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Digital twin systems for musculoskeletal applications: A current concepts review

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Abstract

Digital twin (DT) systems, which involve creating virtual replicas of physical objects or systems, have the potential to transform healthcare by offering personalised and predictive models that grant deeper insight into a patient's condition. This review explores current concepts in DT systems for musculoskeletal (MSK) applications through an overview of the key components, technologies, clinical uses, challenges, and future directions that define this rapidly growing field. DT systems leverage computational models such as multibody dynamics and finite element analysis to simulate the mechanical behaviour of MSK structures, while integration with wearable technologies allows real-time monitoring and feedback, facilitating preventive measures, and adaptive care strategies. Early applications of DT systems to MSK include optimising the monitoring of exercise and rehabilitation, analysing joint mechanics for personalised surgical techniques, and predicting post-operative outcomes. While still under development, these advancements promise to revolutionise MSK care by improving surgical planning, reducing complications, and personalising patient rehabilitation strategies. Integrating advanced machine learning algorithms can enhance the predictive abilities of DTs and provide a better understanding of disease processes through explainable artificial intelligence (AI). Despite their potential, DT systems face significant challenges. These include integrating multi-modal data, modelling ageing and damage, efficiently using computational resources and developing clinically accurate and impactful models. Addressing these challenges will require multidisciplinary collaboration. Furthermore, guaranteeing patient privacy and protection against bias is extremely important, as is navigating regulatory requirements for clinical adoption. DT systems present a significant opportunity to improve patient care, made possible by recent technological advancements in several fields, including wearable sensors, computational modelling of biological structures, and AI. As these technologies continue to mature and their integration is streamlined, DT systems may fast-track medical innovation,

Abbreviations: 3D, three-dimensional; ACL, anterior cruciate ligament; AI, artificial intelligence; ASME, American Society of Mechanical Engineers; CFD, computational fluid dynamics; COU, context of use; CT, computed tomography; DCGAN, deep convolutional generative adversarial network; DT, digital twin; EMA, European Medicines Agency; FDA, Food and Drug Administration; FE, finite element; FEA, finite element analysis; MBD, multibody dynamics; ML, machine learning; MoCap, motion capture; MONAI, Medical Open Network for AI; MRI, magnetic resonance imaging; MSK, musculoskeletal; NASA, National Aeronautics and Space Administration; PMMA, polymethyl methacrylate; sEMG, surface electromyography; TKA, total knee arthroplasty; UQ, uncertainty quantification; VR, virtual reality; VVUQ, verification, validation and uncertainty quantification.

ushering in a new era of rapid improvement of treatment outcomes and broadening the scope of preventive medicine.
Level of Evidence: Level V.

KEYWORDS
artificial intelligence, digital twin, musculoskeletal, orthopaedic surgery, personalised medicine, rehabilitation

INTRODUCTION

A digital twin (DT) is a virtual replica of a physical object or system that uses data-driven simulations for various applications [91, 108, 118, 119]. These applications include predictive maintenance, performance optimisation, product development, operational efficiency, personalisation, safety, and monitoring across multiple fields such as healthcare, manufacturing, infrastructure, energy, telecommunications, and retail [11, 75, 118, 119].

Personalised medicine, including precision medicine, entails tailoring treatments, and healthcare decisions to the patient's specific characteristics [66, 114] and has recently emerged to address some of the most difficult challenges in healthcare. Such challenges are partly related to rising costs and increasing complexity, including efficient resource allocation while ensuring high-quality care and providing focused treatment while fostering a holistic view of the patient [126]. However, significant obstacles must be addressed to implement personalised medicine approaches, including combining patient data from different sources and the need for extensive research to utilise this data effectively [65]. Unfortunately, the exponential growth of medical knowledge [35] outpaces our ability to effectively and efficiently integrate new information into clinical practice and research [115]. As a result, the medical field often struggles to iterate efficiently, leading to the slow adoption of novel techniques, treatments, and technologies [41, 106], further complicating the development of personalised care approaches.

DTs could be a potentially transformative solution, offering a platform to integrate and analyse vast amounts of data, accelerate medical research, and simulate personalised treatments efficiently [3, 118]. Moreover, DTs may offer a deeper understanding of complex biological systems, diseases, and injuries [118]. Accordingly, DTs have recently received considerable attention in healthcare and across several industries, further propelled by generative artificial intelligence (AI) developments [27]. The global DT market was valued at 10.1 billion USD in 2023 and is projected to reach 110.1 billion USD by 2028, growing at a compound annual growth rate of 61.3% over the forecast period [78].

DT systems can potentially address key challenges in orthopaedics, including optimising implant design, tailoring surgical indications, and techniques to individual patients, and improving the monitoring of postoperative rehabilitation and recovery [33, 49]. Apart from enhancing the precision and efficiency of surgical planning, these systems can facilitate real-time intraoperative decision-making through integration with augmented reality [109], while leveraging predictive analytics to identify and mitigate potential complications such as implant failure [33].

This paper reviews current concepts related to DT systems for musculoskeletal (MSK) applications. It explores the components of such systems, their validation, clinical MSK applications, present challenges, and future directions.

OVERVIEW OF DT SYSTEMS

The National Aeronautics and Space Administration (NASA) first implemented a concept akin to a DT in the 1970s to model aircraft and address real-time problems as they arose [15]. This concept proved essential during the Apollo 13 mission following an explosion in one of the oxygen tanks [89]. Using simulation, NASA could simulate the conditions on Apollo 13, test various scenarios and solutions, and ultimately ensure the safe return of the spacecraft and astronauts to Earth [15].

The concept of DTs was presented by Grieves in 2002 while discussing product lifecycle management, but the term was not formally introduced until 2005 [51]. Since then, numerous related terms and descriptors have emerged [68]. A synthesis of these terms, their meanings, and other relevant concepts are provided in Table 1. In 2010, Grieves and Vickers, while working at NASA, further explored DTs as virtual models of physical systems [51]. According to their description, a DT consists of three components: the physical object or system, its virtual replica, and a connection between the two, allowing the virtual model to be mapped to the actual system in real time.

Thus, DTs are often dynamic virtual models that mirror the behaviours and states of physical entities in real time [11, 24, 66]. A crucial characteristic for some authors is *bidirectional mapping*, where real-time, real-world data updates the DT, and insights from the DT

TABLE 1 Here's a table with concise definitions for the terms aimed at orthopaedic surgeons: Key concepts and definitions regarding digital twin (DT) systems.

Term	Definition
Bidirectional mapping	Real-time, real-world data updates the DT, and insights from the DT inform actions on the physical system [11, 24, 66].
Computational fluid dynamics	A numerical method dividing fluid domains into finite control volumes to study fluid flows by solving Navier–Stokes equations [124].
Data-driven DTs	Utilise data analytics, ML, and statistical methods to model and predict system behaviour [84].
DT	A virtual replica of a physical object or system using data-driven simulations for various applications [91, 108, 118, 119].
Edge computing	Processes data near its source and, with federated learning, enhances security by keeping sensitive information local while storing processed data remotely [3].
Finite element analysis	A numerical method divides complex systems into finite elements to predict responses to forces, heat, and other agents [30].
Hybrid DTs	Integrate empirical data with physical models to enhance DTs' accuracy, reliability, and scope [84].
Imaging segmentation	Identifying and classifying anatomical structures like bones, cartilage, tendons, muscles, and ligaments in medical images [47].
Multi-modal data fusion	Integrates data from various sources, such as imaging, biomechanical, and clinical data [3].
Multibody dynamics	Studies the movement and behaviour of interconnected, rigid or flexible bodies under external forces [60].
Personalised medicine	Tailoring treatments and healthcare decisions to the patient's specific characteristics [66, 114].
Physics-driven DTs	Based on mathematical models and physical laws, effective for well-described simulations of physical events [105].
Verification, validation and uncertainty quantification	Processes ensuring model accuracy, reliability, and understanding variability in simulations [91].

