A Model of Health

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Models are crucial in the biomedical sciences since they provide information that is not otherwise accessible and help in discriminating among possible schemes of interpretation of complex phenomena. Italian research teams have been very active in this field with important contributions in the area of heart mechanics, which typically requires sophisticated three-dimensional (3-D) approaches to simulate wall and blood fluid mechanics. These models are increasingly being used to assess the patient-specific pathological scenario and to predict possible therapy outcomes.

Heart failure is considered the disease of the 21st century in the western world, and its etiology, progression, and therapy are still poorly understood.

The most popular numerical approaches are the finite-element model (FEM) and the finite-volume method (FVM), which are used to simulate structures and fluids, respectively. Numerical methods are based on the domain discretization in geometrically simple domains—tetrahedrons, hexahedrons, wedges, or pyramids—each represented by a set of element equations to the original problem (e.g., balance of the momentum), which are then recombined in a global system of equations describing the overall system behavior. FEM was first introduced in the late 1950s for solving structural problems where it was possible to approximate the description of the problem physics to a linear algebraic system; its use was then expanded in the 1970s to include large deformations and fluid dynamics applications, which are intrinsically nonlinear problems. In the 1990s, it was partially replaced by FVM for the analysis of fluid dynamics problems due to an advantage in memory usage and solution speed. FEM and FVM share the ability to visualize or estimate events and physical quantities within a complex 3-D domain that are difficult or impossible to observe or measure.

Due to the inherent complexity of biomechanical problems, the use of numerical modeling methods in this area was particularly attractive, giving rise to a discipline known as computational biomechanics. In Italy, computational biomechanics was first applied to the area of cardiovascular sciences in general and

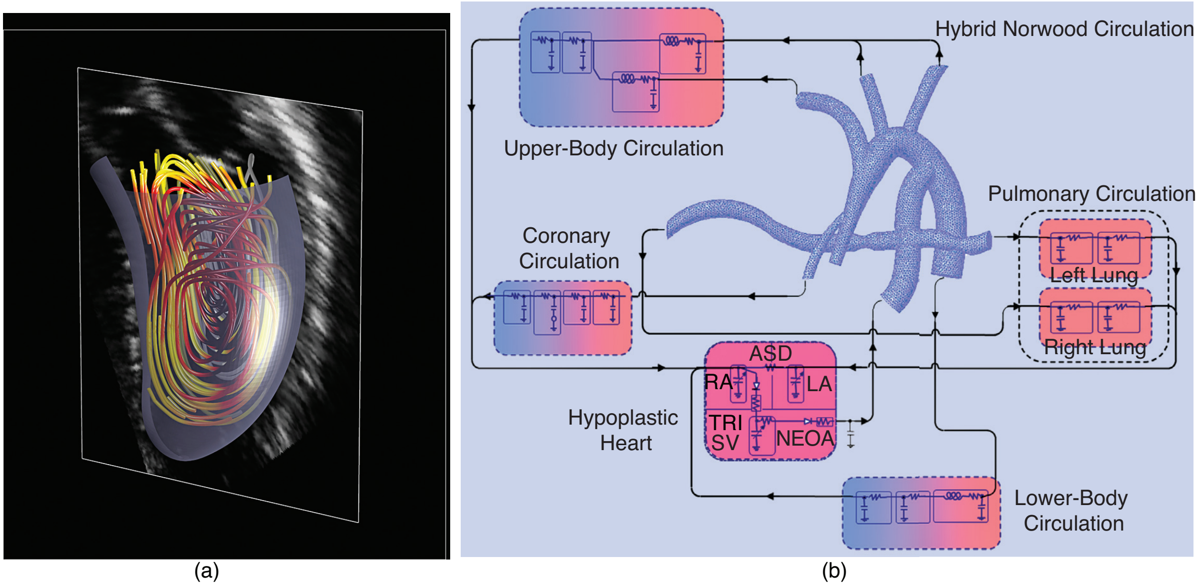

FIGURE 1 (a) Streamlines of blood flowing inside a normal left ventricle at the onset of systole. The streamlines are computed from a velocity field estimated by echographic particle image velocimetry in biplanar echographic acquisition. The flow pattern shows the rotatory motion that developed during diastole and persists to the onset of systole directing the flow toward the outflow track situated on the top left of the image. (Image courtesy of Gianni Pedrizzetti; more info can be found at www.dica.units.it/perspage/gianni/ and in [4]). (b) A multiscale model of the hybrid Norwood circulation where a stent is inserted to open the ductus arteriosus. (Image courtesy of Francesco Migliavacca; more info can be found at modelingventricle.clemson.edu and in [5]. ASD: atrial septal defect; RA: right atrium; LA: left atrium; TRISV: tricuspid stenotic valve; NEOA: neo aorta.

