Dear Snape College Chemistry Department search committee,

Please consider my candidacy for the position of Assistant Professor of Chemistry. I received my Ph.D. in Biophysics from University of Anywhere in 2014 with a thesis on computational research in the lab of Prof. Minerva McGonagall. I currently hold a Competitive postdoctoral fellowship working with Prof. Albus Dumbledore at R1 University (R1U), another top research institution. My career goal is to teach at an elite liberal arts college where I can continue to conduct high-quality research while teaching and mentoring a diverse group of undergraduates. I am a strong supporter of liberal arts education, having earned my B.A. at Beauxbatons University, and I believe my interdisciplinary scientific background will enhance your mission of creative thought. In addition to general and advanced chemistry courses, I am prepared to teach cross-disciplinary computing or biology courses. My research is primarily computational, allowing for flexibility of resources, and also has an experimental component, offering students experience in a range of methods. I hope that undergraduate students will become deeply involved and perform an instrumental role in my research projects, while simultaneously enhancing their own learning.

I am passionate about teaching science to students from all backgrounds, and I have continuously developed my teaching skills while engaging in doctoral and postdoctoral research. This includes participating in the Summer Institute for Preparing Future Faculty at Anywhere, and the Preparation for Teaching Program at R1U. Since R1U does not have any undergraduate students, I sought out opportunities to teach at other Coastal City institutions. Teaching as the sole instructor for an entire quarter of Introductory Physics at Fantastic College, I gained invaluable perspective on how to teach the skills that new college students need to analyze and solve problems effectively. Before teaching at Fantastic, I assisted with Biophysical Chemistry courses at Anywhere. I also developed my own course material for a 5-week Coding course that I proposed, designed and taught as a graduate student. These experiences have prepared me to create my own curriculum and course material, something I am eager to do at Snape College as part of the interdisciplinary first-year seminar program or for advanced chemistry electives. I would also like to develop cross-listed courses such as Scientific Computing or Biophysics.

I am excited to involve undergraduate students in my research program at Snape College as I investigate the biophysics and function of dolores umbridge proteins (DUPs). At Anywhere, I developed a research interest that applies quantitative physical chemistry techniques to biological problems and engaged in both computational and experimental research. I improved our understanding of Huntington Disease by studying the DUP cho-chang protein using both simulations and NMR spectroscopy. This work yielded new computational methods and resulted in three first-author publications. At R1U I proposed a project on HPV, studying a flexible human-virus protein complex. This project was granted funding by the NIH through a postdoctoral fellowship, and this independence will allow me to bring that research program with me to a faculty position. Collaboration with experimentalists (Argus Filch at Anywhere and Filius Flitwick at R1U) has been integral to my research. I look forward to forming collaborative relationships with colleagues at Snape, such as Prof. Irma Pince or Prof. Aurora Sinistra, as I develop an independent research program studying DUPs and their interactions.

I particularly look forward to mentoring undergraduate students if I am hired at Snape College. Because not all students at Snape share my background, my experience advising

undergraduates is critical to informing my mentorship strategies. I have had the opportunity to work with several outstanding undergraduate students as their primary research mentor while completing my Ph.D. These students came from a variety of countries as well as different cultures within the United States. I developed individual research projects for them, and by working with them I have learned that different styles of interaction and guidance work well for students with different experience and work habits. All of the students I mentored have gone on to further scientific accomplishments, and one exceptional undergraduate, Katie Bell, contributed to a publication. At Fantastic College, the group of students I taught contained a range of cultural backgrounds and high school preparations. I tried to make my classroom a space for inclusive learning, implementing several methods based on recent research on improving outcomes for underrepresented groups in science, such as conducting a 10-min ungraded essay on student values. I look forward to improving my strategies for working with a diverse student population as I learn more about effective approaches.

By contributing an expertise in biophysics and computational modeling as well as a strong foundation in general chemistry, I hope to enhance the diversity of learning opportunities for undergraduates at Snape. The interdisciplinary nature of my research will attract certain students who might not ordinarily seek out chemistry research. The applications to biology and disease can motivate students to ask interesting questions and apply physical concepts from thermodynamics and statistical mechanics to answer these questions. In addition to learning computational techniques, students will evaluate experimental data through projects that combine experiment and computation. Although computational research can be difficult for undergraduate students with no experience, the connection to disease and experiments can help students grasp the important concepts. Students I mentored at Anywhere with no prior research experience ultimately completed independent work running and analyzing simulations.

