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Cardiovascular patient-specific modeling: Where are we now and what does the future look like?

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THE RISE OF PATIENT-SPECIFIC COMPUTATIONAL MODELS: FROM 3D RECONSTRUCTIONS TO DIGITAL TWINS

The clinical and bioengineering arenas are experiencing tremendous technological progress. Imaging technologies yield images with continuously improved time- and space-resolution; image processing is being boosted by the introduction of artificial intelligence (AI) techniques allowing for time-efficient, automated, and reliable segmentation of tissues or organs; and the performance of computational infrastructures is increasing exponentially. In this scenario, it is becoming easier and faster to exploit the anatomical and functional information generated by medical imaging to feed computer models meant to gain insights into clinically relevant scenarios.

In their most basic version (Fig. 1), such models are detailed reconstructions that allow for the 3D quantification of the anatomy and of its motion, as well as for the quantification of clinically relevant functional metrics, e.g., 3D strain distributions as computed from ultrasound imaging (Rego *et al.*, 2018) and fluid dynamic footprints of blood velocity fields as derived from 4D flow magnetic resonance imaging (Piatti *et al.*, 2017). In clinics, these models provide physicians with exhaustive and non-misleading information to plan interventions: relevant examples are the choice of the best access and path to reach a target without harming noble structures, as in neurosurgery (Ferroli *et al.*, 2013). The advent of augmented reality and virtual reality is empowering this type of model by providing the end-user with fully 3D and immersive renderings that allow for the better understanding of particularly complex anatomies, as in the case of patients whose anatomy is deranged by major congenital diseases (Butera *et al.*, 2019).

In their most sophisticated version (Fig. 1), patient-specific models simulate the physics of the analyzed organ or tissue (see, e.g., Krishnan *et al.*, 2015; Collia *et al.*, 2019). To this aim, the information on anatomy and motion of organs is complemented by the quantitative description of tissue micro-architecture (Lee *et al.*, 2014)—e.g., myocardial fiber organization derived from diffusion tensor imaging (Whittaker *et al.*, 2019)—and physical properties—e.g., mechanical properties, porosity, and electrical conductivity (Avazmohammadi *et al.*, 2017). These models are expected to be high-fidelity replicas, or digital twins, of the tissues of organs affected by the disease. As such, they are used to simulate potential treatments and quantify the associated response of the relevant tissue or organ in terms of, e.g., tissue stresses (Rausch *et al.*, 2017) or tissue remodeling (He *et al.*, 2019; Boland *et al.*, 2019). The computed variables are considered relevant, and sometimes pivotal, to predict potential acute intra- or peri-operative adverse events and longer-term effects of surgery. The potential of these models as tools to support decision making is in the possibility to define a set of parameters characterizing the envisioned treatment (e.g., type of technique; type, size, and location of the devices to be implanted and changes in patient conditions driven by drug therapy) and to systematically quantify the effects of the corresponding changes.

Owing to their potential, these patient-specific image-based computational models are becoming ubiquitous in (i) industrial R&D, where they are used to virtually test the effects of prototypal devices and, consistently with the 3R principles, they are coupled with *in vitro* testing to reduce the need for animal models; (ii) regulatory processes, where not only the results of computational modeling of medical devices are considered crucial to their approval by agencies but also computational modeling can embody the actual medical device (Software as Medical Device—SAMD); and (iii) clinical practice, where computational models are used as SAMDs for the analysis of pathological conditions, prognosis, and decision making.

PATIENT-SPECIFIC DIGITAL TWINS IN THE CLINICAL ARENA

To be adopted in the clinical routine, patient-specific digital twins must provide evidence of additional values as compared to standard approaches.

