UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi Biomolecolari – XL CICLO

Research Topic ID: XL – 1.9

Proponent: Prof. Luca De Gioia

Project Title: From Computational Insights to Rational Design: Investigation of Structure-Activity Relationships in Bio-Molecular Ratchets for Tailored Performance

Scientific background and 'open issues'
Molecular ratchets, which are autonomously powered by chemical reactions, have become crucial elements in the development of synthetic molecular motors and pumps. These processes, which are common in biological systems, offer significant potential for the progression of synthetic molecular nanotechnology and artificial energy conversion systems. The performance of these molecular ratchets is evaluated based on their speed, power, and efficiency. For autonomous chemically powered molecular ratchets, these factors are closely linked with the directionality, catalytic rate, and efficiency of the energy conversion process. Gaining a deep understanding of these features and their interconnections is essential for improving the design of molecular ratchets for specific biological applications.

Objectives
The main objective of this Ph.D. project is to explore the complex relationships between the stereo-electronic properties and reactivity in recently studied molecular ratchets, with the ultimate goal of rationally design novel biomolecular ratchets of biotechnological relevance.

Methodologies
Several computational methods will be used, including Molecular Dynamics, DFT calculations, and Knowledge-based methods (Machine Learning and other AI approaches).

Collaboration / Co-tutoring opportunities
The project will be carried out in collaboration with experimental laboratories involved in the synthesis and characterization of molecular ratchets with tailored characteristics.

Project's Sustainability & Mobility

- The laboratory has a long-standing experience in the characterization of structure-activity relationships in biomolecules using computational approaches.

- *Recent publications:*

Mechanism of RGD-conjugated nanodevice binding to its target protein integrin $\alpha_V\beta_3$ by atomistic molecular dynamics and machine learning
Frigerio, G., Donadoni, E., Siani, P., ...De Gioia, L., Di Valentin, C.
Nanoscale, 2024, 16(8), pp. 4063–4081

Use of the Asymmetrical Chelating N-Donor 2-Imino-Pyridine as a Redox [Fe4S4] Cubane Surrogate at a Di-Iron Site Related to [FeFe]-Hydrogenases
Mele, A., Arrigoni, F., De Gioia, L., ...Schollhammer, P., Zampella, G.
Inorganics, 2023, 11(12), 463

Molecular Dynamics for the Optimal Design of Functionalized Nanodevices to Target Folate Receptors on Tumor Cells
Donadoni, E., Frigerio, G., Siani, P., ...De Gioia, L., Bonati, L., Di Valentin, C.
ACS Biomaterials Science and Engineering, 2023, 9(11), pp. 6123–6137

Assessing the Performance of Non-Equilibrium Thermodynamic Integration in Flavodoxin Redox Potential Estimation
Silvestri, G., Arrigoni, F., Persico, F., ...De Gioia, L., Vertemara, J.
Molecules, 2023, 28(16), 6016

- *Foreign institutions for achieving the required ordinary mobility:* Department of Chemistry, University of Manchester (UK)

References

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2. D. R. S. Pooler, A. S. Lubbe, S. Crespi, B. L. Feringa, *Chem. Sci.* **2021**, *12*, 14964–14986.
3. A. Mondal, R. Toyoda, R. Costil, B. L. Feringa, *Angew. Chem. Int. Ed.* **2022**, *61*, e202206631.
4. S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan, A. L. Nussbaumer, *Chem. Rev.* **2015**, *115*, 10081–10206.
5. Y. Feng, M. Ovalle, J. S. W. Seale, C. K. Lee, D. J. Kim, R. D. Astumian, J. F. Stoddart, *J. Am. Chem. Soc.* **2021**, *143*, 5569–5591.
6. I. Aprahamian, *ACS Cent. Sci.* **2020**, *6*, 347–358.