CARDIOPULSE

Global Spotlights

Use of computer models in cardiovascular therapy to advance precision medicine

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The complexity of living organisms has always required approaches to investigate their behaviour in a different way from those required for the study of inanimate matter. The methodologies employed in biology and medicine differ substantially from those used in physics and engineering, the former being guided by field experience and statistical approaches, while the latter is based on theory followed by field demonstration. However, these distinctions have blurred in recent decades as principles and methodologies once unique to particular scientific fields are now being applied across disciplines. This cross-disciplinary trend is perhaps best exemplified by the emergence of *in silico* technologies,[1] which leverage computational models to investigate problems with an unprecedented level of complexity. Indeed, when coupled with imaging and molecular diagnostics, *in silico* technologies can provide granular information on the physiology and pathology of single individuals in a non-invasive way. Thanks to these developments, there are several examples showing how computer models are capable of predicting quantities of a specific patient that would be impossible, or very difficult, to measure directly, allowing physicians to make the best possible decision regarding the clinical management of that patient.

As the study of living organisms is called *in vivo* and that of bench experiments is called *in vitro*, by analogy, today, the use of computational technologies to study living organisms has led to the coining of the term 'in silico medicine' in reference to the *in silico* technologies used in these applications. *In silico* medicine adopts state-of-the-art methodologies to create computer models of individual subjects that can optimize the diagnosis, predict the prognosis, and simulate the effect of available therapeutic strategies, with the potential of becoming a valid, practical, and effective tool for cardiovascular diseases in view of the intrinsic characteristics of the cardiovascular system.

Application of computer models in cardiovascular medicine

There are three main categories of computer models used in the cardiovascular field: computational fluid dynamics (CFD),[2] structural or finite element analyses (FEA),[3] and fluid–structure interaction (FSI)[4,5] models (*Table 1*). Computational fluid dynamics is used to analyse systems involving fluid flow, such as blood flow patterns within the heart and the vessels. Finite element analysis models consider the behaviour of the structural parts of the cardiovascular system in terms of stresses and deformations. Fluid–structure interaction approaches allow to consider simultaneously the effects of the flow and the structural parts.

In each of these categories, a patient-specific analysis follows a common set of steps. Vessels, valves, or cardiac chambers are virtually reconstructed based on medical images from non-invasive (i.e. ultrasound, computed tomography, or magnetic resonance imaging) or invasive imaging techniques (i.e. quantitative coronary angiography, intravascular ultrasound, or optical coherence tomography). Once the anatomy is reconstructed, the model is divided into small parts, called elements or volumes, to create the computational mesh or grid. In these elements, the flow and solid equations are solved with the definition of the properties of the fluid or structure (e.g. blood density and viscosity, arterial stiffness), boundary conditions (e.g. pressures and flows at the inlet and outlet of the model, structural constraints and contacts), and the mesh kinematic approach (e.g. Eulerian, Lagrangian, FSI boundary-fitted, and FSI non-boundary-fitted). The simulation is then run on a computer workstation or

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Table 1 Characteristics of the three main categories of computer models: FEA, CFD, and FSI

	FEA	CFD	FSI
Input	• Imaging or computer-generated anatomical and/or device structures • Measured or assumed constraints and contacts	• Imaging or computer-generated anatomical fluid domains • Measured or assumed fluid boundary conditions	• Imaged or computer-generated anatomical fluid domains and device structures • Measured or assumed fluid boundary conditions, structural constraints and contacts
Considerations	• Structural components (i.e. anatomy and device)	• Only fluid (i.e. blood)	• Fluid and structural components
Output	• Stresses and strain of native anatomy and devices • Post-processed variables as principal or von Mises stresses, damage index	• Pressure and velocity fields of blood domains • Post-processed variables as wall shear stresses, haemolysis index	• Stresses and strain of native anatomy and devices and pressure and velocity fields of blood domains • Post-processed variables from both the domains
Advantages	• Less computing power required than FSI	• Less computing power required than FSI	• Considers interactions between solid and fluid components
Disadvantages	• Does not consider blood domains	• Assumes patient, valve, and device domains as rigid structures	• Requires intense computing power
Applications to Tavi	• Evaluation of device deployment in native anatomy • Quantification of stress/strain/damage in both anatomy and device domains	• Quantification of wall shear stresses • PVL location and regurgitant volume quantification	• Quantification of both structural and fluid variables

