Building digital twins for personalized cardiovascular medicine: Advances, challenges, and future directions

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Editorial

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The concept of the digital twin, already widely adopted in traditional engineering domains such as aerospace, automotive, and manufacturing, is now gaining traction in the healthcare sector, including the cardiovascular domain. Various definitions of digital twins exist, ranging from broad to more restrictive interpretations [1]. According to the EDITH support action [2], digital twins can be defined as "virtual representations of a physical object, process or system across its life-cycle" [3]. These systems use "data and other sources to enable learning, reasoning, and recalibrating (either dynamically or through human-in-the-loop decision making) for monitoring, diagnostics and prognostics" [3]. These virtual tools integrate, in a coherent and potentially dynamic way, the clinical data acquired over time for an individual by applying physics-based (mechanistic) models and/or data-driven approaches, including standard statistical methods or artificial intelligence (AI) -based approaches [4,5]. Although still rarely implemented in healthcare [1], the dynamic nature of digital twins represents a key feature. It refers to their ability to incorporate a real-time component, allowing ongoing interaction between the models and patient or application, and regular updates with clinical measurements and imaging data [6]. In general, digital twins can support the three main phases of the clinical workflow [5]: (i) optimizing data acquisition and the extraction of clinically relevant information, (ii) assessing current health status to guide diagnosis and risk stratification, and (iii) supporting the selection and optimization of medical devices and therapeutic strategies to ensure effective, personalized treatment.

Within this context, the Special Issue titled "Building digital twins for personalized cardiovascular medicine" aims to showcase recent advances in subject-specific digital twins for cardiovascular applications. The Special Issue brings together 32 articles (31 full-length research articles and 1 review), accepted for publication out of 38 submissions received by the journal between 2024 and 2025, and selected from approximately 50 total expressions of interest. Collectively the articles highlight the potential of digital twins as virtual and high-fidelity representations of individual patient conditions or cardiovascular devices to support key clinical tasks such as personalized risk assessment, outcome prediction, and therapy planning.

The contributions included in this Special Issue present digital twins covering a wide spectrum of anatomical regions, ranging from the whole circulation [7] to vascular territories such as the aorta (i.e., ascending aorta [8,9], ascending and thoracic aorta [10–13], thoracic aorta [14,15], abdominal aorta [16], fetal aortic arch [17]), coronary arteries [18], pulmonary artery [19], liver vasculature [20], Circle of Willis [21], and peripheral microvasculature [22,23], to the aortic valve [24] and the heart (i.e., atrial regions [25–28], left ventricle [29–33] and both ventricles or the whole heart [34–37]). Several of these studies specifically focus on modeling of cardiovascular devices or treatment procedures. Device modeling includes stent-grafts used in thoracic endovascular aortic repair (TEVAR) [10] and abdominal endovascular repair [16], transcatheter aortic valve implantation (TAVI) [13,24], coronary artery stents [18], left ventricular assist devices [9], and left atrial appendage occlusion devices [25]. Treatment procedure modeling covers the surgical repair of thoracic aortic aneurysms [14] and Type A aortic dissection [8], excision [28] or inversion [26] of the left atrial appendage, and the surgical ventricular restoration [30].

From a methodological viewpoint, most contributions are grounded in physics-based (mechanistic) models, which rely on established physical laws governing cardiovascular physiology and biomechanics, and use computational simulations to investigate hemodynamics, structural mechanics, or electrophysiology in clinically relevant scenarios. Among the proposed modeling strategies, computational fluid dynamics (CFD) and fluid-structure interaction (FSI) simulations are employed to analyze blood flow in patient-specific anatomies and to assess the fluid dynamic performance of vascular devices under physiological or pathological flow conditions. Various numerical strategies are represented in this Special Issue, underscoring that no single methodological approach is favored within the research community in this

