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REVIEW

On the multiscale modeling of heart valve biomechanics in health and disease

Eli J. Weinberg · Danial Shahmirzadi · Mohammad Reza Kaazempur Mofrad

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Abstract Theoretical models of the human heart valves are useful tools for understanding and characterizing the dynamics of healthy and diseased valves. Enabled by advances in numerical modeling and in a range of disciplines within experimental biomechanics, recent models of the heart valves have become increasingly comprehensive and accurate. In this paper, we first review the fundamentals of native heart valve physiology, composition and mechanics in health and disease. We will then furnish an overview of the development of theoretical and experimental methods in modeling heart valve biomechanics over the past three decades. Next, we will emphasize the necessity of using multiscale modeling approaches in order to provide a comprehensive description of heart valve biomechanics able to capture general heart valve behavior. Finally, we will offer an outlook for the future of valve multiscale modeling, the potential directions for further developments and the challenges involved.

Keywords Heart valve · Multiscale modeling · Computational modeling · Simulation · Cardiovascular biomechanics

1 Healthy heart valve mechanics

The heart is a pump system consisting of four chambers and valves. As the chambers contract and expand to eject and receive blood, the valves open and close in sequence to control the direction of flow. Like many other biological systems, the heart valves function at different length-scales and demonstrate distinct biomechanical features at each length-scale (Sacks and Yoganathan 2007), see Fig. 1. In the following, healthy heart valve is described at different organ-, tissue-, cell- and molecular-scales.

Working as an organ, each of the heart valves consists of a number of tissue flaps.[1] The aortic, pulmonary, and tricuspid valves each normally have three flaps (or leaflets) and the mitral valve has two. Leaflets are passive elements, opening and closing when forced by the blood flow. Healthy heart valves become fully wide when open, providing an unobstructed flow path, and fully sealed when close, avoiding any pressure drop or retrograde flow (Humphrey 2001). Opening and closing of healthy heart valves occur based on an exquisite timing which generates a smooth blood circulation throughout the body. Healthy valves move quickly between the open and close states and require little force to do so (Milnor 1990).

At tissue-scale, the valve leaflet is composed of three layers with overall thickness of about 0.2–2.0 mm (Grande et al. 1999), see Fig. 2a. The thinnest layer, ventricularis, is below the inflow surface and consists mostly of a dense plexus of collagen with some elastin fibers. Below the outflow surface is the thicker layer, fibrosa, which is composed of organized collagen structure (Schoen and Levy 1999). The aligned collagen fibers make fibrosa the main load-bearing layer in the valve. Collagen fibers are crimped when the tissue is unstressed and flatten when the tissue is tensed due to pressurization of the valve (Sacks et al. 1998). Between the two fibrous layers exists the gel-like layer called spongiosa, which is composed of proteoglycans (Schoen and Levy 1999).

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[1] Generally the tissue flaps of the aortic and pulmonary valves are referred to as the "cusps" and those in the mitral and tricuspid valves are referred to as "leaflets". Throughout this article, the term leaflet refers to natural valves together, bioprosthetic valves, or mechanical valves, and the term "cusps" is used specifically to address the natural aortic or pulmonary valve.

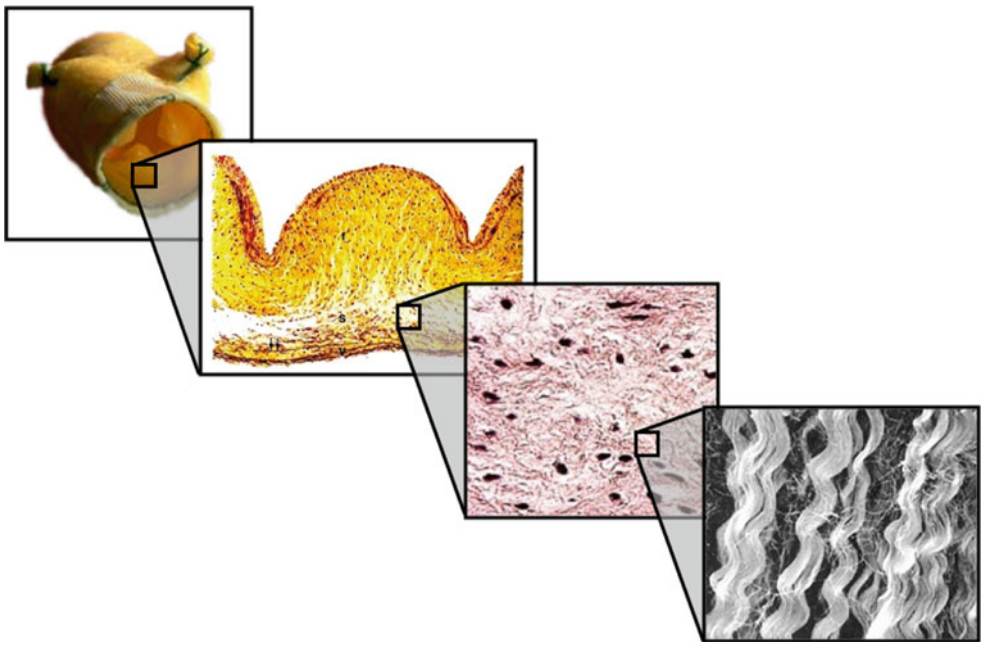


Fig. 1 Representation of the multiscale nature of heart valve mechanics: organ-, tissue-, cell-, and molecular-scale features (Schoen and Levy 1999; Schenke-Layland et al. 2004; Fastenrath 1995)

