Computational Modelling and Digital Twin in Personalized Treatment for Cardiac Electrophysiology: A Survey

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Abstract

This survey paper explores the integration of computational modeling and digital twin technology in personalized treatment for cardiac electrophysiology, focusing on conditions such as atrial fibrillation, ventricular tachycardia, ischemic heart disease, and heart failure. It examines the transition from reactive to proactive healthcare, highlighting the role of Human Digital Twins (HDTs) in continuous health monitoring and personalized interventions. The paper discusses advanced modeling techniques, including graph-based, hybrid, inverse problems, and surrogate modeling approaches, and their application in simulating complex cardiac dynamics. The integration of real-time data and predictive analytics in digital twins is emphasized, showcasing their potential to enhance patient-specific interventions and optimize treatment outcomes. The survey also addresses the challenges in distinguishing responders from non-responders and the predictive capabilities of digital twins in this context. Intra-operative applications and the use of digital twins in cardiac resynchronization therapy (CRT) are explored, highlighting their potential to improve surgical precision and patient outcomes. The paper concludes by discussing real-world applications, future directions, and the ethical, legal, and implementation challenges associated with digital twin technology in healthcare. Overall, this survey underscores the transformative potential of computational modeling and digital twin technology in advancing personalized medicine and optimizing patient care.

1 Introduction

1.1 Structure of the Survey

This survey provides a comprehensive analysis of the integration of computational modeling and digital twin technology in personalized treatment for cardiac electrophysiology. The paper is organized into several key sections: Section 2 presents a detailed background and definitions of fundamental concepts, including computational modeling, digital twin technology, and relevant cardiac conditions. Section 3 examines computational modeling techniques in cardiac electrophysiology, covering graph-based, hybrid, inverse problems, surrogate modeling approaches, as well as advanced machine learning and Bayesian methods [1]. Section 4 discusses digital twin technology in personalized treatment, focusing on the integration of real-time data and predictive analytics [2], patient-specific interventions, applications of human digital twins, and associated challenges. Section 5 explores diagnostic tools in cardiac assessment and the role of computational models in treatment selection. Section 6 analyzes challenges in distinguishing responders from non-responders and the predictive capabilities of digital twins in this context. Section 7 highlights intra-operative applications of digital twins in cardiac resynchronization therapy (CRT) to enhance surgical outcomes [3]. The survey concludes with Section 8, summarizing key findings, discussing real-world applications, future directions, and addressing ethical, legal, and implementation challenges.

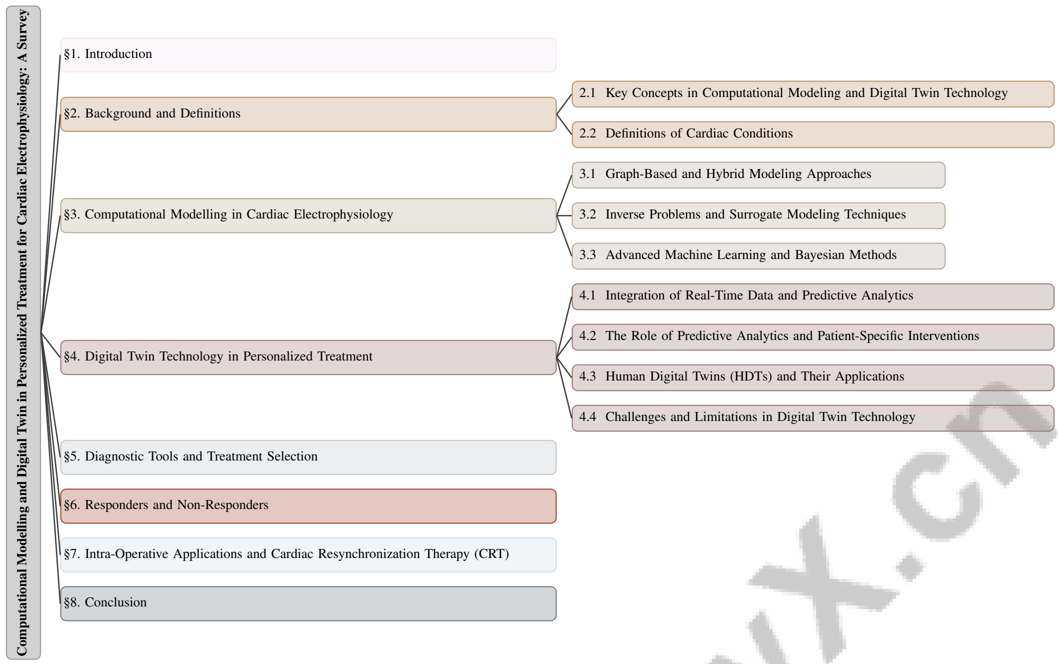


Figure 1: chapter structure

1.2 Transition from Reactive to Proactive Healthcare

The transition from reactive to proactive healthcare signifies a fundamental shift in the medical field, emphasizing personalized, precise, and systemic treatment approaches. Traditional healthcare models, reliant on retrospective data and reactive management strategies, are increasingly inadequate for addressing complex chronic conditions [4]. Digital twin technology plays a critical role in this transition, providing sophisticated solutions to decode intricate physiological processes and anticipate disease trajectories through high-fidelity virtual simulations and robust data interactions.

Human Digital Twins (HDTs) are pivotal to this proactive model, enabling continuous health state monitoring and offering a dynamic framework for simulating disease manifestations in real patients. This innovation surpasses traditional data collection methods, such as ECG, by delivering nuanced and individualized health assessments. Moreover, HDTs facilitate the integration of diverse patient data types, addressing computational challenges and enhancing the precision of complex disease modeling [5].

The benefits of HDTs are substantial, promising improvements in patient outcomes and healthcare system efficiency. By leveraging predictive analytics and uncertainty quantification, digital twins refine treatment plans and enhance decision-making processes, fostering more proactive and effective healthcare delivery. This approach not only tackles existing challenges in personalized healthcare but also lays the groundwork for future advancements in digital twin technology implementation. However, significant obstacles remain, including the lack of a standardized definition for digital twins, high IT infrastructure costs, data privacy and security concerns, and the necessity for strong trust in AI systems [6].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Key Concepts in Computational Modeling and Digital Twin Technology

Computational modeling and digital twin technology are crucial for advancing personalized healthcare, particularly in cardiac electrophysiology. These methodologies employ mathematical models to simulate biological systems, thereby improving the understanding of complex physiological processes. Graph-based models are instrumental in integrating diverse clinical data, simulating patient-specific conditions, and predicting health trajectories, which are vital for visualizing cardiac behaviors and refining diagnostic and therapeutic strategies [4]. Digital twin technology serves as a dynamic digital replica of physical entities, such as the human heart, by integrating real-time data with complex simulations to enable continuous monitoring and personalized healthcare interventions. The architecture of Human Digital Twin (HDT) systems typically includes components for physical representation, digital modeling, and human-computer interfaces, facilitating a comprehensive approach to digital twin development [7, 8].

