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Utilizing Computational Fluid Dynamics in Cardiovascular Engineering and Medicine—What You Need to Know. Its Translation to the Clinic/Bedside

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Biological flows involve complex fluids flowing through three-dimensional (3D) deformable and permeable tissues and organs and within artificial organs that support either intra- or extracorporeal circulation. Biofluid mechanics analysis involves mathematical and computational modeling of the nonlinear Navier–Stokes equations governing such flows, and was initially limited to simplified models and geometries. The advent of computational fluid dynamics (CFD) made the simulation of complex transport phenomena in medicine and biology feasible. Tackling more challenging and clinically relevant problems in realistic physiologic geometries was achieved by concomitant advancements in high performance computing (HPC) and the development of cutting edge clinical visualizing modalities and graphics software. Presently, those are readily integrated into numerical simulations of physiological flows and complex flow fields within artificial devices that circulate them. It opens tremendous opportunities for harnessing the power of CFD to solving problems at the clinical forefront. It led to breakthroughs such as patient specific fluid–structure interactions (FSI) modeling of disease processes for improving clinical diagnostics, designing optimized implantable prosthetic devices, and improving outcomes of surgical procedures. In recent years several organizations and regulatory federal agencies such as ASME and the US Food and Drug Administration (FDA) are fully engaged in formulating verification and validation (V&V) guidelines to help speed up the FDA approval process of medical devices that utilize CFD during their research and development (R&D) phase (1), with groundbreaking implications for the legal, medical, and engineering realms. While there is a growing recognition within the clinical community and regulatory agencies of the tremendous benefits in employing CFD for such purposes, with CFD steadily gaining traction in the clinic, it is paramount that modelers apply CFD correctly and that they are fully aware of the assumptions made and the limitations of their modeling approaches. For a successful translation of CFD to the clinic and bedside and to serve for augmenting the clinical decision making tool, CFD output should be readily tuned for specific clinical scenarios and clinician needs.

When formulating a CFD simulation problem, several considerations and steps need to be followed at the preprocessing stage. The desired level of complexity and the scale of the problem to be modeled combined with the accuracy needed, dictates reconciling the CFD code capabilities with the computational resources available. The size of the simulation will determine whether it can be solved using a PC or a workstation or a supercomputer (such as large computational clusters that are collectively known as HPC resources). This may also

dictate whether serial or parallel platforms with compatible codes should be used. The clinical visualization modalities that may be used for creating the in silico numerical model can become a challenge, given the inherent resolution limitations of modalities such as CT or MRI that are increasingly utilized nowadays for solving patient specific CFD problems. While medical imaging provides the anatomical and physiological details needed for the model reconstruction by segmenting and defining its geometric boundaries, its resolution does not come close to the level of granularity that CFD can offer—at times requiring interpolation or extrapolation for reconstructing the missing information and/or smoothing the model geometries because of lower resolution artifacts.

CFD is solved by discretizing the geometry into finite elements or volumes, where physical conservation laws are applied to each small volume/elements formed by grid or mesh generation using various approaches. The grid (mesh), consisting of indexed points in space upon which continuous functions that follow conservation laws may be approximated, can be constructed using various methods of discretization, for example, fine or coarse, structured or unstructured, uniform or nonuniform. Mesh generation algorithms can be programmed to automate the process and adapt it to special needs, for example, finer mesh where stronger gradients are present, or combining structured with unstructured meshing for dealing with complex geometries. The CFD solver then produces the pressure and velocity field over all elements at each time step.

