

**AI DRIVEN DIGITAL TWINS FOR DRUG REPURPOSING: CURRENT EVIDENCES,
APPLICATIONS, TRANSLATIONAL CHALLENGES AND FUTURE DIRECTIONS**

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ABSTRACT

Conventional drug discovery and development is associated with substantial financial costs, lengthy development timelines, and high attrition rates during preclinical and clinical evaluation. Drug repurposing provides an alternative strategy by identifying new therapeutic applications for existing drugs with previously characterized pharmacological and safety profiles. Recent advances in artificial intelligence, multimodal biomedical data integration, mechanistic modelling, and digital twin technology have created new opportunities to improve computational drug repurposing and patient-specific treatment prediction. This review examines the emerging integration of AI-driven digital twins with drug repurposing, focusing on digital twin architectures, artificial intelligence methodologies multi modal data integration, drug target prediction, pharmacokinetic or pharmacodynamic modelling, treatment-response simulation, and personalized therapeutic decision-making. The review also discusses applications across cancer, neurodegenerative, cardiovascular, infectious, metabolic, and rare diseases. Particular emphasis is placed on the development of patient-specific digital twins, integration of multi-omics and clinical data, virtual treatment simulation, and validation through computational, experimental, and clinical approaches. Major challenges include data heterogeneity, interoperability, model reliability, uncertainty quantification, interpretability, algorithmic bias, cybersecurity, privacy, clinical workflow integration, and regulatory acceptance. Emerging approaches, including causal AI, federated learning, multimodal foundation models, virtual clinical trials, and real-time adaptive digital twins, may further enhance the translational potential of AI-enabled drug repurposing. However, prospective clinical validation and standardized regulatory frameworks remain necessary before widespread clinical implementation.

KEYWORDS: Artificial intelligence; Digital twins; Drug repurposing; Drug repositioning; Machine learning; Precision medicine; Multimodal data; Virtual clinical trials; Drug discovery.

1. INTRODUCTION**1.1 Difficulties with Traditional Drug Discovery**

The process of finding and developing new drugs is costly, time-consuming, and dangerous. It is estimated

that the average cost of launching a new medication is \$1.24 billion. Preclinical research, clinical trials, post-marketing safety monitoring and drug discovery are the four main phases of traditional drug development

processes as seen in. The time needed to produce a new medication is roughly 12–17 years due to regulatory regulations for safety, efficacy, and quality in animal research and clinical trials.^[1]

1.2 Drug Repurposing

Drug repositioning, reprofiling, redirection, and drug rediscovery are other names for drug repurposing.^[2] New and creative approach to drug development is called "drug repurposing" which entails looking into how current medications might be used to treat conditions other than those for which they were designed.^[3] Compared to the de-novo development of completely new medications, drug repurposing provides a number of advantages, such as the potential to expedite the discovery process and lower failure rates throughout the clinical development and testing phase.

By finding new therapeutic applications for already-approved medications, drug repurposing also referred to as drug repositioning offers a convincing substitute. Remdesivir, which was repurposed for COVID-19 treatment, and sildenafil, which was once created for hypertension but is now commonly used for erectile dysfunction, are two notable examples for drug repurposing.^[4] Clinical, Preclinical, experimental, and computational approaches are used in the drug repurposing; computational approaches are becoming more popular as a result of improvements in the algorithmic sophistication and the data availability.^[5]

1.3 Drug Discovery Using Artificial Intelligence

In pharmaceutical research, artificial intelligence, which includes machine learning, deep learning, graph neural networks, reinforcement learning, generative AI, explainable AI, and huge language models, has been developed quickly.^[6] In drug repurposing, AI can facilitate drug–target interaction prediction, disease–drug association mining, molecular similarity analysis, transcriptomic signature matching, network-based prioritization, treatment-response prediction, toxicity assessment, and identification of patient subgroups likely to benefit from specific therapies. More precise and effective drug discovery and repurposing activities are made possible by AI's capacity to evaluate large and intricate biomedical datasets.^[7]

1.4 Digital Twin Technology In Healthcare

A healthcare digital twin is a computational representation of an individual, biological system, or clinical process that integrates relevant data and computational models to represent, monitor, simulate, and predict the behaviour of its corresponding physical entity.⁸ DTs are frequently displayed as 3D models or dashboards; a cardiac DT for instance might show up as a visual, realtime simulation of a patient's heart. By testing various treatment scenarios, such as modifying drug dosages or mimicking surgical procedures, clinicians can engage with the model and watch how the heart behaves, displaying changes in blood flow,

function, or possible consequences in real time. This technology allows for monitoring, simulation, and predictive insights by utilizing sensors, analytics, and machine learning.

