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Review

Utilization of precision medicine digital twins for drug discovery in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) presents significant challenges in drug discovery and development due to its complex and poorly understood pathology and etiology. Digital twins (DTs) are recently developed virtual real-time representations of physical entities that enable rapid assessment of the bidirectional interaction between the virtual and physical domains. With recent advances in artificial intelligence (AI) and the growing accumulation of multi-omics and clinical data, application of DTs in healthcare is gaining traction. Digital twin technology, in the form of multiscale virtual models of patients or organ systems, can track health status in real time with continuous feedback, thereby driving model updates that enhance clinical decision-making. Here, we posit an additional role for DTs in drug discovery, with particular utility for complex diseases like AD. In this review, we discuss salient challenges in AD drug development, including complex disease pathology and comorbidities, difficulty in early diagnosis, and the current high failure rate of clinical trials. We also review DTs and discuss potential applications for predicting AD progression, discovering biomarkers, identifying new drug targets and opportunities for drug repurposing, facilitating clinical trials, and advancing precision medicine. Despite significant hurdles in this area, such as integration and standardization of dynamic medical data and issues of data security and privacy, DTs represent a promising approach for revolutionizing drug discovery in AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and significant cause of worldwide dementia that is intrinsically linked to aging [1]. As people are living longer, societies will be challenged by a corresponding rise in AD prevalence. It is currently estimated that in the United States alone around 6.7 million people over the age of 65 are living with AD, and that without discovery of effective treatments this number will rise to upwards of 14 million by 2050 [1,2]. AD progression is characterized by depression, cognitive decline, memory loss, and ultimately the inability to execute basic life skills. It poses an enormous challenge and burden to individuals, families, and society [1,3,4]. Thus, there is an urgent need to develop effective therapeutic interventions and preventive measures.

AD has a complex pathophysiology characterized by accumulation of amyloid plaques and tau tangles, as well as general protein aggregation, epigenetic alterations, peripheral effects on the brain, neuroinflammation, blood-brain barrier (BBB) deterioration, DNA damage, lipid dysfunction, mitochondrial impairment, axonal degeneration, impaired postnatal neurogenesis, and synaptic dysfunction [5]. Many of the therapeutic strategies currently being investigated are based on these mechanisms, although many have not yet been validated in clinical trials [5]. Out of all Phase III clinical trials for AD that were active as of January 1, 2024, targeting neurotransmitter receptors accounted for 34 %,

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amyloid targeting accounted for 22 %, synaptic plasticity and neuroprotection accounted for 12 %, neuroinflammation, proteostasis/proteopathies, and metabolism/bioenergetics each accounted for 6 %, and tau, postnatal neurogenesis, growth factors/hormones, and circadian rhythm targets each accounted for 3 % [1]. However, despite decades of extensive and expensive research, effective treatments for AD patients remain severely limited. While to date two anti-amyloid monoclonal antibodies, lecanemab and aducanumab, have been approved for patients, they are currently controversial due to high expense, limited ability to slow cognitive decline, and significant risk of dangerous side effects [1,6]. Sadly, the vast majority (over 99 %) of clinical trials in AD to date have shown profound lack of efficacy, highlighting the need to improve discovery of new and effective AD therapies.

AD research is receiving increasing attention as the problem grows in magnitude, with different organizations initiating large-scale projects to address this important problem. For example, the nonprofit Brain Health Medicines Center of the Harrington Discovery Institute of University Hospitals of Cleveland is implementing a novel approach to specifically support academic researchers who have made innovative discoveries in AD, outside of the mainstream of biotech and industry, with scientific, industry, and business development expertise to help them traverse the valley of death between academic discovery and commercialization steps required to access the clinic [7]. Other notable efforts include the Religious Orders Study or Rush Memory and Aging Project (ROS-MAP) [8,9], the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) [10], and the Alzheimer's Disease Sequencing Project (ADSP) [11] (Table 1). These initiatives, along with databases like the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS) [12], have generated or collected a large amount of data at different dimensions. These include genomics, transcriptomics, epigenomics, proteomics, phenomics, and metabolomics. For example, the NIAGADS database includes genomic data (genome-wide association studies (GWAS) and whole genome sequencing (WGS) data) and phenotypic data, while the SEA-AD, ROSMAP and ssREAD databases provide a large amount of RNA sequencing data including bulk-RNA-seq, single-cell/nuclear RNA sequencing (sc/snRNA-seq) and spatial transcriptomics data. As well, ADNI includes a variety of clinical data, including imaging data such as magnetic resonance imaging (MRI) and positron emission tomography (PET). Lastly, metabolomic data sets (such as the Human Metabolome Database, HMDB) [13] contain comprehensive analysis of all metabolites in any given biological specimen (i.e. brain, blood, cerebrospinal fluid) to characterize of metabolic derangements in disease and facilitate discovery of new therapeutic targets and biomarkers (Table 1). These massive datasets are the cornerstone of many advanced and emerging technologies.

