

BENCH MARK

January 2018 issue ...

- Near-Future Directions of Multiscale & Multiphysics Modeling & Simulation
- Personalized Healthcare in the Age of Simulation
- Co-simulation - Art or Science?
- Large Deformation of Rubber Sleeves in Valves Using Strongly Coupled Fluid-Structure Interaction
- Multiphysics Analysis of Lithium Ion Battery
- What is The Functional Mock-up Interface?
- Aero-Vibro-Acoustics for Wind Noise Applications
- An Introduction to Multiphase Flow Modelling
- Why do I need Multiscale Modeling?
- Multiphysics of Sloshing in the Nuclear Industry
- Benchmarking Accuracy and Parallel Performance of an Open Source Framework for Fluid Structure Interaction Problems
- Building the Credibility of Engineering Simulation in Aerospace
- Co-Simulation - What is it?
- Excel for Engineers and other STEM Professionals

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Bringing it all Together
Multiphysics, Multiscale & Co-Simulation

Personalized Healthcare in the Age of Simulation

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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. This model is now available on the cloud and is delivering the power of multiphysics-multiscale simulation to medical device makers, pharma companies, and clinicians, and in doing so, democratizing simulation and making personalized healthcare a reality.

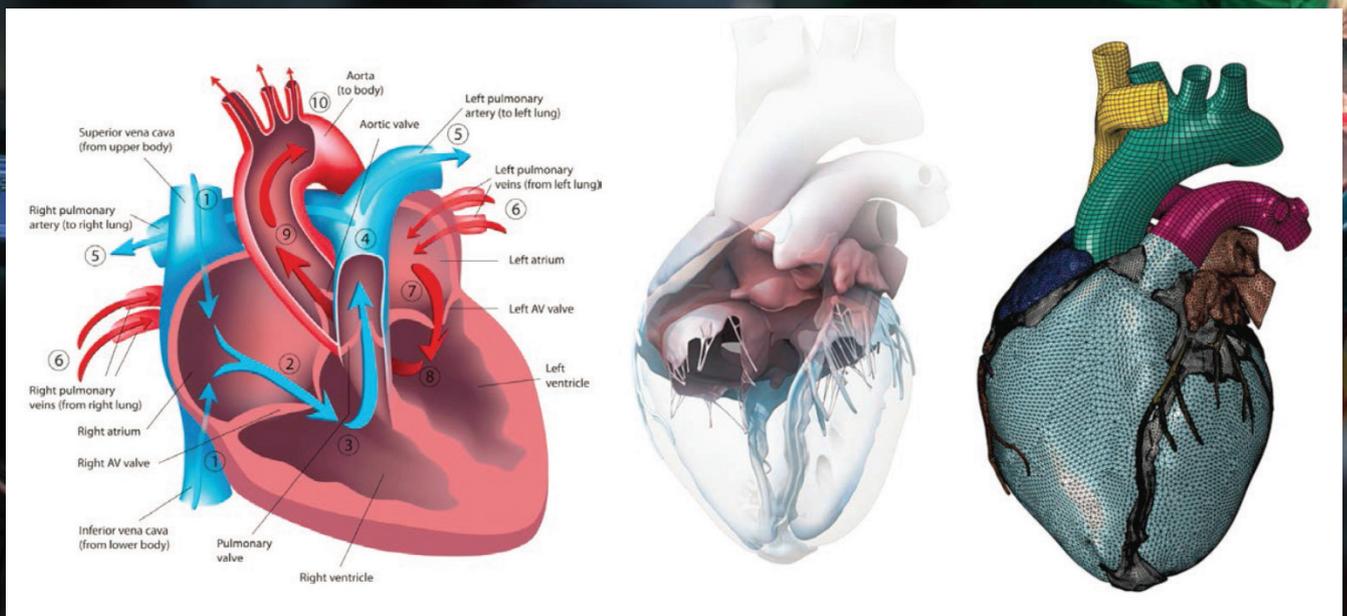


Figure 1: Schematic of human heart (left), cardiac geometry used to create the LHM (from Zygote Media Group) [center]; FE mesh representation of LHM (right)