Innovations in the field have introduced Digital Twin Generators (DTGs) that utilize neural networks to create patient-specific digital twins capable of predicting future health outcomes [9]. The integration of mobile AIGC further enhances HDT capabilities by enabling real-time data generation and analysis [10]. Novel pipelines that incorporate subject-specific clinical data, such as ECG and MRI, have significantly improved the fidelity of simulations of ventricular activation, including Purkinje networks [11]. Hybrid models, such as the HyPer-EP framework, combine physics-based and data-driven approaches to address complexities in personalized cardiac electrophysiology [12]. The Med-Real2Sim method exemplifies the use of physics-informed self-supervised learning algorithms, pretraining neural networks on synthetic data to create differentiable simulators of physiological processes.

Digital twin technologies can be categorized into Virtual Twin, Predictive Twin, and Twin Projection, emphasizing their roles in real-time prediction and optimization. Despite advancements, challenges remain, particularly concerning the identifiability of cardiovascular model parameters from electronic health records (EHR). Traditional optimization and Bayesian inference methods, such as Bayesian PROCOVA, often impose regularization constraints that limit the discovery of multiple solutions [1]. Innovative techniques like Gaussian process surrogates enhance model discrimination in complex biological systems [13]. The JHgRF-Net architecture, which integrates Spatio-Temporal Hypergraph Convolutional Network (STHgCN) and Spatio-Temporal Transformer Network (STTN), improves forecasting accuracy and reliability in healthcare applications [14].

These developments underscore the transformative potential of computational modeling and digital twin technology in personalized healthcare, ensuring that key therapy targets are mathematically represented for reliable virtual predictions of therapy outcomes [3]. Hierarchical federated learning frameworks facilitate collaboration among healthcare organizations without sharing sensitive patient data, advancing the collective development of digital twin technologies [15].

2.2 Definitions of Cardiac Conditions

Electrophysiology examines the electrical properties and activities of biological cells and tissues, focusing on cardiac function. This field encompasses the development of advanced techniques such as cardiac digital twins (CDTs), which are patient-specific virtual models replicating the heart's electrical behavior for personalized diagnostics and treatment planning. Innovations include hybrid modeling frameworks that merge physics-based approaches with machine learning to enhance model accuracy and probabilistic methods for identifying critical components like the Purkinje network from non-invasive electrocardiograms (ECGs), improving model calibration against clinical data for individualized cardiac care [16, 17, 18, 19]. Understanding action potentials and electrical impulse conduction is crucial for diagnosing arrhythmias and cardiac disorders, forming the foundation for effective diagnostic and therapeutic strategies.

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia characterized by rapid and irregular atrial electrical activity, leading to inefficient blood flow and increased stroke risk. Disruptions in the heart's electrical conduction system, influenced by anatomical and physiological factors, necessitate accurate modeling for effective diagnosis and treatment. Advanced computational techniques, including cardiac digital twins, are being developed to simulate individual heart function and optimize therapeutic interventions, enhancing AF management [20, 21, 19, 18, 3]. Understanding AF's electrophysiological basis is essential for developing effective treatments and interventions.

Ventricular tachycardia (VT) is a rapid heart rhythm originating from the ventricles, characterized by abnormal electrical impulses that disrupt normal rhythm, potentially leading to severe complications. Recent advancements in cardiac electrophysiology, including the identification of the Purkinje network through probabilistic modeling and the development of personalized virtual heart models, underscore the importance of understanding VT mechanisms for improving precision medicine and patient-specific treatment strategies [16, 19]. If unmanaged, VT can be life-threatening, leading to ventricular fibrillation and sudden cardiac death, often requiring precise electrophysiological mapping and interventions to restore normal rhythm.

Ischemic heart disease (IHD), or coronary artery disease, occurs when blood flow to the heart is reduced due to narrowing or blockage of the coronary arteries, leading to heart attacks and significant morbidity and mortality. Computational modeling and digital twin technology facilitate understanding hemodynamic changes in IHD and optimizing treatment strategies by identifying patient-specific parameters using noninvasive data such as echocardiograms [22].

Heart failure is a chronic condition where the heart fails to pump blood effectively to meet the body's needs, arising from various underlying health issues, particularly ischemic heart disease and hypertension, which significantly impact cardiovascular function and overall health [4, 23]. As a major public health issue, advancements in computational modeling present new opportunities for personalized treatment approaches, enhancing the management of this complex condition.

In recent years, the field of cardiac electrophysiology has seen significant advancements driven by computational modeling approaches. These methodologies not only enhance the accuracy of cardiac models but also contribute to the personalization of patient care. To elucidate the complexity and organization of these approaches, Figure 2 presents a comprehensive overview of their hierarchical structure. This figure illustrates the various computational modeling approaches, categorizing them into three primary groups: Graph-Based and Hybrid Modeling Approaches, Inverse Problems and Surrogate Modeling Techniques, and Advanced Machine Learning and Bayesian Methods. Each of these categories is further subdivided into specific methodologies, demonstrating their respective applications and implications for improving cardiac model accuracy and patient outcomes. By examining this structured representation, we can better appreciate the interplay between different modeling techniques and their collective impact on the future of cardiac research and treatment.

3 Computational Modelling in Cardiac Electrophysiology

3.1 Graph-Based and Hybrid Modeling Approaches

Graph-based and hybrid modeling approaches are essential in advancing cardiac electrophysiology by providing sophisticated frameworks for simulating complex cardiac dynamics. These approaches leverage the structural and functional connectivity inherent in cardiac tissues, enabling detailed simulations of electrophysiological processes and predictions of arrhythmogenic events [4]. Graph neural networks (GNNs) and generative adversarial networks (GANs) form the core of these models, capturing the intricate dynamics of cardiac systems.

The development of personalized Purkinje networks from clinical data exemplifies the application of graph-based models in enhancing ventricular activation simulations, supporting tailored therapeutic interventions [11]. This personalized approach deepens the understanding of individual cardiac function and aids in formulating targeted treatment strategies.

Hybrid modeling approaches, such as the HyPer-EP framework, integrate physics-based and data-driven methodologies to address unmodeled complexities in personalized cardiac electrophysiology [12]. By combining various modeling paradigms, these approaches accurately represent physiological processes and enhance predictive model precision.

Digital twins in cardiac electrophysiology emphasize maintaining continuous data links between virtual and physical counterparts, allowing for dynamic updates and personalized treatment strategies [24]. These digital representations enable the continuous integration of real-time data, improving the accuracy and applicability of computational models in clinical settings.

Graph-based frameworks model relationships between health indicators and their impact on health states, providing a comprehensive understanding of patient-specific conditions [25]. This methodology supports the development of high-fidelity digital twins capable of distinguishing between normal and disease-indicative features, refining diagnostic and therapeutic strategies [20].