The complexity level of the CFD simulation is determined by the physical and physiological phenomena to be modeled. The level of complexity is also dictated by the fluid properties used in the simulations, for example, Newtonian versus non-Newtonian fluid behavior models (in blood flow problems for example this may depend on the range of shear rates that the phenomenon to be modeled is characterized by), whether the fluid is to be modeled as a single or multiphase flow—such as may be required if the particulate/cellular phase in the fluid needs to be taken into account—and the expected range of Reynolds number (dictating whether the flow can be assumed laminar or may require the use of turbulence models). As most of the CFD problems are solved today as unsteady (time dependent) flow problems, the accuracy is dictated by the spatiotemporal resolution and the need to achieve numerical convergence of the solution. This, in turn, dictates the degree of both the spatial resolution (the number of the finite elements or cell grids) and the time steps needed to stabilize the solution. A typical numerical mesh for solving a 3D cardiovascular problem reconstructed from medical imaging may consist of millions of elements and thousands of time steps that are run over several cardiac cycles. Obviously, a trade-off between accuracy and computational viability should be considered.

Appropriate boundary conditions at the inlet(s) and outlet(s) are mandatory for achieving high fidelity and accurate physiological flow scenarios. The boundary conditions are extracted from physiological parameters (that could be time dependent) such as pressures and velocities that may be patient specific or assumed, and/or from measurements in devices. As in recent years the size of cardiovascular simulations is rapidly increasing to incorporate larger sections of the cardiovascular system, an efficient approach is to couple zero order (0 D) “lumped-parameter models” that lack a spatial dimension into the 3D models for applying systemic boundary conditions. Following a successful converged

solution, a postprocessing stage provides the tools needed for visualization of the solution to both quantify and interpret the results. In CFD those typically consist of velocity flow field and profiles within the flow domain, pressure distribution and parameters such as wall shear stress, shear rates, and oscillating shear index. Those are typically visualized using color rendering.

The applications of CFD in biomedical engineering and medicine are wide ranging, most notably in the cardiovascular system and in cardiovascular engineering. They are currently used to enhance diagnostic capabilities and progress toward patient specific precision medicine. CFD simulations of the circulation help to shed light on biological and cardiovascular disease processes and their progression by analyzing those from a biomechanics perspective. Few examples of the numerous CFD applications can be found in: studying the complex relation between pathological hemodynamic flow patterns and lesion-prone regions in coronary atherosclerosis, diagnosing the risk of rupture in abdominal aortic aneurysms (2), cerebral aneurysms, and in vulnerable plaques (3), improving surgical procedures to achieve better clinical outcomes, for example, the growing use of CFD for refining transcatheter aortic valve replacement (TAVR) procedures (4), optimization approaches to improve the hemodynamic performance of mechanical circulatory support (MCS) and cardiovascular devices to enhance their thromboresistance, for example, in coronary and carotid stents and endovascular devices, in prosthetic heart valves (5,6), ventricular assist devices (VADs) (7), and in the total artificial heart (TAH) (8).

The few CFD applications mentioned above require special considerations. In recent years, fluid structure interaction (FSI) is increasingly incorporated into CFD simulations to study the interaction of the hemodynamics with the vascular wall, or for simulating blood flow interacting with moving parts of cardiovascular devices. FSI simulations can be loosely or strongly coupled, where the latter require solving the structural and the fluid mechanics equations simultaneously. These are more challenging simulations that, for example, in the case of the vascular wall biomechanics require the incorporation of advanced soft tissues material models (elastic, hyperelastic, orthotropic, and advanced anisotropic models that take into account the vascular wall fibers content and their orientation, etc.). Such FSI simulations also require detailed time varying boundary conditions (some can be extracted from patient specific clinical measurements, and may also require testing specimens from patients to fine tune the many parameters of these advanced material models). Many such parameters are difficult to obtain and may remain unknown, requiring the use of certain assumptions. The challenges in coupled FSI simulations are device dependent. For the case of pulsatile devices such as the TAH (8) heart valves leaflets deflections and VADs, these involve large motions and deformation of a thin membrane that may also undergo buckling, coupled with the prosthetic valves leaflets motion during their rapid opening and closure-requiring applying appropriate kinematic and traction conditions. One of the major challenges in such FSI simulations is developing advanced remeshing strategies to accommodate the large deformations involved (9).

