Challenges and Advances
in Computational Chemistry and Physics 30
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Huixiao Hong *Editor*

Advances in Computational Toxicology

Methodologies and Applications in Regulatory Science

Springer

Challenges and Advances in Computational Chemistry and Physics

Volume 30

Series Editor

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Huixiao Hong
Editor

Advances in Computational Toxicology

Methodologies and Applications in Regulatory Science

Springer

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Foreword

Given the ever-increasing panoply of human and animal drugs, food products, and environmental chemicals, the need for science-based risk/safety regulation is greater than ever. From a pharmaceutical perspective, accurate and effective toxicity evaluation is critical in several areas such as dose–response characteristics including organ exposure and first-in-human dosages, reproductive and carcinogenicity toxicity, exposure assessment, and biological pathway characterization. Food product assessment requires understanding of gastrointestinal delivery, metabolic breakdown into metabolites, context of use, and dietary exposures. Lastly, environmental toxicity necessitates system-level approaches considering chemical mixtures and chemical transport into target organs in multiple species. Despite these extensive efforts, idiosyncratic toxicities can occur, suggesting the need for personalized toxicity approaches.

Conventional approaches along with some new methodologies like "organ-or-a-chip" have been developed to address key questions in this area. Many of these approaches are limited in cost, time, translational accuracy, and scalability. Consequently, scientific endeavors in the computational space have inspired new and powerful tools, ushering in the era of computational toxicology. This exciting field facilitates the paradigm shift from bench-based toxicology to the computational assessment and will provide regulators globally with the benefit of fast, accurate, and low-cost methods to supplement conventional toxicity assessment. Moreover, integrative predictive approaches may enhance personalized toxicological prediction to prevent idiosyncratic events.

To inform not only regulators around the world but also key stakeholders, industry, and academic trainees, this textbook provides a deep dive into computational toxicological approaches needed to advance toxicological regulation through research. It includes sections outlining theory, methods, applications, as well as tangible examples and covers development through implementation. Information in this book will apprise the reader with a greater understanding of computer-based toxicological predictive capabilities. Information in this book will also enable the reader to develop their own cutting-edge computational strategy to address a toxicological question of interest. The provided information may also

foster collaboration by providing inspiration for scientific discourse among readers with diverse training backgrounds.

Currently, computational toxicology has gained acceptance as an "alternative" testing method compared to traditional approaches for rapid toxicity assessment. The toxicology community of scientists and regulators look forward to the validation of computational methods that may supplement and, in some cases, replace traditional assays. The contents of this textbook, inspired by new computational methods and approaches, provides a comprehensive overview of the representative methodologies in the land of computational toxicology with an emphasis on regulatory science research.

Jefferson, AR, USA

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Preface

In comparison with the field of toxicology which dates back to ancient civilizations, the field of computer science is just coming of age. After many years of focused development, computational tools, methods, hardware, and knowledge have advanced enough to be of utility in other fields. Computational techniques are now employed in toxicology for regulatory, research, and development purposes. We compiled this book with the ambition to capture the latest advancements at the intersection of computer science and toxicology together in one location.

Our motivation in creating this book was twofold. First of all, the number of new chemical entities being developed by the ever-growing pharmaceutical, biotechnology, and food industry is dizzying. Absolutely all of these products must be screened for safety at various stages of development. Secondly, the ecosystem of our planet is increasingly bathed in an assortment of molecules, many of which nature has never experienced before. The surge of new molecules and entities entering the human body and the environment presents an insurmountable challenge to traditional toxicology. Impressively, the novel computational toxicology methods described herein are rising to meet the challenge.

Machine learning, artificial intelligence, quantitative structure–activity relationship (QSAR), bioinformatics, genomics, proteomics, molecular dynamics, and more are described via examples of applications to toxicology. Both safety evaluation and risk assessment are topics of consideration across multiple chapters. A background introduction followed by details is provided for computational toxicology methods, as well as applications. Toxicology from the perspective of medicines, food products, and the environment is described in multiple chapters.

