Three-year PhD position at the Enzyme and Cell Engineering Lab, Amiens, France

Title : Simulation of the translocation of peptides across biological membranes for future pharmacological applications

Scientific context

Cell-penetrating peptides (CPPs) are small peptides (30 aminoacids or shorter) that can cross the outer membranes of cells without affecting their integrity.[1] They are able to reach specific cell compartments, where they can potentially facilitate the delivery of therapeutic or imaging-related drugs. The therapeutic potential of CPPs is huge, and still largely untapped despite the recent increase in peptide-derived drugs approved by the Food and Drug Administration. In particular, CPPs could replace traditional antibiotics that have become ineffective against the highly virulent and resistant bacteria of the ESKAPE class, which raise global public health concerns acknowledged by the World Health Organization.[2] However, current limitations in the understanding of the interactions between CPPs and membranes strongly hinder the rational design of CPPs, which is crucial to target specific therapeutic applications. The goal of this project is to contribute to a better understanding of the mechanisms and free energy costs driving the recognition and translocation of a set of peptides across membranes, using molecular dynamics simulations.

Research project

Because CPP/membrane recognition and translocation are slow processes, two simulation techniques will be combined to obtain accurate yet computationally cost-effective simulations: coarse-graining, which represents atom groups as pseudoparticles (limiting computational cost), and enhanced sampling, which accelerates transitions along user-defined collective coordinates related to the process under study and yields the associated free energy penalties. These collective coordinates will be carefully chosen to account both for peptide flexibility and membrane deformation, based on previous work in the lab.[3] We will especially focus on two crucial phases of the global mechanism: the adsorption of the peptide on the membrane, and the first steps of its translocation through it. The studied peptides will be chosen as variations on the sequence of well-known naturally-occurring CPPs (Tat, penetratin…), as well as exemplars of the main classes of CPPs selected using the ADAPTABLE antimicrobial peptide (AMP) database hosted in the lab.[4] Novel hybrid CPPs studied in the lab as part of a collaborative project with microbiologists will also be considered, providing stimulating interactions between experiments and *in silico* predictions. If time allows, the simulation results will be confirmed in the lab by experimental techniques (NMR, fluorescence). Beyond the mechanisms specific to each CPP, which are valuable *per se*, we hope to derive guidelines facilitating the choice of CPP sequences for a given application.

The lab

Research at GEC focuses on cell biochemistry in plants and animals. Transdisciplinary by nature, it combines experience in the preparation of biological membranes with expertise in NMR and computational methods to study the structure and dynamics of biomolecules (all-atom and coarse-grained molecular dynamics, docking, free energy simulations, software development...). Involved in the study of AMPs for several years, GEC hosts the ADAPTABLE database of AMPs. It has

privileged access to the high-performance computing platforms in Amiens and Reims (more than 4000 CPU computing cores, 300 GPUs, 500 teraflops).

Living in Amiens

Amiens, the capital of Picardy, is one hour away from Paris and Lille by train. University students represent more than 25% of its population of 140,000, accounting for a rich cultural life and lively atmosphere. It hosts one of the largest university hospitals in France, powering cutting-edge medical research. Home to the largest gothic cathedral in France (a UNESCO world heritage site) and famous floating gardens, its situation in the Somme valley (with more than 200 km of cycling paths) and the vicinity of the Somme bay (ranked amongst the world's most beautiful bays) also makes it ideal for nature lovers.

Eligibility

Successful candidates should hold a master's degree (or equivalent) in chemistry, physics, molecular biology or related disciplines and possess an intermediate English level. Knowledge or experience in computational chemistry, molecular modeling and/or computer programming is highly desirable.

How to apply

Applications should be sent to **Benjamin Bouvier** (benjamin.bouvier@u-picardie.fr) or **Nicola D'Amelio** (nicola.damelio@u-picardie.fr) **before June 1st, 2023**, comprising:

- a curriculum vitae detailing the completed university courses;
- grades and ranking sheets for the courses followed during bachelor's and master's degrees;
- a letter of motivation in which the candidate advertises her/his suitability to the project;
- the contact details of at least two of the candidate's previous supervisors or lecturers willing to recommend their application.

The selected candidate will be required to participate in a competitive selection process between applicants to PhD projects shortlisted by the doctoral school; it is therefore essential that the application file be of high quality. **The PhD position will start in October 2023.**

References

[1] Lindgren, M. ; Hällbrink, M. ; Prochiantz, A. ; Langel, U. *Trends Pharmacol. Sci*. 2000, **21**, 99–103.
[2] Abadi, A. T. B. ; Rizvanov, A. A. ; Haertlé, T. ; Blatt, N. L. *BioNanoScience* 2019, **9**, 778–788.
[3] Bouvier, B. *J. Chem. Theory Comput.* 2019, **15**, 6551–6561.
[4] Ramos-Martín, F. ; Annaval, T. ; Buchoux, S. ; Sarazin, C. ; D'Amelio, N. *Life Sci. Alliance* 2019, **2**, e201900512.