When CFD incorporation during the R&D phase of cardiovascular devices started in earnest, it was intended to circumvent ad hoc approaches which seemed to pervade the field back then (unfortunately some still do), as to establish a more methodological and rigorous

approach to device development (10). CFD was mostly incorporated only at a late stage of the device design process, having limited utility for effective design alterations. Fortunately, since then and with the rapid advance in numerical modeling techniques and computing capabilities that facilitated the application of relevant and sophisticated CFD modeling techniques for studying blood flow in the complex confines and geometries characterizing devices and cardiovascular pathologies, CFD has advanced in huge strides and is steadily gaining acceptance both by device manufacturers and the clinical community. As mentioned earlier, the FDA is actively involved in incorporating CFD into the regulatory process and issued corresponding guidelines for device manufacturers that are including CFD studies results when seeking approval for their devices.

An example of utilizing CFD to optimize the performance of MCS devices concerns simulations of blood flow within rotary blood pumps such as rotary VADs that typically spin at approx. 10 000 RPM and involve both rotating and stationary components. A cost-effective approach for such FSI simulations is using a sliding interface approach (11). Beyond that, VAD is also highlighted here as a specific example – representing any blood recirculating device to illustrate how to extract from CFD specific information that is useful and relevant to various stakeholders such as clinicians, device designers, and regulatory agencies. All such devices are burdened with thrombotic and thromboembolic complications that mandate complex anticoagulation/antithrombotic drug regimen for their recipients. To harness the power of CFD to better understand the flow induced mechanisms that may induce blood damage and promote thrombogenicity and hemolysis—information that can be used to optimize the devices' thromboresistance—special CFD approaches need to be utilized. For quantifying the thrombogenic potential of VADs the CFD simulation should be solved as a two-phase flow problem, for example, where a large population of platelets is represented in the particulate phase and a Lagrangian approach is employed for resolving individual platelet trajectories within the flow field. Such approach is based on the well-established shear induced platelet activation concept (12). Briefly, exposure to fluid shear stresses will activate and aggregate platelets irreversibly in the absence of any exogenous agonist, showing consistent “dose” and time response characteristics of equivalent chemical agonists (13). The shear loading histories of each individual platelet, that is, its stress accumulation (SA) along its flowing trajectory, is computed by incorporating the cumulative product of the instantaneous shear stress and exposure time (either as linear or power law summation rule). To quantitatively analyze and compare the SA values from the large number of platelet trajectories, a probability density function (PDF) is employed to statistically represent the distribution of the SA of all trajectories, representing the device “thrombogenic footprint” (7,14,15). This information can be used for example to optimize the device design for better hemodynamic performance, to study the thrombogenic potential of various implantation configurations, as well as to inform clinicians how to fine tune a patient's medication regimen, for example, by testing the patient blood sample in a microfluidic device that exposes it to MCS-specific dynamic shear stress patterns that are extracted from the CFD simulations (16). Hemolysis response is very similar, and several models for hemolysis have been developed over the years, for example, local rate of hemolysis as a power function of the average local rate of mechanical energy dissipation (17), and relating hemolysis to shear stress (18,19). In these predictive phenomenological

models, which are based on the theory of damage in solid mechanics, internal damage accumulates in a red blood cell until it reaches a critical value of damage, either as a function of the instantaneous stress level and the previous damage history (20), or as weight average damage accumulation over a number of cycles.

As in all CFD simulations, caution should always be practiced when using it to quantify blood damage. The influence of various numerical implementation assumptions on predicting blood damage in cardiovascular devices using Lagrangian methods with Eulerian computational fluid dynamics should be carefully examined as those may affect the results. Implementation assumptions in SA computations may include various platelet seeding patterns, stochastic walk models, or simplified trajectory calculations with pathlines. Those can significantly affect the resulting stress accumulation, that is, the blood damage model predictions. The appropriate assumptions should be considered based on the physics of the flow of the specific case and a sensitivity analysis (21). For example, when quantifying the thrombogenic potential of stents where the vortical blood flow structures that promote thrombus formation are mostly confined to regions in between the stent's struts, the seeding patterns of the platelets should be completely different than of those applied in scenarios such as flow through VADs where mixing occurs throughout the flow field.

