Coronavirus through Delaware's Computational Microscope

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ABSTRACT

The Perilla/Hadden-Perilla research team at the University of Delaware presents an overview of computational structural biology, their efforts to model the SARS-CoV-2 viral particle, and their perspective on how their work and training endeavors can contribute to public health.

INTRODUCTION

Since the beginning of the current global pandemic, COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2, Figure 1, left*), has infected over eight million people worldwide,[1] and more than 10,000 in the state of Delaware.[2] The rapid spread and severity of SARS-CoV-2 has placed significant strain on our public health infrastructure and exerted pressure on our STEM workforce to quickly develop strategies to combat the virus.

We are constituents of that STEM workforce at the University of Delaware. Our team, including members of two research laboratories in the Department of Chemistry and Biochemistry, have received funding from the National Science Foundation (NSF) and the Delaware Established Program to Stimulate Competitive Research (EPSCoR) to develop a new model of SARS-CoV-2. The model, a structure of the SARS-CoV-2 viral particle that encompasses all its constituent atoms, will provide an important basis for understanding the virus that causes COVID-19 from the bottom up. The approaches we are employing to develop the model are derived from a field of research referred to as computational structural virology and utilize an instrument we call the "computational microscope" (*Figure 1, right*).

In this article, we invite our fellow Delawareans to learn more about computational structural virology, how we are leveraging it to characterize SARS-CoV-2, and how this basic science approach can ultimately impact public health. We also underscore the role of academic research in recruiting and training our next-generation STEM workforce to combat future viral outbreaks and introduce members of our highly diverse computational team at the University of Delaware.

THE COMPUTATIONAL MICROSCOPE

While most people are familiar with biomedical research that takes place at the laboratory benchtop or in a clinical setting, health-related research can also take place *in silico* or entirely within a computer. Computer-based investigations of viral diseases include epidemiological modeling to predict infection risk or spread in the population, sequencing studies to characterize similarities between pathogens or trace their evolution, data science initiatives to extract statistics and trends from accumulated public health information, and high-throughput screening of drug compounds to identify potential antiviral treatments. Within computational structural virology, investigations also include modeling to develop virtual replicas of viruses or their components and simulations to investigate the dynamics of virus structures, as well as how the structures interact with each other, drugs, or the host cell during infection.[3–5] Our SARS-CoV-2 project involves modeling and simulation of the atomistic viral particle.

For scientists like us, the computer is a research instrument. By combining theory from chemistry, physics, and biology to accurately describe the behavior of biomolecules, the computer transforms into a "computational microscope" (*Figure 1, right*), allowing us to examine realistic virtual virus structures and their dynamics at a level of detail that is unattainable by even the most powerful material microscopes.[6] Importantly, the work we perform with our "computational microscope" integrates experimental data and is validated against experimental results to ensure that our models and simulations are representative of reality.[7,8] The experimental data we incorporate comes from a variety of sources, including biochemical assays, X-ray

