

Dr. Amar Nath GUPTA

Assistant Professor

Department of Physics

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Research Interest

I am interested in doing research in the field of Biophysics of proteins (mostly on intrinsically disordered proteins) and DNA . How biological molecules fold (and unfold) is a question of immense importance in both the physical sciences and life sciences. The single-molecule experiments offer several advantages over conventional ensemble methods through the removal of ensemble averaging. By conducting many sequential measurements the distributions and fluctuation of molecular properties can be characterized, transient intermediates can be revealed. Single-molecule trajectories provide dynamic and statistical information that is often hidden in ensemble-averaged results and also permit real-time observation of rarely populated transients, which is difficult or impossible to capture using conventional methods.

Free-energy landscape formalisms provide the fundamental conceptual framework for understanding of the biophysics of folding: in principle, the microscopic rates, diffusion constant at different point of the landscape and pathways for folding of protein. Theoretical studies suggest that single-molecule experiments, performed at different temperatures, might allow exploration of the roughness of protein-folding energy landscapes. It would be nice to explore this aspect from the energy landscape profile. I am always keen to learn new techniques to explore more in the field of Biophysics to improve our understanding of living world.

Education

- **PhD** (2008) from School of Physical Sciences, Jawaharlal Nehru University, New Delhi, India

Thesis Title: *Kinetics of Phase Transitions in Aqueous Polyelectrolytes and Gels*

Supervisor: Prof. Himadri B. Bohidar

- **Pre-PhD** (2003-2004) School of Physical Sciences, JNU, New Delhi, India; **CGPA:** 7.4/9.0

Course taken :

Advanced Statistical Mechanics

Special Topics in Classical and Quantum Mechanics

Experimental Methods in Physics

Research Course I and II in Biophysics

- **M.Sc. Physics** (2001-2003), School of Physical Sciences, JNU, New Delhi, India; **CGPA:** 6.41/9.0

Project worked on : *Rheology of gelatin gel*

Special course taken : Biophysics, Laser Physics, and Advanced Solid State Physics

CSIR JRF-NET: Qualified for JRF *in* Physical Sciences, December 2002

GATE: 95.8 percentile *in* Physics (February 2003), All India Rank: 97

Sponsored/Funded Projects undertaken

- §1. Unraveling cancer transformation and progression through biological, electro-mechanical and computational techniques
Total Grant: 35 Lakhs
- §2. Study misfolding and amyloid formation of amylin protein by laser light scattering
Total Grant: 25 Lakhs

Conference/Workshop organized

- §1. Photonics-2014; member organizing committee, session chair and accommodation-in-charge
- §2. 10th National conference on solid state ionics, IIT Kharagpur, 2014

Research/Teaching Experience

- **Assistant Professor** (12th Sept 2013-) Department of Physics, IIT Kharagpur, West Bengal, India
- **Research Associate** (8th July 2013–8th September 2013)
Worked on project *Investigating the effects of an anti-prion ligand on the folding of PrP at the single-molecule level with force spectroscopy* at the University of Alberta, Edmonton, AB, Canada.
- **Postdoctoral Fellow** (16th Dec 2009–7th July 2013)
Worked on project entitled *Developing Single-Molecule Force Spectroscopy and Fluorescence Assays to Study Protein misfolding and Aggregation* at the University of Alberta, Edmonton, Canada.
- **Postdoctoral Fellow** (29th Oct 2007–30th Nov 2009)
Worked on project titled *Entropy driven liquid crystalline compaction of super coiled DNA* at the Department of Physics, National University of Singapore, Singapore.
- **Teaching Assistantship** for the following M. Sc Courses at SPS/JNU, New Delhi.
 1. Biophysics, Jan–May 2004, Course taken by Prof. Himadri B. Bohidar.
 2. Solid State Physics, Aug–Dec 2005, Course taken by Prof. Deepak Kumar.
 3. Mathematical Physics II , Jan–May 2006, Course taken by Prof. Shankar P. Das

Safety induction training

- At faculty of science, National University of Singapore, Singapore in August 2008

Computer experience

- Proficient in LabVIEW, IGOR-Pro, FORTRAN, MATLAB, MATHEMATICA, Sigma Plot, Latex, Adobe Illustrator etc..

