I+D Recio BIO2010-22324: Docking entre proteínas y otros aspectos: avances en la descripción biofísica y computacional de las interacciones proteína-proteína y proteína-ADN

Description

The proposed project will study molecular recognition phenomena in proteins, at structural, physico-chemical and functional levels. After the vast amount of data generated from the genomics and proteomics projects, the next grand challenge is the characterization of all the interactions between proteins and other biomolecules, and the present project aims to contribute in this direction.

During the past ten years, we have developed algorithms for predicting a complex structure from its subunits (docking problem), based on scoring of rigid-body poses with optimized energy function, and they yielded excellent results in blind tests such as CAPRI (http://www.ebi.ac.uk/msd-srv/capri/). The models describe the pseudo-rigid-body encounters during association, and in several cases, they are of sufficient quality for biological and functional predictions. Several challenges still remain though: multi-protein complexes, highly transient interactions, and cases with large movements upon binding. We will study the binding phenomena in detail, based on our current models. A deeper knowledge of the role of flexibility during the different steps of the docking energy landscape will improve our knowledge of protein association mechanism and will be useful to develop new modelling tools. Local flexibility will be explored with molecular dynamics and Monte-Carlo sampling, while large domain movements will be described with coarser-grained description like normal mode analysis and our new algorithms for the flexible link/tethered docking, especially relevant for modelling multi-protein complexes.

Related to this, one of the major goals is to achieve realistic docking predictions on homology-based models, in order to apply these tools at proteomic scale.

The final challenge will be the design of small compounds capable of inhibiting protein-protein interactions, important for drug design. This will require the computational identification of protein-protein interfaces and ‘hot-spots’ in the absence of structural information, search of transient pockets in protein interfaces, and the integration of protein-protein and protein-ligand docking algorithms.

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