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Academic Appointments

2024/Feb – present Postdoctoral associate in Chemistry, Massachusetts Institute of Technology, US

Education

2019/Sep – 2024/Jan Ph.D. in Chemistry, University of Massachusetts at Amherst, US
2015/Jun – 2019/Jul B.S. in Chemistry and Molecular Science, Wuhan University, China

Research Summary

Biomolecular Systems: 1. specific binding in protein–protein interactions (PPIs) and enzymes; 2. dynamic client selectivity in intrinsically disordered proteins (IDPs) and PTM-regulated or multidomain systems; and 3. multivalent assembly in biomolecular condensates and dynamic protein assemblies.

Disease- and Health-Relevant Biophysical Mechanisms: mechanisms of dynamic protein signaling, regulatory or pathological processes: 1. bacterial immune evasion; 2. membrane pore transport and regulation; 3. neurodegeneration-associated protein phase separation; 4. nanopore-based single-molecule detection; 5. viral protease conformational dynamics and activity; and 6. oncogenic fusion proteins in cancer.

MD/ML-Integrated Biomolecular Modeling: 1. physics-based molecular dynamics, multiscale coarse-grained and atomistic force-field development, and theory-based off-lattice model development; 2. explainable and generative ML/AI methods for physical-model development and biomolecular analysis.

Bioinformatics: 1. protein language models (pLMs); 2. sequence–ensemble–function relationships; 3. evolutionary conservation and fitness landscapes; and 4. network biology.

Research Experience

02/2024 – : Postdoctoral Associate, Massachusetts Institute of Technology (Advisor: Bin Zhang)

1. Decoding IDP functional roles using protein language model (*2024/02 – 2024/10*).
   We identified the biophysical roles of the fitness landscape predicted by the ***pLM***, which reflects evolutionary conservation, and applied it to interpret how IDP sequences encode their phase separation functions. Our findings show that scaffold IDPs that drive phase separation are enriched in evolutionarily conserved residues, with chemical identities aligning with the 'sticker-and-spacer' model. (*eLife*)
2. Investigating structural roles in regulating elastin-like protein phase separation (*2024/07 – 2025/12*).
   Collaborating with Dr. Xin Zhang's lab, I am using a physics-based model to investigate the dynamics of biological condensate formation and to explore how protein conformational properties correlate with their phase behavior. (*JACS*)
3. Developing a transferable coarse-grained protein model (*2025/09 -2026/06*).
   In collaboration with lab mate, I am developing a transferable coarse-grained protein force field that integrates machine-learning approaches with physical insights, aiming to achieve balanced interactions capable of describing disordered, folded, and multi-domain proteins. (*bioRxiv*)
4. Exploring the physical role of protein phase separation based on mean-field theory (*2024/07 - 2026/07*).
   I am using the sticker-and-random-spacer theoretical model to investigate how the balance between specific and non-specific interactions synergistically affects phase separation in homo- and heterogeneous systems. (*bioRxiv*)

09/2019 – 02/2024: Graduate Research Assistant, University of Massachusetts Amherst (Advisor: Jianhan Chen)

1. Developing multi-scale enhanced sampling methods to study protein conformational dynamics.

   ### 1.1. Physics-based protein coarse-grained model: HyRes II/HyRes-GPU (2021-2022)

   I developed HyRes II, a novel ***coarse-grained protein model that incorporates solvent effects*** through the inclusion of a solvation term. This model was specifically calibrated to achieve a quantitative description of long-range non-specific interactions, making it accurate for simulating the conformational dynamics and interactions of IDPs. HyRes II has been further optimized for GPU implementation (HyRes-GPU),

significantly improving computational efficiency (achieves ~ 500 ns/day for system with 100K beads). This model has been widely applied to study short- and long-timescale (nanosecond to microsecond) biological activities, such as protein-protein interactions and protein phase separation. (*JCIM*)

1.2. Collective-variable independent enhanced sampling method: REST3 (2021-2022)

I developed REST3, a novel collective-variable independent enhanced sampling method for efficient conformational sampling of IDPs. This method optimizes the scaling of solute-solvent interaction strengths as a free parameter, overcoming limitations in previous ***replica-exchange with solute tempering*** protocols. REST3 effectively resolves the issue of fictitious conformational collapse at high temperatures observed in REST2, allowing for more efficient (~ 2x) conformational exchange and sampling. (*JCTC*)

1.3. Transferable atomistic protein model: C36mrb-disp (2023-2024)

Collaborating with Dr. Xiping Gong, we developed C36mrb-disp, a transferable atomistic model for both folded and disordered proteins. We identified *the side chain of charged residues as a major limitation* in the CHARMM36m force field and demonstrated that both charge adjustment and switching to the TIP4P-D water model are necessary to rebalance the force field. The new version, C36mrb-disp, presents higher accuracy in describing disordered protein conformational ensembles while also showing robust conformational sampling for folded proteins. (*JPCB*)

