Student Responses to RENEWAL Questions

The following apply only for renewal applications. Please consider these responses in making your assessment of the application.

1. Please describe how successful you were in achieving the intended outcomes of and adhering to the plan/timeline of your original proposal.

While research rarely progresses as intended, I would say that I've been fairly successful in adhering to the original research plan. My original plan suggests that I can explore "straightforward extensions of the existing 2D models [in] 3D". However, crystallization of the simple 3D models is less "straightforward" than anticipated. 3D models have a higher propensity for glass formation, which makes creating a set of models more difficult.
We have adapted our procedure to accommodate this difficulty, but it has taken some time. Therefore, I am just beginning the process of "developing a set of models that reproduce the qualitative crystallization outcomes found in experiments". This stage of the project was intended to begin in October and extend into November, so I'm about a half-month behind my original timeline.

2. Please describe how successful you think your relationship with your mentor was during your first semester of UROP.

My relationship with my mentor, Professor [redacted], has been incredibly rewarding. Professor [redacted] is very approachable and helpful whenever I have questions about research, coursework, or graduate school. I truly consider him a role model for my future career in chemistry. The group environment has facilitated learning and given direction to my research. Each week each group member has the opportunity to present the results of the previous week's simulations, then the group takes the time to analyze the results and think of new directions for research or potential solutions to any encountered problems. This has transformed something that could potentially cause a considerable amount of stress into an opportunity to progress my research project and grow as a presenter.

3. Please explain what you think the impact of an additional semester in UROP would be to your educational and career goals.

During my first semester of research through UROP I've gained an incredible amount of knowledge and learned valuable skills. I've been given the opportunity to contextualize my coursework and develop important transferable skills. I'm grateful for the opportunity, and the value is ongoing. Another semester in UROP would further solidify what I've learned this semester and provide continued support while I grow into a confident researcher. I'm particularly excited about moving forward with my project. I've never taken a research project towards completion, and I'd relish the opportunity to experience a more complete project life cycle. This experience would greatly benefit my career goals, because, as a professor, I would be expected to complete and publish my research. Another semester in UROP would allow me to develop that continued focus and follow-though.

UROP Proposal

Title of Proposal

Simple molecular models for chiral crystallization

Problem/Topic of Research or Creative Work

Chiral molecules play an important role in many biological processes. [1] Chiral molecules have enantiomers, mirror-image isomers that cannot be superimposed on each other. The classic analogy to enantiomers is a pair of hands. A pair of hands mirror each other, yet no matter the orientation of the right hand it remains distinct from the left. Many organisms produce organic molecules with selective "handedness", also known as chirality. A solution that contains a molecule and its enantiomer is a racemic solution. Enantiomers often have very different biological effects, necessitating the separation of enantiomers during the production of many pharmaceuticals. [2,3] Spontaneous chiral resolution, the crystallization of a racemic solution into a conglomerate of enantiopure crystals, is a simple, scalable, and inexpensive method of separating enantiomers. However, the majority of organic racemic solutions form racemic crystals rather than enantiopure conglomerates. [4] It is still unclear why some molecules can spontaneously resolve into separate enantiopure crystals, while the majority form racemic structures. [4,5]

Molecular dynamics simulations are a promising way to reveal the microscopic mechanisms underlying spontaneous resolution. Simulations can probe the kinetic and thermodynamic factors in the crystallization of chiral molecules. [6] While simple two-dimensional models have recently shed some light on the thermodynamics of chiral crystallization, predictions made with these two-dimensional simulations are not necessarily applicable to three-dimensional systems. In fact, experiments have shown that quasi two-dimensional systems of chiral molecules on surfaces have a much higher propensity to separate into conglomerates than bulk solutions. [7] Recent effort focuses on the development of coarse-grained three-dimensional models of chiral molecules that reproduce the experimentally observed crystallization trends. By analyzing the thermodynamic landscape and crystallization kinetics of these models, we aim to predict the likelihood of spontaneous separation based on molecular structure and interactions.

