Fine-tuning of Conditional Transformers Improves the Generation of Functionally Characterized Proteins

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Abstract: Conditional transformers improve the generative capabilities of large language models (LLMs) by processing specific control tags able to drive the generation of texts characterized by specific features. Recently, a similar approach has been applied to the generation of functionally characterized proteins by adding specific tags to the protein sequence to qualify their functions (e.g., Gene Ontology terms) or other characteristics (e.g., their family or the species which they belong to). In this work, we show that fine tuning conditional transformers, pre-trained on large corpora of proteins, on specific protein families can significantly enhance the prediction accuracy of the pre-trained models and can also generate new potentially functional proteins that could enlarge the protein space explored by the natural evolution. We obtained encouraging results on the phage lysozyme family of proteins, achieving statistically significant better prediction results than the original pre-trained model. The comparative analysis of the primary and tertiary structure of the synthetic proteins generated by our model with the natural ones shows that the resulting fine-tuned model is able to generate biologically plausible proteins. Our results confirm and suggest that fine-tuned conditional transformers can be applied to other functionally characterized proteins for possible industrial and pharmacological applications.

1 INTRODUCTION

Recent years witnessed remarkable developments in natural language models, greatly enhancing capabilities in natural language processing (NLP) and machine translation. Particularly noteworthy are generative models, which excel in creating text that is both structurally and semantically coherent (Bommasani et al., 2021). A key milestone in this field was the introduction of the transformer architecture (Vaswani et al., 2017), which constitutes a foundational element for many advanced language models, including the widely recognized BERT (Devlin et al., 2019) and GPT (Brown et al., 2020; OpenAI, 2023) models.

One of the key advantages of transformers in NLP is their ability to learn representations that capture both syntactic (grammatical arrangement of words) and semantic (meaning of words) information. The self-attention mechanism enables the model to weigh the importance of different words or tokens in the input sequence, considering their contextual relationships. This attention-based approach has shown remarkable performance in tasks such as machine translation, sentiment analysis, text summarization, and question-answering (Wolf et al., 2020). Transformers models are pre-trained on vast amounts of textual

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data, enabling them to learn rich linguistic patterns and structures using self-supervised learning techniques. The pre-training phase involves predicting masked tokens or next tokens in a sequence, enabling the model to acquire knowledge about syntax, grammar, and semantic relationships.

The scope of large language models (LLMs) goes well beyond linguistic applications, as exemplified by their use in protein modeling, indicating their expansive potential and transformative role in scientific inquiry (Valentini et al., 2023). Indeed, both text and proteins rely on a vocabulary. In text, words serve as the basic units of meaning, forming an alphabet of sorts. Similarly, proteins are encoded by amino acids, which can be viewed as an alphabet of building blocks to be combined to create diverse protein sequences. In text, phrases are sequences of words, whereas, in the realm of molecules, proteins are sequences of amino acids. Just as different phrases convey different ideas or sentiments, different protein sequences result in unique molecular structures. The relationship between meaning and structure can be observed in both text and proteins. In text, the meaning of a sentence arises from the arrangement and interaction of words. Similarly, in proteins, patterns, domains, and more in general the structure of the molecule determines its function and meaning within a biological context. The folding and arrangement of amino acids in a protein sequence contribute to its structural properties, which in turn govern its functional characteristics.

Several protein language models have been recently proposed to model and generate proteins, by training transformers on large corpora of proteins from public databases (Ferruz and Höcker, 2022). Several works showed that fine tuning pre-trained language models, by using relatively small well-focused data, enhance their predictive and generative power (Devlin et al., 2019). Moreover, conditional transformer architectures, enabling the use of keywords to direct the generation of specific types of text (Keskar et al., 2019), recently paved the way to similar models for the generation of functionally characterized protein sequences (Madani et al., 2023).

In this work, we show that by combining a pre-trained conditional transformer and transfer learning we can fine tune a model to boost the generation of specific functionally characterized protein families. This is of paramount importance for the automatic generation of proteins for specific applications in pharmacology and precision medicine (Moor et al., 2023).

