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

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 (Regó 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 perioperative 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 prototypical 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
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 vorticity 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 (Ruysink et al., 2020) and myocardial tissue characterization (Payol-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 (Raiiisi 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.

REFERENCES

Avazmohammadi, R., Soares, J. C., Li, D. S., Raut, S. S., Gorman, R. C., and Sacks, M. S., “A contemporary look at biomechanical models of myocardium,” Annu. Rev. Biomed. Eng. 21, 417–442 (2019).

Avazmohammadi, R., Hill, M., Simon, M., and Sacks, M. S., “Transmural remodeling of right ventricular myocardium in response to pulmonary arterial hypertension,” APL Bioeng. 1, 016105 (2017).

Ayoub, S., Howson, D. P., Lee, C. H., and Sacks, M. S., “On the role of predicted in vivo mitral valve interstitial cell deformation on its biosynthetic behavior,” Biomech. Model. Mechanobiol. (published online, 2020).

Boland, E. L., Grogan, J. A., and McHugh, P. E., “Computational modelling of magnesium stent mechanical performance in a remodelling artery: Effects of multiple remodelling stimuli,” Int. J. Numer. Methods Biomed. Eng. 35(10), e3247 (2019).

Butera, G., Sturla, F., Pluchinotta, F. R., Caimi, A., and Carminati, M., “Holographic augmented reality and 3D printing for advanced planning of sinus venous ASD/partial anomalous pulmonary venous return percutaneous management,” JACC: Cardiovascular Interventions 12(14), 1389–1391 (2019).

Collia, D., Zovatto, L., and Pedrizetti, G., “Analysis of mitral valve regurgitation by computational fluid dynamics,” APL Bioeng. 3, 036105 (2019).

Elgeti, T., Knebel, F., Hättasch, R., Hamm, B., Braun, J., and Sack, I., “Shear-wave amplitudes measured with cardiac MR elastography for diagnosis of diastolic dysfunction,” Radiology 271(3), 681–687 (2014).

Ferroli, P., Tringali, G., Acerbi, F., Schiariotti, M., Broggi, M., Aquino, D., and Broggi, G., “Advanced 3-dimensional planning in neurosurgery,” Neurosurgery 72(Suppl.,) A54–A62 (2013).

He, Y., Zuo, D., Hackl, K., Yang, H., Mousavi, S. J., and Avril, S., “Gradient-enhanced continuum models of healing in damaged soft tissues,” Biomech. Model. Mechanobiol. 18(5), 1443–1460 (2019).

Hollender, P. J., Wolf, P. D., Gooswami, R., and Trahey, G. E., “Intracardiac echocardiography measurement of dynamic myocardial stiffness with shear wave velocimetry,” Ultrasound Med. Biol. 38(7), 1271–1283 (2012).

Kim, D., Bresette, C., Liu, Z., and Ku, D. N., “Occulsive thrombosis in arteries,” APL Bioeng. 3, 041502 (2019).

Kissas, G., Yang, Y., Hwuang, E., Witschey, W. R., Detre, J. A., and Perdikaris, P., “Machine learning in cardiovascular flows modeling: Predicting arterial blood pressure from non-invasive 4D flow MRI data using physics-informed neural networks,” Comput. Methods Appl. Mech. Eng. 358, 112623 (2020).

Krishnan, K., Ge, L., Haraldsson, H., Hope, M. D., Saloner, D. A., Guccione, J. M., and Tseng, E. E., “Ascending thoracic aortic aneurysm wall stress analysis using patient-specific finite element modeling of in vivo magnetic resonance imaging,” Interact. Cardiovasc. Thorac. Surg. 21(4), 471–480 (2015).

Latorre, M., and Humphrey, J. D., “Critical roles of time-scales in soft tissue growth and remodeling,” APL Bioeng. 2, 026108 (2018).

AIP Bioeng. 4, 040401 (2020); doi: 10.1063/5.0031452
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Lee, C. H., Amini, R., Gorman, R. C., Gorman, J. H., 3rd, and Sacks, M. S., "An inverse modeling approach for stress estimation in mitral valve anterior leaflet valvuloplasty for in-vivo valvular bioprosthesis assessment," J. Biomech. 47(9), 2055–2063 (2014).

Li, L., Liu, M., Martin, C., and Sun, W., "A deep learning approach to estimate stress distribution: A fast and accurate surrogate of finite-element analysis," J. R. Soc. Interface 15(138), 20170844 (2018).

Mard, M., Kilner, P. J., and Ebbers, T., "Comprehensive 4D velocity mapping of the heart and great vessels by cardiovascular magnetic resonance," J. Cardiovasc. Magn. Reson. 13(1), 7 (2011).

Min, J. K., Taylor, C. A., Achenbach, S., Koo, B. K., Nørgaard, B. L., Markl, M., Kilner, P. J., and Ebbers, T., "Comprehensive 4D velocity mapping of the heart and great vessels by cardiovascular magnetic resonance," J. Cardiovasc. Magn. Reson. 13(1), 7 (2011).