Along with student mentoring, I am eager to participate in community outreach activities at Snape. This is something I have actively pursued by volunteering with elementary school classrooms and other community science service projects, as well as mentoring women in science. As a science professor, I hope to engage not only in advanced research in my field, but also in Snape's academic and campus life as an integral member of the community.

Sincerely,

Ginny Weasley, Ph.D.
Competitive Postdoctoral Fellowship Recipient
Department of Chemistry
R1 University
Address
City, USA
Phone: 000-000-0000
e-mail: email.email@mail.edu

CURRICULUM VITAE

Ginny Weasley

Dumbledore Lab
Address, City, USA
e-mail: email.email@mail.edu | phone: 000.000.0000
web: sites.google.com/websitehere

EDUCATION

PhD **University of Anywhere**, Biophysics, May 2014

Prof. Minerva McGonagall – advisor, Bioengineering & Chemistry

Thesis Committee: Argus Filch, Pomona Sprout, Sybill Trelawney

Title of Thesis here

BA **Beauxbatons University**, Physics, *summa cum laude,* departmental honors, May 2008 French minor, studied abroad at **University of Durmstrang, France**, Spring 2007

RESEARCH

NIH National Research Service Award Postdoctoral Fellow (F32), ***R1 University, R1 City, USA*** (April 2016 – present)
Fellowship co-mentored by Prof. Albus Dumbledore and Prof. Filius Flitwick. Title of research project here.

R1 University, R1 City, USA (October 2014 – present)

Postdoctoral research conducted with Prof. Albus Dumbledore, R1U Chemistry and former Biophysic Program Chair. Summary of research project here. Resulted in one first author publication submitted to *PLoS Computational Biology* and currently under revision.

Biophysics Program, *University of Anywhere, Anywhere, USA* (May 2009 – August 2014)

Thesis research conducted with Prof. Minerva McGonagall in collaboration with Prof. Argus Filch. Summary of Research Project here. Developed new methods for incorporating experimental and simulation data. Compared the conformations of different isoforms of the mandrake protein and investigated the biophysical mechanism for their different toxicities. Resulted in 3 first author publications in *The Journal of Physical Chemistry B*, *Biophysical Journal*, and *Biochemistry*.

Physics department, *Beauxbatons College, Beauxbaton CIty, USA* (Sept. 2007 – May 2008)

Undergraduate research thesis mentored by Prof. Rubeaus Hagrid and inspired by summer research with Prof. Rolanda Hooch at the University of Firenze. Summary of research project here.

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Physics REU, *University of Firenze, Firenze City, USA* (Summer 2007)

Undergraduate research with Prof. Rolanda Hooch. Summary of research project here.

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Physics REU, *College of Slughorn, Slughorn City, USA* (Summer 2006)

Undergraduate research with Prof. Alastor Moody. Summary of research project here.

TEACHING

Molecular Simulations Workshop, *Remus Lupin University, Lupin City, USA* (June 2016)
Instructor for 3-day Simulations Training Workshop conducted by Prof. Gilderoy Lockhart. Gave one lecture and assisted students during the extensive hands-on portion of the workshop.

Physics Department, *Fantastic College* (March 2016 – June 2016)

Instructor for Physics, the second course in the introductory physics series for physicists and engineers (52 students). Created the lectures, activities, and assessments for a full course covering topics: oscillations, fluids, waves, sound, light, thermodynamics, and gravity. Gave all lectures, held office hours, and graded exams as the sole instructor for the course.

Chemistry Department, *University of Anywhere, USA* (Jan. 2014 – May 2014)

Graduate Teaching Assistant for Biophysical Chemistry taught by Prof. Silvanus Kettleburn, Prof. Minerva McGonagall, and Prof. Wilhelmina Grubbly-Plank. Taught 2 weekly discussion sessions of 16 second and third year students. Wrote homework, quiz, and exam questions. Graded homeworks and quizzes. Prepared practice problems and review material for discussion sections.

