Novel discovery framework: harnessing adaptive learning for breakthroughs in drug development and clinical applications

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Abstract The costly process of bringing new therapeutics to market and high attrition rates have motivated the search for new frameworks in drug research and development (R&D). These challenges extend to the clinical space with the need for better patient stratification and therapy matching. Moreover, despite significant leaps in deep learning, even the most sophisticated methods rely on static analytical structures. Thus, unaddressed needs in therapy development and applications call for unconventional thinking to capture dynamic processes across preclinical and clinical spaces. With this review, we trace how crucial algorithmic pieces have been coming together over the past decades for the next generation of deep learning, which we define as adaptive learning. This new class of robust analytical architectures will be enabled through self-organised models where inputs changing over time can guide deep networks to adapt to biases and optimise learning. There have already been glimpses of such groundbreaking solutions in liquid neural networks (LNNs), graph attention algorithms, digital twins, and engineering research. As we review multiple examples and applications, we want to highlight the emerging fundamental shifts in discovery and analytical paradigms. Only by continuing to develop new frameworks can we capture complex disease interactomes and identify or improve therapeutic avenues.

Insight Box Our work underscores the emerging shifts in research and development (R&D) and drug discovery from a deep learning perspective. First, we identify and discuss the missing link in drug discovery that affects multiple areas in translational research. We then demonstrate how critical algorithmic, analytical, and technological pieces have been coming together to address these challenges. Furthermore, we illustrate how applied AI and deep learning frameworks will need to change and what solutions are already available. Consequently, we employ examples of novel deep learning architectures, digital twins, and clinical research. Notably, there has been very little discussion to acknowledge current limitations in deep learning from a translational perspective. Thus, our work offers not only new insights but also a direction of travel for future developments, which we define as adaptive learning.

Keywords: machine learning (ML); deep learning; systems medicine; systems biology; drug discovery; digital twins

Introduction

Drug discovery is a long and expensive process, with approximately only 10% of clinical programmes succeeding [1, 2]. Notably, expenditure for new drugs has risen sharply, with the reported cost of bringing a new drug increasing from US $1.2 billion in 2007 [3] to US $2.8 billion in 2016 (adjusted for inf lation, US $1.8 billion and US $3.7 billion, respectively) [4], which ref lects changing research and development (R&D) trends. While these observations are nothing new to industry folks, the growing num- ber of chronic and pandemic diseases compels us to reconsider old paradigms, improve translational success, and expedite drug development.

In the past ten years, the industry has started to slowly shift from 'low-hanging fruit' or well-defined targets to exploring more complex regulatory networks [5]. However, challenges remain. A good illustrative example is the 16 IGF1R inhibitors tested in 183 cancer trials, with an estimated US $1.6–2.3 billion spent— without a single oncology approval [6]. This and other similar cases raised questions about whether our traditional methodologies for establishing targets, developing candidate molecules, and predicting therapeutic potential needed revisiting. At about the same time, digital twins, deep learning, and causal inference methods emerged as attractive solutions that could help us com- bine multivariate biological processes into a system that can be modelled and studied [7]. However, current artificial intelligence (AI) approaches cannot self-update their architectures based on continuous inputs or emergent internal biases, which results in static learning. For example, Apple researchers have raised concerns about the current state of large language models (LLMs) and the fragility of their mathematical reasoning [8–10]. Further- more, improvements in LLMs depend on a substantial increase in training data and the size of the model. This also brings into question whether the research is biased because only big tech companies have the resources for this scale of model building and training [10]. In other words, deep learning progress can be viewed as motivated by certain

commercial interests, and we may be missing important research areas, as evidenced by the fact that self-organising and self-correcting architectures are not yet developed. However, these advancements will be crucial for the analyses of causally complex biological networks, which exhibit unpredictability and a continuous f low of high-dimensional infor- mation (Fig. 1) [11]. Our goal is to uncover the main direction of travel for the next generation of applied solutions in indus- try and the clinic, which we define as adaptive learning. Precisely, adaptive learning can be thought of as architectures, algo- rithms, or deep learning frameworks where the system dynam- ically changes and self-adjusts to optimise learning based on evolving inputs. Reframing established methodologies—such as digital twins and dynamic models—through the lens of emerging frameworks like liquid neural networks (LNNs) enables a deeper exploration of their clinical applicability and how novel architectures arise (Fig. 1). In particular, biologically-informed neu- ral architectures, which continuously adapt to environmental perturbations by restructuring themselves and thereby exem- plify adaptive learning, have yet to be critically examined in the context of drug development and therapeutic innovation. Thus, this review not only highlights novel architectures but also pro- poses a translational roadmap to take advantage of continuous-time adaptability and real-time responsiveness to address current therapeutics development and implementation challenges. We structure our discussion into several parts: the analysis of the 'missing link' in drug discovery and motivations for adaptive learning; early implementations of adaptive learning principles; and clinical opportunities for this new framework.

