DynAA: Characterizing the dynamics of antibody-antigen interfaces using Molecular Dynamics simulations

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Abstract

Studying the antibody-antigen (Ab-Ag) interfaces is crucial for understanding the molecular basis of antibody recognition and for designing effective therapeutics. Current studies mainly focus on static structures coming from experimental methods such as X-ray crystallography, which do not capture the dynamic nature of these interfaces known to present specific binding behavior. This is why, in this work, we used trajectories from all-atom classical Molecular Dynamics (MD) simulations to add a temporal dimension to the analysis of Ab-Ag interfaces. We performed simulations on 212 non-redundant protein-protein complexes from the well-known open-source Docking Benchmark 5.5 dataset [1], including 57 Ab-Ag complexes classified as AA (Ag-Double chain Ab) or AS (Ag-Single chain Ab). These runs were made possible by an exceptional grant of 90 million CPU hours from GENCI, allowing us to generate at least 3 replicates of 100 ns-long trajectories for each complex. All simulation data, now accessible through DynaRepo [2] and DynaBench [3] repositories, were analyzed using DynaPIN [4], a new analysis pipeline that combines structural stability metrics, interface quality assessment, residue-level energetics, and interaction network analysis to comprehensively characterize protein-protein interaction (PPI) dynamics. To our knowledge, this work will constitute the first large-scale analysis comparing Ab-Ag interface dynamics to other PPI types, with future extensions focusing specifically on AA versus AS interaction mechanisms. The results are expected to reveal dynamic signatures specific to Ab-Ag interfaces and pave the way for the identification of key residues/structures critical for AA and AS assembly stability, with important implications for therapeutic antibody design targeting specific antigens.

Keywords: Antibody-Antigen interfaces, Molecular Dynamics simulations, Therapeutic antibodies, Protein-protein interactions, Computational biology

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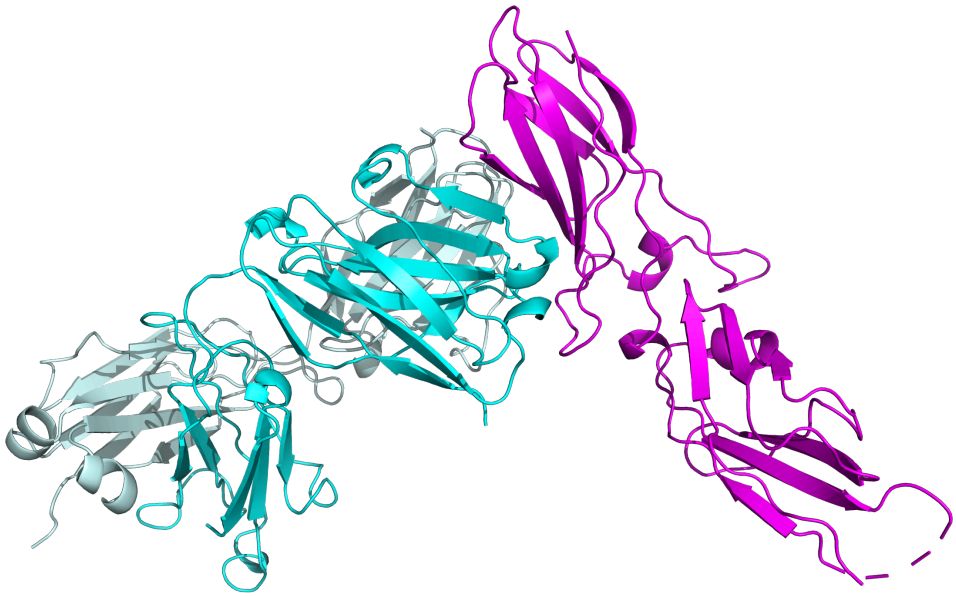

Figure 1 – A complex from the AA group of the Docking Benchmark 5.5: Tissue factor extracellular domain with an inhibitory immunoglobulin Fab fragment (PDB ID: 1AHW) [5]. The antigen is shown in magenta and the antibody in cyan, with the heavy and light chains colored in dark and pale cyan, respectively.

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