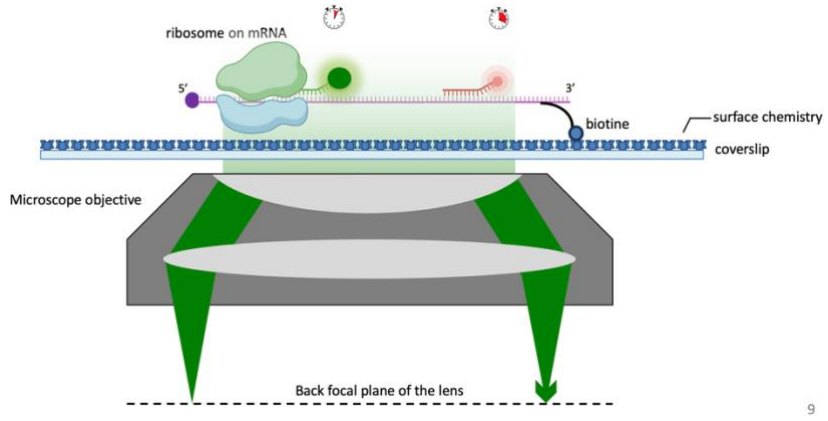
M2 Internship Offer with Opportunity for PhD

FRAME: Role of RNA modifications in translation Fidelity. Example of translational fRAmeshifting studied at the single-MoleculE level

Translation is the step in gene expression during which the genetic code carried by mRNAs is decoded into proteins by the ribosome. For proper cellular function, it is essential that the ribosome ensures optimal translation fidelity, meaning that the synthesized protein corresponds accurately to the genetic message. To achieve this objective, translation is subject to numerous regulatory mechanisms. In recent years, chemical modifications of RNA (the epitranscriptome) have emerged as a major regulatory pathway for translation efficiency. Despite recent advances in this field, the effect of these modifications on decoding fidelity—and particularly on maintaining the reading frame—remains largely underexplored. In certain viruses, such as HIV and SARS-CoV-2, RNA secondary structures manipulate the ribosome to force a change in reading frame, a process known as programmed frameshifting. This event enables viruses to express proteins that are essential for their replication. While these frameshifts are well described from a structural perspective, the influence of chemical modifications within these mRNA structures on the ribosome and its function remains unexplored. Indeed, very few approaches make it possible to measure the physical forces exerted by the ribosome on these mRNA structures and how these forces are altered by RNA modifications.

The proposed PhD project aims to determine the importance of RNA modifications in translation fidelity using biophysical approaches. It will be structured around two major axes at the single-molecule level to account for the heterogeneity of RNA modifications: 1) adaptation of our reporter system to measure real-time translation speed via fluorescence microscopy, directly in *in vitro* systems where RNA chemical modifications are tightly controlled ; 2) study using magnetic tweezers to measure the physical forces exerted by the ribosome to unwind structures present on all mRNAs. For this second part, we will build upon our collaboration with David Dulin (Vrije Univ. Amsterdam), with whom Karen Perronet currently co-supervises a PhD student, to develop our own magnetic tweezers setup at LuMIn.



Reporter assay to time a single ribosome during translation using Total Internal Reflexion Fluorescence Microscopy.

The Interdisciplinary Nature of the Project

These approaches require both biological expertise and extensive skills in physics and optics to track and quantify single-molecule translation events. Consequently, these methods are highly interdisciplinary and, to date, have never been applied to address these questions.

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