On the one hand, they can provide objective forecast capabilities and quantitative information, allowing for choosing among different

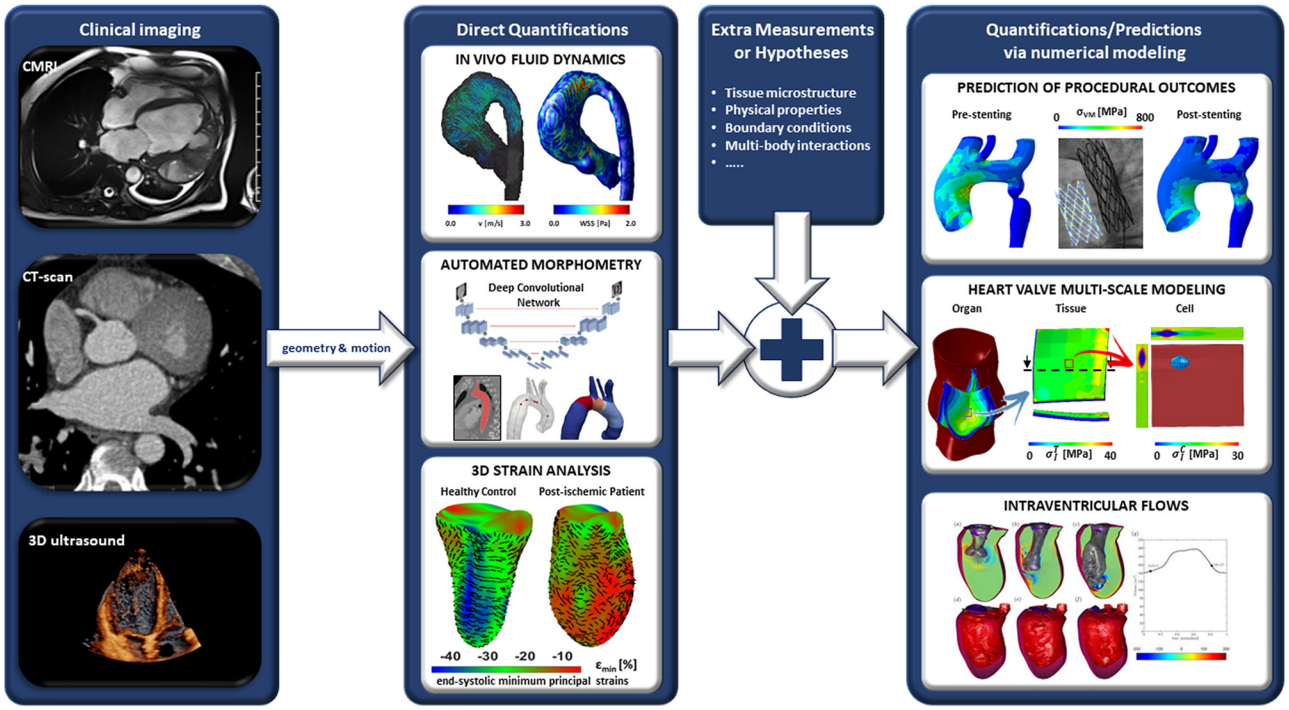

FIG. 1. Different types of patient-specific models and corresponding applications. Left panel: examples of medical imaging that can yield information on geometry and motion of tissues and organs. From top to bottom: CMRI = cardiac magnetic resonance imaging, CT-scan = computed tomography, and 3D ultrasound = three-dimensional echocardiography. Central panel: models based on the direct processing of clinical images to yield quantitative information. From top to bottom: space-resolved 3D blood velocity field in the aorta and associated wall shear stress (WSS) as derived from 4D flow CMRI sequences; automated AI-based classification of landing zones for the endovascular stenting of the thoracic aorta; and 3D strain field, complemented by the information on minimum principal strain directions, over the endocardial surface of a healthy and a post-ischemic left ventricle. Right panel: models that simulate the physics of organs and tissues through numerical modeling, based on the information from medical imaging complemented by extra measurements or hypotheses on the relevant aspects of the simulated system. From top to bottom: predictive simulation of the effects of endovascular stenting in a coarcted descending aorta; multiscale simulation of the structural mechanics of the aortic valve, relating the mechanics observed at the organ length scale to the mechanics observed at the tissue and cell length scales; and flow field within the left ventricle as computed through fluid–structure interaction modeling.

surgical approaches, devices, or sizes. Possibly, they should be capable of reducing the need for invasive planning procedures by identifying those cases where the surgical approach is actually beneficial. This is the case, for instance, of software to support the planning of transcatheter valve implantation by assessing the device post-implant deformation, as well as the risk for device migration, paravalvular leakage and, in the case of the aortic valve, conduction abnormalities (Rocatello *et al.*, 2019).

