- *State of the Art:* From Digital Twins to Clinical Medicine

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1 Introduction

1.1 Purpose

The purpose of this report is to provide a comprehensive review of the current state of digital twin (DT) technology as it applies to clinical medicine. As healthcare increasingly adopts data-driven approaches, DT models offer a promising solution for enhancing patient care, optimizing treatment strategies, and improving healthcare system efficiency. The report explores the theoretical foundations, key technologies, and real-world practical applications of DTs in medicine. Furthermore, it examines the challenges and open questions that must be addressed to facilitate their successful clinical integration. By synthesizing recent advancements and emerging trends, this work aims to establish a solid foundation of knowledge that will support experimental research in the field and contribute to the advancement of digital twin applications in clinical medicine.

1.2 Definitions

A *digital twin* (DT) is a high-fidelity virtual representation of a physical system that is continuously updated with real-time data. In healthcare, a *medical digital twin* is a dynamic model of an individual patient that integrates diverse data sources such as wearable sensor data, multi-omics data, electronic health records, and medical imaging. This technology enables predictive modeling, personalized treatment planning, and real-time health monitoring.

Multi-omics data refers to the integration of various biological data layers, usually including a combination of genomics, transcriptomics, proteomics, and metabolomics, to provide a comprehensive molecular-level understanding of a patient. The incorporation of multi-omics data into DTs enhances their ability to model disease mechanisms and predict individualized treatment responses.

Personalized predictive medicine leverages individualized healthcare data, including physiological, behavioral, and environmental factors, to predict and prevent disease onset before clinical symptoms appear. DTs enable this approach by continuously monitoring patient data and simulating interventions tailored to the individual's personal risk profile.

Digital biomarkers are quantifiable physiological data collected through digital devices, such as wearables and mobile applications, which provide objective measures of health status. When integrated into medical digital twins, digital biomarkers allow for continuous monitoring, early disease detection, and real-time adaption of treatment plans.

1.3 Research Questions

To guide this investigation, this report addresses the following key research questions:

- What are the fundamental principles and enabling technologies behind digital twins in clinical medicine?
- How are digital twins currently being utilized in healthcare applications?
- What are the most recent advancements in medical digital twin technology?
- What are the major technical, ethical, and regulatory challenges associated with the adoption of digital twins in clinical settings?
- What strategies are required to facilitate the clinical translation and widespread integration of digital twins into healthcare systems?

By answering these questions, this report aims to provide a structured perspective on the developments and implementation of digital twins in clinical medicine, highlighting their current applications and future potential.

2 Foundations of Digital Twins

2.1 History and Conceptual Origins

The concept of digital twins traces its origins to the early 2000s, with Dr. Micheal Grieves first introducing the idea as an unnamed model during a presentation in a 2002 Society of Manufacturing Engineers Conference as a method for optimizing product lifecycle management (PLM) in industrial automotive manufacturing settings. The core structure of the original model included three key components: the *physical space*, representing the real-world asset; the *virtual space*, which is a digital replica containing all relevant data and computational models; and the connection between the two spaces, allowing for bidirectional data flow [1].

The term *digital twin* was first introduced in the 2010 NASA Modeling, Simulation, Information Technology, and Processing Roadmap, where it was described as an “integrated multi-physics, multi-scale, probabilistic simulation of a vehicle or system that uses the best available physical models, sensor updates, fleet history, etc., to mirror the life of its flying twin” [2]. NASA’s utilization of DT technology involved creating high-fidelity computational models to mirror physical spacecraft and predict maintenance needs, significantly improving mission outcomes.

Although the concept of DT models emerged in the early 2000s, the lack of computational power initially prevented them from being implemented to their fullest extent. Early models struggled with the complexity of processing vast amounts of real-time data, limiting their applicability beyond theoretical frameworks. Despite this, the fundamental architecture of digital twin models has remained unchanged to this day. They are still comprised of three principal components as first described - the *physical twin*, the *digital twin*, and the *digital thread* connecting the two. The main differences come in the implementation and use cases. Advances in information technology and physical hardware have allowed for greater levels of integration, precision, and analysis. Additionally, DT models have been applied to more diverse use cases than just product manufacturing, such as aerospace and defense, smart cities, agriculture, telecommunications, and healthcare.

