Life as a Function: Why Transformer Architectures Struggle to Gain Genome-Level Foundational Capabilities.

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Abstract

Recent years have seen a flurry of generative nucleotide models, mostly of limited utility. In this paper, we use the functional representation of DNA as a complex, composite function on the plane of evolution to extend the theoretical unification of ecological and evolutionary change to the problem of synthetic DNA models. Through experiments on synthetic and real DNA sequences we show that next-token prediction decoder transformer architectures are limited in their capacity to learn such functions.

Keywords: Synthetic Biology, DNA

1. Introduction

DNA/RNA molecules are the physical substrate for which life carries information. They allow for the exploration of vast combinatorial spaces and in doing so, form the backbone of evolution as a driver of change [1]. Learning how the subcomponents of these molecules are arranged to achieve specific goals (e.g. viral replication in mammalian cells) is a key problem of synthetic biology [2].

To that end, Duthie & Luque [3] have proposed a unified equation of biological evolution and population ecology. In their paper, they state, that individuals give rise to new individuals through birth such that β_i is the number of births attributable to individual i. Individuals are removed from the population through death such that δ_i is an indicator variable that takes a value of 1 (death of i) or 0 (persistence of i). All individuals are defined by some characteristic z_i, and Δz_i defines any change in z_i from one time step t to the next $(t+1)$. The total number of individuals

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in the population at t is N. From this foundation, we can define Ω to be a summed characteristic across N entities:

$$\Omega = \sum_{i=1}^{N} (\beta_i - \delta_i + 1) * (z_i + \Delta z_i) \tag{1}$$

As a result of the above equation, since the rates of deaths and births are ultimately a function of the optimality of an individuals traits at a particular niche, represented by x, the sum of a genomes characteristics simplifies to:

$$\Omega(x) = f(x) + \varepsilon\sigma_\Omega \tag{2}$$

Here, f represents a function that selects for optimal traits, while $\varepsilon\sigma_\Omega$ accounts for non-fatal variations. As Ω is a summation of characteristics, we expect the cumulative summation of the nucleotides of trait-relevant genes to be fairly stable at ecological niche points. This is because all biological traits (in the limit) are determined by nucleotides, as even epigenetic changes are dependant on genetic capacity.

Focusing on DNA/RNA as the backbone of biology, many projects have aimed to learn this function using different architectures and datasets, all ultimately aiming to scale to foundational level capabilities ala Claude, GPT-4 etc. Benegas et all [4] provide a good overview of the current state-of-art for Genomic Language Models.

The key goals of this paper are to discuss two questions:

1. What is Ω?
2. What are the limits of the current paradigm with respect to learning f?

We hypothesize that the overall structure of Ω should be detectable and f learnable. The structure of Ω, in the context of genomic modeling, does not refer to 3D-chromatin structures such as topologically associated domains (TADs) as described by Rowley et al. [5], but rather to the composition of the one-dimensional symbolic representation of the genome. These include repeating elements such as tandem repeats [6], regular sequence motifs and cis-regulatory regions such as TATA boxes [7] and the differences between coding and non-coding regions [8], [9],[10], [11]. We focused our study on viral genomes, as they are small and easy to handle with low computational resources.

2. Ω is the output of evolution.

There are a few essential points we should be aware of regarding evolution as a highly context specific, complex, adaptive framework. One, whether the framework is considered deterministic or stochastic depends on the specific particularities of the organism [12]. Two, its constraints are