2 PROTEIN GENERATIVE MODELS

During the last decade, advancements in protein generative models revolutionized protein engineering (Ferruz et al., 2022a). By leveraging machine learning techniques, these models offer new opportunities to design proteins with desired properties, overcoming the limitations of traditional methods (Valentini et al., 2023).

In recent years, deep neural networks, specifically generative architectures, have emerged as promising tools for protein science and engineering (Shin et al., 2021; Jumper et al., 2021; Ferruz et al., 2022b; Das et al., 2021; Kilinc et al., 2023). These models, such as attention-based models trained on protein sequences, have shown remarkable success in classification and generation tasks relevant to artificial intelligence-driven protein design. They have the potential to learn complex representations and effectively utilize vast amounts of unaligned protein sequence data from public databases such as Pfam and UniProt (The UniProt Consortium, 2022).

Protein language models (PLMs) offer a robust framework for learning from extensive collections of amino acid sequences within various protein families, facilitating the generation of diverse and realistic protein sequences. These language models leverage the power of natural language processing techniques to comprehend and extract meaningful patterns from vast sequences of data. ProGen (Madani et al., 2023), ProteinGPT2 (Ferruz et al., 2022b), and IgLM (Shuai et al., 2022) are all PLMs decoder-only models developed in the last few years. It is noteworthy that both ProGen and IgLM generate sequences conditioned on prefix(es) at the start of the sentences, providing additional constraints during the generation process. IgLM is specifically trained for unpaired antibody sequence modeling.

By employing PLMs, researchers can generate protein sequences that exhibit well-folded structures, despite their divergence in sequence space. This capability is achieved by capturing relationships and dependencies within the sequence data. To tailor PLMs for specific protein families of interest, a fine-tuning approach can be adopted, where the models are trained on a subset of relevant proteins. This targeted training allows the PLMs to learn the specific characteristics associated with the desired protein family, enhancing the quality and specificity of the generated sequences.

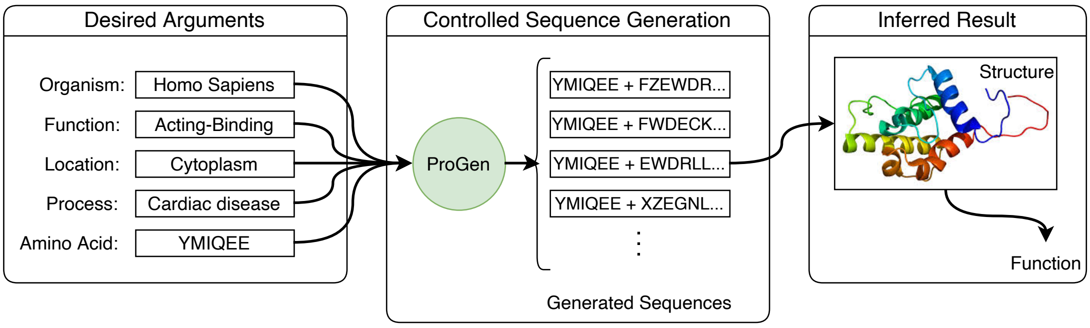


Figure 1: An example of ProGen protein generation using multiple control sequences and an amino acid prefix (in desired argument box). The generation process can create multiple output sequences with the same Input (controlled sequence generation box). For each generated sequence, it is possible to compute its structure with tools like AlphaFold-2.

3 THE PROGEN MODEL

ProGen (Madani et al., 2023) uses a LLM to generate novel protein sequences that are not present in any database; specifically, it implements and uses the conditional transformer architecture (CTRL) proposed in (Keskar et al., 2019) that relies on the use of keywords to guide the generation of texts. Instead of training the whole model from scratch, the weights in ProGen were initialized to those of a trained CTRL model. Examples of ProGen protein generations are shown in Figure 1.

Madani et al. proposed protein engineering as a self-supervised sequence generation problem. Using 280 million protein sequences, the authors trained ProGen with 1.2 billion parameters.