The Human Heart: A Multiphysics-Multiscale Simulation 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 well-defined anatomical details of internal (e.g., heart valves) and external (e.g., aortic arch) structures that are necessary to accurately model cardiac hemodynamics and device-heart interactions, as well as microstructural features such as continuously varying muscle fiber orientations that strongly influence the dynamic behavior of the heart. 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. The structural behavior of cardiac tissue includes both passive and active components. Passive tissue response uses an anisotropic hyperelastic formulation while active tissue response uses a time-varying elastance model to account for the excitation-contraction coupling. 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 1D 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 (e.g., PV loops) 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. For example, artificial heart valves must not only exhibit stable structural contact with surrounding tissue, but must also generate blood flow patterns that resemble those seen in healthy hearts to prevent cardiac remodeling, tissue damage, and other unintended consequences. 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. For intermediate levels of accuracy and run time, smoothed particle hydrodynamics (SPH) can be an attractive alternative as it can handle complex cardiac phenomena such as flow pinching (heart valves) and requires minimal fluids modeling expertise.

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. In addition to a 3D conduction model for bulk tissue behavior, the LHM also includes electrically important 1D anatomical features (e.g., the Purkinje fiber network) to generate physiologically realistic propagation patterns. In summary, The LHM is an adaptable multiphysics-multiscale framework for cardiac simulation that can facilitate the diagnosis and treatment of cardiovascular disease. We now describe how this technology is being applied in medical devices, pharma/biotech, and patient care.

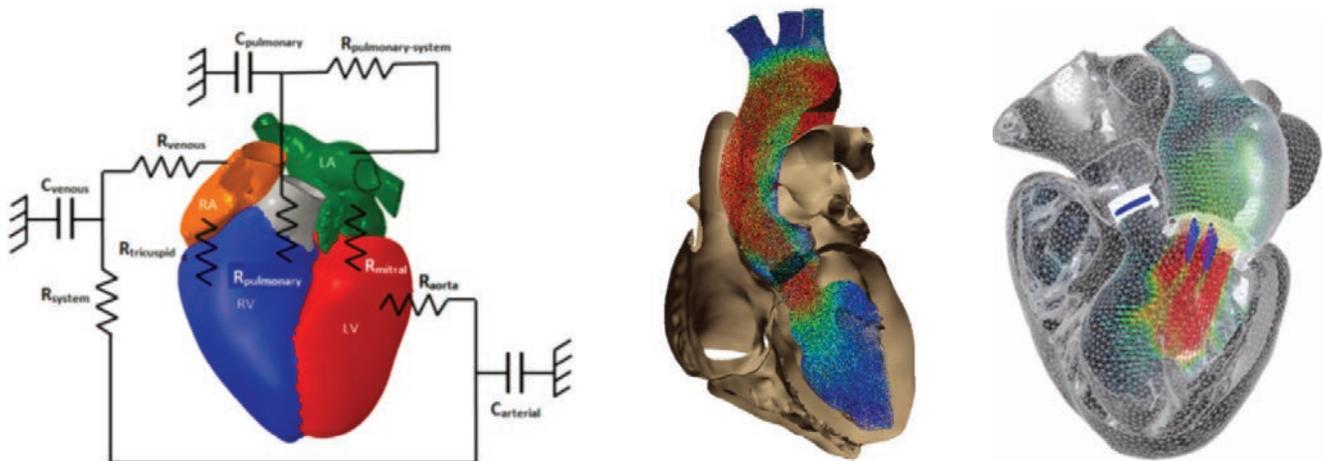


Figure 2: 1D blood flow model in the LHM (left); 3D FSI using SPH (center) and cosimulation with Flow Vision (right) for simulating the hemodynamic characteristics of artificial heart valves

