Improve Antibody Humanization with Monte-Carlo Tree Search

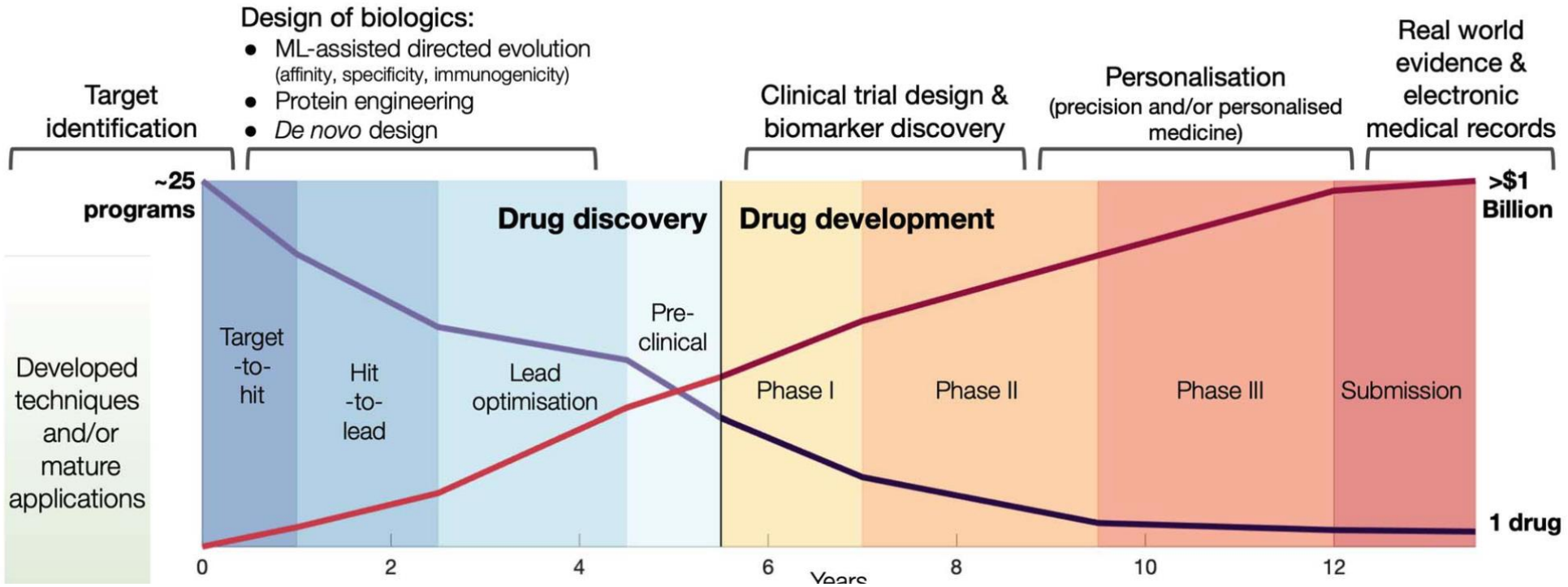
Zhihao Zhan, Huan Zhang

2024.12.19

IFT6269 Course Project

Motivation: AI-Driven Antibody Discovery

- Antibody development is costly and has a low success rate.
- AI-powered large-scale preliminary screening could be transformative.



Background: Antibody Humanization

- Antibody humanization aims to reduce immunogenicity in humans while preserving the specificity and binding affinity of the original non-human antibody.
- Prior to this stage, the lead antibody's ability to bind effectively to the target has been validated.