This book is intended as a text for established computer scientists looking to enter the toxicology field, experienced toxicologists seeking to enable research through computational methods, or students and trainees curious about stepping into the field. Thus, this book includes not only introductory sections to help readers become familiar with new concepts but also detailed actionable methods which can be deployed by the reader. Each chapter of this book can stand alone to update the reader on a specific topic of interest. Alternatively, this textbook can be read in sections as chapters that are roughly organized in topical order. For a graduate

course on computational toxicology, this book would provide excellent reading material. Studying the entire book will provide the reader with not only a broad but also a deep understanding of the field.

While this book does focus on computational toxicology, it does not contain any learning exercises, quizzes, or snippets of computer code for the reader to advance and test knowledge. In the case of the classroom setting, these materials would be left to the course instructor. Moreover, herein we do not review basic toxicology concepts as they are effectively covered by other established bodies of work. We would be appreciative of any corrections, feedback, comments, or criticism from readers on how to improve for a future body of work.

Inspired by how computational toxicology is rising to meet the challenges currently facing traditional toxicology methods, we put forth this book for the community as an educational tool. The broad scope and deep depth of this textbook would not be possible without the herculean efforts of and tremendous cooperation from the authors, for which we are tremendously appreciative. This book also would not have been possible without the support and vision of Springer, who we acknowledge for having a visionary understanding of the importance of the topic at hand.

This preface reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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Chapter 1
Computational Toxicology Promotes Regulatory Science

Rebecca Kusko and Huixiao Hong

Abstract New tools have become available to researchers and regulators including genomics, transcriptomics, proteomics, machine learning, artificial intelligence, molecular dynamics, bioinformatics, systems biology, and other advanced techniques. These new advanced approaches originated elsewhere but over time have perfused into the toxicology field, enabling more efficient risk assessment and safety evaluation. While traditional toxicological methods remain in full swing, the continuing increase in the number of chemicals introduced into the environment requires new toxicological methods for regulatory science that can overcome the shortcoming of traditional toxicological methods. Computational toxicology is a new toxicological method which is much faster and cheaper than traditional methods. A variety of methods have been developed in computational toxicology and some have been adopted in regulatory science. This book summarizes some methods in computational toxicology and reviews multiple applications in regulatory science, indicating that computational toxicology promotes regulatory science.

Keywords Computational toxicology · Regulatory science · Risk assessment · Safety evaluation · Chemicals

Abbreviations

3D	Three dimensional
AI	Artificial intelligence

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CYP	Cytochrome P450 enzyme
DA	Department of Agriculture
DILI	Drug-induced liver injury
EDC	Endocrine disrupting chemical
EDSP	Endocrine disruptor screening program
EPA	Environment Protection Agency
FDA	Food and Drug Administration
ML	Machine learning
MD	Molecular dynamics
MDDT	Medical Device Development Tools
MOA	Mechanism of Action
MoA	Mode of Action
NCATS	National Center for Advancing Translational Sciences
NIEHS	National Institute of Environmental Health Sciences
NN	Neural Networks
POD	Point of Departure
QSAR	Quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
TsTKB	Target-specific Toxicity Knowledgebase
US	United States

1.1 Computational Toxicology

Toxicology as a broad field seeks to predict and eliminate substances which may cause a living body harm, including pharmaceuticals, natural products, food products, and environmental substances. Toxicology has been performed since the ancient Greeks and Chinese [1]. It is currently a major field of study around the world. The study of toxicology is of importance not only to governmental regulatory agencies, but also to the pharmaceutical/biotech industry, the veterinary industry, food manufacturers, and academics. Toxicology also spans many sub-disciplines as it must consider the entire path of a potential toxicant, including exposure, absorption, distribution, metabolism, excretion, as well as interactions with cellular machinery throughout this entire pathway (Fig. 1.1). Pinpointing the exact mechanism or mode of toxicity as a potential toxicant interacts with a living organism is paramount. Adding to an already complex system, nearly any known substance can be toxic at a high enough exposure. Moreover, toxicity is dependent on an array of other factors including organism size, species, age, sex, genetics, diet, combination with other chemicals, overall health, and/or environmental context.

