

Multiscale Hemodynamics

accelerated computation and multiphysics modeling
may help predict deadly arterial plaques



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Selected accomplishments

- Coupled simulations of fluid and molecular dynamics in a real system
- Acceleration of multiphysics code using graphics processing units
- Mapping of endothelial shear stress in a coronary system based on medical imaging
- Progress in visualizing hemodynamics of human coronary arteries, with possible applications to real-time screening and intervention to prevent death

In the last several decades, there has been growing interest in understanding the circulation of blood (hemodynamics) in the human cardiovascular system. This is a very complex system: the heart pumps the blood through the large arteries to the smaller diameter arteries, which become capillaries and eventually venules, where the deoxygenated blood is passed through veins back to the heart, imposing a circular road map through the whole body. In such diverse morphological conditions blood exhibits a wide variety of behavior, ranging from the continuum to the corpuscular nature of the biofluid, rich in red blood cells and other suspended particles.

The phenomenology of hemodynamics has several implications for the initiation and evolution of cardiovascular diseases. Atherosclerosis is the

of lipid molecules and inflammatory cells at specific locations within the wall of the coronary arteries.

The main objective of the Multiscale Hemodynamics project is to develop and deploy a general purpose, multi-scale methodology to study flow patterns in complex morphological environments. A direct benefit of this study would be the enhanced biomedical understanding of the causes and evolution of plaques in the heart arteries, with important implications for predicting the course of atherosclerosis and possibly preventing or mediating its effects. The principle underlying our multi-scale approach is to resolve the motion of the relevant degrees of freedom (particles, molecules, red blood cells, etc.) and their fluid “environment” in a consistent way. The irrelevant components of the system are handled in effective terms, without

sacrificing the realism of the overall description. In this way, we are able to approach systems of mesoscopic or macroscopic size, with a number of elemental components that cannot be handled by conventional simulation methods.

Studying complex flow patterns in irregular geometries implies the simulation of suspended bodies and particles convected by the underlying fluid plasma. The interaction exerted between the fluid (solvent) and suspended bodies (solute) is

bi-directional, with an action-reaction principle underlying the motion of both solute and solvent. We have thus developed a method to couple two computational approaches by combining methods borrowed from different contexts, the Lattice Boltzmann (LB) method from the computational fluid dynamics community, and Molecular Dynamics (MD) from the atomistic computational community. The developed concurrent multi-scale methodology is stable, reliable and suitable for a number of extensions and applications. We have initially applied the method to the study of biopolymer translocation in solid-state narrow pores, as a simple test case for which a large volume of experimental results are available to test the computational approach; in this physical

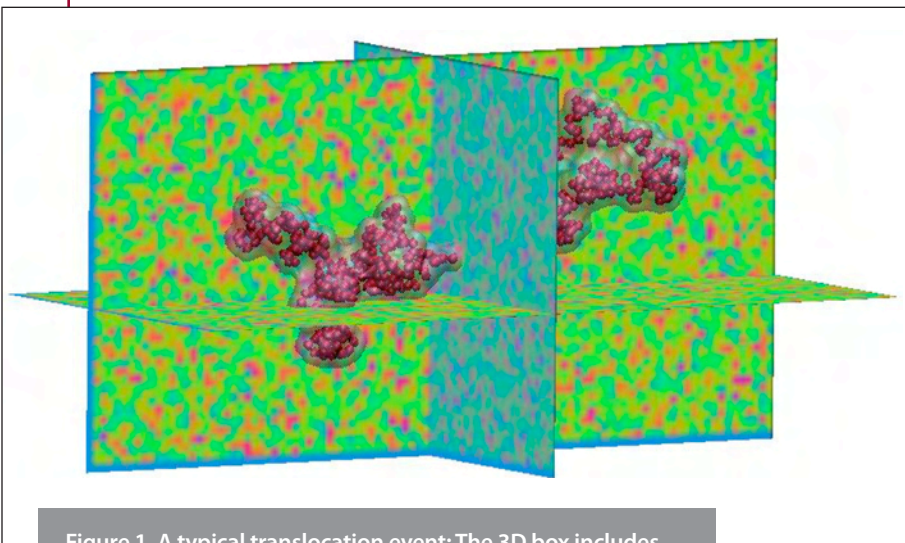


Figure 1. A typical translocation event: The 3D box includes the fluid, the polymer, and a wall (not shown) that separates the box into two chambers. A polymer (red beads) represents double-stranded DNA and the fluid velocity magnitude is shown on 2D planes by color shading. Red denotes high value, green low value.