Abbreviation: ML, machine learning.

inform actions on the physical system; for these authors, that is the main distinction from other forms of computational modelling [11, 24, 66]. Nevertheless, the necessity of DTs to have real-time data has been questioned in healthcare [101], and what differentiates DTs from other forms of computational modelling is still being debated [119]. This on-going debate highlights the complexity and the evolving nature of the field of DT systems. As stated by Tang and Dai, DTs definitions and categorisations are not uniformly agreed upon, as DTs lack 'a unifying approach', especially regarding classification and roadmaps for developing DTs of the human body [118], with these authors having proposed such a plan.

Broadly, DTs can be categorised into data-driven, physics-driven, or hybrid [91]. Data-driven DTs utilise data analytics, machine learning (ML), and statistical methods to model and predict system behaviour [84]. These are more suited towards scenarios with abundant data and fuzzy processes. Physics-driven DTs (Figure 1) are based on mathematical models and simulations of physical laws, requiring detailed knowledge of the system's mechanisms [105]. These are effective in well-described simulations of physical events. Hybrid DTs, however, offer a promising future as they integrate both approaches, combining empirical data with physical models to enhance the accuracy, reliability, and scope of DTs and have been shown to outperform data- and physics-driven versions [84].

Notable examples of DT systems in medicine include applications in cardiology, such as the Living Heart Project developed by Dassault Systèmes [14]. The Living Heart Project is a collaborative initiative uniting cardiovascular researchers, medical device developers, and regulatory agencies to create highly accurate, personalised digital human heart models [31]. These models aim to support medical device design/testing, clinical diagnosis, and education advancements [16, 80, 128]. Another example is the Swedish Digital Twin Consortium initiative, which focuses on developing patient-specific drug therapies [18]. This approach involves creating unlimited copies of network models encompassing all molecular, phenotypic, and environmental factors relevant to disease

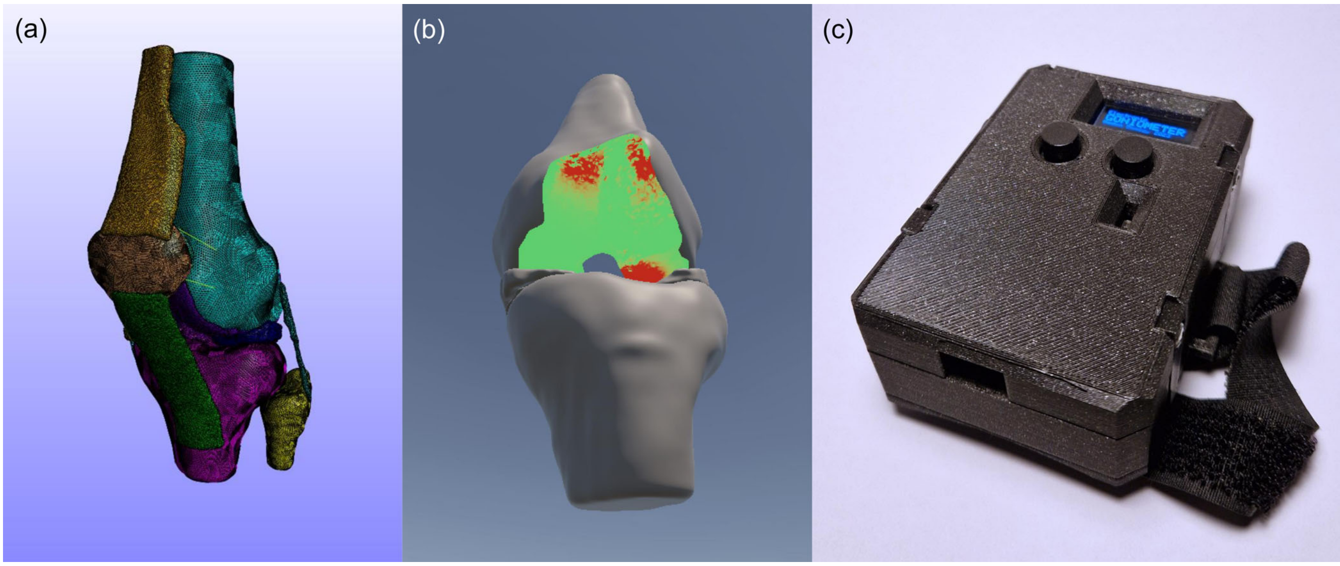

FIGURE 1 Example of a physics-driven digital twin of the knee. Model created using Unity (Unity Technologies) based on a finite element model from the Open Knee(s) open-source library [25]. Using results of a finite element analysis using FEBio [77] (a), simulating a passive knee flexion-extension, the 3D geometry of the knee was imported into Unity and Cauchy stress tensor values at the trochlea cartilage were mapped in real-time as a function of knee joint position (b). A wearable sensor based on an Arduino Nano 33 BLE microcontroller (Arduino) was used to track knee joint position in real time (c).

mechanisms in individual patients. These DTs are then computationally *treated* with thousands of drugs to identify the best-performing treatment. Finally, one of the first examples of DTs is using glucose monitors and insulin injectors to manage diabetes [82]. These systems continuously monitor blood glucose levels in real time and adjust insulin delivery accordingly.

The field of DTs is rapidly evolving [51]. The introduction of Computer-Aided Design in the 1980s marked the ability to store geometrical information in computers. Still, it was in the 2000s that the DT era truly began, with the development of 3D modelling [51]. Other noteworthy technological landmarks include the Internet of Things, 5G communication technology, cloud computing, and AI [61, 76, 121]. The following section lists the main concepts and technological enablers related to DTs, but it should be noted that such a list is far from exhaustive.

COMPONENTS OF MSK DTs

Several architectures have been proposed for DTs [32, 110], with their discussion being beyond the scope of this review. However, regardless of their specific features and architecture, DTs tendentially have a common characteristic: a modular nature [29]. Thus, DT components may be developed and function independently [79].

AI can significantly enhance MSK DTs' design, development, and deployment by improving data processing and integration, fine-tuning simulations, providing real-time anomaly detection, generating synthetic data for scenario analysis, offering outcome predictions, and enabling an improved understanding of the underlying logic behind them [50, 56, 118]. While specific instances where AI can be used to improve the development and operation of DTs are mentioned, the readers are referred elsewhere for an extensive discussion on the practical implementation of AI in orthopaedic clinics and research [93, 134, 135].

This section provides readers with an overview of the common concepts and components that may be part of MSK DTs. However, it should be noted that this list is not exhaustive and that only some of the following items must be present for the implementation to be considered a DT. As a simplification, these are grouped into the three main aspects of a DT, as defined by the Industrial Internet Consortium: data, models, and services [69]. These three aspects, however, are closely related and often overlap [69].