heart mechanics in particular. Since the advent of the heart–lung machine in 1953, Italy has been a pioneer in the development of cardiac surgery, with important contributions in mitral valve repair, valve sparing techniques, ventricular surgical restoration, and aortic valve repair, just to mention a few examples. An Italian company, Sorin Group, is a world leader in cardiopulmonary bypass technologies and a primary competitor in cardiac rhythm management treatment. Computational biomechanics studies were initially developed in the area of ventricular fluid dynamics and left hypoplastic ventricle syndrome, moving in later years to stenting procedures and cardiac valve mechanics. All of these topics will be briefly addressed in the following sections.

The "fil rouge" among these different applications is the need for an accurate replication of the pathological condition and the subsequent simulation of different post-therapeutic scenarios to provide surgeons with support in the decision-making process. This approach, known as personalized health care, is a paradigm based on the detailed comprehension of the pathophysiology of the tissue and/or organ under examination and is aimed at more effective treatment of disease.

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Ventricular Mechanics

Heart failure (HF) affects more than 2% of the adult population in western countries and carries a high mortality rate, about 50% at five years after diagnosis, with morbidity being the most frequent cause of acute hospital admissions in patients over 65. The impact of HF in terms of age-adjusted hospitalization rates and short- and long-term postdischarge mortality is similar to or greater than the six most common cancers combined.

Heart failure is considered the disease of the 21st century in the western world, and its etiology, progression, and therapy are still poorly understood. We cite just two new paradigms in the study of ventricular mechanics in this field: first, the 3-D evaluation of ventricular wall strains to assess regional wall motion and synchronicity with standard in vivo imaging. In particular, it has been proposed that an intrinsically tomographic imaging technique, such as magnetic resonance imaging, can be used to evaluate the regional 3-D strains of the ventricular wall by selecting reference points that are then tracked throughout the cardiac cycle by means of a nearest-neighbor search. The tomographic image is mapped on a 3-D surface, which is classified in terms of longitudinal and circumferential curvatures; the latter are then used to identify the reference point motion frame by frame. Finally, following the rationale adopted in the FEM, their time-dependent displacement is interpolated within predefined wall sectors to obtain the continuous displacement field [1]. This approach yields the full strain tensor. As compared to the in-plane strain data that can be extracted from tagged magnetic resonance imaging (MRI) or echocardiographic images via spackle tracking, which are inherently two-dimensional (2-D), this information is intrinsically 3-D and consistent with the actual deformation modes experienced by the ventricle during the cardiac cycle.

The second paradigm is a new image-based approach—echographic particle image velocimetry (Echo-PIV) in biplanar echographic acquisition—designed to evaluate blood flowing inside the left ventricle (Figure 1); this approach is aimed at providing evidence of a relationship between the abnormal distribution of hemodynamic forces and the long-term adaption of cardiac geometry. Indeed, there is evidence that blood flow may manifest as an early sign of mechanical dysfunction, thus providing an early diagnostic marker for the risk of pathologic progression as well as evaluation of therapeutic options. The proposed method utilizes B-mode harmonic imaging seeded with ultrasound microbubbles contrast agent. Such bubbles are visual evidence of the swirling intracardiac motion, and the images can be processed by Echo-PIV, an echocardiographic adaptation of the particle image velocimetry (PIV) technology long used in fluid dynamics laboratories. Research is now moving in the direction of overcoming two major limitations: 1) the need for injecting microbubbles with preliminary tests, demonstrating a spontaneous signal from the moving blood itself and 2) the inherent 2-D nature of the information recorded, which could be solved by implementing a multiplanar acquisition strategy.

