COMPUTER-AIDED FORMULATION DESIGN FOR IMPROVED NANOFORMULATION OF ANTICANCER THERAPEUTICS: USING SIMULATION TO IMPROVE THE EFFECTIVENESS OF CANCER DRUGS

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EXECUTIVE SUMMARY

Typical anticancer drugs produce harmful side effects and can be ineffective. Computational tools that elucidate the fundamental interactions in advanced drug formulations help to understand and predict the composition of next-generation therapeutics. Choosing an ideal drug carrier vehicle is difficult, and there are very few established design processes for the development of new nanoformulations. This has resulted in calls from government, industry, and academic institutions for the development of new design processes. To overcome the challenges preventing successful clinical adoption, and to further integrate nanoformulation into the industrial research and development process, quantitative, standardized methods of evaluating and designing nanomedicine must be developed. We used molecular simulation to show how nanoparticle formulations form on a molecular level in order to inform the design of new and better formulations. By observing the interactions among molecules, we can develop methods to formulate drugs that have better targeting, fewer side effects, and cheaper developmental costs.

RESEARCH CHALLENGE

Development of new nanoformulations usually requires extensive synthesis and experimental evaluation. Ways to guide experiments and to better understand what makes a "good" formulation could dramatically reduce development time and cost. This research is of importance to clinicians in cancer research as well as materials scientists and cancer researchers who are seeking to develop better cancer therapies.

METHODS & CODES

We used the molecular dynamics programs GROMACS and NAMD to model molecular systems across multiple size scales. We began by modeling single polymer strands and then graduated to multistrand systems and systems that included polymer molecules as well as organic dye molecules acting as surrogate drug molecules. By using dye molecules, we could compare our simulation results to experiments, further expanding the information available on the interactions in nanoformulations that are of importance. We used fluorescence spectroscopy as well as static and dynamic light scattering to observe the simulated systems in an experimental setting to confirm and explain the simulation results.

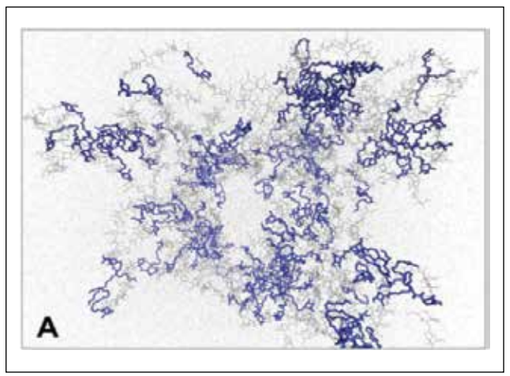

Figure 1: Simulation of a polymeric nanoparticle to be used for drug delivery. These polymers assemble around hydrophobic pockets, which trap hydrophobic drug molecules.

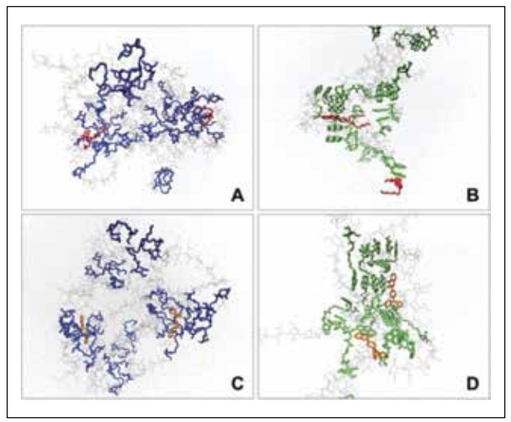

Figure 2: Simulation of different polymer strands interacting with dye molecules. This process demonstrates drug loading into a polymeric nanoformulation, but the use of dye molecules in place of drugs allows for better experimental evaluation.

RESULTS & IMPACT

This work was among the first to investigate self-assembled polymeric nanoformulations using simulations and correlating simulations to experimental observations. The simulations have enabled our lab to focus experimental investigation of new lead formulations as well as to begin working with new polymers in a more effective, methodical design process.

WHY BLUE WATERS

As an experimentalist seeking to develop computational chemistry skills, the support, tools, and knowledge provided by the Blue Waters staff dramatically reduced the learning curve. The Blue Waters supercomputer increased my ability to perform simulations, as queue times were shorter and Blue Waters performed simulations faster than other available resources.

William Payne is a third-year PhD student in pharmaceutical sciences at the University of Nebraska Medical Center. He is working under the supervision of Dr. Aron Mohs and plans to graduate in May 2019.