# Enhancing Antibody Discovery: Genetic Algorithms and Risk-aware Protein Modeling


## Abstract

In this study, we introduce an innovative framework for antibody design that synergizes protein language models with risk-aware batch Bayesian optimization and genetic algorithms. Our objective is to enhance the sample efficiency of antibody design while reducing experimental costs and time. By leveraging protein language models, we generate candidate sequences with higher naturalness. The integration of risk-aware Bayesian optimization allows for effective exploration of the sequence space with an emphasis on managing uncertainties. Additionally, we incorporate genetic algorithms to further refine our search strategy, combining their robustness in finding global optima with our model's predictive power. Our experimental results demonstrate a significant improvement in identifying promising antibody candidates compared to traditional methods. This framework not only advances the field of antibody design but also provides a versatile approach applicable to other areas of protein engineering.


## 1 Introduction


Figure 1: Future antibody design pipeline. Image generated by DALLE.

Immunoglobulins, commonly referred to as antibodies, are the immune system's arsenal against pathogenic incursions, essential for warding off illness and maintaining health [18]. These molecules possess variable regions that are remarkably diverse, enabling the specific detection of antigens. Within these regions, a trio of complementarity-determining regions, known as CDR1, CDR2, and

NeurIPS 2023 AI for Science Workshop.

CDR3, are found, with CDR3 being notably variable and thus dubbed the "hypervariable region" [21]. The CDR3 region, with its high variability, is crucial for the specificity of antigen recognition, making its diversity a key focus in the design of tailored antibodies. This strategic antibody design is essential for accelerating the development of novel treatments and advancing vaccine research [10, 9].

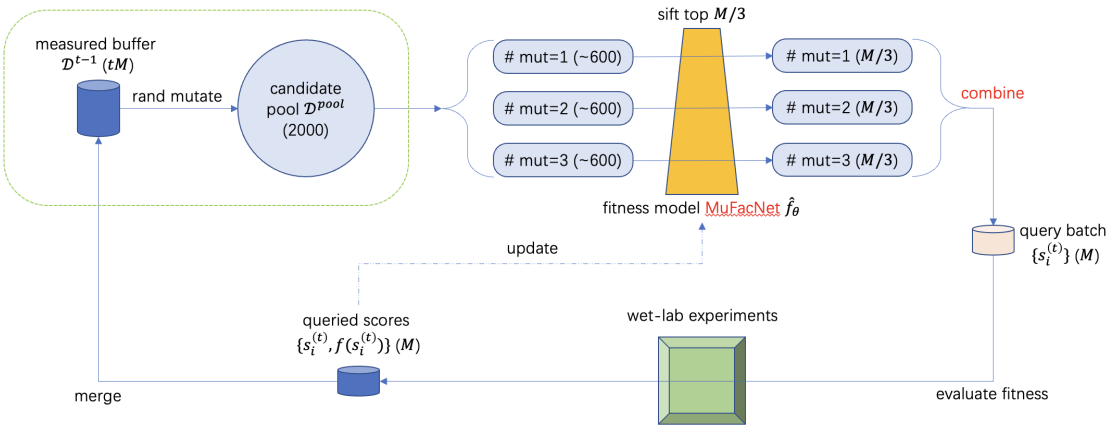


Figure 2: Framework overview. The proposed framework in the provided diagram outlines a process for optimizing antibody design through a computational and experimental approach. Initially, a measured buffer of candidate sequences is generated from existing data, which is then randomly mutated to create a diverse pool of candidates. This pool is processed by the fitness model, MuFacNet, which evaluates and ranks the candidates based on predicted fitness, sifting the top third for further consideration. These selected sequences are divided into three groups based on the number of mutations, and a combined query batch is formed. This batch is then subjected to wet-lab experiments to evaluate the actual fitness of each candidate. The results of these experiments are used to update the fitness model, thereby closing the loop and providing a refined set of sequences for the next iteration. This iterative process is designed to efficiently converge on the most promising antibody designs by integrating computational predictions with experimental validation.

The ambition of antibody engineering is to fine-tune these biological molecules to specific therapeutic or diagnostic objectives. By refining attributes such as their binding efficiency and structural resilience, these custom antibodies are shaping the future of precision medicine, with far-reaching potential across diagnostic and therapeutic domains [13, 2].

Antibody design is a multifaceted process that integrates both experimental and computational techniques. The initial step involves identifying the target antigen, typically using methods such as X-ray crystallography, NMR spectroscopy, or bioinformatics analysis. Following antigen identification, the appropriate antibody type is selected, which may include monoclonal antibodies, polyclonal antibodies, or engineered variants. A diverse antibody library is then generated, encompassing a

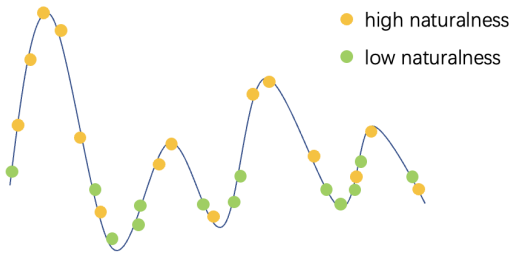


Figure 3: Process of lane scape learning

wide range of sequences. This library is subsequently screened to identify antibodies that exhibit the desired properties, such as high affinity and specificity for the target antigen. The selected antibodies are then optimized to improve key characteristics, including binding affinity and stability. Finally, the optimized antibodies undergo rigorous in vitro and in vivo testing to evaluate their efficacy and safety.

However, experimental antibody design and screening can be time-consuming and expensive. Computational tools facilitate the virtual screening of a large number of potential candidates, enabling investigators to select the most promising ones for further experimental validation. Simulations [22] can provide insight into the antibody protein landscape, which aims to capture the sequential, structural, and functional diversity of antibodies and provides insights into properties such as binding affinity and specificity [11, 5]. However, the sheer number of possible CDR3 sequences in the combinatorial space makes it infeasible to exhaustively examine any antibody [15]. The vast diversity of possible CDR3 sequences in the combinatorial space makes it impractical to exhaustively explore every potential antibody. As a result, computational tools are essential to guide the search through this complex protein landscape. Additionally, the antibody development process is inherently multifaceted, requiring the integration of various techniques, such as constructing structural models for different antibody components, generating antigen-derived structures, and performing docking studies [22].

Numerous machine learning-based sequence design methods have been proposed to enhance antibody development. For example, Robert et al. developed a software suite that enables the generation of synthetic, lattice-based 3D structures for antibody-antigen binding, providing access to ground-truth data such as conformational paratopes, epitopes, and affinity measurements *Absolut!*. Furthermore, common immunological challenges associated with antibody specificity prediction were formalized as machine learning tasks, with results confirming that machine learning models trained on experimental data can be applied to generated datasets *Absolut!*. This framework offers a robust platform for the development and benchmarking of machine learning strategies in the design of biotherapeutics *Absolut!*.