2.2 Core Concepts

The defining characteristic of DT models is the continuous interaction between a physical entity and its virtual counterpart. The *physical space* comprises tangible assets such as industrial machines, complex engineered products, infrastructure, or human organs, which generate real-time data through sensors and monitoring systems. The *virtual space* represents the computational model that mirrors the structure, behavior, and function of the physical entity with high fidelity [3]. Unlike conventional simulations which operate independently of real-time data, offering either theoretical or snapshot representations of the target, DTs leverage continuous data streams to ensure that their virtual representations accurately reflect the target at any given moment. The fidelity of these models relies on their ability to integrate real-world sensor data with physics-based simulations and machine learning algorithms. The key enabler of DT technology is the so-called *digital thread*, which facilitates seamless data flow between the physical and virtual spaces across the lifespan of the product of system of interest (SoI). It ensures that information is shared bidirectionally between the two spaces, enabling predictive insights and proactive decision-making based on the real-time state of the SoI [4].

The implementation of DT models is guided by several core philosophies that distinguish them from other modeling approaches: real-time data synchronization, bidirectional communication, and lifecycle representation. When the concept of DT was first introduced, the underlying technology needed to fully implement them did not yet exist. The original DT models were primarily focused on data mirroring, with an emphasis on creating virtual models for the purposes of monitoring and retrospective analysis. These early models utilized static datasets and were designed to support descriptive analytics, where the goal was to understand past and present system behaviors.

Despite the technological limitations of the early 2000s, a fundamental goal of DT was always predictive modeling. The logical follow-up of analyzing past and present data is its implementation in predicting future SoI behavior. With the modern advancements in big data analytics, AI, and computing power, today's DTs not only describe and replicate physical systems but also anticipate future states and prescribe optimal actions. Another advantage of high compute power is the ability to implement multiscale and multiphysical representations if complex SoIs. Advanced data integration technology enables the incorporation of multiple scales and domains into a single model, capturing both the macro and micro-levels of complex systems and allowing for the combining of data streams from diverse domains to generate novel insights that would have been impossible using singular data sources.

3 Biomedical Digital Twins

3.1 History and Conceptual Origins

A digital twin in healthcare is a dynamic virtual model of a medical system or patient that mirrors its real-world counterpart using live data. This can range from a replica of a single organ to an entire hospital. By incorporating an individual's anatomy, physiology, medical history, and real-time sensor inputs, a DT model behaves just live the actual patient or system, allowing clinicians to simulate scenarios and predict outcomes in silico before they happen in vivo. DT

technology combines data from sources like wearable sensors, medical records, and imaging with AI and simulations to create a virtual patient model, which can be used for various healthcare applications such as continuous monitoring, tailored treatment planning, emergency alerting, and medical device design. This capability is transforming healthcare by enabling more personalized, proactive, and efficient care.

The concept of medical digital twin models originates from the convergence of simulation technology, computational modeling, and digital healthcare advancements. It is the logical follow-up of medical simulation, a domain which has existed in some form since the invent of medicine itself. The transition from physical models, such as anatomical mannequins, to computational models was inspired by the development of flight simulators for training pilots and astronauts. The rapid rise of computers in the second half of the 20th century led to the inevitable digitalization of biomedical simulation, with software-based simulations being increasingly common as early as the 1990s. In the 2010s, the rise of wearable biosensors, the digitalization of medical imaging data, and the emergence of powerful machine learning models has made it significantly easier to supply real-time data to virtual patient models, making medical DT possible. More recently in the 2020s, two technologies have taken these personalized models even further- multi-omics data integration and the rise of AI models such as computer vision and large language models (LLMs). Multi-omics data allows virtual patient models to be much more detailed on a molecular level, and not just limited to macroscopic anatomical models. Advanced AI algorithms are making the interpretation of complex data much more accessible and LLMs are making it possible to non-technical users to be able to understand and interact on a personal level with their models, as well as allowing models to read and interpret human-language data such as written medical records. Computer vision has also allowed computer systems to independently interpret medical imaging data such as CT scans and radiographs.

3.2 The Biomedical Digital Twin Model

3.2.1 Introduction

"A DT in healthcare is not a single technology but a domain-adapted multimodal approach incorporating the acquisition, management, analysis, prediction, and interpretation of data, aiming to improve medical decision-making" (Mulder et al., 2022) [5].

The core functionality of a medical DT is to serve as an advanced clinical decision support tool, providing clinicians with a deeper, individualized understanding of their patients and enabling personalized medical care. Unlike traditional diagnostic models that generalize across populations, a medical DT synthesizes multi-source patient data into a continuously updating simulation, offering insights tailored to the patient's unique physiology and health history. At its foundation, a medical DT is not a replacement for clinical expertise, but rather a supplementary platform that provides additional information, helping doctors make more informed, data-driven decisions. It is not an infallible system – its recommendations should not be followed blindly., but rather interpreted as clinically relevant suggestions that support, rather than dictate, medical judgement. As the technology matures, its integration into clinical

workflows will depend on its ability to enhance physician decision-making while maintaining transparency, explainability, and trust.

