frontiers | Frontiers in Drug Discovery

TYPE Perspective
PUBLISHED 04 October 2022
DOI 10.3389/fddsv.2022.1019706

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to In silico Methods and Artificial Intelligence for Drug Discovery,
a section of the journal
Frontiers in Drug Discovery

RECEIVED 15 August 2022
ACCEPTED 14 September 2022
PUBLISHED 04 October 2022

CITATION
DiNuzzo M (2022), How artificial intelligence enables modeling and simulation of biological networks to accelerate drug discovery.
Front. Drug. Discov. 2:1019706.
doi: 10.3389/fddsv.2022.1019706

How artificial intelligence enables modeling and simulation of biological networks to accelerate drug discovery

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The pharmaceutical industry suffered a significant decline of innovation in the last few decades, whose simple reason is complex biology. Artificial intelligence (AI) promises to make the entire drug discovery and development process more efficient. Here I consider the potential benefits of using AI to deepen our mechanistic understanding of disease by leveraging data and knowledge for modeling and simulation of genome-scale biological networks. I outline recent developments that are moving the field forward and I identify several overarching challenges for advancing the state of the art towards the successful integration of AI with modeling and simulation in drug discovery.

KEYWORDS

modeling and simulation, biological networks, systems biology, drug discovery, artificial intelligence

1 Introduction

The worldwide spending on pharmaceuticals (i.e., prescription drug sales) hit US 1.3 trillion in 2020 and is forecast to reach US 1.7 trillion by 2026 at a compound annual grow rate (CAGR) in the range 3–6% (IQVIA, 2021). Pharma companies invest on average 15% of their revenues in R&D, which is about five-fold more than the public expenditure, a trend that has run unchanged over the last 30 years (Prokop and Michelson, 2012). Nonetheless, the last 2 decades have seen a clear deterioration in productivity, with an approximately 50% reduction in peak sales per asset and a >80% decrease in return of investment (ROI) for the pharmaceutical industry during the years 2010–2019 (Hay et al., 2014; Steedman and Taylor, 2020). While the Covid-19 pandemic somewhat mitigated these figures, the cost of developing a new drug and bringing it to the market is still on the rise and it is now estimated at around US 2 billion (i.e., roughly doubled in the last 10 years) (May et al., 2022).

Such decline in innovation is easily explained by the complex, and often hidden, biology of diseases, which makes it difficult to identify and validate biological targets of physiopathological significance (Prokop and Michelson, 2012). Our lack of disease understanding is a major reason for the high failure rate of clinical trials, which stands at about 90% (but possibly underestimated by the successful development of "me-too" drugs) (Kola and Landis, 2004). Indeed, most drugs fail as a result of low efficacy

(45–65% of cases) or high toxicity (15–35% of cases), and seldom because of strategic, commercial, or operative reasons (Harrison, 2016; Takebe et al., 2018; Dowden and Munro, 2019). Clinical trials have even occasionally had serious adverse effects on trial participants, including death or severe injuries like hepatotoxicity (e.g., fialuridine) or multi-organ failure (e.g., TGN 1412, BIA 10–2474) (Institute et al., 1995; Attarwala, 2010; Peck et al., 2022). Additional complications are sometimes due to unforeseen side effects of drugs already on the market that have therefore to be recalled for safety issues.

Given the recent advances in computational biology and bioinformatics, it seems a particularly good time to seek support from modeling and simulation, i.e., carry out virtual experiments using digital copies of human cells, tissues, and/or organ systems, especially when *in vitro* or animal models are notoriously unpredictive of human biology [for example, see (Booth et al., 2003)]. The ability to predict clinical efficacy and toxicity *in silico* can indeed be a time- and cost-effective solution for the pharmaceutical industry, thus empowering sponsors to take go/no-go decision earlier in the drug discovery and development process (Pritchard et al., 2003). Gaining information about a drug's effects (including mechanism of action, biological targets, network interactions, and so on) is likewise important for small and medium-sized biotech companies as they are largely reliant on venture capital funding and are often unable to generate sufficient efficacy and toxicity data to avoid failures happening further down the line (Roberts, 2018).

