω_1, the ventricularis and fibrosa were each assigned their proper extensibilities. These values were based on published experimental studies. The stretches required to move from one configuration to the next were then calculated using the extensibility data. These reference configurations were used as the framework for the multiscale simulations. Simulations were first performed in the organ scale and the resulting element strains were then used as boundary conditions imposed on the tissue-scale model. Similarly, the strains from the tissue scale model were then used as boundary conditions for the cell scale model. In this manner, simulations are executed with data passing down from the largest to smallest scale.

The organ scale simulations were computed using LS-DYNA (LSTC, Livermore, CA, USA), an explicit commercial finite element package capable of fluid-structure interaction. A constitutive model was used for the material in which discrete isotropic solid elements had embedded one-dimensional cable elements on their top and bottom perimeters. These cable elements were defined so that those running parallel are in the same family, distinguished from those that run perpendicularly. This scale's model was characterized in accordance with configuration Ω_2; experimentally-derived stress-strain curves and cross-sectional areas were assigned appropriately to the cable elements, recreating the fibers of the valvular tissue. The isotropic solid elements were defined using a single-term Mooney-Rivlin adapted from valve leaflet bending data. This model is particularly computationally efficient in the explicit method compared to a continuum material model. The aortic root was modeled as an anisotropic material also using an experimentally-derived single-term Mooney-Rivlin. Valve geometry was based on experimentally-measured parameters, and symmetry was assumed so that only one-sixth of the valve was simulated. The solid structures of the root and valve are immersed within a fluid domain to capture the fluid-solid interplay, and time-varying physiological pressures were applied as boundary conditions to the fluid inlet and outlet sources to model the dynamic function of the valve throughout the entire cardiac cycle. The motion created by ventricular contraction was also included in the model by applying experimentally-derived radial displacements to the base of the valve. For continuation to the tissue-scale model, the element deformations at three points throughout the radius of the leaflet were tracked to be transferred to the tissue scale model.

An implicit commercial finite element program, ADINA (ADINA R&D, Watertown, MA), was used for the tissue level simulations. The ventricularis and fibrosa were modeled as isotropic exponential materials (single-term Fung material, initial modulus modeled with single-term Mooney-Rivlin) with embedded exponential fibers (Holzapfel model, [27]) which traversed in the circumferential direction, whereas the spongiosa was modeled using a single-term Mooney-Rivlin strain energy function. The constants for these functions, as well as values for extensibilities and locking moduli, were adapted from published experimental data with respect to configurations Ω_0 and Ω_1. Experimental values for tissue thicknesses were also referenced to construct the geometry of the tissue model with the appropriate assembly of the three layers (Ω_1). A radial stretch was then applied to modify the tissue from Ω_1 to Ω_2, and the element deformations from the organ scale model were imposed for configurations Ω_2 to Ω_t. Three element positions were tracked for element deformations to use for the cell scale model: a location of large deformation in the undulated fibrosa, a location of low deformation in the undulated fibrosa, and a location in the ventricularis.

The model for the cell scale was also performed using implicit ADINA software, and was comprised of a single cell surrounded by matrix. The same constitutive models as the tissue scale model were utilized for that of the cell level, and the matrix could represent either the fibrosa or the ventricularis. Symmetry was also assumed in this model level, and one-eighth of the cell and matrix was modeled. The entire interface between the cell and matrix was assumed to be perfectly bonded and to remain so throughout deformation. The element deformations from the tissue scale model were applied as boundary conditions to the outer faces of the matrix, and simulations began from reference configuration Ω_2. The results obtained from this level of simulation were cell aspect ratio (CAR) data.

Validations were executed for all three model levels. For a full list of references for the experimental data used for property derivations and validations, see Weinberg and Mofrad [58]. The constitutive models used for the organ and tissue scale simulations were verified against experimental data on bending response and radial and circumferential stresses from biaxial experiments. To verify the deformations occurring throughout the dynamic simulations of the organ scale model, displacement and strain computations were compared to experimentally obtained measurements and were found to be in acceptable agreement. The fluid-structure interaction was observed to be free from leakage and allowed for proper leaflet coaptation which disallowed flow. Results characterizing the fluid flow, such as bulk flow rate through the valve, velocity profiles, and flow rates, were compared to experimental values and found to be similar. CAR results were also compared to experimental data for a static case, as it varied with pressure and through the thickness of the leaflet, and were found to be agreeable.

