

Characterizing Broadly Neutralizing Antibody Maturation Pathways Using Reinforcement Learning.

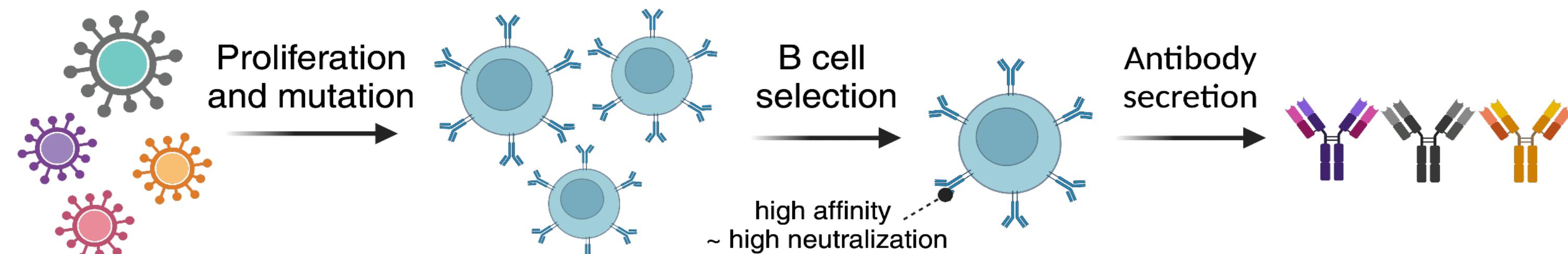
^{1,2}Ivan Rivera, ¹Fatima Talib, ¹Jeffrey Gray.

¹Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore.

²Department of Biomedical Engineering, Columbia University, New York.

Background

- Affinity maturation (AM): B cells evolve antibodies with increased binding affinity towards an antigen.
- Hyper-somatic mutation drives AM by selecting neutralizing antibodies
- Broadly neutralizing antibodies (bnAbs) arise through AM by targeting conserved epitopes, resulting in **high neutralization breadth**



Motivation

Significance

- Traversing AM landscapes for bnAbs can give insight into optimal vaccination protocols against the most variable (and dangerous) viruses.

Previous work

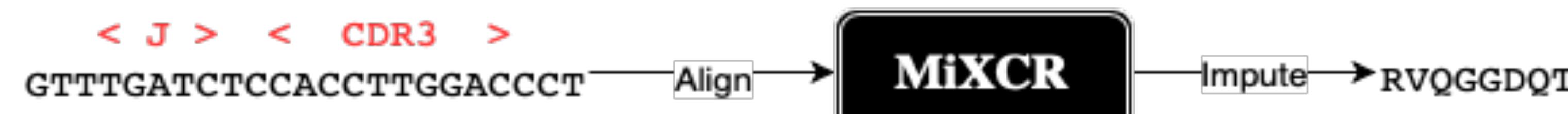
- Greedy search algorithms for path finding
- Deep reinforcement learning for optimal vaccination protocols

