# Probabilistic Transformer: Modelling Ambiguities and Distributions for RNA Folding and Molecule Design

**Jörg K.H. Franke**[1], **Frederic Runge**[1], **Frank Hutter**[1,2]
[1]Department of Computer Science, University of Freiburg, Germany
[2]Bosch Center for Artificial Intelligence, Renningen, Germany
{frankej,runget,fh}@cs.uni-freiburg.de

## Abstract

Our world is ambiguous and this is reflected in the data we use to train our algorithms. This is particularly true when we try to model natural processes where collected data is affected by noisy measurements and differences in measurement techniques. Sometimes, the process itself is ambiguous, such as in the case of RNA folding, where the same nucleotide sequence can fold into different structures. This suggests that a predictive model should have similar probabilistic characteristics to match the data it models. Therefore, we propose a hierarchical latent distribution to enhance one of the most successful deep learning models, the Transformer, to accommodate ambiguities and data distributions. We show the benefits of our approach (1) on a synthetic task that captures the ability to learn a hidden data distribution, (2) with state-of-the-art results in RNA folding that reveal advantages on highly ambiguous data, and (3) demonstrating its generative capabilities on property-based molecule design by implicitly learning the underlying distributions and outperforming existing work.

## 1 Introduction

Transformer models [1] are the architecture of choice for many applications. Next to a wide range of NLP applications, such as language modelling [2, 3, 4] and machine translation [1, 5], they are also very effective in other disciplines, such as computer vision [6, 7], biology [8, 9], and chemistry [10, 11]. An additional challenging application for which transformers are promising is RNA folding, where the goal is to model a secondary structure (represented in dot-bracket notation [12]) based on a given sequence of nucleotides. RNA data is highly ambiguous since it is collected with different techniques, resolutions, protocols, and even contains natural ambiguities since there exist multiple structures for the same RNA sequence in the cell [13, 14] and the same structure can be caused by multiple sequences. Similar to RNA structures, molecules can be represented as sequences by using the *simple molecular line entry system* (SMILES) [15] and transformers arise as the architecture of choice in the flourishing field of molecule design [11, 16].

Although Transformers have outstanding performance, the deterministic core of the architecture could harm performance in real-world applications like RNA folding. If collected data contains noisy labels or ambiguous samples, a vanilla Transformer model can only express uncertainties in the softmax output but not in the latent space. When sampling, sequential interdependencies can only be modelled in a decoder setting but not in an encoder-only setting. We address these limitations by proposing a Probabilistic Transformer[1] (ProbTransformer) that models a hierarchical latent distribution and performs sampling in the latent space. The ProbTransformer can represent ambiguities in these

[1]Source code is available at github.com/automl/ProbTransformer

36th Conference on Neural Information Processing Systems (NeurIPS 2022).

distributions and refine the sampled latent vectors within the computational graph. This is in line with recent findings in cognitive science that suggest that the human brain both represents probability distributions and performs probabilistic inference [17, 18]. Our approach is based on the idea of combining the transformer architecture with a conditional variational auto-encoder (cVAE) [19], but in a hierarchical fashion similar to the hierarchical probabilistic U-Net [20]. Therefore, we introduce a new probabilistic layer and incorporate it after the attention and feed-forward layer (Section 3). In this way, we preserve the global receptive field through the attention mechanism and remain independent of other enhancements in the transformer ecosystem [21]. To train the latent distributions, we make use of the generalized evidence lower bound (ELBO) with constrained optimization (GECO) [22] and introduce an annealing technique to adapt a hyperparameter online.

We see our contributions in three aspects:

- The introduction of the ProbTransformer, a novel hierarchical probabilistic architecture enhancement to the Transformer ecosystem.
- Our training procedure using GECO, the analysis of the sensitivity of its hyperparameter $\kappa$, and the introduction of the online adaption technique *kappa annealing* which could be beneficial for variational training with ELBO in general.
- A comprehensive empirical analysis that verifies the ProbTransformer's capability to learn and recover data distributions on a novel synthetic sequential distribution task, assesses its capability of handling data ambiguities in practice by achieving state-of-the-art performance in RNA folding, and demonstrates its generative character by outperforming existing work in Molecule Design.

We first clarify notation and recap the cVAE [19] (Section 2), and then introduce the ProbTransformer (Section 3). We then present our experiments on the sequential distribution task (Section 4.1), RNA folding (Section 4.2), Molecule Design (Section 4.3), as well as our ablation study (Section 4.4), discuss related work (Section 5) and conclude (Section 6).

## 2 Background

**Transformer Notation** The Transformer [1] is a self-attention based sequence-to-sequence model introduced as an encoder-decoder architecture. However, both encoder-only and decoder-only versions are very successful by themselves [2, 23], and in our work, we focus on either of these two versions. An encoder or decoder has $N$ blocks and each block consists of a multi-head (masked) attention followed by a feed-forward layer. Around both of these layers there are residual connections [24] followed by layer normalization [25]. We use the parameterization with $D_{model}$ dimensions in the residuals and attention, $H$ heads per attention, $D_{ff}$ latent dimensions in the feed-forward layer, and $N$ for the blocks in the Transformer. In addition, we define $X \widehat{=} (x_1, \ldots, x_S)$ as the input sequence of length $S$, $Y \widehat{=} (y_1, \ldots, y_S)$ as the target sequence, and $\hat{Y} \widehat{=} (\hat{y}_1, \ldots, \hat{y}_S)$ as the predicted sequence.

**Conditional Variational Auto-Encoder (cVAE)** The cVAE [19] is a deep conditional generative model and an extension of the Variational Auto-Encoder [26, 27]. During inference, the cVAE aims to generate a distribution for an output $\mathbf{y}$ conditional on an input $\mathbf{x}$. More specifically, given an input $\mathbf{x}$, a latent variable $\mathbf{z}$ is drawn from a (conditional) prior model $p_\theta(\mathbf{z}|\mathbf{x})$ and used as an additional input to the generation model $p_\rho(\mathbf{y}|\mathbf{x}, \mathbf{z})$ in order to generate the prediction $\hat{\mathbf{y}}$. The cVAE is trained by minimizing the negative evidence lower bound (ELBO), $\mathcal{L}_{ELBO}$:

$$\mathcal{L}_{ELBO}(\mathbf{x}, \mathbf{y}; \theta, \rho, \psi) = \mathbb{E}_{\mathbf{z}^{post} \sim q}(-\log p_\rho(\mathbf{y}|\mathbf{x}, \mathbf{z}^{post})) + \mathrm{D}_{\mathrm{KL}}(q_\psi(\mathbf{z}|\mathbf{x}, \mathbf{y}) \parallel p_\theta(\mathbf{z}|\mathbf{x})) \quad , \quad (1)$$

where $q_\psi(\mathbf{z}|\mathbf{x}, \mathbf{y})$ describes the posterior model (called "recognition network" in [19]). All models are neural networks, and the prior and posterior models each output a mean and variance of a Gaussian distribution which represents the distribution of the latent $\mathbf{z}$. During training, $\mathbf{z}^{post} \sim q_\psi(\mathbf{z}|\mathbf{x}, \mathbf{y})$ is sampled from this posterior model and used as input to the generation model $p_\rho(\mathbf{y}|\mathbf{x}, \hat{\mathbf{z}})$, whose output $\hat{\mathbf{y}}$ is compared to the ground true with a cross-entropy loss. This objective at training time can be viewed as a reconstruction task due to the target sequence input to the posterior, which is an easier task than prediction. The Kullback-Leibler (KL) divergence term $\mathrm{D}_{\mathrm{KL}}(\cdot \parallel \cdot)$ aims to align the (conditional) prior model $p_\theta(\mathbf{z}|\mathbf{x})$ and the posterior model $q_\psi(\mathbf{z}|\mathbf{x}, \mathbf{y})$. The two losses are added and then used to train the prior, posterior, and generation models jointly, employing the reparameterization trick [28].

## 3 Probabilistic Transformer

Building on concepts of the cVAE, we enhance the Transformer model to a probabilistic Transformer (ProbTransformer) by adding a probabilistic feed-forward layers (prob layer) to $M \in \{1, \ldots, N\}$ of the existing blocks. We introduce our approach for an encoder-only model to simplify notation. It also applies to the decoder-only model but not directly to an encoder-decoder model because our training setup requires the alignment of the source and target sequences in the posterior input, see Section 3.2. Whether all or only a selection of blocks are enhanced with prob layers is a design decision and examined empirically in Section 4.4. In a block, we place the prob layer after the attention and feed-forward layer. The prob layer parameterizes a multivariate Gaussian distribution $\mathcal{N}(\boldsymbol{\mu}, \Sigma)$ with a diagonal covariance $\Sigma = \boldsymbol{\sigma}^2\mathbf{I}$, where $\mathbf{I}$ is the identity matrix, used to sample a latent vector $\mathbf{z} \in \mathbb{R}^{D_z}$ for each position in the sequence. We denote by $X$ and $Y$ the input and target sequences of length $S$, by $Z_m \widehat{=} (\mathbf{z}_{m,1}, \ldots, \mathbf{z}_{m,S})$ the position-wise sampled sequence of latent distributions in block $m$, by $\mathbf{Z} \widehat{=} (Z_1, \ldots, Z_M)$ all sequences of latent distributions of all blocks, and by $\mathbf{Z}_{<m} \widehat{=} (Z_1, \ldots, Z_{m-1})$ all sequences of latent distributions of all blocks before $m$. At inference time, we sample $Z_m$ and add it to the computation graph of the current block, similar to sampling from the (conditional) prior in the cVAE. However, in contrast to the cVAE, our sampling is conditioned hierarchically; the latent realization $\mathbf{z}_{m,s}$ at block $m$ and sequence position $s$ depends on all previously sampled latent vectors of any position in previous Transformer blocks due to the Transformer architecture:

$$\mathbf{z}_{m,s} \sim p(\mathbf{z}_{m,s} | \mathbf{Z}_{<m}, X). \tag{2}$$

A sequential relation between the positional distributions is achieved by the attention mechanism: while the samples $\mathbf{z}_{m,s}$ are drawn independently for each position $s \in \{1, \ldots, S\}$, the following attention operations relate them and turn the position-wise samples into a joint distribution over sequences refined in higher blocks.

As a result of the hierarchical composition of the ProbTransformer and the sequential relation, prior model $p_\theta(Z_m | \mathbf{Z}_{<m}, X)$ and the generation model $p_\rho(Y|X, \mathbf{Z})$ effectively become a single *predictive model* $P_\phi(Y|X)$, which differs from the modeling strategy of the cVAE. This model approximately marginalizes over latent variables $\mathbf{Z}$: $P_\phi(Y|X) = \int_{\mathbf{Z}} p_\phi(\mathbf{Z}|X) \times p_\phi(Y|X, \mathbf{Z}) \; d\mathbf{Z}$, and we can sample from it by hierarchically sampling $p_\phi(\mathbf{Z}|X)$ decomposed as

$$p_\phi(\mathbf{Z}|X) = p_\phi(Z_M | \mathbf{Z}_{<M}, X) \cdot \ldots \cdot p_\phi(Z_0|X), \tag{3}$$

followed by sampling from $p_\phi(Y|X, \mathbf{Z})$. At inference time, we can sample different predictions from the predictive model $\hat{Y} = P_\phi(Y|X)$.

However, we can also use the mean of the respective (Gaussian) distributions instead of sampling from them. We denote this as *mean inference* in contrast to *sample inference*. In the following, we introduce the prob layer architecture in detail before explaining our training setup and the learning objective.

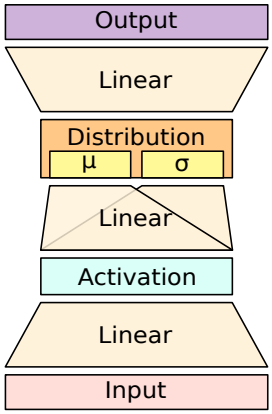

Figure 1: Probabilistic Feed-Forward layer.

### 3.1 Position-wise Probabilistic Feed-Forward Network

Similar to the feed-forward layer, the prob layer is applied to the latent representation of each position $s \in \{1, \ldots, S\}$ of the input sequence $X$ independently. Figure 1 provides a visual description. It consists of a linear layer that transforms from the model dimension $D_{model}$ to the distribution dimension $D_z$ of the probabilistic latent space, followed by an activation function. Further, two linear layers with $D_z \times D_z$ weight matrices generate the latent representation of a conditional Gaussian distribution with mean $\boldsymbol{\mu}_{m,s} \in \mathbb{R}^{D_z}$ and log variance[2] $\log \boldsymbol{\sigma}^2_{m,s} \in \mathbb{R}^{D_z}$ for the prob layer in

[2] We use $\log \boldsymbol{\sigma}^2_{m,s}$ to avoid negative variance values and for numerical stability. We obtain the variance $\boldsymbol{\sigma}^2_{m,s}$ by $\boldsymbol{\sigma}^2_{m,s} = e^{\log \boldsymbol{\sigma}^2_{m,s}}$.

block $m$ at position $s$:

$$\boldsymbol{\mu}_{m,s} = \text{Linear}_{\mu,m}(\text{Act}(\text{Linear}_{\text{In},m}(\mathbf{x}_{m,s}))) \tag{4}$$

$$\log \boldsymbol{\sigma}^2_{m,s} = \text{Linear}_{\sigma,m}(\text{Act}(\text{Linear}_{\text{In},m}(\mathbf{x}_{m,s}))) \tag{5}$$

$$\mathbf{z}_{m,s} \sim \mathcal{N}(\boldsymbol{\mu}_{m,s}, \boldsymbol{\sigma}^2_{m,s}\mathbf{I}) =: p(\mathbf{z}_{m,s}|\mathbf{Z}_{<m}, X) \tag{6}$$

$$\mathbf{y}_{m,s} = \text{Linear}_{\text{Out},m}(\mathbf{z}_{m,s}) \tag{7}$$

As mentioned before, during *sample inference*, we can sample from the distribution (Equation 6) and during *mean inference* we use $\mathbf{z}_{m,s} \widehat{=} \boldsymbol{\mu}_{m,s}$. An additional linear layer is used to compute the layer's output $\mathbf{y}_{m,s} \in \mathbb{R}^{D_{model}}$ (Equation 7). Similar to the attention and feed-forward layer, we employ a residual connection [24] followed by a layer normalization [25].