Like the preceding computational models of the aortic valve, this model can demonstrate the deformation occurring during the opening and closing of the valve, and the stress and strain distributions which result. With its FSI facilities, the mutual effects of the solid and fluid domains are included in the analysis, and fluid flow data can be acquired in addition to that of the solid structures. However, unlike previous developed models of the valve, the capabilities of this model extend beyond the organ scale (see Fig. 9). The mechanical response of the individual layers of the tissue can be investigated, examining the distributions of stress and strain throughout the

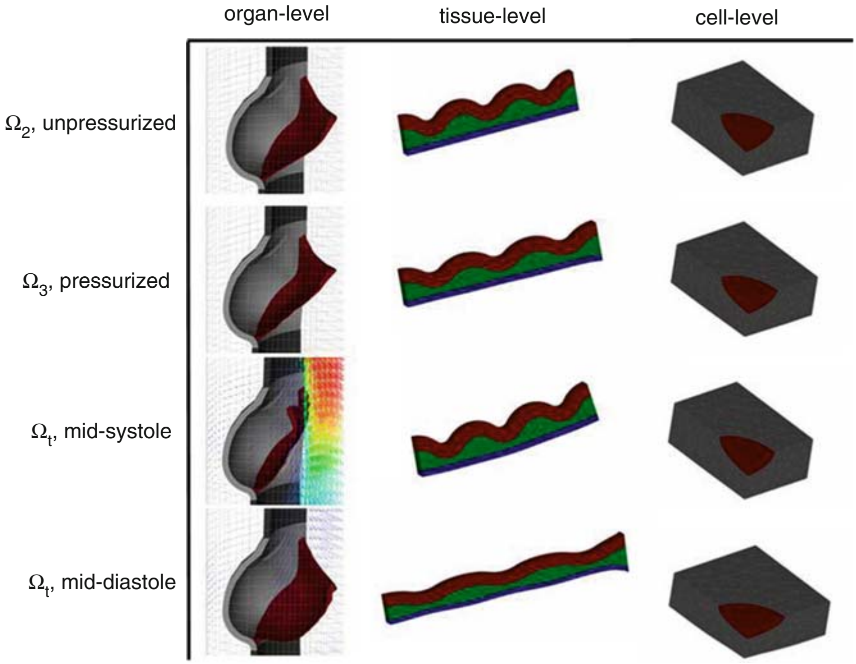


Fig. 9 Deformations experienced at each of the three levels of the multiscale model [58]

layers accounting for the unique corrugated nature of the fibrous layers. Most interesting is the information available on cellular deformation at key points in the tissue assembly, to better ascertain which conditions are truly sensed on the cellular level and therefore capable of eliciting a biological change. Like other computational models, this model incorporates simplifications such as symmetrical idealized geometries, material models, continuous cell-matrix interface, etc. The major limitation of a multiscale approach is that the error associated with approximations on the larger scales may be amplified as information is passed on to the smaller scales. At each scale level, more simplifications are incorporated and subsequently more opportunities for error. The sum total of the model's limitations must be considered when making final conclusions on the cell scale level. This utile model has already been employed to investigate the mechanical effects of an aortic valve with only two cusps as opposed to the typical trileaflet configuration [59]. This multiscale model shows great promise as a tool to investigate other pathologies which may have a strong mechanical influence such as aortic calcification, which has been speculated to be triggered by the interstitial cells of the leaflet tissue in response to abnormal mechanical stimuli.

7 Applications

7.1 Natural Aortic Valve

Organ-scale models have previously simulated the aortic valve and have provided information on the native state of the undiseased valve. These studies have demonstrated that computational modeling can be a very expedient tool for investigating the mechanics of the native aortic valve and can quantify values such as stress which are difficult to obtain in an in vitro or in vivo setting. These simulations have shown how the three leaflets and three sinuses function together in a complex manner to distribute the heavy pressure load of diastole and to be capable of the high flexion required during systole.

For example, Grande et al. [23] used ANSYS (ANSYS, Inc., Houston, PA) commercial software to model the aortic valve and the aortic root to investigate regional variations in stress and strain. The valve geometry was obtained from MRI images of ex vivo specimens and also accounted for local variations in leaflet and root thickness. Many FEM studies assume leaflet symmetry, uniform thickness, and that all three leaflets and corresponding sinuses are identical; in contrast, this study had a very complex geometry by which to more accurately characterize and compare local stress and strain magnitudes. The study was a static simulation of end systole to the end of left ventricular isovolumetric relaxation, focusing on the stresses generated as the pressure across the valve reaches a maximum during diastole (the coupling of fluid was not included in this model). The results showed that the asymmetrical and nonuniform nature of the simulated geometry led to asymmetrical and nonuniform distributions of stress and strain values in both the leaflets and sinuses (see Fig. 10).

