

Thesis subject:

Characterization of the nanomechanical properties of biological lipid membranes with a new Atomic Force Microscopy mode: the Circular mode AFM.

PhD Advisors:

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Context of the thesis:

The thesis is part of the project activities of the Laboratory of Excellence (LABEX) at the Université de Technologie de Compiègne (UTC) in France on the Control of Technological Systems of Systems (MS2T) (www.utc.fr/labexms2t).

Nanoscience is a "horizontal" field because it brings together different technological sectors in converging approaches ("top-down" or "bottom-up") and common principles. Therefore, nanosciences are expected to produce innovations addressing many technological problems. Among the fields of applications of nanosciences, instrumentation for the characterization of the structures/properties of matter on the nano-scale is already considered as essential in a wide range of sectors. Indeed, **the characterization of nano-mechanical properties and the unambiguous identification of nanoobjects constitute a bottleneck for industrial exploitation of nanoobjects**. There is an enormous **need for instrumentation and protocols allowing to identify, characterize, manipulate, handle, combine, or protect against man-made nanosized matter**. These issues must be addressed in areas such as **toxicology, nano-based medicines (drug delivery)**, nano-based sustainable technologies to ensure the development of nano(bio)technologies, as stated in FP7 NMP and H2020 guide documents. One should note that **few studies address interactions of nanosized materials at biological interfaces**.

This project proposal will address these challenges by **the development of a new atomic force microscopy (AFM) mode based on circular scanning for biological applications**. In this project, circular mode AFM will characterize biomimetic lipid membranes in order to address the relation between lipid membranes' nanomechanical properties and their use as nanovectors in drug delivery applications. Lipid-based nanovectors are used to deliver specifically drugs to diseased cells. This innovative application of nanomedicine is based on the ability of nanovectors to undergo fusion with the membrane of living cells, thereby releasing their drug load into cell interior (see figure 1). The mechanism of membrane fusion involved in drug delivery is controlled by the nanomechanical properties of lipid-based assemblies (i.e., both the nanovector and cell envelope) but there are still not accurately determined to date, especially regarding friction properties.^{1,2}

The self-assembly of lipid molecules produces membranes with an organization, an elasticity and a viscosity to be determined. **Lipid-membranes are considered as a system formed by assembly of single systems (lipids) with own properties/behaviour**.

Adequation to Labex MS2T scientific fields: Optimized design of technological SoSs // Multi-level and multi-physical optimization of a set of complex systems. We propose a **new characterization method** to improve and enhance the development of **biomimetic lipid nano-systems (made up of several sub-systems, i.e. individual lipids)** designed for drug delivery.

PhD thesis description:

We propose to apply a new circular AFM mode developed by P.E. Mazeran (Roberval Lab) and O. Noel (Univ. du Maine) [Nasrallah et al., 2010] to measure the friction force of biomimetic lipid membranes in order to demonstrate the usefulness of this new mode in biomechanics. Experiments will be scheduled as follows: **Year 1:** characterization of lipid monolayers (2 components models) by circular mode AFM; **Year 2:** characterization of lipid bilayers (2 components models) by circular mode

¹El Kirat K, Morandat S, Dufrêne YF. (2010) Biochim Biophys Acta 1798(4):750-65.

² Morandat S, Azouzi S, Beauvais E, Mastouri A, El Kirat K. (2013) Anal. Bioanal. Chem. 405:1445-1461.

AFM; and **Year 3**: characterization of complex biomimetic models of lipid membranes by circular mode AFM. During the three years, experimental procedures and treatment/analysis of force/friction curves will be improved to have well-defined recipes and tools dedicated to circular mode AFM. Circular mode AFM is already patented, and all the biological applications are the most promising ways of exploitation by industrials (Bruker AFM company already interested if applicable to Biology).

Candidate's profile: M.Sc in Physics, BioPhysics or Mechanics with notions of Biology.

Financial Support requested: 36 months salary of Ph D student. Equipment (Langmuir-Blodgett trough 25 keuros, hardware upgrade of multimode AFM for circular mode 32 keuros) and 24 keuros of consumables (lipids, surfaces, AFM tips, mica surfaces, tweezers...) and missions/congress fees (6 keuros).

Other related projects submitted: project submitted to Région Picardie (circular mode AFM on organic/biologic thin layers), and ANR submitted (circular mode AFM to measure bioaffinity).

