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Current Opinion in Pharmacology

In silico models in drug development: where we are

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The use and utility of computational models in drug development has significantly grown in the last decades, fostered by the availability of high throughput datasets and new data analysis strategies. These *in silico* approaches are demonstrating their ability to generate reliable predictions as well as new knowledge on the mode of action of drugs and the mechanisms underlying their side effects, altogether helping to reduce the costs of drug development. The aim of this review is to provide a panorama of developments in the field in the last two years.

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Current Opinion in Pharmacology 2018, **42**:111–121

This review comes from a themed issue on **New technologies**

Edited by **Antoine Bril**, **Oliver Nosjean** and **Patrick Genissel**

https://doi.org/10.1016/j.coph.2018.08.007

Introduction

Quantitative Systems Pharmacology (QSP) is a relatively new discipline that combines systems biology approaches with methods of quantitative pharmacology [1]. The combination of computational and experimental methods via QSP approaches provides a systems level understanding of the mechanism of action of drugs while leveraging on the accumulated data on approved or failed drugs. In a similar way, Quantitative Systems Toxicology (QST), emerged as new paradigm for toxicity assessment [2], focuses on understanding the adverse effects of drugs, from molecular alterations to phenotypic observations, by integrating computational and experimental methods [3]. QST merges methods of classic toxicology with systems biology modeling and quantitative measurements of molecular and functional changes occurring upon drug treatment at different levels of biological organization (cell, tissue, organ, organism) [2]. QST approaches have proven useful to optimize dose and schedule drug regimens, potentially minimizing costly phase I/II clinical trials [4,5]. By integrating *in vitro* cell toxicity data with multiscale *in silico* modeling of drug exposure, QST models could become an efficient tool to assess and predict drug toxicity [3]. Moreover, a better understanding of biological responses to drugs will reduce uncertainties in species extrapolations, and allow the prediction of treatment responses considering the patient genetic variability or pre-existing diseases.

The present review is focused on presenting and discussing the recent advancements in computational methods used in QSP and QST, which support three crucial aspects of the drug development process: firstly, the understanding and prediction of drug pharmacokinetics, secondly, the understanding and prediction of drug toxicity, and thirdly, the translational perspective of the preclinical assessment.

Physiologically based pharmacokinetic models

Physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling has become a widely adopted tool in the industry to obtain a quantitative characterization of concentration–time profiles in different organ and tissues across human populations. A recent survey showed that around 70% of pharmaceutical companies use pre-clinical PBPK/PD modeling in all therapeutic areas [6]. The wide adoption of these modeling approaches has been facilitated by the availability of several PBPK commercial platforms [7], and by recommendation of regulatory agencies [8]. The main goal of PBPK modeling is to describe drug absorption, distribution, metabolism and elimination (ADME) within the body. The prediction of drug exposure in plasma but especially in the site of action of the drug is of high pharmacological relevance, because drug concentration in certain body compartments may be difficult or impossible to be experimentally measured [7]. State of the art PBPK/PD models are composed of hundreds of ordinary differential equations (ODEs) describing physiological processes involved in ADME. The parameters in the model are obtained from prior knowledge available in the literature or calculated from specific and carefully validated formulas [7]. Although the primary focus of a PBPK model is on physiological variables, biochemical information is considered for drug transporters and metabolic enzymes, which play a role in drug transport and metabolism.

PBPK models have been used to represent particular disease states or specific patient groups, such as pediatric patients or pregnant women [9] as well as to predict drug-

drug interactions [10–16], food-drug interactions [17–19], drug formulation effects [20,21], cross-species extrapolation [22–24], and constitute key components of multiscale models [25••].

PBPK models can be combined with transcriptomics data to investigate mechanisms of drug toxicity [26•,27] and carcinogenicity [28]. Furthermore, PBPK models can be expanded by adding mechanistic models of gene regulation and signaling pathways. For instance, a PBPK model was coupled with the miRNA-BDNF pathway to study perfluorooctanesulfonic acid induced neurotoxicity [29]. In another study, Mason *et al.* combined PK and mechanistic models to estimate the dose and time of ingestion in paracetamol poisoning, using traditional and experimental serum biomarkers in mice [30•].