Recently, Bayesian optimization has demonstrated its efficiency in exploring the sequence design space [11, 3]. Bellamy et al, compared how noise affects different batched Bayesian optimization techniques and introduces a retest policy to mitigate the effect of noise. [19] discussed the use of Bayesian optimization (BO) for the design of chemical-based products and functional materials, showing that BO can significantly reduce the number of experiments required compared to traditional approaches. However, traditional BO may be ineffective for antibody sequence design where the search space dimension is extremely large. The choice of the acquisition function used to guide the optimization process can also impact its effectiveness, and there may be a trade-off between exploration and exploitation that must be carefully balanced.

We propose GRAAB-BO, an efficient way for antibody sequence optimization to address the above challenges. Our main contributions are improving exploration efficiency by using protein language models to filter out mutants with low fitness scores, and designing a risk-aware acquisition function based on the uncertainty of the prediction to improve the explorer's ability. We demonstrate the effectiveness of our proposed method on multiple antibody datasets. Our model can identify the sequence with the best fitness score in the fewest rounds compared to other baselines.

- We introduce an advanced approach where protein language models are utilized to enhance exploration efficiency. This is achieved by filtering out mutants with low fitness scores, thus prioritizing high-potential candidates.
- We incorporate a risk-aware acquisition function, leveraging the uncertainty in predictions. This strategic element enhances the explorer's ability to navigate the complex sequence space more effectively.
- The integration of genetic algorithms plays a crucial role in our framework. These algorithms help in refining the search strategy, thereby optimizing the process of identifying sequences with high fitness scores.
- Our methodology is validated across multiple antibody datasets. The results showcase not only the ability of our model to identify sequences with the highest fitness scores but also its superior overall speed and efficiency in acquiring sequences with high naturalness, outperforming other baseline methods.

## 2 Related work

### 2.1 Protein Landscape modeling

Modeling the protein landscape is crucial for understanding the vast structural and functional variety of proteins. This understanding aids in comprehending protein folding patterns, dynamics, molecular interactions, and their correlation with biological functionalities.

In particular, the application of fitness scores is instrumental in assessing the biofunctional aspects of sequences, a key factor in antibody design. These scores are pivotal in determining the functional integrity and structural soundness of antibodies. Generally, higher fitness scores correlate with enhanced binding affinity, stability, and other sought-after traits. Recent advancements have seen the development of innovative frameworks for modeling diverse protein sequences, notably those utilizing pre-trained language models. These models exhibit remarkable capabilities in transfer learning, adept at predicting fitness scores as cited in works like [19] and [16]. In antibody design, the ability to predict fitness scores is invaluable. This approach presents an efficient and cost-effective alternative to labor-intensive, expensive laboratory experiments. Through the use of computational models and machine learning techniques, researchers can swiftly evaluate the fitness of numerous antibody sequences, focusing on those with higher predicted scores for subsequent empirical validation.

### 2.2 Exploration algorithms for sequence design

The relationship between sequence design and antibody development is crucial for creating antibodies with desired properties. However, sequence design presents significant challenges due to the vastness of sequence space and the complex structure-function relationships involved. To overcome these challenges, researchers have proposed various approaches to improve the efficiency and effectiveness of sequence design in antibody engineering.

One such approach is batch Bayesian optimization (BO), which has garnered attention as a powerful tool to enhance exploration in sequence design. Belanger et al. explored the application of batched Bayesian optimization in biological sequence design, addressing the unique challenges associated with it and evaluating design choices for creating robust and scalable solutions [4]. Additionally, they proposed a heuristic method based on estimating the function's Lipschitz constant to better capture interactions between evaluations within a batch. This method uses a penalized acquisition function to optimize batch selection, thereby minimizing non-parallelizable computational effort [8]. Similarly, Khan focused on using a CDRH3 trust region to narrow the search space, restricting it to sequences that show favorable developability scores.

These studies highlight the ongoing efforts to address the challenges in sequence design for antibody engineering. By incorporating bayesian optimization, researchers aim to enhance the efficiency and effectiveness of antibody design and improve the sequence diversity.

## 3 Problem Formulation and Background

### 3.1 Antibody Sequence Design

Antibody Sequence Design can be formulated as a constrained optimization problem [1, 20, 11, 17]. Let $x$ be a vector representing the CDRH3 amino acid sequence, and let $f(x)$ be a fitness function that quantifies the quality of the antibody sequence in terms of target specificity and developability. The problem is to find the optimal sequence $x^*$ that maximizes the scoring function subject to constraints:

$$\max_x \ f(x) \text{ s.t. } x \in \mathcal{X},\ g(x) \leq 0, \tag{1}$$

where $\mathcal{X}$ is the set of all possible amino acid sequences for the CDRH3 region and $g(x)$ represents constraints on the biophysical properties of the sequence, such as stability and solubility. The optimization problem aims to find the best antibody sequence that satisfies the biophysical constraints and has the highest target specificity and developability scores. Bayesian optimization methods can be used to efficiently solve this optimization problem by iteratively proposing candidate sequences that are subsequently evaluated by a surrogate model and passed to an acquisition function that balances exploration and exploitation.

### 3.2 Bayesian optimization

Bayesian Optimization (BO) is a sequential model-based optimization technique used to solve expensive black-box optimization problems with a limited budget of function evaluations [11]. BO involves modeling the unknown fitness function using a surrogate model, and iteratively selecting the next evaluation point by optimizing an acquisition function that balances the trade-off between exploration and exploitation. The overall goal is to find the global optimum of the unknown function with a minimum number of function evaluations.

We can express the BO process as follows: Let $f(x)$ be the unknown fitness function we aim to optimize, where $x \in \mathcal{X}$ is the input variable. Our goal is to find the global optimum $x^*$ that maximizes $f(x)$. However, doing wet lab experiment to evaluate $f(x)$ is expensive and time-consuming. The acquisition function, denoted by $\alpha(x)$, measures the utility of evaluating a point $x$ based on the current surrogate model. $\alpha(x)$ balances exploration and exploitation by favoring points with high uncertainty (exploration) or high expected improvement (exploitation). Popular acquisition functions include expected improvement (EI), upper confidence bound (UCB), and probability of improvement (PI) [23, 11].

We can approximate $f(x)$ using a Gaussian process (GP), which provides a probabilistic model that captures the uncertainty of the unknown function. The GP model assumes that the function values follow a multivariate Gaussian distribution with a mean function $\mu(x)$ and a covariance function $k(x, x')$:

$$f(x) \sim GP(\mu(x), k(x, x')) \tag{2}$$

Based on the current set of evaluated points, denoted by $\mathcal{D} = (x_i, y_i)_{i=1}^n$, where $y_i = f(x_i)$, we can obtain a posterior distribution over $f(x)$ that conditions on $\mathcal{D}$:

$$P(f(x)|D) \sim \mathcal{N}(\mu_{n+1}(x), \sigma_{n+1}^2(x)) \tag{3}$$

where $\mu_{n+1}(x)$ and $\sigma_{n+1}^2(x)$ are the posterior mean and variance of $f(x)$, respectively.