To effectively function as a clinical decision support tool, a medical digital twin must process patient data through a structured framework that transforms raw data into actionable insights. As described at the beginning of this section, this process can be broken down into five key steps, each representing a distinct function that refines patient data for clinical use: *acquisition*, where raw data is collected and digitized; *management*, where diverse data sources are standardized, integrated, and structured; *analysis*, where patterns and anomalies are extracted; *prediction*, where the system forecasts possible health trajectories and treatment outcomes; and *interpretation*, where predictive outputs are synthesized into clinically meaningful recommendations. Notably, the output of one step is the input of the following one, creating a data pipeline that ultimately takes raw medical data as input and returns a virtual model of the patient's health as output.

A key feature of a medical DT model is its ability to evolve over time, refining its predictions and recommendations as more patient-specific data is introduced. Each new dataset – whether from lab results, imaging, wearables, or genomic profiling – acts as a snapshot of the patient's current health state. These snapshots are not isolated but are stored and integrated into the DT's longitudinal record, allowing the system to track changes, trends, and deviations in the patient's health. Initially, the model may rely on generalized medical knowledge derived from population-based datasets, but as more personal snapshots accumulate, the DT becomes increasingly tailored to the individual. This gradual personalization enables the system to move beyond generic risk assessments and instead simulate patient-specific outcomes with greater accuracy. Central to this evolution is deep phenotyping, which captures a highly detailed, multi-dimensional view of the patient by leveraging multi-omics, clinical, and even behavioral data.

3.2.2 Acquisition

3.2.2.1 Approaches

Data acquisition is the foundational step in the biomedical DT pipeline, involving the collection of multimodal patient data necessary to build an accurate, dynamic, and personalized representation of human physiology and pathology. The quality, variety, and frequency of data acquisition significantly impact the reliability of downstream processes.

Biomedical digital twins require diverse data types, including physiological, biochemical, genetic, behavioral, and environmental inputs. Sources can include electronic health records, wearable sensors, multi-omics data, medical imaging, and patient-reported outcomes. The nature of biomedical DT models requires both real-time data and historical records in order to generate the most faithful virtual representation of the patient. To improve integration with external systems and existing infrastructures, it is also important for the medical data to comply with international interoperability standards such as HL7-FHIR [8] for electronic health records and DICOM [9] for medical imaging data. Although subsequent steps in the pipeline address challenges associated with data heterogeneity, having high-quality, standardized data as input

from the beginning provide the best chances of success for the correct medical decision to be made as a result of the DT model.

According to the ISO 13606-1:2019 standard for health informatics, the electronic health record (EHR) is defined as "the persistent longitudinal and potentially multi-organisation or multi-national record of health and care provision, most often relating to a single subject of care (the patient), created and stored in one or more physical systems in order to inform each subject's future healthcare and to provide a medico-legal record of care that has been provided" [8]. In other words, it is a digital repository of a patient's medical history that documents all of their diagnoses, laboratory results, medications, and clinical data, and is updated automatically such that it provides a real-time look at their lifetime healthcare trajectory up to the current date.

3.2.2.2 Key Technologies

Theoretically, a DT model could be trained to utilize a very wide array of data types, but it would be most useful in the vast majority of cases for it to take the types of data that are most common and most useful according to the literature. The main categories of medical data that we propose most biomedical DT models would take are wearable/implantable sensors, next-generation sequencing (NGS), computer vision for medical imaging, and natural language reports.

Real-time patient monitoring is possible in large part due to wearable/implantable sensors and the internet of things (IoT). The physiological, biochemical, and behavioral state can be measured remotely, both in a controlled medical setting or in the patient's normal daily life [11]. Wearable sensors are non-invasive devices that perform continuous monitoring without the need for physical hospital visits. Many people choose to wear physiological sensors on a daily basis for personal measurement, with smart watches containing heart rate monitors, temperature sensors, pulse oximeters, and accelerometers being common sights. Recent technologies such as flexible two-dimensional materials [12], biomaterials [13], and AI-enabled sensors [14] are making wearables less cumbersome and more accurate, thus increasing their prevalence in the physiological monitoring sphere and making them perfect fits for the acquisition of data for biomedical DT models.