most common disease that affects the arterial blood vessels resulting in coronary heart disease, the most common cause of mortality and morbidity in developed countries; about 50% of annual deaths due to this disease occur suddenly and with no prior symptoms. Although the development of the disease depends on the presence of systemic risk factors, such as high cholesterol, diabetes and high blood pressure, the clinical manifestations—heart attack, sudden coronary death and angina pectoris—are focal, resulting from the accumulation

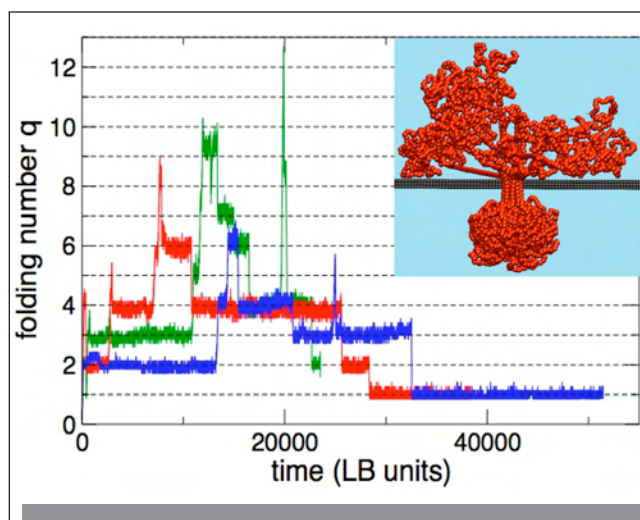


Figure 2. Three trajectories of the folding number (corresponding to fast, green; intermediate, red; and slow, blue, events) illustrating the quantized signal during multi-file translocation through pores much wider than the polymer cross-section. The inset shows a multi-file configuration.

system, issues of coupling of scales arise which are essentially the same as in hemodynamics, although the physics of polymer translocation is different. Having proved the viability and the reliability of the approach on the simpler problem of translocation, we then tackled the more challenging problem of multiscale hemodynamics.

For a number of years, highly tuned, system-specific application codes have been used to run large-scale simulations in many different fields of computational physics. However, attempts at coupling such application codes to simulate more complex, interdisciplinary, phenomena have been often based on a simple sequential paradigm, that is, the output of the microscopic code provides the input of the macroscopic code, with limited (if any) run-time concurrency and system integration. The end result of our effort has been the development of the software package MUPHY, a general-purpose multi-scale simulation tool that can be used to study a variety of systems. Due to a number of technical advancements in high-performance computing, MUPHY can seamlessly handle real-life geometrical set-ups, such as blood flows in human arteries in the presence of white cells, lipids, drug-delivery carriers and other suspended bodies of biological interest. Moreover, MUPHY has been designed to exploit cutting-edge hardware resources, such as the BlueGene platform

available at Harvard, or clusters of general-purpose graphical processing units (GPGPUs) that are currently attracting considerable attention in the computational physics community. Benchmark tests have shown that MUPHY can sustain highly competitive performances on these architectures, notwithstanding the underlying general-purpose design of the software components.

Concept development in a model system:

Biopolymer translocation

Motivated by recent experimental studies, we first developed, tested and applied our multi-scale approach in the model system of biopolymer translocation through nanopores. Biopolymer translocation is a complex phenomenon involving the competition between many-body interactions at the atomic or molecular scale, fluid-atom hydrodynamic coupling, as well as the interaction of the biopolymer with the wall in the region of the pores. Accordingly, all the important features of scale coupling between a continuum fluid flow through a complex geometry and the motion of a discrete, molecular-scale object that might be encountered in the hemodynamics context are already present in the translocation problem.

Biopolymer (such as long DNA strands) translocation is an important biophysical process

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occurring in phenomena like viral infection by phages, inter-bacterial DNA transduction and gene therapy. In addition, it is argued that this type of process may open a path toward ultrafast DNA-sequencing by sensing the base-sensitive electronic signal as the biopolymer passes through a nanopore with attached electrodes. We have investigated the process of DNA translocation and found that the translocation time obeys a power-law dependence on the polymer length in excellent agreement with experimental measurements, revealing that the coupling of the polymeric motion to hydrodynamic correlations (shown in Figure 1) results in a significant acceleration of the translocation process.