### 3.2 Training Setup and Learning Objective

We optimize the ELBO as the standard practice for conditional training [19]. This requires a variational posterior $Q_\psi(\mathbf{Z}|X, Y)$ that depends on both the input sequence $X$ and target sequence $Y$. We model this posterior with a separate ProbTransformer with the same architecture as the predictive model except for an additional input embedding for the target sequence $Y$ and no output generation layers, since we are only interested in the latent sampling $\mathbf{Z}^{post}$ and not in the actual model output. During training, we first run the posterior model and sample the latent $\mathbf{Z}^{post} \sim Q_\psi$. In a second step, we run the predictive model but use the latent realization $Z^{post}_m$ instead of sampling an own $Z_m$ in each prob layer $m$. Figure 2 illustrates this training setup.

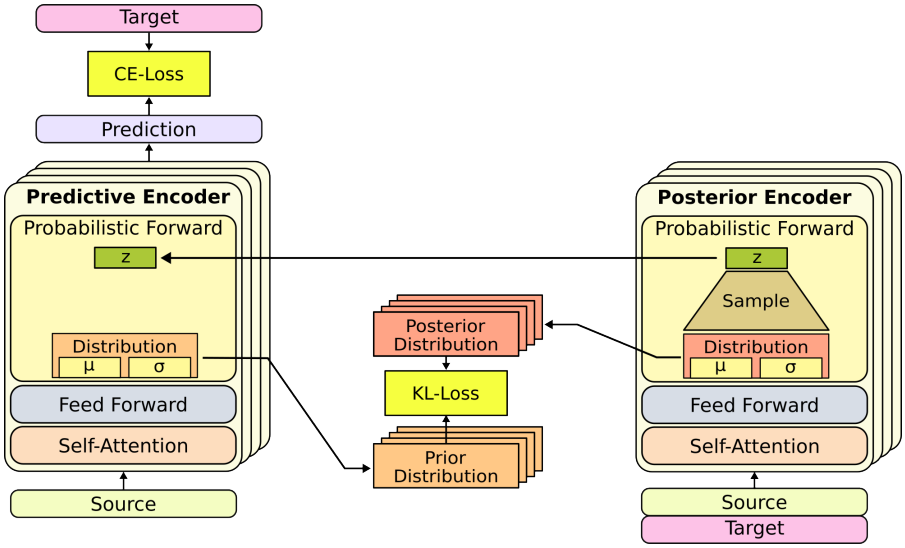


Figure 2: Training setup of the ProbTransformer: The predictive and posterior encoder trained jointly.

The negative ELBO loss $\mathcal{L}_{ELBO}$ (Equation 1) is composed of a reconstruction loss $\mathcal{L}_{rec}$ and a KL divergence $D_{KL}$ between the prior distribution $P_\phi$ conditioned on the latent $\mathbf{Z}^{post}$ and the posterior distribution $Q_\psi$. The reconstruction loss is the cross-entropy between the predicted sequence $\hat{Y}$ and the true sequence $Y$ while using the latent $\mathbf{Z}^{post}$ from the posterior model:

$$\mathcal{L}_{rec} = \mathbb{E}_{\mathbf{Z}^{post} \sim Q}\big( - \log p_\phi(\mathbf{y}|X, \mathbf{Z}^{post})\big), \tag{8}$$

and $D_{KL}$ is the sum of KL divergences between the hierarchically decomposed distributions $P$ and $Q_\psi$ at each prob layer $m$ for all positions $s$:

$$\mathcal{D}_{KL} = \frac{1}{S}\sum_{s=1}^{S}\sum_{m=1}^{M} D_{\text{KL}}\big(q_\psi(\mathbf{z}^{post}_{m,s}|\mathbf{Z}^{post}_{<m}, X, Y) \parallel p_\phi(\mathbf{z}_{m,s}|\mathbf{Z}^{post}_{<m}, X)\big) \tag{9}$$

With the default $\mathcal{L}_{ELBO}$ loss, we discovered instability in the training and performance issues, even with a weighting factor $\beta$ [29]. Therefore, we follow [20] to avoid convergence issues with the classic

ELBO objective and make use of the Generalized ELBO with Constrained Optimization (GECO) objective [22], optimizing the Lagrangian

$$\mathcal{L}_{GECO} = \lambda(\mathcal{L}_{rec} - \kappa) + \mathcal{D}_{KL}. \tag{10}$$

The Lagrange multiplier $\lambda$ balances the terms and is initialized to 1, added to the learnable parameter space and updated as a function of the exponential moving average of the reconstruction loss [20]. In the beginning of the training, there is high pressure on the reconstruction loss due to an increasing $\lambda$. Once the desired reconstruction loss $\mathcal{L}_{rec} \approx \kappa$ is reached, the pressure moves to the KL-term. Please find more information about the training dynamics in Appendix A.

$\kappa$ was set to a constant in the original work of [22], but this is problematic since it is a sensitive hyperparameter due to the training dynamics. Specifically, if $\kappa$ is chosen *too small*, possible failure modes include that $\mathcal{L}_{rec}$ never reaches it (with the pressure staying only on the reconstruction loss), that $\kappa$ will be reached by over-fitting, or that the posterior distribution collapses which leads to high $D_{\mathrm{KL}}(Q_\psi \parallel P_\phi)$ and destabilizes the training. On the other hand, if $\kappa$ is chosen *too large*, the model can underfit or the reconstruction loss drops below $\kappa$, leading to a negative loss value and harming the training success significantly. To address this issue we introduce **kappa annealing** and adjust $\kappa$ during training. Let $\mathbf{L}_c = \frac{1}{K}\sum_{k=0}^{K} \mathcal{L}_{rec}(X_k, Y_k) - \kappa$ be the mean constrained difference for $K$ training samples in one epoch of training or a defined number of update steps. In our experiments, we find that initializing $\kappa$ slightly larger than the optimal CE loss value and updating it every epoch with

$$\kappa = \begin{cases} \kappa + \mathbf{L}_c & \text{if } \mathbf{L}_c < 0 \text{ and } \lambda \leq 1 \\ \kappa & \text{otherwise} \end{cases} \tag{11}$$

leads to more stable training behaviour, improved final performance, and reduces the need for expensive tuning of $\kappa$.

# 4 Experiments

We demonstrate the benefits of the ProbTransformer in three experiments: (1) using a novel synthetic sequential distribution task, we show the advantages of distributions in the latent space over the standard softmax output distribution of a vanilla Transformer. (2) We show the benefits of the ProbTransformer in dealing with ambiguous data in RNA folding. (3) We use the ProbTransformer to improve property-based Molecule Design by sampling from the latent space instead of a softmax-output. In an additional ablation study, we provide insights on the impact of kappa annealing and hierarchical prob layers.

## 4.1 Synthetic Sequential Distribution Task

In real-world generation tasks, the true distribution is not available and is only implicitly accessible by a dataset. To provide insights on the quality of distribution learning, we created a synthetic sequential distribution task and compare the ProbTransformer to two sampling methods of a vanilla Transformer.

**Data** We design the task to map a sequence of tokens from a source vocabulary $x \in \mathcal{V}_i^*$ to a sequence of target tokens from a target vocabulary $y \in \mathcal{V}_o^*$ with the same length. The tokens in the source sequence are used to build 'phrases" $\mathbb{P}$. Each phrase exists of $l$ tokens sampled with replacement (similar to the combination of words to phrases in a sentence). For each source token in each phrase, we randomly generate a unique distribution $p(y|x, \mathbb{P})$ over the target tokens depending on the current phrase. Further, we design the distribution sparsely so that no more than $k$ tokens from the target vocabulary have a non-zero probability. The training data consists of source and target sequence pairs with input sequences sampled with replacement from all phrases and target sequences sampled from the corresponding distributions.

**Setup** We use an encoder-only ProbTransformer model and enhance each block with a prob layer. We configure the task and the model to run on one GPU within few hours. Please find more information about the task and the configuration in Appendix B. For the inference of the vanilla Transformer we use MC dropout (using dropout during inference time, based on [30]) and sampling from the softmax distribution. For the inference of the ProbTransformer we sample from the predictive model and use the token with the highest output value. We generate 50 realizations per sample to create a predictive distribution of the target vocabulary.

**Results** We measure the generative performance of a model or sampling method with two metrics: The *Validity* describes the percentage of predicted tokens whose probability in the true distribution is not zero. Second, we measure the *KL-divergence* between the sampled distribution and the true distribution since sampling should reproduce the true target token distribution. As shown in Table 1, the ProbTransformer outperforms the MC dropout and softmax sampling, demonstrating its strong performance in probabilistic sequence modelling. Please note that this task does not consider interdependence sampling, where the sampling of one token in a sequence depends on the realization of others, while the next task on RNA folding does.

Table 1: The mean measures of five random seeds in the synthetic task.

| Model | | Validity | KL-div. |
|---|---|---|---|
| ProbTransformer | | **0.99** | **0.52** |
| Transformer | dropout | 0.93 | 12.71 |
| | softmax | 0.73 | 7.84 |

### 4.2 RNA Folding

An RNA's structure influences its function drastically [31] and the functional importance of RNA arguably is on par with that of proteins [32]. Since cellular RNAs typically have extensive secondary structures but limited tertiary structures [33], RNA folding is typically modeled as a function $\mathcal{F} : \Upsilon^* \rightarrow \Gamma^*$, where $\Upsilon$ and $\Gamma$ denote sequence and secondary structure alphabets, respectively. However, this is a simplified view on the RNA folding process, which ignores the fact that RNAs alter their structures dynamically, resulting in an ensemble of structures occurring with different probabilities [13, 14]. Further, real-world applications often require structure analysis of very similar sequences [34], sometimes folding into the same secondary structure. These ambiguities can hardly be captured with common approaches and ambiguous data is often removed for a better training result [35, 36, 37]. We address these issues with probabilistic modelling using our ProbTransformer and by keeping ambiguous training data, while implicitly measuring overfitting by explicitly removing similarity to the test data.

**Data** We collect a large data pool of publicly available datasets from recent publications [38, 39, 37, 40, 41] and split the predefined validation and test sets, VL0 and TS0 [37], from the pool. We derived a separate testset, *TSsameStruc*, from 149 samples of TS0 that share the same structure with at least one other sequence in TS0 and uniformly sampled a disjoint set of 20 sequences with more than one annotated secondary structure from the remaining pool to produce an ambiguous testset, *TSsameSeq*. Samples without pairs and with a sequence similarity greater than 80% to the test and validation sets were removed from the training pool. However, in contrast to previous work [37, 39, 42], we kept all remaining samples for training to capture ambiguities and the influence of small sequence changes on the structures. The final data consists of 52007 training and 1299 validation samples, and 1304 samples in the testset TS0 and 46 samples in the testset TSsameSeq. We observe 48092, 1304, and 20 unique sequences with up to 7 different structures for a single sequence, and 27179, 1204, and 46 unique structures with up to 582 different sequences for a single structure in the training, TS0, and TSsameSeq sets, respectively. This indicates that many sequences map to the same structure and different structures to the same sequence. We refer to Appendix C.1 for more information about the data.

**Setup** We use a 6-block encoder-only architecture with $D_{model}$ of 512 for the vanilla Transformer and ProbTransformer. We train them for 200 epochs or 1M training steps. We compare them against the state-of-the-art deep learning algorithms, *SPOT-RNA* [37], MXFold2 [39], and a commonly-used dynamic programming approach, *RNAfold* [43] on the testset TS0 and its subset TSsameStruc using mean inference. To analyse the capabilities of the ProbTransformer to reconstruct structure distributions, we also infer the model 5, 10, 20, 50, and 100 times using sample inference on TSsameSeq, and compare against three commonly-used algorithms specialized on the prediction of structure ensembles via sampling from the Boltzmann distribution based on experimentally derived thermodynamic parameters: *RNAsubopt* [43], *RNAshapes* [44], and *RNAstructure* [45]. In contrast to previous work [37, 41, 39, 42], we do not use ensembling nor limit the set of accepted base pairs or secondary structures for post-processing, but independently train a CNN head on the output of the ProbTransformer that maps the string representation to an adjacency matrix representing the structure for evaluations on TS0 and TSsameStruc. Although we are aware of the problems with exact evaluations via F1 Score due to the dynamic nature of RNA structures [46], we report F1 Score for reasons of comparability to previous work; however, we further report the number of solved structures

Table 2: Structure fidelity of different RNA folding approaches on TS0 and TSsameStruc. For the ProbTransformer and the vanilla Transformer we show mean results of three random seeds.

| Model | TS0 | | | TSsameStruc | | |
|---|---|---|---|---|---|---|
| | F1 Score | Hamming | Solved | F1 Score | Hamming | Solved |
| ProbTransformer | **62.5** | **27.4** | **0.118** | **93.2** | **3.2** | **0.550** |
| Transformer | 50.5 | 35.3 | 0.084 | 89.5 | 4.6 | 0.481 |
| SPOT-RNA | 59.7 | 39.6 | 0.005 | 78.0 | 14.6 | 0.020 |
| MXFold2 | 55.0 | 42.1 | 0.014 | 74.6 | 17.1 | 0.067 |
| RNAFold | 49.2 | 48.0 | 0.008 | 59.2 | 25.5 | 0.020 |

(the ultimate goal of the task), and the average Hamming distance to achieve a better measure of distance. For more details on the setup, CNN head, and metrics, we refer to Appendix C.2.

