

Utsab R. Shrestha

CONTACT INFORMATION

UT/ORNL Center for Molecular Biophysics
Biosciences Division
Oak Ridge National Laboratory
1 Bethel Valley Rd,
Oak Ridge, TN 37831, USA

Mobile: +1 (313) 806 4782
E-mail: shresthaur@ornl.gov
utsab.shrestha@gmail.com

HIGHLIGHTS

Study of biomolecular flexibility using molecular dynamics (MD) simulations and neutron/X-ray scattering experiments.

Generation of 3D ensemble of structures of intrinsically disordered proteins using enhanced sampling MD simulations and validation by experiments.

News: Supercomputing, neutrons unite to unravel structures of intrinsically disordered protein.
[<https://www.ornl.gov/news/supercomputing-neutrons-unite-unravel-structures-intrinsically-disordered-protein>]

APPOINTMENT

Postdoctoral Research Associate, May 2017 - Present.
Biosciences Division, Oak Ridge National Laboratory.

- *Project 1*: Integrating small-angle neutron scattering (SANS) with MD Simulations to Determine Structural Ensembles of Flexible Biological Systems.
- *Project 2*: Investigation of Structure of Plant Hemicellulose and its Binding Properties to Cellulose using SANS and MD Simulations.

EDUCATION

Department of Physics & Astronomy, Wayne State University

Ph.D. in Physics, **Fall 2012 - Winter 2017** (*Advisor*: Dr. Xiang-Qiang Chu, Professor).

Dissertation title: Exploring the Physics of Proteins at Molecular Level by Neutron and X-ray Scattering.

- *Project 1*: Photoactivation Mechanism of G Protein-Coupled Receptor using Contrast Match SANS and quasielastic neutron scattering (QENS).
- *Project 2*: Effects of High Temperature and Pressure on Structure and Dynamics of Hyperthermophilic Protein from a Deep-Sea Microorganism studied by SANS, QENS and Neutron Spin-Echo (NSE).
- *Project 3*: Investigation of Phonon-like Excitations in Globular and Denatured Proteins using Inelastic Neutron/X-ray Scattering (INS/IXS) Experiments.

Department of Physics, University Campus, Tribhuvan University, Nepal

Master of Science in Physics, **2007-2009** (*Advisor*: Dr. Binil Aryal, Professor).

Dissertation title: Study of Visual Flux Emitted from Saturn's Ring System.

Tri-Chandra Multiple College, Tribhuvan University, Nepal

Bachelor of Science in Physics, **2004-2007**.

RESEARCH EXPERIENCE

- Flexibility-function relationship in globular, membrane and intrinsically disordered proteins.
- MD simulations of intrinsically disordered proteins, membrane protein and plant cellulose.

- X-ray/neutron scattering techniques to probe molecular structure and femtosecond to nanosecond dynamics of proteins.
- **MD simulations:** All-atom standard and enhanced sampling (replica-exchange) MD simulations.
- **Scattering experiments:** Small-angle X-ray/neutron scattering, inelastic X-ray/neutron scattering and quasielastic neutron scattering.

TEACHING
EXPERIENCE

- A lecture on the topic “Neutron Scattering (II)” for a course *Introduction to Molecular Biophysics* at Biochemistry & Cellular & Molecular Biology Department, University of Tennessee - Knoxville.
- A “Journal Club” discussion, Biochemistry & Cellular & Molecular Biology Department, University of Tennessee - Knoxville.
- Teaching assistant for Research in Biomedical Physics course, Department of Physics & Astronomy, Wayne State University, **2015-2017**. Major duties to demonstrate/teach the experiments to senior undergraduates, which are useful for biomedical research and applications.
- Graduate teaching assistant (duties to teach undergraduate level laboratories and quiz classes), Department of Physics & Astronomy, Wayne State University, **2012-2015**.
- Senior teacher for high school level Physics and Math courses at Gyankunj Higher Secondary School, Kathmandu, Nepal, **2009-2012**.

MENTOR
EXPERIENCE

Mentored senior undergraduate and graduate students:

<u>Wayne State University</u>	<u>University of Tennessee</u>
Resiola Neli (2014)	Jordan Finley (2017)
Everett Hall (2015)	Viswanathan Gurumoorthy (2017)
Victor McCastle (2015)	Rupesh Agarwal (2018 - Present)
Kurt Van Delinder (2014-2016)	

- Mentor for “*The Appalachian Regional Commission (ARC)/Oak Ridge National Laboratory (ORNL) High School Summer Math-Science-Technology Institute*” held from **July 7-20, 2018** at Oak Ridge National Laboratory, USA. Major duties to organize and teach high school science and math teachers a molecular dynamics simulation of protein at grass root level and design a coursework for the students.