2 Target-based vs. phenotypic drug discovery

Target-based drug discovery (TDD) is a top-down approach where the desired target is known (i.e., a protein thought to be relevant for a disease) and compounds are screened against their interaction with the target. Conversely, phenotypic drug discovery (PDD) is a bottom-up approach where the desired phenotype is known (i.e., healthy condition readouts) and compounds are screened against replication of the phenotype. Both approaches have the generation of chemical compounds as their endpoint, yet they are characterized by one profound difference. While TDD requires only the biological target for drug screening, PDD requires a full biological system, like cultured cells, animal models, or human subjects/patients. Such difference is very likely the reason for why *in silico* applications have found their main success in TDD. For example, computer-aided drug design (CADD) uses a variety of techniques, including quantitative structure-activity relationship (QSAR), molecular docking, ADMET (absorption, distribution, metabolism, excretion, toxicity), which can predict drug-target binding using feature descriptors, e.g., physicochemical properties (Jiménez-Luna et al., 2020; Jiménez-Luna et al., 2021; Paul et al., 2021; Galati et al., 2022; Göller et al., 2022; Jia and Gao, 2022; Mamada et al., 2022). Similarly, approaches based on artificial intelligence (AI) have been very successful in drug design, where generative models for *in silico* screening (for example, generative adversarial neural networks, GANNs) are capable of sampling the chemical space at an incredible pace compared with physics-based simulation such as molecular dynamics (Díaz et al., 2019; Prykhodko et al., 2019; Tong et al., 2021a; Blanchard et al., 2021; Gaudelet et al., 2021; Abbasi et al., 2022). On the other hand, our level of insight into the biological complexity of disease has been thus far deemed as insufficient for a fruitful *in silico* PDD approach.

Strategies for TDD are very popular due to their cost-effectiveness compared with PDD approaches, yet they carry the risk of having an incomplete preclinical validation and a lot of false positives. The problem is that the generation of a promising lead compound that successfully interact with a target does not immediately translate into the expected biological outcomes, because many targets are disease-associated (which is relatively easy to identify) but not disease-modifying [for example, see (Florez, 2017)]. In addition, many drugs, including most of the commercialized medicines, are pleiotropic (i.e., they interact with more than one target) and thereby interfere with several cellular processes including signal transduction, receptor-mediated signaling, and metabolic homeostasis. The ensuing changes in cell biochemistry stimulate feedback and feedforward loops acting either to amplify or suppress the activity of specific biological pathways within very complex networks. As a consequence, the final net biological outcome cannot be inferred from the individual effect of the drug on a given target. The relatively low relevance of target-specific effects is evidenced by the fact that for up to 20% of currently approved drugs the biological targets and mechanisms of action are actually unknown (Moffat et al., 2017).

The multiple interactions between drugs and biological targets might well underlie unwanted side-effects, but often they also contribute to therapeutical efficacy (Vincent et al., 2022). In particular, even mild modulation of several targets simultaneously can be much more efficient than strong modulation of a single target. This notion forms the basis of post-hoc polypharmacology (i.e., multi-target drug discovery and combination therapy), which illustrates the idea that it is not the target that should be treated, but rather the state of the biological network (van Hasselt and Iyengar, 2019). Arguably, there is an increasing demand on achieving a mechanistic understanding of biological targets that takes into account the fact that such targets are immersed in intricate networks and pathways often spanning multiple cell types (Arrell and Terzic, 2010; Benson, 2015). Given the high complexity and redundancy of biological networks, predicting how perturbing multiple targets affects cell biology, possibly at distinct points in space and time, requires the development of computational tools that are capable of capturing the holistic nature of living systems (Pujol et al.,