The next evaluation point is selected by optimizing the acquisition function over the input space $\mathcal{X}$:

$$x_{n+1} = \underset{x \in X}{\operatorname{argmin}}\, \alpha(x) \tag{4}$$

After evaluating $f(x_{n+1})$, we update the surrogate model with the new observation $(x_{n+1}, y_{n+1})$ and repeat the process until the budget of function evaluations is exhausted or a satisfactory solution is found. Batch BO improves this by minimizing the exploration rounds.

### 3.3 Protein language model

A protein language model can be utilized for filtering out sequence with lower fitness scores. For the training of the masked language model, it involves randomly masks amino acid tokens in the sequence, similar to models such as BERT [6] and RoBERTa [14]. In our research, we could utilize the power of protein language model's ability for naturalness evaluation.

## 4 Method

In this section, we introduce our proposed framework, GRA-BO (Genetic Risk-Aware Bayesian Optimization), which integrates fitness-guided mutation generation, protein language model filtering, and an information-theoretic acquisition strategy to efficiently navigate the antibody sequence space.

### 4.1 Fitness Model-Guided Mutation Generation

We first aim to generate mutation candidates that potentially exhibit higher naturalness and fitness. The mutation process maintains a growing pool $\mathcal{D}_i^{\text{Mutation}}$ for the $i^{th}$ amino acid position and updates it iteratively:

$$\mathcal{D}_{i+1}^{\text{Mutation}} = \begin{cases} \mathcal{D}_i^{\text{Mutation}} & \text{if } |\mathcal{D}_i^{\text{Mutation}}| \geq \mathcal{N} \\ \mathcal{D}_i^{\text{Mutation}} \cup \{x_t\} & \text{otherwise} \end{cases} \tag{5}$$

where $x_t$ is the offspring generated at iteration $t$ with the highest fitness score:

$$x_t = \arg \max_{x \in \text{Offspring}} f(x) \tag{6}$$

This process continues until the mutation pool reaches a predefined size $\mathcal{N}$.

### 4.2 General Language Model-Guided Candidate Pool Generation

We employ a General Language Model (GLM-Ab), adapted from GLM [7] and trained on antibody sequences from the Observed Antibody Space [12], to filter candidates based on sequence naturalness. GLM-Ab is trained using both understanding (e.g., token masking and blank filling) and generation tasks.

Let $\mathcal{C}$ be the full candidate pool of $N$ sequences. The language model provides perplexity-based fitness estimates $f(x_i)$ for each $x_i \in \mathcal{C}$. We define a fitness threshold $t$ such that the bottom $m\%$ of sequences are filtered out:

$$\mathcal{C}' = \{x_i \in \mathcal{C} \mid f(x_i) \geq t\} \tag{7}$$

This yields a reduced candidate pool $\mathcal{C}'$ that retains sequences with higher naturalness and predicted fitness, reducing the search space for subsequent optimization.

### 4.3 Genetic Risk-Aware Bayesian Optimization

The GRABO strategy combines the global search power of genetic algorithms with Bayesian optimization's sample efficiency. A population of sequences is evolved through selection, crossover, and mutation, guided by a fitness model. To avoid local optima and ensure robust exploration, we define the acquisition function:

$$\alpha_{\text{GRABO}}(x) = \mu(x) + k_g \cdot \phi_g(x) - k_r \cdot \phi_r(x) \tag{8}$$

where:

- $\mu(x)$ is the predicted fitness score by the surrogate model;
- $\phi_g(x)$ quantifies the sequence's diversity relative to the current population;
- $\phi_r(x)$ penalizes high epistemic uncertainty (risk);
- $k_g$ and $k_r$ are hyperparameters balancing exploration and risk aversion.

This acquisition function promotes the selection of diverse, high-fitness, and low-risk candidates for evaluation.

### 4.4 Information-Theoretic Risk-Aware Acquisition Function

To further enhance sampling efficiency, we incorporate an information-theoretic acquisition function that selects candidates based on their expected information gain. The mutual information between a candidate's fitness and the model is defined as:

$$\alpha_{\text{info}}(x) = \mathbb{I}[f(x); D] = H[f(x)] - \mathbb{E}_{p(y|x,D)}\left[H[f(x) \mid y]\right] \tag{9}$$

This formulation favors candidates that can most reduce uncertainty in the fitness landscape. We integrate this term into our acquisition function:

$$\alpha_{\text{GRABO+Info}}(x) = \mu(x) + k_g \cdot \phi_g(x) + k_i \cdot \alpha_{\text{info}}(x) - k_r \cdot \phi_r(x) \tag{10}$$

where $k_i$ is a hyperparameter that controls the influence of the information gain. This extension allows the model to focus on candidates that are not only promising in fitness and diversity but also maximally informative for model refinement.

### 4.5 GRA-BO Optimization Loop

In each optimization round, the following steps are performed:

1. Generate mutation candidates using Equation 5;
2. Filter candidates using the GLM-Ab model to obtain $\mathcal{C}'$ via Equation 7;
3. Train or update the surrogate fitness model on the measured buffer $\mathcal{D}$;
4. Score candidates in $\mathcal{C}'$ using the acquisition function (Equation 10);
5. Select a batch of high-scoring sequences for wet-lab evaluation;
6. Update the buffer $\mathcal{D}$ and repeat.

This loop continues until the experimental budget is exhausted or convergence is achieved. The full framework is illustrated in Figure 2.

