Protein-protein interactions in the purinosome metabolon

The goal of the project is to investigate by multi-scale computer simulations the structure, dynamics and ultimately function of a metabolon: the purinosome. The project will be carried out under the supervision of Fabio Sterpone at the LBT/IBPC in collaboration with S. Melchionna (Lexma-Technology, Rome, Italy), and it will benefit from the tight collaboration with the experimental group of S. Ebbinghaus (TU Braunschweig, Germany).

Metabolic enzymes form regulatory clusters in cells, the metabolons, where enzymes are spatially and temporally organized into multienzyme complexes. One example is the purinosome that controls the metabolic pathway for de novo purine synthesis in eukaryotes involving ten chemical steps catalyzed by six enzymes [1]. We apply a unique combination of multi-scale simulations to investigate the complex and its individual enzymes on a molecular level. We will identify protein-protein interactions between the enzymes that lead to the assembly/disassembly of the complex under different cellular conditions. We will analyze structural changes, conformational dynamics of the individual enzymes in the complex compared to their counterparts in the cytoplasm. By characterizing the structure of the purinosome we will gain molecular insights into the control of a metabolic flux and its regulation, and possibly unravel novel therapeutic strategies.

The computational investigation will be based on the innovative technique developed in the host laboratory, the lattice Boltzmann Molecular Dynamics based on coarse-grained models for proteins [2,3], combined to atomistic simulations. The group of F. Sterpone has already applied the approach to study protein stability and dynamics in crowded solutions and cellular environments, see figure 1 and Ref. [4,5]. The multi-scale strategy will allow to explore the time-dependent aggregation of the core of the purinosome and its packing organization, tracing the assembling pattern, the preferential interactions among the constituents, the local clustering under different cellular crowding conditions. The investigation will be partnered by the experimental investigation carried out on the same system in the laboratory of S. Ebbinghaus (TU Braunschweig, Germany) and based on single molecule spectroscopy [6]. The candidate will also contribute, in collaboration with S. Melchionna (Lexma-Technology) to the software development in order to improve performance and scalability so to handle in the future very large biomolecular systems/complexes in the cellular environment. The natural secondment for this project is the start-up Lexma-Technology.

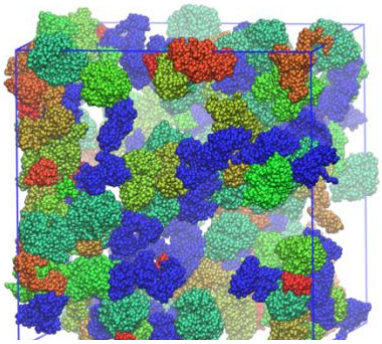

Figure 1. Model of E. coli cytoplasm simulated by LBMD

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The project can be associated to axis 1 because of the role of purine synthesis in ATP production, or axis 2 because of the supposed spatial localization of the purinosomes near mitochondria.

References

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