Biophysics Program, *University of Anywhere, USA* (Sept. 2012 – Oct. 2012)

Creator and Instructor for 5- week Introduction to Coding course for graduate students and postdocs. Developed and the concept and curriculum for this basic programming course as part of the pilot Biophysics Graduate Group module course program. Gave lectures, conducted hands-on workshops, developed assignments, and provided feedback.

Bioengineering Department, *University of Anywhere, USA* (Aug. 2010 – Dec. 2010)
Graduate Teaching Assistant for Computational Methods in Biology an upper level undergraduate and graduate level course taught by Prof. Minerva McGonagall. Helped create assignments, graded all assignments, held computer lab sessions.

Physics Department, *Beauxbatons University, Beauxbaton, USA* (Jan. 2005 – May 2008)
Undergraduate Teaching Assistant for introductory physics classes: Newtonian Physics; Electricity & Magnetism; Thermo, Fluids, Waves & Optics taught by Prof. 1, Prof. 2, Prof. 3, Prof. 4. Graded problem sets and held help sessions for the homework.

MENTORING

Name	Institution	Department	Project Type & Details	Dates	Current Position
Colin Creevey	R1U	Biophysics Graduate	Computational	2014-present	R1U Ph.D. Student
Hannah Abbott	Anywhere	Chem Eng Graduate	Computational	2012-2013	Anywhere Ph.D. Student
Blaise Zabini	Anywhere	Chemistry Graduate	Computational	2012-2013	Software Engineer at Somewhere
Lavender Brown	Anywhere	Chem Biology Undergraduate	Exp* & Comp – *I created this project*	2012-2013	Chemist at Industry Laboratories
Katie Bell	Anywhere	Integrated Biology Undergraduate	Experimental* – paper in *Protein Expression and Purification*	2011-2012	University of Crabbe Ph.D. Student
Parvati Patil	Anywhere (Elsewhere University)	Physics Visiting Masters Student	Computational – *I created this project*	2011	Granger University Ph.D. Student
Neville Longbottom	Anywhere	Bioengineering Undergraduate	Experimental* **Only experimental supervisor*	2010	Finnigan University Medical Student

FUNDING

- **Competitive Postdoctoral Fellowship,** $XX,XXX annual (2016)
- Molecular Biophysics **Training grant,** $XX,XXX annual (2008-2011, 2012-2013)

PROFESSIONAL DEVELOMPENT

- **Preparation for Teaching Program** (PTP)**,** R1U (2016)
- Coastal City Postdocs: **Teaching Science Workshop,** Another University (2015)
- **Navigating the NIH Grant Application Process** seminar series, R1U (2014)
- Institute Fellowship at **Summer Institute for Teaching Preparation,** Anywhere University (2014)
- Workshop on **Teaching and the Academic Job Search**, Anywhere University (2013)
- Workshop on **How to Teach a Course**, Anywhere University (2013)
- **Teaching Techniques** for students semester course, Anywhere University (2010)
- **Teaching Conference** for Graduate Student Instructors, Anywhere University (2010)

ACADEMIC & UNIVERSITY SERVICE

- Organizer, **R1U Some Department Seminar Series** (Spring 2016 – present)
- Chair, **Carrow Research Seminar** on A Topic (July 2015)
- Founder & Coordinator, **Subject here Module Courses**, Anywhere University (2012 – 2013)
- Participant, **Committee to improve the Student's graduate program**, Anywhere University (2012)

HONORS & AWARDS

- Women's organization **Founder Region Fellowship Semifinalist** (2013)
- **A Society Poster Award Semifinalist** at Biophysical Society Annual Meeting (2013)
- **NSF** Graduate Student Fellowship **Honorable Mention** (2008, 2009, 2010)
- **Phi Beta Kappa** honors society as a Junior, top 2% of class, Beauxbatons University (2009)

OUTREACH

- Science demonstrations in elementary schools, **Organization here** (2010-2014)
- Mentor for female physics undergraduates, **Society here**, Anywhere Univ. (2010)
- Volunteer with afterschool science program for girls in Oakland, **Company here** (2009-2010)

PUBLICATIONS

In Review

1. **Ginny Weasley**, Name, Name, Name, Name, Name, Albus Dumbledore. Publication title. *PLoS Computational Biology*. (Invited to revise and resubmit)