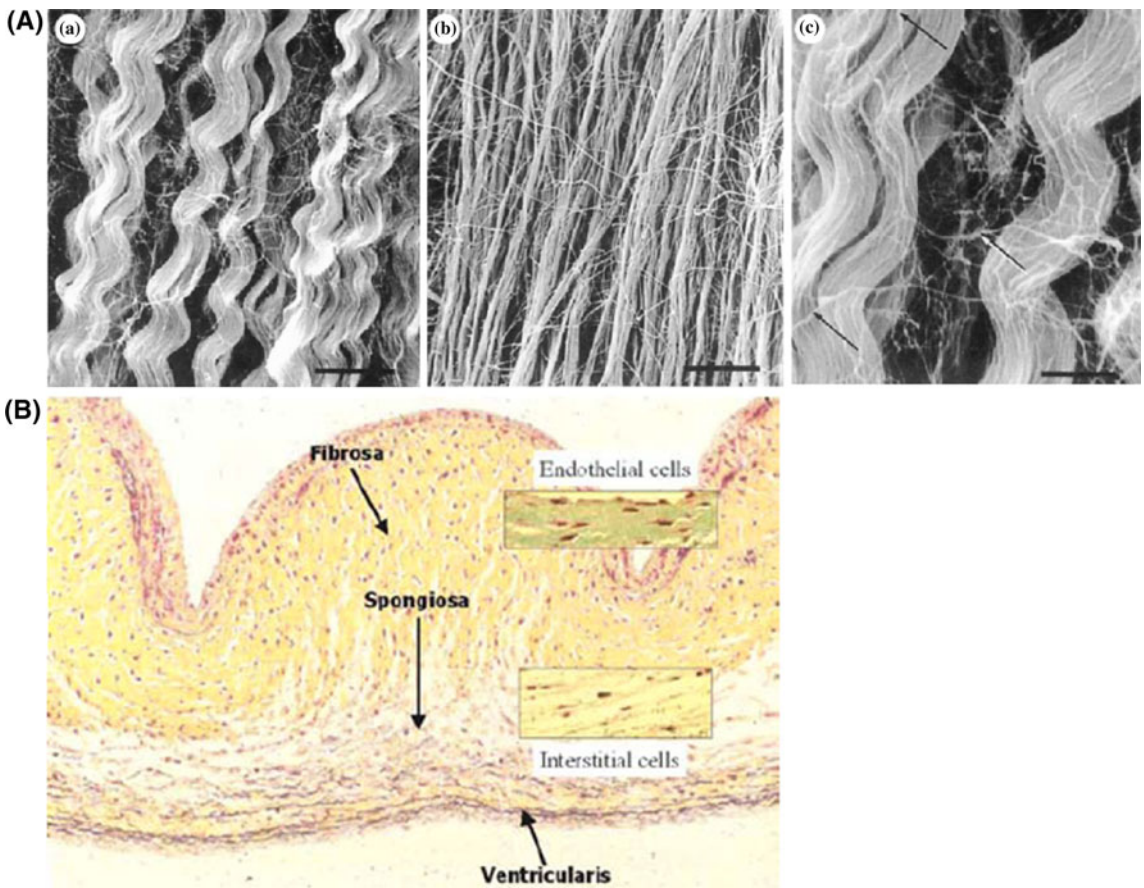


Fig. 2 Aortic valve leaflet micrographs showing: (A) tissue layers and cells (Mendelson and Schoen 2006) (B) Matrix structure (Fastenrath 1995; Misfeld and Sievers 2007)

At cell-scale, heart valve leaflets consist of two types of cells: valvular interstitial cells (IC) and endothelial cells (EC), see Fig. 2a. ICs are distributed throughout, and are responsible for maintaining, the leaflet tissue matrix and modulating disease pathology (Liu et al. 2007). In the valve, ICs display a number of different phenotypes at different locations, and share some characteristics with fibroblasts and some with skeletal, cardiac, and smooth muscle cells (Roy et al. 2000; Taylor et al. 2003; Merryman et al. 2006a; Chester and Taylor 2007). ICs are known to remodel over the human lifetime (Rabkin-Aikawa et al. 2004), respond to physical deformations (Gupta et al. 2008), and engage in signaling with other ICs and the extracellular matrix (Chester and Taylor 2007). On the other hand, ECs coat all of the blood-facing surfaces and have spatially varying phenotypes (Simmons et al. 2005), respond to mechanical stimuli (Weinberg et al. 2010), regulate valve pathologies (Butcher and Nerem 2007), and engage in signaling (Butcher and Nerem 2007).

At molecular-scale, heart valve leaflets are composed of a sponge-like fibrous matrix of elastin which surrounds bundles of collagen fiber (Taylor et al. 2003), see Fig. 2b. The fibers are aligned in the plane of the leaflet and organized into tissue's three layers of fibrosa, spongiosa, and ventricularis. The collagen and elastin exist in a hydrated gel-like ground substance composed of proteoglycans and glycosaminoglycans (Taylor 2007). Collagen and elastin are kinked fibers that can straighten under small loads, allowing large extension of the tissue at low stress. The pure elastin acts as a brittle glass-like polymer with no sign of rubbery properties as it possesses in healthy cardiovascular tissue (Pezzin et al. 1976). Rather, hydrated elastin—as found in healthy cardiovascular system—shows signs of viscoelasticity—revealed for instance by creep or stress relaxation tests—which rises due to the interaction of elastin molecules with water molecules available in aqueous extracellular matrix (Lillie and Gosline 1990). It is shown that a considerable stiffening of vascular elastin occurs by losing only 10% of tissue water content (Gosline and French 1979). The mature cross-linked elastin molecule is so inert and stable that in normal circumstances, it lasts for the entire lifetime of the species (Fung 1993). Elastin has a denaturation temperature of about 200°C, which is much higher than collagen's denaturation temperature of about 50°C (Pezzin et al. 1976; Fung 1993; Samouillan et al. 2000).

Overall behavior of heart valves is regulated by different mechanisms at different length scales. Distinct mechanical behavior can be observed at the organ, tissue, cell, and molecular scales. Additionally, functional communication exists among different scales meaning that alteration in behavior at one scale impacts behavior at other scales. For example, extensibility and geometric organization of the fibrous molecules determine the tissue stiffness and anisotropy (Billiar and Sacks 2000a,b), which furthermore—along with the tissue-scale geometry—determines the cusps motion at organ-scale (Weinberg and Kaazempur Mofrad 2007). In addition, there is active communication between the cell and tissue scales, where contraction of the ICs significantly affects tissue stiffness (Merryman et al. 2006b). On the other hand, mechanical communication from the larger scales down toward the smaller scales affects active biochemical processes as well. Fluid motion at organ-scale applies shears to the ECs at cellular-scale. Solid motion at the organ scale causes deformation at tissue scale, which in turn deforms the ICs in the cellular scale. It is thus increasingly realized that there is a crucial and inherent connection between the behaviors of heart valve at different length scales which undermines studying the valve behavior at each individual length scale separately.

2 Heart valve disorder mechanisms

Healthy heart valves move easily between the unobstructed open and the fully sealed closed configurations, and change shape in a regular pattern during the cardiac cycle. As the heart ages over the species lifetime, the valves must grow proportionally and must maintain certain material properties in order to adapt to the increasing flow pressure, to be able to take regular configurations during cardiac cycle, and to deform rapidly. Any deviation of heart valve from regular shape, size, or material properties can be a source of pathological conditions. Similar to healthy conditions, pathological conditions can be caused by various factors at different length scales. Such factors at different length scales can potentially have mutual effect on each other. For example, gene expression in diseased ECs and ICs of heart valve may be controlled by mechanical signals at the cell scale which are transferred from mechanical signals at tissue- and organ-scales through mechanotransduction (Roy et al. 2000; Taylor et al. 2003; Butcher and Nerem 2007; Liu et al. 2007; Weinberg et al. 2010). In the following, we provide a brief overview of some of the most common pathological conditions at different length scales which lead to heart valve major disorders.

