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Computing Traversability of Protein Tunnels using Motion Planning

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Abstract

Chemical interactions between proteins and other molecules (ligands) take place in specific locations, called active sites. The active sites are usually deeply buried inside the protein structure and they are accessible through one or more tunnel pathways. Chemists usually analyze accessibility of these tunnels assuming a spherical ligand (probe). The obvious disadvantage of this approach is that the shape of the ligand, neither its flexibility, is considered when evaluating the tunnels. The traversability of ligand molecules through protein tunnels can be formulated as a path planning problem. In this poster, we describe a sampling-based motion planning method to find trajectories for non-spherical ligands through protein tunnels. Besides considering the shape of the ligand, the conformational changes of the ligand (i.e., its flexibility) are considered as well.

1. Introduction and Motivation

The reactivity of proteins with other molecules plays a crucial role in many research disciplines, including protein engineering and drug design. In the virtual screening, the task is to identify which small molecule (ligand) can possibly bind to a given protein. The reactivity between the ligand and the protein is tightly connected with the presence of the protein void space. This space, forming a path called a tunnel, can be utilized by the ligand which can enter the protein inner space and react with the amino acids surrounding the protein active site [MDB*17]. The biochemists use various computational methods for tunnel detection to estimate the possibility of interactions between the protein and a ligand. This can help them to reduce the number of necessary in-vitro experiments.

The most common tools detect the tunnels using Voronoi diagrams [YFW*08, CPB*12], assuming a spherical ligand (probe), i.e., they approximate the ligand by a bounding sphere. The main disadvantage of this analysis is that the shape of the ligand is not considered. Consequently, it is not easy to determine if a non-spherical ligand can pass the tunnel by evaluating only the bottleneck (or length) of the tunnel. To evaluate the traversability more precisely, the shape of the ligand has to be taken into account.

The poster presents a motion planning algorithm to find the trajectories for the flexible ligand in proteins. The method utilizes the concept of sampling-based planning [LaV06]. The ligand is considered as a point moving in a high-dimensional configuration space. The dimensions of the space are determined by the considered degrees of freedom: translation, rotation and also the dihedral angles responsible for the conformational changes of the ligand. The configuration space is randomly sampled and the samples are classified as free or non-free using collision detection. Free samples are then stored and connected, if possible, with their close neighbors. This results in a roadmap approximating the free space, where the ligand can move. The configuration space is sampled using non-uniform samples; the probability of generating a sample near the tunnels is increased, which allows us to find trajectories around the selected tunnel. During the planning, potential energy of the ligand is evaluated and high-energy conformations (that would not likely occur in a real system) are discarded. The computed trajectories can be evaluated e.g., using potential energy which provides more information about the tunnel than can be obtained using the knowledge about its bottleneck.

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