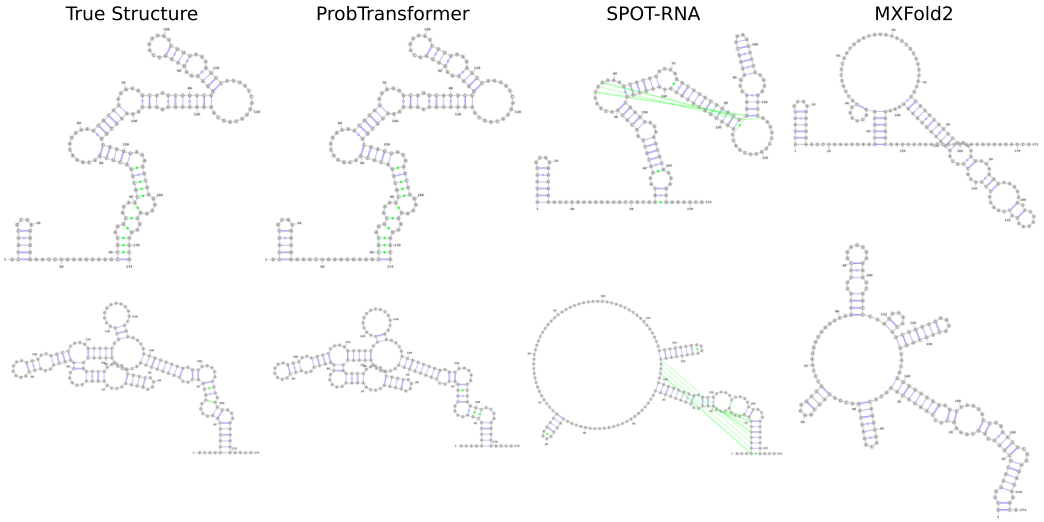


Figure 3: Example predictions of deep learning-based approaches for challenging RNAs from TS0. We show (top) a Group II catalytic intron (RF02001) and (bottom) a M-box riboswitch (RF00380).

**Results** Table 2 summarizes the results of all approaches on TS0 and TSsameStruc. Both attention-based approaches generally achieve strong results, but we observe that the ProbTransformer outperforms the vanilla Transformer across all measures on both sets. The ProbTransformer achieves the best performance in terms of F1 Score, solves more than eight times the structures compared to the next best approach (MXFold2) on both sets and achieves four times lower Hamming distance on TSsameStruc compared to SPOT-RNA, indicating that it has learned to handle ambiguous sequences. Our model is further capable of accurately reconstructing challenging structures, exemplarily shown for two structures that contain long-range interactions in Figure 3. A functional important class of base pairs are pseudoknots [47, 48], non-nested base pairs present in around 40% of RNAs [41] that are overrepresented in functional important regions [49, 48] and known to assist folding into 3D structures [50]. While RNAFold and MXFold2 cannot predict this kind of base pairs due to the underlying nearest neighbour model, Figure 3 as well as further results shown in Appendix C.3.2 suggests that the ProbTransformer can predict pseudoknots more accurately than SPOT-RNA if these are contained in the structures (Figure 9) and further rarely predicts pseudoknots if the structure is nested. However, a detailed analysis on the quality of pseudoknot predictions would be out of the scope of this work. When inferring the model multiple times on TSsameSeq, the ProbTransformer is the only model in our evaluation that could reconstruct more than one structure for a given sequence (for two sequences this was already achieved when inferring the model only five times). The average Hamming distances of the best predictions on TSsameSeq for every approach are summarized in Table 15 in Appendix C.3.2. The ProbTransformer improves the Hamming distance by up to 44%,

Table 3: Multi-property (TPSA+logP+SAS) conditional training on GuacaMol dataset (mean on five different seeds).

| Model | Validity | Unique | Novelty | TPSA MAD/SD | logP MAD/SD | SAS MAD/SD |
|---|---|---|---|---|---|---|
| ProbTransformer | **0.981** | 0.821 | 1.0 | **2.47/2.04** | **0.22/0.18** | **0.16/0.14** |
| MolGPT | 0.973 | **0.969** | 1.0 | 3.79/4.80 | 0.27/0.35 | 0.18/0.26 |

indicating that the ProbTransformer reconstructs the overall structure ensemble very well. Additional results and example predictions for RNA folding are reported in Appendix C.3.

### 4.3 Molecule Design

In the field of generative chemistry [51], deep generative models are employed to explore the chemical space [52, 53, 54]. However, biological applications typically require that the designed molecules have certain desired properties. For example, to penetrate the blood-brain barrier in order to interact with receptors of the nervous system, a molecule typically requires a certain permeability score [55, 56]. Conditional generation then refers to the problem of exploring the chemical space conditioned on molecule properties; a well-suited task to evaluate the ProbTransformer in a decoder-only setting against the state-of-the-art transformer decoder model, *MolGPT* [11].

**Data** We use the GuacaMol [57] training data and the evaluation protocol provided by [11]. For more information about the data we refer to Appendix D.1.

**Setup** We employ the same architecture as [11], enhanced with probabilistic layers, and train our model for 20 epochs or 300k training steps. During training, the model implicitly learns the properties of the training data by conditioning generation on molecular properties together with the input SMILES. At inference, novel molecules with multiple desired property values are generated by providing the model with a start token alongside with the desired property values while predicting the next token until either a maximum length is reached or the model produces an end-token. We condition the generation of molecules on three properties: the *synthetic accessibility score (SAS)*, the *partition coefficient (logP)*, and the *topological polar surface area (TPSA)*, using the same domains of values described in [11]. For each combination of property values, the model generates a total of 10000 molecules. Results are reported in terms of the mean average deviation (MAD) and the standard deviation (SD) relative to the range of the desired property values, as well as the *validity* of the generated compounds, their *uniqueness* in terms of the internal diversity of valid predictions, and their *novelty* compared to the training data. For more information about the measures and the general setup, we refer to Appendix D.2.

**Results** The results for the conditional generation of molecules are summarized in Table 3. We observe a high validity score and a novelty of 1.0, indicating that our ProbTransformer has learned the underlying SMILES grammar very well and does not suffer from overfitting to the train data. For the main task of conditional generation, the ProbTransformer clearly outperforms *MolGPT* across all measures, which highlights its ability to control multiple molecular properties during generation. The largest improvement can be observed for the SD and MAD scores of TPSA, an important measure for drug delivery in the body, improving the standard deviation (SD) by 57.5% and the mean average deviation (MAD) score by nearly 35%. We do not observe improvements in uniqueness compared to *MolGPT* but note that nearly perfect uniqueness could, e.g., be achieved by adding carbons *a posteriori* [58]. Additional results and prediction examples are shown in Appendix D.3.

### 4.4 Ablation Studies

We perform two ablation studies to provide more evidence for the usefulness of hierarchical probabilistic construction and kappa annealing. For this ablation, we use the RNA Folding task described in Section 4.2 with the same architecture and training steps. We provide more details in E.

**Hierarchical probabilistic design** Due to the possibility of having a prob layer in any block, we tested different setups from one prob layer (middle) up to all blocks enhanced with a prob layer. In Figure 4, we measure the performance improvement in Hamming distance compared to a vanilla Transformer on the TS0 and TSsameStruct sets. Performance saturates at 4 prob layers for the TS0

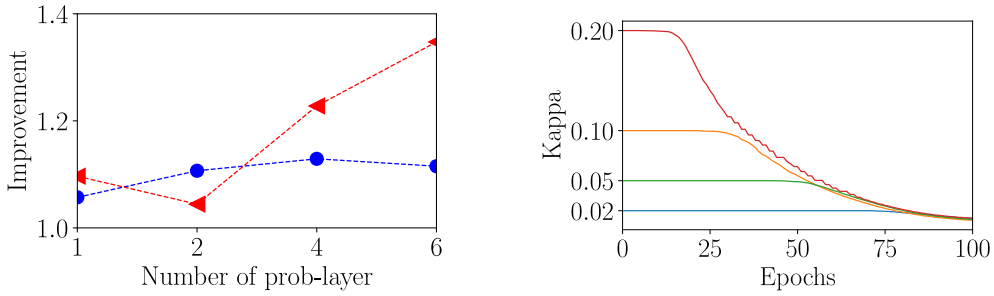


Figure 4: (Left) Performance improvement by number of prob layer: Dot (blue) on TS0 and triangle (red) on TSsameStruc. (Right) Kappa annealing with different initialization over 100 training epochs.

set but keeps improving on the TSsameStruct set. This is in line with our hypothesis that especially ambiguous samples profit more from the hierarchical architecture.

**Kappa Annealing** We assess the effect of kappa annealing when initializing $\kappa$ with different values. In this ablation, we compare a constant $\kappa$ to kappa annealing on the Hamming distance, see Table 4. In these results, kappa annealing always improves the performance and substantially stabilizes final performance across a range of initialization values. Figure 4 shows the adaption of $\kappa$ over a training run, demonstrating that it smoothly converges to a smaller value. Initializing with such a small value would yield much worse performance.

Table 4: Hamming distance with and w/o kappa annealing on different initialization.

| Kappa | w/o | annealing |
|---|---|---|
| 0.02 | 29.4 | 29.2 |
| 0.05 | 28.0 | 28.0 |
| 0.1 | 29.4 | 27.9 |
| 0.2 | 32.2 | 29.2 |

## 5 Related Work

**Related Transformer Models** A series of works enhanced the encoder-decoder Transformer architecture with a distribution in the latent space between encoder and decoder. During inference, the model samples from these distributions. There is work in the field of music representation [59] which does not use a posterior model. Work in neural machine translation [60, 61] has a separate posterior encoder and enhances the ELBO objective. This is similar to the work of Lin et al. [62] which introduces a variational decoder layer for dialogue modelling and has a separate posterior encoder. Other work in text generation [63, 64, 65] uses the encoder for the predictive and posterior model. In contrast to our work, neither of the methods mentioned above model hierarchical distributions or use the GECO objective. The work of Pei et al. [66] introduces a hierarchical stochastic multi-head attention mechanism aiming at uncertainty estimation. In contrast, we preserve the original attention mechanism by adding a new layer. The work of Liu et al. [64] also introduces a $\beta$ scheduling in $\beta$-VAE ELBO objective [29] similar to our kappa annealing but focused on the KL loss instead of the reconstruction objective.

**Related work in RNA folding** Until recently, RNA folding was dominated by dynamic programming (DP) algorithms using either thermodynamic, statistical, or probabilistic scoring functions [67]. Learning-based approaches to the problem benefit from making few assumptions on the folding process and allowing previously unrecognized base pairing constraints [42], which recently led to state-of-the-art performance using deep learning [37, 42]. We discuss these state-of-the-art deep learning approaches in detail in Appendix C.4 and refer to a recent review [68].

**Related Work in Molecule design** While a plethora of deep learning-based models have been proposed for *de novo* generation of molecules in the past five years [69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79], only some methods yet approached the challenging task of generating molecules with (multiple) predefined property values (conditional generation). These include conditional RNNs [80], cVAEs [81], conditional adversarially regularized autoencoders [82], and more recently

also Transformers [11]. Since [81] considers inorganic molecules and conditional generation is only performed in a case study in [82], and because of the usage of different evaluation protocols in [80] and [11], a correct evaluation and fair comparison of these approaches is out of the scope of this work. We, therefore, compare the ProbTransformer to the most similar and recent work in the field, *MolGPT*, which, to our knowledge, is the current state-of-the-art in the field. For more details on the different methods, we refer to multiple excellent reviews [83, 84, 51, 53].

## 6 Discussion and Conclusion

We propose a novel probabilistic layer to enhance the transformer architecture with hierarchical latent distributions while keeping the global receptive field via the attention mechanism. The ProbTransformer samples interdependent sequences in one forward path. This sampling happens in the latent space, and the ProbTransformer can refine or interpret a sampled latent representation in a further layer. Compared to sampling from the softmax output distribution, this approach yields greater flexibility. It also is compatible with other enhancements to the Transformer model since it only adds a new layer but keeps everything else unchanged.

We showed the benefits of our approach in several experiments. To our knowledge, the ProbTransformer is the first learned RNA folding model that can provide multiple correct structure proposals for a given RNA sequence, which opens the doors to novel research paths in RNA structure prediction that are in line with experimental evidence for RNA structural dynamics from, e.g., NMR studies, such as fraying [85], bulge migration [86], and fluctuating base pairs [86]. On the challenging multi-objective optimization task [54] of designing molecules with desired properties, we demonstrate superior control over molecule properties during the generation in a decoder-only setting compared to a state-of-the-art vanilla Transformer architecture. We want to point out that molecular research inevitably bears the risk of misuse [87], but we strongly distance ourselves from any such attempts.

However, our approach also has limitations. The additional layer and the posterior model increase the computational and memory needs up to a factor of two. Our approach is also limited to encoder-only or decoder-only setups since it requires a target of the same length as the input sequence. We have not applied our model in natural language processing yet, e.g. as a language model, which could improve predictive performance and save compute at inference time due to the probabilistic encoder. Another future application could be in text-to-speech or automated speech recognition since natural speech contains many ambiguities. In general, our approach and especially the conditional variational training using the GECO objective and kappa annealing, could be used in future probabilistic models. Kappa annealing reduces the need for exhaustive hyperparameter optimization and increases performance. Therefore, we expect that the positive impact of our work is not limited to RNA folding and molecule design but also to generative models in general.

## Acknowledgments and Disclosure of Funding

Jörg Franke, Frederic Runge, and Frank Hutter acknowledge funding by European Research Council (ERC) Consolidator Grant “Deep Learning 2.0” (grant no. 101045765). Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the ERC. Neither the European Union nor the ERC can be held responsible for them.

Funded by the European Union

A part of this work was supported by the German Federal Ministry of Education and Research (BMBF, grant RenormalizedFlows 01IS19077C) and by the German Research Foundation (DFG, grant no. 417962828). Furthermore, the authors acknowledge support by the state of Baden-Württemberg through bwHPC and the DFG (grant no. INST 39/963-1 FUGG). We also thank Tom Kaminski, Fabio Ferreira, Mahmoud Safari and Arbër Zela for useful comments on the manuscript.

