BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Miao, Yinglong

eRA COMMONS USER NAME (credential, e.g., agency login): yinglongmiao

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Science and Technology of China, Hefei, Anhui, China	B.S. B.E.	06/2004	Chemistry Computer Science and Technology
Indiana University, Bloomington, IN, USA	Ph.D.	08/2009	Computational Chemistry
UT/ORNL Center for Molecular Biophysics, Oak Ridge, TN, USA	Postdoctoral	08/2012	Molecular Biophysics
University of California, San Diego, CA, USA	Postdoctoral	08/2015	Computational Chemistry and Pharmacology

A. Personal Statement

I develop novel theoretical and computational methods and Deep Learning techniques, which speed up biomolecular simulations by orders of magnitude[a-b]. I apply these methods for unprecedented simulations of biomolecular dynamics such as protein folding, drug binding and protein-peptide/protein interactions[a-b]. 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 such as γ-secretase, RNA-binding proteins and RNA[c-d]. My research has yielded ~100 peer-reviewed publications with 38 H-index and 70+ invited talks. I have enjoyed mentoring of students with diverse academic backgrounds. Using Individual Development Plans, I provide students with training that match their skills, interest and values. This also helps the students to explore career opportunities and acquire skills they need to succeed in their future careers. I am dedicated to training in rigorous and unbiased research design, methodology, analysis, interpretation and reporting of results.

Ongoing projects that I would like to highlight:
NIH R01 GM132572
Miao, Y (PI)
04/01/2019 – 03/30/2024
Enhanced Sampling of G-Protein-Coupled Receptor–G protein interactions

NIH R01 CA244504
Miao, Y (Co-I; PI: Wolfe)
01/01/2020 – 12/30/2024
Structure and Function of γ-Secretase in Familial Alzheimer's Disease.

NSF 2121063
Miao, Y (PI)
09/01/2021 – 08/30/2024
A public workflow for predicting peptide binding structures

Jared Grantham Kidney Institute pilot grant, University of Kansas Medical Center

Miao, Y (PI)
01/01/2023 – 12/31/2023
Mechanism of polycystin-1 signal transduction in complex with polycystin-2

NSF MRI 2117449
Miao, Y (co-PI)
08/01/2021 – 07/30/2023
Acquisition of a High-Performance Computing Cluster for Science and Engineering Research at the University of Kansas

Citations:

a. Do HN & **Miao Y*** (2023) Deep Boosted Molecular Dynamics (DBMD): Accelerating molecular simulations with Gaussian boost potentials generated using probabilistic Bayesian deep neural network. *Journal of Physical Chemistry Letters,* **14** (21): 4970-4982. PMCID: PMC10081221
b. Wang J & **Miao Y*** (2022) Protein-protein interaction-Gaussian accelerated molecular dynamics (PPI-GaMD): Characterization of protein binding thermodynamics and kinetics. *Journal of Chemical Theory and Computation*, 18(3):1275–1285. PMCID: PMC9817007.
c. Su, M.[#], Wang, J.[#], Xiang, G., Do, H.N., Levitz, J., **Miao, Y.***, Huang, X.-Y.* (2023) Structural Basis of Agonist Specificity of α_{1A}-Adrenergic Receptor. *Nature Communications*. **14**: 4819. PMCID: PMC10415349.
d. Vuckovic Z[#], Wang J[#], Pham V[#], Mobbs J[#], Belousoff MJ, Bhattarai A, Nawaratne V, Leach K, Burger WAC, Westhuizen ETvd, Khajehali E, Thompson G, Yeasmin M, Liang Y-L, Glukhova A, Wootten D, Lindsley CW, Tobin AB, Sexton PM, Danev R, Valant C, **Miao Y***, Christopoulos A*, & Thal DM* (2023) Pharmacological hallmarks of allostery at the M4 muscarinic receptor elucidated through structure and dynamics. *eLife*, 12:e83477. PMCID: PMC10229135.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-	Associate Professor, Department of Pharmacology and Computational Medicine Program, University of North Carolina – Chapel Hill
2022-23	Associate Professor, Computational Biology and Molecular Biosciences, University of Kansas
2021-23	Faculty Member, University of Kansas Cancer Center, Kansas City
2020-23	Courtesy Faculty Member, Department of Medicinal Chemistry, University of Kansas
2017-22	Assistant Professor, Computational Biology and Molecular Biosciences, University of Kansas
2015-17	Assistant Project Scientist, Department of Pharmacology, UCSD, La Jolla, CA
2015-17	Research Specialist I, Howard Hughes Medical Institute, UCSD, La Jolla, CA
2014-	American Heart Association, member
2012-	American Chemical Society, member
2010-	American Association for the Advancement of Science, member
2009-	Biophysical Society, member