We have conceptualized this behavior by means of a new mean-field model accounting for the anisotropy of both translocated and untranslocated segments, which are crucial aspects for interpreting the basic mechanisms behind the physics of biopolymer translocation.

We have further investigated a number of intriguing phenomena related to biopolymer translocation and its application to automatic sequencing devices, most notably the so-called current-blockade quantization. This is a phenomenon related to discrete jumps of the ionic current through the pore observed during the translocation process. Our simulations showed that these jumps are indirect evidence that the polymer crosses the pore in the form of discrete folded configurations associated with integer values of the folding number, that is, the number of strands simultaneously occupying the pore during the translocation (see Figure 2). Our studies

showed that for long polymers, new features appear related to the reduction of friction through the pore region. The observed behavior elicited an intriguing analogy with quantum systems, whereby the observed translocation time was formulated as a weighted average over the whole set of multi-folded configurations (the “pure states” of the polymer-pore system). The modulation of the dwell time with the folding states explains the general trend elicited by simulations.

Simulation of hemodynamics in real coronary arteries

Prior research, primarily observational and in vitro, has established that the foci of atherosclerosis appear in regions of disturbed blood flow, where the local endothelial shear stress (ESS) is low or of alternating direction. Therefore, atherosclerotic lesions frequently form near arterial branches and bifurcation, where there always is disturbed flow. Moreover, it primarily affects the luminal side of