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## Checklist

1. For all authors...
   (a) Do the main claims made in the abstract and introduction accurately reflect the paper's contributions and scope? [Yes] We describe our new approach in detail and provide a experimental evaluation with state-of-the-art results.
   (b) Did you describe the limitations of your work? [Yes] We mention them in Section 6.
   (c) Did you discuss any potential negative societal impacts of your work? [Yes] We are not aware of negative impacts of RNA folding or foundation in probabilistic modelling but in molecule design and mention this in Section 6.
   (d) Have you read the ethics review guidelines and ensured that your paper conforms to them? [Yes] We read it and our paper is conform.
2. If you are including theoretical results...
   (a) Did you state the full set of assumptions of all theoretical results? [N/A]
   (b) Did you include complete proofs of all theoretical results? [N/A]
3. If you ran experiments...
   (a) Did you include the code, data, and instructions needed to reproduce the main experimental results (either in the supplemental material or as a URL)? [Yes] We include the source code and scripts to build the data in the supplemental material.We also open source our code upon acceptance as mentioned in Section 4
   (b) Did you specify all the training details (e.g., data splits, hyperparameters, how they were chosen)? [Yes] Details about hyperparameter and data can be found in Appendices B,C, and D.
   (c) Did you report error bars (e.g., with respect to the random seed after running experiments multiple times)? [Yes] We report all experimental results including standard deviation on multi-seed runs in the Appendix.
   (d) Did you include the total amount of compute and the type of resources used (e.g., type of GPUs, internal cluster, or cloud provider)? [Yes] Details about compute resources can be found in Appendices B.2,C.2, and D.2.
4. If you are using existing assets (e.g., code, data, models) or curating/releasing new assets...
   (a) If your work uses existing assets, did you cite the creators? [Yes] We cite used open source libraries in the Appendix B.2.
   (b) Did you mention the license of the assets? [No] We use only open source software.
   (c) Did you include any new assets either in the supplemental material or as a URL? [No] We do not include any new assets.
   (d) Did you discuss whether and how consent was obtained from people whose data you're using/curating? [No]
   (e) Did you discuss whether the data you are using/curating contains personally identifiable information or offensive content? [No] Our data does not contain personally identifiable information or offensive content.
5. If you used crowdsourcing or conducted research with human subjects...
   (a) Did you include the full text of instructions given to participants and screenshots, if applicable? [N/A] We do not use crowdsourcing nor conducted research with human subjects.
   (b) Did you describe any potential participant risks, with links to Institutional Review Board (IRB) approvals, if applicable? [N/A] We do not use crowdsourcing nor conducted research with human subjects.
   (c) Did you include the estimated hourly wage paid to participants and the total amount spent on participant compensation? [N/A] We do not use crowdsourcing nor conducted research with human subjects.

# Appendix

## A Training Dynamics of ProbTransformer

In this section, we provide insights into the training dynamics of the ProbTransformer using the RNA folding task. In Figure 5 we visualize the progress of the training. The first row pictures the hamming distance on the validation set, in the second we show the learning rate schedule, in the third the annealing of kappa, in the fourth the cross-entropy loss $\mathcal{L}_{rec}$, in the fifth the KL loss $\mathcal{D}_{KL}$, in the sixth the adjustment of $\kappa$, and at the bottom the reconstruction constraint $\mathcal{L}_{rec} - \kappa$.

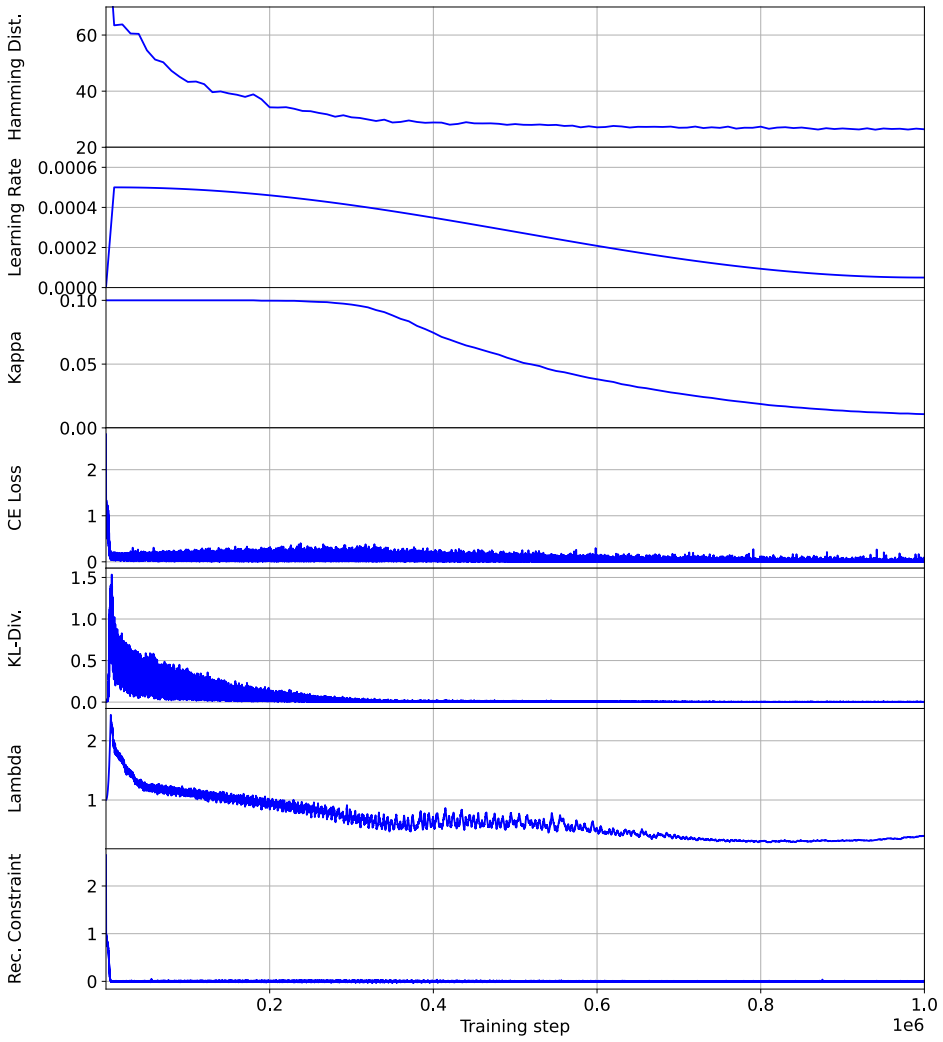


Figure 5: The training dynamics of the ProbTransformer in the RNA folding task.

We observe that the $\kappa$ decreases over time due to a low $\lambda$ which allows an increase in the pressure on the reconstruction. In Figure 6, we show the same training but with a log scale on the x-axis to focus on the early training phase. At the beginning of the training, the reconstruction constraint is not satisfied and the Lagrange multiplier $\lambda$ is increasing which results in pressure on the reconstruction loss. At the same time, the KL divergence increases due to reconstruction via $\mathbf{Z}^{post}$, leading to an increase in the initial distance of $P_\phi$ and $Q_\psi$. Once the reconstruction constraint is satisfied, $\lambda$ decreases and the pressure moves to the KL term. Also, the performance, measured in terms of the Hamming distance, does not improve even when the CE loss drops, since the CE loss only trains the posterior reconstruction. It only starts to improve when the KL divergence begins to decrease and the predictive model learns to create a useful internal latent representation.

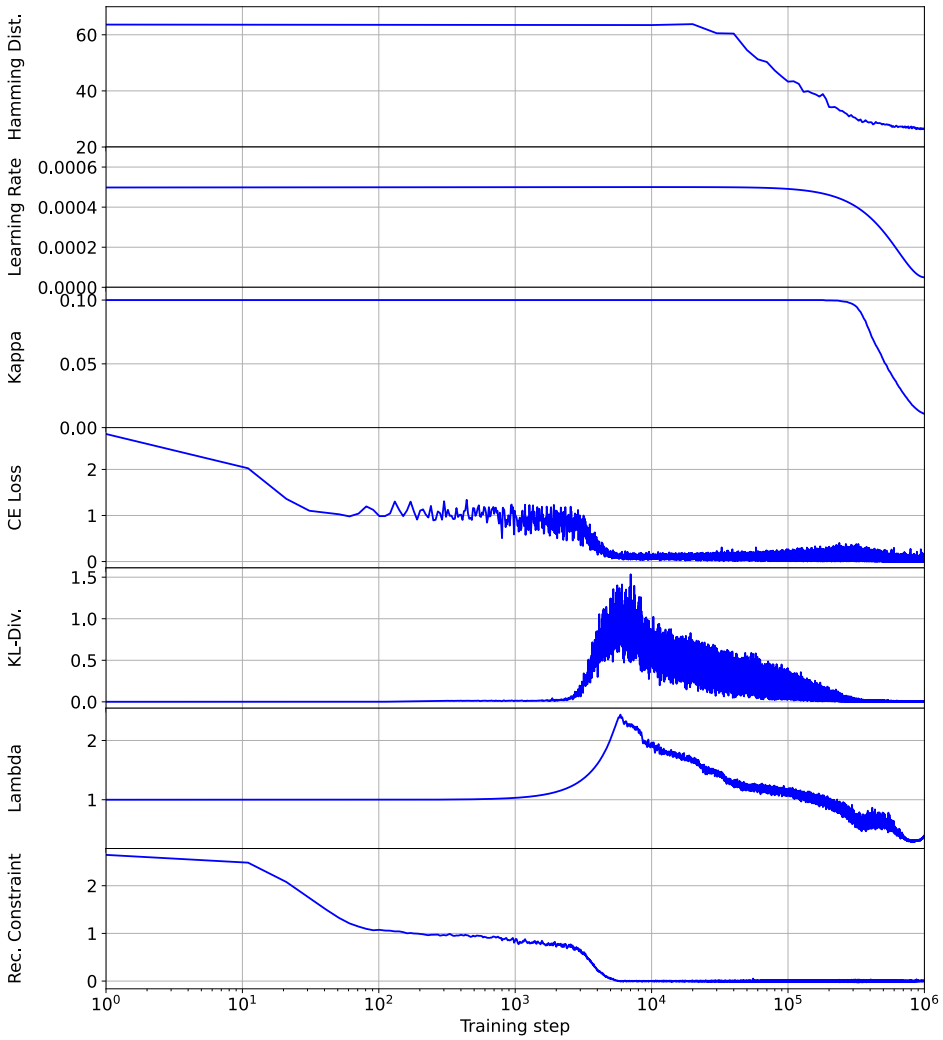


Figure 6: The training dynamics of the ProbTransformer in the RNA folding task but with log scale on the x axis to focus on the early phase of the training.

## B Synthetic Sequential Distribution Task

This section provides more details about the synthetic sequential distribution task itself, the configuration of the used Transformer and ProbTransformer model, the training process, and the results.

### B.1 Data

We design the task to map a sequence of tokens from a source vocabulary $x \in \mathcal{V}_i^*$ to a sequence of target tokens from a target vocabulary $y \in \mathcal{V}_o^*$ with the same length. The tokens in the source sequence are used to build 'phrases" $\mathbb{P}$. Each phrase consists of $l$ tokens sampled with replacement (similar to the combination of words in a sentence). We randomly generate a unique distribution $p(y|x, \mathbb{P})$ over the target tokens for each source token in each phrase, depending on the current phrase. Further, we design the distribution sparsely so that no more than $k$ tokens from the target vocabulary have a non-zero probability. The training data is generated by sampling input sequences from all phrases (with replacement) and sampling the target sequence from its corresponding distribution. The size of the source and target vocabulary is 500, a phrase exists of three tokens, and we create 1000 different sections. Each target token is drawn from a sparse distribution with 1 to 10 non-zero token probabilities. The sequence length is uniformly drawn from a length of 15 to 90. We created 100.000 training samples and 10.000 validation and test samples. Please find the detailed configuration of the task in Table 5.

Table 5: Configuration of the synthetic sequential distribution task.

| | |
|---|---|
| Max token length | 90 |
| Min. token length | 15 |
| Number of phrases | 1000 |
| Number of training samples | 100000 |
| Token per phrase $l$ | 3 |
| Possible target tokens $k$ | 10 |
| Vocabulary source tokens | 500 |
| Vocabulary target tokens | 500 |

Figure 7 shows an example of target distribution depending on the source phrase. On the x-axis, we show the target vocabulary consisting of number-tokens. On the y-axis, there are two phrases of source tokens. The yellow-green-blue color scheme represents the distribution of the target token mapping to a source token depending on the source phrase. Please note that the tokens in the second and third rows are the same but have different distributions due to the position in the phrase. A target sequence is sampled from this distribution, and in the optimal case, the model should be able to reproduce this distribution.

### B.2 Setup

In general, we implement our models and tasks in Python 3.8 using mainly PyTroch [88], Numpy [89], and Pandas [90]. We use Matplotlib [91] for the plots in the paper.

For experiments on the synthetic sequential distribution task, we use the configuration listed in Table 6 for the Transformer and ProbTransformer. For MC dropout, we employed a grid search to find the optimal Dropout rate $(0.1, 0.2, \cdots, \mathbf{0.5})$. The other hyperparameters were tuned manually based on preliminary work [1] or based on preliminary experiments. We use SiLU [92] as activation function in both models. Furthermore, we use automatic mixed-precision during the training, initialize the last linear of each layer (feed-forward, attention, or prob layer) with zero, and use a learning rate warm-up in the first epoch of training as well as a cosine learning rate schedule. We use the squared softplus function to ensure a positive $\lambda$ value during training and update $\lambda$ with a negative gradient scaling of $0.01$. For the moving average of the reconstruction loss, we use a decay of $0.95$.

### B.3 Results

We provide detailed results of our models and sampling methods with mean and standard deviation for five random seeds and evaluate two additional metrics: (1) We count the different output variations.

