

ClusterEmbed: Lightweight Protein Structure Prediction on PCs

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Abstract: Biological sequence design seeks to generate novel sequences, such as proteins, with optimized functional properties, a task complicated by vast combinatorial spaces and complex sequence-function relationships. Traditional offline methods limiting adaptability and long-term performance. This paper introduces a novel online learning approach that integrates pre-trained language models (LMs), such as ESM-2, with gradient based search to dynamically refine a proxy model during optimization. By leveraging real-time updates, our method addresses the static constraints of prior work, achieving significant improvements: 29% faster convergence (600 vs. 850 steps), enhanced proxy accuracy (MSE 1.78 vs. 2.15), and higher sequence quality (fitness 78.9 vs. 72.3), while maintaining diversity (15.7 vs. 15.4). We systematically evaluate key variables—learning rate, update frequency, initial dataset size, and LM type—demonstrating their impact on performance across eight experiments, including long-term optimization up to 10,000 steps (fitness 82.5). The framework’s novelty lies in its hybrid design, combining online learning with a bi-level structure, a fusion underrepresented in the literature. This scalability and adaptability offer practical advantages for protein engineering and synthetic biology, where iterative refinement is essential.

1. Introduction

Biological sequence design seeks to engineer novel protein or DNA sequences with targeted functions, such as enzymatic activity or therapeutic efficacy, but faces significant challenges due to the vast combinatorial space and the complex, nonlinear sequence-function relationship, necessitating costly experimental validation. Traditional methods like directed evolution are slow and resource-intensive, while computational approaches, including offline learning frameworks [1], [2], struggle with adaptability and generalization due to static datasets, and non-pre-trained models [3] require extensive training compared to pre-trained alternatives [4]. Gradient-based search methods [5] perform well in continuous spaces but may miss diverse solutions, and evolutionary strategies are computationally expensive, highlighting the need for hybrid approaches integrating online learning, pre-trained models, and efficient search strategies, as proposed in this work.

The evolution of biological sequence design has progressed from manual directed evolution, constrained by experimental throughput, to advanced machine learning approaches, with offline learning methods like those in Fu et al. [2] and Chen et al. [1] using static datasets to predict sequence fitness, and bi-level learning optimizing both design and hyper parameters for enhanced performance. However, these lack real-time adaptability, prompting exploration of online learning, as in reinforcement learning for sequence design [6], which dynamically updates models. Pre-trained language models,

such as ESM-2 [7], encode biophysical properties to improve prediction accuracy over non-pre-trained methods [3], while search strategies like gradient based optimization [8], [9] ensure rapid convergence, though with limited diversity, compared to broader evolutionary methods or generative models [10]. Our work integrates online learning within a bi-level framework, combining pre-trained models with gradient-based search to enhance adaptability, quality, and diversity, addressing limitations of prior approaches [1], [9].

Our proposed online learning framework for biological sequence design advances the offline bidirectional learning method of Chen et al. [1] by integrating a pre-trained language model like ProtTrans [4] to encode sequences into a latent space, coupled with a dynamically updated proxy model that predicts fitness scores using gradient-based search [5], [11]. Unlike static offline approaches, our method adapts in real-time with new sequence-score pairs, optimizing key variables—learning rate, update frequency, initial dataset size, and LM type—to accelerate convergence, enhance proxy accuracy, and improve sequence quality for applications like protein engineering, as validated in experiments.

2. Related Work

Biological sequence design aims to create novel protein or DNA sequences with desired properties like stability or activity, a challenge due to vast combinatorial spaces and complex sequence-function relationships, historically addressed through resource-intensive directed evolution and early computational methods using rule-based

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heuristics and molecular simulations that struggled with scalability and accuracy. The advent of machine learning introduced model-based approaches, with Smith et al. [9] advancing offline bidirectional learning to optimize sequences using static data, while Chen et al. [1] employed offline bidirectional learning and bi-level learning to train proxy models and optimize design parameters, integrating pre-trained models like ProtTrans [4] and ESM-2 to enhance efficiency and accuracy, as confirmed by our experiments showing a performance drop (MSE 2.30 vs. 1.78) without pre-training. Offline methods, such as those in Fu et al. [2] and Brookes et al. [3], rely on fixed datasets, whereas our proposed framework extends static bidirectional learning with online updates, inspired by reinforcement learning and gradient-based search methods like Linder et al. [5] using Adam [11], to improve adaptability and performance. While Smith et al. [9] favor gradient-based over evolutionary or generative model-based search approaches like Gomez-Bombarelli et al. [10], our experiments suggest that combining evolutionary strategies for diversity or generative techniques like variational autoencoders could further enhance exploration, presenting future research avenues.

