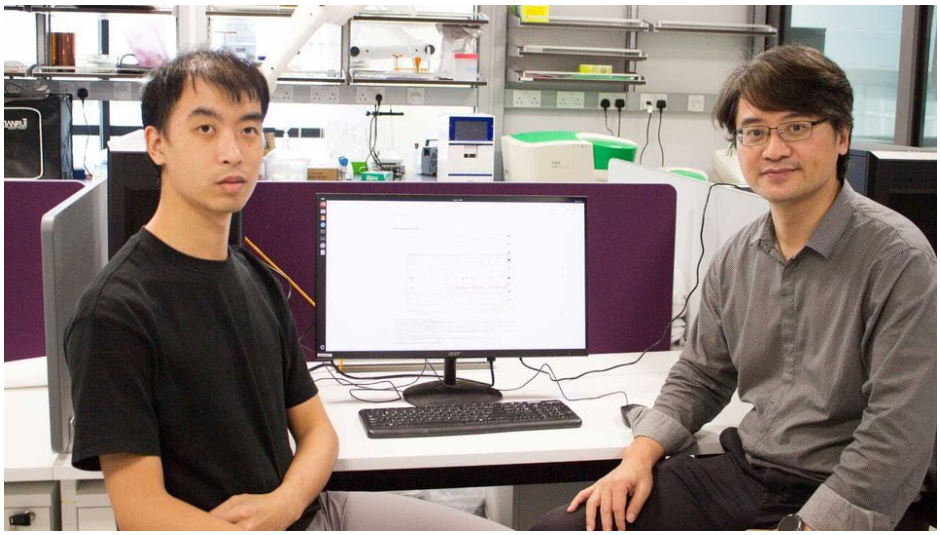
Technology Networks
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20 October 2026

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AI Tools Map Protein Phase Separation Across the Tree of Life

PLATO and PhaseHub predict protein phase separation and support research into aging and disease.



From left: Dr. Liang Qiyu, research fellow at the Institute for Digital Molecular Analytics and Science (IDMxS) at NTU, and Prof Miao Yansong, School of Biological Sciences and IDMxS, NTU. Credit: NTU Singapore.

An AI-powered database and a platform, PLATO and PhaseHub, have been developed to help predict proteins that undergo phase separation and form droplet-like compartments within cells.

These tools could advance aging research by identifying proteins whose condensates may develop into harmful aggregates, enabling studies of age-related cellular dysfunction and neurodegeneration. Built on systematic analysis across diverse organisms, the platforms also reveal insights into the biological roles of phase separation and its relationship with genome size.

Exploring the links between protein phase separation, aging, and disease

We undertook this work to address a key challenge: identifying which proteins undergo phase separation and how this behavior contributes to cellular function, aging, and disease.

Phase separation creates droplet-like compartments that organize molecules and regulate cellular reactions and stress responses. When this process becomes

dysregulated, abnormal condensates or aggregates can arise, potentially contributing to age-related cellular decline and neurodegenerative disorders such as Alzheimer's disease. Yet reliable prediction remains difficult because protein assembly is dynamic and depends on interactions with many cellular components.

By systematically analyzing proteins across diverse organisms, we aim to improve prediction and provide a foundation for investigating how functional protein assemblies become harmful, supporting future research into healthy aging and disease.

Mapping protein phase separation across the tree of life

We built PLATO through large language model-assisted literature mining and data curation of experimentally tested proteins and their phase behavior.

We also used our machine-learning tool, MolPhase, to predict phase-separating proteins across 1,106 species, spanning animals, plants, fungi, and bacteria. For PhaseHub, we integrated these predictions with experimental protein abundance and interaction data to explore potential multicomponent signaling hubs and their biological roles.

The platforms allow researchers to visualize predicted interactions and examine features such as homorepeats—stretches of repeated amino acids—that may influence phase separation.

We also found that eukaryotes generally had higher predicted proportions of phase-separating proteins than bacteria. These proportions increased with genome size among smaller genomes before plateauing. This pattern suggests a relationship between genome size and phase-separation capacity, providing a basis for investigating how this balance might influence harmful protein aggregation in aging and disease.

The key findings of the papers were:

- Molecular features, including homorepeats, help shape proteins' propensity for phase separation.
- Eukaryotes have a higher predicted proportion of phase-separating proteins than prokaryotes.
- Among organisms with smaller genomes, the predicted proportion of phase-separating proteins increases with genome size before reaching a plateau.
- Integration of phase separation predictions with protein abundance and interactome data enables the identification of complex, multicomponent signaling hubs.

Providing a comprehensive understanding of phase separation

Together, PLATO and PhaseHub provide a framework for exploring how phase separation helps organize cellular processes across the tree of life.

The relationship between genome size and the predicted proportion of phase-separating proteins suggests that this capacity expands with genomic complexity but eventually plateaus. This pattern raises questions about how cells balance the benefits of molecular compartmentalization with the potential risks of inappropriate protein assembly.

PLATO also captures shortened versions of proteins, mutations, and engineered variants that are rare in existing phase-separation datasets.

By integrating predictions with protein abundance, interaction data, and molecular features, these platforms help researchers prioritize proteins and interactions for experimental investigation.

For aging research, they offer a starting point for examining why some functional condensates become persistent or harmful aggregates, and how changes in protein abundance or cellular conditions might influence this transition.

Although the predictions require experimental validation, these resources could support studies of age-related cellular dysfunction and guide future investigations into maintaining healthy protein organization.

Combining AI, systems biology, and experimental evidence, PLATO and PhaseHub help researchers identify proteins likely to undergo phase separation and prioritize targets for further study. PLATO combines LLM-assisted curation and filtering to compile the most comprehensive database of experimentally validated protein variants, enabling the development of a more accurate AI predictor of phase separation.

These accessible resources could advance understanding of how protein organization supports cellular health and how its disruption contributes to aggregation, aging, and disease. Beyond biomedical research, they could support studies of plant stress responses and resilience, opening opportunities for applications in sustainable agriculture.

However, the current analysis would benefit from further experimental validation to confirm the phase-separating proteins and their roles.

Towards more precise predictions of protein phase separation

Future work will use the PLATO database to train and refine AI predictors, integrating protein sequence features with information on abundance, interactions, and cellular context.

By incorporating these associated features and experimentally validated examples, we aim to improve prediction accuracy and identify conditions that favor phase separation. This could help researchers investigate how functional condensates become harmful aggregates, supporting studies of protein organization in aging and disease.

References:

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