Honors

2021	OpenEye Outstanding Junior Faculty Award, ACS Computational Chemistry
2017-19	Scientist Development Grant Award, American Heart Association
2008	Registration Fellowship, American Conference on Theoretical Chemistry
2007-08	Oak Ridge Institute for Science and Education (ORISE) Participant Fellowship

C. Contributions to Science

1. **Development of accelerated molecular simulation methods**. I have created the Gaussian accelerated molecular dynamics (GaMD) simulation methodology[e,f]. Since publication in 2015, GaMD has received >600 citations. It has been implemented in widely used simulation packages including AMBER, NAMD, OpenMM, Tinker-HP and GENESIS. 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)[g], Peptide GaMD (Pep-GaMD)[h] and Protein-Protein Interaction GaMD (PPI-GaMD)[b]. 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. 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[a].

e. **Miao Y***, Feher, V., McCammon, J.A. (2015). Gaussian Accelerated Molecular Dynamics: Unconstrained Enhanced Sampling and Free Energy Calculation. *J Chem Theory Comput* **11**: 3584-3595. PMCID: PMC4535365.

f. Wang J, Arantes P, Bhattarai A, Hsu R, Pawnikar S, Huang Y-m, Palermo G* and **Miao Y*** (2021) Gaussian accelerated molecular dynamics: principles and applications. *WIREs Computational Molecular Science*: e1521. PMCID: PMC8658739.

g. **Miao, Y***, Bhattarai, A., and Wang, J. (2020) Ligand Gaussian accelerated molecular dynamics (LiGaMD): Characterization of ligand binding thermodynamics and kinetics. *Journal of Chemical Theory and Computation*, **16**(9): 5526–5547. PMCID: PMC7768792.

h. Wang, J. and **Miao, Y*** (2020) Peptide Gaussian accelerated molecular dynamics (Pep-GaMD): Enhanced sampling and free energy and kinetics calculations of peptide binding. *Journal of Chemical Physics*, **153**, 154109. PMCID: PMC7575327.

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) I have published *the first reports* of accelerated molecular dynamics simulations that revealed the activation mechanism of a muscarinic GPCR[i], as well as the pathways and mechanisms of agonist binding and G protein coupling in muscarinic and adenosine GPCRs. (ii) My lab has revealed critical residue contacts for activation and allosteric modulation of different classes of GPCRs through sequence coevolution and structural contact analysis. (iii) My lab has 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[d,j]. (iv) My lab has reported *the first study* of a novel allosteric signaling mechanism of polycystin-1. Our model was validated by collaborative mutagenesis and cellular assay experiments[k]. (v) I have discovered new allosteric modulators as selective drug leads of the M_2 muscarinic GPCR using a computational structure-based approach[l].

i. **Miao, Y.***, Nichols SE, Gasper PM, Metzger VT, & McCammon JA (2013) Activation and dynamic network of the M2 muscarinic receptor. *Proc Natl Acad Sci U S A*, 110(27):10982-10987. PMCID: PMC3703993.

j. Draper-Joyce CJ, Bhola R, Wang J, Bhattarai A, …, **Miao Y**, Glukhova A, Wendy LI, & Christopoulos A (2021) Structural basis of analgesic action of an adenosine A1 receptor allosteric modulator. *Nature*, **597** (7877): 571–576. PMCID: PMC8711093.

k. Pawnikar S, Magenheimer BS, Nevarez-Munoz E, Maser RL*, & **Miao Y*** (2022) Mechanism of Tethered Agonist-Mediated Signaling by Polycystin-1. *Proc Natl Acad Sci U S A*, 119(19):e2113786119. PMCID: PMC9171645.

l. **Miao, Y.***#, Goldfeld D, Moo EV, Sexton PM, Christopoulos A, McCammon, J. A.* and Valant, C.*# (2016) Accelerated structure-based design of chemically diverse allosteric modulators of a muscarinic G protein-coupled receptor. *Proc Natl Acad Sci U S A*, **113**(38): E5675–E5684. PMCID: PMC5035859.