Published

2. Name, Name, **Ginny Weasley**, Name, Name, Argus Filch, Minerva McGonagall. Publication title. *Protein Expression and Purification.* 2016. (In Press)

3. **Ginny Weasley**, Argus Filch, Minerva McGonagall. Publication title. *The Journal of Physical Chemistry B,* 2015.
4. Name, **Ginny Weasley,** Name, Name, Name, Minerva McGonagall, Name, Name. Publication title. *Neurobiology of Disease,* 2015.
5. **Ginny Weasley**, Name, Argue Filch, Minerva McGonagall. Publication title. *Biophysical Journal,* 2014. *Featured on issue cover.*
6. **Ginny Weasley**, Name, Gilderoy Lockhart, Name, Argue Filch, Minerva McGonagall. Publication title. *Biochemistry,* 2012.
7. Name, Name, **Ginny Weasley**, Minerva McGonagall. Publication title. *Journal of the American Chemical Society,* 2010.

POSTERS & PRESENTATIONS

1. **Conference here:** Presentation title (Location), September 2016. *Poster presenter.*
2. **Conference here:** Presentation title (Location), August 2015. *Speaker.*
3. **Conference here:** Presentation title (Location), June 2015. *Poster presenter.*
4. **Conference here:** Presentation title (Location), July 2015. *Poster presenter.*
5. **Conference here:** Presentation title (Location), Jan. 2014. *Poster presenter.*
6. **Conference here:** Presentation title (Location), July 2013. *Poster presenter.*
7. **Conference here:** Presentation title (Location), Feb. 2013. *Poster presenter.*
8. **Conference here:** Presentation title (Location), Jan. 2013. *Poster presenter.*
9. **Conference here:** Presentation title (Location), July 2011. *Poster presenter.*
10. **Conference here:** Presentation title (Location), Feb. 2011. *Poster presenter.*
11. **Conference here:** Presentation title (Location), Jan. 2011. *Speaker.*
12. **Conference here:** Presentation title (Location), Jan. 2011. *Poster presenter.*

On my first day leading a discussion section for undergraduate students in Biophysical Chemistry, I stood in the front of the class, looking out at unresponsive faces for 15 minutes as I dutifully reviewed the key points of the material covered in lecture. I waited patiently after each question I posed to the class, attempting to elicit student participation, but the same two students responded to every inquiry. I had no idea if I was reaching the rest of the class at all. Then I moved on to a practice problem I had chosen, and I broke the class up into groups of three to work on the problem. Almost as an afterthought, I said "Please show your work on the board," hoping to get them out of their chairs and more active. Suddenly in the next 30 seconds the atmosphere in the classroom had changed completely. Students in each group were talking to each other and trying to figure out the problem. As I walked from group to group asking questions about how they were solving the problem, even the most hesitant students responded, and I had a sense of what concepts they understood and where they were having trouble. Students were eager to ask me questions, something they rarely did during the lecture style teaching. Through the next few months of working with these students, I created an informal group learning environment that allowed me to work constructively with students at all levels while maintaining high standards of understanding and performance. This approach to working with students is motivated by my **four main teaching goals: concepts, applications, engagement, and inclusion.**

Concepts & applications: In the basic sciences, conceptual understanding and application to problem solving operate side-by-side in the classroom, feeding off of one another. Conceptual knowledge allows students to apply the same method in many different situations with ease, and problem solving illustrates and clarifies concepts while revealing areas of weakness. For example, when teaching about the statistical mechanics partition function, I found that writing out the partition function for many different systems was more useful in allowing students to begin grappling with the concept than simply defining it. However, once the students were able to calculate the partition function for any given system, many of them did not grasp the fundamental reason for creating a partition function. When I realized this, I went back to the definition and reminded them of the underlying purpose, which is to normalize the probability.

While teaching first-year physics and engineering students in Introductory Physics at Fantastic College, I encouraged conceptual learning by asking students to apply concepts from lecture to problems on homework and exams that were posed very differently. This was very challenging for students, who came from a variety of high school preparations and were not used to college course expectations. After working one-on-one with struggling students, providing opportunities to improve grades with extra credit, and offering practice problems before the exams, all of my students passed the course and improved their understanding of the material. However, I learned just as much from this experience, and when I teach an introductory course in the future, I will emphasize problem solving skills that will help students apply concepts to a wide variety of problems. Instead of making sure students follow each of the steps in a derivation in class, I will focus more on the overall result of the derivation and why this is important for solving problems. Moving back and forth between applications and concepts is a fundamental scientific skill that I hope to instill in all of my future students.

