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Optimizing a coarse-grained model for the recognition of protein-protein binding

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Abstract- *We are optimizing a force-field to be used with our coarse-grained protein model for the recognition of protein -protein binding. We have found that, apart from ranking correctly the ligand-receptor conformations generated in a protein-protein docking algorithm, our model is able to distinguish binding (experimental structure) from nonbinding (false positive) conformations for many complexes. This suggests us that the model could have a good performance in complete cross-docking, a method aimed to recognize the possible binding between any two proteins that are unknown to interact.*

VIII. INTRODUCTION

We have applied our coarse-grained protein model [1] to the simulation of protein complexes. The protein model uses a force field parametrized to reproduce correct association and dissociation rates of intrinsically disordered proteins [1]. Our aim in this work is to test the stability of experimental protein complexes during molecular dynamics simulations with our protein coarse-grained model and force-field, and to test if our force field is able to identify false positives. Stability of experimental complex structures together with dissociation of false positives after simulation would suggest that our model might able to recognize which proteins associate with each other and which is their binding conformation [2].

IX. METHODS

We have used the Discrete Molecular Dynamics (DMD) algorithm [3] for the simulation of the proteins complexes. In DMD the particles interact through stepwise potentials, therefore move with constant velocity until they reach the pairwise distance corresponding to a potential energy step, when the collision happens. At this point a transfer of momentum between the two particles occurs, changing the velocity of them. The velocity of the particles is updated by imposing conservation of linear momentum and energy at the collision, instead of integrating the equations of motion as made in standard molecular dynamics (MD). The simplicity of the calculations made in DMD makes it much faster than MD, with a negligible loss of accuracy respect to it. This together with the low number of particles in the simulation due to the use of implicit solvent and coarse-graining of the system make the simulations orders of magnitude faster than conventional explicit solvent MD simulations.

We have used the coarse-grained model of Marrink et al. [4] for the sidechains plus an atomistic representation of the amide atoms N,H,C,O, in order to be able to include explicitly hydrogen bonds in the model. The number of beads of each sidechain depends on the aminoacid, mapping generally four heavy atoms in each bead.

We have reparametrized our force field [1] in order to improve the predictive performance in protein-protein complexes. Following the same idea as used in the optimization of scoring functions for protein-protein docking [5], we have modified the nonbonded part of the force-field changing the weight of the following terms: i) Van der Waals; ii) electrostatic; iii) implicit solvation

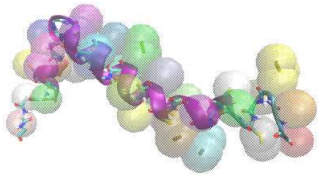

Fig. 1 Coarse-grained protein structure in our model. An atomistic representation is used for the amide atoms of the backbone, and a coarse-grained representation for the side chain beads (transparent spheres with a different color for each residue)

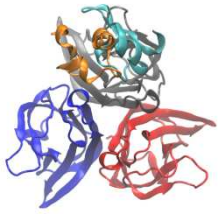

Fig.2 Movement of the ligand along the DMD simulation with our force field for the experimental structure of the complex of PDB code 1XU1. The ligand in the experimental structure is in gold color, and after the simulation in cyan color.

X. RESULTS

We have made simulations on all the experimental complex structures of Weng's protein docking benchmark 4.0 [6]. In figure 2 is shown the movement of the ligand of an experimental complex structure after a simulation of 1 ns. The simulation of the best scored false positive for this complex generated by a standard docking algorithm [5] produces a fast dissociation of the ligand and the receptor.
In a previous work [7] we simulated this benchmark using an atomistic representation of the proteins, finding that all the

docking conformations kept stable during the simulation, because we were using a standard molecular dynamics with implicit solvent force field not parametrized to give de correct association/dissociation rates in systems of interacting proteins.

Here found that the majority of the experimental structures keep stable during the simulation, as shown in the figure 3. We found that only 20% of the complexes of the benchmark showed dissociation.

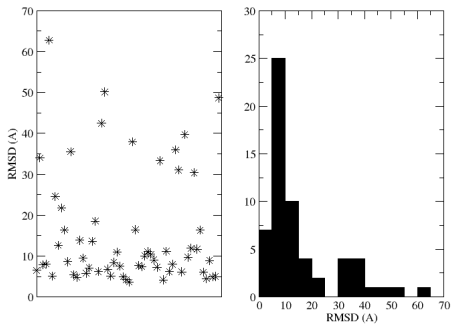

Fig. 3 RMSD respect to the experimental structure after the DMD simulation with our force-field for the complexes of the protein benchmark.

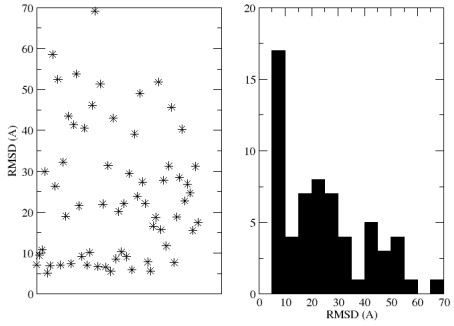

Fig. 4 RMSD respect to the initial structure of the best scored false positive generated by a docking algorithm for the complexes of the protein benchmark.

When we made the simulations of the best scored false positives, we found (figure 4) that in 60% of the complexes ligand and receptor dissociated. This suggests us that our approach is able to recognize stable receptor-ligand configurations and discard false positives for the majority of the complexes in the benchmark, opening the perspective to obtain a higher performance after further optimization of the force field.

REFERENCES

[1] A. Emperador et al., "A coarse-grained model for the study of protein structure, dynamics and interactions", unpublished.

[2] S. Sacquin-Mora et al., "Identification of protein interaction partners and protein-protein interaction sites", *J. Mol. Biol.* **382**, 1276-1289 (2008)

[3] A. Emperador et al., "Protein felsibility from discrete moleular dynamics simulations using quasi-physical potentials", *Proteins* **78,** 83-94 (2010)

[4] L. Monticelli et al., "The MARTINI coarse-grained force field: extension to proteins", *J. Chem. Theory and Comput.* **4**, 819-934 (2008)

[5] J. Fernandez-Recio et al., *Protein Science* **11** 280-291 (2002)

[6] H. Hwang, *Proteins* **78** 3111-3114 (2010)

[7] A. Emperador et al., "Efficient relaxation of protein-protein interfaces by discrete molecular dynamics simulations", *J. Chem. Theory and Comput.* **9** 1222-1229 (2012)