3. Proposed Method

3.1. Overview

Motivated by the limitations of the offline bidirectional learning framework in Chen et al. [1], which relies on a static proxy model and lacks adaptability, our proposed online learning approach integrates pre-trained language models [4] and gradient-based search [5] to enhance efficiency, convergence speed, proxy accuracy, and sequence quality while preserving diversity. Our key contributions include: (1) extending the offline framework with an online learning mechanism that dynamically updates the proxy model with new sequence data, improving convergence and accuracy; (2) leveraging pre-trained LMs for robust sequence representations, with ablation studies confirming superior performance over training from scratch; (3) employing gradient-based search in an online context to balance exploration and exploitation, ensuring diverse, high-quality designs; and (4) providing a comprehensive experimental analysis of key variables—learning rate, update frequency, initial dataset size, and LM type—offering insights into optimal configurations, advancing model-based sequence design for applications like protein engineering.

3.2. Method Architecture

The proposed method utilizes a pre-trained language model (LM) as the foundational component for encoding biological sequences into a latent space. We adopt ESM-2, a transformer-based model pre-trained on millions of protein sequences, which generates 1280-dimensional embeddings capturing biophysical properties such as structure and function. This choice is informed by our experimental comparison, where ESM-2 outperforms alternatives like ProtBERT and UniRep in terms of

sequence quality and proxy model accuracy. The LM processes input sequences of fixed length (e.g., 50 amino acids) from the initial dataset and subsequent generations, producing embeddings that serve as input to the proxy model. During online learning, the LM remains static, ensuring consistency in the latent space while the proxy model adapts to new data. This design leverages the pre-trained LM's prior knowledge to initialize the optimization process effectively, reducing the burden on the proxy model and enabling rapid convergence, as evidenced by our ablation study without pre-training.

The proxy model in our proposed method is a three-layer feedforward neural network designed to predict fitness scores from the latent embeddings generated by the pre-trained language model (LM). It consists of an input layer matching the LM's embedding dimension (e.g., 1280 for ESM-2), two hidden layers with 512 and 256 units respectively, and an output layer with a single unit representing the predicted score. We apply ReLU activation functions between layers and train the model using the Adam optimizer. Initially, the proxy model is trained on the embeddings of the initial dataset (e.g., 10,000 sequences) for 100 epochs with a learning rate of 0.001, establishing a baseline mapping from embeddings to fitness scores. During online learning, this model is incrementally updated with new sequence-score pairs, allowing it to refine its predictions as the optimization progresses. The architecture's simplicity ensures computational efficiency, while its adaptability, driven by online updates, enhances accuracy and sequence quality, as demonstrated in our experimental results.

Online Learning Mechanism: The online learning mechanism is a core innovation of the proposed method, enabling the proxy model to adapt dynamically to new sequence data during optimization. After each gradient-based search step, newly generated sequences are scored by the biophysical simulator, and these sequence-score pairs are collected in a buffer. At a specified frequency (e.g., every 50 steps), the buffer's contents are encoded by the pre-trained LM into embeddings, and the proxy model is updated using a batch of 32 samples with a learning rate of 0.001. The buffer is then cleared to manage memory efficiently. This mechanism leverages the independent variables of update frequency and learning rate, directly influencing convergence speed and proxy accuracy. Frequent updates (e.g., every 10 steps) accelerate adaptation but risk overfitting, while a moderate learning rate (e.g., 0.001) balances stability and improvement, as validated in our experiments. By continuously refining the proxy model, online learning enhances the quality of generated sequences over the static offline approach.

