NDnano
Notre Dame Nanoscience and Technology

NDnano Summer Undergraduate Research
2020 Project Summary

1. Student name & home university:
Sarah Bluhm – Northeastern University

2. ND faculty name & department:
Dr. Jonathan K. Whitmer – Department of Chemical and Biomolecular Engineering

3. Summer project title:
Effects of Acidity and Salinity on Polymer Drug-Delivery Complexes

4. Briefly describe new skills you acquired during your summer research:
I began this summer research program with no background in molecular dynamics simulations (MDS) nor in physical chemistry. Thus, embarking on this largely independent project entailed building both a theoretical and practical foundation in the field. Computer Simulation of Liquids [1] and Understanding Molecular Simulation [2] were my principle references for constructing a knowledge base. The ground-up build of this system required gaining proficiency with many major molecular dynamics tools, including Gromacs, Martini, Packmol, VMD, and Pymol.

5. Briefly share a practical application/end use of your research:
Polymer drug-delivery complexes are one of many use cases for complex coacervates. Coacervates are good candidates for delivery of therapeutic molecules because they are able to encapsulate a variety of molecules whilst possibly improving their uptake into tissues and protecting them from degradation [3]. They are also useful because changes in pH or salinity can be used to trigger the coacervate to deliver the cargo at the target site [3]. The uptake and release properties of coacervates are thus of great interest to the medical field.

6. 50- to 75-word abstract of your project:
The effect of acidity on the partition coefficients of molecules into coacervates remains an open area of inquiry. This summer project succeeded in setting up a preliminary system that will be appropriate for testing the uptake of a variety of molecules into a coacervate phase consisting of 10-mer polylysine and polyglutamic acid peptides.

7. References for papers, posters, or presentations of your research:
[1] Allen, M. P., & Tildesley, D. J. (2017). *Computer simulation of liquids*.
[2] Smit, B., & Frenkel, Daan. (2001). *Understanding Molecular Simulation*. Academic Press.
[3] Blocher, Whitney C, & Perry, Sarah L. (2017). Complex coacervate-based materials for biomedicine. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 9(4), E1442-N/a.
[4] Rathee, Vikramjit S, Sidky, Hythem, Sikora, Benjamin J, & Whitmer, Jonathan K. (2018). Role of Associative Charging in the Entropy–Energy Balance of Polyelectrolyte Complexes. *Journal of the American Chemical Society, 140*(45), 15319-15328.
[5] Yesylevskyy, Semen O, Schäfer, Lars V, Sengupta, Durba, & Marrink, Siewert J. (2010). Polarizable Water Model for the Coarse-Grained MARTINI Force Field. *PLoS Computational Biology, 6*(6), E1000810.
[6] Ileri Ercan, Nazar, Stroeve, Pieter, Tringe, Joseph W, & Faller, Roland. (2018). Molecular Dynamics Modeling of Methylene Blue−DOPC Lipid Bilayer Interactions. Langmuir, 34(14), 4314-4323.

One-page project summary that describes problem, project goal and your activities / results:

Problem:

This research topic was inspired by a paper published by the Whitmer group investigating entropic and enthalpic contributions to polyelectrolyte complex (PEC) formation [4]. One of the results of this paper predicts that enthalpy, rather than entropy, is the driving force for polyelectrolytes that are not strongly charged, which may arise depending on the acidity of the solution [4]. This discovery sparked an interest in the tendency of coacervates to uptake and retain molecules depending on pH, as there is a dearth of studies in this area. Thus, this summer project aimed to lay to groundwork for studying the dependency on pH of cargo encapsulation.

Project Goal:

The primary objective within the ten week period was to prepare a novel coarse-graining molecular dynamics system. The desired system contains a film composed of polylysine and polyglutamic acid surrounded by an aqueous phase containing ions. Setup included the creation of molecule topologies and a protocol for system minimization, equilibration, and production runs.

Of interest was also the development of a protocol for umbrella sampling (US). US uses an umbrella potential to sample unfavorable states along a reaction coordinate that would otherwise not be visited [1]. In conjunction with the weighted histogram analysis method (WHAM), it allows the estimation of the relative free energy difference between two systems [1]. US would in this way enable the calculation of the partition coefficient of a wide variety of solutes between the aqueous and coacervate phase.

Activities and Results:

The initial system created consisted of a 4 x 4 x 7 nm box with periodic boundary conditions in the x, y, and z directions. The general Martini 2.2 force field and the Martini 2.0 ion force field were used with the Gromacs molecular dynamics package. Polylysine and polyglutamic acid were coarse grained using the Martinize script and placed using Packmol along with a mixture of water, antifreeze water, Na+, and Cl- beads. Qualitative inspection of the system's speed distribution and the water beads' radial distribution function were used to assess if the system was behaving as expected.

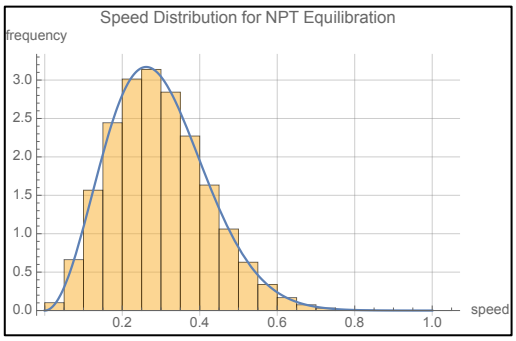

Fig. 1: The Maxwell distribution function fit over the speed distribution of all molecules. P-value = 0.0668103 and n = 2,365,182.

