Deciphering the dynamics of small-Heat-Shock Protein by Atomic-Force-Microscopy and multi-scale molecular dynamics simulations.

Laboratory:
Laboratoire ICB, UMR 6303 UB-CNRS
Département Nanosciences, Université de Bourgogne Franche-Comté, Dijon
Advisors:
Prof. E. Lesniewska, eric.lesniewska@u-bourgogne.fr
Dr. A. Nicolaï, adrien.nicolaï@u-bourgogne.fr
Prof. P. Senet, psenet@u-bourgogne.fr

In collaboration with:
Laboratoire PAM, UMR AgroSup-UB
Equipe VAlMiS**,** Université de Bourgogne Franche-Comté, Dijon
Contacts :
Pr. Jean Guzzo
Dr. Stéphanie Weidmann-Desroche

General introduction

For a physicist, protein is a very exciting smart nanoparticle! A protein is a polymer which folds on itself to adopt a well-defined shape and a specific intrinsic dynamic. Both the shape, protein surface and protein dynamics are important for the protein to function *in vivo*. Nowadays, proteins can be studied at the single-molecule level, both numerically and experimentally. Interactions between proteins, between proteins and cell membranes can be monitored by Atomic-Force-Microscopy (AFM). AFM reveals the diffusive motions of proteins, their shape and dynamics at the nanoscale. The group of AFM team of ICB (lead by Prof. Lesniewska) is a world-wide recognized group in development of AFM microscopies.

Detailed interpretation of the observed protein motions required theoretical models based on the forces between the atoms and molecules: molecular dynamics simulations provided such information on time-scales from the ps to the ms with the appropriate methods. The group PhaP of ICB (lead by Prof. Senet) is a leader theoretical group in the field of simulations of protein dynamics.

The project aims to understand the dynamics of an important class of specific proteins, the small Heat-Shock-Proteins (sHSP), present in all cells. The project will focus on a model sHSP, Lo18, of a bacteria *Oenococcus oeni* involved in wine factoring and exposed during the growth in wine to multiple stresses as acidic stress and ethanolic stress. The thesis will be carried on in close collaboration with the molecular biology group VAlMiS (lead by Prof. Guzzo) which is an international recognized expert group in sHSP and in particular of stress response in bacteria and specifically the role of small Hsp as Lo18.

The present project is unique as it involves experimental and theoretical physicists and molecular biologists to tackle the challenging question of understanding the sHSP conformational changes and its interactions with a membrane. Taking into account that sHSP are universal HSP mainly involved in cellular adaptation to stress but also with several implications in diseases, this fundamental understanding will have potential applications in technological processes (wine) and in medicine (immune response, cancer,…).

Summary of the PhD thesis project

Most of the proteins occur as a single-chain of amino-acids (monomeric protein). For the sHSP Lo18, the most stable state is however a dimer. Lo18, as all sHSP, participates to the protein chaperoning system and this activity is based on its ability to self-assemble into large and highly dynamical structures with up to 16-18 monomers. In these super-structures, the monomers are linked by non-covalent interactions. Preliminary High-Speed AFM data of Lo18 on a solid surface shown that the dynamics of Lo18 was depending on the pH. HS-AFM allowed us to follow individual dimers and their organization into a highly cohesive multimer structure as a function of time. Fundamental questions to answer in the thesis by AFM and simulations are: what drives the aggregation of Lo18? Why the dimer is more stable than the monomer? Why the dynamics of Lo18 is suppressed at pH5? How this dynamical aggregation depends on the surface on which the proteins are observed (solid surface, model of cell membranes,…)? An intriguing question is the dependence of Lo18 affinity for the membrane as function of the fluidity level, a complex multi-phase physical fluid. Answers to these fundamental questions will have possible applications in food industry and in medicine. Model membranes will be studied both in AFM and in molecular dynamics simulations. As the Lo18 muti-meric structure is out of reach for all-atom simulations, the student will have to develop multi-scale models from the atomistic description of the proteins, to coarse-grained models where an amino-acid or even the whole monomer is represented by an effective interaction center.

Profile of the applicant

Background in **physics** (condensed matter physics, statistical physics at the master/bachelor level) or **physical-chemistry** (physical chemistry and statistical physics at the master/bachelor level)**.** No background in biology is required. The applicant should have some experience of programming and be willing to perform a phD thesis including both numerical simulations (using mainly Molecular Dynamics) and experimental measurements (using Atomic Force Microscopy) and to work in an interdisciplinary project.