Goals

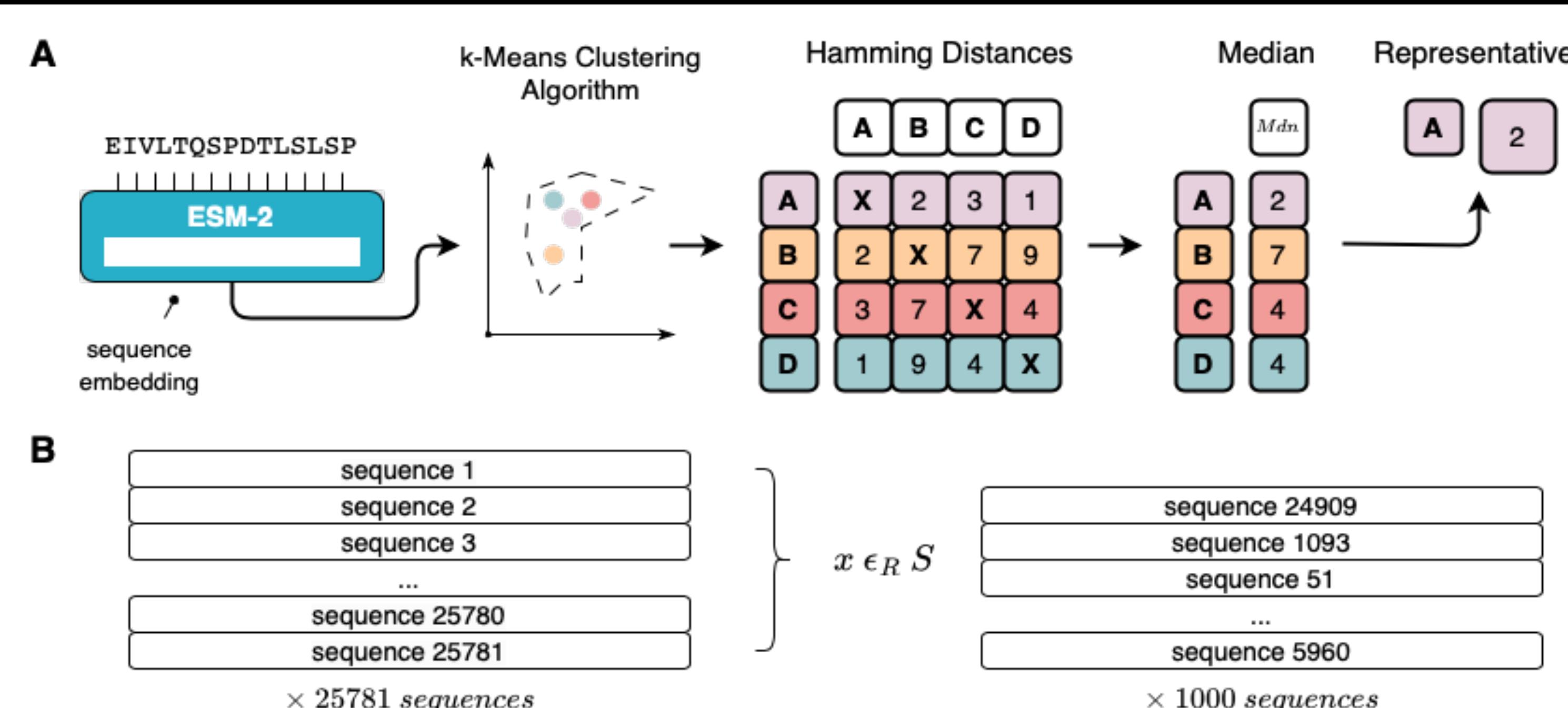
- Develop a graph representation of the AM landscape
- Traverse this landscape using informed search algorithms and reinforcement learning

Methods

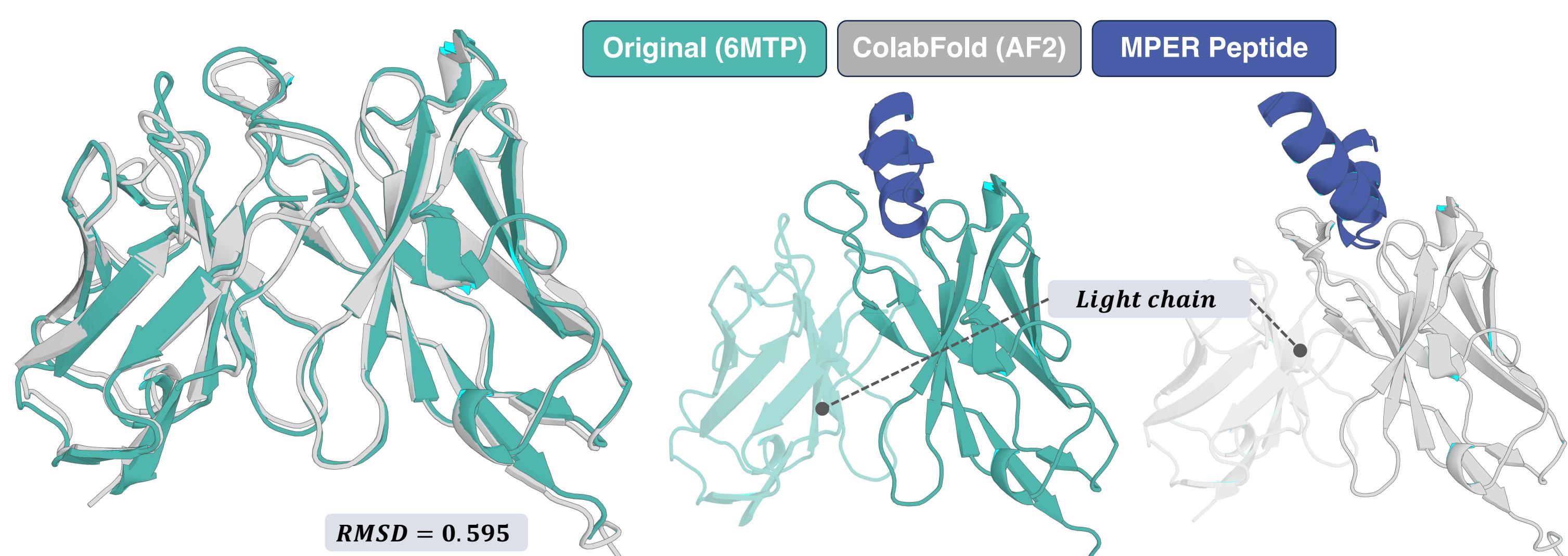
✓ Generate protein sequences from a nucleotide repertoire.



