AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Large-scale Application Of Free Energy Perturbation Calculations For Antibody Design

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Antibodies can be designed and manufactured as effective countermeasure against biological threats such as the viral infection caused by SARS-CoV-2 and its variants. Our interdisciplinary team at the Lawrence Livermore National Laboratory has been developing the infrastructure for rapid response to emerging virus threats by designing neutralizing antibodies with good efficacy and manufacturability. Our platform employs a large variety of computational and experimental techniques for rapid antibody development. In this presentation, we focus on the alchemical free energy perturbation (FEP) method, a rigorous and powerful physics-based technique to calculate the free energy difference between distinct chemical systems. We report our implementation of automated large-scale FEP calculations, using the Amber software package, to facilitate the antibody design and evaluation. In combination with Hamiltonian replica exchange, our FEP simulations aim to predict the effect of mutations on both the binding affinity and the structural stability. Importantly, we incorporate multiple strategies to faithfully estimate the statistical uncertainties in the FEP results. As a case study, we apply our protocols to systematically evaluate variants of the m396 antibody for their conformational stability and their binding affinity to the spike proteins of SARS-CoV-1 and SARS-CoV-2. By properly adjusting relevant parameters, the particle collapse problems in the FEP simulations are avoided. Furthermore, large statistical errors in a small fraction of the FEP calculations are effectively reduced by extending the sampling, such that acceptable statistical uncertainties are achieved for the vast majority of the cases with a modest total computational cost. Finally, our predicted conformational stability for the m396 variants is qualitatively consistent with the experimentally measured melting temperatures. FEP thus plays a valuable role in our platform of antibody design and development and in the mission of biological countermeasure.