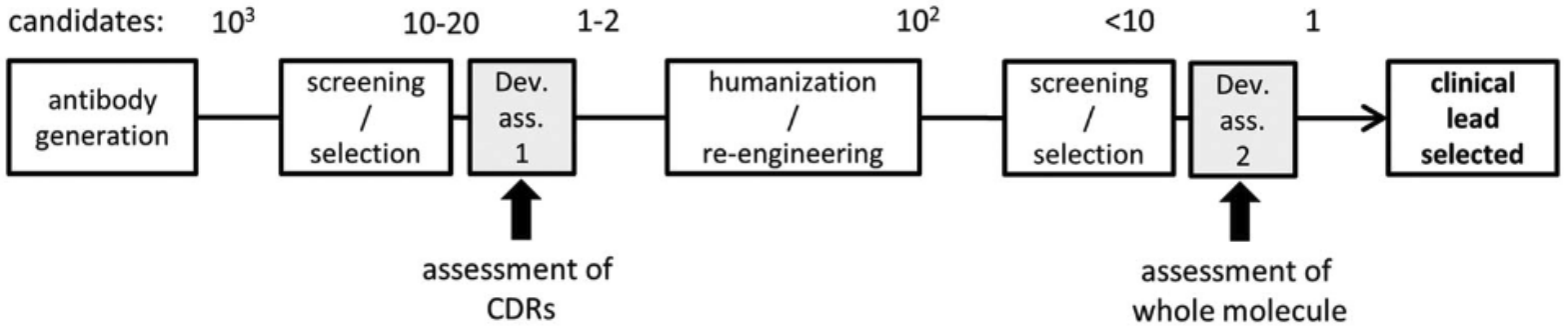
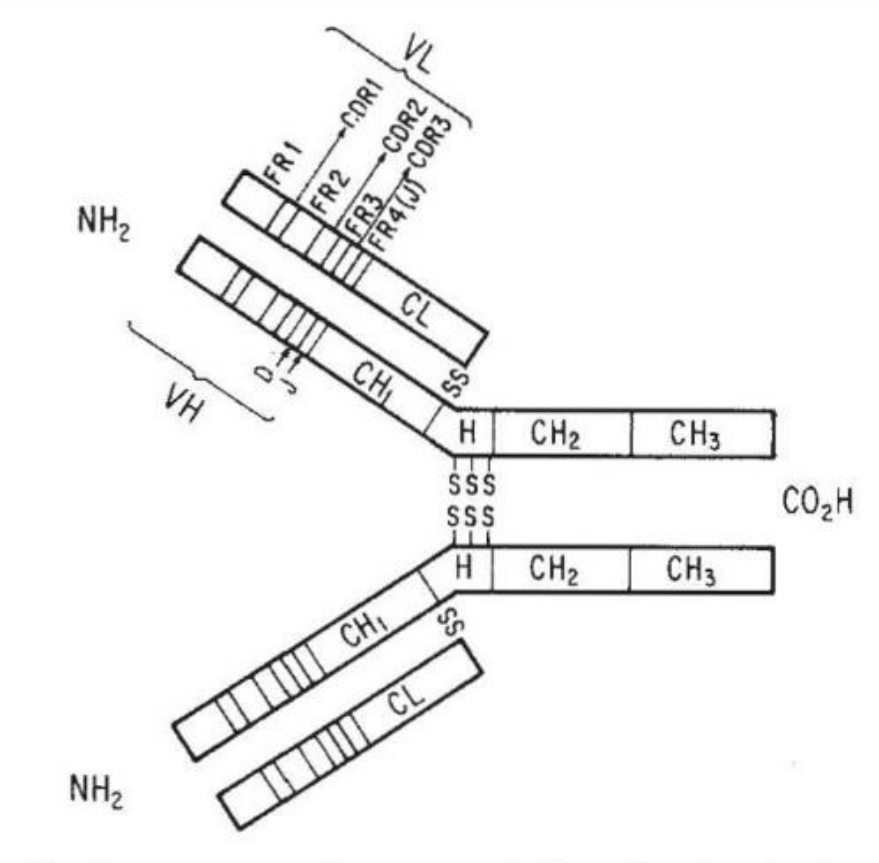


Figure 1. Developability workflow. The various stages of protein drug discovery are shown as boxes with the number of candidates typically tested indicated above. Arrows mark the time points at which developability assessment is performed.

