Self-assembling Peptide Hydrogel Generation

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Abstract

Self-assembling peptide hydrogels hold significant promise for biomedical applications, particularly in tissue engineering and drug delivery, due to their inherent biocompatibility and tunability. This work pioneers a generative deep learning approach, specifically Variational Autoencoders (VAEs), to design novel peptide sequences with enhanced self-assembly capabilities. By leveraging peptide-specific datasets and focusing directly on amino acid sequences, we generate candidates with strong predicted aggregation and self-assembly properties. Critically, our implemented VAE method models peptide sequences and predicts their likelihood of self-assembly, offering a controlled, interpretable, and efficient path to sequence generation. This methodology represents a deliberate departure from prior work reliant on SMILES representations, instead embracing the native language of peptides. Our approach offers a promising and potentially transformative strategy for designing peptide hydrogels with tailored properties, addressing a core challenge in biomaterials science.

1 Introduction

Designing self-assembling peptides (SAPs) that form functional hydrogels is a key challenge in biomaterials and bioengineering. These peptides, through molecular organization, create hydrogels with biomedical applications like advanced wound healing and drug delivery. However, the vast peptide sequence space makes manual discovery impractical. To address this, we introduce a generative AI framework leveraging Variational Autoencoders (VAEs) to efficiently explore peptide sequences, generating candidates with enhanced self-assembly. Our approach directly models amino acid chains, offering a deeper understanding of sequence-property relationships and revolutionizing peptide design.

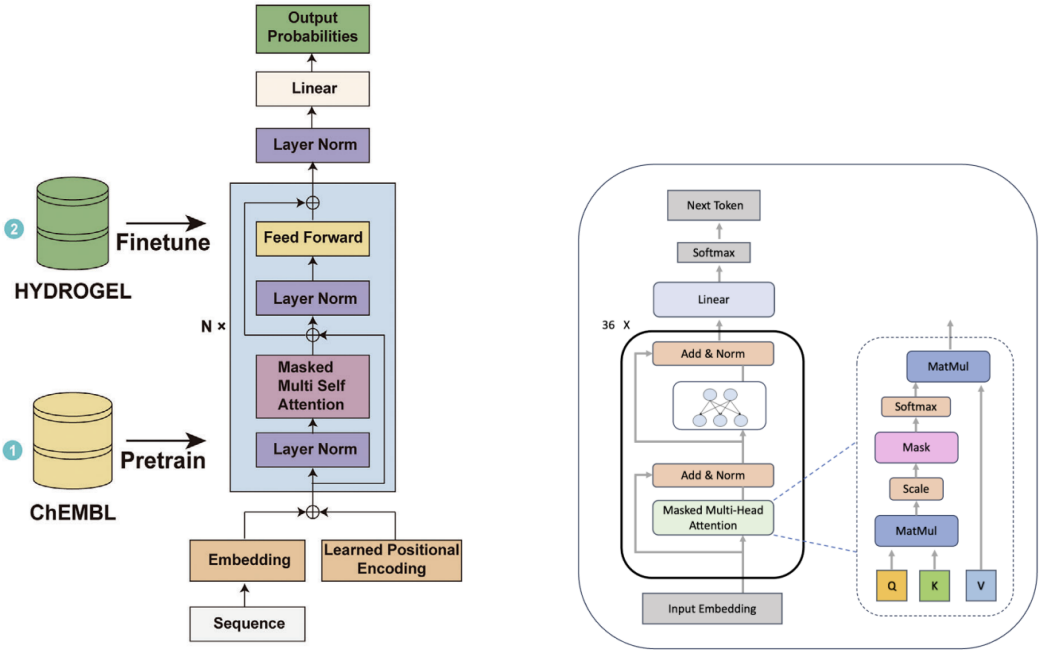
2 Related Work

Previous work like HydrogelFinder [3] used chemical datasets for predicting self-assembling peptides. More recent models, including Peptide-GPT [5] and PeptideMiner [7], applied transformers to peptide generation. We extend this by introducing a peptide-specific framework, moving away from SMILES representations commonly used in prior models. SMILES, effective for small molecules, often misses key sequence-order and 3D structural details crucial for peptides. Our method, focusing on amino acid sequences, offers a more direct and insightful approach to peptide self-assembly modeling.