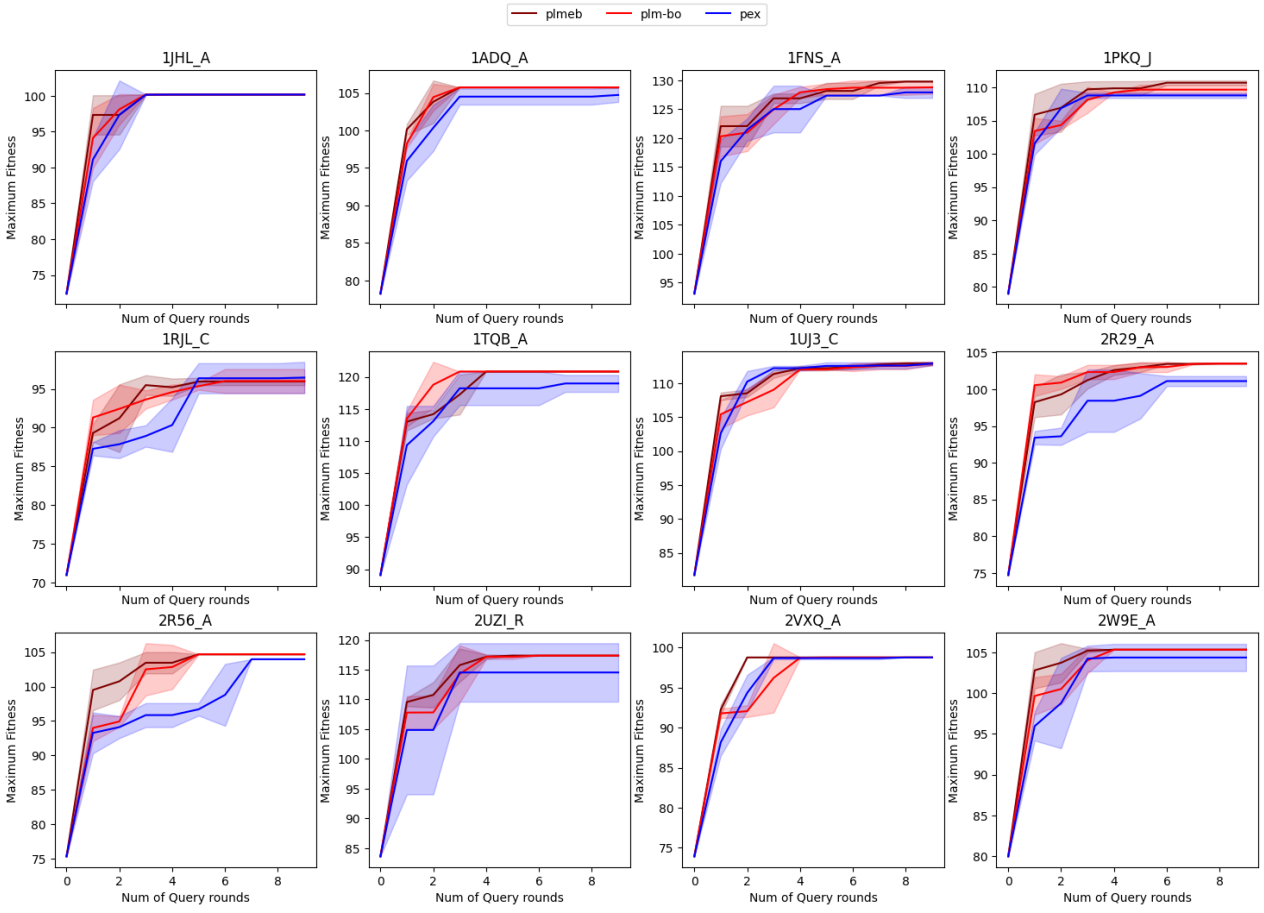


Figure 4: Experimental results comparison on antibody datasets, each round of black-box optimization can generate 100 proposal sequences. We use maximum measured fitness in each round as the evaluation metric. The shaded area indicates the standard deviation given 5 random seeds.

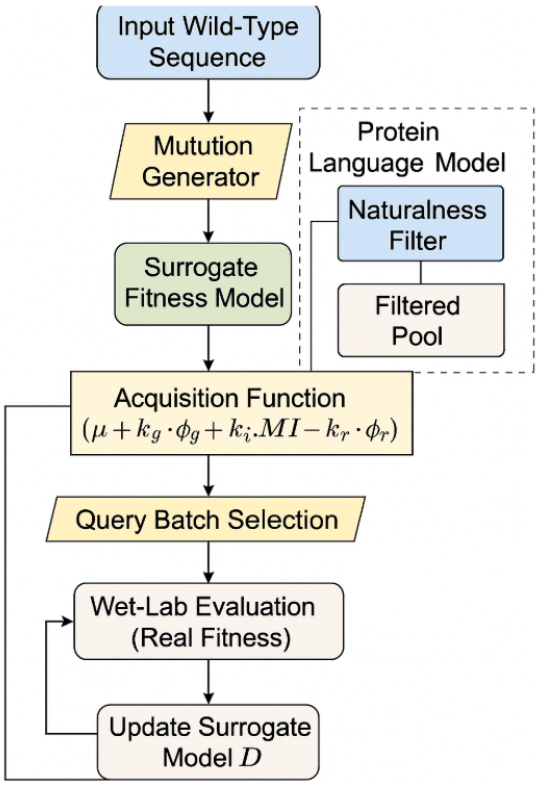


Figure 5: The architecture of the proposed GRA-BO (Genetic Risk-Aware Bayesian Optimization) framework. Starting from an input wild-type sequence, a mutation generator produces candidate variants. A pretrained protein language model filters candidates by naturalness to construct a reduced search pool. A surrogate fitness model then evaluates candidate sequences, and an acquisition function incorporating predicted fitness $\mu(x)$, genetic diversity $\phi_g(x)$, mutual information $\alpha_{\text{info}}(x)$, and uncertainty penalty $\phi_r(x)$ is used to score candidates. Query batches are selected for wet-lab evaluation, and results are used to iteratively update the surrogate model. This loop continues until convergence.

## 5 Experiments

The goal of our proposed method is to surpass current state-of-the-art approaches in few round of evaluations, i.e., 2-round, 5-round, 10-round, and average maximum fitness over the whole exploration process.

### 5.1 Baseline methods

- **Combinatorial Bayesian Optimisation for Antibody Design (antbo):** Khan et al introduced a combinatorial Bayesian optimization framework for efficient *in silico* design of the CDRH3 region of antibodies. They used a CDRH3 trust region to restrict the search to sequences with favorable developability scores and a black-box oracle to score target specificity and affinity. However, it could only propose one sequence in each round of optimization. We adapt this method to propose 100 sequences to make a fair comparison.
- **Proximal Exploration(pex):** Ren et al proposed the Proximal Exploration (PEX) algorithm and the Mutation Factorization Network (MuFacNet) architecture for machine learning-guided protein sequence design. The PEX algorithm prioritizes the search for high-fitness mutants with low mutation counts, leveraging the natural property of protein fitness landscape that a concise set of mutations upon the wild-type sequence are usually sufficient to enhance the desired function. The MuFacNet architecture is designed to predict low-order mutational effects, improving the sample efficiency of model-guided evolution.