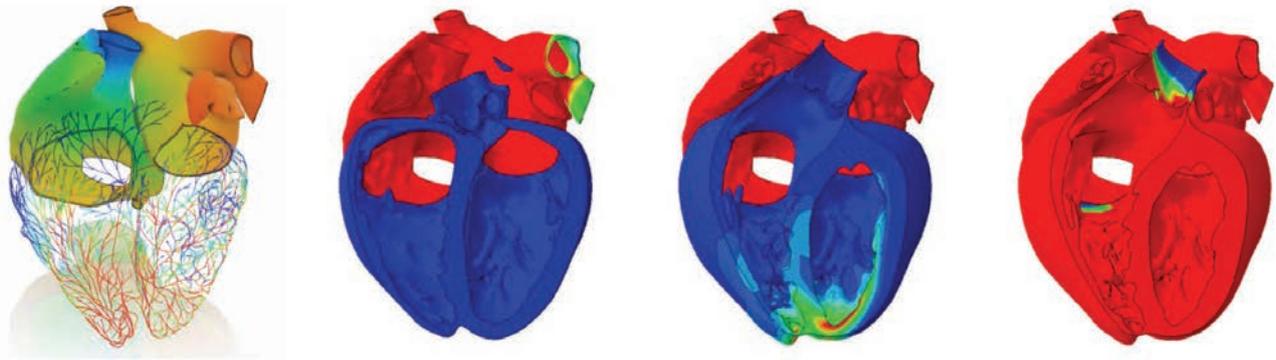


Figure 3: Purkinje fiber network in the LHM (left); electrical potential at various times over the cardiac cycle (right): maximum (red) = 20mV; minimum (blue) = -80mV

Medical Devices: Including the Patient in the Design

Medical devices for cardiovascular applications have to perform effectively, reliably, and safely in unpredictable conditions to win regulatory approval and meet the exacting standards of today's healthcare industry. Currently, designing a device capable of meeting these rigorous criteria involves high costs, long development times, and a certain degree of luck. Moreover, the high variability among heart 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. Consequently, there is much interest in moving away from one-size-fits-all solutions to designing and selecting devices based on a specific patient's anatomical and physiological characteristics. The LHM is specifically designed to facilitate the development of population or patient-specific computational models that better represent real-world variability.

The LHM can be adapted to recapitulate a known disease state in two complementary ways – disease-specific and patient-specific. In some cases, patient-specific image data may be available that can be used to determine the region of the heart that is affected (e.g., the location of a myocardial infarction or heart attack). Alternatively, the parameters governing cardiac electrical or mechanical behavior can be adjusted such that the modified model is able to reproduce specific clinical metrics (e.g., cardiac output, ECG patterns, etc.). However, this is a nontrivial task since the physical underpinnings of heart disease are poorly understood and brute force approaches can be computationally prohibitive.

To mitigate this problem, we have developed a cardiovascular (CV) systems model that reproduces key structural and hemodynamic characteristics of the LHM, yet runs in matter of seconds. Using this model, it is possible to conduct systematic multi-parameter modifications to match patient or disease-specific metrics. Once the relevant systems parameters are determined, they can be translated into appropriate

material coefficients and boundary conditions for the LHM thereby allowing the model to be personalized. In the example below, this methodology was used to introduce a myocardial infarction into the LHM based on patient-specific image data; the model parameters were then tuned to match relevant clinical metrics.

Having represented the underlying disease state, device makers can then simulate the interaction of a new device with the diseased heart, thereby gaining actionable insight on the influence of the heart on the device and vice versa. Multiple device design modifications can then be made until an optimal design is identified. Moreover, to account for real world variability, rather than using a single diseased heart model (based on a specific or average patient), 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. Such virtual patient studies are currently being conducted and are expected to revolutionize the design, testing, and deployment of medical devices in the near future.

Pharma/Biotech: Drug Safety from Cell to Organ

Cardiac arrhythmia can be a potentially lethal side effect of drug action on the human body. During this condition, the electrical activity of the heart becomes chaotic and circulation of blood through the body is compromised. 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; as a consequence, many potentially efficacious compounds never make their way to the market. The LHM provides a foundation for virtual safety studies that can offer mechanistic insight into drug action at the cellular and organ levels.