Reviewer of scientific journals

Applied Surface Science (Elsevier) , Mettalamics (Royal Society of Chemistry)

Membership of scientific organisation

- Material Research Society, Singapore

Fellowship/Awards

- §1. Jawahar Bhavan Trust Yojna Fellowship for one year in 2nd year of M.Sc.
- §2. Junior/Senior Research Fellowship during PhD from CSIR, New Delhi.
- §3. Travel award of C\$ 1000 to present poster in ‘PrP Canada 2012 and Protein Folding and Disease Conference’ in Toronto.

Citation and *h*-index

Citation: more than 500 [Google Scholar](#) *h*-index: 11 Average impact factor: > 7

Sponsored Projects

Current/Ongoing

- §1. Study misfolding and amyloid formation of amylin protein by laser light scattering (APL)
(Funding Agency: ISIRD, SRIC, IIT Kharagpur)
- §2. Unravelling cancer transformation and progression through biological, electro-mechanical and computational techniques (CPT)
(Funding Agency: MHRD, Department of higher education, New Delhi)

Laboratory Responsibility

§1. In-charge of Teaching Laboratory: M.Tech Teaching lab

Theses Supervision

§1. Ph.D Theses: **1 (completed)**; **4 (ongoing)**

§2. M. Tech: **2 (completed)**; **1 (Ongoing)**

§3. M.Sc. Theses: **5 (completed)**; **3 (Ongoing)**

Course Taught/Teaching

§1. M.Sc./M. Tech/ PhD:

- (a) PH61003 (Physics for Medicine and Biology)(Core Course)(3 semester)
- (b) PH60402 (Biophysics) (Elective)(3 semester)
- (c) PH49009 (Condensed Matter Physics Lab-I) (2 semester)
- (d) PH69003 (M.Tech. Lab)(2 semester)
- (e) PH49006 M.Sc Optics Lab (2 semester)

§2. B.Tech

- (a) BS20001 (Science of Living System) (Core Course) (3 semester)
- (b) PH20003 Physics-II (3 semester)
- (c) PH11001 (Physics-I) (1 semester)
- (d) PH19001 (B.Tech Lab) (4 semester)

Department Level Activities

- §1. Associated with 'School of Bioscience'
- §2. Associated with 'School of Medical Science and Technology'
- §3. Member of various departmental committees
- §4. Assisted in conducting PhD entrance exam and viva every year
- §5. Evaluation of MSC final year thesis Presentations
- §6. MTech Lab-in-charge
- §7. Member of purchase committee
- §8. Training and Placement in-charge Physics department