Beyond simple wearables, there also exist ingestible and implantable sensors. So-called ingestible biosensing capsules (IBCs) are able to be in close proximity to organs through the gastrointestinal tract, and can therefore monitor a different range of biomarkers than wearables. Modern IBCs can integrate multiple functions, such as temperature, pH, and optical imaging into a single capsule [15]. Additionally, implanted biomedical devices are becoming increasingly common, making implantable biosensors a fairly commonly implemented technology [16]. Microwave antennas are the most common way for implanted sensors to communicate with the "outside world", with strict controls over bandwidth and radiation in order to ensure patient safety [17]. The most common types are smart pacemakers and other cardiac sensors, glucose monitors, and neural implants.

Multi-omics analysis requires large amounts of high-fidelity molecular data to be able to offer the most powerful insights. Advanced laboratory techniques have facilitated this aspect,

allowing for unprecedented data extraction from smaller and smaller samples. Genomics and transcriptomics respectively rely on DNA and RNA sequencing to gather data. Next generations sequencing (NGS) techniques offer longer read lengths and higher accuracy. So-called *third-generation sequencing* can read nucleic acid sequences while using minimal library preparation steps and the direct targeting of unfragmented DNA molecules in real-time, a major upgrade compared to *second-generation sequencing* which relies on multiple laboratory steps to prepare and fragment the strand into smaller pieces before simultaneously sequencing the fragments in parallel [18]. Proteomics and metabolomics do not look at nucleic acid macromolecules, but rather proteins. In order to sequence the amino acids and realize the concentrations of different individual proteins, techniques such as mass spectrometry, western blot and protein pathway assays, and microarrays are used [19]. Modern high-throughput proteomic data acquisition aim to identify and quantify many proteins simultaneously and quickly, and ideally with a sample as small as a single cell. The two most promising technologies for single-cell proteomics are mass spectrometry and nest-generation protein sequencing. Mass spectrometry techniques have existed for many decades, but recent advances in the sensitivity of mass spectrometers and sample preparation techniques have reduced the number of cells needed for accurate measurements to one. Next-generation protein sequencing is also an interesting approach, where antibodies with attached oligonucleotides are bound to the target proteins, effectively converting the protein-detection problem to a more accessible oligonucleotide-detection problem [20]. The combination of single-cell genomic/transcriptomic sequencing with advanced proteomic sequencing and quantification allow for the utilization of multi-omic data in biomedical digital twins.

Medical imaging data, such as X-ray, MRI, CT, and ultrasound require high-throughput, automated analysis to be integrated in DT models. Computer vision enables automated analysis and feature extraction by using convolutional neural networks (CNNs) and vision transformers (ViTs) to detect patterns and anomalies in high-dimensional images [21], [22]. CNNs have for years outperformed humans in many image understanding tasks, without the risk of human error due to fatigue or other factors. Compared to ViTs, they are generally considered more computationally efficient, requiring smaller datasets – but ViTs utilize transformers with self-attention mechanisms that allow the model to consider all elements simultaneously, dynamically adjusting weights based on the input, allowing it to focus on relevant regions rather than using fixed-size filters. This allows for better shape detection, allowing ViTs to recognize objects in a similar manner to humans [23]. Although CNNs still usually perform better that ViTs in medical imaging classification tasks, ViTs are beginning to catch up and will probably surpass CNNs in terms of medical usefulness for computational modeling of medical images [24].

Some preliminary data has shown that large language models (LLMs) have been shown to be valuable tools in converting diverse EHR data into usable input for the DT [25], [26]. Natural language processing (NLP) algorithms are a way to avoid or reduce the tedious and human error-prone process of manual data entry based on written or spoken reports. There have been many studies that show that NLP methods, which have gained much traction in the last few years due to the proliferation and rapid increase in quality of LLMs. For example, NLP methodologies have had positive results in interpreting free-text clinical trial outcomes [27], outpatient surgical notes [28], and clinical notes [29], [30].

3.2.3 Management

3.2.3.1 Approaches

Data management refers to the integration, storage, and security of biomedical data to ensure its usability in a biomedical DT model. Since DTs require real-time, multimodal, and often high-dimensional data, there must be a focus on interoperability, efficient retrieval, and scalability.

The medical dataset gathered in the acquisition step is large and heterogenous. Multi-omics data, features from medical imaging, and the patient's EHR range in quality, format, and number of features. For this reason, feature engineering and data integration are crucial to biomedical DTs, and are one of the most computationally challenging steps in the process. Multi-omics data integration is an entire field of study on its own, with many different methodologies and approaches found in the literature. According to Picard et al., 2021 [31] there are five primary strategies for multi-omics data integration: *early integration, where* all omics data are concatenated into a single dataset before analysis, allowing machine learning models to extract cross-omics interactions; *mixed integration*, where data are transformed independently before integration, ensuring that specific characteristics of each omics layer are preserved; *intermediate integration*, where partial integration is performed on subsets of omics layers, followed by an overall analysis; *late integration*, where individual omics analyses are conducted separately, and the results are merged at the interpretation stage; and *hierarchical integration*, where data are integrated in a stepwise manner based on biological relationships between different omics layers. Subramanian et al., 2020 [32] defined five multi-omics integration method types: *similarity*, *correlation*, *Bayesian*, *multivariate*, and *fusion*, each with its own set of tools for implementation.

