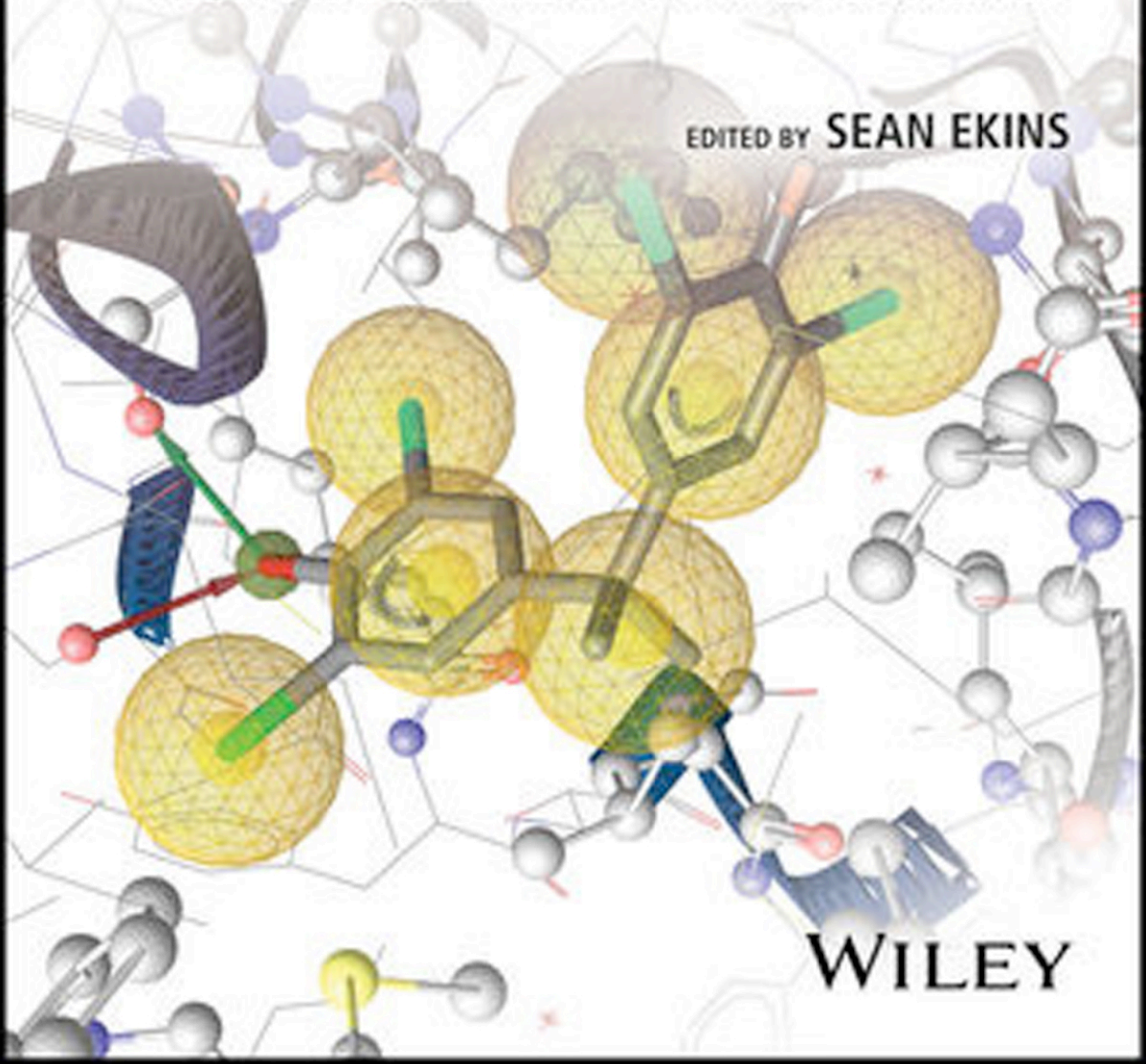
Wiley Series on Technologies for the Pharmaceutical Industry

Sean Ekins, Series Editor

COMPUTATIONAL TOXICOLOGY

RISK ASSESSMENT FOR CHEMICALS

EDITED BY SEAN EKINS



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Computational Toxicology: Risk Assessment for Chemicals
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Computational Toxicology

Risk Assessment for Chemicals

Edited by

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I should have no objection to go over the same life from its beginning to the end: requesting only the advantage authors have, of correcting in a second edition the faults of the first.