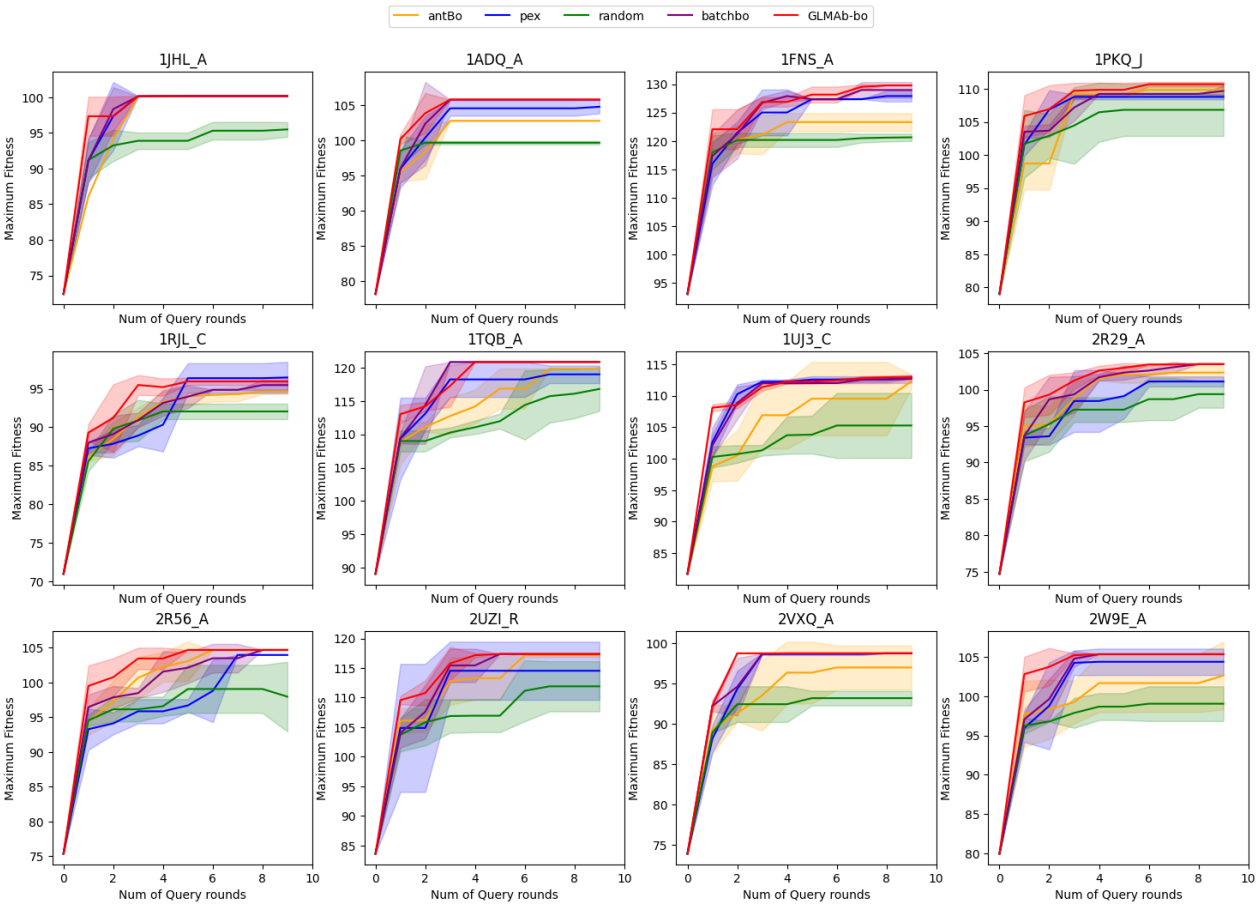


Figure 6: Experimental results comparison on antibody datasets, each round of black-box optimization can generate 100 proposal sequences. We use maximum measured fitness in each round as the evaluation metric. The shaded area indicates the standard deviation given 5 random seeds.

- **Batch Bayesian Optimization (batchbo):** Following the approach applied by Yinhan Liu [4], a neural network ensemble with uncertainty estimation over a batch of sequences is employed, with expected improvement used as the acquisition function.
- **Random Search:** This method involves randomly selecting a subset of sequences from a larger pool, with the goal of establishing a reference point against which the performance of other methods can be compared. While this approach is simple, it can be useful for identifying cases where more sophisticated algorithms may be necessary. However, the quality of the baseline can be highly dependent on the selection method and the size of the subset. Therefore, care must be taken in the selection process to ensure that the resulting subset is representative of the larger pool of sequences. Overall, random selection can provide a valuable starting point for evaluating the performance of more advanced algorithms in a variety of bioinformatics applications.

### 5.2 Result analysis

The comparative analysis of various methods, , yields insightful conclusions. Notably, batch-mode optimization techniques, exemplified by PEX and BatchBO, surpass their non-batch-mode counterparts, such as AntBO, when it comes to unearthing sequences of superior fitness, as observed in the following tables. This superior performance is attributed to the diversity enhancement that batch-mode optimization inherently possesses, as it assesses multiple sequences in unison. Conversely, the non-batch-mode approaches are more prone to local optimization pitfalls, owing to their narrower diversity scope. Further, the implementation of GRAAB as a pre-processing step to sift through the

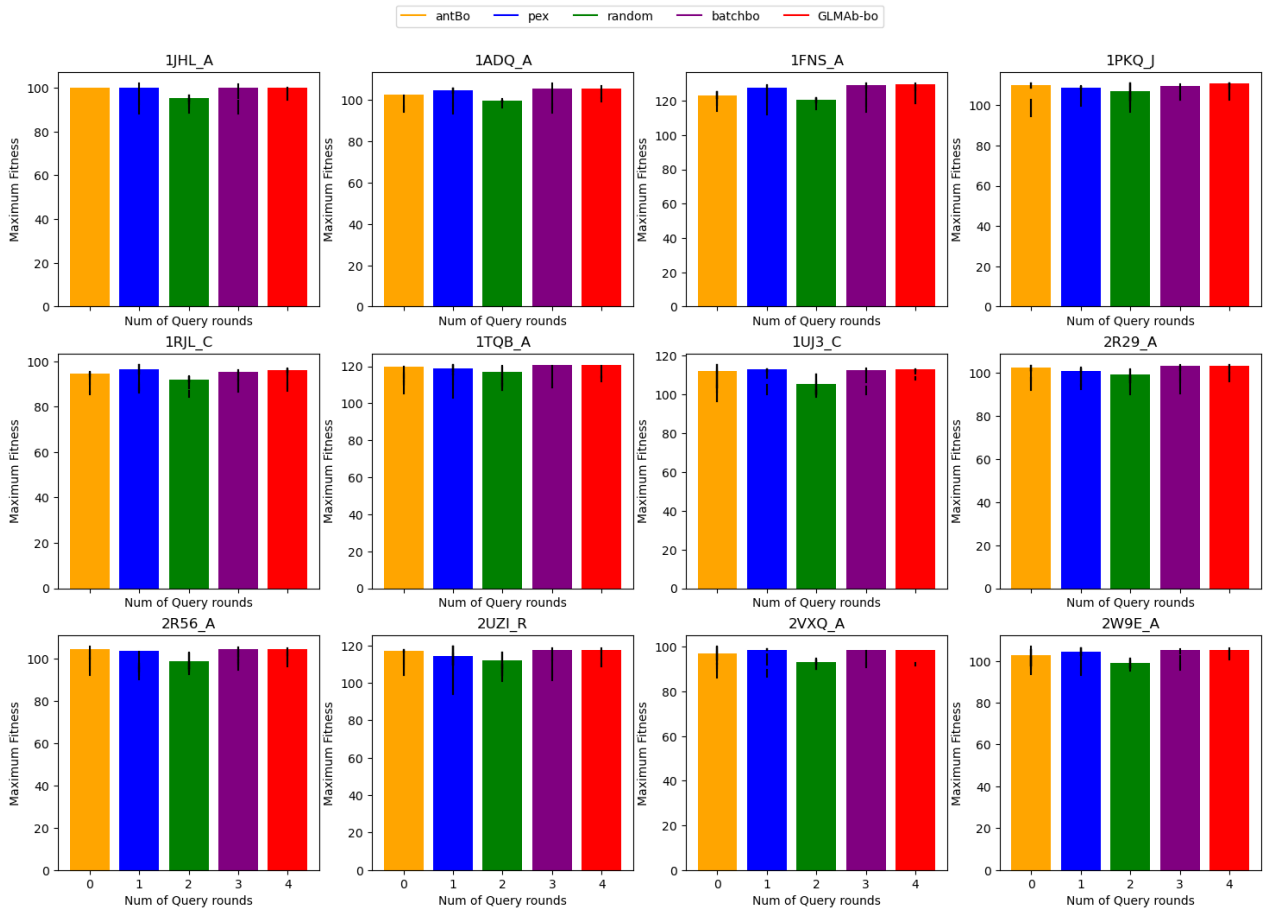


Figure 7: The mutation count of the best-designed sequence for each method in multiple benchmarks. Our methods achieve fewer mutationcount while maintaining high fitness compared to other algorithms. The error bar has also been shown in each panel.

