

M2 internship — Computational Chemistry/ Biophysics (start Feb. 2027)

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). They 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 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. Accumulation of PAR and dysregulated PAR condensates have been linked to various diseases, including cancer and neurodegenerative disorders such as Alzheimer's and Parkinson'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.

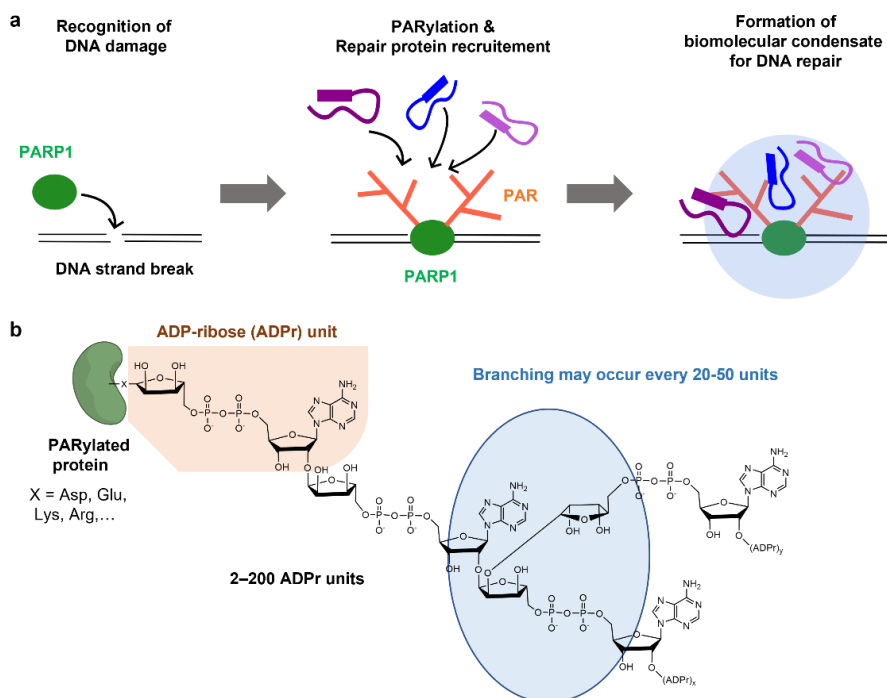


Figure
1: a) Schematic steps of DNA damage recognition leading to the formation of PAR-seeded condensates. b) Chemical structure of PAR

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. Starting from coarse grain simulations of PAR-FUS condensates, our goal will be to setup and validate a protocol for all-atom MD simulations of these systems that will allow us to reveal the molecular level structure of these condensates and illuminate the factors modulating their properties. We will pay specific attention to 1) the choice of refined force fields (including

benchmark of machine-learning potentials) to characterize PAR-FUS interactions in dilute solutions; 2) the setup of an adequate enhanced strategy techniques to sample such disordered systems ; 3) validation against experimental data obtained by our collaborators.

A PhD fellowship in my team may be available for the fall 2027 (awaiting decision in the upcoming weeks).

Techniques/Methods Molecular dynamics; all atom simulations ; Enhanced sampling ; programming for simulation analysis (Python) ; machine learning potentials.

Research environment The research will take place in the lab of Theoretical Biochemistry (LBT) with Élise Duboué-Dijon (specialist 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@cnr.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).
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6. Rhine, K. et al. Poly(ADP-ribose) drives condensation of FUS via a transient interaction. *Mol. Cell* 82, 969-985.e11 (2022).