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VIRTUAL PATIENTS AND DIGITAL BIO PRINTING SIMULATION IN THE DEVELOPMENT OF PERSONALIZED MEDICINE

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ABSTRACT:

The medical paradigm is evolving from generalized treatment regimens to individualized, targeted treatments based on the specific biological and clinical traits of every patient. Advances in technology such as digital twin simulations, which provide dynamic, data-based representations of individual patients, and virtual patients computational models, which simulate human physiology and treatment outcomes, are enabling this transformation. At the same time, 3D bio printing offers the physical platforms for the duplication of organ and tissue assemblies, complementing digital approaches in translational medicine. Integrated with the digital twin simulation and virtual patient model, bio printing technologies are also explored in this paper with a focus on how the technologies complement each other to accelerate the development of personalized medicine. Virtual patients and digital twins have been found to enhance predictive accuracy for therapeutic decisions, reduce animal testing requirements, and enable virtual clinical trials. Patient-specific 3D constructions are also made available by 3D bio printing for regenerative purposes. Case studies in cardiology, chronic disease, and cancer illustrate clinical utility. Problems with data integration, privacy, validation, and regulatory clearance still exist, however. Digital twin simulation, bio printing, and virtual patient technology converge to give a disruptive pathway toward personalized therapy. Next-generation studies must focus on regulatory paradigms to enable translation to clinics, real-time adaptive models, and integration with wearables and the IoT Technologies.

INTRODUCTION:

Industry has been employing digital twins, or virtual copies of actual objects, since 2002 to enhance manufacturing and the product life cycle (1). But "health digital twins" (HDT) are a comparatively fresh concept in the medical world (2). HDTs hold revolutionary applications in clinical trials, precision medicine, and public

health if utilized appropriately. A concrete or potential physical made product is assembled from the micro atomic scale to the macro geometrical scale by means of a collection of virtual information referred to as a "digital twin." Any data that may be extracted by studying a product that is physically manufactured might, at best, be



dynamically read in real time from its virtual counterpart. To generate thoughtful observations that could later be used on the actual equivalent, these virtual models are employed to test performances, simulate improvements, model difficulties, and develop potential solutions. (3) Digital Twins (DTs), i.e., virtual copies of existing systems or objects connected through mutual data and information exchange, can also be formed due to generative AI [4]. A novel field of in silico drug discovery is referred to as DTs [5]. From individual cells [6–11] (Figure 1a) to cell cultures [12–14], tissue samples [15,16], whole organs [17–19] (Figure 1b), animal models [20–23], and whole human representations [24–26] (Figure 1c), DTs can essentially represent any biological object. With the aid of advanced computational and algorithmic methods, the respective DT can simulate the results of real tests after being initialized with the start state of a biological object. For example, DTs, or healthcare DTs, are computerized replicas of patients employed in clinical trials that are representative of the longitudinal aspects of actual patients [6,26]. Realistic clinical patient pathways can be generated with the assistance of DTs [24–26]. Patients and their DTs are thus composed in both directions: information flows from the patient to their virtual DT representations in order to represent its current and future states, and vice versa from the DTs to the patient to support medical decision-making. A DT's predictions or simulations, i.e., model outputs for a specific patient, determine the flow of information from the DT to the patient. I.e., if a DT predicts a negative event, measures can be taken to immediately counter it, e.g., by using

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additional health monitoring. As for their observed characteristics, i.e., their monitored clinical data and disease prognosis, DTs should ideally be the same as real patients. In the following sections, we provide a short overview of AI methods in DTs and address the status of generative AI-based DTs in clinical trials and pharmaceutical drug development today. Finally, we review our idea for DTs and explain in depth the challenges of their development and employment. We believe that in the near future AI-powered DTs will transform clinical trials and drug discovery.