Benjamin Franklin

To my family and collaborators.

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Preface

Since the publication of *Computational Toxicology: Risk Assessment for Pharmaceutical and Environmental Chemicals* in 2007 a lot has happened both in the career of the editor and in science in general. For one, my focus has expanded towards many computational applications to drug discovery rather than solely focused on ADME/Tox. I have also garnered new collaborators some of whom have very graciously agreed to contribute to this volume. Science is changing. Publishing may be adjusting slowly too. This book will likely be read as much on mobile devices or computers as in physical hard copies. Computational toxicology has also evolved in the past decade with the dramatic increase in public data availability. There have also been a number of more collaborative projects in Europe around toxicology (e.g. e-Tox and OpenTox), in addition we have seen a growth in open computational tools and model sharing (QSAR toolbox, Chembench, CDD, Bioclipse etc.). Groups like the EPA have developed and expanded ToxCast which represents a valuable resource for toxicology modeling. We are now therefore in the age of truly Big Data compared with a decade ago and there have been several efforts to combine different types of data for toxicology. To round this off, the growth in nanotechnology has seen the emergence of computational nanotoxicology which would not have been predicted my earlier book.

This book is therefore aimed at this next generation of computational toxicology scientist, comprehensively discussing the state-of-the-art of currently available molecular-modelling tools and the role of these in testing strategies for different types of toxicity. The overall role of these computational approaches in addressing environmental and occupational toxicity is also covered. These chapters before you aim to describe topics in an accessible manner especially for those who are not experts in the field. My goal with this book was to not cover too much of the same ground as the earlier book because much of what we published then is still generally valid, but to make the book focused on newer topics. I hope this book also serves to introduce some of the younger scientists from around the world who will likely drive this next generation of computational toxicology for many years to come. Finally, I hope this book inspires scientists to pursue computational toxicology so that it continues to expand across different industries from pharmaceutical to consumer products and its importance increases, as it has over the past decade.

Sean Ekins
November 12, 2017 Fuquay Varina, NC, USA

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Part I

Computational Methods

1

Accessible Machine Learning Approaches for Toxicology

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CHAPTER MENU

1.1 Introduction

Computational approaches have in recent years played an increasingly important role in the drug discovery process within large pharmaceutical firms. Virtual screening of compounds using ligand-based and structure-based methods to predict potency enables more efficient utilization of high throughput screening (HTS) resources, by enriching the set of compounds physically screened with those more likely to yield hits [1–4]. Computation of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties exploiting statistical techniques greatly reduces the number of expensive assays that must be performed, now making it practical to consider these factors very early in the discovery process to minimize late-stage failures of potent lead compounds that are not drug-like [5–11]. Large pharma have successfully

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integrated these *in silico* methods into operational practice, validated them, and then realized their benefits, because these firms have (i) expensive commercial software to build models, (ii) large, diverse proprietary datasets based on consistent experimental protocols to train and test the models, and (iii) staff with extensive computational and medicinal chemistry expertise to run the models and interpret the results. Drug discovery efforts centered in universities, foundations, government laboratories, and small biotechnology companies, however, generally lack these three critical resources and, as a result, have yet to exploit the full benefits of *in silico* methods. For close to a decade, we have aimed to used machine learning approaches and have evaluated how we could circumvent these limitations so that others can benefit from current and emerging best industry practices.

