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Integrating Molecular Dynamics and Phylodynamics to Unravel Sialic Acid and HA Interactions Patterns in Avian H5 2.3.4.4b Influenza

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Abstract & Keywords

Abstract

The hemagglutinin (HA) receptor binding switch in the avian H5 2.3.4.4b clade is crucial for understanding influenza virus host specificity and transmission, especially after the 2024 cattle outbreak. This study investigates **receptor binding properties** and affinity changes due to mutations in this clade across different hosts. We modeled HA proteins, performed molecular docking with sialic acids, and ran molecular dynamics simulations to refine interactions and calculate **free binding energies**. Key variants will be validated via glycan microarray and Biolayer Interferometry (BLI) assays. Phylodynamic analyses will trace **receptor binding evolution**. We will then retrain a **machine learning model** to predict **receptor binding switches** for new HA sequences.

Keywords & Definitions

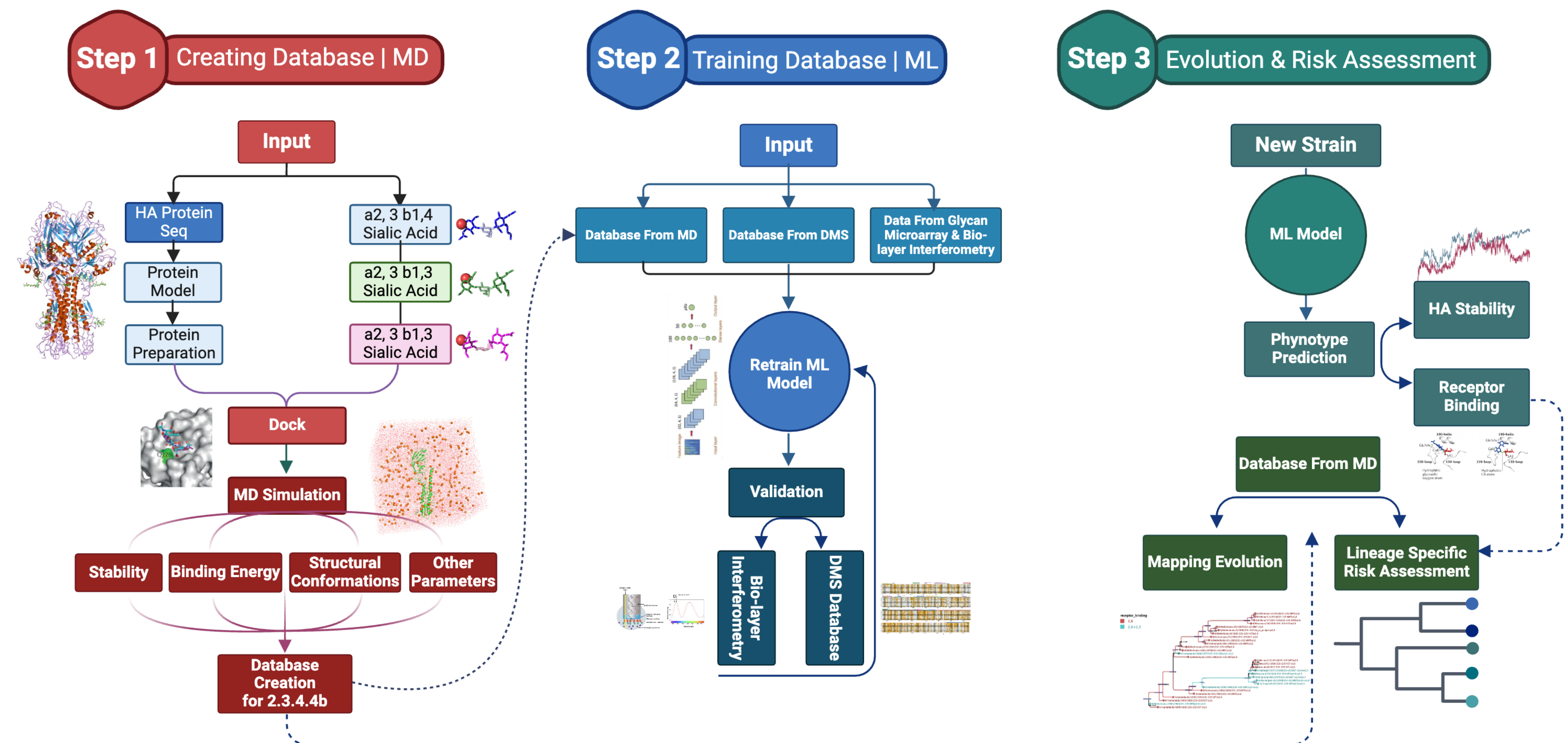
MD Simulation: Molecular Dynamics simulation is a biophysical method of studying motion of molecules.