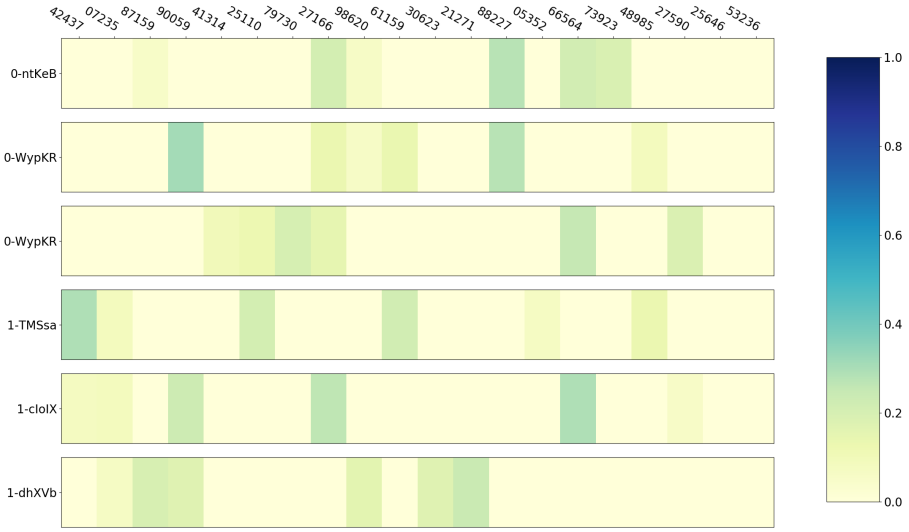


Figure 7: Target distribution depending on the source phrase.

Table 6: Hyperparameters of the Transformer and ProbTransformer training in the synthetic sequential distribution task.

| | |
|---|---|
| Feed-forward dim | 1024 |
| Latent Z dim | 256 |
| Model dim | 256 |
| Number of layers | 4 |
| Number of heads | 4 |
| Prob layer | all layer |
| Kappa | 0.1 |
| Dropout | 0.1 |
| Optimizer | adamW |
| Beta 1 | 0.9 |
| Beta 2 | 0.98 |
| Gradient Clipping | 100 |
| Learning rate schedule | cosine |
| Learning rate high | 0.001 |
| Learning rate low | 0.0001 |
| Warmup epochs | 1 |
| Weight decay | 0.01 |
| Epochs | 50 |
| Training steps per epoch | 2000 |

A perfect model creates the same *diversity* as nonzero probabilities in the true distribution. We normalize this measure to one; high values suggest more different tokens than non-zero tokens in the true distribution, and smaller values suggest fewer tokens. (2) Another measure for the distance between two distributions is the *total variation* which can deal with zero probabilities. Please find the results in Table 7.

Table 7: The mean and standard deviation of five random seeds for runs with Transformer and ProbTransformer in the Synthetic Sequential Distribution Task.

| Model | | Validity | | Diversity | | KL-divergence | | Total Variation | |
|---|---|---|---|---|---|---|---|---|---|
| | | mean | std | mean | std | mean | std | mean | std |
| ProbTransformer | | 0.99 | 0.0024 | 0.99 | 0.0002 | 0.52 | 0.0165 | 0.11 | 0.0007 |
| Transformer | dropout | 0.93 | 0.0198 | 0.72 | 0.0014 | 12.71 | 0.0357 | 0.35 | 0.0004 |
| | softmax | 0.73 | 0.0075 | 0.90 | 0.0020 | 7.84 | 0.0654 | 0.31 | 0.0016 |

# C RNA Folding

In this section, we detail our data pipeline, the general experimental setup and evaluation protocol, and show additional results, including standard deviations for multiseed runs, for our experiments on the RNA folding problem. We start, however, with a brief introduction to RNA functions and the importance of their secondary structure.

RNAs are one of the major regulators in the cell and have recently been connected to diseases like cancer [93] or Parkinson's [94, 95]. They consequently arise as a promising alternative for the development of novel drugs, including antiviral therapies against COVID-19[96] and HIV[97], or vaccines[98].

The vast majority of RNAs that are differentially transcribed from the human genome do not encode proteins [99, 100] and revealing the functions of these so-called non-coding RNAs (ncRNAs) is one of the main challenges for understanding cellular regulatory processes [31]. Similar to proteins, the function of an RNA molecule strongly depends on its folding into complex shapes, but unlike protein folding, which is dominated by hydrophobic forces acting globally, RNAs exhibit a hierarchical folding process [101]. In a first step, the corresponding nucleotides of the RNA sequence connect to each other by forming hydrogen bonds, resulting in local geometries and a distinct pairing scheme of the so-called secondary structure of RNA[3]. The secondary structure defines the accessibility of regions for interactions with other cellular compounds [31] and dictates the formation of the 3-dimensional tertiary structure [101, 102]. However, RNA structures are highly dynamic, which dramatically influences their functions [13, 14]. A learning algorithm that tackles the problem of predicting these structure ensembles is currently lacking in the field and we consider our work a major step in the direction of accurate RNA structure prediction.

## C.1 Data

In this section, we detail the datasets used during training and for our experiments. RNA sequences are chains of the four nucleotides (bases) *adenine*, *cytosine*, *guanine*, and *uracil*. However, RNA data often considers an extended nucleotide alphabet using IUPAC nomenclature[4] and we note that the datasets used in this work include IUPAC nucleotides.

A RNA secondary structure is typically described as a list of pairs where a pair $(i, j)$ denotes two nucleotides at the positions $i$ and $j$ of a RNA sequence that are connected by hydrogen bonds to form a base pair. In the simplest case, all pairs of the secondary structure are nested, i.e. if $(i, j)$ and $(k, l)$ describe two pairs of a secondary structure with $i < k$, then $i < k < l < j$. A functional important class of base pairs [47, 48], however, is called pseudoknots, where the nested pairing scheme is disrupted by one or more pairs of type: $i < k < j < l$. Canonical base pairs are formed between A and U, G and C (Watson-Crick pairs) or between G and U (Wobble pairs), while all other pairings of nucleotides are called non-canonical base pairs. We use the dot-bracket notation [12] for description of secondary structures where a dot corresponds to unpaired nucleotides and a pair of matching brackets denotes a pair of two nucleotides.

For our experiments we collect a large pool of annotated RNA secondary structures and their corresponding sequences from recent publications [41, 39, 37, 103, 38]. In particular, we collect 102098 samples from the BpRNA [103] meta database, two versions of the RNAStralign [104] dataset provided by [41] and [39] with 28168 and 20897 samples, respectively, two versions of the ArchiveII [105] dataset provided by [41] and [39] with 2936 and 3966 samples, the TR0, VL0, and TS0 datasets provided by [37] with 10814, 1300, and 1305 samples, respectively, the TrainSetA [106] and the TrainSetB [106] with 3164 and 1094 samples, respectively, and all available data from the RNA-Strand [38] database (3898 samples). For all data provided in `.bpseq`, .ct or similar file formats that only provide base pairs, we use BpRNA [103] to consistently annotate secondary structures with our major data source, the BpRNA metadatabase. We split the testset TS0 and the validation set VL0 from the pool and uniformly sampled a novel testset, TSsameSeq, from sequences of the remaining pool as described in Section 4.2. The highly redundant raw data consists of 177035

[3] We note that there is a longstanding discussion in the field of structural biology on what is called an RNA secondary structure and we use the broadest definition of secondary structure, i.e. including non-nested structures, in this work.

[4] We refer to the IUPAC nomenclature described by the International Nucleotide Sequence Database Collaboration (INSDC) at `https://www.insdc.org/documents/feature_table.html#7.4.1`.

training samples, 1300 validation samples and 1351 test samples. We remove duplicates from the data as well as samples that did not contain any pairs. We applied `CD-HIT-EST-2D` [107] to remove sequences from the training data with a sequence similarity greater than 80% to the validation and test samples, the lowest available threshold [37]. In accordance to [37], we limit the length of sequences to 500 nucleotides to save computational budget and since especially for longer RNAs, experimental evidence is generally still lacking because of challenges in crystallization and spectral overlap [108]. Table 8 summarizes the final datasets used for our experiments.

Table 8: Statistics of the different datasets used for our experiments on RNA folding.

| Dataset | # Samples | Unique Seq. | Unique Struc. | Avg. Length | Pair Types | | |
|---|---|---|---|---|---|---|---|
| | | | | | Canonical | Non-Canonical | Pseudoknots |
| Train | 52007 | 48092 | 27179 | 137.46 | 1701469 | 106208 | 47382 |
| VL0 | 1299 | 1299 | 1218 | 131.94 | 35301 | 4096 | 1001 |
| TS0 | 1304 | 1304 | 1204 | 136.09 | 36702 | 4083 | 1206 |
| TSsameStruc | 149 | 149 | 49 | 85.04 | 2849 | 211 | – |
| TSsameSeq | 46 | 20 | 46 | 176.46 | 2273 | 60 | 150 |

### C.2 Setup

In this section, we provide the configuration of the models and training details. We list the hyperparameters of the Transformer and ProbTransformer training in the RNA folding experiment in Table 9. We use the squared softplus function to ensure a positive $\lambda$ value during training and update $\lambda$ with a negative gradient scaling of $0.1$. For the moving average of the reconstruction loss we use a decay of $0.95$. We performed the training on one Nvidia RTX2080 GPU and the training time for one ProbTransformer model is $\sim$63h and for one Transformer $\sim$33h. The training time for the ProbTransformer nearly doubles due to the posterior model.

Table 9: Hyperparameters of the Transformer and ProbTransformer and training details of the RNA folding experiment.

| | |
|---|---|
| Feed-forward dim | 2048 |
| Latent Z dim | 512 |
| Model dim | 512 |
| Number of layers | 6 |
| Number of heads | 8 |
| Prob layer | 2,3,4,5 |
| Kappa | 0.1 |
| Dropout | 0.1 |
| Optimizer | adamW |
| Beta 1 | 0.9 |
| Beta 2 | 0.98 |
| Gradient Clipping | 100 |
| Learning rate schedule | cosine |
| Learning rate high | 0.0005 |
| Learning rate low | 0.00005 |
| Warmup epochs | 1 |
| Weight decay | 0.01 |
| Epochs | 100 |
| Training steps per epoch | 10000 |

#### C.2.1 CNN Head

Although the Transformer's and ProbTransformer's output prediction has a high quality, its still sometimes flawed. This hinders the evaluation of the F1 score and therefore the comparison on this metric to related work. Instead of manually designing an error correction heuristic we decided to learn a simple model which takes the Transformer's last latent and predicts an adjacency matrix which is use to evaluate the F1 score of our prediction.

We use a fixed-size CNN without up or down scaling. The detailed hyperparameters and training configuration of our CNN is listed in Table 10. The input is a concatenation of the vertical and horizontal broadcast of the last latent from the Transformer as well as the embedded nucleotide sequence. The output are two classes, one for a connection between nucleotides and one for no connection. We train our CNN head on the same training data as the Transformer and pre-compute the Transformer output to save computational resources during the CNN training, i.e. we do not train them jointly. We use early stopping based on the Hamming distance of the validation set. We perform the training on one Nvidia RTX2080 GPU and the training time is $\sim$3h.

Table 10: Hyperparameters of the CNN head and training configuration.

| | |
|---|---|
| Model dim | 64 |
| Number of layers | 8 |
| Stride | 1 |
| Kernel | 5 |
| Dropout | 0.1 |
| Optimizer | adamW |
| Beta 1 | 0.9 |
| Beta 2 | 0.98 |
| Gradient Clipping | None |
| Learning rate schedule | cosine |
| Learning rate high | 0.005 |
| Learning rate low | 0.0005 |
| Warmup epochs | 1 |
| Weight decay | 1e-10 |
| Epochs | 10 |
| Training steps per epoch | 2000 |

### C.3 Results

In this section, we describe our evaluation protocol in detail and show additional results for the predictions on the three test sets, TS0, TSsameStruc, and TSsameSeq, including standard deviations. For drawing of RNA secondary structures, we use `VARNA` [109] provided under GNU GPL License.

#### C.3.1 Evaluation

We evaluate all approaches concerning Hamming distance, the number of solved tasks, and the F1 score. The Hamming distance is the raw count of mismatching characters in two strings of the same length. A dot-bracket structure with a Hamming distance of zero counts as solved. F1 score describes the harmonic mean of precision (PR) and sensitivity (SN) and is computed as follows:

$$\text{PR} = \frac{\text{TP}}{(\text{TP} + \text{FP})} \quad , \tag{12}$$

$$\text{SN} = \frac{\text{TP}}{(\text{TP} + \text{FN})} \quad , \tag{13}$$

$$\text{F1} = 2 \cdot \frac{(\text{PR} \cdot \text{SN})}{(\text{PR} + \text{SN})} \quad , \tag{14}$$

where TP, FP and FN denote true positives, false positives and false negatives, respectively. For TSsameSeq, we only evaluate the best predictions concerning Hamming distance.

**SPOT-RNA** The output of SPOT-RNA is in `.ct` tabular format with columns for indication of pairs. Deriving pseudoknots from base pairs is not trivial [110, 103] and we, therefore, convert the output to `.bpseq` format and apply BpRNA [103], the same annotation tool as we used during data generation, to yield annotated secondary structures for all predictions of SPOT-RNA.

**MXFold2** MXFold2 directly outputs secondary structures in dot-bracket format, which we evaluate directly.

**RNAfold** As for MXFold2, RNAfold's predictions can be evaluated directly from the output in dot-bracket format.

We note that RNAfold and MXFold2 are not capable of predicting pseudoknots due to their underlying dynamic programming approach.

**UFold** In contrast to all other approaches, UFold cannot handle IUPAC nucleotides in the input sequences. When evaluating the exact same test data used for all other approaches, the recommended webserver of UFold at `https://ufold.ics.uci.edu/` as well as the standalone version generates predictions with different lengths compared to the inputs which cannot be evaluated. A fair comparison with UFold thus was not possible and we decided to exclude UFold from the evaluations in the main paper. However, we resolved IUPAC nucleotides by uniformly sampling corresponding canonical nucleotides for IUPAC nucleotides to create a dataset accepted by UFold. We use the dot-bracket output of UFold for evaluations since provided `.ct` files resulted in errors when trying to obtain secondary structures using BpRNA similar as described for SPOT-RNA due to predictions with nucleotides pairing with themselves. The results of UFold on TS0 and TSsameStruc are shown in Table 11.

Table 11: Structure fidelity of UFold and the ProbTransformer on TS0 and TSsameStruc.

| Model | TS0 | | | TSsameStruc | | |
|---|---|---|---|---|---|---|
| | F1 Score | Hamming | Solved | F1 Score | Hamming | Solved |
| ProbTransformer | **62.5** | **27.4** | **0.118** | **93.2** | **3.2** | **0.550** |
| UFold | 58.8 | 33.3 | 0.038 | 82.7 | 9.4 | 0.141 |

**ProbTransformer** Regarding Hamming distance and the number of solved structures, we directly evaluate the predictions of the ProbTransformer from the raw model outputs. For the F1 Score, however, we use a post-processing step using the CNN head to obtain an adjacency matrix as described above.