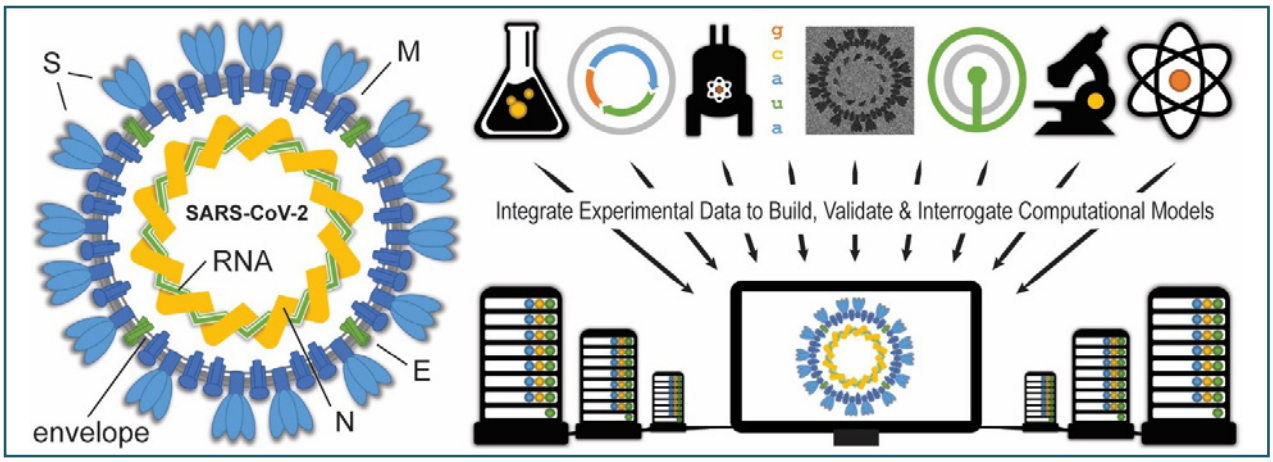

Figure 1. Virus models via supercomputers. Schematic of the SARS-CoV-2 viral particle, left. Conceptual diagram of the "computational microscope," right.

crystallography, cryo-electron microscopy, and nuclear magnetic resonance spectroscopy. Some of the experimentalists that we collaborate with to obtain this data have their laboratories right here in the State of Delaware. Since the accuracy of the "computational microscope" depends on the availability and quality of experimental data, our SARS-CoV-2 project will benefit from the plethora of structural information that has already been collected for the virus, as well as other related coronaviruses.

Importantly, the models that we construct and study with the "computational microscope" describe the structures of biomolecular systems down to the individual atoms that they are composed of. The simulations that we run include every atom in the model, as well as the atoms of water molecules and salt ions that surround the system and mimic its native physiological environment. When we model and simulate virus structures, the atoms that we must consider can number in the millions, and we require high-performance supercomputing resources to carry out the work. While studying the smaller structural components of SARS-CoV-2 (*Figure 2*) is amenable to local resources, such as the Delaware Advanced Research Workforce and Innovation Network (DARWIN) supercomputer, our model of the SARS-CoV-2 viral particle requires partnering with national resources, namely the leadership-class Frontera supercomputer at the Texas Advanced Computing Center, which is ranked fifth in the world.[9]

MODELING THE SARS-COV-2 VIRAL PARTICLE

Developing a model of the SARS-CoV-2 viral particle is a monumental task. Fortunately, our groups have many years of combined experience in computational structural virology and have worked on viruses like HIV-1 and hepatitis B in the past.[10–13] To model an entire virus, we begin with modeling the individual structural components of SARS-CoV-2 (*Figure 2*), integrating as much experimental data as we have available and using computational approaches to fill in the gaps. Structures we are working on include the spike (S) protein, which mediates adhesion and entry of the virus, the membrane (M) protein, which plays an essential role in assembly of new viral particles, the envelope (E) protein, which forms a pentameric ion channel, and the helical nucleocapsid (N) protein, which encases the viral RNA (*Figure 2*).[14–19]

While the genome-containing nucleocapsid is packed into the core of the virus, numerous copies of the S, M, and E proteins are embedded in its surface, which is composed of a lipid bilayer envelope (*Figure 2*). The SARS-CoV-2 envelope encompasses a complex combination of lipid species, and the composition may be unique to the virus. We are separately developing a model of the envelope, including the realistic lipid composition, which will ultimately allow us to bring all the structural components together to produce a cohesive model of the viral particle. When completed, the SARS-CoV-2 model will incorporate the envelope, its surface-embedded proteins, the glycans that decorate those proteins, the viral RNA encased by the helical nucleocapsid packed within the particle core, as well as other non-structural and accessory proteins known to be packaged by the virus. While not the first atomistic model of a viral particle produced by our field,[20–22] our final SARS-CoV-2 model aims to be the most comprehensive virtual representation of a virus ever constructed.