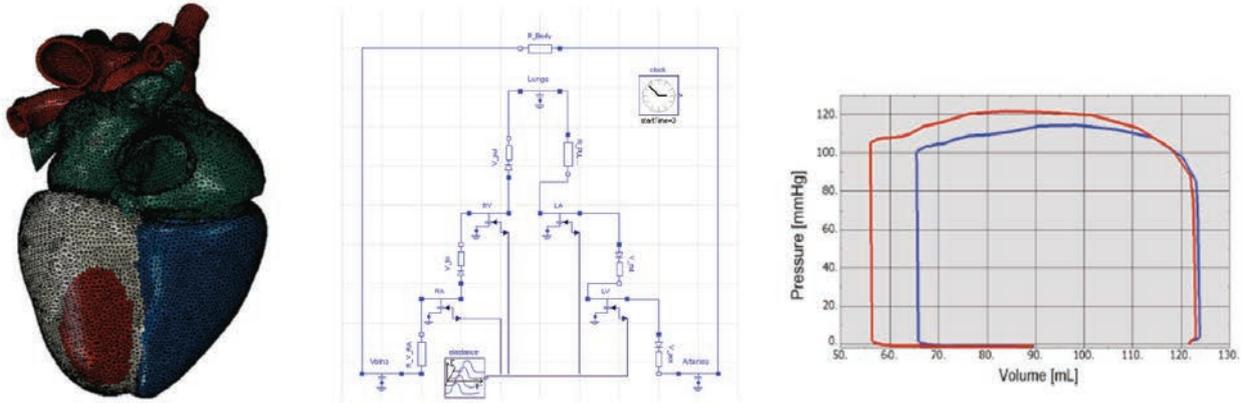


Figure 4: LHM with myocardial infarction in left ventricle (left); CV systems model in Dymola (center); modified clinical characteristics showing reduction of ejection fraction from 55% (red) to 45% (blue) (right)

To enable this novel functionality, members of the Living Matter Lab at Stanford University developed computational models of single cardiac cells capable of modeling the activities of individual ion channels (e.g., Na^+ , K^+ , Ca^{2+}) that determine the electrical activity of the heart as a whole. After verifying the accuracy of these single cell models for various types of cardiac tissue, they were introduced into the LHM to simulate how changes at the cellular level affect macroscopic electrical behavior at the whole heart level.

The first challenge for this enhanced, multiscale LHM was to reproduce the normal whole heart electrical propagation patterns and ECG traces. Next, the parameters governing the activities of ion channels were modified using published data for various drugs, and the enhanced LHM was able to correctly simulate the spontaneous onset and propagation of abnormal electrical patterns characteristic of arrhythmia. The enhanced LHM uses a large number of elements (~10 million) to maintain global spatial accuracy as well as around 250 million internal variables to track local ionic current fluctuations. Moreover, as the concentration of a drug can significantly affect ion channel behavior, it is necessary to conduct multiple simulations with different drug dosage scenarios to determine the full toxicity profile of the drug. Both the multiscale LHM framework and the availability of inexpensive HPC resources are therefore critical to practical application of this

methodology, for instance, to guide early stage drug discovery or to interpret 1D clinical data in the context of the whole 3D organ. As in the previous case, it is also possible to develop patient or population-specific cellular profiles from genomic data and other sources. Future work in this area will focus on these personalization aspects.

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 a series of surgical procedures that enable the right ventricle to assume complete circulatory control and a critical step is the reconstruction of the aortic arch to restore systemic and coronary oxygenation. However, there is no consensus on optimal arch reconstruction and neonates often exhibit unique cardiac anatomies. This means that clinicians must rely almost entirely on intuition for critical surgical decisions. While modeling and simulation can provide valuable guidance, few clinicians possess the necessary knowledge or tools. In an effort to overcome these challenges, we are working with clinical teams in Belgium and Germany to leverage the methods used to build the LHM to help HLHS patients.