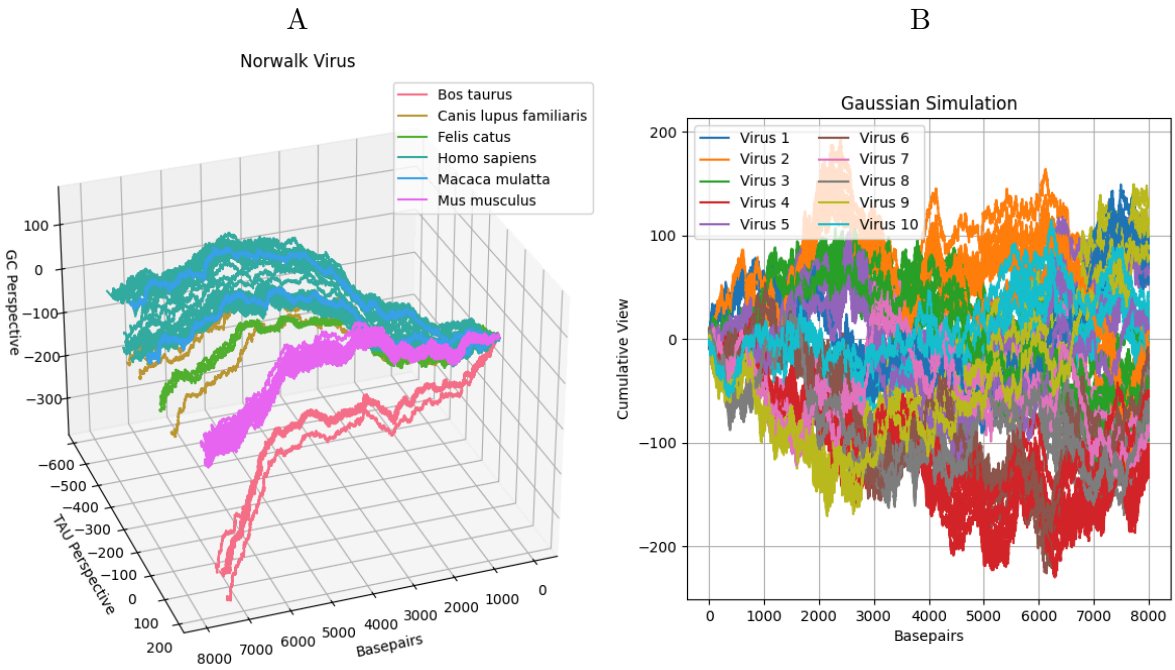

Figure 1: A. 3D representation of Norwalk virus samples colored by their hosts. The x-axis represents the basepairs, for every basepair we move exactly one. TAU perspective represents the cumulative summation of T (0,1,1), A (0,-1,1) or U (0, 1, 1) basepairs along the y-axis. GC perspective represents the cumulative summation of G (1,0,1) and C (-1,0,1). The viruses adapted to different host species clearly occupy different regions in the overall information representation space of Norwalk virus genomes. Hosts that are closer to each other taxonomically result in overlapping regions, e.g. humans and rhesus monkeys. B. Gaussian simulation of sub-region development in the space of related viral sequences. The simulation uses 10^-5 as the mutation rate, similar to RNA viruses. x-axis represents the basepair equivalent, y-axis represents cumulative summation of selected random values, mutated by the mutation rate.

functional not sequential, backward not forward looking, developmental not constructive [12], [13]. There is no goal or aim to evolution. Three, much the same as selection, mutations are non-random [14]. Four, evolution's fitness landscape is non-static [12], [15]. And finally five, it operates at the systemic level. No organism exists outside of an ecosystem [13], [15].

Taking Norwalk virus as an illustrative example, in Fig. 1 A, we can see evolutionary constraints guide sequences towards predictable patterns (particular loci based on host), with deviations from those patterns correlated. This is due to the fact that each virus can only exist if it can successfully replicate, thus forcing emphasis on genomes with the most useful traits for a particular niche (which in this case is represented by the host). Said differently, although the change at any replication point is necessarily Brownian (through different mutations occurring at each replication) and viral-cell interactions are chaotic, viral genomes adapted to the host (the

particular niche) approximate a temporary Lyapunov stable point to minimize system-wide energy expenditure (the system representing the viral cell populations along with the host's cells).

To simulate this in a Gaussian framework, we can sample 10 sequences from a random sequence matrix of shape [samples, length, basepairs]. Those 10 sequences represent successful replications within a host. Each of those sequences can then be replicated 1000 times with a level of accuracy similar to viral mutation rates (10^{-5} per bp [16]). The results of such a simulation can be seen in Fig. 1 B, showing clear speciation of the initial samples, similar to what we observe in nature. What we observe here arises just from the initial randomness combined with Brownian noise. Together, this means that for any model to learn biological dynamics, it must learn a complex, modular, compositional function that takes into account epigenetic regulation, regulatory networks of host cells, and the constructive, interchangeable and fractal nature of development [17].

3. The limits of the current paradigm with respect to learning the Ω generating function

3.1. Transformer decoder models suffer from a power law when learning complex, modular, compositional functions

To test our hypothesis in a controllable fashion, we conducted an experiment with synthetic sequences, represented as composite functions, based on combining sinusoidal terms with varying wavelengths, exponential modulation, polynomial growth, and additive noise. Samples from these functions can be found in Fig. A.1. Similar to the DNA representation above, they exhibit micro and macro structure, although with stronger periodicity. We trained a transformer model of the Pythia variant on these sequences on model scales from 1.2 million to 800 million parameters and evaluated performance on out-of-distribution (OOD) sequences. See Section B.1.2.1 for a description of the sequence generating process.

As shown in Fig. A.2 A, although model size was positively correlated with OOD performance, that correlation followed a power law and did not increase strongly after 300 million parameters. This is inline with the literature [18] and what we find from other experiments. Fig. A.2 B shows the training loss also stagnating after 300 million parameters, pointing at a bound for possible learning of these functions for transformer architectures.