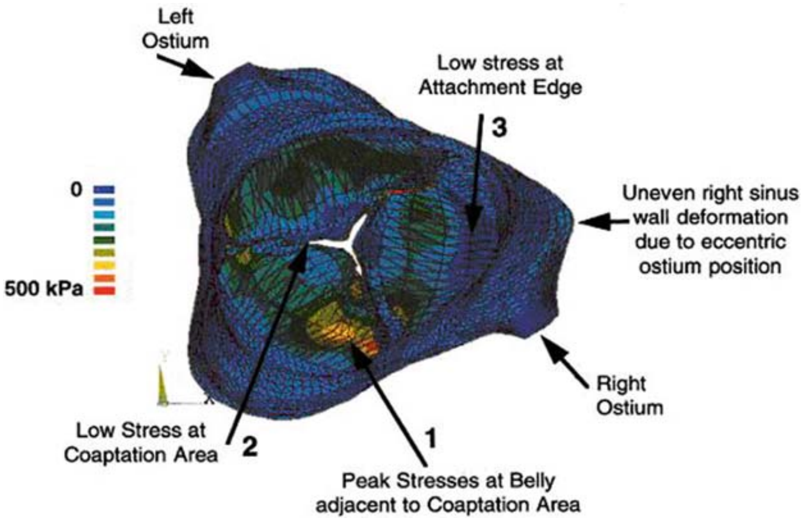


Fig. 10 Stress distributions obtained by Grande et al. [23], revealing local differences between the three leaflets

The noncoronary leaflet was shown to have the highest values of peak principal stress, which the author conjectured to be partially due to the fact that it is the leaflet with the greatest area, perimeter, and thickness as well as radius of curvature which could cause higher values of stress. Peak principal stresses in leaflets were seen in the free margin and in the belly near regions of coaptation, and stresses in the sinuses were higher near the annulus of the valve as opposed to near the sinotubular junction. Of the sinuses, the right coronary sinus and the noncoronary sinus had the greater values of stress. These results correspond well with clinical results which show that these two sinuses more commonly develop dilatation or an aneurysm [12]. This study showed that the regional anatomical differences of the aortic valve and root do have influences on the stresses and strains imposed during diastole, which could provide further information on which localized areas are more susceptible to disease or require special consideration during repair.

A contrasting study is that by Gnyaneshwar et al. [21], who performed a dynamic simulation of the aortic valve and root using an idealized geometry using ABAQUS software (Hibbitt, Karlsson, and Sorensen, Inc., Pawtucket, RI). Pressure waveforms were applied to mimic the cardiac cycle; fluid was not included in this simulation. Deformation of the aortic leaflets and root wall and the von Mises stresses throughout the leaflets were obtained during systole and diastole. At the level of the commissures, the aortic root was seen to dilate before the leaflets began to open, and when the pressure load on the leaflets was removed in the simulation, the leaflets still opened up to 20% in response to the aortic root dilation alone. During closure, the von Mises stresses of the leaflets were greater near the attachment to the root wall than near the free surface. At the moment of closure, an instantaneous increasing spike in stress was observed in the coaptation area. This study further helped elucidate the stress distributions present in the aortic valve as well as depicting the deformation of the natural valve throughout the cardiac cycle. Another interesting finding from this simulation was that it demonstrated the important relationship between the leaflets of the valve and the aortic root. The loss of the ability of the aortic root to dilate and function alongside the leaflets could be a factor in some diseased conditions and could be important to maintain or recreate during repair or replacement.

While both these studies have made different simplifications and assumptions to the complex problem of the aortic valve, their results can aid scientists and physicians alike to better comprehend the mechanics of the natural valve and its associated structures. Grande's work sheds light on the differences in stress experienced by the three different leaflets and sinuses, essential information on understanding the local variation within the valve. Although Gnyaneshwar's study is unable to detect differences between leaflets, it was able to characterize the regions of the leaflets which experienced the greater stresses. A main focus of the study was temporal rather than spatial, being able to obtain information throughout the cardiac cycle, and this enabled the model to provide further insight on the complete role of the aortic root. Using computational modeling, a variety of studies are possible, examining different details to focus on investigating different types of problems associated with the valve. A thorough understanding of the condition of the physiological undiseased state provides a basis with which to compare the mechanics of pathological, repair, and replacement settings. A severe deviation from the native conditions could indicate a potential site for a pathological response or, in the case of repairs and replacements, a region of comprised durability.

7.2 Diseased Aortic Valve

In addition to modeling the normal state of the aortic valve, finite element models have been employed to investigate the effects of pathological conditions which may significantly change the deformations and stresses imposed on the valve. Such comparative studies have demonstrated the mechanical implications of disease conditions such as a dilated aortic root, a stiffened aortic root, and a bicuspid aortic valve.