ProGen processes not only the sequence of amino acids $x = (x_1, \ldots, x_n)$, where each x_i represents an amino acid, but also includes functional tags during training. More precisely, its input prefixes one or more functional tags t to the sequence x of amino acids. The functional tags represent a protein family or a Gene Ontology term, or whatever property of the protein. The objective of conditional protein language modeling is to acquire knowledge about the probability distribution $p(x)$ given a functional tag t. Given that (t,x) represents a sequence of amino acids prefixed by a functional tag, using an approach similar to (Bengio et al., 2000), it is reasonable to factorize the conditional probability $p(x|t)$ using the chain rule of probability:

$$p(x|t) = \prod_{i=1}^{n} p(x_i|x_{<i},t) \quad , \tag{1}$$

in which $p(x_i|x_{<i},t)$ denotes the conditional probability of x_i given all the preceding elements $x_1, \ldots, x_{i-1}$ and the functional tag t.

This decomposes protein language modeling into next-amino-acid prediction. Hence we can train a deep neural network with parameters θ to minimize the negative log-likelihood over a dataset of $|D|$ sequences $D = \{(t,x)^{k=1}, \ldots, (t,x)^{k=|D|}\}$:

$$\mathcal{L}(D) = -\sum_{k=1}^{|D|} \sum_{i=1}^{|x^k|} \log p_\theta(x_i^k|x_{<i}^k, t^k) \quad , \tag{2}$$

The functional tag provides a point of control over the generation process, and it constraints the protein generation toward proteins having a specific property t^k.

Since protein language models acquire knowledge about the conditional probability distribution $p_\theta(x_i|x_{<i},t)$, it is possible to generate a new sequence $\tilde{x}$ of length m that is obtained by sequentially sampling its constituent symbols: $p_\theta(x_0|t)$, $p_\theta(x_1|\tilde{x}_0,t)$, $\ldots$, $p_\theta(x_m|\tilde{x}_{<m},t)$.

The overall architecture of ProGen is borrowed from CTRL. The model has internal embedding dimension $d = 1028$, inner dimension $f = 512$, 36 layers, and 8 heads per layer. Dropout with probability 0.1 follows the residual connections in each layer. Token embeddings are tied with the embeddings of the final output layer.

4 FINE-TUNING OF THE PRE-TRAINED PROGEN MODEL

The objective is to harness the knowledge ProGen has acquired from millions of sequences, and transfer its "learned knowledge" (represented by the model weights) to the task of generating a specific family of proteins. We selected the family of phage lysozymes, i.e., enzymes that can act as anti-microbials through the hydrolysis of the peptidoglycan component of the cell wall.

To specialize the model on phage lysozyme data we downloaded 19473 sequences from the Pfam API (hosted by InterPro) (Mistry et al., 2020). We randomly split the data in a test set (2000 sequences, about 10% of the total data), and in a training set (17473 sequences, roughly 90% of the data) for fine-tuning the model. The average sequence length of the phage lysozyme dataset is 201.6 amino acids.

During the learning process, since proteins are invariant to the temporal notion of sequence generation, each amino acid sequence has a certain probability of being flipped, allowing the model to receive both the direct sequence and its reverse. Additionally, the input sequence for fine-tuning may sometimes (with a certain probability) lose its keyword that represents the phage family, to allow for generation also without an initial keyword. In total, a training sequence can be transformed into four distinct training inputs: the sequence with its family keyword, its reverse with the keyword, the sequence without the family keyword, and its reverse without the keyword.

The fine-tuning process involved different parameters, described below.

Flip probability. A feature was introduced to randomly flip the amino acid sequence with a 0.2 probability. In other words, there's a 20% chance that the sequence will be read from the end to the beginning, acting as a data augmentation technique.

Omitted keyword probability. We introduced a probability with which the phage family keyword can be dropped from the sequence. Specifically, the overall probability of dropping the keyword while using different transformation objects for data loading stands at 0.13, similarly to the implementation of Madani et al.

Maximum sequence length for training. The sequence length was limited to 512 tokens, including the keywords. This is because, during the initial training phase, the model was not trained to generate inputs longer than 512 tokens, due to inherent limitations in the model size and architecture.

Adam optimizer. The optimization algorithm that computes adaptive learning rates for each parameter used is Adam (Adaptive Moment Estimation) (Kingma and Ba, 2014).

Learning rate. The learning rate determines the step size at each iteration while moving towards a minimum of the loss function. In our experiments, we tested two distinct learning rates: 0.0001 and 0.001.