On the other hand, they can provide information in a cheaper or most effective way or a combination of the two. This is the case, for instance, of computational fluid-dynamics models for the estimation of the coronary Fractional Flow Reserve (FFR) in stenosed coronary vessels. This approach has proved a valid alternative to coronary angiography, showing a comparable sensitivity, i.e., capability to correctly identify patients with coronary obstruction, and specificity, i.e., capability to correctly identify those without coronary obstruction but at a significantly lower cost and without the risks associated with catheterism (Min *et al.*, 2015).

At the same time, to be effectively exploited in real clinical settings, a patient-specific digital twin must be (i) easy to use, i.e., it must not require end-users to master simulations; this may require the creation of an automated black-box system, where pre-operative medical imaging is uploaded and the computational results are then presented, through a completely automated processing system or by using an outsourcing service completing the model setup upon clinical data input; (ii) fast, i.e., the time-expense to obtain results must be compatible with clinical agendas; this can be obtained through state-of-the-art and robust supercomputing platforms available on the supervised computing system in the cloud; and (iii) reliable, i.e., the simplifications in the model must not lead the end-user to misjudge the simulated scenario. At this purpose, since computational results can be driven by many model parameters, these should be systematically changed within reasonable ranges to exhaustively explore the parameter space and assess the corresponding changes in model outputs, thus yielding results to the end user with confidence intervals.

THE ISSUE OF ACCURACY AND UNCERTAINTIES

Patient specific modeling is still far from being standardized. The most delicate issue related to patient specific models is their verifiability and validation. Verification consists in evaluating whether the model meets the requirements and specifications; it typically consists of the careful check of the hypotheses underlying the model and of the equations and parameters chosen for the description of the phenomenon.

Validation consists of the assessment of the capacity of the model to fulfill its intended purpose and to replicate the behavior of the real system.

The problem of accuracy is related mainly to the validation process and to the model robustness to "perturbations," i.e., the possibility that model inputs are, to some extent, uncertain.

Each aspect of the modeling process is a potential source of uncertainty. Even the initial, and apparently most basic, step, i.e., the 3D *reconstruction* of the relevant anatomies, is no exception. Despite the use of cutting-edge imaging technology, some anatomical structures may be not clearly visible or not visible at all because of insufficient space-resolution or contrast of the images. For example, with reference to cardiac biomechanics, valve leaflets are too thin for their thickness distribution to be captured from CMR or CT images; zoomed-in 3D ultrasound images can be used to this aim, but measurements are very operator-dependent. The chordal apparatus of atrioventricular valves cannot be reconstructed from *in vivo* clinical imaging. In small vessels, the space-resolution of clinical images is comparable to the lumen of the vessel and greater than the wall thickness.