3.1.1. Performance on real OOD sequences does not benefit from scale

With the already lacking performance in synthetic and considerably less chaotic sequences, we also tested this on a dataset of all genetic sequences of virus genomes from NCBI [19]. Genomes were fed into the models with a context window size of 2048 basepairs and an overlap of 400

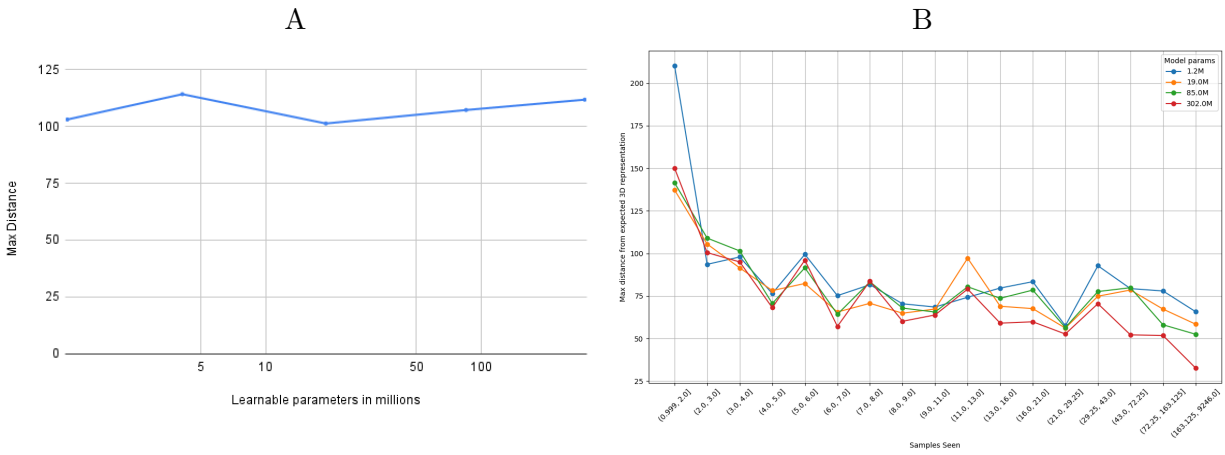

Figure 2: A. The first chart shows the maximum euclidean distance between expected 3D representations of OOD sequences and generated sequences on the y-axis against the model size log on the x-axis. This indicates that the model cannot learn OOD sequences irrespective of scale. B. The second chart shows the maximum euclidean distance between original sequences and their respective generated sequences against the number of samples of a species seen during training. The distance decreases as the number of examples per species in the training set increases.

basepairs. A simple 8 word tokenizer was used. See section B.1.4 for a description of the dataset and tokenizer.

When training on genetic sequences, we find the results of our experiments similar to those of the synthetic sequences. Transformer models need to be of sufficient size with ample examples to learn from complex datasets, as can be seen from Fig. 2 B. However, Fig. 2 shows that OOD sequences, as well as sequences with low samples in the training set (left-hand side of Fig. 2), maintain a high distance from their expected Euclidean representation. This trend persists regardless of the model's scale, contrasting sharply with the synthetic experiment. These results highlight that transformers struggle to capture the underlying functions of DNA sequences.

Taking a closer look at single sequences, Fig. 3 compares a virus with low numbers of samples in the dataset (Gallivirus A) with a more abundant virus type (Enterovirus C). The true sequence is given in violet and the generated sequences are colored by the parameter size of the generating model. Note that in Gallivirus A (panel A) none of the models can generate a sequence close to the original after being prompted with the first half of the original sequence. Only the largest model is able to learn the direction of the sequence representation in the function space. However, in panel B models larger than 82M learned the function almost identically, pointing at memorization rather than learnt knowledge, which is a known issue of the LLM paradigm [20]. Also note from Fig. 2 that OOD scores do not improve with model size. That's because OOD samples in viral genomes come from completely different populations unlike those in the synthetic experiments.

