OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Miao, Yinglong

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-3714-1395

Position Title: Associate Professor

Organization and Location: Department of Pharmacology, Computational Medicine Program and Lineberger Comprehensive Cancer Center, University of North Carolina – Chapel Hill, Chapel Hill, North Carolina, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of California San Diego/Howard Hughes Medical Institute, San Diego, CA, United States	Postdoctoral Fellow	09/2012	08/2015	Computational Chemistry and Pharmacology
Oak Ridge National Laboratory/University of Tennessee, Oak Ridge, TN, United States	Postdoctoral Fellow	09/2009	08/2012	Molecular Biophysics
Indiana University, Bloomington, IN, USA	DOCTOR OF PHILOSOPHY	08/2004	08/2009	Computational Chemistry
University of Science and Technology of China, Hefei, Anhui, China	BACHELOR OF ENGINEERING	01/2002	06/2004	Computer Science and Technology
University of Science and Technology of China, Hefei, Anhui, China	BACHELOR OF SCIENCE	09/2000	06/2004	Chemistry

Appointments and Positions

2023 - present	Associate Professor, Department of Pharmacology, Computational Medicine Program and Lineberger Comprehensive Cancer Center, University of North Carolina – Chapel Hill, Chapel Hill, North Carolina, United States
2022 - 2023	Associate Professor, Computational Biology and Molecular Biosciences, University of Kansas, Lawrence, KS, United States
2017 - 2022	Assistant Professor, Computational Biology and Molecular Biosciences, University of Kansas, Lawrence, KS, United States
2015 - 2017	Assistant Project Scientist, Department of Pharmacology, University of California, San Diego, San Diego, CA, United States
2015 - 2017	Research Specialist I, Howard Hughes Medical Institute, San Diego, CA, USA

Products

Products Closely Related to the Proposed Project

1. Miao Y, Goldfeld DA, Moo EV, Sexton PM, Christopoulos A, McCammon JA, Valant C. Accelerated structure-based design of chemically diverse allosteric modulators of a muscarinic G protein-coupled receptor. Proc Natl Acad Sci U S A. 2016 Sep 20;113(38):E5675-84. PubMed Central PMCID: PMC5035859.
2. Pawnikar S, Magenheimer BS, Munoz EN, Maser RL, Miao Y. Mechanism of tethered agonist-mediated signaling by polycystin-1. Proc Natl Acad Sci U S A. 2022 May 10;119(19):e2113786119. PubMed Central PMCID: PMC9171645.
3. Pawnikar S, Magenheimer BS, Joshi K, Nevarez-Munoz E, Haldane A, Maser RL, Miao Y. Activation of polycystin-1 signaling by binding of stalk-derived peptide agonists. Elife. 2024 Oct 7;13 PubMed Central PMCID: PMC11458180.
4. Bhattarai A, Wang J, Miao Y. Retrospective ensemble docking of allosteric modulators in an adenosine G-protein-coupled receptor. Biochim Biophys Acta Gen Subj. 2020 Aug;1864(8):129615. PubMed Central PMCID: PMC7261249.
5. Wang J, Nguyen ATN, Adediwura VA, Lu CS, McNeill SM, Jörg M, Scammells PJ, Christopoulos A, May LT, Miao Y. Dissociation kinetics of G proteins from G protein-coupled receptors and effects of allosteric modulation. Proc Natl Acad Sci U S A. 2025 Nov 18;122(46):e2512423122. PubMed Central PMCID: PMC12646235.

Other Significant Products Highlighting Contributions to Science

1. Wang J, Arantes PR, Bhattarai A, Hsu RV, Pawnikar S, Huang YM, Palermo G, Miao Y. Gaussian accelerated molecular dynamics (GaMD): principles and applications. Wiley Interdiscip Rev Comput Mol Sci. 2021 Sep-Oct;11(5) PubMed Central PMCID: PMC8658739.
2. Draper-Joyce CJ, Bhola R, Wang J, Bhattarai A, Nguyen ATN, Cowie-Kent I, O'Sullivan K, Chia LY, Venugopal H, Valant C, Thal DM, Wootten D, Panel N, Carlsson J, Christie MJ, White PJ, Scammells P, May LT, Sexton PM, Danev R, Miao Y, Glukhova A, Imlach WL, Christopoulos A. Positive allosteric mechanisms of adenosine A(1) receptor-mediated analgesia. Nature. 2021 Sep;597(7877):571-576. PubMed Central PMCID: PMC8711093.
3. Bhattarai A, Devkota S, Do HN, Wang J, Bhattarai S, Wolfe MS, Miao Y. Mechanism of Tripeptide Trimming of Amyloid β-Peptide 49 by γ-Secretase. J Am Chem Soc. 2022 Apr 13;144(14):6215-6226. PubMed Central PMCID: PMC9798850.
4. Hegde S, Akhter S, Tang Z, Qi C, Yu C, Lewicka A, Liu Y, Koirala K, Reibarkh M, Battaile KP, Cooper A, Lovell S, Holmstrom ED, Wang X, Piccirilli JA, Gao Q, Miao Y, Wang J. Mechanistic studies of small molecule ligands selective to RNA single G bulges. Nucleic Acids Res. 2025 Jun 20;53(12) PubMed Central PMCID: PMC12188297.
5. Miao Y, McCammon JA. Graded activation and free energy landscapes of a muscarinic G-protein-coupled receptor. Proc Natl Acad Sci U S A. 2016 Oct 25;113(43):12162-12167. PubMed Central PMCID: PMC5087018.