DIGITAL TWINS AND GENERATIVE AI :

AI increasingly integrates with human intelligence and subject-matter knowledge to support drug development decision-making [27]. A summary of relevant AI keywords and concepts appears in Table 1. As such, the field is embracing machine learning (ML), a subset of artificial intelligence that employs algorithms that learn from data. Consequently, interest in ML's application to medication discovery and research has increased [28, 29]. The architecture of the human brain is the model for machine learning algorithms called artificial neural networks (NNs). NNs employ stacks of neurons to map the incoming signal. The key feature that provides NNs a powerful algorithm for data-driven modeling are the hidden layers, which are the layers that are between the input and output and perform non-linear data transformation. Although NNs are able to process high-dimensional data directly and automatically learn feature representations, conventional machine learning methods such as logistic

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regression and decision trees most often require dimension reduction or manual feature extraction. Apart from this, NNs have spearheaded developments in the area of DTs because of their demonstrated appropriateness for complicated, multimodal, multidimensional, and longitudinal data [30]. The feature

learning capability of a neural network can be enhanced based on how many hidden layers it possesses. In an attempt to enhance the quality of DTs, recent NN architectures with many hidden layers deep NNs or deep learning (DL) [31] are used.

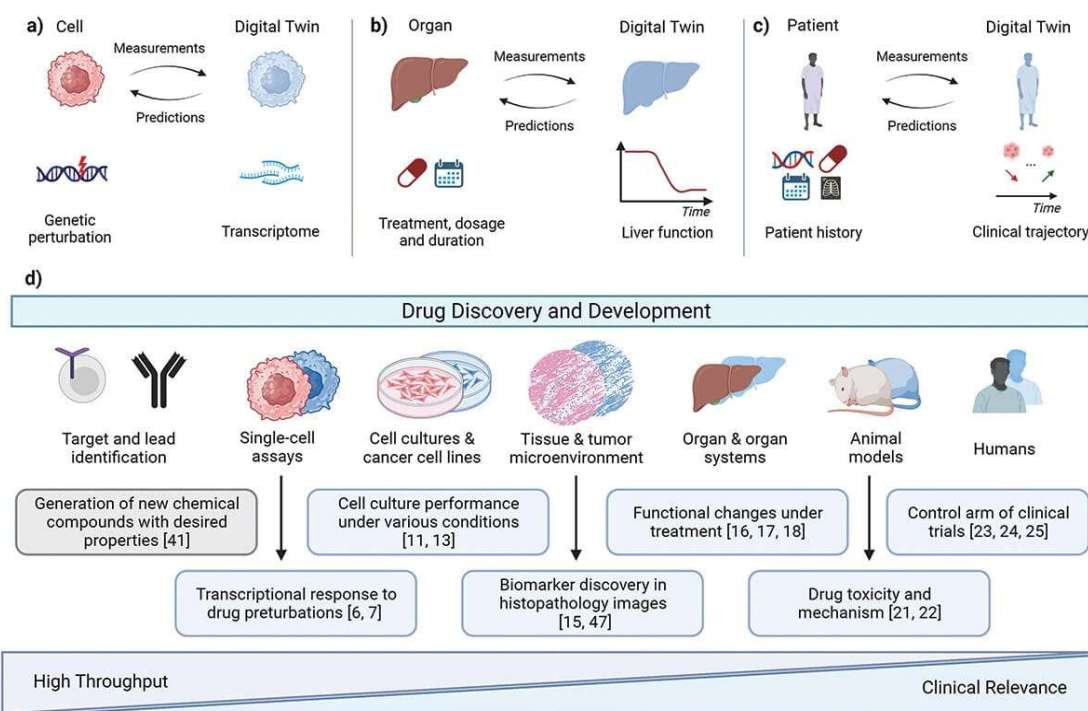


Figure 1: Virtual representations of actual biological organisms are called digital twins (DTs). Here, DTs of (a) cell lines, (b) complete organs, and (c) entire human patients are used as examples. A biological entity and its DT exchange information in both directions. A DT is initialized with measurements from a genuine biological entity and then delivers simulation results or predictions from virtual experiments that impact the biological entity's decision-making. (d) DTs affect clinical trials as well as every phase of drug development and discovery. used BioRender.com to create it.