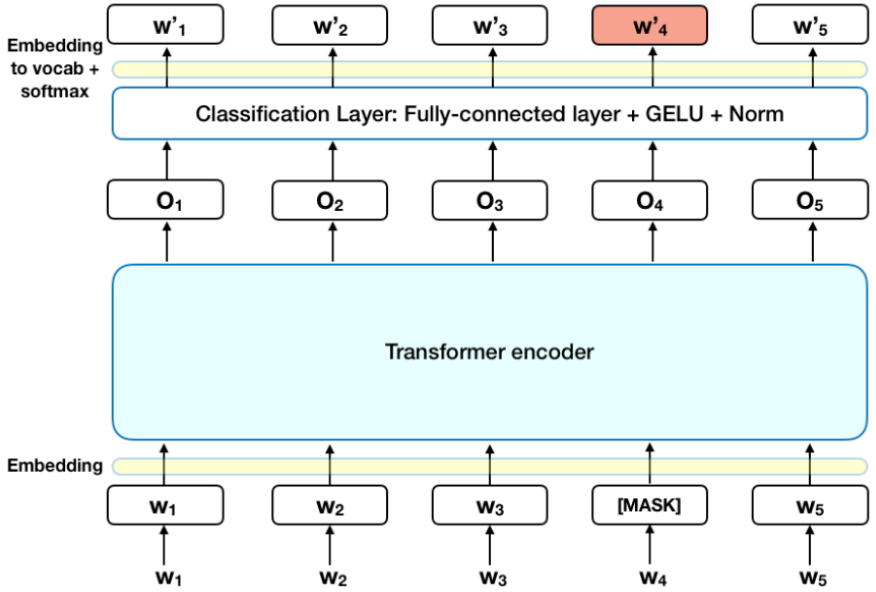
Setup: Antibody Humanization

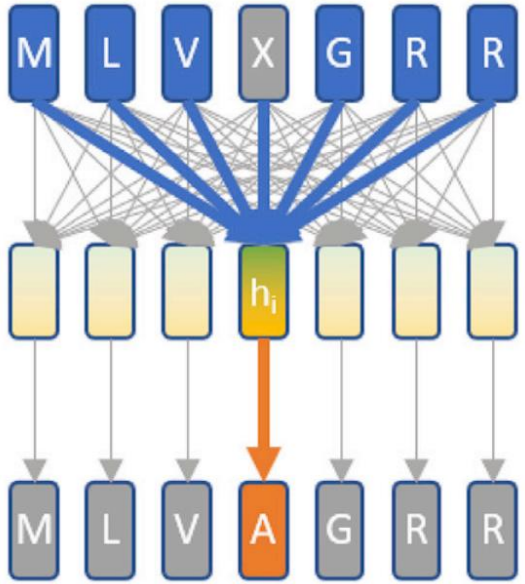
- The goal is to mutate the framework (FR) regions while preserving the binding (CDR) regions.