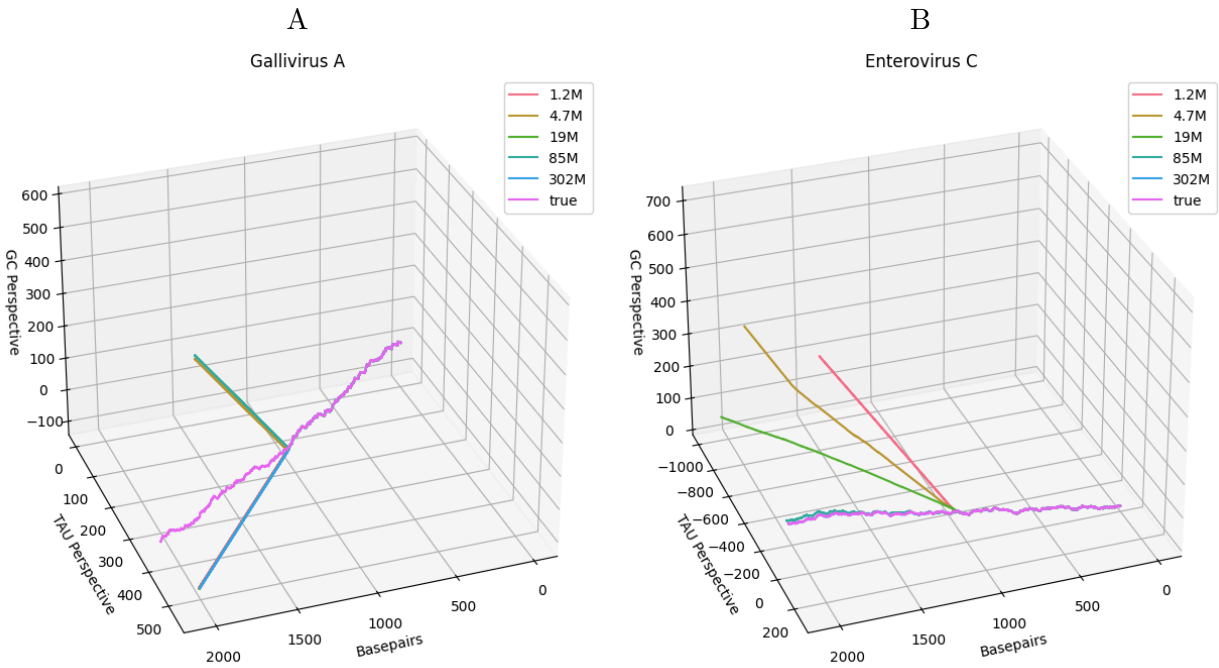

Figure 3: A. 3D representation of generated subsections of Gallivirus A virus sequences colored by model size vs. true sequence. Note that half the sequence (1024 base pairs) is fed into each model before generation. Only the 302M parameter model correctly assigns the right direction; however, none learn the microstructure. B. 3D representation of Enterovirus C virus sequences colored by model size vs. true sequence. As model size increases, output correctness improves, likely due to copying. This difference in behavior is likely due to the number of samples for each species: Enterovirus is much more abundant with 4141 samples compared to 15 for Gallivirus A. The model memorizes the species' overall structure when it sees enough samples and has a sufficiently large parameter size. However, small sample sizes are insufficient to memorize a species' profile, and the model cannot learn underlying functions that could enable knowledge transfer between species. Figure axes are as in Figure 1.

4. Discussion

With this work, we want to provoke a discussion about the feasibility of using the currently favored LLM training paradigm (next-token prediction decoder transformer models) to learn DNA sequences as well as its application to downstream tasks in the life sciences and medicine. We discuss findings from mathematical evolutionary theory that we see as applicable to the general problem of biological dynamics and use them to reason about what a model needs to learn for foundational level capabilities that depict biology in a sufficient approximation to make predictions or connections. We show that with 3D representation of sequences, the character of DNA as a function is apparent and provide intuition on how evolution in viruses shapes the function space of said sequences.

Based on this we show with synthetic composite functions, similar to what we observe in our numerical representations of DNA, that transformer models struggle to learn the underlying functions of these sequences and suffer from a power law when it comes to predicting OOD samples. Moving on to the real sequences, we observe this shortcoming to an even larger extent: OOD samples, and even sequences of viral species that have been seen, but with low abundance, are not correctly generated and result in large differences between the original and generated sequence.

Although transformers are in theory Turing-complete under reasonable conditions, as shown by Jesse et al. [21], these findings point at the known problem of their inability to learn complex functions. We suggest that these models' ability to learn the macro and micro structure of the DNA as a function could be improved with knowledge infusion. For example, this could be achieved by using topological losses to inform the model. Such a loss could be based on representations similar to what we see in this work or Yau et al. [22]. Similarly, persistent homology based losses could be used to learn the macrostructure of the sequences and enable the model to keep direction and recurring patterns during the generation process.

Another possibility to gain foundational capabilities and generate viable DNA sequences at the genomic scale might be a switch in training paradigms/perspectives to one that addresses the

