PhD PROJECT PROPOSAL

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Learning the rules of confined cell migration in complex flow environments

Lead supervisor: Ankur D. Bordoloi (**ADB**), ankur-deep.BORDOLOI@univ-amu.fr, IRPHE, ED353

Co-supervisor: Pierre Ronceray (**PR**), pierre.RONCERAY@univ-amu.fr, CINaM, ED352

Abstract (10 lines)*

Cell migration in confinement is a fundamental process underlying tissue morphogenesis, wound healing, immune surveillance, and cancer metastasis. During metastasis, tumor cells navigate through extracellular matrices and capillary networks where confinement and interstitial fluid flow create complex mechanical cues (see illustrating image A). How cells sense and adapt to these physical constraints remains poorly understood. In this project, we propose to tackle this problem by combining microfluidic experiments in controlled complex environments with data-driven stochastic modeling. We will vary physical and biological parameters to integrate multi-experiment datasets into a unifying inferred model. This model will quantitatively capture cell migration dynamics as an outcome of cell-environment, cell-flow and cell-cell interactions, revealing physical and mechanobiological rules governing confined cell migration under fluid flow.

Keywords*

Confined cell migration, microfluidics, data-driven modeling, stochastic dynamics, complex media, fluid shear stress, mechanotransduction

Scientific question and Objectives (10 lines) *

Building upon the expertise of two supervisors in experimental bio-microfluidics (ADB) and data-driven stochastic modeling (PR), this project will use an interdisciplinary approach combining biophysical experiments and data-driven statistical physics modeling. The main goal will be to **learn a mechanistically grounded "migration strategy" that predicts how single cells transduce local confinement, fluid shear and a crowded environment into navigational decisions across heterogeneous networks**. By quantitatively capturing the dynamics of cell position and shape descriptors from high-resolution microfluidic experiments, the model will enable the prediction of cell behavior across different confinement and flow regimes. Complementary biological perturbations, such as modulating cytoskeletal contractility or mechanosensitive signaling pathways, will be used to probe the mechanotransduction mechanisms that couple local mechanical cues to cell migration decisions.

*: Mandatory

Proposed approach (experimental / theoretical / computational) and research plan (20 lines)*

Our strategy is to explore parameter space of confined migration under flow by systematically perturbing the intrinsic motility of cells by mechanical stimuli along three axes: (1) the geometry of the confining network, (2) the external fluid shear stress, and (3) cell-cell interactions (see illustrating image B).

During the preparatory stage, the PhD student will receive training in microfluidic design and fabrication using soft lithography, as well as mammalian cell culture, fluorescence microscopy, and early-stage data analysis. In parallel, initial inference tests using the available pilot data in simplified test cases (e.g. network without flow) will validate the modeling framework and guide in optimizing the experimental parameters (e.g. frame rate, resolution, cell concentration, etc.).

In the second stage, we will probe the three axes of the parameter cube in depth by performing microfluidic experiments with two epithelial cell lines (benign MCF-10A and metastatic MDA-MB-231). Fluorescence microscopy will quantify single-cell trajectories, morphological dynamics, and interactions within controlled microfluidic networks of tunable pore size distribution. By systematically modulating the confinement geometry, interstitial flow rate and cell concentration, we will map their effects on migration speed, persistence, and directional bias. We will integrate the resulting datasets into our inference framework that will predict deterministic and stochastic contributions from local features (e.g., constriction size, local fluid shear stress, neighbor positions).

Finally, we will probe the mechanotransduction mechanisms that couple local mechanical cues to migration decisions by applying biological perturbations, such as modulating cytoskeletal contractility (e.g. blebbistatin) and mechanosensitive signaling (e.g. Rho/ROCK and YAP/TAZ). This will allow us to link migration model parameters to the underlying signaling pathways that govern cellular adaptation under confinement and flow.

Interdisciplinarity and Implication of the two labs (15 lines)*

(In this section the collaboration of the two laboratories will be explained in details to explain why the project cannot be conducted by one team alone)

This project is inherently interdisciplinary combining experimental biophysics, fluid mechanics, statistical physics and data-driven modeling to understand how cells migrate through complex microenvironments under flow. This collaboration will operate in a rapid feedback loop, where the experiments will guide model refinement and the modeling outcomes will guide the experimental parameter selection.