The cardiac digital twin pipeline (CDTP) exemplifies these approaches by personalizing ventricular anatomy and electrophysiological function based on routine clinical data, facilitating virtual therapy evaluations [3]. Additionally, the JHgRF-Net architecture effectively models complex spatio-temporal dynamics within multivariate time series data, achieving superior multi-horizon forecasting accuracy compared to existing methods [14].

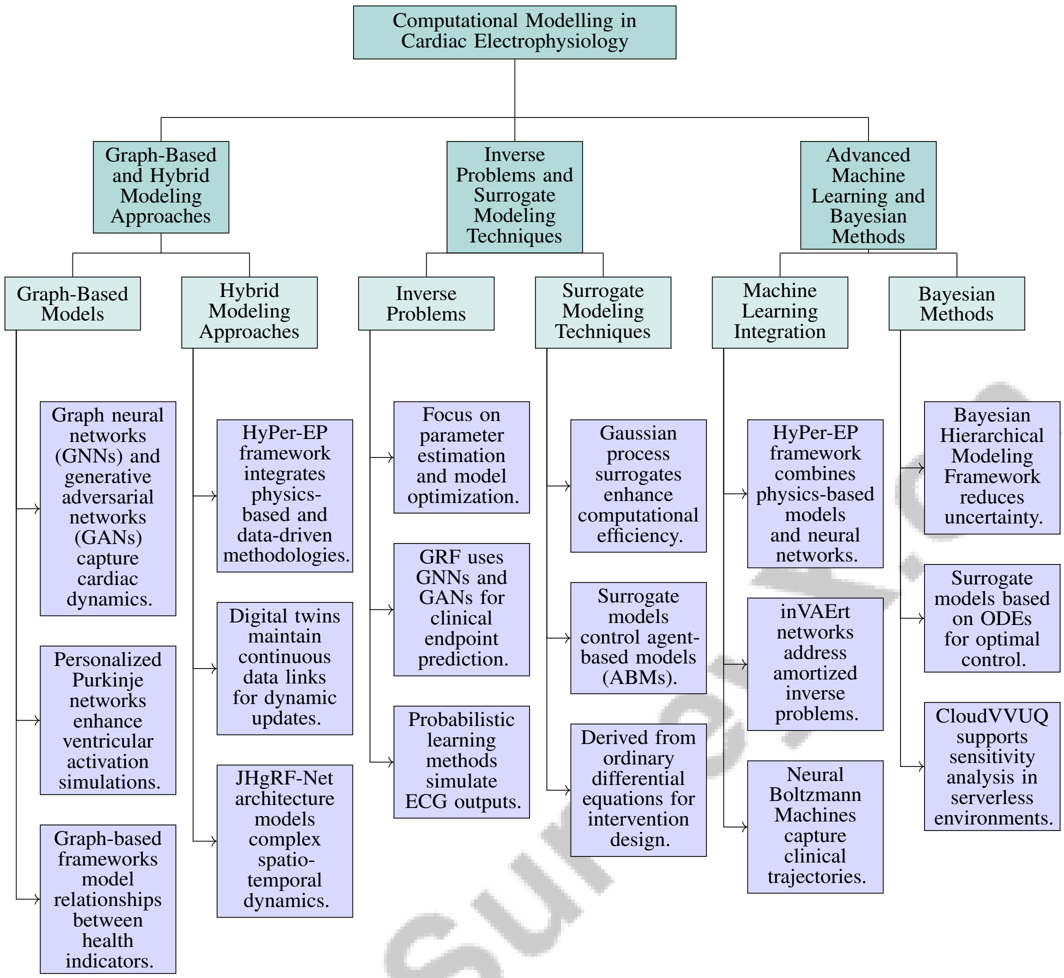


Figure 2: This figure illustrates the hierarchical structure of computational modeling approaches in cardiac electrophysiology, highlighting three primary categories: Graph-Based and Hybrid Modeling Approaches, Inverse Problems and Surrogate Modeling Techniques, and Advanced Machine Learning and Bayesian Methods. Each category is further divided into subcategories, detailing specific methodologies and their applications in improving cardiac model accuracy, personalization, and patient care.

These methodologies involve accessing electroanatomic mapping (EAM) data, assessing its quality, and converting it into modeling formats according to the openCARP standard, thereby standardizing and streamlining the modeling process [17]. These advancements underscore the transformative potential of graph-based and hybrid modeling approaches in personalized medicine, enhancing predictive accuracy and optimizing patient care. Interdisciplinary collaboration required for effective implementation addresses ethical and practical challenges, paving the way for future innovations in digital twin technology.

3.2 Inverse Problems and Surrogate Modeling Techniques

Inverse problems and surrogate modeling techniques are essential for enhancing precision and applicability in cardiac electrophysiology computational models. These methodologies focus on parameter estimation and model optimization, crucial for developing accurate and personalized cardiac models. In cardiac applications, inverse problems often involve estimating patient-specific parameters from noninvasive measurements, complicated by structural and practical non-identifiability due to overparametrization and poor data quality in existing models, as well as the complexity of

Method Name	Methodological Approaches	Application Domains	Computational Efficiency
pyCEPS[17]	Graph Neural Networks	Cardiac Electrophysiology	Surrogate Modeling
MRS[22]	Self-supervised Learning	Cardiac Hemodynamics	Physics-informed Neural
IVAE[26]	Invaert Networks	Cardiovascular Parameters	Amortized Inference
GPSM[13]	Gaussian Process Surrogates	Pharmacokinetic-like Models	Computationally Efficient Solution

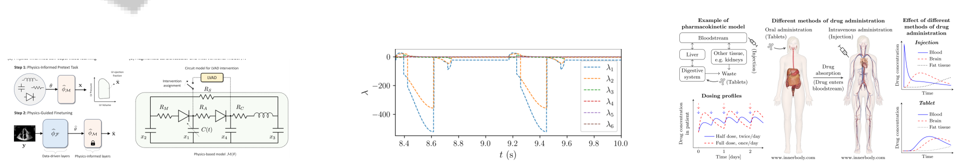
Table 1: This table summarizes various methodological approaches employed in inverse problems and surrogate modeling techniques within cardiac electrophysiology. It highlights the specific application domains and computational efficiency of each method, demonstrating their relevance in enhancing personalized cardiac models.

accessing, parsing, and converting electroanatomic mapping (EAM) data exported from commercial mapping systems [17].

To address healthcare challenges, methods like Graph Representation Forecasting (GRF) use Graph Neural Networks (GNNs) to predict clinical endpoints, such as blood pressure, while employing Generative Adversarial Networks (GANs) to generate synthetic data that enhances patient condition modeling. This integration of AI techniques and mechanistic computational modeling aims to create a comprehensive digital twin of the patient, facilitating personalized and effective treatment plans and improving predictive accuracy of clinical outcomes [9, 27, 5, 28, 4]. This approach effectively addresses the inverse problem by leveraging the structure of physics-based models to identify patient-specific parameters, linking noninvasive measurements with physiological states. Probabilistic learning methods, such as those generating parametric representations of the Purkinje network, simulate ECG outputs to tackle inverse problems in cardiac electrophysiology, enhancing the accuracy of patient-specific models.

