A deep learning based approach for genetic risk prediction

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Whole Genome Sequencing vs. Genotype array

Full Data
(whole genome sequencing)

```
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 0 0 1 0 1 1 0
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 1 0 1 1 1 0 1 1 1 1 0 1 1 0 1
```

Sparse Data
(genotype array)

```
0 0 ? ? ? 0 0 1 1 ? ? 0 ? ? ? ?
0 0 ? ? ? 0 0 1 1 ? ? 0 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
0 0 ? ? ? 0 0 1 1 ? ? 1 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
```

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Whole Genome Sequencing vs. Genotype array

Full Data
~80M genetic variants

```
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 0 0 1 0 1 1 0
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 1 0 1 1 1 0 1 1 1 1 0 1 1 0 1
```

Sparse Data
~4 million genetic

```
0 0 ? ? ? 0 0 1 1 ? ? 0 ? ? ? ?
0 0 ? ? ? 0 0 1 1 ? ? 0 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
0 0 ? ? ? 0 0 1 1 ? ? 1 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
0 1 ? ? ? 1 0 1 1 ? ? 0 ? ? ? ?
```

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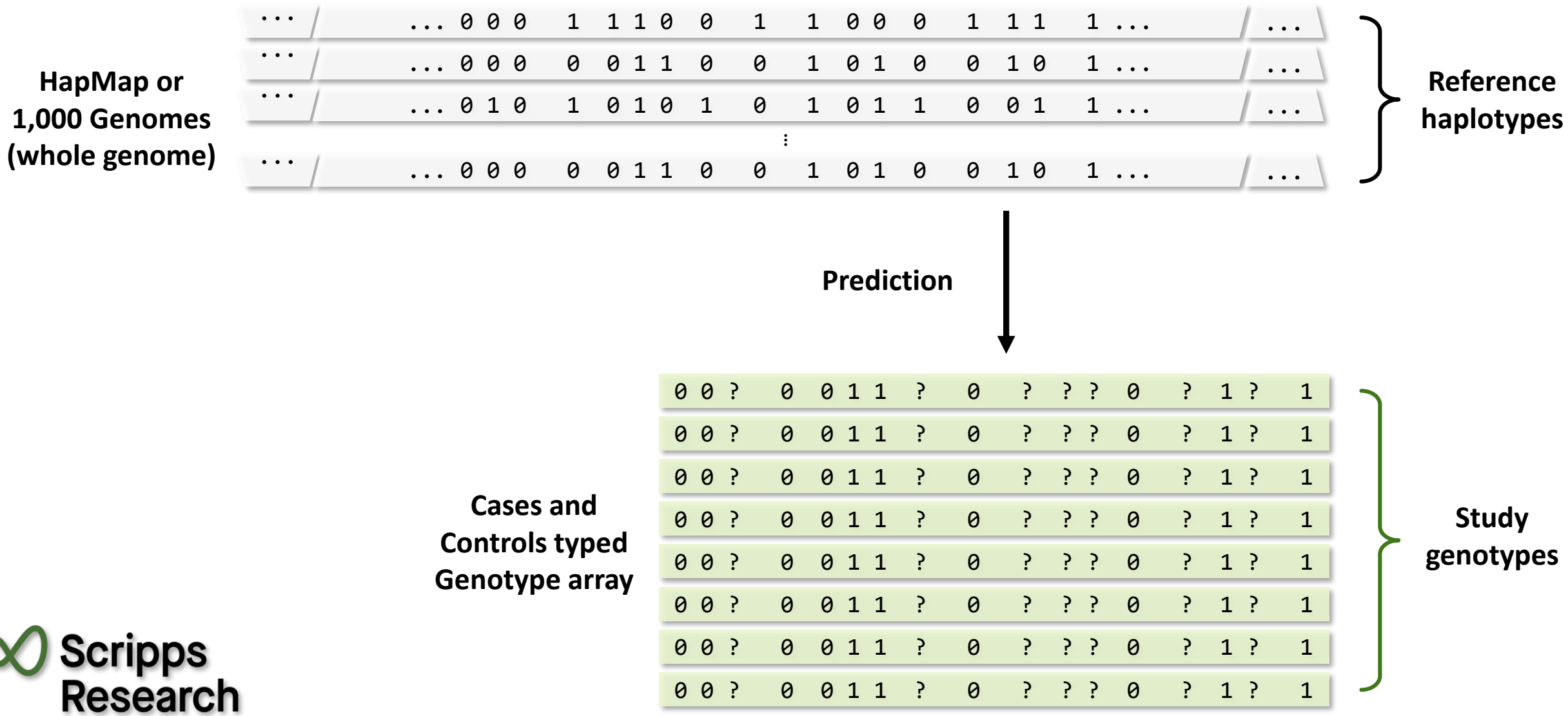
Genetic imputation problem



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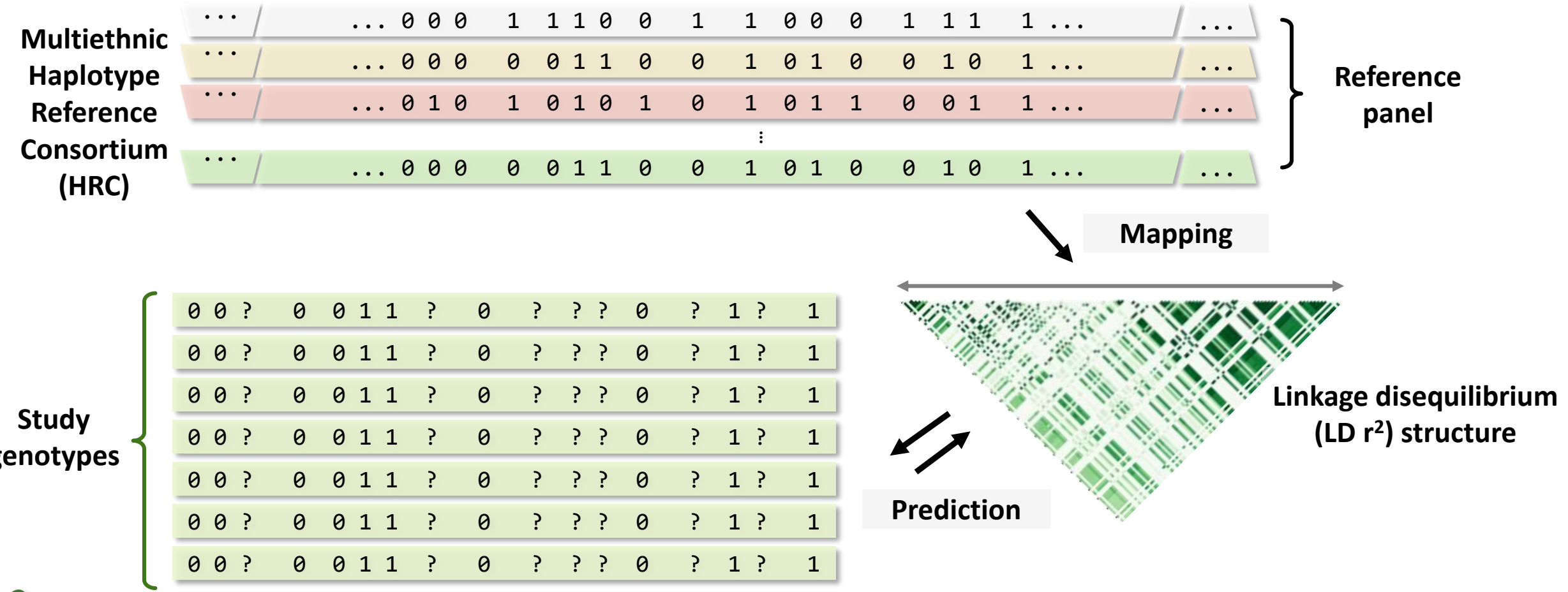
A typical imputation approach



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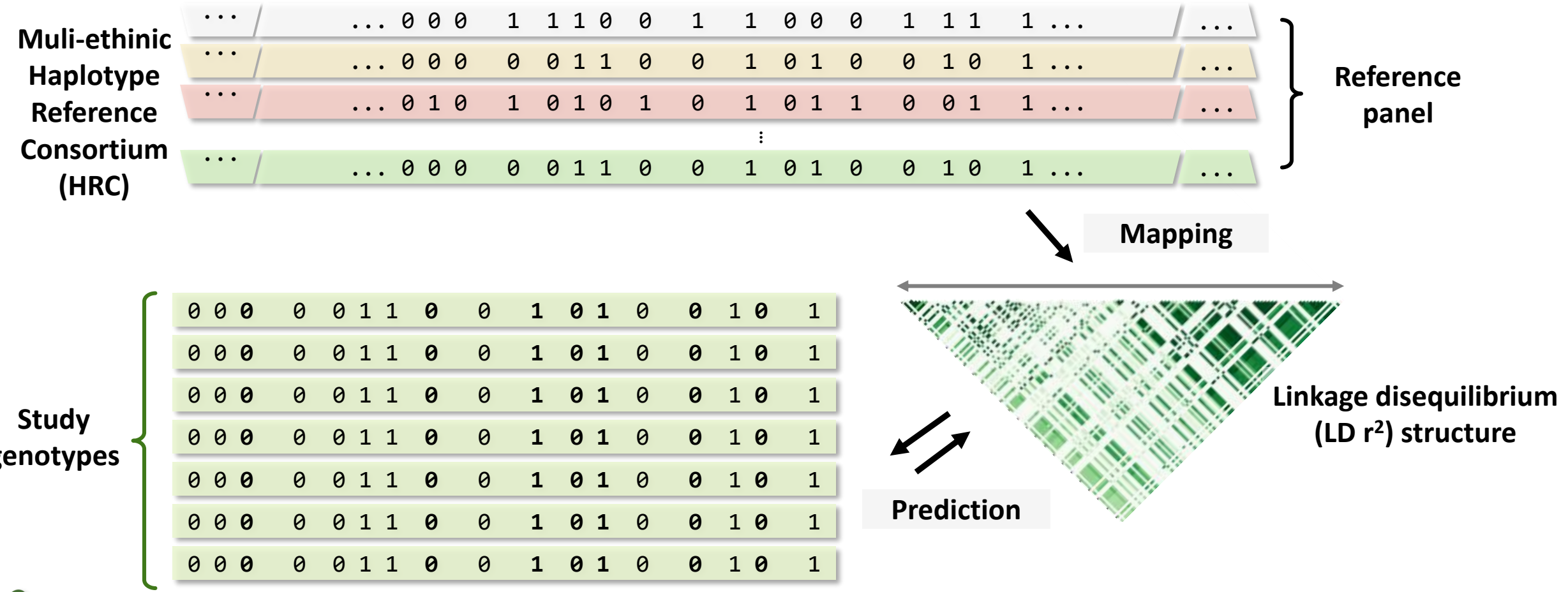
A typical imputation approach



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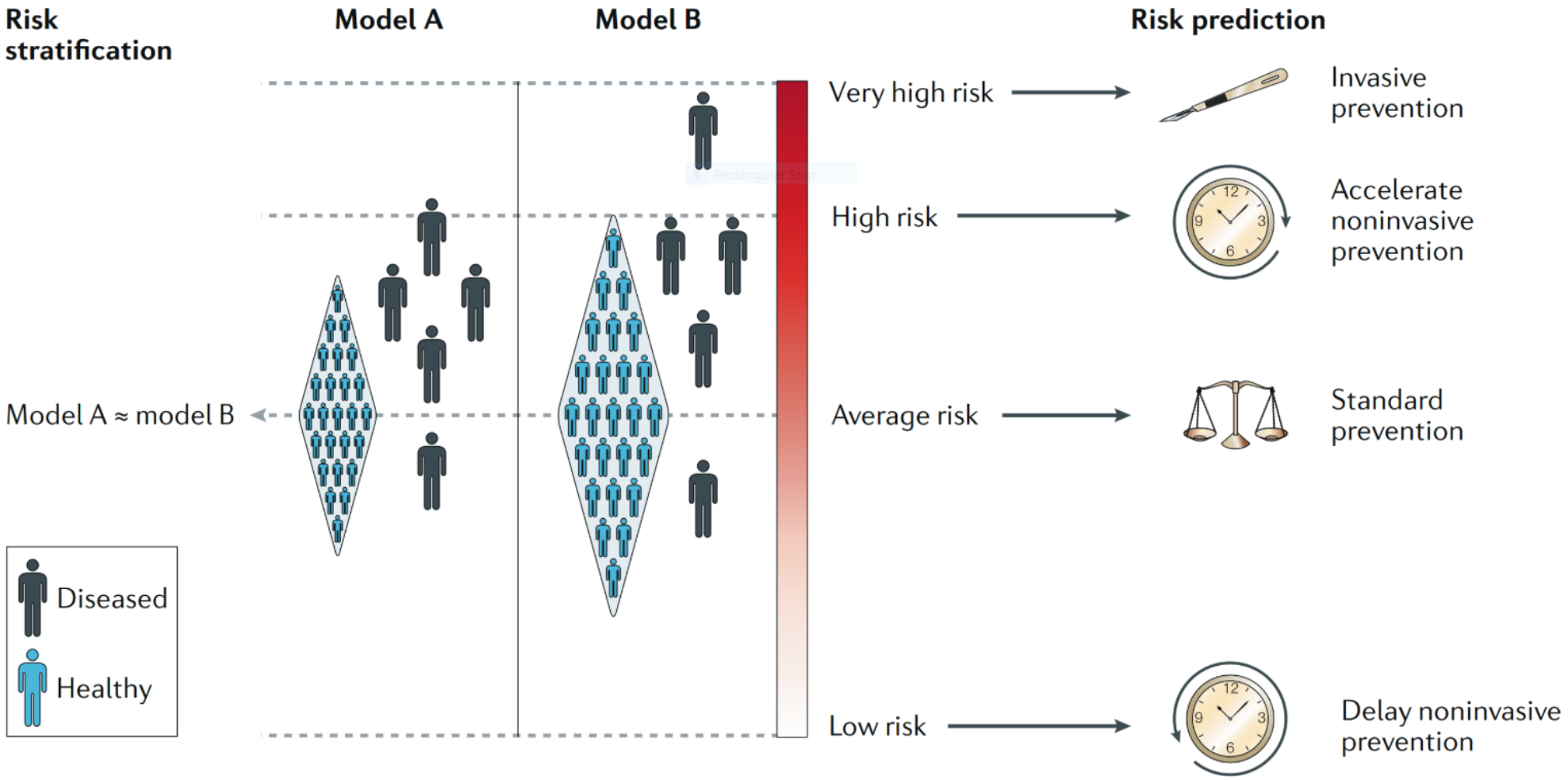
Polygenic Risk Score (PRS)