CONCEPT AND STRATEGIES FOR VIRTUAL PATIENTS

SIGNIFICANCE AND EXTENT:

Computer-synthesized simulations that resemble the clinical characteristics of real

patients are referred to as virtual patients [32]. Without the need for initial human or animal testing, these models are applied in *in-silico* studies to predict the impact of drugs. These studies depend mostly on

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virtual patient cohorts, or cohorts of virtual patients, which might make trials possible to conduct entirely in a computer environment [33].

METHODS FOR CREATING DIGITAL PATIENTS

AGENT-BASED MODELING (ABM):

ABM enables the investigation of complex behavior and outcomes using simulation of the interactions of individual agents (virtual patients) within a system. This method is particularly useful for the simulation of immunological reactions and disease spread [33,34,35]. In cancer, for example, ABM has been utilized to simulate tumor growth and combination treatment outcomes, enabling researchers to predict treatment efficacy in a variety of scenarios [35].

AI AND ML: Artificial intelligence (AI) and machine learning (ML) examine large datasets to detect patterns and make predictions. They enhance the accuracy of simulations, reveal hidden connections, and help generate virtual patients from real patients' data [36–38]. AI has become universal in its acclaim for its process automation capabilities and driving

innovation in the healthcare sector following the launch of ChatGPT (OpenAI, San Francisco, USA). AI and ML can assist in drug development as they can be employed to forecast in uncommon diseases [40] and make artificial datasets for short trials [39].

BIO SIMULATION/STATISTICAL

METHODS: Bio simulation involves the use of mathematical models to simulate biological processes at small and large scales of data [41, 42]. Some of the methods used include Monte Carlo simulations and ordinary differential equations (ODEs) [43]. From existing data sets, statistical methods like regression and bootstrapping generate simulated patient data [44]. Regression can predict drug dose-response relationships [45–46], and bootstrapping resamples data to assess variability [24]. Monte Carlo simulations apply random sampling to predict clinical outcomes and uncertainty modeling [47–48]. These methods are especially useful in pharmacokinetics, pharmacodynamics, and the study of rare diseases, and they assist in trial design optimization, dosage optimization, and disease modeling [49].

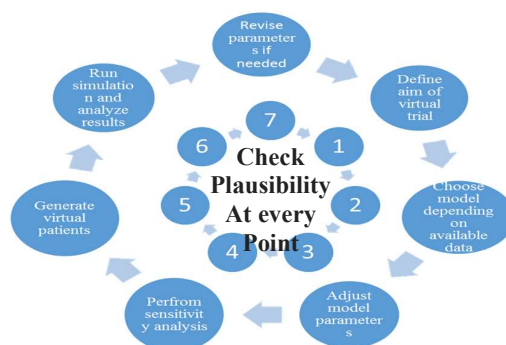


FIGURE 2: Cycle for generation of virtual patient

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The idea of the digital twin, later used in medicine, started in engineering as a virtual model of an existing system. Constructed with EHRs, imaging, genomics, wearables, and ambient data, it is a dynamic model of one patient in the healthcare sector that is real-time and dynamic. Through the simulation of biology and drug reactions, the twin makes safe testing of therapy possible before patient administration.

TECHNOLOGICAL FOUNDATIONS OF MEDICATION DIGITAL TWINS:

Three technologies are required to develop digital twins that can replicate a patient's response to medicine: predictive analytics, computational modeling, and data integration.

1. Data Integration and Acquisition Systems

This is how the process of collecting and consolidating all relevant patient information works. An electronic source for a patient's medical history, prescription medication, lab test results, and diagnoses was created by the adoption of Electronic Health Records (EHRs) by 2008. Moreover, real-time, patient-specific information is created by devices such as implanted cardiac devices and continuous glucose monitors. For certain medications, such as warfarin, even pharmacogenomics testing, which analyzes how genetics affect drug response, is becoming increasingly available.

