molecular pharmaceutics

editorial

In Silico Pharmaceutical Property Prediction

It is hardly a secret that pharmaceutical research and development is being transformed at a fundamental level in response to increasing demands for important new products in an increasingly difficult drug discovery environment. Much of the focus is on the application of new technologies to speed all of the components of the process. Automated parallel medicinal chemistry enabling the synthesis of at least an order of magnitude more compounds in the same time frame that it took to synthesize a single analogue is ably supported by automated high throughput biology. Compound tracking and distribution technologies now enable both, and automated data capture and analysis is standard in the industry. The resulting increase in speed and efficiency of the drug discovery process has created demands for new drug design technologies. In parallel, an appreciation for the reasons underlying the failure of drug candidates has created demand for new methods to determine risks based on intrinsic properties of compounds.

In silico prediction of basic properties of molecules is a well-established practice. In many pharmaceutical R&D enterprises, cLogP calculations have been institutionalized within cheminformatics databases and are now well-accepted as reliable predictors of potential issues relating to pharmaceutical and pharmacokinetic properties, and are one of the four properties that in aggregate comprise the basis for Lipinski's rules. By applying computed properties such as cLogP to analogue design, chemists are now able to predict physicochemical issues and focus precious chemistry and biology resources on synthesis candidates with more drug-like properties. However, despite the fact that cLogP methodologies have been in use for over three decades, computational prediction of other important properties such as solubility and pK_a has lagged behind because until recently the available methods were deemed to be too unreliable.

In this issue, we hope to illustrate the present state of the computational sciences relating to the prediction of pharmaceutical properties from a molecular structure. In keeping with the scope of *Molecular Pharmaceutics*, we focused on papers which address the most important molecular properties to pharmaceutics: solubility, pK_a, and stability. Recent advances in the prediction of solubility are the subject of contributions by Johnson et al. and Zhang et al. Johnson describes an empirical computational model for aqueous solubility that consists of a multivariate QSAR model for the intrinsic solubility, the ionization using a predicted pK_a, and the effects of crystal packing through molecular dynamics simulations. Zhang describes a novel approach to the generation of an individually tailored "local" training set for predicting the solubility of an individual compound wherein contributors to the training set are selected from a global database of compounds with experimentally determined solubilities on the basis of their similarity to the structure of interest.

As important as solubility is to the biopharmaceutical behavior of a compound, perhaps equally important is the ionization state of the molecule. Since the great majority of drugs possess one or more ionizable functionalities, prospective knowledge of this attribute would also enable more sophisticated and accurate assessment of a compound's pharmaceutical properties. Lee et al. apply an established methodology for prediction of physical properties and chemical reactivities of molecules to the prediction of pK_a values for drugs and drug candidates, appropriately treating ionization as a reversible chemical reaction. Narazaki et al. describe a new method which capitalizes on knowledge about the ionization properties of a drug to predict the extent to which a compound in solution may precipitate from solution after being injected into a buffer with different pH. This tool is intended to enable the prediction of compounds which may precipitate out of solution after administration by injection into biofluids, and to facilitate the design of formulations which would be predicted to keep the compound in solution for maximum therapeutic benefit.

Two contributions present some recent new thinking about the prediction and use of the property of lipophilicity. Schroeter et al. describe the modeling of the lipophilicity using the Gaussian process on large public and in-house data. The model provides not only the prediction but also the domain applicability and the prediction confidence. Bhal et al. present an adapted Rule of 5 using log *D* instead of log *P* as a more pharmaceutically representative measure of lipophilic character. Finally, we are pleased to include a contribution by Pole et al. which describes DELPHI, an expert system for the prediction of chemical degradation of drug substances, including prediction of likely degradant products by finding relevant degradation pathways.

One consistent attribute of all of the contributions to this special topic issue on in silico pharmaceutical property prediction is the requirement for a simple two-dimensional structure as the only input. It must be acknowledged that medium- to high-throughput methods are now well-estab-

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lished for the measurement of kinetic solubility, pK_a, log *D*, and log *P*, with throughputs in the range of a few hundred compounds per week for a well-equipped laboratory. However, the costs of establishing and operating a facility to support these methods is substantial, and such services consume substantial amounts of compound: much more than are needed for most in vitro biological screening. We hope that the contents of this special topic issue on in silico pharmaceutical property prediction will illustrate the potential for new computational tools and techniques as reliable low-cost alternatives to experimental data as enablers of more efficient and effective drug discovery.

Pil H. Lee
Guest Editor
Pfizer Research and Development, 2800 Plymouth Road, Ann Arbor, Michigan 48105
E-mail: pilhlee@gmail.com

Michael F. Rafferty
Guest Editor
10325 South Greentree Court, Olathe, Kansas 66061
E-mail: raffe01@mac.com

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