【Grant-in-Aid for Transformative Research Areas（B）】

Multi-scale understanding of Self-condensation mechanism from Dynamic solution perspective（Dynamic Solution）

Head Investigator	Kyoto University, Graduate School of Science, Assistant Professor SEKIYAMA Naotaka　Researcher Number:50758810
Research Area Information	Number of Research Area : 22B308　Project Period (FY) : 2022-2024 Keywords : LLPS, Amyloid fibrillization, Neurodegenerative diseases

Purpose and Background of the Research

●Outline of the Research

Phase separation is a phenomenon in which two substances separate into two phases, like the demixing of oil and water. It has become clear that this phenomenon, called liquid-liquid phase separation (LLPS), also occurs in cells. LLPS is the formation of liquid-like aggregates, named membrane-less organelles, driven by the self-condensation of intrinsically disordered proteins (IDPs) which have no three-dimensional structures. LLPS is also associated with neurodegenerative diseases because of its propensity to mature into amyloid fibrils. However, it has remained unclear that what controls the self-condensation and how is the self-condensation regulated.

We focus on the dynamic solution environment, in which the chemical and physical states fluctuate with time and space. In this research area, we identify the factors of the dynamic solution environment that control the self-condensation and elucidate the self-condensation mechanism regulated by the dynamic solution environment (Figure 1).

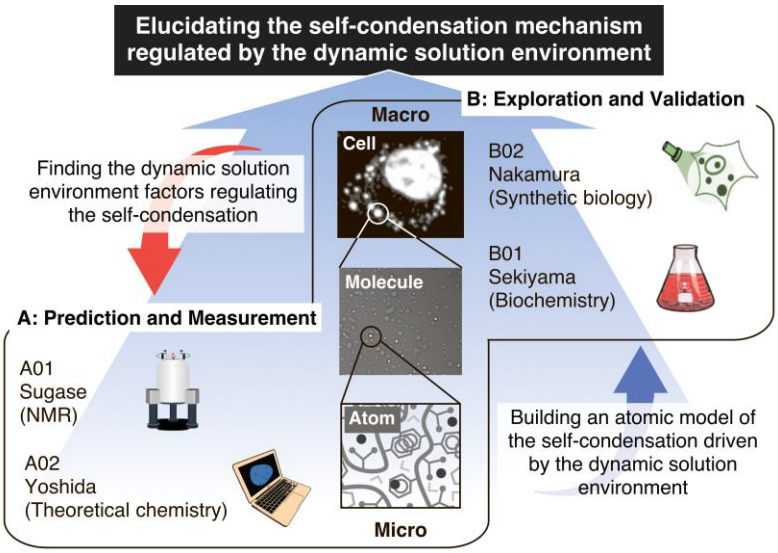

Figure 1. Overview of our research area

●Background

In our human bodies, blood glucose levels and adenosine triphosphate (ATP) levels fluctuate widely. The spatial distribution of other chemical compounds, such as amino acids and metabolites, also fluctuate. In addition, physical perturbations such as blood flow and electric fields in neurons are present in vivo (Figure 2). Recently, it has become clear that these dynamic solution environments regulate the self-condensation of IDPs.

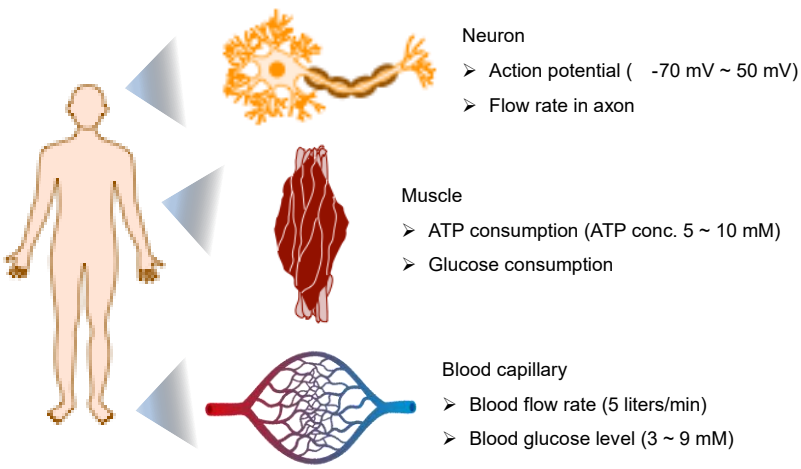

Figure 2. Conceptual images of the dynamic solution environment

●Objective（subtitle: optional）

Physiological functions controlled by the self-condensation of IDPs are implemented by the linkage of atomic, molecular, and cellular events. However, conventional experimental methods do not allow the solution environments to be perturbed freely, and the unavailability of the experimental data prevents an establishment of the theories.