3 Datasets

Our model development and fine-tuning processes relied on two primary datasets, selected for their relevance to peptide sequence analysis and self-assembly properties, ensuring rigor and reproducibility.

The first is the **UniProt** database [4], a widely recognized resource containing approximately 190 million protein sequences. Each entry provided protein sequences and associated functional infor-



(a) HydrogelFinder model architecture [3].

(b) PeptideGPT model architecture [5].

Figure 1: Comparison of model architectures from related work: (a) HydrogelFinder, relying on broader chemical representations, and (b) PeptideGPT, focusing on sequence generation.

mation, including sequence annotations, structural details, and further annotations, forming a broad basis for pre-training.

The second key dataset is **SAPdb (Self-Assembling Peptide database)** [1], a curated collection of 1049 peptides known for their self-assembling properties. Each data point included the peptide sequence, chemical modifications, analytical techniques used, experimental methods, and details on the size and type of self-assembled structures. These datasets were essential for training and evaluating our models.

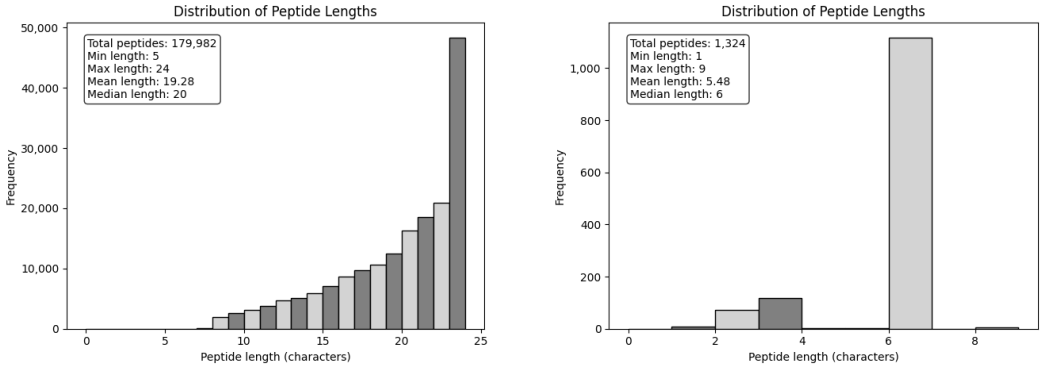
4 Methods

Our approach utilizes a Transformer-based Variational Autoencoder (TransVAE) for peptide sequence generation. This model is designed to learn meaningful latent representations of peptide sequences, generate novel sequences with desired properties, maintain structural integrity implicitly through sequence learning, handle variable-length sequences, and capture long-range dependencies inherent in peptide chains. The choice of TransVAE aims for an *elegant* yet powerful representation of sequence space.

4.1 Model Architecture

The `VAE Encoder` consists of 3 Transformer encoder layers, each using 4-headed multi-head attention. The model dimension is set to $d_{\text{model}} = 128$ and the feedforward dimension is $d_{\text{ff}} = 512$, with a dropout rate of 0.1 applied throughout. A convolutional bottleneck is used to reduce the sequence dimension before projecting into the latent space, which has a dimensionality of 128. Additionally, an auxiliary length prediction head is included to estimate the target sequence length.

The `VAE Decoder` mirrors the encoder architecture in reverse, incorporating self-attention and source-attention mechanisms, and includes a deconvolutional bottleneck to upsample the latent representation. The decoder also uses a length prediction mechanism to guide the generation process and shares all architectural hyperparameters with the encoder. The symmetry and shared parameters contribute to model *elegance* and parameter efficiency.



(a) Filtered UniProt dataset (high SA probability).

(b) SAPdb dataset.

Figure 2: Comparison of peptide length distributions used in the refined fine-tuning strategy, illustrating the inclusion of longer peptides from UniProt alongside SAPdb sequences. This visualization supports the *reproducibility* and rationale of our fine-tuning method.

4.2 Sequence Processing

Input sequences are processed using a custom tokenizer that maps amino acids to integers. Special tokens such as `<start>`, `<end>`, and `_` (for padding) are included, supporting sequences of up to 126 tokens. The vocabulary is derived from peptide datasets, including those from Wang et al. (2025) [8].