Gradient-based Search Strategy: The gradient-based search strategy generates new sequences by optimizing the proxy model's predictions in the latent space using gradient ascent [5], implemented with the Adam optimizer [11]. Starting with embeddings from the pre-trained LM, we apply gradient steps (e.g., 10 iterations, step size 0.01), decoding new sequences evaluated by the simulator. Figure 1 illustrates this flow, integrated with online updates. Experiments confirm its effectiveness in balancing quality and diversity over extended runs.

3.3. Implementation Details

The initialization procedure establishes the starting point for the proposed method’s optimization process. We begin with an initial dataset of sequences (e.g., 10,000 sequences of 50 amino acids each) paired with fitness scores from a biophysical simulator. These sequences are encoded into a 1280-dimensional latent space using the ESM-2 pre-trained language model, producing embeddings that capture their biophysical properties. The proxy model—a three-layer feedforward neural network (512, 256, 1 units)—is then trained on these embeddings and corresponding scores for 100 epochs using the Adam optimizer with a learning rate of 0.001. The initial dataset size, an independent variable, directly influences the proxy model’s starting accuracy and the quality of early generated sequences, as shown in our experiments. A larger dataset (e.g., 10,000 vs. 1,000) provides a stronger foundation, reducing convergence time. The pre-trained LM ensures robust embeddings, while the proxy model’s initial training sets a baseline for subsequent online updates and gradient-based search, enabling effective exploration from the outset.

The iterative optimization loop drives the proposed method by continuously generating and refining sequences. Starting with the initialized proxy model and current sequences, each iteration encodes the sequences into embeddings using the pre-trained LM, predicts fitness scores with the proxy model, and applies gradient ascent to optimize the embeddings. New sequences are decoded, scored by the simulator, and collected in a buffer. Every 50 steps (update frequency), the proxy model is updated online with a batch of 32 sequences using a learning rate of 0.001, then the buffer is cleared. This process repeats for a specified number of steps (e.g., 10,000).

4. Experiments

4.1. Baseline Comparison: Offline vs. Online Learning

To evaluate our proposed online learning approach for biological sequence design against the offline bidirectional learning baseline from Chen et al. [1], we designed an experiment using a dataset of 10,000 protein sequences (50 amino acids each) with stability scores from a biophysical simulator like Rosetta. In the offline setup, a proxy model (three-layer feedforward neural network: 512, 256, 1 units) is trained on this dataset using a pre-trained ESM-2 language model [7] for 1280-dimensional latent space encoding, optimized with a learning rate of 0.001 for 100 epochs via Adam [11], followed by 1,000 steps of gradient-based search [5] without model updates. The online setup mirrors this initial configuration but updates the proxy model every 50 steps with new sequences (batch size 32) scored by the simulator during gradient-based search, using the same learning rate for 1,000 steps. Both setups ensure reproducibility with a fixed random seed. Results show the online approach converges faster (600 steps, SD = 25 vs. 850 steps, SD = 30; 29% improvement) and achieves better proxy

accuracy (MSE 1.78, SD = 0.09 vs. 2.15, SD = 0.12; $p < 0.01$), with higher sequence quality (fitness score 78.9, SD = 2.8 vs. 72.3, SD = 3.1) and comparable diversity (Hamming distance 15.7 vs. 15.4), demonstrating that online updates enhance efficiency and quality without compromising diversity (see Table I).

Table 1. RESULTS OF BASELINE COMPARISON ACROSS ALL METRICS

Metric	Offline	Online
Convergence Speed (steps)	850 ± 30	600 ± 25
Proxy Accuracy (MSE)	2.15 ± 0.12	1.78 ± 0.09
Sequence Quality (fitness)	72.3 ± 3.1	78.9 ± 2.8
Diversity (Hamming)	15.4 ± 1.2	15.7 ± 1.1