Surrogate modeling techniques further enhance computational efficiency and accuracy in cardiac models. The use of Gaussian process surrogates, constructed from experimental data and simulated outputs, facilitates efficient model discrimination and optimization in complex biological systems. Surrogates enable comprehensive exploration of parameter spaces and precise quantification of variabilities in cardiac models, as evidenced by methodologies analyzing the impact of anatomical variations—such as heart orientation, size, and electrical conductivity—on electrocardiogram (ECG) morphology, enhancing the reliability of cardiac digital twin models in both healthy and pathological scenarios [19, 18, 17, 16, 3].

Utilizing surrogate models in the control of agent-based models (ABMs) significantly enhances the application of optimal control methods to complex rule-based systems, often resistant to traditional mathematical analysis. This approach is particularly relevant in personalized medicine, where high-dimensional and stochastic medical digital twins require simplification into low-dimensional surrogate models for effective intervention design. By deriving these surrogate models from ordinary differential equations, researchers can effectively compute tailored interventions for ABMs, bridging the gap between data-driven insights and the intricacies of dynamic biological systems. This methodology addresses optimal control challenges in ABMs and has broader implications for managing complex dynamical systems across various domains [29, 30, 12, 31, 13]. Integrating these advanced modeling techniques enables the development of more accurate, reliable, and personalized cardiac models, significantly improving patient outcomes in clinical settings.



(a) Physics-Informed Self-Supervised Learning and Augmented Cardiovascular and Interventional Models[22]

(b) The image shows a graph with six lines representing different lambda values over time.[26]

(c) Pharmacokinetic Model and Drug Administration Methods[13]

Figure 3: Examples of Inverse Problems and Surrogate Modeling Techniques

As shown in Figure 3, computational modeling in cardiac electrophysiology serves as a pivotal tool for understanding complex physiological processes and addressing inverse problems through surrogate modeling techniques. The first approach, "Physics-Informed Self-Supervised Learning and Augmented Cardiovascular and Interventional Models," integrates physics-based tasks with neural networks to enhance predictions of cardiovascular metrics, such as left ventricle ejection fraction. This technique leverages a physics-informed pretext task to improve model accuracy and reliability. The second illustration presents a graph depicting six lambda values over time, providing insights into dynamic changes within the cardiovascular system. Lastly, the "Pharmacokinetic Model and Drug Administration Methods" diagram offers a comprehensive view of how various drug administration routes affect drug concentration in the bloodstream, underscoring the importance of pharmacokinetic understanding in optimizing therapeutic strategies. Together, these examples highlight the multifaceted nature of computational modeling in cardiac electrophysiology, showcasing its potential to address inverse problems and refine surrogate modeling techniques for improved clinical outcomes. Table 1 provides a comprehensive overview of the diverse methodologies applied in cardiac electrophysiology to tackle inverse problems and improve surrogate modeling techniques, emphasizing their application domains and computational efficiencies.

3.3 Advanced Machine Learning and Bayesian Methods

Method Name	Modeling Frameworks	Hybrid Approaches	Uncertainty Quantification
IVAE[26]	Variational Encoding	Invaert Networks	Bayesian Inference Methods
HyPer-EP[16]	Hybrid Modeling Framework	Hybrid Modeling Approach	Bayesian Methods
PPNI[19]	Bayesian Optimization	Machine Learning Techniques	Quantify Uncertainty
BHM[32]	Bayesian Hierarchical Models	Physics-based Models	Bayesian Methods
DTGs[9]	Neural Boltzmann Machines	Energy-based Modeling	Probabilistic Forecasts
SMOC[31]	-	Hybrid Modeling Techniques	Uncertainty Quantification
CVV[33]	-	-	Probabilistic And Bayesian

Table 2: Overview of advanced machine learning and Bayesian methods in cardiac electrophysiology modeling, highlighting various modeling frameworks, hybrid approaches, and uncertainty quantification techniques. The table presents a comparative analysis of different methods, including their unique contributions to improving cardiac model accuracy and personalization through integration with digital twin technologies.

Advanced machine learning and Bayesian methods are crucial in enhancing computational models for cardiac conditions by providing robust frameworks for parameter estimation, uncertainty quantification, and predictive modeling. Table 2 provides a comprehensive analysis of advanced machine learning and Bayesian methods applied to cardiac electrophysiology, emphasizing their roles in enhancing model accuracy and personalization through innovative frameworks and hybrid approaches. The integration of hybrid modeling frameworks and automated cardiac digital twin pipelines into cardiac electrophysiology improves the understanding of intricate cardiac dynamics by combining physics-based models with deep learning techniques, thereby enabling more accurate personalization of treatment strategies through improved parameter estimation and uncertainty quantification from patient-specific data [16, 3, 17, 19].

The proposed inVAErt networks offer a novel approach to digital twin representations by addressing amortized inverse problems and assessing identifiability, thereby refining the accuracy of cardiac models [26]. This approach complements traditional modeling techniques by leveraging machine learning strengths to enhance model predictions' precision.

The HyPer-EP framework exemplifies the integration of machine learning with physics-based models, combining known expressions with neural network models to bridge the gap between theoretical models and real-world observations [16]. This hybrid approach allows for a more accurate representation of cardiac electrophysiology, accommodating discrepancies between models and reality.

Probabilistic learning techniques further enhance modeling cardiac structures, such as the Purkinje network, by quantifying uncertainty and improving the identification of these critical components [19]. This probabilistic framework enables more reliable predictions of cardiac behavior and supports the development of targeted therapeutic interventions.

Bayesian methods, such as the Bayesian Hierarchical Modeling Framework (BHM), leverage shared information across individuals to reduce uncertainty in parameter estimates, enhancing prediction accuracy [32]. This approach is particularly effective in digital twins, where individualized data can inform more precise healthcare strategies.

The use of Neural Boltzmann Machines (NBMs) in creating flexible, conditional generative models represents a significant advancement in capturing clinical trajectories across multiple disease indications [9]. These models provide powerful tools for understanding cardiac condition progression and tailoring interventions accordingly.

Additionally, developing surrogate models based on systems of ordinary differential equations (ODEs) facilitates optimal control and effective interventions in ABM-based medical digital twins [31]. These surrogate models enable high-throughput analysis and optimization of treatment strategies, improving patient outcomes in clinical settings.

The implementation of CloudVVUQ in a serverless computing environment further supports executing VVUQ tasks, allowing efficient sensitivity analysis and model validation [33]. This capability enhances the scalability and applicability of computational models in personalized medicine.

Integrating advanced machine learning techniques and Bayesian methods into cardiac electrophysiology modeling signifies a pivotal advancement towards achieving more accurate, reliable, and personalized healthcare solutions. This innovative approach combines traditional physics-based models with neural network enhancements, addressing conventional methods' limitations while maintaining interpretability. By facilitating the creation of personalized digital twins through patient-specific data analysis, these technologies improve cardiac disease detection precision and enable therapeutic response simulations in virtual clinical trials. Consequently, this integration highlights the transformative potential of these methodologies to revolutionize cardiac care, paving the way for tailored treatment strategies that adapt to individual patient needs [16, 3, 20, 19].