The boom in artificial intelligence (AI), especially generative AI technologies, has greatly accelerated biomarker identification, prediction of disease progression, and identification of drug targets in human disease, including AD [2,14–16]. However, these approaches usually rely on massive amounts of data for overall static prediction, whereas implementing dynamic and personalized models is a challenge. Digital twins (DTs) represent a way to potentially address this challenge. A DT is a virtual representation of a physical individual, process, or system and is already widely used in industries [17–19]. The feature of dynamization and the bi-directional interaction between the virtual realm and reality allows the digital space to be continuously updated in real time in response to the complex physical space [20]. In recent years, the concept of DTs has been introduced to the health and medical fields, and the dynamic and bi-directional interplay between the virtual realm and reality offers promising applications for drug discovery and precision medicine [21,22]. In this review, we discuss the prospective applications of DTs in predicting AD progression, discovering biomarkers, identifying new drug targets and opportunities for drug repurposing, facilitating clinical trials, and advancing precision medicine.

Current AD drug development landscape

AD neuropathology

AD is characterized by a complex neuropathological landscape, traditionally characterized by accumulation of amyloid-beta (Aβ) plaques composed of aberrantly cleaved amyloid precursor protein and other proteins, as well as generation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [19,20]. In addition to amyloid and tau, other neuropathological features, such as neuroinflammation, blood-brain barrier (BBB) deterioration, DNA damage, lipid dysfunction, mitochondrial impairment, axonal degeneration, impaired postnatal neurogenesis, and synaptic dysfunction also play significant roles in AD's progression [6,23–26]. For instance, microglia are resident innate immune cells in the brain, and activated microglia are a chronic source of various neurotoxic factors and also propagate a chronic inflammatory response that steadily damages neurons in AD [27–29]. Researchers have also found a close relationship between cerebrovascular disease (CVD) and AD. Cerebrovascular lesions are often found in the brains of AD patients and the most common vascular lesions are cerebral amyloid angiopathy and small vessel disease [30,31]. Indeed, increasing evidence in recent years suggests that AD most frequently results from a synergistic effect of multiple neuropathologies that occur to varying degrees across different people and also across time within any given patient. For example, cerebral amyloid angiopathy (CAA), limbic-predominant

Table 1
A list of data resources and tools for Alzheimer's disease (AD) research.

Name	Overview	Data type	Website	Reference
AD knowledge portal	Comprehensive collection of data, tools, and resources for AD and AD-related dementia	Genomic, transcriptomic, proteomic, metabolomics, and clinical data	https://adknowledgeportal.synapse.org/	[83]
NIAGADS	Centralized data repository of genomic data related to AD	Genetic, genomic, and phenotypic data	https://www.niagads.org/	[12,84]
ADNI	Longitudinal data of neuroimaging and biomarker data for AD	MRI and PET scans, cerebrospinal fluid (CSF) biomarkers, and cognitive assessments	https://adni.loni.usc.edu/	[85]
NCRAD	Biorepository of AD and other related dementia	DNA, plasma, serum, cerebrospinal fluid (CSF), and other types of biosamples	https://ncrad.iu.edu/	[86]
AlzGPS	Integrative platform for drug discovery and development for AD	Multi-omics data, genetic information, and clinical data	https://alzgps.lerner.ccf.org/	[87]
TACA	Comprehensive resource of AD at cellular level	scRNA-seq	https://taca.lerner.ccf.org/	[88]
SEA-AD	Comprehensive resource of multi-omics data at cellular level for AD	snRNA-seq, snATAC-seq, snMultiome, spatial transcriptomics	https://portal.brain-map.org/explore/seattle-alzheimers-disease	[10]
ssREAD	Database of sn/scRNA-seq for AD	sc/snRNA-seq, spatial transcriptomics	https://bmblx.bmi.osumc.edu/ssread/	[89]
scREAD	Database of sn/scRNA-seq for AD	scRNA-seq & snRNA-seq	https://bmbls.bmi.osumc.edu/scread/	[90]
HMDB	Human metabolome database	Chemical data, clinical data, and molecular biology/biochemistry data.	https://hmdb.ca/	[13]

age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC), and Lewy body disease (LBD) increase dramatically in incidence and severity in AD [32,33], suggesting that relationships and interdependence of various comorbid conditions with AD pose challenges for developing effective diagnostic tools and therapies [24,33]. This multifactorial nature of AD pathology highlights the complexity of the disease and the need for multifaceted therapeutic approaches.

