Institut de Biologie et Chimie des Protéines
7, Passage du Vercors - 69367 Lyon Cedex 07 – France
Tél : 33 (0)4.72.72.26.65 - Fax: 33 (0)4.72.72.26.02 - http://www.ibcp.fr

Molecular Microbiology and Structural Biochemistry (UMR 5086)
Luca Monticelli
Team: Modeling Biological Macromolecules (MOBI)
luca.monticelli@ibcp.fr

Laboratory of Tissue Biology and Therapeutical Engineering (UMR 5305)
Claire Monge
Team: Colloidal Vectors and Tissue Transport
claire.monge@ibcp.fr

Master 2 project

This project will take place in a highly interdisciplinary environment at IBCP, in the group of Luca Monticelli (molecular modeling) and in close collaboration with Claire Monge (experiments), who develops layer-by-layer (LbL) assemblies for vaccine delivery.
To apply, please send a CV and a motivation letter by e-mail to luca.monticelli@ibcp.fr.

Molecular modelling for a vaccine delivery system

Vaccine delivery is an important problem in pharmaceutical and medical technology. Among the different vaccine vectors developed so far, the layer-by-layer system is particularly interesting because of its simplicity of fabrication and low cost. Layer-by-layer assemblies are generated by dipping a charged solid surface into a polyanion and then into a polycation solution, multiple times; such procedure leads to the progressive formation of films on the solid support, consisting of alternating layers of the polyelectrolytes [Decher 1997]. This self-assembly method is based on the strong electrostatic forces between the charged polymers. The multilayers are versatile tools for the delivery of macromolecules such as proteins, nucleic acids, or polypeptides with targeted properties [Monge 2015]. A vaccine for the HIV virus is currently being studied by Dr. Monge at LBTI (CNRS, Lyon). Understanding the molecular origin of the properties of the film and deciphering the interactions with the biomolecules they contain is necessary to tune the properties and increase the efficacy of the final medical device. However, explaining the behaviour of the polyelectrolytes in the LbL assembly remains a challenge due to major difficulties in structural characterization of the materials.

Here we propose to characterize the self-assembly, the mechanical properties, and the interactions of LbL multilayers using molecular simulations. During the past decades, molecular simulations have become a powerful tool for interpreting experimental results in terms of nanometre-scale structures and interactions, particularly for biological systems such as proteins, nucleic acids, carbohydrates, and lipid membranes. In the first phase of the project we will build molecular models for two charged polysaccharides, chitosan and hyaluronic acid, experimentally used in LbL systems for drug delivery. All-atom models, with the highest level of accuracy, are already available and will be used as a basis for the parameterization of coarse-grained models, featuring higher computational efficiency, which is essential to reach the large time and length scales needed to characterize the properties of

polyelectrolytes. Coarse-grained simulations will allow the characterization of dynamic and elastic properties of the polymers in solution, and will be carried out with the MARTINI model, one the most widely used coarse-grained models. MARTINI has successfully been used for the description of a wide variety of biological and synthetic systems, including liposomes, models of complex biological membranes, polymers, and nanoparticles [Marrink 2007; Monticelli 2008; Marrink 2013]. Simulations will be validated by comparison with experimental data whenever possible.

Once the models of each polyelectrolyte will be built and characterized, in the second phase of the project we will perform self-assembly simulations, exposing a charged, solid surface alternatively to solutions of each polyelectrolyte – mimicking the experimental layer-by-layer deposition process. This will allow characterization of the multi-layer assembly in terms of internal structure (e.g., density profiles), dynamics (self-diffusion of the polymers), and elastic properties (e.g., Young modulus). Simulations of material swelling with aqueous solutions will also be possible, allowing changes in material properties and structural rearrangements upon modifications of pH and ionic strength, as well as exposition to other materials – allowing predictions on the interaction between LbL multilayers and proteins or nanoparticles. Such predictions will be used, in turn, to guide the experimental design of novel LbL materials with improved properties.

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