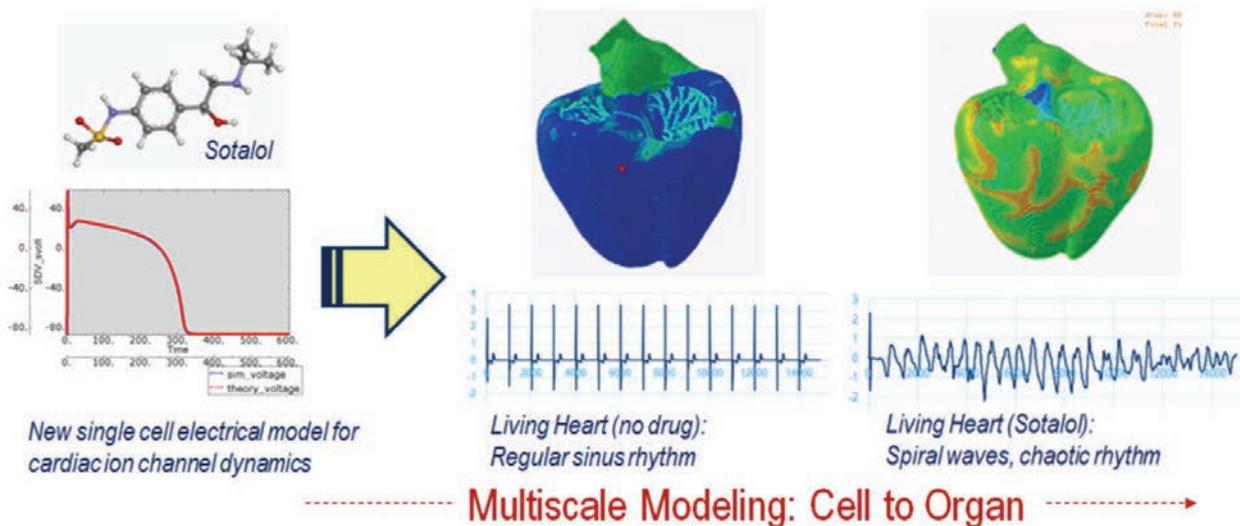


Figure 5: Multiscale framework enabling the development of cellular dynamic models and their coupling to the LHM

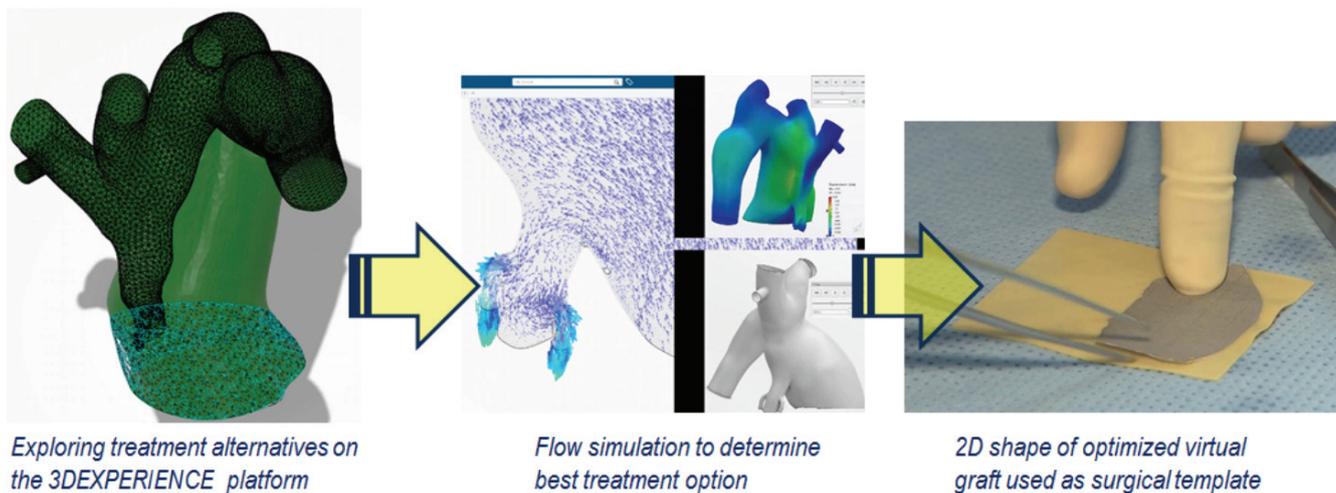


Figure 6: Process for blood flow simulation guided reconstruction of the aortic arch for HLHS patients

Pre-operative MRI data was used to construct a patient-specific anatomical model using segmentation and geometry clean-up techniques similar to those used to create the LHM. Geometry morphing tools were then used to define the design envelope of the reconstructed arch with guidance from cardiac surgeons on sizing and maneuverability. The model was then subjected to a steady state CFD analysis using ultrasound data for inlet mass flow rate and a distribution of outlet mass flow rates based on literature data. 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 flattened 2D stencil for use during the actual surgery. Having demonstrated the feasibility and ease of use of the LHM for HLHS, next steps will include co-simulation with the CV systems model for more accurate time-varying boundary conditions as well as including physiological constraints in the topology optimization loop. As these kinds of tools grow in functionality and usability, we expect patient-specific modeling and simulation to be increasingly integrated into the regular practice of healthcare for children as well as adults.

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 define personalized healthcare in the age of simulation.

As a Senior Solution Consultant with Dassault Systemes, **Karl D'Souza** has extensive experience in technical consulting, product management, and market strategy as they pertain to simulation-based solutions for science and technology companies. He is currently focused on developing novel digital health solutions for the medical device, pharmaceutical, and clinical care segments of the Life Sciences industry.