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Invited Perspective

Molecular mechanism matters: Benefits of mechanistic computational models for drug development

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ABSTRACT

Making drug development a more efficient and cost-effective process will have a transformative effect on human health. A key, yet underutilized, tool to aid in this transformation is mechanistic computational modeling. By incorporating decades of hard-won prior knowledge of molecular interactions, cellular signaling, and cellular behavior, mechanistic models can achieve a level of predictiveness that is not feasible using solely empirical characterization of drug pharmacodynamics. These models can integrate diverse types of data from cell culture and animal experiments, including high-throughput systems biology experiments, and translate the results into the context of human disease. This provides a framework for identification of new drug targets, measurable biomarkers for drug action in target tissues, and patient populations for which a drug is likely to be effective or ineffective. Additionally, mechanistic models are valuable in virtual screening of new therapeutic strategies, such as gene or cell therapy and tissue regeneration, identifying the key requirements for these approaches to succeed in a heterogeneous patient population. These capabilities, which are distinct from and complementary to those of existing drug development strategies, demonstrate the opportunity to improve success rates in the drug development pipeline through the use of mechanistic computational models.

1. Current strategies for drug development

It is well established that traditional drug development is a long and increasingly costly process, due in large part to high attrition of drugs throughout the development pipeline [1,2]. As of 2010, the estimated cost to develop a single new molecular entity (novel active ingredient) was $1.8 billion dollars [3]. In addition, only about 5–6 mechanistically innovative (first-in-class) drugs are approved in the US per year [3,4]. The most common reasons for drug failure, particularly in Phase 2 trials, are lack of efficacy and toxicity due to off-target drug effects, which were not apparent in cellular and animal systems [5–7]. A better understanding of potential drug targets and mechanisms of action promises to aid in earlier identification of ineffective drugs, or drugs with unsafe off-target effects, as well as to inform the necessary properties (e.g. precise targets and binding affinities) for more effective compounds.

Traditionally, drug efficacy and safety are assayed by characterizing the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. PK describes what the body does to a drug (e.g. drug absorption, clearance, and distribution throughout the body), while PD characterizes what a drug does to the body (i.e. drug action in target tissue). Drug PK and PD are typically estimated using a combination of cell culture and animal models, along with human data for similar, previously developed drugs. This empirical PK and PD characterization allows drug developers to estimate drug half-life in the body and uptake within tissues. Computational models incorporating both PK and PD (PK/PD models) are used to simulate drug distribution in the body, predicting the time delay from administration to drug action in the target tissue, and potential issues such as drug accumulation leading to toxicity. As such, these simulations have the potential to aid in establishing safety margins [8]. While PK/PD work is a critical component of drug development, traditional PK/PD studies do not identify the most effective targets for new drugs, or account for complex biological compensation mechanisms. This lack of predictiveness is a result of the data-driven nature of these studies, which makes extrapolation to other dosing ranges or to related drugs, as well as prediction of patient-specific

Abbreviations: ECM, extracellular matrix; PAD, peripheral arterial disease; PD, pharmacodynamics; PK, pharmacokinetics; VEGF, vascular endothelial growth factor.

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Box 1: What is a mechanistic computational model?
A *mechanistic computational model* simulates interactions between the key molecular entities (e.g. proteins, ATP, RNA), and the processes they undergo (e.g. expression, subcellular trafficking, degradation, phosphorylation, deactivation), explicitly by solving a set of mathematical equations that represent the underlying chemical reactions (e.g. $[A] + [B] \rightleftarrows [A \cdot B]$). The *key distinguishing feature* of a mechanistic model is incorporation of detail *based on prior knowledge* of the regulatory network, as opposed to inferring interactions using a data-driven approach.

responses, difficult. The missing piece is a detailed understanding of the molecular mechanisms of action underlying pharmacodynamic responses. Mechanistic models (Box 1) can incorporate this understanding into PK/PD models.

The sequencing of the human genome brought hope that newly identified genetic components of health and disease would clearly guide advances in therapies for a wide variety of conditions. While bioinformatics approaches have identified new therapeutic targets for some diseases, in many cases there is no clear disease-associated genetic signature that is consistent across patients. Even when a disease-related molecule is identified, it does not necessarily represent an effective drug target; thus far, target-based screening has not been more effective than traditional phenotypic drug screening [9]. As such, many researchers interested in drug development have turned to systems biology, which combines high-throughput experiments and mechanistic computational modeling to better understand the interactions of the molecules that regulate cell behavior.