**Structure Ensemble Predictions** We use the dot-bracket output of all approaches for evaluations on TSsameSeq. The predictions with the lowest Hamming distance to the respective ground truth structure were used for the evaluation of performance.

### C.3.2 Detailed results

In this section, we provide further results for our experiments on the RNA folding problem, including standard deviations for multiseed runs.

**TS0** We provide additional results for predictions on TS0. In Table 12 we provide results with standard deviations. Figure 8, 9 and 10 show example predictions of different approaches. Figure 13 shows the F1 score for different base-pairs in comparison with related work.

Table 12: Mean and standard deviation for three random seeds of the ProbTransformer and Transformer on TS0.

| Model | TS0 | | | | | |
|---|---|---|---|---|---|---|
| | F1 Score | | Hamming | | Solved | |
| | mean | std | mean | std | mean | std |
| ProbTransformer | 62.5 | 0.004 | 27.4 | 0.3425 | 0.118 | 0.0037 |
| Transformer | 50.5 | 0.0109 | 35.27 | 0.5911 | 0.084 | 0.0019 |

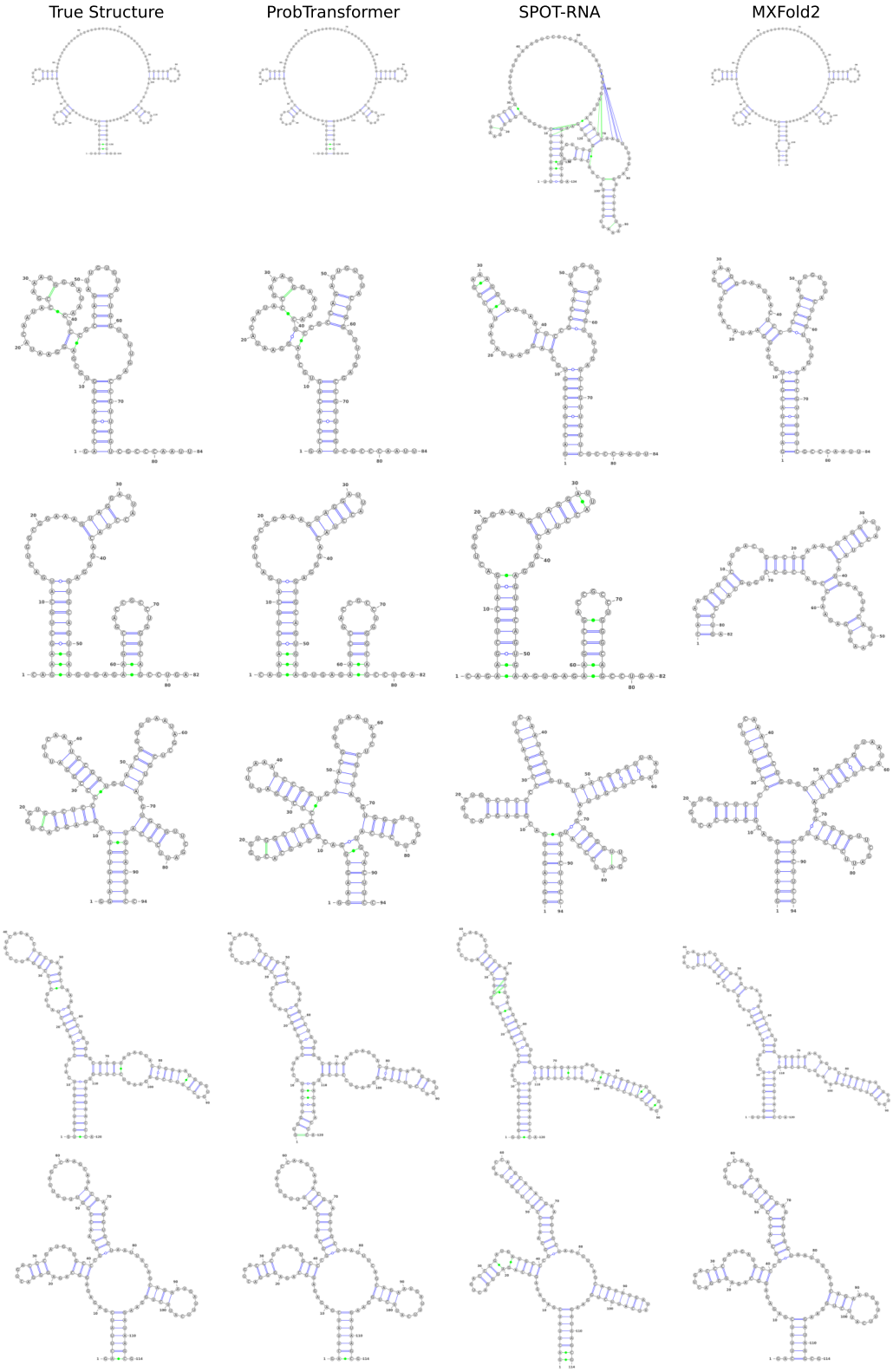


Figure 8: RNA Structure prediction examples for the test set TS0. The shown structures for the ProbTransformer are derived from the raw model outputs without further post-processing.

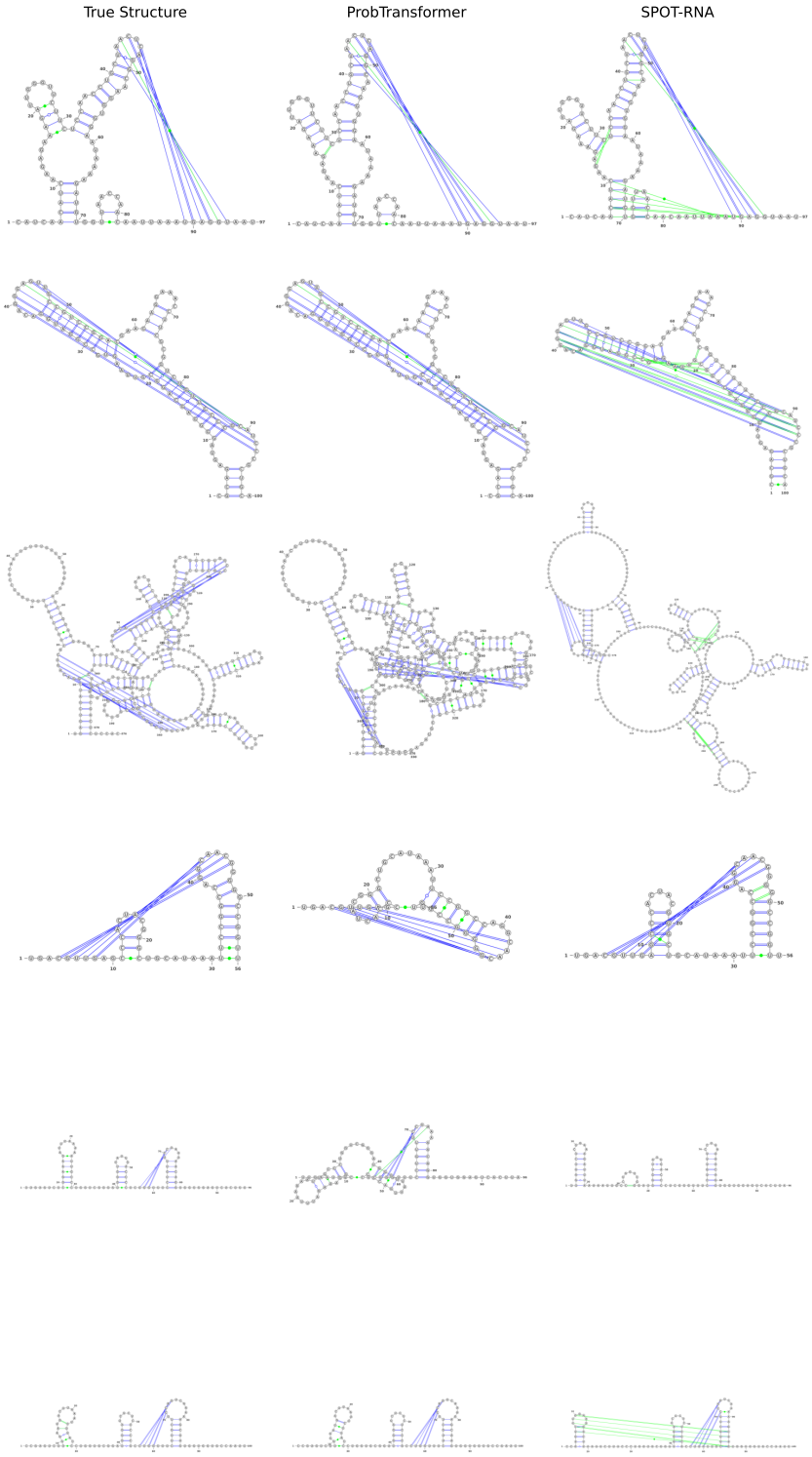


Figure 9: RNA Structure prediction examples for targets that contain pseudoknots from the test set TS0. The shown structures for the ProbTransformer are derived from the raw model outputs without further post-processing. We only show the two algorithms that are capable of predicting pseudoknots.

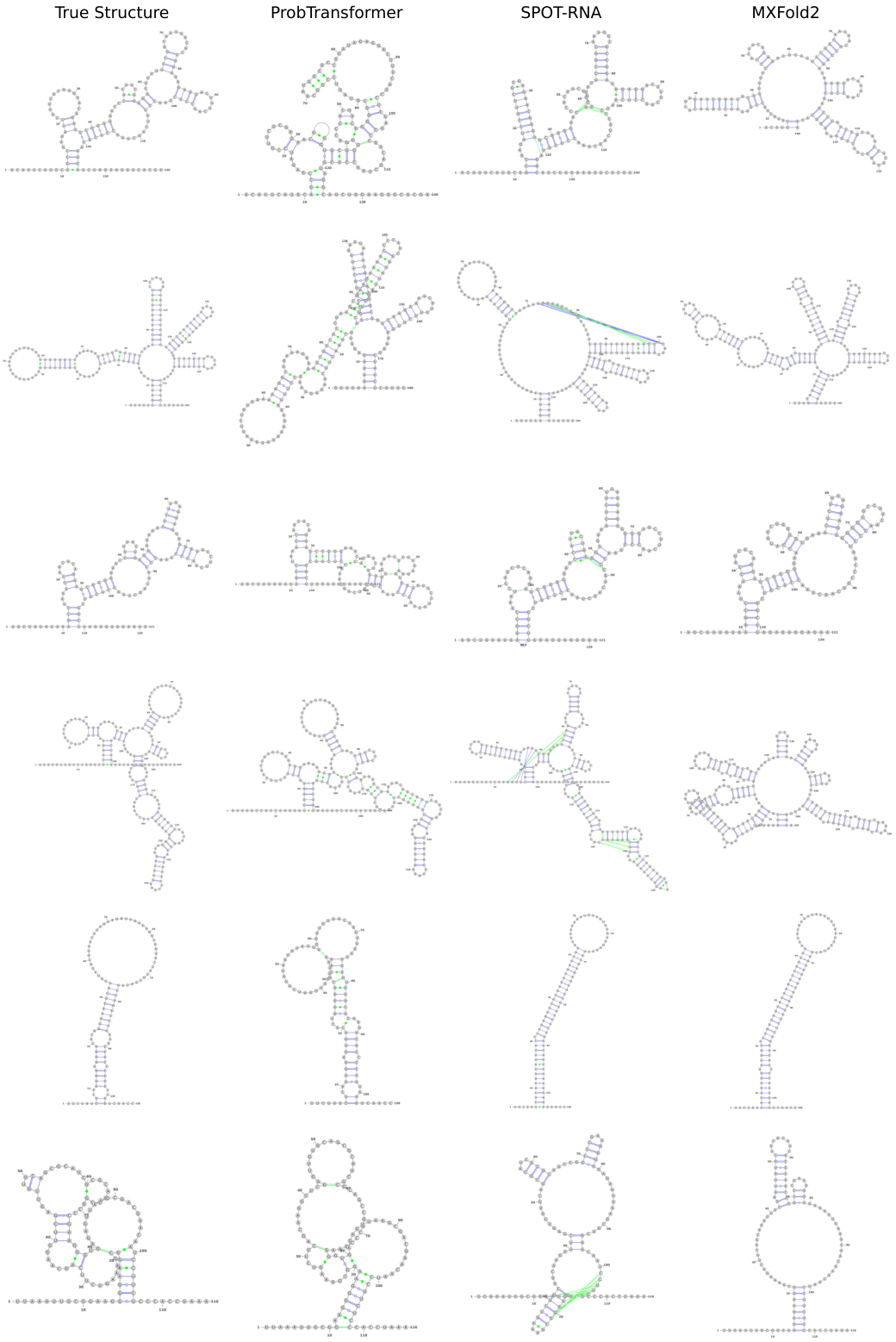


Figure 10: RNA Structure prediction examples for the test set TS0 for inaccurately predicted structures. The shown structures for the ProbTransformer are derived from the raw model outputs without further post-processing.

Table 13: The F1 score of different base-pairs of the ProbTransformer, Transformer and related work on TS0.

| Method | F1-All | F1-WC | F1-canonical | F1-wobble | F1-NC |
|---|---|---|---|---|---|
| ProbTransformer | 62.5 | 65.7 | 64.7 | 58.1 | 39.5 |
| Transformer | 50.5 | 53.4 | 52.5 | 47.7 | 36.3 |
| SPOT-RNA | 59.7 | 63.7 | 62.7 | 43.9 | 15.6 |
| MXFold2 | 55.0 | 58.0 | 57.0 | 41.7 | 0.0 |
| RNAFold | 49.2 | 52.0 | 50.8 | 36.9 | 0.0 |

**TSsameStruc** We provide additional results for predictions on TSsameStruc. Table 14 shows results with standard deviation.