Data

Imaging segmentation

The foundation of physics-driven or hybrid MSK DTs is an accurate reconstruction of the patient's anatomy, typically derived from medical imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) [4, 56, 82, 83, 116]. Imaging segmentation involves identifying and classifying anatomical structures such as bones, cartilage, tendons,

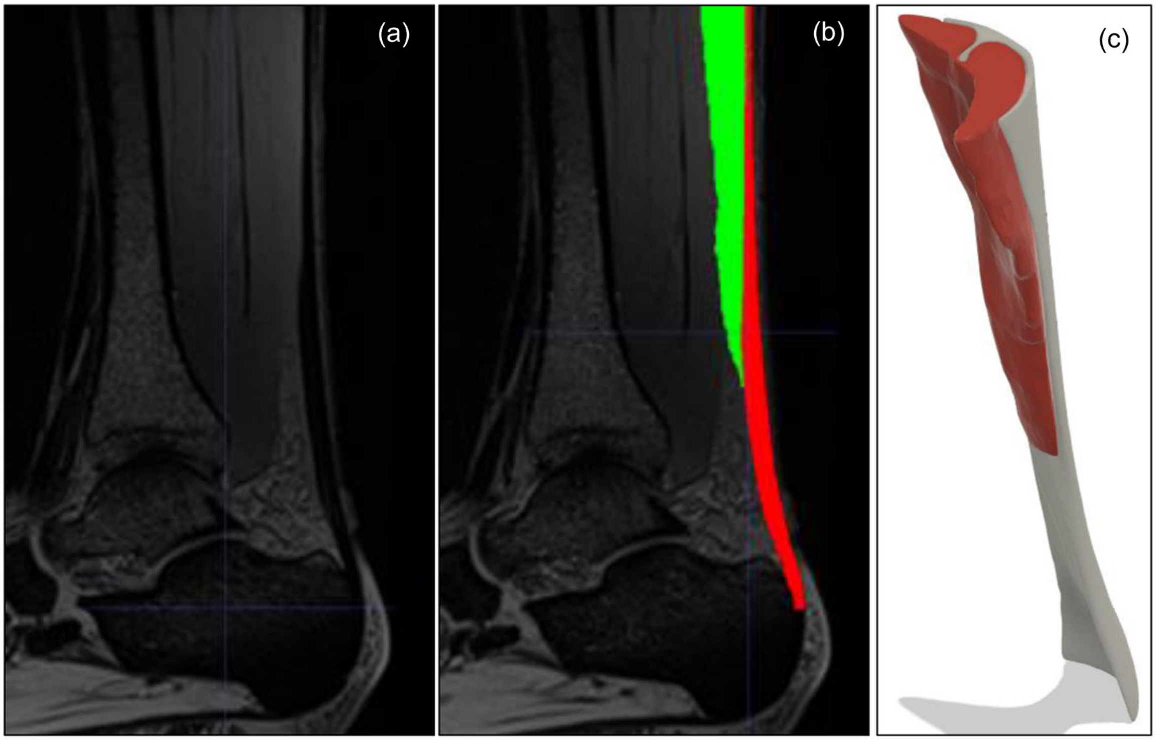

FIGURE 2 Segmentation of an Achilles tendon and distal portion of the soleus muscle. (a) Magnetic resonance imaging (MRI) of an ankle captured using a 1.5 T MRI machine (Siemens Magnetom Aera 1.5 T, Siemens), with the image depicting a T2*-FS sagittal scan slice (repetition time 6.34 ms/echo time 2.54 ms; field of view, 240 mm; matrix 0.8 × 0.8 × 2 mm^3, 320 × 320 pixels; slice thickness, 2 mm; and 20% distance factor). (b) segmentation of the Achilles tendon (green) and distal portion of the soleus muscle (red). (c) Three-dimensional model generated from the segmented images after post-processing.

muscles, and ligaments in medical images (Figure 2) [47]. Each voxel in the image slice is categorised based on the type of tissue it represents; then, these classified voxels are stacked to reconstruct a three-dimensional (3D) model [47]. Segmentation can be performed manually, semi- or fully automatically [70], with several open-source software suites, like InVesalius, 3D Slicer and ITK-SNAP, often leveraging ML algorithms, being available for streamlined imaging segmentation and 3D geometry generation [9, 44, 133].

Motion capture (MoCap) and force plate systems

Data acquired via MoCap and force plate systems (Figure 3) can be used to perform kinematic and kinetic analyses, which can inform prevention strategies [46], be valuable in diagnosing MSK conditions [53], for example, assessing the outcomes of surgical interventions such as anterior cruciate ligament (ACL) reconstructions [127], and guiding rehabilitation of patients with shoulder disorders [73]. In addition, MoCap and force plate analyses, for example, from Kistler and Bertec have a long history of use in sports technique- and performance-related biomechanical research [132]. Markerless MoCap systems, for example, such as the one developed by Qualysis, have evolved significantly over the past few years, possibly overcoming the practical obstacles to using typical marker-based systems, which tend to be expensive and require an extensive experimental setup [113]. Moreover, considerable research efforts have been devoted to single-camera approaches [17], which have the potential to make kinematic analyses much more ubiquitous. FreeMoCap is an open-source markerless MoCap tool designed to make motion analysis more accessible [81]. In addition, fusion of camera and inertial measurement unit data can achieve higher accuracy than either modality alone [97]. Finally, data from these systems can be used to parameterise multibody and finite element (FE) simulations, as explained in the 'Computational Modelling' sub-section. OpenSim is an open-source source, frequently used tool to process MoCap data and perform MSK modelling [34].

Wearable sensors and surface electromyography (sEMG)

Wearable sensors can integrate real-time data into MSK DTs [11]. These sensors may continuously monitor physiological and biomechanical parameters, such as muscle electrical activity and joint angles, which may be used to,

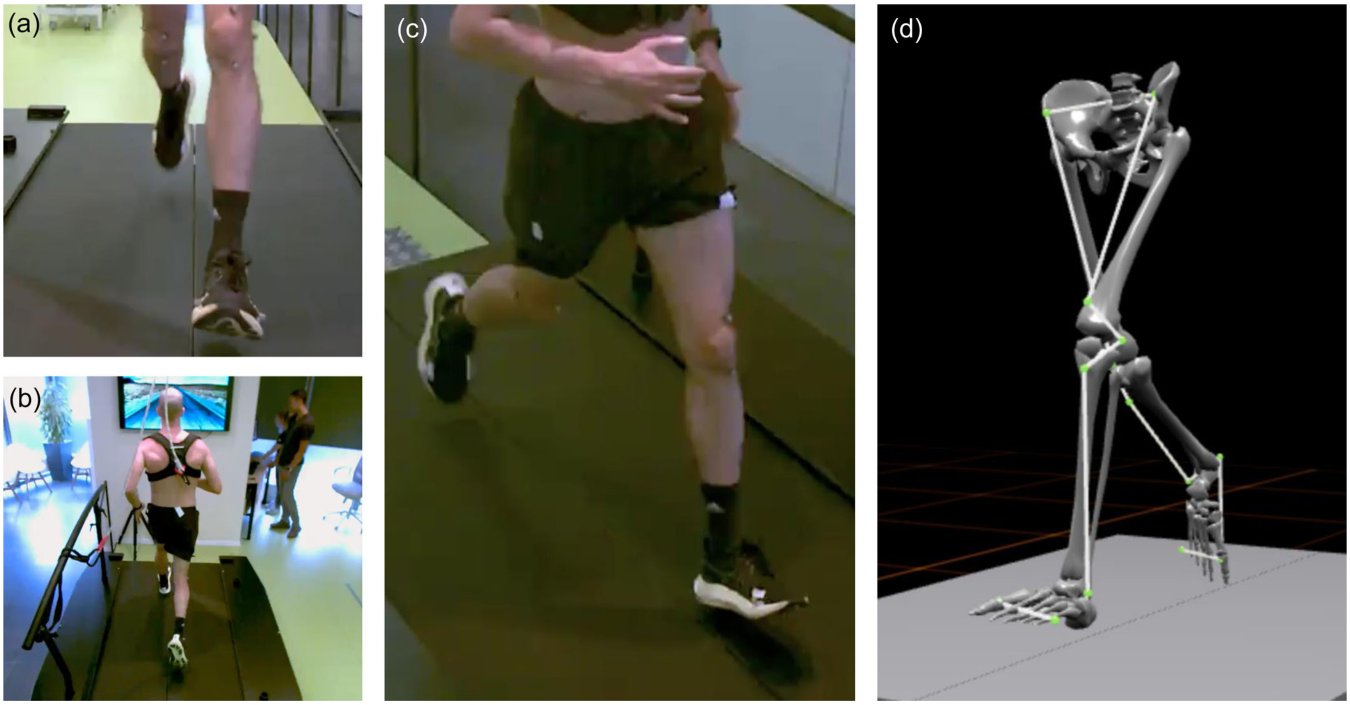

FIGURE 3 State-of-the-art human motion analysis lab. Marker-based and markerless systems are used concomitantly for added accuracy (a–c). Note the real-time 3D model created from the motion capture procedure (d). Data collected from the lab may be exported and used to parameterise multibody dynamics and finite element models. 3D, three-dimensional.

for example, predict early functional recovery after MSK injury [19]. Other parameters that may be recorded include step count, gait velocity, ground reaction forces, and heart rate. sEMG data can noninvasively assess muscle activation and coordination patterns [117], which can validate or improve biomechanical models' accuracy. Additionally, sEMG can offer insights into impairments in injured or recovering athletes, for example, in CrossFit athletes with shoulder pain or in patients subjected to ACL reconstructions [98, 112] and give patients feedback to enhance muscle control and overall function [129].