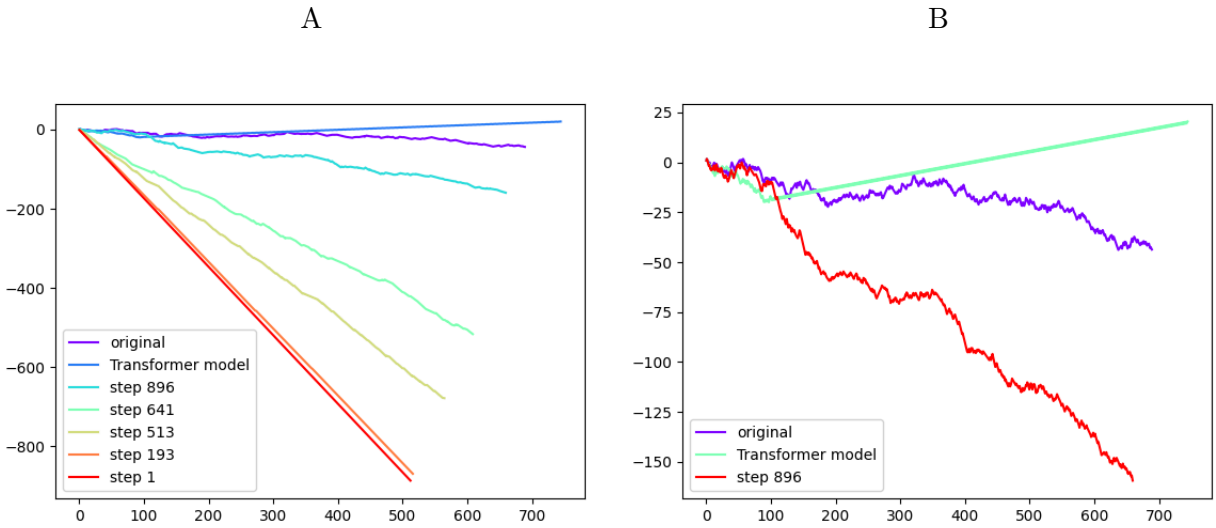

Figure 4: A. shows the diffusion process, by sampling from a trained model. The diffusion is guided by the first half of the sequence, comparable to the prompting of the transformer models above. The sequence is depicted by 2D-representation as per [22]. The axes are cumulative representations of the sequence similar to our 3D version, assigning a 2D-vector to each base. Colors show the different steps of the process, as well as the expected sequence (violet) and the transformer model output (blue). B. shows our selected final step for the diffusion models (red) compared to the expected sequence as well as the output of a transformer model (green) of comparable size, trained on the same data.

nature of DNA as the output function of life. There are multiple ways to model DNA as such. Firstly, we can model DNA sequences as the solution to branching random walks in a random environment as per König [23]. Due to the differing strengths of potentials within this environment, we should expect concentration of solutions to be localized islands, these islands can be viewed as our species or genera. Secondly, we can model viral DNA sequences as the phase transition between one organism and the next, gaining the capacity to build multi-scale models [24]. Finally, viral genomes can be considered as sequences operating on a hierarchical topological space, with species/genera represented by topological balls.

Discrete diffusion models can also be used to learn the underlying function by modelling the evolutionary genome generating path [25]. As can be seen in Fig. 4, a discrete diffusion model performs significantly better with OOD sampling than a transformer model of comparable size when trained on the same dataset.

We can go further with flow matching models and disaggregate the problem of synthetic sequences into their natural domains (e.g. target & sequence). As can be seen in Fig. 5, flow matching models are able to generate OOD samples based just on target description.

The dual use risk of generative models in biology has recently started to get traction in the general discussion about the use and risk of AI, with key opinion leaders in the field voicing ethical concerns about biological foundation modals [26], [27], [28].

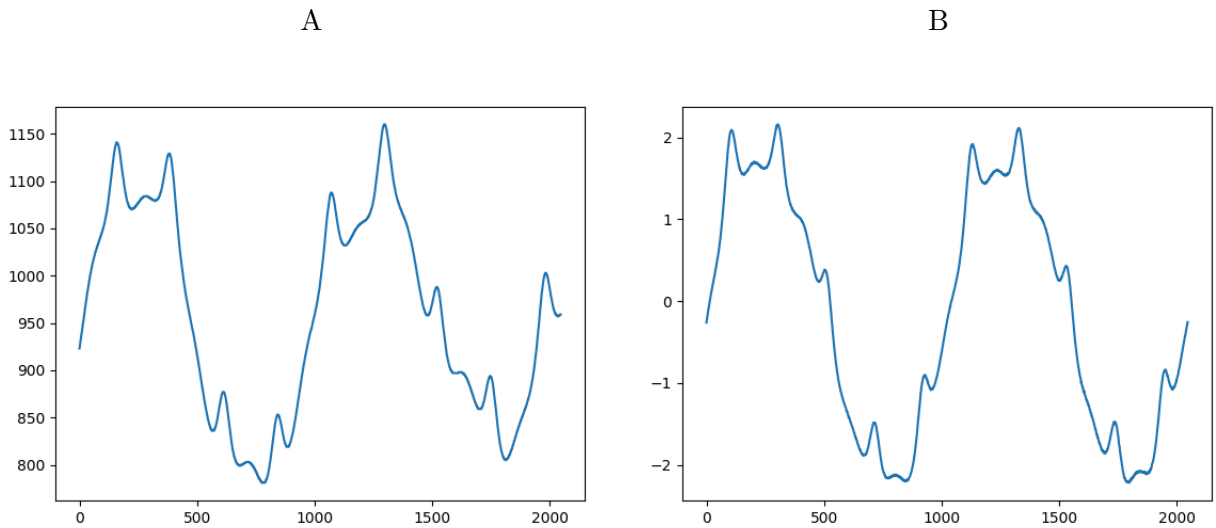

Figure 5: A. shows the output of a flow matching model, prompted by a target description as per Appendix B.1.3. B. shows the expected output based on the target description used to prompt the model in A.