2010; Rai et al., 2018). Specifically, in order to link TDD and PDD it is necessary that such computational tools implements target deconvolution, i.e., the identification of the biological targets that are responsible for a specific drug-induced phenotypic response (Hughes et al., 2021). Attempts in this direction have recently employed AI and static interaction networks [reviewed by (Cuperlovic-Culf, 2018; Zampieri et al., 2019)], e.g., compound-protein and phenotype-protein interactions (Iwata et al., 2020). However, as discussed below PDD and target deconvolution would greatly benefit from the integration of AI with dynamical modeling and simulation of genome-scale biological networks. Accordingly, cheminformatics, *in silico* target prediction, as well as pathway network analysis are thought to be critical tools along with the advancements in experimental drug target deconvolution (e.g., chemical proteomics) [reviewed by Hughes et al. (2021)]. This argument is especially important for multiple or non-protein biological targets, where computational methods provide prioritized recommendations for subsequent *in vitro* and *in vivo* experiments for target identification and validation (Leon and Markel, 2006).

3 Artificial intelligence in biological modeling and simulation

3.1 Overview

Systems biology aims at deciphering the complexity of biological networks based on the formulation and use of mathematical models. In particular, dynamical modeling and simulation investigates the behavior and the relationships between the elements of a particular biological system while it is functioning and responding to perturbations (Ideker et al., 2001). Typically, the dynamics of the biological network is modeled by a set of ordinary differential equations (ODEs) containing balance equations describing the time derivatives of chemical species as well as rate equations describing the velocities and mechanisms of action of chemical processes. The ODE-based approach represents one of the most detailed solutions for time-dependent analysis of biological networks (Tangherloni et al., 2017). However, it requires the knowledge of a large number of initial conditions and kinetic parameters, and until recently only relatively simple biological systems have been analyzed using such approach. Yet, being able to quantitatively interrogate how complex biological networks at the genome-scale (e.g., whole-cell level) respond to perturbations holds great potential for gaining critical insights into the mechanisms of diseases and the relevant therapeutic interventions (Kell and Goodacre, 2014).

Biological networks can be studied at various spatial scales spanning ~10 orders (nm to m) of magnitude (e.g., atomic/molecular, molecular-complexes, sub-cellular, cellular, multi-cellular, tissue, organ, multi-organ, organism) (Sali, 2021). In order to cope with such complexity, multi-scale ODE-based models commonly neglect spatial heterogeneity, for example pools are considered instead of individual molecules, and/or populations instead of individual cells. Even with these simplifications, genome-scale models might still contain up to tens of thousands molecular species and reactions within different cells and cellular compartments, eventually across distinct body organs (Thiele et al., 2020). The interactions between system components are critically dependent on network architecture, or topology, which brings about emergent properties and behaviors so that phenotypic traits arise from the collective action of genes (and conversely, genetic diversity results in a variety of phenotypes). Collective phenomena include steady-state multiplicity (e.g., bistability), hysteresis, oscillations, whose details are outside the scope of this paper [for reviews, see (Goldbeter, 2018; Goldbeter and Yan, 2022)]. As for the relevance in drug discovery, the deterministic nature of ODE-based model simulation has the critical advantage of allowing the study of "emergence" in terms of quantitatively monitoring and analyzing the phenotypic response of the whole biological system to pharmacological, genetic, environmental, or pathophysiological perturbations.

3.2 Model construction

Genome-scale biological network models typically include gene-regulatory, signal transduction, and metabolic pathways. Metabolic models are among the most studied, as metabolism is an exquisite indicator of the homeostatic functional state of the cell and thus it is diagnostic of the patient's disease phenotype (Angione, 2019). Reconstructions of biological network topology have recently advanced to the whole-body level, with genome-scale single-cell networks [e.g., (Brunk et al., 2018)] scaled to multi-cellular/multi-tissue systems (Thiele et al., 2020). Such a process is supported by large community efforts across research disciplines (Singla and White, 2021) that constantly generate petabytes of publicly accessible datasets from high-throughput biological experiments (Camacho et al., 2018). As highly complex multi-omics information (e.g., abundance of genes, proteins, and metabolites) are progressively more available, data-driven AI techniques become increasingly important for efficient model construction, validation and refinement.

