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Quantitative systems toxicology

Peter Bloomingdale[1], Conrad Housand[2], Joshua F. Apgar[2], Bjorn L. Millard[2], Donald E. Mager[1], John M. Burke[2] and Dhaval K. Shah[1]

Abstract

The overarching goal of modern drug development is to optimize therapeutic benefits while minimizing adverse effects. However, inadequate efficacy and safety concerns remain to be the major causes of drug attrition in clinical development. For the past 80 years, toxicity testing has consisted of evaluating the adverse effects of drugs in animals to predict human health risks. The U.S. Environmental Protection Agency recognized the need to develop innovative toxicity testing strategies and asked the National Research Council to develop a long-range vision and strategy for toxicity testing in the 21st century. The vision aims to reduce the use of animals and drug development costs through the integration of computational modeling and *in vitro* experimental methods that evaluates the perturbation of toxicity-related pathways. Towards this vision, collaborative quantitative systems pharmacology and toxicology modeling endeavors (QSP/QST) have been initiated amongst numerous organizations worldwide. In this article, we discuss how quantitative structure-activity relationship (QSAR), network-based, and pharmacokinetic/pharmacodynamic modeling approaches can be integrated into the framework of QST models. Additionally, we review the application of QST models to predict cardiotoxicity and hepatotoxicity of drugs throughout their development. Cell and organ specific QST models are likely to become an essential component of modern toxicity testing, and provides a solid foundation towards determining individualized therapeutic windows to improve patient safety.

Addresses

[1] Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, The State University of New York at Buffalo, Buffalo, NY, USA

[2] Applied BioMath, LLC, 55 Old Bedford Road, Suite 208, Lincoln, MA 01773, USA

Corresponding authors: Shah, Dhaval K (dshah4@buffalo.edu); Burke, John M (john.burke@appliedbiomath.com)

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1. Introduction

While the origin of systems toxicology lies in studying the cumulative effects of various environmental exposures on human health, there has been a tremendous increase in the application of this approach in the field of medicine. The Food, Drug, and Cosmetic Act (FDCA) passed by Congress in 1938, in response to the 1937 sulfanilamide tragedy where over 100 people died from nephrotoxicity, has set the precedence for the current toxicity testing strategy, which assesses the effects of a drug on animals prior to administration in humans. However, toxicity testing performed in animals is not always translatable to the clinic. For example, the teratogenic effects of thalidomide, which led to over 10,000 cases of birth defects, was not identified in rat toxicity studies [1]. In response to this event, the Kefauver-Harris amendment was made to the FDCA, requiring proof of drug effectiveness and safety. Thus, inaccuracies in preclinical-to-clinical translatability, significant worldwide resource cost, and the sacrifice of millions of animals for toxicity testing, warrants a novel toxicity testing strategy that moves away from traditional animal toxicity testing. In fact, a decade ago, the National Academy of Sciences published a report titled, '*Toxicity Testing in the 21st Century*', which advocated the development of a systems approach to replace current toxicity testing. Accordingly, organ/disease specific quantitative systems toxicology models, which integrate *in vitro* human cell toxicity assays with multi-scale *in silico* modeling of drug exposures, could serve as an efficient tool to assess and predict human toxicity of drug molecules.

Quantitative systems pharmacology (QSP) has been defined as, "an approach to translational medicine that combines computational and experimental methods to elucidate, validate, and apply new pharmacological concepts to the development and use of small molecule and biologic drugs." [2] Here we provide a working definition for quantitative systems toxicology (QST) as an approach to quantitatively understand the toxic effects of a chemical on a living organism, from molecular alterations to phenotypical observations, through the integration of computational and experimental methods. A quantitative understanding of holistic drug effects will allow the distinction between three forms of toxicity, on-