Other data sources

Other data sources that may be incorporated into DT models include patient anthropometric data and patient-reported outcome measures related to physical and mental health [74]. Furthermore, genomic data may be included [18]. Genomic data may be used in data-driven DTs as part of a model's feature set or to parameterise computational biology models in physics-driven or hybrid DTs [24, 67], as further discussed in the 'Models' subsection.

Data transfer and storage

The need for high-speed internet connections and cloud storage solutions grows as data volume grows, as relying only on locally stored data may not be feasible [54]. In addition, such an approach has notable problems related to data safety, for example, data loss in case of catastrophic equipment failure [54]. Fortunately, recent developments in 5G and 6G technologies and cloud storage solutions have made the increasing volume of data generated by personal health devices, such as wearable fitness trackers, smartwatches, and remote monitoring systems, more manageable [11, 24, 66]. On the other hand, cloud computing may raise questions about patient privacy in the event of malicious or unwitting actions from third-party agents [11, 54]. As an alternative, edge computing processes data near its source and, when combined with federated learning, enhances security by keeping sensitive information local while remotely storing the processed data [3].

Data processing

The rising complexity of simulations and the increasing depth of AI models have increased the demand for computational power. For real-time DTs to become a reality, they must be supported by an efficient information technology infrastructure [66, 68]. Furthermore, several steps in developing DTs, such as training ML-based imaging segmentation algorithms [99], finite element analysis (FEA) [30], and computational fluid dynamics (CFD) [4], are computationally intensive

[103], possibly benefiting from high-performance computing for faster implementation. Cloud computing, however, has made it possible to implement compute-hungry tasks without a significant investment in on-premises hardware [11], which is essential for the scalability of DT systems [91].

Multi-modal data fusion

Multi-modal data fusion integrates data from various sources [3], like imaging, biomechanical, and clinical data, thus being an essential feature in developing MSK DTs effectively. However, considerable limitations exist regarding this field, as no uniformly accepted algorithms or evaluation methods exist [96]. Multi-modal data fusion can be approached using different architectures [3], but deep-learning methods have shown promise [48]. Data fusion can occur at various stages of the data processing and analysis pipeline [3, 96]. Data can be fused early on, that is, before feeding to the simulation and analysis modules, with predictions being made on the fused data [3, 96], which can be helpful, especially in the context of data-driven DTs. Data fusion can also occur later in the DT workflow, for example, by combining the results of different simulation modules [3, 96]. Open-source frameworks like MONAI (Medical Open Network for AI) facilitate the fusion of medical imaging data with other modalities [23]. Regardless of the approach chosen, research shows that multi-modal data fusion improves the accuracy of ML models in classification tasks [96].

Models

Multibody dynamics (MBD)

MBD studies the movement and behaviour of interconnected, rigid, or flexible bodies under external forces [60]. Simulations using MBD use equations of motion to predict how these segments will move in response to applied forces and torques [60]. In practice, these simulations may be used to study the loads acting on the MSK system during activity, such as during swimming [103], injury mechanisms [125], and the effects of surgical interventions, like arthroscopic superior capsule reconstruction and total knee arthroplasty (TKA) [10, 83]. *Inverse dynamics* is a method within the scope of MBD used to estimate internal forces and moments acting on the MSK system by analysing external motion data [10], for example, movement patterns and ground reaction forces during walking. *Forward Dynamics*, on the other hand, predicts how the MSK system will respond to known forces and moments by solving the equations of motion [60].

FEA

FEA is a numerical method to make approximate predictions of how materials or structures will respond to forces, heat, and other physical agents. Using FEA, complex systems can be divided into smaller, simpler parts called FEs (Figure 4) [30, 77], whose behaviour can be mathematically described using comparatively simple equations. The mechanical behaviour of something as intricate as the knee joint can be predicted by assembling these equations into a system of equations and solving said system [25], using, for example, open-source software such as FEBio [77]. S*tress–strain analysis* can be performed using FEA and is useful, for example, in designing orthopaedic implants [49] or understanding tear progression in partial Achilles tendon ruptures (Figure 5) [39]. *Material properties* can significantly impact the accuracy of FEA simulations [116]. Biological tissues often show heterogeneous physical behaviours, which include anisotropy, viscoelasticity, and non-linearity, that must be incorporated into the material models as they influence the simulation's results [40]. Non-destructive assessment of biological tissues' material properties for patient-specific FEA simulations can be achieved, for example, through advanced imaging techniques, with methods such as magnetic resonance or ultrasound elastography and high-resolution CT, particularly quantitative CT [47, 85].

CFD

CFD is a numerical method used to study problems related to fluid flows. Like FEA, CFD divides the fluid domain, that is, that part of the computational domain occupied by a fluid or vacuum, into finite control volumes to solve the Navier-Stokes equations [124], which describe the motion of fluids by representing the conservation of mass, momentum, and energy. In orthopaedic surgery, CFD models can be used, for example, to predict the effect of vertebroplasty on the mechanical integrity of a vertebral body in a patient with a lytic metastatic tumour [4]. Recent research has shown the added potential of CFD when used in conjunction with ML algorithms [4, 124].

Computational biology

Computational biology relates to using numerical methods, including statistical analysis and mathematical modelling, to understand and predict the behaviour of biological systems. Computational biology faced notable expansion in the 1980s and 1990s, driven by the exponential growth of biological data and the need for novel methods to analyse, interpret, and integrate

