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Docking to Solvated and Flexible Macromolecules

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To achieve potent enzyme inhibition, the inhibitors must benefit from optimal molecular recognition with the macromolecular biological target structure, a principle that has been the basis for the development of computational drug design methods. Two aspects contribute to the success of structure-based drug design: the generation of reasonable binding modes and highest scoring of those that correspond to the experimentally observed data. Predicting the correct binding mode of an inhibitor in an enzyme active site invokes the prior positioning of the ligand by a search engine that ensures an efficient and unbiased sampling (conformation/orientation/translation). However, most of the developed models do not account for conformational changes upon binding. When activity is correlated to conformational changes, usual approaches often lead to misleading results. The binding mode of interest must next be identified. For this purpose, a variety of scoring functions have been developed. However, to date, the existing scoring functions rank (to some extents) compounds according to their biological activity but their predictiveness still relies heavily on the target under study. The presence of bridging water molecules is a main issue that also remains to be addressed.

To account for the side-chain or backbone adjustments, the presence of water molecules and to address the scoring function predictiveness, we have developed new strategies that will be presented. Application to a variety of enzymes, receptors, and RNA aptamers is used to validate the methods.

Nicolas Moitessier graduated from the University of Nancy, France (PhD in Chemistry, 1998). He carried out thesis research on computer-aided design and synthesis of carbohydrate-based biologically relevant molecules. In 1998, he moved to Montréal where he joined Prof. Stephen Hanessian's group. His interests involved the docking study and the asymmetric synthesis of conformationally constrained MMP inhibitors. In 2001, he moved back to Nancy to start his academic career before taking up an Assistant Professor position in the Department of Chemistry at McGill University in 2003. His current interests include the development of software for molecular design, medicinal chemistry, and asymmetric synthesis.