Selected Publication

- §1. Suparna Khatun, Anurag Singh, Debabrata Mandalb, Amreesh Chandraab and **Amar Nath Gupta** *Quantification of protein aggregation rates and quenching effects of amylininhibitor complexes* *Phys. Chem. Chem. Phys.* DOI: 10.1039/C9CP03238J; (2019)
- §2. S Khatun, A Singh, N Pawar, **AN Gupta** *Aggregation of amylin: Spectroscopic investigation* *International journal of biological macromolecules* 133, 1242-1248 (2019)
- §3. Debabrata Mandal, Suparna khatun, **Amar Nath Gupta**, Amreesh Chandra *DNA supported graphene quantum dots for Ag ion sensing* *Nanotechnology* 30 (25), 255501 (2019)
- §4. S Khatun, K Shikha, A Ganguly, N Pawar, **AN Gupta** *Repulsive interaction induces fibril formation and their growth* *International journal of biological macromolecules* 123, 20-25 (2019)
- §5. A Sudha, SL Sharma, **AN Gupta** *Achieving sensitive and stable indium oxide thin films for gamma radiation monitoring* *Sensors and Actuators A: Physical* 285, 378-385 (2019)
- §6. A Sudha, TK Maity, SL Sharma, **AN Gupta** *An extensive study on the structural evolution and gamma radiation stability of TeO₂ thin films* *Materials Science in Semiconductor Processing* 74, 347-351 (2018)
- §7. A Sudha, SL Sharma, **AN Gupta**, SD Sharma *Tuning the properties of tin oxide thin films for device fabrications* *The European Physical Journal B* 90 (11), 219 (2017)
- §8. **Amar Nath Gupta**, Johan RC van der Maarel *Compaction of plasmid DNA by macromolecular crowding* *Macromolecules*, 50, 4, 1666-16671, (2017)
- §9. **Amar Nath Gupta**, K P Neupane, Negar Rezaiooei, Leonardo Cortez, Valerie Sim, M. T. Woodside *Pharmacological chaperone reshapes the energy landscape for folding and aggregation of the prion protein* *Nature Communication*; (doi:10.1038/ncomms12058 ; 2016)
- §10. **Amar Nath Gupta**, Hao Yu, Xia Lu, K P Neupane, Angela M. Brigley, Iveta Sosova, M. T. Woodside *Energy landscape analysis of native folding of the prion protein yields the diffusion constant, transition path time, and rates* *Proceeding of National Academy of Sciences, (USA)*, 109, 14452-14457, (2012)
- §11. **Amar Nath Gupta**, Derek R. Dee, Max Anikovskiy, Iveta Sosova, Elena Grandi, Laura Rivera, Abhishash Vincent, Angela M. Brigley, Nils O. Petersen, Michael T. Woodside *Phthalocyanine tetrasulfonates bind to multiple sites on natively-folded prion protein* (*BBA-Proteins and proteomics (Elsevier)*), 1824, 826-832, (2012)
- §12. Hao Yu, Xia Liu, Krishna Neupane, **Amar Nath Gupta**, Angela M. Brigley, Allison Solanki, Iveta Sosov, Michael T. Woodside *Direct observation of multiple misfolding pathways in a single prion protein molecule* *Proceeding of National Academy of Sciences (PNAS), USA*, 109, 5283 (2012); This article was Editor's choice in science magazine, 336, number 6080issue of 27 April 2012 in *Biophysics: Taking the wrong path*
- §13. **Amar Nath Gupta**, A. Vincent, K. Neupane, Hao Yu, F. Wang, M. T. Woodside *Experimental validation of free energy landscape reconstruction from non-equilibrium single-molecule force spectroscopy measurements*, *Nature Physics (Letter)*, 7, 631 (2011); this article was cited in **news and view** in *Nature Physics* 7, 591 (2011)
- §14. Xiaoying Zhu, Siow Yee Ng, **Amar Nath Gupta**, YP Feng, B Ho, A Lapp, Stefan U. Egelhaaf, VT Forsyth, M Haertlein, M Moulin, Ralf Schweiwins and JRC vd Maarel *Effect of crowding on the conformation of interwound DNA strands from neutron scattering measurements and Monte Carlo simulations* *Phys. Rev. E* 81, 061905 (2010)
- §15. **Amar Nath Gupta** and H.B. Bohidar *Phase separation in aqueous solutions of similarly charged Biopolymers* *J. Surface Sc. Technol.* 25, 1 (2009)

- §16. **Amar Nath Gupta**, H. B. Bohidar *Temporal evolution of self-organization of gelatin molecules and clusters on quartz surface* *Phys. Rev. E* **76**, 051912 (2007)
- §17. **Amar Nath Gupta**, V. K. Aswal, H. B. Bohidar *Surface patch binding induced intermolecular complexation and phase separation in aqueous solutions of similarly charged gelatin-chitosan molecules* *J. of Phys. Chem. B* **111**, 10137 (2007)
- §18. B. Mohanty, **Amar Nath Gupta**, H. B. Bohidar *Effect of gelatin molecular charge heterogeneity on formation of intermolecular complexes and coacervation transition* *Journal of Polymer Science Part B: Polymer Physics* **45**, Issue 13, 1511 (2007)
- §19. Shilpi Boral, **Amar Nath Gupta** and H. Bohidar *Swelling and De-swelling kinetics of gelatin hydrogels in ethanol-water marginal solvent* *I J of Bio. Macromol.* **39**, 240 (2006)
- §20. **Amar Nath Gupta**, Reena and H.B.Bohidar *Free energy landscape of alcohol driven coacervation transition in aqueous gelatin solutions* *J. Chem. Phys.* **125**, 054904 (2006)
- §21. **Amar Nath Gupta** and H.B.Bohidar *Kinetics of Phase separation in System Exhibiting Simple Coacervation* *Phys. Rev. E* **72**, 011507 (2005)
- §22. **Amar Nath Gupta**, B. mohanty and H.B.Bohidar *Flory Temperature and Upper Critical Solution Temperature of Gelatin Solution*, *Biomacromolecules* **6**, 1623 (2005)

