Absorb & Escape: Overcoming Single Model Limitations in Generating Genomic Sequences

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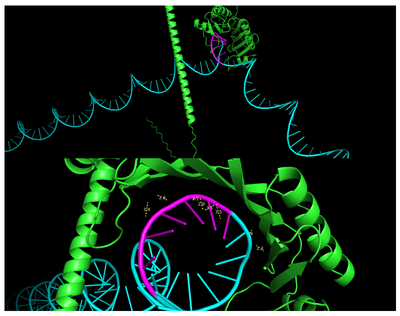
Abstract

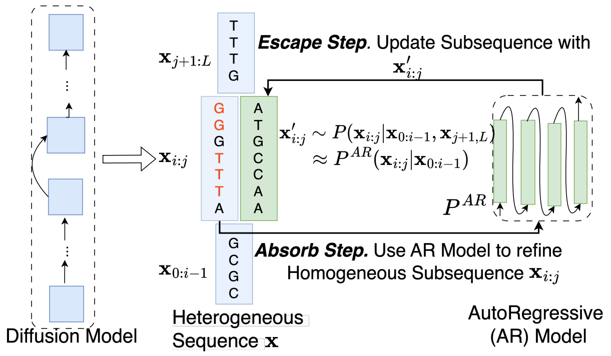
Recent advances in immunology and synthetic biology have accelerated the development of deep generative methods for DNA sequence design. Two dominant approaches in this field are AutoRegressive (AR) models and Diffusion Models (DMs). However, genomic sequences are functionally heterogeneous, consisting of multiple connected regions (e.g., Promoter Regions, Exons, and Introns) where elements within each region come from the same probability distribution, but the overall sequence is non-homogeneous. This heterogeneous nature presents challenges for a single model to accurately generate genomic sequences. In this paper, we analyze the properties of AR models and DMs in heterogeneous genomic sequence generation, pointing out crucial limitations in both methods: (i) AR models capture the underlying distribution of data by factorizing and learning the transition probability but fail to capture the global property of DNA sequences. (ii) DMs learn to recover the global distribution but tend to produce errors at the base pair level. To overcome the limitations of both approaches, we propose a post-training sampling method, termed **A**bsorb **&** **E**scape (A&E) to perform compositional generation from AR models and DMs. This approach starts with samples generated by DMs and refines the sample quality using an AR model through the alternation of the Absorb and Escape steps. To assess the quality of generated sequences, we conduct extensive experiments on 15 species for conditional and unconditional DNA generation. The experiment results from motif distribution, diversity checks, and genome integration tests unequivocally show that A&E outperforms state-of-the-art AR models and DMs in genomic sequence generation. A&E does not suffer from the slowness of traditional MCMC to sample from composed distributions with Energy-Based Models whilst it obtains higher quality samples than single models. Our research sheds light on the limitations of current single-model approaches in DNA generation and provides a simple but effective solution for heterogeneous sequence generation. Code is available at the Github Repo[1].

1 Introduction

DNA sequences, as the blueprint of life, encode proteins and RNAs and directly interact with these molecules to regulate biological activities within cells. The success of deep generative models in image [28], text [27], and protein design [35] has drawn the attention of deep learning researchers to the problem of DNA design, i.e. applying these models to genomic sequence generation [4, 34, 38]. However, one rarely explored issue is how well existing methods can handle the unique property of DNA sequences: heterogeneity. DNA sequences are highly heterogeneous, consisting of multiple

[1]https://github.com/Zehui127/Absorb-Escape


(a) **A DNA generated by A&E, interacting with TATA-binding protein.** The DNA sequences highlighted in magenta are the TATA-box motif. The confirmation is predicted by AlphaFold 3 [1]: the DNA bends at the TATA-box position.



Diffusion Model
$\mathbf{x}_{j+1:L}$
T T T G
$\mathbf{x}_{i:j}$
G G G T T T A
A T G C C A A
$\mathbf{x}_{0:i-1}$
G C G C
Escape Step. Update Subsequence with $\mathbf{x}'_{i:j}$
$\mathbf{x}'_{i:j} \sim P(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1,L}) \approx P^{AR}(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$
P^{AR}
Absorb Step. Use AR Model to refine Homogeneous Subsequence $\mathbf{x}_{i:j}$
Heterogeneous Sequence $\mathbf{x}$
AutoRegressive (AR) Model

(b) The proposed framework Fast **A**bsorb **& E**scape (Fast A&E): The DM and AR models jointly optimize a given sequence by alternating between the A-step and the E-step. See Section 4 for a detailed explanation.

Figure 1: (a) Generated DNA interacting with TATA-binding protein. (b) Proposed A&E framework.

connected functional regions (e.g. Promoter Regions, Exons, and Introns) in sequential order. While elements within each functional region might be homogeneous (coming from the same distribution), the overall sequence is non-homogeneous. This heterogeneity, along with the discrete nature of genomic sequences, poses challenges to popular deep generative methods.

Limitations of Existing Single-Model Approaches in Generating Genomic Sequences AutoRegressive Models (AR) [8, 17, 24] are one of the most dominant approaches for discrete sequence generation. To model the data distribution of a sequence x of length T, the probability of x is factorized as:

$$p^{AR}(\mathbf{x}) = \prod_{i=1}^{T} p_\theta(x_i|x_1, x_2, \dots, x_{i-1}). \tag{1}$$

An issue arises when modeling heterogeneous data, where the value of θ may vary significantly from one segment to another. Additionally, AR models assume a dependency between the current element and previous elements; this assumption may not hold true for heterogeneous sequences, potentially hindering the learning process (see Section 3 for details).

On the other hand, Diffusion Models (DMs), initially proposed by [30], have been dominant in image generation. In the probabilistic denoising view [16], DMs gradually add noise to the input data x_0, and a reverse diffusion (generative) process is trained to gradually remove the noise from the perturbed data x_t. DMs directly model the data distribution without AutoRegressive factorization, thereby avoiding the issues associated with AR models. However, it has been shown that DMs are less competent than AR models for discrete data generation [21, 36]. When it comes to modeling heterogeneous genomic sequences, it remains unclear how the performance of DMs compares to AR models within each homogeneous segment.

Model Composition As a Solution Balancing the ability of generative algorithms to capture both local and global properties of the data distribution is central to the problem. An obvious solution could be to combine these two types of models and perform generation using the composed models. However, this typically requires converting these two models into an Energy-Based Model and then sampling using Markov Chain Monte Carlo (MCMC), which can be inherently slow due to the sampling nature of the algorithm [10], and the potential long inference time of individual models. With the goal of accurate and efficient DNA generation, we aim to investigate two key questions in this work: (i) How well does a single AR model or DM perform in DNA generation, given the heterogeneous nature of genomic sequences? (ii) Is there an efficient algorithm to combine the benefits of AR models and DMs, outperforming a single model? In answering these two questions, *our contribution is three-fold*:

(a) We study the properties of AR models and DMs in heterogeneous sequence generation through theoretical and empirical analysis (Section 3).

(b) We design the theoretical framework **A**bsorb **&** **E**scape (A&E) to sample from the compositional distribution of an AR model and a DM (Section 4.1). Furthermore, as shown in Figure 1b, we propose an efficient post-training sampling algorithm termed Fast A&E to sample from the composed model, requiring at most one forward pass through the pretrained DM and AR model (Section 4.2).

(c) We design a comprehensive evaluation workflow for DNA generation, assessing the sequence composition, diversity, and functional properties of generated genomic sequences. Extensive experiments (15 species, 6 recent DMs, 1 AR model, and 3 types of evaluations) reveal: 1) the limitations of existing models in DNA generation (Section 5.3), and 2) that the proposed algorithm Fast A&E consistently outperforms state-of-the-art models as measured by motif distribution and functional property similarity to natural DNA sequences (Sections 4.2 and 5.3).

2 Preliminaries and Related Work

2.1 Problem Formulation: DNA Generation

DNA generation aims to produce synthetic sequences that functionally approximate real DNA sequences. Formally, let $\mathbb{N}_4 = \{1, 2, 3, 4\}$, where each element represents one of the four nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C). A DNA sequence of length L can be represented as $\mathbf{x} \in \mathbb{N}_4^L$, with each element/nucleotide denoted by $\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_L$.

Unconditional Generation: Given a dataset of real-world DNA sequences $\mathcal{X} = \{\mathbf{x}^{(n)}\}_{n=1}^N$ collected from some distribution $p(\mathbf{x})$, where each sequence $\mathbf{x}^{(n)} \in \mathbb{N}_4^L$ represents a chain of nucleotides, the objective is to develop a generative model $p_{\boldsymbol{\theta}}(\mathbf{x})$ of the data distribution $p(\mathbf{x})$ from which we can sample novel sequences $\tilde{\mathbf{x}} \sim p_{\boldsymbol{\theta}}(\mathbf{x})$. These sequences should be structured arrangements of A, T, G, and C, reflecting the complex patterns found in actual DNA. Earlier works applying Generative Adversarial Networks (GANs) [13] to generate protein-encoding sequences [14] and functional elements [33, 34, 38] fall into this category.

Conditional Generation: In this task, the dataset of DNA sequences $\mathcal{X} = \{\mathbf{x}^{(n)}, c^{(n)}\}_{n=1}^N$ is sampled from the joint distribution $p(\mathbf{x}, c)$, where c represents the condition associated with each sequence. The objective is to develop a model $p_{\boldsymbol{\theta}}(\mathbf{x}|c)$ that generates new DNA sequences $\tilde{\mathbf{x}}$ given condition c. Recently, a discrete diffusion model DDSM [4] and an AutoRegressive model RegML [20] have used expression level as the condition, while DNADiffusion [26] has used cell type as the condition.

2.2 Homogeneous vs. Heterogeneous Sequences

Homogeneous Generation Process In the context of sequence generation, a homogeneous Markov Chain is characterized by constant probabilistic rules for generating the sequence at each time step t. More generally, a process is defined as **homogeneous** if the transition probabilities are independent of time t. This means there exists a constant $P_{\mathbf{c},j}$ such that:

$$P_{\mathbf{c},j} = \Pr[\mathbf{x}_t = j \mid \mathbf{x}_{1:t-1} = \mathbf{c}] \tag{2}$$

holds for all times t, where $P_{\mathbf{c},j}$ is a constant, and $\mathbf{c}$ represents a specific sequence of past values, i.e., $\mathbf{c} = (c_1, c_2, \ldots, c_{t-1})$.