The Hypoplastic Left Heart Syndrome

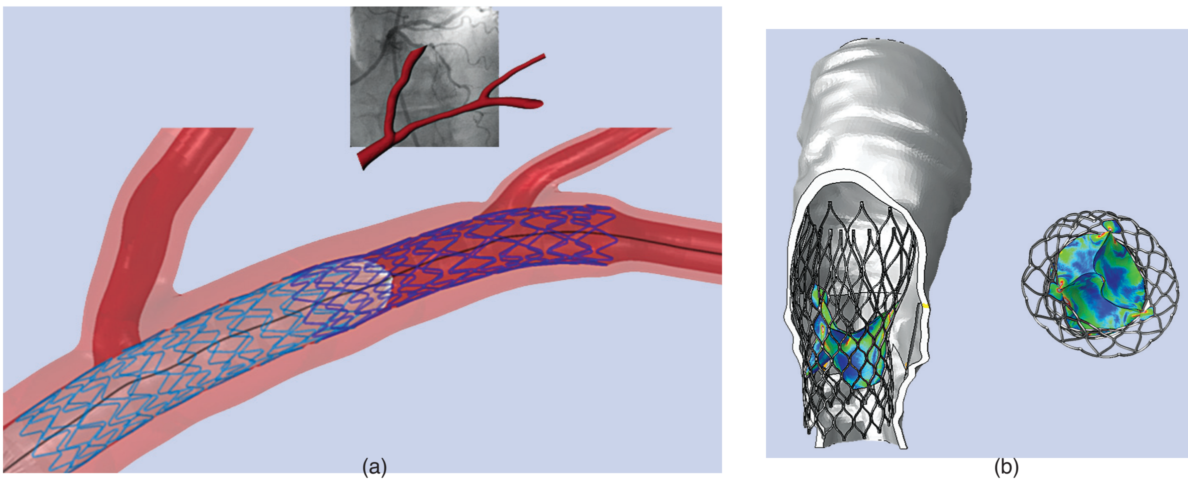
The hypoplastic left heart syndrome (HLHS) describes a spectrum of cardiac abnormalities characterized by marked hypoplasia of the left ventricle and ascending aorta. HLHS accounts for 2–3% of all congenital heart disease, although the overall incidence is likely underestimated because of the indeterminate rate of spontaneous abortions and the elective termination of pregnancy of affected fetuses. HLHS is characterized by atretic, hypoplastic, or stenotic aortic and mitral valves, and atrial septal defects. It is lethal if left untreated, and children must undergo surgery shortly after birth. Currently, the standard surgical approach consists of a series of three operations: the Norwood procedure (stage I), the hemi-Fontan or bidirectional Glenn procedure (stage II, six months after the Norwood procedure), and the Fontan procedure (stage III, 18–36 months after the Glenn procedure).

Numerical modeling can be used to predict local fluid-dynamics changes and to assess the overload of the right ventricle, which feeds both the systemic and the pulmonary circulations.

The surgical repair of congenital heart disease involves significant modifications to the circulatory tree. Resections, reconstructions, and graft insertions significantly impact local and systemic hemodynamics, which may be difficult to foresee or to assess quantitatively by clinical investigation alone.

Numerical modeling can be used to predict local fluid-dynamics changes and to assess the overload of the right ventricle, which feeds both the systemic and pulmonary circulations. The accurate design of vessel reshaping can minimize the energy losses and impact the success of surgery. However, for an accurate prediction, information on two aspects is needed: detailed anatomy, which can now be attained with different imaging techniques (e.g., MRI, computed tomography, and 3-D echo), and inflow and outflow conditions. Indeed, the hemodynamic analysis cannot be localized on the shunt region alone since the effects of the procedure on the whole circulation have to be accounted for to ensure proper coronary perfusion, minimal ventricular volume overload, and pulmonary hypertension.

Consequently, from the original idealized models dating back to the 1990s, the research has been progressively focusing on more realistic 3-D models coupled with detailed closed-loop lumped-parameter models [2] aimed at accounting for the interaction with the entire circulation of the patient (Figure 2). So



(a) (b)

FIGURE 2 (a) Virtual coronary stenting: from medical images to simulations. A longitudinal view, obtained by cutting a portion of aortic root, showing the postoperative configuration of the prosthetic valve. (Image courtesy of Francesco Migliavacca; more info can be found in [6].) (b) A computer-based simulation of a patient-specific transcatheter aortic valve implantation (TAVI) of the Corevalve device by Medtronic. The top view of the implanted device highlighting nonoptimal valve performance due to asymmetric postoperative placement (Image courtesy of Ferdinando Auricchio; more information is available in [7] and [8].)

far, this methodology has been applied extensively to investigate the hemodynamic effects of a central shunt, a modified Blalock–Taussig shunt, a right-ventricle-to-pulmonary-artery shunt, and the hybrid approach, respectively.