Toxicological methods can be classed into experimental and computational [2]. Experimental methods consist of two types: in vivo and in vitro experiments indicated by the blue arrows in Fig. 1.1. Traditional experiments in toxicology are conducted on non-human animals such and mice and rats [3]. Though in vivo experiments are generally treated as the gold standard method in toxicological studies and remain as

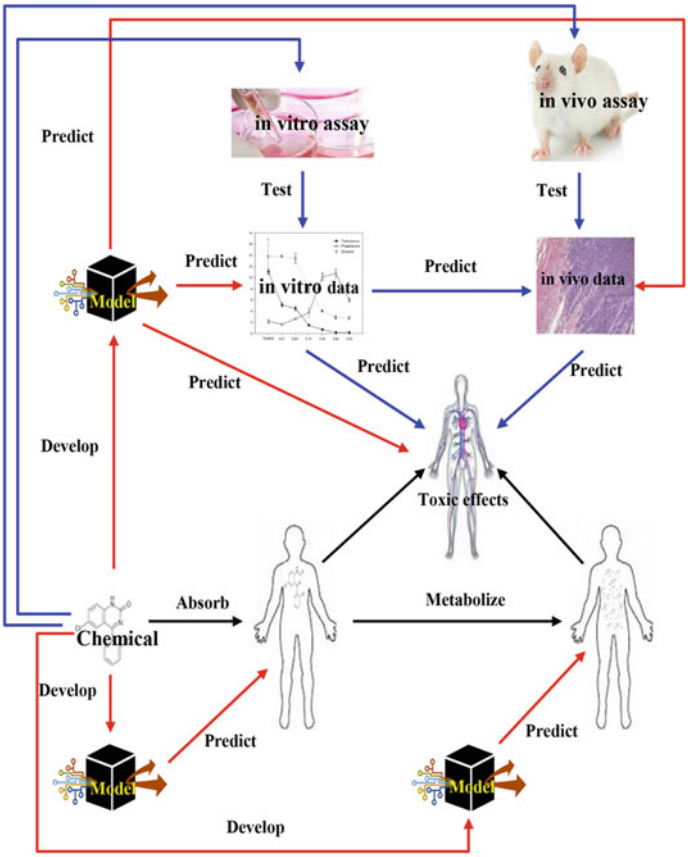

Fig. 1.1 Predictive toxicology schematic. A potential route of a toxicant is represented as black arrows. In vivo and in vitro toxicology as well as connections between components are represented as blue arrows. Computational toxicology's key role is represented as red arrows. Arrows are labeled by actions that achieve the arrow targets

a major approach of estimating human effects of substances, ethical, economic, and technical concerns on use of animals make toxicologists search for alternative testing methods [4–6]. Computational toxicology, an emerging component in toxicology, is an alternative method where computational methods are used to understand and predict toxicological effects of substances in the environment such as drugs, food, and environmental chemicals [7–9]. Many computational methods have been developed for predicting absorption, metabolism of chemicals, estimating in vitro and in vivo experimental data, and assessing human risk solely based on chemical structures as illustrated by the red arrows in Fig. 1.1 [10–17].

Given impressive advances recently in computing power as well as developments in advanced computational algorithms, many toxicologists are now reaching out to computer science to enable prediction of toxicological effects or outcomes. Thus,

the intersection of computer science and toxicology is what we here call "Computational Toxicology." Computational toxicology integrates both the long-standing computational methods and the newer approaches including neural networks (NNs) and artificial intelligence (AI). Rather than individual scientists and researchers trying to understand multiple complex phenomena via bench experiments, these complex biological systems can now be modeled and predicted in the computational space. Issues which may have previously seemed impossible or intractable are increasingly becoming solvable due to the scalability of computational toxicology.