The disorder in which the aortic valve is not opening fully is called aortic stenosis (AS). Aortic stenosis is the most common valve disease, occurring in 2–4% of adults of ages 65 and over (Freeman and Otto 2005). In calcific aortic stenosis (CAS), calcified nodes develop on the aortic valve cusps and the subsequent stiffenning will prevent the valve from opening fully, leading to obstruction of blood flow (Thubrikar 1990; Otto 2003). It has been shown that calcification causes change in valve properties at different scales (Pohle et al. 2001; Mazzone et al. 2006; Weinberg and Kaazempur Mofrad 2008). For instance, matrix-maintaining functions

of valvular ICs are regulated by healthy valves (Taylor et al. 2003), and in calcified valves, abnormal mechanical signals lead to the dysfunction of the ICs (Otto 2002). Aortic stenosis may be caused either by age-related wear on the valve or by rheumatic disease (Lilly 2003), the latter of which might also cause mitral stenosis (MS).

The disorder in which the aortic valve is not closing sealed is called regurgitation or insufficiency (Humphrey 2001), which is most commonly observed in the mitral valve. Mitral regurgitation (MR) is caused by a variety of conditions, including valve degeneration and stiffening (Grande-Allen et al. 2005), papillary muscle dysfunction, infective endocarditis, rheumatic disease, and enlargement of the left ventricle (Lilly 2003), some of which occur in organ-, tissue-, cell-, and molecular-scales. Aortic regurgitation (AR) can also occur with similar causes of either tissue disease or orifice enlargement (Otto 2003). Specifically, dehydration of elastin molecules because of water molecules blockade, either through binding of elastin to cholesterol esters or due to high density of glycosaminoglycans, causes aortic stiffening (Lillie and Gosline 1990). Tricuspid and pulmonary valve regurgitation are generally functional rather than structural, meaning they develop in response to pressure overload and not due to a mechanical defect of the valve itself (Lilly 2003).

Besides the heart valve diseases of stenosis and regurgitation, there exist other less severe disorders which are often precursors to stenosis and regurgitation (Thubrikar et al. 1986; Lilly 2003). Mitral valve prolapse (MVP) refers to a condition wherein the mitral valve bulges out significantly under pressure. Bicuspid aortic valve (BAV) is another valve disorder in which the aortic valve has two cusps instead of three and it occurs congenitally in 1–2% of the population (Thubrikar 1990; Otto 2002; Weinberg and Kaazempur Mofrad 2008).

Since different pathological conditions of valve can be caused by factors at different organ-, tissue-, cell- and molecular-scales, treatment schemes should also be developed at appropriate length scales. For example, progression of calcification in stenotic valves can potentially be inhibited at cell- and molecular-scales through pharmaceutical statins (Rosenhek et al. 2004; Moura et al. 2007; Otto 2007). On the other hand, surgical methods at tissue scale might be used to repair abnormal valve; however, surgery is currently possible only for specific cases of stenosis and regurgitation (Yacoub and Cohn 2004a,b), with new methods continuously being developed (Dagenais et al. 2005; Carmody et al. 2006). In the vast majority of cases, the existing treatment method is through implant surgery at organ scale. Development of valve replacement methods has traditionally proceeded using both mechanical and bioprosthetic valve types (He et al. 1995; Vlessis et al. 1997; Yau et al. 2000) and autologous valves in more recent years (Mol et al. 2006). For a comprehensive up-to-then review on artificial heart valve, see pioneering work of Grunkemeier et al. (Grunkemeier and Rahimtoola 1990). The current focus in valve replacement research is on reducing thrombogenicity of mechanical valves (Dumont et al. 2007), increasing durability of bioprosthetic valves (Sacks et al. 2006), and development of tissue-engineered solutions (Mendelson and Schoen 2006). Much research has thus been carried out on simulating biomechanics of mechanical and bioprosthetic valves than that of the native valves.

3 Existing approaches in modeling heart valve

Enabled by the experimental and theoretical methods, an increasing number of investigations has been carried out to model heart valve biomechanics. Except few studies, existing approaches in modeling heart valve, experimental and theoretical, have been developed by focusing on a single length scale, whether organ-, tissue-, cell-, or molecular-scale. Experimental methods in studying heart valve biomechanics at each length-scale rely on advancements in techniques from a disparate range of disciplines. The field of mathematical modeling of heart valve mechanics has grown from nonexistent in three decades ago to a broad discipline today. This expansion is due both to development of mathematical approaches in describing relevant mechanical behavior and to the increased availability of computational power necessary for simulating complex biomechanical dynamics. In the following, we will highlight the existing heart valve models at each length-scale, with highlighting the fact that no single-scale model is capable of capturing the overall behavior of the heart valve. In particular, merely capturing the heart valve bulk material properties by a model does not guarantee the capability of the model in predicting any arbitrary valve behavior. The incapability of single-scale models emphasizes the need for developing multi-scale models, which will be discussed in the next section.

3.1 Organ-scale

Organ-scale heart valve models have traditionally been of great significance, both in clinical diagnosis and in valve implant researches. Majority of clinical models have been developed with the aim of detecting valve abnormal conditions based on organ-scale symptoms. The classic method of listening to heart sounds can detect and, along with other physical examination, diagnose abnormalities (Lilly 2003; Bonow et al. 2006). Cardiac catheterization can be used to examine the valve for calcification or other defects (Bonow et al. 2006). Valve disease is most commonly evaluated by chest echocardiograph (Handke et al. 2003; Otto 2006), which allows measurements of fluid motion and valve geometry that can be compared to various indices for valve disease (Antonini-Canterin et al. 1999; Garcia et al. 2000; Blais et al. 2001; Antonini-Canterin et al. 2002; VanAuker 2006).