We are still missing critical links for translating research into clinical applications

Numerous studies have investigated the underlying causes of why ~90% of drug development programmes are unsuccessful, despite the ever-expanding new methodologies and screening tools [2, 12]. The most common themes in these reports can be condensed into the following conclusions: nonexistent strategies for bridging preclinical and clinical research, over-dependence on a narrow spectrum of translational methods or a single approach, and the lack of retrospective studies to better understand the causes of past failures. We refer to this as the 'missing link' in drug discovery.

The first prominent challenge is the largely unknown biological mechanisms responsible for pathophysiology in many complex diseases. Poor linkage between early discovery models and the underlying disease biology, as well as limited efficacy of new drugs, are predicted to account for ~50% of clinical failures [2]. Furthermore, many historical examples reveal that therapeutic discoveries were either serendipitous or relied on complex in vivo models [13]. Only recently have research organisations started to develop models and assay systems more suitable to tackle complex disease interactomes [14–16]. For example, cell-based assays, 2D/3D co-cultures, organoid models, tissue-organ chips, and microphysiological systems are now being integrated into a 'chain of translatability' to capture disease-related and drug response-dependent phenotype dynamics [17]. Nonetheless, data capture is still fragmented and discrete, which does not encourage framing pipelines to support

continuous adaptability. A clear example of this is drug screening and diagnostic applications in 3D cultures and organoids, where the drug's mechanistic action is limited to a single time point [18]. This lack of accurate physio- logical models contributes to less methodological diversity.

Correspondingly, R&D remains highly dependent on a limited number of analytical strategies, which is the second predomi- nant problem we have identified [13, 19, 20]. Until the 1980s, drugs were developed through the observation of their therapeu- tic effects and disease phenotype modulation. With the advent of molecular biology and genetics, there was a shift towards target- centric approaches. Subsequently, high-throughput (HTS) screen- ing started to dictate drug development programmes, enabling a fast turnaround of targets and compound libraries [13]. Neverthe- less, target-focused studies plateaued between 1999 and 2008 as the majority of first-in-class drugs were discovered empirically. It was becoming clear that 'low-hanging fruit' targets were depleted and the remaining disease space spanned complex interactome and pathophysiology [21]. Therefore, phenotypic drug discovery (PDD) re-entered the R&D scene in 2011 with an expanded array of tools and a focus on disease-modulating strategies [13, 17]. Specifically, PDD relies on screening new drugs by evaluating their effects on a biological model. Instead of a single target, this method helps to find compounds that modulate the phenotype without needing to define a specific therapeutic mechanism first. Consequently, this offers a robust testing and discovery plat- form for detecting active compounds [13]. While examples of iva- caftor and lumacaftor for cystic fibrosis, risdiplam and branaplam for spinal muscular atrophy, and SEP-363856 for schizophrenia demonstrate the power of PDD, the industry's slow shift from the 'one target-one disease' paradigm ref lects the fact we are still looking for the best strategies [13]. Many recent advances in com- putational methods and AI are also part of the same narrow focus with a select few methods dominating. Interestingly, even though AI-native companies had entered 67 molecules into clinical trials by 2023 [22], the AI contributions to pipeline assets are often not disclosed. Importantly, these historical and current examples accentuate that relying just on one strategy often leads to 'herd- like' thinking without proper retrospection on performance or potential improvements.

In addition to methodological overreliance, the last part of the 'missing link' draws attention to the fact that past failures of clinical programmes are underreported, which prevents understanding what was overlooked and where better optimisation is needed [2, 12, 20, 23]. A good case example is thalidomide, where the drug's anti-inf lammatory properties were coincidentally discovered through a leprosy patient taking the drug for its sedative effects [24]. The optimised analogue several of blood cancer indications and after gaining Food and Drug thalidomide—lenalidomide—was repurposed for Figure 1. Key algorithmic developments and applications motivating adaptive learning. The order of occurrence is primarily based on how widespread the adoption was and when the method became more prominent in research. The schematics outline key features of different algorithmic and modeling concepts [25–34]. Administration (FDA) approval, led to sales in excess of $12 billion in 2020 [13]. Evidently, enabling retrospective analysis could be

consequential in reducing discovery costs and attrition rates. This would also diversify therapeutic modality search and allow the integration of different research methodologies.