The patient-specific *mechanical properties* of solid tissues are typically unknown. Their displacement can be estimated from imaging, as for the compliance of blood vessels. However, mechanical properties also depend on further parameters that may not be measurable, as, for vessel, wall thickness. The modeling of mechanical properties becomes particularly prone to uncertainty when dealing with soft tissues, whose stress–strain response is non-linear and in some cases anisotropic and viscoelastic. In the absence of patient-specific data, this complex response may be modeled based on data obtained from *ex vivo* mechanical testing. However, these are often obtained from animal models and, even when obtained from human tissue, are rarely specific to, e.g., the age, gender, ethnicity, and pathophysiological condition of the patient. The reliable modeling of tissue mechanical properties becomes even more complicated when dealing with contractile tissue, as for myocardium. Muscle contraction is dictated by the arrangement of myofibers, which can be appreciated with diffusion tensor magnetic resonance imaging (MRI) (Avazmohammadi *et al.*, 2019), but only in *ex vivo* studies or on animals, by the inotropic state of the heart as a whole, and by regional contractility, which can be dramatically heterogeneous especially in the case of post-ischemic and dilated pathological hearts. Similarly, the rheological properties of fluids (density and viscosity) in fluid dynamics simulations are, in almost every work in the literature, assumed regardless of the real situation of the patient. Although in this case it is possible to take a blood sample and carry out characterization tests and derive viscosity from the hematocrit measurement, this is never done. It has been estimated that the error made using data distributed within the physiological range can be of the order of 10% (Morbiducci *et al.*, 2011). Concerning blood, the comprehension of the mechanisms underlying its susceptibility to abnormal flow conditions is also crucial since abnormal flows determined by pathologic vessel morphologies or implanted devices can trigger thromboembolic events, which are ultimately responsible for a wide class of cardiovascular diseases (Kim *et al.*, 2019; Slepian *et al.*, 2017). Finally, there is a problem related to the simulation of the adaptive response of tissues and organs to surgical or pharmacological treatments: on the short and medium-terms, these may induce tissue growth and changes in solid tissue mechanical properties or in fluid tissue rheology. Such responses may be modeled mathematically, but predicting their time-evolution, even for the average patient, requires feeding the adaptation models with data gathered from longitudinal studies on wide cohorts of patients.

The boundary conditions and the associated uncertainty are also crucial. It is the case of patient-specific fluid dynamics simulations, where the 3D inflow velocity profile can significantly impact the domain flow field. However, clinical imaging has strong limitations in this perspective. Echo-Doppler can measure peak velocities, but it is strongly operator dependent and cannot provide information about the 3D velocity profile. Phase contrast magnetic resonance imaging (PC-MRI) in through-plane mode allows for the indirect measurement of blood through-plane velocity component distribution, and in 3D mode, the in-plane components can also be assessed (Pirola *et al.*, 2018). However, the use of to impose boundary conditions to patient specific models is not yet widespread, and PC-MRI data are hampered by relatively poor space- and time-resolution as compared to computational settings and by noise. As a result, PC-MRI does not yield accurate data on the small vessels; this limitation can affect also the simulation of blood fluid dynamics in medium- and large-size vessels with bifurcations (as in carotid arteries) or lateral branches (as for the supra-aortic vessels stemming from the aortic arch). Correctly imposing the flow rate repartition among outflow vessels is also pivotal, and even small errors can determine unrealistic velocity flow fields, e.g., with artificially created vorticosity and pressure gradients immediately upstream from the outlet sections (Morbiducci *et al.*, 2010; Pirola *et al.*, 2017). The setting of percentage distribution between the various outflow vessels, an option typically present in simulation codes, generates macroscopic errors. The use of one-dimensional lumped or 1D models connected to the 3D domain is a valid alternative that preserves the physics of the system but is sometimes complex to implement.

FROM DIGITAL TWINS TO *IN SILICO* TRIALS

Uncertainty in the definition of the various aspects of patient-specific models takes a different spin in the context of industrial R&D and regulatory science, where models are used to understand the safety and the effectiveness of a treatment/device not on a specific patient but rather in a specific clinical scenario, i.e., on an entire class of patients affected by a pathology of interest, whose intra- and inter-subject variabilities have to be accounted for. As a result, the concept of "virtual patient" has been introduced to indicate not only the anatomical and physical modeling of organs but also a broader approach that can combine patient-specific modeling as discussed earlier with statistical techniques. In this way, key factors such as age, gender, and activity level of the considered type of patients or tolerances in the design of the device whose implant is being simulated are accounted for (Morrison *et al.*, 2018). This approach leads to predicting endpoints relevant to safety and effectiveness, along with confidence intervals of the results.