1.2 Domain of Computational Toxicology

Safe drugs, safe food products, and a safe environment for living organisms are of concern in all countries around the world. Toxicology leadership usually stems from governmental regulatory agencies, in the USA including the FDA (Food and Drug Administration), EPA (Environment Protection Agency), DA (Department of Agriculture), NCATS (National Center for Advancing Translational Sciences), NIEHS (National Institute of Environmental Health Sciences) and others. These regulatory agencies are responsible for maintaining the health and well-being of a population and actively seek to prevent any exposures to toxic chemicals. Additionally, the pharmaceutical and biotechnology industry strive to improve patient lives by bringing both new and generic medicines to the market and must do so while minimizing harm to human life. Safety and toxicity screening is critical throughout the steps of any drug development program, starting from the preclinical stage, during clinical trials, and even in post-market surveillance. For the food and agriculture industry, safety screening is also a key step in establishing safe exposure levels to new additives or pesticides. Academics, while rarely developing a product for commercial purposes, do seek to create and test toxicity screens and also assess toxicity mechanism of action (MOA) or mode of action (MoA). This textbook emphasizes the methods of computational toxicology and their potential applications in regulatory science, but the topic is clearly relevant across sectors and around the world.

1.3 Need for Computational Toxicology

The field of computational toxicology has been blooming due to the fundamental limitations of experimental toxicology. While a dizzying array of novel chemical matter is being created every day, traditional experiments are bottlenecked by throughput and cost. In other words, the need for fast toxicity screening and prediction is ever increasing and traditional in vivo and in vitro approaches cannot keep pace. Moreover, there is a global push to avoid the use of animals for experimental testing. Traditional approaches are also limited in the number of doses, time points, organ systems, and combinations that can possibly be tested sanely in one experiment or laboratory.

When using research to guide toxicology regulation, reproducible and rigorous analysis are absolutely required. Bench experiments often have many variables which are difficult to control, including variations in technician, machinery, laboratories, reagent lots, reagent age, or other protocol subtleties. Advances in computer science offer not only faster experiments, but also more reproducible ones. For example, a computational analysis can be exactly repeated by an independent scientist provided that the raw data is available, code is captured in a publicly available source such as GitHub and the compute environment is dockerized. The ease of sharing experiments not only allows computational toxicology to be more rigorous and reproducible, but fosters collaboration between researchers as protocols are readily shared.

1.4 Methods in Computational Toxicology

Many computational techniques, including the ones originated from other fields such as computational chemistry and pure computer science, have been developed and applied in toxicology. To summarize, this book solicited chapters to review some popular methods in computational toxicology that can be used to assess risk, evaluate safety, and/or predict toxicology of a drug or other substance.

Chapter 2 introduced the modeling framework of computational toxicology, defined its scope, listed the major tasks, reviewed the methods, and discussed the challenges in computational toxicology.

Structural alerts and quantitative structure–activity relationship (QSAR) models are two of the most popular methods for predicting toxicological activity of chemicals, especially for the simple toxicological endpoints [18, 19]. Chapter 3 reviewed the applications of structural alerts and QSAR models in computational toxicology and summarized some lessons learned from some successful models. It also discussed some challenges such as making negative predictions, moving to quantitative predictions and weight of evidence approaches.

Emerging technologies such as next-generation sequencing enable fast generation of huge amounts of data. Computational analysis is challenging and crucial to extract knowledge from such big data [20]. Machine learning algorithms have been developed and applied in computational toxicology for prediction of unexpected, toxic effects of chemicals. Moreover, computer science has enabled computational prediction to scale to supermassive sizes. For example, the field of machine learning has birthed matrix and tensor factorization. These two approaches have been used to analyze $>2.5 \times 108$ data points spanning 1300 compounds. It would be absolutely impossible to analyze such a dataset in a simple traditional program such as Microsoft Excel! Chapter 4 reviewed the recent progresses in machine learning-based computational methods and tools and further detailed matrix and tensor factorization approaches.