ADB brings his expertise in microfluidics, quantitative live-cell imaging and data analysis, providing the experimental framework to recreate the heterogeneous confined environment with flow. The project will also benefit from ADB's pilot experiments on confined cell migration through heterogeneous confinement network under flow, which provides the experimental foundation for model development. PR contributes with his skills in statistical physics and will provide the inference framework, stochastic force inference, that his group has been developing over the past years. PR has several years of experience in data driven modeling of cancer cells within complex environment. This tight integration of experimental biophysics and data-driven modeling lies beyond the scope of either team; only their combined expertise can bridge the cell level observation with the predictive mechanistic modeling.

Specify with whom the person recruited will collaborate and on what aspects *

The student will work with ADB on the microfluidics experiments related to the project, jointly with ADB and PR on the data analysis aspects, and with PR on the data-driven modeling aspects of the project.

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PhD student's expected profile*

The PhD candidate is expected to have a physics background, with both theoretical and experimental experience in biological physics, soft matter and/or statistical physics. The student should have lab experience, preferably including some experience with microscopy, as well as strong proficiency with theoretical statistical physics tools (fluctuation-dissipation relation, Langevin Dynamics…). Experience in programming (Python or MATLAB) is mandatory. Prior experience in image analysis (FIJI,Trackmate or alternatives), and/or in data-driven approaches / machine learning would be a plus.

Is this project the continuation of an existing project or an entirely new one? In the case of an existing project, please explain the links between the two projects (5 lines)*

This is an entirely new collaboration, joining pre-existing expertise of the two supervisors. Some pilot experiments were carried out during a Master's End Project at TU Delft under the supervision of ADB., where the initial microfluidic design, experimental protocol for generating interstitial flow in heterogeneous confinement networks, and image analysis workflow were developed. This prior work establishes the technical foundation and feasibility of the experimental approach for the PhD project.

Two to five references related to the project*

- Van der Net, A., Rahman, Z., Bordoloi, A.D., Muntz, I, Ten Dijke, P., Boukany, P., and Koenderink, G. EMT-related cell-matrix interactions are linked to states of cell unjamming in cancer spheroid invasion iScience, 27, 12, 111424, 2024
- Lautscham, L. A., Kämmerer, C., Lange, J. R., Kolb, T., Mark, C., Schilling, A., Strissel, P. L., Strick, R., Gluth, C., Rowat, A. C., Metzner, C., & Fabry, B. (2015). Migration in confined 3D environments is determined by a combination of adhesiveness, nuclear volume, contractility, and cell stiffness. Biophysical Journal, 109(5), 900–913
- Pries, A. R., Cornelissen, A. J. M., Sloot, A. A., Hinkeldey, M., Dreher, M. R., Höpfner, M., Dewhirst, M. W., & Secomb, T. W. (2009). Structural adaptation and heterogeneity of normal and tumor microvascular networks. PLOS Computational Biology, 5(5), e1000394
- Amiri, S., Zhang, Y., Gerardos, A., Sykes, C., & Ronceray, P. (2024). Inferring geometrical dynamics of cell nucleus translocation. Physical Review Research, 6(4), 043030.
- Brückner, D. B., Arlt, N., Fink, A., Ronceray, P., Rädler, J. O., & Broedersz, C. P. (2021). Learning the dynamics of cell–cell interactions in confined cell migration. PNAS, 118(7), e2016602118

Two main publications from each PI over the last 5 years*

ADB:

- Rahman, Z., Bordoloi, A.D., Rouhana, H, Tavasso, M., van der Zon, G., Garbin, V., Ten Dijke, P. and Boukany, P. Interstitial flow potentiates TGF-β/Smad-signaling activity in lung cancer spheroids in a 3D-microfluidic chip Lab-on-a-Chip 24, (422-433), 2024

- Bordoloi, A.D., Scheidweiler, D., Dentz, M., Bouabdellaoui, M., Abbarchi, M. and de Anna, P. Structure induced laminar vortices control anomalous dispersion in porous media Nature Communications 13, 3820, 2022