2. Application of multiscale simulation methods to studies of dynamic protein interactions.

2.1. Regulation of mitochondrial pore opening: interactions between p53-TAD/CypD (2020-2021)

Collaborating with Dr. Chunyu Wang's lab, we demonstrated that p53-TAD can dynamically bind to cyclophilin D (CypD), mediating mitochondrial permeability transition pore (mPTP) opening. The predicted binding interface and the electrostatic nature of the interaction were further confirmed through NMR and SPR experiments. Integrated simulations, NMR, and SPR measurements revealed how disordered p53-TAD binds the mPTP regulator CypD through a dynamic electrostatic interface and promotes mPTP opening. (*JMB*)

2.2. Bacterial infection: immune evasion of staphylococcus (2020-2021)

Inspired by Dr. Brian V. Geisbrecht's studies, I investigated how the conformational dynamics of Staphylococcal peroxidase inhibitor (SPIN) help the bacteria evade immune responses. The *coupled binding and folding process* of the natively disordered SPIN N-terminal domain (SPIN-NTD) likely plays a central role in inhibiting the human oxidative immune enzyme's activity. I demonstrated that SPIN species with more ordered NTDs exhibit stronger binding affinity to the enzyme's active site via a conformational-selection mechanism, resulting in higher inhibition efficacy. (*Frontiers*)

2.3. Real-time biomolecule sensing: nanopore engineering for tracking flavivirus proteases functional conformations (2021-2023)

Collaborating with Dr. Min Chen's lab, we identified a functional site on the ClyA protein nanopore and engineered a new pore with enhanced protease interactions. Molecular simulations and electrophysiology revealed that West Nile Virus proteases could be captured and stabilized in the new nanopore lumen through electrostatic interactions, resolving open and closed states at the single-molecule level. This platform paves the way for high-throughput screening of novel allosteric inhibitors targeting the NS2B-NS3 interface. (*Biophys. J.*)

2.4. IDP phase separation: how local structure affects the phase separation (2023)

I investigated how the dynamic secondary structures of IDPs regulate their phase behaviors. Using the elastin-like protein GY-23 as a model, I observed the increased β-structure formation upon condensation, consistent with experimental CD data. In the case of TDP-43, I successfully recapitulated the effects of disease-related mutations on helicity and phase separation propensity. The analyses revealed that the balance between backbone- and side chain-mediated interactions, rather than helicity itself, governs the phase separation propensity in these systems. (*JACS*)

07/2018-05/2019: Undergraduate Researcher, Wuhan University, China (Advisor: Fuan Wang)

1. Hybrid HCR-CHA circuit for phosphorylase kinase signal amplification (2018-2019)
   We developed an HCR-CHA circuits to amplify the FRET signal during a continuous chain reaction, which can sensitively and specifically detect the signals of phosphorylase kinase at nanomolar concentrations.

Publications (#: co-first authors; *: corresponding authors ; []†: key publications with PDF attached)

At MIT:

[15]. **Y. Zhang**#, A. Sood#, A.Athreya, B. Zhang*, "Valency-Limited Molecular Dynamics Simulations of Stickers-and-Spacers Polymers Reveal a Tradeoff Between Condensation and Organization." (**2026**) *bioRxiv*

[14]†. S. Liu#, **Y. Zhang**#, I. Riveros, C. Wang, B. Zhang*, "MOFF2: A Transferable Coarse-Grained Protein Force Field for Predictive Condensate Simulations." (**2026**). *bioRxiv* (under minor revision from *JCTC*)

[13]†. L. Zhu#, G. Liao#, **Y. Zhang**#, Y. Guo, J. Chen, S. Zhou, Z. Wu, Y. Huang, X. Lu, C. Chen, H. Chen, Y. Weng*, X. Zhang*, "A Glimpse into the Initial Microsecond of Biomolecular Condensation." *J. Am. Chem. Soc.* (**2026**). *ACS*

[12]†. **Y. Zhang**, J. Zheng, B. Zhang*, "Protein Language Model Identifies Disordered, Conserved Motifs Implicated in Phase Separation." *eLife*. (**2025**). *eLife*

At UMass Amherst:

[11]. **Y. Zhang**# , X. Liu# and J. Chen*, "Intrinsically disordered proteins", in "Generalized-Ensemble Algorithms - Ideas and Applications", Edited by Sugita and Okamoto, Springer, 2026. (*In Press, Submitted to Springer*)

[10]. S. Barethiya#, S. Schultz#, **Y. Zhang**, J. Chen*, "Coarse-Grained Simulations of Phosphorylation Regulation of p53 Autoinhibition." *Biochemistry.* (**2025**). *ACS*

[9]. S. A. Shorkey#, **Y. Zhang**#, J. Sharp#, S. Clingman, L. Nguyen, J. Chen* and M. Chen*, "Tracking flaviviral protease conformational dynamics by tuning single-molecule nanopore tweezers.", *Biophys J*. (**2025**). *ScienceDirect*

[8]. X. Gong#, **Y. Zhang**#, J. Chen. "Likely Over-Stabilization of Charge-Charge Interactions in CHARMM36m(w): A Case for a99SB-disp Water.", *J. Phys. Chem. B.* (**2024**). *ACS*