One feature of modern science is diverse data for a specific scientific question such as specific risk of chemicals to humans and the environment. Thus, integrating diverse data sources from toxicological research to extract more consistent and

reliable knowledge than that provided by any individual data source for risk assessment of chemicals attracts attention of computational toxicologists [21]. Network analysis-based algorithms have been developed for analyzing such large, diverse, and sparse data in computational toxicology [22, 23]. To shed insight into this new method, Chap. 5 presented a network-based systems pharmacology approach that integrates the networks of proteins, genes, drug target, and the human protein–protein interactome for assessing the risk of drug-induced cardiotoxicity in humans.

MoA is the functional or anatomical change caused by chemicals, at the cellular level or at the molecular level that is often used as mechanism of action [24]. It is important knowledge for understanding toxicology of chemicals when the molecular target of chemicals has not yet been determined. It can be used to guide development of predictive models in computational toxicology. Chapter 6 introduced a MoA-guided novel computational toxicology approach that is based on molecular modeling and is implemented in the target-specific toxicity knowledgebase (TsTKb) that contains a pre-categorized database of MoA for chemicals and provides pre-built and category-specific predictive models.

Predictive models in computational toxicology are often developed based on many molecular descriptors using different machine algorithms [25]. One of the key steps in development is to select important descriptors. Chapter 7 discussed different methods for removal of redundant and irrelevant molecular descriptors to improve the performance and interpretability of the model. The strengths and shortcomings of some feature selection and extraction methods in current computational toxicology practices were summarized.

Genomics is the study of genomes, including all molecules such as DNA and RNA and their structures and functions. Adverse effect of a chemical could be caused by the interactions between the chemical and the target genome such as human genome, such is the scope of toxicogenomics [26]. Toxicogenomics has been widely applied in current toxicology practices. A database spanning disciplines of toxicogenomics is the DrugMatrix, which includes gene expression of some 600 therapeutics at multiple doses and 96 signatures relating to phenotypes. Chapter 8 gave a comprehensive description of a legacy resource of toxicogenomics, DrugMatrix and its automated toxicogenomics reporting system, the largest molecular toxicology reference database and informatics systems, which contains thousands of gene expression datasets generated using different microarray platforms.

Given the increasing prevalence of toxicogenomics resources such as the DrugMatrix database, a methodology known as pair ranking was developed to compare transferability between the systems used for testing. Chapter 9 introduced the pair ranking (PRank) method that is developed for quantitative evaluation of assay transferability between the different toxicogenomics platforms.

Several computational toxicology approaches have emerged as a hybrid with computational chemistry. For example, molecular dynamics (MD) simulation was originally used in chemistry to detail interactions between chemicals and biological molecules (including DNA and proteins). For computational toxicologists, MD simulation allows for surveillance of potential fluctuations or conformational changes that a chemical might induce on a biomolecule [27]. Chapter 10 reviewed available

software tools for MD simulations and the challenges to apply these software tools to computational toxicology and summarized key protocols to run MD simulations.

The applicability domain of a prediction model is defined as the structural space that is covered by the chemicals of the training set. It is expected that the predictions from the model for new compounds within the structural space are more accurate than the predictions of chemicals out of the space. Analysis of applicability domains in computational toxicology is important for assessing QSAR models [28]. Chapter 11 reviewed different perspectives of the applicability domain and the existing methods for analysis of applicability domain. It also formalized a holistic approach for utilization of the applicability domain in computational toxicology.