While at University of Anywhere, I proposed and taught a 5-week course in Introductory Scripting for graduate students without computational backgrounds. This course provided a series of tools for manipulating quantitative data as well as the accompanying basic programming skills. I believe that this type of applied computational learning can be

incorporated into core science courses at an undergraduate level through short assignments in introductory courses and longer projects in advanced undergraduate courses. Future scientists will be expected to be proficient in an array of computational methods that are essential for analyzing data and modeling new hypotheses, and I look forward to addressing these learning goals when teaching undergraduate students.

Engagement: While canonical examples and practice problems can help to illustrate and cement concepts, students engage with the material and retain the most information when they see a connection that makes the ideas relevant to them. This task will be different for every class and group of students. When teaching Introductory Physics to engineering students at Fantastic, I provided practice problems in class that related to problems they might encounter as engineers. I also screened a series of five 2-5 minute interviews that I recorded with a professional in engineering who worked in a field related to the current course topic, making sure that these professionals included women and people of color. As an undergraduate teaching assistant for Introductory Physics courses, I realized that many of the students were from chemistry or biology, and were required to take physics for their major or medical school. I saw that the courses might be more relevant to them if biological applications of physics were described and used as examples. With my training in biophysics, I can bring an interdisciplinary perspective to general chemistry courses, emphasizing the broad applications of the concepts I am teaching.

Another way to engage students in learning is to relate course material to my research. While advising undergraduate researchers in the lab, I have seen their motivation to learn about new ideas when looking for solutions to a research problem. Lavender Brown, an undergraduate chemical biology student I mentored at Anywhere, was struggling to understand why the relative frequency of conformational states was important to characterizing the protein ensemble he was simulating. I explained this by connecting it to her formal training on statistical mechanics and the idea that more populated states are lower in energy. In the Biophysical Chemistry classroom, I have used a molecular dynamics simulation from my research to illustrate the flexibility of proteins, which triggered many questions about how my research relates to the course. I hope to create a learning environment that extends beyond the classroom by mentoring students, both in research and in planning for their future academic and career goals.

Inclusion: The classroom environment is key to ensuring all students are included in the learning process. This was particularly true in my experience mentoring and teaching students from underrepresented groups. Using active learning strategies from the Preparation for Teaching Program at R1U, I strive to break down the barrier between (passive) student and (active) teacher. In the 52-student Physics course I taught at Fantastic, I incorporated clicker questions, problem solving in small groups, and demonstrations into traditional lectures. These activities allow students with different learning styles, including those who are not as comfortable talking in class, to actively connect with the material. In a survey I conducted halfway through the course asking which was most helpful for learning, there was an almost even split in preference between these four types of in-class activity, showing how important it was to vary my teaching strategies. Because teaching can act as a tool for learning, I also encourage my students to explain problems to others when they are studying on their own. Using a wide variety of teaching formats to facilitate class participation is an effective way to engage all students in my classroom.

My future research program will engage undergraduate students in interdisciplinary biophysics research on the structure and dynamics of protein molecules. I will use computer simulations to investigate ***how regions of beta pleated sheets affect the structure and dynamics of folded proteins***. This research area will allow students to investigate systems that are important to biological function and human disease from a physical and chemical perspective, and learn valuable computational skills. Students will apply concepts related to physical chemistry, statistical mechanics, and classical and quantum physics to model proteins and their interactions. In addition, they will have the opportunity to develop new methods in the analysis of protein dynamics, and collaborate with structural biologists, biochemists, and computational chemists.