Table 14: Mean and standard deviation for three random seeds of the ProbTransformer and Transformer on TSsameStruc.

| Model | TSsameStruc | | | | | |
|---|---|---|---|---|---|---|
| | F1 Score | | Hamming | | Solved | |
| | mean | std | mean | std | mean | std |
| ProbTransformer | 93.2 | 0.005 | 3.22 | 0.163 | 0.55 | 0.0055 |
| Transformer | 89.5 | 0.0111 | 4.55 | 0.0316 | 0.481 | 0.0084 |

**TSsameSeq** We provide results for the predictions on TSsameSeq to analyze the ability of the ProbTransformer to capture the structure distribution of RNA sequences that map to different structures. For all experiments, we inferred the model 5, 10, 20, 50, and 100 times using sample inference and analyzed the raw predictions without further post-processing. We observe that the ProbTransformer has learned the structure distributions from the data, producing predictions closer to the desired structures as indicated by a low Hamming distance shown in Table 15. The mean and standard deviations of the predictions are shown in Table 17, results for individual samples are summarized in Table 16. Remarkably, the ProbTransformer is the only model that reproduces both true structures for two of the 20 RNA sequences from the raw model predictions directly using only 5 inferences (with two out of three random seeds, results not shown).

Table 15: Average minimum Hamming distance of the different approaches on TSsameSeq.

| Model | Hamming Distance | | | | |
|---|---|---|---|---|---|
| | N=5 | N=10 | N=20 | N=50 | N=100 |
| ProbTransformer | **26.51** | **25.16** | **24.47** | **23.60** | **23.09** |
| Transformer | 49.17 | 49.17 | 49.17 | 49.17 | 49.17 |
| RNAsubopt | 42.59 | 42.83 | 38.09 | 34.22 | 31.30 |
| RNAshapes | 47.65 | 45.83 | 45.24 | 39.04 | 37.59 |
| RNAstructure | 47.22 | 42.02 | 38.04 | 35.20 | 32.59 |

Table 16: Minimal Hamming distances per Structure for all samples of TSsameSeq. We show results for one random seed of the ProbTransformer only.

| Family | #Structures | ProbTransformer | RNAsubopt | RNAshapes | RNAStructure |
|---|---|---|---|---|---|
| 5S rRNA | 2 | 0/0 | 8/12 | 12/16 | 8/12 |
| 5S rRNA | 2 | 8/0 | 16/12 | 14/10 | 24/22 |
| 5S rRNA | 2 | 8/0 | 10/2 | 12/4 | 12/4 |
| Group I catalytic intron | 2 | 24/24 | 44/47 | 51/53 | 50/56 |
| N/A | 2 | 76/88 | 51/65 | 59/71 | 60/72 |
| Antizyme RNA frameshifting stimulation element | 2 | 14/2 | 12/0 | 16/6 | 15/4 |
| N/A | 3 | 7/5/1 | 6/4/0 | 6/4/0 | 6/4/0 |
| tRNA | 2 | 0/4 | 4/0 | 4/0 | 4/0 |
| transfer-messenger RNA | 3 | 17/33/29 | 91/62/112 | 140/111/152 | 107/77/119 |
| tRNA | 2 | 0/2 | 2/0 | 2/0 | 2/0 |
| N/A | 2 | 14/13 | 12/2 | 12/2 | 10/0 |
| Bacterial small signal recognition particle RNA | 2 | 6/7 | 10/6 | 10/6 | 10/6 |
| Hammerhead ribozyme (type I) | 2 | 36/35 | 14/14 | 8/8 | 8/8 |
| Group I catalytic intron | 2 | 118/116 | 54/53 | 102/101 | 66/65 |
| 5S rRNA | 2 | 9/1 | 10/6 | 10/6 | 12/8 |
| 5S rRNA | 2 | 11/1 | 12/12 | 16/8 | 20/14 |
| Bacterial RNase P class A | 3 | 14/15/15 | 63/60/52 | 55/51/46 | 61/59/54 |
| Bacterial RNase P class A | 3 | 9/6/6 | 50/47/42 | 61/58/55 | 43/43/38 |
| Bacterial RNase P class B | 4 | 65/66/68/69 | 78/79/101/99 | 80/78/104/101 | 65/67/89/91 |
| 5S rRNA | 2 | 3/1 | 4/0 | 6/2 | 4/0 |

Table 17: Mean and standard deviation of the ProbTransformer and Transformer on TSsameSeq for three random seeds.

| Model | TSsameSeq | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N=5 | | N=10 | | N=20 | | N=50 | | N=100 | |
| | mean | std | mean | std | mean | std | mean | std | mean | std |
| ProbTransformer | 26.51 | 0.7754 | 25.16 | 0.4687 | 24.47 | 0.3388 | 23.60 | 0.2310 | 23.09 | 0.4820 |
| Transformer | 49.17 | 2.6304 | 49.17 | 2.6304 | 49.17 | 2.6304 | 49.17 | 2.6304 | 49.17 | 2.6304 |

### C.4 Related work RNA folding

In this section, we discuss state-of-the-art deep learning approaches for the RNA folding problem in detail.

*SPOT-RNA* [37] was the first algorithm using deep neural networks for end-to-end prediction of RNA secondary structures. In this work, an ensemble of residual networks (ResNets) [111] and bidirectional LSTMs [112] (BiLSTMs) [113] was pre-trained on a large set of RNA secondary structure data and then fine-tuned on a small set of experimentally-derived RNA data, including tertiary interactions. Although the authors claimed the possibility of predicting RNA tertiary interactions, the performance for these types of base pairs was poor and the currently available version of the algorithm excludes tertiary interactions from its outputs. We thus consider this work as RNA secondary structure prediction.

*E2efold* [41] uses a Transformer encoder architecture to learn the prediction of RNA secondary structures. The algorithm was trained on a very homologous set of RNA data and showed strongly reduced performance when evaluated on data of other publications [39, 42], indicating strong overfitting. Since we use the same data set as the respective work, we exclude *E2efold* from our evaluations.

*MXFold2* [39] combines deep learning with a DP approach by using a CNN/BiLSTM architecture to learn the scoring function for the DP algorithm. The network is trained to predict scores close to a set

of thermodynamic parameters to increase robustness. *MXFold2* is restricted to predict a reduced set of base pairs due to limitations in the DP algorithm.

*UFold* [42] employs a UNet [114] architecture for solving the RNA folding problem. Similar to *SPOT-RNA*, the authors additionally report results for predictions on data that contains tertiary interactions after fine-tuning the model on experimental data with slightly worse overall performance compared to *SPOT-RNA*. In contrast to the previously described works, however, *UFold* treats an RNA sequence as an image of all possible base-pairing maps (16 maps corresponding to 16 possible pairs) and an additional map for pair probabilities, represented as square matrices of the provided sequence.

# D Molecular Design

In this section, we provide further information on our experiments for the conditional generation of molecules based on multiple desired properties.

Estimations of the size of the chemical space [52] vary widely [115] (typically between $10^{20}$ and $10^{100}$) with a common consensus that it contains too many molecules to be explicitly enumerated [53]. Deep generative models recently attracted huge interest in exploring this practically infinite space for the use in drug discovery and deep learning-based molecular *de novo* generation has emerged as the most interesting and fast-moving field in cheminformatics [53] during the last five years. In this so-called generative chemistry [51], deep generative models are typically trained on a large part of enumerated chemical space to learn a biased distribution of molecular representations and evaluated for their ability to generate novel compounds and explore the unseen chemical space. Common evaluation protocols include metrics to measure e.g. the *novelty* of the designed compounds concerning the examples visited during training, their *uniqueness* to measure the internal diversity of predictions, and *validity* of the generated compounds regarding e.g. the underlying SMILES grammar [57]. However, besides general exploration which could be achieved using uniform sampling approaches [53], biological applications typically require that the designed molecules have certain desired properties. For generative models, the task is then to explore the chemical space conditioned on molecule properties (conditional generation).

## D.1 Data

For sequence-based approaches, a common way of representing molecules is the simple molecular line-entry system (SMILES) [15]. This notation was originally proposed to represent molecules as strings and uses a sequence of elements combined with special characters to enable branching, ring-closure, and different bond orders as well as indications for properties like charges [53]. To train the ProbTransformer, we use the training data of the GuacaMol [57] benchmark suite provided by [11]. Overall, the training data consists of 1259543 SMILES with a vocabulary of 94 unique characters.

## D.2 Setup

In this section, we provide the configuration of the models and training details. We list the hyperparameters of the Transformer and ProbTransformer training for the molecule design experiment in Table 18. Furthermore, we use automatic mixed-precision during the training, initialize the last linear of each layer (feed-forward, attention, or prob layer) with zero, and use a learning rate warm-up in the first epoch of training. We use the squared softplus function to ensure a positive $\lambda$ value during training and update $\lambda$ with a negative gradient scaling of $0.01$. For the moving average of the reconstruction loss, we use a decay of $0.95$. We performed the training on one Nvidia RTX2080 GPU and the training time for one ProbTransformer model is $\sim$25h and for one Transformer $\sim$13h.

We condition the generation of molecules on three properties:

The *synthetic accessibility score (SAS)* is a measure of how difficult it is to synthesize a compound. The values for *SAS* could generally range between 1 (easy to synthesize) and 10 (very difficult to make).

The *partition coefficient (logP)* describes the logarithm of the partition coefficient of a compound. This measure compares the solubilities of a solute in two immiscible solvents at equilibrium. If one of the solvents is water and the other one is non-polar, *logP* is a measure of hydrophobicity.

The *topological polar surface area (TPSA)* measures the ability of a drug to permeate cell membranes and describes the contributions of all polar atoms, such as oxygen and nitrogen and their attached hydrogens, to the molecular surface area. The polar surface area is a good estimator of the absorption, distribution, metabolism, excretion, and toxicology (ADMET)-relations of a compound and provides a rule-of-thumb for chemists to avoid dead-ends during the development process in drug discovery pipelines [116].

For our experiments, we follow the protocol described for *MolGPT* by choosing a value for each property from the following domains of values. *SAS*: 2.0, 4.0; *logP* 2.0, 6.0; *TPSA*: 40, 80. The model then conditionally generates molecules with the task to match all chosen values. Following *MolGPT*,

Table 18: Hyperparameters of the Transformer and ProbTransformer and training details of the molecule design experiment.

| | |
|---|---|
| Feed-forward dim | 1024 |
| Latent Z dim | 64 |
| Model dim | 256 |
| Number of layers | 8 |
| Number of heads | 8 |
| Prob layer | 2-7 |
| Kappa | 0.1 |
| Dropout | 0.1 |
| Optimizer | adamW |
| Beta 1 | 0.9 |
| Beta 2 | 0.98 |
| Gradient Clipping | 100 |
| Learning rate schedule | cosine |
| Learning rate high | 0.0005 |
| Learning rate low | 0.00005 |
| Warmup epochs | 1 |
| Weight decay | 0.01 |
| Epochs | 60 |
| Training steps per epoch | 5000 |

results are reported in terms of the mean average deviation (MAD) and the standard deviation (SD) relative to the range of the desired property values. While our experiment focuses on conditional generation to match the desired property values, we also report the following scores.

*Validity* describes the fraction of generated molecules that are expressed as valid SMILES. High validity indicates strong learning of the underlying SMILES grammar.

*Uniqueness* is a measure of the prediction diversity. Uniqueness is the fraction of unique predictions from all generated valid SMILES. Although this metric is known to be not well-defined [16] and can be tricked by very simple means [58], we report uniqueness scores for reasons of comparability to previous work in the field.

*Novelty* is the fraction of valid molecules that are different from the training samples. A high novelty indicates strong exploration while a low novelty indicates overfitting.

We use `rdkit` [117] for computations of TPSA and logP and use the provided script by [11] for computations of SAS.

### D.3 Results

We provide detailed results with standard derivation in Table 19. Figure 11 shows the distributions of properties for all valid predictions of the ProbTransformer and MolGPT. We observe less deviation from the desired property values for the predictions of the ProbTransformer compared to MolGPT. In line with these results, we observe that the ProbTransformer generates more unique molecules with properties close to the desired property values compared to MolGPT as indicated in Table 20. Example predictions of these molecules are shown in Figures 12, 13, 14, 15, 16, 17, 18, and 19. We use `rdkit` [117] for drawing of the molecules.

Table 19: Results of the ProbTransformer in multi-property (TPSA+logP+SAS) conditional training on GuacaMol dataset on five different seeds.

| | | | | TPSA | | logP | | SAS | |
|---|---|---|---|---|---|---|---|---|---|
| | Validity | Unique | Novelty | MAD | SD | MAD | SD | MAD | SD |
| mean | 0.981 | 0.821 | 1 | 2.47 | 2.04 | 0.22 | 0.18 | 0.16 | 0.14 |
| std | 0.0123 | 0.0858 | 0 | 0.3727 | 0.3715 | 0.0544 | 0.0449 | 0.0767 | 0.0623 |

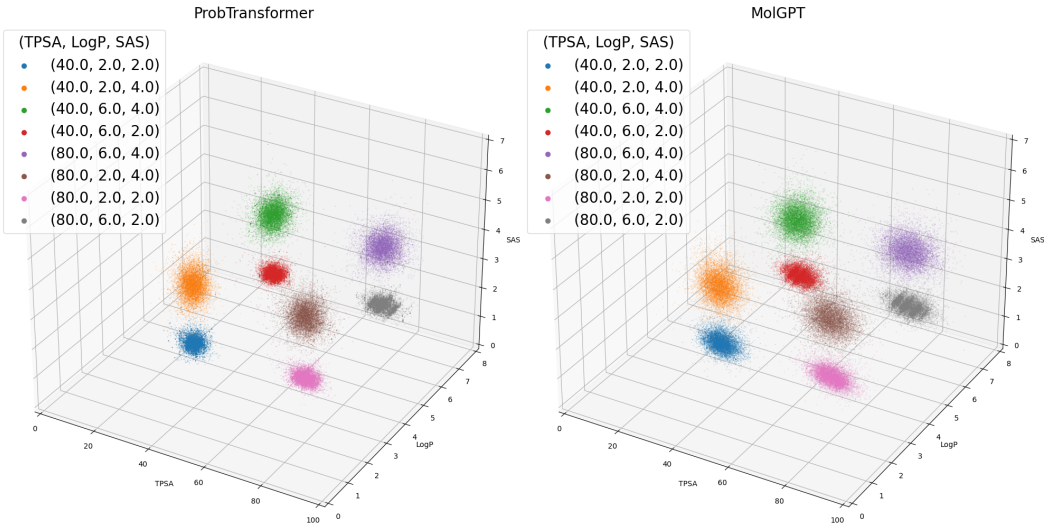


Figure 11: Distributions of predicted properties of the ProbTransformer and MolGPT. Results are shown for a representative seed for the ProbTransformer.