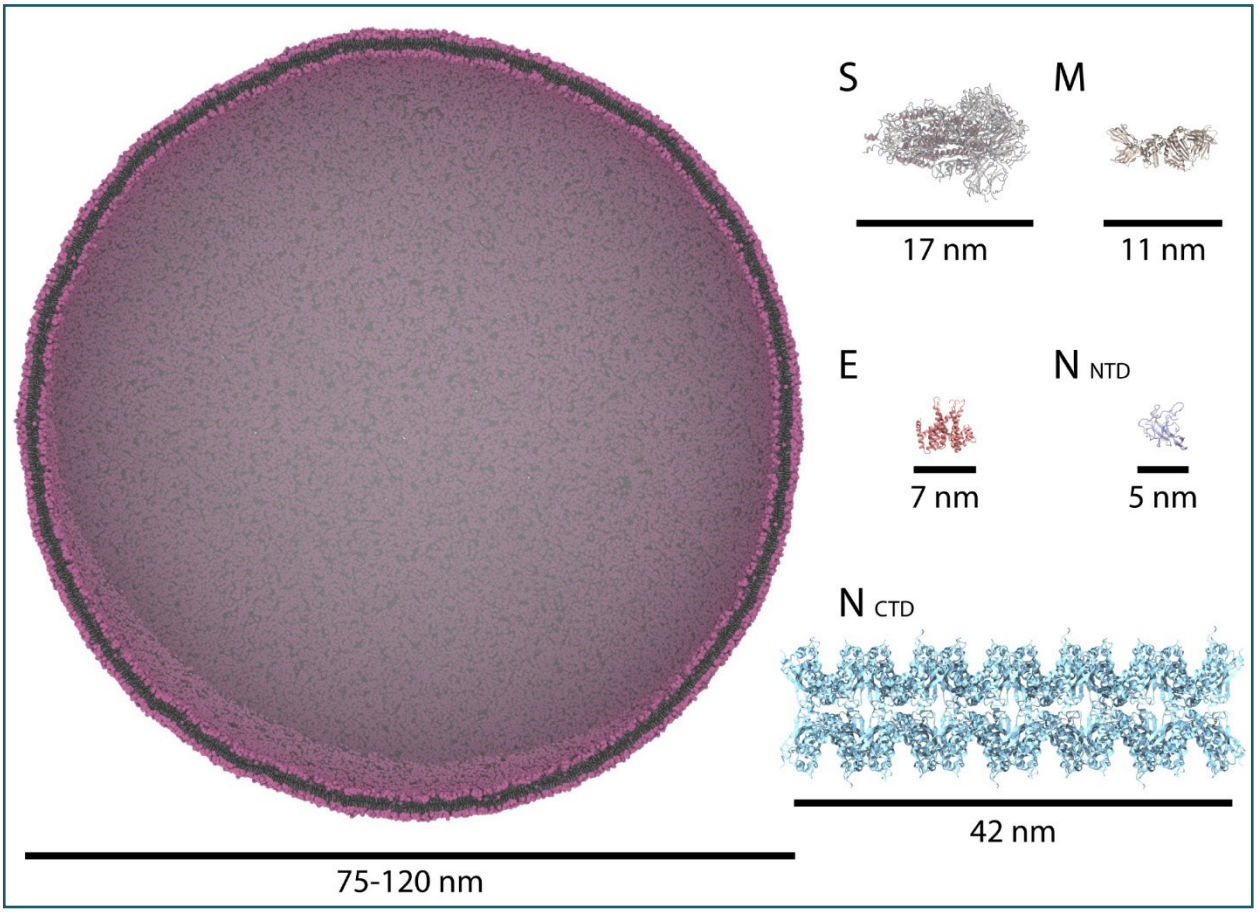

Figure 2. Structural components of the SARS-CoV-2 viral particle. Lipid bilayer envelope, left. Structural proteins, right, including the spike (S) protein, membrane (M) protein, envelope (E) protein, and N-terminal and C-terminal domains of the nucleocapsid (N) protein.

