PERSONALIZED CARDIOVASCULAR MODELING FOR MEDICAL DEVICE EFFICACY, DRUG SAFETY, AND CLINICAL GUIDANCE

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SUMMARY

Cardiovascular disease is the leading cause of death in developed nations and imposes a high socioeconomic cost. In 2014, Dassault Systemes launched the Living Heart Project to harness the power of realistic simulation to tackle the problem of cardiovascular disease. The cornerstone of the project is the Living Heart Model (LHM), an anatomically and physiologically realistic model of a human heart that can be used for in silico diagnosis and treatment of cardiovascular disease. In this paper, we describe applications of the model in medical device design, drug safety, and patient care.

1: The Human Heart: A Multiphysics-Multiscale Challenge

A realistic model of the human heart must account for both its anatomical and physiological characteristics. The LHM is constructed from real patient image data and contains anatomical details necessary to accurately model cardiac hemodynamics and device-heart interactions. From a functional viewpoint, the heart can be considered as a pump wherein blood flow is driven by myocardial contractions and in turn influences cardiac motion. The timing and magnitude of the contractions are controlled by waves of electrical excitation that travel across the heart. To account for these physiological phenomena, the LHM uses a multiphysics framework to simulate the dynamic structural, fluid, and electrical behavior of the heart. Pathological conditions can be modeled by modifying the material coefficients, changing the loads and boundary conditions, or adding user-defined material models to simulate complex phenomena such as tissue growth and remodeling.

A fluid network is used to represent blood flow between the heart chambers and through the external circulation. It is implicitly coupled with the structural model and calibrated such that clinically relevant metrics are within their published ranges. Users may modify local vascular compliances and resistances to simulate exercise, hypertension, and other physiological or disease states. While the blood flow network model is computationally efficient and adequate for many applications of practical interest, there are situations in which a spatially resolved (3D) blood flow model is required. The LHM can be augmented to include 3D blood flow representations if required. Bidirectional fluid-structure interaction (FSI) with both “traditional” Navier-Stokes solvers as well as with “meshless” Lattice-Boltzmann solvers is enabled; users may choose a flow solver based on the specific application and the degree of accuracy required.

Tissue electrical response is characterized by an action potential whose spatiotemporal evolution is governed by both extrinsic (global) and intrinsic (biochemical) variables. In many cases of practical interest, it is common to modify the extrinsic variables (e.g., heart rate, conduction blocks) to study their effects on cardiac function and device efficacy, while holding the biochemical variables constant over the duration of the simulation. However, to study some types of arrhythmias, it may be necessary to model the evolution of the biochemical variables explicitly. The LHM allows the mechanistic modeling of cellular electrophysiological dynamics and uses a multiscale framework wherein cellular dynamics can affect and be affected by organ level phenomena.

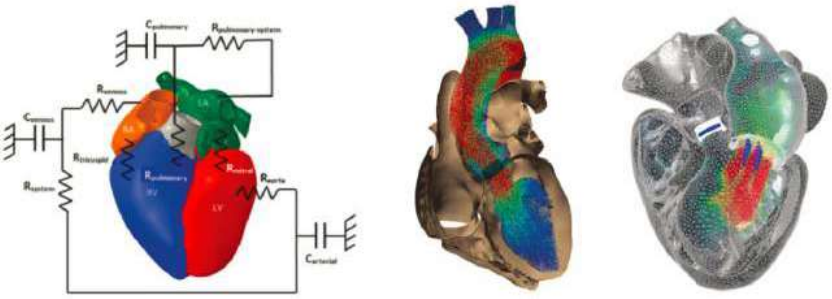

Figure 1: Blood flow network model (left), 3D FSI using SPH (center) and Co-simulation with FlowVision (right)

2: Medical Devices: Including the Patient in the Design

Medical devices for cardiovascular applications have to perform effectively, reliably, and safely in unpredictable conditions. Moreover, the high variability among patients means that, even when the underlying disease is the same, a device that works well for some patients may prove ineffective or unsafe for others. The LHM is specifically designed to facilitate the development of population or patient-specific computational models that better represent real-world variability. In some case, patient-specific image data can be used to determine the region of the heart that is affected. Alternatively, the parameters governing cardiac behavior can be adjusted such that the modified model is able to reproduce specific clinical metrics.