BLI: Biolayer Interferometry is an optical technique to measure molecular interactions in real time.

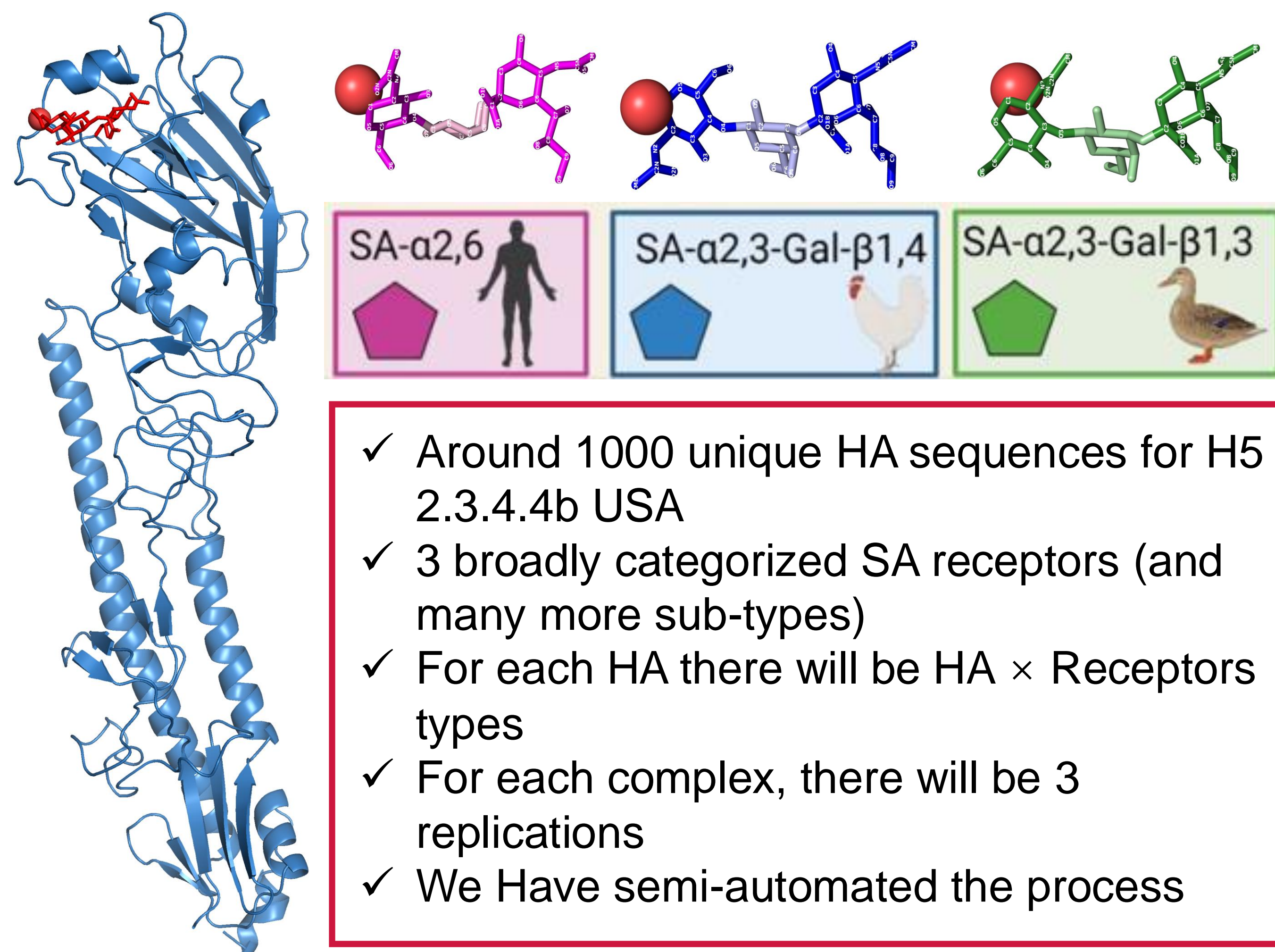
Glycan Microarray: High-throughput method for analyzing glycan-binding interactions by spotting diverse glycans on a chip.