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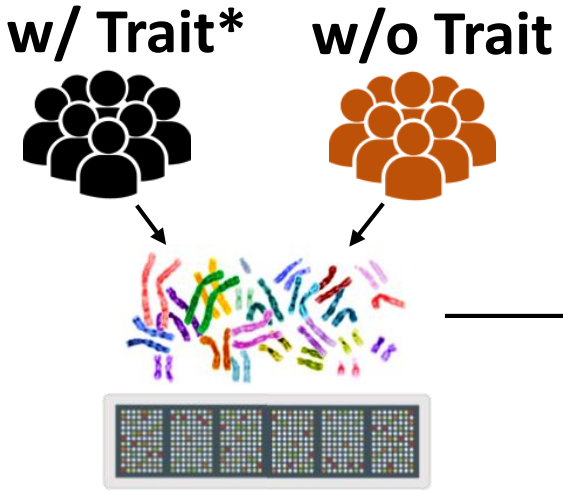
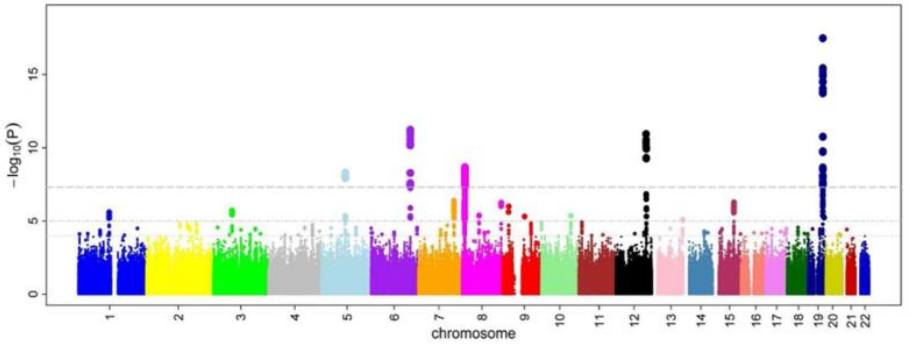
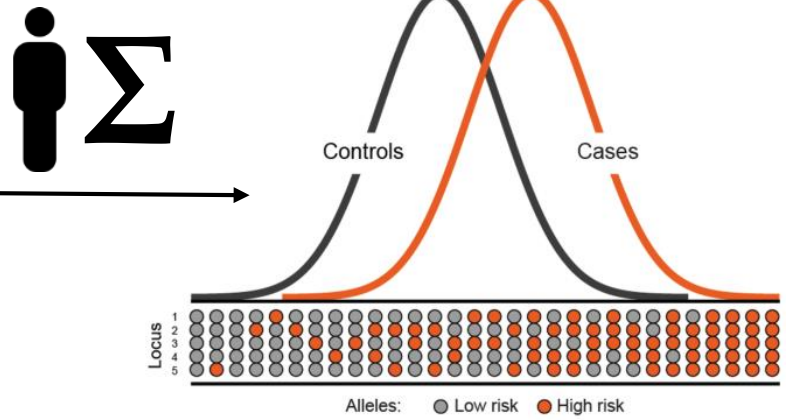
Polygenic Risk Calculation







Design
100,000+ subjects

Results
Millions of known variants

Polygenic Risk Score
Cumulative sum

***Trait** can often be heterogeneous
e.g. coronary artery = heart attack, stroke, bypass surgery, etc.

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Objectives

1. More accurate and faster imputation
2. Find important genetic variants
3. Better polygenic risk score calculation

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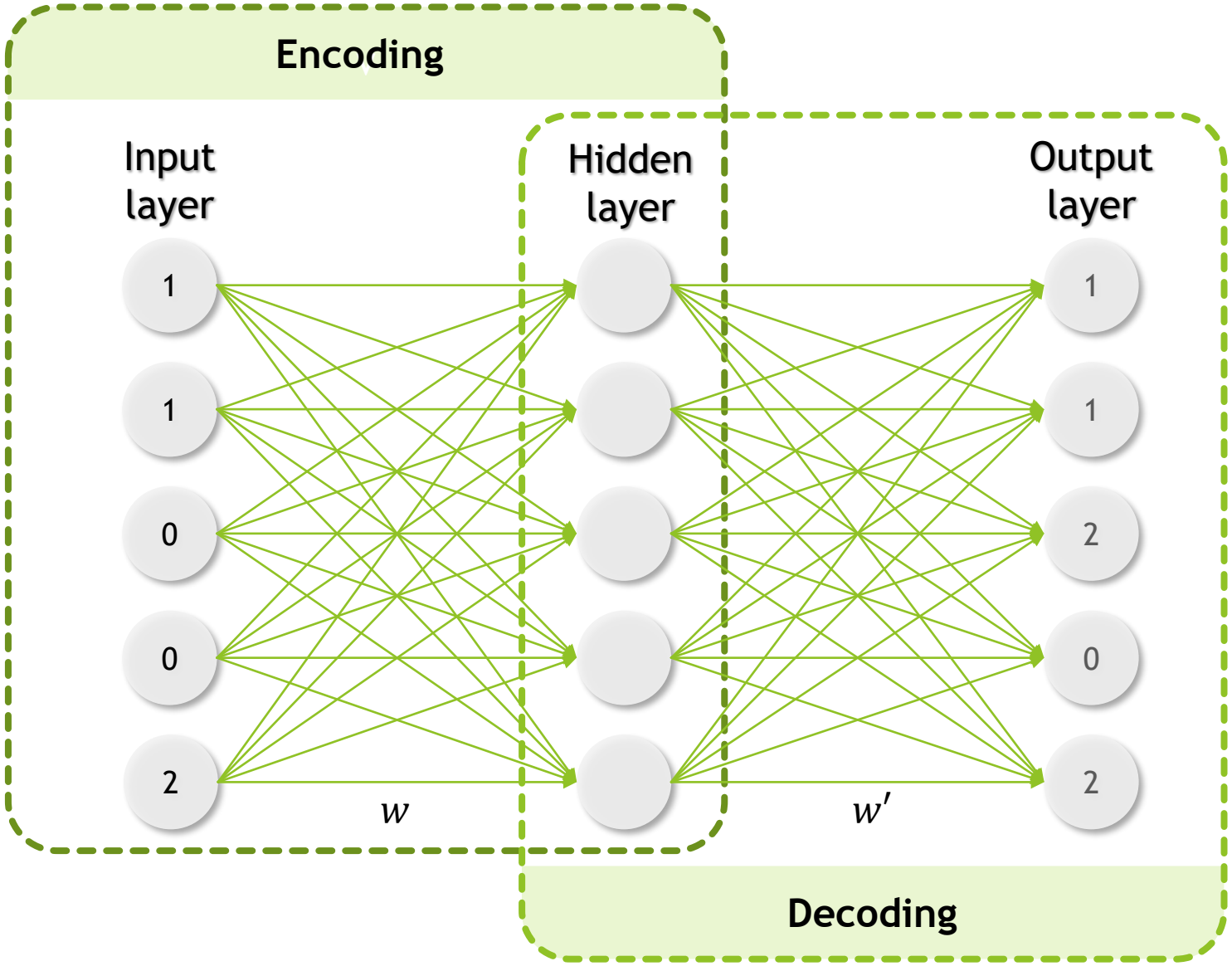
Our proposed approach



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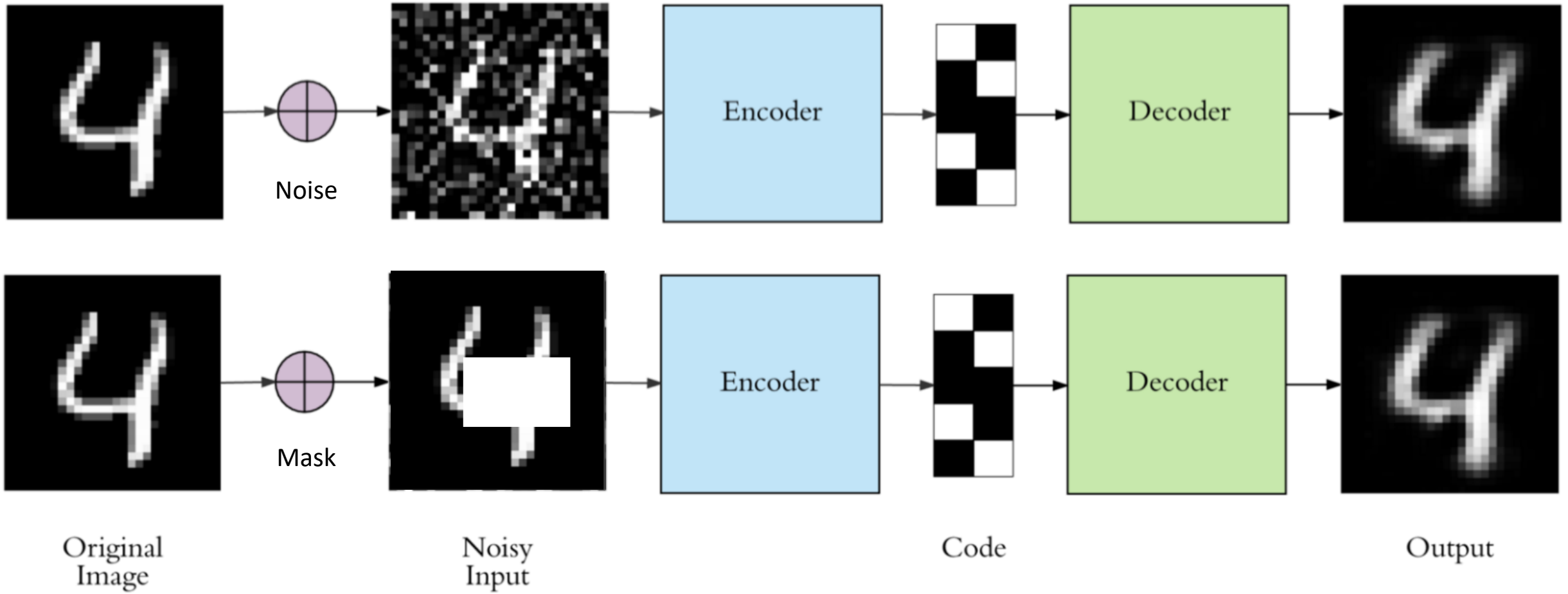
Denoising autoencoder for image restoration



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Bigdeli, Siavash Arjomand, and Matthias Zwicker. "Image restoration using autoencoding priors." *arXiv preprint arXiv:1703.09964* (2017).