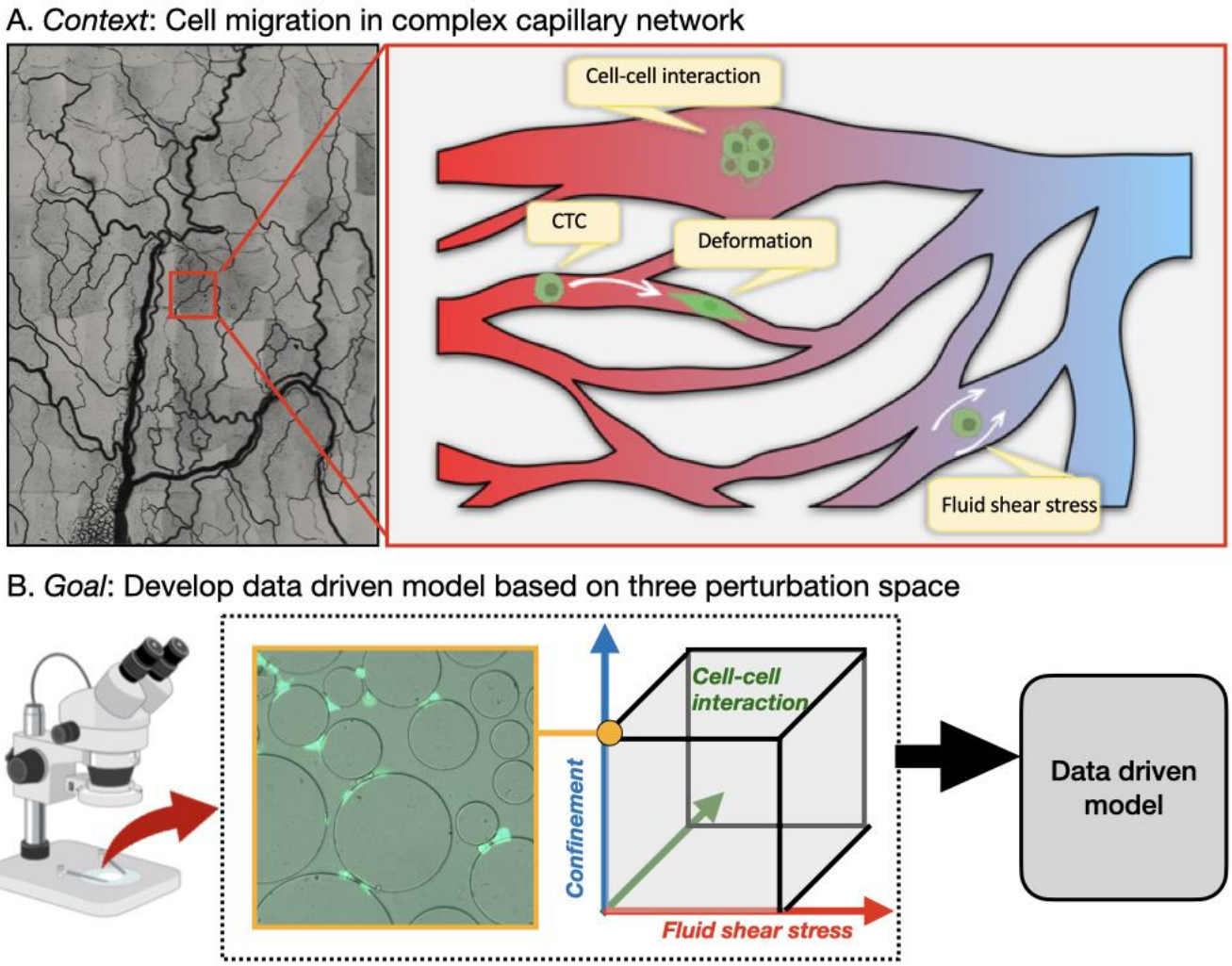
PR:

- Andonis Gerardos and Pierre Ronceray. Principled Model Selection for Stochastic Dynamics. Phys. Rev. Lett. 135, 167401, 2025.

*: Mandatory

- Anna Frishman and Pierre Ronceray. Learning Force Fields from Stochastic Trajectories. Phys. Rev. X 10, 021009, 2020.

Project's illustrating image



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