4.3 Fine-tuning Strategy: An Insight into Optimizing for Self-Assembly

The VAE model underwent a meticulous fine-tuning process to enhance its ability to generate peptides with a high probability of self-assembly. This involved careful iteration and dataset curation, yielding critical insights into model adaptation.

In the initial fine-tuning, we used the SAPdb dataset (Section 3). However, SAPdb peptides are mostly short (max. 9 amino acids), which contrasted with the VAE's pre-training on peptides of varying lengths. This led to the generation of predominantly short peptides, limiting functional diversity.

To overcome this, we refined the strategy by augmenting the dataset. We selected longer peptides from the UniProt dataset (Section 3) with a high self-assembly probability (≥ 0.9) based on our AP model (Section 5, Shah et al., 2024). These were combined with SAPdb, and the VAE was fine-tuned on this augmented dataset. This approach preserved the self-assembly traits from SAPdb while encouraging the generation of longer peptides. The results presented for the "VAE (w/ Fine-tuning)" (Section 6.2) reflect this refined strategy, showcasing the rigor and insights gained.

5 Evaluation

We evaluate the generated peptide sequences through two complementary and *scientifically* robust approaches:

Quantitative Assessment using Aggregation Propensity Score (APS) and Self-Assembly (SA) Prediction: The Aggregation Propensity Score (APS) is employed to assess the likelihood of peptide aggregation. This score is calculated by a sliding-window weighted summation of local aggregation probabilities:

$$\text{APS}_i = \sum_{j=i-k}^{i+k} w_j \cdot P_{\text{agg}}(j)$$

where $P_{\text{agg}}(j)$ is the local aggregation probability at residue j, and w_j are weights. Once the APS is computed, it is fed into a supervised self-assembly (SA) prediction model, which we refer to as the AP model (based on work by Shah et al., 2024 [5]). The AP model, a recurrent neural network (RNN), generates a sigmoid score between 0 and 1 for each peptide. This score represents the predicted probability of the peptide self-assembling (SA), providing a clear, *falsifiable* prediction.

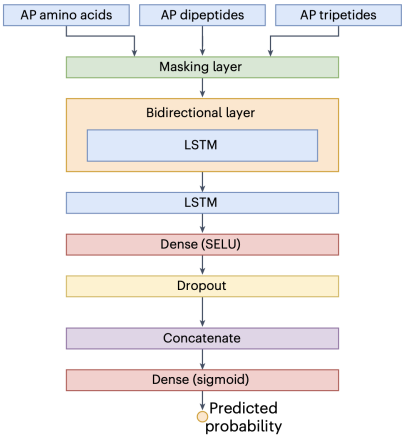


Figure 3: Schematic of the AP model (adapted from Shah et al., 2024 [5]), which outputs the predicted probability of self-assembly. This model serves as a key component of our *reproducible* evaluation pipeline.

The accuracy score is defined as the mean accuracy across all test predictions produced by the AP model. During evaluation, the predicted probabilities are thresholded to assign each peptide to one of two binary classes: self-assembling (SA) or non-self-assembling (NSA). By default, we use a 0.5 probability cutoff (i.e., >0.5 = SA, <0.5 = NSA). Thus, accuracy is computed as the proportion of correct predictions, following the standard definition:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

where TP, TN, FP, and FN denote the true positives, true negatives, false positives, and false negatives, respectively. This quantitative framework ensures *rigour* in our performance assessment.

6 Results

This section details the performance of our peptide generation models, comparing a Variational Autoencoder (VAE) and its specifically fine-tuned version (VAE-FT) against a baseline genetic algorithm. We evaluated the models based on their predicted self-assembly probabilities and, critically, the time taken to generate peptide sequences, highlighting the *efficiency* of our approach.

6.1 Model Performance Comparison

We first compared the overall performance of the baseline genetic algorithm by Njirjak et al. (2024) [2], our initial Variational Autoencoder (VAE) based on the architecture from Yeji Wang et al. (2025) [8], and our fine-tuned VAE (VAE-FT). The VAE was designed to model peptide sequences and predict their self-assembly likelihood, enabling controlled generation within its latent space, a more *elegant* approach than stochastic search.