Heterogeneous Generation Process Assuming homogeneous properties simplifies modeling but can be overly restrictive for certain modalities, leading to inaccuracies. For example, DNA sequences consist of various functionally distinct regions, such as promoters, enhancers, regulatory regions, and protein-coding regions scattered across the genome [11]. Each region may be assumed to be homogeneous, but the overall sequence is non-homogeneous due to the differing properties of these elements.

For sequences like DNA, which consist of locally homogeneous segments, we define them as **heterogeneous sequences**. Formally, a heterogeneous sequence is defined as follows: Suppose a sequence $\mathbf{x}$ is divided into segments $\mathcal{S}_1, \mathcal{S}_2, \ldots, \mathcal{S}_m$, where each segment $\mathcal{S}_i$ is homogeneous. For each segment $\mathcal{S}_i = (\mathbf{x}_t, \mathbf{x}_{t-1}, \mathbf{x}_{t-2}, \ldots, \mathbf{x}_{t-k})$, there exists a constant $P_{\mathbf{c}_i,j}$ such that:

$$P_{\mathbf{c}_i,j} = \Pr[\mathbf{x}_t = j \mid \mathbf{x}_{t-k:t-1} = \mathbf{c}_i] \tag{3}$$

holds for all times t within segment $\mathcal{S}_i$, where $P_{\mathbf{c}_i,j}$ is a constant, and $\mathbf{c}_i = (c_{i,t-1}, c_{i,t-2}, \ldots, c_{i,t-k})$ represents values characterizing the history within that segment. While segment $\mathcal{S}_i$ is homogeneous, the entire sequence is non-homogeneous due to the varying properties across different segments.

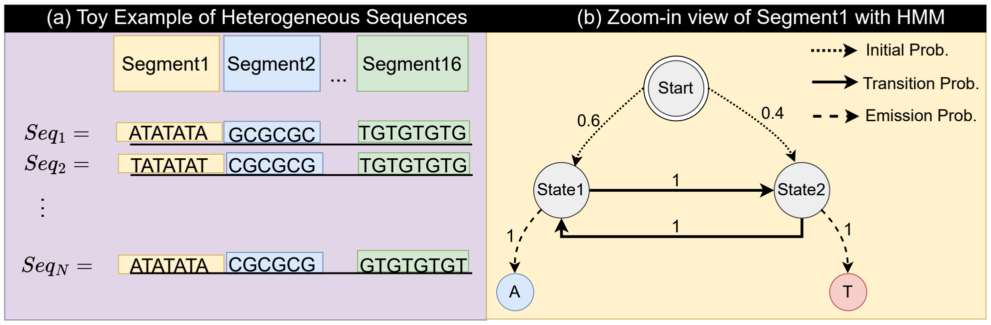

(a) Toy Example of Heterogeneous Sequences
Segment1
Segment2
...
Segment16
$Seq_1 =$ ATATATA GCGCGC TGTGTGTG
$Seq_2 =$ TATATAT CGCGCG TGTGTGTG
$Seq_N =$ ATATATA CGCGCG GTGTGTGT
(b) Zoom-in view of Segment1 with HMM
Start
0.6
0.4
State1
State2
1
1
1
1
A
T
Initial Prob.
Transition Prob.
Emission Prob.

Figure 2: A toy example with heterogeneous sequences: (a) The overall training set consists of $N = 50,000$ heterogeneous sequences, where each sequence further consists of 16 homogeneous segments. We apply an autoregressive and a diffusion model to learn the underlying distribution. (b) Within each segment, the sequences are generated with a simple Hidden Markov Model (HMM), with deterministic transition probability and emission probability.

3 Single Model Limitations in Heterogeneous Sequence Generation

How powerful are AR models and DMs in modelling heterogeneous sequences? We first provide a theoretical analysis, and then perform experiments on synthetic sequences to validate our assumption.

AutoRegressive (AR) Models Suppose a heterogeneous sequence $\mathbf{x}$ consist of two homogeneous segments of length k, then $\mathbf{x} = \{\{x_1, x_2, \cdots, x_k\}, \{x_{k+1}, x_{k+2}, \cdots, x_{2k}\}\}$. AR models factorize $p(\mathbf{x})$ into conditional probability in eq. (4); consider the case where the true factorisation of $p(x)$ follows eq. (5).

$$p^{AR}(\mathbf{x}) = p_\theta(x_1)p_\theta(x_2|x_1)\cdots p_\theta(x_k|\mathbf{x}_{1:k-1}) \cdot p_\theta(x_{k+1}|\mathbf{x}_{1:k})p_\theta(x_{k+2}|\mathbf{x}_{1:k+1})\cdots p_\theta(x_{2k}|\mathbf{x}_{1:2k-1}) \tag{4}$$

$$p^{data}(\mathbf{x}) = \underbrace{p_1(x_1)p_1(x_2|x_1)\cdots p_1(x_k|\mathbf{x}_{1:k-1})}_{\text{Segment 1}} \cdot \underbrace{p_2(x_{k+1})p_2(x_{k+2}|\mathbf{x}_{k+1})\cdots p_2(x_{2k}|\mathbf{x}_{k+1:2k-1})}_{\text{Segment 2}} \tag{5}$$

AR factorisation allows the accurate modelling of the first homogeneous segment; however, it may struggle to disassociate the elements of the second segment from the first segment. More precisely, sufficient data is needed for AR model to learn that $p_\theta(x_{k+1}), p_\theta(x_{k+2}), \cdots, p_\theta(x_{2k})$ should be independent to the elements $\{x_1, x_2, \cdots, x_k\}$ in the first segments. Secondly, when the context length of the AR model is shorter than the sequence length $2k$, it could struggle to capture the difference between p_1 and p_2 with a single set of parameters θ.

Diffusion Models (DMs) On the other hand, DMs estimate the overall probability distribution $p(\mathbf{x})$ without factorization. The elements of $\mathbf{x}$ are usually generated in parallel. Thus, they do not suffer from the conditional dependence assumption. However, the removal of the conditional dependence assumption may also decrease the accuracy of generation within each homogeneous segment compared to AR models, as DMs do not explicitly consider previous elements.

3.1 A Toy Example

To evaluate the performance of Autoregressive (AR) models and Diffusion Models (DMs) in generating heterogeneous sequences, we consider a toy example with 50,000 heterogeneous sequences $\mathcal{X} = \{\mathbf{x}^{(n)}\}_{n=1}^{50000}$. Each sequence contains 16 segments, as illustrated in Figure 2(a), and each segment comprises 16 elements, resulting in a total sequence length of 256 ($\mathbf{x} \in \mathbb{N}_4^{256}$). A simple Hidden Markov Model (HMM) is used to generate each segment, as shown in Figure 2(b), with deterministic transition and emission probabilities that ensure homogeneity within each segment. The emitted tokens differ from one segment to another, mimicking the properties of real DNA sequences. Whilst it is possible to use more complex distributions for each segment, doing so could complicate the evaluation of the generated sequences.

Evaluation Under our toy HMM setup, a generative model could make two types of mistakes within each segment: **1) Illegal Start Token**: The generated sequence starts with a token which has zero emission probability. E.g. in Figure 2(b), the starting token could only be $\{A, T\}$. $\{G, C\}$ at the beginning of the sequence are classified as illegal start tokens. **2) Incorrect Transition**: The generated sequence contains tokens with zero transition probability. E.g. in Figure 2(b) given the start of the sequence is (A, T, A, T), the next token must be A, any other tokens such as $\{T, G, C\}$ are classified as incorrect transitions. We use the number of incorrect tokens as the metric for evaluation.

Experiment We use HyenaDNA [20, 24] as the representative autoregressive (AR) model. For the diffusion model, we develop a simple latent Discrete Diffusion model termed DiscDiff. It resembles the design of StableDiffusion [28], a latent diffusion model for image generation. DiscDiff consists of a CNN-based Variational Encoder-decoder, trained with cross entropy, to map the discrete DNA data into a latent space, and a standard 2-D UNet as the denoising network (detailed in appendix A). The training dataset consists of $\mathcal{X} = \{\mathbf{x}^{(n)}\}_{n=1}^{50,000}$. For detailed training procedures see Appendix B. We generate 4,000 sequences from each model and present the evaluation results in Table 1. As expected, the diffusion model DiscDiff makes fewer errors regarding Illegal Start (IS) tokens but tends to generate more Incorrect Transition (IT) tokens. Conversely, while the AR model HyenaDNA generates some IS token errors, it produces significantly fewer IT token errors. This motivates the question: *can we combine the strengths of both algorithms to achieve better sequence generation?*

Table 1: **Number of Incorret Tokens on Synthetic Dataset**. The performance metrics used are the number of Illegal Start (IS) Tokens and Incorrect Transition (IT) Tokens. Note that there are a total of $4,000 \times 256 = 1024,000$ tokens.

	HyenaDNA	DiscDiff
# IS Tokens ↓	812	**0**
# IT Tokens ↓	**3,586**	110,192

4 Method

Algorithm 1 Absorb & Escape Algorithm

```
Require: Pretrained AutoRegressive model $p_\theta^{AR}(\mathbf{x})$ and pretrained Diffusion Model $p_\beta^{DM}(\mathbf{x})$
 1: Initialize $\tilde{\mathbf{x}}^0 \sim p_\beta^{DM}(\mathbf{x})$
 2: Set $t = 0$
 3: Assume $\mathbf{x} = \{\mathbf{s}_1, \mathbf{s}_2, \ldots, \mathbf{s}_n\}$, where each $\mathbf{s}_k = \{\mathbf{x}_i, \mathbf{x}_{i+1}, \cdots, \mathbf{x}_j\}$ is a segment
 4: while not converged do
 5:     Sample a segment $\mathcal{S} \in \{\mathbf{s}_1, \mathbf{s}_2, \ldots, \mathbf{s}_n\}$
 6:     Set $i$ = start index of $\mathbf{s}_k$, $j$ = end index of $\mathbf{s}_k$
 7:     Absorb step:
 8:     $\tilde{\mathbf{x}}'_{i:j} \sim p(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1:L}) \approx p_\theta^{AR}(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$ //Refine segment $\mathbf{s}_k$ using the AR model
 9:     Escape step:
10:     $\tilde{\mathbf{x}}^t_{i:j} = \tilde{\mathbf{x}}'_{i:j}$ //Update $\tilde{\mathbf{x}}^t$
11:     Increment $t = t + 1$
12: end while
13: Output: Final sample $\tilde{\mathbf{x}}^t$ with improved quality
```

