

Deep generative model of genetic variation data improves imputation accuracy in private populations



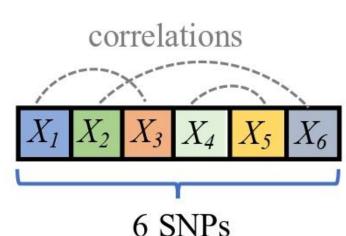
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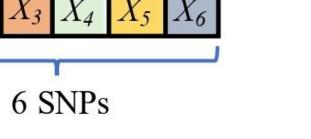
Introduction

- Artificial Genomes (AGs) enable sharing and benchmarking without exposing sensitive genetic data, supporting reproducibility and equity in population genomics
- Coalescent and PAC/HMM approaches are interpretable and tractable but often computationally intensive, and may not fully capture fine-scale genomic dependencies
- GANs, VAEs, and RBMs offer expressiveness but lack tractable inference, reliable likelihood computation, and are challenging to train and tune
- We propose a novel tractable and expressive deep generative model of genetic variation based on Hidden Chow-Liu Trees (HCLTs) represented as Probabilistic Circuits (PCs), enabling efficient learning and inference

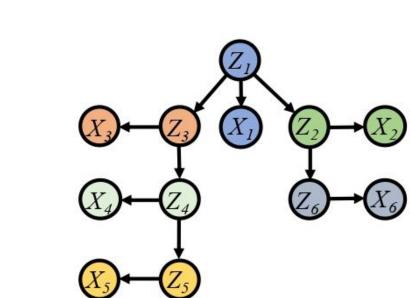
Methods



(a) Genetic data with 6 SNPs



(b) Learned CLT structure captures strong pairwise correlation between SNPs.

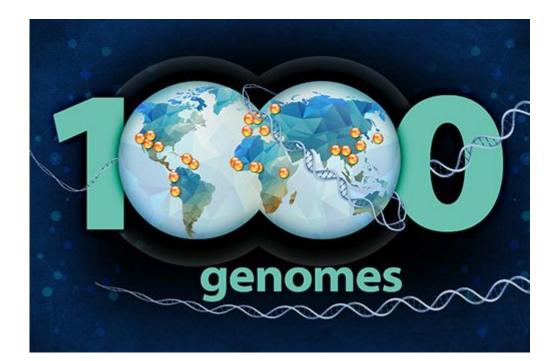


(c) Learned HCLT structure given the SNPs in (a).

- After constructing the HCLT, we convert to a PC via PyJuice [1]
- PCs are <u>efficient</u> to train and contain a <u>single hyperparameter</u>
- PCs can generate samples and quickly query marginals and conditionals → <u>probabilistic</u> convergence and direct <u>imputation</u>