Relevant Background/Literature Review

Critical biological processes such as the replication of DNA and RNA require nucleic acid monomers of a specific chirality. [2] Many pharmaceuticals also require specific chirality, due to the different toxicology of each enantiomer. For example the l-isomer of dihydroxy-3,4 phenylalanine, or dopa, is used as a treatment for Parkinson disease, while the d-isomer is quite toxic. [3] There are many more examples of enantiomers with dramatically different medical and toxicological effects. [2,3] Industry primarily uses two separation methods for chiral resolution; chiral chromatography and diastereomeric salt formation. Diastereomeric salt formation utilizes a pure enantiomer as a resolving agent to produce diastereomeric salts; many methods exist to separate these salts. An acid/base reaction removes the resolving agent after the diastereomeric salts are separated.

Diastereomeric salt formation relies on the compatibility of the resolving agent. Chiral chromatography relies on differing binding energies of enantiomers with the stationary phase of a high-performance liquid chromatography (HPLC) instrument. Determining the correct column for chiral separation proves time- consuming and expensive due to the innate similarities between enantiomers. Many pharmaceuticals are sold as racemic mixtures because of the high production costs associated with these methods. [3] A simple method of separating enantiomers has existed since the discovery of chirality. In 1848 Louis Pasteur recrystallized a racemic mixture of tartaric acid. The resulting crystal had two different crystal forms, each corresponding to a separate enantiomer. These crystals separate easily resulting in enantiopure samples. [2] This separation method, called spontaneous chiral resolution, represents an exciting way to separate enantiomers

because of its simplicity. It relies only on the interactions between enantiomers in solution. Spontaneous chiral resolution needs no catalysts, salts, or special HPLC columns, making it a good option for large scale separation. The primary challenge in implementing spontaneous chiral resolution is that few chiral molecules form conglomerates despite having similar densities and lattice energies. Consideration of kinetic effects and accurate computer simulations will be necessary to predict spontaneous resolution. [4]

A useful simulation method is the molecular dynamics simulation, where the classical equations of motion are iteratively solved for each particle during the simulation. [8] Molecular dynamics simulations have been used for decades to explore the relaxation of systems to their equilibrium behavior. As early as 1957 Alder and Wainwright were running computer simulations to explore the phase transitions of hard spheres. [9] Molecular dynamics simulations have since been used to solve problems in many different fields from protein folding to solar cells. [10,11] Several researchers have implemented molecular dynamics simulations to uncover the mechanisms of chiral molecules. For example, Latinwo et al. developed an effective three-dimensional model for chiral tetramers. Their detailed model was tunable and incorporated chiral inversion, where a molecule interconverts between enantiomers, allowing them to provide a detailed description of many phenomena produced by chiral tetramers. [12] Despite the impressive progress in exploring chiral molecule crystallization, the vast array of possible chiral molecules, as well as the lack of understanding behind the infrequence of conglomerate formation, makes continued computational research invaluable.

Specific Activities to be Undertaken and Timeframe for Each Activity

I plan to work approximately 10-15 hours a week. Accommodations to my course load have been made so that I can dedicate this time to the project.

Preliminary work (completed):

During the ongoing semester I familiarized myself with Python [13] and the GPU-accelerated molecular dynamics simulation package HOOMD-blue. [8,14] Significant effort has been made to establish a reliable procedure to nucleate and crystallize molecular dynamics simulations of solutions of rigid molecules. Several factors make observing crystallization more difficult in three-dimensional simulations than two dimensional simulations. The first reason is that three-dimensional systems have a higher propensity for glass formation, which is also observed in experiments. [7] The second reason is that three-dimensional simulations have a larger computational burden. These difficulties prevent simple adaptation of the two-dimensional simulation procedures. Finding solutions to these difficulties has defined the first semester of my work, and several promising directions have emerged. For example, I am simulating the crystallization of coarse-grained molecules with more appropriate atomic bond distances and radii to increase the physical accuracy of our coarse-grained molecular models. Preliminary simulations suggest that this improves the likelihood of crystallization.

January:
I will utilize the procedures I have developed to crystallize solutions of coarse-grained chiral molecules to develop new families of molecular models. By altering the molecular shape and interactions, I will develop a set of models that reproduce the qualitative crystallization outcomes found in experiments and, at the same time, allow for efficient simulations.
I will present the preliminary results from this project at the poster session of the Berkeley

Statistical Mechanics Meeting at UC Berkeley.
This stage of the project should take approximately 50 hours.