Background

The study of protein structure and function has focused mainly on proteins that fold into a single well-defined structure that determines its function (catalyzing a reaction, signaling, etc.). However a large fraction of human proteins contain disordered regions that transition between multiple chain geometries, called conformations, on biologically relevant timescales (nanoseconds-minutes). These highly dynamic regions are not visible in X-ray crystal structures (1). Often, structural biologists ignore these unstructured regions when attempting to explain protein function because they have no structural data to work from; however, dolores umbridge proteins (DUPs) and luna lovergood regions (LLRs) of folded proteins can be important to cellular function and dysfunction (2). These disordered regions could play critical roles in protein regulation, interaction, and stability, but their functions are largely unknown.

Methods

Experimentally, Nuclear Magnetic Resonance (NMR) can provide data on DUP or LLR ensembles by measuring the slightly different chemical environments that atomic nuclei encounter. We can study which protein atoms are in contact by using quantum mechanics to measure coupling between nuclei. However, this only yields an average conformation and cannot reproduce the full ensemble of protein states. In order to fully characterize an DUP, we must apply statistical mechanics to represent the ensemble of DUP conformational states.

The computational technique of molecular dynamics (MD) uses classical mechanics to model atomic interactions and simulate molecular motions on the timescale of femtoseconds to seconds. MD can access length and timescales not reached by experiments, and has applications in fields like material science, nanophysics, and environmental chemistry as well as biophysics.

The force on every atom in the simulation system is determined by taking the derivative of an interatomic potential function such as,

$$U(r^N) = \sum_{\text{bonds}} k_b (l - l_0)^2 + \sum_{\text{angles}} k_a (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} \frac{1}{2} V_n \left[1 + \cos(n\omega - \gamma)\right]$$

$$+ \sum^{N-1} \sum^{N} \left\{ \varepsilon \left[\left(\frac{r}{r_{0ij}} \right)^{6} - 2 \left(\frac{r_{0ij}}{r} \right)^{} \right] + \frac{q_i q_j}{4} \right\}$$

This equation uses a harmonic potential to approximate covalent molecular bonds with the first two terms. The third term restricts the geometry of the protein chain for atoms connected by

three covalent bonds. The sum over all pairs of atoms approximates repulsion between non-bonded atoms at small distances due to the Pauli exclusion principle, as well as attraction at longer distances due to quantum induced instantaneous multipoles. The final term applies Coulomb's Law of charged particle interaction. After the force on each atom is calculated, Newton's equations of motion are used to calculate the acceleration and propagate the positions one femtosecond into the future. The forces are then recalculated based on the new positions and this is repeated 10^6 times or more.

The result of the MD simulation is a trajectory of molecular motion in atomic detail with high temporal resolution. The short length and timescales of MD can describe DUP motions more precisely than experiments alone.

Doctoral thesis

During my doctoral work on the DUP implicated in Huntington Disease, Cho-Chang (CC), I improved methods for determining the DUP conformational ensemble (3). Often NMR observables, such as chemical shifts (resonant frequencies of atomic nuclei) and J-couplings (nuclear spin coupling through chemical bonds), are used to determine the structural propensity of an DUP. Then an ensemble of conformations is created by choosing structures with this propensity from a pool of randomly generated DUP structures. We found that in the case of CC, NMR data alone were not sufficient to determine the DUP ensemble. The best results came from generating a pool of conformations with MD simulations and refining based on the experimental data. Two example conformations are shown in Figure 1.

Figure 1 here

Figure 1. Example structures from the CC42 conformational ensemble generated by MD (5).

I also investigated the causes of Huntington Disease by comparing the MD-generated conformational ensembles of different length CC peptides (4, 5). Huntington Disease is characterized by large aggregates of many proteins stuck together between neurons in the brain, and CC is the most common protein in these aggregates. The 42-amino acid CC is more aggregation prone and more toxic than the slightly shorter 40-amino acid CC. We saw different structures in the CC42 and CC40 conformational ensembles that helped explain these different behaviors (5).

Studying CC has allowed me to contribute to understanding both the causes of Huntington Disease and the biophysics of DUPs. I am actively involved in this research community, and I proposed and chaired a DUP Research Seminar on student and postdoc research. The DUP field has been rapidly growing, with 109 papers published in 2015 compared to only 3 papers in 2005, according to PubMed. This is an exciting time to work in the field, when methods and paradigms are being established, and newcomers, including undergraduate researchers, have the potential to make an impact.

