
PhD project : **Heterogeneous transport of circulating tumor cells in blood flow (HetFlow)**

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Context. **Blood is a dense suspension** of numerous Red Blood Cells (RBCs, 95% of the cells) and much more rare circulating cells, such as immune cells, progenitors, fetal cells or tumor cells. **All these cells travel through a highly complex and ramified vascular network** and each cell type has created its proper strategy to efficiently circulate through the network. In particular, Circulating Tumor Cells (CTCs), which are larger and more rigid than RBCs, are prone to be pushed towards the vessel walls (a phenomenon called margination) or retained at bifurcations. Understanding how rare CTCs interact with a heterogeneous and RBC-rich microenvironment is still an open question in the fields of hydrodynamics and biophysics. The HetFlow project aims at establishing the **physical principles underlying transport of CTCs through the vascular network under the influence of surrounding RBCs**.

State-of-the-art. Most previous studies focused solely on either RBCs or rare circulating cells and have neglected the biophysical interactions between heterotypical cells. For example, self-organization of RBCs under flow has been extensively studied in vitro [1-5] and in silico [2,6], including by our group. We also characterized the adaptive transport of monocytes (one type of white blood cells) under flow in a confined geometry mimicking the pulmonary bed [7]. However, so far, mixed suspensions of RBCs and other cells have been barely explored. Two recent studies showed the promoting role of cell-cell interactions between CTCs and platelets or RBCs in tumor proliferation [8,9] but in static conditions and not under flow, which is different from what CTCs undergo in vivo in the microcirculation. The HetFlow project aims at filling this gap by studying the **coupled dynamics of CTCs in a RBC-rich flowing environment**.

Project. The main objective of HetFlow is to **set a biophysical framework for the heterotypic cell transport in the RBC-rich blood flow**, and establish the physical mechanisms that drive the vascular architecture, the RBC dynamics, and the CTC transport. Our project will combine **soft matter physics, fluid dynamics, and cell biology approaches**, such as cell biomechanics, microfluidics, brightfield and fluorescence microscopy of living cells. We will design microfluidic networks mimicking the vascular network geometries at various complexity levels; microscopy imaging will allow to track in real time flow events such as margination, transit through confined/bifurcating regions, or arrest. We will develop **numerical simulations** with our collaborator, S. Mendez, to identify the crucial parameters to be tuned, like cell concentration, cell mechanical features (size or shape), or microfluidic device geometry (branching). Microfluidic experiments will firts performed with CTCs and abiotic particles (rigid beads or deformable particles) mimicking RBC mechanical features but unable to interact biologically with the CTCs : this first series of experiments will allow understanding the **mechanical and hydrodynamical effects** of the environment geometry and of the surrounding particles on the CTC behavior. The same experiments will be next repeated with CTCs mixed with RBCs to state the **impact of cell-cell biological interactions** (typically, adhesion). **The interdisciplinary approach of HetFlow will establish the understanding of CTC transport in the blood flow** by explicitely identifying the mechanical and biological interactions between the CTCs and the surrounding RBCs.

The team and its collaborators. Emmanuèle Helfer is a biophysicist with a large expertise in physics of the cell cytoskeleton and membranes. She uses microfludics in routine to study the response of cells (RBCs [2,10] and other cell types [7,11]) to various mechanical constraints, either in healthy or pathological conditions. The PhD project involves her collaborator, Simon Mendez (IMAG, Montpellier), researcher in fluid and mechanics and main developer of the YALES2BIO solver dedicated to blood flow predictions [2,6].

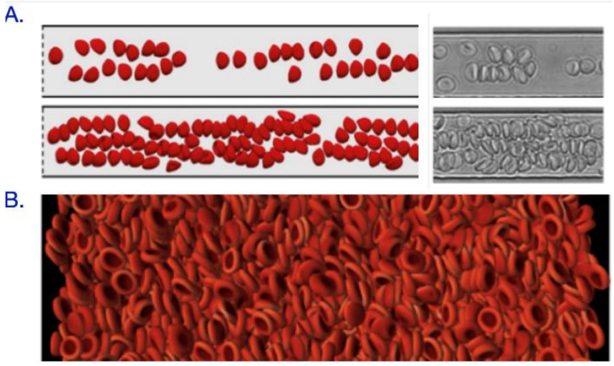

Figure 1. (A) Self-organization of RBCs under quasi-2D confined flow (in the horizontal direction) in channels of 9 µm in depth (perpendicularly to the screen) and 30 µm in width: validation of YALES2BIO simulations (left) by microfluidic experi-ments (right). Volume fractions are 8% (top) and 20% (bottom). Adapted from [2]. (B) YALES2BIO simulation of a dense RBC suspension (30% vol. fraction) in a shear flow (in the vertical direction).

Role of the PhD student. The PhD student will perform microfluidic experiments on suspensions of cells/cells and cells/particles, and videomicroscopy data analysis. She/he will be trained on the various techniques used in the project: design/fabrication of microfluidic devices, cell handling, optical microscopy, image analysis. We are looking for a student with a training in physics, preferentially in soft matter physics and/or biophysics. She/he is expected to have a strong interest for interdisciplinarity, and more particularly for living systems.

References (publications from the team and collaborator are highlighted in bold)

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