1.5 AI-Powered Digital Twins for Repurposing Drugs

By providing continuous learning, predictive analytics, and adaptive simulations, the integration of AI with digital twins improves their capabilities. AI-powered digital twins are capable of simulating medication reactions, modelling complicated disease progression, seeing potential for repurposing, and assisting with customized treatment choices. Through precision therapy optimization and virtual patient simulations, this collaboration has the potential to revolutionize drug repurposing.^[9]

1.6 Objectives

This review compares AI approaches and digital twin architectures, summarizes recent research on AI-driven digital twins for medication repurposing, highlights obstacles, and explores potential avenues for future study. The objective is to present a thorough understanding of technical developments and how they could be applied to precision medicine.

2. METHODOLOGY

2.1 Study Design

In order to summarize the state of the art on AI-driven digital twins used in drug repurposing, this review employs a methodical narrative approach. The following are the main research questions: Which digital twin architectures and AI techniques are currently being used? What is the integration of multi-omics data? What are the main obstacles and potential paths in this developing field? In order to incorporate information from various study approaches, the review places a strong emphasis on qualitative synthesis.^[10]

2.2 Strategy for Literature

Search Electronic databases such as PubMed, Scopus, Web of Science, IEEE Xplore, Science Direct, SpringerLink, and ACM Digital Library were searched thoroughly for relevant material. In order to catch recent developments, the search period included publications from 2018 to 2026. Boolean operators were mixed in search terms, such as: ("artificial intelligence" or "machine learning" or "deep learning" or "graph neural networks") and ("digital twin") and ("drug repurposing" or "drug repositioning") and ("healthcare" or "precision medicine").

To find other studies, manual reference searches of pertinent papers were also carried out.^[11]

2.3 Qualifications

Peer-reviewed journal publications or conference papers published in English, research using AI-driven digital twin models in medication repurposing or closely related

healthcare applications, and those offering methodological or validation information were all required for inclusion. Reviews lacking original data, studies unrelated to digital twins or medication repurposing, and non-English publications were among the exclusion criteria.^[12]

2.4 Choosing a Study

Two reviewers separately assessed titles and abstracts based on eligibility after duplicates were eliminated. Disparities were settled by consensus after full texts were evaluated for inclusion. The study selection procedure is depicted in a PRISMA flow diagram.^[13]

2.5 Extraction of Data

Study features (authors, year, illness emphasis), AI approaches (algorithms, architectures), digital twin components, datasets used, validation strategies, major findings, performance measures, and limitations were among the data retrieved.^[14]

2.6 Evaluation of Quality

AI model reproducibility, dataset robustness, validation rigor, interpretability, and potential biases were all taken into account while evaluating methodological quality. It was stated that certain studies lacked sufficient validation or methodological clarity.^[15]

2.7 Synthesis of Data

AI approaches, digital twin frameworks, disease-specific applications, validation procedures, and new trends were compared using a thematic synthesis methodology. The results were arranged to emphasize research gaps, strengths, and limitations.^[16]

3. Fundamentals

3.1 The Development of Digital Twin Technology

In industrial engineering, digital twins were first used as virtual copies of real assets for simulation and monitoring.^[17] Digital twins are being used in healthcare thanks to developments in sensor technology, cloud computing, the Internet of Things (IoT), and artificial intelligence (AI). This allows for dynamic, real-time virtual representations of biological systems and patients.^[18]

3.2 Healthcare Architecture

Health care digital twins are made up of a number of interrelated parts including biological system that is modelled, encompassing molecular, cellular, tissue, organ, or whole-body scales is referred to as the physical entity(patient).Data acquisition systems include wearable technology i.e. sensors, electronic health records (EHR), and imaging technologies that gather both historical and current biomedical data. Multimodal data, such as genomes, proteomics, metabolomics, clinical data, and environmental exposures, are processed and harmonized using a data integration platform.^[19]

AI Analytics Engine: Uses knowledge graphs, graph neural networks, machine learning, and deep learning for pattern detection and predictive modelling.