February:
If I am successful in developing a set of models that reproduce qualitative experimental crystallization outcomes, I will begin analyzing the crystallization trends of the set of models. We will analyze the effect of the molecular shape, the location of interactions, and the interaction strength on crystallization.
This stage of the project should take approximately 30 hours.

March-April:
If the previous stage of the proposed work is successfully completed, I will determine the thermodynamic landscape of crystal polymorphs for the three-dimensional models. This will be done by using a crystal structure prediction software (MGAC) developed by the Facelli group at the University of Utah. Thermodynamic landscapes obtained with MGAC will be analyzed together with crystallization propensities observed in MD simulations.
I will formally document my research in an Honors Thesis.
I will present my findings at the American Chemical Society's National Meeting in Philadelphia and at the Undergraduate Research Symposium at the University of Utah.
This stage of the project should take approximately 60 hours.

Relationship of the Proposed Work to the Expertise of the Faculty Mentor

Dr. [redacted] is an Assistant Professor whose research uses statistical mechanics and molecular simulation to study important nanoscience questions. He develops and utilizes computer simulations to reveal the underlying mechanisms responsible for the self-assembly of materials. Professor [redacted]'s expertise in enhanced statistical sampling methods and his proficiency with a plethora of molecular dynamics simulation packages makes him the ideal mentor for this project. Professor [redacted] is currently working on modeling the crystallization of chiral molecules. I am collaborating with other members of the group to complete my project and have ample support from Professor [redacted] and other lab members. In addition to meeting with Professor [redacted] weekly to discuss my progress and adapt the project to unforeseen challenges, I attend group meetings to further enable collaboration between myself and the rest of the group, and to broaden my understanding the group's other projects.

Professor [redacted] has proven an excellent mentor. He has motivated both personal and professional growth. I took Thermodynamics and Kinetics (Chem 3070) and Statistical Thermodynamics (Chem 7040) from Professor [redacted], where I found his teaching style engaging and his demeanor kind and nurturing. I look to Professor [redacted] as a role model. If I am successful in my plan to become a professor, I hope that I can emulate both his engaging teaching and research proficiency. In him I have a mentor who can provide excellent guidance as I move towards an academic career in the sciences.

Relationship of the Proposed Work to Student's Future Goals

Participating in the UROP program has given me invaluable exposure to exciting and applicable research. I am a senior studying chemistry with an emphasis and a minor in physics, and I hope to continue my education by pursuing a PhD in physical chemistry. The fundamental laws of the universe have always fascinated me. The closer I look, the more I realize that everything is

constructed from simple repeating patterns. All my prior, current, and future research experiences complement this desire to explore the emergent patterns of matter. I spent last summer participating in an NSF funded REU program with Columbia University's Materials Research Science and Engineering Center. My mentor for this program was Professor Xiaoyang Zhu. For the duration of my time with the Zhu group, I studied electron-phonon coupling in ferroelectric semiconductors. This research taught me advanced ultra-fast spectrographic techniques used to study the properties of materials after synthesis. In Professor [redacted]'s lab, I approach the field of study from yet another angle. In particular, I am learning how to model the formation of materials using molecular dynamics simulations. This research will continue to provide valuable experience with direct applicability to my future goals. Molecular dynamics simulations have given me a better appreciation of the mechanisms behind chemical processes. Developing coarse-grained molecular models has given me a better appreciation of the significance of different molecular properties. Additionally, through my research in Professor [redacted]'s lab, I am learning incredibly useful and transferable skills such as programming in Python. Through this incredible research experience, I will gain a broad understanding of physical chemistry and statistical mechanics. I hope to study the properties of interesting materials and understand how molecular properties lead to their formation. These diverse experiences will prove invaluable when I pursue a PhD in physical chemistry. My experiences in the [redacted] group will continue to provide valuable learning opportunities and exciting application of my classwork, and it will provide context to the decisions I will make when choosing a research topic in graduate school. Participation in the UROP program for another semester would greatly facilitate this research experience and give me the opportunity to follow my curiosity.

References

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