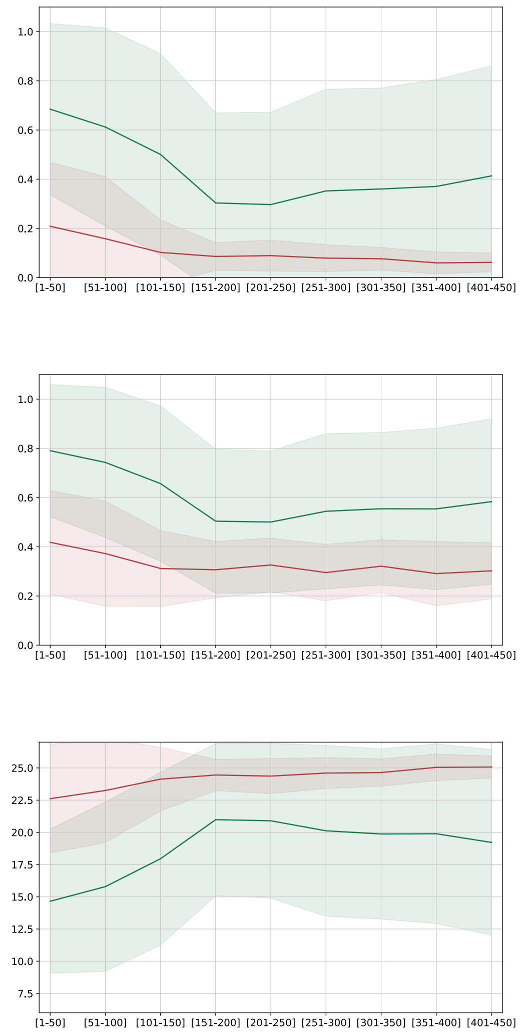


Figure 2: Accuracy (top), soft accuracy (middle) and perplexity (bottom) comparison of the fine-tuned and general ProGen models on the phage lysozyme family (PF00959). Results are computed on different ranges of 50 amino acids with standard deviation represented by shaded regions. Fine-tuned and general model results are in green and red, respectively.

Batch size and epochs. The batch size, set at 2, represents the number of training examples utilized in one iteration. A smaller batch size often provides a regularizing effect and lower generalization error. The training process was conducted over 4 epochs, meaning the entire dataset was passed forward and backward through the model four times.

Gradient norm clipping. The gradients were clipped with a norm of 0.25, to avoid the "exploding gradient" issue that afflicts deep neural networks.

Warmup iteration. This parameter, set at 100 in our experiments, defines the number of iterations over which the learning rate will be gradually increased.

The code for the experiments is available from `https://github.com/AnacletoLAB/ProGen`. We used PyTorch libraries and data from InterPro and UniProt. For training and testing the models we used two multi-processor servers equipped with 128 GB of RAM and NVIDIA A100 GPU accelerators.

4.1 Testing the Fine-tuned Model on Phage Lysozymes

In this section, we evaluate the performance of the ProGen model that has been fine-tuned for the phage lysozyme family (PF00959). Classification here involves predicting the next amino acid in a sequence based on the current sequence input.

Figure 2 shows that the fine-tuned model significantly outperforms the general model (Wilcoxon rank-sum test $\alpha = 0.01$) on the test set. Results are averaged across the 2000 phage lysozyme proteins of the test set, with the top-*k* parameter fixed to 1 (i.e., we predicted the amino acid with the highest predicted probability), repetition penalty set to 0 and keywords usage. Data are tested up to input length 512.

4.2 Generating New Functionally Characterized Proteins

In this section, we show the results of the application of our fine-tuned model to the generation of synthetic protein sequences with functional characteristics that closely resemble those of natural proteins.

We considered two generation processes: a) generation from scratch using only the input keyword; b) prefix generation, i.e., generation from an initial sequence of amino acids. For this second generation process we selected three phage lysozymes involved in the degradation of peptidoglycans and in the programmed host cell lysis: RddD (UniProt entry P78285), P1 (UniProt entry Q37875), and T4 (UniProt entry P00720). We started the generation from the 25, 50, and 75% amino acid position for each protein.