✓ Extract representative protein sequences.

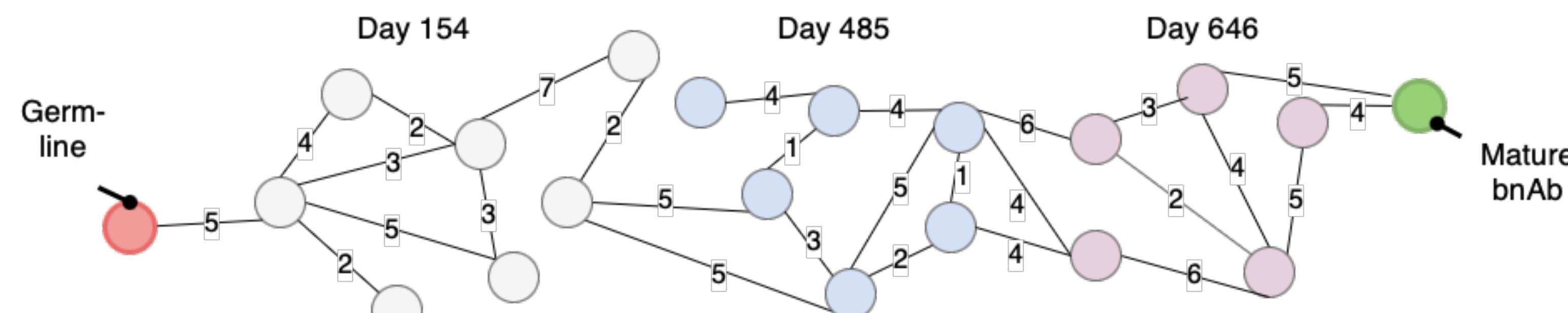


✓ Build bound antibody-antigen structures using AF2.



□ Calculate Rosetta binding energies (REU).

□ Build AM graph landscape.



□ A* implementation using heuristic functions

- Levenshtein distance (LD): $h_{LD}(n) = |LD(T) - LD(n)|$
- Binding energies: $h_{\Delta\Delta G}(n) = |\Delta\Delta G_T - \Delta\Delta G_n| + \Delta\Delta G_n - \Delta\Delta G_{n-1}$
- pLDDT: $h_{pLDDT}(n) = |pLDDT_T - pLDDT_n| - pLDDT_n + pLDDT_{n-1}$
- Aggregate: $h_{Agg}(n) = h_{LD}(n) + h_{\Delta\Delta G}(n) + h_{pLDDT}(n)$