Algorithm 2 Fast Absorb & Escape Algorithm

```
Require: Absorb Threshold $T_{Absorb}$, Pretrained AutoRegressive model $p_\theta^{AR}(\mathbf{x})$ and pretrained Diffusion Model $p_\beta^{DM}(\mathbf{x})$
 1: Initialize $\tilde{\mathbf{x}}^0 \sim p_\beta^{DM}(\mathbf{x})$
 2: for $i$ in $len(\tilde{\mathbf{x}})$ do
 3:     if $p^{DM} < T_{Absorb}$ then
 4:         Absorb step:
 5:         j = i+1
 6:         $\tilde{\mathbf{x}}'_j \sim p_\theta^{AR}(\mathbf{x}_j|\mathbf{x}_{0:i})$
 7:         while $p^{AR}(\tilde{\mathbf{x}}'_j) > p^{DM}(\tilde{\mathbf{x}}_j)$ do
 8:             Increment $j = j + 1$
 9:             $\tilde{\mathbf{x}}'_j \sim p_\theta^{AR}(\mathbf{x}_j|\mathbf{x}_{0:i}, \mathbf{x}_{i:j-1})$ //Refine Inaccurate region of the sequence token by token
10:         end while
11:         Escape step:
12:         $\tilde{\mathbf{x}}_{i:j} = \tilde{\mathbf{x}}'_{i:j}$ //Update $\tilde{\mathbf{x}}$
13:         Increment i = i + j
14:     end if
15: end for
16: Output: $\tilde{\mathbf{x}}$ with improved quality
```

4.1 The Absorb & Escape Framework

Given a pretrained AutoRegressive model $p_\theta^{AR}(\mathbf{x})$ and a Diffusion Model $p_\beta^{DM}(\mathbf{x})$, we aim to generate a higher quality example $\tilde{\mathbf{x}}$ from the composed distribution $p_{\theta,\beta}^{C}(\mathbf{x}) = p_\theta^{AR}(\mathbf{x}) \circ p_\beta^{DM}(\mathbf{x})$. However, directly computing $p_{\theta,\beta}^{C}(\mathbf{x})$ is generally intractable, as both the autoregressive factorizations from p^{AR} and score functions from p^{DM} are not directly composable [9, 10]. We propose the **A**bsorb **& E**scape (A&E) framework, as shown in Algorithm 1, to efficiently sample from $p_{\theta,\beta}^{C}(\mathbf{x})$.

Absorb-Step Inspired by Gibbs sampling [12], which iteratively refines each dimension of a single sample and moves to higher density areas, our algorithm starts with a sequence $\mathbf{x}^0 \sim p^{DM}(\mathbf{x})$, generated by the diffusion model and then refines the samples through the Absorb step and Escape step. By exploiting the heterogeneous nature of the sequence, we assume that $\mathbf{x}^0$ can be factorized into multiple segments $\{\mathbf{s}_1, \mathbf{s}_2, \ldots, \mathbf{s}_n\}$. For each segment $\mathbf{s}_k$, we set i and j as the start and end indices, respectively. During the Absorb step, we sample a subset of segments $\mathcal{S} \subseteq \{\mathbf{s}_1, \mathbf{s}_2, \ldots, \mathbf{s}_n\}$ and refine each segment $\mathbf{s}_k$ by sampling $\tilde{\mathbf{x}}'_{i:j} \sim p(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1:L}) \approx p_\theta^{AR}(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$, using the autoregressive model to approximate the conditional probability.

Escape-Step After refining the segment in the Absorb step, we proceed with the Escape step where we update the refined segment $\tilde{\mathbf{x}}^t_{i:j}$ to $\tilde{\mathbf{x}}'_{i:j}$. This iterative process continues for each selected segment $\mathbf{s}_k$, with t incrementing after each update. By leveraging the ability of the diffusion model to capture the overall data distribution and the autoregressive model to refine homogeneous sequences within each segment, our algorithm efficiently improves the quality of the generated samples. The final output $\tilde{\mathbf{x}}^t$ is hereby closer to the true data distribution $p(\mathbf{x})$ compared to the initial sample $\tilde{\mathbf{x}}^0$. A proof for the convergence in Proposition 1 is provided in Appendix C.

Proposition 1. *The Absorb & Escape (A&E) algorithm converges to the target distribution $p_{\theta,\beta}^{C}(\mathbf{x}) = p_\theta^{AR}(\mathbf{x}) \circ p_\beta^{DM}(\mathbf{x})$, under the assumptions that both models are properly trained, the segments of $\mathbf{x}$ are homogeneous, the subset of segments is chosen randomly, and the conditional distribution $p(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1:L})$ is accurately approximated by $p_\theta^{AR}(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$.*

4.2 Practical Implementation: Fast A&E

While A&E offers a method to sample from a compositional distribution, two practical issues remain unresolved. Firstly, the algorithm may take a considerable amount of time to converge. Secondly, a crucial step in Line 3 of Algorithm 1 involves splitting $\mathbf{x}$ into homogeneous segments $\{\mathbf{s_1}, \mathbf{s_2}, \cdots, \mathbf{s_n}\}$ and then sampling a subset of these segments. Segmentation is straightforward when the boundaries of functional regions of the DNA sequence are known, such as protein-coding regions, exons, or introns, where each region naturally forms a homogeneous segment. However, this information is often unavailable in practice.

To address these challenges, we propose a practical implementation termed Fast A&E. For generating a sequence $\mathbf{x} \in \mathbb{N}_4^L$, it requires at most L forward passes through the AR model. As shown in Algorithm 2 and Figure 1b, Fast A&E adopts a heuristic-based approach to select segments for refinement. It scans the sequence from left to right, identifying low-quality segments through a thresholding mechanism. Tokens with predicted probabilities smaller than the T_{absorb} threshold trigger the absorb action, while the autoregressive process terminates once the probability of a token generated by the AR model $p^{DM}(\tilde{\mathbf{x}}'_j)$ is smaller than that of the diffusion model $p^{AR}(\tilde{\mathbf{x}}_j)$. In this manner, Fast A&E corrects errors made by the diffusion model with a maximum running time of $O(T_{DM} + T_{AR})$, where T_{DM} and T_{AR} are the times required for generating a single sequence from the diffusion model and autoregressive model, respectively.

5 Experiment

5.1 Transcription Profile (TP) conditioned Promoter Design

We first evaluate Fast A&E in the task of TP-conditioned promoter design, following the same evaluation procedures and metrics as used by DDSM [4] and Dirichlet Flow Matching (DFM) [32].

Data Format & Evaluation Metric: Each data point in this task is represented as a (DNA, signal) pair, where *signal* corresponds to the CAGE values for a given DNA sequence, providing a quantitative measure of gene expression around the transcription start site (TSS). Both the DNA sequence and the signal have a length of 1024. The goal of this task is to generate DNA sequences conditioned on specified signals. During evaluation, for a given test set data point (x, c), the generated sequence $\tilde{\mathbf{x}}$ and the ground truth sequence are processed through the genomic neural network Sei [37]. The performance metric is the mean squared error (MSE) between $Sei(x)$ and $Sei(\tilde{\mathbf{x}})$.

Table 2: **Evaluation of transcription profile conditioned promoter sequence design.** A&E achieves the smallest MSE with Language Model and DFM distilled being the AR and DM components.

Method	**MSE↓**
Bit Diffusion (bit-encoding)*	.0414
Bit Diffusion (one-hot encoding)*	.0395
D3PM-uniform*	.0375
DDSM*	.0334
Language Model*	.0333
Linear FM*	.0281
Dirichlet FM (DFM)*	.0269
Dirichlet FM distilled (DFM distilled)*	.0278
A&E (Language Model+Dirichlet FM distilled)	**.0262**

Results: As shown in Table 2, we ran Fast A&E on this task with a default threshold of $T_{\text{absorb}} = 0.85$, using the pretrained model as both the autoregressive (AR) model and the denoising model (DM) component. The evaluation followed the same procedure as described in the DFM repository. The Fast A&E model, comprising AR and DM components (i.e., the language model and the distilled DFM checkpoints provided in the DFM repository), achieved state-of-the-art results with an MSE of 0.0262 on the test split.

5.2 Multi-species Promoter Generation

5.2.1 Experimental Setup

Dataset Construction Prior efforts in DNA generation have been constrained by small, single-species datasets [19, 34]. To better evaluate the capability of various generative algorithms in DNA generation, we construct a dataset with 15 species from the Eukaryotic Promoter Database (EPDnew)[23]. Table 3 compares our EPD dataset with those used in previous studies, including DDSM[4], ExpGAN [38], and EnhancerDesign [33]. The key advantage of EPD is its diversity in both species types and DNA sequence types. Additionally, although the number of sequences in EPD is on a similar scale to that of DDSM, EPD offers greater uniqueness: each sequence corresponds to a unique promoter-gene combination, a guarantee not provided by the other datasets.

Baseline Model We evaluate the state-of-the-art diffusion models for DNA sequence generation: *DDSM* [4], *DNADiffusion* [26], *DDPM* [2, 3], and a AR model *Hyena* [20, 24]. In addition, we implement a VAE with a CNN-based encoder-decoder architecture. Adding UNet as the denoising network to VAE results in another baseline latent diffusion model termed *DiscDiff*. For a fair evaluation, we maximally scale up the denoising networks of each diffusion model to fit into an 40GB NVIDIA A100. Additionally, we adapt four pretrained *Hyena* models from HuggingFace for comprehensive fine-tuning. The additional details of the network architectures are shown in Appendix D.

Table 3: **A comparison of DNA generation datasets.** EPD used in this work is significantly larger in size and contains fifteen species. Reg. represents the regulatory regions, and Prot. represents the protein encoding region.

Dataset	# DNA	Multi Species	DNA Regions
EPD (Ours)	**160,000**	✓	Reg. & Prot.
DDSM [4]	100,000	×	Reg. & Prot.
ExpGAN [38]	4238	×	Reg.
EnhancerDesign [33]	7770	×	Reg.