Researchers have recently demonstrated MRI (John et al. 2003) and CT (Alkadhi et al. 2005; Feuchtner et al. 2006a,b) imaging technologies able to resolve valve motion, holding promise that modern imaging methods may be applied to clinical examination of valves. However, some of the laboratory methods available to examine organ-scale valve motion cannot be practically used on patients. A pulse chamber can be used to subject physiological flows to valves, wherein the valve deformation can be monitored by optical methods (Fenner et al. 1995; Gao et al. 2000; Iyengar et al. 2001; He et al. 2005; Sun and Sacks 2005) and fluid motion can be measured by particle velocimetry (Chandran et al. 1989). Valve motion has been measured in large-animal models by tracking sonocrystals attached to the leaflets (Thubrikar 1990) and fluid velocity profiles have been measured in the animal models by hot-wire anemometry (Falsetti et al. 1972).

Attempts in developing replacement for native heart valve, whether with mechanical or bioprosthetic substitutes, primarily aim to capture organ-scale features of the natural valve. The organ-scale motion of native and bioprosthetic valves is very similar, but quite different from that of mechanical valves. Simulation of mechanical valves, however, carries attention because the simulation methods developed for mechanical valves can provide guidelines for analyzing bioprosthetic valves. The simplest organ-scale valve simulation is the static case of a mechanical valve closed against pressure. This situation can be examined without a fluid phase, representing the fluid simply as a pressure load against the valve leaflets which are modeled as isotropic and linear solid (Cataloglu et al. 1976, 1977; Chong and Missirlis 1978; Hamid et al. 1985a,b). Analysis of the static, closed-valve case has continued (Beck et al. 2001), and present models include rigorous accompanying work in material modeling and experimental verification (Sun et al. 2005). The next step in complexity of organ-scale models is to move from the static to the dynamic case. The fluid can again be represented simply as a pressure load applied on the surfaces of the solid, but in dynamic simulation of the valve the leaflets are moving through large deformations. The first dynamic solid-phase models were developed a few years after, tending to include more advanced descriptions of both geometry and material properties. Grande-Allen et al. simulated the aortic valve including realistic asymmetric geometry and the aortic root (Grande et al. 1998, 1999; Grande-Allen et al. 2001), whose simulation geometry is shown in Fig. 3a. Other models added anisotropic (Kunzelman et al. 1993) and nonlinear (Black et al. 1991; Howard et al. 2003) material descriptions. As with the static case, the dynamic solid-phase case is presently being used with advanced material models and relevant experimental work (Kim et al. 2006, 2008), whose simulation results are shown in Fig. 3b. An entirely new level of complexity and computational expense is added by incorporating the presence of fluid through a fluid-solid interaction (FSI)

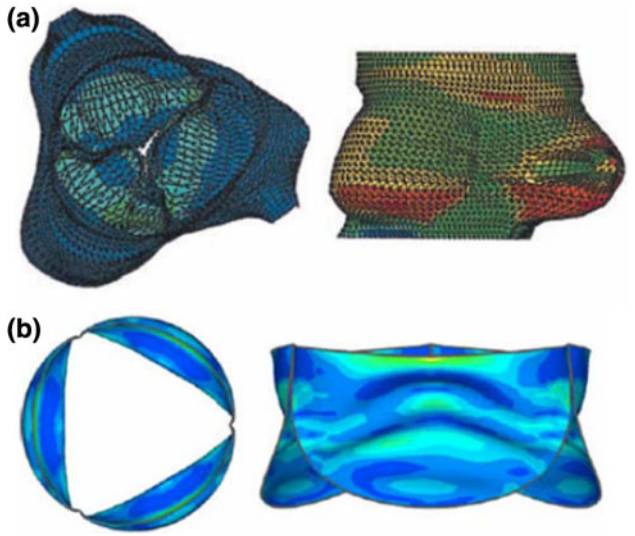


Fig. 3 Results of aortic valve dynamic, solid-only simulation with **a** realistic geometry (Grande-Allen et al. 2001) and **b** realistic material model (Kim et al. 2006)

analysis. These models were created after the solid-phase models, and thus usually include more advanced material models as well. Possessing realistic geometries, well-defined fibrous material models, and the interaction of fluid and solid, these models represent the current state of the art.

Application of finite element (FE) methods in enhancing the heart valve organ-scale simulation results has also been considered. A major challenge in simulating valve organ-scale motion with FE is related to the leaflets' large strains (up to 40%) as well as the valve's large displacements and rotations. Simulation of these deformations has been enabled by the development of the nonlinear "updated Lagrange" and "total Lagrange" approaches in large-deformation solid mechanics (Bathe 1996; Bathe et al. 1999). Another challenge in FE simulation of valve organ motion is modeling the fluid-solid interaction (FSI) between the leaflets and blood, both of which move dynamically throughout the cardiac cycle. Using ALE (Arbitrary Lagrange–Eulerian) mesh smoothing method, FSI models have been developed for leaflet-blood large displacement interactions. The fluid and solid computational grids can be modeled as either conforming with a Lagrangian interface, or non conforming with an interpolated interface, two different methods being used by commercial FE software packages ADINA (Watertown, MA) (Bathe 1996) and LS-DYNA (LSTC, Livermore CA) (Hallquist 2006), respectively. Many other finite element simulation methods have been used to capture the FSI behavior in heart valves. The De Hart group impressively has coded fictitious domain software to perform the FSI and included a fibrous material (De Hart et al. 2003a,b, 2004) to model a bioprosthetic valve, see Fig. 4a. Loon et al. extended fictitious domain method through coupling a Navier-Stokes

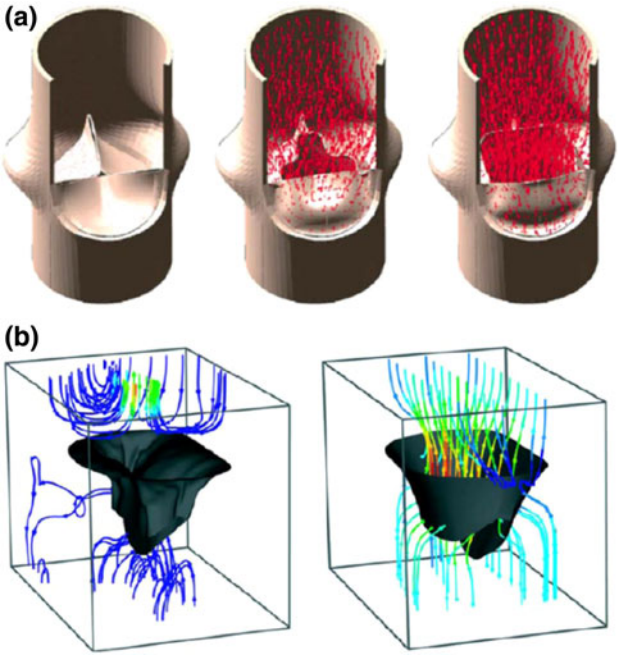


Fig. 4 Organ-scale simulations with realistic geometries, fibrous material models, and fluid-structure interaction. **a** Bioprosthetic valve simulation (De Hart et al. 2003b) and **b** mitral valve simulation (Einstein et al. 2004)