AD drug development pipeline

Currently, the AD drug development pipeline is centered around two strategies: disease-modifying therapy (DMT) and symptomatic therapy [1]. Symptomatic treatments, such as the acetylcholinesterase inhibitor Donepezil that is intended to enhance cognition, offer temporary relief from cognitive symptoms, but they do not alter the underlying disease process [1]. In contrast, DMTs focus on addressing the underlying mechanisms of AD, such as targeting neurotransmitter receptors, neuroinflammation, amyloid beta protein processes, synaptic plasticity/neuroprotection, or tau pathology, with the goal of slowing or halting disease progression [1,3]. Based on the statistics of all clinical trials on clinicaltrials.gov, there are currently (as of January 1, 2024) 96 DMT trials, accounting for 76 % of the new drugs being tested. Of these drugs, 12 % have a therapeutic goal of cognitive enhancement and 13 % are intended to treat neuropsychiatric symptoms [1]. Among the total of 127 drugs that are reported in clinical trials for AD as of January 1, 2024, 22 % target neurotransmitter receptors, 20 % target neuroinflammation, 18 % target amyloid-beta protein processes, 12 % target synaptic plasticity and neuroprotection, 9 % target tau-related processes, and 6 % target metabolism and bioenergetics [1].

Notably, recent advancements in DMTs, including monoclonal antibodies like aducanumab and lecanemab, have been approved for use in slowing the cognitive decline of AD [1]. Both aducanumab and lecanemab target the amyloid-β protein. Aducanumab has been approved for treatment of patients with mild cognitive impairment (MCI), while lecanemab is the first drug to receive full approval from the U.S. Food and Drug Administration (FDA) for slowing progression of mild AD [34]. These developments of DMTs indicate a paradigm shift in Alzheimer's treatment, moving from symptomatic treatment to interventions that could potentially alter the disease trajectory. Notably, there are currently no drug development programs aimed at reversing AD and recovering function.

Challenges of AD treatment

Despite significant progress, numerous challenges remain in the fight against AD (Fig. 1). One of the most pressing issues is the high failure rate of clinical trials of agents that have shown high success in preclinical studies. Clearly, there are important problems with translation of AD therapies from animal model species to humans [35,36]. Additionally, the heterogeneity of AD, which manifests as variations at the cellular level, differences in pathology, incongruent patient responses to treatment, and gender disparities in incidence, poses significant challenges to developing universally effective therapies [25]. Single-cell genomic approaches have shown that AD involves complex interactions between almost all major brain cell types, as summarized by Murdock et al. with respect to cell-specific molecular and metabolism pathway changes [25]. For example, neurons account for the majority of differentially expressed genes in AD, such as those associated with presynaptic, postsynaptic, and inhibitory synaptic mechanisms. *SYN1*, the gene encoding the synaptophysin 1 protein that is essential for synaptic vesicle function, is up-regulated in AD neurons, whereas *TSPAN7*, the gene encoding the tetraspanin protein that regulates the structure of postsynaptic dendritic

