LABORATOIRE DE BIOLOGIE ET MODELISATION
DE LA CELLULE

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M2 Internship offer

Academic year 2024/2025

Exploration and expansion of conformational states of the ABC transporter BmrA

LBMC laboratory at École Normale Supérieure de Lyon
DAMM team - Dynamics and Control of Macromolecular Assemblies and Molecular Machineries

Starting date: beginning of 2025 (as early as possible)
Duration: 6 months
Supervisor: Nicoletta Ceres (nicoletta.ceres@ens-lyon.fr)

Keywords: machine learning, transmembrane transporter, conformational state, allostery

Context

The DAMM team develops *in silico* methods and conducts computational experiments using both physics-based and machine learning approaches to address the fundamental relationship between protein structure and function from different, complementary perspectives.
One class of proteins of interest for the team is the family of transmembrane (TM) ATP-binding cassette (ABC) transporters. These ubiquitous proteins, that play a crucial role in both physiological and pathological conditions, mediate the transport of a wide range of small organic molecules across the lipid bilayer by coupling ATP binding and hydrolysis with significant conformational changes.

Project description

Despite the structural determination of numerous ABC transporters over the past 20 years, a detailed description of the conformational space explored during a transport cycle, based on experimental models, is available for just a few transporters. Additionally, the impact of transmembrane helix deformations on functional conformational changes, as well as the allosteric effect of ATP and ligand binding, are still poorly understood.
The student will contribute to addressing these aspects of the structure-function relationship for the multidrug-resistant protein BmrA, overexpressed by the bacterium *Bacillus Subtilis* to confer resistance in vivo to cervimycin C, an antibiotic produced by *Streptomyces tandæ* against Gram-positive bacteria.
A collaboration with an experimental team, which conducts structural and enzymatic experiments on BmrA to further characterize this transporter, is currently ongoing.

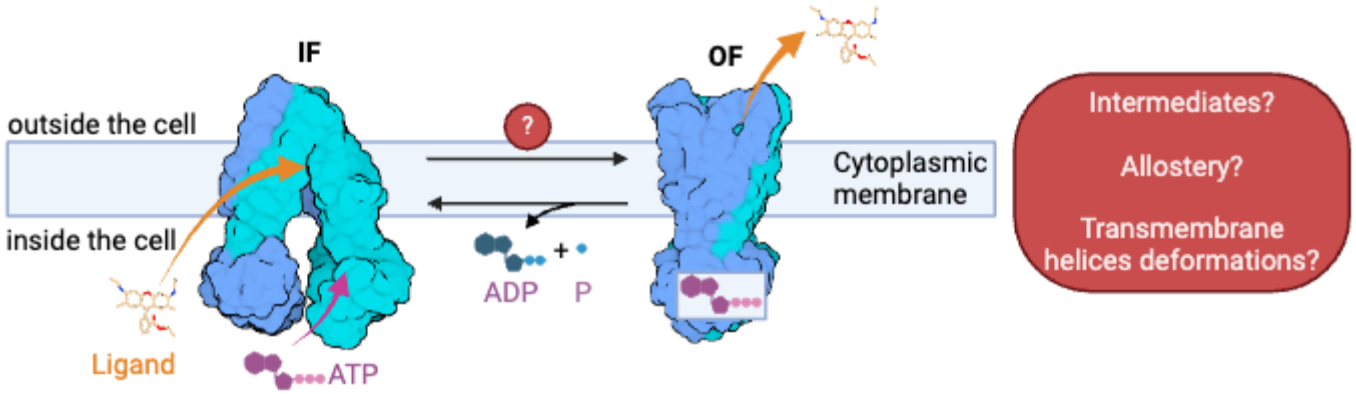

Figure 1. Scheme of the transport cycle. The homodimeric BmrA transporter alternates between inward-facing (IF) and outward-facing (OF) states. In the IF state, ligands bind inside the cell. ATP binding triggers the transition to the OF state, releasing ligands outside. ATP hydrolysis drives the return to the IF state. Despite existing atomistic models of the IF and OF states, the transition mechanism remains unclear. Chains A and B of BmrA are colored respectively in cyan and blue.

What you will learn

- How to use diverse and complementary approaches to better understand the functional implications of conformational changes in BmrA through the application of:
  - machine learning algorithms (notably AlphaFold)
  - physics-based methods (such as those related to normal modes theory)
  - static 3D protein structure analysis and visualization tools
- How to organize and manage your work in a collaborative environment using tools like GitLab, Jupyter notebook, JupyterLab, including the development of pipelines for executing and analyzing computational experiments
- How to effectively communicate in both oral and written forms with computational and structural biologists

Host environment and contact

Our team of computational biologists, with diverse expertise, aims to advance the understanding of the relationships between structure and function of biological systems. We integrate *in silico* approaches, including molecular dynamics simulations and machine learning, across atomistic and coarse-grain scales. Our focus is primarily on proteins: their assemblies and interactions with other proteins and biological membranes.

Send a CV and cover letter to nicoletta.ceres@ens-lyon.fr and juliette.martin@ens-lyon.fr.

References

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