On the Applicability of Normal Modes in Small-Molecule Docking

Matthias Dietzen[1], Elena Zotenko[2], Andreas Hildebrandt[3], Thomas Lengauer[1]

[1]Max-Planck-Institut für Informatik Saarbrücken, [2]Garvan Institute of Medical Research Sydney, [3]Johannes-Gutenberg-Universität Mainz

Incorporating protein backbone flexibility into protein-ligand docking is still a challenging problem in computer-aided drug design. In related fields, normal mode analysis (NMA) has become increasingly popular as it is able to determine the collective motions of a biological system. Its application areas range from the prediction of protein flexibility over the determination of protein domains and the guidance of MD simulations along the predicted collective motions to the fitting of proteins into electron density maps.

While incorporating normal modes from coarse-grained models into macromolecular docking has become a popular approach, the question whether they can also be useful in predicting the conformational changes observed upon small-molecule binding has only been addressed in some case studies [1, 2] . However, the interfaces for binding a macromolecule are usually much larger than those for binding a small molecule, a fact that requires a more detailed investigation.

We therefore have performed a large-scale study on the applicability of NMA in small-molecule docking by establishing a best-case scenario as follows. Using normal modes, we have generated intermediate structures from apo/holo pairs of the Astex Diverse [3] and Non-Native Sets [4] by projecting the conformational difference between both partners onto normal mode subsets of increasing size. The resulting C_α traces optimally reproduce the holo conformation w.r.t. the given normal mode subspace. Subsequently, the all-atom structures have been reconstructed and energy-minimized, C_α atoms were kept fixed. These structures were then docked using AutoDock [5] , GOLD [6] , and FlexX [7] to assess how the docking performance changes over a series of increasingly well reproduced holo structures and to estimate the number of modes required to sufficiently reproduce the conformational change induced by the ligand.

The results of our study indicate that even for such a best-case scenario, the use of normal mode analysis in small-molecule docking is restricted and that a general rule on how many modes to use might not exist or at least not be easy to find.

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