INTERNSHIP PROPOSAL

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Thesis possibility after internship: YES
Funding: YES If YES, which type of funding: Impulscience (Fondation Bettencourt Schueller)

Impact of antibiotics on mutations in bacteria

Our fight against infectious diseases is underpinned by an evolutionary arms race with pathogens, in which mutations fuel the evolution of virulence and antibiotic resistance. Similar issues arise in cancer therapy, where cancer cells accumulate mutations and escape chemotherapy. It has been proposed that mutation rates are environment-dependent. For instance, **mutagenesis in bacteria was proposed to increase in presence of sublethal concentrations of antibiotics**, which are often found in our environment due to our extensive use of antibiotics in agriculture and medicine.

However, previous studies on the environmental control over mutagenesis lead to many controversies, due to the limitations of classical experimental approaches. We recently developed a new approach to overcome these limitations, allowing **detecting mutations and assessing their effects directly in single bacterial cells**[1,2,3] (figure 1). In this approach, bacteria grow in a microfluidic chip called the "mother machine" (figure 1A), and they express a fluorescent marker which tags mutations (figure 1B). The growth of the bacteria and the occurrence of mutations is followed on a long time-scale (several days) by time-lapse microscopy.

In this project we will **visualize and quantify mutations in the bacterium *Escherichia coli* in presence of sublethal doses of antibiotics**. This internship is interdisciplinary and will combine experimental methods from physics (microfluidics, microscopy) and biology (genetics, molecular biology), with image analysis techniques using deep learning[3] and data analysis in the framework of probability theory and statistical physics.

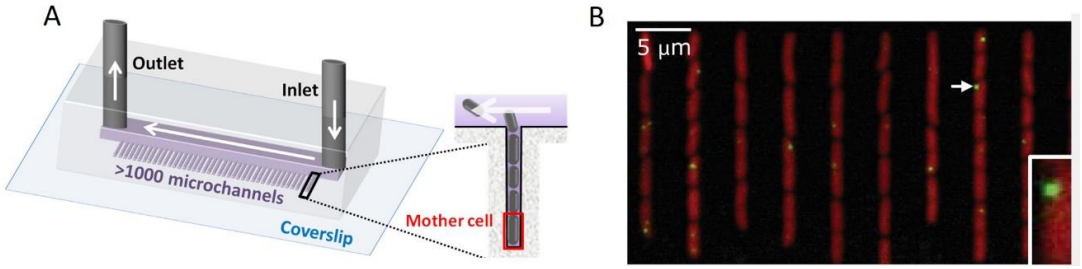

Figure 1: Mutation Visualization experiments. A) The "mother machine" microfluidic chip used to grow bacteria in precisely controlled conditions on a long time-scale. B) Overlay of red (to see the bacteria growing in the microchannels) and yellow fluorescence images (YFP-MutL tags the mutations). The inset shows a magnified image of a cell with a YFP-MutL spot (arrow), i.e. a mutation.

1)Robert L, et al. (2018) Mutation dynamics and fitness effects followed in single cells *Science* 359(6381):1283-1286
2)Robert L, Ollion J, Elez M, (2019) Real-time visualization of mutations and their fitness effects in single bacteria. *Nat. Protoc.* 14(11):3126-3143
3)Ollion J, Elez M, Robert L, (2019) High-throughput detection and tracking of cells and intracellular spots in mother machine experiments. *Nat. Protoc.* 14(11):3144-3161.

Please, indicate which speciality(ies) seem(s) to be more adapted to the subject:
Condensed Matter Physics: YES Soft Matter and Biological Physics: YES
Quantum Physics: NO Theoretical Physics: NO