Despite the advantages brought by the combined methodology into the study of surgical procedures, hemodynamic outcomes are still hard to predict from a clinical point of view; this is mainly due to the still-poor comprehension of the response of the peripheral circulation to the surgical operation and the complex regulatory mechanisms that intervene in the postoperative scenario. The inclusion of these factors into numerical simulations represents the next challenge in this field.

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Stent Modeling

Coronary artery diseases are the major cause of death when it comes to cardiovascular disease. Transcatheter treatment options, i.e., angioplasty and stenting procedures, are currently the preferred treatments due to their lower invasiveness as compared to coronary artery bypass. However, stenting efficacy is still debated due to some recurring clinical issues affecting the arterial healing process, such as neointimal hyperplasia, in-stent restenosis, and late-stent thrombosis.

In the last two decades, numerical models have been extensively used to investigate stenting procedures from both a structural and a fluid dynamic point of view (Figure 3). Early studies only involved simplified cases and idealized stented arteries. In the mid-2000s, the first computational analyses including stent deployment were published, and the effect of stent deployment on vessel configuration was accounted for. More recently, numerical models have allowed for simulating stent implantation in a realistic coronary anatomy or to simulate the implantation of multiple stents in bifurcations or curved vessels. These advances have led to the ability to tackle those anatomically complex conditions that are still characterized by low clinical success.

To date, we are able to mimic stent implantation, accounting for the simulation of the deployment of realistic models of stents, accounting for both their actual structure and material behavior, into realistic implantation sites. What is still missing is the inclusion of algorithms that are able to predict the long-term outcome of implanted stents by implementing reliable methods for the estimation of fatigue fracture, the simulation of biodegradable stents resorption, the multiscale modeling of in-stent restenosis, and the assessment of the kinetics of drug release from drug-eluting stents.