4 Digital Twin Technology in Personalized Treatment

Digital twin technology represents a transformative approach in personalized healthcare, particularly in cardiac care, by integrating real-time data and predictive analytics. This section examines the core elements of digital twins, focusing on their role in enhancing personalized interventions. It explores how these components interact to create dynamic, patient-centered models that inform clinical decisions and improve health outcomes.

4.1 Integration of Real-Time Data and Predictive Analytics

In cardiac electrophysiology, the integration of real-time data and predictive analytics is crucial for developing digital twins that personalize healthcare interventions. These digital twins use advanced AI techniques to dynamically represent patients, allowing continuous health monitoring and outcome forecasting [4]. This integration enables the assimilation of diverse data streams, such as EHR and clinical time-series data, to tailor interventions to individual needs.

The Med-Real2Sim approach exemplifies the extraction of patient-specific parameters, enhancing intervention precision [22]. InVAErt networks tackle identifiability and inverse problem challenges, improving digital twin accuracy [26]. Digital twin generators use generative models to predict health trajectories and assess treatment impacts, supporting personalized plans [9, 1].

Incorporating human factors ensures digital twins remain synchronized with patient health, facilitating continuous feedback and adaptation [34]. The cardiac digital twin pipeline demonstrates predictive analytics by inferring cardiac properties from CMR and ECG data, simulating drug effects for virtual treatment evaluation [3].

Forecasting supports decision-making and risk reduction, enhancing healthcare efficiency and cost-effectiveness [14]. By leveraging real-time data and predictive analytics, digital twins transform personalized healthcare, improving intervention precision across clinical contexts.

4.2 The Role of Predictive Analytics and Patient-Specific Interventions

Predictive analytics is essential for customizing interventions in cardiac electrophysiology. By integrating computational models and real-time data, predictive analytics personalizes treatment strategies, improving clinical outcomes. Digital twin technology, incorporating predictive analytics, allows high-fidelity cardiac activation simulation, capturing individual variability for accurate in silico trials [11].

AI-generated, for reference only.

These models identify patient-specific parameters and predict health trajectories, crucial for targeted interventions. The feedback loop between patient status and digital twin ensures dynamic intervention adjustments, enhancing treatment effectiveness and minimizing adverse effects by considering patient characteristics and real-time data, thus optimizing outcomes [10, 27, 23].

Predictive analytics evaluates treatment scenarios, allowing pre-implementation impact assessment. Digital twin integration enhances decision-making by utilizing real-time data, analytics, and simulations, reducing ineffective treatments and enabling personalized care, ultimately improving patient satisfaction and healthcare efficiency [10, 27, 23].

By leveraging digital twin technology and machine learning, predictive analytics advances personalized medicine in cardiac care. It creates accurate simulations of patients' physiological states, facilitating early diagnosis and tailored treatment plans, thus enhancing intervention precision and safety [20, 23, 16, 10, 4].

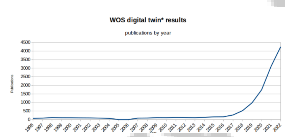
4.3 Human Digital Twins (HDTs) and Their Applications

Human Digital Twins (HDTs) are a cutting-edge advancement in personalized healthcare, providing dynamic digital counterparts for real-time monitoring and tailored interventions. HDTs integrate comprehensive data streams, including physiological, behavioral, and environmental factors, to create holistic health representations [35]. These digital replicas simulate disease progression and evaluate treatment outcomes, enhancing healthcare precision and efficacy [34].

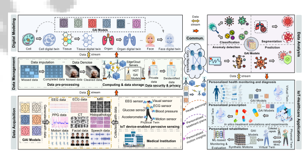
HDTs revolutionize patient management by enabling continuous monitoring and proactive interventions. Advanced networking architectures and real-time data integration allow HDTs to adapt to dynamic patient needs [36]. This capability is crucial for managing chronic conditions, where timely treatment adjustments significantly impact outcomes [10].

Innovations in HDTs include mobile AI-generated content, improving synthetic data generation and real-time personalized healthcare services [10]. This integration enhances health assessment accuracy and predictive model development for future health event anticipation and clinical decision-making.

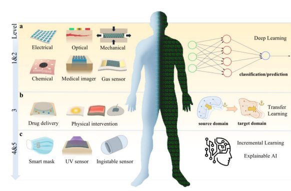
Despite HDTs' promise, challenges exist, such as defining HDTs, establishing design guidelines, and modeling complex human attributes [7, 34, 6, 10]. Addressing these challenges is crucial for HDT advancement and effective implementation in healthcare.



(a) WOS digital twin* results[35]



(b) Healthcare Applications and Digital Twins: A Comprehensive Framework for Personalized Health Monitoring and Diagnosis[28]



(c) Human Body and AI Applications[2]

Figure 4: Examples of Human Digital Twins (HDTs) and Their Applications

As shown in Figure 4, Digital Twin Technology is revolutionizing personalized treatment through Human Digital Twins (HDTs). This approach uses computational models to create digital replicas of human systems, enabling personalized healthcare solutions. The figures illustrate HDTs' dimensions and applications. The first figure shows rising scholarly interest in digital twin technology, indicating HDTs' potential in healthcare transformation. The second figure presents a framework for personalized health monitoring and diagnosis, highlighting digital twins and machine learning synergy. This framework covers digital modeling, data analysis, and management, progressing from cellular to tissue levels. The third figure explores AI integration with human systems, detailing AI applications at various levels. These examples underscore HDTs' transformative potential in advancing personalized treatment and healthcare innovation [35, 28, 2].

4.4 Challenges and Limitations in Digital Twin Technology

Benchmark	Size	Domain	Task Format	Metric

Table 3: This table provides an overview of the representative benchmarks used in digital twin technology across various domains. It includes details on the size, domain, task format, and metrics associated with each benchmark, highlighting the diversity and scope of current research efforts.

Digital twin technology in healthcare faces significant challenges and limitations. Data heterogeneity complicates the integration of diverse sources needed for accurate digital twins [7]. Privacy concerns also pose barriers, as continuous sensitive data collection requires robust security against unauthorized access [7]. Table 3 presents a comprehensive summary of the representative benchmarks in digital twin technology, illustrating the challenges and limitations faced in integrating diverse data sources and establishing standardized frameworks.

Modeling human behavior adds complexity, as these factors are dynamic and hard to predict [7]. High computational costs in simulating electrotonic coupling with human-based ionic currents limit digital twin scalability [3].

Lack of standardized definitions and frameworks for digital twins in healthcare causes inconsistencies, hindering real-time data integration, predictive analytics, and personalized treatment plans across systems. This inconsistency affects clinical operations, care, and limits innovation [6, 23]. Misconceptions about digital twin capabilities and limitations can undermine adoption and effectiveness.