Morbiducci, U., Gallo, D., Massai, D., Consolo, F., Ponzini, R., Antiga, L., Bignardi, C., Deriu, M. A., and Redaelli, A., "Outflow conditions for image-based hemodynamic models of the carotid bifurcation: Implications for indicators of abnormal flow," J. Biomech. Eng. 132(9), 091005 (2010).

Morbiducci, U., Gallo, D., Massai, D., Ponzini, R., Deriu, M. A., Antiga, A., Redaelli, A., and Montevereci, F. M., "On the importance of blood rheology for bulk flow in hemodynamic models of the carotid bifurcation," J. Biomech. 44(13), 2427–2438 (2011).

Morrison, T. M., Pathmanathan, P., Adwan, M., and Magrerrison, E., "Advancing regulatory science with computational modeling for medical devices at the FDA’s office of science and engineering laboratories," Front. Med. 5, 241 (2018).

Piatti, F., Sturla, F., Bisell, M. M., Pirola, S., Lombardi, M., Nesteruk, I., Della Corte, A., Redaelli, A., and Votta, E., "4D flow analysis of BAV-related fluid-dynamic alterations: Evidence of wall shear stress alterations in absence of clinically-relevant aortic anatomical remodeling," Front. Physiol. 8, 441 (2017).

Pirola, S., Jarral, O. A., O’Regan, D. P., Asimakopoulos, G., Anderson, J. R., Pepper, J. R., Athanasiou, T., and Xu, X. Y., "Computational study of aortic hemodynamics for patients with an abnormal aortic valve: The importance of secondary flow at the ascending aorta inlet," APL Bioeng. 2, 026101 (2018).

Pirola, S., Cheng, Z., Jarral, O. A., O’Regan, D. P., Pepper, J. R., Athanasiou, T., and Xu, X. Y., "On the choice of outlet boundary conditions for patient-specific analysis of aortic flow using computational fluid dynamics," J. Biomech. 60, 15–21 (2017).

Puyol-Antón, E., Ruijsink, B., Baumgartner, C. F., Masci, P., Sinclair, M., Konukoglu, E., Razavi, R., and King, A. P., "Automated quantification of myocardial tissue characteristics from native T1 mapping using neural networks with uncertainty-based quality-control," J. Cardiovasc. Magn. Reson. 22(3), 60 (2020).

Raisi, M., Perdirakis, P., and Karniadakis, G. E., "Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations," J. Comput. Phys. 378, 686–707 (2019).

Rausch, M. K., Zöllner, A. M., Genet, M., Baillargeon, B., Bothe, W., and Kuhl, E., "A virtual sizing tool for mitral valve annuloplasty," Int. J. Numer. Method Biomed. Eng. 33(2), e02788 (2017).

Rego, B. V., Khalighi, A. H., Drach, A., Lai, E. K., Pouch, A. M., Gorman, R. C., Gorman, J. H. III, and Sacks, M. S., "A noninvasive method for the determination of in vivo mitral valve leaflet strains," Int. J. Numer. Methods Biomed. Eng. 34(12), e3142 (2018).

Ruijsink, B., Puyol-Antón, E., Olsouf, I., Sinclair, M., Bai, W., Schnabel, J. A., Razavi, R., and King, A. P., "Fully automated, quality-controlled cardiac analysis from CMR: Validation and large-scale application to characterize cardiac function," JACC. Cardiovasc. Imaging 13(3), 684–695 (2020).

Rocatello, G., Faquir, N. E., De Backer, O., Swaans, M. J., Latih, A., Vicentini, L., Segers, P., De Beule, M., de Jaegere, P., and Mortier, P., "The impact of size and position of a mechanical expandable transcatheter aortic valve: Novel insights through computational modelling and simulation," J. Cardiovasc. Transl. Res. 12(5), 435–446 (2019).

Ronneberger, O., Fischer, P., and Brox, T., "U-net: Convolutional networks for biomedical image segmentation," International Conference on Medical Image Computing and Computer-Assisted Intervention (Springer, Cham, 2015).

Slepian, M. J., Sheriff, J., Hutchinson, M., Tran, P., Bajaj, N., Garcia, J. G. N., Scott Saavedra, S., and Bluestein, D., "Shear-mediated platelet activation in the free flow: Perspectives on the emerging spectrum of cell mechanosensory mechanisms mediating cardiovascular implant thrombosis," J. Biomech. 50, 20–25 (2017).

Thomas, V. S., Lai, V., and Amini, R., "A computational multi-scale approach to investigate mechanically-induced changes in tricuspid valve anterior leaflet microstructure," Acta Biomater. 94, 524–535 (2019).

Whittaker, D. G., Benson, A. P., Teh, J., Schneider, J. E., and Colman, M. A., "Investigation of the role of myocyte orientations in cardiac arhythmia using image-based models," Biophys. J. 117(12), 2396–2408 (2019).