A specific risk that should be highlighted with flow matching models, is their ease in interpolating between latents to produce potentially biologically viable results [29]. This is because they do not require their source distribution to be sampled from noise and are thus capable of learning a mapping from any distribution to another (e.g a virus hosted by one specie to another). To test this, we trained a model on (genus, host) pairs and sampled the model to produce sequences that have been perturbed from one host into another. As can be seen in Fig. 6, the model is able to learn the macro patterns associated with particular hosts. Note this is GC perspective normalized and not the full view.

In future research we will develop flow matching models capable of generating DNA sequences at scale. Additionally, we will explore possibilities to improve the performance of next-token prediction models by designing better topological losses. During the research of these models we aim to explore physical and in-silico risk mitigation methods, accommodating both current and potential future risks. Models of foundational capability could be applied to myriad socio-medical use cases, such as pandemic surveillance (via zoonosis prediction), synthetic bacteriophage generation for antimicrobial resistent bacteria, developing safer oncolytic phages or other biopolymers.

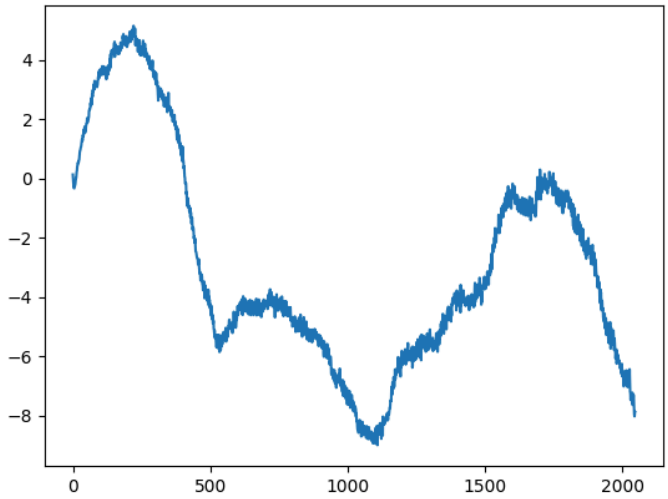

Figure 6: Virus interpolated from one host to another. The depicted line is the GC part of the 3D representation used in Section 3. It resembles the real distribution of GC representation of this virus species in the target host.

5. Data and Code availability

All models, code, and links to the datasets used will be available on GitHub at https://github.com/dna-llm/life-as-a-function. However, pre-trained models will only be available at reasonable request as the training data includes pathogenic viruses. All sequences were acquired off NCBI in Q2 2024.