The current practice in pharma is to integrate *in silico* predictions into a combined workflow together with *in vitro* assays to find "hits" that can then be reconfirmed and optimized [12]. The incremental cost of a virtual screen is minimal, and the savings compared with a physical screen are magnified if the compound would also need to be synthesized rather than purchased from a vendor. Imagine if the blind hit rate against some library is 1%, and the *in silico* model can pre-filter the library to give an experimental hit rate of 2%, then significant resources are freed up to focus on other promising regions of chemical property space [13]. Our past pharmaceuticals collaborations [14, 15] have suggested that computational approaches are critical to making drug discovery more efficient.

The relatively high cost of *in vivo* and *in vitro* screening of ADME and toxicity properties of molecules has motivated our efforts to develop *in silico* methods to filter and select a subset of compounds for testing. By relying on very large, internally consistent datasets, large pharma has succeeded in developing highly predictive proprietary models [5–8]. At Pfizer (and probably other companies), for example, many of these models (e.g., those that predict the volume of distribution, aqueous kinetic solubility, acid dissociation constant, and distribution coefficient) [5–8, 16] are believed (according to discussions with scientists) to be so accurate that they have essentially put experimental assays out of business. In most other cases, large pharma perform experimental assays for a small fraction of compounds of interest to augment or validate their computational models. Efforts by smaller pharma and academia have not been as successful, largely because they have, by necessity, drawn upon much smaller datasets and, in a few cases, tried to combine them [11, 17–22]. However, this is changing rapidly, and public datasets in PubChem, ChEMBL, Collaborative Drug Discovery (CDD) and elsewhere are becoming available for ADME/Tox properties. For example, the CDD public database has >100 public datasets that can be used to generate community-based models, including extensive neglected infectious disease structure–activity relationship (SAR) datasets (malaria, tuberculosis, Chagas disease, etc.), and ADMEdata.com datasets that are broadly applicable to many projects. Recent efforts with them have led to a platform that enables drug discovery projects to benefit from open source machine learning algorithms and descriptors in a secure environment, which allows models to be shared with collaborators or made accessible to the community.

In the area of pharmaceutical research and development and specifically that of cheminformatics, there are many machine learning methods, such as support vector machines (SVM), *k*-nearest neighbors, naïve Bayesian, and decision trees, [23] which have seen increasing use as our datasets, have grown to become "big data" [24–27]. These methods [23] can be used for binary classification, multiple classes, or continuous data. In more recent years, the biological data amassed from HTS and high content screens has called for different tools to be used that can account for some of the issues with this bigger data [26]. Many of these resulting machine learning models can also be implemented on a mobile phone [28, 29].

1.2 Bayesian Models

Our machine learning experience over a decade [14, 30–46] has focused on Bayesian approaches (Figure 1.1). Bayesian models classify data as active or inactive on the basis of user-defined thresholds using a simple probabilistic classification model based on Bayes' theorem. We initially used the Bayesian modeling software within the Pipeline Pilot and Discovery Studio (BIOVIA) with many ADME/Tox and drug discovery datasets. Most of these models have used molecular function class fingerprints of maximum diameter 6 and several other simple descriptors [47, 48]. The models were internally validated through the generation of receiver operator characteristic (ROC) plots. We have also compared single- and dual-event Bayesian models utilizing published screening data [49, 50]. As an example, the single-event models use only whole-cell antitubercular activity, either at a single compound concentration or as a dose–response IC_{50} or IC_{90} (amount of compound inhibiting 50% or 90% of growth, respectively), while the dual-event models also use a selectivity index ($SI = CC_{50}/IC_{90}$, where CC_{50} is the compound concentration that is cytotoxic and inhibits 50% of the growth of Vero cells). While single-event models [13, 51, 52] are widely published, dual-event models [53] attempt to predict active compounds with acceptable relative activity against the pathogen (in this case, *Mtb*), versus the model mammalian cell line (e.g., Vero cells). Our models identified 4–10 times more active compounds than random screening did and the models also had relatively high hit rates, for example, 14% [54], 71% (Figure 1.1) [53], or intermediate [55] for *Mtb*. Recent machine learning work on Chagas disease has identified *in vivo* active compounds [56], one of which is an approved antimalarial in Europe. Most recently, we