Although PBPK models are widely used for the prediction of ADME, other types of modeling approaches are required to gain insight on the mode of action of compounds, especially at the cellular level.

Toxicogenomics data analysis

The use of transcriptomics to characterize the cell response to a particular compound is widely applied in both QSP and QST. DNA microarray technologies have allowed monitoring the changes of the expression levels of thousands of genes simultaneously after the exposure to a given drug, setting the foundations for the field of toxicogenomics. The most popular resources for toxicogenomics are summarized in Box 1. One of the challenges in the field is how to translate changes in gene expression into actionable information for understanding the biological mechanism of toxicity of drugs. To address this challenge, several approaches have been proposed, including the analysis of gene signatures, gene set enrichment analysis, and gene co-expression networks.

Box 1 Glossary of terms or abbreviations

ADME: drug absorption, distribution, metabolism and elimination

DILI: Drug-Induced Liver Injury

DTNI: Dose-Time Network Identification

ILP: Integer Linear Programming

GEO: Gene Expression Omnibus

GSEA: Gene Set Enrichment Analysis

GSMN: Genome Scale Metabolic Networks

ODE: Ordinary Differential Equations

ORd: O'Hara–Rudy dynamic cardiac ventricular model

PBPK/PD: Physiologically based pharmacokinetic/pharmacodynamics

QSP: Quantitative Systems Pharmacology

QST: Quantitative Systems Toxicology

WGCNA: Weighted Gene Co-expression Network Analysis

Gene signature analysis

Gene signatures analysis aims at obtaining a minimal list of genes that can be used to predict the toxic response to a compound. The underlying assumption is that compounds with similar mechanisms of action will have similar gene expression profiles, and that these gene expression profiles can be used to build gene expression signatures predictive of drug toxicity. A variety of methodologies have been proposed to identify these gene signatures. Among them, Connectivity Map-like analysis [31] aims at detecting similarities among gene expression signatures of different compounds using pattern-matching algorithms. This method has been successfully used to group chemicals based on their mode of action [32], to select potential new drug candidates for several cancer types [33], to characterize genes involved in the cell response to different chemicals by means of different features, such as evolution, topological properties in a protein interaction network and disease SNP density [34], and by integrative analysis with chemical structures and drug sensitivity data, to improve drug taxonomy and provide a comprehensive picture of drug-drug relationships [35•].

Another type of methods uses machine-learning techniques to derive the gene signatures. For example, Rempel *et al.* obtained a classifier that allows to separate histone deacetylase inhibitors from mercurials using human embryonic stem cells, thus demonstrating that the system is suitable for toxicant classification [36] and Giordano *et al.* used different machine-learning approaches to derive gene signatures from whole blood gene expression data to predict cigarette smoke exposure in humans [37] (Box 2).

Box 2 Toxicogenomics data resources

One of the most commonly used resources in QSP and QST analysis is open access TG-GATEs database [115]. This resource contains toxicogenomics data for 170 compounds, in human and rat primary hepatocytes, linked to phenotype data and pathology findings. The US Broad Institute Connectivity Map [116,117] contains thousands of gene expression profiles of most FDA approved drugs tested in multiple cell types. It has been used for identifying modes of action and defining biologically similar compounds. The US National Cancer Institute (NCI) 60 tumor cell line screen includes results on GI50 (50% growth inhibition), total growth inhibition (TGI), and LC50 (50% lethal concentration) for many compounds tested in the major Connectivity Map cell lines [118]. The Library of Integrated Network-based Cellular Signatures (LINCS) catalogs how cells respond to different types of perturbations using a variety of assays [119]. The Chemical Effects in Biological Systems (CEBS) database is a toxicology resource containing animal data from the National Toxicology Program (NTP) testing program and other depositors. CEBS currently covers over 8000 studies including carcinogenicity, short-term toxicity and genetic toxicity studies [120].