THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

An Integrated Structural Biology Platform For Rapid Discovery And Development Of Diagnostics And Therapeutics

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Responsiveness to emerging threats requires the agile and rapid development of diagnostics, countermeasures and therapeutics. There is a need for tunable yet tailored platforms and frameworks to design, characterize, iteratively refine and develop diagnostics and countermeasures. AI-based structure prediction in conjunction with targeted structural biology methods enables a framework by which protein structure, dynamics and interactions can be rapidly measured and validated. At the Advanced Light Source (ALS; als.lbl.gov) at the Lawrence Berkeley National Laboratory (LBNL), a resource operated by the United States Department of Energy, we have integrated the structural biology methods of crystallography, small angle X-ray scattering (SAXS), and X-ray footprinting mass spectrometry (XFMS) together with associated expertise in generating and using current structure modeling and prediction methods. We additionally have the ability to incorporate cryoEM and soft X-ray tomography as required. This integration of capabilities and expertise at the ALS uniquely positions LBNL to provide a flexible and rapid pipeline for structural characterization. During the SARS-CoV-2 pandemic, for example, macromolecular crystallography was used at the ALS synchrotron to provide atomic level structures, whereas SAXS provided solution state global dynamics information, and XFMS provided solution state residue-level epitope mapping. Together, these formed an integrated, holistic system level characterization of the pathogen and its interaction with host proteins. We are now currently deploying this pipeline for rapid assessment of antibody:antigen interactions. More generally, this integration of methods enables on-demand characterization of protein structure and interactions, and validation of atomic models of pathogenic proteins. Highlights from this effort will be showcased in this presentation.

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