A genetic disorder called Marfan syndrome has been shown to have an adverse effect on elastic fibers. As these fibers become fragmented and disorganized, the aortic root can begin to stretch and stiffen. Grande-Allen et al. [26] investigated the mechanical effects which this abnormal aortic root could have on the leaflets of the valve. Using a similar computational model to that discussed previously [23], the three aortic leaflets and sinuses were modeled based on normal human specimens. The geometry of the model was altered to recreate four levels of aortic root dilation, 5%, 15%, 30% and 50%, which subsequently moved the leaflets radially outward. The elastic modulus of the root for the four models of Marfan syndrome was doubled to simulate the stiffened aortic root. A static analysis of diastolic loading was investigated. Regional stresses and strains of the leaflets were significantly increased by root dilation and stiffening as compared to the undiseased model, particularly near the attachment to the root and the coaptation area. For the 30% and 50% dilation models, leaflet coaptation decreased. For the 5% and 15% dilation models, increases in stress and strain were present without loss of coaptation, a scenario which could also be representative of leaflet calcification. This study illustrated that the abnormal aortic root which develops in patients with Marfan syndrome can significantly alter the natural stresses and strains on the aortic valve leaflets and can decrease coaptation, evidence which supports the instances of leaflet thickening and regurgitation often seen in such cases. Information on the resulting leaflet conditions including coaptation area, regional stresses, and regional strains can better inform surgeons on the most effective surgical repair or replacement to proceed with for patients with a dilated and stiffened aortic root such as that associated with Marfan syndrome.

Sripathi et al. [49] and Howard et al. [28] also studied the effects of aortic root stiffening on the leaflets of the valve; however, in these cases root dilation was not included, isolating the effects of root stiffening alone. A healthy aortic root is elastic and able to expand and contract during the cardiac cycle. The increasing rigidity of the aortic root and sinuses is associated with several conditions including aortic root disease as well as the loss of elastic fibers due to aging. Sripathi's study employed a similar computational model to that used by Gnyaneshwar et al. [21]

for the undiseased compliant root model, and the stiffened root model was simulated by increasing the elastic modulus of the aortic root from 2 MPa to 10 MPa. Howard's model was similar to that of Sripathi as it was a dynamic simulation, did not incorporate fluid-structure interaction, and had idealized geometry. Both studies saw that wrinkling of the leaflets became present with the rigid root model, whereas the leaflets of the compliant root opened smoothly and symmetrically. Results by Sripathi indicated that no significant increase in maximum principal (tensile) stress was observed due to the wrinkling present in the stiffened root model; however, increased values of minimum principle (compressive) stress did exist and in increased area. Results by De Hart et al. [16], as well as those in studies on artificial valves, also support the findings that the ability of the root to expand produces more favorable opening and closing leaflet configurations and reduces leaflets stresses (Fig. 11). Both Howard [28] and Sripathi [49] had agreeing results that the compliant aortic root facilitated leaflet opening, allowing opening to occur sooner and at lower pressures than compared to the rigid root; without the dilation of the aortic root, the orifice area of the rigid root model was also reduced. As described, the loss of elasticity of the aortic root does likely have adverse effects on the root's ability to dynamically aid valve function. It has been speculated in a study with similar findings that the loss of compliance in the aortic root and sinuses and the resulting effects including wrinkling of the leaflets may lead to the abnormal stresses which may cause leaflet calcification [45]. These results by Sripathi and Howard also have implications for surgical procedures; repairs and replacements such as

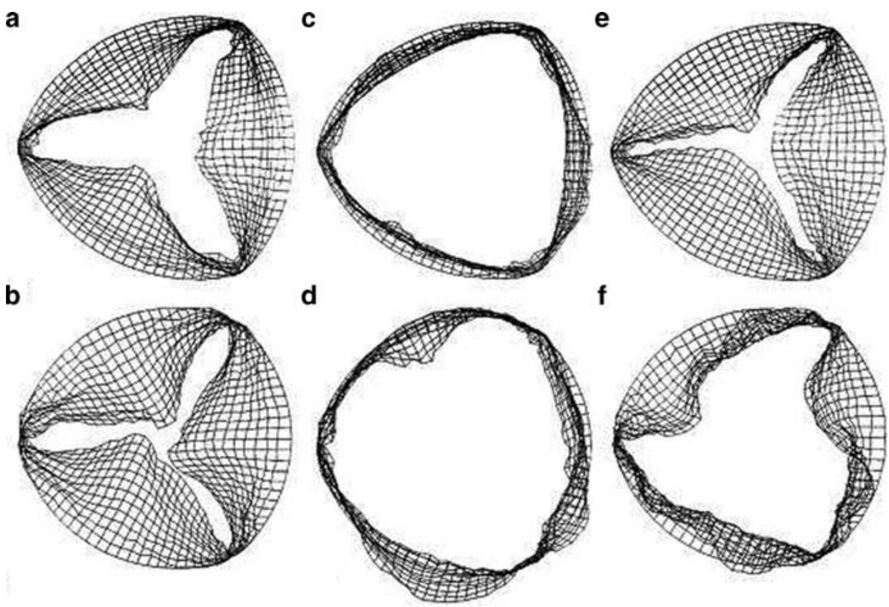


Fig. 11 The opening (**a**, **b**), opened (**c**, **d**), and closing (**e**, **f**) configurations of the leaflets (Top row represents a compliant root model, bottom row represents a rigid root model [49])

some leaflet-sparing techniques or stented replacement heart valves could interfere with the function of the natural compliant aortic root. This topic will be discussed further in Section 9.