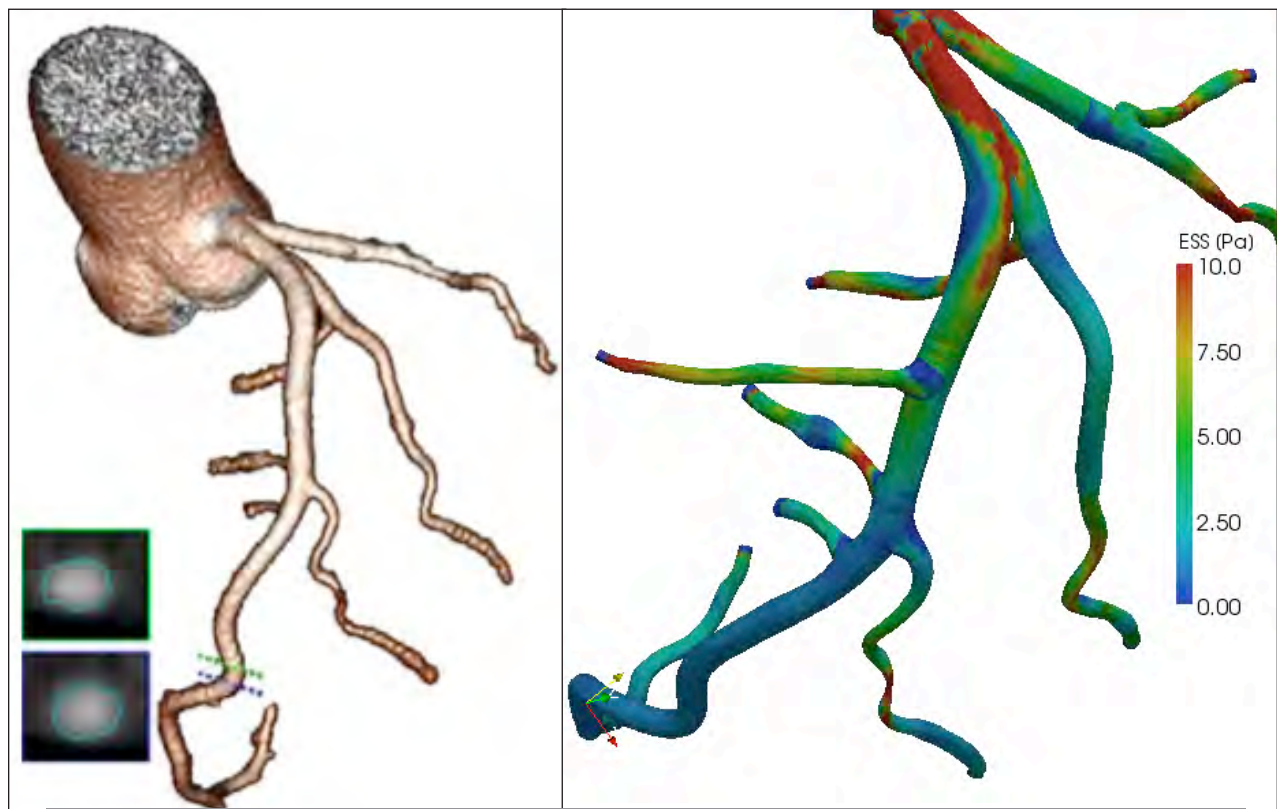


Figure 3. *Left*: Human Left Coronary Artery as imaged by a multi-detector computed tomography scan, with the coronary artery system descending from the aorta. The upper region is directly attached to the aorta and subdivides in nine different bifurcations. *Right*: The Left Coronary Artery colored according to the local ESS (endothelial shear stress). The regions of pathologically low ESS correspond to the deep blue coloring, occurring in proximity of bifurcations, for local enlargements of the vessel diameter, and generally along the inner region of vessel bending.