Data

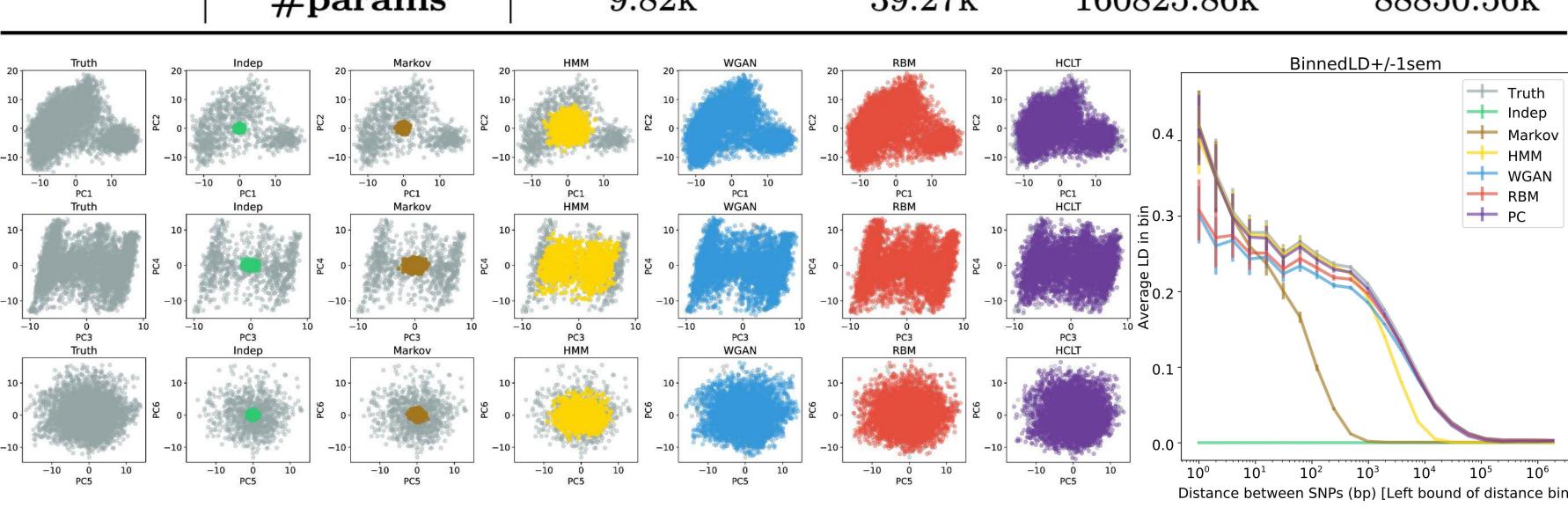
- Phased haplotype data (0/1)
- 1000 Genomes Project Phase 3 (low-coverage) 15:27379578 - 15:29625035 (5008 x 10000)
- UK Biobank
- 22:29456546 22:32665772 (26924 x 9820)
- 1000 Genomes Project Phase 3 (high-coverage) 15:27134431 - 15:29332831 (5008 x 14670)





Reconstructing Global and Local Population Structure

Dataset	Category	INDEP	Markov	HMM	PC
1KG	train LL	-2386.81	-1806.33	-591.08	-202.51
	test LL	-2404.51	-1819.96	-599.88	-265.06
	#params	10.00k	39.99k	163774.98k	88473.73k
UKBB	train LL	-1642.62	-1360.86	-554.88	-120.10
	test LL	-1648.03	-1362.16	-554.38	-127.75
	#params	9.82k	39.27k	160825.86k	88850.56k



- Log-likelihood of models that support tractable likelihood inference
- **Bottom:** Left shows top 6 principal components of ground truth vs. samples, while right shows binned LD as a function of SNP distance