Model Training All the models are implemented in Pytorch and trained on a NVIDIA A100-PCIE-40GB with a maximum wall time of 48 GPU hours per model; most of the models converged within the given time. Adam optimizer [7] is used together with the CosineAnnealingLR [22] scheduler. The learning rate of each model are detailed in Appendix D. For the evaluation of various diffusion models in unconditional generation (see Section 5.2.2), we sample 50,000 sequences from each model. For the conditional generation across 15 species (see Section 5.3), we generate 4,000 sequences. In both cases, we use the DDPM sampler [31] with 1,000 sequential denoising steps.

5.2.2 Evaluating Diffusion Models on Mammalian Model Organisms

Table 4: Comparison of diffusion models on unconditional generation evaluated on EPD (256 bp) and EPD (2048 bp). Metrics include S-FID, Cor_{TATA}, and MSE_{TATA}. The **best** and <u>second-best</u> scores are highlighted in bold and underlined, respectively.

	EPD (256 bp)			EPD (2048 bp)		
Model	S-FID ↓	Cor_{TATA} ↑	MSE_{TATA} ↓	S-FID ↓	Cor_{TATA} ↑	MSE_{TATA} ↓
Random (Reference)	119.0	-0.241	8.21	106.0	0.030	1.86
Sample from Training Set	0.509	1.0	0	0.100	0.999	0
VAE	295.0	-0.167	26.5	250.0	0.007	9.40
BitDiffusion	405	0.058	5.29	100.0	0.066	5.91
D3PM (small)	<u>97.4</u>	0.0964	4.97	<u>94.5</u>	0.363	**1.50**
D3PM (large)	161.0	-0.208	<u>4.75</u>	224.0	0.307	8.49
DDSM (Time Dilation)	504.0	<u>0.897</u>	13.4	1113.0	<u>0.839</u>	2673.7
DiscDiff (Ours)	**57.4**	**0.973**	**0.669**	**45.2**	**0.858**	<u>1.74</u>

One prerequisite of Fast A&E (Algorithm 2) is that the diffusion model P_β^{DM} should be properly trained and provide accurate approximations of underlying data distribution. We first evaluate existing Diffusion Models on a subset of EPD datasets. This subset includes sequences from four mammalians *H. Sapiens* (human), *Rattus Norvegicus* (rat), *Macaca mulatta*, and *Mus musculus* (mouse), which collectively represent 50% of the total dataset. Training on this subset allows for a more precise assessment of the generative algorithm's accuracy in a unconditional generation setting.

Metrics

1. **Motif Distribution Correlation (Cor_M)** and **Mean Square Error (MSE_M)**: Cor_M is the Pearson correlation between the motif distributions of generated and natural DNA sequences for motifs like TATA-box, GC-box, Initiator, and CCAAT-box. MSE_M is the average squared differences between these motif distributions.
2. **S-FID (Sei Fréchet Inception Distance)**: Measures the distance between distributions of generated and natural DNA sequences in latent space similar to the FID metric [15] for images, replacing the encoder with the pre-trained genomic neural network, Sei [37].

The results are presented in Table 4, indicating that most existing models perform worse than the simple baseline DiscDiff proposed here, as measured by S-FID, Cor_{TATA}, and MSE_{TATA}. TATA is one of the most fundamental motifs for gene transcription – a special type of protein called transcription factors binds to TATA tokens on the DNA as shown in Figure 1a. It changes the shape of DNA and then enables the gene transcription. The failure of existing diffusion models to capture the TATA-box distribution indicates a potential gap in existing research. In the following, we hereby use DiscDiff as the p_β^{DM} to initialize the A&E algorithm.

5.3 Multi-species DNA Sequences Generation

We compare our model Fast A&E with *Hyena* [24] and the best-performing diffusion model from Section 5.2.2, *DiscDiff*, on the task of generating species-specific DNA sequences.

Motif-centric Evaluation We consider four types of motifs closely related to promoter activities $\{\text{TATA-box}, \text{GC-box}, \text{Initiator}, \text{CCAAT-box}\}$. We calculate 4 types of motif distributions for 15 species across 3 models, resulting in 180 frequency distributions.

Figure 3 shows the average MSE and Correlation between generated and natural DNA distributions for each model and motif type across 15 species. Fast A&E improves upon *Hyena* and *DiscDiff*, generating the most realistic sequences across almost all species and motif types. It achieves the lowest MSE and highest Correlation across all four motifs. This pattern is consistent across all 15 species. The motif plots for all 15 species are provided in Appendix F. As an example, Figure 4 shows the motif distributions of sequences generated by the three models versus real DNA sequences

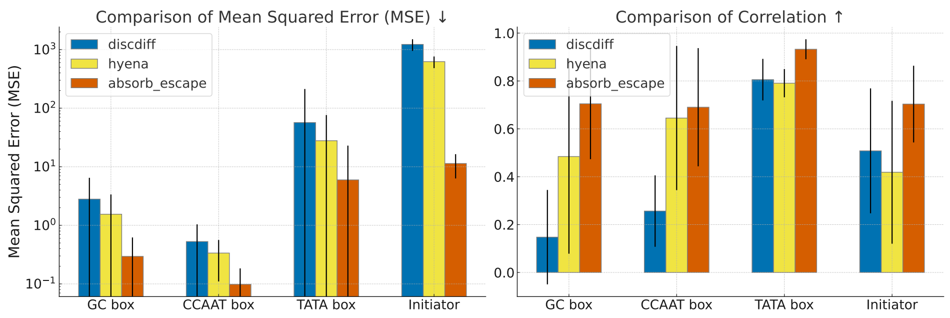


Figure 3: **The average MSE and Correlation between generated and natural DNA distributions for each model and motif type across 15 species.** Fast A&E outperforms *Hyena* and *DiscDiff*, generating the most realistic sequences with the lowest MSE and highest Correlation across four motif types. This pattern is consistent across all 15 species.

for *macaque*. Fast A&E closely resembles the natural motif distribution, especially for the TATA and GC box motifs, while *Hyena* and *DiscDiff* fail to capture the values or trends accurately.

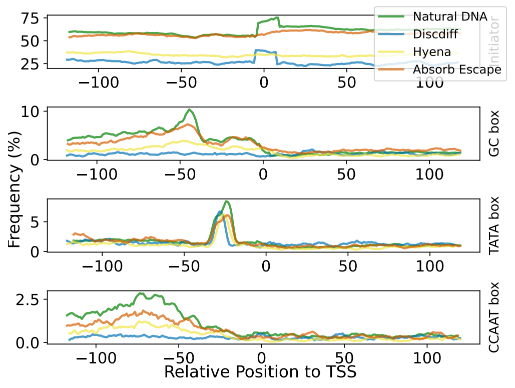


Figure 4: **Motif distributions in macaque DNA compared across natural DNA, FAST A&E, DiscDiff, and Hyena**. FAST A&E closely aligns with natural DNA, especially for the TATA and GC motifs.

Sequence Diversity To assess the diversity of the generated sequences, we applied BLASTN [18] to check (1) the similarity between the training set (Natural DNA) and generated sequences from three models, and (2) the similarity within the generated sequences. BLASTN takes a query DNA sequence and compares it with a database of sequences, returning all the aligned sequences in the database that are similar to the query. For each alignment, an alignment score, the alignment length (AlignLen), and statistical significance (eValue) are provided to indicate the quality of the alignment, where a larger alignment score, a smaller statistical significance (eValue), and a longer alignment sequence (AlignLen) indicate a higher similarity between the query sequence and the database sequences. Ideally, when using generated sequences to query the training dataset, a good generative sequence should align better than a random sequence, but not replicate the sequences in the training set.

Table 5 shows the results of the BLASTN algorithm. From the table, *DiscDiff*, *Hyena*, and A&E all satisfied the mentioned criteria. In terms of the diversity within the groups, none of the algorithms generated repetitive sequences. Furthermore, A&E tends to lie between Hyena and DiscDiff in terms of the diversity of the generated sequences, implying that A&E may combine the properties of AR and DM models. One notable fact is that the alignment scores are very high within the natural sequences, potentially indicating that natural sequences naturally have repetitive properties (conservative motifs), while the generative sequences do not have this characteristic.

Table 5: **BLASTN Results**

Query vs. Database	Score↑	eValue↓	AlignLen↑
Random vs. Natural DNA	17.78	1.1769	24.2
A&E vs. Natural	21.39	0.1695	35.9
Hyena vs. Natural	22.89	0.2895	40.1
DiscDiff vs. Natural	20.25	0.2098	31.4
A&E vs. A&E	20.14	0.0968	33.69
Hyena vs. Hyena	19.57	0.0843	28.7
DiscDiff vs. DiscDiff	20.95	0.1029	37.6
Natural vs. Natural DNA	57.06	0.0633	77.6

Genome Integration with Promoter Sequences As shown in Figure 5, to evaluate the functional properties of sequences generated by *Hyena*, *DiscDiff*, and *A&E*, we inserted the generated promoter sequences of length 128 bp upstream (5') of three commonly studied genes in oncology: **TP53**,

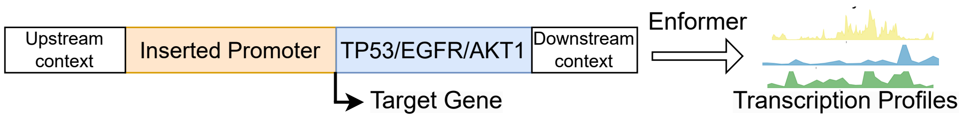


Figure 5: **Evaluation of Generated Promoters for gene regulation through Genome Integration EGFR**, and **AKT1** [6, 25, 29], which are closely related to tumor activities. Our goal was to determine which model generates promoter sequences that produce gene expression levels closest to those of natural promoters when reinserted into the human genome.

Table 6: **Sum of Squared Errors (SSE) of Transcription Profiles between Real and Generated Sequences**

	TP53↓	EGFR↓	AKT1↓
Random	278.18	8.09	65.70
A&E	**17.21**	**0.28**	**1.65**
Hyena	36.25	0.89	2.88
DiscDiff	124.03	2.17	25.50

We use Enformer [5] to predict transcription profiles. Enformer takes a DNA sequence of 200k bps as input and outputs a matrix $P \in \mathbb{R}^{896\times 638}$, representing a multi-cell type transcription profile. We sampled 300 promoter sequences from each source: *Natural DNA promoters*, *Hyena*, *DiscDiff*, and A&E. For each set, we calculated the average transcription profile across the sequences. The Sum of Squared Errors (SSE) between these average transcription profiles of the generated sequences and those of natural promoters are shown in Table 6. The results indicate that A&E produces the smallest SSE, suggesting it best captures the properties of natural DNA. This finding highlights the potential of generative algorithms to create promoter sequences that effectively regulate gene expression, with applications in bioproduct manufacturing and gene therapy.

