How could the protein-protein complexes be modelled?

ID - 192

Costantini Susan[1,2], Colonna Giovanni[1], Facchiano M Angelo[1,2]

[1]Laboratorio di Bioinformatica e Biologia Computazionale, Istituto di Scienze dell'Alimentazione, CNR, Avellino, Italy

[2]Centro di Ricerca Interdipartimentale di Scienze Computazionali e Biotecnologiche, Seconda Università di Napoli, Italy

Motivation

Proteins may assume different stable conformations, depending on the different environment or their interaction with other molecules. In fact, when a protein interacts with another molecule, it modifies its protein-unbound conformation to assume a protein-bound conformation more suitable for the interaction. The prediction of a protein-protein complex structure can be a very difficult task, and expecially when the protein structure is unknown. How can be predicted the protein structure and the conformational changes occuring during the complex formation? The best method for predicting the three-dimensional structure of proteins is the homology modelling strategy, but the models are created as unbound conformations and the prediction of a protein-protein complex requires a more specific strategy.

Methods

We selected proteins for which both the protein-unbound and protein-bound conformation have been determined by experimental methods. Theoretical complexes by structural superimpositions, compared to the experimental ones and subjected to different strategies of modeling refinement and optimization aimed to improve the side chain geometry. The protein-protein interactions were analyzed by different tools able to evaluate specific parameters, in particular HBPLUS for putative H-bonds, NACCESS for interface accessible surface area (ASA), DCOMPLEX for binding affinity, FOLDX for protein complexes stability. Comparative modelling strategy was applied to create protein models to be used in the creation of protein-protein complexes. We used BLAST for sequence similarity searches, MODELLER to build full-atom protein models, SCWRL3 to model the side chains of the amino acids, PROCHECK and PROSA to evaluate their stereo chemical quality and a scoring function and DSSP for secondary structure assignment to three-dimensional models.

Results

Different model refinement strategies have been evaluated. The theoretical complexes subjected to the enhanced modeling of the side chain conformations of complexed proteins followed by optimization procedure, resulted more similar to the experimental ones in term of free binding energy, of interface ASA value and of H-bond number. The same procedure was applied within an homology modelling experiment. We have modelled the IL-1beta sequences from mouse and trout using as template the protein-bound and protein-unbound structures of human IL-1beta, and simulated the complexes with the related receptors on the basis of experimental human complex. The results confirm the same refinement strategy as the better one. Other refinement strategies are under investigation in order to improve the whole modelling protocol.

Email: susan.costantini@isa.cnr.it