Systems biology approaches have deepened our understanding of the pathways involved in cellular survival and behavior, and how cellular signaling changes in disease [10]. One particularly valuable benefit of mechanistic computational models is their ability to incorporate the specifics of different experimental protocols (e.g. drug/ligand concentration, measurement time, cell line), allowing for reconciliation of apparent discrepancies in experimental results from different groups, protocols, or cell types. Along with deriving more insight from experimental results, these models can be used to design the next sets of experiments, in order to answer key unsolved questions. A second key strength of mechanistic computational models is the ability to examine the sensitivity of individual signaling pathway components to perturbation (e.g. change in receptor expression or ligand concentration). Proteins to which the model is highly sensitive likely represent key nodes and promising drug targets. Despite these advantages, translation of systems biology into the context of the human body for use in the drug development pipeline has been limited [5,11], due in part to the prevalence of empirical PK/PD modeling in industry, while mechanistic computational modeling occurs primarily in academic research laboratories (with some notable exceptions).

The emerging field of systems pharmacology aims to bridge systems biology and PK/PD modeling, translating the mechanistic insight emerging from systems biology into a therapeutically relevant context [12,13]. To do this, mechanistic models (Box 1) are used to describe the pharmacodynamics in quantitative detail, and are integrated with drug pharmacokinetics in a PK/PD model. Several excellent examples of systems pharmacology models incorporating mechanistic intracellular signaling detail have been published in recent years [12,14,15]. However, such models remain the minority; it is more common for drug pharmacodynamics to be represented by empirical drug-tissue binding curves (e.g. Hill equation) [16,17]. While useful, such data-driven binding curves have limited ability to reliably extrapolate to other species, to humans with different genetics and body mass, to related drugs, to combination therapies, or even to different dosing schedules and administration routes for the same drug [11]. One reason for a semi-mechanistic representation of PD in many models to date is a lack of sufficient mechanistic information available from experiments. While this is a challenge, the amount of useful information increases quickly, e.g. due to high-throughput experiments using new molecular imaging and gene expression measurement techniques [18–20]. Additionally, because computational models can integrate diverse data types into a single framework, data from experiments designed for very different purposes, or obtained from different groups using different protocols, can be leveraged [21]. For example, in our PK/PD models, the geometric parameters for the PK component are obtained from histological studies, while the PD are based on a combination of binding assays, receptor trafficking studies, and measurements of receptor phosphorylation under different conditions, from experiments performed in multiple cells lines by different research groups [22,23].

One of the areas where systems pharmacology holds the most promise is in accounting for changes in PK and PD between animal models and humans, both due to geometric differences, and to species-specific genes and gene expression patterns (Fig. 1) [13]. Detailed systems pharmacology models can be built and validated using in vitro data and pharmacokinetic studies in animals, and then converted into human- and disease-specific models [10,24]. In order for these models to make clinically relevant predictions, they must then be validated against human data to the maximum extent possible. While human data is limited, levels of drug and other biomarkers in plasma can be measured with relative ease. Mechanistically detailed systems pharmacology models can then connect predictions of important but difficult-to-measure quantities, such as drug concentration, occupancy of receptors with drug versus native ligand, and cellular signaling at the target site, to measurable biomarkers [10]. By providing a window into the site of disease, these models have great promise to improve our understanding of both disease and therapy in the human body.

In light of the capabilities of mechanistic computational models (Box 2), we propose that inclusion of detailed mechanistic information into pharmacodynamic models is critical to understand drug PD in an insightful and predictive way. We present three brief examples where inclusion of mechanistic detail was necessary to: (1) meaningfully discriminate between effective and ineffective drugs, (2) identify promising new drug targets, or (3) understand why existing therapeutic approaches have been ineffective. We chose case studies that focus on mechanistic modeling of receptors and channels, as they are subject to complex regulation, but provide targets more specific than downstream signaling pathways, which are common to many cellular processes. These examples involve different biological systems, highlight different advantages of mechanistic models, and use different techniques to translate the mechanistic insight into the human body. All, however, demonstrate the promise of mechanistic computational models to aid in drug development for a wide range of diseases (Box 2).

2. Case study 1: drug discrimination for cardiac arrhythmia

A promising application for mechanistic computational models is to perform virtual drug screening, eliminating candidate drugs that appear to work in single-cell systems, but have emergent properties in the context of human physiology that may result in adverse effects. The multi-scale mechanistic computational models built by Colleen Clancy and collaborators to compare anti-arrhythmia drugs, both in the context of a single cell and within tissues, provide an elegant example. Cardiac arrhythmia is a complex condition involving the (dis)coordinated electrical