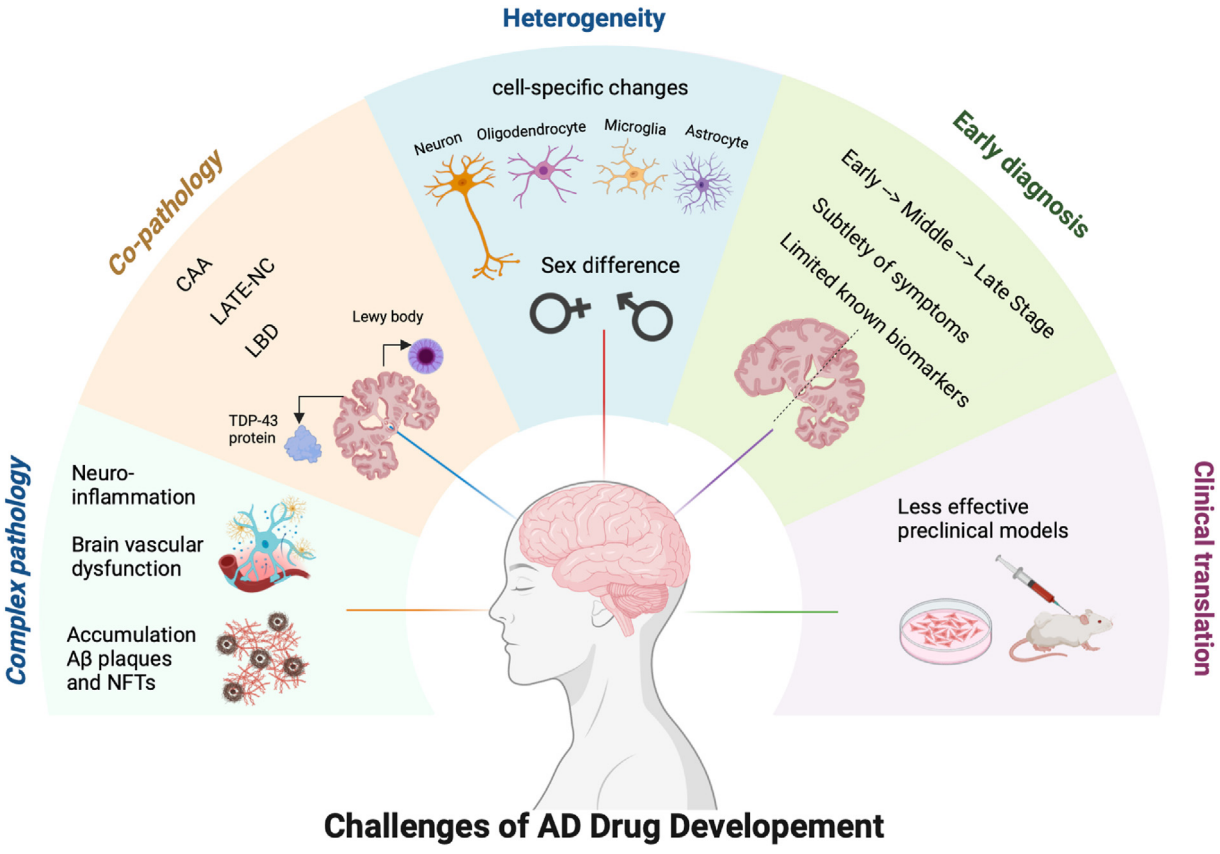

Fig. 1. The complex biology and etiology of Alzheimer's disease. It includes complex pathology and co-pathology, heterogeneity, difficulty of early diagnosis, and high failure rates in clinical translation. CAA: Cerebral amyloid angiopathy; LATE-NC: Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes; LBD: Lewy body disease. This figure created with BioRender.com.

spines, is down-regulated in AD neurons [25]. In addition, differentially expressed genes in microglia are also involved in regulating synaptic function, phagocytosis and immune responses in AD, such as *LINGO1*, which negatively regulates myelination, *and VSIG4* and *FCGBP*, which regulate the immunoglobulin response in AD [25]. Moreover, there is growing evidence of sex-specificity in AD manifestations, as well as sex differences in the rate of cognitive decline and brain atrophy, suggesting that sex is a key variable in disease heterogeneity [37].

Another critical challenge is generating accurate early diagnosis of AD. Current diagnostic methods often detect the disease only after significant neuronal damage has already occurred, limiting the efficacy of any given intervention [38]. The development of reliable biomarkers for early detection and monitoring of disease progression is crucial for the optimized success of future therapeutic strategies. Complex pathology and co-pathology are another impediment to AD drug development. For example, CAA, LATE-NC, and Lewy bodies increase dramatically in incidence and severity in AD. CAA interacts with plaques and tangles, especially in *APOEε4-positive* individuals; LATE-NC is associated with tangles later in the course of the disease; and most Lewy bodies are associated with moderate to severe plaques and tangles [33].

Digital twins

The features of digital twins

The term "digital twin" first appeared around 2010 in the National Aeronautics and Space Administration (NASA)'s technology roadmap, where it was defined as the pairing of a virtual representation with a physical entity, system, or process. This virtual model is continuously updated with real-time data to mirror its real-world counterparts [17,20,39,40]. Much of the early work and development of digital twins took place in industry and aerospace engineering. For example, digital twins can be used for structural health monitoring and predictive maintenance of airframes and aircraft engines [20]. It can also be used to monitor and control DC-DC converters in electric vehicles [41]. Today, interest in and development of digital twins extends to different application areas, such as healthcare [20]. The main features of DTs are to create a dynamic digital model based on multi-scale real-time data that can simulate, predict, and optimize the performance of its physical twin by virtue of the information gleaned from examining the bi-directional interaction between physical and digital space.

In healthcare, digital twins rely on AI technologies, statistical methods, and network approaches to obtain virtual representations from multimodal biomedical data. It is complementary to advanced technologies like AI [42]. While on the one hand AI technologies and statistical approaches provide powerful analytical capabilities, digital twin provides the framework for dynamic, integrated and actionable insights. The key advancements in DTs compared to AI/ML models lie in their dynamic adaptability, real-time interaction, and holistic integration [43]. Unlike AI models, which remain static until retrained with new data, DTs continuously evolve with real-time updates, enabling users to reflect the current state of the system and support more responsive and informed decision-making (Fig. 2).