Simulation Engine: Conducts simulated tests to mimic the course of a disease and reaction of medication

Decision Support Module: Offers clinicians useful information on dose optimization, medication selection.

Enables adaptive and customized interventions by continuously adding new patient data to the digital twin model.^[20]

3.3 Digital Twin Types

The biological scale of digital twins in healthcare varies:

Molecular twins: Simulate drug binding and molecular interactions.

Cellular twins: Mimic signalling pathways and cellular activity.

Tissue and Organ Twins: Mimic the diseases, physiological processes of particular organs.^[21]

Whole-Patient Twins: Use multi-scale data to model systemic diseases.

Population Twins: Combine information from several cohorts to investigate epidemiology.

Each kind has unique benefits for example; whole-patient twins facilitate individualized care, whereas molecular twins are excellent at predicting drug-target interactions.^[22]

3.4 Technologies for Artificial Intelligence

The following are important AI technologies used in digital twins:

Algorithms that extract the predictive patterns from data are known as machine learning (ML). Multiple-layer neural networks that record the intricate feature hierarchies are known as deep learning(DL).

Graph Neural Networks (GNNs): Simulate drug interactions and biological network linkages. Knowledge graphs are organized depictions that incorporate a variety of biomedical knowledge. Through trial and error, reinforcement learning facilitates adaptive decision-making. Generative AI mimics biological processes and produces artificial data.

Explainable AI (XAI): By making model judgments more transparent, XAI increases clinician trust. Beyond correlations, causal AI models cause-and-effect linkages.^[23]

3.5 Sources of Biomedical Data

Digital twins combine a variety of data sources including Multi-omics profiles reveal molecular disease pathways in the fields of genomes, transcriptomics, proteomics, metabolomics and the epigenomics.^[24] Clinical histories & treatment information are stored in electronic health

records **Medical imaging:** PET, CT, and MRI scans providing functional and anatomical information. **Wearable Sensor Data:** Constant physiological observation. Validation and outcome data from clinical trials and real-world evidence. Missing values, longitudinal data integration, and data standards are challenges.^[25]

4. AI- Driven Digital Twin Framework for Drug Repurposing

4.1 Overview of the System

From multi-source data collection to clinical decision support, the AI-driven digital twin platform for drug repurposing includes a full process. It simulates illness states and medication reactions by combining AI analytics with patient-specific models.^[26]

4.2 Gathering and Integrating Data

Omics, imaging, clinical records, wearable sensors, and other multimodal data are gathered and processed. Compatibility for model input is ensured by data normalization, feature extraction, and harmonization. Integration effectively combines disparate datasets by utilizing sophisticated workflows.^[27]

4.3 Construction of Digital Twins

Among the computational modelling techniques are Mechanistic simulations of biological processes are known as systems biology models

Hybrid Mechanistic AI Models: For improved accuracy, integrate data-driven AI with biological understanding.

Patient-Specific Models: Personalized digital twins that represent individual differences.^[28]

4.4 AI-Based Predictive Modelling AI models forecast Disease Progression:

Project long-term clinical results.

Drug-Target Interaction: Determine whether medications and biological targets may interact. **Drug Response:** Model side effects and treatment efficacy. Finding molecular markers of treatment response is known as biomarker identification. Evaluate drug safety profiles in order to predict toxicity.

Optimize Combination Therapy: Assess synergistic effects of drugs. Metrics including accuracy, AUC, precision, recall, and interpretability are used to assess the model's performance.^[29]

4.5 Online Drug Testing

In silico screening of current drug libraries is made possible by digital twins, which rank candidates according to expected safety and efficacy. Repurposing decisions are guided by simulated therapeutic responses prior to experimental validation.^[30]

4.6 Techniques for Validation

Cross-validation and dataset benchmarking are examples of computational validation. Animal models and organoids are used in laboratory experiments.