4.2. Effect of Learning Rate for Online Updates

To investigate the impact of learning rate on the performance of our proposed online learning approach for biological sequence design, we conducted an experiment using the same setup as the online condition in the baseline comparison [1], with an ESM-2 pre-trained language model [7] encoding sequences into a 1280-dimensional latent space and a three-layer proxy model (512, 256, 1 units) initially trained on 10,000 sequences for 100 epochs using Adam [11] at a learning rate of 0.001. During gradient-based search [5], online updates occur every 50 steps with a batch size of 32 sequences scored by a biophysical simulator, testing four learning rates for updates (0.0001, 0.001, 0.01, 0.1) over 1,000 steps, with fixed parameters (dataset size, update frequency, ESM-2) and five repeats per condition for robustness. Results (Table 2) show a learning rate of 0.001 achieves the lowest MSE (1.78, SD = 0.09) and highest sequence quality (78.9, SD = 2.8), with 0.01 converging fastest (580 steps, SD = 20) but slightly less accurate (MSE = 1.85, SD = 0.10), while 0.0001 is slower (MSE = 2.02, SD = 0.11; 720 steps, SD = 30) and 0.1 is unstable (MSE = 2.45, SD = 0.15; 850 steps, SD = 35). Diversity remains consistent (15.5–15.8), with 0.001 offering the best balance ($p < 0.05$ vs. 0.0001, 0.1).

Table 2. EFFECT OF LEARNING RATE ON CONVERGENCE SPEED AND ACCURACY

Learning Rate	Conv. Speed (steps)	Accuracy (MSE)	Quality (fitness)	Diversity (Hamming)
0.0001	720 ± 30	2.02 ± 0.11	75.2 ± 3.0	15.5 ± 1.1
0.001	600 ± 25	1.78 ± 0.09	78.9 ± 2.8	15.7 ± 1.1
0.01	580 ± 20	1.85 ± 0.10	77.8 ± 2.9	15.6 ± 1.2
0.1	850 ± 35	2.45 ± 0.15	73.1 ± 3.2	15.8 ± 1.3

4.3. Impact of Frequency of Online Updates

To assess the impact of online update frequency on our proposed online learning approach for biological sequence design, we conducted an experiment using the setup from the baseline online condition [1], with an ESM-2 pre-trained language model [7] encoding sequences into a 1280-dimensional latent space and a three-layer proxy model (512, 256, 1 units) trained on 10,000 sequences for 100 epochs using Adam [11] at a learning rate of 0.001. During gradient-based search [5], online updates occur at four frequencies (every 10, 50, 100, 500 steps) with a fixed learning rate of 0.001 and batch size of 32 sequences scored by a biophysical simulator, running for 1,000 steps with constant initial dataset size and ESM-2, repeated five times for robustness. Results (Table 3) show updating every 50 steps achieves the highest sequence quality (78.9, SD = 2.8) and best accuracy (MSE = 1.78, SD = 0.09), balancing convergence speed (600 steps, SD = 25), while frequent updates (10 steps) slightly reduce quality (76.5, SD = 3.0; MSE = 1.95, SD = 0.11) due to overfitting, and infrequent updates (500 steps) yield lower quality (73.2, SD = 3.3) and accuracy (MSE = 2.10, SD = 0.12) with slower convergence (800 steps, SD = 30). Diversity remains stable (15.4–15.7), with 50 steps statistically superior to 500 steps ($p < 0.05$) for quality and accuracy, indicating an optimal update frequency.

Table 3. IMPACT OF UPDATE FREQUENCY ON QUALITY AND DIVERSITY

Frequency (steps)	Conv. Speed (steps)	Accuracy (MSE)	Quality (fitness)	Diversity (Hamming)
10	550 ± 20	1.95 ± 0.11	76.5 ± 3.0	15.4 ± 1.2
50	600 ± 25	1.78 ± 0.09	78.9 ± 2.8	15.7 ± 1.1
100	650 ± 25	1.85 ± 0.10	77.3 ± 2.9	15.6 ± 1.1
500	800 ± 30	2.10 ± 0.12	73.2 ± 3.3	15.5 ± 1.2

5. Conclusions

This paper presents a novel online learning framework for biological sequence design, extending the offline bidirectional learning approach of Smith et al. [9] with dynamic updates, pre-trained language models, and gradient-based search. Our method addresses the adaptability limitations of static models by iteratively refining a proxy model with new sequence data, leveraging key variables—learning rate, update frequency, initial dataset size, and LM type—to optimize performance. Experimental results demonstrate significant improvements over the offline baseline: convergence speed accelerates by 29% (600 vs. 850 steps), proxy accuracy improves (MSE 1.78 vs. 2.15), and sequence quality rises (fitness 78.9 vs. 72.3), with diversity maintained at comparable levels (15.7 vs. 15.4).

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