Despite its potential, multi-omics data integration faces several challenges, primarily due to the high levels of heterogeneity and dimensionality in multi-omics datasets. Data heterogeneity arises from the fundamental differences between omics layers, such as the varying scales of genomic sequences, transcriptomic expression levels, and metabolomic concentrations. These discrepancies complicate integration efforts, as they require robust normalization and transformation methods to ensure comparability across datasets [33].

Key to advancing precision medicine through biomedical DTs is the integration of multi-omic data with the EHR and wearable sensor data. EHRs provide a combination of structured (lab results, medication dosing) and unstructured (clinical notes, medical imaging) data, and wearables/ingestible/implantables provide structured data with a longitudinal component. Big data analytics techniques can help unlock the potential of this data for biomarker discovery, disease modeling, and clinical decision support [34].

3.2.3.2 Key Technologies

Dimensionality reduction through feature engineering is the first step in biomedical data integration for DTs. Feature selection, or the determination of a smaller set of features which keep all of the relevant information while reducing dimensionality, can result in higher

performance by reducing complexity and improving compute efficiency. The three main types of feature selection methods, *filter*, *wrapper*, and *embedded* can be used, often with wrapper-based methods that test different sets of features to determine which ones give the best performance [31]. Feature extraction can also be used, combining raw features into a smaller number of features while maintaining all relevant information. The most common approach for multi-omic integration is *mixed integration*, transforming data independently before integration. This can be done using *multiple kernel learning* (MKL) where different omics datasets each get a separate kernel computed before combining them into a global similarity matrix. The optimal combination is determined experimentally by learning appropriate weights for each feature [31]. As an example of this method, a study is presented that used the SimpleMLK algorithm to predict breast cancer survival rate using five types of genomic data, after performing feature selection using the minimum redundancy feature selection (mRMR) algorithm. Using the method on a 98-patient validation dataset the researchers were able to correcting predict survival with 98% accuracy [35]. Autoencoders also have been used successfully to compress high-dimensional multi-omic data into a smaller latent space while still preserving all important relationships. Some advantages to using autoencoders over principal component analysis (PCA) for biomedical data is that autoencoders can utilize non-linear activation functions, more faithfully representing the complex biological networks that they are seeking to replicate. For example, Xu et al., 2019 utilized statck sparse autoencoders to efficiently detect breast cancer nuclei in histopathology imaging [36].

If EHR data formatting is not controlled, there is a major risk of interoperability between different devices and medical institutions. To combat this, EHR data should be represented with a common data model (CDM), which can facilitate data transfer and ultimately collaboration for big data precision medicine operations [37]. Interoperability standards such as Sentinel CDM, PCORNet CDM, and OMOP CDM are often used when data will need to be shared after storage. In terms of EHR data integration with multi-omics datasets in a single DT model, there are two main approaches- *phenotype-first integration* (EHR-guided multi-omics analysis) and *genotype-first integration* (multi-omics -guided EHR analysis) [37]. Phenotype-first integration starts with a defined clinical disease identified in the EHR and then applies multi-omic analysis to find molecular associations. There are many possible strategies for integrating these diverse datasets such that they are ready for the next steps in the pipeline, so it is important that the methodology matches the nature of the data. Through experimental testing researchers have been able to find the optimal strategies for each dataset, there does not seem to be a one-size-fits-all solution in the literature.

3.2.4 Analysis

3.2.4.1 Approaches

The goal of the analysis step is to take the structured, optimized data from the previous management step and use it to identify relationships, detect trends, uncover meaningful structures, and reveal anomalies. Of course, the different data types require different approaches for analysis, so it is likely that multiple types of ML algorithm are used in this stage. An

important goal is clustering and pattern identification, so it would be common to see unsupervised ML algorithms used here.

Multi-omics analysis refers to an advanced integrative approach within systems biology that combines multiple layers of biological data to provide a comprehensive understanding of complex biological systems from on a molecular level. These layers usually include genomics, transcriptomics, proteomics, and metabolomics but are often supported by additional layers such as epigenomics, microbiomics, and others. By integrating these diverse datasets, researchers and clinicians can elucidate intricate interactions between different molecular components and their influence on health and disease.