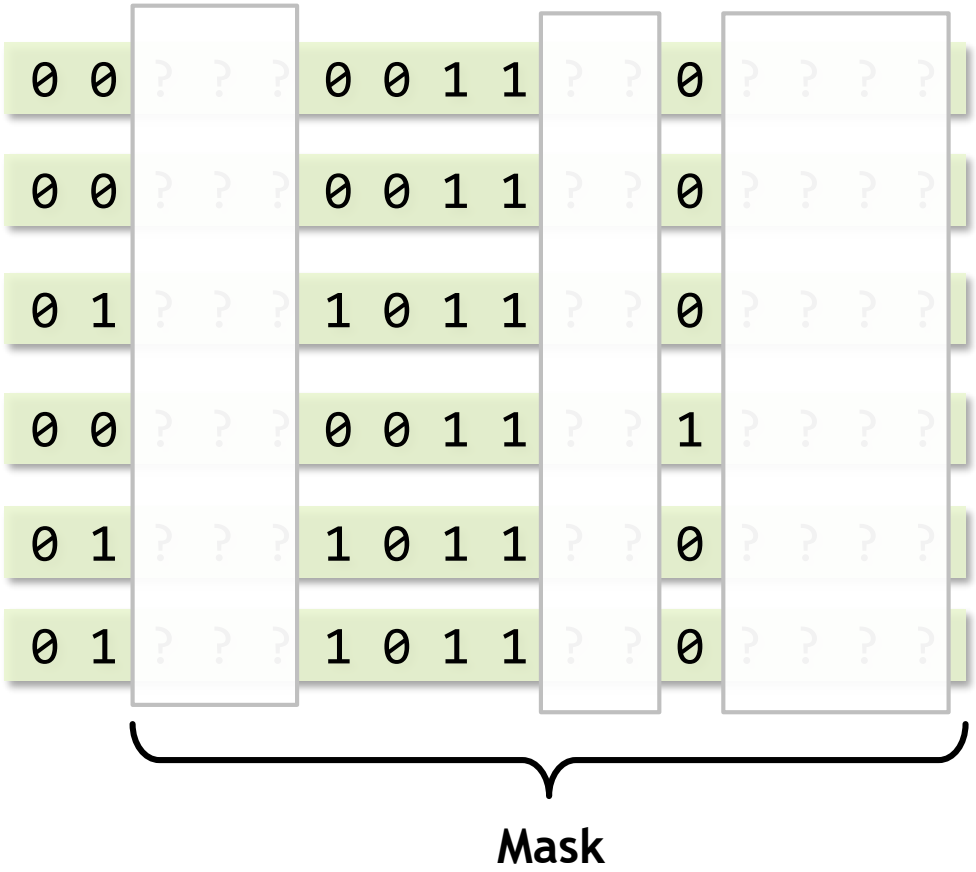
Wang, Ruxin, and Dacheng Tao. "Non-local auto-encoder with collaborative stabilization for image restoration." *IEEE Transactions on Image Processing* 25.5 (2016): 2117-2129.

Genotype imputation case study example

Ground truth
(whole genome sequencing)

```
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 1 1 0 1 1 0 1
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 0 1 0 0 0 0 1 1 0 0 1 0 1 1 0
0 1 0 1 0 1 0 1 1 1 1 0 1 1 0 1
0 1 0 1 1 1 0 1 1 1 1 0 1 1 0 1
```

Masked input
(genotype array)



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Case study: 9p21.3 region of the genome

- **Length: 59846 bp**
- **846 genetic variants in reference panel (whole genome data)**
  - Approx. 200 common variants
  - Approx. 600 rare variants
- **Only 17-47 variants in genotype array!!!**
- **Strong association to coronary artery disease (CAD)**
- **Genotyped and sequenced in many studies**

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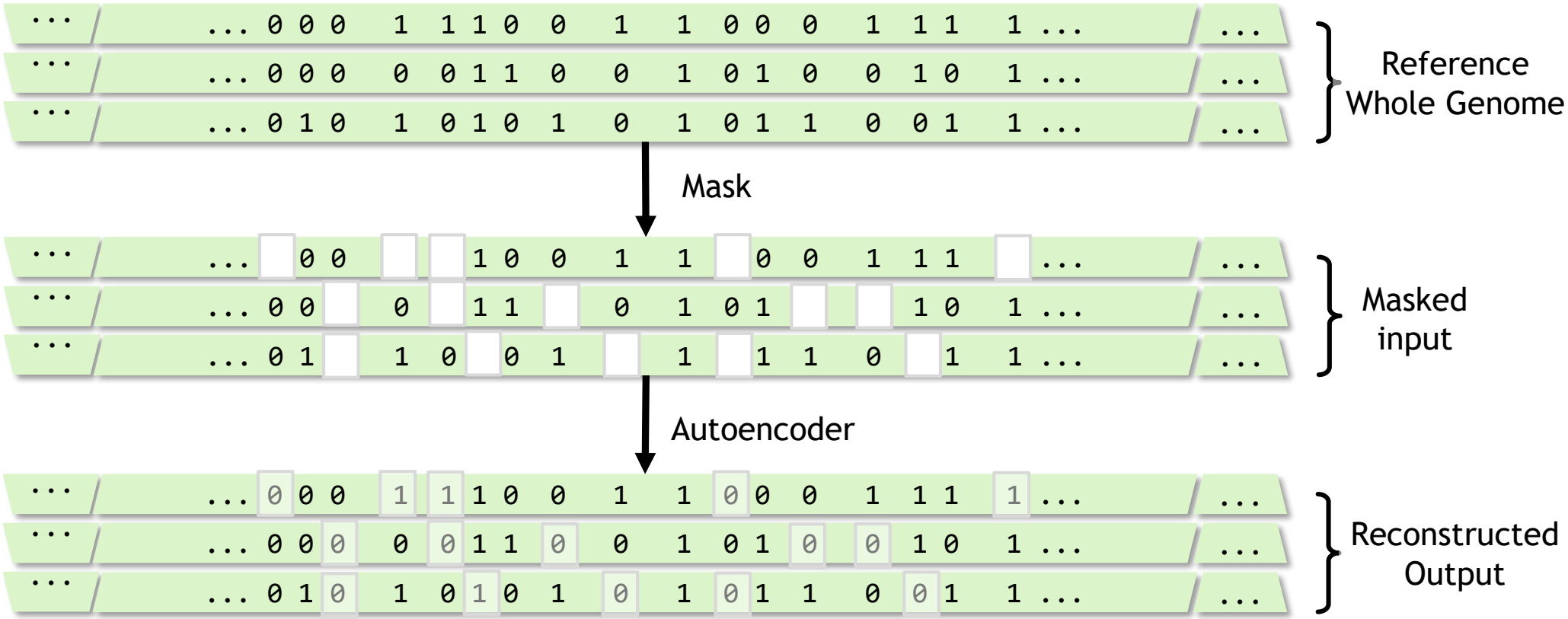
Training on the reference panel: Data augmentation strategy



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Customized Sparsity Loss Function

- Sparsity loss with Kullback-Leibler (KL) / cross entropy element:

$$D_{KL}(\rho||\hat{\rho}) = \rho * \log\left(\frac{\rho}{\hat{\rho}}\right) + (1-\rho) * \log\left(\frac{1-\rho}{1-\hat{\rho}}\right)$$

- Customized loss adjusted for hidden activation sparsity:

$$loss = MSE + \beta * \sum_{i=1}^{n} D_{KL(i)}$$

- Mean Squared Error:

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)$$

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Hyper parameters to be optimized

- β
- ρ
- Activation functions
- L1/L2 regularizers
- Learning rate
- Batch size

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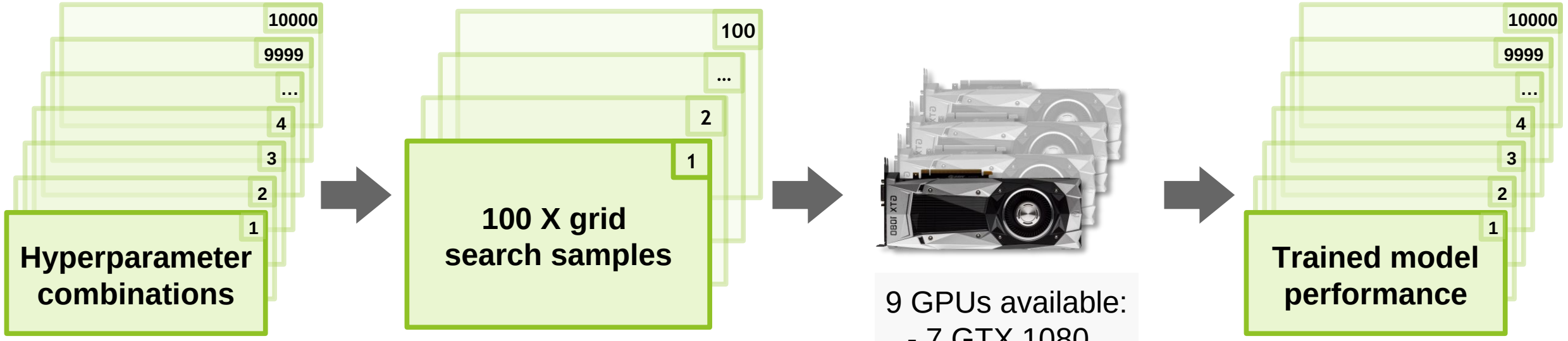
Parallel Grid Search
Hyperparameter optimization approach



860 hours
(sequential run,
100 epochs)

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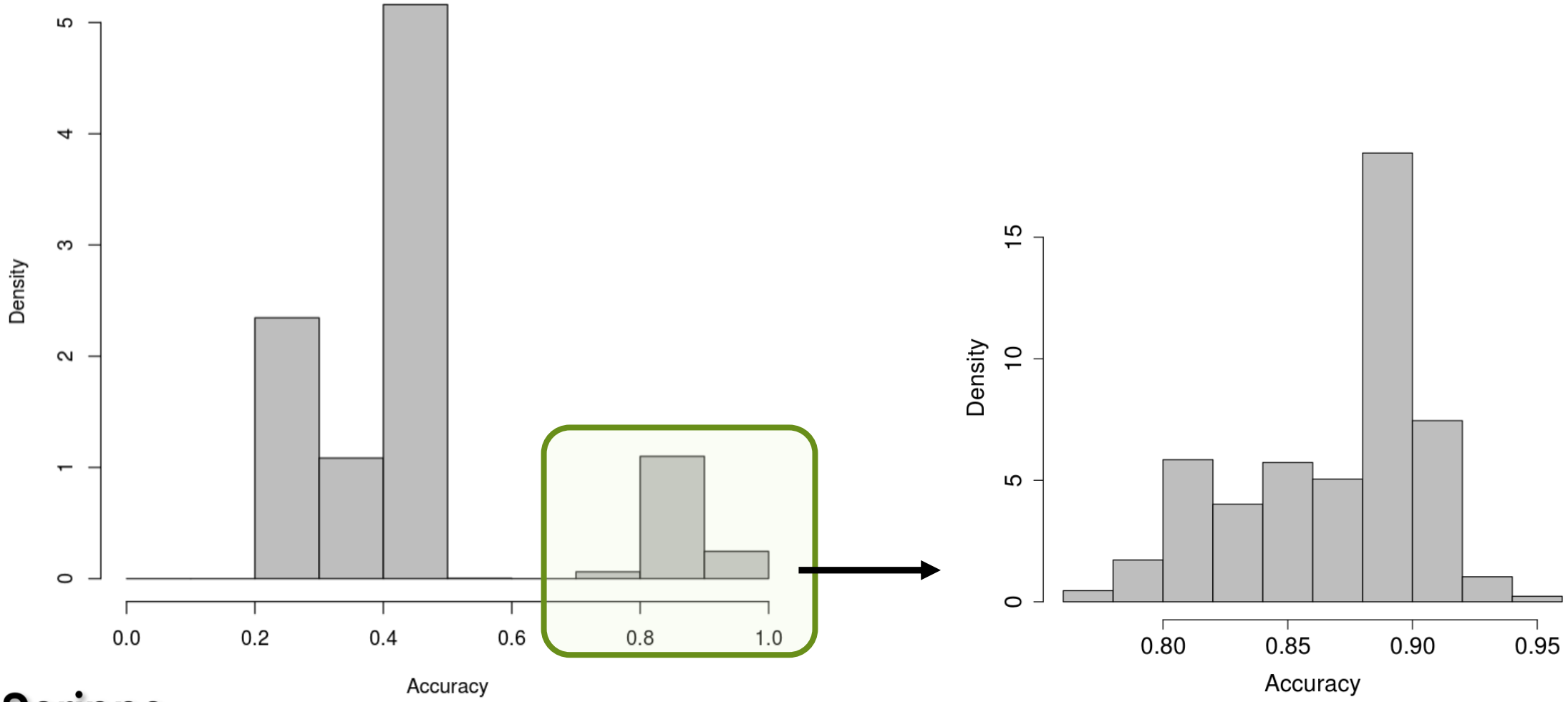
Grid Search Results: training accuracy