FUTURE PERSPECTIVE: CHALLENGES AND OPPORTUNITIES

There are several challenges that must be tackled to move forward to the next-generation patient-specific models. First, concerning imaging, it is necessary to develop new algorithms for the estimation of deformations starting from 4D images. This information can be useful either for the model setting or for the model validation. There are interesting techniques under investigation such as nearest neighbor

search, optical flow, and spackle-tracking methods that can, once validated, directly produce information on the effective regional stiffness. This information can be used to assign patient-specific mechanical properties to tissues and to identify regions prone to rupture or with altered mechanical properties. In this context, an interesting approach recently proposed is elastography, a technique that allows us to know the properties of materials starting from the application of a known stimulus by observing its response through ultrasound or magnetic resonance (Elgeti *et al.*, 2014; Hollender *et al.*, 2012).

PC-MRI and 4D flow can be used to properly set fluid dynamics boundary conditions; velocity vectors can be acquired on specific planes defined by the radiologist during PC-MRI acquisitions. 4D flow could theoretically allow us to capture the entire fluid dynamics domain (Markl *et al.*, 2011; Piatti *et al.*, 2017) and replace computational fluid dynamic simulations. As a matter of fact, however, its spatiotemporal resolution is still inadequate, and it does not allow us to evaluate the effect of any therapeutic action since it does not possess any predictive capabilities. Also, 4D flow is affected by artifact due to the presence of metal objects in the patient. Novel approaches combining simulations and 4D flow acquisitions need to be set up for validation purposes, for the fine tuning of the model, or to improve the resolution of 4D flow.

There is a need for multiscale models to predict how changes at the organ and tissue length-scale can affect the cell response and identify mechanotransduction pathways (Ayoub *et al.*, 2020; Thomas *et al.*, 2019; Latorre and Humphrey, 2018). This approach can pave the way to the understanding of tissue and organ remodeling mechanisms for improved prognosis practice.

Artificial intelligence (AI) can play a key role in all these challenges. The use of convolutional neural network (CNN) for image segmentation is gaining interest since it allows us to obtain rapid, precise, and operator independent 3D imaging reconstruction. These approaches are based on training of an artificial intelligence system that learns to autonomously segment a specific anatomical domain from a large number of pre-segmented images. In this field, U-Net, first proposed in 2015 (Ronneberger *et al.*, 2015) specifically for biomedical image segmentation, is rapidly establishing itself as the gold standard thanks to its end-to-end settings and the need of relatively small image training datasets. Fully automatic image segmentation can pave the way for building deep learning-based frameworks for automating geometric and functional analysis, including ventricular function assessment (Ruijsink *et al.*, 2020) and myocardial tissue characterization (Puyol-Antón *et al.*, 2020).

Prospectively, machine learning algorithms could be fed with computational models to perform surrogate and real time simulations, providing fast alternatives to structural finite element methods for stress distribution assessment (Liang *et al.*, 2018) and to hemodynamic analysis (Liang *et al.*, 2020). However, despite the promising potential shown so far by AI-based algorithms and, in particular, by deep neural networks, the great variability of geometry and boundary conditions typical of biological systems, as well as the interplay between them, leads to the "curse of dimensionality," making data-driven models difficult, if not impossible, to train in high-dimensional feature spaces.

Eventually, another class of machine learning models that can actually change the rules of the game are physics informed neural networks (PINNs). PINNs are supervised learning algorithms that embed physics constraints into data-driven modeling, minimizing the discrepancy between measurements and partial differential equation solutions to perform data super-resolution or to infer the underlying physics equations from data (Raissi *et al.*, 2019). These models can be trained on noisy and sparse clinical data of blood flow and arterial wall displacement to obtain intravascular pressure and pulse wave velocity from noninvasive 4D flow MRI measurements (Kissas *et al.*, 2020).

In conclusion, after 20+ years from their conception, patient specific models can now really drive the pace in the biomedical arena, providing evidence of efficacy of novel medical devices, making available huge *in silico* patient populations for medical trials, allowing for real time simulation of different therapeutic scenarios thanks to a strict symbiosis of sophisticated *in vivo* data and advanced *in silico* technologies.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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