Conference Publication

- §1. K Neupane, H Yu, D Ritchie, **AN Gupta**, X Liu, DAN Foster, F Wang, I Sosova, Micahel T Woodside, *Transition Path Times for the Folding of Nucleic Acids and Proteins Determined from Experimentally-Reconstructed Energy Landscape Profiles* Biophysical Journal 104 (2), 165a
- §2. X Liu, H Yu, **A N Gupta**, K Neupane, AM Brigley, I Sosova, MP Woodside *Reconstruction of the Energy Landscape Profile for Native Folding of the prion Protein from Single-Molecule Force Spectroscopy* Biophysical Journal 102 (3), 54a (2012)
- §3. A Vincent, **AN Gupta**, K Neupane, H Yu, M Woodside *Experimental Validation of Free Energy Landscape Reconstructions from Non-Equilibrium Single-Molecule Pulling Experiments* Biophysical Journal 100, 484 (2011)
- §4. I Sosova, A Vincent, **A Gupta**, M Anikovskiy, A Brigley, MT Woodside *Characterizing the Interaction Between Phthalocyanine Tetrasulfonates and Mammalian Prion Protein* Biophysical Journal 100, 553 (2011)
- §5. H Yu, X Liu, AM Brigley, A Solanki, **AN Gupta**, I Sosova, MT Woodside *Force Spectroscopy of Mammalian Prion Protein Folding and Misfolding* Biophysical Journal 100, 23 (2011)
- §6. **Amar Nath Gupta**, Xiaoying Zhu, Johan RC Van der Maarel *Study of Salt Effect on Supercoiled Plasmid DNA by Light and Neutron Scattering* DNA Nanoscience and Physics, ICMAT, Singapore 2009
- §7. **Amar Nath Gupta**, Xiaoying Zhu, Bow Ho, Johan RC Van der Maarel *Purification of PHSG298 Supercoiled Plasmid DNA Using Anion-exchange Chromatography at Lab Scale* DNA Nanoscience and Physics, ICMAT, Singapore 2009

Book Chapter

- §1. H. B. Bohidar and **Amar Nath Gupta** *Nano-scale self-organization of polyampholytes* Recent trends in Surface and colloid Science; [Statistical Science and interdisciplinary Science Vol. 12, chapter 6](#), (2008)
- §2. H. B. Bohidar and **Amar Nath Gupta** *Kinetics of phase separation in polyampholytes* in Current Physics Index by American Institute of Physics (2005)