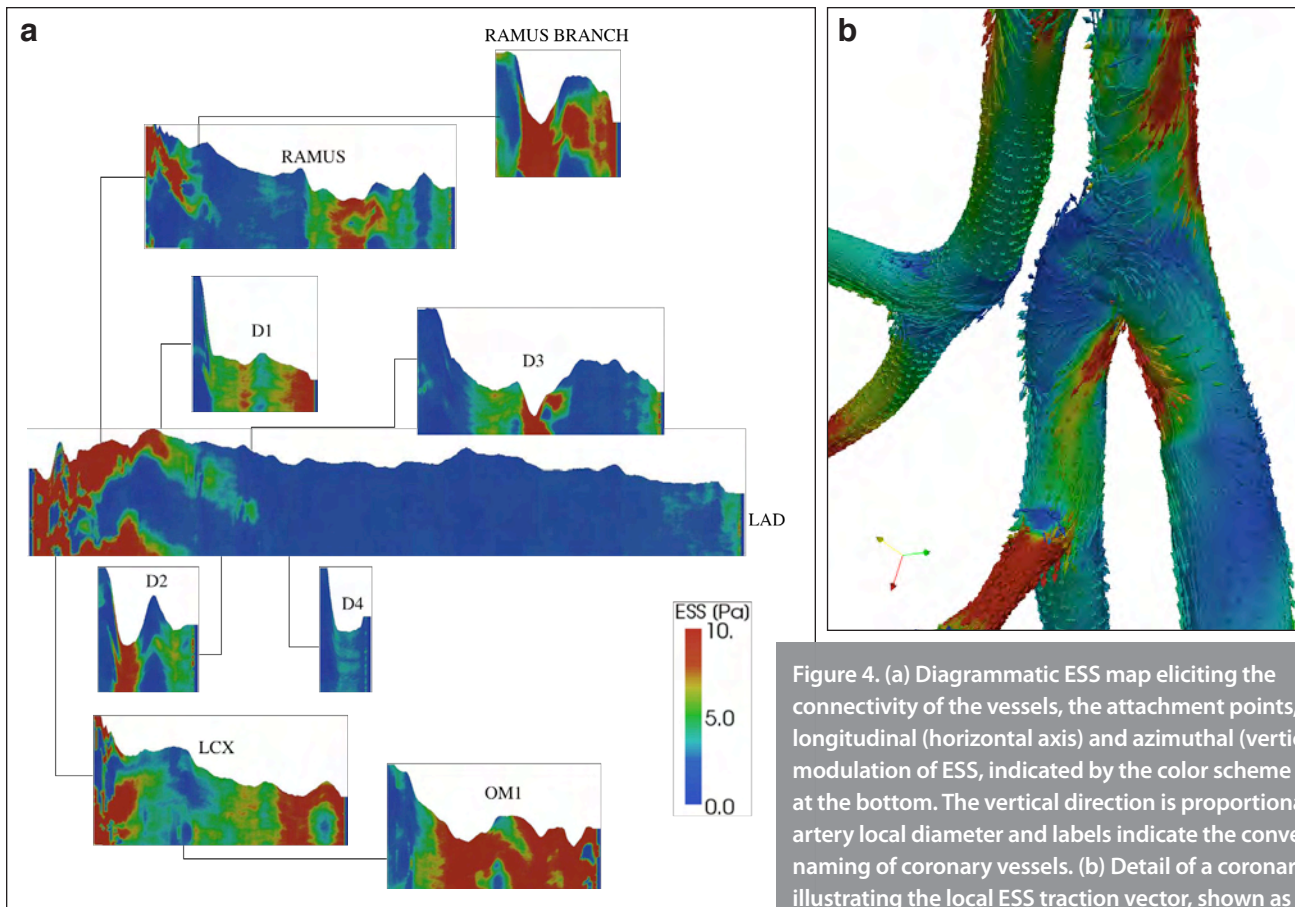


Figure 4. (a) Diagrammatic ESS map eliciting the connectivity of the vessels, the attachment points, and the longitudinal (horizontal axis) and azimuthal (vertical axis) modulation of ESS, indicated by the color scheme shown at the bottom. The vertical direction is proportional to the artery local diameter and labels indicate the conventional naming of coronary vessels. (b) Detail of a coronary system illustrating the local ESS traction vector, shown as surface arrows and colored according to the ESS intensity map. A good alignment of arrows indicates physiologically safe (high) ESS values, whereas misalignment corresponds to irregular or disturbed flow patterns, that is, regions with high risk of plaque formation.

arteries since the distribution of wall stress through the thickness of the wall arising from pressure is higher on the inner surface of the artery.

The evidence for ESS in the localization and progression of atherosclerosis is compelling and widely accepted. However, to date there is no direct route to predict the occurrence of atherosclerosis. In fact, because there is no direct method for measuring ESS *in vivo*, the prediction where disease is likely to develop and what form it would take is basically impossible.

In close collaboration with the Cardiovascular and Radiological Units of the Brigham and Women's Hospital, we have undertaken a systematic investigation of extended coronary systems enveloping the complete human heart. The joint usage of vascular profiling techniques, such as Multi-Detector Computed Tomography (MDCT), and MUPHY, allowed us to simulate coronary systems of unprecedented size and accuracy. MDCT is an emerging noninvasive modality for coronary artery imaging with the potential to assess the coronary artery lumen, the wall, and plaque with improved spatial and temporal resolution as

compared to prior acquisitions, permitting the creation of a 3D image of the entire coronary artery system in a few minutes.

We have developed a set of tools to reconstruct, regularize and finally simulate coronary arteries *in silico*. The Lattice Boltzmann method proves particularly favorable in handling complex arterial geometries since the use of a regular cartesian mesh greatly facilitates handling irregular coronary geometries, as compared to traditional fluid-dynamic approaches. Moreover, one can measure the interesting quantities, such as ESS, locally on the mesh, without awkward interpolation methods, as illustrated in Figure 3, for a real-life example of a coronary artery.

Our study focuses on the reconstruction of ESS maps in left and right coronary arteries. Given the high level of ramification in coronaries, sophisticated 3D graphical software allows us to

system	execution time (in sec)	MFLUPS
1 C870 GPU	760	53
2 G200 GPUs	159	252
8 GT200 GPUs	41.9	955

Table 1. Timing of 10,000 iterations on an irregular domain with 4,000,000 fluid nodes. The performance is measured by using the “de facto” standard unit for lattice Boltzmann code, that is a Million FLuid node lattice Updates Per Second (MFLUPS). A MFLUPS is equal, approximately, to 200 million floating point operations per second (MFLOPS). Going from one C870 GPU to 8 GT200 GPUs, performance improves by a factor of 18.

visualize scalar, vectorial and tensorial fields and locate the foci of low ESS (see Figure 4). We can thus monitor the coronary hot spots in different hemodynamic conditions, for steady state as well as pulsatile flow conditions and for different values of the inlet and outlet flow rates. In particular, we have identified a number of observational quantities, such as the ESS traction vector (Figure 4(b)), that allow us to characterize irregular flow patterns, with repercussions on the underlying endothelial cell alignments and adhesion properties of lipid-rich material by the inner coronary wall. Such quantities

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prove of great interest for a correct interpretation of incipient pathologies by the medical community.