The framework of digital twins

A DT involves the following components: data, modeling, connectivity, evaluation, and feedback (Fig. 3). High quality, multi-dimensional, and real-time datasets are the foundation of any DT [20,39]. Modeling and simulation based on multi-scale and time-series data to create virtual representations of physical counterparts is also a key element of DTs. DTs connect the virtual and physical worlds with bi-directional interaction creating a feedback loop that continuously updates the models and optimizes decisions [20]. How to effectively utilize medical DTs is a challenge that needs to be addressed urgently. First, DTs cannot be separated from analysis of various biomedical data, such as integration of multi-omics data, processing of image data, network analysis, and machine learning or generative AI to construct different levels of representations and models of clinical data and disease states. For instance, commercial enterprises are incorporating AI to create DTs of human cells using multi-omics data to perform pathway analysis, as well as for simulating responses to drugs and genetic perturbations [14,44,45].

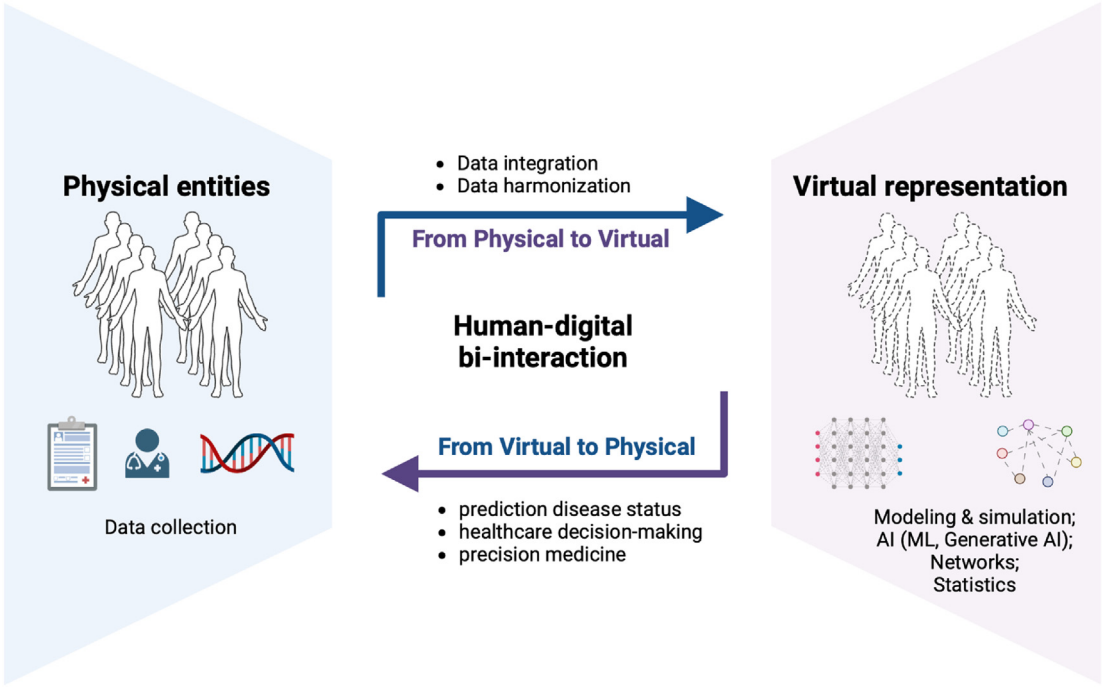

Fig. 2. The features of digital twins. The input data features of DT contain multi-scale real-time datasets. Models and simulations that can integrate all state-of-the-art methods, and models and decisions-making that can be updated in real time based on bi-interactions between virtual and real. This figure created with BioRender.com.