flow solver in Eulerian description to a Neo-Hookean solid model in Lagrangian description to model valve-leaflet blood interaction (Loon et al. 2006). Nicosia et al. modeled the aortic valve using an anisotropic elastic material model (Nicosia et al. 2003), followed by Weinberg et al. modeling the aortic valve with a discrete fiber model (Weinberg and Kaazempur Mofrad 2007) and Einstein modeling the mitral valve with a splayed-fiber model (Einstein et al. 2004, 2005a,b; Kunzelman et al. 2007). The last two models notably are verified against various experimental measures, and Einstein's model is able to predict heart sounds (Einstein et al. 2004); see Fig. 4b for a representation of the mitral valve model which also includes the chordae tendinae, not depicted. Progress in simulation of mechanical heart valves has perhaps outpaced that of bioprosthetic valves. Unlike in native valves, latest models for mechanical valves have incorporated FSI analysis with a sophisticated description of blood as a non-Newtonian fluid and were able to predict thrombogenicity of the valve (Bluestein et al. 2000; Cheng et al. 2003, 2004; Yin et al. 2004; Bluestein et al. 2004; Fallon et al. 2006; Dumont et al. 2007), see Fig. 5. We expect that future bioprosthetic valve models will also incorporate these advancements in blood flow modeling. Increased computational power has enabled more complete models of heart valve organ-scale behavior. While running a solid-phase simulation of a valve linear elastic model once required nearly a day on a supercomputer (Gnyaneshwar et al. 2002), only 5 years later a full

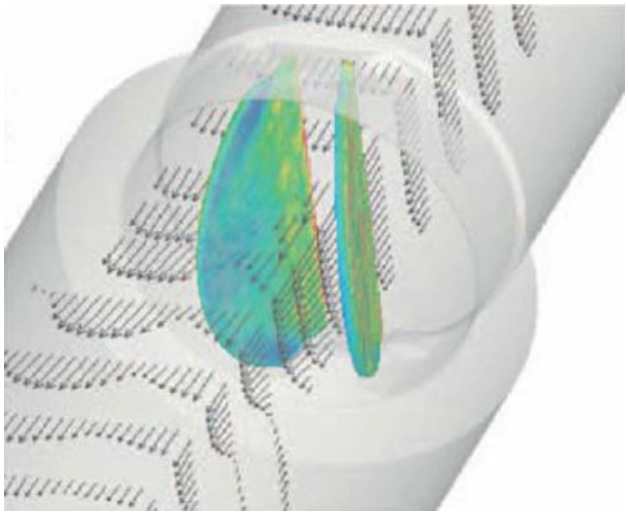


Fig. 5 FSI simulation of a mechanical heart valve (Dumont et al. 2007)

FSI simulation of a valve nonlinear model was performed in a few hours on a personal computer (Weinberg and Kaazempur Mofrad 2007).

3.2 Tissue-scale

With primary focus on quantifying the material properties of heart valve leaflets, efforts have been made on modeling heart valve properties at the tissue scale. Like for many other soft tissues, initial measurements of valve leaflet tissue were measured by Instron-type uniaxial tester (Clark 1973; Missirlis and Chong 1978; Thubrikar et al. 1980; Rousseau et al. 1983; Sauren et al. 1983; Vesely and Noseworthy 1992; Vesely and Lozon 1993). Valve tissue, even compared to other biological tissues, is particularly nonlinear, nonhomogeneous, and anisotropic. The Sacks group has pioneered use of optically measured methods that, in concert with development of theoretical tools, has enabled rigorous description of multilayer, anisotropic and nonlinear tissue properties in both biaxial and bending deformations (Sacks and Sun 2003; Sacks and Yoganathan 2007). Standard histology methods give two-dimensional pictures of tissue microstructure. New high-frequency ultrasound imaging methods extend this capability to three dimensions (Lacefield et al. 2004). The two main advancements in mechanical modeling at the tissue scale are the development of constitutive models for biological tissues and the tools to implement those models in the FE setting. Constitutive modeling of tissue behavior requires the theoretical framework provided by continuum mechanics (Fung 1993; Holzapfel 2000a). The initial insight upon which the rest of the field is based was Fung's demonstration that biological tissues behave in a pseudoelastic manner. That is, these matrices of fiber and water have nonlinear, usually exponential loading curve, which matches closely

to unloading curve (Fung 1967, 1993). There exist other reports on heart valve tissue demonstrating pseudoelastic (May-Newman and Yin 1998) and viscoelastic behaviors (Billiar and Sacks 2000a; Grashow et al. 2006a); nevertheless modeling the valve tissue as an elastic material is currently an accepted practice, primarily due to tissue's low level of viscoelasticity (Grashow et al. 2006b) enabling the valvular tissue to function with little viscous dissipation. With the assumption of elasticity, and the additional assumption that the tissue can be represented as continuous, the material behavior can be described by an elastic strain energy density function. Once energy function is defined, the stress in the tissue can be calculated by taking the derivative with respect to strain. One approach for defining strain energy function is through constructing sum of simple terms expected to give the correct behavior, and then fit constants to the experimental data. Li et al. extended the linear transverse isotropy to nonlinear in order to model aortic valve tissue (Li et al. 2001). May-Newman and Yin constructed a Fung-like exponential strain energy function from the three usual strain invariants and two directional pseudo-invariants (Holzapfel et al. 2000b; Humphrey 2003) for modeling mitral valve leaflet behavior (May-Newman and Yin 1998). Researchers are now able to construct strain energy functions that can describe the complex behavior of biological tissues such as anisotropy, nonlinearity, and nonhomogeneity, all with large deformations. For implementation in FE software, the function must additionally be numerically well-behaved. Some reasonably constructed models for biological tissue have been shown to not possess a necessary feature, namely convexity (Holzapfel et al. 2000b). Once an appropriate energy function has been formulated, it is another matter to implement the model in FE software. A number of examples have been published wherein analytical models for valve tissue are implemented for use in FE simulations. Since the valve leaflets are fairly thin, most researchers have modeled them with shell, rather than three-dimensional, elements (Holzapfel et al. 1996; Klinkel and Govindjee 2002). For these elements, a separate and equally significant effort has been made toward creating a theoretical framework for using shells to model large deformations in general (Dvorkin et al. 1995; Betsch et al. 1996; Basar and Kintzel 2003; Chapelle et al. 2004; Sze et al. 2004; Weinberg and Kaazempur-Mofrad 2006) and developing tools for handling complex material models (Klinkel and Govindjee 2002). Bioprosthetic valves have been modeled with shells having aligned-fiber models (Black et al. 1991; Carmody et al. 2004). Shell models have also been implemented for mitral valve leaflet tissue (Prot et al. 2007), including the effect of changes in thickness (Weinberg and Kaazempur-Mofrad 2006). Currently, the most widely used models incorporate a splayed-fiber model into a shell. This approach has been used successfully in simulating bioprosthetic valves (Sun et al. 2005; Sun and Sacks 2005) and mitral valves in healthy and diseased states (Einstein et al. 2004, 2005a,b). Modeling of valve tissue-scale mechanics has been recently reviewed (Weinberg and Kaazempur Mofrad 2005; Sacks and Yoganathan 2007), and the field continues to progress rapidly. A great deal of effort has gone into the creation of rigorous methods for modeling three-dimensional materials in FE. Sussman et al. have created the mixed formulation commonly used to model arbitrary incompressible materials with three-dimensional finite elements (Sussman and Bathe 1987), Driessen et al. have developed valve tissue models with preferably directed collagen structure (Driessen et al. 2003, 2005), and others have implemented anisotropic and biological material models (Almeida and Spilker 1998; Ruter and Stein 2000).