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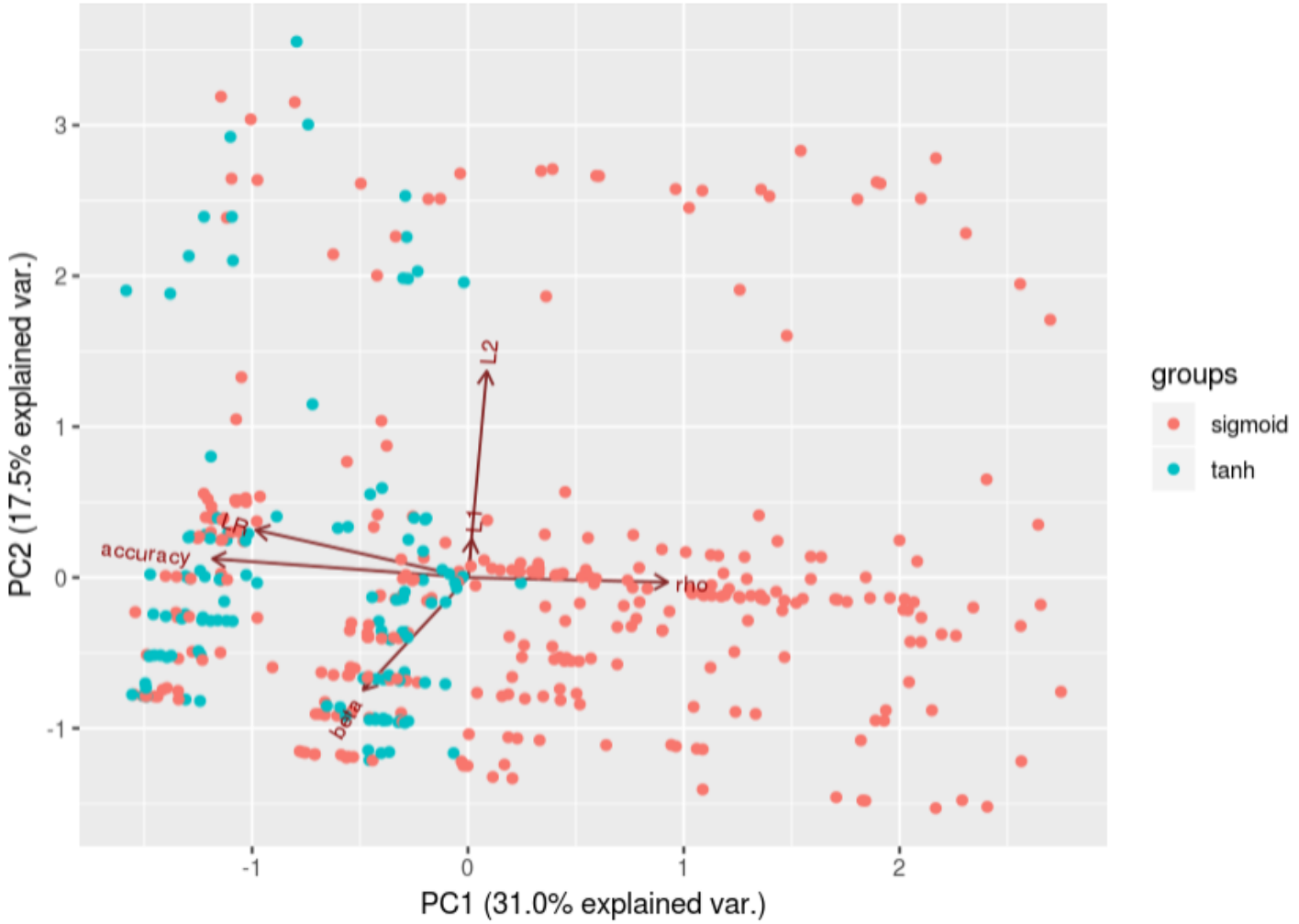
Grid Search results: assessing best hyperparameter values



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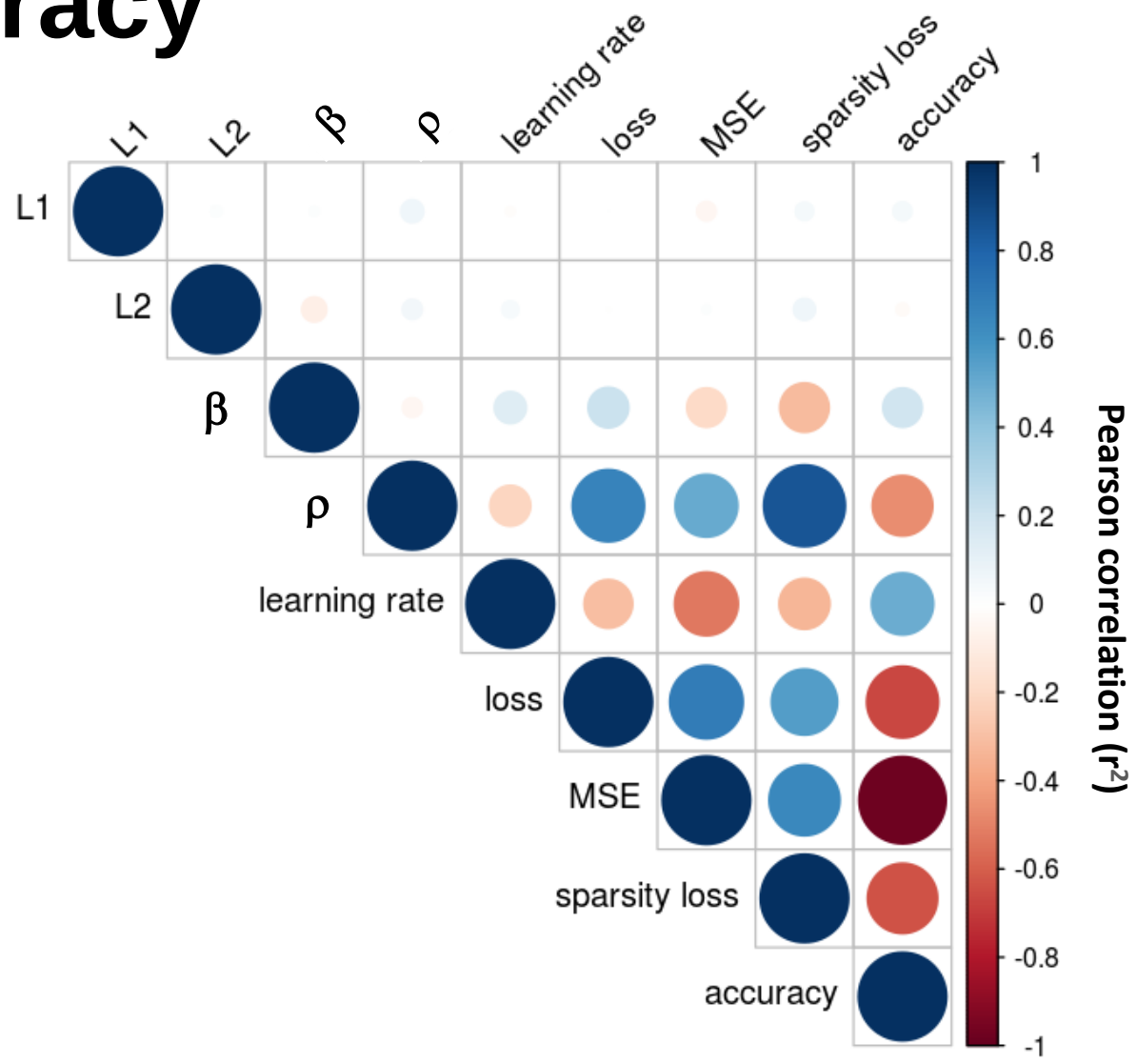
Effect of hyper parameter values in training accuracy

- β
- ρ
- Learning rate



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Effect of hyper parameter values in training accuracy

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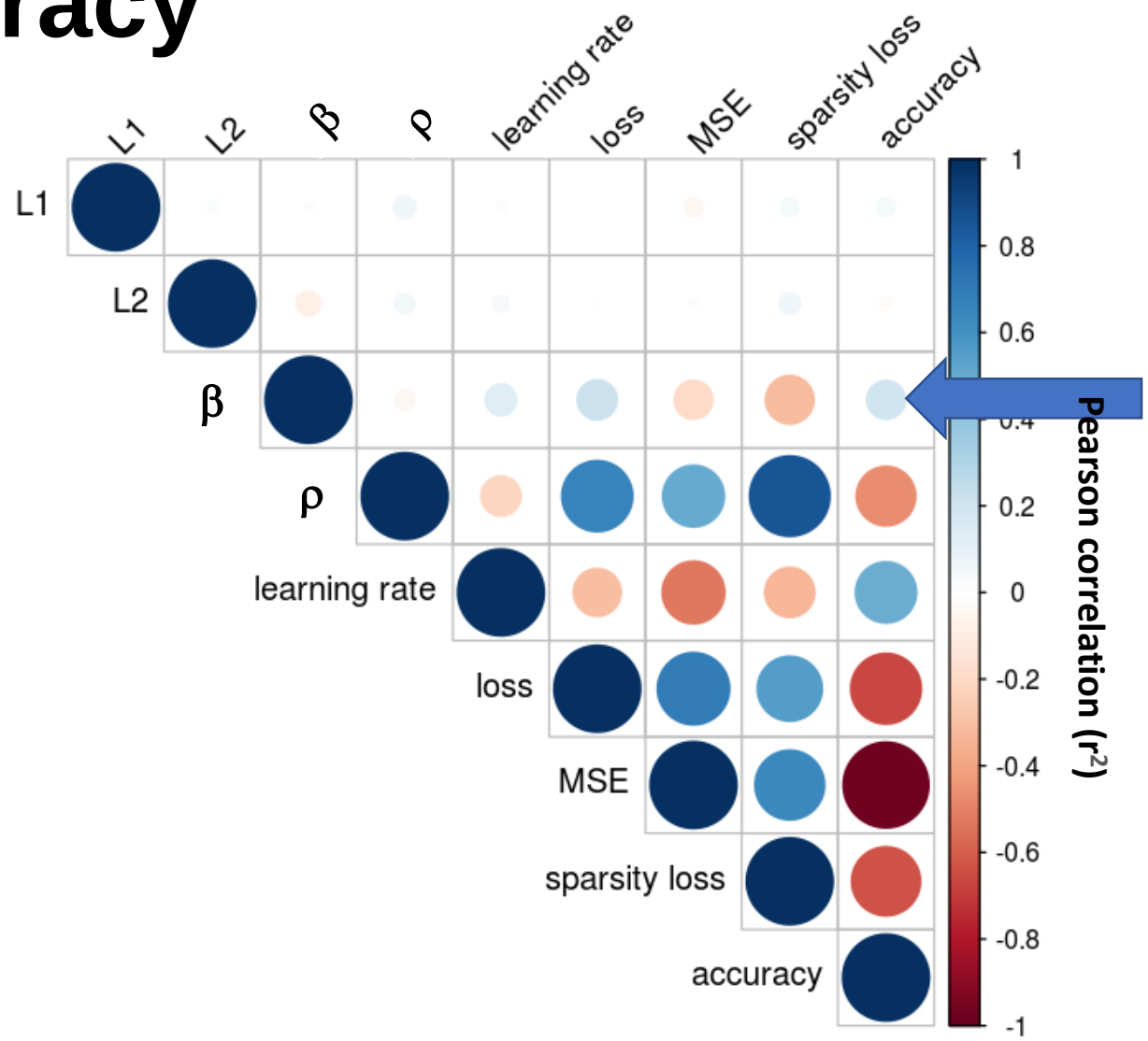
- Learning rate



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Effect of hyper parameter values in training accuracy

