Generating Synthetic Genotypes using Diffusion Models

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Why do we need Synthetic Data?

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- Large high quality datasets are becoming available but getting access is a long and costly process (for example UKBB [1])
- High quality synthetic data would allow genomics data to be freely distributed (i.e. Kaggle dataset) without privacy concerns.

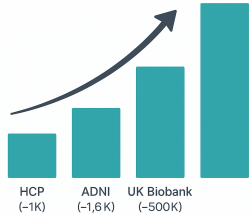
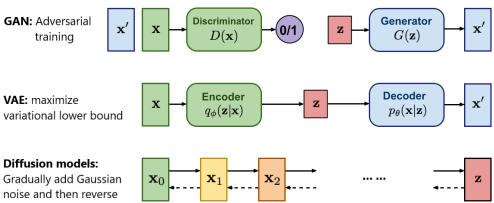


Figure: Increasing availability of large scale genomics datasets.

[1] UK Biobank – cohort of 500 000 participants with extensive health, genetic and imaging data. "About our data" page, UK Biobank. https://www.ukbiobank.ac.uk/enable-your-research/about-our-data.

Possible Generative Models

- Variational Autoencoder
- Generative Adversarial Networks
- Generative Markov Models
- Diffusion Models
- Autoregressive Models (LLM Style)



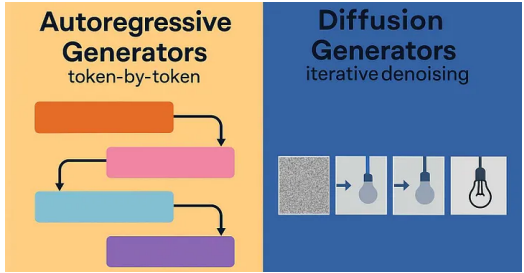
Possible Generative Models

- Variational Autoencoder - Output quality not state of the art, does not scale well, ...
- Generative Adversarial Networks - Unstable, hard to train, ...
- Generative Markov Models - Not very powerfull or general, ...

Possible Generative Models

- Diffusion Models - best suited for fixed length generation with causal interactions in all directions, can produce very high quality output by refining over multiple passes
- Autoregressive Models (LLM Style) - best suited for non-fixed length with causal interactions left to right, produces good output, mostly used for high level tasks

Genome has interactions in all directions, fixed length, high quality needed
-> Diffusion Models



Related Work

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Table: An overview of related work on generating synthetic genomes and its differences / similarities in comparison with our work. Our novelties are **highlighted**.

Reference	Model	Data Type	Genome Length	Cond.
DNAGPT (Zhang et al., 2023)	Autoregressive	Base-Pairs	24k BPS	x
HyenaDNA (Nguyen et al., 2023)	Autoregressive	Base-Pairs	10^6 BPS	x
HAPNEST (Wharrie et al., 2023)	LD & Markov	SNPs	1 Chromosome	x
(Perera et al., 2022)	GMMNs	SNPs	1 Chromosome	✓
(Yelmen et al., 2021)	GAN,RBM	SNPs	10k SNPs	x
(Yelmen et al., 2023)	WGAN	SNPs	10k SNPs	x
(Szatkownik et al., 2024)	WGAN	PCA+SNPs	65k SNPs	x
(Ahronoviz and Gronau, 2024)	GAN	SNPs	10k SNPs	✓
(Burnard et al., 2023)	VAE	SNPs	1 Chromosome	x
(Dang et al., 2023)	HCLTs	SNPs	10k SNPs	x
GeneticDiffusion (Ours)	**Diffusion**	PCA+SNPs	**Full Genome**	✓

