Computing and Displaying Intermolecular Negative Volume for Docking

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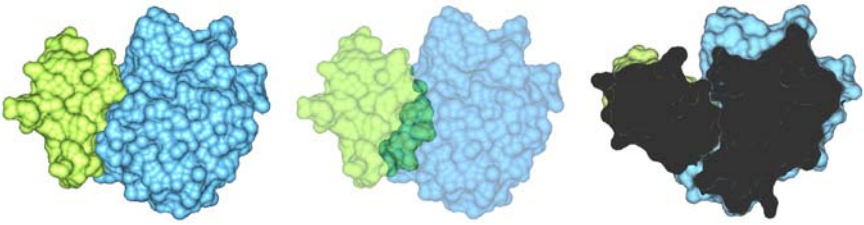
Summary. Protein docking is a Grand Challenge problem that is crucial to our understanding of biochemical processes. Several protein docking algorithms use shape complementarity as the primary criterion for evaluating the docking candidates. The intermolecular volume and area between docked molecules is useful as a measure of the shape complementarity. In this paper we discuss an algorithm for interactively computing intermolecular negative volume and the area of docking site using graphics hardware. We also present the design considerations for building an interactive 3D visualization tool for visualizing intermolecular negative volumes.

1 Introduction

Several drug development processes have so far begun with large-scale random screening of candidate inhibitors. These initial discoveries are improved through well-defined approaches to find new drugs. As molecular structure determination techniques and computational methods progress, protein docking methods using structure-based molecular complementarity have become an important substitute for random screening in the drug design process [10].

Among many factors involved in protein-protein interactions such as electrostatics, hydrophobicity, and hydrogen bonding, shape complementarity is of major importance for protein docking. Purely geometric approach can restrict the time-consuming calculations of interaction energy to be performed only for those cases that have a good geometric fit. Geometric methods can also be used as foundations for more complete approaches considering chemical and energetic characteristics [2]. A complete search of all possible geometric fits of two flexible molecules takes too much time because of the extremely large degrees of freedom. Therefore, molecules have been often assumed as rigid bodies. Even with the rigid body assumption, finding accurate shape complementarities remains a challenging problem. Most existing methods provide a list of candidates sorted by complementarity criteria and the final decision by human is needed. Therefore, an interactive tool for visualizing the shape complementarity would be useful.



(a) Solid Surfaces (b) Translucent Surfaces (c) Cross Sections

Fig. 1. Traditional Complementarity Visualization Methods

There are many methods for visualizing the steric fit between molecules. These include visualization using solid solvent-accessible smooth molecular surfaces, translucent molecular surfaces, and cross-sections of molecular surfaces (See Fig. 1). The solid molecular surface representation is unsuitable for complementarity visualization because the interface between molecules is difficult to observe due to occlusions from the solid surfaces. Translucent molecular surfaces allow the visualization of the interface between molecules. However, visual interference from other parts of the molecules prevents a clear visualization of the intermolecular interface. The cross-section method, also called the Z-clip method in graphics, visualizes the molecular interface by displaying cross sections of the molecules at varying depths from the viewer. Although the interface can be visualized clearly using two-dimensional cross sections, it is difficult to construct a mental model of the three-dimensional spatial structure of the interface. Therefore, in addition to the visualization of molecular surfaces, we need new and more informative methods for the visualization of the interface between molecules.

In this paper we present a method that computes *the negative volume* between molecules to visualize their interface. Our method leverages the recent advances in the 3D graphics hardware to achieve interactive rates of performance. Using this method scientists can interactively study various possible docking conformations and visualize the quality of the steric fit.

The remaining paper is organized as follows. In Sect. 2, we give an overview of the previous work. The concept of intermolecular negative volume and the description of the algorithm for computing intermolecular negative volume are given in Sects. 3, 4, and 5. The algorithm for computing the area and volume of the docking site is described in Sect. 6. In Sect. 7, we describe our interactive 3D visual tool to assist protein docking. We conclude this paper and discuss future work in Sect. 8.

2 Previous Work

The early research on drug design focused on geometric shape complementarity. Connolly [2] has proposed a protein docking algorithm based on geometric shape complementarity. He defines a molecule's *shape function* parameterized by scale R, at a surface point p as the volume of the molecule that lies inside a sphere of radius