In the following sections, we detail how the emerging modelling approaches can enable the required analytical transformation to address these multifaceted discovery challenges. Starting with the evolution of dynamic models and algorithms (Fig. 1), we highlight what inf luenced their development and how that informs future trajectories of applied solutions in adaptive learning for better screening and therapeutics development.

Towards analytical plasticity: adaptive learning

Before neural networks and modelling approaches started to resemble attentive processes and specialised computational hardware was designed to support them, the ability to change internal architecture arguably first emerged within mechanical and electrical systems developed for various tasks, from engineering to biotechnology [32, 35, 36]. Later, increasing data traffic across networks and data centres also necessitated greater f lexibility for network topology designs, with solutions such as optical switches allowing architectures to adapt based on demand [37]. Self-adjusting networks (SANs) are built to support dynamic physical network reconfiguration via algorithmic and physical solution interfaces (Fig. 1) [31]. Systems capable of self-tuning inspired further applications bridging physical and computational interaction systems. For example, microf luidics for organoid cultures illustrates how a dynamic culture environment can be automatically maintained by changing medium f low and other micro-environment parameters based on the system's feedback [38]. This has proven to be especially valuable in drug research [38, 39]. Thus, engineering challenges motivated the emergence of new methodologies that can process multimodal, stochastic, and time-evolving data.

Building on these needs, the groundwork for adaptive learning was laid out with adaptive boosting, graph-based, probabilistic machine learning, network diffusion, self-organising map, genetic, and other algorithmic advances (Fig. 1) [30, 40–43]. Some of the earliest works raising the question of 'self-aware' model architec- tures can be traced back to multilayer feedforward networks that, under supervision, can develop their own output labels through a self-coding backpropagation algorithm [44]. 'Self-awareness' can be interpreted as the model's ability to not only perform a specific task but also optimise its learning. This study by Sarukkai was primarily biologically motivated, as pre-specifying output labels in advance is often not possible. Moreover, self-learning systems have roots in reinforcement learning where there is an active com- ponent of interacting with an environment and learning from that experience [30]. Later, advances in training deep neural networks were used to develop an artificial agent, a deep Q-network, further conceptualising end-to-end reinforcement learning [30, 43]. Thus, self-supervised learning, which mimics independent adaptability, has been originally developed with the premise of automatically deriving relations based on the input data. Convolutional neural networks (CNNs) and recurrent neural networks (RNNs), and their variants, are also an important

class of the deep discrimina- tive learning models that have memory for features and within- model information sharing (Fig. 1) [45, 46]. Further progress with transformer-based architectures and attention mechanisms has resulted in effective vector-based embeddings that enable net- works to selectively focus on relevant input components to gener- ate specific outputs [47, 48]. However, these algorithms and mod- elling frameworks remain constrained by discrete learning cycles and cannot restructure themselves based on input perturbations. Continuous adaptability in model development became a more focused research trajectory for improving temporal processing (Fig. 1) in the early 2000s with echo state networks (ESNs) [49] and liquid state machines (LSMs) [50]. ESNs employ a fixed, random internal network (a 'reservoir') to process input and train output weights. The reservoir's nonlinear dynamics result in an 'echo' of the input history. The network is made adaptive by training only the simple, linear output weights that map this dynamic state to the output. As a result, this design prevents the vanish- ing or exploding gradient problem and increases computational efficiency [51]. In a similar fashion to ESNs, LSMs use a random, sparse 'reservoir' to map input data into a higher-dimensional space, by employing a trainable readout layer. The reservoir con- tains predetermined, spiking neurons (the 'liquid') to react to the input spikes by generating their own spikes [52]. This recurrent connection enables neurons to use their recent output history and create complex temporal patterns. LSMs also illustrate how emerging deep learning models are inspired by biological neu- rons [52]. Furthermore, a pivotal shift came in 2018 with neu- ral ordinary differential equations (NODEs) [53], which enabled continuous-time and differentiable dynamics for adaptive deep learning systems. NODEs represent an important class of deep learning models where the transformation between layers is not a discrete sequence of operations, but a solution to an ordinary dif- ferential equation (ODE) (Fig. 1). Such a continuous-time system handles irregular data better, allows complex nonlinear learning without assuming a fixed structure, and provides tools for study- ing time-evolving relationships [54, 55]. This is especially relevant in clinical research where prediction of cell differentiation trajec- tories, gene regulation patterns, or patient-specific drug response depend on how the system of interest changes over time [54–56]. Among the most notable outcomes of these methodological advances is the emergence of LNNs (Fig. 1) [57–59]. The key feature of LNNs is the ability to adapt dynamically to system perturba- tions, which allows efficient processing of time-series data [57– 59]. The network's behaviour and structure can be reconfigured based on the data f low, allowing for continuous learning even after training. This new type of neural network architecture uses fewer nodes than RNN models and is more robust to noise. LNNs achieve this plasticity by using a liquid time constant, which depends on the input and alters the network's connections as new information becomes available. In other words, the liquid time constant ensures the 'liquidity' of the network as it is not static but dynamically computed as a function of the input and the previous hidden state of the network. This serves as an adaptive memory because the neuron learns how long to retain a memory of past states [60, 61]. LNNs have been tested in tasks such as autonomous driving, weather prediction, and speech recognition, demonstrating real-world adaptability [58, 59]. Importantly, LNNs address the static nature of reservoir computing and offer a trajec- tory towards dynamical system