Bottom-up biological network reconstruction is an iterative process that requires both well annotated genome sequences and literature-driven manual curation. For example, starting from raw whole genome/exome sequences, similarity-based (e.g., sequence homology or local alignment) and *ab initio* algorithms for gene-finding are used to predict the protein coding regions and the functional sites of genes (Wang et al., 2004; Ghorbani and Karimi, 2015; Chavali and Rhee, 2017). Recently, deep learning has been employed to annotate enzymes

and capture functional difference of enzyme isoforms on the basis of raw sequence data (Li et al., 2018). Additional biochemical information is needed on a protein-specific basis (e.g., substrates and products for enzymes, or phosphorylation state for receptors), which is typically obtained using basic research (Reed et al., 2006). Other machine-learning algorithms predict the cellular localization of proteins from both the amino-acid sequence and high-throughput experimental approaches (Schneider and Fechner, 2004; Nakai et al., 2007). A combination of automatic and manual gap analysis (e.g., due to genome misannotations) is then required to obtain gap-filled biological networks (Karp et al., 2018; Pan and Reed, 2018). Finally, gene-expression profiling *via* transcriptomic data or reference atlases (Lähnemann et al., 2020), possibly with the help of machine learning (ML) (Abdolhosseini et al., 2019), is utilized to prune the biological network in order to generate the single-cell reconstruction (Raškevičius et al., 2018).

The topology of a biological network already containts lots of information. For example, biological network analysis with graph neural networks (GNNs) (Muzio et al., 2020) has been used to predict novel disease-relevant protein-protein and ligand-protein (i.e., drug-target) interactions (Li and Gao, 2019; Zhang et al., 2021). Network inference and graph representations can also be exploited to learn and predict across different types of -omics data (e.g., learn from bulk RNA-seq and predict single-cell RNA-seq) (Hasibi and Michoel, 2021). Molecular interpretation of single-cell RNA-seq data has been also obtained using knowledge-primed neural networks by matching biological and neural network topology (Fortelny and Bock, 2020).

Biochemical profiling of biological fluids (e.g., serum, urine, sweat) as well as tissue samples/extracts can be employed to determine the extracellular and intracellular pools that serve as initial conditions of the model. In particular, the steady-state concentrations of chemical species (e.g., small molecules) can be estimated using experimental metabolomics, whereas proteomics can be used to confirm gene expression patterns, since changes in mRNA levels often correlate poorly with changes in protein expression (Weston and Hood, 2004). Recently, ML has been applied to chromatographic techniques (e.g., liquid or gas chromatography) coupled to mass spectrometry for the identification of specific (e.g., disease-associated) metabolic pathways (Pirhaji et al., 2016; Toubiana et al., 2019). Processing of proteomic and metabolomic datasets have also been used in combination with systems biology and deep learning to discriminate among different disease phenotypes (Kopylov et al., 2021). Using ML, metabolite concentrations have been even predicted from proteomic data (Zelezniak et al., 2018) or from network topology-based optimizations (Tepper et al., 2013; Küken et al., 2019). Protein abundance can be also estimated by integrating network models with transcriptomics (Li et al., 2022) or metabolomic (Di Filippo et al., 2022) data.

Experimental fluxomics data can be used to estimate substrate flow rates within the biological networks. Steady-state and isotopically non-stationary flux analysis is typically based on labeling experiments, like metabolite isotopic enrichment studies that employ ^{13}C-NMR spectroscopy (Winter and Krömer, 2013; Niedenführ et al., 2015). In the case of metabolic networks, flux analysis requires the knowledge of the labeling patterns (i.e., atomic transitions) of each chemical reactions. Since fluxomics data is generally very difficult to obtain, predicting fluxes using ML is highly advised. As an illustration, protein levels have recently been used for training artificial neural networks in order to predict glycolytic reaction fluxes (Ajjolli Nagaraja et al., 2019).

