Improving Rigid Body Protein-Protein Docking Using Fine-Grained Normal Mode Analysis

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INTRODUCTION

Treating flexibility in protein-protein docking presents several challenges, the most obvious being the computational complexity involved\(^1\)\(^2\). In order to make calculations more tractable, current docking algorithms typically treat proteins as rigid bodies and employ soft scoring functions that allow for a limited amount of flexibility. Alternatively, cross docking of ensembles generated from molecular dynamics (MD) may be performed\(^3\)\(^4\). However, this produces thousands or possibly millions of docking solutions and therefore, fast scoring and refinement techniques are desirable. In order to accelerate the calculations, we use Graphics Processing Units (GPUs). Here, we present a novel normal mode analysis (NMA) based approach that avoids the need for combinatorial cross docking. Rigid body docking orientations output by HEX\(^5\) are perturbed by stepping along the NMA eigenvectors. The NMA-perturbed structures are then further refined by an evolutionary Monte Carlo (MC) method which locally optimises each putative solution using fast van der Waals and pairwise desolvation terms. The utility of the approach is demonstrated using docking searches performed on selected examples from the protein docking Benchmark 2.0\(^6\). Preliminary results indicate improvement in quality of the initial rigid body orientations.

METHODS

We have developed a computationally efficient approach to incorporate a moderate degree of flexibility into the docking process for a given starting orientation. Our results show that the use of soft rigid body Monte Carlo minimization increases the number of near-native docking solutions for most of the cases. The inclusion of soft normal modes leads to a three-fold increase in the number of high quality models for 1PPE, and significant improvements in the all-atom RMSDs are observed for the others.

RESULTS

Figures 2-5 show the refinement results obtained for four Benchmark 2.0 cases. Table 1 summarises the performance of the NMA-based optimization.

CONCLUSIONS

We have developed a computationally efficient approach to incorporate a moderate degree of flexibility into the docking process for a given starting orientation. Our results show that the use of soft rigid body Monte Carlo minimization increases the number of near-native docking solutions for most of the cases. The inclusion of soft normal modes leads to a three-fold increase in the number of high quality models for 1PPE, and significant improvements in the all-atom RMSDs are observed for the others.

Performance improvements can be achieved by implementing more of the calculations on GPUs. This would facilitate a finer-grained sampling that could further improve the quality of the solutions.

REFERENCES