Barrier Trees for Continuous Fitness Landscapes

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Extended Abstract

Local minima of a fitness landscape are separated by barriers. A barrier tree (Flamm et al., 2002) is a representation of a fitness landscape as a binary tree, where each leaf represents a local minimum; the barriers connecting the local minima are represented as the internal horizontal nodes of the barrier tree. To reflect the fitness values of barriers and minima, each node in the barrier tree is positioned relative to the height of the represented point in the fitness landscape.

Until now, barrier trees have been applied to discrete fitness landscapes. This contribution extends the concept to multi-dimensional continuous landscapes; a generalization that allows the use of the approach in various areas of life sciences. Methods for generating barrier trees for continuous fitness landscapes will be presented, ranging from a coarse grained view of the landscapes by converting them to discrete ones, to the use of heuristic approaches, where local minima are found via the Nelder-Mead simplex method, and the minima are then connected via biased random walks. Advantages and disadvantages of the approaches will be demonstrated and methods to compare generated trees will be explained.

In order to exemplify the power of the approach, the real-life problem of molecular docking will be treated. In molecular

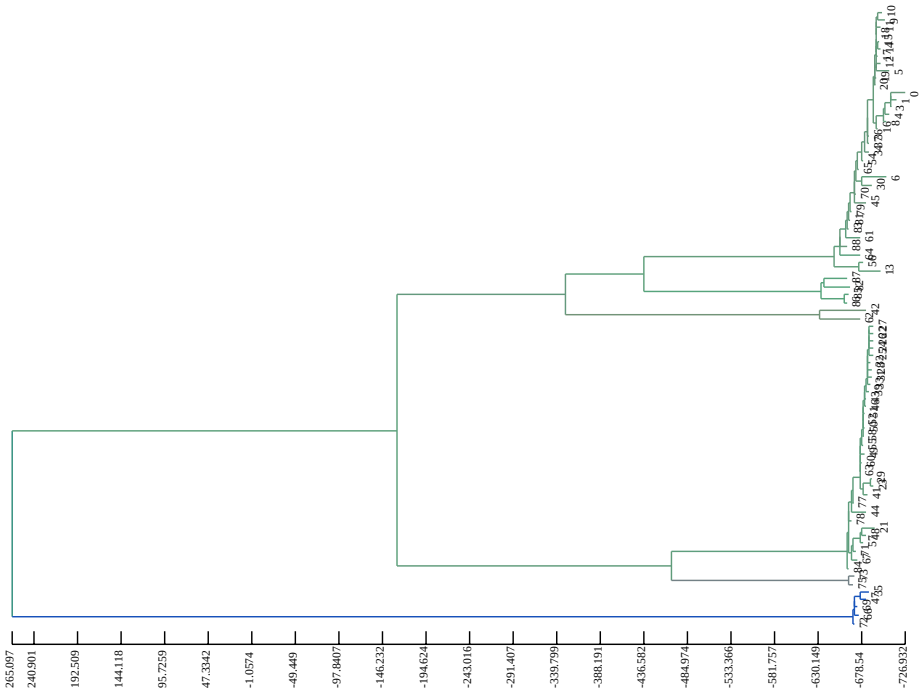

Figure 1: Barrier tree for docking of Buxaminol-E with AChE. Colored by Cartesian coordinates of the center of the ligand.

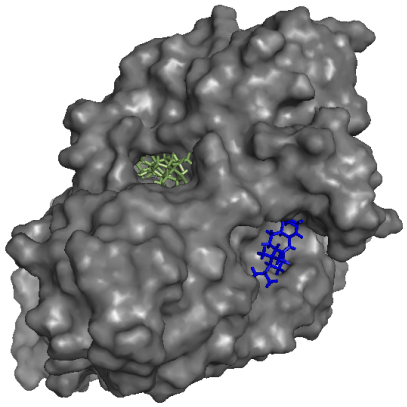

Figure 2: An illustration of the best nodes of the barrier tree from each subtree of the largest barrier. Id 35 (blue) from the lower subtree and id 0 (green) from the upper. The gray molecular surface represents the receptor AChE; the two ligands are illustrated in a stick view with the color of their respective subtree in Figure 1.

docking the interactions between small (ligand) and large (receptor) molecules are investigated in the search for the correct binding pose, which means in which ligand and receptor form a stable complex. Modeling the interaction between molecules is a complicated problem; the system's degrees of freedom include the position in Cartesian space, the orientation of the ligand, and internal flexibility of the ligand or of ligand and receptor. The ruggedness of the landscapes resulting from the different possible fitness functions makes sampling and optimization challenging. As the backbone for doing molecular docking landscape analysis, we make use of the fitness function from molecular docking software PARADOCKS (Meier et al., 2010). We used a test set with pharmaceutical relevance, a small library of known ligands and decoys of acetylcholinesterase.

Docking test illustrated in this abstract were done with acetylcholinesterase (AChE, Kryger et al. 1999) and Buxaminol-E, a natural occurring steroid isolated from Boxwood that is a known inhibitor of AChE (Thomson Scientific, 2001). First 10,000 local minima were located with the Nelder Mead method (Nelder and Mead, 1965), then removing any of those having a neighbor with a lower fitness value, neighbor again meaning within a certain step size range, and finally keeping only the 150 lowest points remaining. The barrier tree created is shown in Figure 1. The structure of the tree indicates that there are two groups of local minima separated by a high barrier, where the one group is again subdivided into smaller groups by smaller barriers.

With the barrier trees it can be seen how the search space of docking the ligand Buxaminol-E to the receptor AChE is structured. This is confirmed when we look at a figurative of the actual structure of the molecules. Figure 2 illustrates the difference in position for the ligands of the left and right subtree of the highest barrier of the barrier tree. The ligands are positioned in two distinct regions of space, which indicates two possible binding sites at the receptor.

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