Open issues in model construction include the quality of the reconstructed biological networks (eventually including epigenomic data), because many genes have an unknown function and the literature is often ambiguous or incomplete. In this regard, AI can be used to support/validate the prediction of gene network topology starting from a desired biological function (Shen et al., 2021). Another outstanding challenge is the development of automatic and reliable computational methods for the prediction of the baseline values of concentrations and fluxes, something that as discussed necessarily goes along with the improvement of experimental high-throughput methods and availability of transparent high-quality multi-omics data.

3.3 Model simulation

The successful parametrization of biological network models with AI and multi-omics data allows the implementation of ODE-based simulation for the phenotype of interest, thereby revealing mechanisms and pathways that are likely to contribute characterizing drug actions as well as systemwide side-effects (Michelson et al., 2006; Prokop and Michelson, 2012). Model parametrization is a daunting task, but fortunately biological systems do obey multiple constraints, from simple ones (e.g., flux and mass balance) to more complex ones (e.g., genomic stability). For instance, metabolic network models are inherently constrained by reaction stoichiometry and thermodynamics (e.g., Gibbs free energy and Haldane equations) (Chen et al., 2016; Kiparissides and Hatzimanikatis, 2017). Biological constraints make the corresponding high-dimensional mathematical problems amenable to physics-informed neural networks (PINNs) (Raissi et al., 2019; Karniadakis et al., 2021). Embedding physics into ML is particularly relevant for incorporating incomplete or noisy data in complex models and obtain reliable predictions that can be used to e.g., solve prohibitively expensive inverse problems such as target deconvolution. Accordingly, model parameter estimation has

been enhanced by incorporating the system of ODEs into deep fully connected neural networks (Yazdani et al., 2020; Daneker et al., 2022). In particular, loss functions for ML methods can be formulated on the basis of specific simulation outputs that depend on model equations. Notably, systems biology-informed AI can be used to select among different reaction kinetic schemes (e.g., mass-balance, S-systems, log-linear/lin-log, Michaelis-Menten, generalized Hill, convenience, modular) according to the available mechanistic knowledge, experimental datasets, and desired level of details (Du et al., 2016; Kim et al., 2018). Several approaches combining deep learning with GNNs or GANNs have been recently used to fully parametrize ODE-based genome-scale metabolic models in terms of Michaelis-Menten affinity constants (Choudhury et al., 2022) or enzyme turnover numbers (Li et al., 2021), respectively. Bayesian meta-modeling is another systems biology-based approach that uses different mathematical representations, scales, and levels of granularity from prior models in order to simulate cell activity (Raveh et al., 2021). In addition, using ML some aspects of the system's dynamics can be learned from time-series data whenever these are available (Costello and Martin, 2018).

Due to the high cost and difficulty underlying the experimental determination of kinetic information, ODE-based systems are often underdetermined (e.g., the number of variables is greater than the number of known parameters). The increasing availability of useful curated data notwithstanding, at the moment the sole viable solution to the underdetermination problem is to step up the number of different parametrizations of the same system. Statistical approaches [e.g., (Liepe et al., 2014; Valderrama-Bahamóndez and Fröhlich, 2019)] can be used to obtain good coverage of the parameters space in independent realizations that can thus be numerically solved in parallel (i.e., using ensemble solving). Massively parallel resolution is also beneficial for parameter estimation procedures as well as for neural networks training in surrogate modeling (Renardy et al., 2018; Engel et al., 2019; Vanhaelen, 2022). Recent developments in graphics processing unit (GPU)-accelerated ODE solvers allows investigating large-scale models of complex biological systems at reduced computational costs [for example, see (Tangherloni et al. (2017)].

