Multiscale molecular simulations to develop inhibitors of the SARS-CoV-2 coronavirus membrane fusion protein

PI: **Carlos Simmerling**, Professor, Department of Chemistry (CAS), Laufer Center for Physical & Quantitative Biology

Co-PI: **Evangelos Coutsias**, Professor, Department of Applied Mathematics & Statistics (CEAS), Laufer Center for Physical & Quantitative Biology

Summary

The surface “spike” glycoprotein of the SARS-CoV-2 coronavirus recognizes and binds to the ACE2 receptor on the surface of human cells. This leads to attachment of the spike to the human cell membrane, and a dramatic conformational change in the spike that brings the two membranes into close proximity, leading to membrane fusion and cell infection. Due to this critical role, the spike is the main target of antibodies, which eventually give immunity by binding the spike and blocking its rearrangements. We hypothesize that a well-designed small molecule drug could play the same role. Unfortunately, experimental structures of the spike are incomplete, prohibiting use of modern structure-based drug design methods. With our combined expertise in molecular geometry and large-scale biomolecular simulations, we will address this challenge by modeling the structure and dynamic mechanism of the coronavirus spike. Predictions will be tested by experimental labs at Stony Brook and elsewhere. The project has potential for high impact; the spike is a feature of all coronaviruses, such as those causing SARS and MERS. Success in this project could be a vital step leading to a broadly effective therapy for present and future coronavirus-borne illnesses. Our initial models are already receiving attention.