integration with modern machine learning. Similarly, graph neural networks (GNNs) and their exten- sions represent how deep learning and related algorithms evolved with more f lexible and adaptable designs (Fig. 1) [34]. In particular, graph-enabled methods offer adaptive solutions with temporal adjustments where learning attention is directed towards specific parts of the graph with transductive capabilities [62]. For example, hybrid graph architectures draw from continuous-time neural models and graph-enabled topology mapping. BioLNN is one such example where liquid time constant cells are embedded into nodes of a temporal knowledge graph to capture co-evolving drug– target–pathway interactions [63]. Specifically, causal pathways of interest can be captured by liquid state constants dynamically adjusting their computational graphs [63]. These illustrative cases demonstrate how advanced deep learning architectures evolved and how gradual design choices of adaptive feature incorporation were motivated by specific research needs, concerning spatiotem- poral and variable inputs. Nevertheless, next-generation intelli- gent systems depend not only on algorithmic developments but also on suitable hardware.

Computational hardware represents an important research area to overcome the limitations of traditional von Neumann architectures (i.e. CPU can only access either data or instructions at a time) for successful advancement and adoption of adaptive deep learning. As a result, brain-inspired neuromorphic com- puting has emerged with new solutions for energy efficiency, interfaces and intelligent massive parallelism, and co-located memory and processing [57, 64]. Notably, neuromorphic computing aims to mimic the way the human brain works, which includes both hardware and software solutions to replicate the neural structures and functions of the brain's information processing [64]. Major advances in the 1990s and 2000s, and initiatives such as DARPA's SyNAPSE programme fueled innovations in silico neurons, synapse models, and memristor-based designs for efficient pattern recognition and sensory processing [65]. For example, multimodal learning algo- rithms implemented in neuromorphic chips have shown potential robotics [66]. in brain-computer Accordingly, LSMs, ESNs, and LNNs are some of the models tested for the adoption within neuromorphic computing frameworks and applications [57, 67]. Therefore, neuromorphic computing is a powerful and evolving alternative to conventional architectures.

Collectively, the adaptive deep learning approaches have been evolving together with the supporting hardware. From a perspec- tive of drug development and clinical applications, it becomes evident that biological processes—which are time-evolving and inherently stochastic—require the adoption of new methodolo- gies to study them effectively [27, 68]. This is also ref lected in technological developments of hybrid systems, such as digital twins or microf luidic screening devices. As such, adaptive deep learning stands at the forefront of a paradigm shift—offering the f lexibility, responsiveness, and spatiotemporal awareness needed to transform how we investigate, predict, and intervene in com- plex biomedical systems.

The emergence of adaptive learning principles in studying complex systems

In this section, we explore digital twin, digital twin-like, physics- inference, and decision-driven systems as informed, causal instructive examples of adaptive frameworks. Their responsive- ness to inputs and environmental variables was an early moti- vator for adoption to study multimodal biological phenomena. Importantly, they also offer real-world-tested insights for novel adaptive applications and algorithm development [69, 70].