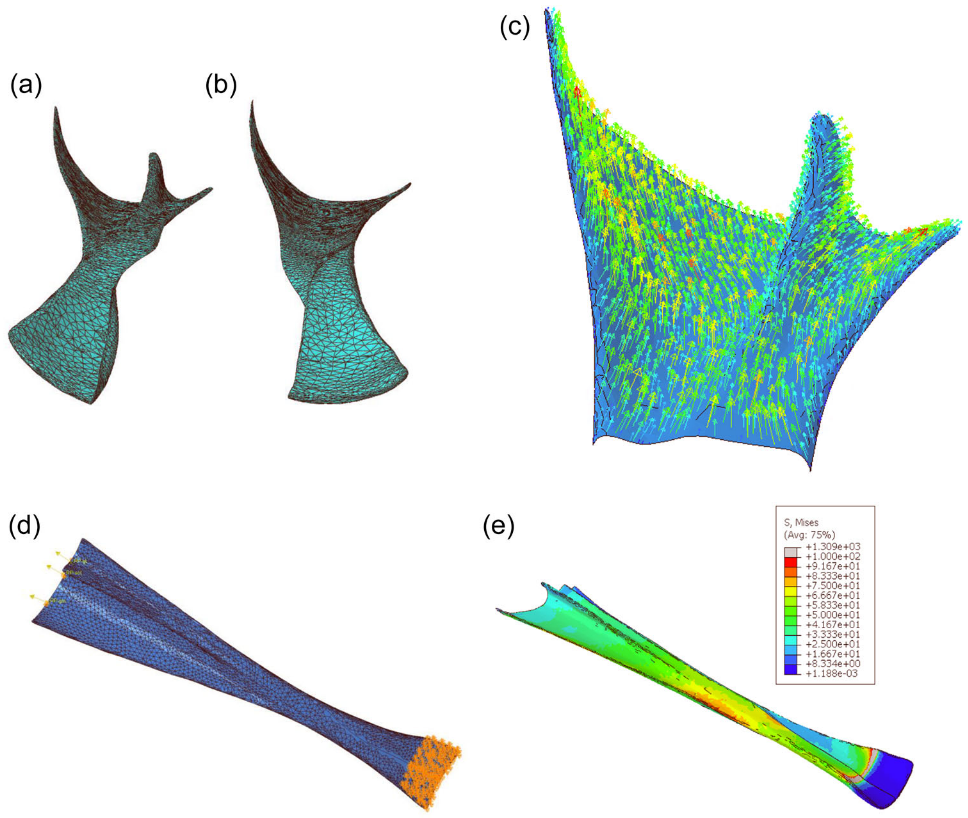

FIGURE 4 Finite element model of the aponeurotic and free Achilles tendon [40]. The finite element meshes of the soleus (a) and gastrocnemius (b) subtendons and the force vectors on the ventral aspect of the tendon simulating the contraction of the distal portion of the soleus muscle (c). (d) Loads and boundary conditions. (e) Results of simulated isometric plantarflexion contraction with 3000 N.

it [58, 94]. Computational biology models are sometimes incorporated into multi-modal, multi-scale simulations [102]. Examples of such models in orthopaedic research include modelling fracture healing under different loading conditions [130] or internal fixation implants [104] and rat Achilles tendon healing, considering load-dependent changes in tissue production and material properties over time [92].

ML

ML models can aid in creating MSK DTs, for example, in preparing the 3D geometrical model [11] and optimising simulation parameters [56]. In addition, ML models can be used for pre-processing and make predictions directly on patient data [3, 118]. Surrogate models of multi-modal simulations can be developed using ML [116]. After deployment, these models will be faster-solving than their original counterparts, allowing real-time predictions [116]. Open-source tools like PyTorch and TensorFlow are widely used for training ML models [1, 95]. Finally, as the next section mentions, explainable AI techniques can illuminate the reasoning behind data-driven conclusions and future predictions [118].

Services

DT platforms

Data integration is crucial for DTs, as different data sources must be intertwined to function correctly (Figure 6). Masison et al. have described a modular open-source computational framework for medical DTs [79]. The advantage of such architecture over other implementations of DTs is that 'it eliminates direct dependencies between different model components', allowing changes in model components without needing to track the effects those changes have on the rest of the model [79]. Cloud-based platforms have also been proposed [72]. The Auckland Bioengineering Institute's 12 LABOURS Digital Twin Platform project aims to provide researchers with a platform to develop and customise computational physiology models based on an individual's health data and integrate them into clinical workflows [13]. Such initiatives are essential because native interconnectivity between the different components of DTs does not usually exist [24]. Nonetheless, standards like Fast Healthcare Interoperability Resources and frameworks like CONNECTED are being explored to foster multi-modal data integration and interoperability in healthcare DTs [3, 22].

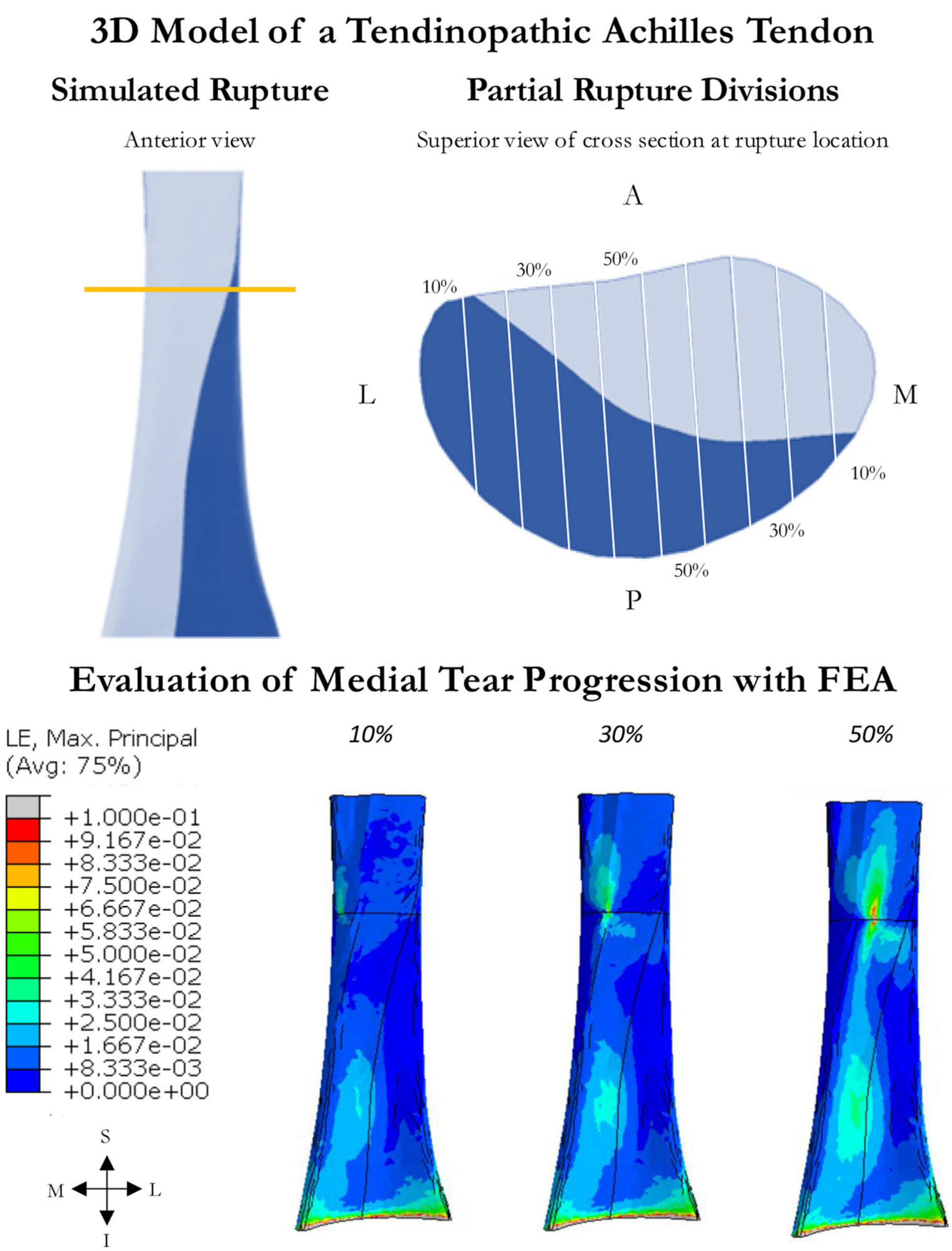

FIGURE 5 Maximum principal strain field (LE, Max Principal), computed for a 200 N load in an Achilles tendon partial rupture model with moderate twisting of the subtendons and tendinopathic geometry and material properties. The tendinopathic tendon geometry was generated from a healthy tendon using free-form deformation. Strain fields are represented in the non-deformed geometry. Results are displayed for a 10%, 30%, and 50% partial rupture from the medial side. FEA, finite element analysis; L, lateral; LE, logarithmic strain; M, medial; MP, material properties. 'Avg. 75%' in the figure means that if the relative difference of an output parameter between neighbouring elements or regions is less than 75%, the values are averaged; otherwise, values are displayed separately. Partial ruptures were considered to progress if a volume of at least 3 mm^3 exhibited a maximum principal strain above 10% [39].