SUPPORTING PUBLIC HEALTH WITH BASIC SCIENCE

Computational structural virology is a field of basic science research. Its objective is ultimately to further our fundamental understanding of viruses. Generally, we are interested in elucidating structure-function relationships, or discovering how the details of viral architecture drive the biological processes involved in successful infection, replication, and propagation. Once we establish the mechanisms by which the structural components operate and work together to form the functional whole, then we can devise interventions that disrupt those operations to thwart the virus. For example, by characterizing a component known to play an essential role in particle assembly or mediate a key interaction with the host cell, our model can guide rational design or optimization of antiviral drugs that inhibit these events; by characterizing a component known to elicit a host immune response during infection, our model can facilitate the mapping of antigenic sites and support the development of vaccines. Further, by investigating the SARS-CoV-2 viral particle in aggregate, we can analyze emergent properties of the system that may be related to host-level factors such as infectivity, pathogenicity, and virulence.

Overall, basic science builds a foundation of knowledge for applied science to stand upon. Cultivating an understanding of SARS-CoV-2 from the bottom up will provide a powerful advantage over the virus. A model of an intact, atomistic virus particle will equip researchers with a detailed structural map of the pathogen and a depth of insight into its inner workings that will enhance biomedical research across other STEM fields, guiding new experiments and data interpretation. By promoting the development of prophylactic and therapeutic interventions, basic science translates into disease control and patient care; by expanding our fundamental understanding of the virus, basic science can lead to improved public health recommendations, education, policy, and outcomes. Moreover, the more we learn about viruses in general, the more prepared we become to combat and contain future outbreaks. Supporting basic science research is ultimately essential to maintaining the welfare of our population long-term, in Delaware and beyond.

TRAINING RESEARCHERS FOR FUTURE PANDEMICS

Our project to model the SARS-CoV-2 viral particle is NSF-funded. In keeping with NSF's strategic plan to develop a high-quality, diverse national STEM workforce,[23] we are actively training new researchers in the state-of-the-art computational skills they need to participate in addressing the current pandemic, as well as any that may arise in the future. Remarkably, a significant portion of our SARS-CoV-2 work is being carried out by students and postdoctoral researchers at the University of Delaware. Being engaged in biomedical research with the potential to impact an ongoing global health emergency has empowered these trainees at critical stages of their scholarly careers. As academics, we must always prioritize the recruitment and training of capable individuals who will become our next generation of scientists. Importantly, we should also aim to diversify the STEM workforce going forward.

Our research laboratories actively seek to attract diverse individuals to the field of computational structural virology. Notably, our team (*Figure 3*) is currently 50% male and 50% female, made up of domestic and international scholars, and includes members who identify as White, Black, Asian, Hispanic or Latino, LGTBQ, disabled, first-generation college student, first-generation immigrant, and Delaware native. *Figure 3* shows a picture of our team during a recent video conference meeting. To support social distancing on the University of Delaware campus, the team has been working remotely since March 2020.

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Figure 3. Members of the Perilla/Hadden-Perilla research team.

A. *Olivia Shaw, undergraduate student (Hadden Lab);* **B.** *Dr. Jodi Hadden-Perilla, Assistant Professor;* **C.** *Dante Freeman, postbaccalaureate researcher (Hadden Lab);* **D.** *Dr. Nidhi Katyal, postdoctoral researcher (Perilla Lab);* **E.** *Chaoyi Xu, graduate student (Perilla Lab);* **F.** *Tanya Nesterova, undergraduate student (Perilla Lab);* **G.** *Hagan Beatson, undergraduate student (Perilla Lab);* **H.** *Dr. Juan Perilla, Assistant Professor;* **I.** *Oluwatoni Akin-Adenekan, undergraduate student (Perilla Lab);* **J.** *Alexander Bryer, graduate student (Perilla Lab);* **K.** *Fabio González, graduate student (Perilla Lab);* **L.** *Carolina Pérez Segura, graduate student (Hadden Lab).*

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