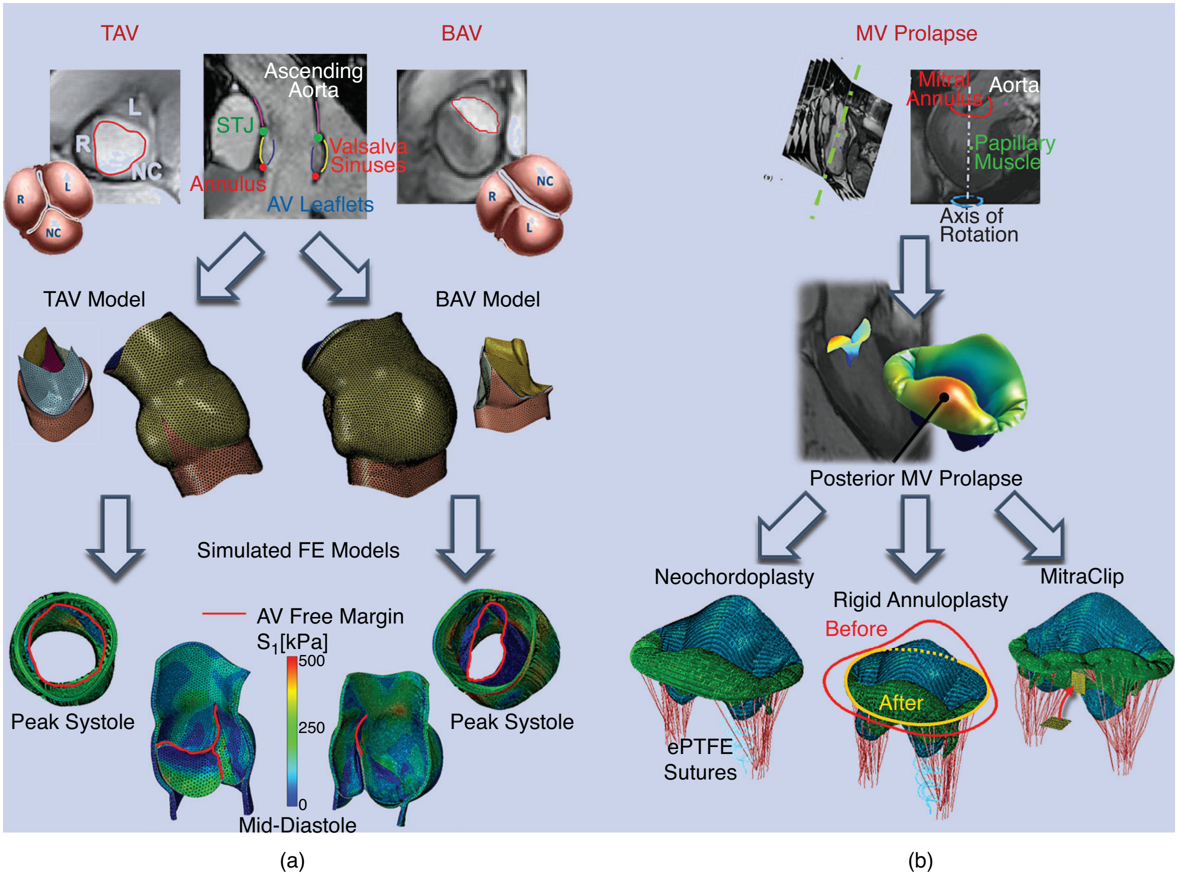

FIGURE 3 A biomechanical evaluation of cardiac valves: (a) a comparison of tricuspid and bicuspid valve behavior and (b) from cardiac imaging to the simulation of three different mitral valve surgical corrections. (Image courtesy of Francesco Sturla; more info can be found in [9].) TAV: tricuspid aortica valve; BAV: bicuspid aortica valve; AV: aortic valve; STJ: sinotubular junction; MV: mitral valve; FE: finite element; ePTFE: expanded polytetrafluoroethylene.

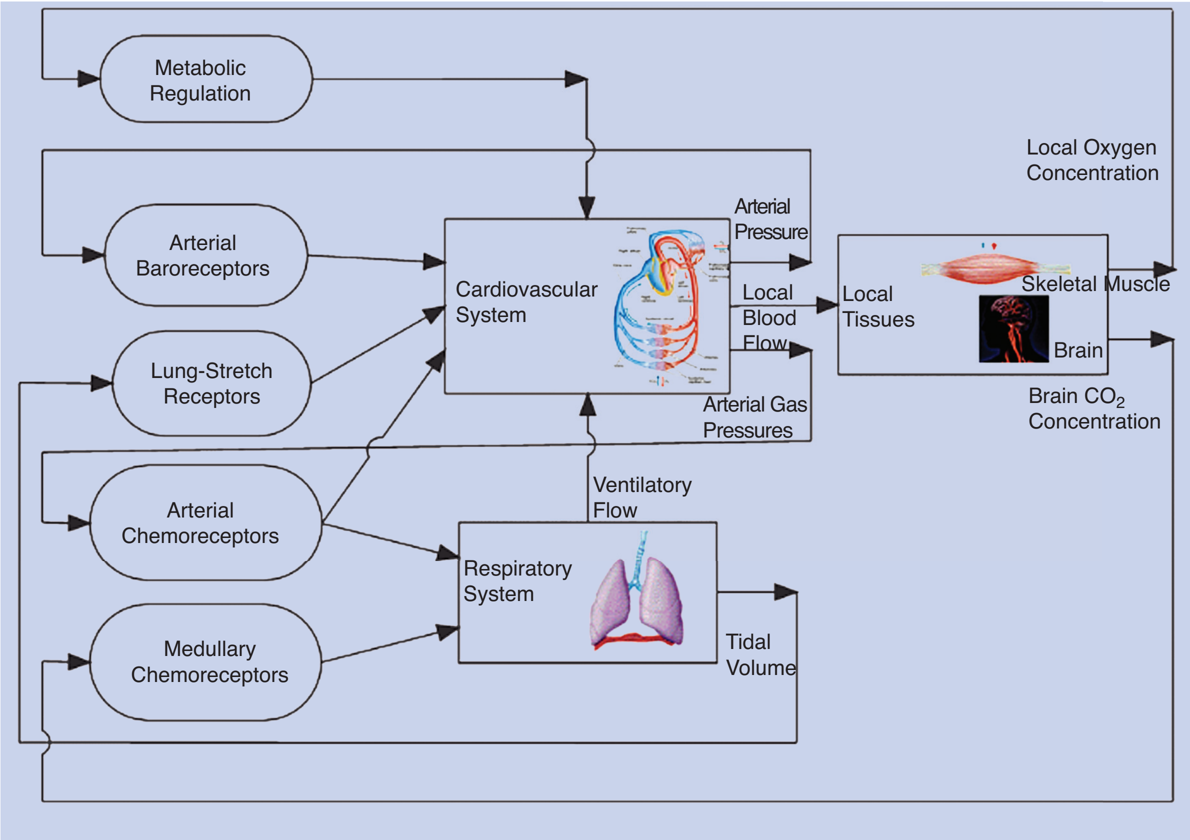

FIGURE 4 The main factors operating in concert in the closed-loop cardiorespiratory system. The controlled system is composed of the heart and vessels, lungs, and peripheral tissues. Several feedback mechanisms operate on it to maintain the vital quantities adequate to metabolism and function CO_2: carbon dioxide.