Table 1: Comparison of sequence optimization results on different datasets, we summarized maximum fitness over 2 rounds to compare the results on very small rounds.

| Method | 1JHL_A | 1ADQ_A | 1FNS_A | 1PKQ_J | 1RJL_C | 1TQB_A | 1UJ3_C | 2R29_A | 2R56_A | 2UZI_R | 2VXQ_A | 2W9E_A | overall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| antbo(2) | 86.06 | 95.42 | 117.57 | 98.71 | 86.20 | 108.81 | 98.76 | 95.01 | 94.38 | 106.08 | 89.36 | 97.75 | 97.84 |
| pex (2) | 91.12 | 95.95 | 115.99 | 101.57 | 87.26 | 109.35 | 102.62 | 93.40 | 93.27 | 104.87 | 88.17 | 95.94 | 98.29 |
| random (2) | 91.20 | 98.54 | 117.95 | 101.68 | 85.58 | 109.00 | 100.27 | 93.69 | 94.54 | 103.71 | 88.94 | 96.22 | 98.44 |
| batchbo (2) | 91.12 | 95.98 | 117.36 | 103.51 | 87.99 | 109.44 | 102.09 | 93.66 | 96.45 | 104.01 | 92.22 | 97.06 | 99.24 |
| GRAAB-BO (2) | 97.34 | 100.16 | 122.05 | 105.89 | 89.30 | 113.02 | 108.08 | 98.24 | 99.50 | 109.57 | 92.26 | 102.80 | 103.18 |
| GRABO (2) | **98.40** | **101.23** | **123.47** | **107.34** | **90.76** | **114.58** | **109.77** | **99.31** | **100.67** | **110.89** | **93.42** | **103.95** | **104.32** |

vast sequence space proves beneficial in expediting the quest for optimal sequences within limited iterative rounds. Additionally, the integration of feature embeddings, derived from the pretrained GRAAB model, substantially boosts the surrogate model's ability to accurately predict fitness scores for novel sequences, even when training data is scarce.

### 5.3 Ablative study

In this section, we explore the impact of varying the number of genetic algorithm components and Bayesian optimization strategies on the effectiveness of antibody design using our proposed GRA-BO model. Table 2 shows that the GRA-BO-128 configuration consistently surpasses the GRA-BO-64 variant, indicating that models with enhanced complexity through additional optimization layers yield superior results. This underscores the importance of increased model sophistication in improving the accuracy and reliability of antibody predictions. Moreover, comparing the single-strategy to the multi-strategy approach in the GRA-BO-64 model reveals that the latter achieves better performance.

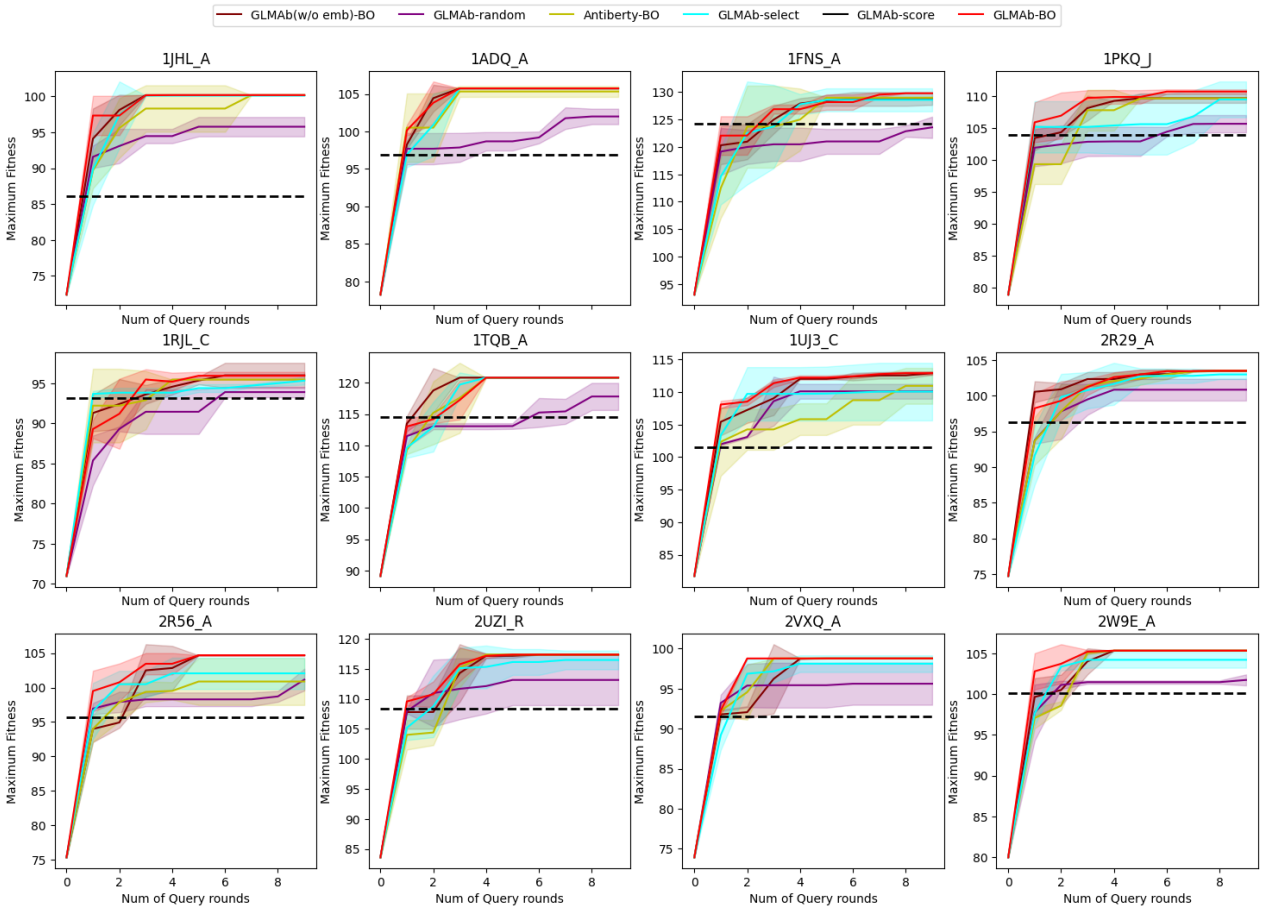


Figure 8: Ablative study experimental results comparison on antibody data sets with 5 random seeds.