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field and that a consensus on this aspect still appears distant. Specifically, CFD analyses rely on the finite volume method [11,17,19,20] or the finite element method [10,12], implemented in commercial (i.e., ANSYS CFX and ANSYS Fluent) [11,17,19,20] or open-source software (i.e., SimVascular [38]) [10,12]. FSI analyses in Ref. [14] make use of the finite element-based open-source software CRIMSON [39], which enables the use of the coupled momentum method to model compliant vessel walls. These approaches are applied to study altered hemodynamics in thoracic or abdominal aortic segments following stent-graft implantation [10,11], evaluate the hemodynamic effectiveness of surgical repair of thoracic aortic aneurysms [14] and intervention for fetal coarctation of the aorta [17], characterize turbulence and postoperative flow redistribution in complex reconstructions such as the Norwood procedure [12], and explore pulmonary hemodynamics and right ventricular adaptation in the context of pulmonary hypertension [19]. Additionally, CFD simulations coupled with an optimization strategy are employed to model the delivery of radioactive microspheres into the hepatic artery aimed at improving anti-tumor therapy efficacy [20]. Structural simulations based on finite element analysis are used to model cardiovascular device implantation and treatment procedures. Most of the simulations presented were performed using the commercial DASSAULT SYSTEMS SIMULIA Abaqus solvers [8,13,16,25,26], with the exception of those in Ref. [24], which utilized the commercial explicit solver available in ANSYS LS-Dyna. Applications include the analysis of braided occlusion devices for the left atrial appendage [25], stent-grafts in the abdominal aorta [16], and TAVI [13,24], as well as Type A aortic dissection repair [8], or minimally invasive surgical procedures [26]. Electrophysiology models simulate atrial and ventricular activation sequences, scar-related conduction abnormalities, and the influence of anatomical variability on cardiac electrical propagation. In this Special Issue, contributions span patient-specific models investigating the influence of scar morphology on ablation strategies [32], which, from a methodological viewpoint, rely on the Reaction-Eikonal formulation of cardiac electrophysiology [40] implemented in the commercial package NumeriCor CARPentry-Pro; a computational framework for prescribing highly detailed myofiber orientations and providing robust regional annotation in bi-atrial morphologies combined with electrophysiology simulations based on an in-house implementation of the Eikonal-diffusion model [27]; a computational framework for assessing arrhythmogenesis, which is based on a modified version of the Ten Tusscher-Panfilov model [41] that incorporates ionic variations occurring during the early phase of acute myocardial ischemia [33]; and platform-level electrophysiology toolboxes that facilitate model personalization and simulation workflows, using monodomain solvers to simulate cardiac electrical activity [37].

A smaller subset of contributions is based on data-driven approaches to characterize cardiovascular dynamics, estimate parameters, or predict relevant clinical outcomes. The methodologies adopted range from traditional machine learning techniques to more advanced deep learning approaches. In particular, metamodeling techniques are employed to accelerate parameter estimation and uncertainty quantification in lumped cardiovascular models [7]. Neural operator transformer architectures are used to reconstruct cerebral hemodynamics in the Circle of Willis from sparse clinical data [21]. Physics-informed neural networks are applied to reconstruct complex blood flow in the presence of aortic stenoses [15]. AI-driven system identification methods are used to capture heart rate dynamics through zero-poles modeling and evolutionary learning [36]. Machine learning is also adopted to support cardiovascular parameter identification and scenario simulation in patients undergoing extracorporeal membrane oxygenation and continuous renal replacement therapy [23], and to enhance personalized hypertension risk prediction by integrating diverse clinical, lifestyle, and genetic data sources [42]. In most of these studies, models were implemented in Python, leveraging widely used open-source libraries for AI, such as TensorFlow [43], Open TURNS [44], scikit-learn [45], and PyTorch [46].

The importance of integrating physics-based models with data-driven tools capable of identifying task-specific patterns and correlations is increasingly recognized, as this synergy can potentially leverage the complementary strengths of both approaches [4]. A representative example is provided by the integration of data-driven modeling with electrocardiographic imaging and cardiac digital twins to improve the localization of premature ventricular contractions [34]. In this work [34], synthetic datasets generated through electrophysiological simulations are used to optimize a computational model capable of markedly reducing localization errors compared to standard electrocardiogram-based methods. This hybrid approach shows how data-driven analysis, informed by patient-specific physics-based models, can enhance the diagnostic accuracy and clinical applicability of non-invasive mapping of arrhythmic sources.

Across the contributions presented in this Special Issue, model credibility and its assessment clearly emerge as central themes for the development of clinically applicable digital twins. Assessing model credibility involves performing verification, validation, and uncertainty quantification within a standardized process, as recommended by the ASME Verification and Validation 40 standard [47]. Several contributions address these aspects explicitly. For instance, Grossi et al. [24] validate patient-specific finite element simulations of TAVI by comparing them against clinical imaging data. Tunedal et al. [31] propose a structured approach to quantify uncertainty in model-derived hemodynamic biomarkers from non-normal data distributions. Hanna et al. [7] present a pipeline integrating metamodeling with sensitivity analysis, parameter estimation, and uncertainty quantification for lumped cardiovascular models of circulation and transport, as previously mentioned.