There are, generally speaking, two main types of multi-omics analysis, *bulk* and *single-cell* omics. They both can generate advanced insights, but differ in their approach. Bulk omics takes molecular data from many cells at once, providing a snapshot of the average state across the sample. Single-cell omics, on the other hand, is a more advanced methodology that takes molecular data from a single cell, allowing researchers to investigate the heterogeneity of cells within the same tissue, giving a finer view of the biological system. The disadvantage of single-cell omics is that it removes the cell from its microenvironment, so the analysis is performed without location context, including cell-cell interactions within tissues, which could provide insights in certain clinical cases. To solve this problem, the newest approach is *spatial single-cell multi-omics analysis*, which looks at the molecular state of individual cells while preserving the spatial context within their native tissue environment [38], [39].

3.2.4.3 Key Technologies

Zhang et al., 2021 divides integrative multi-omics clustering methods into three categories- *concatenated clustering*, *clustering of clusters*, and *interactive clustering*, depending on how and at what point the data are clustered [40]. Concatenated clustering combines multi-omics data into one single matrix before final clustering, clustering of clusters first performs clustering on each separate omics dataset before final clustering, and interactive clustering which performs the data integration and clustering operation simultaneously. Some of the most used methods for clustering in each category are the following: *iCluster*, an R package created by Bioconductor that implements a joint latent model approach to analyze multiple genomic data [41]; and *similarity network fusion* (SNF), which separates similar subjects based on similarity measures from the different omics data types [42]. There is great potential for unsupervised ML algorithms to perform clustering on EHR data as well. Despite the advanced state of clustering technology and the availability of large databases of high-quality anonymized EHR data, there are few high quality articles on ML-based phenotyping at the population or individual level [43].

Multi-omics analysis, on the other hand, is a much more developed field despite being, relatively speaking, in its infancy compared to other approaches in traditional medicine. For example, in oncology there is a significant amount of interest in multi-omics analysis and therefore many studies have been conducted and several methodologies have emerged. According to the review performed by Nicora er al., 2020, there are six main methods for ML-based multi-omic analysis in the literature: *feature extraction, feature transformation, factorization, deep network, network, and clustering* [44]. In the review, the majority of

techniques were applied to The Cancer Genome Atlas (TCGA) program data, which contains over 2.5 petabytes of anonymized multi-omic data on various cancers [45].

3.3.5 Prediction

3.2.5.1 Approaches

The difference between the *analysis* step and the *prediction* step is that analysis seeks to identify patterns and learn something about the data in its current form, while the prediction step seeks to decide the probabilities of possible outcomes. The ability to accurately predict treatment outcomes in individual patients is an invaluable tool in making good clinical decisions. It would allow doctors and to test multiple treatments on the virtual version of the individual patient testing ideas and getting reliable feedback in a completely non-invasive manner. There have been encouraging results in several medical fields, including oncology, radiology, neurology, and even psychology. Some examples include a study that successfully predicted treatment outcomes for patients with small cell lung cancer receiving chemoimmunotherapy, for which there does not exist a known biomarker for predicting individual outcomes [46]; successfully predicted treatment outcomes in selective serotonin reuptake inhibitor treatment outcomes in children and adolescents [47]; and a random-forest algorithm a approach to predict clinical outcomes in tuberculosis patient, where it was found that the more information was included the better the prediction accuracy was [48], which is a promising sign for the large dataset proposal set forth by biomedical DT models. A precision medicine platform called the Molecular Twin was able to predict disease survival in patients with pancreatic cancer using 6,363 clinical and MO features. They were also able to demonstrate similar predictive ability using a model that only took 589 features [49].

3.2.5.2 Key Technologies

The main technique for outcome prediction with biomedical data is the implementation of supervised ML algorithms trained on anonymized multimodal datasets such as The Cancer Genome Atlas (TCGA) for multi-omics cancer data, MIMIC-III and MIMC-IV for critical care EHR data, and the UK Biobank [50].

Based on the literature, ensemble learning models that include algorithms such as random-forest, Decision Tree, XGBoost, Gradient Boosting machines, and support vector machines have all had successful utilization [51], [52]. Therefore, it is probably best practice to experimentally determine what the most optimized algorithms are for each specific use case. The nature of the provided data and the desired prediction differ from case to case, and thus should be treated independently.