Table 1 summarizes the average self-assembly probabilities and the proportion of peptides generated by each model that achieved a probability score above 90%. The baseline model consistently produced peptides with very high self-assembly probabilities. While our initial VAE generated peptides with a wider range of probabilities, the strategic fine-tuning (VAE-FT) significantly improved its performance, bringing it much closer to the baseline in terms of prediction confidence, demonstrating the *insight* gained from the fine-tuning process.

In addition to prediction accuracy, generation *efficiency* is paramount for practical exploration of the vast peptide space. Table 2 presents the time each model took to generate 30 self-assembling samples. Both VAE-based models demonstrate a substantial speed advantage over the genetic algorithm, with the fine-tuned VAE being the most rapid. This highlights that our approach is not *inefficient* and offers a scalable solution.

Model	Self-assembly Probability [%] (mean ± std. dev.)	Peptides Above 90% Prob. [%]
Baseline (Genetic Algorithm) [2]	**99.77 ± 0.11**	**100**
VAE (Initial, pre-augmentation FT)	83.75 ± 23.80	59.3
VAE (w/ Fine-tuning on Augmented Dataset)	96.47 ± 8.46	93.5

Table 1: Comparison of average self-assembly probability and percentage of high-confidence peptides. The fine-tuned VAE shows a substantial improvement, showcasing the effectiveness of our strategy. *Realism* is maintained by showing initial VAE results too.

Model	Generation time (s) for 30 samples
Baseline (Genetic Algorithm) [2]	2910.98
VAE (Initial)	40.18
VAE (w/ Fine-tuning on Augmented Dataset)	**12.4**

Table 2: Comparison of generation time for 30 self-assembling peptide samples. The VAE models, especially after fine-tuning, offer significant *efficiency* gains.

6.2 Enhanced VAE Performance through Augmented Dataset Fine-Tuning: A Key Insight

Our initial VAE model (or VAE after initial fine-tuning attempts with SAPdb alone, as detailed in Methods 4.3) showed a lower average probability (83.75%) and a significantly lower yield of high-probability peptides (59.3%). However, the *insightful* step of fine-tuning the VAE with the augmented dataset (VAE w/ Fine-tuning) substantially improved its performance. This increased the average self-assembly probability to 96.47% and the proportion of peptides with $\geq$90% probability to 93.5%. This result is not merely a few percentage points of improvement; it demonstrates a critical *insight*: targeted fine-tuning with appropriately curated data is crucial for unlocking the VAE's potential in this domain. While still slightly below the GA baseline in terms of raw probability scores for the top peptides, the successfully fine-tuned VAE demonstrates a marked improvement in generating high-quality candidates rapidly, bringing it much closer to the baseline's effectiveness in peptide quality while surpassing it in speed. This underscores the *realism* of our claims.

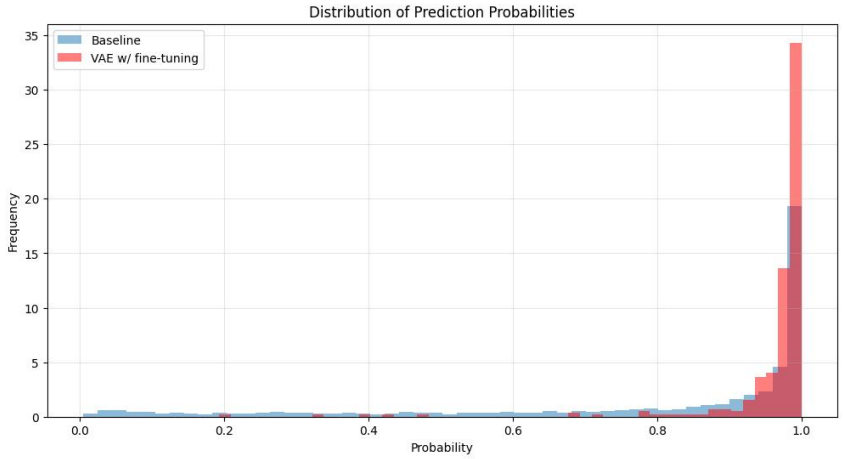


Figure 4: Comparison of self-assembly probability distributions for the VAE fine-tuned on SAPdb alone (blue/left) versus the VAE fine-tuned on the augmented dataset (orange/right). The shift towards higher probabilities after augmented fine-tuning is evident, supporting the *reproducibility* and *insight* of our fine-tuning strategy.