The barriers to the effective clinical use of cardiovascular digital twins remain numerous [1,48], as also reflected in the contributions to this Special Issue. In particular, challenges related to feasibility, methodology, and performance are frequently highlighted. First, the limited availability of high-quality patient-specific data often limits model personalization and hinders the accurate definition of boundary conditions, particularly for CFD and FSI simulations where direct in vivo measurements are often lacking. Second, model credibility remains a key issue. Verification, validation, and uncertainty quantification activities should consistently be performed to ensure reliability and support regulatory acceptance. In addition, clinical validation of digital twin predictions is essential and requires dedicated prospective studies, which have not yet been conducted. Third, computational demands remain high, particularly for high-fidelity CFD, FSI, and electrophysiology simulations, as well as for tasks such as sensitivity analysis, parameter estimation, and uncertainty quantification, along with the training of large deep learning models, thereby limiting real-time or routine clinical application. Most of the simulations presented in the Special Issue were executed on high-performance computing resources, from dedicated workstations to GPU-accelerated clusters, typically requiring several hours or even days to complete. Such prolonged runtimes can be especially critical in clinical contexts where the time window between diagnosis and treatment is extremely limited. Potential optimizations, such as the implementation of efficient reduced-order models (see, for instance, Ref. [7]), remain uncommon. Fourth, the absence of standardized modeling workflows hinders reproducibility and comparison across studies. Lastly, translating simulation outputs into clinically meaningful insights and integrating digital twins into decision-making tools within the highly regulated information systems of medical centers remains a major challenge. A critical aspect of this challenge is finding the right balance between the sophistication of digital twin models, the accuracy of their predictions, and their feasibility in real-world clinical settings, which are often resource-constrained and frequently limited in the availability of clinical input data as part of standard of care protocols [49]. Beyond technical aspects, sustainable business models must also be considered, since the clinical adoption of digital twins will depend on mechanisms such as

insurance reimbursement and the demonstration of economic value for developers of these computational technologies [50]. Furthermore, the long-term success of digital twins will require acceptance from key stakeholders [50]: clinicians must view them as reliable and practical tools that enhance, rather than complicate, decision-making, while patients need to trust predictions and recommendations generated through digital twins. The road ahead on these aspects remains long, and achieving an overall balance between technical rigor and feasibility, economic sustainability, and social acceptance will be decisive for enabling digital twins to progress from research tools to scalable solutions for everyday medical practice in the cardiovascular field.

Despite the barriers described above, the adoption of cardiovascular digital twins holds promise across multiple points of the healthcare value chain, from supporting clinicians with advanced tools for risk stratification, pre-operative planning, and therapy optimization, to enabling virtual trials that can accelerate research, reduce costs, and provide evidence at a scale not achievable with traditional studies [5]. However, realizing this potential will require dedicated revenue models that ensure accessibility and usability. Examples include per-case or per-procedure fees, pre-trial or virtual cohort pricing, as well as licenses for application programming interfaces or marketplace platforms hosting third-party solvers. At the same time, the benefits of cardiovascular digital twins must be demonstrable and quantifiable in terms of clinical impact, such as reducing the need for invasive measurements or radiation exposure, saving procedure or diagnosis time, preventing complications, shortening hospital stays, lowering readmissions, and decreasing both size and duration of clinical trials [51]. In this regard, aligning digital twin adoption with the principles of value-based healthcare could provide a strategic pathway to maximize health outcomes per unit cost, shifting the focus from service volume to measurable improvements in patient outcomes and cost-efficiency [52].

From a clinical perspective, it is important to consider how cardiovascular digital twins can remain aligned with the dynamic nature of patient care. They should evolve in parallel with a patient's life cycle by continuously integrating longitudinal data from diverse sources, including information collected over months or years through continuous monitoring, real-time updates, and personalized parameter adjustments [51]. Such dynamic enhancement is crucial for developing adaptive digital twins that accurately mimic the evolving complexities of patient-specific physiological and pathological conditions, enabling tailored insights and guidance for optimal cardiovascular care. Achieving truly functional digital twins, such as those envisioned in cardiac electrophysiology, requires the seamless incorporation of new data, allowing models to predict both immediate therapeutic responses and long-term disease progression [53]. In cardiac surgery, continuously updated digital twin models could significantly improve post-operative monitoring by enabling early detection of complications and supporting more effective recovery assessments during follow-up. Ultimately, this evolution will allow cardiovascular digital twins to inform and enhance personalized risk assessment, prevention, and treatment of disease.

In conclusion, although the path toward widespread, safe, and standardized clinical adoption of digital twins in cardiovascular medicine is still in its early stages, this Special Issue highlights a field undergoing rapid progress. The contributions showcase current digital twin applications across a broad spectrum of cardiovascular regions and therapeutic devices, leveraging both mechanistic and data-driven methodologies. While technical, clinical, and regulatory challenges remain, the diversity and quality of the studies presented underscore the strong potential of subject-specific digital twins to advance personalized cardiovascular care in the near future. Over the next five years, the development of credible and trustworthy digital twins is expected to become increasingly central, supported by assessment standards endorsed by regulatory agencies for medical device evaluation. At the same time, concrete progress is anticipated in reducing computational time and resource demands, particularly for physics-based models, thereby moving closer to an effective integration of digital twins into decision-support tools for clinical practice.

CRediT authorship contribution statement

Claudio Chiastra: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Selene Pirola:** Writing – review & editing, Conceptualization. **Simone Saitta:** Writing – review & editing, Conceptualization. **Francesco Sturla:** Writing – review & editing, Conceptualization. **John F. LaDisa:** Writing – review & editing, Conceptualization.

Ethics statement

This article is an Editorial. No research activities were conducted, and therefore, no Ethics statement is required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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