2. Computational Modeling

This is the mathematical "brain" of the digital twin. They imitate the body's biological processes, including the metabolism of drugs and the onset of disease. Compartmental models can be

used to forecast the transit of a drug in the body and its duration of action. System biology models can imitate more complex relations between organs and genetic parameters. To this end, scientists in 2008 utilize computer systems like SimBiology, COPASI, and NONMEM. A customized digital twin for every patient can be created by customizing these generic models with their information (e.g., weight, renal function).

3. Analytics for Prediction

This method predicts the future by applying computational models and interlinked data. Depending on a patient's age, genetics, and other health issues, initial machine learning techniques like logistic regression and decision trees were utilized as early as 2008 to predict the expected efficacy of a drug and potential adverse effects. Three technologies' integration is the main advantage of the digital twin. The system may update the model and refine its predictions as it follows changes in a patient's actual world data (e.g., receipt of a new test result, weight change), potentially suggesting adjustments to therapy to achieve better outcomes. (50)

CLINICAL TRIALS WITH DIGITAL TWINS:

Complete and correct clinical patient trajectories may be developed due to DTs [5,51]. There is a high failure rate for drugs that enter clinical trials, with only one of ten making it to regulatory approval, which is incentive enough for DTs in the clinical context [52]. Phase 1 clinical trials aim to determine a compound's safety and effectiveness as soon as possible utilizing patient data of enrolled patients [53]. Decreasing the number of people required

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to quickly assess a molecule is important to fast-tracking medication development with less cost and societal impact, since patient recruitment delays in around 80% of all studies [54]. Clinical trials can be significantly fast-tracked and enhanced in quality by adding them to patient DTs. DT-generate data can reduce protracted patient recruitment processes (Figure 3a), e.g., trials in rare diseases, where the number of patients recruited is sometimes drastically limited [55]. Phase I and II oncology clinical trials offer another example. In this case, DTs can be used as comparison arms, making possible an earlier assessment of efficacy. In principle, with more simulation data, DTs have the potential to increase statistical power and accelerate clinical decision-making. As part of their commercial offering, Unlearn.AI built one of the very first DTs for clinical trials using generative NNs from conditional restricted Boltzmann machines (CRBM; Figure 3b) [24,25]. They trained generative models imitating patient courses for multiple sclerosis [25] and Alzheimer's disease [24] on data from observational studies and placebo control arms of prior treatment trials. One limitation of CRBMs is that, unlike deep NNs, they are shallow NNs with only a single hidden layer, i.e., they are less powerful at feature learning. DL models are accountable for the bulk of the latest advancements in generative AI. VAE for stroke patient trajectory prediction was explored by [26] in the context of DTs (Figure 3c). For counterfactual placebo therapy, in the treatment arm, they modeled the stroke patients' trajectories with EHR data. Patient trajectories were progressively generated by a VAE that decoded data from a low-dimensional

embedding space of trajectories learned. Generative DT models with the current limitations of the models constrain their generalizability and utility. Firstly, most of the efforts are limited to the exclusive target application of creating a control arm that is DT-based, where each patient in the treatment arm has a DT counterpart. Secondly, most of the methods employ training data of fewer than 5,000 patients, which is considered minimal for deep learning [58] and may restrain the generalizability of the models. Finally, comparing distribution characteristics with statistical tests or statistical indistinguishability i.e., showing that linear or non-linear classifiers cannot distinguish between real patients and DTs is the main way DTs are validated [24–26]. Further clinical information, like DTs of multiple sclerosis, was utilized for validation only in exceptional situations [56]. Deep learning architectures of today are not yet implemented by most DT models currently in clinical trials. On a related note, GANs (Figure 3d) successfully simulated synthetic clinical trial participants that statistically replace actual trial participants to preserve anonymity while allowing data sharing [57]. As these artificial objects are not attached to any real patients, they cannot be considered DTs; however, the approach might in the future be adapted for DTs. Numerically more sophisticated DTs, such as diffusion models, which are current leaders in image generation (Figure 3e) [58], neural ODEs, which enable learning of continuous dynamic systems (ODEs; Figure 3f) [60], and transformers, which have transformed language and speech generation (Figure 3g) [59], might be applied in clinical trials using advanced generative DL models.

