PhD project 2023

Laboratory: **Dpt « Physics and Engineering for Living Systems »**
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Multiphysics modeling of confined cell migration

Keywords: cell mechanics, mechanobiology, confined migrationmicrofluidics, image analysis

Context. Mechanobiology studies the response of cells and tissues to their mechanical environment during different pathophysiological processes such as carcinogenesis or embryogenesis. Although major advances have made it possible to observe *in vitro* the behaviour of cells, observations are still often qualitative since **it is challenging to quantify the stresses, strains and mechanical parameters** associated with a specific cellular process. Therefore**, mechanical and mathematical modelling** plays a fundamental role as it allows many scenarios to be explored with less time and cost compared to laboratory tests.

Project. We focus on cell migration under confinement, a mechanobiological process which can be observed during embryogenesis, immune response or tumour progression. During confinement, cells migrate through sub-cellular (10–30 µm width) or sub-nuclear (2–10 µm width) pores. The nucleus, which is the largest and the stiffest cellular organelle, plays a critical role in confined environments since it may inhibit and gradually slow down migration. **Our objective is to study the influence of the cellular and nuclear mechanical properties during migration under confinement.**
We will use a microfluidic device with microchannels to constrain the cells. The PhD student will first assess the passive viscoelastic properties of the cells by pushing them through the microchannels under controlled pressure drop, as previously done (Figure) [1]. Second, similar experiments will be performed with cells freely migrating through microchannels without pressure drop, to assess the mechanical properties involved in active migration. In both series of experiments, the PhD student will modulate cellular components (chromatin, cytoskeleton, nucleo-cytoskeletal links), track various fluorescent markers of cellular dynamics (calcium fluxes, nucleus integrity and chromatin compaction state, cytoskeletal components), and correlate the changes to cellular mechanics. Specific cell responses to targeted modulations will give insight into the molecular mechanisms at play. Our experimental data will feed a sophisticated numerical model coupling both the molecular and the mechanical framework of the biological process of confined migration [2]. Our experimental and numerical approaches will be a consistent diagnostic tool to identify pathological cells.

This project will be done in collaboration with a computational group expert in numerical simulation of single and collective cell migration as well as nuclear mechanics (R. Allena, Univ. Nice) and a biology group expert in epigenetics and cell modulation (S. Ait Si Ali, Univ. Paris Cité).

Position description. The funding is conditioned on being selected by the Physics Doctoral School (ED 352, Aix Marseille Univeristé), in May 2023. Starting date is planned on October, 2023.

Expected profile. Preferentially a physicist with interest towards biological questions, the subject is however flexible and can be adapted to fit specific interest and skills of the candidate.

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References

[1] Enhanced cell viscosity as a marker of premature senescence induced by lamin A/C alterations. C. Jebane, A.-A. Varlet, M. Karnat, L. M. Hernandez-Cedillo, A. Lecchi, F. Bedu, C. Desgrouas, C. Vigouroux, M.-C. Vantyghem, A. Viallat, J.-F. Rupprecht, E. Helfer, C. Badens. BioArXiv: https://doi.org/10.1101/2022.07.18.500411

[2] Nuclear Stress-Strain State over Micropillars: A Mechanical In silico Study. R Allena, D Aubry. Mol Cell Biomech 19 (2022).

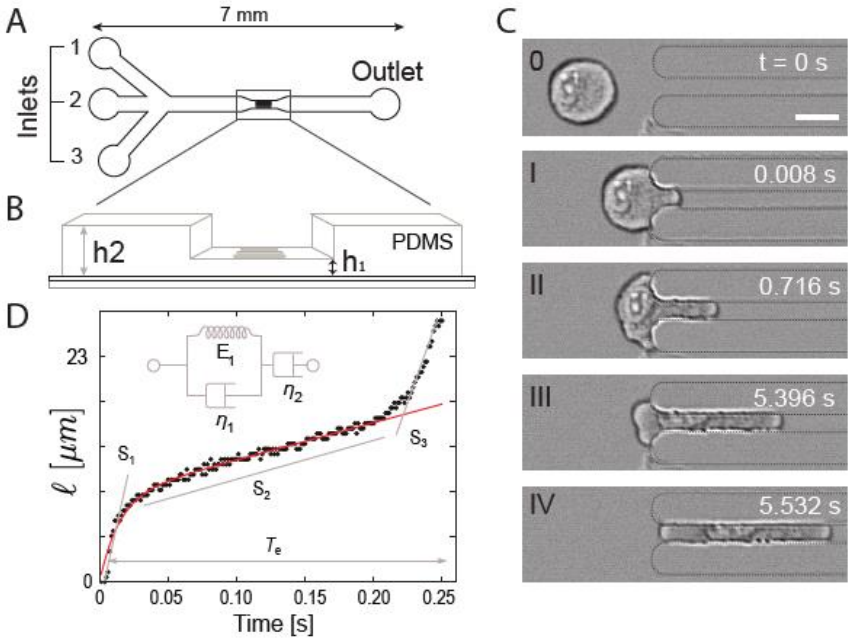

Figure. *A-B) Schematics of the microfluidic device (A, top view) and of the microchannel region (B, zoomed 3D-view) made of polydimethylsiloxane (PDMS). C) Timelapse of a 24-µm cell entering a 6-µm wide constriction. Scale bar: 15 µm. D) Typical time evolution of the tongue length l(t) of a cell entering a microchannel, with linear approximation of the 3 displayed regimes (slopes S_1-S_3) and analytical fit of the 2 first regimes (in red) using a rheological model.*