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Nicolas Moitessier
McGill University, Canada

FITTED, an evolving docking programs addressing unmet medicinal chemistry needs

Docking methods have been prominent in the discovery of novel drugs. Over the 15 years ago, we have been developing a docking program which has been modified to address unmet needs in medicinal chemistry. Initially, our applications of docking programs to integrin antagonists, BACE-1 inhibitors, and aminoglycosides binding to bacterial RNA revealed the limitations of available docking programs, which were essentially docking flexible ligands to rigid proteins. Over the following year, we developed our own program, Fitted, implementing algorithms for protein flexibility, displaceable water molecules, and ligand-based pharmacophore-oriented docking. Other medicinal chemistry projects motivated most of the concepts and implementation within an ever-evolving docking program. We will present examples of medicinal chemistry-driven implementations such as methods considering drug-zinc coordination and its effect on the pKa of surrounding residues, for HDAC inhibitor design, routines to identify reactive groups and form bonds with a given residue to enable the development of covalent prolyl oligopeptidase (POP) inhibitors, methods to compute transition states while docking for studying the metabolism of POP inhibitors by cytochrome P450 enzymes (CYPs) and others.

Biography

Nicolas Moitessier is an Associate Professor at McGill University, Montréal, Canada. He received his undergraduate training and his PhD from Université Henri Poincaré-Nancy I (France) under the guidance of Dr. Yves Chapleur within the Groupe SUCRES. He carried out thesis research on computer-aided design and synthesis of carbohydrate-based biologically relevant molecules. He was first involved in the design and preparation of IP3 and Adenophostin A mimics using Sharpless asymmetric dihydroxylation as a key reaction. In collaboration with a theoretical chemistry group (headed by Dr. Maigret), he then focused on the computer-aided design and synthesis of carbohydrate-based antagonists of integrins.

nicolas.moitessier@mcgill.ca

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