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Finally, we have witnessed that DTs are being adapted already for clinical trials; however, existing approaches have limitations. We describe our vision of

generative AI models and DTs in drug discovery and development in the next section, highlighting clinical trial use cases for DTs (Figure 3h-j).

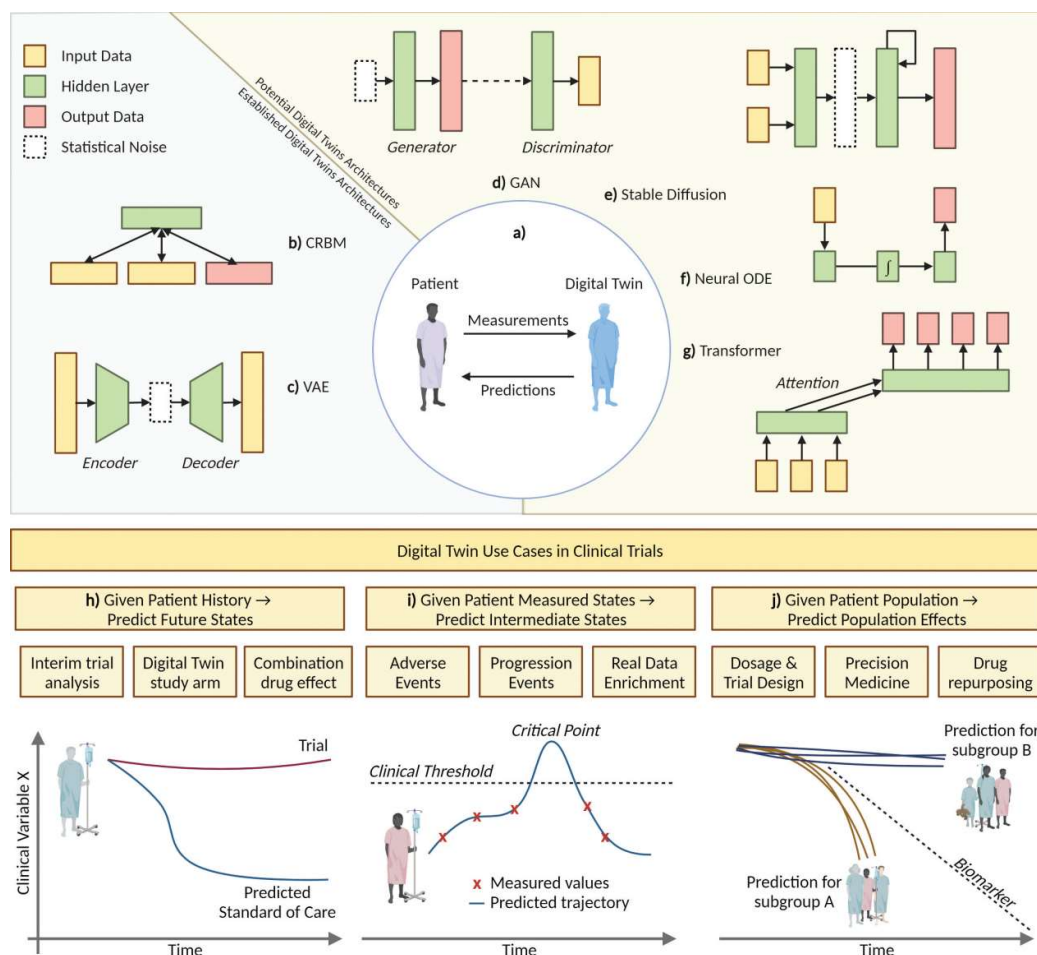


Figure 3: Clinical trial use scenarios and digital twin (DT) designs. (a) Since DTs are virtual representations of patients that can aid in better patient care, information exchange between them and actual patients is two-way. A simplified representation of the two generative DT architectures currently in use: the vibrational auto encoder (VAE) and the conditional restricted Boltzmann machine (CRBM). Generative adversarial networks (GAN), stable diffusion, neural ordinary differential equations (neural ODE), and transformers are possible generative DT structures. (h) DT use cases made possible by forecasting future patient conditions based on past data. (I) use cases that, given their measured states, are supported by

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DT predictions of intermediate states. Cases made possible by forecasting the patient's future conditions based on their medical history. (j) DT use cases by forecasting population effects and their parameters for a specific population, such as establishing clinical trial inclusion criteria. used BioRender.com to create it.