RELEVANT
SKILLS

MD Simulation:	GROMACS, NAMD, VMD.
Scripting:	bash/shell, Python, MATLAB.
Neutron/X-ray data reduction:	DAVE, MANTID.
Neutron/X-ray data analysis:	IGOR, SASVIEW, ATASAS, DAVE.

PUBLICATIONS

14. **U. R. Shrestha**, J. C. Smith, L. Petridis. Full structural ensembles of intrinsically disordered proteins from unbiased molecular dynamics simulations. [under review]
Preprint: (DOI: <https://doi.org/10.1101/2020.06.16.155374>)
13. **U. R. Shrestha**, E. Mamontov, H. M. O’Neill, Q. Zhang, A. Kolesnikov, X.-Q. Chu. Collective excitations in protein: a measure of flexibility and precursor to bioactivity. [under review]
12. R. Agarwal, **U. R. Shrestha***, X.-Q. Chu, L. Petridis, J. C. Smith*. Mesophilic enzyme function at high temperature: molecular dynamics of hyperthermophilic and mesophilic pyrophosphatases. *Biophys. J.* (2020), in press [DOI: <https://doi.org/10.1016/j.bpj.2020.05.021>]

*co-corresponding author

11. **U. R. Shrestha**, P. Juneja, V. Gurumoorthy, J. M. Borreguero, Q. Zhang, V. Urban, X. Cheng, S. V. Pingali, J. C. Smith, H. M. O'Neill, L. Petridis. Generation of the configurational ensemble of an intrinsically disordered protein from unbiased molecular dynamics simulation. *Proc. Natl. Acad. Sci. U. S. A.*, 116(41): 20446-20452 (2019). [DOI: 10.1073/pnas.1907251116]
10. O. N. Demerdash, **U. R. Shrestha**, L. Petridis, J. C. Mitchell, J. C. Smith, A. Ramanathan. Using small-angle scattering data and parametric machine learning to optimize forcefield parameters for intrinsically disordered proteins. *Front. Mol. Biosci.*, 6: 64, (2019). [DOI: 10.3389/fmolb.2019.00064]
9. **U. R. Shrestha**, S. Smith, S. V. Pingali, H. Yang, M. Zahran, L. Breunig, L. A. Wilson, M. Kowali, J. D. Kubicki, D. J. Cosgrove, H. M. O'Neill, L. Petridis. Arabinose substitution effect on xylan rigidity and self-aggregation. *Cellulose*, 26(4): 2267-2278 (2019). [DOI: 10.1007/s10570-018-2202-8]
8. I. Dhiman, **U. R. Shrestha**, D. Bhowmik, D. R. Cole, S. Gautam. Influence of molecular shape on self-diffusion under severe confinement: A molecular dynamics study. *Chem. Phys.*, 516: 92-102 (2019). [DOI: 10.1016/j.chemphys.2018.08.033]
7. J. M. Borreguero, F. Islam, **U. R. Shrestha**, L. Petridis. idpflex: Analysis of intrinsically disordered proteins by comparing simulations to small angle scattering experiments. *J. Open Source Softw.*, 3(32): 1007 (2018). [DOI: 10.21105/joss.01007]
6. S. M. D. C. Perera, U. Chawla, **U. R. Shrestha**, D. Bhowmik, A. V. Struts, S. Qian, X.-Q. Chu, M. F. Brown. Small-angle neutron scattering reveals energy landscape for rhodopsin photoactivation. *J. Phys. Chem. Lett.*, 9: 7064-7071 (2018). [DOI: 10.1021/acs.jpcclett.8b03048]
5. I. Dhiman, D. Bhowmik, **U. R. Shrestha**, D. R. Cole, S. Gautam. Effect of molecular shape on rotation under severe confinement. *Chem. Eng. Sci.*, 180: 33-41 (2018). [DOI: 10.1016/j.ces.2018.01.027]
4. **U. R. Shrestha**, D. Bhowmik, K. W. Van Delinder, E. Mamontov, H. O'Neill, Q. Zhang, A. Alatas, X.-Q. Chu. Collective excitations in protein as a measure of balance between its softness and rigidity. *J. Phys. Chem. B*, 121(5): 923-930 (2017). [DOI: 10.1021/acs.jpcc.6b10245]
3. D. Bhowmik, G. K. Dhindsa, **U. R. Shrestha**, E. Mamontov, X.-Q. Chu. Effect of nanodiamond surfaces on drug delivery systems. *arXiv:1609.02656 [physics.bio-ph]* (2016)
2. **U. R. Shrestha**, S. M. D. C. Perera, D. Bhowmik, U. Chawla, E. Mamontov, M. F. Brown, X.-Q. Chu. Quasi-elastic neutron scattering reveals ligand-induced protein dynamics of a G-protein-coupled receptor. *J. Phys. Chem. Lett.*, 7: 4130-4136 (2016). [DOI: 10.1021/acs.jpcclett.6b01632]
1. **U. R. Shrestha**, D. Bhowmik, J. R. D. Copley, M. Tyagi, J. B. Leao, X.-Q. Chu. Effects of pressure on the dynamics of an oligomeric protein from deep-sea hyperthermophile. *Proc. Natl. Acad. Sci. U. S. A.*, 112(45): 13886-13891 (2015). [DOI: 10.1073/pnas.1514478112]