target/on-pathway, on-target/off-pathway, and off-target. Although QST may be considered to be a part of QSP modeling by many, we believe QST will likely find its own niche in the development of organ specific toxicity platforms. With collaborations between academic/non-profit institutions, pharmaceutical industries, and regulatory agencies, current toxicity testing could begin to be replaced with *in silico* modeling, which would be of best interest to all parties. The Comprehensive in Vitro Pro-Arrhythmia (CIPA) and Drug Induced Liver Injury (DILI)-sim initiatives are two such collaborative efforts that aim to improve patient safety, decrease resource expenditure in drug development, and reduce the need for animal toxicity testing through the development of cardiac and hepatic QST models. Although in this chapter we have covered QST modeling in the context of its applications in pharmaceutical sciences, it should be noted that this type of modeling would also be of interest to other fields such as environmental sciences and ecotoxicology. Here, we have discussed the foundation and application of QST models in drug development, along with a discussion of the different mathematical modeling approaches that could be incorporated into QST model development.

2. Modeling approaches in systems toxicology

Several systems toxicology-modeling approaches have been developed to predict the adverse effects of drugs on human health. Here we briefly review QSAR/ADMET, network-based, and PK/PD modeling approaches, since these three are integral in the development of QST models.

2.1. Quantitative structure-activity relationship (QSAR) and ADMET modeling

The history of quantifying toxicity based upon similarities in chemical structure dates back to 1863, where Cross identified that the toxicity of primary aliphatic alcohols to mammals increased as its water solubility decreased [3]. At the end of the 19th century, Meyer and Overton separately showed that the anesthetic potency of narcotics is correlated with their olive oil/water partition coefficient, reflective of increased membrane permeability due to greater lipophilicity [4,5]. In 1937, Hammett formulated the first quantitative relationship between molecular structure and activity to describe electronic effects of organic reactions. The foundation of modern day QSAR has been attributed to Hansch and Fujita. They integrated Hammett's constant (σ) with oil-water partition coefficients, later defined as a hydrophobicity parameter (π), in order to relate the physicochemical properties of phenoxyacetic acids with their plant growth activity [6]. The major advancement in QSAR occurred when it was shown that the concentration required to induce a biological response could correlate with the linear sum of different physicochemical parameters. The ability to make accurate *in silico* predictions of biological, pharmacological, and toxicological activity/properties of a compound, based upon molecular descriptors and physicochemical properties, is the underlying goal of QSAR modeling.

QSAR modeling has served as a useful tool throughout the drug discovery and development process. QSAR modeling has facilitated the discovery and development of new drugs through the ability to screen compounds for activity and favorable drug properties, complementing high throughput screening approaches [7]. QSAR offers the ability to design out unwanted drug properties, such as hERG inhibition and CYP450 modification, which is a powerful application. In terms of QSP/QST modeling, QSAR can be utilized to make initial predictions of parameters when no experimental information is available. QSAR predictions of parameters that relate to the absorption, distribution, metabolism, excretion, and toxicity of a drug is referred to as ADMET modeling. One of the most notable examples, although not quantitative, is Lipinski's rule of five [8]. Due the ability to provide predictions of model parameters in the absence of experimental data, QSAR modeling can provide a bridge backwards for the utilization of QST models in the earliest stages of drug discovery and development.

2.2. Network-based modeling

The study of biology in the context of a system can be traced back to generalized systems theory [9]. The application of network theory in the study of biological systems has gained popularity within the past couple of decades due to the transition from a reductionist viewpoint of biological research back to one that is holistic [10,11]. A holistic viewpoint is one that aims to understand how the integration of molecular events give rise to biological processes across different scales of organization. The surge of interest in systems biology/pharmacology is met with advances in computational methods and software, curated databases, and analytical techniques. Genomics, proteomics, and metabolomics has enabled the generation of large quantities of data, which can be utilized in order to gain a systems-level understanding of biological phenomena through the complex dynamics of subcellular components.

Network models of biological systems, derived from the mathematical formalism of graph theory, aim to describe the complex qualitative relationships between biological components. There are different types of biological networks, which are dependent upon how nodes and edges are defined. Vertices, or nodes, typically represent genes or gene products, such as DNA, RNA, or proteins. Edges between nodes indicates a regulatory interaction. Analysis of network topology through applying measures of connectivity, centrality, and clustering, provides