M2 internship — Computational Chemistry/ Biophysics

(start Feb. 2026)

CNRS, Laboratoire de Biochimie Théorique, Paris, France

Multiscale computational investigation of PAR-seeded condensates in DNA damage response

Biomolecular condensates are dynamic membraneless cellular compartments composed of proteins and nucleic acids that condense into liquid-like droplets formed through liquid-liquid phase separation (LLPS). Among many other cellular processes, biomolecular condensates play a key role in the response to DNA damage by concentrating and organizing repair proteins at sites of DNA lesions.[1] The formation of such condensates relies on the recognition of DNA damage by the PARP-1 enzyme, that then catalysis its (auto)Poly(ADP-ribose)-ylation (PARylation), i.e. the addition of PAR tags at various sites (Figure 1a).[2–4] PAR is an unstructured and highly charged biopolymer that serves as a multivalent platform for non-covalent binding of proteins.[3] PAR chains are believed to serve as a seed for condensates, formed through non covalent interactions between the multivalent PAR chains and proteins with low complexity domains. These condensates selectively recruit and concentrate proteins involved in DNA damage repair, such as FUS (Fused in Sarcoma), p53 and EWS (Ewing Sarcoma), thus organizing the damage repair process.[4,6] Accumulation of PAR and dysregulated PAR condensates have been linked to various diseases, including cancer and neurodegenerative disorders such as Alzheimer's and Parkison's diseases. However, the formation, structure and dynamics of these condensates are still poorly understood, as well as the molecular aspects of PAR-protein recognition and determinants of selective protein recruitment within the condensates. There is thus a strong need to better understand at the molecular level the rules governing the formation and physical properties of PAR-seeded condensates, as well as their impact on both protein and DNA structure within the condensates.

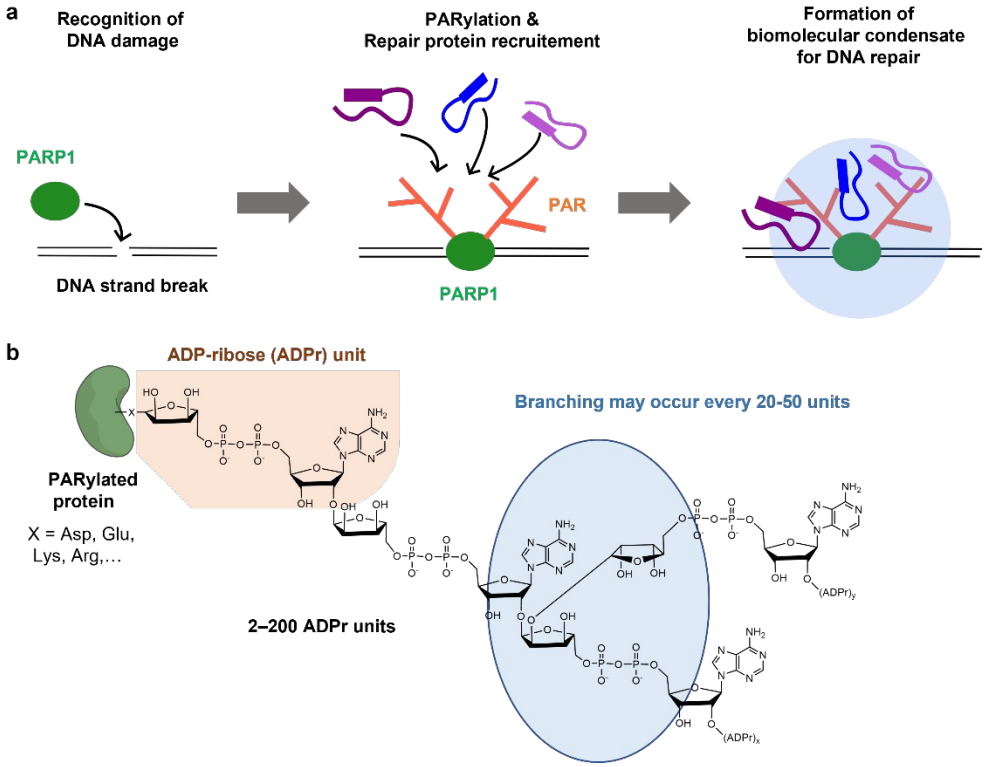

Figure 1: a) Schematic steps of DNA damage recognition leading to the formation of PAR-seeded condensates. b) Chemical structure of PAR

We propose in this M2 project to **setup a multiscale simulation methodology to obtain a molecular understanding of the formation and properties of PAR-triggered condensates.** The project will focus on the interaction between PAR and the FUS protein. We propose a multiscale simulation approach combining simulations at different levels (atomistic and coarse grain) of PAR/FUS interactions and PAR-FUS condensates that will allow us to reveal the molecular level structure of these condensates and illuminate the factors modulating their formation. The internship will be divided in two tasks: 1) Atomistic simulations with refined force fields to characterize PAR-FUS interactions in dilute solutions; 2) Coarse-grained simulations to explore the physical properties of PAR-FUS condensates under varying conditions.

Techniques/Methods Molecular dynamics; Coarse-grain and all atom simulations ; Enhanced sampling ; programming for simulation analysis (Python).

Research environment The research will take place in the lab of Theoretical Biochemistry (LBT) with Élise Duboué-Dijon (specilist of nucleic acid simulations at the all-atom scale) and Fabio Sterpone (modeling of condensate with coarse grained approaches). Our team is specialized in the simulation, at different scales, of biologically relevant processes. It is located in the very stimulating research environment of the Latin Quarter, at the heart of Paris.

Contact information Interested candidates should contact Élise Duboué-Dijon (elise.duboue-dijon@cnrs.fr) and Fabio Sterpone (sterpone@ibpc.fr) together with a curriculum vitae and contact information for one or two references.

References

1. Spegg, V. & Altmeyer, M. Biomolecular condensates at sites of DNA damage: More than just a phase. DNA Repair 106, 103179 (2021).
2. Altmeyer, M. et al. Liquid demixing of intrinsically disordered proteins is seeded by poly(ADP-ribose). Nat. Commun. 6, 8088 (2015).
3. Rhine, K., Odeh, H. M., Shorter, J. & Myong, S. Regulation of Biomolecular Condensates by Poly(ADP-ribose). Chem. Rev. 123, 9065–9093 (2023).
4. Leung, A. K. L. Poly(ADP-ribose): A Dynamic Trigger for Biomolecular Condensate Formation. Trends Cell Biol. (2020).
5. Wang, T. et al. Cation-induced intramolecular coil-to-globule transition in poly(ADP-ribose). Nat. Commun. 15, 7901 (2024).
6. Rhine, K. et al. Poly(ADP-ribose) drives condensation of FUS via a transient interaction. Mol. Cell 82, 969-985.e11 (2022).