Another pathological condition which has been studied with the use of finite element modeling is the congenital defect of the bicuspid aortic valve. Whereas the normal aortic valve has three leaflets and three sinuses, 1–2% of the population is born with only two leaflets and two corresponding sinuses. These patients are more likely to develop valvular diseases such as calcific aortic stenosis and generally present symptoms at an earlier age. Weinberg and Mofrad [59] utilized the multiscale model described previously [58] to investigate the mechanical effects of this leaflet geometry on the organ, tissue, and cellular levels (see Fig. 12). At the organ level, the bicuspid valve did not open as fully, creating a jet formation differing from that seen in the fluid phase of the tricuspid valve. Higher levels of flexure were observed for the bicuspid valve in both the coaptation area and the region near the leaflet attachment to the root wall, and the leaflets opened with visible wrinkling. Cellular deformation values were computed for the regions of high flexure on the aortic surface of the leaflet (the surface where calcification develops) for both the bicuspid and tricuspid valves and compared. Although the bicuspid had aberrant deformation on the organ level, cellular deformations were similar for both models, and therefore no significant difference may be detected on the cellular level. Since calcific aortic stenosis is thought to be regulated at the cellular level, this study concluded that the higher occurrence of calcification in bicuspid valves is not necessarily caused solely by the geometric difference of the reduced number of leaflets. Bicuspid valves may be more susceptible to disease due to other genetic differences such as abnormal matrix components. Further information outside the capabilities of computational modeling is needed to identify the reason bicuspid valves are vulnerable to disease; however, computational modeling was successful in providing evidence against the simple assumption that the geometric difference of two leaflets was fully responsible for diseases such as calcification and demonstrates that further investigation is warranted.

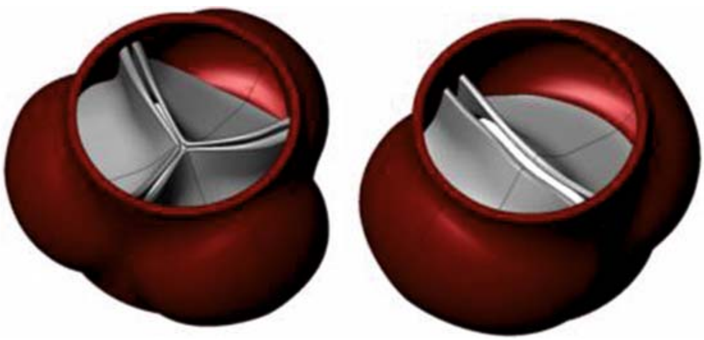


Fig. 12 Trileaflet (*left*) and bileaflet (*right*) geometries used in [59]

Computational modeling can provide detailed information on how deviant conditions in the aortic valve and root can have a significant impact on the mechanics of the valve. These subsequent changes have the potential to further precipitate abnormal biological responses. As more information on the effects of diseased conditions becomes available using this modality, clinicians can obtain a better understanding of the implications of these valvular pathologies. These types of studies also enable physicians to make a more informed decision on the course of treatment or surgical procedure, keeping in mind the mechanics which play a vital role in maintaining valve function.

7.3 Modeling Surgical Repair

Although the primary surgical procedure for patients with aortic stenosis is valve replacement, surgical repairs which leave the native leaflets intact are an option for patients with aortic insufficiency due to aortic dilatation. While the leaflets are spared, the aortic root is replaced with a synthetic graft. As discussed previously, the naturally compliant aortic root and sinuses aid in valve function. These grafts, which replace the native root, may have mechanical effects on the leaflets of the valve. The optimal design of these grafts should be determined to provide the most restorative and durable repair. Computational studies have been performed examining different shapes and materials of such grafts and the comparative stress and strain values present in the leaflets in the presence of these grafts.

Two graft shapes were investigated by both Grande-Allen et al. [25] and Ranga et al. [44]: a cylindrical tubular graft and a graft remodeled to have a "pseudosinus" shape, shown in Fig. 13. Geometrical and material properties were redefined in the portion of the model representing the graft. Grande-Allen used a static computational model that simulated the load experienced during diastole, this model has been described in Section 7 [23]. The model used by Ranga was a dynamic model with idealized geometry which incorporated fluid-structure interaction of the full cardiac cycle. While both graft shapes increased stresses from those of the normal undiseased valve, Grande-Allen noted that both grafts decreased stress and strain concentrations as compared to models of untreated aortic dilatation.