DIGITAL TWINS DURING THE AGE OF PERSONALIZED MEDICINE: DIGITAL DEVICE TO DIGITAL PATIENT:

A revolutionary question is prompted by the proven success of digital twins in keeping complex medical devices in working order: can the same technology be used with a human? To build a digital twin of an organ and, ultimately, an integrated model of a person's anatomy and physiology, the aim is to include longitudinal patient data [61].

THERE IS PLENTY OF POTENTIAL IN HEALTHCARE FROM THIS SHIFT IN PARADIGMS:

Better Clinical Procedures: By automatically including medical imaging to more accurately guide complex interventional procedures, digital organs can potentially revolutionize radiology-guided therapy [61].

ADVANCED MEDICAL EDUCATION:

By allowing young physicians and medical students to hone and rehearse their abilities on extremely realistic "digital patients" without any risk, these models are excellent for teaching [61]. The ultimate goal is to reach truly individualized medicine. We might shift the focus from treating disease to anticipating and preventing it by incorporating ongoing data to patient-specific models [62]. A full digital twin that tracks an individual from birth through to dying may enable highly personalized diagnostics, recommend

dietary or lifestyle changes, and forecast potential health risks. This encourages healthy living and early interventions to extend life [61]. With the advancements in artificial intelligence (AI), this is more than theory. Today, we can build dynamic, personalized simulations that are fully updated in real time based on lifestyle and health information. This information is already being employed in test digital twin investigations to track the impact of life style modifications, measure responses, and adapt therapies [66, 67, 63, 64, 65]. The assembly of digital twins extends beyond individualized care to yield massive cohorts of "virtual patients." This enables:

VIRTUAL CLINICAL TRIALS & POPULATION STUDIES: Researchers can investigate the progression of diseases and effects of treatments at scale using large-scale simulations, accelerating research and reducing costs [63].

DATA-DRIVEN RESEARCH INVESTMENT: Priceless evidence is generated by aggregating results and assessing how projections matched or mismatched with reality. It helps in channeling funds and research funds into the treatments and innovations that have proven to be most effective [63]. Finally, a networked health ecosystem a system that integrates data from wearable technology, patients, physicians, healthcare facilities, and the pharma industry can be established through digital twins [3, 65]. Thanks to AI and advanced biotechnologies such as

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genomics ("-omics") [68], an entire lifetime, constantly changing personal model is the promise of the future. This model will be applied to simulate situations, improve diagnostics, and facilitate highly individualized treatment plans, from focused medication therapy to tailored lifestyle interventions. It is directed by genetic information, laboratory

findings, and medical images. In essence, the digital twin will first be utilized to try out medical judgments. By incorporating these virtual investigations into clinical procedures, they will enhance patient decision-making and establish a system of continuous learning that emulates an infinite number of clinical trials