Preserving Privacy of the Training Data

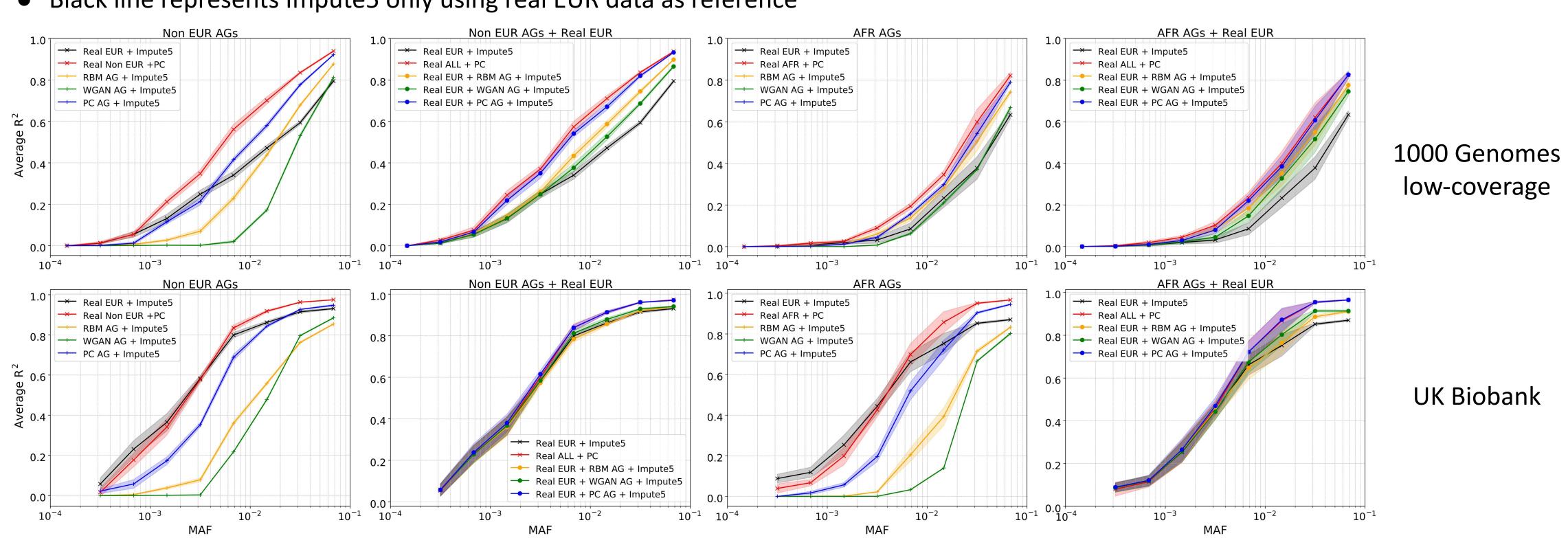
$$\mathcal{AATS} = \frac{1}{2} \left(\frac{1}{n} \sum_{i=1}^{n} \mathbf{1} \left(d_{TS}(i) > d_{TT}(i) \right) + \frac{1}{n} \sum_{i=1}^{n} \mathbf{1} \left(d_{ST}(i) > d_{SS}(i) \right) \right)$$
• Nearest Neighbor Adversarial Accuracy [2]
• T = Truth, S = Synthetic

Dataset	Metric	RBM	WGAN	\mathbf{PC}
1KG	AA_{TRUTH} (Train) AA_{TRUTH} (Test) AA_{SYN} (Train) AA_{SYN} (Test)	0.9561 0.9928 0.0024 0.0276	0.8103 0.7764 0.7356 0.7847	0.7185 0.7680 0.4225 0.5304
UKBB	AA_{TRUTH} (Train) AA_{TRUTH} (Test) AA_{SYN} (Train) AA_{SYN} (Test)	0.9954 0.9962 0.0064 0.0160	0.9674 0.9688 0.7768 0.7582	0.9204 0.9198 0.5324 0.4630

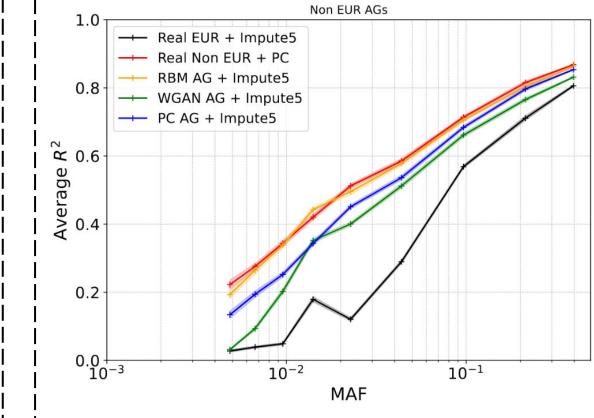
- AA_{TRITH} : Low \rightarrow synthetic mimics real too closely(overfit, low privacy). $High \rightarrow synthetic$ is far from real (high privacy, lower utility).
- AA_{SYN} : Low \rightarrow synthetic copies real samples (low privacy). High \rightarrow synthetic has its own structure (high privacy, may reduce utility if too different).
- **Ideal:** Both around $0.5 \rightarrow$ realistic synthetic data that balances privacy and utility
- Only report components since average can hide poor performance