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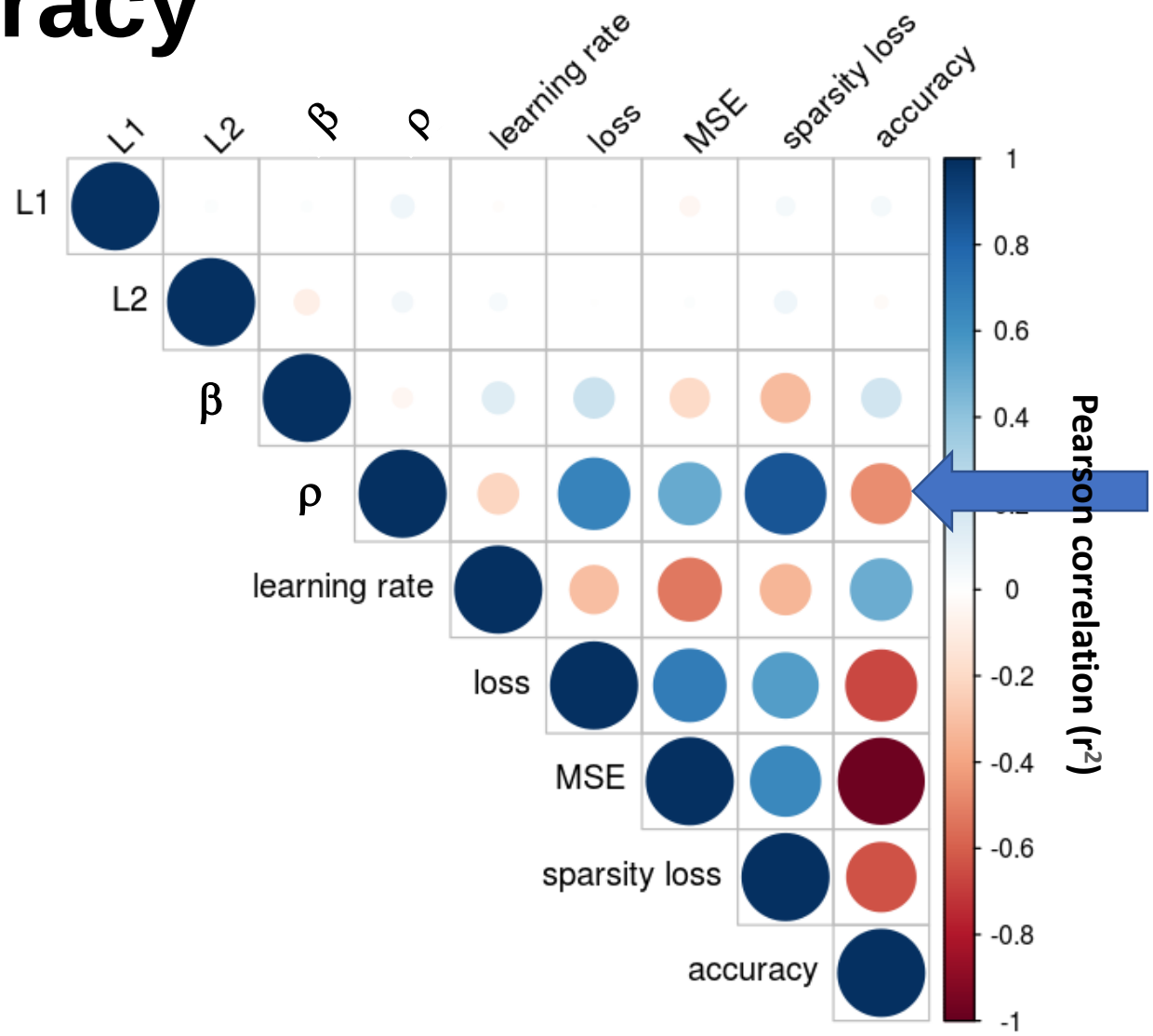

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Effect of hyper parameter values in training accuracy

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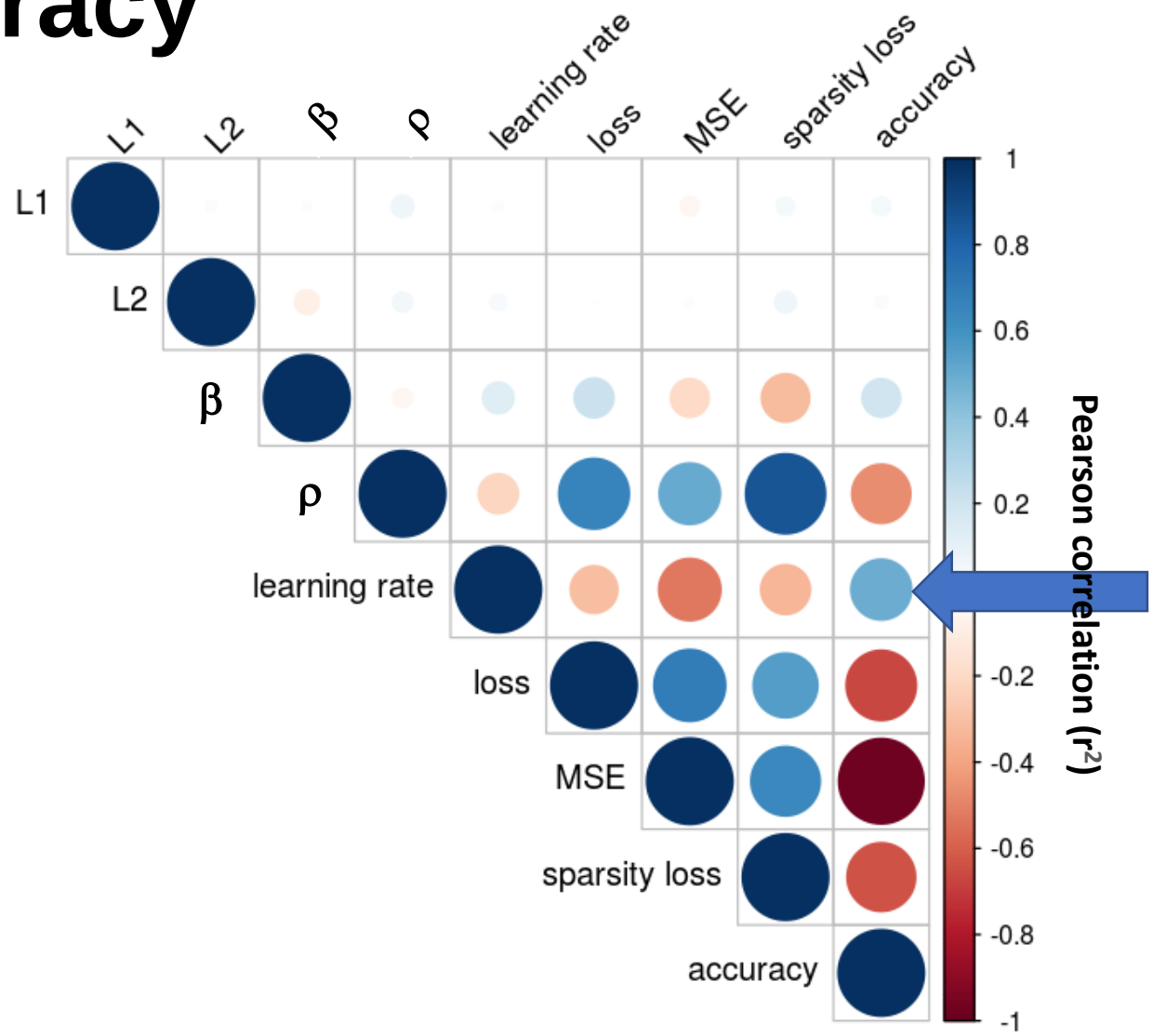

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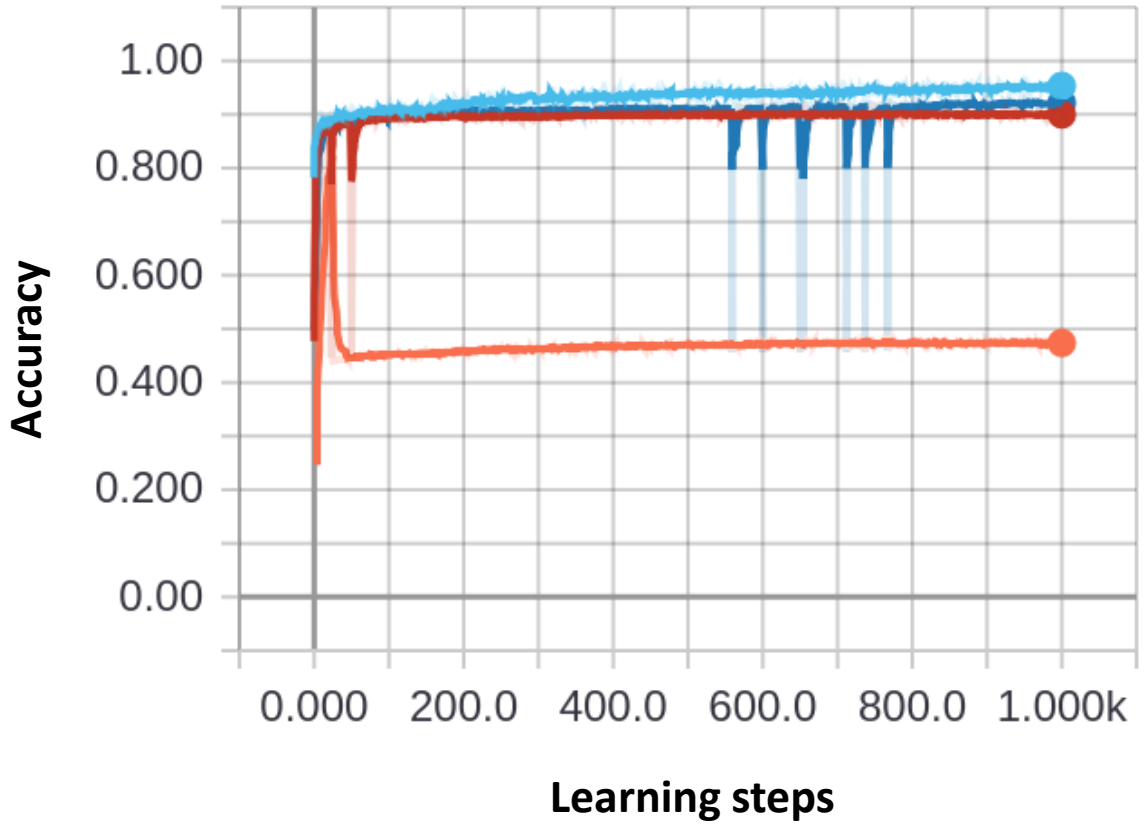
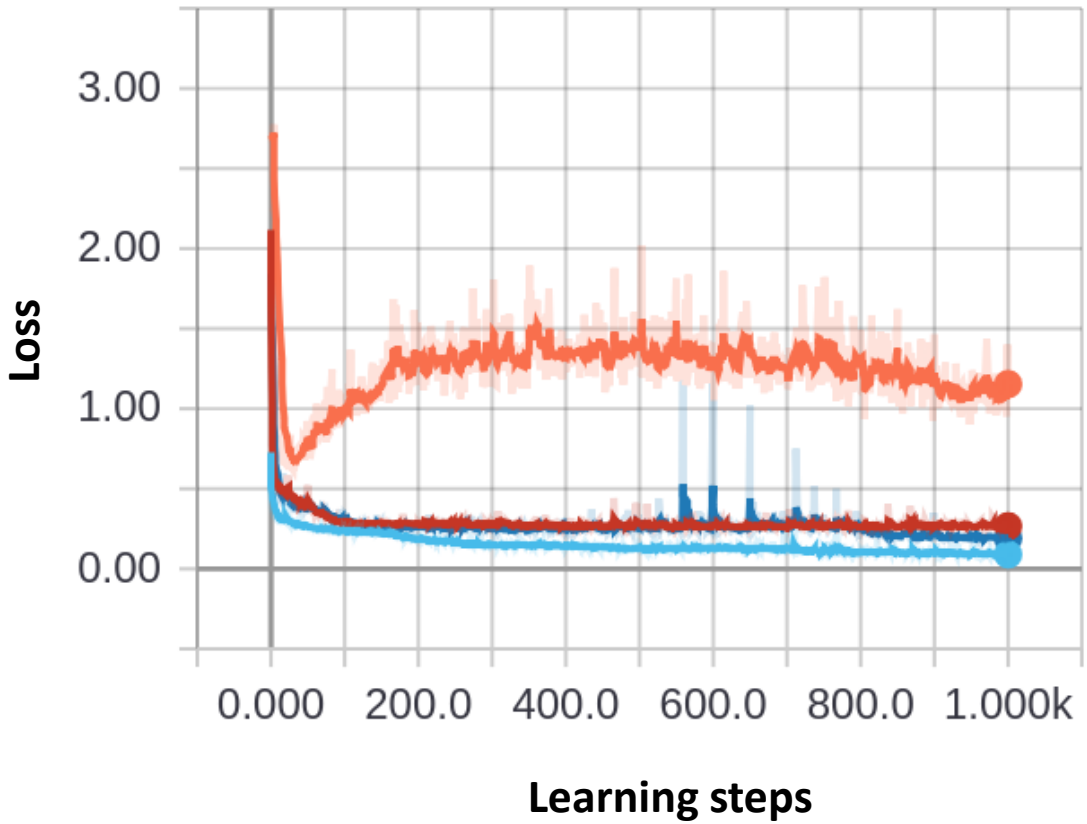
Optimizing batch size: training accuracy