In this research area, we aim to develop experimental methods and theories that can handle the dynamic solution environments, and to elucidate the mechanisms of the self-condensation regulated by the dynamic solution environments from a multi-scale perspective at the atomic, molecular, and cellular levels. Specifically, we focus on the chemical environments of molecules surrounding IDPs, such as water, ions, and metabolites, and the physical environments of material flow, physical vibrations, and electric fields. Our goal is to clarify WHAT kind of dynamic solution environment causes the self-condensation process and HOW each dynamic solution environment controls the self-condensation process of IDPs.

Expected Research Achievements

● Description of Our study

Our research area is divided into two subgroups: A: Prediction and Measurement Group and B: Exploration and Validation Group. We will circulate the findings obtained from each group within our research area and elucidate the mechanism of the IDPs self-condensation regulated by the dynamic solution environment.

1. Building an atomic model of the self-condensation driven by the dynamic solution environment

We analyze the interaction of IDPs with water molecules and ATP oligomers at the atomic level using nuclear magnetic resonance (NMR) and Rheo-NMR which can analyze the structure and dynamics of IDPs in flow. We also investigate the distribution of water and ATP oligomers around IDPs and a thermodynamic analysis for the self-condensation using a statistical mechanics approach .

2. Finding the dynamic solution environment factors regulating the self-condensation

We extract membrane-less organelles from cells and search for the solution environment factors that alter the solvation structures. We also manipulate the self-condensation by light and chemical compound stimulations in living cells and evaluate the effects of the dynamic solution environment in cells.

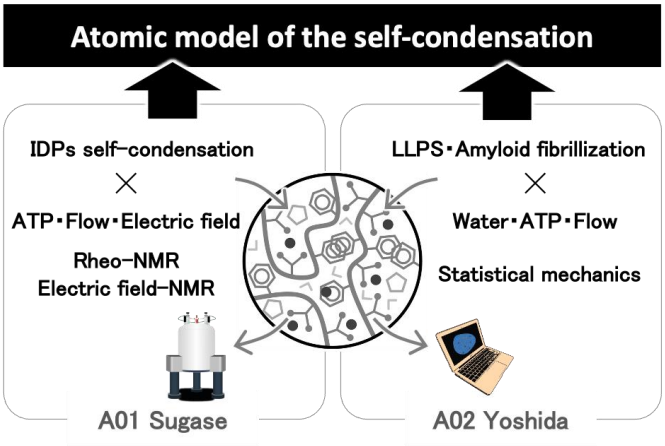

Figure 3. Prediction and Measurement group

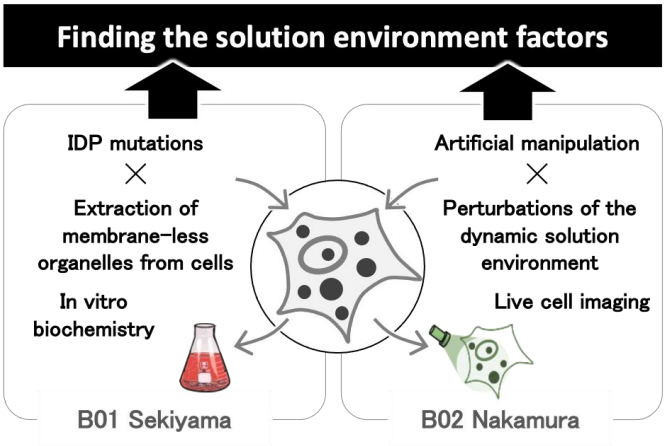

Figure 4. Exploration and Validation group

Homepage Address, etc.	https://dynamicsolution.biophys.kyoto-u.ac.jp/