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european union 21

A shift in focus on brain disorders

Should we start from the beginning?

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An Independent Review

Computer-aided methods in biochemistry and biomedicine

To rationalise, increase efficiency, speed and cost-effectiveness of the drug discovery process…

Proteins are key components of the machinery in all living organisms' metabolic routes. The alteration of their particular characteristics can induce deleterious effects for the cell. Knowledge of the mechanisms by which proteins carry out their biological functions, usually by interacting with other proteins or with different ligands, is essential not only for the manipulation of processes involving proteins (for example to make them exhibit functions different from those for which they were synthesised), but also to identify aberrations in their behaviour that might be lethal for the cell. These might include the up or down-regulation of the production of a particular protein, the appearance of particular mutations that modify the 3D conformation of an enzyme or receptor active site, or the induction of unfolding causing cellular stress due to accumulation of proteins unable to carry out their functions. In addition, many diseases are caused by infectious micro-organisms and viruses. A way to fight against them consists of annulling a vital function by the blockading of a key enzyme.

The drug discovery process has traditionally relied on experimental high-throughput screening to identify biologically active compounds, an extremely laborious and expensive procedure that often failed to identify potent lead series. Similarly, despite the fact that mechanism of action of many vital proteins and enzymes has been widely analysed, key clues are still far from being understood at the electronic and atomic level. Complementary structure-based computer-aided methods for drug design and analysis of reaction paths, which incorporate the knowledge from high-resolution 3D protein structures, offer an alternative to rationalise, increase efficiency, speed and cost-effectiveness of the drug discovery process, as well as in the understanding of biochemical reactions.

The challenge at the Institute for Biocomputation and Physics of Complex Systems (BIFI) is to use a combination of biochemical, biophysical and computational methodologies to investigate the physical-chemistry of systems depending on protein-protein, protein-DNA and protein-ligand interactions in the frame of a structural biology multidisciplinary approach. It can provide an important advance in knowledge, understanding and use of biological systems with profitable aims for the society. Computer-aided structure-based approaches for lead optimisation and screening of chemical libraries based on ligand-protein docking are increasingly becoming part of many drug discovery projects and in the understanding of enzyme mechanism projects, mainly due to the technical improvements in crystallography, the support of modern software and the ever increasing computational power.

A combination of these technologies is presently being used at BIFI to shed light on the biochemical nature and possible solutions to illnesses caused by protein misfolding (human hypercholesterolemia), loss of enzymatic activities (rescue of phenylalanine hydroxylase activity), degeneration of protein structures and alteration of vital and apoptotic activities (Alzheimer's disease and mitochondrial activities), as well as by the action of viruses (Hepatitis C) or pathogens (*M. tuberculosis, L. monocytogenes, H. pylori*). Additionally, several projects run with potential biotechnological relevance, including the structural and functional characterisation of transcriptional regulators, as well as different applications of proteins and peptides produced by cyanobacteria and fungi.

Nevertheless, the underlying physical and theoretical models based on classical mechanics force-fields, coupled with the number of approximations involved, still result in a modest predictability for ligand binding free energies and chemical reaction steps. The actual solution to this problem lies in improving the level of physical representation of the molecular system. Considering the current increase in computational power and storage, and the decrease of CPU time cost, researchers at BIFI move to use semi-empirical quantum mechanical methods coupled with an enhanced description of entropic changes to provide lead discovery and optimisation of structure-based methods with the accuracy and predictability they presently lack. The multidisciplinary nature of our research – experimental, methodological and applied – coupled with highly novel and innovative methods must have a tremendous impact to treat different diseases and to develop reaction mechanisms of biotechnological interest.

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