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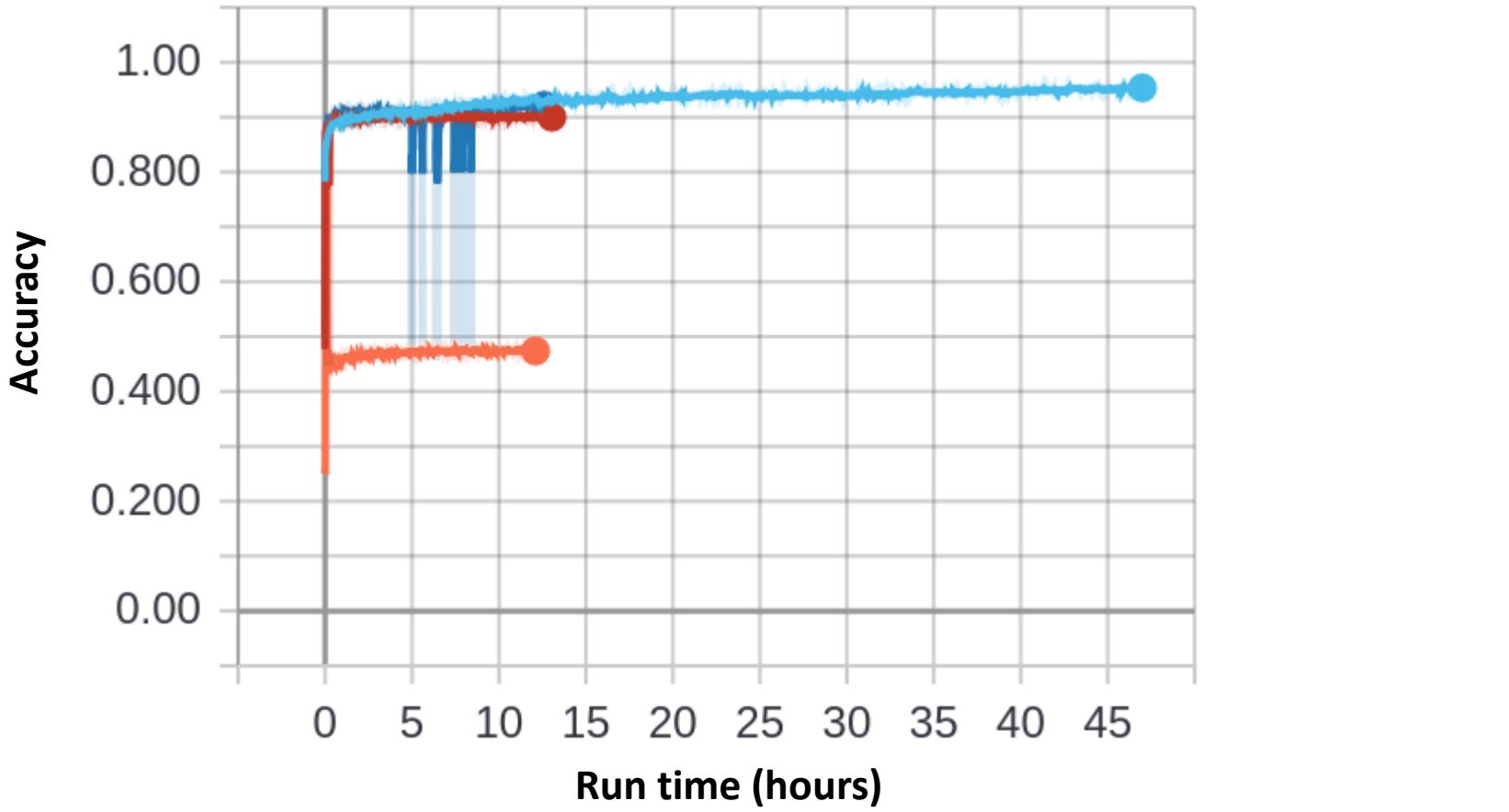
10 batches
50 batches
100 batches
1000 batches

Optimizing batch size: training run time



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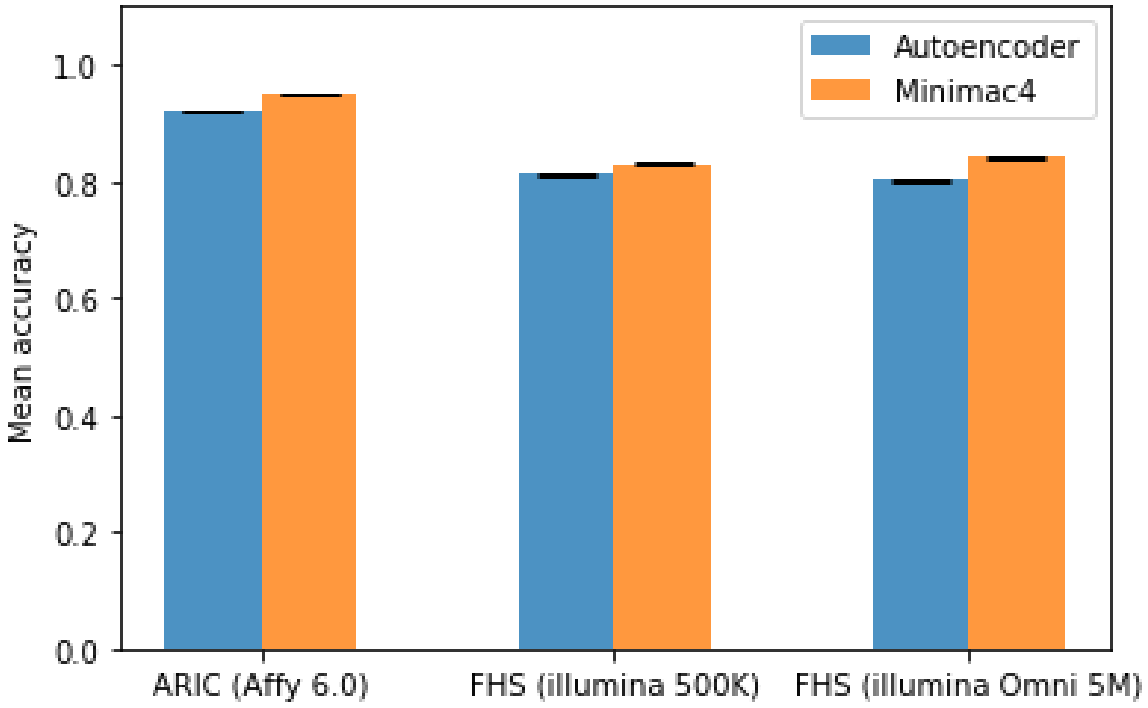
Testing on multiple case studies

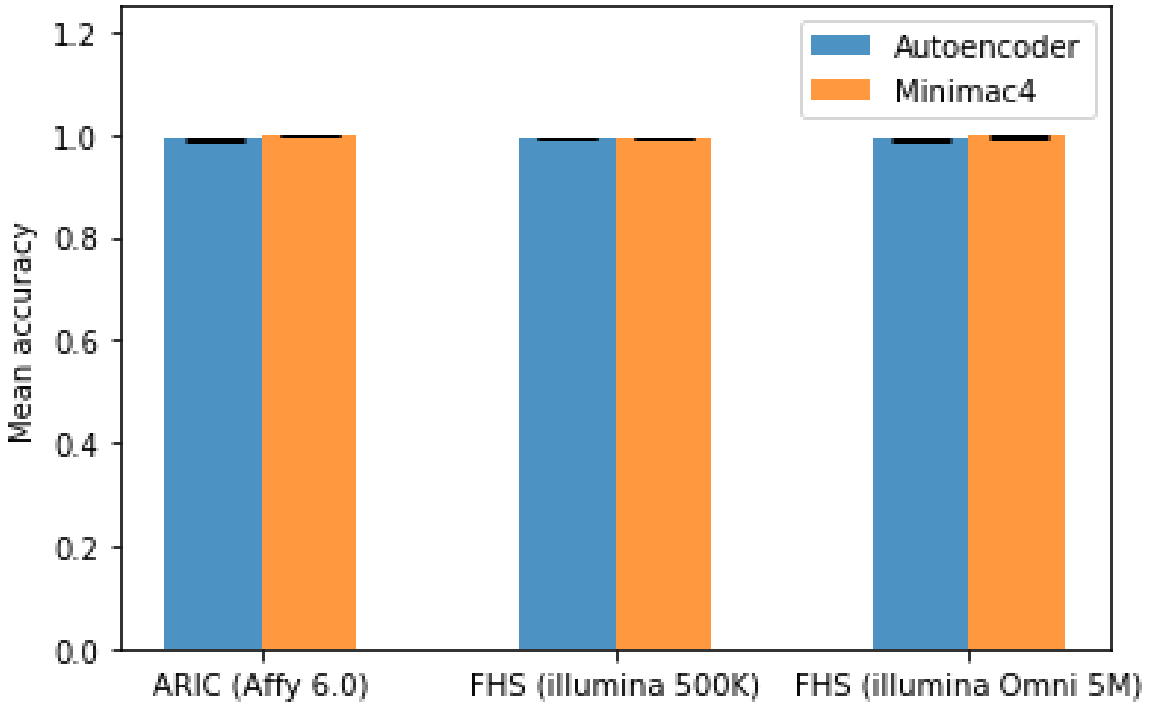
- **Atherosclerosis Risk in Communities (ARIC)**
  - More than 3000 samples
  - Whole genome sequencing (846 variants, 0% mask, ground truth)
  - Affymetrix 6.0 genotype array (17 variants, 98% mask, input data)
- **Framingham Heart Study (FHS)**
  - More than 500 samples
  - Whole genome sequencing (846 variants, 0% mask, ground truth)
  - Illumina 500K genotype array (47 variants, 95% mask, input data)
  - Illumina 5M (93 variants, 89% mask, input data)

Accuracy in additional case studies: Proposed approach versus common statistic methodology

Performance: all variants



Performance: rare variants



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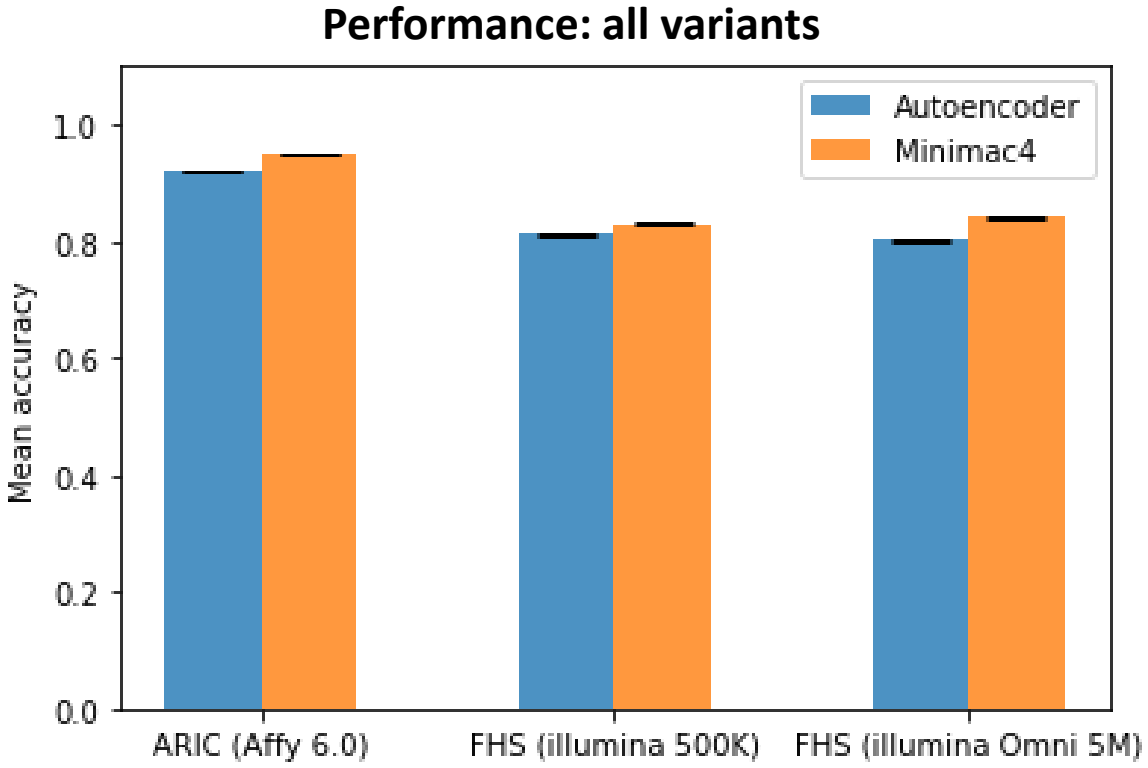
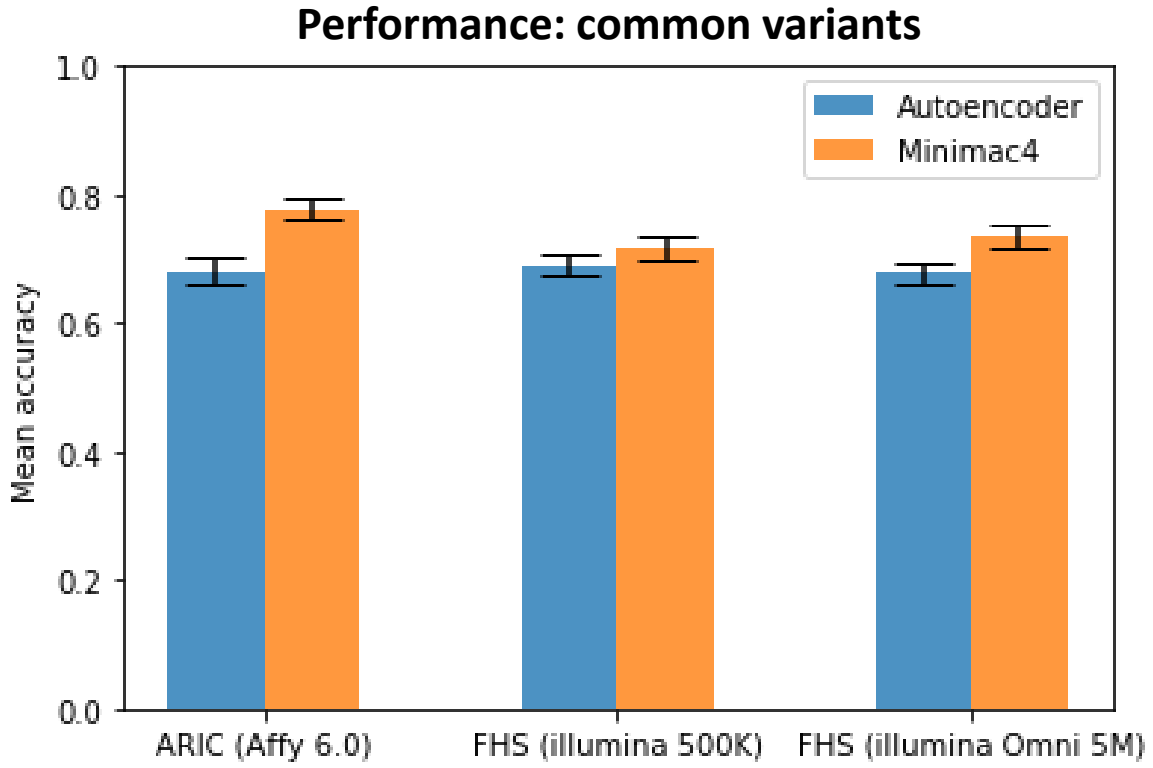
Accuracy in additional case studies: Proposed approach versus common statistic methodology