DMS: Deep mutational scanning evaluates every possible mutation at each position in a protein to assess its impact on function or stability.

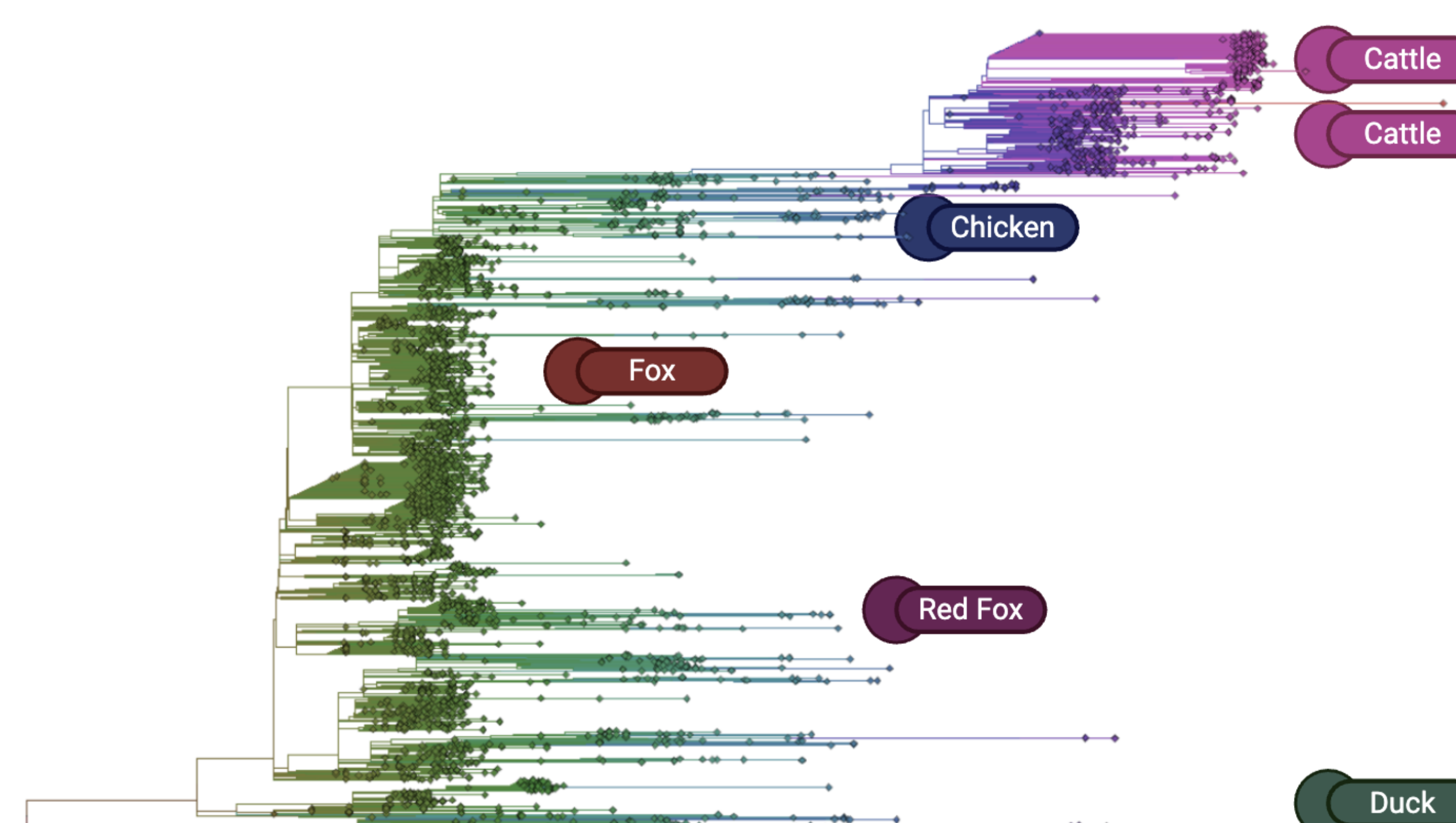
From Molecular Dynamics (MD) Simulation to Risk Assessment



