

You are cordially invited to a talk in the **Edmond J. Safra Center for Bioinformatics Distinguished Speaker Series**.

The speaker is **Dr. Giorgio Colombo**, Head of the Computational Biochemistry Group at ICRM-CNR, Milano.

**Title:** "Structure-function-dynamics relationships in proteins: implications for drug discovery"

**Time:** Tuesday, **May 16, 2017**, at **10:15** sharp (refreshments from 10:00)

**Place:** Kaplun 324, Exact Sciences Faculty

**Host:** Prof. Haim Wolfson, [wolfson@tau.ac.il](mailto:wolfson@tau.ac.il), School of Computer Science, TAU

**Abstract:** In this study, we will present recent results on the development of computational biology strategies for the discovery of new inhibitors of protein-protein interactions with drug-like properties, and for the study of the functional dynamics and allosteric signal propagation mechanisms in proteins.

In the first part, we present a computational analysis of signal propagation mechanisms and long-range communication pathways in the molecular chaperone Hsp90. The analysis is carried out using molecular dynamics (MD) simulations of the full-length Hsp90 dimer, combined with essential dynamics, correlated motions analysis and a signal propagation model. All-atom MD simulations with the time scales of 100ns have been independently carried out for Yeast Hsp90 in complexes with the natural substrates ATP and ADP and for the unliganded dimer. We elucidate the mechanisms of signal propagation and determine hot spot residues involved in the inter-domain communication pathways from the nucleotide-binding site to the C-terminal domain interface. Interestingly different communication mechanisms are triggered by different ligands. This information is then used to select for new allosteric inhibitors of the chaperone. The new molecules show the ability to allosterically inhibit the chaperone's functional motions.

In the second part, we discuss new methods to investigate the role of sequence mutations on the stability and interaction properties of proteins and domains. Given a certain structure, a native sequence and a set of mutants, we show that our model discriminates the ability of a mutation to yield a more or less stable protein, in agreement with experimental data, capturing the principal energetic determinants of protein stabilization. The approach is then extended to investigate the interaction properties of proteins, and in particular to the prediction of antibody-binding sites. Epitope prediction has proven challenging. The antibody binding properties of an antigen depend on its structure and related dynamics. To this end, we have developed an integrated analysis of the dynamical and energetic properties of antigens, to identify non-optimized, low-intensity energetic interaction-networks in the protein structure isolated in solution. The method is based on the idea that recognition sites may correspond to localized regions with low-intensity energetic couplings with the rest of the protein allowing them to undergo conformational changes, to be recognized by a binding partner and to tolerate mutations with minimal energetic expense. Analyzing the results on isolated proteins and benchmarking against antibody-complexes, the method successfully identifies binding sites located on the protein surface and accessible by putative binding partners. The combination of dynamics and energetics can thus discriminate between epitopes and other substructures based only on physical properties.

Finally we will discuss the implication of these methods in drug and vaccine discovery.