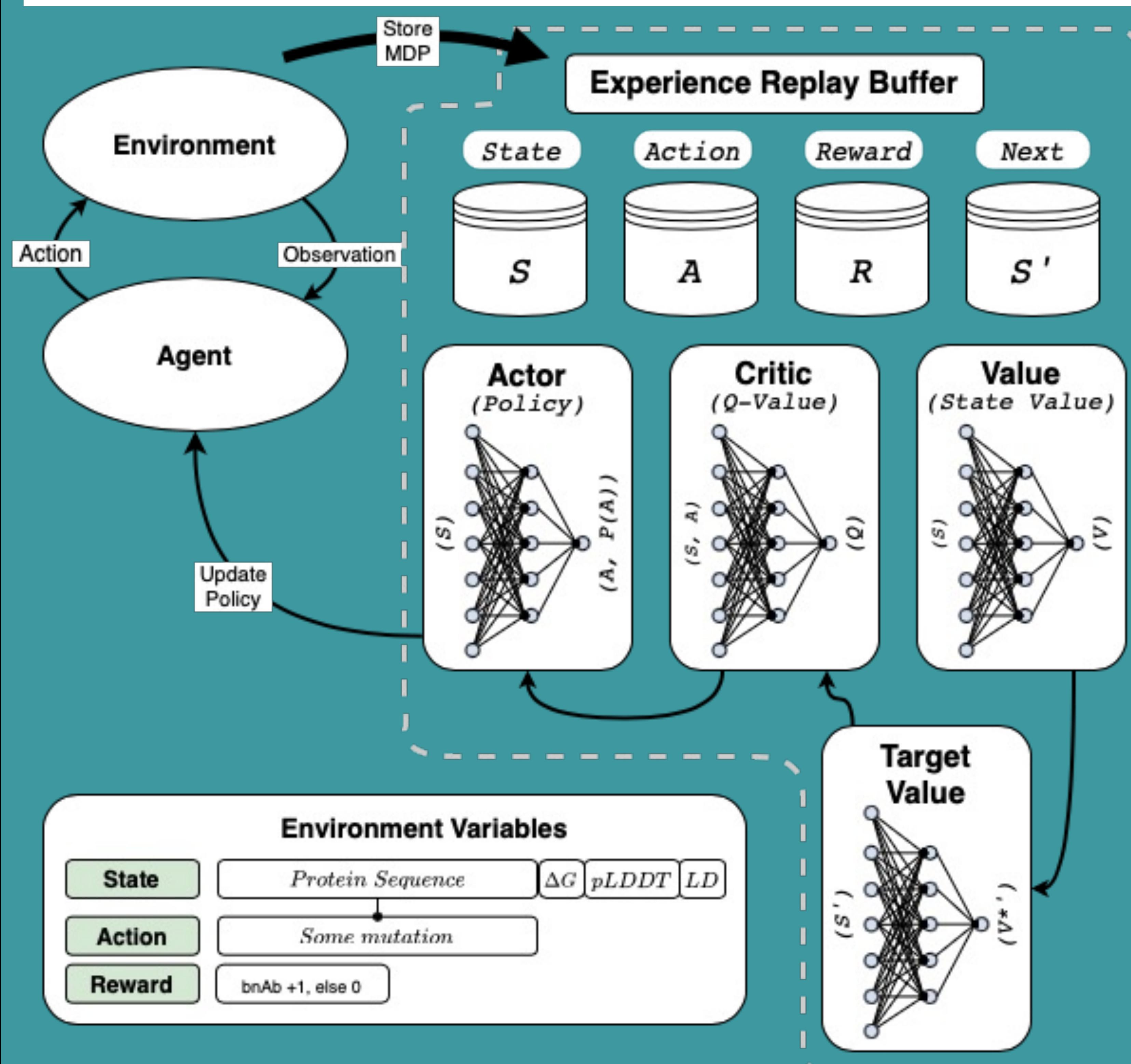
□ Deep reinforcement Learning (DRL).

Data

Unpaired, longitudinal repertoire of a patient who developed **three bnAb lineages (VRC42, VRC43, VRC46)** against the **MPER epitope**, a known highly conserved region of the HIV-1 gp41 envelope protein.

Taken over 654 days after identification of Fiebig I infection stage

Affinity Maturation Soft Actor-Critic (AMSAC)



Expectations and Future Directions

- Language model for Actor network
- Policy learned by DRL agent characterizes an AM pathway for bnAbs
- Binding energy generally decreases throughout pathway

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