Clinical trials include both prospective and retrospective research. Analyses of longitudinal patient data provide real-world evidence.^[31]

4.7 Assistance with Clinical Decisions

Precision medicine is made possible by AI-driven digital twins, which help physicians by suggesting customized medication choices, optimizing dosages, anticipating side effects, and continuously tracking treatment response.^[32]

5. Current Evidences & Applications Of AI Driven Digital Twins For Drug Repurposing

5.1 Cancer

The use of Digital Twin [DT] technology is revolutionizing the field of cancer. DTs provide powerful solutions in this context by creating digital human representations that are able to translate their physiological and anatomical characteristics with remarkable fidelity.^[33] The current research and development activity in cancer remains particularly resource-intensive and encounters a significant failure rate. DTs develop cancer models in a virtual environment for research, clinical trials, and treatment planning optimization by gathering data from multiple sources, including imaging, genetics, clinical histories, and patient self-reported outcomes. By simulating intricate biological processes like drug metabolism, distribution, target engagement, and possible toxicities, these virtual models can offer important insights prior to human exposure.^[34]

5.2 Cardiovascular diseases

Cardiovascular disease (CVD) is still the leading cause of death globally and its incidence is gradually increasing. DT technology is currently being used in an increasing number of medical fields, including cardiovascular medicine. By modelling illness progression and precisely forecasting treatment results, AI-powered DT technologies create patient-specific simulations that support early diagnosis, optimal therapy, post-intervention monitoring.^[35] They also improve clinical decision making. The digital twin has a lot of potential in the field of cardiovascular illness, but its practical application and general adoption are still in their infancy. There are still issues with data quality, model complexity, clinical usefulness, and privacy.^[36]

5.3 Personalised Medicine

Personalised medicine also known as precision medicine, is a novel approach to medicine that tailors therapies and treatments to each patient's particular need.³⁷ Recently, digital twin technology has been introduced to the healthcare industry, and it has the potential to revolutionize precision and individualized medicine.³⁸ For decades, the medical world has struggled to produce personalized medicine, or treatment planning based on patient-specific data. Digital twins allow medical personnel to make data-driven decisions, personalize treatment approaches, and obtain a thorough

understanding of patients health by utilizing cutting edge technologies to create digital replicas of persons.^[39]

5.4 Neurodegenerative diseases

Neurodegenerative diseases are particularly suitable for AI-driven digital-twin applications because of their complex molecular mechanisms, substantial inter-individual heterogeneity, progressive disease trajectories, and variable responses to treatment. Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are emerging areas in which AI, multiomics, network medicine, and computational modelling can support drug repurposing.

A. Alzheimer's disease

Alzheimer's disease (AD) is a promising area for the use of digital twins in drug discovery and repurposing because of its complex nature, involving the interplay of amyloid and tau pathology, neuro inflammation, vascular dysfunction, metabolic changes, genetic factors, and cellular dysfunction. Digital twins can integrate AI, clinical data, and multi-omics information to predict disease progression, identify biomarkers and therapeutic targets, prioritize repurposable drugs, and improve patient stratification. A recent single-cell digital-twin approach by Ren *et al.* combined AI, network medicine, and multi-omics data to identify AD-related therapeutic targets and potential repurposed drugs. This enables drug repurposing based on cell-type-specific mechanisms rather than only general drug-disease associations. Additionally, AI-generated patient trajectories using electronic health records can act as clinical digital twins, helping predict individual disease progression and potentially supporting treatment selection and clinical trials.^[40]

B. Parkinson's disease

Parkinson's disease represents another promising area for the use of digital twins, as patients show considerable heterogeneity in motor symptoms, cognitive impairment, disease progression, genetic background, and treatment response. A Parkinson's disease digital twin could integrate genomic information, neuro imaging data, clinical motor and cognitive assessments, medication history, and molecular biomarkers. AI-based models can identify disease-associated molecular pathways and potential therapeutic targets, whereas the digital twin can provide a patientspecific framework for evaluating candidate interventions. Such an approach could enable precision drug repurposing, in which existing drugs are prioritized according to the predicted biological characteristics and treatment response of individual patients or molecular subgroups. Potential applications include prediction of disease progression, identification of molecular subtypes, evaluation of treatment response, identification of repurposable drugs, and simulation of combination therapies. However, compared with AD, patient-specific digital-twin applications in PD remain less mature and should currently be regarded as an emerging research direction.^[41]

C. Huntington's disease

Huntington's disease is particularly suitable for integrating AI, causal modelling, systems biology, and digital-twin concepts because its initiating genetic abnormality is well characterized, while its downstream molecular and clinical effects are highly complex.