To assess the quality of the generated proteins we compared:

1. the primary structure (sequence) of the generated proteins versus the natural ones of the family of the phage lysozymes;
2. the phylogenetic relationships of generated sequences versus the natural ones;
3. the tertiary (three-dimensional) structure of the generated sequences versus the natural ones.

4.2.1 Comparison by Sequence Alignment

We initially compared the sequences newly generated by our fine-tuned model with those of the phage lysozyme family. More precisely, we searched for similar natural proteins by using NCBI BLAST+ integrated into Galaxy to estimate similarity scores (Cock et al., 2015). BLAST searches were conducted versus the whole phage lysozyme dataset.

Figure 3 shows that most of the sequences generated from scratch or starting from a prefix sequence have a relevant sequence similarity with respect to the natural proteins belonging to the phage lysozyme family. Nevertheless, several newly generated sequences show only a partial similarity, showing that our model can explore protein spaces unexplored by the natural evolution.

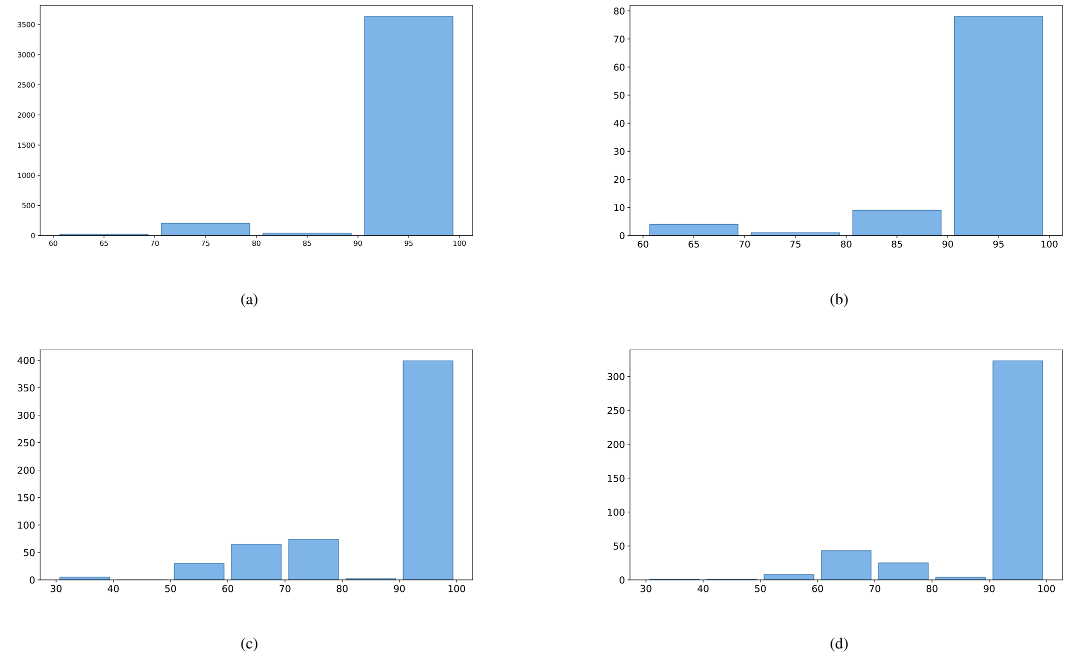
4.2.2 Phylogenetic Tree Construction

We initially used CD-HIT (Fu et al., 2012) to cluster protein sequences generated by our model, in order to reduce redundancy in the generated sequence data (several generated sequences are very similar, data not shown) and to optimize the subsequent multiple alignment analysis and phylogenetic tree construction. To this end we employed CLUSTAL-W (Larkin et al., 2007) for the multiple alignment of the centroid sequences found by CD-HIT, and FAST-TREE (Price et al., 2009), a maximum likelihood algorithm designed to construct phylogenetic trees using a multiple alignment of the sequences. This analysis allows us to discern the evolutionary relationships within the group of representative sequences generated by our fine-tuned model. Figure 4 shows the evolutionary relationships found by FAST-TREE between Q37875 and the new proteins generated by our model starting from half of protein Q37875 itself. Only the newly generated sequences considered representative by CD-HIT are shown.