An approach used widely in modeling other hyperelastic materials and biological tissues but not, to our knowledge, in heart valve mechanics yet, is the unit-cell approach (Bischoff et al. 2002). Unit-cell models base their strain energy functions on the theoretical behavior of a unit cell of entropic chains. While it might be helpful to incorporate cell-scale information in strain energy function, unit-cell models alone are not sufficient to describe complex multiscale behavior of valve mechanics. The most advanced strain energy functions for valve mechanics include fiber splay as well as fiber direction. Such models have been constructed and fit to experimental data for aortic (Billiar and Sacks 2000a,b) and mitral (Einstein et al. 2004) valves. Current research in continuum models for leaflet mechanics aims to create a multi layered model of the tissue with continuum models for each layer. Using existing microdissection techniques (Vesely and Noseworthy 1992), Stella et al. have microdissected different layers of aortic valve leaflet to characterize material properties of each layer through biaxial testing. Based on their results, they have created a model having multiple layers with different splayed-fiber material descriptions (Stella and Sacks 2007). Also drawing from that data, Weinberg et al. have modeled each layer with a continuum model and added the undulated geometry and transversely isotropic behavior for each layer (Weinberg and Kaazempur Mofrad 2007), see Fig. 6. While most existing constitutive models for aortic valve tissue mechanics are continuum-based, in some cases other approaches may be useful. Weinberg et al. have created a discrete fiber tissue model, illustrated in Fig. 7, that is computationally efficient when particularly used in explicit finite element codes such as LS-DYNA (Weinberg and Kaazempur Mofrad 2007).

3.3 Cell-scale

Enabled by the methods for quantifying cell properties, cell-scale models have been developed for heart valve. Recently developed methods to measure cell mechanical properties (Lim et al. 2006) have been applied to heart valve ICs

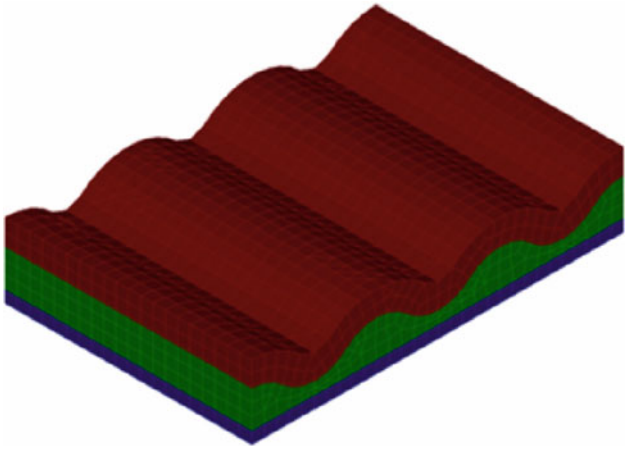


Fig. 6 Geometry of multilayered, undulated tissue model (Weinberg and Kaazempur Mofrad 2007)

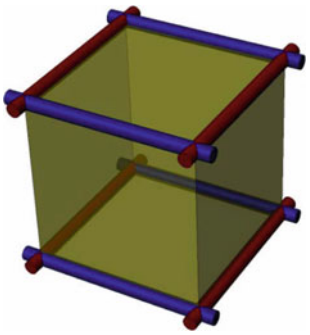


Fig. 7 Single solid element of discrete fiber model for aortic valve tissue (Weinberg and Kaazempur Mofrad 2007)

(Merryman et al. 2006b) whose results indicate IC being probed by micropipette aspiration. Pressure is applied to the cell via the pipette, and cell mechanical properties are deduced from the observed deformations. Two main types of models have been proposed for cell mechanical behavior: Majority of models follow the continuum assumption and describing the cell as some combination of fluid and solid enveloped by the cell membrane (Lim et al. 2006; Mofrad and Kamm 2006), while others take a structural approach, treating the cytoskeleton as the main structural component (Lim et al. 2006; Mofrad and Kamm 2006). Although many groups have reported simulation of organ- and tissue-scale heart valve mechanics over the past three decades, simulation at the cell-scale has been reported only recently and rarely. Huang et al. modeled the deformation of ICs in pressurized valves and compared results to experiment (Huang et al. 2007), see Fig. 8a. Weinberg et al. extended that work to the three-dimensional dynamic deformations (Weinberg and Kaazempur Mofrad 2007) as well as to the pathological conditions (Weinberg and Kaazempur Mofrad 2008).