5.3.1 Sensitivity Analysis of T_{Absorb}

We perform a *sensitivity analysis* of A&E algorithm over hyperparameter T_{absorb}. As shown in Figure 6, with a small T_{absorb}, the sequences generated by A&E are dominated by the diffusion model. As T_{absorb} increases, the AR helps to correct the errors made by the DM. Finally, when T_{absorb} is larger than 0.7, the correlation flattens and fluctuates. In conclusion, A&E is robust under different values of T_{absorb}, and it is best to use the validation dataset to choose the optimal value. However, a wide range of T_{absorb} can still be used with improved performance.

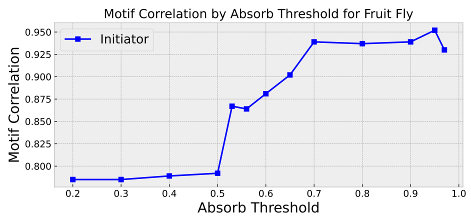


Figure 6: **Sensitivity of A&E under various T_{absorb}**. For each value of T_{absorb}, 3000 sequences are generated and compared with natural DNA. The correlation between the generated sequences and natural DNA increases initially as T_{absorb} increases, and then it flattens. An optimal T_{absorb} can be selected based on the validation set, or a default value of 0.85 can be used.

6 Conclusion

This paper demonstrates that (i) both the AutoRegressive (AR) model and Diffusion Models (DMs) fail to accurately model DNA sequences due to the heterogeneous nature of DNA sequences when used separately, and (ii) this limitation can be overcome by introducing A&E, a novel sampling algorithm that combines AR models and DMs. Additionally, we developed a fast implementation of the proposed algorithm, Fast A&E, which enables efficient generation of realistic DNA sequences without the repetitive function evaluations required by conventional sampling algorithms. Experimental results across 15 species show that Fast A&E consistently outperforms single models in generating DNA sequences with functional and structural similarities to natural DNA, as evidenced by metrics such as Motif Distribution, Sequence Diversity, and Genome Integration. Regarding the future work, the generated DNA sequences still require validation through wet-lab experiments before they can be directly used in clinical settings.

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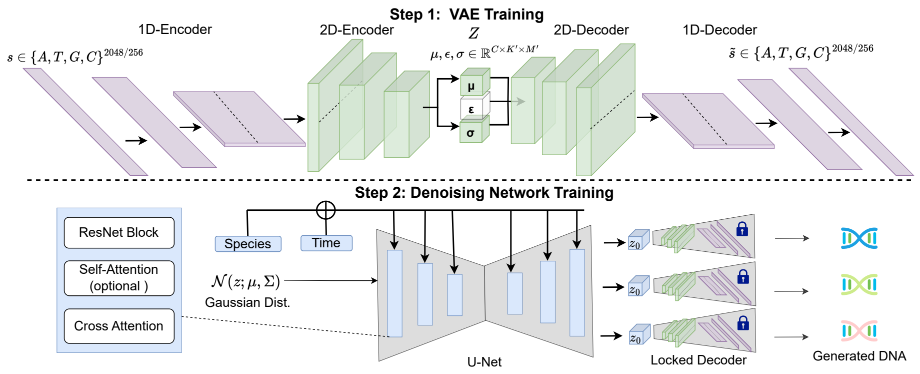
Step 1: VAE Training
1D-Encoder
2D-Encoder
2D-Decoder
1D-Decoder
$s \in \{A,T,G,C\}^{2048/256}$
Z
$\mu, \epsilon, \sigma \in \mathbb{R}^{C\times K'\times M'}$
$\tilde{s} \in \{A,T,G,C\}^{2048/256}$
Step 2: Denoising Network Training
ResNet Block
Self-Attention (optional)
Cross Attention
Species
Time
$\mathcal{N}(z;\mu,\Sigma)$
Gaussian Dist.
U-Net
Locked Decoder
Generated DNA

Figure 7: DiscDiff Model: A two-step process for DNA sequence generation. **Step 1: VAE Training**: A sequence $s \in \{A, T, G, C\}^{2048/256}$ is encoded via a 1D-Encoder to a 2D-Encoder. The latent space representation Z with parameters μ, ϵ, σ is then decoded back to $\tilde{s}$ through a 2D-Decoder and 1D-Decoder. **Step 2: Denoising Network Training**: The latent representation Z is processed through a denoising network comprising a ResNet Block, optional Self-Attention, and Cross Attention, with species and time information. The network outputs a Gaussian distribution $N(z; \mu, \Sigma)$. A U-Net architecture takes this distribution to produce various z_0 representations, which a Locked Decoder (fronzen parameters) used to generate the final DNA sequences.

A A simple baseline latent diffusion model for discrete data: DiscDiff

A.1 The DiscDiff Model

We design DiscDiff, a Latent Discrete Diffusion model for DNA generation tasks. As shown in Figure 7, this model is structured into two main components: a Variational-Auto-Encoder (VAE) and a denoising model. The VAE consists of an encoder $\mathbf{E} : \underline{s} \mapsto \underline{z}$, which maps discrete input sequence $\underline{s}$ to a continuous latent variable $\underline{z}$, and a decoder $\mathbf{D} : \underline{z} \mapsto \underline{\tilde{s}}$, which reverts $\underline{z}$ back to $\tilde{s}$ in the discrete space. The denoising model $\varepsilon_\theta(\mathbf{z}_t, t)$ is trained to predict the added noise ε in the latent space.

A.1.1 VAE Architecture

The choice of VAE architecture in LDMs is critical and often domain-specific. We find that mapping the input data to a higher dimension space can help to learn a better denoising network, generating more realistic DNA sequences. We hereby propose to use a two-stage VAE architecture as shown in Figure 7.

The first stage encoder $\mathbf{E}_{\phi_1} : \mathbb{N}_4^L \to \mathbb{R}^{K\times M}$ maps $\underline{s} \in \mathbb{N}_4^L$ to a 2D latent space $\underline{z}_1 \in \mathbb{R}^{K\times M}$, where K is the number of channels and M is the length of the latent representation. The second stage encoder $\mathbf{E}_{\phi_2} : \mathbb{R}^{1\times K\times M} \to \mathbb{R}^{C\times K'\times M'}$ first adds a dummy dimension to $\underline{z}_1$ such that $\mathbf{z}_1 \in \mathbb{R}^{1\times K\times M}$ and then maps it to 3d latent space $\mathbf{z} \in \mathbb{R}^{C\times K'\times M'}$, where C is the number of channels, K' and M' are the reduced dimensions of K and M respectively. The decoder in the first and second stage are $\mathbf{D}_{\theta 1}$ and $\mathbf{D}_{\theta 2}$ respectively. Which are symmetric to the encoders. Overall, we have $\mathbf{z} = \mathbf{E}_\phi(\mathbf{s}) = \mathbf{E}_{\phi_2}(\mathbf{E}_{\phi_1}(\mathbf{s}))$, and the reconstruction is $\tilde{\mathbf{s}} = \mathbf{D}_\theta(\mathbf{z}) = \mathbf{D}_{\theta 1}(\mathbf{D}_{\theta 2}(\mathbf{z}))$.

A.1.2 VAE Loss

When training the VAE, we propose to use Cross Entropy (CE) as reconstruction loss. The loss function is given by:

$$\mathbf{L}_{\theta,\phi} = \underbrace{\mathbb{E}_{p(\mathbf{s})}\left[\mathbb{E}_{q_\phi(\mathbf{z}|\mathbf{s})}\left[-\sum_{l=1}^{L}\sum_{i=1}^{4}\delta_{is_l}\log p_\theta(\mathbf{s}_l|\mathbf{z})\right]\right]}_{\text{Reconstruction Loss}} + \beta\cdot\underbrace{\mathbb{E}_{p(\mathbf{s})}\left[\mathrm{KL}(q_\phi(\mathbf{z}|\mathbf{s})\,||\,\mathcal{N}(\mathbf{z};\mu,\mathbf{\Sigma}))\right]}_{\text{KL Divergence}}$$

where δ_{ij} is the Kronecker delta, $p_\theta(\mathbf{s}|\mathbf{z})$ is the probabilistic decoder output from $\mathbf{D}_\theta$; $q_\phi(\mathbf{z}|\mathbf{s})$ is the probabilistic output from encoder $\mathbf{E}_\phi$ that represents the approximate posterior of the latent variable $\mathbf{z}$ given the input s; $\mathcal{N}(\mathbf{z};\mu,\mathbf{\Sigma})$ is the prior on $\mathbf{z}$. Here we use a simple isotropic. β is a mixing hyperparameter. β is set to 10^{-5} in the experiments used in this paper.

A.1.3 Denoising Network Training

Once $\mathbf{D}_\theta$ and $\mathbf{E}_\phi$ are trained in the first step, we train a noise prediction ε_θ in the latent space $\mathbf{z} = \mathbf{E}_\phi(\mathbf{s})$ with Equation (6).

$$\mathbb{E}_{\mathbf{z},t\sim U[1,T],\varepsilon\sim\mathcal{N}(\mathbf{0},\mathbf{I})}\left[\|\varepsilon - \varepsilon_\theta(\mathbf{z}_t,t)\|_2^2\right] \tag{6}$$

B Toy Experiment Training Details

We train both HyenaDNA and DiscDiff on an NVIDIA A100-PCIE-40GB using the Adam optimizer. For HyenaDNA, the learning rate is set to 0.0001, and we use the model `heyenadna-large-1m-seqlen` for this task. The maximum number of epochs is set to 100, with early stopping enabled to facilitate early convergence.

For DiscDiff, the VAE is trained with a learning rate of 0.0001, while the UNet is trained with a learning rate of 0.00005. DiscDiff is trained for 600 epoches; during the inference time, we use DDPM [16] sampler with 1000 denoising steps.

C Convergence Proof of the Absorb & Escape Algorithm

In this section, we provide a proof for the convergence of the Absorb & Escape (A&E) algorithm under certain assumptions. The convergence proof will demonstrate that the sequence generated by the A&E algorithm converges to a sample from the target distribution $p^C_{\theta,\beta}(\mathbf{x})$.