Setup: Language Model as Reward Model

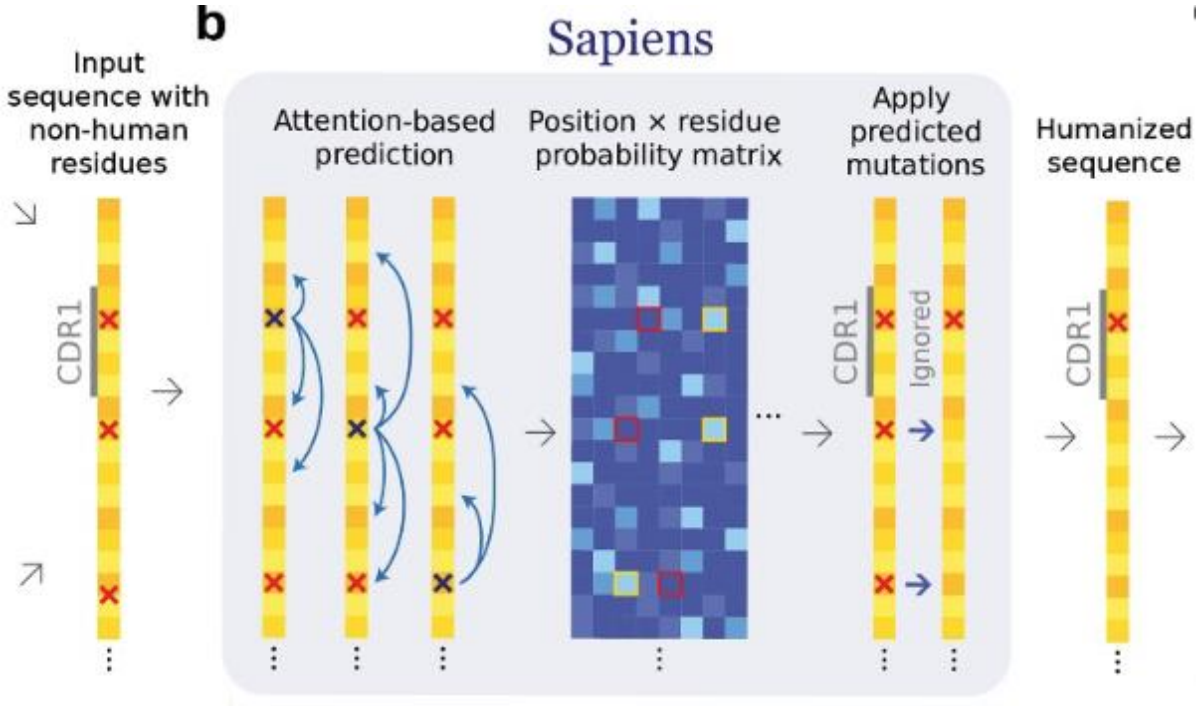
- We use a language model, large-scale pre-trained with masked-language-modeling on the human antibody database OAS, to calculate a sequence score as a reward model. It also predicts the probability of each amino acid at every position.
- Previous studies have shown a negative correlation between language model zero-shot scores and experimental immunogenicity.





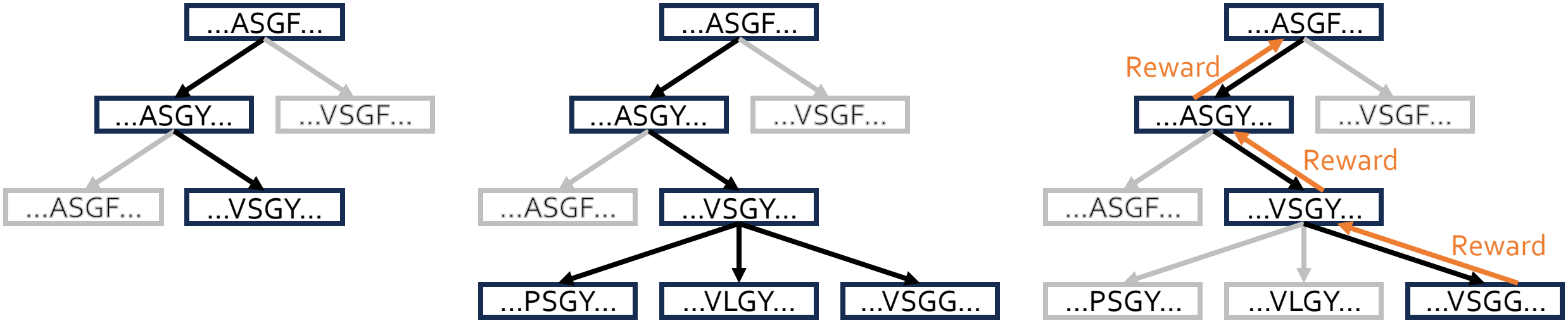
Baseline: Greedy Algorithm

- The greedy algorithm iteratively replaces every amino acid with the one having the highest probability at its position.
- However, it may get stuck in a local maximum.



