MOLECULAR DOCKING WITH A VIEW: THE INTEGRATION OF A MONTE CARLO DOCKING PROGRAM INTO A VIRTUAL REALITY ENVIRONMENT

Trevor N. Hart¹, Richard E. Gillilan², Ryan Lilien²,*
Steven R. Ness¹† and Randy J. Read¹

¹ Department of Medical Microbiology and Immunology,
University of Alberta, Canada
² Cornell Theory Center,
Cornell University, U.S.A.

Abstract: Molecular docking has become a fundamental tool in both the process of drug discovery and the understanding of protein structure and function. While much effort has gone into faster and more effective automated docking algorithms, the visualization of molecular structures remains an important tool for the correct interpretation of structural predictions. The integration of the Research docking algorithm into the Virtual Reality facility at the Cornell Theory Center offers a unique tool for understanding of protein-ligand interactions. The docking program Research is a fast Monte Carlo docking method employing a full force-field interaction model to represent molecular interactions. The program is integrated as a function call within the VR/3D workspace environment and connected with a sophisticated molecular viewer that displays docking results in real time. The workspace viewer allows the user to change perspective, style of molecular display, and parameters of the Research algorithm during the docking procedure. Multiple docking processes can be run simultaneously and interactively attached or detached from the viewing workspace. The integrated docking/viewing environment is not only a practical tool for drug discovery and design, but also offers an inside look at the molecular docking process.

Keywords: molecular docking, drug design, protein structure, molecular graphics, virtual reality.

*Current address: Department of Computer Science, Dartmouth College, U.S.A.
†Current address: Department of Biochemistry, University of British Columbia, Canada.
30.1 INTRODUCTION

The problem of molecular docking is that of determining, by computation, the preferred mode of interaction between two given molecular structures. When only a small number of atoms is involved, there are few possible configurations and the problem is relatively easy. For systems with large numbers of atoms, biological molecules in particular, the problem is much more difficult because of the enormous number of possible modes of interaction. Molecular docking has become an important problem in structural biochemistry, the solution of which will have impact not only on drug design but on our fundamental understanding of protein structure and function.

Proteins are large macromolecules, typically containing hundreds to thousands of atoms, and are fundamental to the function of life as we know it (Stryer, 1981). While DNA represents the blueprint of life, proteins are the workers: they build, maintain and recycle the chemical structures necessary for biological function. Perhaps the most important aspect of protein structure is the specificity of protein shape: proteins adopt specific shapes\(^1\) in order to perform specific functions (Cantor and Schimmel, 1980). Enzymes are proteins that perform specific chemical reactions by recognizing complementary shapes. Drugs, such as antibiotics, often act by binding to specific enzymes in the pathogen, thereby disabling their function.

The basic purpose of docking methods is to predict and study the binding of a molecule to a protein. Protein structures lend themselves well to computational analysis, since the protein is represented as a set of three-dimensional coordinates, specifying a position for each atom in the protein. A docking algorithm will then model the interaction between the bound molecule (the ligand) and protein, searching for optimal binding modes. Current algorithms are limited both by the computational expense of computing interactions and by the ability to search for modes efficiently (Blaney and Dixon, 1993; Hart and Read, 1994).

While docking algorithms have been an active area of research, particularly in the past eight years, the use of graphical representations of structures has remained an important aspect of predicting protein/ligand interactions. As recent results from blind docking tests show (Dixon, 1997), docking methods are still not completely reliable in determining correct ligand binding, although they can effectively reduce the problem to a small number of possibilities (Hart et al., 1997). Other methods must be used to discriminate between correct and incorrect results, the primary being visualization by the trained structural biochemist. Thus, ability to examine solutions to a docking problem is almost as important as generation of the solutions themselves.

Our research groups at the Cornell Theory Center and the University of Alberta have developed an interactive molecular docking and viewing environment for Virtual Reality (VR). VR is being used in an increasing number of scientific disciplines for visualization of data, design and remote manipulation (Ihlenfeldt, 1997). As more

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\(^1\)This is a simplification, since not only the shape but also the chemical nature of the molecule is important for specificity. The specific atoms, bonds and shape of a molecule give rise to a distribution of electric charge; regions of negative charge on one molecule prefer to associate with positive regions on another molecule, etc.