Current research

My initial postdoctoral work focused on how attachment of a folded polymerase protein can perturb protein structure and function. This perturbation can be mediated by subtle internal

rearrangements of the protein chain, known as allostery. Using MD simulations of a polymerase protein, we find that although the polymerase is very flexible, it can nonetheless affect the protein structure. In particular, we see opposite effects when the polymerase protein is attached at two different amino acids. In my future independent work, I will use what I have learned by researching the allosteric effects of polymerases to study how LLRs perturb folded proteins.

My current NIH fellowship involves the study of the Human Papilloma Virus (HPV) protein Draco Malfoy factor (Dmf), which is an DUP (6), but folds when it binds to human proteins (7, 8). Since Dmf still has a disordered tail region after binding to the complex, it is an ideal system on which to begin my study of how an LLR can affect a folded protein.

Research Plan

My independent research program will focus on LLRs rather than DUPs. LLRs, like DUPs, sample an ensemble of conformational states, but in addition can allosterically affect the conformation and dynamics of the folded protein to which they are attached. Increasingly, examples of how LLRs serve critical protein functions are being identified, but the emphasis has been on how these disordered tails and loops directly interact with active sites or binding partners (9, 10). However, the conformational ensemble occupied by an LLR could allosterically affect the more ordered conformational state of the folded protein. I will use MD simulations to investigate the question of whether the LLR ensemble can allosterically alter the conformation and dynamics of a folded domain on the same protein. Understanding the physical mechanisms at play is crucial to structural biology because many proteins contain disordered regions that are not typically included as part of structure-function models. My research findings will be particularly relevant to biologists studying proteins with disordered regions and biophysicists interested in the interplay between protein structure and function.

For each of the projects described below, students will use concepts from chemistry and physics to model protein motions, characterize conformational ensembles, and compare computational results to experiments. In order to understand the equation for the interatomic potential used to calculate atomic forces, students must use electorstatics and quantum chemistry. Thermodynamic concepts of energy and entropy are also important for understanding molecular simulations and the principles determining how proteins interact. As students progress in their research they will use statistical mechanics to understand ensembles of protein states and how these ensembles can be perturbed. Biochemistry will be used to interpret computational and experimental data and understand the big picture of how proteins function in the cell. Many courses in the chemistry curriculum will relate to student research projects in my group.

HPV Dmf

Dmf is a 192-amino acid HPV DUP that binds a complex of human proteins (Fig. 2). This complex is part of the cell's machinery to destroy unwanted proteins, and HPV uses Dmf to hijack it and neutralize antiviral proteins. The formation and function of this complex is critical to HPV disease propagation. Although Dmf adopts a folded structure as part of this complex, its C-terminal tail, amino acids 177 to 192, are not visible in the crystal structure of the complex because they are disordered (7). We will run MD simulations of this complex, varying the length of the disordered Dmf region to reveal the biophysical effect of this LLR on the conformation flexibility, and stability of the protein complex.

Project 1: (3 students, 3 years) Test whether the Dmf LLR affects the flexibility and conformation of the Dmf-human protein complex by comparing simulations of the complex with and without the disordered Dmf tail, amino acids 177-192. Students will run MD simulations and perform NMR experiments on the complex with and without the disordered tail, analyzing the data to identify significant differences in structure and flexibility.

Figure 2 here

Figure 2. Crystal structure of Dmf (pink) in complex with human proteins (7).

Project 2: (1-3 students, 2-3 years) Investigate whether the LLR sequence can affect the structure or flexibility of the HPV Dmf complex. Based on the above simulations of the complex with the disordered Dmf tail, students will propose mutations that would affect the LLR's interaction with the folded complex and use MD to test these predictions.

Protein kinase XYZ

Kinases are proteins which function in signaling many important cellular processes, including transcription regulation, immune response, and cell growth. Protein kinase XYZ (PKXYZ) and protein kinase MNP (PKMNP) are two related kinases. PKXYZ contains a long tail that is mostly disordered but contains sequences that are critical to kinase regulation (11). PKMNP has a similar fold, but its tail is more ordered in the crystal structure. We will use MD simulations to compare the flexibility of the PKXYZ and PKMNP tails and how they can allosterically affect kinase conformation. Because these proteins function in the crowded environment of the cell, we will also investigate the effect of crowding on the LLR and its regulation of the kinase.