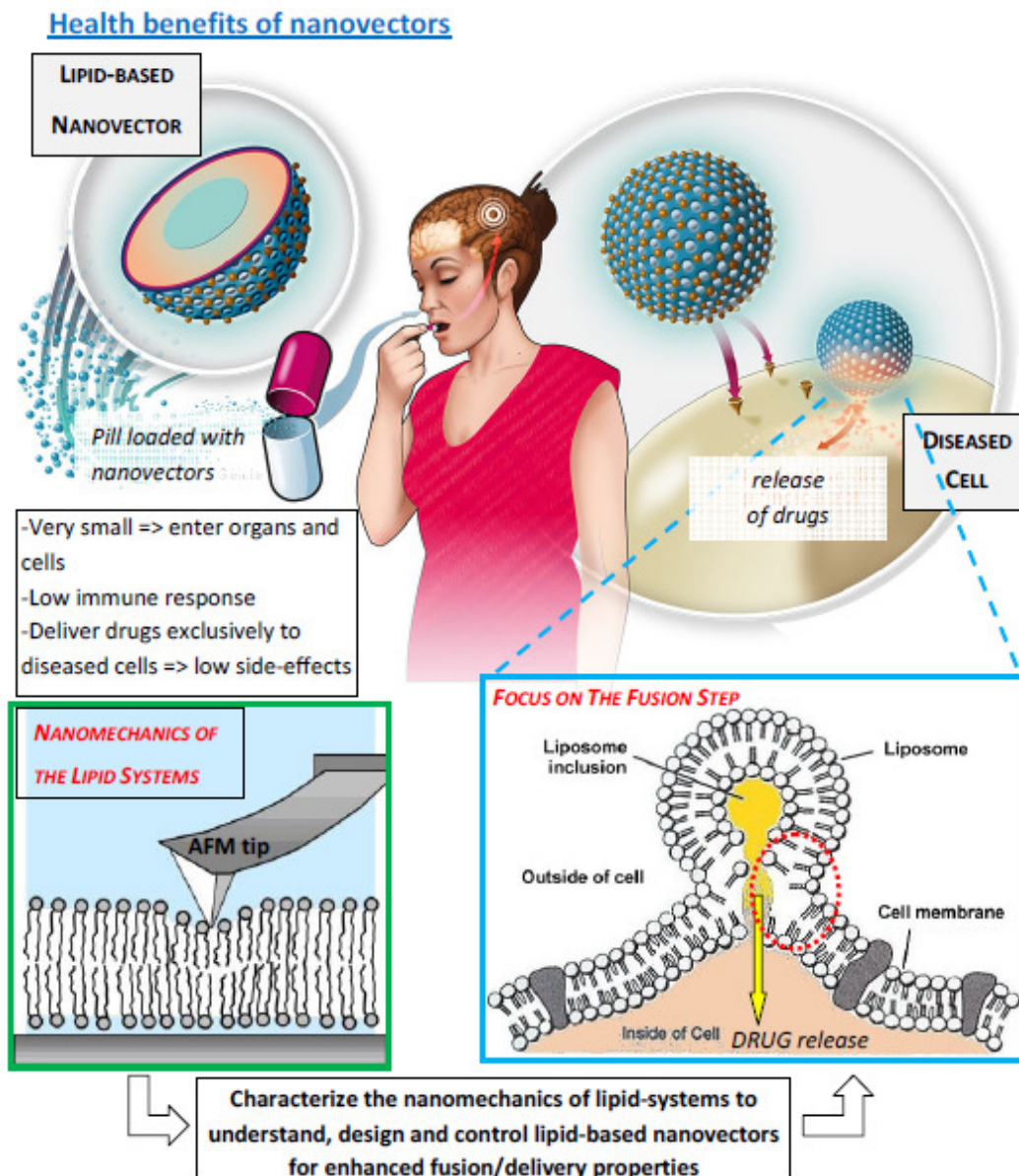


Figure 1: Biomimetic nanovectors (nm-sized capsules) designed for drug delivery are a system of self-assembled lipid molecules. The fusion of the nanovector with the lipid membrane of the target cell is crucial to the efficiency of drug release. This is controlled by the nanomechanical properties of both the lipid-based nanovector and of the target cell's lipid membrane (see dashed circle in bottom-right panel - reorganization of lipids and change in membranes' nanomechanics).