We can now handle disparate geometries and flow conditions at the centimeter and millimeter level. Further work is in progress aimed at reproducing the rheological properties of blood in arterioles and capillaries. Here, the corpuscular nature of blood modulates viscosity in specific ways, and needs to

be taken into account via the reproduction of motion of red blood cells, with full deployment of the multi-scale methodology.

Computational tool development: MUPHY on GPGPUs

The result of an intensive two-year effort co-sponsored by the IIC and the Cyber-Infrastructure Lab of the School of Engineering and Applied Sciences, our simulation software, MUPHY, swiftly pipelines the different phases of the hemodynamic simulation and exploits the power of ultrafast, massively parallel hardware architectures in a highly efficient manner. The code was successfully run on two parallel architectures, the IBM BlueGene (BG) and a cluster of general purpose graphics processing units (GPGPUs). The BG implementation was developed at Harvard’s 2-rack machine (4,096 cores) and then run on a 16-rack machine (32,768 cores) at the IBM T. J. Watson Research Center made available to our group by special arrangement. This run demonstrated the excellent scalability of the code. More recently, we have developed a version of the code that takes advantage of the capabilities of low-cost parallel platforms based on GPUs, which we discuss in more detail, due to its interest and promise for future applications.

Given its particularly favorable price/performance ratio, the GPGPU-based architecture represents the latest technological breakthrough in scientific computing, accessible as commodity hardware. Among the GPGPUs, those developed by NVIDIA appear particularly suitable to support general purpose processing thanks to their programming technology named CUDA. We had access to a NVIDIA Tesla C870 equipped with 16 multiprocessors with 8 processors each, for a total of 128 computational cores that can execute at a clock rate of 1.3 GHz. The total on-board global memory on the Tesla C870 amounts to 1.5 GByte with a 384-bit memory interface to the GPU that delivers 76.8 GByte/sec memory bandwidth. The latency for the access to this global memory is approximately 200 cycles (two-orders of magnitude slower than access to shared memory) with any location of the global memory visible by any thread, whereas shared memory variables are local to the threads running within a single multiprocessor.

The CUDA software development toolkit offers an extended C compiler. The extensions to the C language supported by the compiler allow starting

computational kernels on the GPU, copying data back and forth from the CPU memory to the GPU memory and explicitly managing the different types of memory available on the GPU. The programming model is a Single Instruction Multiple Data (SIMD) type. Each multiprocessor is able to perform the same operation on different data 32 times in two clock cycles, so the basic computing unit (called warp) consists of 32 threads. MUPHY is the first lattice Boltzmann code with indirect addressing ported to GPU architecture.

To highlight the computing capabilities provided by the GPU, we report in Table I the results of the multi-GPU version of MUPHY parallel code obtained on a cluster of GPUs composed of 4 Quad core Xeon 2.8 GHz connected by Infiniband and each equipped with two pre-production S1070 GPU systems (for a total of 8 GT200 GPUs). For the test we used an irregular domain with a large bounding box ($1057 \times 692 \times 1446$ dimension) and a total number of fluid nodes 4,000,000. To obtain overall high performances, we took special care of the communication patterns among the GPUs due to an intermediate passage through the host CPUs. Overall, the reconstruction of extremely accurate ESS maps of complete coronary systems requires to have mesh spacing of $20 \mu\text{m}$ resulting in 250,000,000 fluid mesh points, that is, a global

memory allocation of 60 GByte in single precision representation. Such requirement is currently met by exploiting the cluster of 8 Tesla GT200 each equipped with 16 GByte of global memory currently available at the Harvard School of Engineering and Applied Sciences.

Our most recent results are shown in Figure 5.

Conclusions and outlook

In this project, we developed both the conceptual/theoretical framework and the computational tools to perform highly realistic simulations of blood flow patterns in arteries, and the effects of the continuum flow patterns on the artery wall stress and structure. The computational tools (MUPHY code) were optimized for performance on massively parallel architectures, including the IBM BlueGene and a cluster of general-purpose graphics processing units.

We applied the code to calculate endothelial stress patterns in a real left coronary artery system of a human heart, as measured by computed tomography scan at the Cardiovascular and Radiological Units of the Brigham and Women's Hospital. As these results demonstrate, MUPHY exploits multi-GPU hardware capabilities to deliver fast and accurate measurement of endothelial shear stress patterns in real clinical samples.

