Efficient Inclusion of Receptor Flexibility in grid-based Docking

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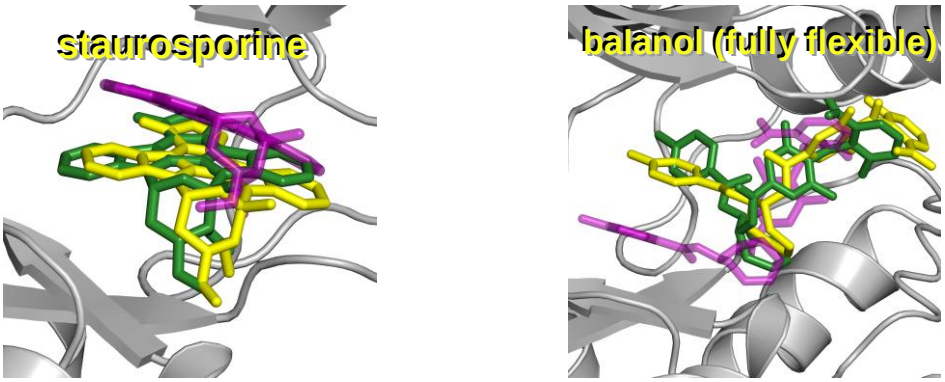
Receptor flexibility is by now considered an essential component for successful protein-ligand docking but still marks a major computational challenge [1]. Docking programs such as AutoDock [2] employ a grid-based potential representing the receptor and allow efficient docking of flexible ligands. However, global receptor flexibility is not yet properly accounted for in such methods.

Here, we present a new approach [3] to efficiently include receptor flexibility by combining normal mode calculations [4] with grid-based energy calculations in AutoDock. Similar to many other proteins, the Protein Kinase A (PKA) undergoes global structural changes upon inhibitor binding which makes it an especially challenging docking target. It serves as test case for our method. Docking ligands to apoPKA using standard AutoDock (rigid receptor) returns ligand placements that differ strongly from experiment (see figure below: compare stick representations in magenta from rigid docking to apoPKA with yellow stick models showing the placement in the experimental complex). In contrast, inclusion of normal mode based receptor flexibility calculated for the apoPKA structure yields significantly better docking results (indicated in green).

The computational effort to calculate elastic network based normal modes is negligible compared to AutoDock's genetic algorithm runtime, hence, a significant improvement of docking results at small computational cost is accomplished. The computational method and several applications will be presented.



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