6. Acknowledgements

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A. Appendix A

A.1. Synthetic Sequences Experiment

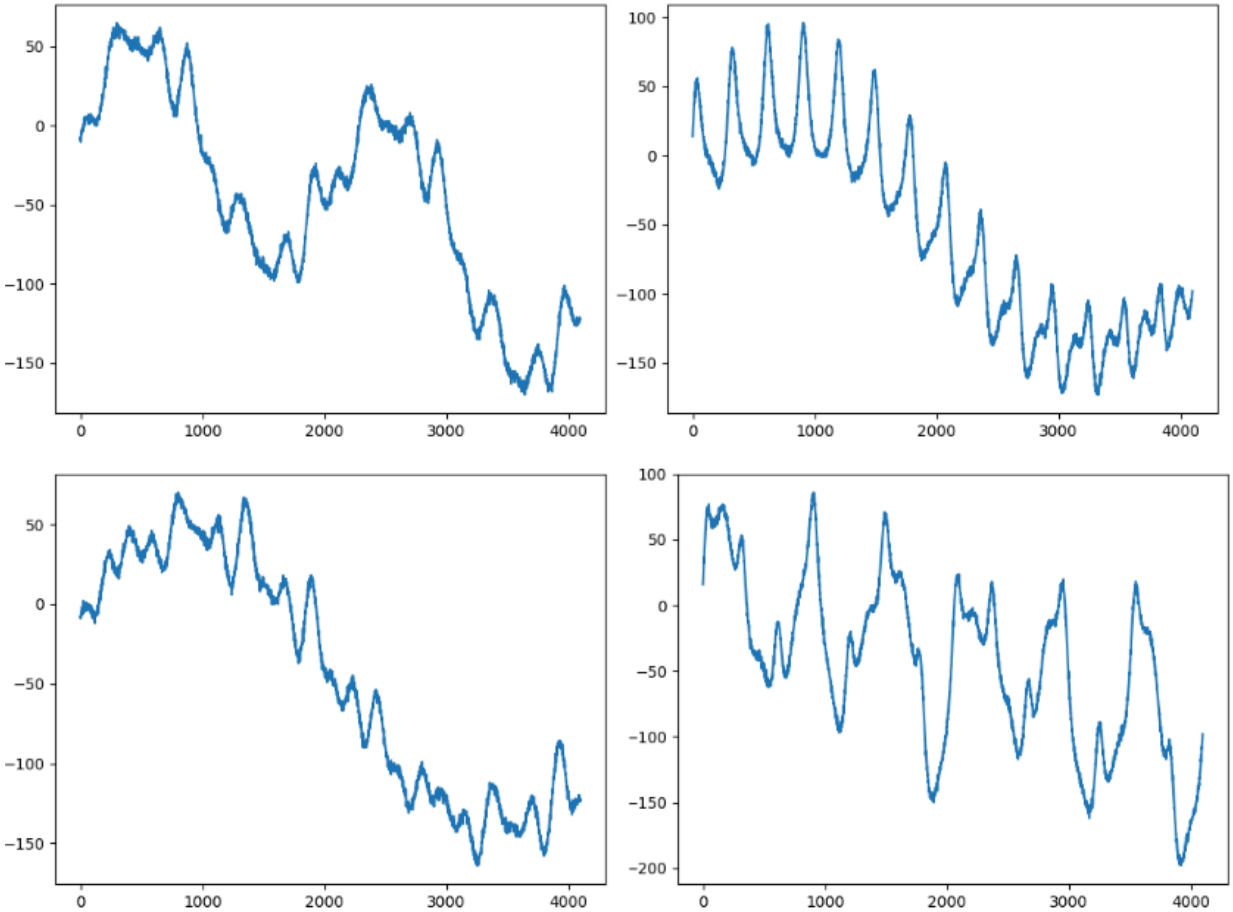

Figure A.1: Example synthetic sequences. The x-axis represents token location and the y-axis represents the token value, which is an integer conversion of our synthetic sequence generator described in Section B.1.3.

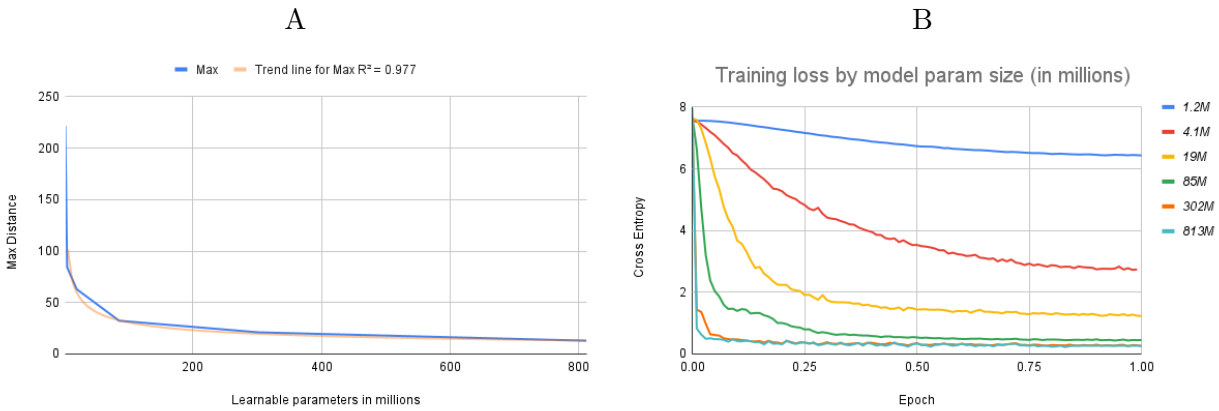

Figure A.2: A. shows the maximum euclidean distance between expected 3D representations of OOD sequences and generated sequences on the y-axis against the model size on the x-axis. In contrast to DNA sequences, learning our simpler synthetic sequences improves with scale. However even then, learning is restricted to a power law, approaching negligible error decrease after 300 million parameters. B. shows cross-entropy loss across a single epoch, labelled by learnable model parameter size in millions.

B. Appendix B

B.1. Methods

All code, as well as additional code linked to this and potential follow up projects can be found at https://github.com/dna-llm/life-as-a-function.

B.1.1. Simplified 3D Representation of DNA

To investigate the spatial and energetic properties of viral DNA sequences, we utilized a dataset of viral genetic material obtained from NCBI Virus [19]. This dataset included detailed annotations of viral sequences.