Future research should focus on standardized protocols and data integration enhancement to tackle digital twin challenges. This will improve scalability, reliability, and application across domains like manufacturing, healthcare, and smart cities, where seamless data exchange is crucial for decision-making and analysis [27, 6, 37, 38]. Overcoming these obstacles will realize digital twin technology's potential in providing precise and effective personalized healthcare solutions.

5 Diagnostic Tools and Treatment Selection

5.1 Integration of Diagnostic Tools in Cardiac Assessment

The integration of advanced diagnostic tools, such as PET scans, plays a critical role in cardiac assessment by providing detailed insights into the physiological and metabolic underpinnings of cardiac diseases. PET scans, through radiotracer utilization, deliver high-resolution images crucial for evaluating myocardial perfusion and viability, thereby enhancing diagnostic accuracy and treatment planning. Coupling these imaging modalities with computational models facilitates the creation of personalized digital twin models, reflecting individual anatomical and physiological nuances, ultimately improving cardiovascular health outcomes [39, 18].

Incorporating PET scans into digital twin frameworks and computational modeling significantly enhances patient-specific model accuracy and reliability. This integration supports the development of highly personalized virtual representations of human anatomy and physiology, enabling real-time simulations and predictive modeling that improve healthcare delivery [39, 27, 9, 23]. Combining PET data with MRI and ECG provides a comprehensive cardiac function overview, supporting precise and personalized treatment strategies.

Deploying these diagnostic tools within advanced computational frameworks, such as Kubernetes cluster environments for healthcare data streaming, underscores the need for robust data integration techniques [40]. These environments facilitate seamless data assimilation, ensuring digital twin models remain reflective of the patient's health status.

The integration of diagnostic tools, including personalized cardiac digital twins and high-resolution imaging, enhances cardiac assessment accuracy and informs tailored treatment strategies. These tools improve diagnostic precision and facilitate real-time predictive modeling and individualized treatment planning, leading to better patient outcomes in heart disease management [39, 20, 16, 18, 3]. Leveraging insights from PET and other modalities, healthcare providers can optimize therapeutic interventions, advancing personalized medicine.

5.2 Role of Computational Models in Treatment Selection

Computational models are essential in optimizing treatment selection for cardiac conditions, offering a framework for evaluating therapeutic interventions—such as stents, surgeries, and pharmacological therapies—through the integration of machine learning with mechanistic modeling. This integration enables the creation of personalized digital twins that simulate physiological conditions and predict treatment responses. Utilizing extensive clinical datasets and sophisticated computational resources, these models facilitate virtual clinical trials, accelerating therapy development and enhancing treatment plan precision tailored to individual needs [21, 3, 13, 4].

The flexibility of inVAErt networks in modeling complex input-output relationships allows exploration of multiple solutions to the inverse problem in treatment selection [26]. This capability is crucial for understanding cardiac system interactions and tailoring interventions. Additionally, information-based model discrimination quantifies model accuracy in explaining system behavior, guiding optimal treatment strategy selection by indicating higher information gain for accurate dynamic representations [30].

Integrating mobile AI-generated content (MAIGC) within Human Digital Twins (HDTs) leverages mobile edge computing to deliver low-latency healthcare services, enhancing treatment recommendation precision through effective multi-modal data management [10]. This ensures computational models are responsive to real-time patient data, facilitating timely clinical decision-making.

The cardiac digital twin pipeline exemplifies computational model application in personalized virtual therapy testing, supporting treatment selection by simulating therapeutic scenarios [3]. This approach enhances clinical trial precision and improves treatment recommendation accuracy by tailoring digital twins to individual patients [9].

Bayesian PROCOVA refines treatment selection processes by demonstrating improved bias control and variance reduction in treatment effect inferences compared to traditional methods [1]. This advancement enables reliable treatment efficacy predictions, contributing to personalized therapeutic strategies.

Computational models offer a transformative approach to treatment selection in cardiac care, enabling data-driven decisions that optimize patient outcomes. By leveraging advanced analytics and real-time data integration through technologies like mobile AIGC and digital twin frameworks, these models enhance understanding of individual conditions. This facilitates the development of high-fidelity digital replicas and predictive analytics for early diagnosis, personalized treatment plans, and optimized surgical strategies, paving the way for precise and tailored healthcare solutions [23, 4, 10, 5].

6 Responders and Non-Responders

Distinguishing responders from non-responders in cardiac treatment is pivotal for tailoring therapeutic strategies, especially with the advent of digital twin technology. This technology integrates real-time patient data with predictive analytics to craft personalized treatment plans, enhancing clinical operations and patient outcomes. By leveraging machine learning for early health risk detection, healthcare providers can initiate proactive interventions, improving patient safety and fostering innovative treatment methods [24, 23]. Understanding the determinants of patient response is crucial for informed clinical decision-making and highlights the complexities of treatment outcomes, paving the way for discussions on the role of digital twin technology in predicting these outcomes.

6.1 Challenges in Distinguishing Responders and Non-Responders

Identifying responders and non-responders in cardiac treatment is challenging due to the variability in patient responses influenced by genetic, comorbid, and environmental factors. Digital twin technology offers a solution by using real-time data and advanced analytics to create personalized treatment plans that account for individual patient characteristics. These digital twins simulate unique health trajectories, facilitating predictive analytics and proactive interventions, thereby enhancing clinical outcomes [27, 4, 23, 9]. The complexity of these systems necessitates sophisticated analytical frameworks capable of integrating diverse data sources for accurate treatment outcome predictions.

The effective implementation of digital twins is often hindered by computational model constraints and data quality issues. For example, while the adaptive service function chain method is effective in certain scenarios, it may struggle in dynamic environments with rapid resource changes [40]. This limitation underscores the need for ongoing advancements in computational methodologies to improve predictive accuracy.

Variability in treatment adherence and lifestyle factors further complicates the differentiation between responders and non-responders, potentially obscuring intervention efficacy. Digital twin technology enhances personalized treatment plans by modeling individual characteristics and historical data, allowing for more precise assessments of treatment outcomes. The interplay of adherence, lifestyle factors, and advanced modeling techniques necessitates a nuanced evaluation of intervention effectiveness [1, 23, 27]. Addressing these challenges requires robust predictive models that accommodate variability and provide reliable insights into patient-specific treatment responses.

A comprehensive multidisciplinary strategy is essential to navigate the complexities of differentiating responders from non-responders in healthcare. This approach should combine advanced computational techniques, such as machine learning for predictive analytics, real-time data integration, and personalized healthcare methods exemplified by digital twin technology. By leveraging these elements, healthcare systems can enhance patient care through tailored treatment plans, early health risk detection, and optimized clinical operations, ultimately improving patient outcomes and safety [10, 23].