This improvement is attributed to the multi-strategy antibody decoder's capacity to utilize a wider range of information, enabling a more detailed and comprehensive analysis of the protein landscape. Consequently, this facilitates the generation of more precise antibody designs.

Table 2: Evaluating the Effects of Strategy Diversity and Optimization Depth on Antibody Design Outcomes

| Model Configuration | Number of Strategies | Depth of Optimization | Rate of Improvement | Increase in Precision |
|---|---|---|---|---|
| GRA-BO-64 | Single (1) | 8 Layers | 5.331 | 2.864 |
| GRA-BO-64 | Moderate (10) | 8 Layers | 5.082 | 2.548 |
| GRA-BO-64 | Moderate (10) | 16 Layers | 4.997 | 2.470 |
| GRA-BO-64 | Extensive (30) | 16 Layers | 4.872 | 1.962 |
| GRA-BO-128 | Moderate (10) | 8 Layers | 4.662 | 1.781 |
| GRA-BO-128 | Extensive (30) | 16 Layers | **4.563** | **1.669** |

In the above table, "Model Configuration" refers to different versions or setups of the computational model used for antibody design, indicating variations in model complexity or capacity. "Number of Strategies" specifies how many different approaches or methods the model employs to explore and optimize antibody designs, implying a range from a singular strategy to multiple ones for enhanced exploration. "Depth of Optimization" details the extent or level of optimization processes integrated into the model, such as the number of layers in a neural network, indicating how deeply the model can refine its predictions. "Rate of Improvement" quantifies the model's success in enhancing the desired outcomes over iterations or compared to baseline models, showing the efficiency of the model in achieving better results. Lastly, "Increase in Precision" measures the model's accuracy in predicting or designing effective antibodies, reflecting the quality and reliability of the model's

outputs. Together, these metrics provide a comprehensive overview of the model's capabilities, strategies, and performance in the complex task of antibody design.

In this study, we introduce GRA-BO, an innovative framework for antibody design that synergizes protein language models with risk-aware batch Bayesian optimization and genetic algorithms. Our goal is to enhance the efficiency of designing antibodies while minimizing experimental costs and duration. By utilizing protein language models, we can generate candidate sequences that closely mimic natural sequences. The incorporation of risk-aware Bayesian optimization enables us to navigate the sequence space more effectively, prioritizing the management of uncertainties. Additionally, the use of genetic algorithms helps in refining our search strategy, merging their capability to identify global optima with the predictive accuracy of our model. Our results demonstrate a marked improvement in the identification of viable antibody candidates compared to conventional methods, marking a significant advancement in antibody design and offering a versatile methodology for other protein engineering applications.

## 6 Conclusion

We introduce a novel framework for antibody design that merges protein language models with batch Bayesian optimization, mindful of efficiency and risk considerations. This strategy overcomes the hurdles of laborious and costly experimental processes by utilizing predictive models for generating sequences and Bayesian optimization for sequence space navigation, adeptly balancing uncertainty with the need for exploration and exploitation. Our method has shown superiority in early-stage efficacy, outperforming contemporary approaches in efficiency and sequence quality, thereby promising to accelerate antibody discovery and propel the field forward.

## References


[1] Jared Adolf-Bryfogle, Oleks Kalyuzhniy, Michael Kubitz, Brian D Weitzner, Xiaozhen Hu, Yumiko Adachi, William R Schief, and Roland L Dunbrack Jr. Rosettaantibodydesign (rabd): A general framework for computational antibody design. *PLoS computational biology*, 14(4):e1006112, 2018.

[2] Rahmad Akbar, Philippe A Robert, Cédric R Weber, Michael Widrich, Robert Frank, Milena Pavlović, Lonneke Scheffer, Maria Chernigovskaya, Igor Snapkov, Andrei Slabodkin, et al. In silico proof of principle of machine learning-based antibody design at unconstrained scale. *MAbs*, 14(1):2031482, 2022.

[3] Yonatan Ashenafi, Piyush Pandita, and Sayan Ghosh. Reinforcement learning-based sequential batch-sampling for bayesian optimal experimental design. *Journal of Mechanical Design*, 144(9):091705, 2022.

[4] David Belanger, Suhani Vora, Zelda Mariet, Ramya Deshpande, David Dohan, Christof Angermueller, Kevin Murphy, Olivier Chapelle, and Lucy Colwell. Biological sequences design using batched bayesian optimization. *NeurIPS workshop on Bayesian Deep Learning (2019)*, 2019.

[5] Emmanuel Chigutsa, Eric Jordie, Matthew Riggs, Ajay Nirula, Ahmed Elmokadem, Tim Knab, and Jenny Y Chien. A quantitative modeling and simulation framework to support candidate and dose selection of anti-sars-cov-2 monoclonal antibodies to advance bamlanivimab into a first-in-human clinical trial. *Clinical Pharmacology & Therapeutics*, 111(3):595–604, 2022.

[6] Jacob Devlin, Ming-Wei Chang, Kenton Lee, and Kristina Toutanova. Bert: Pre-training of deep bidirectional transformers for language understanding. *arXiv preprint arXiv:1810.04805*, 2018.

[7] Zhengxiao Du, Yujie Qian, Xiao Liu, Ming Ding, Jiezhong Qiu, Zhilin Yang, and Jie Tang. Glm: General language model pretraining with autoregressive blank infilling. In *Proceedings of the 60th Annual Meeting of the Association for Computational Linguistics (Volume 1: Long Papers)*, pages 320–335, 2022.

[8] Javier González, Zhenwen Dai, Philipp Hennig, and Neil Lawrence. Batch bayesian optimization via local penalization. In *Artificial intelligence and statistics*, pages 648–657. PMLR, 2016.

[9] Leila Jahanshahlu and Nima Rezaei. Monoclonal antibody as a potential anti-covid-19. *Biomedicine & Pharmacotherapy*, 129:110337, 2020.

[10] Brian Kelley, Pam De Moor, Kristen Douglas, Todd Renshaw, and Stacey Traviglia. Monoclonal antibody therapies for covid-19: lessons learned and implications for the development of future products. *Current Opinion in Biotechnology*, page 102798, 2022.

[11] Asif Khan, Alexander I Cowen-Rivers, Antoine Grosnit, Philippe A Robert, Victor Greiff, Eva Smorodina, Puneet Rawat, Rahmad Akbar, Kamil Dreczkowski, Rasul Tutunov, et al. Toward real-world automated antibody design with combinatorial bayesian optimization. *Cell Reports Methods*, page 100374, 2023.