AI-driven models can connect the genetic alteration associated with the disease to transcriptomic, proteomic, metabolic, cellular, motor, and cognitive changes. These models can subsequently be used for virtual perturbation of disease-associated pathways and prioritization of existing drugs.

The major advance represented by this approach is the transition from conventional drug-target prediction to mechanism-based therapeutic simulation. Instead of simply identifying drugs that interact with a disease-associated protein, the digital twin can theoretically simulate how perturbation of a biological pathway could alter disease progression.^[42]

5.5 Rare diseases

Rare diseases represent another important area for the use of AI-driven digital twins. Drug development in rare diseases is often limited by small patient populations, sparse clinical data, delayed diagnosis, heterogeneous phenotypes, incomplete natural-history information, and limited understanding of disease mechanisms. A recent systematic review of digital twins in rare diseases identified approaches based on physiologically based pharmacokinetic, population pharmacokinetic, quantitative systems pharmacology, physiome, and combined modelling approaches. The review concluded that digital-twin implementation in rare diseases remains at an early stage, but these approaches have considerable potential for disease-progression modelling, drug development, precision dosing, and clinical decision support.

One important application is the development of virtual patients. AI and mechanistic models can integrate limited patient information to create computational representations of disease states. These virtual patients can subsequently be used to evaluate drug exposure, pharmacokinetics, pharmacodynamics, and potential treatment responses.

Drug repurposing is particularly attractive for rare diseases because existing drugs have established pharmacological and safety information. AI can identify relationships between disease-associated genes, proteins, pathways, phenotypes, and existing drugs, while the digital twin can provide an individualized framework for evaluating the potential response to those candidates.^[43]

5.6 Infectious diseases

Infectious diseases provide a distinctive application for AI-driven digital twins because therapeutic outcomes depend on dynamic interactions between the host,

pathogen, immune system, drug, and environment. AI is already being applied to infectious-disease drug discovery and repurposing through molecular docking, virtual screening, drug–target prediction, network pharmacology, machine learning, and deep learning.

A. Viral infections

The COVID-19 pandemic accelerated AI-based drug repurposing because rapid computational screening was required to identify potential therapeutic candidates. AI models can analyse drug–viral protein interactions, host factors, molecular pathways, and clinical information to prioritize existing drugs.

Digital twins could extend these approaches by integrating pathogen genomic information with patient-specific characteristics, immune status, laboratory measurements, pharmacokinetics, and clinical outcomes. A host–pathogen digital twin could therefore simulate alternative therapeutic strategies and predict potential treatment responses.

Current applications include antiviral candidate prioritization, host–pathogen interaction modelling, disease-progression prediction, treatment-response prediction, virtual evaluation of therapeutic combinations, and patient-specific treatment selection.

AI is also increasingly being applied to infectious-disease surveillance and epidemic modelling. A 2025 Nature perspective highlighted the expanding role of AI in infectious-disease epidemic modelling, while recent digital-twin research has proposed AI-based frameworks for precision surveillance of emerging infectious diseases.^[44]

B. Antimicrobial resistance

Antimicrobial resistance (AMR) represents an important opportunity for AI-driven precision medicine. Treatment selection depends on pathogen susceptibility, infection site, patient physiology, antimicrobial exposure, immune response, and the possibility of resistance emergence.

AI models can predict antimicrobial susceptibility and resistance patterns, while digital twins can potentially simulate the effects of different antimicrobial agents, doses, combinations, and treatment durations. This creates an opportunity to identify the most appropriate existing antimicrobial for a specific patient–pathogen combination.

Current AI applications in AMR include resistance prediction, pathogen identification, antimicrobial discovery, susceptibility prediction, and treatment optimization. When combined with digital-twin modelling, these approaches could support individualized antimicrobial selection and dosing and potentially reduce unnecessary antimicrobial exposure.^[45]

6. Translational Challenges

6.1 Data challenges

Data Quality and Completeness: Model accuracy is hampered by inconsistent data, missing variables and noise.