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)[m]. 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 KU Medicinal Chemistry[n]. 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[o] and effects of Familial Alzheimer's Disease mutations on γ-secretase activation for APP substrate cleavage[p].

m. Wolfe MS & **Miao Y** (2022) Structure and mechanism of the gamma-secretase intramembrane protease complex. *Curr Opin Struct Biol*, 74:102373. PMCID: PMC9189058.
n. Bhattarai, A., Devkota, S., Bhattarai, S., Wolfe, M. S.* & **Miao, Y.*** (2020) Mechanisms of gamma-secretase activation and substrate processing. *ACS Central Science*, 6(6), 969–983. PMC7318072.
o. Bhattarai A, Devkota S, Do HN, Wang J, Bhattarai S, Wolfe MS*, & **Miao Y*** (2022) Mechanism of Tripeptide Trimming of Amyloid β-Peptide 49 by γ-Secretase. *Journal of American Chemical Society,* **144**(14): 6215–6226. PMCID: PMC9798850.
p. Do HN[#], Devkota S[#], Bhattarai A, Wolfe MS*, & **Miao Y*** (2023) Effects of Presenilin-1 Familial Alzheimer's Disease Mutations on γ-Secretase Activation for Cleavage of Amyloid Precursor Protein. *Communications Biology*, **6**(1):174.

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[q]. My lab has successfully carried out computer-aided drug design of inhibitors for the Musashi and human antigen R (HuR) RBPs[r]. 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[s]. In collaboration with the Jingxin Wang lab in KU Medicinal Chemistry, my lab has performed GaMD simulations that captured spontaneous splicing drug binding to single-stranded RNA. We have uncovered a novel ligand-binding pocket formed by two sequential GAAG loop-like structures in pre-mRNA of the survival of motor neuron 2 (SMN2). Our simulations were highly consistent with NMR and structure-affinity-relationship experiments[t].

q. Wang J, Lan L, Wu X, Xu L, & **Miao, Y*** (2022) Mechanism of RNA recognition by a Musashi RNA-binding protein. *Current Research in Structural Biology*, 4:10-20. PMCID: PMC8695263.
r. Wu X, Ramesh R, Wang J, Zheng Y, Armaly AM, Wei L, Xing M, Roy S, Lan L, Gao FP, **Miao Y**, Xu L, & Aube J (2023) Small Molecules Targeting the RNA-Binding Protein HuR Inhibit Tumor Growth in Xenografts. *J Med Chem*, **66**(3):2032-2053. PMCID: PMC10101218.
s. Gao Y, Cao D, Pawnikar S, John KP, Ahn HM, Hill S, Ha JM, Parikh P, Ogilvie C, Swain A, Yang A, Bell A, Salazar A, **Miao Y***, & Liang B* (2020) Structure of the Human Respiratory Syncytial Virus M2-1 Protein in Complex with a Short Positive-Sense Gene-End RNA. *Structure*, 28(9):979-990. PMC7484405.
t. Tang Z, Akhter S, Ramprasad A, Wang X, Reibarkh M, Wang J, Aryal S, Thota S, Zhao J, Douglas J, Gao P, Holmstrom E, **Miao Y***, & Wang J* (2021) Recognition of single-stranded nucleic acids by small-molecule splicing modulators. *Nucleic Acids Research, **49**(14):7870–7883*. PMCID: PMC8373063

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[u,v], binding of G-protein mimic to a GPCR[w], and multiple times of ligand dissociation and binding in human ACE2 receptor[x].

u. **Miao, Y.*** and McCammon, J. A. (2016) Graded activation and free energy landscapes of a muscarinic G protein-coupled receptor. *Proc Natl Acad Sci U S A*, **113**(43): 12162–12167. PMCID: PMC5087018.
v. Do, H. N., Akhter, S. & **Miao, Y.*** (2021) Pathways and Mechanism of Caffeine Binding to Human Adenosine A2A Receptor. *Frontiers in Molecular Biosciences* **8**, 242. PMCID: PMC8111288

w. **Miao Y*** & McCammon JA* (2018) Mechanism of the G-Protein Mimetic Nanobody Binding to a Muscarinic G-Protein-Coupled Receptor. *Proc Natl Acad Sci U S A*, 115(12):3036-3041. PMC5866610.
x. Bhattarai A, Pawnikar S, & **Miao Y*** (2021) Mechanism of Ligand Recognition by Human ACE2 Receptor. *J Phys Chem Lett*, 12:4814-4822. PMC8146134.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44817316/?sort=date&direction=descending