Certification:

I certify that the information provided is current, accurate, and complete. This includes but is not limited to information related to domestic and foreign appointments and positions.

I also certify that, at the time of submission, I am not a party to a malign foreign talent recruitment program.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§ 287, 1001, 1031 and 31 U.S.C. §§ 3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Miao, Yinglong

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-3714-1395

Position Title: Associate Professor

Organization and Location: Department of Pharmacology, Computational Medicine Program and Lineberger Comprehensive Cancer Center, University of North Carolina – Chapel Hill, Chapel Hill, North Carolina, United States

Personal Statement

I develop novel theoretical and computational methods and Deep Learning techniques, which speed up biomolecular simulations by orders of magnitude. I apply these methods for unprecedented simulations of biomolecular dynamics such as protein folding, drug binding and protein-peptide/protein interactions. In collaboration with leading experimentalists, my lab combines complementary simulations and experiments to uncover functional mechanisms and design novel drug molecules of important biomolecules, including G-protein-coupled receptors (GPCRs), membrane-embedded proteases, RNA-binding proteins and RNA. My research has yielded ~130 peer-reviewed publications with 45 H-index and 90+ invited talks.

I have enjoyed mentoring of graduate students and postdocs. Using Individual Development Plans, I provide lab members with training that matches their skills, interest and values. This also helps them to explore career opportunities and acquire skills they need to succeed in their future careers. I am dedicated to training in rigorous research design, methodology, analysis, interpretation and reporting of results. Four of my graduate students have obtained PhDs recently, with excellent academic record, high research productivity and different award recognitions. I have also participated in various mentoring training programs at UNC.

In this project, I will collaborate with the Hahn and Dohlman labs to design membrane-permeable small-molecule and peptide biosensors to decode compartmentalized G protein signaling in living cells. Our team will integrate state-of-the-art computational techniques with novel biosensor approaches to design subtype- and state-selective biosensors of G protein activation. We will map not only nanoscale organization and rapid transitions of endogenous G proteins, but also how protein dynamics differ during transit between plasma membrane and endomembrane compartments. By resolving these spatially distinct activation signatures, we will reveal modes of G protein signaling that have remained invisible to existing technologies.

I have not published or created research products under another name.

Honors

2026 - 2031	Maximizing Investigators' Research Award, National Institutes of Health
2024 - 2027	Editor-in-Chief, npj Drug Discovery
2022 - 2024	Associate Editor, Frontiers in Molecular Biosciences
2021	OpenEye Outstanding Junior Faculty Award, ACS Computational Chemistry
2019	Keynote Lecture, 5th Biennial Symposium – Optical Micro-spectroscopy & Molecular Imaging, University of Wisconsin, Milwaukee
2017 - 2019	Scientist Development Grant Award, American Heart Association
2008	Registration Fellowship, American Conference on Theoretical Chemistry
2007 - 2008	Participant Fellowship, Oak Ridge Institute for Science and Education (ORISE)

Contributions to Science

1. Development of accelerated molecular simulation methods: I have created the Gaussian accelerated Molecular Dynamics (GaMD) simulation methodology (Wiley Interdiscip Rev Comput Mol Sci, 2021). It has been implemented in widely used simulation packages including AMBER, NAMD, OpenMM, Tinker-HP, GENESIS and Discovery Studio. GaMD, called “time-accelerated computational microscope”, enables short simulations to capture long-timescale events. Applications of GaMD have revealed mechanisms of protein folding and conformational changes, ligand binding, protein-protein/membrane/nucleic acid interactions and carbohydrate dynamics. GaMD has also been applied to explore different protein structures and account for protein flexibility for drug design. Based on GaMD, my lab has developed innovative

simulation algorithms, including Ligand GaMD (LiGaMD), Peptide GaMD (Pep-GaMD) and Protein-Protein Interaction GaMD (PPI-GaMD). These new methods, for the first time, enabled microsecond atomic simulations to capture repetitive dissociation and binding of small-molecule ligands, flexible peptides and proteins, thereby allowing for highly efficient and accurate calculations of their binding free energies and kinetics. The GaMD methods have so far received >1600 citations. In addition, my lab has built the GaMD, Deep Learning and free energy prOfiling Workflow (GLOW) for predicting molecular determinants and mapping free energy landscapes of biomolecules. Furthermore, my lab has developed a new Deep Boosted Molecular Dynamics (DBMD) method in which probabilistic Bayesian neural network models are implemented to construct boost potentials that exhibit Gaussian distribution with minimized anharmonicity, thereby allowing for more accurate energetic reweighting and further improved sampling of biomolecules.

