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Designing binding pockets on protein surfaces using the A* algorithm

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The *in silico* design of ligands binding to the protein surface instead of deep binding pockets is still a great challenge. Representative examples are small molecules that target protein-protein interactions [1]. The unbound experimental protein structures often lack appropriate binding pockets and thus standard virtual screening techniques will fail. We previously presented a pocket detection protocol that provides a starting point for *in silico* drug design for such cases [2]. Unfortunately, the underlying molecular dynamics simulations make this protocol quite time-consuming. However, if the potential binding site of a ligand is known, conformational sampling focused on this region appears more promising than scanning the whole protein surface for transient pockets. Here, we present two new algorithms for designing tailored ligand binding pockets on the protein surface that account for backbone and side chain flexibility. At first, a predefined region of the protein surface is scanned for potential pocket positions using a program named PocketScanner. This program minimizes the protein energetically in the presence of generic pocket spheres representing the binding pockets whose positions remain fixed. The side chains of the relaxed protein conformations are then further refined by a second program named PocketBuilder that searches for the best combination of side chain rotamers using the A* algorithm. The approach was tested on the proteins BCL-XL, IL-2, and MDM2 which are involved in protein-protein interactions and hence challenging drug targets. Although the native ligand binding pocket was not or not fully open in the unbound crystal structure, PocketScanner and PocketBuilder successfully generated conformations with pockets into which the known inhibitors could be docked in orientations similar to those seen in the inhibitor bound crystal structures.

References

1. Wells JA, McClendon CL: *Nature* 2007, **450:**1001.
2. Eyrisch S, Helms V: *J Med Chem* 2007, **50:**3457.