Will computational simulation in congenital heart disease ever make it out of the engineering lab and into the clinic?

"Despite an abundance of research, publications and PhD theses, there have been only a few clinical advances with regard to the Fontan operation or care for these 'single-ventricle patients' directly resulting from the use of simulation methods."

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The day-to-day application of computational simulation (the technology, not the role-playing technique) is commonplace in a wide-ranging group of industries, including, but certainly not limited to, meteorology, geology and aviation/aeronautics. While there are a number of advantages to using these technologies, the two greatest advantages usually focus on cost savings and risk minimization. Perhaps nowhere is this more important than in medicine, yet we have long relied on the 'build and test' surgical paradigm. Little effort, and far less headway, has been made to incorporate computational modeling into the diagnostic arsenal of medical and surgical clinicians.

In the area of congenital heart disease, the application of computational simulation techniques has most often been applied to the investigation of the total cavopulmonary connection (also known as Fontan) procedure (Figure 1). Performed in patients born with an abnormality of the heart in which only one of the two ventricles forms properly, it serves to separate the oxygenated and deoxygenated blood. The developed ventricle pumps blood to the body, while passive flow delivers blood to the lungs.

Given this lack of a pump to the lungs, minimizing inefficiencies in the system is critical, and lends itself nicely to the use of computational simulation. Despite an abundance of research, publications and PhD theses, there have been only a few clinical advances with regard to the Fontan operation or care for these 'single-ventricle patients' directly resulting from the use of simulation methods. This is due to several factors:

- Lack of truly realistic simulations as a result of limited anatomical models, physiologic parameters and an almost myopic approach to evaluating performance;
- Lack of validation and/or outcome studies incorporating simulation-based parameters;
- Lack of a critical mass and a concerted effort dedicated to this cause.

In a recent review article, DeGroff [1] issued a 'call to arms' to increase the sophistication and impact of Fontan simulations. At the most basic level, this work provides an outstanding bibliography of the work to date in this arena. More importantly, it has caused more attention and effort to be focused on what it will take to bring the use of simulation in congenital heart disease out of the lab and into the hospital.

That being said, it remains far easier to write about modeling than to actually do the modeling. Constructing accurate models requires anatomic data from either magnetic resonance imaging or computed tomography. Due to both imaging and computational advances, there has been substantial progress in model-building capabilities in recent years, and we now have the potential to incorporate fairly detailed anatomy. However, these processes remains cumbersome, and still require a vast amount of intensive user participation to identify the structures to be modeled, recognize and remove noise in the image data, and/or differentiate closely approximated structures (e.g., pulmonary arteries and veins). Inexperience in any of these facets leads to an inaccurate model, which, in turn, leads to an inaccurate simulation.

> *"It remains far easier to write about modeling than to actually do the modeling."*

Other sources of error are found within the simulations themselves. Models of such complexity (often over 1 million elements) require solving time-dependent equations on a supercomputer, and may take as long as 2 days to complete for even a relatively straightforward geometry. Simulations resulting in faster run times are most likely

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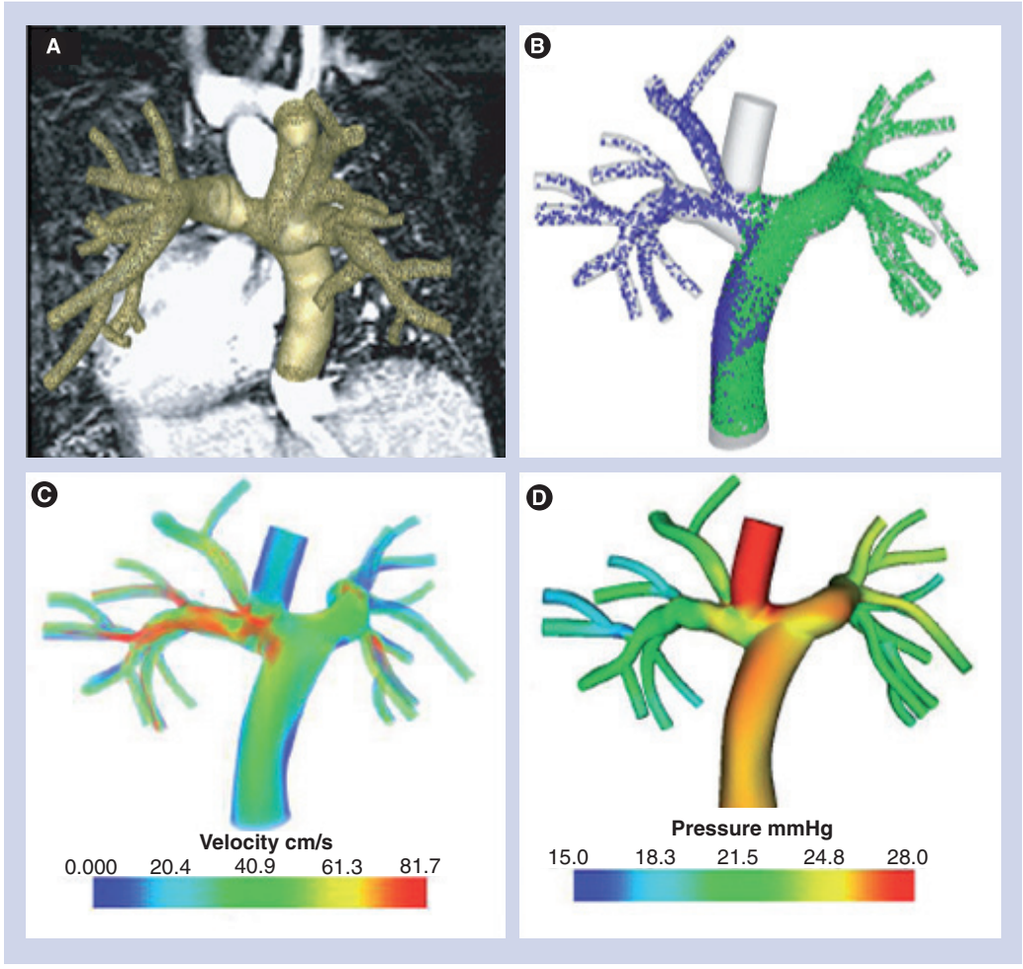