Grande-Allen observed that for both graft shapes the stresses in the root region were increased and strains were decreased. The stresses near the leaflet attachment area were lower than those of other regions such as near the sinotubular junction, creating an altered stress distribution from that of the natural aortic root. Both graft shapes increased leaflet coaptation as compared to the normal valve, but the percent increase for the cylindrical graft shape was double that of the pseudosinus graft, and directional strains implied that the valve may be displaced into the left ventricular outflow. The cylindrical grafts also produced the more severely altered stress and strain patterns and magnitudes in the leaflets; the grafts which recreated the sinus regions had the more comparable values to that of normal valves. Ranga also observed that the cylindrical graft significantly altered the distribution of stress in the

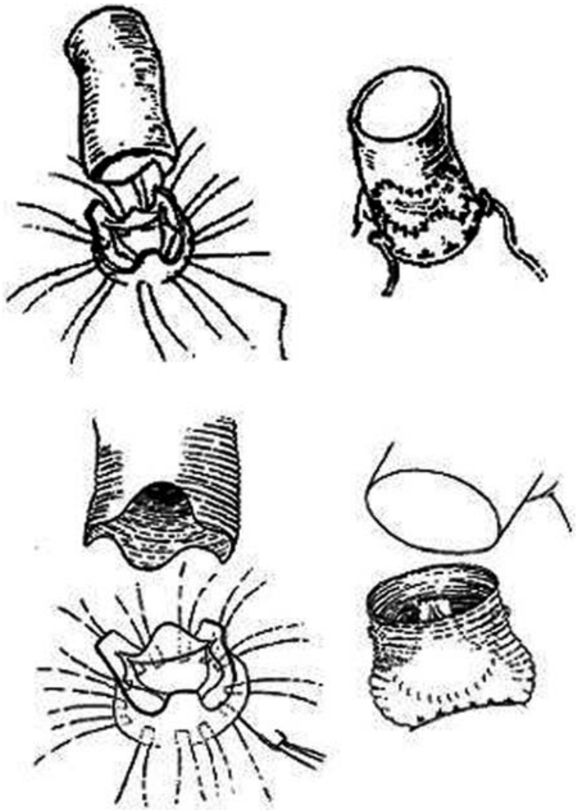


Fig. 13 Valve-sparing surgical grafts: top row showing a cylindrical graft, the bottom row showing a pseudosinus graft [24]

leaflets, and compressive stresses were increased as compared to that of the normal valve, whereas the results of the graft with sinuses were relatively similar to the native condition. Another computational study by Beck et al. [1], which compared a cylindrical graft to the native root, also found that the tubular graft increased deformation and stress, particularly along the leaflet attachment region, which was also the site where Grande-Allen observed the greatest increases in stress and strain in the leaflets. The normal allocation of load between the root/graft and leaflets was disturbed, causing atypical stress and strain distributions in the aortic root and leaflets, more severely so in the case of the cylindrical graft which was the greater anatomical change from the natural state.

The cylindrical conduit also affected the normal function and dynamics of the valve as seen in Ranga's simulation of the complete cardiac cycle. These results indicated loss of expansion of the commissures during opening, decreased opening and closing times, and the introduction of abnormal folding of the leaflets. Grande-Allen also concluded that the leaflets within the cylindrical graft may experience folding as a consequence of increased coaptation and increased leaflet strains in the attachment and belly regions. The fluid component of Ranga's study provided further information on the implications of the absence of the sinuses. Peak velocities were increased in the cylindrical graft model (those of the pseudosinus graft were similar to normal values), and without the sinuses the vortices which aid in closing were no longer present. The repair which retained the native geometry of the aortic root and sinuses had the more favorable mechanical impact on the leaflets and fluid flow as compared to the more commonly used cylindrical graft.

The study by Grande-Allen also tested three different synthetic materials for the grafts: crimped polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), and polyurethane (PCU). The elastic modulus of PCU was the lowest and closest to that of native arteries, PET was the stiffest in the circumferential and radial directions, and ePTFE was the stiffest in the longitudinal direction. The portion of the model which represented the graft was given the anisotropic material properties and thickness of the specific synthetic material. For the cylindrical shaped graft, the use of PET induced the greatest increases on the stresses and strains on the leaflets as well as the greatest increase in coaptation length. The results of ePTFE and PCU were comparable and closer to those of a normal valve. For the pseudosinus shaped graft, the PCU material had the least overall changed stress and strain values from the leaflets in the normal condition, and the PCU model's root also exhibited the most similar values to those within the natural aortic root. These results indicate that the more compliant material is most suitable for manufacturing a durable and effective aortic root graft. The differences between graft materials on minimizing negative mechanical impact were not as significant as the increased adverse impact which the cylindrical shape graft had as compared to the pseudosinus graft.

A valve-sparing surgical repair transforms the environment in which the native leaflets function. Grafts which increase stresses and strains or which shift peak stresses to regions less adapted to and less capable of handling a high load could compromise durability or create a setting in which further complications may develop. The model developed by Grande-Allen et al. [25] showed that grafts that are made from a stiffer material produce unfavorable results. These results agree with the studies discussed in Section 8, which observed that a rigid aortic root can have damaging effects on the mechanical behavior of the valve function and leaflets. Several studies gave evidence that a graft that included the sinuses was advantageous to a cylindrical tubular graft which imposed greater alterations on the native mechanical state of the valve; a logical conclusion as the pseudosinus graft more closely mimics the anatomy of the aortic root.