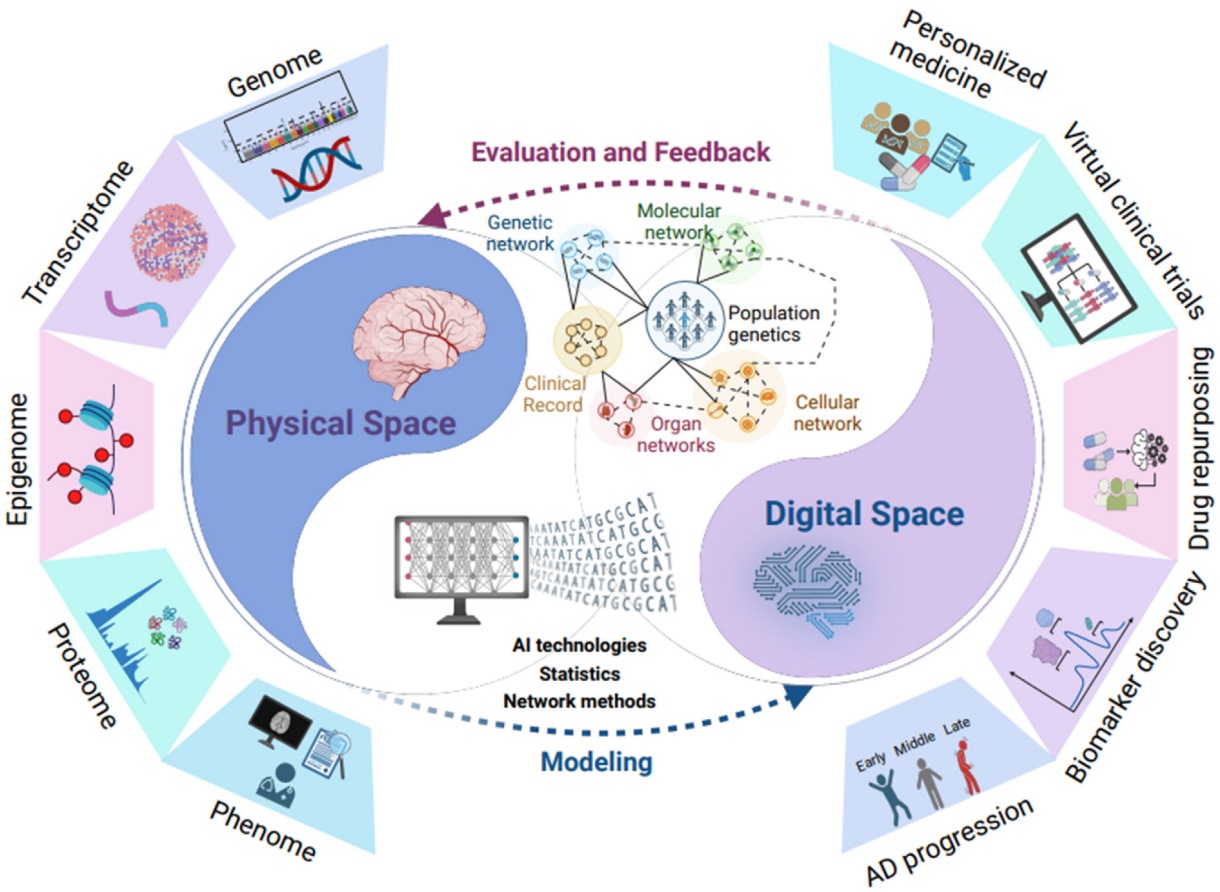

Fig. 3. The general framework of medical DT and its application in AD. It typically consists of three main components, where the physical space includes multi-scale input data, genomic data (e.g. GWAS), transcriptomic data (e.g. scRNA-seq, spatial transcriptomics) and epigenomic data (e.g. ATAC-seq data and methylation data), proteomic data (e.g. MS and PPI), and phenomics data, that is clinical data, including such as MRI, EHR. The middle space is modeling component, which uses AI, statistics, and network approaches to connect the physical and digital components for bi-directional interactions. The digital part can be constructed as cell-DT, individual-DT, organic-DT, and population-DT depending on whether the input data is at the cellular level, the organ level, the individual level, or the population level. It then can be applied to different aspects such as in AD, which including prediction of AD progression, biomarker identification, drug repurposing, virtual clinical trials, and personalized medicine. This figure created with BioRender.com.

Potential applications of digital twins in AD

DTs typically serve as a foundational framework via integrating AI models, statistical methods, and network-based approaches. A key advancement of DTs lies in their real-time bidirectional feedback capabilities. This enables precise predictive insights from even small amounts of new data, paving the way for precision medicine. As foundational models continue to flourish, DTs are emerging as a powerful tool in healthcare, particularly for addressing complex diseases such as cancer, type 2 diabetes, multiple sclerosis, heart failure, seasonal allergic rhinitis, post-hepatectomy liver failure, viral infection, and dental issues [46–49]. For example, dynamic single cell-based DTs have been used to prioritize disease-associated genes and drug targets by network-based method for seasonal allergic rhinitis, which provides a foundational framework for biomarker discovery and identification of drug targets [50]. This framework can be continuously refined with new data and validated for treatment efficacy over time. By accelerating the discovery of biomarkers and drug targets, this approach not only shortens the drug development timeline but also enhances precision in identifying individual-specific biomarkers, revolutionizing the drug discovery process. In addition, the company DeepLife has leveraged single-cell omics data, AI, and systems engineering to develop a platform for creating DTs of human cells, enabling rapid assessment of how cells respond to potential drug candidates [44]. This approach streamlines drug discovery, reduces costs, and enhances safety in drug testing compared to traditional pre-clinical methods. Despite these advancements, the application of DTs in AD remains largely underexplored, highlighting an opportunity for future research to unlock their potential in understanding and managing this complex neurodegenerative diseases.