1.5 Potential Applications of Computational Toxicology in Regulatory Science

Computational toxicology has been accepted in the regulation of products. One of the examples is the International Council for Harmonisation M7 (ICH M7) guideline that describes the assessment of carcinogenic risk of mutagenic impurities in drug products [29]. This indicates the state of the art of a computational toxicology method and is the milestone for regulatory acceptance of computational toxicology for pharmaceutical products [30, 31]. In the USA, the FDA accepted QSAR modeling results for impurities in applications of drug products. The FDA developed the Medical Device Development Tools (MDDT) program to qualify tools that can be used in evaluation of medical devices [32]. In the newly released FDA' predictive toxicology roadmap, computational toxicology is listed as one of the new technologies might be able to address some of the needs in regulatory science [33]. The EPA's Endocrine Disruptor Screening Program (EDSP) in the twenty-first century is using computational toxicology, coupling with in vitro methodologies, to prioritize and identify EDSP Tier 1 information needs for pesticide active ingredients that will be included in the registration review program [34]. In Europe, read-across, a commonly used computational toxicology method, is adopted for data gap filling in registrations submitted under the REACH regulation [35]. Computational toxicology is gaining attention in chemical risk assessment and management in China [36]. This book's solicited chapters shed lights on examples of potential applications of computational toxicology in regulatory science in USA, Europe, and China.

In terms of consumer food safety, toxicokinetics, QSAR modeling, and bioinformatics approaches are currently in use. Over time, certainly many more approaches will be added to screen for toxic food products. Chapter 12 reviewed quantitative structure–activity relationships, toxicokinetic modeling and simulation, and bioinformatics in the FDA's Center for Food Safety and Applied Nutrition in-house food ingredient knowledgebase to show the scientific utility of computational toxicology for improving regulatory review efficiency.

In the space of drug development, log regression analysis has predicted drug-induced liver injury, which has proven challenging for both the pharmaceutical industry and regulators. Chapter 13 briefed the drug-induced liver injury (DILI) research efforts at the National Center for Toxicological Research (NCTR), FDA, including drug-label-based-approach to annotate the DILI risk associated with individual drugs including a series of models developed to assess the potential of DILI risk.

Alternative methods including computational toxicology have been considered to inform regulation of drugs, foods, and environmental chemicals. Spanning all three of these fields, a collaborative project across US governmental agencies known as Tox21 screened 10 k chemicals against a large panel of cell-based assays in a quantitative high-throughput screen [37]. Chapter 14 described the efforts to build in vivo toxicity prediction models based on the Tox21 in vitro activity profiles of compounds and discussed the limitations of the current data and strategies for selection of optimal assays to improve the performance of the developed models. The Tox21 project served as powerful fuel for computational predictive modeling across many projects and institutions including predicting point of departure (POD). Chapter 15 reviewed common data modeling approaches that use gene expression profiles to estimate the PODs and compared with the PODs determined using Tox21 data.

From an environmental perspective, endocrine disrupting chemicals (EDCs) are of grave concern and the MOA has been effectively detailed by target-based molecular modeling methods. Computational toxicology methods are an essential and powerful tool to elucidate the MOA of endocrine disruptors. Chapter 16 reviewed the critical processes to perform the molecular modeling of EDCs, including preparation of three-dimensional (3D) structures of the biomacromolecules and EDCs, generation and optimization of the structures of EDC–biomacromolecule complexes, and investigation of the underlying interaction mechanism.

The metabolism of xenobiotics by cytochrome P450 enzymes (CYPs) represents an important mechanism for in vivo compound processing via environmental exposure. Density functional theory (DFT) calculations have been used to highlight the underpinnings of the mechanisms of various environmental toxicants by CYPs including brominated flame retardants. Chapter 17 reviewed the recent progress in molecular simulations of xenobiotic metabolism catalyzed by the typical phase I enzyme CYPs.

Computational toxicology methods including QSAR and read-across are gaining acceptance in regulatory science in the USA, Europe, and Japan [38]. To facilitate the applications of computational toxicology in regulatory science, tools for utilization of QSAR models and read-across have been developed. Chapter 18 introduced a tool (VEGA) that was designed to reduce the barriers between the different read-across and QSAR models for the evaluation of specific chemicals for the assessment of populations of substances. VEGA provides multiple tools for different purposes.

Rigorous and reproducible in silico workflows are needed for toxicological databases and analysis to be successful. OpenTox is stepping in to fill this gap. OpenTox advocates the establishment of good practice and guidance for tracking computational toxicology models to enhance reproducibility, a very important parameter for acceptance of the computational models in regulatory science. Chapter 19 dis-