Journal of Medicinal Chemistry

Editorial

pubs.acs.org/jmc

Advances in Computational Medicinal Chemistry: A Reflection on the Evolution of the Field and Perspective Going Forward

We are pleased to introduce the Special Issue "*Computational Methods for Medicinal Chemistry*", which was envisioned to showcase computational approaches with particular relevance and utility for medicinal chemistry.

Back in the early 1990s, when purple-frilled reptiles lounged in lazy splendor in Jurassic jungles, the evolution of computation in medicinal chemistry was open to question. Whereas many companies had computational chemistry groups, their integration with the central chemistry enterprise was thin, and their main contribution was often restricted to pretty pictures. Academically, though techniques like free energy perturbation and structure-based docking had had a few precocious successes, most medicinal chemistry remained anchored in empiricism and synthesis. Structure-based "rational" drug design, having overpromised during the 1980s, was suffering through an inevitable crash.

Over the past quarter century, a few breakthroughs, gambles, and a steady pace of incremental improvements have conspired to increase computation's role in the field. Just as computational chemistry was reaching its nadir in pharmaceutical research, the dam was bursting on protein structure determination: a combination of molecular biology, new tools for protein purification, and new techniques for solving structures synergized to release upon the field a flood of structurally enabled targets. A recent high-water mark has been the determination of membrane-bound receptors, especially G-protein-coupled receptors.

Moreover, Moore's law continued to have its way, and calculations that were unthinkable in the 1990s are, a quarter of a century later, being prosecuted almost routinely (such as, for example, millisecond long molecular dynamics simulations). In docking, no single breakthrough occurred, but incremental improvements, and a great leap in the number of compounds readily available, eventually had an impact. Today there are few major pharmaceutical research organizations without a structure-based discovery group. Meanwhile, a few companies such as Vertex and Agouron, and later Astex and Heptares, had been founded exclusively around the idea of structure-based drug design, and by the mid- to late-1990s, the first drugs that could be clearly attributed to such methods were beginning to appear.

The award of Nobel Prizes in Chemistry for computational work, the first to Pople and Kohn in 1998, partly for "computational methods in quantum chemistry", and the second to Warshel, Karplus, and Levitt for the development of "multiscale models for complex chemical systems" in 2013, has also raised the standing of the field.

As much as anything else, a flood of data from experiment has made resistance to computation futile in pharmaceutical research, and there is no area in drug discovery and development that is really free from it any more.

The papers in this Special Issue of the *Journal of Medicinal Chemistry*, including perspectives and original research articles, reflect the increasing penetration of computation into the field. Some areas are as well represented as one might expect: there are five papers on molecular docking and four on ligand design, both of long interest in the community. Other areas are more surprising, such as the three papers on decision and sensitivity analysis in lead optimization. Some papers represent areas of more recent emphasis, such as the role of ligand binding kinetics on understanding efficacy, while others represent areas that were more central to computational medicinal chemistry in the 1980s and 1990s than today, such as pharmacophore-based design and quantum mechanics; these are experiencing a renaissance by integrating with the wealth of structural data now available. Several other established, or nearly established, areas of computation appear to be under-represented, for example, with only one paper on fragment-based discovery, chemoinformatics, and phenotypic screening each and none in the design of protein therapeutics, an area falling outside the conventional medicinal chemistry spectrum.

A great difference for the field overall, relative to 25 years ago, is that over half of the papers in this Special Issue integrate computational prediction with experimental testing. It is in such integration that the field has gained the traction it now has in pragmatic drug discovery.

Predictions are fraught, "especially about the future", but still it is entertaining to speculate on themes for the next possible Special Issue of the *Journal of Medicinal Chemistry* devoted to computation. The alloy between computation and experiment should continue to be illuminating and increasingly pragmatic. The orders-of-magnitude increase in available compounds, both as specific molecules from vendors and in new formats such as DNA-encoded libraries, will continue, and methods that can capture that growth are expected to have a great run. Furthermore, methods that could accurately calculate free energies of binding, or even accurately rank-order choices, have been the computational holy grail of the future for 30 years and remain so, but breakthroughs in long simulation times portend opportunities in prospective affinity calculations to experimental accuracy (1 kcal/mol). Moreover, a marriage between structure-based methods and chemoinformatics, the latter of which has had a successful run over the past decade, but which lacks the theoretical foundations of the former, may be fruitfully explored. Last but not least, methods that integrate ligand and protein design may offer great rewards. This is the perspective going forward.

However, returning to our current Special Issue, we are delighted to see that "*part of the future is now*" and to expose to the scientific community an array of computational papers that reflect the state-of-the-art and new developments in this field and should be of interest to computational experts as well as practicing medicinal chemists. First and foremost, we thank our

Special Issue: Computational Methods for Medicinal Chemistry

Published: April 7, 2016

DOI: 10.1021/acs.jmedchem.6b00511
J. Med. Chem. 2016, 59, 4033−4034

authors for making this Special Issue a success and the *Journal of Medicinal Chemistry* for supporting this timely publication.

Brian K. Shoichet, Guest Editor
W. Patrick Walters, Guest Editor
Hualiang Jiang, Associate Editor
Jürgen Bajorath, Associate Editor

AUTHOR INFORMATION

Notes

The views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

DOI: 10.1021/acs.jmedchem.6b00511
J. Med. Chem. 2016, 59, 4033−4034