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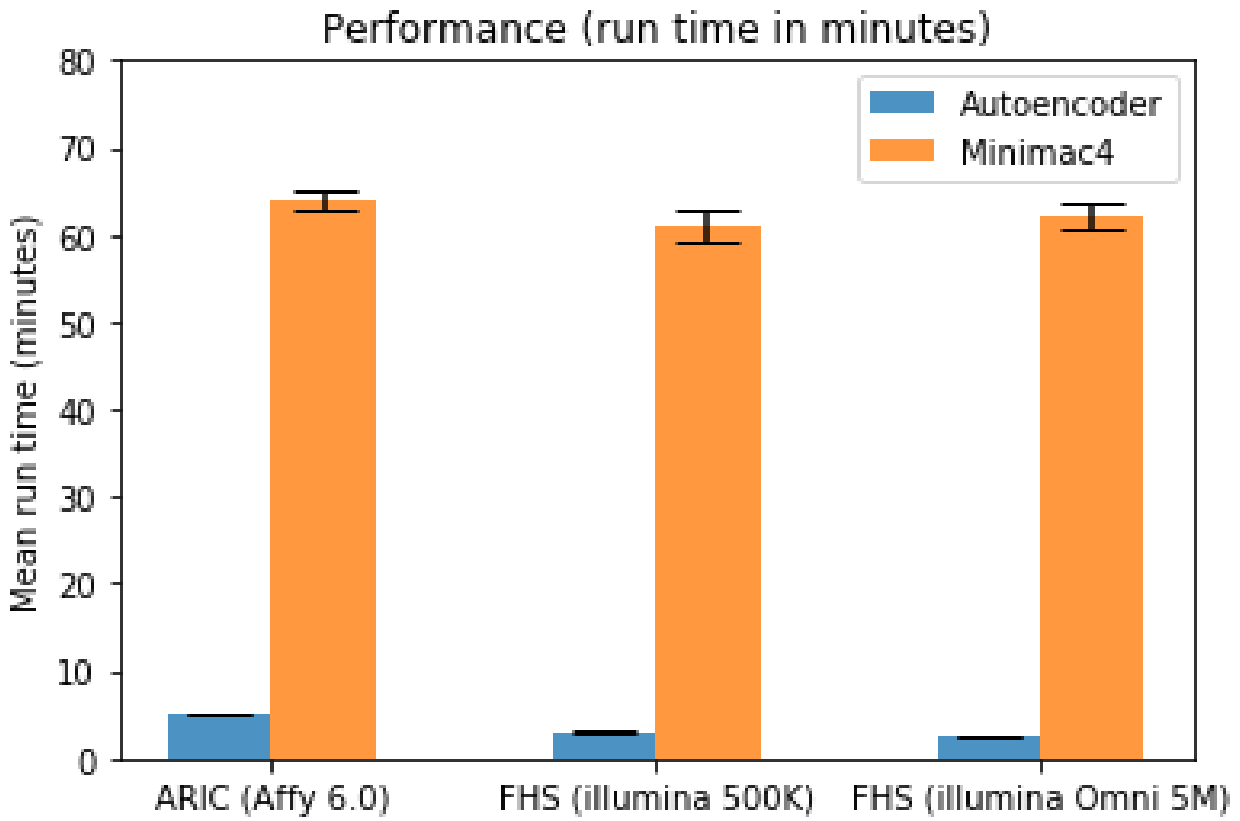
Run time: Proposed approach versus common statistic methodology



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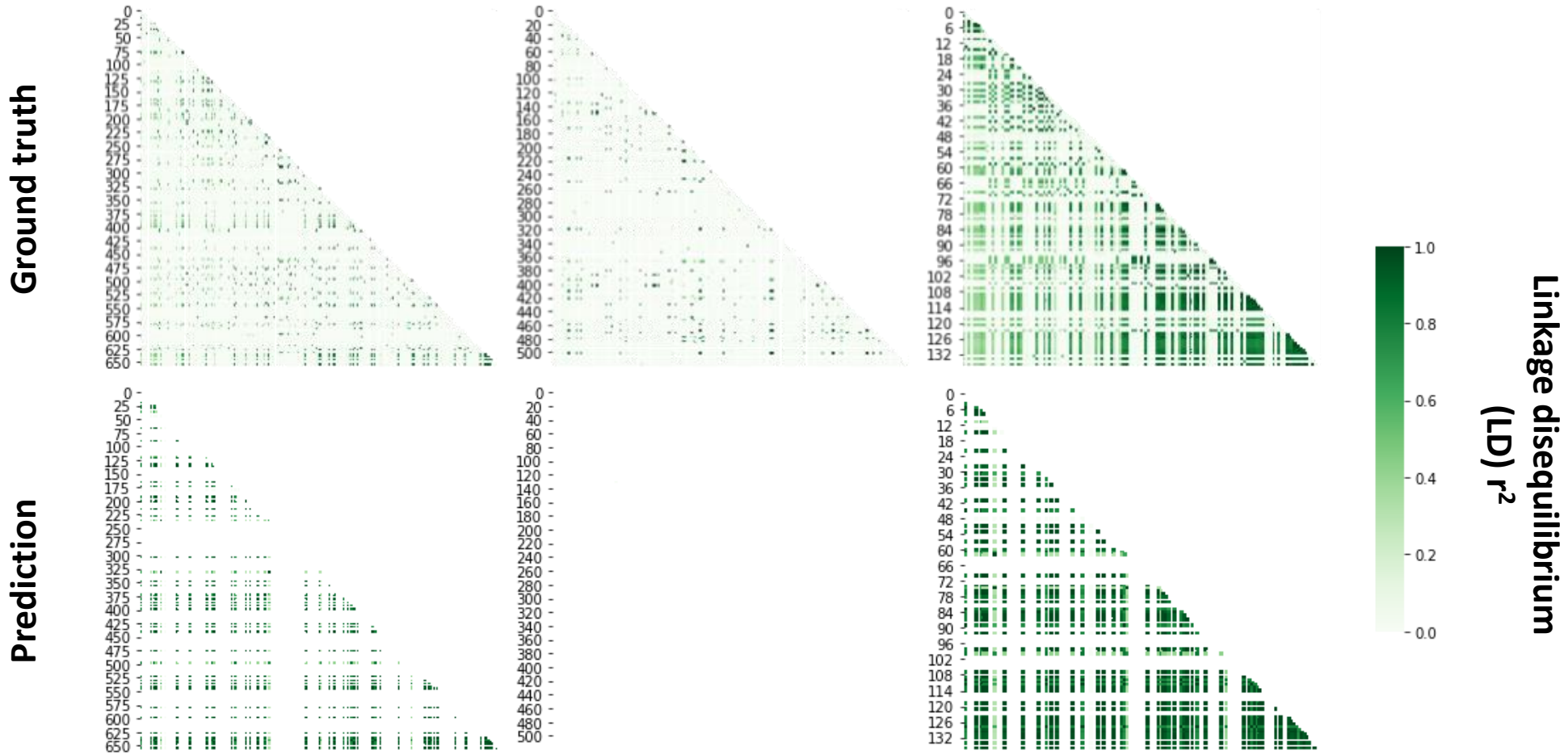
Linkage disequilibrium structure: ARIC



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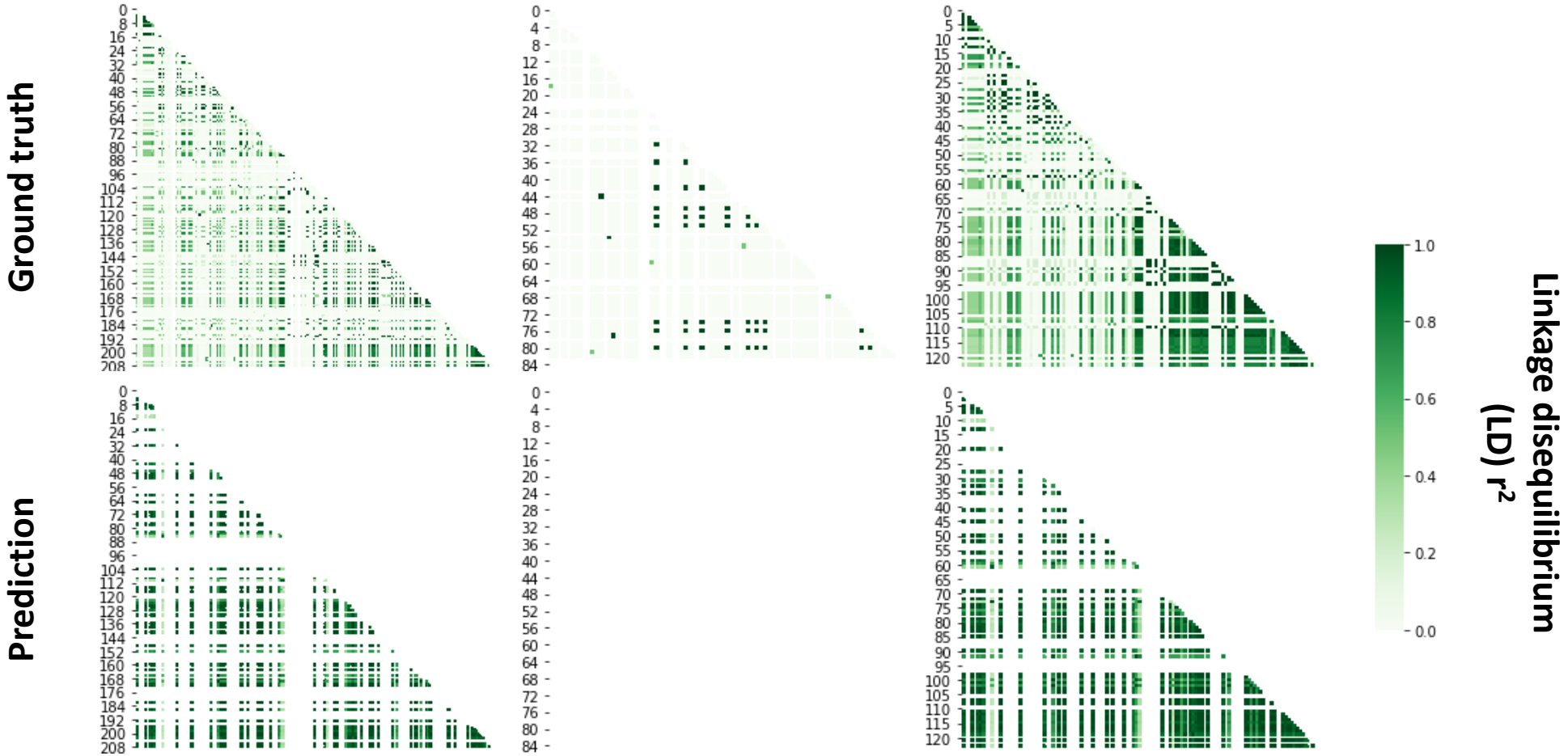
Linkage disequilibrium structure: FHS



