Review of Digital Twin Modeling Strategies in Medicine: Methodological Approaches, Applications, and Emerging Trends

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Introduction

- **Digital Twins (DT)**: A specialized engineering approach pairing physical entities with digital models that dynamically mirror their status.[1]
- **Emerging Technology**: Creates in silico representations of individuals, continuously reflecting their molecular state, physiological condition, and lifestyle changes.[1]
- **Hypothesis**: Access to detailed biophysical and lifestyle information over time redefines 'normality' or 'health' as patterns typical for a specific person, compared to broader population patterns.[1]
- **Modeling and Simulation**: Widely used in various industrial sectors for designing and de-risking new products. In biomedical research, these tools enhance experimental and clinical research by enabling detailed mechanistic and systematic investigations.[2]
- **Credibility and Adoption**: Modeling and simulation have gained significant traction within regulatory agencies and the industry, leading to the emergence of human in silico clinical trials as a key paradigm in medical therapy development.[2]
- **Applications**:
  - **Virtual Testing**: Used for the virtual testing of pharmacological therapies and devices.[3]
  - **Animal Experimentation**: Helps reduce, refine, and replace animal experimentation and traditional bench tests.[3]
- **Cancer Treatment Challenge**: Cancer, a leading cause of death globally, has the lowest success rate for clinical trials among complex diseases. Computational tools are needed to expedite the testing and comparison of dose levels, therapy combinations, and predictive biomarkers.[4]
- **Related Concepts**: Virtual patients, virtual twins, digital patients, and digital twins aim to speed up drug development and improve patient outcomes, each with distinct limitations.[4]
- **Model-Informed Drug Development (MIDD)**: Mathematical models guide clinical trial design, with semi-mechanistic approaches like pharmacokinetic-pharmacodynamic (PK/PD) models integrated into regulatory submissions.[5]
- **Advanced Mechanistic Models**: Physiologically-based pharmacokinetic (PBPK) models and quantitative systems pharmacology (QSP) models predict drug effectiveness and support clinical trial design through in silico or virtual clinical trials.[6]
- **Precision Medicine**: Digital twins monitor and optimize treatment for individual patients using personalized models, emphasizing close correspondence with their physical counterparts.[7]
- **Data Utilization**: Virtual patients are created using aggregated data from multiple sources, while digital twins use data from individual patients, regularly updated from future measurements.[8]

METHODS

➢ **Search Strategy**

- **Databases**: PubMed, Scopus, Web of Science
- **Date Range**: Up to June 1, 2024
- **Keywords**: "digital twin", "virtual twin*", "digital patient*", "virtual patient*", "in silico*", "simulation*"

➢ **Inclusion and Exclusion Criteria**

- **Inclusion**: Original research articles in English focusing on digital twins and related modeling strategies in medical applications.
- **Exclusion**: Reviews, meta-analyses, editorials, letters, and non-research articles.

➢ **Selection Process**

- **Screening**: Titles and abstracts reviewed for relevance.
- **Full-Text Review**: Articles assessed against inclusion criteria.
- **Final Selection**: 373 papers included, with duplicates removed.

➢ **Data Extraction and Analysis**

- **Data Extraction**: Structured form capturing article details, modeling strategy, medical discipline, objectives, and findings.
- **Qualitative Analysis**: Categorized by modeling strategy and medical specialty to identify trends and gaps. Results are visualized through charts and tables.

Article Example (Title)	Modeling Strategy	pecialty
Development of Digital Twins to Optimize Trauma Surgery and Postoperative Management	Digital Twin	Orthopedics
Systems-based digital twins to help characterize clinical dose-response in a Phase I study	Digital Twin	Oncology
Virtual patient framework for testing mechanical ventilation settings	Virtual Patient	Anesthesiology & Critical Care
Use of virtual patients in orthopedic teaching	Virtual Patient	Medical Education
Estimating long-term effects of treatment using virtual twins	Virtual Twin	DT in Clinical Trials
In Silico Trials Guide Optimal Stratification of Atrial Fibrillation Patients	In silico	Cardiology
Predicting Pregabalin Treatment Response using Machine Learning	Simulation	Endocrine

RESULTS

➢ **Distribution of Modeling Strategies:**

- **Virtual Patient Models**: The most utilized strategy, accounting for **57.3%** of studies.
- **Digital Twin Models**: Represent **30.5%** of the reviewed papers.
- **In Silico Methods**: Used in **9.2%** of the studies.
- **Virtual Twin Models**: Less frequently applied, present in **2.7%** of papers.
- **Simulation**: Rarely used, making up only **0.3%** of the studies.

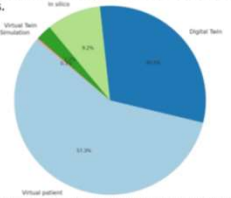

Figure 1: Distribute modeling strategy applied. proportion of papers categorized by the modeling strategy applied in each study.

➢ **Distribution of Medical Specialties**

- **Medical Education**: 157 publications (42.1%)—dominates research focus on integrating DTs in medical training.
- **Prominent Fields**: **Endocrine** (25 papers, 6.7%), **Cardiology** (21 papers, 5.6%), **Oncology** (18 papers, 4.8%), **Neurology** (17 papers, 4.6%)—strong focus on applying DTs to complex diseases.
- **Underrepresented Fields**: OBGYN, Dermatology, Nephrology, Nuclear Medicine, Ophthalmology, Rehabilitation—each with just **1 paper** (0.3%).
- **Low Representation**: Genetics, Hematology, Occupational Therapy—each with 2-3 papers.
- **Emerging Interest**: Digital Twin in Clinical Trials—8 papers (2.1%)—growing interest in applying DTs in clinical trials.

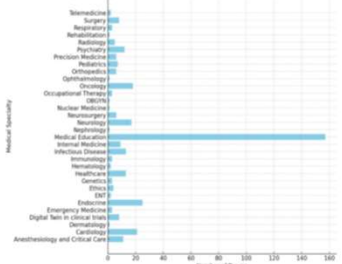

Figure 2: Distribution of medical specialty, varying application of advanced modeling strategies across different fields.

Discussion

- **Key Findings:**
  - Digital Twin (DT) technology is mainly applied in medical education, cardiology, oncology, neurology, and endocrinology.
- **Medical Education:**
  - Mostly uses Virtual Patients (154 out of 157 papers), but DTs have potential for enhancing personalized learning.
- **Cardiology & Oncology:**
  - DTs are often used in cardiology (14 out of 21 papers) and oncology (13 out of 18 papers) to manage complex diseases and personalize treatments.
- **Neurology & Endocrinology:**
  - Neurology (11 out of 17 papers) and endocrinology use DTs to explore disease management and predictive care.
- **Gaps in Research:**
  - Fields like nephrology, OBGYN, and respiratory medicine are underexplored, representing opportunities for future research.

Conclusion

- **Growing Importance:**
  - DTs are increasingly used in healthcare for personalized treatment, especially in cardiology and oncology.
- **Research Gaps:**
  - More research is needed in fields like nephrology, OBGYN, and respiratory medicine.
- **AI and DTs:**
  - AI integration improves real-time monitoring and personalized care.
- **Economic Impact:**
  - DTs can reduce healthcare costs and improve resource allocation.
- **Future of Healthcare:**
  - Expanding DT use will enhance personalized medicine across more medical fields.

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