BIOGRAPHICAL SKETCH

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NAME: Chapagain, Prem P.

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

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tribhuvan University, Kathmandu, Nepal	B.Sc.	06/1996	Physics
Tribhuvan University, Kathmandu, Nepal	M.Sc.	12/1998	Physics
Florida International University, Miami, FL	Ph.D.	08/2005	Physics/Biophysics
Cornell University, Ithaca, NY	Postdoc	08/2006	Infectious disease Modeling

A. Personal Statement

Over the last few years, my research has focused on the computational investigations of protein dynamics and function including membrane interactions, assembly, and budding of filovirus and flavivirus proteins. I have extensive research experience in computational investigations of protein dynamics. As the PI of an NIH funded grant, I investigated the protein barrel flexibility and oxygen diffusion pathways in red fluorescent proteins (RFP). More recently, in collaboration with Stahelin lab (Purdue), I have been investigating viral replication and budding in Filoviruses, which include Ebola virus (EBOV) and Marburg virus (MARV). I have expertise on epitope mapping for identifying potential epitopes as potential vaccine candidates and have worked on MARV and Lassa virus (LASV) epitopes. I also have expertise in molecular docking and virtual screening, and have performed in silico screening of potential inhibitors for a variety of protein systems. I am currently involved in drug screening against both human and bacterial topoisomerases. With my expertise in computational modeling and simulation, I am well positioned to make a significant contribution towards molecular modeling and drug screening.

I have a highly successful record of mentoring both graduate and undergraduate students. I received the 2019 FIU *Faculty Excellence in Teaching* Award and *Outstanding Research Award* in 2016 and 2018. The PhD students I supervised have been recognized by FIU as the "*Worlds Ahead*" graduates and have continued their research in biophysics as postdocs. Currently, several graduate and undergraduate students, including minority and female students, are currently carrying out research in biophysics under my supervision. I was promoted to full professor in 2021. In 2019, I was appointed as the Associate Director of Biomolecular Sciences Institute, which was founded in 2012 to facilitate interdisciplinary research in molecular and cellular biophysics and biochemistry.

B. Positions and Honors

Positions and Employment

2021-	Professor, Department of Physics, Florida International University, Miami, FL
2019-	Associate Director, Biomolecular Sciences Institute, Florida International University.
2012-	Associate Professor, Department of Physics, Florida International University, Miami, FL
2006-2012	Assistant Professor, Department of Physics, Florida International University, Miami, FL
1999-2000	Medical Physicist, Bhaktapur Cancer Hospital, Nepal
1998-2000	Assistant Lecturer, Tribhuvan University, Nepal

Other Experience and Professional Memberships

2020	NSF Panel **-** Phase I: COVID 19 Pharmaceutical Tech Therapeutic Molecule I Virtual Panel
2019	Member, American Chemical Society
2019	Grant Reviewer for the National Fund for Scientific and Technological Development, Chile
2018	NIH Ad-hoc Reviewer, MSFD
2013-	Member, Biophysical Society
2011,12,16	Reviewer Alzheimer's Association International Research Grant Program
2009	Mail Reviewer for Human Frontier Science Program (HFSP)
1998-	Life member, Nepal Physical Society

Honors

2019	Innovative Course Design, FIU Online, Florida International University, Miami, FL
2019	Faculty Excellence in Teaching Award, Florida International University, Miami, FL
2018	Outstanding Research Award, CASE, Florida International University, Miami, FL
2016	Outstanding Research Award, CASE, Florida International University, Miami, FL
2012	American Physical Society International Travel award.
2010	Faculty Summer Research Award, Florida International University, Miami, FL
2008	Faculty Summer Research Award, Florida International University, Miami, FL
2004	National Science Foundation (NSF) Travel Award (STATPHY22)
2004	Dissertation Year Fellowship, Florida International University, Miami, FL
1998	Distinction (Topped the list of MSc physics recipients from the entire country), Nepal
1996	Medal for Excellence in Education (Topped the list of BSc recipients, local), Nepal

C. Contributions to Science

I. My research has focused primarily on protein structural dynamics that allow proteins to perform a myriad of functions to maintain life. In the last few years, I have been focusing on the structure and dynamics as well as membrane interactions various viral proteins. Specifically, I have extensively worked on the dynamics and membrane interactions of filovirus protein VP40, which is the main component of the virus matrix. In collaboration with the Stahelin lab, I have investigated how Ebolavirus and Marburgvirus VP40 assemble at the host membrane surface and facilitate viral budding. I have uncovered important details of VP40-membrane interactions, such as how VP40 enhances the clustering of the PIP_2 lipids. I have also investigated the structural changes in the receptor-binding domain of the SARS-CoV-2 spike protein. I conceived the ideas, designed the computational strategies, and led the projects in the following representative publications:

1. Bhattarai, N., Baral, P., Gerstman, BS. and **Chapagain, PP.**, Structural and Dynamical Differences in the Spike Protein RBD in the SARS-CoV-2 Variants B. 1.1.7 and B.1.351. *The Journal of Physical Chemistry B* 125, 7101-7107 (2021) [**Featured on the journal cover].**

2. Pokhrel R, Gerstman BS, and **Chapagain PP***, “Membrane pore formation and ion selectivity of the Ebola virus delta peptide” Currently under revision stage at *Physical Chemistry Chemical* Physics **21**, 5578-5585 (2019).