C.1 Assumptions

We make the following assumptions for the convergence proof:

1. The autoregressive model $p^{AR}_\theta(\mathbf{x})$ and the diffusion model $p^{DM}_\beta(\mathbf{x})$ are both properly trained and provide accurate approximations of the underlying data distribution.
2. The initial sample $\mathbf{x}^0 \sim p^{DM}_\beta(\mathbf{x})$ is a valid sample from the diffusion model.
3. The segments $\{\mathbf{s}_1, \mathbf{s}_2, \ldots, \mathbf{s}_n\}$ of the sequence $\mathbf{x}$ are chosen such that each segment is homogeneous.
4. The subset of segments $\mathcal{S}$ is chosen randomly and includes all segments over multiple iterations.
5. The conditional distribution $p(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1:L})$ approximated by $p^{AR}_\theta(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$ is accurate.

C.2 Proof

We aim to show that the A&E algorithm produces samples from the target distribution $p^C_{\theta,\beta}(\mathbf{x})$. We do this by showing that the Markov chain defined by the A&E algorithm has $p^C_{\theta,\beta}(\mathbf{x})$ as its stationary distribution.

Step 1: Initialization The initial sample $\mathbf{x}^0 \sim p_\beta^{DM}(\mathbf{x})$ is drawn from the diffusion model. This ensures that $\mathbf{x}^0$ is a valid sample from $p_\beta^{DM}(\mathbf{x})$.

Step 2: Absorb Step For each segment $\mathbf{s}_k$ in the subset $\mathcal{S}$, the Absorb step samples $\tilde{\mathbf{x}}'_{i:j}$ from the conditional distribution $p(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1}, \mathbf{x}_{j+1:L})$. Under the assumption that $p_\theta^{AR}(\mathbf{x}_{i:j}|\mathbf{x}_{0:i-1})$ accurately approximates this conditional distribution, the refined segment $\tilde{\mathbf{x}}'_{i:j}$ is a valid sample from the target conditional distribution.

Step 3: Escape Step The Escape step updates the segment $\tilde{\mathbf{x}}^t_{i:j}$ to $\tilde{\mathbf{x}}'_{i:j}$. This ensures that the updated sequence $\tilde{\mathbf{x}}^t$ incorporates the refinement from the autoregressive model.

Step 4: Stationary Distribution To show that the Markov chain defined by the A&E algorithm converges to $p_{\theta,\beta}^C(\mathbf{x})$, we need to show that $p_{\theta,\beta}^C(\mathbf{x})$ is the stationary distribution of this Markov chain.

The transition probability for the A&E algorithm is given by the product of the probabilities of the Absorb and Escape steps:

$$P(\mathbf{x} \to \mathbf{x}') = P_{\text{Absorb}}(\mathbf{x} \to \mathbf{x}')P_{\text{Escape}}(\mathbf{x}' \to \mathbf{x}).$$

Given that $p_\beta^{DM}(\mathbf{x})$ captures the overall structure and $p_\theta^{AR}(\mathbf{x})$ refines the segments, the composed distribution $p_{\theta,\beta}^C(\mathbf{x})$ is achieved by iteratively applying the Absorb and Escape steps. We need to show that the stationary distribution satisfies:

$$\int p_{\theta,\beta}^C(\mathbf{x})P(\mathbf{x} \to \mathbf{x}')d\mathbf{x} = p_{\theta,\beta}^C(\mathbf{x}').$$

Using the detailed balance condition for the Markov chain:

$$p_{\theta,\beta}^C(\mathbf{x})P(\mathbf{x} \to \mathbf{x}') = p_{\theta,\beta}^C(\mathbf{x}')P(\mathbf{x}' \to \mathbf{x}).$$

Given that the Markov chain is ergodic, the detailed balance condition implies that $p_{\theta,\beta}^C(\mathbf{x})$ is the stationary distribution.

Step 5: Ergodicity Ergodicity ensures that the Markov chain will visit all possible states given sufficient iterations. The random selection of segments $\mathcal{S}$ and the iterative updates in the A&E algorithm guarantee that all parts of the sequence are refined over time.

Conclusion By satisfying the detailed balance condition and ergodicity, we have shown that the Markov chain defined by the A&E algorithm converges to the target distribution $p_{\theta,\beta}^C(\mathbf{x})$. Therefore, the A&E algorithm produces samples from the composed distribution $p_{\theta,\beta}^C(\mathbf{x})$ as the number of iterations t approaches infinity.

D Experiment Details

Baselines The details about the **architecture and implementation** of the baseline models are as below:

- DNADiffusion [26]: We enhance the current DNADiffusion implementation for DNA synthesis, originally from the DNA-Diffusion project[2], by expanding the models to encompass 380 million parameters. This network is composed of Convolutional Neural Networks (CNNs), interspersed with layers of cross-attention and self-attention. The learning rate is set to 0.0001.
- DDSM [4]: We scale up the original implementation of the denoising network used for promoter design in DDSM[3] to what is the corresponding size of the network given 470 million parameters. It is a convolution-based architecture with dilated convolution layers. The learning rate is set to 0.00001.

[2]https://github.com/pinellolab/DNA-Diffusion

[3]https://github.com/jzhoulab/ddsm

- D3PM [3]: We take the implementation of D3PM for biological sequence generation from EvoDiff [2][4], adopting the algorithm for DNA generation. We use the original implementation of the denoising network, which has two versions: with sizes of 38M and 640M. We hereby have D3PM (small) and D3PM (big), respectively. The learning rate for both D3PM (small) and D3PM (large) are set to 0.0001.
- Hyena [24]: We modify the RegLM [20][5], a existing work uses hyena for DNA generation. Four pretrained Hyena models of different sizes (hyenadna-large-1m-seqlen, hyenadna-medium-160k0seqlen, heynadna-small-32k-seqlen, and hyenaana-tiny-16k-seqlen-d128) are downloaded from HuggingFace[6] and used for full-size fine-tuning, we apply the fine-tuned models for generations on EPD-GenDNA. The learning rate for fine-tuning is set to 0.0001.
- DiscDiff: A 2D-UNet of 500 Million parameters are used as the denoising network. See Appendix A for the implementation details. The learning rate is set to 0.00005 for UNet training, 0.0001 for VAE training.

For the Fast A&B algorithm, we set the T_{absorb} to 0.80.

E Content List of Supplementary Code and Data

Our code folder includes the following sub-folders, within each folder there is a readme file, detailing the steps to run the code. The below is the list of sub-folders.

E.1 Toy Experiment

Include the source code to reproduce Section 3. No external package is required to run the code except for python

E.2 DiscDiff

A implementation of the discdiff baseline in Appendix A. Please follow the readme for running the code.

E.3 AbsorbEscape

This includes an implementation of the proposed algorithm in Section 4.2; however, it depends on the external AR models, please adopt it accordingly to AR models which you want to try.

E.4 EPD Data

We include the training dataset used for producing the main results, which includes 160K DNA sequences from EPD, each sequence has a length of 256 bp.

F Motif Distributions for 15 species

We plot TATA-box, GC content, Initiator, and CCAAT-box for 15 speces as below.