[7]. S. Li**, Y. Zhang** and J. Chen*, "Backbone Interactions and Secondary Structures in Phase Separation of Disordered Proteins.", *Biochem. Soc. Trans.* (**2024**). *Portland Press*

[6]†. **Y. Zhang**#, S. Li#,*, X. Gong and J. Chen*, "Toward Accurate Simulation of Coupling between Protein Secondary Structure and Phase Separation.", *J. Am. Chem. Soc.* (**2024**). *ACS*

[5]. **Y. Zhang**, X. Liu* and J. Chen*, "Re-balancing replica exchange with solute tempering for sampling dynamic protein conformations", *J. Chem. Theory Comput*. 19, 1602 (**2023**). *ACS*

[4]. **Y. Zhang**#, X. Liu# and J. Chen*, "Coupled binding and folding of SPIN N-terminal region in myeloperoxidase inhibition", *Front. Mol. Biosci*.(**2023**). *frontiers*

[3]†. **Y. Zhang**, X. Liu* and J. Chen*, "Towards Accurate Coarse-Grained Simulations of Disordered Proteins and Their Dynamic Interactions", *J. Chem. Inf. Model*. 62, 4523-4536 (**2022**) *ACS*

[2]. J. Zhao, X. Liu, A. Blayney, **Y. Zhang**, L. Gandy, F. Zhang, R. J. Linhardt, J. Chen, C. Baines, S. N. Loh and C. Wang, "Intrinsically disordered N-terminal domain (NTD) of p53 interacts with mitochondrial PTP regulator Cyclophilin D" *J. Mol. Biol.* 434, 167552 (**2022**). *JMB*

[1]. X. Gong#, **Y. Zhang**# and J. Chen, "Advanced Sampling Methods for Multiscale Simulation of Disordered Proteins and Dynamic Interactions" *Biomolecules*, 11, 1416 (**2021**) (Invited Review). *MDPI*

Research Interests

1. Network biology including protein-protein interactions, gene regulatory networks, and signaling networks.
2. Bioinformatics for biomolecular function and evolutionary analysis.
3. Explainable MD/ML model for biomolecular functional investigation and prediction.
4. Predictive and generative model for peptides/small molecules design targeting pathological biological activities.
5. Biophysics in human diseases including immunology, cancer, and neurodegeneration.

Collaboration Experience

- Dr. Min Chen's lab at UMass Amherst: Nanopore tweezer engineering for enzyme functional states detecting.
- Dr. Brian V. Geisbrecht's lab at Kansas State University: Immune inhibition mechanism by bacteria.
- Dr. Chunyu Wang's lab at Rensselaer Polytechnic Institute: PPI regulation for mitochondrial pore opening.
- Dr. Xin Zhang's lab at West Lake University: Early-stage condensate assembly.

Talks and Poster Presentation Experience

Talks:

- 2023, Chemistry ResearchFest, UMass Amherst
- 2022, Chemistry-Biology Interface (CBI) Chalk Talk, UMass Amherst

Posters:

- 2024, Biophysics Retreat, MIT.
- 2023, American Chemical Society Spring
- 2022, Biophysical Society Annual Meeting
- 2020 - 2022, Chemistry ResearchFest, UMass Amherst

Teaching and Mentoring Experience

Teaching (as teaching assistant):

- General Chemistry (Chem 111 & Chem 112), UMass Amherst
- Advanced Physical Chemistry (Chem 585), UMass Amherst

Mentoring:

- Graduate students: Samantha Schultz, Juni Campbell, Shrishti Barethiya and Kairong Dong.
- Undergraduate students: Anik Dey, Ryan Pham, Jiayue Wang, Sasha Zhang.

Technical Skills

Programming Skills: Highly proficient in Linux operating systems, Python, and PyTorch

Computational and Molecular Modeling: Extensive experience in biological system modeling and analyzing. Rich experience in multi-scale state-of-the-art force fields such as CHARMM, Amber, HPS, and Martini. Expertise in advanced sampling methods, including Umbrella Sampling, Replica Exchange, Free Energy Perturbation, and Thermodynamic Integration.

Data Analysis: Highly skilled in data curation and large-scale data analysis, including deep learning-based clustering, principal component analysis (PCA), factor analysis, and feature extraction techniques.

Machine Learning: Proficient in large language model, contrastive learning, diffusion model, score/flow-matching

Professional Service

2021- Peer Reviewer for: ***Biophysical Journal, Scientific Reports, Proteins, Journal of Chemical Information and Modeling, Journal of Chemical Theory and Computation, International Journal of Biological Macromolecules, Physical Chemistry Chemical Physics, Journal of Physical Chemistry B, ACS Omega, JACS Au, PLOS Computational Biology.***

Honors and Awards

2023 Dr. Paul Hatheway Terry Endowment Award in Chemistry ResearchFest, UMass Amherst

2020 1st place prize in Chemistry ResearchFest poster presentation, UMass Amherst

2016 2nd Class Freshman Scholarship, Wuhan University, China

2015 Freshman Scholarship, Wuhan University, China