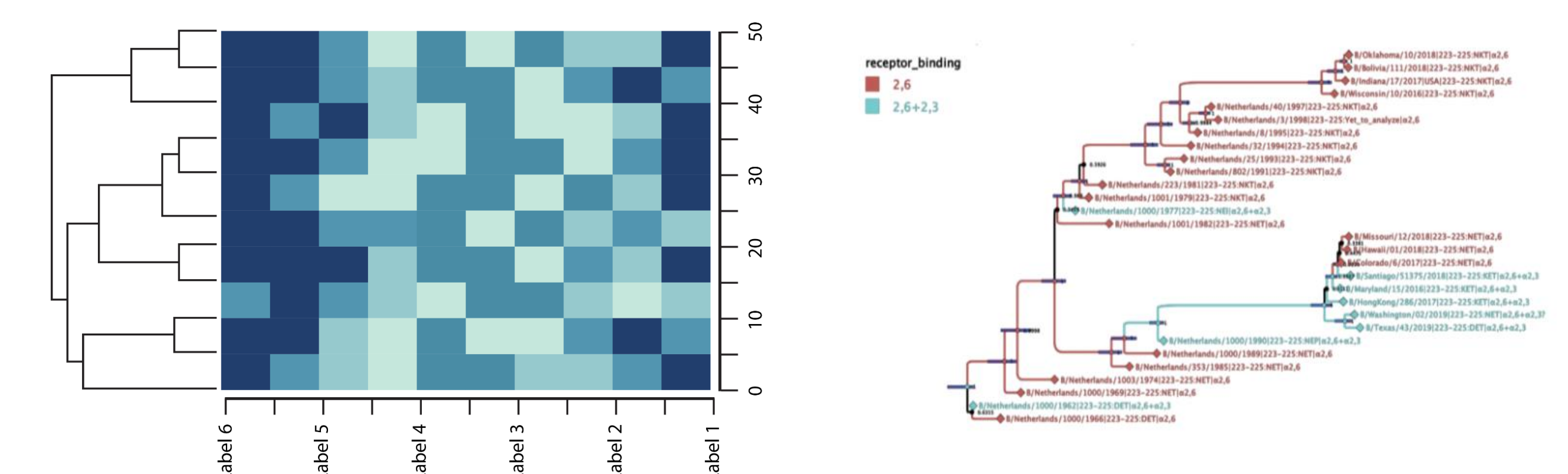
HA Protein and Sialic Acid Receptors



2.3.4.4b USA as Dataset



Binding Energy and Evolution



Future Works

- ✓ Complete modeling, docking, & simulation for all the systems.
- ✓ Calculate the binding energy to create the database.
- ✓ Retrain OnionNet/ESM3 with this dataset and DMS dataset.
- ✓ Validate using glycan microarray & biolayer interferometry technique.
- ✓ Develop tool for risk assessment of new strains.