Reformulation: Monte-Carlo Tree Search

- We define a state to be an antibody sequence, and an action to be a mutation at single position. Both state and action space are discrete and relatively large.
- Standard MCTS has 4 stages: selection, expansion, simulation and back-propagation.



Selection

Expansion

Simulation and Back-Propagation

Limitations of MCTS

- Duplicated states and actions.
  - Can we avoid searching the same state more than once?
- Random expansion.
  - Can we improve the expansion process with heuristics?
- Inefficient tree climbing.
  - Can we directly access the best node for expansion?

Our Improvements of MCTS

- Change of reward estimation.
  - We maintain maximal futural reward instead of expected futural reward during back-propagation.
- Deduplication.
  - If a newly expanded state has been encountered before, it is discarded.
  - Once an action is performed at a position, future actions can no longer modify that position.
- Heuristic expansion.
  - We calculate the estimated reward of the next state instead of the current state:
  - We prioritize expanding next states with higher rewards.
- Eliminate selection and back-propagation.
  - We use a heap to maintain the node with maximal estimated reward.

Our Algorithm

- At each step, we start from a state s, $s_i \in A$, A is the set of 20 amino acids.
- A language model takes s as input, and outputs $r_{s,p,X}$, $X \in A$, representing the predicted probability for the p-th amino acid in s to be X. The sequence score is calculated as:

$$R = \sum_i r_{s,i,s_i}$$

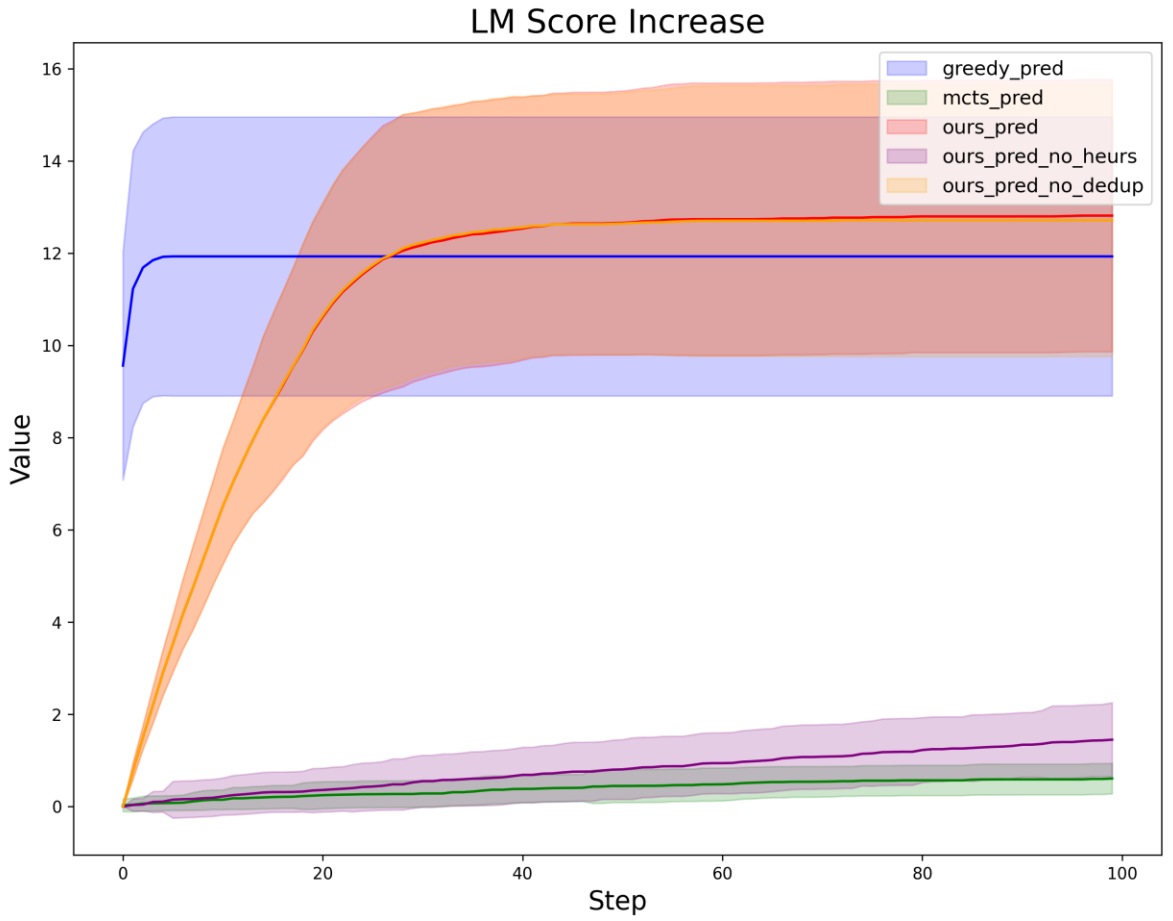
- We define the next states $\tilde{s}_{p,X}$ and their estimated rewards $\tilde{R}_{p,X}$ as:

$$\tilde{s}_{p,X,i} = \begin{cases} s_i & (p \neq i) \\ X & (p = i) \end{cases} \qquad \tilde{R}_{p,X} = \sum_i r_{s,i,\tilde{s}_{p,X,i}}$$

- According to our heuristics, we maintain the largest unvisited $\tilde{R}_{p,X}$ in a heap and choose the corresponding $\tilde{s}_{p,X}$ as the next state.

Benchmark

- We apply our method to Hu-mAb dataset, which contains 25 non-human antibodies.
- We compare our method with:
  - greedy baseline;
  - standard MCTS baseline;
  - our method without heuristics;
  - our method without deduplication.



Benchmark

- We also report drug likeliness (OASis percentile), human antibody likeliness (OASis Identity), human germline likeliness (Germeline content percentile).

Method	OASis Percentile	OASis Identity	Germline Content Percentile	Language Model Score Increase
Greedy	59.66	83.44	84.67	11.93
MCTS	7.33	52.63	69.50	0.61
Ours	62.39	84.68	87.04	12.81
-deduplication	62.26	84.62	87.02	12.72
-heuristics	4.72	49.24	69.22	1.45

Limitations and Future Work

- We consider mutation only.
  - We will consider insertion and deletion as well.
- Reward model may not be as accurate as expected.
  - A regression model trained on experimental immunogenicity will be a better solution.
- Our heuristics can also cause MCTS to get stuck in a local maximum.
  - We will discover more effective ways to incorporate randomness.

Reference

- Gaudelet, T., Day, B., Jamasb, A. R., Soman, J., Regep, C., Liu, G., Hayter, J. B. R., Vickers, R., Roberts, C., Tang, J., Roblin, D., Blundell, T. L., Bronstein, M. M., and Taylor-King, J. P. Utilizing graph machine learning within drug discovery and development. Briefings in Bioinformatics, 2021.
- Jarasch, A., Koll, H., Regula, J. T., Bader, M., Papadimitriou, A., and Kettenberger, H. Developability assessment during the selection of novel therapeutic antibodies. Journal of Pharmaceutical Sciences, 2015.
- Prihoda, D., Maamary, J., Waight, A., Juan, V., Fayadat-Dilman, L., Svozil, D., and Bitton, D. A. Biophi: A platform for antibody design, humanization, and humanness evaluation based on natural antibody repertoires and deep learning. mAbs, 2022.
- Tonegawa S. Somatic generation of antibody diversity. In Nature. 1983.
- Horev R. BERT Explained: State of the art language model for NLP. In Towards Data Science. https://towardsdatascience.com/bert-explained-state-of-the-art-language-model-for-nlp-f8b21a9b6270. 2018.
- Bepler T, Berger B. Learning the protein language: Evolution, structure, and function. In Cell Systems. 2021.