Cardiac Valve Modeling

Heart valve diseases (HVDs) affect approximately 2.5% of the population with an increasing rate as patients age (U.S. estimations are 13% for the population 75 and older). The majority of HVDs concern mitral regurgitation and aortic stenosis, which are associated with significant morbidity and mortality.

Regurgitant mitral valves are mainly repaired. Repairing techniques include valve leaflet resection to restore the proper shape of the valve leaflets; annuloplasty, i.e., the use of a rigid or flexible ring to reduce the orifice area; the use of artificial chordae in the case of chordae tendineae rupture; and edge-to-edge repair, consisting in suturing the edges of the leaflets at the site of regurgitation (often leading to a double orifice valve). On the other hand, aortic stenosis treatment often requires valve replacement with a mechanical or bioartificial valve, valve-sparing root replacement, which consists in the implantation of an artificial graft while the patient's aortic valve is kept (although it may be repaired and reimplanted), or both. In both cases, the best therapeutic solution to HVDs is still an open issue despite the continuous improvements and the introduction of innovative approaches such as minimally invasive surgery and percutaneous heart valve repair/replacement.

These new approaches can be optimized with the help of numerical tools, particularly for the quantitative assessment of the effects of different therapeutic options. A limitation in the use of numerical tools is that, with respect to other cardiovascular regions, mitral and aortic valves are quite complex structures whose functioning is dictated by the mutual interplay of the different subcomponents. However, advances in image acquisition and processing allow for capturing most of the relevant data. On the other hand, an interesting feature of these valvular apparatuses is that their behavior is mainly dictated by their morphology and by the kinematic boundary conditions (i.e., the mitral annulus and papillary muscle tip motion and the aortic root dilation) rather than mechanical properties in most cases (with the exception of degenerative diseases causing major tissue alteration such as Marfan syndrome and aortic leaflet calcification). Consequently, in the last five years, heart valve patient-specific modeling has evolved from pilot studies testing the possibility to effectively integrate image processing with FE modeling (Figure 4) to the development of tools that exploit the information from routinely adopted imaging modalities that can be systematically adopted to simulate valve function on a patient-specific basis [3].

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These models are proving capable of actually capturing the specific functional defects of prolapsed valves, for example, and can be used to quantify the associated alterations in tissue tensions or the nonphysiological stresses occurring in the congenital bicuspid aortic valve. Moreover, they have successfully been used to predict the effects of heart valve surgical repairs [Figure 4(b)] as in the case of mitral annuloplasty, mitral prolapse correction by means of the edge-to-edge approach, the neochordae apposition, and aortic sparing techniques. In particular, a systematic approach to predict the postoperative performance of implantation devices is particularly useful in the case of minimally invasive transcatheter procedures such as TAVI and the MitraClip approach (an approach resembling the edge-to-edge procedure obtained through the transcatheter plication of the leaflet edges) since it may guide the surgeon in the preoperative decision-making process toward the optimal choice in terms of prosthesis type, size, and positioning for a specific patient.

Conclusions

Recent advances in imaging and image processing techniques, together with increasing computational hardware and software resources, have made possible the realistic patient-specific simulation of complex biomechanical phenomena. Its application to clinical cases, although still not routine, is at least feasible. The major limitations to its use are the resources that would be needed to achieve this digital clinical revolution in terms of personnel, infrastructure, and mentality. However, a major challenge needs to be addressed in the near future related to the long-term evolution of patient status in terms of tissue remodeling, tissue–prosthesis interaction and system response (e.g., other organs adaptation, biochemical, and humoral responses, and sympathovagal response). This scenario is much wider than the biomechanical one and requires a comprehensive data-mining approach that is able to correlate data derived from different and heterogeneous sources to provide the most reliable patient outcome.

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