- §1. *Transition path time, diffusion constant and folding rates of protein determined from reconstructed free energy landscape analysis* an invited talk at Indian Institute of Technology Kanpur on 12th December 2012
- §2. *Observing protein folding and misfolding in the single-molecule regime with optical tweezers* an invited talk at National Center for Biological Sciences Bangalore on 3rd December 2012
- §3. *Free energy landscape reconstruction of native folding prion protein* an invited talk at Indian Institute of Technology Hyderabad on 30th November 2012
- §4. *Reconstruction of free energy landscape of prion protein from non-equilibrium force spectroscopy data* an invited talk at TIFR TCIS on 29th November 2012
- §5. *Observing folding and misfolding of a single prion protein by optical tweezers* an invited talk at Indian Institute of Technology Bombay on 27th November 2012
- §6. *Transition path time, diffusion constant and folding rate of protein determined from free energy landscape analysis* an invited talk at Indian Institute of Science Bangalore on 22nd November 2012
- §7. *Observing protein folding and misfolding in the single-molecule regime with optical tweezers* an invited talk at Indian Institute of Scientific Education and Research Mohali on 19th November 2012
- §8. *Direct observation of protein folding/misfolding using single-molecule force spectroscopy* an invited talk at Indian Institute of Technology Ropar on 16th November 2012
- §9. *Reconstruction of free energy landscape of prion protein from non-equilibrium force spectroscopy data* an invited talk at Indian Institute of Technology Delhi on 15th November 2012
- §10. *Energy landscape analysis of native folding of the prion protein yields the diffusion constant, transition path time, and rates* an invited talk at Young Investigator Meeting Boston, USA on 8th October, 2012
- §11. *Reconstruction of Free Energy Landscape for Native Folding of the Prion Protein from Single-Molecule Force Spectroscopy using Optical Tweezers* an invited talk at Regional Centre for Biotechnology, Gurgaon, India on 18th January, 2012
- §12. *Free Energy Reconstruction and Verification of Jarzynski Equality from Single Molecule Force Spectroscopy Experimental Data* an invited talk at Indian Institute of Science Education and Research Mohali, India on 28th July, 2010
- §13. *Study of Salt Effect on Supercoiled Plasmid DNA by Light and Neutron Scattering* an Oral presentation in ICMAT 2009 on 2nd July, 2009 in Singapore
- §14. *Purification of pHSG298 Supercoiled Plasmid DNA Using Anion-exchange Chromatography at Lab Scale* an oral presentation at ICMAT 2009 on 2nd July, 2009 in Singapore

- §1. Poster title *Energy landscape analysis of the native folding pathway of the prion protein: diffusion constant, transition path time, and rates* in PrP Canada 2012 and Protein Folding and Disease Conference in Toronto, Canada from 25th-27th June 2012
- §2. Poster title *Reconstruction of Free Energy Landscape for Native Folding of the Prion Protein from Single Molecule Force Spectroscopy* in YIM2012 at Lonavala, India on 7th-11th January 2012
- §3. Poster title *Reconstruction of the Energy Landscape Profile for Native Folding of the prion Protein from Single-Molecule Force Spectroscopy* in Biophysical Society Meeting in San Diego, USA (2012)
- §4. Poster title *Direct observation of Misfolding in single Prion Protein Molecules* presented in PRION2011 in Montreal, Canada on 15th-19th May 2011
- §5. Poster title *Characterizing the interaction between phthalocyanine tetrasulfonates and mammalian prion protein* presented in 55th Biophysical Society meeting in Baltimore, USA on March 5th-9th, 2011
- §6. Poster title *Experimental validation of free energy landscape reconstructions from non-equilibrium single-molecule pulling experiments* presented in 55th Biophysical Society meeting in Baltimore, USA on March 5th-9th, 2011
- §7. Poster title *Direct observation of multiple misfolding pathways in a single prion protein molecule* presented in 55th Biophysical society annual meeting, Baltimore, USA, March 5th-9th, 2011
- §8. Poster title *Single Molecule Force Spectroscopy of Prion Protein Folding/Unfolding Studied with Optical Tweezers* presented in ASM 2010 meeting in Vancouver, Canada on 26th Oct 2010
- §9. Attended in *PrP Canada 2010* Scientific meeting in Ottawa, Canada on 9th-10th March 2010
- §10. Presented a poster on purification and characterization of supercoiled plasmid DNA in the same conference in ICMAT 2009 in June-July.
- §11. Participated in 1st NUS Academic Entrepreneurship Workshop on 10th November 2009
- §12. Participated in 2nd Mechanobiology Workshop 2008 which was held from 3 to 5 November 2008 at the Center for Life Sciences, NUS
- §13. Participated in Singapore Nanomedicine Workshop 2008 which was held on 22-25th October 2008 at BIOPOLIS, matrix Building Singapore
- §14. Participated in join 5th Structural Biology and functional genomics and 1st Biophysical Physics international Conference, held at NUS Singapore on 9th-10th Dec 2008
- §15. Participated in Institute of Future Workshop about future of science and innovation on 24th July 2008 at NUS
- §16. Participated in workshop on the *frontiers of nano-Science and nano-technology*, held at faculty of engineering in NUS Singapore on 7th Aug 2008
- §17. Participated in Workshop on BioMEMS-Micro/Nano-fluidic devices: Simulation and Experimentation Organised by Computational Engineering (CE) Programme at NUS 22nd July 2008
- §18. Participated in INFECTIOUS DISEASE SYMPOSIUM: "The Genomics of hosts, pathogens, and their interaction" held at BIOPOLIS, Singapore on 17-18th June 2008
- §19. Participated in the XII workshop on Neutron as probes of condensed matter on 24th-25th Feb 2006 organized by UGC-DAE CSR and SSP Division at BARC, Mumbai
- §20. Poster title *Flory temperature and UCST of gelatin solution* presented in ICBC-2005, International Conference on Advances in polymer Blends, composites, IPNS and Gels: Macro to Nano scales held at school of chemical sciences, Kottayam, Kerala on 21st-23rd March 2005
- §21. Presented a poster on *Synthesis of gelatin nanoparticles via simple coacervation* in ICSM 2004 at Jadavpur University, Calcutta