SCHOLARLY
ACTIVITIES

- Reviewed journal articles for *Scientific Reports*, Nature Publishing Group.

MEDIA COVERAGE

- Supercomputing, neutrons unite to unravel structures of intrinsically disordered protein. [https://www.ornl.gov/news/supercomputing-neutrons-unite-unravel-structures-intrinsically-disordered-protein]
- Molecular shape dictates the dynamic course in narrow channels. [https://advanceseng.com/molecular-shape-dictates-the-dynamic-course-in-narrow-channels]

- ‘Neutron Scattering and Molecular Simulations to Study Biological Flexibility and Function’, **invited talk** at workshop on ‘Neutrons in Biology: Emergent Topics’, University of Tennessee/Oak Ridge National Laboratory, November 8, 2019.
- ‘Modeling IDPs using Enhanced Sampling Molecular Dynamics Simulations’, **invited talk** at the workshop on ‘Intrinsically Disordered Protein Regions in the Context of Polymer Physics’, Oak Ridge National Laboratory, September 10-11, 2019.
- ‘Accurately Modeling the Heterogeneous Ensemble of Structures of Intrinsically Disordered Proteins using Enhanced Sampling Molecular Dynamics Simulations’, contributed a talk at 256th American Chemical Society Meeting and Exposition, March 30 - April 4, 2019.
- ‘Heterogeneous Interconverting Conformations of N-terminal Intrinsically Disordered Domain of c-Src’, poster presentation at 6th annual Oak Ridge National Laboratory Postdoctoral Association Research Symposium, August 7, 2018.
- ‘Intramolecular Interaction in N-terminal Regulatory Region of c-Src Kinase: A Combined Study of Molecular Dynamic Simulation and Small-Angle Scattering’, contributed talk at 255th American Chemical Society Meeting and Exposition, March 18-22, 2018.
- ‘Quasielastic Neutron Scattering Reveals the Effects of Pressure on Dynamics of a Hyperthermophilic Protein from Deep-Sea’, contributed talk at American Conference on Neutron Scattering, 2016.
- ‘Effects of Pressure on the Dynamics of a Hyperthermophilic Protein Revealed by Quasielastic Neutron Scattering’, contributed talk at APS March meeting, 2016.
- ‘Mechanism of Activation of G-Protein Coupled Receptor Revealed by Neutron Scattering Experiments’, poster presented at 6th Graduate Research Day, Department of Physics and Astronomy, Wayne State University, 2015.
- ‘Neutron Scattering Experiments Revealed the Conformational Change and Flexibility in Rhodopsin upon Light Activation’, contributed talk at 6th Annual Midwest Graduate Research Symposium, University of Toledo, 2015.
- ‘Small-Angle Neutron and X-ray Scattering Reveal Conformational Changes in Rhodopsin Activation’, contributed talk at APS March Meeting, 2015.
- ‘Probing the Domain Motions of an Oligomeric Protein from Deep-Sea Hyperthermophile by Neutron Spin Echo’, poster presented at 59th Annual Meeting of Biophysical Society, 2015.
- ‘Rhodopsin Photoactivation Dynamics Revealed by Quasielastic Neutron Scattering’, poster presented at 59th Annual Meeting of Biophysical Society, 2015.
- ‘Small-Angle Neutron and X-ray Scattering Reveal Conformational Differences in Detergents Affecting Rhodopsin Activation’, contributed talk at 59th Annual Meeting of Biophysical Society, 2015.
- ‘Dynamics of a Large Oligomeric Protein Under High Pressure Studied by Neutron Scattering’, poster presented at American Conference on Neutron Scattering, 2014.
- ‘Photoactivation of a GPCR-Rhodopsin Studied by Small-Angle Neutron Scattering’, poster presented at American Conference on Neutron Scattering, 2014.
- ‘Dynamic behavior of a Large Oligomeric Protein IPPase under Extreme Conditions’, poster presented at 9th Annual Midwest Conference on Protein Folding, Assembly and Molecular Motions, University of Notre Dame, 2014.
- ‘Investigation of Phonon-like Excitations in Hydrated Protein Powders by Neutron Scattering’, presented at 58th Annual Meeting of Biophysical Society, 2014.
- ‘Dynamic Behavior of Oligomeric Inorganic Pyrophosphatase (IPPase) Studied by Quasielastic Neutron Scattering’, poster presented at 58th Annual Meeting of Biophysical Society, 2014.