Using an integrated modeling methodology that extracts additional information from the CFD simulations as illustrated in the few examples above, informs device developers how to reconcile conflicting demands by modifying the device design. Once the appropriate numerical models are developed and their predictive capabilities demonstrated (through testing), their efficacy becomes evident as modifying and optimizing the model geometries and testing the effects of design modifications are all performed in silico. Such methodologies are already transforming current devices design and testing practices, by facilitating design changes and optimization before going into preclinical testing. It is envisioned that it will greatly facilitate the use of blood recirculating devices for long term and destination therapy. Following an iterative optimization process, device prototypes are then fabricated and tested in vitro and/or in vivo. Such an integrated methodology has the potential to significantly improve clinical outcomes, for example, where the device optimization leads to a significant reduction in the rate of cardioembolic complications, in mortality rates, and in the ensuing health care costs.

A current simulation trend that is aimed at a longer term goal is to extend these models over the multiscales characterizing the multifactorial phenomenon of clotting in blood flow while efficiently combining biochemical events of the coagulation cascade, morphological changes of the blood constituents during the process, and the mechano-transduction events involved in it. With the exponential growth in computational power, multiscale modeling is currently being incorporated into the modeling toolbox. Such innovative modeling approaches will be readily extended and applicable to many types of implantable and extracorporeal blood recirculating devices in which cardioembolic complications are a significant problem, such as the TAH, stents, geometries of vascular surgical reconstruction, and tubular constrictions of extracorporeal circulation devices. It will also enable to model the effects of various drugs under device relevant flow conditions and fine tune it to patient specific conditions, promoting the rise of precision medicine.

The above are just a very few specific examples of clinically relevant CFD applications. Such applications are rapidly becoming very wide ranging. There is a strong drive to harness the CFD power to improve clinical diagnostic capabilities and bring its benefits to the bedside. In silico approaches are becoming available to test the efficacy of surgical interventions, and also used to accelerate the pace and minimize risks associated with long and costly human clinical trials, as well as preclinical animal trials. However, to gain better traction and credibility by the clinical community and other stake holders, modelers need to carefully analyze and apply critical judgment to their simulation results. They need to adopt clear V&V approaches and metrics (22), by developing appropriate in vitro and where needed in vivo experimental approaches that can be used to test the validity of their models' predictions. As mentioned and discussed above, it is important that the simulations do provide results that can be readily interpreted by clinicians. In that, the onus also lies on the clinical community that needs to both raise the awareness and promote medical education that will prepare clinicians to be able to include simulation results into their clinical decision making toolkit and incorporate those in the clinical practice. Such acceptance will pave the way toward a transformation in clinical practice and translate its benefits to the clinic and the bedside.

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Biography

Danny Bluestein, PhD, a Professor of Biomedical Engineering at Stony Brook University, is internationally known as a leader in the study of thrombosis, cardiovascular pathologies, and cardiovascular devices thrombogenicity. His research interests include the elucidation of physical forces that regulate cellular function in flowing blood, and translation of this knowledge to numerical and experimental strategies aimed at improving the design of blood recirculating devices such as prosthetic heart valves, ventricular assist devices and the total artificial heart, developing multiscale modeling approaches to describe blood clotting, and enhancing clinical diagnostics of cardiovascular diseases by using patient based numerical simulations. He is the author of over 100 peer reviewed scientific articles. Dr. Bluestein has received several major honors and awards including the Established Investigator Award from the American Heart Association and the Quantum award from the NIBIB, and was elected as a Fellow of the American Institute of Medical and Biological Engineering. His research

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