Although these results all imply that reimplantation with a cylindrical graft is not a durable repair, clinical results indicate otherwise. Long-term results by David et al. [13] showed that 94% of patients with a cylindrical graft were free from moderate or severe aortic insufficiency after 10 years and 96% did not require reoperation. The long-term clinical results of a remodeling procedure, which tailored the graft to the patient's valve and more physiologically recreated the sinuses and normal valve motion, were also examined. In this case, only 75% of patients were free from returning aortic insufficiency after 10 years. While computational studies can characterize the stresses and strains present under very controlled conditions, the studies did not consider the biological processes which may ensue after surgery. In many cases, annular dilation will continue or return depending on the pathology, and a more rigid constraining repair may better prevent future remodeling and the reoccurrence of aortic insufficiency. Further development of grafts which reproduce the sinuses is being pursued; while these clinical results are still not as positive as those of the standard cylindrical graft, they are promising [40].

Computational modeling is an informative tool to perform a detailed analysis on the mechanical implications of a surgical repair. As the capabilities of the modality improve, more information can be obtained. The addition of fluid-structure interaction to the computational model by Ranga et al. [44] enabled researchers to investigate the impact of the graft on blood flow in addition to the solid mechanics of the leaflets and root, and visualizing the entire cardiac cycle provided information on the opening and closing dynamics of the valve as well. It is important to keep in mind with a mathematical model that biological processes may further alter the conditions of the environment, and that there are factors which exist that are not included within the model. Also, while the results of a study may demonstrate that one simplified scenario is superior to another, these results may not translate to the real world application.

7.4 *Optimizing Artificial Heart Valve Design*

Another application for valve computational models is to simulate artificial valves in the physiological setting and to investigate design factors in order to produce the most mechanically favorable design. Performing preliminary tests using computational methods can provide greater information to both the design engineers and the physicians and can reduce the number of in vitro or animal tests required in the optimization and testing process. Data such as stress magnitudes and distributions is particularly difficult to acquire using other testing modalities, and this information is critical to assessing valve integrity and long-term durability. Computational models have been shown to be an informative tool to study the mechanical behavior and impact of mechanical, bioprosthetic, and synthetic artificial heart valve replacements (Fig. 14).

Models which incorporate the fluid aspect of the problem are ideal for analyzing mechanical heart valves. The primary concern with the use of mechanical heart

Fig. 14 Artificial heart valves: Bileaflet mechanical valve (**a**) [22], bovine pericardial bioprosthetic valve (**b**) [47], synthetic valve with sinusoidal fiber reinforcement (**c**) [14]

valves is the tendency for these patients to develop thrombi or emboli, leading to a possible stroke or heart attack. The geometry of this type of valve distinctly differs from the native aortic valve, and therefore generates non-physiological flow distributions and conditions. Using FSI techniques, researchers can study unfavorable hemodynamic conditions, such as recirculation, turbulence, and abnormal levels of shear stress. These conditions can damage blood cells or platelets, increasing the likelihood of thrombotic events. Studies such as that performed by Ge et al. [20] further clarify the mechanical process by which hemolytic damage develops, providing insight on the specific biological pathway by which the damage propagates. Parameters other than shear stress can also negatively influence hemolytic activity. Adverse pressure gradients, squeeze flow, vortex formation, and valve rebound can contribute to cavitation, in which case small vapor bubbles form and then collapse, possibly initiating hemolysis, platelet activation, or increased stress on neighboring structures. Blood damage is particularly a concern in areas of the valve such as hinges or clearance regions. Lai et al. [32] employed computational modeling to compare different leaflet tip geometries and different allowances for the gap between the leaflet tip and housing of the bileaflet valve investigated. This type of study is an excellent approach in optimizing valve design to prevent a thrombolytic response. These types of FSI computational models help illustrate the mechanical processes which affect hemolytic activity and can improve the design of this type of commonly used valve replacement so as to minimize the negative impact on the patient.

Bioprosthetic and synthetically manufactured valves provide an alternative to mechanical heart valve replacements and the high risk of thrombosis. These valves mimic the native geometry (trileaflet) and are constructed from materials which do not illicit such an immunological response. The main trade-off for this advantage is reduced durability compared to their mechanical counterparts. Numerical simulations can aid engineers in developing valves which have a more uniform stress distribution and minimized bending moments, producing valves which are therefore less prone to fatigue or calcification. For the construction of synthetic valves, De Hart has explored the use of fiber-reinforcements within the leaflet material, not unlike the native valve tissue which has a network of collagen fibers. The use of fiber-reinforcement compared to a non-reinforced valve stabilized the leaflets in the open configuration, eliminated high bending deformations during closure, and reduced stresses in the leaflets. The number and orientation of the fibers was seen to have an effect on stress distribution and magnitudes [14, 16]. Research has also been conducted to examine which materials may be more subject to tears and fatigue and to examine the mechanical changes occurring upon structural damages. One study on BHVs showed that initial tears had the tendency to propagate, and damage to collagen fibers due to bending could compromise the strength of the tissue and lead to failure [11]. Further understanding of the modes of BHV and synthetic leaflet failure can be attained through computational research, and simulations can be used to test new proposed materials.

