PhD subject

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Title: **Physical model of the cell nucleus mechanics: towards a chip-based diagnostic of premature cellular aging**

Project. Cellular aging (or *senescence*) is a normal process defined as the progressive decline of all cellular functions ending with cell cycle arrest. The process may happen prematurely in some pathological diseases, inducing symptoms akin to diabetes and/or cardiovascular dysfunction. Studies of rare premature aging syndromes like Progeria have identified a pathway to senescence related to a defect in lamin A, a major constituent of the nuclear lamina. This protein meshwork, part of the nuclear envelop, controls the shape of the cell nucleus and provides its mechanical rigidity (Fig. 1A). Using microfluidic tools and physics-based modelling (Fig. 1B), we will establish the correlation between well-characterized senescence of premature aging syndromes and the mechanical properties of nuclei. Experimental results will be integrated into a multiscale rheological model, in order to establish a phase diagram between rheological properties and pathology level.

Objectives. The aim of the project is to correlate the well-scored senescence of premature aging syndromes with the cell nucleus rheological properties. From combined experiments and modelling on cells from patients affected by these pathologies we will establish a complete set of quantitative, biological and physical data and infer mechanical criteria, beyond the usual nucleus shape one, for cell type classification.

Proposed approach (experimental / theoretical / computational). Cell lines with controlled senescence (lamina defective or biochemically treated) will be provided by a collaborating biologist (C. Badens, Marseille Medical Genetics (MMG), La Timone campus).
Experiments – Microfluidic experiments on single cell/nucleus will be conducted to assess nucleus shape, fragility and deformability, and correlate nucleus rheological properties with

lamina defect level. Another setup will mimic the situation in a blood vessel to characterize the response of endothelial cells to shear flow, with healthy or abnormal lamina.
Modelling and computing – We will develop a physical model connecting the global nuclear rheology to the dynamics of the local lamina meshwork. Deep learning will be included in the data analysis process to design new experiments optimized for data classification and to determine rheological criteria specific of the cell pathological state.

Expected profile. The PhD candidate should preferentially be a physicist with some knowledge in programming or a theoretician with strong interest towards experimental approaches. She or he must be motivated to work at the interface of physics and biology as she/he will handle biological samples and perform both experiments and computations.

Keywords. Premature aging, nucleus mechanics, lamin mutations, mechanotransduction, microfluidics, viscoelasticity, rheology, theory and numerical simulations, machine learning

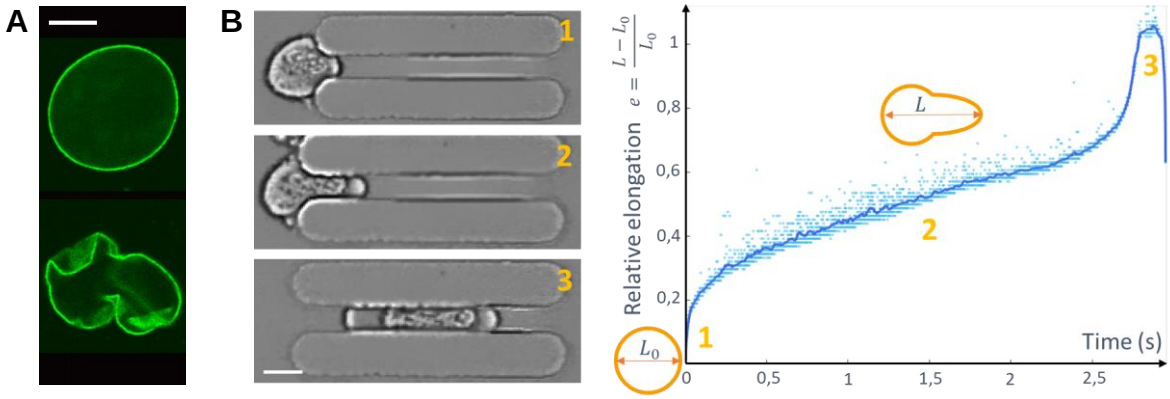

Figure 1. A) Cell nuclei of a healthy (top) and a Progeria-affected patient (bottom). Scale bar: 5 µm. B-C) Typical temporal elongation of a cell passing through a 6x10-µm^2 constriction. Scale bar: 10 µm.

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