6.2 Role of Digital Twins in Predicting Treatment Outcomes

Digital twins have become transformative tools in personalized medicine, enabling the development of individualized computational models that reflect patient health trajectories. Utilizing advanced machine learning techniques and extensive datasets, including electronic health records, digital twins accurately forecast patient responses to treatments. The TWIN-GPT model, for instance, employs large language processing to generate personalized digital twins, enhancing clinical trial outcome predictions and facilitating tailored treatment recommendations. Advancements in medical imaging further enhance the precision and applicability of these digital twins, enabling real-time simulations and personalized treatment planning that contribute to improved patient outcomes [39, 27, 9]. The integration of digital twins in healthcare allows for highly individualized models that simulate and predict therapeutic intervention outcomes, optimizing treatment plans and improving patient care.

A key advantage of digital twins is their ability to dynamically incorporate historical control data, as demonstrated by the Bayesian PROCOVA method. This approach enhances outcome prediction precision by adjusting the weight assigned to historical data, controlling bias, and improving the reliability of treatment forecasts [1]. Such dynamic adjustments are essential for accommodating variability in patient responses and ensuring treatment plans are tailored to individual needs.

Methodologies addressing model discrepancies further enhance the predictive accuracy of digital twins by providing more accurate estimates of physical parameters and significantly reducing uncertainty, thus offering a reliable basis for clinical decision-making [32]. This capability is particularly valuable in complex biological systems, where precise parameter estimation is critical for predicting treatment efficacy.

Moreover, digital twin frameworks preserve diagnostically relevant features, such as ECG characteristics, despite uncertainties. This retention of critical diagnostic information enhances the reliability of cardiac digital twins (CDTs) and supports accurate treatment outcome predictions [18]. By ensuring that key clinical features are maintained within the digital twin model, healthcare providers can make more informed decisions regarding patient care.

The collaborative development of digital twins, illustrated by hierarchical federated learning frameworks, offers additional benefits, including enhanced patient data privacy, reduced latency in anomaly detection, and improved model accuracy through collaborative learning [15]. These frameworks enable the sharing of insights across multiple healthcare organizations without compromising patient confidentiality, thereby advancing the collective understanding of treatment responses.

6.3 Frameworks and Methodologies for Optimizing Therapy

Optimizing therapy through digital twin insights relies on sophisticated frameworks and methodologies that employ advanced computational techniques to tailor interventions to individual patient needs. A critical component of therapy optimization is the systematic evaluation of model quality through multiple information criteria, which facilitates accurate model selection and enhances the predictive accuracy of digital twins [30]. This approach ensures that the most appropriate models are utilized in simulating patient-specific conditions, thereby improving the reliability of therapeutic recommendations.

In cardiac care, these frameworks integrate real-time data and predictive analytics to continuously refine treatment plans. By leveraging advanced predictive models that encompass a wide array of patient data—including genetic, physiological, and lifestyle factors—healthcare providers can create highly personalized treatment strategies tailored to each patient's unique characteristics. This process is further enhanced by innovative technologies such as digital twins, which simulate individual health trajectories based on comprehensive historical data, and machine learning techniques that refine these models using large datasets. Consequently, healthcare professionals can improve prediction precision, optimize clinical trial outcomes, and develop effective, individualized care plans that address the complex interplay of factors influencing each patient's health [27, 4, 9]. Such customization is vital for optimizing therapeutic outcomes and minimizing adverse effects.

The implementation of hierarchical federated learning frameworks significantly enhances collaborative digital twin model development in healthcare by allowing multiple organizations to share insights and improve model accuracy while protecting patient privacy. This decentralized data processing reduces risks associated with centralized data storage, such as response time delays and security threats. Additionally, it facilitates data aggregation at various levels, supporting a multi-party collaboration model and employing advanced machine learning techniques to generate personalized insights and predictive analytics for patient care [9, 23, 27, 15, 5]. This collaborative approach accelerates digital twin technology advancements and ensures therapy optimization is informed by a comprehensive understanding of patient variability.

The integration of advanced frameworks and methodologies in digital twin technology represents a transformative step toward more effective and personalized healthcare solutions. By systematically assessing model quality and utilizing collaborative learning techniques, healthcare providers can enhance therapeutic strategies informed by insights from personalized digital twins. This approach aims to improve patient outcomes and supports the advancement of precision medicine through real-time analytics, personalized treatment planning, and early diagnosis via comprehensive patient data integration. Recent innovations, such as the TWIN-GPT framework and advanced medical imaging technologies, further facilitate the creation of unique digital twins that preserve individual patient characteristics, ultimately contributing to more effective clinical trial predictions and optimized patient care [39, 27, 5].

7 Intra-Operative Applications and Cardiac Resynchronization Therapy (CRT)

7.1 Virtual Twin in Intra-Operative Settings

Virtual twins represent a cutting-edge advancement in surgical care, employing advanced imaging and real-time data analytics to create personalized anatomical models. These models enhance surgical outcomes by enabling precise simulations and predictive modeling, facilitating individualized treatment plans based on real-time physiological data. This technology not only aids in early health risk detection but also optimizes clinical workflows, enhancing patient safety and driving surgical innovation [**?** 23]. Real-time simulations provided by virtual twins allow surgeons to visualize and predict surgical interventions' consequences, which is crucial for complex procedures.

During operations, virtual twins continuously integrate intra-operative data, allowing surgical plans to be adjusted based on real-time insights, thereby improving intervention accuracy and reducing complications. By simulating surgical scenarios, virtual twins leverage computational models and personalized data to identify optimal strategies, enhancing decision-making and patient outcomes through tailored treatment plans and analytics [**? ? ?** 22].

Predictive analytics within virtual twin frameworks further enhance their intra-operative utility. These sophisticated models predict potential complications and recommend proactive strategies, thus optimizing treatment outcomes and patient safety. Advanced machine learning and comprehensive medical data integration allow for personalized simulations that account for individual patient characteristics [**?** **?** **?** 2**?** , 4]. Such predictive capabilities are essential for optimizing surgical procedures.

Robust data integration techniques support virtual twin development, ensuring seamless assimilation of diverse data sources, including imaging and physiological data. This comprehensive approach uses advanced imaging and digital twin technology to create highly personalized models of anatomy and physiological functions, enabling precise interventions and enhancing diagnostic accuracy and treatment effectiveness [**?** **?** 23, 10, 25].

Integrating virtual twins into intra-operative settings marks a groundbreaking step in surgical care, utilizing real-time data, advanced analytics, and simulations to create personalized treatment plans. This method improves surgical outcomes and patient safety by enabling early risk detection and predictive analytics, streamlining clinical operations, and providing a realistic training environment for healthcare professionals. By leveraging computational models and high-resolution imaging, virtual twins empower surgeons to optimize strategies and interventions, driving innovation and precision in healthcare [**?** 23**?**].