In addition to the artificial leaflets, many BHV or synthetic valves have a stent structure which supports the leaflet structure, and the construction of the stent or lack of one altogether is a matter of debate in valve design. A static analysis of a polyurethane valve in the closed position compared rigid and flexible stents [8]. The maximum normal and shear stress concentrations were located near the commissures where the leaflets attach to the stent. The use of a flexible stent reduced the maximum principal stress within the leaflets as well as reduced the maximum shear stress near the commissures. Chandran also examined the effects of varying stent height and found that leaflet stresses were decreased as stent height was increased. The results of this study only provided information on the high pressure loading of diastole. Another study by Krucinski et al. [31] used a model of a bioprosthetic valve to further investigate the problem, focusing on the high flexure stresses experienced during opening. The areas of high curvature were also seen near the commissures and attachment to the stent and produced high compressive stresses in result. Krucinski modeled the use of an expansile stent, which allowed dilation at the commissures like that of the natural aortic root, and this stent significantly reduced the compressive stresses experienced in the commissural region. As discussed earlier, aortic root contraction and expansion of the commissures aids valve opening and is an important component of the complex valvular stress-sharing and dynamics. Additional computational studies have also demonstrated that trileaflet valve replacements that retain the ability of the root to dilate and contract minimize leaflet stresses [6, 16].

Much research and exploration has gone into heart valve prosthesis development. The use of computational modeling has broadened the capabilities of valve testing, allowing for a greater number of studies. As compared to in vivo or clinical testing, modeling allows for parametric testing in which case individual variables can be isolated and investigated. Most importantly, this modality is able to provide detailed data on the solid and fluid mechanics associated with the problem. Hemodynamic data can provide insight on the valve's influence on non-physiological flows and the possible subsequent thrombotic consequences, and stress distribution data can elucidate the vulnerability of a prosthesis to failure or possible calcification. Comparative studies can help indicate which geometric or material design qualities fare the best in the physiological environment, eliminating some designs before they reach animal or clinical testing. Modeling is an excellent tool to fully appreciate the complete valve replacement problem and to best optimize a valve design for the dynamic living setting.

8 Future Directions

The use of computational modeling to study the aortic valve is far from being exhausted. As more advanced and complex models are developed, the research possibilities continue to grow. The addition of FSI has allowed for more thorough studies of the normal valve state, but there is still opportunity for improvement. The capability of simulating turbulent flow and better resolution of shear stress of the fluid would greatly improve the quality of hemodynamic data and would particularly improve the computational evaluation of mechanical prostheses. Constitutive material models continue to include more complexities of the valve tissue. Material models which can be implemented into commercial finite element software are of particular applicability; such a model which included anisotropy, in plane and bending behavior, and nonlinear pseudoelastic characteristics would improve the accuracy of simulations and the relevancy of solid mechanics data obtained. The development of multiscale models has also expanded the scope of computational studies. The ability to examine mechanical effects on the cellular or tissue level lends itself excellently to study diseased conditions such as calcified aortic stenosis, which may be mediated on the cellular level by changes which occur on the organ or tissue scale. Examining the status of current cell scale methods, a model which more accurately portrayed cell surface-extracellular matrix interaction would improve the relevancy of cellular level models. The extension of multiscale methods to relay information from the smaller scales up to the larger scales, instead of solely one-way transfer of information, would also broaden the faculties of multiscale models. As also described, computational models can be used to test new surgeries or replacement valve designs. As techniques advance these models could be adapted to be patient specific and used in the clinical setting to aid in deciding which repair or replacement would be most favorable for a specific patient. The field of aortic valve computational biomechanics has significantly advanced and expanded in just over a decade and future progress in these techniques will further enhance the relevancy and impact of computational studies.

9 Conclusion

Computer simulations of the aortic valve have provided mechanical information on the valve which may have otherwise been unattainable. Heart valve diseases are a widespread problem and in many cases are linked to mechanical factors and abnormalities. Modeling studies have presented a platform to elucidate the mechanical environment of the healthy valve, and this type of research has provided insight on the progression of pathological conditions and the favorability of proposed surgical repairs and valve replacements. Continuing improvements in numerical simulations are eliminating past modeling limitations so that new models can more closely replicate the physiological problem. This field shows great promise in continuing to supply vital information to improve heart valve healthcare.

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