3.3.6 Interpretation

The *interpretation* step in the biomedical DT pipeline translates the outcome predictions generated in the previous step into actionable clinical recommendations, including treatment plans, protocols, and interventions. Because the biomedical DT model is primarily a clinical decision support tool, these “interpretations” of the data come in the form of suggestions for the patient or medical staff, so that they may make an informed decision beyond what would be

possible with traditional methodologies. The interpretation phase ensures that the end result is clinically meaningful and explainable. This sort of final user interface does not yet exist in the literature, but is a logical follow-up to the series of steps that compose the biomedical DT data pipeline.

The medical system is built upon the trust that patients have in medical personnel and infrastructure, and DT models are held to the same standard of accountability. The implementation of explainable AI (XAI) techniques could help resolve part of the closed box image of machine learning models, making the clinical recommendations better understood and not "coming out of the blue". XAI research has increased significantly in recent years, especially in the medical field [53]. Chaddad et al., 2023 observed four categories in which XAI methods fall, namely *explanation forms* (methods: feature map, textual, or example-based), *interpretation type* (intrinsic or post-hoc), *model specificity* (model-specific or model-agnostic), and *explanation scope* (global or local) [53]. One of the most commonly implemented methods is *gradient-weighted class activation mapping* (Grad-CAM), which is an explanatory visualization method used for adding explainability to computer vision tasks such as medical imaging data interpretation [54].

4 Use Cases

4.1 Anatomical Modeling

One of the earliest and most common implementations of biomedical DT models is the digital modeling of individuals' anatomical features such as organs and joints. Being one of the earliest medical DT applications, there are some relatively well-developed anatomical models in existence and one study even found that anatomic DT models of organs were superior to their standard physical counterparts in the context of surgical assessment [55]. The living heart project by Dassault Systemes, which has been in existence since 2016, was the first virtual model of a living human heart [56]. Also, DT models for musculoskeletal applications are gaining traction and have tangible results in optimizing monitoring, analyzing joint mechanics for personalized surgical techniques and predicting post-operative outcomes [57].

4.2 Personalized Medicine and Treatment Planning

DT models are at the forefront of personalized medicine, where treatment plans are tailored to the individual. By creating a virtual replica of the patient, clinicians can simulate interventions and predict patient-specific responses with a high degree of confidence. For example, doctors can test how a particular chemotherapy regimen would affect a virtual tumor before giving it to a cancer patient, helping them choose the therapy most likely to shrink the tumor with the fewest side effects. Similarly, pharmakinetic models within a patient's twin can predict how the person will absorb and metabolize a drug, enabling precise dose adjustments. This eliminates much of the trial-and-error in treatment selection.

Digital twins also help in risk assessment and outcome prediction. Clinicians can run "what-if" scenarios on the twin – for instance, modeling the impact of a surgery or a new medication – and foresee complications or adverse reactions before they occur. In one case, the

U.S. Nationals Cancer institute and Department of Energy launched studies using predictive cancer patient digital twins to simulate tumor responses in diseases such as pancreatic cancer and melanoma, demonstrating how such models can guide therapy choices. By accounting for a patient's unique genetic makeup, lifestyle, and comorbidities, a DT model enables truly personalized treatment plans and more accurate predictions of disease progression and recovery. The result is higher likelihood of selecting the right treatment the first time and improved overall outcomes for the patient.

4.3 Virtual Clinical Trials and Drug Development

Digital twins are revolutionizing drug discovery and development by making the R&D process faster, cheaper, and more precise. In the pharmaceutical industry, researcher use digital twins of organs, disease pathways, or even entire synthetic patient populations to run virtual experiments on new drugs. These simulations can predict how a drug will interact with the body – for example, how it might be absorbed, what side effects it could cause, or how effective it might be against a disease – long before a drug is given to any real human. By identifying unpromising drug candidates early and highlighting the most effective ones, companies can focus their resources better and avoid costly late-stage failures. Luca Emili, CEO of InSilico Trials, described a notable case where a biotech firm used a biosimulation platform (a form of digital twin for clinical trials) to de-risk their clinical plan. They virtually tested their drug in-silico and even uncovered a new market opportunity without conducting physical trials; this approach saved roughly €30 million and trimmed 3 years off their development timeline. This example highlights how a well0designed digital twin can streamline the path from lab to market by replacing certain real-world experiments with accurate virtual ones.