- §1. **Single-Molecule Force Spectroscopy:** By Dual Trap Laser Optical Tweezers
- §2. **Binding Kinetics of Protein with Drug:** By Surface Plasmon Resonance (**SPR**); Iso-Thermal Calorimetry (**ITC**) and Fluorescence Correlation Spectroscopy (**FCS**)
- §3. **Size and structure Measurements:** By Atomic Force Microscopy (**AFM**)
- §4. **Making of DNA handles:** By Polymerase chain reaction (**PCR**)
- §5. **Thin film deposition:** Chromium and gold deposition on SF-10 glass by thermal evaporation and making of sensor chip for **SPR**
- §6. **DNA and Protein Purification:** By HPLC (**AKTA** Explorer/Purifier)
- §7. **Aggregation Assay for Prion / Alpha-Synuclein Protein:** Th-T assay By Microplate Reader
- §8. **Making of Micron-sized channel:** By PDMS casting on the stamp made by proton ion beam writing
- §9. **Helicity of protein:** By Circular Dichroism (**CD**); **Turbidity Measurement:** By Colorimeter
- §10. **Gel electrophoresis:** Agarose / SDS PAGE and Chloroquine gel electrophoresis
- §11. **Protein/DNA expression:** in *E. Coli* for plasmid DNA and proteins like HU/HNS, Prion and their mutant
- §12. **Surface charge measurement (Zeta Potential):** by **ZEECOM**
- §13. **Bio-Nanoparticle Preparation-**Gelatin nanoparticles by simple coacervation
- §14. **Size of nanoparticles:** By Dynamic & Static Light and Small Angle Neutron Scattering (**SANS**)
- §15. **Drug Release Kinetics:** By Dialysis and UV-Visible Spectrophotometry
- §16. **Rheological Properties:** By Rheometer AR 500 (**TA instrument**)

Research experience in various reputed labs

- §1. **National Institute for Nanotechnology, University of Alberta, Canada** with **Prof. Nils O. Petersen** on drug binding kinetics by Surface Plasmon Resonance
- §2. **Institut Laue-Langevin, Grenoble, France** with **Dr. Ralf Schweins** for Small angle neutron scattering (SANS) measurements on Plasmid DNA under zero average contrast
- §3. **Department of Microbiology, NUS, Singapore**, with **Prof. Ho Bow** for Expression of protein and DNA in *E. coli* bacteria
- §4. **Biophysics and Complex fluids lab, NUS, Singapore** with **Prof. Johan RC van der Maarel** on Plasmid DNA and protein purification and their characterization
- §5. **Centre for Ion Beam Application, NUS, Singapore** with P.G. Shao for making of micron-sized channel
- §6. **SSP Division, Bhabha Atomic Research Centre (BARC), India** with **Dr.VK Aswal** for SANS measurements on gelatin and complex of gelatin-chitosan coacervates.
- §7. **Departmental of Biotechnology, JNU, India** with **Prof. Santosh Kar** on curcumin and chitosan
- §8. **Department of Physics, IIT Delhi, India** with **Prof. BR Mehta** for AFM measurements
- §9. **School of Physical Sciences, Semiconductor Lab, JNU, India** with **Prof P. Sen** for AFM measurements