Having represented the underlying disease state, device makers can then simulate the interaction of a new device with the diseased heart. Multiple device design modifications can be made until an optimal design is identified. Moreover, to account for real world variability, rather than using a single diseased heart model, multiple diseased models can be generated that collectively represent the target patient population. This methodology can be used to further optimize the device design, or to produce multiple designs each of which is best suited to a subset of the target patient group. We discuss a methodology to facilitate such analyses.

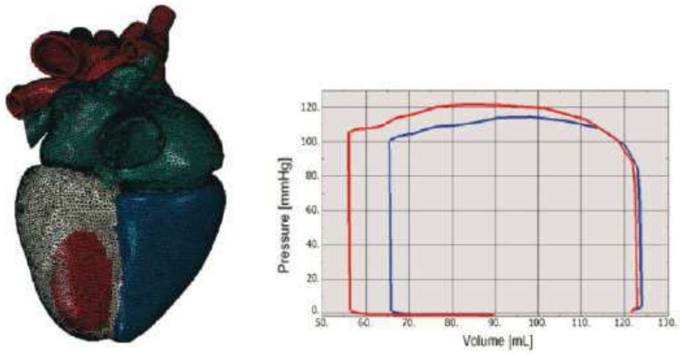

Figure 2: LHM with myocardial infarction (left) and resultant reduction in cardiac ejection fraction (right)

3. Pharma/Biotech: Drug Safety from Cell to Organ

Cardiac arrhythmia can be a potentially lethal side effect of drug action on the human body. Before a new drug is approved, pharmaceutical companies must assess the risk of arrhythmia posed by the drug. Current early stage safety assessment protocols are unable to accurately predict the effect of a drug on real 3D hearts. The LHM provides a foundation for virtual safety studies that can offer mechanistic insight into drug action at the cellular and organ levels.

To enable this functionality, we developed computational models of single cardiac cells capable of modeling the activities of individual ion channels that determine the electrical activity of the heart as a whole. These models were introduced into the LHM to simulate how changes at the cellular level affect macroscopic electrical behavior at the whole heart level. Next, the parameters governing the activities of ion channels were modified and the enhanced LHM was able to correctly simulate the spontaneous onset and propagation of abnormal electrical patterns characteristic of arrhythmia. We discuss the methodology and results of this effort.

4. Patient Care: Virtual Surgery guides the Real

Hypoplastic Left Heart Syndrome (HLHS) is a condition in which the neonatal left ventricle and aorta are underdeveloped, and is invariably fatal if left untreated. Treatment typically involves reconstruction of the aortic arch to restore systemic and coronary oxygenation. However, there is no consensus on optimal arch reconstruction. This means that clinicians must rely almost entirely on intuition for critical surgical decisions. To overcome these challenges, we are working with clinical teams in to leverage the methods used to build the LHM to help HLHS patients.

Pre-operative MRI data was used to construct a patient-specific anatomical model. Geometry morphing tools were then used to define the design envelope of the reconstructed arch with guidance from cardiac surgeons. The model was then subjected to a steady state CFD analysis. Having established a baseline solution, topology optimization was then used to identify the shape of the aortic arch that minimizes overall pressure loss while maximizing coronary perfusion. Once the optimal arch geometry was selected, it was used to create a 2D stencil for use during the actual surgery.

Exploring treatment alternatives on the 3DEXPERIENCE platform

Flow simulation to determine best treatment option

2D shape of optimized virtual graft used as surgical template

Figure 3: Process for blood flow simulation guided reconstruction of aortic arch

5: Conclusion

The applications discussed here demonstrate that in silico personalized healthcare is now within our reach and that it requires several important elements – a diverse ecosystem of experts contributing their knowledge and skills, high performance simulation tools capable of modeling the multiphysics-multiscale nature of the human body, modern data science techniques to manage complexity and reduce uncertainty, and novel visualization and interactive settings to expand participation from specialists to everyone. In bringing together these key ingredients, the Living Heart is helping make personalized heath care a reality.