Project 1: (2 students, 2 years) Determine whether the disordered regions of the PKXYZ tail affect kinase conformation by comparing PKXYZ and PKMNP tail flexibility, and interactions with the folded protein. Students will run simulations on PKMNP and PKXYZ and look for differences in tail dynamics, including how the tails interact with regulatory elements of the kinase.

Project 2: (1-3 students, 1-2 years) Ascertain whether particular disordered PKXYZ amino acids are important for kinase regulation and identify PKXYZ mutations that would affect activity. Based on the above simulations of PKXYZ, students will design and run simulations on PKXYZ mutants to test how mutations affect kinase conformation. Students can also experimentally test the activity of the mutated kinase using a phosphorylation assay.

Project 3: (2-3 students, 1-2 years) Determine whether crowding of the disordered PKXYZ tail changes its effect on the folded kinase. Students will run simulations of PKXYZ in the presence of spherical crowding particles, varying the size and concentration of particles. They will measure the flexibility and compactness of the PKXYZ tail under different crowding conditions, and make predictions for how crowding would affect the ability of the tail to regulate the kinase.

For both of these systems, we will investigate the relationship between the sequence of the LLR and its degree of disorder, and how this affects the folded domain. Because there are

several variables to study for each system, it will be easy to mentor several undergraduate students on separate but related research projects. I anticipate involving undergraduates in the development of new methods for analyzing and comparing MD simulation data, using techniques from statistics, information theory, and machine learning. I will also seek the expertise of other computational scientists in the department when developing new analysis methods. I will maintain an experimental aspect to my research, as I have done in the past. Fostering collaborations with structural biologists and biochemists will benefit this aspect of the research plan. NMR data will provide information about the degree of flexibility of the LLRs and their molecular interactions. A kinase activity assay will allow us to test predictions about the role of the LLR in PKXYZ regulation. I expect my students to do these experiments themselves while sharing resources and expertise with collaborators.

Involving undergraduate researchers

I will involve undergraduate researchers at all stages of the projects described above. Having mentored undergraduate and graduate students during my graduate studies at University of Anywhere and as a postdoc at R1U, I am confident that I can formulate individual projects for students that are appropriate to their level of experience and allow them to learn important research skills. Each individual project will answer an important scientific question and contribute to a publication.

Students will need only one year of introductory chemistry coursework to join my research group. Many of the computational skills needed to run MD simulation software and analyze the resulting data will initially take time to learn, but can then be applied to many different research questions. I will also cultivate an atmosphere of teamwork among my research students and encourage them to take advantage of the fact that they are using similar techniques in their projects. Students will work independently, but they will also help each other make progress, both through formal group meetings and informally as they struggle with writing programs to run MD or applying statistical mechanical interpretations to their simulation data.

Career development for the students I mentor will also be a priority. Because my research is interdisciplinary, students who work with me will gain the skills needed to tackle problems at the intersection of multiple domains, including chemistry, computer science, math, physics, and biology. Students will learn the languages and methods of these fields, adapting them to a modern scientific context in which the boundaries between traditional disciplines are increasingly fluid. Students will gain communication skills by presenting their work at conferences. The data analysis and programming skills used in my research group will also be useful in future scientific or quantitative activities students choose to pursue such as physical chemistry, cheminformatics, or data science.

Research Program Feasibility

Because my research is primarily computational, it can be realistically performed at a small undergraduate institution. The main cost is for workstations and computer clusters on which to run large-timescale (biologically relevant) simulations in atomic detail, as well as accompanying storage. I anticipate maintaining a small GPU cluster for my lab, as well as applying for additional compute time at a supercomputing facility such as the DOE NERSC facility, which I used as a graduate student, or the NSF XSEDE facility, which I used as a postdoc.

In addition to applying for supercomputer allocations, I will apply for federal funding in the form of NSF CAREER grants and NIH R15 grants. This funding will go toward computer workstations, allowing students to present at conferences, student summer research stipends, and upgrading my in-house cluster. Having successfully applied for an NIH postdoctoral fellowship award (F32), I am motivated to continue to apply for federal funding, and I am optimistic that my research interests overlap with the interests of these agencies, both in terms of basic research and mentoring of undergraduate researchers.

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