Predictive AD progression

AD progresses with age and is categorized into early, middle and late stages [51]. Diagnosing AD at its early stage is challenging due to the subtlety of symptoms, which are often masked by routine age-related changes, and the subjective nature of commonly used cognitive tests [51]. Previous studies have investigated AD progression with different approaches. For example, to characterize the spatiotemporal atrophy staging of AD at the whole-brain level, Planche et al. modeled lifetime volumetric changes of brain structure in both healthy and AD brain by integrating multiple large-scale databases, comprising 3512 MRIs across nine subject cohorts spanning the entire lifespan [52]. Furthermore, several studies have predicted AD progression by evaluating the AD Course Map, which is a statistical model that forecasts the progression of a patient's neuropsychological assessments and imaging biomarkers based on early-stage medical and radiologic data [16,53]. Additionally, researchers have explored the molecular changes across AD progression at the single-cell level. For instance, Mathys et al. and Gabitto et al. studied molecular regulation of major brain cell types across AD progression through single-cell multi-omics data [10, 54]. These studies provide essential data resources for developing a DT model that accurately represents AD progression, paving the way for more precise predictions of disease trajectories.

Biomarker discovery

A comprehensive understanding of the molecular changes underlying AD development across cellular, genomic, individual, and population levels is essential for identifying biomarkers for diagnosis, discovering drug targets, and gaining precise insights into AD mechanisms. At the cellular level, researchers are leveraging multi-omics single-cell data integration, network analysis, and machine learning methods to construct spatial transcriptomics and an epigenetic atlas of AD, uncovering cell-specific molecular changes [50,54–58]. At the population level, continuous or lifelong learning methods applied to electronic health records (EHR) and longitudinal genomic data provide valuable insights into disease progression, facilitating the identification of mechanisms driving AD development and enabling the prediction, prevention, and treatment of the disease [2,17,29,59,60]. Although general machine learning methods are also effective for biomarker discovery, particularly when leveraging large datasets, these methods typically analyze static data or snapshots in time, uncovering general patterns and associations at the population level [39]. In contrast, the DT framework is designed for continuous model updates and real-time feedback, even with minimal or individual-specific data. This capability allows DTs to simulate the dynamic progression of a disease over time, facilitating the discovery of biomarkers that reflect early disease stages, progression, or therapeutic response, as well as pinpointing optimal temporal windows for intervention [20]. Additionally, DTs have the potential to generate individualized, dynamic simulations within a continuous feedback loop. By integrating multi-scale data—genomic, proteomic, and clinical—these simulations capture the unique trajectory of disease progression for each individual. This approach accelerates biomarker and drug discovery, enhancing precision and efficiency even in scenarios with limited data availability. Furthermore, DTs can conduct virtual trials to evaluate the efficacy of biomarkers before proceeding to clinical validation [61]. This innovative approach not only enhances the precision and efficiency of biomarker discovery but also significantly accelerates drug development while reducing associated costs.

Drug repurposing

Traditional drug discovery continues to be challenged by long lead times and drug safety risks, even after entering clinical trials. Drug repurposing - finding new uses for existing FDA-approved drugs – is an important area for discovering new treatments for patients. For example, Cheng et al. developed a Genome-wide Positioning System Network (GPSnet) algorithm that enables drug repurposing through localization of disease-specific modules in individual patient DNA and RNA sequencing profiles that are mapped to the human protein-protein interactome network, as well as a protein-network-based approach for identification of combinations of drugs with clinical efficacy for specific diseases [62,63]. Furthermore, Fang et al. and Xu et al. developed a network-based artificial intelligence framework for drug repurposing that integrates bulk-RNA-seq and multi-omics data at the single-cell/nucleus level as well as the human protein-protein interactome network to accurately infer drug targets affected by disease-associated genetic variants identified by genome-wide association studies (GWAS) [29,64,65]. Overall, this important area is particularly amenable to application of DT technology [66]. For example, by modeling how existing drugs interact with disease models in patient-specific DTs, utilizing large-scale perturbation databases such as Connectivity Map (CMap) or the Library of Integrated Network-based Cellular Signatures (LINCS), the efficacy of potential drug candidates can be efficiently screened [29,67,68]. These candidates can then be validated using real-world data (RWD) from extensive clinical databases like OneFlorida and MarketScan, which collectively encompass over a decade of clinical records for more than 170 million patients [69–72]. Drug repurposing not only saves time and resources, but also leverages the safety profile of approved drugs to deliver effective treatments to patients faster. Future application of DTs to drug repurposing in AD holds great promise for accelerating the discovery of new treatment approaches.