CFD, computational fluid dynamics; FEA, finite element analysis; FSI, fluid–structure interaction; PVL, paravalvular leak.
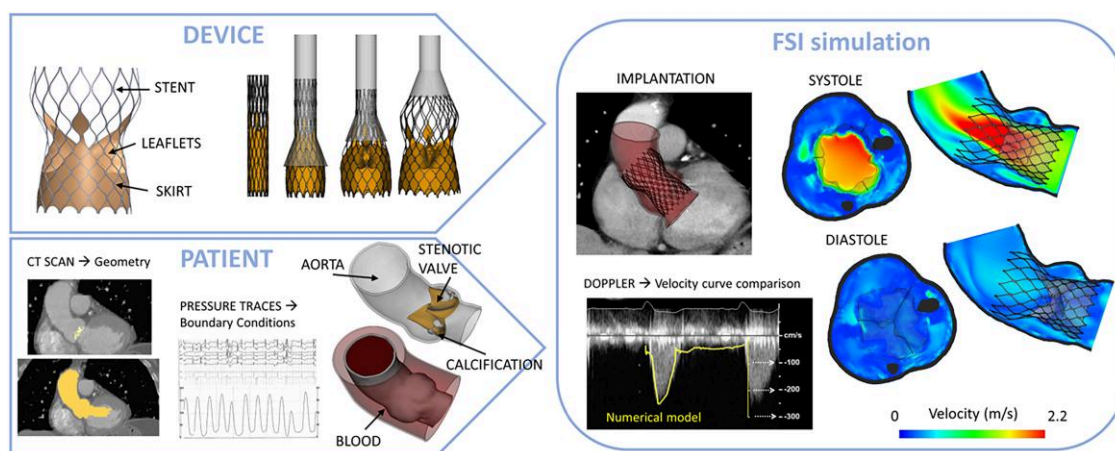

Figure 1 Required elements of a reliable *in silico* model. (Top-left panel) Device domain: high-fidelity device model consisting of the metallic valve frame, leaflets, and skirt. Stages of device release from the delivery system during deployment. (Bottom-left panel) Patient domain: patient-specific aortic root segmentation and 3D reconstruction from computer tomography imaging. Invasive pressure readings used to apply boundary conditions. (Right panel) Completed *in silico* transcatheter aortic valve implantation with structural and haemodynamic results.

high-performance computing cluster by taking advantage of their parallel computing features. Finally, the solution of the analysis is obtained and the results are post-processed in order to extract the haemodynamic or arterial structural quantities of interest.

As the field of cardiovascular medicine increasingly adopts computer modelling, the scope of research has expanded to include diverse applications, including studying flow patterns after coronary stenting,[6] simulating interventions for congenital heart disease,[7] predicting the

progression of vascular aneurysms,[8] and characterizing cerebral thrombus mechanics,[9] among others.

A practical example: a transcatheter aortic valve implantation model

We recently developed an FSI model for patients with aortic stenosis undergoing transcatheter aortic valve implantation (TAVI), showing that the development of patient-specific FSI models can be a valuable tool to support procedural planning.[5] In order to achieve this, we obtained pre-procedural and post-procedural echocardiography and computer tomography (CT) images, as well as intraprocedural haemodynamics, which were subsequently analysed using patient-specific FSI modelling. The resulting *in silico* model simulated the implantation of the prosthetic valve and the interaction of the device with the haemodynamics during systolic–diastolic cycles after the implantation. In this way, the FSI model allowed to evaluate the haemodynamic alterations due to the valve implantation and accurately predict the risk of paravalvular leakage (PVL), a pivotal complication of TAVI, with coherent values of the regurgitant volume and effective regurgitant orifice area. Moreover, we compared the final release configuration of the device and the velocity field with post-operative imaging, demonstrating an optimal qualitative and quantitative match (*Figure 1*).

Future outlook

The rise of *in silico* medicine has paved the way for exciting possibilities in improving patient care. The ability to create high-fidelity patient-specific models and perform virtual procedures on patients who are otherwise excluded from clinical trials has captured the interest of medical professionals and researchers alike.

Despite the promise of *in silico* medicine, several current challenges facing *in silico* technologies in cardiology persist. The foremost challenge is the need for reliable and accurate data to create patient-specific models. This requires detailed information on cardiac anatomy, electrophysiology, and haemodynamics, which can be arduous to obtain. Moreover, incorporating biological and physiological variability, such as age, sex, and comorbidities, into models to ensure their clinical relevance poses another obstacle. The exponential growth of this field has led to the development of a plethora of models, each claiming relevance. Consequently, the verification, validation, and uncertainty quantification of these models are of paramount importance in determining their reliability and clinical utility. Finally, computational challenges, such as the need for high-performance computing and advanced algorithms, to accurately simulate complex physiological processes also need to be overcome.

In silico medicine can have a significant impact on health technology assessment (HTA) by providing valuable insights into the safety and effectiveness of medical devices and therapies. By creating computational models that can simulate the behaviour of a device or therapy in the human body, *in silico* medicine can help identify potential risks and benefits before actual clinical trials are conducted. This can save time and resources, as well as minimize the risk of harm to patients and reduce reliance on animal and human trials.[10] In addition, *in silico* medicine can also be used to assess the cost-effectiveness of new medical technologies. By creating models that incorporate data on the costs and benefits of a technology, HTA agencies can make more informed decisions about which technologies to fund and which to reject. In fact, the US FDA has recently announced that *in silico* evidence from numerical simulations can be considered for biomedical device approval. This will have implications on the time to market of biomedical devices and overall costs related to device development and animal and human testing.

In conclusion, it is clear that the impact of *in silico* medicine on the cardiovascular field has yet to be fully realized. Collaboration between engineers and physicians will be pivotal to unveiling the full potential of this technology, ultimately potentially leading to major advancements in patient care.

Data availability

No new data were reported or analysed in support of this manuscript.

Conflict of Interest

All authors declare no conflict of interest for this contribution.

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