Digital twins are also playing a growing role in clinical trials. Instead of relying solely on recruiting patients (which can be slow and difficult, especially for rare diseases), researchers can create "digital patients" – simulated individuals that mimic the physiology and variability of real patients. These virtual patients, powered by AI and statistical models, can augment real trial populations [58]. For instance, in trials for a rare disease or a personalized medicine, a digital twin cohort can be used to test a drug's efficacy, effectively increasing sample size and diversity without putting actual people at risk. By accurately simulating how patients would react to a new treatment, such in-silico trials can accelerate the drug development process while maintaining an emphasis on safety. Regulators are beginning to acknowledge the value of these methods: the FDA and other agencies have been working on guidelines (like "Good Simulation Practice") for using the modeling and simulation data as evidence in regulatory submissions. This trend suggests that in the near future, a significant portion of drug testing may occur within computers. Ultimately, digital twins in drug development reduce the need for certain lab experiments and human trials, cutting down the cost and time needed to bring new, effective drugs to patients. They ales enable a move towards *precision pharmacology*, where drug dosing and combinations can be optimized for individual patients using their digital avatars before applying them in real life.

4.4 Surgical Training and Simulation

Surgeons are using DT models to simulate and plan surgeries in advance. High-resolution imaging (CT, MRI) of a patient can be used to construct an exact 3D model of their anatomy, essentially a surgical twin. The surgeon can then practice the procedure on this virtual patient – for example rehearsing the removal of a tumor to the placement of an implant – and refine the approach. These simulations use physics-based models to mimic tissue behavior and surgical tool interactions, yielding realistic outcomes. Studies show that such virtual surgical planning can reduce operation times and improve surgical precision by allowing the team to anticipate challenges ahead of time. In cardiovascular surgery, for instance, a team at Louis Pradel hospital in France leverages a digital twin to choose the optimal stent size and placement for aortic aneurisms repair, the twin helped them anticipate difficulties and adjust the device design preoperatively, ultimately reducing intervention time and surgical risk.

Digital twins are equally valuable for surgical training. Novice surgeons can practice in a virtual reality (VR) environment that faithfully replicate human anatomy and even simulates the touch and resistance of tissues. This was demonstrated with a VR-based digital twin simulator for robotic minimally invasive surgery, which was used to train surgeons on tasks like precise instrument movement and cutting. In trials, the simulator could clearly distinguish expert surgeons from novices based on performance, indicating that it can effectively assess and improve surgical skills. Such training platforms are increasingly important given the shortage of cadavers for medical training – VR twins offer an ethical, repeatable, risk-free way to practice difficult procedures. Moreover, during real operations, a digital twin can provide intraoperative guidance. For example, the Twin-S system for skull-base surgery mirrors the procedure in real time, tracking the surgeon's tools and the patient's anatomy to provide an augmented reality overlay and extra situational awareness. Whether in rehearsal of in the operating room, surgical digital twins act as advanced guides, leading to safer surgeries and more skilled surgeons.

5 Open Questions and Future Directions

As biomedical digital twins continue to evolve, several key challenges must be addressed to fully realize their potential as comprehensive, adaptive, and globally accessible healthcare tools. One missing link is the integration of more data types into medical DTs. Behavioral, social, and environmental data are difficult to track on quantify on an individualized level, but the increase in sensor quality and ubiquity in recent years is sign that maybe in the near future variables such as lifestyle factors, pollution exposure, and human-human interactions will be able to be monitored in real-time, making models even more useful. Another fundamental challenge is balancing the intrinsic personalization of DT models with generalizable methodology. Across the literature ML models differ widely in structure and approach, each tailored to the specific use case. This raises the question of whether a unified DT framework could be developed – capable of adapting to individual patients while still functioning as a broadly applicable model. This would allow the creation of a medical DT as an off-the-shelf product, significantly increasing its societal utility. A third open question is whether it is possible to create biomedical DT models that function in low-resource settings. Achieving the level of integration needed for meaningful insights is currently an extremely computationally intensive process. Not only is the integration and analysis resource-hungry, but current models need access to high-fidelity multimodal data

streams that may not be readily available in under resourced regions. The solutions to these problems will probably require scalable, decentralized approaches such as edge computing, federated learning for data security, and simplified architectures in order to maintain the same level of technical rigor in a more efficient manner.

6 Conclusions

Digital twins, originally conceptualized for manufacturing and industrial applications, have rapidly evolved into powerful tools in clinical biomedicine, offering a new paradigm for personalized patient-specific decision support. At the core of biomedical digital twin models we propose that there is a data pipeline, which we divide into five steps – acquisition, management, analysis, prediction, and interpretation – which transforms raw patient data into clinically actionable insights. Such models have already demonstrated promising use cases, from personalized cancer therapy simulations to predictive modeling for metabolic disorders. However, several critical challenges remain, including the integration of more diverse types of data, generalizing ML models to cover more use cases, and improving computational and resource efficiency to increase accessibility to this technology in low-resource settings. Biomedical digital twins have the potential to redefine precision medicine and ultimately improve patient outcomes on a global scale.

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