Clinical trial emulation

Clinical trial emulation using DTs is another innovative application that could be applied to AD research. Clinical trials are costly and time-consuming, and it can be difficult to recruit patients. Developing DTs of trial participants, however, allows for in silico simulations of experimental therapies, enabling the prediction of outcomes and identification of potential side effects before human trials are conducted [73,74]. This approach can significantly reduce costs, save time, and minimize the risk associated with clinical testing. Importantly, virtual DT clinical trials more accurately reflect real-world changes than traditional cell and animal models, and thus could be uniquely applicable in AD for which there is a particular high discordance between preclinical data and clinical efficacy. For example, Bertolini et al. developed a machine learning model for predicting AD progression using a conditionally constrained Boltzmann machine. The model utilized nearly 7000 clinical records from placebo groups of AD clinical trials and observational studies to generate DTs in the form of synthetic clinical records that reflect baseline characteristics and the most likely disease progression of real patients under the standard of care with or without placebo [73]. Companies like Unlearn.AI [75] are also designing virtual clinical trials with large amounts of data on diseases such as AD and Parkinson's disease, which they named TwinRCT. TwinRCT is a randomized trial that uses DTs to predict individual outcomes to optimize the trial process. Notably, creation of DTs of trial subjects by AI models trained on patient-level data helps in conducting subsequent human trials with higher power and smaller control groups [18,76]. In summary, clinical trial emulation using DTs can help optimize trial design, reduce the number of participants needed, and increase the likelihood of success, ultimately accelerating the development of new treatments.

Precision medicine

It is hoped that in the future DTs will deliver personalized medicine to AD patients, with continuous updating of a patient's DT based on new data (e.g., biomarkers at multi-scales level, imaging results, and clinical assessments), to help physicians customize their treatment plans in real time [21,77]. In this respect, we propose future utilization of cellular DTs (CDTs) across AD progression, as many AD risk genes are differentially expressed in various cell types. For example, multiple GWAS studies suggest that the ε4 allele of the apolipoprotein E (APOE) gene is the most potent genetic risk factor for sporadic late-onset AD, and APOE genes are relatively highly expressed in microglia and astrocyte cells [25,78]. In addition, integrative analysis of multi-omics single-cell data has shown that somatostatin-expressing neuronal subtypes are reduced in early AD, intracranial suprachiasmatic projection excitatory neurons and parvalbumin-expressing neurons are reduced in late AD, and disease-associated microglial and astrocytic cells are increased in late AD [10]. These results suggest that cell type- and disease progression-specific effects are an important consideration in treatment. The construction of a cellular DT for AD progression could potentially mirror the molecular changes of AD progression at the cellular level, which could enable identification of key biomarkers and drug targets. In addition, machine learning and network-based approaches, combined with drug databases such as CMap, could enable drug perturbation trials to identify cell-specific drugs that are effective against a given stage of AD progression. This dynamic, personalized approach utilizing DTs could ensure that each patient receives the most effective interventions and treatments based on their unique disease characteristics.

Another potential application for DTs in AD drug discovery is development of whole brain DT (BDT). Lu et al. [79] and Feng et al. [80] have

already introduced the BDT computing platform that simulates spiking neuronal networks at the scale of the entire human brain, containing up to 86 billion neurons and 478,000 billion synapses [79,80]. In this work, they incorporated imaging data from a variety of biological brain structures, including structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET), while using a hierarchical random graph model with constraints and multiple edges to simulate synaptic interactions between neurons [79]. This BDT under development is projected to emerge into a powerful platform for enhancing our understanding of brain dynamics, thereby supporting development of new therapeutic approaches and improving clinical decision-making through personalized brain simulation.

Challenges and future directions

To summarize, DT technology is already showing great potential application in healthcare, and we propose that it is particularly promising for accelerating drug discovery and development for AD, as well as aspects of personalized precision medicine. However, there are still some limitations for DT in healthcare. DT currently lacks well-defined, systematic theories and algorithms, often relying on existing statistical models and various machine learning approaches. Advancing DT requires a highly interdisciplinary effort: mathematicians and computer scientists are needed to provide foundational theoretical support and develop robust models, while biologists and medical scientists contribute domain expertise to accurately represent biomedical systems. Additionally, the integration of mechanistic modeling, Internet of Things (IoT) technologies, and other tools is essential to seamlessly connect the virtual and physical worlds, ensuring the fidelity and applicability of DT. It is also important to note that DT validation in biology is more challenging than in industry. One of the main challenges is that biological processes and diseases themselves are not as straightforward as objects in industry, and their inherent complexity complicates multi-scale real-time data collection as well as integration and coordination of data in different dimensions. It should also be noted that sensitive personal health information may be used in constructing DT, and data privacy and data security should be taken into account. Some current advanced techniques, such as federated learning and distributed learning, are methods that can effectively reduce data security issues [81,82]. In the future, as DT technologies and theories mature, DT has the potential to revolutionize drug discovery in AD and provides patients with more accurate, personalized, and efficient care.

Author contributions

Y.R., A.A.P, and F.C. wrote and critically revised the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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