Model adjustment

Adjustment mechanisms are an essential feature of DTs, ensuring that models remain accurate. In DTs, collected data can be compared with model predictions, leading to refinement of the model and increasing trueness [91]. In the blood-glucose monitor-insulin-injector example mentioned earlier, the model predictions of blood glucose are continuously compared with current values, prompting adjustments in the model as needed [24]. Similarly, in MSK DTs, simulation and analysis modules may be fine-tuned using, for example, data from wearables, MoCap and force plate systems [83]. As previously stated, ML algorithms are instrumental in effectively and efficiently optimising the operation of DTs [56].

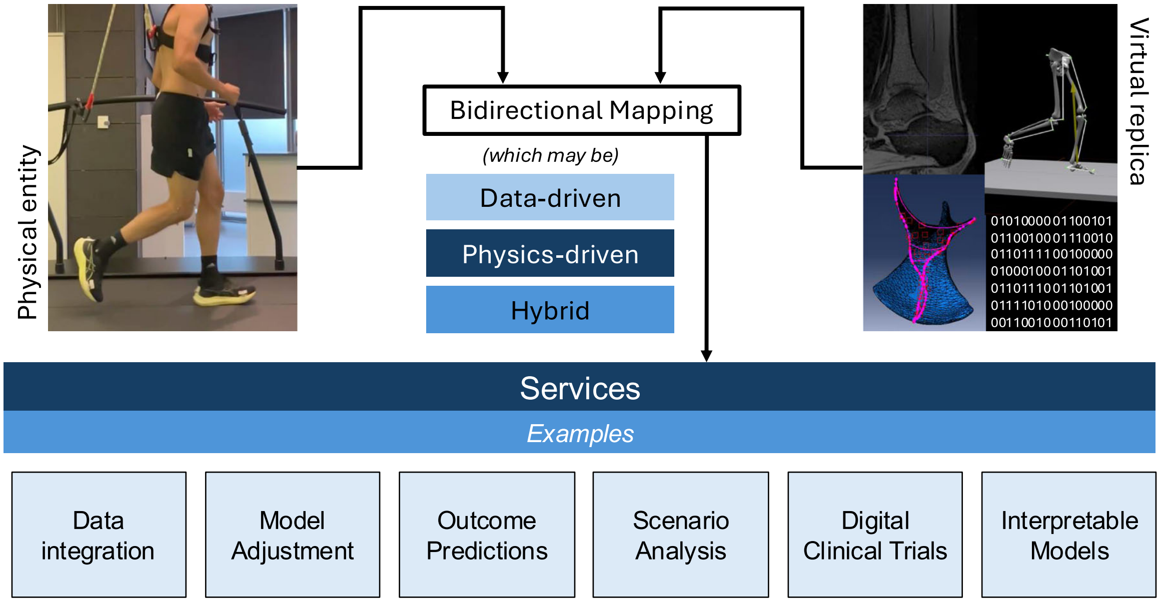

FIGURE 6 Overview of digital twin (DT) conceptual framework and components in musculoskeletal applications, illustrating the bidirectional mapping between physical entities and their virtual replicas. Several examples of DT services are provided.

Predictions

DTs may predict clinical outcomes and potential health issues [3, 11, 118]. Additionally, similarly to the manufacturing industry, DTs may be used for *predictive maintenance* [11, 118], for example, predicting implant failure [6]. AI is critical to the predictive ability of DTs [21, 68]. For instance, ML algorithms may be used to predict local gene expression from medical images [3], which can be the target of drug-screening DTs [18]. Another potential use of outcome-predicting DTs is detecting deviations from normal functioning or expected recovery patterns, allowing for timely interventions or modifications to the treatment regimen [3, 68, 118]. For example, DTs may detect complications early, such as infections or non-unions.

Scenario analysis

Particular implementations of DTs could be used to predict the outcomes of different treatment strategies [118]. For example, DTs may be used to choose between different fracture fixation methods [12]. DTs for scenario analyses are also called *editable* models, where the *edits* may be drugs or surgeries [118].

Digital clinical trials

The randomised controlled trial is the gold standard for evidence regarding novel diagnostic, therapeutic, and prognostic interventions in clinical medicine [3]. However, running such clinical trials is increasingly expensive and time-consuming [3, 11]. In addition, underrepresenting particular patient groups is another recognised issue [3, 131]. DTs may provide an alternative approach by allowing in silico testing of novel drugs or implants before clinical application [3, 13, 18, 24, 66, 68]. Additionally, in silico testing may 'reduce, refine and replace animal experimentation' or substitute bench testing [123]. Accordingly, the DTs may allow fast-tracking of the drug screening and approval process, with regulatory agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) taking steps to integrate DT-like technologies in their regulatory standards [68].

Interpretable models

Interpretable or explainable models are useful for successfully integrating DTs in MSK applications, ensuring that the insights generated are understandable and trusted by clinicians, researchers, and patients. These models may enhance clinical trust and adoption by providing transparency in decision-making processes [111], which is highly valuable for regulatory compliance and patient engagement. Techniques such as SHapley Additive exPlanations and Local Interpretable Model-Agnostic Explanations help identify significant features influencing model predictions, making the decision-making process more transparent [118]. Visualisation tools like augmented- and virtual reality (VR) [11] may help healthcare researchers and providers work effectively and intuitively with DTs [68].

VERIFICATION, VALIDATION AND UNCERTAINTY QUANTIFICATION (VVUQ)

Over the past two decades, considerable investment has been made in computational science on VVUQ, to the point where, for example, FEA is used to support high-stakes decisions [91]. However, verification and validation remain significant concerns regarding the application of DTs [90]. Moreover, the development of hybrid-DT, that is, those combining data- and physics-driven approaches, has put additional demands on VVUQ methodologies [91].

Regulatory frameworks

Key initiatives

Over the past decade, organisations like the American Society of Mechanical Engineers (ASME), the FDA, and the European Commission have fostered modelling and simulation for in silico trials, especially for medical devices and pharmaceuticals [123]. Key initiatives include ASME's VV-40-2018 standard [45], the Avicenna project, a Support Action launched by the European Commission [123], and the EMA's guideline on reporting physiologically based pharmacokinetic modelling and simulations [43]. No document equivalent to the ASME's VV-40-2018 standard has been produced in Europe [7].

ASME VV-40-2018 credibility assessment process

The ASME VV-40-2018 standard outlines a risk-informed credibility assessment framework for the computational modelling of medical devices [45]. It begins with defining a *question of interest*, that is, the question the model intends to answer, followed by specifying the *context of use* (COU) for modelling and simulation. COU defines the specific role and scope of the computational model in addressing the question of interest, that is, how the model's output will be used to answer the *question of interest* [88, 123]. The framework identifies *model risk*, sets *credibility goals*, and details model verification and validation steps, including *UQ*. *Model risk* relates to the combined assessment of the risk of the model outputting a false or incorrect conclusion with the consequences of such a decision [88, 123]. Finally, the *applicability* of the *credibility goals* and model *verification and validation* to the model's COU is evaluated to determine if sufficient model credibility is achieved to support its use.

Verification and validation

Verification and validation

Verification and validation are standard steps in general software deployment and integration [59], including computational models. Briefly, *verification*, which includes steps such as code verification and calculation verification (detailed below), confirms that the product meets the pre-established requirements for integration, that is, integrating different software components or systems to function cohesively [59]. Conversely, *validation* ensures that the integration meets the practical application requirements [59] and that the model produces outputs consistent with real-world data.

Code verification

Code verification ensures the reliability of the software implementation, including its numerical accuracy, that is, the correctness of the outputted values [7]. Computational modelling and simulation software vendors must provide evidence of adequate code verification [7, 88]. However, it should be noted that in multi-modal, multi-scale simulations, like DT systems, errors may still occur anywhere in the data integration pipeline.