[4]https://github.com/microsoft/evodiff

[5]https://github.com/Genentech/regLM

[6]https://huggingface.co/LongSafari

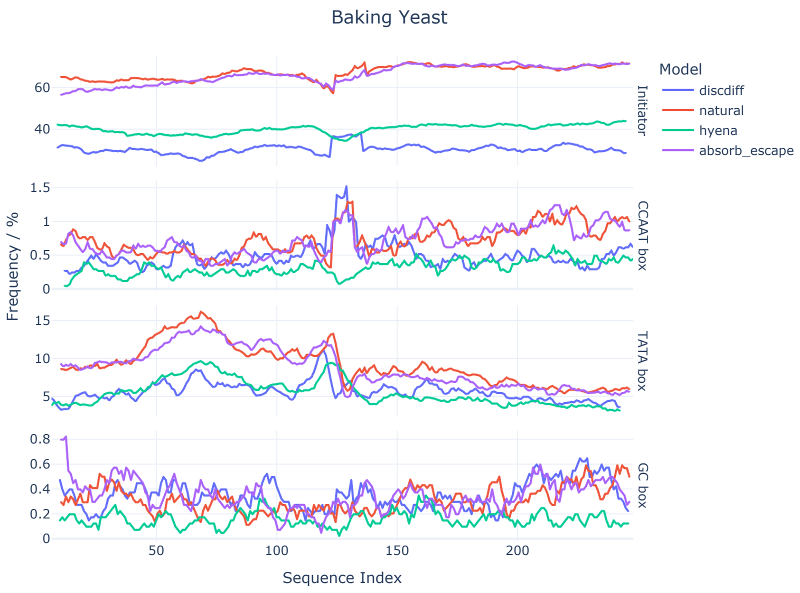

Figure 8: Baking Yeast

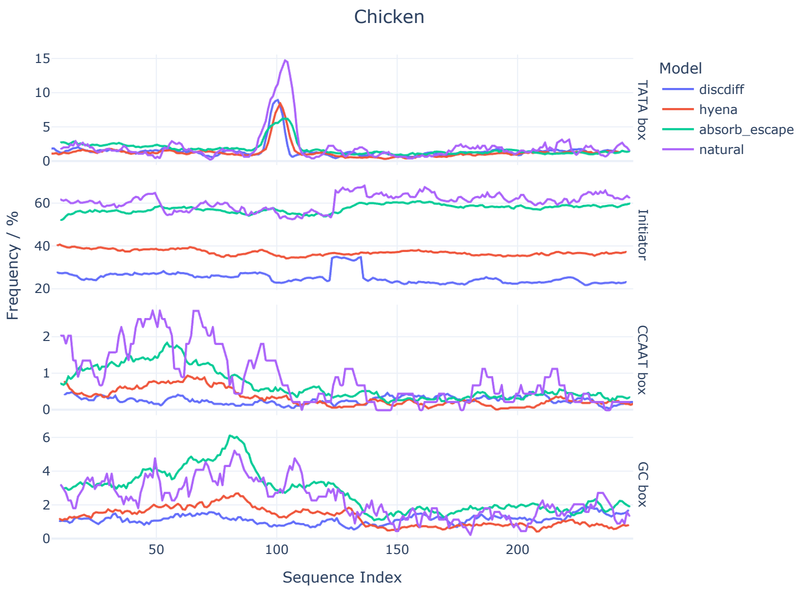

Figure 9: Chicken

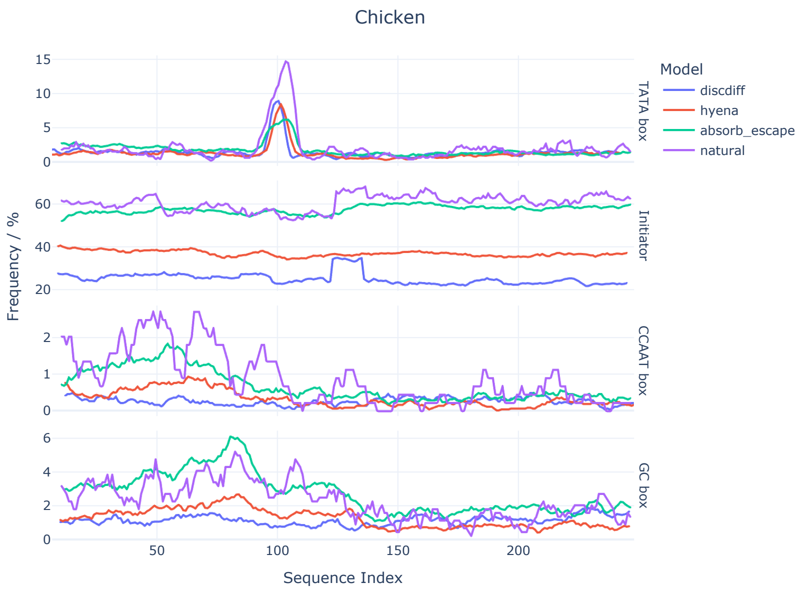

Figure 10: Chicken

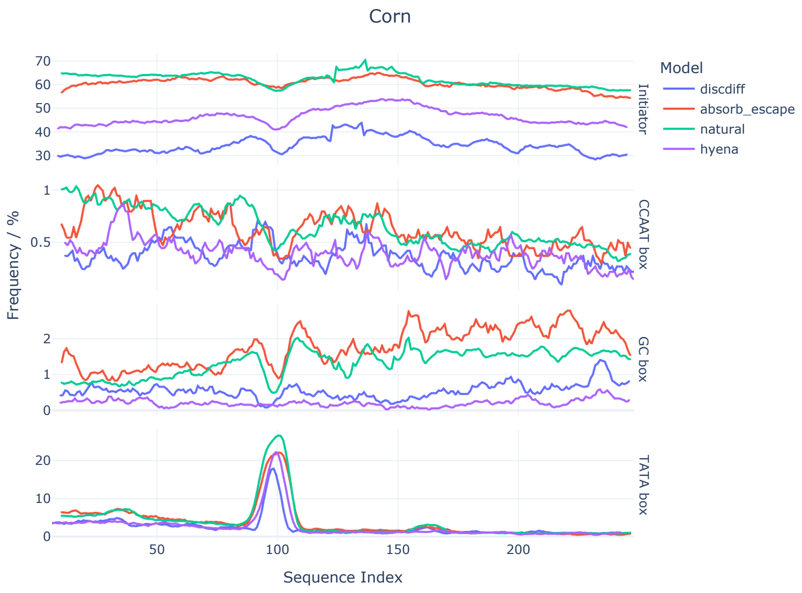

Figure 11: Corn

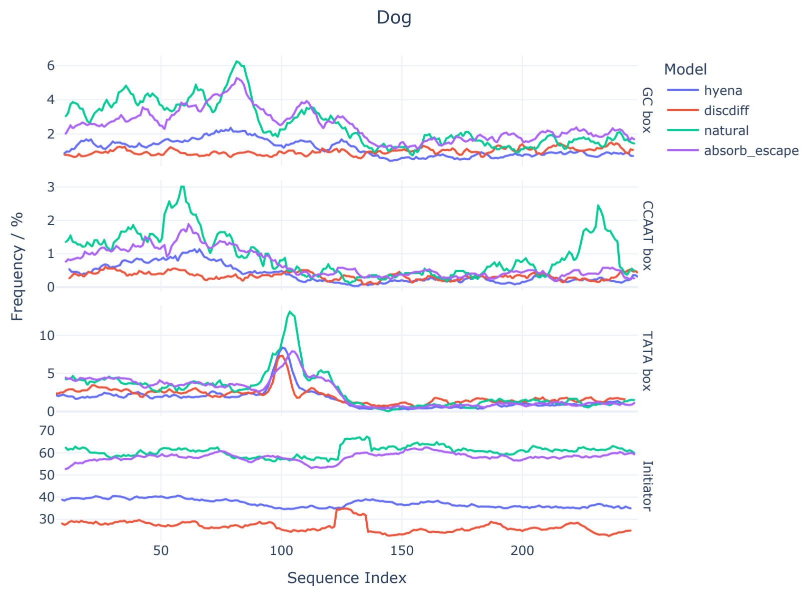

Figure 12: dog

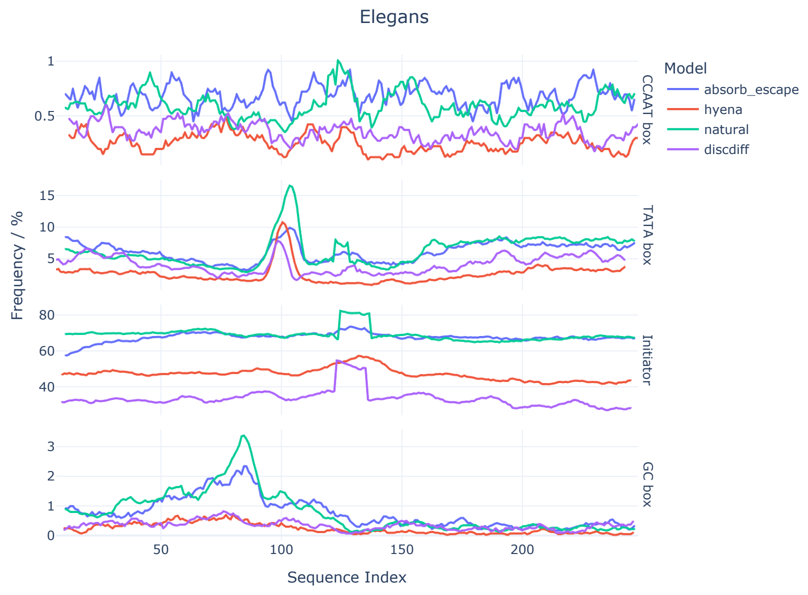

Figure 13: elegans

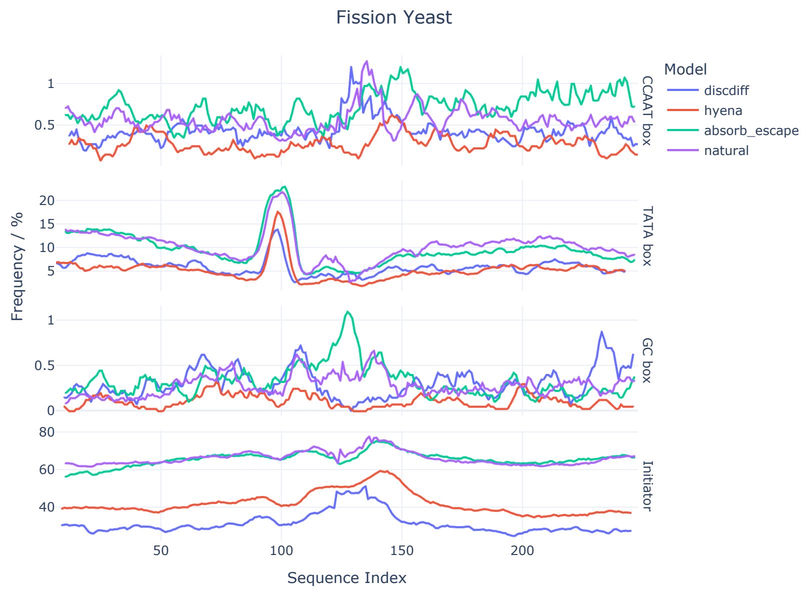

Figure 14: fission yeast