Digital twins are an excellent example of the emergence of adaptive learning principles, as they use a bidirectional automatic data f low between a physical system or an object and the model (Fig. 1) [71]. More precisely, digital twins can be described as an in silico replica of an object, a system, or a process [25]. As a result, digital twins represent an emerging technology encompassing computer science, mathematics, engineering, as well as life and clinical sciences [72, 73]. While the term 'digital twin' was first mentioned in 1994 based on the idea of digitisation of 3D arterial phantoms [74] and later in NASA's 2010 technological roadmap [75], their use can be traced back to Apollo missions and radiologists' work dating to the early 1960s [25, 76]. At present, in the pharmaceutical industry, digital twins are primarily used to manage processes, such as biomanufacturing, and their use case examples are scarce [7, 25]. This has prompted more research in the HTS designs to better capture continuous information f low, enabling real-time input-driven adjustments, and minimising the accumulation of noise or error [77, 78]. For example, digital twin controllers could serve as a replica of a complex network of experimental machinery or pipelines via continuous performance readout integration. Such digital counterparts can enable adaptive decision making by detecting faults in real-time or anticipating how input changes might inf luence outputs and adjusting the system accordingly [79]. Digital twin technology could also ensure that initial data processing accounts for potential batch effects during biomanufacturing. Batch effects are commonly defined as technical variations that are distinct from factors being studied. These effects can be detrimental to screening quality by distorting a meaningful biological signal, obscuring a relevant response, and leading to nonreproducible results [80–82]. For example, such an unwanted bias can result from the use of different equipment, changes in experimental conditions over time, or nonstandardised analytical protocols [81]. Consequently, high-throughput data generation, such as genomics, transcriptomics, proteomics, or other omics, can be especially sensitive to unaccounted batch effects [80, 82]. By leveraging dynamic information received from HTS monitoring systems, bioprocessing-integrated digital twins can perform real- time identification, quantification, and correction of noise and variance sources in the HTS pipeline [80, 82, 83]. In particular, various context-aware (or multiple experimental parameters tracking and monitoring) screening solutions are being explored for integrated monitoring in order to capture meaningful biologi- cal signals [82]. Other digital twin technology developments have predominantly been experimental in cell, organoid, and tissue modelling, but more applications and their deployments are being explored [84, 85]. Medical digital twins are particularly advanta- geous for the use in cardiovascular diagnostics, insulin pump control, and surgical applications [7, 86–88]. In addition, patient-specific digital twin models have also been tested for monitoring disease progression and adapting therapy in real time, offering a promising path toward personalised care [89]. It is

important to note that complex technological requirements for digital twins also form the basis for specialised analytical and hydrid systems.

Recently, physics-informed neural networks (PINNs)—which integrate ODEs or partial differential equations (PDEs) into deep learning frameworks—have enabled the fusion of AI with mecha- nistic models [53, 90]. Precisely, PINNs merge the laws of physics, expressed as differential equations or other constraints, into the structure of neural networks. PINNs are especially useful for modelling when only sparse data are available, as well as for complex parameter learning [91]. Clinical and research examples of PINNs include cardiovascular modelling, pharmacodynamics predictions, and biomechanical simulations [92, 93]. Such new approaches are particularly valuable for time-series inputs and the estimation of difficult-to-measure physiological parameters, such as cuff less blood pressure or metabolic dynamics [70, 89, 94]. Moreover, these developments highlight the growing potential of hybrid modeling techniques, such as digital twins in combination with PINNs, to support continuous monitoring, predictive diag- nostics, and adaptive treatment strategies in clinical settings [68, 72, 95].

Feedback integration and adaptive systems have also emerged in other R&D areas. The concept of mechanistic physiological modelling is not new and has been around for the past two decades. Moreover, capturing multidimensional features of ther- apeutically relevant interactomes has roots in systems biology and causal learning, with more recent exploratory work build- ing on causal AI methods [26]. For example, Folkesson and col- leagues demonstrated how their logical modelling framework— ‘a virtual cancer cell’— enabled exploration of new drug com- binations for cancer treatment in a high-throughput manner and captured complex interactions of third- and fourth-order. This was achieved by integrating signalling pathways that are dysregulated in cancer and DNA-damage-associated features [96]. In addition, it is possible to test different cellular effectors via response loops to identify suitable biomarkers and targets [97, 98]. Specifically, endogenous and artificial receptors integrated into sensing systems can be used to detect biomarkers and to translate signals either to modulate cellular responses or to interface with devices [33]. Furthermore, disease progression mapping using single-cell transcriptomics has also been explored with a new generative network, enabling time-series analysis. The developed tool provides a novel approach to study disease progression and drug-induced perturbation, decoding complex cellular dynamics via a variational autoencoder-generative adversarial network [99]. Addressing similar workf low challenges, the HTSplotter software package was launched to capture time-dependent outputs of per- turbagen screens and to facilitate downstream data integration and analysis [77]. These examples underline how closed-loop adaptive designs are being used to support biomarker discovery and clinical applications with improved response tracking and translatability.