Pre-Processing

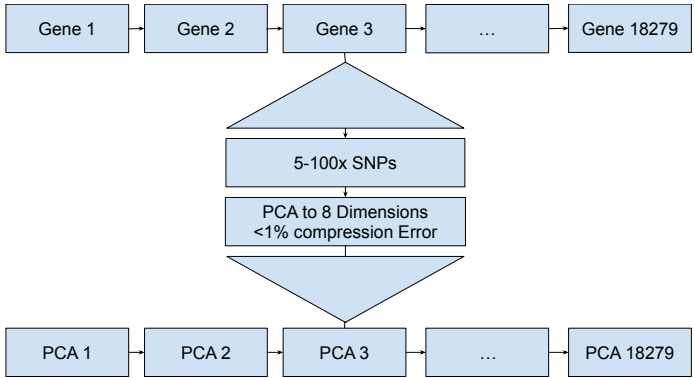
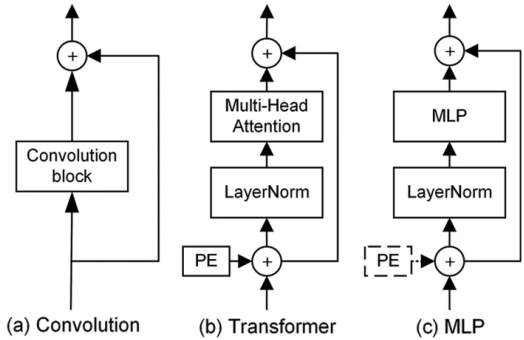


Figure: Overview of the Pre-processing pipeline. Genes, which consist of between 5 to 100 SNPs are each processed by a custom PCA. This is done independently for each Gene.

Model Architecture

Possible options:

- Transformer - No spatial bias, popular, needs high amount of training data
- U-Net CNN - Local spatial bias, few parameters
- U-Net MLP - Overfits easily, hard to train
- Combinations are also possible



Model Architecture

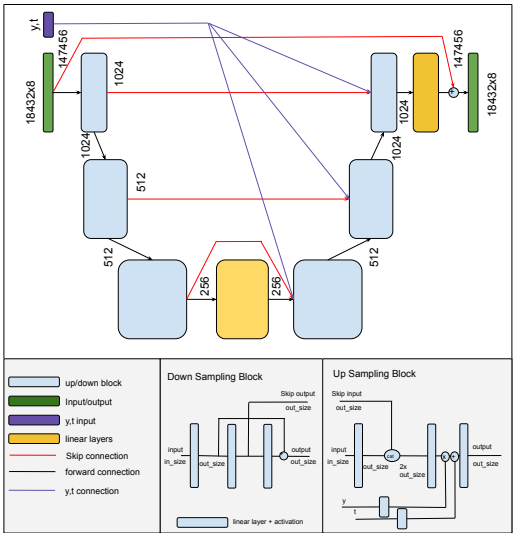


Figure: A structural overview of the architecture of the MLP diffusion model.

Evaluation

We evaluate on 2 different classification tasks:

- ALS classification
- 1KG region classification

Recovery Rate compares the performance of the syn model a_s vs the true model a_r:

$$R(a_r, a_s) = \frac{a_s}{a_r} \tag{1}$$

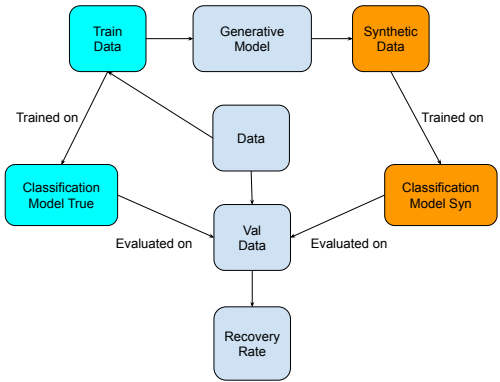
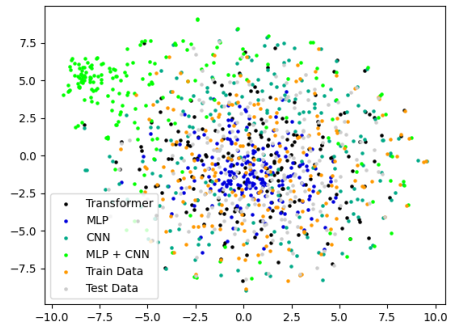


Figure: A diagram of the evaluation pipeline.