3. GC JB, Gerstman BS, and **Chapagain PP*** “Membrane association and localization dynamics of the Ebola virus matrix protein VP40” *Biochimica et Biophysica Acta (BBA) Biomembranes* 10, 2012-2020 (2017).

4. GC JB, Gerstman BS, Stahelin RV, and **Chapagain PP*** "The Ebola virus Protein VP40 hexamer enhances the PIP(4,5)P2 clustering in the plasma membrane" *Physical Chemistry Chemical Physics* 18, 28409-28417 (2016) [PMCID: PMC5084917]. [**Featured on the journal cover].**

II. I have used computational and theoretical techniques to target proteins for identifying novel inhibitors. Specifically, antimicrobial resistance is a growing health concern and novel applications to overcome this issue are urgently needed. Lantibiotic peptides produced by various gram-positive bacteria, constitute a promising class of drugs to battle the threat of antibiotic resistance. I have investigated the molecular mechanisms of pore formation and membrane disruption by various lantibiotic peptides. I am also involved in virtual drug screening for identifying novel compounds against viral and bacterial pathogens, including SARS-CoV-2 and Mycobacterium. I designed and led the computational component in the following representative publications.

1. Sandhaus S, **Chapagain PP**, and Tse-Dinh YC "Discovery of novel bacterial topoisomerase I inhibitors by use of in silico docking and in vitro assays" *Scientific reports* 8, 1437 (2018) [PMCID: PMC5780498].

2. Pokhrel, R., **Chapagain, PP**. and Siltberg-Liberles, J.; Potential RNA-dependent RNA polymerase inhibitors as prospective therapeutics against SARS-CoV-2. *Journal of Medical Microbiology*, 001203 (2020).

3. Pokhrel R, Bhattarai N, Baral P, Gerstman BS, Park JH, Handfield M, and **Chapagain PP**. "Molecular mechanisms of pore formation and membrane disruption by the antimicrobial lantibiotic peptide Mutacin 1140". *Physical Chemistry Chemical Physics*, 21, 12530-12539 (2019).

4. Beddingfield, B.J., Iwanaga, N., Chapagain, P.P., Zheng, W., Roy, C.J., Hu, T.Y., Kolls, J.K. and Bix, G.J., The integrin binding peptide, ATN-161, as a novel therapy for SARS-CoV-2 infection. *JACC: Basic to Translational Science*, 6, 1-8 (2021).

III. For the last several years, my research focused on an NIH-funded project on fluorescent proteins. The goal of the project was to better understand the protein barrel flexibility and the protein protein-chromophore interactions for improving photophysical properties of red fluorescent proteins. I performed Molecular Dynamics (MD) simulations of the dynamics of several variants of red-fluorescent proteins and investigated the correlations between the barrel-chromophore interactions and the photophysical properties of these variants. The computations were carried out in collaboration with JILA experimentalists R. Jimenez and A. Palmer who conducted experiments using multi-parameter screening of RFP variants. Experiments that were guided by MD simulations have resulted in a new FP variant called Kriek (K2C) which has about 2.5-fold photostability of mCherry. Investigations on the role of the barrel-chromophore interactions have revealed that the observed red-shifted emission on far-red FPs depend on the facile switching of the hydrogen bond between direct and water-mediated configurations. Follow up studies by other groups have confirmed that it is not just the presence of the direct H-bond, but its commutable nature is responsible for the large Stokes shift in mPlum. The following are representative publications:

1. **Chapagain PP**, Regmi CK, Castillo W. "Fluorescent protein barrel fluctuations and oxygen diffusion pathways in mCherry", *Journal of Chemical Physics* 135, 235101 (2011). [PMCID: PMC3248888] [**Featured on the Journal Cover**].

2. Regmi CK, Bhandari YR, Gerstman BS and **Chapagain PP** "Exploring the diffusion of molecular oxygen in the red fluorescent protein mCherry using explicit oxygen molecular dynamics simulations" *Journal of Physical Chemistry B* 117, 2247-2253 (2013). [PMCID: PMC3587716]

3. Dean KM, Lubbeck JL, Davis LM, Regmi CK, **Chapagain PP**, Gerstman BS, Jimenez, and AE Palmer "Microfluidics-based selection of red-fluorescent proteins with decreased rates of photobleaching" *Integrative Biology* 7, 263-273 (2015). [PMCID: PMC4323946].