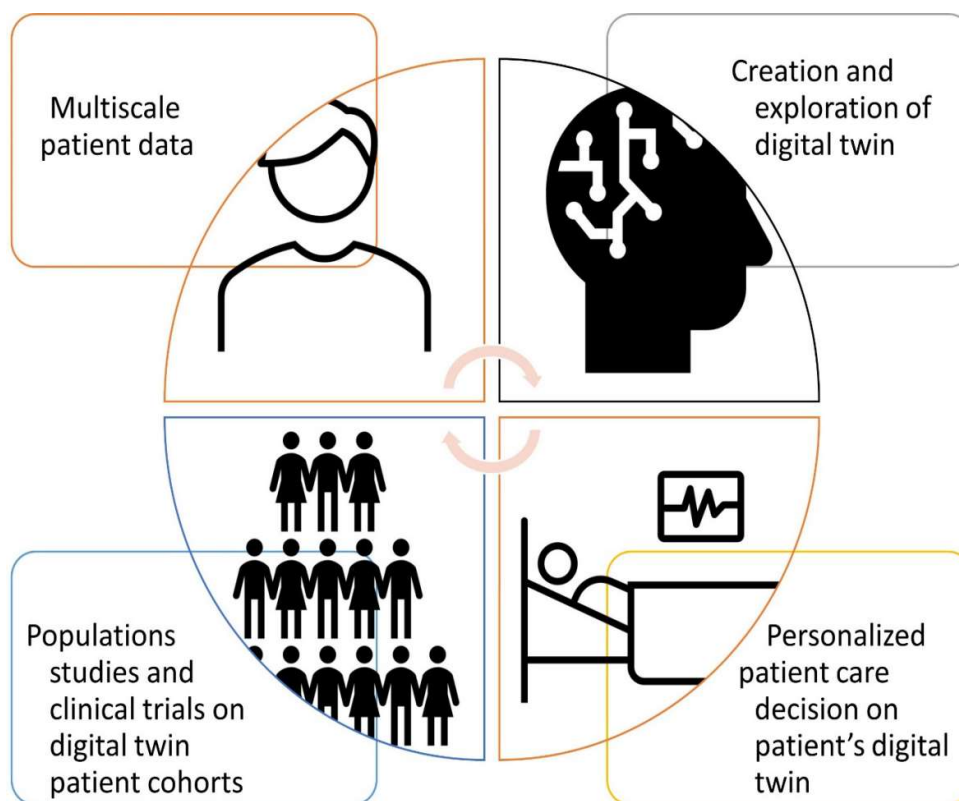


Figure 4: Key concepts and examples of patient digital twin life cycle

CASE STUDIES:

Consider the following applications for illustrating the versatility of digital twin models to better understand their utility:

Case Study 1: Assisting a Diabetic Patient to Prevent Hypoglycemia

Glyburide, a sulfonylurea known to cause hypoglycemia, is prescribed to a 67-year-old female with Type 2 diabetes and chronic kidney disease. Her digital twin runs a simulation and calculates a 78% risk of severe hypoglycemia in the first

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two weeks after being fed her glomerular filtration rate (GFR) and history of vertigo attacks. Sitagliptin, the alternative recommended by the model, is then prescribed with good results and no hypoglycemia attacks. The twin monitors her blood glucose levels and suggests adjusting medication based on trends.

Case Study 2: Enhancing Atrial Fibrillation Anticoagulation

Warfarin is ordered for a 72-year-old male who has atrial fibrillation and a history of stroke. The patient's liver panel, diet history, and genomic data are fed into his digital twin. Due to a forecasted slow metabolism, the model recommends a reduced initial loading dose than usual. Also, it provides an individualized titration plan and forecasts changes in INR in the initial month. As a result, therapeutic INR is achieved earlier and with safety compared to normal therapy.

Case Study 3: Avoiding Adverse Reactions in Oncology

A 50-year-old female breast cancer patient undergoing chemotherapy develops signs of neuropathy. The digital twin predicts deteriorating symptoms if treatment is left unchanged. It includes information on baseline neurological tests, chemotherapy rounds, and genomic markers linked to neurotoxicity. With the model, the oncologist evaluates various dosage regimens and neuroprotective supplements before arriving at a lower dosage in combination with vitamin E, allowing the patient to continue with the treatment without experiencing further nerve injury. [50]

CURRENT DIGITAL TWIN TECHNOLOGY LIMITATIONS AND CHALLENGES:

Even as the above technologies are progressing rapidly, numerous challenges still need to be addressed in the development of digital twins, whose application in the field of healthcare remains in its initial stages. The development and harvesting of high-volume, authenticated, high-quality, multiscale data that capture healthy and ill scenarios is the first challenge. The digital twin is a creation that demands continual and exhaustive data collection of various forms regarding the subject. Data must be gathered by applying the FAIR principles and derived from diverse groups of populations to ensure proper data integration and equal benefits for everyone [66]. But even the best wearable technology today is mostly invisible due to the sheer volume of data that needs to be measured in order to create a model of an individual in a medical context. The creation of multimodal data fusion methods that are able to combine knowledge in order to better delineate disease information, bringing together data-driven and virtual modeling, and data harmonization and aggregation will all be additional challenges. Thus, stringent controls and standards must be ensured to prevent digital twins from driving pre-existing biases and present inequalities within the healthcare system [66] while also governing data use and management [63,68]. This is so because digital twins are influenced by biases as they learn from poor-quality data. Insurance companies and healthcare organizations must gather personal information, including a person's biological, genetic, physical, and lifestyle information, in order to utilize digital twins. Such personal data can be utilized to advance the interests of the business

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instead of the patients [66]. While the technology of digital twins holds the promise of delivering wide-reaching benefits to society, special governance is needed, including measures to ensure data privacy and transparency of data use and benefits derived [66,69]. Otherwise, since such technology may not be universal and since trends observed in a population of digital twins may lead to discrimination and segmentation, it may well prove to be a force of inequality instead of being a social equalizer by facilitating effective equalizing enhancement interventions [66,68].

THE FUTURE OF VIRTUAL PATIENTS AND DIGITAL TWINS IN MEDICINE:

To overcome current challenges, the virtual patient and digital twin technology area is evolving rapidly and is likely to grow exponentially. Future development hinges on several key research and development priorities:

STANDARDIZATION: To make virtual patients widely used, there need to be reliable and consistent approaches to their development and verification.

INTEGRATION: Through the integration of virtual trials with traditional in vitro and in vivo studies, a powerful hybrid approach will be created that leverages the strengths of both digital and traditional methods.

REGULATORY FRAMEWORKS: The ethical and safe application of virtual patients within the drug development and clinical decision-making process is reliant on the adoption of accurate regulatory standards [70].

AI AND ML DEVELOPMENTS: Machine learning and artificial

intelligence need to be improved in order to enhance these models' predictive power. Solving the problem of the "black box" with Explainable AI (XAI) needs to be the highest goal of this effort to ensure safety and legitimacy while providing understandable insight [70]. In addition, access to large amounts of high-quality training data is key to the accuracy and generalizability of these models. Looking from the point of 2008, digital twin technology is expected to evolve along with real-time data gathering improvements, genomics, and computing. Patients will remotely track their medication through wearables in the not-too-distant future, digital twins will be a standard component of Electronic Health Record (EHR) systems, and AI-driven algorithms will keep model accuracy improving with additional data [50]. The creation of regulatory systems will enable this progress and enhance the role of healthcare workers, such as pharmacists, as translators and stewards for these paradigms [70]. A future where every patient receives a personalized, learning digital twin is the ultimate goal. This will guarantee that treatment programs are optimized by harnessing the best of data science and clinical acumen, render adverse medication reactions rare, and obviate trial-and-error prescribing.

CONCLUSION:

Healthcare stands at a crossroads because of digital twin technology, which presents capabilities that were previously unimaginable for simulating patient drug outcomes and guiding treatment decisions. The deployment of digital twins must remain fundamentally aligned to patient needs and physician workflow even as the



sophistication of today's data-driven solutions grows. The ultimate benefit of digital twins requires interdisciplinary collaboration between medicine, biology, data science, and artificial intelligence, similar to the history of previous medical breakthroughs. In addition to tackling ethical concerns and reducing costs, these computer models of patients offer several potential benefits, including enhanced medication safety, personalized treatment, and more efficient drug development processes. Although problems with data integration, interoperability between systems, and legal regimes continue to exist, there is a distinct path forward due to ongoing technological advancements. Digital twin technology can revolutionize patient care and usher in a new precision medicine era, enhancing outcomes all over the world, if academics, politicians, and healthcare professionals collaborate and put effective deployment plans in place

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