3.4 Molecular-scale

Relying on the tools developed in the field of molecular mechanics, there have been attempts to model molecular-scale properties of heart valves. Methods for single-molecule mechanics, such as laser traps demonstrated on collagen (Luo et al. 1997) are directly applicable to heart valve matrix components. Imaging capabilities have reached the molecular-level and have recently been applied to examining heart valve leaflet structure. Figure 9 illustrates an image produced by femtosecond laser pulse of the three-dimensional network of collagenous and elastic fibers in the heart valve leaflet (Schenke-Layland et al. 2004). While mechanics at the cell-, tissue-, and organ-scale can usually be described by continuum mechanics, the continuum assumption does not generally hold at the molecular-scale. Molecular dynamics (MD) simulations must be used to analyze molecule-scale interactions. Like in FE analysis, MD has progressed rapidly in the recent years, due in part to advancements in computational capabilities. To the authors' best knowledge, MD simulation techniques have not yet been applied systematically to model heart valve behavior. See Sotomayor for a review on the MD field (Sotomayor and Schulten 2007). Few efforts do exist, however, that are directly applicable. In particular, research is carried out to simulate various aspects of the behavior of collagen fiber on the molecular-scale (Park et al. 2007; Raman et al. 2006, 2008a,b; Salsas-Escat and Stultz 2008).

4 Multiscale modeling approach for heart valve

The heart valves have been shown to function at multiple length-scales as extensively reviewed by Sacks et al. (Sacks and Yoganathan 2007). Describing the heart valve biomechanics in a single length scale, whether organ-, tissue-, cell- or molecular, is not sufficient to capture valve's overall behavior. In order for a heart valve model to describe any arbitrary behavior, the model should incorporate elements from all different length scales.

While many experimental tools are available to investigate the mechanical behavior at each individual scale, few have been developed that span multiple scales. Huang et al. measured the cell-scale deformations in response to pressures applied at the organ-scale (Huang et al. 2007), Merryman et al. measured the tissue-scale mechanical behavior in response to cellular contraction (Merryman et al. 2006a), Mol et al. quantified cell-scale growth mechanisms when engineered-valve is loaded at tissue-scale (Mol et al. 2003, 2005), and Weinberg et al. measured the cellular response to organ-scale shear (Weinberg et al. 2010).

Computational approaches have also been adapted to incorporate various multiscale effects into cardiovascular

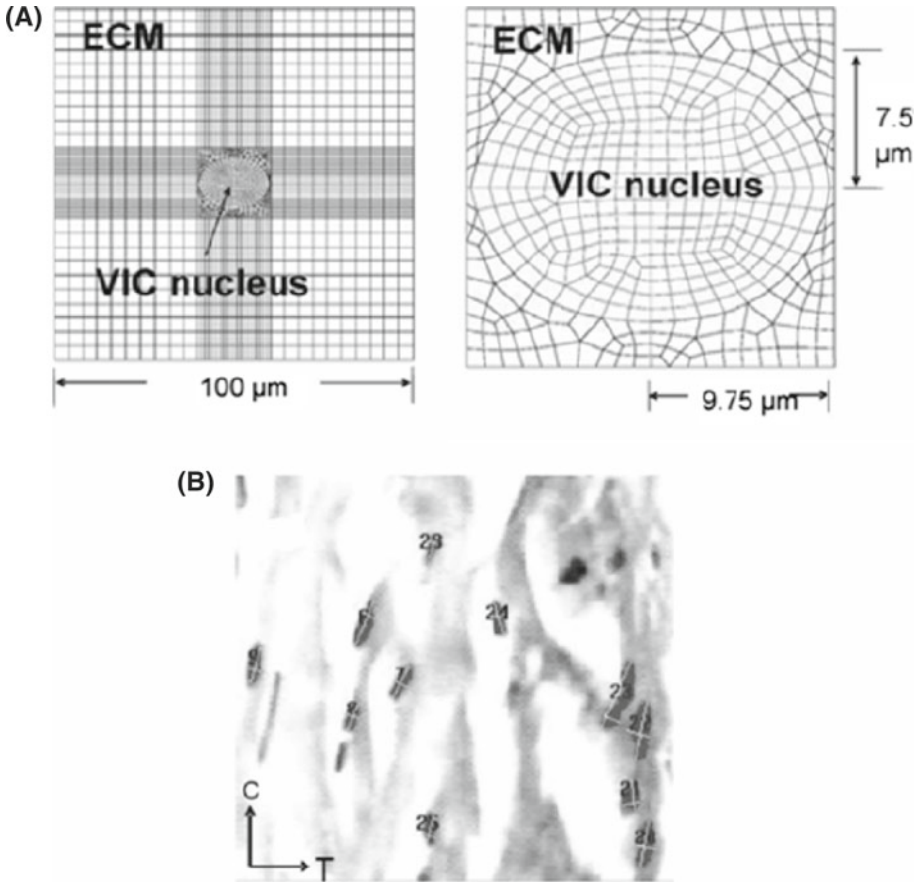


Fig. 8 Theoretical and experimental investigation of IC deformation in valves under pressure. **a** Simulation geometry. **b** Image processing measurement of IC aspect ratios (Huang et al. 2007)

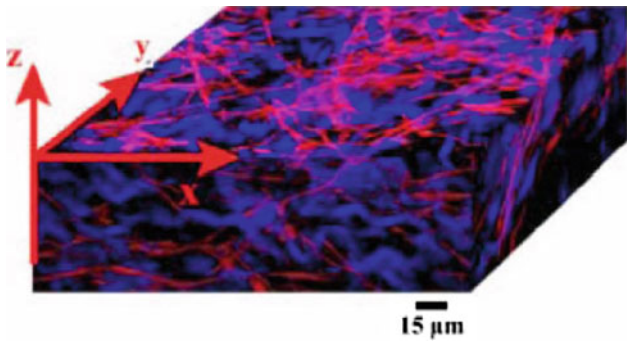


Fig. 9 Three-dimensional reconstruction of ovine aortic heart valve leaflet by femtosecond laser pules. Collagenous fibers are shown in blue and elastic fibers in red (Schenke-Layland et al. 2004)

modeling. Carmody et al. have embedded the valve organ-scale motion to the larger organ-scale motion of the left ventricle (Carmody et al. 2006). Huang et al. have used analytical calculations to link the cell-scale model to pressure applied at the organ-scale, and have notably compared to experimental data with good agreement (Huang et al. 2007). An image from their measurement of IC aspect ratios under pressure is shown in Fig. 8b. Cellular and molecular events have been related to organ-scale physiology in heart left ventricle (Watanabe et al. 2004). Once simulations are created across individual length-scales, new methods are needed to link different scales together. Just recently, few researchers have performed such links for specific cases, such as linking the tissue- and organ-scales in a model of the arterial wall (Stylianopoulos and Barocas 2007) and linking collagen matrix tissue-scale behavior to molecular mechanics (Chandran and Barocas 2007; Katz et al. 2007). Weinberg et al. performed a comprehensive multiscale simulation of heart valve mechanics. They introduced a system of multiple reference configurations set up at different cell-, tissue- and organ-scales, see Fig. 10, with appropriate linkage between scales from top to bottoms (Weinberg and Kaazempur Mofrad 2007). Within this linked framework, illustrated in Fig. 11, they computed organ-scale motion, from which tissue-scale deformations were extracted, and tissue deformation was similarly translated to the cell-scale. The complete effort thus is a dynamic, three-dimensional simulation of AV mechanics spanning the cell-, tissue-, and organ length-scales. The model has been particularly verified with valve experimental data at static case, in which, boundary conditions and deformation were made at organ-scale and the model outcomes were evaluated at cell-scale. This multiscale model has many promising applications in studying valve behavior in health and disease.