Calculation verification

Calculation verification identifies and minimises discretisation errors and other sources such as rounding, numerical solver, and user errors [123]. An example of calculation verification is *mesh convergence analysis* in FEA, where an FE parameter, for example, stress or strain, is calculated and plotted considering different mesh densities [107]. When a mesh converges, the FE parameter remains stable within a specified threshold, regardless of changes in mesh density.

Model comparator

Model validation requires a rigorous comparison of the computational model and the comparator or benchmark [123]. This includes assessing the comparator's parameters and measured values, as the model's credibility depends on the equivalency of inputs and outputs and the rigour of the comparison [123]. Model validation is typically performed by comparing model outputs with experimental data [36]. Validation must be conducted on various levels in computational models and simulations using multiple components, such as DTs [7].

Validation of data-driven models

In data-driven, ML-based models, validation involves using a separate data set during fine-tuning and assessing model performance to avoid overfitting [135]. *Overfitting* may cause a model to perform well with training data but poorly with unseen data [64]. As the ASME VV-40-2018 standard primarily addresses the VVUQ of physics-driven computational models, specific considerations must be considered to validate data-driven models [28]. For example, numerical approximation errors will not be found as there are no equations to solve [28]. The main issue regarding the validation of data-driven models is *concept drift*, which occurs when the predictive accuracy of these models diminishes over time, often because the training data no longer accurately represents the modelled phenomenon [28]. Hence, a predetermined plan should be to reassess the accuracy of data-driven models with newly collected data [28].

UQ

UQ

UQ is essential to establishing the credibility of computational models [2, 123]. It refers to determining the *sensitivities* and *uncertainties* within a computational model and its benchmarks [123]. *Sensitivities*, as in *sensitivity analysis*, involve understanding how variations in model inputs affect outputs [38, 40], and *uncertainties* relate to the degree of confidence in the model's predictions [123].

Sources of model uncertainty

Uncertainty can originate from the inherent variability of model inputs, called aleatoric uncertainty, or from a lack of knowledge, denominated *epistemic uncertainty* [2, 88]. In practical terms, three main sources of uncertainty in computational models can be identified: uncertainties stemming from modelling assumptions and approximations, uncertainties related to the model's input parameters, and uncertainties resulting from the numerical solution of the governing equations [123].

Estimating input uncertainty

The estimation of input uncertainty can be categorised into local or global approaches [88]. The sensitivity coefficient method, for example, in the form of a one-way sensitivity analysis [40], is an example of a local approach. Monte Carlo simulations can be used in UQ, exemplifying a global approach, using repeated random sampling from expected probabilistic distributions [88], providing a probabilistic understanding of potential outcomes, and are commonly used in cost-effectiveness analysis [38].

MSK APPLICATIONS OF DTs

The application of DTs for MSK pathologies is still in its infancy. Regardless, the following sections briefly describe early attempts at using DTs in this field (summarised in Table 2), highlighting the technology's potential. Of note, because the terminology around DTs is not uniformly agreed upon or broadly used by the research community [118, 119], other research works may involve patient-specific multi-modal computational modelling that was not cited but uses similar approaches as those mentioned herein.

Real-time monitoring of exercise and rehabilitation

Movement analysis of the lumbar spine

The authors developed an FE model of the lumbar spine in this study from CT images [55]. A VR system was used for real-time MoCap. Posture information was calculated with an inverse kinematics algorithm, achieving an average time delay of 24.70 ms. An ML model was trained to predict biomechanical parameters, specifically facet joint contact forces and intradiscal pressure, from the posture information based on FE simulations. Afterwards, the DT of the lumbar spine displayed movement and biomechanical parameters in real time using the VR system. This technology can be used, for example, to provide early warnings about dangerous postures.

Upper limb movement monitoring

Guo et al. demonstrated the application of DTs for dynamic monitoring of upper limb muscle forces [52]. MoCap and sEMG data are combined in a mechanical model to predict muscle forces. Immersive interaction is achieved through a VR system, which provides real-time feedback to the user regarding muscle force. According to the researchers, this DT-driven system could be helpful in rehabilitation, exercise, and biomechanical research.

Real-time Achilles tendon strain monitoring

The researchers present a framework for integrating personalised MBD and FEA models to provide real-time feedback on the Achilles tendon strain during activity [100]. In their proof-of-concept study, region-specific Achilles tendon strains of a subject were

TABLE 2 Examples of current applications of digital twin (DT) systems in musculoskeletal pathologies.

Application	Description
Real-time monitoring of exercise and rehabilitation	**Lumbar spine:** FE model integrated with VR for real-time motion and biomechanical monitoring; warns against dangerous postures [55].
	Upper limb: DT with motion capture and sEMG predicts muscle forces; VR feedback aids rehabilitation and exercise [52].
	Achilles tendon: Personalised MBD and FEA models provide real-time strain feedback during activities via smartphone [100].
Understanding MSK pathophysiology	**Knee and hindfoot alignment:** DTs assess hindfoot compensation for knee deformities; higher subtalar joint inclination limits mechanical rebalancing ability [57].
	TKA alignment errors: DT evaluates femoral component malrotation effects on joint kinematics and ligament strain [86].
	Vertebral fracture prediction: ReconGAN-based DT predicts fracture risk in vertebrae with metastasis using FE simulations [5].
Surgical planning and scenario analysis	**Tibiotalar joint motion:** AI-assisted DT identifies personalised joint motion axes that can be used in robotic ankle arthroplasty [56].
	Tibial plateau fracture: Patient-specific FEA evaluates biomechanical parameters under maximum load during gait with different fracture fixations and under various scenarios [12].
Simulating outcomes of surgical procedures	**Patellar tracking**: A DT and a 3D-printed test bench were used to evaluate collision detection algorithms for simulating the patellofemoral joint with TKA implants [83].
	Vertebroplasty: DT integrates ReconGAN and CFD to simulate PMMA injection and its impact on fracture response in vertebrae with lytic metastases [4].

Abbreviations: AI, artificial intelligence; CFD, computational fluid dynamics; FE, finite element; FEA, finite element analysis; MBD, multibody dynamics; PMMA, polymethyl methacrylate; sEMG, surface electromyography; TKA, total knee arthroplasty; VR, virtual reality.

displayed on a smartphone during walking, single-leg hopping, and eccentric heel drops. This framework may be used in a personalised Achilles tendon rehabilitation and training approach.

Understanding of MSK pathophysiology

Relationship between knee and hindfoot alignment

Using ankle CT scans of patients without osteoarthritis and AI, the researchers created DTs to assess whether changes in hindfoot alignment could compensate for coronal plane knee deformities [57]. To this end, the researchers used the DTs to compute the maximum amount of knee varus and valgus that could be accommodated considering the subtalar joint. Results suggest that a higher inclination angle of the subtalar joint axis limits the hindfoot's ability to adjust and rebalance the lower limb's alignment when knee malalignment occurs.

Biomechanical impact of TKA alignment errors

In this study, the researchers used a DT of a joint motion simulator and an MBD model of the knee joint to explore the implications of femoral component malrotation in TKA regarding joint kinematics and ligament strain [86]. The study revealed, as expected, that an externally rotated femoral component resulted in increased knee varus during flexion and lower medial collateral ligament tension in extension compared to a neutrally aligned femoral implant.