Figure 1. Representative results of computational simulation work as applied to congenital heart disease, specifically the Fontan procedure. (A) A sample model (comprised of approximately 1.5 million mesh elements) embedded in the magnetic resonance imaging dataset from which it was built. **(B)** Example of particle tracking techniques that allow investigation of how blood flow is distributed between the right and left lungs – particles are placed at the 'bottom' of the model (inferior vena cava inlet) and followed to their individual exit points. Color coding demonstrates whether they migrate to the patient's left (green) or right (blue). **(C)** Example of a blood flow velocity map, in this case under simulated exercise, which can be investigated for areas of stasis or turbulence. **(D)** Example of a pressure map, in this case under simulated exercise as well, which can be investigated for areas of 'system' inefficiencies and allow, in the case of surgical planning, for prediction of postoperative hemodynamics.

trading anatomic oversimplification and numerical accuracy for this speed. Additionally, to accurately solve the equations governing blood flow (the Navier–Stokes equations), it is essential to have the appropriate physiologic conditions (often referred to as boundary conditions) representing the inputs to the model. The good news is that most of these parameters are readily measured by standard diagnostic techniques such as magnetic resonance imaging or cardiac catheterization. The bad news is that the inaccuracies in these methods (e.g., as much as 15–20% measurement error) become inaccuracies in the final simulation products. The worst news, and perhaps surprising to some, is that it is not at all uncommon for even the most basic physiologic parameters or boundary conditions (e.g., quantification of blood flow to the various lung segments) to be poorly understood, described and modeled. While the potential choices for boundary conditions are far from perfect, there has been considerable sluggishness in the engineering community to adopt more recently developed physiologic alternatives.

In addition to all of the above deficits, significant progress in multiple technical domains within the area of simulation is also still required. Simulations will need to include:

- More realistic and spatially varying wall properties (i.e., fluid–structure interactions);

- Vascular growth and remodeling;
- Techniques for anatomic and physiologic optimization;
- Incorporation of uncertainty techniques to find the 'most likely to succeed or least likely to fail' solution.

With all of these issues as a backdrop, it is a bit disheartening to realize these do not represent, in our mind, the biggest hurdle to the future, routine use of these techniques in the hospital or clinic. That notoriety goes to the lack of effort around validation of these methods. While there has been a reasonable amount of work done on *in vitro* validation of computational fluid dynamics (CFD) codes using glass models, much of this work is more qualitative than quantitative, and this type of study remains a long way from truly representing the complexity of human physiology. Simply put, direct validation of model predictions against clinical outcomes is essentially nonexistent. No longitudinal studies exist, for example, comparing outcomes to simulation-based measures of presumed importance (e.g., power loss or efficiency in Fontan patients). However, the time has come for such longitudinal studies to be undertaken. Of course, in the interim, while time is passing to collect this longitudinal data, short-term investigations of simulation accuracy of pre- and virtual post-operative models will provide critical data with regard to the current assumptions and modeling techniques.

> "*Direct validation of model predictions against clinical outcomes is essentially nonexistent.*"

It is important to realize, while this editorial (and most of the work to date) has focused on the use of congenital heart disease-based computational simulation in the Fontan operation, the techniques are widely applicable to a broad array of other cardiovascular or cardiopulmonary disease states. In fact, simulation-based studies are already underway exploring the risk for venous occlusion due to pacemaker lead implantation, the effects of shear stress on gene expression in pulmonary hypertension and the biomechanical properties of native and repaired coarctation of the aorta as specific examples of this declaration.

As we return to our original question, 'Will computational simulation in congenital heart disease ever make it out of the engineering lab and into the clinic?', you may be surprised to hear a resounding 'Yes' after all the negativism.

There are clearly great hurdles ahead and, until fairly recently, the technology and manpower were greatly outmatched by the complexity of the problem. However, increasing interest in simulation technologies by governmental agencies and funding sources (e.g., US FDA/National Heart, Lung and Blood Institute/National Science Foundation Workshop on Computer Methods for Cardiovascular Devices) begin to level the playing field. Coupled with this, a recent multi-institution, multinational, multimillion dollar grant awarded in this area also lends a great deal of support to this new world sense of optimism.

> "*The true metric of success must be the use of these techniques as part of advancing the understanding and treatment of patients with congenital heart disease.*"

While the banner has long been carried by a small core of devoted individuals, a new critical mass appears to be forming. Perhaps this is best exemplified by the planned conference/workshop in February of 2010 (1st International Conference on Computational Simulation in Congenital Heart Disease), bringing together an international group of some of the best clinicians in pediatric cardiology (both medical and surgical) and engineers (from many different disciplines) involved in modeling to exchange ideas, form new collaborations and set the course for the field. The true metric of success must be the use of these techniques as part of advancing the understanding and treatment of patients with congenital heart disease. It will, in all likelihood, come down to our ability to validate our results and, as such, convince the broader pediatric cardiology community of the value of computational simulation to advance and potentially redefine the field.

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