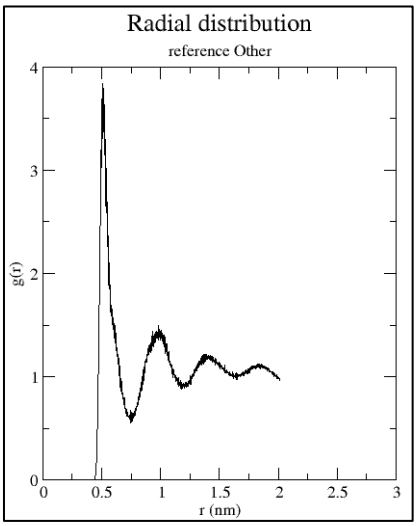

Fig. 2: The water-water RDF. Peaks at approximately 0.5, 1.0, and 1.4 nm match those given in [5].

Umbrella sampling was then performed on this system and some preliminary data was acquired. The impurity was chosen to be methylene blue (MB). Its coarse-grained topology file was created based on the work in [6].

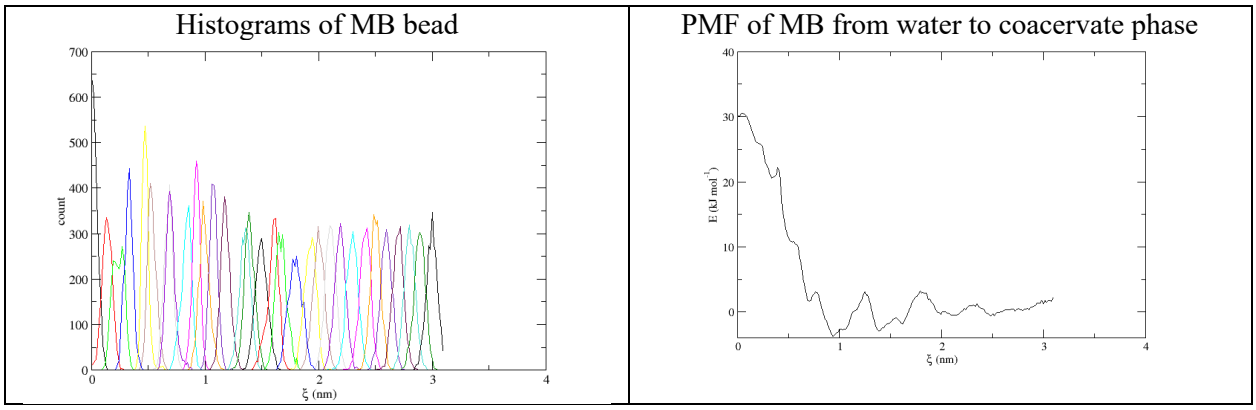

Fig 3: Rough first data collected from the umbrella sampling run on the toy system. Position restraints may need to be applied to the protein phase to retrieve cleaner data from the US simulation.

Finally, the miniature system was enlarged five times in the z-direction. An US simulation remains to be done on this larger system.

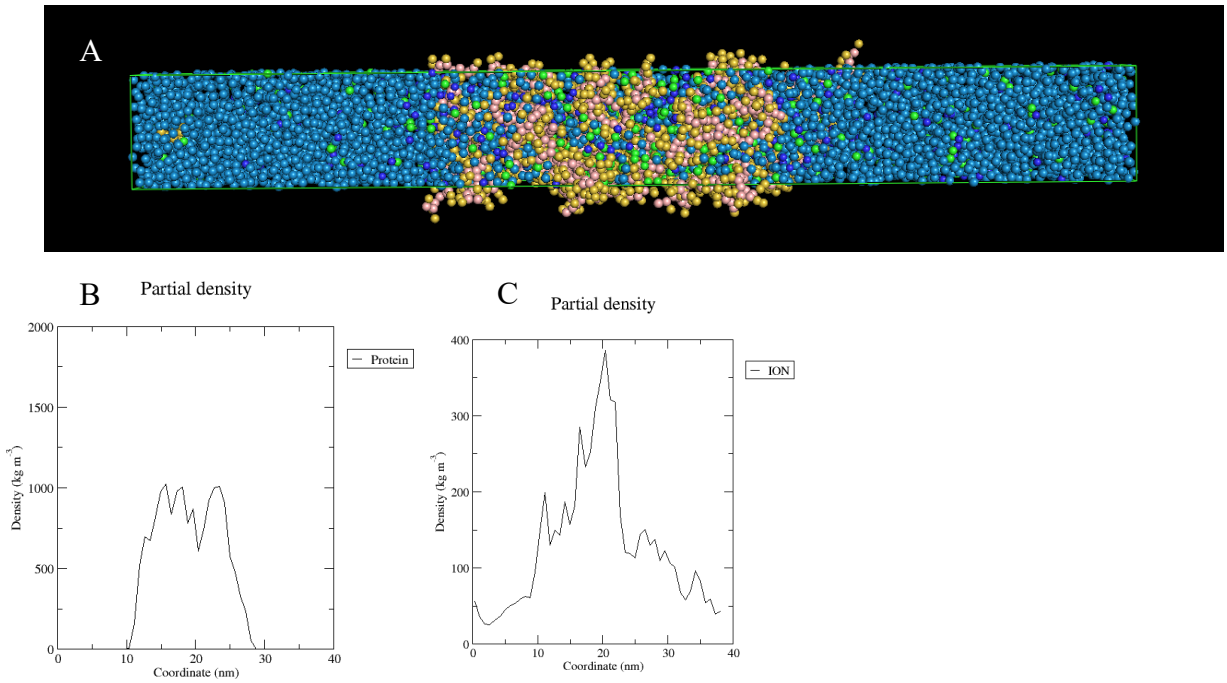

Fig 4: A) Visual of the larger version of the coacervate system. B) Partial density of the polylysine and polyglutamic peptides. C) Partial density of the ions. Ions are more concentrated in the protein phase but are also dispersed through the aqueous phase.