Standardization: Integration is made more difficult by the absence of consistent data formats.

Multi-Modal Integration: It is still difficult to harmonize disparate data from clinical, imaging, and omics sources.

Longitudinal Data Availability: Accurate disease progression modelling is hampered by a lack of time-series data.^[46]

6.2 Computational Difficulties

High Computational Costs: It takes a lot of resources to run simulations and train AI models.

Scalability: It's difficult to modify models for big, varied patient groups.

Real-Time Synchronization: Effective data pipelines are necessary to guarantee that digital twins represent current patient conditions.

Model Maintenance: Constant validation and updating require a lot of resources.^[47]

6.3 AI Difficulties

Interpretability: Clinical trust is limited by complex models, which are frequently opaque.

Algorithmic Bias: Unfair or erroneous predictions can be spread by training data biases.

Overfitting: Beyond training data, models might not be able to generalize well.

Generalizability: Models must be flexible to accommodate a variety of patient demographics & illnesses.

Uncertainty Estimation: Clinical decision-making depends on measuring forecast confidence.^[48]

6.4 Clinical Difficulties

Prospective Validation: Only a small number of models go through thorough prospective clinical testing.

Clinical Workflow Integration: Digital twin instruments must be easily incorporated into current medical procedures.

Physician Acceptance: Adoption is influenced by usability and trust

Patient Engagement: The moral and practical implications of using digital twin monitoring with patients.^[49]

6.5 Regulatory and Ethical Difficulties

Data privacy: It's critical to safeguard private patient data.

Cyber security: Making sure digital twin systems are safe from intrusions.

Regulatory Approval: Handling changing AI-driven tool frameworks.

Accountability and Transparency: Outlining who is responsible for clinical decisions made by AI.

Fairness: Providing advantages to all groups equally.^[50]

7. Future Directions

7.1 Adaptive Digital Twins in Real Time

To enable real-time updating, future digital twins will make use of continuous data streams from wearable technology, remote monitoring, and the Internet of Medical Things (IoMT). Timely interventions and individualized therapy modifications will be made possible by this dynamic flexibility.^[51]

7.2 Foundation

Models with Multiple Modes Comprehensive patient representations will be produced by creating unified foundation models that incorporate genomes, imaging, clinical records, and molecular structures. In a variety of disease situations, these models will increase prediction accuracy.^[52]

7.3 Explainable and Reliable

Clinicians will be able to comprehend and trust AI-driven judgments because to the advancement of explainable AI techniques, which will improve model transparency. Ethical deployment will be encouraged by better uncertainty estimation and fairness evaluations.^[53]

7.4 Federated Learning

By allowing hospitals and research institutions to collaborate on model training without exchanging sensitive patient data, privacy-preserving federated learning techniques will spur innovation while upholding confidentiality.^[54]

7.5 Clinical Research

By simulating treatment outcomes and enhancing trial design, digital twins will enable better patient classification, lower costs, and expedite development times for virtual clinical trials.^[55]

7.6 Uniformity

To guarantee reproducibility, comparability, and regulatory compliance, standardized data models, interoperability standards, benchmarking datasets, and regulatory frameworks must be developed.^[56]

7.7 Customized Precision

Health care AI-driven digital twins for patient-specific therapy optimization will be a crucial part of standard clinical practice, encouraging adaptable treatment plans based on unique biological and lifestyle characteristics.^[57]

8. CONCLUSION

By combining multimodal biological data with sophisticated predictive modelling to speed up the discovery of novel therapeutic indications, AI-driven digital twins are revolutionizing medication repurposing. Disease modelling and treatment response prediction have been improved by methods like explainable AI, knowledge graphs, graph neural networks, and deep learning. Data heterogeneity, model interpretability, strict validation, regulatory approval, and ethical issues like privacy and fairness are among the obstacles that still

exist despite tremendous advancements. The creation of standardized evaluation frameworks, prospective clinical validation, interdisciplinary collaboration between physicians, data scientists, and regulatory agencies, and strong governance frameworks are all necessary for future advancements. These initiatives are essential to turning AI-powered digital twins from research prototypes into standard instruments for effective, patient entered medication development and precision medicine.

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