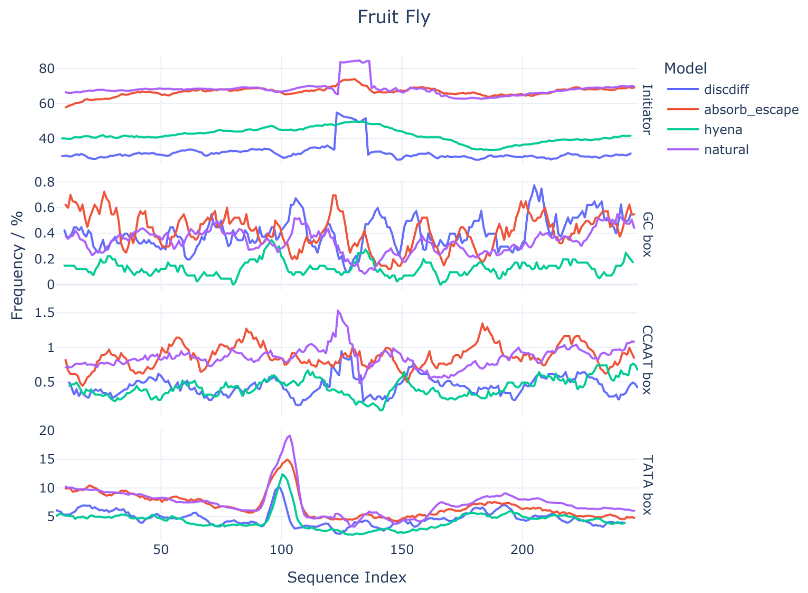

Figure 15: fruit fly

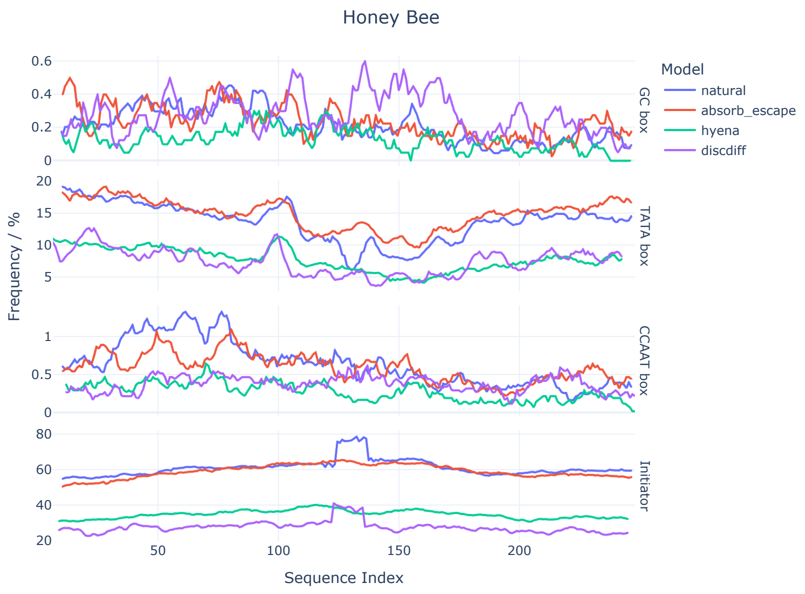

Figure 16: honey bee

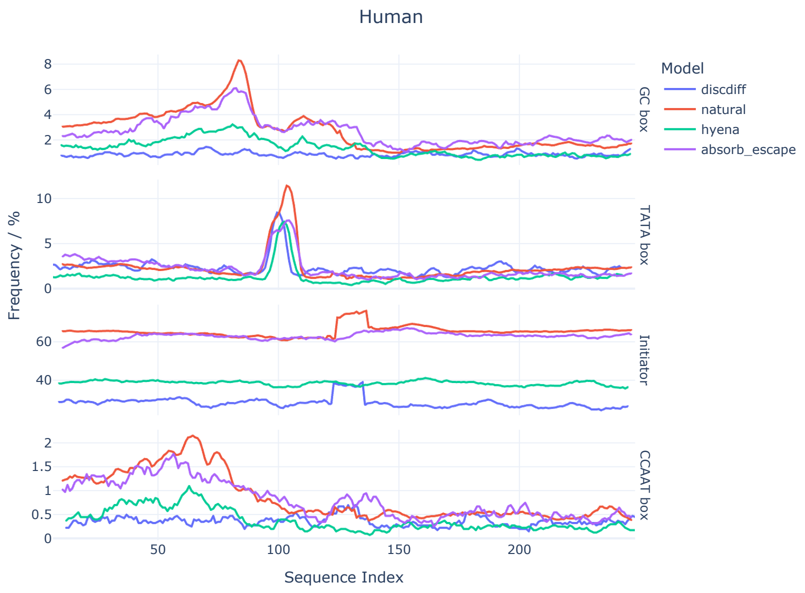

Figure 17: human

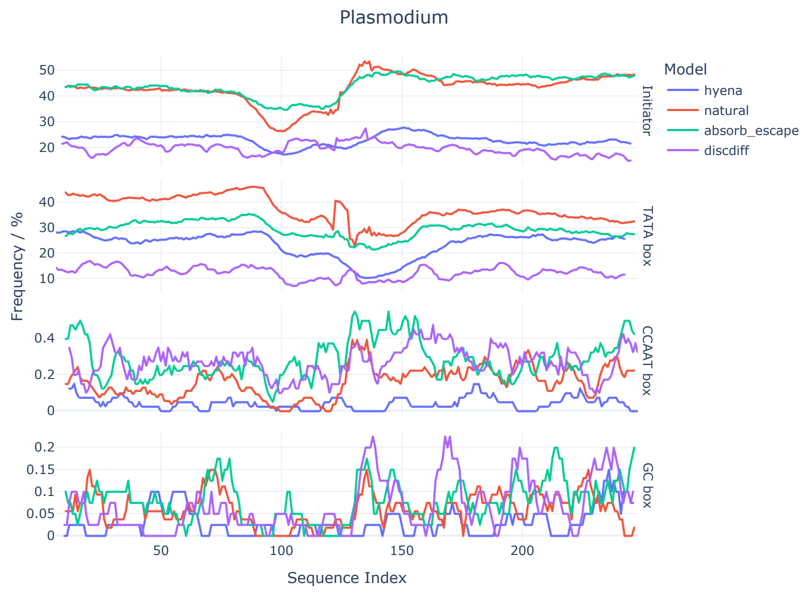

Figure 18: plasmodium

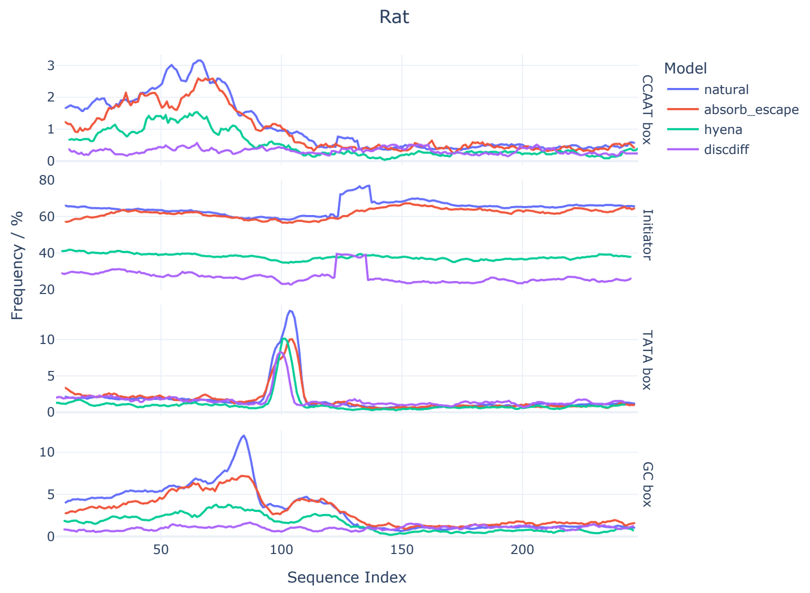

Figure 19: rat

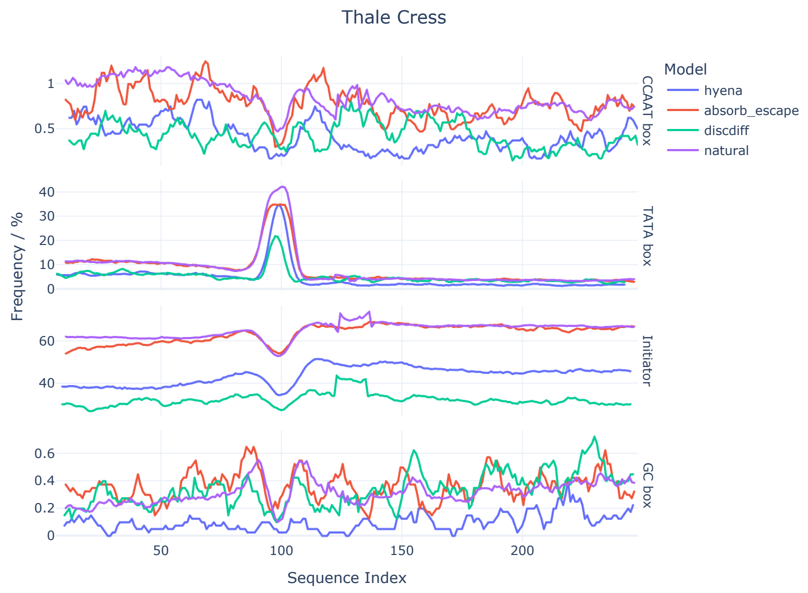

Figure 20: thale cress

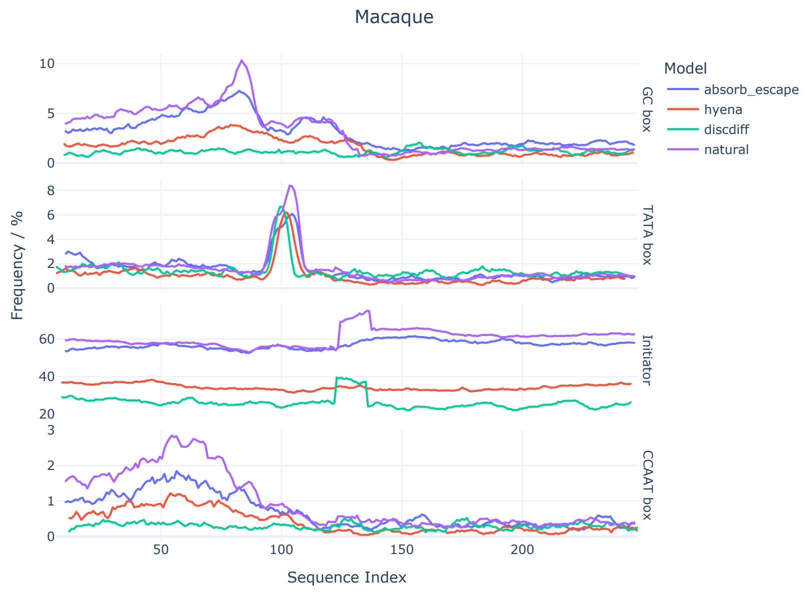

Figure 21: macaque

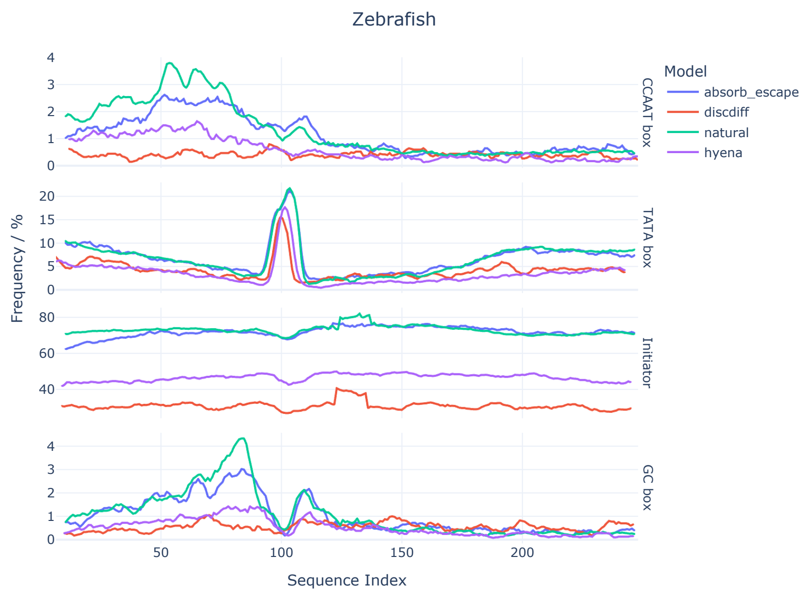

Figure 22: zebrafish

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