4.2.3 Tertiary Structure Comparison

We finally conducted a comparison of the tertiary structure of the generated proteins versus those of the family of natural phage lysozymes. To this end, we compared the three-dimensional structure of the newly generated proteins (obtained by AlphaFold-2 (Jumper et al., 2021)) with that of the reference lysozyme (obtained from the X-ray crystallography protein folding of the swissProt database).

We conducted a comparative analysis by aligning several of the AlphaFold-2 generated protein struc-



(a)

(b)

(c)

(d)

Figure 3: Evaluation of the sequence similarity between proteins generated by the fine-tuned model and proteins from the phage lysozyme family. Histograms display the distribution of BLAST Max-ID for data generated from the fine-tuned model versus the phage lysozyme family. (a) Generation from scratch using only the lysozyme keyword as input. (b) Generation from half of the P78285 protein. (c) Generation from half of the P00720 protein. (d) Generation from half of the Q37875 protein.

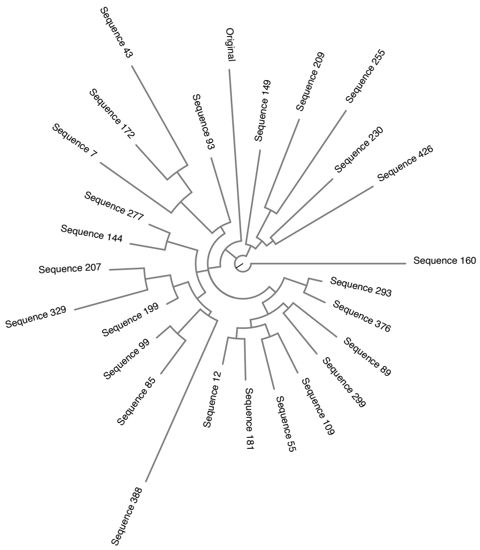


Figure 4: Circular phylogenetic tree representing the evolutionary relationships among protein sequences generated by our model from Q37875 (the original sequence is the root). In the tree the 27 sequences selected as representative by CD-HIT are shown. Each branch of the tree corresponds to a sequence, with the length of the branch indicating the degree of divergence from the ancestral sequence. The tree provides a graphical representation of the sequence similarity and evolutionary distance between the sequences.

tures, represented as PDB files, with the corresponding structures of the original molecules available in the UniProt database. To achieve this, we employed PyMOL (Schrödinger, LLC, 2023), a molecular visualization and analysis tool used in structural biology. PyMOL supports the alignment of protein structures, enabling a detailed examination of the similarities and differences between the predicted structures and their experimentally determined counterparts.

More precisely, after being folded, the structures were compared and aligned with the original natural protein structures from which they were generated using PyMOL. In addition to these alignments, we also calculated the alignment with the tertiary structure of the natural phage lysozyme with the highest match (if the structure was available in UniProt and if a match was found). This step was performed for the sequences 144 of Q37875, and 59 and 78 of P78285 generated by our model. The resulting Root Mean Square Deviation (RMSD) values from these processes are listed in Table 1, which quantifies the alignment quality. The lower the RMSD value, the closer the generated structure is to the compared protein. Figure 5 visualizes the 3D alignment of sequence 144, which was generated from half of the Q37875 protein, with the three-dimensional structure of Q37875

Table 1: RMSD values from PyMOL three-dimensional alignments, using selected sequences generated by the fine-tuned ProGen and folded using AlphaFold-2. The alignments compare these sequences with the structures of the natural proteins obtained from X-ray crystallography or AlphaFold-2 predictions. The natural proteins used are: a) proteins used as prefixes in the model, and b) Max-ID matches found by BLAST (identified by the lines marked with the symbol "†"). The "Protein" column lists the protein identifiers, "Original pdb ID" indicates the file identifier in UniProt of the 3D structure among with the method used to obtain the 3D structure inside the brackets ("X-ray" stands for X-ray crystallography or "AF" for AlphaFold-2 predictions), "Generated ID" refers to the sequence number generated for the related batch with the fine-tuned model, and "RMSD (Atoms)" contains the RMSD value along with the number of atoms used for the alignment.