2. Mechanisms and drug discovery of G-protein-coupled receptors (GPCRs): GPCRs are the largest superfamily of human membrane proteins and serve as primary targets of ~1/3 of currently marked drugs. My contributions in GPCR research include: (i) The first reports of accelerated molecular dynamics simulations that revealed the activation mechanism of a muscarinic GPCR, the pathways and mechanisms of agonist and G protein binding/dissociation in GPCRs, and structural dynamics of an intermediate GPCR-Gαβγ complex. (ii) Discovery of new allosteric modulators as selective drug leads of M2 muscarinic GPCR using a computational structure-based approach. (iii) Discovery of critical residue contacts for activation and allosteric modulation of different classes of GPCRs through sequence coevolution and structural contact analysis. (iv) Uncovered mechanisms of action of allosteric modulators in adenosine and muscarinic GPCRs through GaMD simulations, which were validated by collaborative in-vitro and in-vivo experiments (Nature, 2021). (v) Revealed a general dynamic "conformational selection" mechanism of GPCR allostery through comprehensive Deep Learning analysis of GaMD simulations on the A and B classes of GPCRs using GLOW. (vi) Reported the first study of a novel allosteric signaling mechanism of polycystin-1, an atypical GPCR implicated polycystic kidney disease (PKD). Our model was validated by collaborative mutagenesis and cellular assay experiments. We have also presented the first structural dynamic models for binding of synthetic peptides that can activate signaling of polycystin-1 and ameliorate cystogenesis in embryonic kidney organ cultures from PKD1 mutant mice.

3. Mechanisms of γ-secretase: γ-Secretase, called "the proteasome of the membrane", is a membrane-embedded protease that cleaves 150+ peptide substrates with central roles in biology and medicine, including amyloid precursor protein (APP). Mutations in γ-secretase and APP lead to familial Alzheimer's disease (FAD). My lab has built the first dynamic model for activation and substrate processing of γ-secretase, being highly consistent with collaborative mass spectrometry and western blot biochemical experiments obtained by the Michael Wolfe lab in Medicinal Chemistry. In follow-up studies, our complementary simulations and biochemical experiments have also uncovered the dynamic mechanism of tripeptide trimming of amyloid β-peptide 49 (Aβ49) by γ-secretase (J Am Chem Soc, 2022), effects of Familial Alzheimer's Disease mutations on γ-secretase activation for APP substrate cleavage and mechanism of Notch substrate cleavage by γ-secretase.

4. Mechanisms and drug discovery of RNA-protein interactions and RNA: RNA and RNA-binding proteins (RBPs) have emerged as exciting targets for discovering drugs of new mechanisms. However, they have proven difficult for drug design especially due to their extremely high flexibility and poorly defined targets sites. Mechanisms of ligand-RNA/RBP and RNA-RBP interactions remain largely unknown. My lab has performed GaMD simulations, which, for the first time, captured multiple times of spontaneous and highly accurate binding of RNA from bulk solvent to a Musashi RBP as determined in the NMR structure. My lab has successfully carried out computer-aided drug design of inhibitors for the Musashi and human antigen R (HuR) RBPs. In collaboration with the Bo Liang lab at Emory University, we have combined X-ray crystallography and GaMD simulations that revealed the mechanism of a short positive-sense gene-end RNA binding to the M2-1 viral protein. In collaboration with the Jingxin Wang lab in Medicinal Chemistry, my lab has performed GaMD simulations that captured spontaneous ligand binding to flexible RNA structures (Nucleic Acids Res, 2025). Our simulations were highly consistent with NMR and structure-affinity-relationship experiments. We have also successfully characterized the mechanism, thermodynamics and kinetics of ligand binding to the theophylline RNA aptamer.

5. Mechanisms of biomolecular recognition: Advanced applications of GaMD simulation techniques have allowed us to, for the first time, capture both drug dissociation and binding in one single all-atom GPCR simulations (Proc Natl Acad Sci U S A, 2016), binding of G-protein mimic to a GPCR, and dissociation of G proteins from GPCRs, as well as multiple times of ligand dissociation and binding in human ACE2 receptor.

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