Overall, stoichiometric, thermodynamic, and kinetic information can be extracted from multi-omics data (Caudai et al., 2021) and processed to enable the generation of ODE-based genome-scale biological network models, a methodology that so far has been limited to simple organisms for applications in metabolic engineering and synthetic biology (Karr et al., 2012; Chakrabarti et al., 2013; Almquist et al., 2014; Srinivasan et al., 2015; Miskovic et al., 2019; St. John et al., 2019). However, modeling and simulation of human cells and tissues promises to enhance our understanding of therapeutical and/or toxicological endpoints in drug discovery by quantitatively uncovering the behavior of many molecular species (proteins, enzymes, receptors, small molecules) that we normally do not have access to in experimental settings. The critical contribution of AI to biological modeling and simulation is the adaptive nature of the algorithms to newly generated data and knowledge, which dynamically affects the probability of performing certain operations rather than others. Embedding biological principles into AI-based approaches will strongly facilitate the computational manipulation of biological networks and the association of phenotypes to targets (i.e., target deconvolution). *In silico* drug target deconvolution based on modeling and simulation of genome-scale biological networks is a large combinatorial problem. Deep reinforcement learning (DRL) is a very powerful AI technique that presents unique opportunities to map the high-dimensional states underlying the dynamic behavior of ODE-based systems onto appropriate physics-informed actions, e.g., the allowed set of perturbations that result in the most favourable outcome in the long term (Pawar and Maulik, 2021).

4 Conclusion and outlook

The integration of the predictive power of AI (statistical) with the mechanistic understanding of modeling and simulation (deterministic) is expected to give a substantial contribution to the pharmaceutical industry. In particular, convergence of data-driven and theoretical approaches is an important step to complete the data-model-data cycle that is necessary to solve the problem of parameter estimation and elucidate biological system structure, mechanisms, and dynamics (Wang et al., 2018). AI-enabled modeling and simulation are promising tools to improve data interpretation and distinguish between changes that are caused by a disease from those that cause the disease. Next-generation systems biology will undoubtedly benefit from AI methods capable of converting multi-omics data at different scales into actionable knowledge (Nielsen, 2017; Angione, 2019), especially considering the expected advances in data collection from patients (e.g., biosensors for measuring the concentration of chemical species from body fluids) (Jin et al., 2020; Bhave et al., 2021; Phatak et al., 2021). In turn, personalized datasets are poised to substantially enhance the ability of AI for parametrizing quantitative systems pharmacology (QSP) models that combine systems biology with pharmacokinetics and pharmacodynamics (PK/PD) in order to find optimized therapeutics for individual patients or populations with a given disease [for example, see (McEwen et al., 2021)]. Put in perspective, patient-specific biological network models will form the basis for the construction of medical digital twins (or "virtual patients") [(An and Cockrell, 2022) and references therein]. Genomic data, such as single nucleotide polymorphisms (SNPs), can be incorporated into genome-scale biological network models in terms of enzyme/receptor kinetic parameters (e.g., protein expression/abundance, substrate affinity, reaction or pathway

velocity) (Yamada et al., 2001; Jamshidi et al., 2002; Jamshidi and Palsson, 2006). Accordingly, systems biology and ML can be used (for instance, within genome-wide association studies) to discover SNP-disease association and possibly map individual genetic variations to personalized models (Reilly et al., 2013; Ho et al., 2019; Tong et al., 2021b; Mieth et al., 2021; Foguet et al., 2022).

Overall, the AI-enabled computational framework for the analysis of biological networks is anticipated to play a major role in improving drug target identification and validation, qualify any potentially associated side-effect, identify efficacy and toxicity biomarkers, and help with hypothesis generation, optimal experimental design, as well as testing for disease understanding and identification of disease biomarkers (risk, presence, or treatment selection) (Mardinoglu et al., 2014; Zielinski et al., 2015; Raškevičius et al., 2018; Gu et al., 2019; Turanli et al., 2019; Bintener et al., 2020; Gatto et al., 2020; Proffitt et al., 2022). All these aspects are necessary to support the decision-making process of pharmaceutical companies towards de-risking and ultimately accelerating the time-to-market of new effective and safe medicines for patients.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MD was employed by Netabolics SRL.

Publisher's note

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