Predicting vertebral fracture in a patient with vertebral metastasis

This study introduces ReconGAN, an AI-assisted framework devised to create DTs of vertebrae and predict fracture risk [5]. ReconGAN integrates a 3D deep convolutional generative adversarial network (DCGAN), image processing, and FE-based shape optimisation. The 3D DCGAN model was trained to generate a trabecular bone structure using micro-CT images of cadaveric vertebrae. The synthesised trabecular bone structure is then integrated into a 3D model of the vertebral cortical bone extracted from a patient's diagnostic CT scan. FE-based shape optimisation creates a smooth transition between the trabecular and cortical bone. The final 3D model is converted into an FE model to simulate its damage response to compression and flexion and predict the fracture risk.

Surgical planning and scenario analysis

Personalised motion axis of the tibiotalar joint

Researchers used DTs and AI to identify patient-specific tibiotalar joint motion axes [56]. A *virtual cohort of ankle models* was generated from CT scans and gait lab measurements. In addition, distal extremity 3D models were created from CTs of healthy patients. ML algorithms matched the ankle models in the virtual cohort to the ankles of actual patients. The findings revealed that a specific joint motion axis could be determined for each patient. That axis was represented in a *geodesic system* based on the talus's centre of mass, which may be helpful in robotic ankle arthroplasty.

Optimising osteosynthesis of a tibial plateau fracture

This study demonstrates a workflow for patient-specific FEA to assess the biomechanical behaviour and repeated fracture risk of different fracture fixation [12]. A post-operative CT scan was used to create a 3D model of a patient with a lateral tibial plateau fracture. Four stabilisation methods were modelled, including variations in screw lengths and the use of polymethyl methacrylate (PMMA) cement, resulting in twelve scenarios. These scenarios were combined with three bone healing conditions: early healing, intermediary healing, and bone remodelling. The study assessed mechanical strength, stress distribution, interfragmentary strains, and fragment kinematics under maximum load during gait. The results showed that PMMA injection significantly contributed to the mechanical strength of the osteosynthesis and that a uni-cortical provided similar stiffness to a bi-cortical fixation.

Simulating the outcomes of surgical procedures

Simulation of patellar tracking

This study addresses poor patellar tracking and post-treatment function prediction by exploring using MBD to simulate the patellofemoral joint efficiently [83]. Two collision detection algorithms are compared—generic mesh-to-mesh and analytical contact algorithm—using a DT of a patellofemoral joint with TKA implants. The DT simulates the patellofemoral joint and compares the patella's position, orientation, and contact force with experimental data from a *sensorised* 3D-printed test bench. In this study, the analytical contact detection algorithm was the most computationally efficient.

Simulating vertebroplasty in a patient with lytic vertebral metastasis

In this study, the researchers combined the previously mentioned ReconGAN with CFD to simulate the effect of vertebroplasty in a patient with lytic vertebral metastasis and predict its impact on vertebral fracture risk [4]. CFD, coupled with the level-set method, is used to predict the morphology of the injected PMMA cement. After predicting the cement morphology, a data co-registration algorithm transforms the CFD model into an FE model to forecast the fracture response of the augmented vertebra.

PRESENT CHALLENGES

The practical application of MSK DTs requires overcoming a diverse set of challenges. These can be divided into technical, data-related, ethics and privacy, and those related to intellectual property, costs and reimbursement.

Integrating the various components of DTs and the need for more user-friendly software interfaces present significant challenges for their application in MSK care [11, 79, 91]. Accurate modelling of ageing and material damage over time is another hurdle [91]. The high computational power required for DTs and energy costs impede widespread adoption [37, 91]. DTs also demand specific VVUQ regulatory frameworks [91].

Data-related issues include heterogeneous clinical data collection [11], which needs to adhere to the FAIR principles to leverage ML advancements [63]. The most significant advancements in DTs may come from handling 'small-scale, messy' healthcare data rather than AI research alone [11, 91]. Ensuring high data quality and addressing data shortages are crucial [24, 64, 66, 68, 118]. Effective data integration and interoperability are paramount, given the multi-modal nature of health data [3, 24, 68, 91]. Data loss in sensor networks and the massive data volumes generated by DT systems also pose challenges [64].

Ethical and privacy concerns include obtaining informed consent, especially when discussing data brokerage [62, 68]. Mistrust of ML algorithms, fear of replacement, and loss of clinical skills may hinder DT adoption [11, 118]. Liability issues arising from errors in digital health technologies—who is responsible if a decision influenced by a digital-twin results in adverse outcomes?—requiring clear legal frameworks [24]. Bias in DT models can perpetuate existing inequalities, necessitating efforts to ensure fairness [3, 24, 62, 68, 85], misusing genetic information to select individuals based on genetic profiles is a risk [11]. Despite anonymisation efforts, patient privacy is a concern, particularly when cloud-based platforms are used for data processing and storage, with synthetic data and federated learning being potential solutions [3, 11, 24, 62, 68, 87]. Additionally, the enhanced connectivity of some wearable sensors may expose them to hacking, which may put patients at risk [118]. Over-individualisation of health issues by DTs might overlook socioenvironmental determinants [62], and there is a risk of overdiagnosis and overtreatment [62]. DTs in paediatrics present unique challenges, including unknown vulnerabilities [20, 42].

Technological inequalities and intellectual property issues are among the property costs and reimbursement challenges [11, 66, 68, 119, 120]. Implementing DT systems requires scalable, cost-effective solutions, and robust governance [91]. Business models and reimbursement strategies are crucial for advancing DT health platforms beyond research [26, 68, 114, 122].

FUTURE DIRECTIONS

As implementation of DTs in medicine is remarkably less advanced than in other sectors, particularly industry [71], future directions entail the removal of current hurdles to DTs in healthcare. First, standardisation for reporting studies using DTs, similar to AI-intensive research with the CONSORT-AI and TRIPOD-AI guidelines, is essential for ensuring rigorous reporting of results and minimising bias [134]. Second, developing DT platforms for multi-modal data integration will be a significant step forward [37]. In practice, this will likely involve a 'multi-objective optimisation process', which begins with the lowest-resolution computational model capable of using the available data to simulate potential interventions accurately [71]. Additionally, developing open-source software solutions is anticipated to promote the mainstream adoption of DTs [91]. Third, blockchain-secure frameworks can enhance data sharing, access control, interaction, privacy, and security [8, 68] and be a means to relieve privacy and cybersecurity concerns. Finally, regarding novel applications of DTs, these include medical training and healthcare management, where DTs can be used to simulate operational strategies in clinics and hospitals [24].

The development of DT systems is inherently complex, requiring interdisciplinary expertise from biomedical engineers, data scientists, and clinicians. While clinicians typically lack the technical expertise to develop DTs independently, their input is critical in guiding system design to ensure clinical relevance and practicality. Collaborative teams are, thus, essential to bridge the gap between technical development and clinical application. Additionally, training programmes tailored to physicians are essential. These could include workshops, hands-on demonstrations, and continuing medical education courses focusing on use cases for DT systems, interpretation of outputs and how to integrate them into the decision-making process. As clinical applications of DTs in orthopaedics are mainly experimental, the most straightforward way to engage with these systems is by collaborating directly with the multidisciplinary teams responsible for their development. This approach enables clinicians to contribute their expertise while gaining insights into DTs' capabilities and potential applications, ensuring effective integration into clinical practice.

CONCLUSION

DT systems for healthcare have shown transformative potential in managing MSK conditions. Although the use of DT technologies in this field is still in its early stages, promising use cases can already be found in the literature. DTs may drive medical innovation by addressing current challenges and leveraging ongoing technological advancements, beginning a new chapter of improved MSK injury prevention and management.

AUTHOR CONTRIBUTIONS

Pedro Diniz conceptualised the review, performed the literature search, and drafted the manuscript with contributions from Bernd Grimm, Frederic Garcia, Jennifer Fayad, Christophe Ley and Caroline Mouton. Michael T. Hirschmann, Kristian Samuelsson and Romain Seil revised the manuscript. All authors have read and approved the final submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable as no new data were created.

ETHICS STATEMENT

The ethics statement is not available.

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