Patient stratification and clinical support enabled through adaptive models are also becoming a priority across a number of regulatory bodies [89, 100, 101]. COVID-19 created a precedent demonstrating that drug development and successful clinical trials rest on data-driven decisions that can be adjusted with new evidence [102]. As in silico methodologies

help fill data gaps in preclinical and clinical development, regulatory authorities, namely the FDA, have defined the emerging modelling systems as 'model-informed drug development' (MIDD) [100]. This broad range of digital approaches from statistical predictions to virtual populations is being consolidated as in silico clinical trials, which enable virtual testing of pharmacological therapies and devices [103, 89]. Furthermore, patient-centric trial designs allow for evaluating differences within patient subpopulations and heterogeneous responses to treatment, reducing adverse events [78, 89, 100, 101, 104, 105]. In order to manage multiscale data integration and modelling, adaptive learning principles are also being realised through complex distributed learning architectures designed to support such in silico trial platforms [100]. Notably, this represents an active area of research concerning modern database management systems for dynamic and multimodal data [18, 106–108]. Other examples in this space include a temporal adaptive neural evolutionary algorithm that has been tailored to improve predictive performance in the biomedical internet of things environments [109]. The developed model focuses on cross- domain adaptability with different health conditions, such as respiratory and cardiovascular chronic diseases, where inputs can come from various sources and demographics [109]. Additionally, it has been demonstrated that the merging of AI and mechanistic modelling using neural ordinary equations enables high-fidelity frameworks for designing in silico patients and incorporating complex a priori knowledge about diseases [70, 90, 110]. Our discussed digital twins, physiological and network-centric modelling, in silico trials, and fusion methods of physics-informed AI reveal a new trajectory for deep learning and the potential to bridge drug development with desired clinical outcomes [63, 89]. By drawing insights from real-world testing and early solution implementation, we can outline where the advance- ments are needed and how to best implement next-generation learning.

Adaptive learning: new opportunities for drug discovery and healthcare

Therapy development needs are dictated by the disease preva- lence and the changing population dynamics. Both noncommu- nicable chronic and infectious diseases, by various estimates, are projected to continue to increase in prevalence [111–112, 113]. As a consequence, the ability to deliver new preventative and therapeutic solutions will only grow in importance. In this section, we explore several case examples to showcase how next- generation methods—adaptive learning and related technological advances—can accelerate therapy discovery and improve our readiness for public health challenges.

In light of climate change, the disease borders are predicted to change, with global health challenges becoming more frequent. As a consequence, we will need to establish comprehensive action plans to tackle disease spread [114, 115]. The COVID-19 pandemic exemplified why we need early warning models for infectious diseases with high spreading potential and why models need to be robust in adapting based not only on historical but also on real-time surveillance data [116, 117]. This necessity for improved monitoring and control prompted the exploration of new models and deep learning architectures to enable a better integration of real-world observations and predictive modelling of diverse,

continuously changing multisource data [116, 118–120]. There- fore, a Multi-Phase Physics-Informed Neural Network (MP—PINN) has been proposed to overcome limitations in current population- based forecasting. This network architecture combines PINNs and compartmental models, such as the Susceptible-Infectious- Recovered (SIR) model, allowing parameters to vary across differ- ent phases [118]. Importantly, these phases are argued to enable better modelling of evolving factors during epidemic waves, which is a feature of adaptive learning. MP-PINN experiments using COVID-19 waves data demonstrated the model's superior per- formance for both short-term and long-term forecasting [116]. Additionally, a recent report shifts the paradigm from determin- istic differential equations to data-driven approaches to analyse malaria transmission dynamics. The new methodology integrates artificial neural networks (ANNs), RNNs, and PINNS for both parameter inference and trajectory prediction from observational data. This hybrid neural architecture is capable of autonomously adapting and learning latent patterns, offering a f lexible and scalable framework for modeling complex epidemiological pro- cesses [121]. As a result, these early applications of adaptive learning highlight the potential for modelling stochastic processes and key areas for future research necessary for effective deploy- ment of experimental systems. Furthermore, novel techniques and insights from epidemic spread simulations have broad appli- cations not only concerning diseases but also for drug use, therapy resistance, addictions, and obesity [122].

