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# Preface: Innovations and Current Trends in Computational Cardiovascular Modeling and Beyond: Molecular, Cellular, Tissue and Organ Biomechanics with Clinical Applications

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Innovative computational modeling and methods have been developed and widely used in cardiovascular research and beyond. In this special issue, leading experts in their respective areas were invited to present their novel computational models, numerical methods with new and ground-breaking biomedical and clinical applications in ventrical valve mechanics, arteries, aneurysm, medical devices and treatment techniques, as well as microscale studies at cell and molecule levels, and others. Thirteen papers were selected to form this special issue which has 3 parts: Part I included 5 cardiovascular modeling papers. Part II has 4 papers where numerical methods were developed to design, analyze, and improve various medical devices. Part III selected 4 papers with wide applications including eye, ear, endocytosis, and liver. A brief introduction on each paper is given below.

Cardiovascula disease (CVD) is the leading cause of death worldwide. Huge effort has been made in many disciplines including medical imaging, computational modeling, biomechanics, bioengineering, medical devices, animal and clinical studies, as well as genomic, molecular, cellular and organ-level studies seeking improved methods for early detection, diagnosis, prevention and treatment of these diseases. In Part I, Deng et al. [Deng, Huang, Zuo et al. (2018)] employed novel fluid-structure-interaction (FSI) modeling techniques to construct human left ventricle models to investigate mechanisms of systolic anterior motion (SAM) of the mitral valve in hypertrophic obstructive cardiomyopathy (HOCM). Their FSI models could be used to conduct virtual surgery to quantitatively determine the optimal surgical procedures. Wang et al. [Wang, Wang, Li et al. (2018)] used Dupler-ultrasound to measure human volunteer's carotid diameter and flow rate before and after 30 min exercise. These data were used to construct computational fluid dynamics (CFD) model based on idealized human carotid geometry to study the impact of exercise on carotid wall shear stress (WSS) which is believed to be an important risk factor for cardiovascular diseases. Their numerical results demonstrated that acute exercise significantly increases the magnitudes of blood flow rate and WSS. Moreover, the vessel elastic deformation is a non-negligible factor in the calculation of the WSS induced by exercise. Enhanced external counterpulsation (EECP) is a technique with which doctors use special device to apply external pressure to lower part of patient's

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body (legs, for example) to force more blood to return to the heart to treat myocardial ischemia. However, the underlying mechanisms regarding why this technique is effective in treating myocardial ischemia remains unclear. Chen et al. [Chen, Li, Yang et al. (2018)] used 3D coronary models with different stenosis rates and coupled with a 0-dimensional (0D) lumped parametric model of the blood circulatory system to study the hemodynamic response of the coronary artery. Their findings could provide guidance for clinicians to adjust EECP treatment mode according to patient stenosis severities. Since fractional flow reserve (FFR) is getting accepted in clinical practice as a primary indicator for myocardial ischemia risk, Wang et al. [Wang, Wang, Li et al. (2018)] presented a fast simulation method to estimate FFR value of a coronary artery based on resistance boundary conditions. This simulation method can quickly and accurately assess the influence of coronary stenosis to aid clinicians in their diagnoses. For aneurysm treatment techniques, Mu et al. [Mu, Chi, Ji et al. (2018)] examined the influence of clip locations on hemodynamic factors in patient-specific anterior communicating artery (ACoA) aneurysms with different aneurysmal angle. Their results could preoperatively give useful information for clinicians to optimize their surgical plans.

One important area of computational modeling applications is medical device design, improvement and optimizations. Pan et al. [Pan, Chang and Fu (2018)] performed CFD analysis of shroud design on hemodynamic performance and blood damage in a centrifugal blood pump. Patients with extracorporeal membrane oxygenation suffers from high rates of complication that linked to the flow field within the blood pump. It is essential to optimize the geometry of the pump for improved outcome. They made ten different shroud designs and divided those into two groups according to different covering locations Detailed computational fluid dynamics (CFD) analyses were performed to investigate their effects on hemodynamics and hydraulic performance at the constant flow condition. CFD simulations predicted optimized designing parameters for pump head, hydraulic efficiency, fluid volume, shear stress threshold values and modified index of hemolysis (MIH) with increasing shroud covering proportions from 0 to 1 in the same covering location. Liu et al. [Liu, Liu, Gong et al. (2018)] performed numerical analyses of idealized total cavopulmonary connection physiologies with single and bilateral superior vena cava assisted by an axial blood pump. This paper evaluated the hemodynamic performance of an axial flow blood pump surgically implanted in idealized total cavopulmonary connection (TCPC) models. This blood pump was designed to augment pressure from the inferior vena cava (IVC) to the pulmonary circulation. Their modeling study demonstrated that the pump supported bilateral SVC surgical scheme in balancing flow distribution and reducing the risk of endothelial cell destruction and trauma generation.

Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support (ECLS), is an extracorporeal technique of providing prolonged cardiac and respiratory support to persons whose heart and lungs are unable to provide an adequate amount of gas exchange or perfusion to sustain life. Although pulsatile ECMO, as a novel ECMO, has attracted more attention recently, the differences of the hemodynamic effects of the pulsatile ECMO on the aorta, the cerebral perfusion, and left ventricular work are still under-investigated. Zhang et al. [Zhang, Qian, Zhang et al. (2018)] designed three ECMO support models, named as “constant flow mode”, “co-pulse mode” and “counter pulse mode" to clarify the hemodynamic differences of the cardiovascular system between the pulsatile and non-pulsatile VA ECMO. Their detailed comparisons indicated that ECMO under counter pulse mode could have advantages for the left ventricular unloading. In contrast, the ECMO under co-pulse mode has more benefit for cerebral oxygen perfusion.

Coronary artery bypass grafting (CABG) is a common technique to treat coronary stenosis when the vessel is severely blocked. Graft's poor instant patency may lead to an abnormal hemodynamic environment in anastomosis, which could further cause graft failure after the surgery. Zhao et al. [Zhao, Mao, Liu et al. (2018)] investigated graft hemodynamics with different instant patency, and explored its effect on graft postoperative efficiency. They conducted simulations comparing blood flow characteristics between saphenous vein (SVG) grafts and left internal mammary artery (LIMA) graft. Detailed comparisons for back flow, wall shear stress and oscillatory shear index (OSI) were provided.

The coverage of the special issue include other modeling applications. Cell biology plays an important role in disease development. To investigate mechanical strength and structural basis of $\beta_2$ integrin to mediate neutrophil accumulation on liver sinusoidal endothelial cells.

Li et al. [Li, Zhang, Li et al. (2018)] compared the dynamic force spectra of the binding of $\beta_2$ integrin to intercellular adhesion molecule-1 (ICAM-1) on LSECs using atomic force microscopy (AFM) and performed free and steered molecular dynamics (MD) simulations to analyze their structural bases of LFA-1- or Mac-1-I-domain and ICAM-1-D1 or D3 pair in their force spectra. For drug delivery application, Liu X. et al. [Liu, Liu, Gong et al. (2018)] performed numerical study of passive receptor-mediated endocytosis of nanoparticles to investigate the effect of mechanical properties of nanoparticle, receptor-ligand bonds and cell membrane. Their results showed that passive endocytosis may fail due to the rupture of receptor-ligand bonds during the wrapping process, and the size and rigidity of nanoparticles affect the total deformation energy and the terminal wrapping stage. The success of passive endocytosis also depends on the maximum strength of the receptor-ligand bonds.

One area this issue covered is eye disease. Glaucoma is a series of ocular diseases with the main clinical symptoms of ocular hypertension and can lead to blindness, which is seriously harmful to the health of the affected patients. It is difficult to accurately obtain hydrodynamic parameters of aqueous humor within the trabecular meshwork outflow pathways based on the current technology. Zhang et al. [Zhang, Qian, Zhang et al. (2018)] perfromed FSI simulation to study the pressure difference and velocity in the superficial trabecular meshwork, juxtacanalicular meshwork (JCM) and Schlemm's canal in response to JCM permeability changes. Their study indicated that the fluid dynamics parameters in trabecular meshwork and Schlemm's canal could be considerably affected by the changes of JCM permeability. The study also demonstrated that the finite element modeling of AOS could provide a practical means for studying the outflow dynamics and the biomechanical environment of the AOS. Another coverage of this issue is ear disease. A three-dimensional numerical model of the membranous labyrinth of the semicircular canal of the inner ear was established to investigate the effects of canalithiasis of benign paroxysmal positional vertigo (BPPV) on the balance function of the inner ear. The movement of otolith particles in the membranous labyrinth was simulated when a person turns his head to a specific position. The effects of otolith movements on the balance function of the inner ear were simulated for different numbers, diameters, and initial positions of otoliths [Yu, Wang, Guo et al. (2018)]. The simulation results show that the otolith diameter affects the movement duration of otoliths in the membranous labyrinth. The number and diameter of otoliths, the diameter of the membranous labyrinth, and the initial position of the otoliths can cause changes in the pressure difference on both sides of the cupula of the crista ampullaris (cupula).

The current trend in computational modeling is getting closer to realistic and practical applications. Researchers from clinical front, imaging, enginerring, modeling, cell and molecular biology, and genomics are getting together to form collaborative forces to tackle problems which seemed to be impossible not very long ago and are getting encouraging new discoveries and findings. This special issue is only a limited refelction of the trend and we are looking forward to more exciting contributions from the authors and researchers from all the channles in the coming years.

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