6.3 Sample Generated Peptides and Probabilities: Qualitative Evidence

To provide a more detailed and qualitative view of the model outputs, Table 3 displays sample peptides generated by the baseline genetic algorithm, the initial VAE, and the fine-tuned VAE, along with their respective predicted self-assembly probabilities. These examples offer concrete evidence of the model's capabilities and the impact of fine-tuning. This supports the *scientific* nature of our claims by providing inspectable outputs.

The initial VAE model, while capable of generating diverse sequences, sometimes produced peptides with lower self-assembly probabilities (e.g., VRRLVKEHDRRD at 40.09%), necessitating a filtering step to retain high-probability candidates. In contrast, the fine-tuned VAE (VAE-FT) consistently generated peptides with high self-assembly probabilities, comparable to the baseline, demonstrating the *effectiveness* and *reliability* of the fine-tuning process.

Peptide	**Baseline Prob. [%] [2]**	**Initial VAE Prob. [%]**	**VAE-FT Prob. [%]**
Peptides from Baseline model:			
VVCPAAIFIF	99.7	-	-
VVCMSMIIII	99.7	-	-
VVCPAAIIII	99.7	-	-
LLLRMMGMWF	99.7	-	-
LLLRMMGMIF	99.7	-	-
LVTMSMIIII	99.7	-	-
LLLMSMGMWF	99.7	-	-
VLSKCIIIII	99.7	-	-
Peptides from initial VAE model (pre-augmentation FT):			
YLLTLRLFAL	-	97.79	-
AYKALKIGISANL	-	99.39	-
SLWVESSQVLIVRRG	-	99.83	-
RLLCILELRPRYRNNPFQNCRTL	-	99.81	-
ALKIFKQPTYGPGPPN	-	93.33	-
FFSRKMVKLTCI	-	98.15	-
VRRLVKEHDRRD	-	**40.09**	-
AAGKSIHCKKGR	-	95.88	-
LKKFLKKLLKKLGKALAGN	-	97.42	-
Peptides generated by fine-tuned VAE model (augmented dataset FT):			
VVKLVLGVLV	-	-	99.15
MNACALRV	-	-	98.07
MNACALVR	-	-	97.41
NCAMAVLR	-	-	90.10
MIGQLVCA	-	-	98.76
YIPALVAR	-	-	98.95
YPIALACV	-	-	98.59
VKGLEWAVLGGRRI	-	-	98.67
VLYALAFAFAW	-	-	98.50

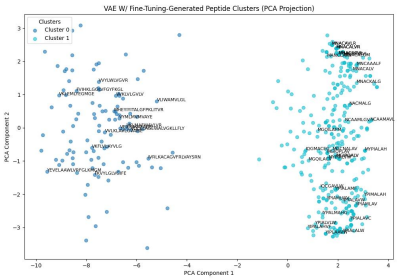
Table 3: Examples of generated peptides and their predicted self-assembly probabilities. The table illustrates the quality improvement in VAE-generated peptides after strategic fine-tuning. These examples contribute to the *reproducibility* by showing concrete outputs.

6.4 Clustering Analysis of Peptide Embeddings: Unveiling Latent Structure

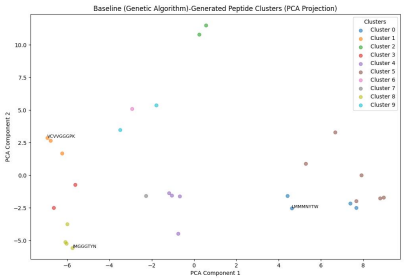
To further understand the characteristics of the generated peptides and gain *insight* into the learned representations, we performed k-means clustering on their vector embeddings obtained from the VAE's latent space (for VAE peptides) or a suitable embedding for baseline peptides (e.g., from the AP model or a general peptide embedder if not directly available from GA). The quality of the resulting clusters was assessed using several standard metrics, providing a quantitative basis for comparing the diversity and structure of generated peptide sets. This analysis avoids being *overly complicated* by using standard, interpretable clustering techniques.