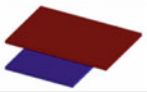
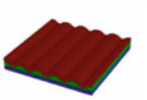
Symbol	Schematic	Description	Extensibilities
Ω_0		unattached layers	fibrosa: $\lambda_C = 1.10$, $\lambda_R = 1.40$ ventricularis: $\lambda_C = 1.20$, $\lambda_R = 1.90$
Ω_1		assembled tissue	fibrosa: $\lambda_C = 1.10$, $\lambda_R = 1.40$ ventricularis: $\lambda_C = 1.20$, $\lambda_R = 1.70$ tissue: $\lambda_C = 1.10$, $\lambda_R = 1.70$
Ω_2		tissue in valve with no external forces applied	tissue: $\lambda_C = 1.10$, $\lambda_R = 1.25$
Ω_3		tissue in valve with baseline pressure applied	tissue: $\lambda_C = 1.05$, $\lambda_R = 1.20$
Ω_t		tissue in functioning valve	tissue, mid-diastole: $\lambda_C = 1.00$, $\lambda_R = 1.00$

Fig. 10 Different reference configurations in multiscale simulation of heart valve (Weinberg and Kaazempur Mofrad 2007)

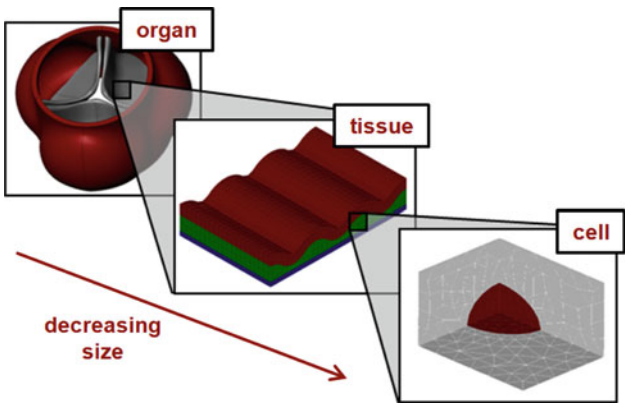


Fig. 11 Linking of multiscale aortic valve mechanical simulations from the organ-scale down to the tissue- and cell-scales (Weinberg and Kaazempur Mofrad 2007)

For instance, the calcific aortic stenosis and aortic stiffening are shown to have initiation and progression factors in different length-scales which can be simulated by this model.

5 Conclusions and future directions

Investigating the health and disease mechanisms in heart valves involves a complex, multiscale, and multidisciplinary process with important clinical outputs. Research in this field has already contributed enormously to patient care, most notably the development of prosthetic and bioprosthetic valve replacements. Simulation of valve biomechanics is a vital tool in improving valve replacement design as well as in increasing our fundamental understanding of valve behavior.

The heart valve has been shown to function at multiple length-scales as reviewed by Sacks et al. (Sacks and Yoganathan 2007). Describing the heart valve biomechanics in a single length scale, whether organ-, tissue-, cell- or molecular-scale, is not sufficient to capture valve's overall behavior. In order for a heart valve model to describe any arbitrary behavior, the model should incorporate elements from all different length-scales.

One key challenge that is common in modeling all biological systems is the fact that these systems are living and actively remodeling. This phenomenon is perhaps more relevant at the cell-scale simulations where the time scale of simulations may be of the same order as those of active response of the cells. Active, remodeling models of cell mechanics are at their infancy (Chandran et al. 2009; Chandran and Mofrad 2010). Modeling heart valve biomechanics at organ- and tissue-scales has been going through generations of refinement over the past three decades; however, it has only been within the past few years that researchers have begun to identify that the need to incorporate the valve mechanics at the cell- and molecular-scale in order to fully appreciate valve biomechanics. Enabled by advances in cutting-edge experimental methods and computational tools in characterizing heart valve properties and behavior in cell- and molecular-scales, further investigations are possible and necessary to bring the smaller-scale simulations to the same level of refinement as the larger-scale models. A number of groups are currently active in developing

experimental tools, numerical methods, and mechanical simulations of heart valves in cell- and molecular-scales (Watanabe et al. 2004; Huang et al. 2007; Sacks and Yoganathan 2007; Weinberg and Kaazempur Mofrad 2007) but the field calls for further investment.

After sophisticated models in each of the length-scales are developed, the next challenge would involve establishing systematic methods to robustly link the single-scale models together. This is an essential step toward developing the multiscale model of heart valve which should be able to describe behavior of valve in any scale caused by behavior of valve at other scales through mechanotransduction (Mofrad and Kamm 2009). Developing the linkage between multiple scales is in its first generation (Weinberg and Kaazempur Mofrad 2007). Except for few attempts, in which specific length-scales have been linked together to study particular multiscale phenomenon (Mol et al. 2003, 2005; Merryman et al. 2006a; Huang et al. 2007; Weinberg and Kaazempur Mofrad 2007, 2008), we are not aware of any model which develops a comprehensive linkage system spanning over multiple length-scales. To the authors' knowledge, Weinberg et al. developed the most comprehensive multiscale model of valve to date, linking organ-, tissue-, and cell-scales (Weinberg and Kaazempur Mofrad 2007). However, their model establishes a unidirectional linkage from organ-scale to tissue-scale and from tissue- to cell-scales and does not yet capture the true bidirectional linkage which can also occur from small scales toward large scales. Major effort is needed to further develop multiscale linkage systems.

Refinement of computational models will surely continue, but to have a significant clinical impact and to increase our fundamental understanding of the heart valves in health and disease, these simulations must be performed in concert with experimental efforts. Recent works combining multiscale modeling with experiment have elucidated the deformation of ICs in response to valve motion (Huang et al. 2007; Weinberg and Kaazempur Mofrad 2007) and the phenotypic expression of ECs in response to blood flow through the valve (Weinberg et al. 2010). Further multiscale, multidisciplinary efforts will similarly increase our ability to understand valve function and treat valve disease.

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