To represent these sequences in a three-dimensional space, we developed a method that maps nucleotide sequences to cumulative 3D coordinates using predefined encoding schemes. The first encoding scheme, referred to as the "simplified encoding", assigned each nucleotide a unique 3D vector based on its structural and chemical properties. The cumulative sum of these vectors across the sequence created a 3D spatial trajectory. A second encoding scheme, the "energy-based encoding", incorporated approximations of the energetic cost of a nucleotide to capture a sequence's energy landscape. Both mappings aimed to provide complementary insights into the spatial and energetic characteristics of a genetic sequence. We chose to go with the simplified version as we found both perspectives to be fairly similar when de-trended.

B.1.2. Gaussian Noise based Virus Sub-Speciation Simulation

To simulate speciation effects induced by evolution, we created 10 random matrices composed of 10,000 random numbers between 0 and 1, to symbolize initial successful viral genomes. These

matrices were then copied a 1000 fold, each copy was penalized with a mutation rate, that induced a mutation at a given base pair by the chance assigned (we went with 10^{-5}) mutated (i.e. a rate of every 100,000 basepairs, selected from the full genome). Note our mutations are completely random, which is different to the modern understanding of mutation [14].

B.1.3. Synthetic Sequence Production

To evaluate the ability of transformer models to learn complex functions, we generated synthetic sequences characterized by a combination of periodic, exponential, polynomial, and noise components. The sequence generation process was driven by a function that combined these components mathematically, incorporating sinusoidal terms with varying wavelengths, exponential modulation, polynomial growth, and additive noise. Key parameters such as amplitude, wavelength, power, and direction were systematically varied using a Cartesian product of predefined ranges. For example, wavelengths ranged from 1 to 10 units, amplitudes from 10 to 50, and amplitude ratios from 1 to 6. This systematic exploration resulted in a diverse dataset of synthetic sequences, each with a length of 4096 samples, generated using the synth_seq_gen function (find the implementation in the notebooks section of our GitHub repository). A total of 240,000 sequences were produced, and metadata for each sequence, including the parameters used, were stored for analysis. Periodically, visualizations of the generated sequences were saved to ensure quality and diversity.

The generated sequences were used to train transformer models, enabling an evaluation of their ability to approximate these synthetic functions and generalize across parameter sizes. We analyzed model performance as a function of dataset size, sequence length, and the complexity of the underlying parameters, focusing on the impact of scaling. Our results revealed that while transformers could partially learn these functions, their generalization capacity was limited, and their performance exhibited a pronounced dependence on scale. Specifically, we observed a power-law degradation in performance, highlighting intrinsic limitations in the transformer architecture for learning such structured, multi-component functions.

B.1.4. Experiments with Viral Genome Data

Viral DNA sequences were sourced from NCBI [19]. The dataset was filtered and only complete non-covid sequences were selected. This resulted in 210,431 samples. Each sequences was then split into 2048 basepairs with an overlap of 400 basepairs, followed by a stratified train, validation, test split.

B.1.5. Models

B.1.5.1. Transformer Architecture

We trained a Pythia transformer using the Hugging Face packages and their APIs [30].

B.1.5.2. Discrete Diffusion

We implemented a framework for training and evaluating a discrete flow matching model for DNA sequence modeling. The model was built on a convolutional backbone with temporal embedding layers to capture the dynamics of discrete time steps, and trained using our preprocessed DNA dataset. Key components of the pipeline included data preprocessing, training with a timestep-dependent noising schedule, and monitoring performance using FLOPs analysis.

The dataset consisted of tokenized DNA sequences from our dataset, processed into input ids for embedding. A discrete scheduler was implemented to manage the noise addition to the sequences over training steps, emphasizing harder-to-learn (more noisy) regions as training progressed. A convolutional neural network (ConvNet) was used for embedding the input sequences and modeling timestep interactions. The model incorporated layers for timestep conditioning and residual connections to capture temporal dependencies.

B.1.5.3. Flow Matching

To allow us to evaluate a flow-matching model's ability to encode and generate structured sequences, we implemented a workflow combining autoencoders and a flow-based transformer model to study the representation and learning of structured synthetic sequences. Using our synthetic sequences dataset, sequences were normalized and paired with integer labels used in their generation to create a paired dataset of sequences and integers. A fully connected autoencoder, with a latent space of dimension 16, was then trained to compress and reconstruct sequences using mean squared error loss. The encoder and decoder employed progressively narrower and wider linear layers, respectively, with dropout regularization and ReLU activations. Training spanned 15,000 steps with the Adam optimizer and noise injection for robustness.

Encoded latent representations served as input to the model, a transformer architecture configured for multi-modal learning. With a latent dimension of 16 and a transformer depth of 8, the model was trained for 100,000 steps, using gradient clipping and exponential moving average (EMA) for stability. Periodically, synthetic samples were generated by decoding latent embeddings back into sequences, and results were regularly visualized and saved. Textual labels were decoded for interpretability using a predefined mapping.