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Integrating computational approaches into high throughput screening for rational drug discovery

Xin Hu
National Center for Advancing Translational Sciences, National Institutes of Health, USA

Abstract

High-throughput screening (HTS) and structure/ligand-based virtual screening (VS) are two well-established techniques that are widely used in drug discovery. Progress on the applications of virtual and biological screening is currently moving towards the integration of these two synergistic approaches. Given the fact that more than 86% of the molecular targets in PubChem have related structural information in PDB, it is expected that a combined campaign with HTS and VS can be conducted in parallel to maximize their output and greatly improve the screening efficiency. Various computational approaches have been introduced to foster the screening process and data integration; however, it remains a challenging task to integrate these two distinct approaches efficiently in practice. Here we present case studies in finding small molecule inhibitors of bacterial virulence effectors combining HTS and computational approaches including molecular modeling and binding-site predication, ligand-based QSAR and pharmacophore search, structure-based docking and virtual screening, MD simulation and binding free energy calculations, and ADME/T modeling. To facilitate the comparative analysis and visualization of VS and HTS data, we developed a web-based tool that integrates the rich biochemical assay data of HTS, 3D structures of protein targets, and predicted protein-ligand binding models from VS into a unified system for efficient data mining. A user-friendly graphical user interface allows users to visualize and manipulate the multidimensional data in an interactive environment, providing a useful informatics platform for computer-aided rational drug discovery.

Biography

Xin Hu received his B.S. in Pharmacy in 1991 from Beijing University, Ph.D. in Pharmaceutical Sciences in 2003 from North Dakota State University, followed by a postdoctoral training at The Rockefeller University. Currently, he is a research scientist at the National Center for Advancing Translational Sciences, National Institutes of Health (NCATS/NIH).