7.2 Predictive Twin for Surgical Outcome Optimization

Predictive twins, a forefront of surgical care innovation, enhance outcomes by integrating real-time data with advanced predictive analytics. These digital replicas simulate and predict surgical outcomes by assimilating real-time data from sensors and medical imaging. By analyzing multimodal health data, predictive twins provide insights that enable optimized surgical plans and enhanced patient care. Leveraging analytics and machine learning, they facilitate personalized treatment strategies, early diagnosis, and improved decision-making, revolutionizing healthcare approaches [**?** **?** **?** 31, 4].

In surgical settings, predictive twins allow for continuous intra-operative data assimilation, enabling dynamic strategy adjustments based on real-time insights. This adaptability is crucial for addressing unforeseen challenges and minimizing complications. By simulating surgical scenarios, predictive twins identify optimal strategies tailored to individual profiles, enhancing decision-making and surgical precision [**?** 23**?** **?** , 31].

Advanced computational models underpin predictive twins, using high-resolution imaging and machine learning to create personalized virtual representations of anatomy and physiological processes. This integration allows for accurate simulation of biological functions and prediction of outcomes, enhancing real-time modeling and individualized treatment planning. Recent advancements improve prediction precision and address anatomical modeling and data integration challenges, contributing to personalized healthcare solutions [**?** **?** 4]. These models utilize diverse data sources to create comprehensive simulations, facilitating complication anticipation and proactive risk mitigation.

Predictive twins support surgical intervention customization by considering patient-specific factors like anatomical variations and comorbidities. Enhanced personalization, facilitated by digital twin technology and analytics, is crucial for optimizing outcomes and ensuring safety through tailored plans that account for individual characteristics and histories. This approach improves predictive analytics, risk detection, clinical operations, and training environments [10, 23]. Detailed and dynamic representations of conditions enhance surgical intervention precision and efficacy.

Integrating predictive twin technology in surgical environments marks a significant advancement, utilizing real-time data integration, analytics, and simulations to enhance outcomes and safety. By offering personalized plans aligned with patient characteristics and histories, predictive twins facilitate early risk detection and proactive interventions. They also optimize workflows and resource allocation, improving operational efficiency. This innovative approach enhances training and skill development in a safe environment, revolutionizing patient care and driving continuous healthcare improvement [23**?**]. Ongoing research and technological advancements are essential to fully realize predictive twins' potential in revolutionizing surgical precision and effectiveness.

7.3 Application of Digital Twins in Cardiac Resynchronization Therapy (CRT)

Digital twins offer transformative potential in enhancing CRT procedures by providing a sophisticated platform for simulating and optimizing patient-specific interventions. CRT is critical for managing heart failure, particularly in patients with dyssynchronous ventricular contraction. Digital twin technology integration into CRT allows for detailed and dynamic cardiac function models, enabling precise simulation of electrical and mechanical patterns [**?**].

The application of digital twins in CRT involves continuous patient data assimilation, including ECG and imaging, to create a comprehensive heart replica. This facilitates simulation of CRT device configurations and pacing strategies, enabling evaluation of different interventions' impacts on cardiac function [18]. Optimizing device settings and lead placements through simulations enhances CRT efficacy and patient outcomes.

Digital twins enable real-time CRT response monitoring, providing feedback for dynamic therapy parameter adjustments. This adaptability accommodates patient condition changes, ensuring therapy alignment with evolving needs. Predictive analytics integration into digital twin frameworks enhances CRT clinical research trials by forecasting complications and offering tailored proactive measures, improving safety and efficacy. This integration uses advanced imaging data and machine learning to develop personalized models reflecting individual characteristics, optimizing trial outcomes and promoting precision medicine [**? ? ? ?**].

Digital twin technology development in CRT is supported by computational models simulating intricate heart interactions. These models leverage diverse data sources for accurate simulations, facilitating optimal CRT strategy identification and improving intervention precision [**?**].

Integrating digital twin technology in cardiac care represents a transformative leap, utilizing imaging and modeling to create personalized heart representations. This innovation enhances diagnosis and treatment planning accuracy, facilitates simulations and analytics, and optimizes interventions. By leveraging clinical datasets and algorithms, digital twins enable virtual trials, accelerating therapy development and improving outcomes through individualized strategies. Digital twins streamline operations and enhance precision and effectiveness in patient management [**? ?** 23**? ?**]. Ongoing research and advancements are essential to fully realize digital twins' potential in revolutionizing CRT and heart failure management.

8 Conclusion

8.1 Real-World Applications and Future Directions

The convergence of computational modeling with digital twin technology heralds a transformative era in personalized medicine, enabling precise patient condition forecasts and customized interventions. By leveraging sophisticated simulations, these technologies enhance healthcare outcomes and broaden their applicability beyond traditional domains. In cardiac care, digital twins facilitate the reproduction of patient-specific ECG profiles and simulate pharmacological responses, thereby refining drug evaluation processes. Digital twin generators further demonstrate their potential by accurately predicting patient outcomes across various diseases, contributing significantly to personalized medicine.

Advanced modeling techniques, such as JHgRF-Net, manage complex data dependencies and provide reliable uncertainty estimates, essential for adapting to dynamic healthcare landscapes. Hybrid approaches, exemplified by the HyPer-EP framework, achieve remarkable accuracy in personalized cardiac modeling, underscoring the efficacy of integrated methodologies. Future research should emphasize efficient data management, privacy-preserving technologies, and the ethical dimensions of Human Digital Twin applications. Additionally, refining surrogate modeling methods and enhancing data assimilation techniques for dynamic model updates are crucial research avenues.

To advance digital twin applications, it is imperative to enhance communication technologies, establish standardized frameworks, and improve data processing capabilities. Addressing current limitations, exploring emerging AI and machine learning trends, and developing robust integration frameworks within existing systems are essential for future research endeavors. The ongoing evolution of digital twin technology promises to significantly impact personalized medicine, optimizing patient care and outcomes across clinical domains. Future efforts will focus on comprehensive performance

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evaluations and real-world model implementations, with additional security measures to mitigate risks.

8.2 Ethical, Legal, and Implementation Challenges

The adoption of digital twin technology in healthcare presents multifaceted ethical, legal, and practical challenges that necessitate careful consideration for responsible clinical integration. Key ethical concerns include data privacy and user trust, particularly in the context of Human Digital Twins. Safeguarding sensitive patient information requires stringent data protection measures and transparent policies, highlighting the need for standardized frameworks and ethical oversight in digital twin development. Legal challenges arise from the scalability of HDT systems and potential misuse, necessitating robust legal frameworks to support integration while preventing exploitation.

Practically, digital twin implementation faces hurdles such as data scarcity, computational complexity, and anatomical registration challenges. Overcoming these barriers demands cost-effective solutions, enhanced data security, and the integration of AI with digital twin technology. Improving computational efficiency and refining models to capture complex anatomical structures are vital steps toward addressing these challenges. Enhancing the robustness of surrogate methods against noisy data is also crucial for addressing ethical and practical challenges in computational model implementation. As digital twin technology continues to evolve, ongoing research and collaboration are essential to navigate these challenges, ultimately enabling more effective and responsible healthcare integration.

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