Protein	Original pdb ID	Generated ID	RMSD (atoms)
P78285	4ZPU (X-ray)	59	20.545 (2043 atoms)
P78285†	A0A854AIC3 (AF)	59	0.642 (812 atoms)
P78285	4ZPU (X-ray)	78	11.356 (1491 atoms)
P78285†	A0A3Y2C086 (AF)	78	0.276 (491 atoms)
P00720	102L (X-ray)	186	1.324 (581 atoms)
P00720	102L (X-ray)	636	2.598 (665 atoms)
Q37875	1XJT (X-ray)	144	0.506 (525 atoms)
Q37875†	A0A2G6EIY6 (AF)	144	7.544 (537 atoms)
Q37875	1XJT (X-ray)	209	1.020 (598 atoms)

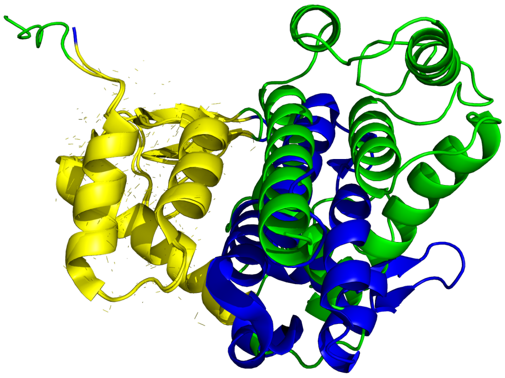


Figure 5: Alignment of the selected protein from Q37875 ProGen generation (sequence identifier 144) with 1XJT (X-ray), i.e., the three-dimensional structure of Q37875 taken from X-ray crystallography. Perfect alignments are in yellow, while the backbone of the protein generated by our model (in green) is superimposed on the experimental X-ray crystallography structure (in blue), illustrating the degree of similarity and differences in the folding patterns.

obtained from X-ray crystallography. This alignment shows the similarity and differences in the folding patterns between the generated and original structures. Additionally, Figure 6 shows the alignment between sequence 144 and its closest phage lysozyme match in nature, identified as A0A2G6EIY6.

5 CONCLUSIONS

We showed that fine-tuning significantly improves the capabilities of a pre-trained LLM model for protein generation on specific specialized tasks. The fine-tuned generative model is able to design new sequences that diverge from their natural counterparts while retaining potential functionality. Additionally, incorporating control tags related to the protein family enhances our ability to design novel protein functions with more refined control. These developments represent a significant step towards the goal of custom-designed proteins well-focused on specific functions.

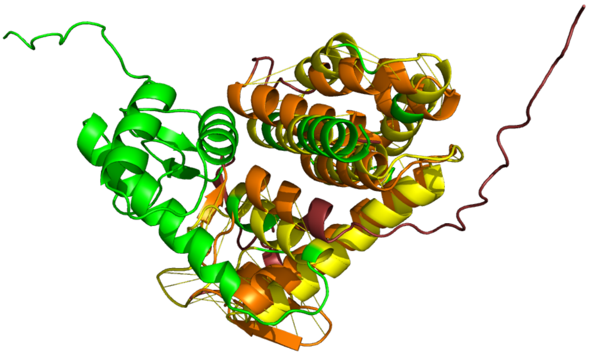


Figure 6: Alignment of the selected protein from Q37875 ProGen generation (sequence identifier 144) with its best match found by BLAST in the phage lysozyme dataset, with identifier A0A2G6EIY6. The three-dimensional structure of A0A2G6EIY6 was taken from AlphaFold-2 prediction (taken form uniProt). In the visualization, the alignment parts of 144 are highlighted in yellow, and the aligned parts of A0A2G6EIY6 are shown in orange. The backbone of the protein generated by our model (in green) is superimposed on the experimental predicted structure of A0A2G6EIY6 (in ruby), illustrating the degree of similarity and differences in the folding patterns.

We outline that fine-tuning the ProGen Conditional Transformer toward specific protein families can enable the generation of new proteins that retain and can also expand their functional characteristics, with possible relevant applications in pharmacology (e.g., for the design of new anti-microbic drugs), or in industrial applications (e.g., for the production of textiles, biofuels or foods).

In perspective, ProGen model can be fine-tuned on more complex tasks. For instance, the generation of functionally characterized protein molecules that can interact with a specific molecular target (i.e., a target protein). This is a challenging task, but it represents our next objective.

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