Improving Imputation Accuracy in Private Populations

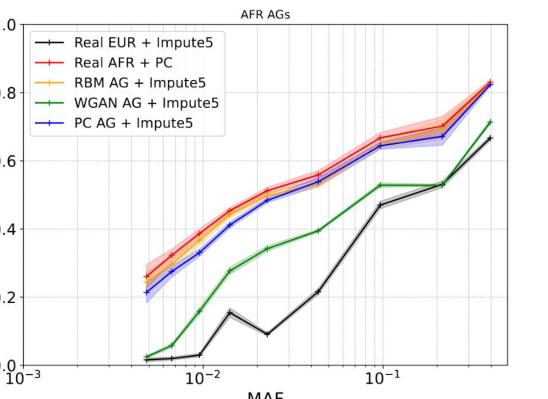
- Imputation of one SNP at a time using AGs as reference panel in Impute5 pipeline (or combined with real EUR data)
- Black line represents Impute5 only using real EUR data as reference



- Imputation of all SNPs not present on InfiniumOmni2-5-8v1-4 A1 array using 1000 Genomes high-coverage as training
- Out of 14670 SNPs, 1302 are present on the array, and remaining are imputed simultaneously (91% missingness)



	\$55. A.S.		- Real EUN + IIIIputes
ALL SNPs Real + Impute5	0.3108 [0.3078, 0.3138]	0.8	Real AFR + PC RBM AG + Impute5 WGAN AG + Impute5
Real + PC RBM AG + Impute5 WGAN AG + Impute5 PC AG + Impute5	0.5294 [0.5273, 0.5315] 0.5215 [0.5188, 0.5242] 0.4289 [0.4257, 0.4321] 0.4725 [0.4696, 0.4754]	Average <i>R</i> ² 6.0	→ PC AG + Impute5
Low-freq (MAF < 1%) Real + Impute5	0.0341 [0.0312, 0.0370]		
Real + PC RBM AG + Impute5 WGAN AG + Impute5 PC AG + Impute5	0.2776 [0.2727, 0.2826] 0.2598 [0.2528, 0.2667] 0.1039 [0.0998, 0.1079] 0.1902 [0.1855, 0.1948]	0.2	-3 10 ⁻²



Method	Mean R^2 [95% CI]		
ALL SNPs			
Real + Impute5	$0.2447\ [0.2392, 0.2501]$		
Real + PC	$0.5224 \ [0.5131, \ 0.5317]$		
RBM AG + Impute5	0.5055 $[0.4950, 0.5159]$		
WGAN AG + Impute5	$0.3370 \ [0.3326, 0.3414]$		
PC AG + Impute5	$0.4889 \ [0.4809, \ 0.4969]$		
Low-freq (MAF $< 1\%$)			
Real + Impute5	$0.0186 \ [0.0138, \ 0.0235]$		
Real + PC	$0.3239\ [0.3051,\ 0.3427]$		
RBM AG + Impute5	$0.3007 \; [0.2816, 0.3198]$		
WGAN AG + Impute5	$0.0759 \; [0.0712, 0.0805]$		
PC AG + Impute5	0.2735 [0.2577, 0.2894]		

Conclusion

- We present a novel deep generative model for genetics based on PCs
- Fast & tractable: Easy to train and use at scale
- Realistic: Matches key genetic patterns, with more accurate LD Privacy-preserving: Balances similarity and separation effectively
- Boosts imputation: Improves accuracy for underrepresented groups
- Direct inference: Enables imputation and likelihood evaluation
- **Enables access:** Supports open, equitable genomic research

References

[1] Anji Liu, Kareem Ahmed, and Guy Van den Broeck. Scaling tractable probabilistic circuits: A systems perspective. In Proceedings of the 41th International Conference on Machine Learning (ICML), jul 2024.

[2] Andrew Yale, Saloni Dash, Ritik Dutta, Isabelle Guyon, Adrien Pavao, and Kristin P. Bennett. Generation and evaluation of privacy preserving synthetic health data. Neurocomputing, 416:244–255, 2020