AWARDS

Knoller Fellowship for PhD Dissertation, Department of Physics and Astronomy, Wayne State University, 2016.

Student Travel Support, American Conference on Neutron Scattering, 2016.

Outstanding Research Poster, 7th Annual Physics Graduate Research Conference, Department of Physics & Astronomy, Wayne State University, 2016.

Thomas C. Rumble University Graduate Fellowship, Wayne State University, 2015-2016.

Neutron scattering travel support by UMCP/NIST (National Institute of Standards & Technology) Outreach Program, 2015.

Outstanding Research Poster, 6th Annual Physics Graduate Research Conference, Department of Physics & Astronomy, Wayne State University, 2015.

The Shirley Chan Student Travel Award, Division of Biological Physics (DBIO), American Physical Society (APS), APS March meeting, 2015

Student Travel Support, American Conference on Neutron Scattering, 2014.

Outstanding Research Poster, 5th Annual Physics Graduate Research Conference, Department of Physics & Astronomy, Wayne State University, 2014.

Education Travel Award, Biophysical Society, 58th Annual Meeting of Biophysical Society, 2014.

Travel Support Award for the participation in Fermi/Swift Conference on Gamma-Ray Bursts, May 7-12, Munich, Germany, 2012.

Fellowship for M.Sc. Dissertation, Ministry of Sports, Science & Technology, Government of Nepal, 2009.

Physics Department Scholarship for M.Sc. Degree, Tribhuvan University, Nepal, 2008.

SCHOOLS & WORKSHOPS

- Neutrons in Biology: Emergent Topics, workshop organized by University of Tennessee/Oak Ridge National Laboratory, November 8, 2019.

- Intrinsically Disordered Protein Regions in the Context of Polymer Physics, Oak Ridge National Laboratory, September 10-11, 2019.

- 17th National School on Neutron and X-Ray Scattering, *Methods & Applications of X-ray and Neutron Scattering*, Argonne National laboratory and Oak Ridge National Laboratory, June 13-27, 2015.

- Summer School on the Fundamentals of Neutron Scattering, *Methods & Applications of Small-Angle Neutron Scattering and Neutron Reflectometry*, NIST Center for Neutron Research, July 13-18, 2014

- X9 SAXS Workbench, National Synchrotron Light Source, Brookhaven National Laboratory, April 24-27, 2014

- Summer School on Methods and Applications of Neutron Spectroscopy, *Inelastic Neutron Scattering Methods*, NIST Center for Neutron Research, June 17-21, 2013

REFERENCES

Xiang-qiang Chu, Ph.D.

Professor (Ph. D. advisor)

Department of Nuclear Science and Technology
Graduate School of China Academy of Engineering Physics
Building 9, East Zone,
ZPark II, No. 10 East Xibeiwang Road,
Haidian District, Beijing 100193, China.
Contact: 86-10-56981796
E-mail: xqchu@gascaep.ac.cn

Loukas Petridis, Ph.D.

R&D Staff Scientist (Postdoc PI)

Biosciences Division
Oak Ridge National Laboratory

Room E340, Building 2040,
Oak Ridge, TN 37831, USA.
Contact: (865)576-2576
E-mail: petridisl@ornl.gov

Jeremy C. Smith, Ph.D.

Director and Governor's Chair

UT/ORNL Center for Molecular Biophysics
University of Tennessee
E344, Bldg. 2040, 1 Bethel Valley Rd.,
Oak Ridge, TN 37831, USA.
Contact: (865) 574-9635
E-mail: smithjc@ornl.gov