Antibiotics are another good case example of why we need network-centric and adaptive approaches since this class of drugs has already faced 'superbug' emergence [123]. Importantly, multidrug resistance to treatment has become one of the major public health threats which, according to World Health Organization (WHO) estimates, causes several million deaths globally every year [123]. As an added challenge, pharma companies are not incentivised to develop new modalities in this clinical space because of the patenting cliff and therapeutic targeting becoming more complex [124]. The latter complication results from the necessity to identify appropriate targets in pathways with enough therapeutic differentiation to avoid new mutations that would ablate efficacy [125]. Promisingly, new deep learning methods capable of adaptively extracting molecular information, using graph-based learning introduced earlier, might help address these challenges. A notable study by Stokes et al., employed a message-passing neural network to predict antibacterial activity that resulted in the discovery of a structurally unique compound among other antibiotics [126]. The novel molecule, Halicin, targeted both bacteria and drug-resistant pathogens with potent bactericidal activity. Based on this research, a follow-up study screened 7500 compounds by employing a GNN model and ensemble learning techniques to identify another antimicrobial compound—Abaucin [127]. These transformative studies have inspired more deep learning- augmented research in the antibiotic space [128]. For example, to overcome certain limitations of existing machine learning-based methods, a multimodal prediction model has been developed by integrating molecular graphs with three types of molecular fingerprints. The attention mechanism is used to assign varying weights, which expands the molecular graph's adaptability and dynamic input learning [129]. AI-integrated knowledge graphs have also been applied to study bacterial enzymology and metabolism, offering new insights for biotechnology and novel bacterial

targets to overcome resistance [130]. In addition, there is a growing number of host-response deep learning studies aimed at predicting infection risk, potential susceptibility, and treatment optimisation by taking advantage of emerging adaptive learning architectures, such as attention mechanisms, recurrent layers, neural ODEs, as well as medical concept embeddings with time- aware attention [114, 131–133]. The discussed adaptive methods highlight that graph or physics-informed models are especially well positioned to deconvolute target networks for antibacterial development. Similarly, these insights can be transferred to noncommunicable diseases.

Chronic diseases -immune and metabolic- and diseases resulting from ageing populations, such as neurodegenerative disorders will also continue to increase the societal burden [134]. Consequently, many discovery programmes are now focused on developing new drugs and therapeutic strategies for these indications [135]. Unfortunately, the discussed therapeutic areas have neither quantifiable phenotypic assays, well-established disease biomarkers nor predictive animal models. For example, lack of suitable end points in neuroscience limits the chain of translatability from in vitro to the preclinical stage [12, 136]. Thus, the development of therapeutic intervention for Alzheimer's disease (ad) has been extremely challenging and in recent years has become more controversial, following a number of Phase 3 failures [12, 137]. A recent study marks a shift from conventional approaches with the development of a novel deep learning model named 3D-CNN-VSwinFormer that leverages several adaptive learning methods [138]. The model consists of a 3D CNN that combines a 3D Convolutional Block Attention Module (3D CBAM) and a fine-tuned Video Swin Transformer [82]. 3D-CBAM integrates two submodules for channel and spatial attention. Specifically, the 3D channel attention module helps to learn and apply weights to the corresponding feature maps, allowing the network to f lexibly focus on the channels that carry useful content [139]. The 3D Spatial attention module enables learning of weights for spatial positions [140]. As a result, utilising the relationships between feature channels and spatial positions allows the generation of attention maps. These adaptive approaches improve the network's performance and learning capacity [82]. The study used extracted features from subject-level 3D Magnetic resonance imaging (MRI) data, achieving accuracy and Area Under the Curve (AUC) of 92.92% and 0.9660, respectively. In contrast to other studies on ad, the model demonstrated superior results with the improved efficiency of ad diagnosis [82]. The attention mechanism employed here exemplifies the potential of adaptive algorithms where CBAM has consistently delivered performance enhancements [82, 141]. While the clinical utility of dynamically adjusting architectures offers many advantages, we need to expand the research focus and incorporate more biomarkers to better address the pathophysiology of ad and other similar indications.