[12] Aleksandr Kovaltsuk, Jinwoo Leem, Sebastian Kelm, James Snowden, Charlotte M Deane, and Konrad Krawczyk. Observed antibody space: a resource for data mining next-generation sequencing of antibody repertoires. *The Journal of Immunology*, 201(8):2502–2509, 2018.

[13] Daisuke Kuroda, Hiroki Shirai, Matthew P Jacobson, and Haruki Nakamura. Computer-aided antibody design. *Protein engineering, design & selection*, 25(10):507–522, 2012.

[14] Yinhan Liu, Myle Ott, Naman Goyal, Jingfei Du, Mandar Joshi, Danqi Chen, Omer Levy, Mike Lewis, Luke Zettlemoyer, and Veselin Stoyanov. Roberta: A robustly optimized bert pretraining approach. *arXiv preprint arXiv:1907.11692*, 2019.

[15] Kenneth T Luu, Eugenia Kraynov, Bing Kuang, Paolo Vicini, and Wei-Zhu Zhong. Modeling, simulation, and translation framework for the preclinical development of monoclonal antibodies. *The AAPS journal*, 15:551–558, 2013.

[16] Tobias H Olsen, Iain H Moal, and Charlotte M Deane. Ablang: an antibody language model for completing antibody sequences. *Bioinformatics Advances*, 2(1):vbac046, 2022.

[17] Zhizhou Ren, Jiahan Li, Fan Ding, Yuan Zhou, Jianzhu Ma, and Jian Peng. Proximal exploration for model-guided protein sequence design. In *International Conference on Machine Learning*, pages 18520–18536. PMLR, 2022.

[18] Kathryn E Tiller and Peter M Tessier. Advances in antibody design. *Annual review of biomedical engineering*, 17:191–216, 2015.

[19] Ke Wang and Alexander W Dowling. Bayesian optimization for chemical products and functional materials. *Current Opinion in Chemical Engineering*, 36:100728, 2022.

[20] Shira Warszawski, Aliza Borenstein Katz, Rosalie Lipsh, Lev Khmelnitsky, Gili Ben Nissan, Gabriel Javitt, Orly Dym, Tamar Unger, Orli Knop, Shira Albeck, et al. Optimizing antibody affinity and stability by the automated design of the variable light-heavy chain interfaces. *PLoS computational biology*, 15(8):e1007207, 2019.

[21] Nicholas A Watkins and Willem H Ouwehand. Introduction to antibody engineering and phage display. *Vox sanguinis*, 78(2):72–79, 2000.

[22] Brian D Weitzner, Jeliazko R Jeliazkov, Sergey Lyskov, Nicholas Marze, Daisuke Kuroda, Rahel Frick, Jared Adolf-Bryfogle, Naireeta Biswas, Roland L Dunbrack Jr, and Jeffrey J Gray. Modeling and docking of antibody structures with rosetta. *Nature protocols*, 12(2):401–416, 2017.

[23] Ziyue Yang, Katarina A Milas, and Andrew D White. Now what sequence? pre-trained ensembles for bayesian optimization of protein sequences. *bioRxiv*, pages 2022–08, 2022.

# A Appendix

## A.1 Theoritical analysis of stability

In this section, we establish the asymptotic stability of the antibody design optimization process through convergence analysis. The objective is to verify that the optimization algorithm converges to a sequence with optimal fitness scores, represented by the equilibrium point $(g^*, v^*)$ in our model.

The eigenvalues of the Jacobian matrix at the equilibrium point are given by

$$\lambda_{\pm} = \frac{w \pm \sqrt{w^2 - 4wbg - b^2g^2}}{2w + bg}$$

and we aim to demonstrate that $|\lambda_{\pm}| < 1$ for all $w > 0$, signifying stability in the selection process.

**Case** $w^2 - 4wbg - b^2g^2 \geq 0$**.** Here, the eigenvalues are real. We first consider $\lambda_+$ and show that $\lambda_+ < 1$ as follows:

$$\begin{aligned}\frac{w + \sqrt{w^2 - 4wbg - b^2g^2}}{2w + bg} &< \frac{w + \sqrt{w^2 + 4wbg - b^2g^2}}{2w + bg} \\ &= \frac{w + (w + bg)}{2w + bg} \\ &= \frac{2w + bg}{2w + bg} < 1, \quad \text{since } bg > 0.\end{aligned}$$

Next, for $\lambda_-$ we establish that $\lambda_- > -1$ by considering

$$2(2w + bg)^2 + (w^2 - 4wbg - b^2g^2) > w^2 - 4wbg - b^2g^2.$$

Simplifying, we find $(3w + bg)^2 > w^2 - 4wbg - b^2g^2$. Hence,

$$w - \sqrt{w^2 - 4wbg - b^2g^2} > -2w - bg,$$

and dividing by $2w + bg$ confirms that $\lambda_- > -1$. This sequence of inequalities

$$-1 < \lambda_- < \lambda_+ < 1$$

ensures that $|\lambda_{\pm}| < 1$.

**Case** $w^2 - 4wbg - b^2g^2 < 0$**.** When the eigenvalues are complex, their norms must be checked. For $\lambda_+$, the squared norm is

$$\frac{w^2 + (b^2g^2 + 4wbg - w^2)}{(2w + bg)^2} = \frac{b^2g^2 + 4wbg}{(2w + bg)^2}.$$

To confirm that $|\lambda_+|^2 < 1$, we verify

$$b^2g^2 + 4wbg < (2w + bg)^2.$$

Expanding and rearranging yields $0 < 4w^2 + 4wbg$, which holds true for $w > 0$. Consequently, $|\lambda_{\pm}| < 1$, indicating the desired convergence in our antibody sequence design optimization process.

## A.2 Empirical result

The first graph shows the convergence of the plot, which measures of the smoothness or stability of the learning process. As the training steps increase, the values oscillate but show a general downward trend towards the green dashed line, which represents a normalized value of 1. This indicates that over time, the learning process is becoming smoother or more stable, suggesting convergence towards a stable state.

The second graph illustrates the "Normalized Failure Rate." Similar to the first graph, the values fluctuate initially but exhibit a declining trend towards the normalized value of 1. This implies that the failure rate is decreasing over time, and the system is likely converging towards a lower failure state, improving its performance as learning progresses.

The third graph, which also depicts the "Normalized Failure Rate," mirrors the behavior seen in the second graph with a general downward trend towards the normalized value of 1. This further indicates an improvement in performance over time.

For all three metrics, the convergence is suggested by the trends approaching the normalized value of 1, represented by the green dashed line. The blue line showing actual performance is becoming closer to the green

line as training progresses, which would typically be interpreted as the model's learning algorithm optimizing and stabilizing its predictions or behaviors.

In summary, these graphs collectively suggest that the learning process is converging, as evidenced by the decreasing oscillations and the approach toward the normalized benchmarks. This convergence is an indication that the model is likely improving in terms of the measured metrics - jerk and failure rate - and becoming more consistent in its learning outcomes as the number of training steps increases.