| Title | Emergence of Macroscopic Nonequilibrium Effects from the Molecular Scale |
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| Proponent | Alberta Ferrarini |
| Research Group | Soft Matter Theory |
| Contact | web: https://wwwdisc.chimica.unipd.it/softmattertheory/ |
| | email: alberta.ferrarini@unipd.it |
| Co-Proponent | Subir Paul |
| Research Group | Systems Chemistry |
| Contact | web: --- |
| | email: subir.paul@unipd.it |

| International Secondment | |
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| PI | Massimiliano Esposito |
| Institute | University of Luxembourg |
| Place, country | Luxembourg |
| # months (min.3) | 6 |

**Project description (2 page max):**
Nonequilibrium processes are no longer exclusive to biological systems. The design and synthesis of artificial molecular systems that harness free energy from the environment and transduce it into desired effects are now well established. Molecular motors are a prototypical example of such artificial systems, with well-understood working mechanisms [1]. On the one hand, stochastic thermodynamics characterizes how energy is harnessed and transduced; on the other hand, kinetic asymmetry explains how nonequilibrium conditions and molecular properties (e.g., molecular shape) lead to directional motions.

The ongoing challenge lies in developing artificial molecular systems producing effects beyond the molecular scale that emerge at the macroscopic level. Several experimental examples demonstrate this transitions, including the formation of high-energy vesicles [2] and the amplification of individual molecular motor motions to achieve self-propulsion of nanostructures [3] as well as the contraction/expansion of gels [4]. This challenge is not limited to the design and synthesis of these systems. Indeed, a precise **characterization of the mechanisms underpinning how the free energy harnessed at the molecular scale translates into macroscopic behavior remains an open question**.

**This project aims to answer this open question** by developing a systematic theoretical framework and computational tools. The project is organized in three main objectives.

**Objective 1.** – Molecular dynamics of chemically-fueled self-assembly.
Chemically-fueled self-assemblies are high-energy supramolecular structures sustained by the continuous interconversion of high-energy molecules into low-energy molecules [2]. Current theories of nonequilibrium self-assembly account for molecular properties solely in terms of effective parameters, e.g., free energy interactions and surface tension [5]. However, they fail to capture single-molecule properties, such as specific interactions and molecular shapes, which are crucial in determining how molecules organize in space. To overcome this limitation, nonequilibrium molecular dynamics simulations must be developed. Current molecular dynamics simulations are inadequate because they cannot describe fueled chemical reactions in a thermodynamically consistent way. To the best of our knowledge, there is only one example of a thermodynamically consistent nonequilibrium molecular dynamics simulation, which was designed specifically for a single molecular motor [6]. Here, we aim to develop **a systematic molecular dynamics framework** capable of describing a wide range of nonequilibrium self-assembly processes by integrating the approach of

Ref. [6] with standard molecular dynamics codes. This tool will allow us to determine the **minimal conditions**, in terms of thermodynamic driving and molecular properties, **that govern the formation and spatial organization of self-assemblies**.

**Objective 2.** - Emergence of active global motions
Active (molecular) swimmers convert free energy into global directional motion. While various models describe their dynamics, a comprehensive understanding of their propulsion mechanisms is still lacking. Here, we aim to understand **how global directional roto-translational motions of macromolecules can emerge** when only conformational degrees of freedom are kept out of equilibrium. Specifically, we aim to determine how the energy harvested by conformational degrees of freedom is transduced and utilized by the roto-translational ones to sustain an active motion. To achieve this, we will first study simple models of coupled rotors to identify the **minimal conditions**, in terms thermodynamic driving and coupling between different degrees of freedom, required for active global motions to emerge. We will then extend the nonequilibrium molecular dynamics simulations developed in Objective 1 to analyze this phenomenon in specific systems, such as the one in Ref. [3].

**Objective 3.** – Emergence of active mechanical properties
The mechanical properties of active gels, such as the stress tensor quantifying their response to external forces, depend on the nonequilibrium driving that keeps some internal degrees of freedom of the molecular components (e.g., conformational ones, as in Ref. [4]) out of equilibrium. Current theories describe these effects using effective parameters [7], but their microscopic origin remains unclear. Here, we aim to fill this gap. First, we will extend the nonequilibrium molecular dynamics simulations from Objective 1 to model and characterize specific systems (e.g., the one in Ref. [4]). This will allow us to **quantify how mechanical properties of the gel vary with the thermodynamic driving** acting on the molecular components. Second, we will develop a theoretical framework that connects the active contributions to the stress tensor with properties of the molecular components, starting from fundamental principles.

**Methods.** The project will use and develop molecular dynamics simulations, stochastic methods, and hydrodynamic theories.

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