Plateau de Modélisation Moléculaire Multiéchelle

Journée Modélisation Moléculaire Multiéchelle

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In silico experiments on biomolecules through the Static Modes: an efficient approach to predict biomechanical response and design functions

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Encompassing biological and non-biological worlds raises new fundamental questions that need to be solved to design high performance materials and achieve industrial development. Their progress is hindered by a lack of fundamental understanding of the rules governing biomolecule properties when integrated in a technological environment. Simulation-based virtual experiments with atomistic precision, but computationally efficient, are necessary to support the viability of future technologies. However, predicting the structure-activity relationship that determines biomolecular function remains an outstanding challenge for computational investigations, and structural biology in general. Main issues are related to the complexity imposed by the number of atoms, the broad range of timescales to simulate, and the treatment of weak interactions that confer to biomolecules a considerable flexibility. This is particularly challenging for large systems, like molecular machines, in which motions are closely related to function, but also to anticipate the response of a biomolecule in a non biological environment, or to design and integrate new active functions. In this competitive background, the Static Mode method developed at LAAS-CNRS, is an innovative approach to anticipate the response of biomolecules when submitted to user-defined external stimuli applied on single or multiple sites and can be used to efficiently identify long-range internal correlation. We will show how the Static Modes can be used to efficiently decipher the molecular mechanisms with atomic precision. We will present selected results on various enzymes and molecular motors, or DNA derivatives, to propose a guideline for efficient, predictive and custom *in silico* experiments.

Simulations of asymmetric and highly curved lipid membranes

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Real cell membranes are remarkably asymmetric and non-planar. The monolayers of real membranes differ by their lipid content and their concentration of components like cholesterol. Surprisingly, numerical simulations of membranes usually operate with symmetric and planar patches of lipid bilayer, which is far from being realistic.
In this talk, we present the methodology of simulating asymmetric and arbitrarily bent lipid membranes. The challenges in the analysis of such systems are discussed. The distribution of the membrane components and their relation to the membrane curvature are studied.

Structure-function studies of self-assembled elastomeric proteins

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Self-assembled elastomeric proteins make up an important and unusual class of structural proteins endowing biological tissues as diverse as spider silks and lung alveoli with extensibility and elastic recoil. In humans, elastin is the polymeric extracellular matrix protein responsible for the elasticity of lungs, skin, the bladder, the uterus, and large blood vessels. Although its self-organization and mechanical properties have spurred interest in elastin as a model for useful biomimetic polymers, the molecular determinants of these properties are poorly understood.
We use atomistic molecular dynamics simulations in explicit solvent to examine the structural and physical basis for the self-assembly and mechanical properties of elastin-like polypeptides. Results indicate that the peptides remain highly disordered even in the aggregated state, and provide an ensemble description of phase-separated peptide aggregates. In this phase-separated state, the peptides are largely solvated by one another, although the polypeptide backbone remains significantly hydrated. Both conformational entropy of the polypeptide chains and the hydrophobic effect drive the formation of this protein-rich phase. Together, our findings support a unified model of self-assembled elastomeric proteins in which th these two types of entropy play essential roles in both self-assembly and elastic recoil. Consistent with this unified model, the elastic modulus of cross-linked, elastin-like networks predicted by the simulations is commensurate with experimental measurements.

Rational design of elastin-based materials: relating structure and mechanical properties

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Elastin is the self-assembling extracellular matrix protein that provides elasticity to tissues. As an entropic elastomer, conformational disorder of the monomer building block, tropoelastin, is essential for elastic function, as returning to a state of higher entropy after extension is one of the main driving forces for elastic recoil. The highly hydrophobic monomer employs a range of strategies for maintaining disorder and flexibility within hydrophobic domains. These include a minimum compositional threshold of proline and glycine residues, regularly spaced prolines and a high proportion of VPG motifs that favour transiently populated β-turns. However, it is becoming clear from the young and rapidly growing field of intrinsically disordered proteins that functional conformational ensembles ("liquid-like" protein states) typically include both disordered and locally structured regions. Indeed, we have recent evidence for local regions of structure formation during stages of assembly, particularly from proline-poor hydrophobic sequences and KA-type cross-linking domains.

Thus, a major emerging question is how structure, disorder and dynamics combine to modulate elastin mechanical properties. Notably, there is limited sequence homology between hydrophobic domains of human elastin. As such, considerable tolerance exists for the insertion of guest residues or sequence blocks for modulating assembly architecture and mechanical properties for the design of materials. Here we replaced regions of disordered sequence in elastin-like polypeptides by residues with propensity for secondary structure formation. These polypeptides self-assembled and could be cross-linked into materials. This study describes the effect of different types of secondary structure (α-helix/ β-sheet) and the location of structure within the polypeptide on elastic mechanical properties such as modulus, resilience and stress-relaxation.