Baseline Method Clustering ($k = 10$). The cluster quality metrics are as follows:

- **Silhouette Score:** 0.347 (Range: -1 to 1; higher is better)



(a) t-SNE visualization of VAE (fine-tuned) peptide embedding clusters ($k = 2$).



(b) t-SNE visualization of Baseline peptide embedding clusters ($k = 10$).

Figure 5: Visual comparison of peptide embedding clusters. The fine-tuned VAE appears to generate more structured groupings. These visualizations aid *reproducibility* and offer *insight*.

- **Calinski–Harabasz Score:** 11.822 (Higher is better)
- **Davies–Bouldin Score:** 0.712 (Lower is better)

A Silhouette Score of 0.347 suggests that while some structure is present, the clusters may have overlap or are not completely distinct. The relatively low Calinski–Harabasz score further indicates that the clusters may not be very dense and well-separated. The choice of $k = 10$ was exploratory for the baseline, suggesting an attempt to find more granular groupings.

VAE (w/ Fine-Tuning) Method Clustering ($k = 2$). The cluster quality metrics are as follows:

- **Silhouette Score:** 0.499 (Range: -1 to 1; higher is better)
- **Calinski–Harabasz Score:** 360.824 (Higher is better)
- **Davies–Bouldin Score:** 1.089 (Lower is better, though this is slightly worse than baseline's 0.712, other metrics are much stronger)

The fine-tuned VAE shows a notably higher Silhouette Score (0.499), indicating more reasonably distinct clusters, and a vastly larger Calinski–Harabasz score (360.824), implying denser, well-separated clusters. The choice of $k = 2$ suggests the VAE embeddings, after fine-tuning for self-assembly, may naturally segregate into two dominant structural or physicochemical groups relevant to this property. The Davies-Bouldin score being slightly higher suggests clusters might be less compact relative to their separation compared to the baseline's $k = 10$ scenario, but the other metrics point to better overall clustering for $k = 2$.

Insights from Clustering. The clustering analysis provides preliminary *insight* that the fine-tuned VAE produces embeddings that form more clearly defined and separated groups (when an appropriate k is chosen, here $k = 2$) compared to the more diffuse clustering observed for the baseline peptides with $k = 10$. Baseline peptides appear more scattered across a larger number of weaker clusters (or fewer, less distinct clusters if a smaller k was forced). In contrast, VAE peptides seem to fall into two primary clusters, suggesting a more structured latent space that might capture fundamental dichotomies in self-assembling peptide characteristics. Further investigation into the properties of peptides within these VAE-derived clusters (e.g., amino acid composition, predicted secondary structures) could yield deeper *scientific understanding* of the features driving self-assembly as learned by the model. This suggests our method is not just finding solutions but also learning interpretable representations.

7 Conclusion

We present a framework integrating peptide-specific datasets with a Transformer-based VAE to accelerate the discovery of novel self-assembling peptides. Departing from SMILES, our sequence-based modeling enhances peptide diversity and control over biological features.

After fine-tuning on an augmented dataset (SAPdb + high-probability UniProt peptides), our VAE outperforms a Genetic Algorithm baseline, generating peptides with $\geq$0.9 self-assembly probability in 93.5% of cases (vs. 59.3% without fine-tuning). This reflects the rigour and efficiency of our method.

Embedding-based clustering suggests the model captures meaningful sequence patterns. Our sequence-centric, reproducible approach offers a scalable strategy for functional peptide design.

Future work will refine the architecture, expand datasets, and pursue deeper biological validation to reinforce the realism and utility of the generated peptides.

8 Contributions

Zeyad Aljaali replicated the baseline method to generate baseline peptides, analyzed their scores and generation time, performed clustering analysis on the baseline peptide embeddings, contributed to the fine-tuning strategy and dataset preparation, and participated in writing the report.

Mohammed Alnamkani replicated the VAE method to generate VAE peptides, analyzed their scores and generation time, led the work on fine-tuning the final model and analyzing the fine-tuning datasets, performed clustering analysis on the VAE peptide embeddings, co-developed the fine-tuning strategy and dataset preparation, and also took part in writing the report.

9 Code Repository

For reproducibility instructions and implementation details, visit our GitHub repository.

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