Evaluation

Additional metric:
Nearest Neighbour Adversarial Accuracy (Yale et al., 2019) - relies on distances of generated samples to original samples.

Problem:
Distances/neighbourhood in high dimensional space are not inherently meaningful (Beyer et al., 1999).



Experiments

We evaluated 4 different generative architectures:

- MLP
- CNN
- MLP + CNN
- Transformer

The metrics we used:

- Recovery Rate
- Nearest Neighbour Adversarial Accuracy
- Accuracy improvement with partial synthetic data

Results Recovery Rate

Table: Recovery rates on a hold out test set of true genotypes after training different ALS or 1KG population classifiers (MLP, Transformer or CNN) on different synthetically generated data types (generated by: MLP, Transformer, CNN, MLP + CNN). The best synthetic data for each classifier type is marked in **bold**.

Classifier	CNN	MLP	MLP+CNN	Transformer
		ALS data		
MLP	71.51	**96.69**	94.26	73.77
Transformer	66.06	93.44	**93.89**	69.30
CNN	69.88	91.72	**93.17**	68.72
		1KG data		
MLP	15.58	65.80	**93.02**	13.28
Transformer	16.23	62.99	**84.98**	8.38
CNN	19.52	56.57	**77.54**	21.21
Average (all)	43.17	78.06	**89.48**	42.56

Results NNAA

Table: Result of Nearest Neighbour Adversarial Accuracy for generated datasets on the ALS and 1KG data; For AA the closer to 0.5 the better, For Privacy Loss the closer to 0 the better; best performance is **highlighted**.

			CNN	MLP	MLP + CNN	Transformer
ALS data	test data	AA_{truth}	0.735	0.255	**0.485**	0.92
		AA_{syn}	0.68	1.0	0.93	**0.66**
	train data	AA_{truth}	0.81	0.005	**0.405**	0.93
		AA_{syn}	**0.67**	1.0	0.92	0.69
		Privacy Loss	0.0325	0.125	0.0475	**0.02**
1KG data	test data	AA_{truth}	0.76	0.0	**0.63**	0.345
		AA_{syn}	0.995	1.0	0.94	**0.92**
	train data	AA_{truth}	0.765	0.0	**0.385**	0.285
		AA_{syn}	1.0	0.99	**0.74**	0.82
		Privacy Loss	0.05	**-0.005**	-0.2225	0.08

Partial Synthetic and Real

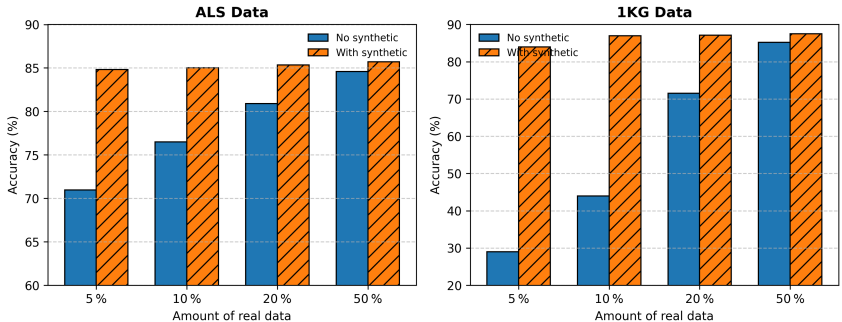


Figure: Accuracy improvements by integration of synthetic data for best performing classification architecture.

Conclusion

- Synthetic data does not just copy real data, while close to real data distribution (see NNAA)
- Recovery Rate indicates high fidelity of synthetic data.

Next Steps:

- Bigger dataset (for example UK Biobank)
- Multimodal data
- Publish synthetic dataset

Questions and Discussion

Feel free to ask anything.

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