Other recent examples in the metabolic disease area also high- light that despite a strong mechanistic rationale, not accounting for the disease interactome and lacking a full understanding of on/off-target dynamics leads to expensive clinical trial fail- ures. This is exemplified by clinical studies focused on increasing high-density lipoprotein cholesterol (HDL-C) since higher levels had been associated with lower risk of atherosclerosis [142]. The main therapeutic mechanism was thought to be mediated by cholesteryl ester transfer

protein (CETP) reducing plasma HDL- C levels [143, 144]. Nevertheless, this target-centric perspective did not translate into efficacious drugs, as demonstrated by a series of clinical studies with multiple Phase 3 failures [12, 145, 146]. One in particular led to ~$800 million lost in the devel- opment of torcetrapib – the first CETP inhibitor [12, 147]. These limitations in studying metabolic diseases and clinical failures have motivated recent efforts to leverage advanced deep learning techniques with embedded adaptivity for a more holistic view of metabolome and associated targets, potentially addressing long- standing hurdles in drug discovery, like those encountered with statin and lipid-lowering therapies. An illustrative example is a study that evaluated different GNN architectures: graph convolutional network (GCN), graph isomorphism network (GIN), and graph attention network (GAT) —to predict the function of novel metabolites based on their structures [148]. Study authors devel- oped a hybrid model with Chemical BiDirectional Encoder Rep- resentations from Transformers (ChemBERTa) embeddings and GAT to identify function-associated structural patterns within metabolite families, enabling interpretable prediction of metabolite functions [148]. Other studies also demonstrated the value of hybrid attention models by combining f lux balance analysis (FBA) and GAT to predict metabolic phenotypes [149]. Hence, a move toward these new modeling approaches, that incorporate adaptive learning elements, could help investigate different metabolite action for next-generation CETP therapies or better understand- ing physiological effects of HDL-C. Moreover, metabolic mod- elling shares many objectives, such as turnover of signalling molecules or genetic cross-decency, with immune processes and regulation.

The necessity of both forward and backward data propagation in clinical settings becomes especially evident when considering other clinical trials for chronic immune diseases. For example, the discrepancies across Phase 2 and Phase 3 patient populations were key determinants for the discontinuation of the Crohn's disease clinical programme after assessing Phase 3 trial results for mongersen, an antisense oligonucleotide for SMAD7 degradation [12, 150]. This well-documented clinical trial failure served as a critical catalyst for acknowledging methodological discrepancies and initiating the search for more innovative solutions [151, 152]. Thus, incorporating sex and population-based differences in drug development, clinical trials, and therapeutic strategies is explored via digital twin applications and in silico clinical trials to increase real-world trial success [104, 105, 151, 152]. One promising application is the forecasting of pharmacokinetics (PK) for individual patients, where sex-specific variables are integrated to predict different outcomes in dosing regimens. Notably, the neural ODE model allowed accurate PK modelling and predicting untested treatment regimens. This was the first study that employed an adaptive model for PK modeling [153]. In parallel, digital patient twins are tested to establish a digital–mechanistic connection—linking device outputs to computational models— for adaptive, continuous learning and predictive modelling by incorporating gender-sensitive factors and patient-specific biomarkers to enhance clinical decision effectiveness [106, 154]. Although progress has been made, the application of deep learning to characterise inter-individual variability in clinical pharmacology is still in its early stages and will require broader validation [152, 155]. Our discussed cases accentuate the need for adaptive feedback loops and self-tuning models to continuously capture new inputs and adjust based

on changes in screening and clinical testing. Nevertheless, more extensive field validation is required to advance adaptive computational tools and frameworks, partic- ularly through the refinement and evolution of deep learning architectures. Such strategies will offer novel approaches ensuring that drug discovery targets and clinical trial endpoints are more objective for the studied populations.

Conclusion

Despite the expansive development in the AI field, we note that the future progress in R&D and clinical applications will hinge on adaptive learning so that variability or certain limitations in data can be compensated, and more complex self-guided architectures can emerge. That is to say, intricate networks, namely genetic, metabolic, pharmacokinetic, and drug interaction, will require more holistic integration in order to bring therapeutic value to the patients. As we saw, there are reasons to be optimistic (Fig. 1)— from early realisations of adaptive learning to more complex applications, such as digital twins, LNNs, hybrid models, and in silico trials—solutions are emerging that provide researchers, clin- icians, and patients with useful tools. We would also like to draw attention to the fact that all advancements need to be incorpo- rated into regulatory frameworks to ensure analytical rigour and product safety. As past examples demonstrate, overlooking early signals can lead to unanticipated harm to patients [156]. Tracing through important analytical and mechanistic breakthroughs, we can conclude that unifying the information f low in a reciprocal manner across research and therapeutic application areas, such as pharmacology, systems biology, deep learning, causal inference, simulation approaches, and patient monitoring, will allow us to advance analytical frameworks that adapt based on the data – leading to adaptive learning.

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