4. Konold PE, Eunjin YE, Junghwa LJ, Samantha L. Allen SL, **Chapagain PP**, Gerstman BS, Regmi CK, Piatkevich KD, Verkhusha VV, Joo T, and Jimenez R, "Fluorescence from Multiple Chromophore

Hydrogen-Bonding States in the Far-Red Protein TagRFP675" *Journal of Physical Chemistry Letters* 7, 3046–3051 (2016). [PMCID: PMC5004773].

III. I have used mathematical modeling techniques to investigate the population dynamics in epidemiology as well as the kinetics in protein structural transitions. I developed mathematical models with coupled non-linear differential equations to describe the spread of Salmonella infections in animal populations. Such models are not only applicable to the spread of infections but also to a wide range of problems, from calcium fluctuations in cells to the cancer progression or the formation of Amyloid fibrils in many neurological disorders. I have modeled the protein aggregation pathways to investigate the kinetics of the fibril formation in Alzheimer's disease and determined kinetic rate constants in various biochemical conditions.

1. Steckmann T. Awan Z. Gerstman B. and **Chapagain PP**, "Kinetics of peptide secondary structure conversion during Amyloid β-protein fibrillogenesis" *Journal of Theoretical Biology* 301, 95-101 (2012). [**Featured as the Model of the Month** by the European Bioinformatics Institute].

2. **Chapagain PP**, Van Kessel JS, Karns JS, Wolfang DR, Hovingh E, Nelen KA, Schukken YH, and Grohn YT, "A mathematical model of the dynamics of Salmonella Cerro infection in a US dairy herd" *Epidemioloy and Infection* 136, 263 (2008).

3. Lanzas C, Brien S, Ivanek R, Lo Y, **Chapagain PP**, Ray KA, Ayscue P, Warnick LD, and Gröhn YT. "The effect of heterogeneous infectious period and contagiousness on the dynamics of Salmonella transmission" *Epidemiology and Infection* 136, 1496-1510 (2008).

4. Lu Z, Mitchell RM, Smith RL, **Chapagain PP**, Schukken YH and Grohn YT, "The importance of culling in Johne's disease" Journal of Theoretical Biology 254, 135-146 (2008).

Complete List of Published Work in MyNCBI:
https://www.ncbi.nlm.nih.gov/myncbi/prem.chapagain.1/bibliography/public/

D. Research Support (in the last three years)

Current Research Support

R01 AI158220 Stahelin (PI) 08/01/2021 – 7/31/2026
NIH/NIGMS
"Computational and Biophysical Analysis of the Filovirus Matrix Protein System"
Role: Co-I

1R41 GM136034 Handfield (PI) 08/01/2021 – 7/31/2022
NIH/NIGMS
"In-silico design of novel lantibiotic peptides"
Role: Co-I

R35 GM139817-01 Tse Dinh (PI) 02/01/2021– 1/31/2025
NIH/NIGMS
"Structure, Mechanism and Interactions of Type IA Topoisomerases".
The goal of this project is to advance our knowledge on the structure, mechanism, interactions and regulation of type IA topoisomerases found in all life forms.
Role: Collaborator

NSF 20-1 2037374 Narasimhan (PI) 07/01/2020 – 06/30/2022
NSF
"RAPID: Bioinformatic Search for Epitope-based Molecular Mimicry in the SARS-CoV-2 Virus using Chameleon**".**

The goal of this project is to use Machine Learning (ML) and Artificial Intelligence (AI) to build a working pipeline to detect molecular mimicry and learn antigen-antibody (Ag-Ab) interaction models.
Role: Co-PI

1R21AI142651-01A1 Stahelin (PI) 03/01/2020 – 02/28/2022
NIH/NIAID
"Investigation of the role of phosphatidic acid metabolism in filovirus budding".
The objective of this project is to understand how the phospholipase D metabolism and phosphatidic acid generation regulates assembly and budding of filoviruses.
Role: Collaborator

Completed Research Support
ORAGENICS Inc. Chapagain (PI) 3/1/2019-2/28/2021
"Computational modeling of lantibiotics interactions with lipid II and membrane".
The goal of this project is to investigate lantibiotic-membrane interactions.
Role: PI

1R03-AI130609 Stahelin (PI) 12/08/2017 – 11/30/2019
NIH/NIAID
Investigation of VP40 mutations found in previous outbreaks on the assembly and budding of filoviruses.
The major goal of this research is to investigate the effects of Marburg VP40 mutations found in previous outbreaks on the viral assembly and budding.
Role: Collaborator

STTR Subcontract with Luna Innovations Inc. Zhou (PI) 21/09/2018 – 20/03/2019
Department of Defense (DoD)
"Marburg Virus Prophylactic Medical Countermeasure".
The goal of this research is to develop an effective vaccine for Marburg Virus infections. Dr. Chapagain's role is to screen the virus genome to identify antigens and run computer simulations for modeling antigen-antibody interactions.
Role: Collaborator