Table 20: Number of unique molecules that meet the desired properties for the ProbTransformer and MolGPT. We allow a deviation from the desired values of 0.5 for TPSA and 0.1 for SAS and LogP. Results show the mean with standard deviation for five random seeds of the ProbTransformer.

| (TPSA, LogP, SAS) | MolGPT | ProbTransformer | |
|---|---|---|---|
| | | Mean | Std |
| (40.0, 2.0, 2.0) | 58.0 | **80.4** | 4.1280 |
| (40.0, 2.0, 4.0) | 25.0 | **48.6** | 4.8415 |
| (40.0, 6.0, 4.0) | 20.0 | **40.4** | 3.7202 |
| (40.0, 6.0, 2.0) | 44.0 | **102.4** | 9.7693 |
| (80.0, 2.0, 2.0) | 105.0 | **220.2** | 16.8333 |
| (80.0, 2.0, 4.0) | 49.0 | **55.4** | 4.4091 |
| (80.0, 6.0, 4.0) | 50.0 | **60.8** | 6.2418 |
| (80.0, 6.0, 2.0) | 246.0 | **430.8** | 57.9876 |

TPSA: 40.0, LogP: 2.0, SAS: 2.0

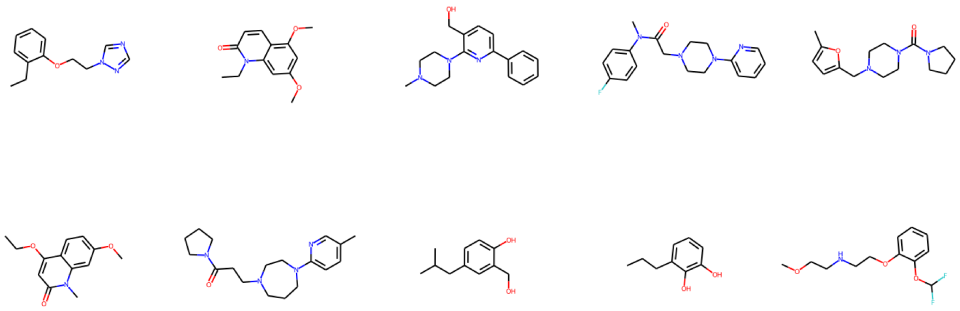

Figure 12: Example predictions of the ProbTransformer for property values of TPSA: 40.0; LogP: 2.0; SAS: 2.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

TPSA: 40.0, LogP: 2.0, SAS: 4.0

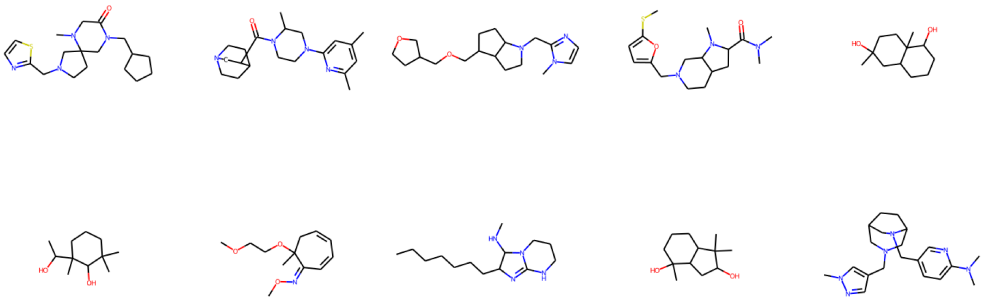

Figure 13: Example predictions of the ProbTransformer for property values of TPSA: 40.0; LogP: 2.0; SAS: 4.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

TPSA: 40.0, LogP: 6.0, SAS: 4.0

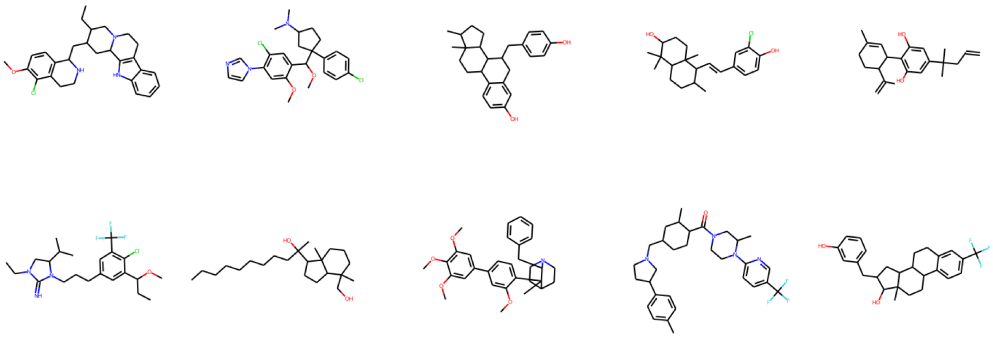

Figure 14: Example predictions of the ProbTransformer for property values of TPSA: 40.0; LogP: 6.0; SAS: 4.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

TPSA: 40.0, LogP: 6.0, SAS: 2.0

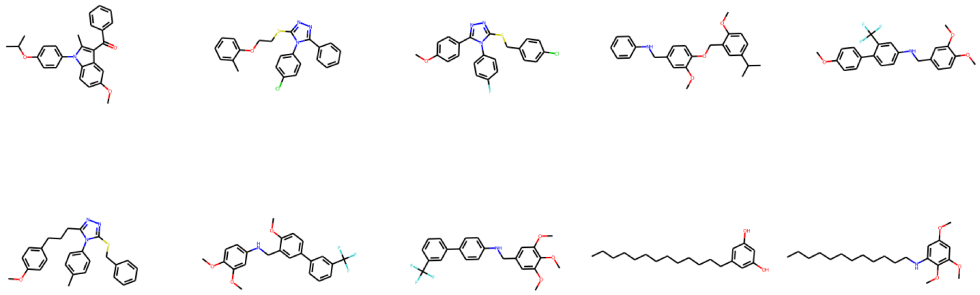

Figure 15: Example predictions of the ProbTransformer for property values of TPSA: 40.0; LogP: 6.0; SAS: 2.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

TPSA: 80.0, LogP: 2.0, SAS: 2.0

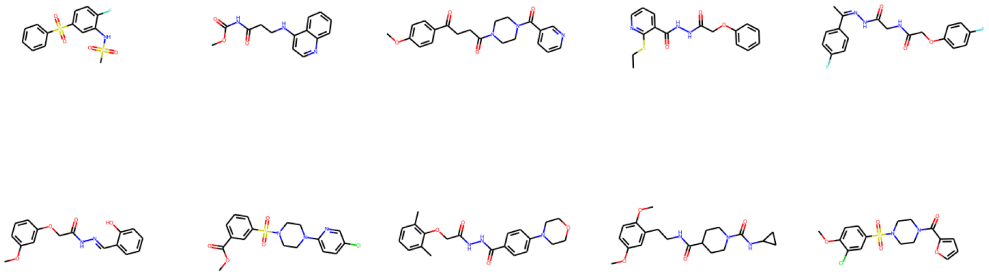

Figure 16: Example predictions of the ProbTransformer for property values of TPSA: 80.0; LogP: 2.0; SAS: 2.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

TPSA: 80.0, LogP: 2.0, SAS: 4.0

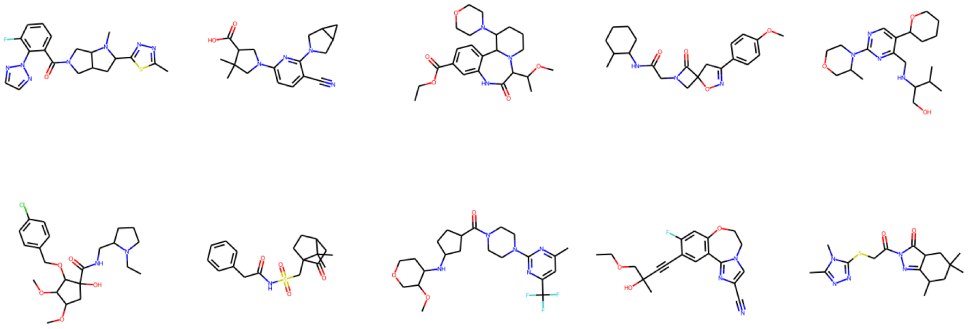

Figure 17: Example predictions of the ProbTransformer for property values of TPSA: 80.0; LogP: 2.0; SAS: 4.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

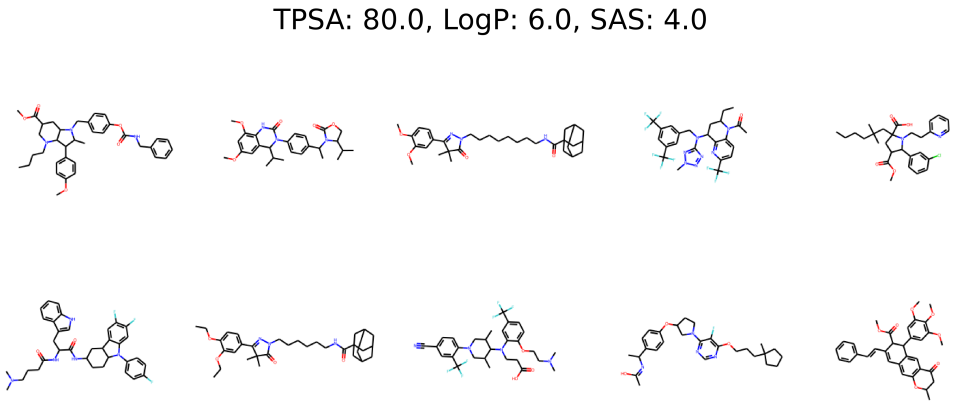


Figure 18: Example predictions of the ProbTransformer for property values of TPSA: 80.0; LogP: 6.0; SAS: 4.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

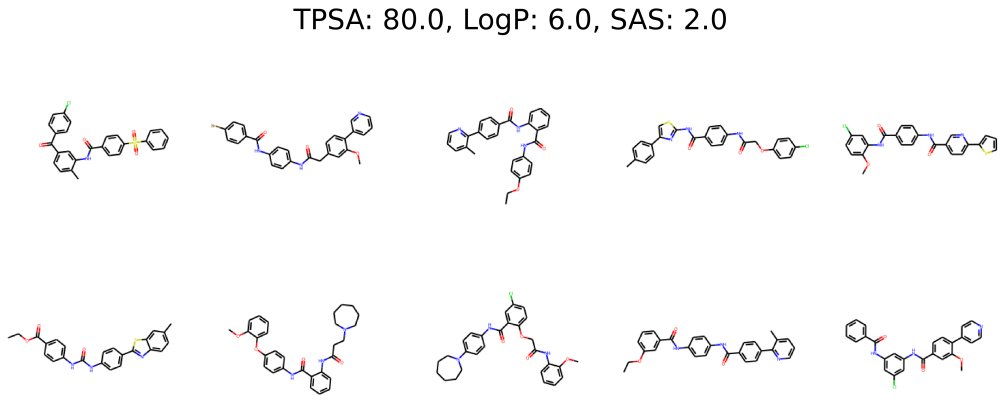


Figure 19: Example predictions of the ProbTransformer for property values of TPSA: 80.0; LogP: 6.0; SAS: 2.0 with an allowed deviation of 0.5, 0.1, and 0.1, respectively.

### D.4 Related Work

Inspired by progress in the field of natural language processing (NLP), early work employed recurrent neural networks (RNNs) to produce focus libraries based on the SMILES notation [73]. Later on, these approaches were coupled with reinforcement learning (RL) to focus the generation on molecules with desirable properties [69, 74]. Additional methods were proposed to tackle the problem, including generative adversarial networks (GANs) [70, 71], variational autoencoders (VAEs) [75, 76], and adversarial autoencoders (AAEs) [72, 77, 78, 79]. For more details on the different methods, we refer the interested reader to multiple reviews of the field [83, 84, 51, 53].

More recently, the success of self-attention mechanisms entered the field and novel methods were developed, adding attention either to RNNs [16] or VAEs [16, 118]. Remarkably, Transformer-based VAEs showed more complex latent representations of molecules and outperformed previous state-of-the-art VAEs [79] in the field [16].

However, as discussed before in Section 5, only some methods yet approached the challenging task of generating molecules with (multiple) predefined property values (conditional generation) [73, 80, 81, 82, 11].

# E Ablation Study

We list the hyperparameters of the Transformer and ProbTransformer as well as the training configuration for the ablation study in Table 21. We performed the training on one Nvidia RTX2080 GPU and the training time for one ProbTransformer model is ∼56h (1 prob layer) to ∼80h (all prob layer) and for one Transformer ∼33h. Also, we reduced the learning rate for the architecture ablation study due to unstable training when using all prob layers.

Table 21: Hyperparameters of the Transformer and ProbTransformer and training details of the ablation study.

| | |
|---|---:|
| Feed-forward dim | 2048 |
| Latent Z dim | 512 |
| Model dim | 512 |
| Number of layers | 6 |
| Number of heads | 8 |
| Prob layer | 4,3-4,2-5,all |
| Kappa | 0.1 |
| Dropout | 0.1 |
| Optimizer | adamW |
| Beta 1 | 0.9 |
| Beta 2 | 0.98 |
| Gradient Clipping | 100 |
| Learning rate schedule | cosine |
| Learning rate high | 0.0001/5 |
| Learning rate low | 0.00001/5 |
| Warmup epochs | 1 |
| Weight decay | 0.01 |
| Epochs | 200 |
| Training steps per epoch | 5000 |