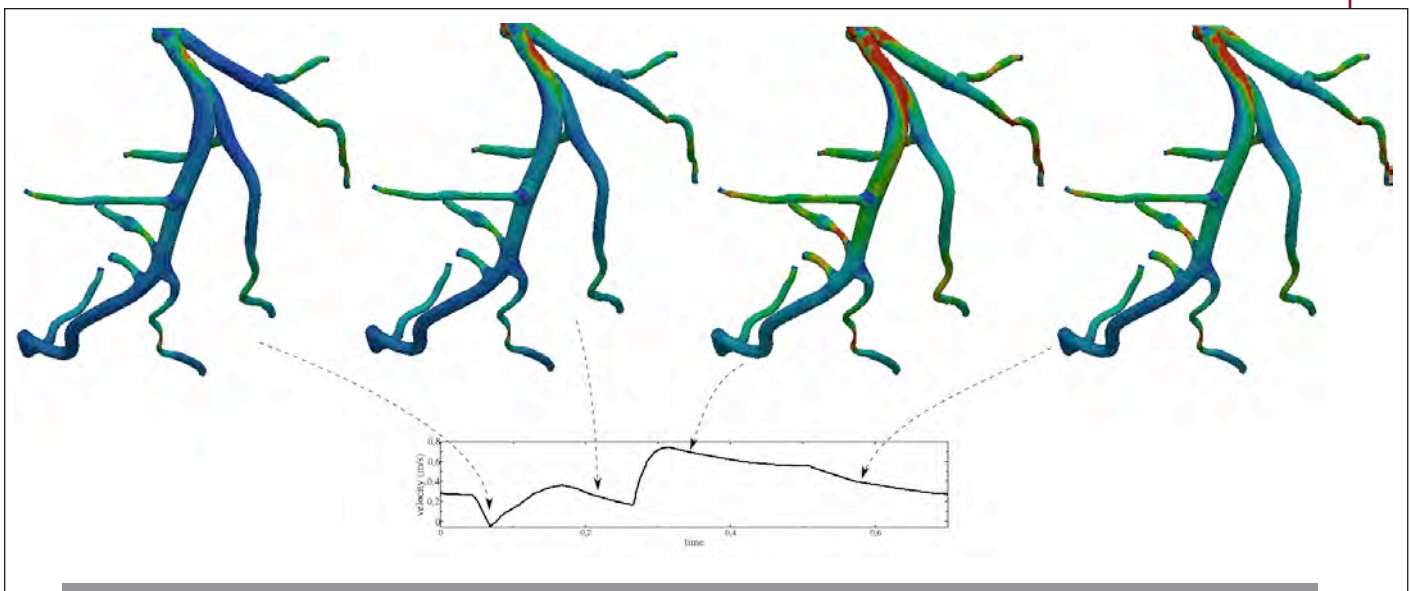


Figure 5. Endothelial shear stress maps of the left coronary arterial tree for pulsatile flow: The velocity of blood is shown in the graph at the bottom as a function of time for one heart beat, and the ESS variation is shown for four instances during this time interval. This simulation took 2 weeks to run on a cluster of 7 NVIDIA Tesla cards, with 4 GPUs in each (28 GPUs total). It involved 200,000,000 voxels and required 700,000 steps per heartbeat.

The output of the simulation is a large volume of numerical data about shear stress on the endothelial wall, as well as flow patterns in the artery interior. Of these results, we have only exploited a small fraction so far. Much additional interesting and useful information is embodied in the data, which needs to be analyzed and interpreted further with the right visualization tools. The implementation of the computational component in graphics-processing hardware has the added advantage of employing the same platform for the numerical simulation and the efficient visualization of the large volume of data produced by the simulation. Our long-term goal is to combine simulation and imaging on the same hardware platform, which will ultimately make it

possible to noninvasively and inexpensively screen large numbers of patients for incipient coronary disease, and intervene at the clinical level prior to the occurrence of catastrophic events.

Much remains to be done in this direction, that is, the integration of the computational component (MUPHY) with a visualization package that seamlessly translates the computed patterns into images useful to clinicians. To this end, we have recently begun a collaboration with another IIC/SEAS faculty member, Prof. Hanspeter Pfister, an expert in visualization, and a HSEAS graduate student, Michelle Borkin. This new phase of the project is expected to take several years and to be the research theme of the student's Ph.D. work.

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