§1. Effect of crowding on the conformation of interwound DNA strands from neutron scattering measurements and Monte Carlo simulations

In this project I learned basic Biophysical characterisation techniques to study the compaction of plasmid DNA. We have measured small angle neutron scattering (SANS) from pHSG298 plasmid (2675 base pairs) dispersed in saline solutions to determine the distance between the two opposing duplexes in supercoiled plasmid DNA. We did SANS experiments under full and zero average scattering contrast using hydrogenated plasmid and a 1:1 mixture of hydrogenated and perdeuterated plasmid, respectively. In the condition of zero average contrast, the scattering intensity is directly proportional to the single DNA molecule scattering function (form factor), irrespective of the DNA concentration and without complications from intermolecular interference. We also did many body Monte Carlo computer simulation for the form factors to match our results. It was observed that the inter duplex distance decreases with increasing concentration of salt as well as plasmid. We showed that besides ionic strength, DNA crowding is also important in controlling the interwound structure and site juxtaposition of distal segments of supercoiled DNA.

§2. Study of folding pathways of a single prion protein molecule using optical tweezers

I am exploring the possible misfolding pathway of prion protein (PrP) by single molecule force spectroscopy measurement using optical tweezers. The optical trap, consisting of a tightly focused, intense laser beam which can hold on to micron-sized plastic beads in solution. An optical trap acts like a spring made out of light, allowing force to be applied to a molecule tethered to a bead by deflecting the bead from the center of the trap. The motion of the molecule is detected by collecting light scattered off the bead. Protein misfolding is a ubiquitous process that is associated with a wide range of diseases. Prion disease such as Creutzfeld-Jacob disease (CJD) in humans is caused by the accumulation of a misfolded form of the prion protein (PrP^{Sc}). Prion-like behavior has also been reported in other misfolding diseases such as Parkinson's and Alzheimer's. PrP^{Sc} is infectious, in the sense that it can recruit natively-folded PrP to make additional PrP^{Sc} and thereby transmit the disease between individuals and even across species. PrP misfolding and conversion remain poorly understood, however, in part because of the difficulty of observing them directly. What we found that PrP unfolded and refolded in its native pathway as a two-state system, without any partially-folded intermediates, despite the important role intermediates are thought to play both in PrP misfolding and protein aggregation more generally. Instead, frequent but fleeting transitions into three distinct misfolded states were observed. Surprisingly, most folding events led to non-native, rather than native, structures. These measurements provide a new insight into the folding dynamics and misfolding mechanism of PrP, demonstrating the power of single-molecule approaches for characterizing protein misfolding through detailed analysis of alternative folding pathways. Partially-folded intermediates of PrP have been proposed to play a key role in this process.

§3. Finding chemical chaperones which can inhibit the formation of PrP^{Sc}

Given the important role played by protein misfolding in prion diseases, one therapeutic strategy has been to focus on finding or developing chemical chaperones which inhibit the formation of PrP^{Sc}. Cyclic tetrapyrroles such as porphyrins and phthalocyanines, which have found use as tumor photosensitizers in cancer therapy and as microbicides for preventing HIV infection, have shown promise as 'anti-scrapie' chaperones. In vitro tests using cell cultures infected with PrP^{Sc} has discovered a variety of tetrapyrroles which are able to inhibit PrP^{Sc} formation. We have further investigated PcTS (3 forms of PcTS: FB-, Zn²⁺-, and Al³⁺) binding to PrP by using several complementary methods based on different physical principles, including surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), fluorescence correlation spectroscopy (FCS), and tryptophan fluorescence quenching. We did the Th-T aggregation assay with the positive hit chaperones identified by above methods. Finally our target is to study the effect of potential drug on the protein misfolding under the trap.