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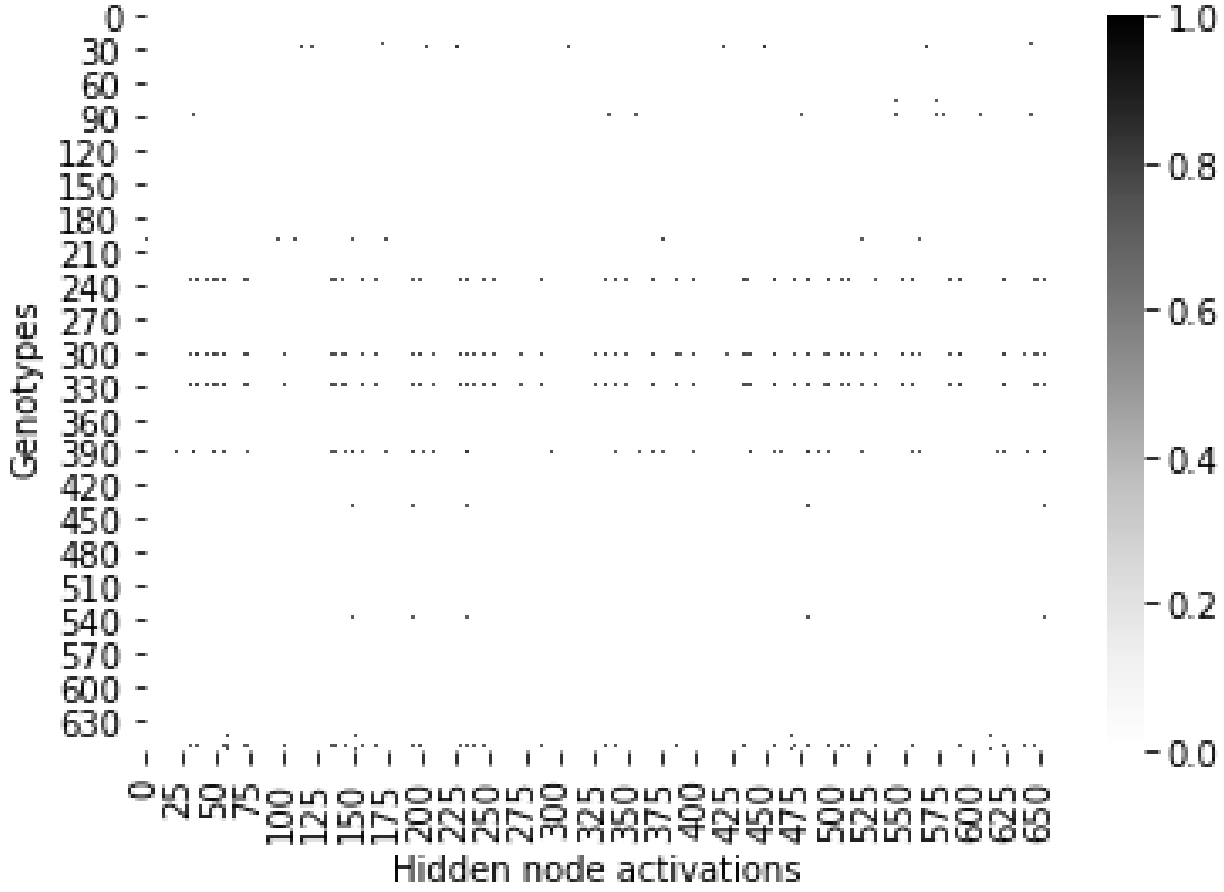
Interpretability: identifying representative genetic variants

Maximal information criteria



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Conclusions

- **Grid search** was able to find high accuracy models (>0.90)
- **Hyperparameters** played an important role in training performance
- Reconstruction of genetic variants from very sparse data with **high accuracy** (>0.80)
- Superior computational performance, **faster predictions**
- **Fine parameter tuning** may be necessary

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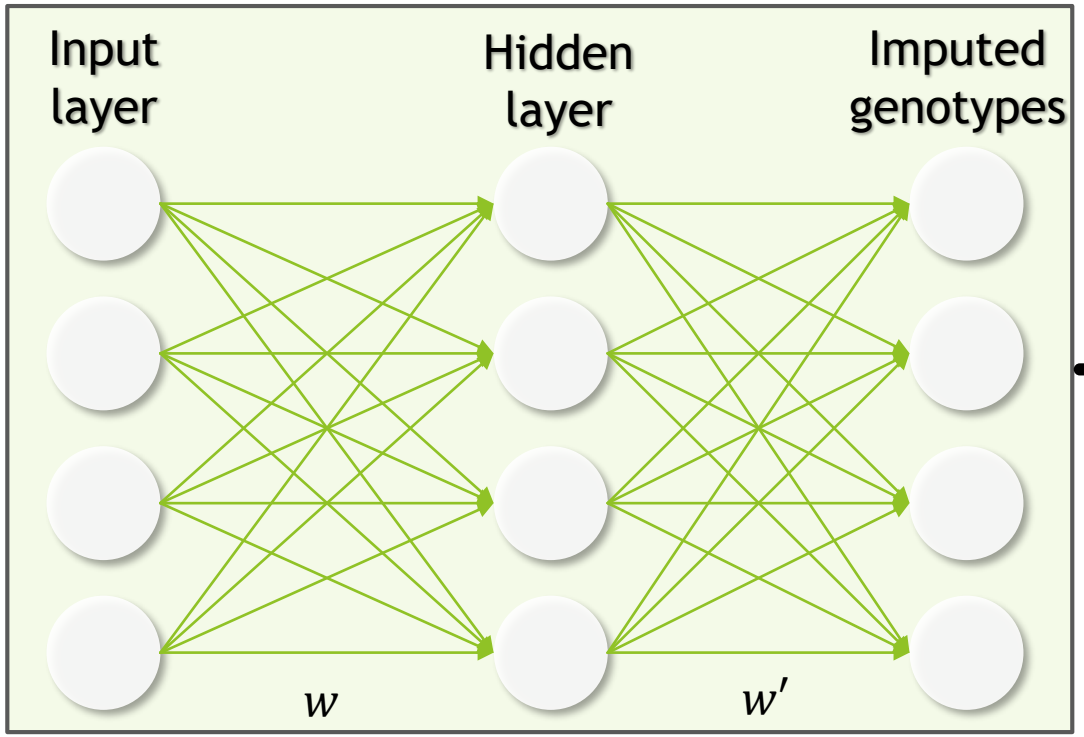
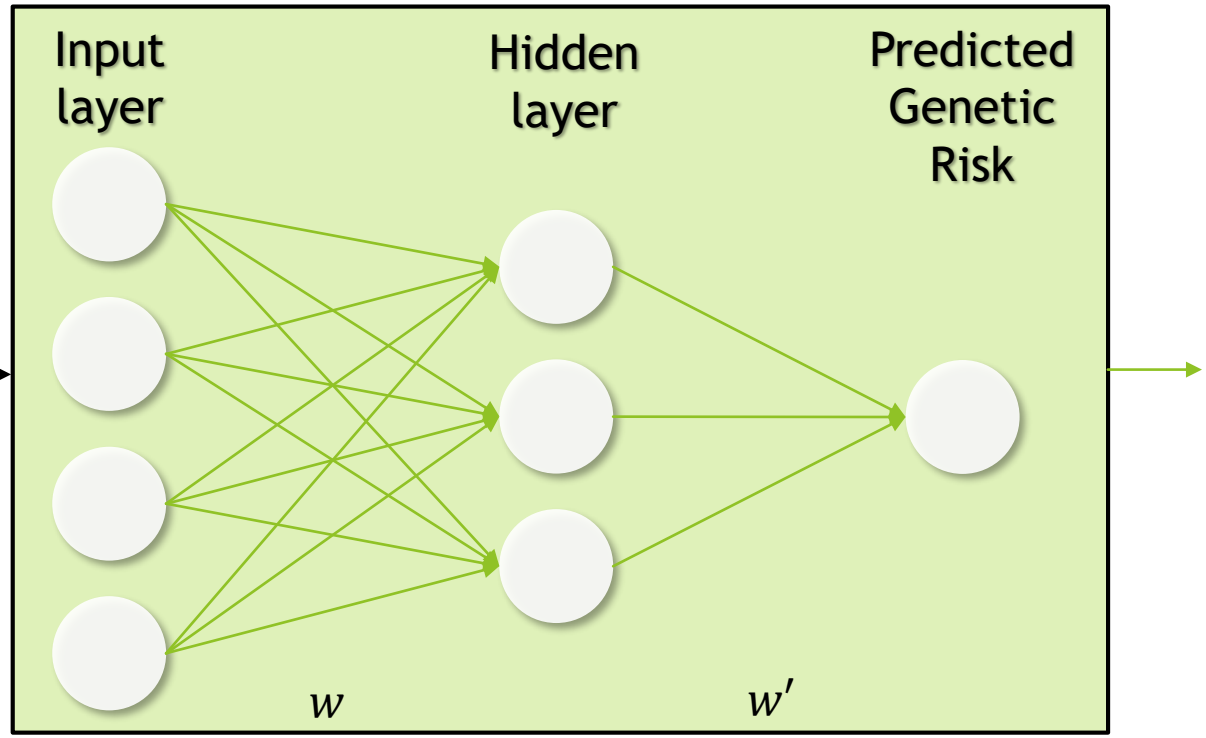
Future steps

- **Expand to other genomic regions, fine parameter tuning**
- **Use imputation autoencoder results as input for polygenic risk score calculation**



Imputation Autoencoder



Feed Forward Neural Network

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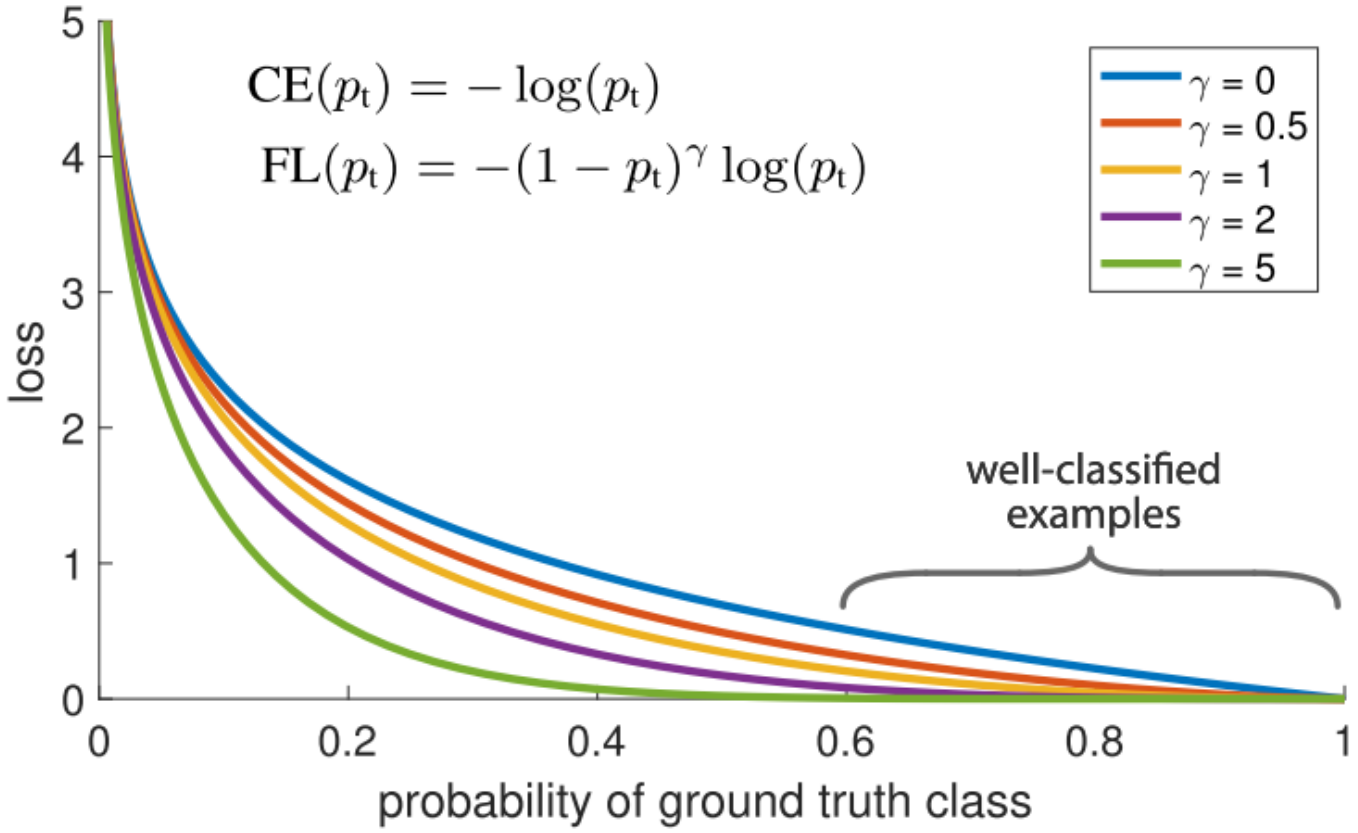
Future steps

- **Focal loss to compensate for rare variants**



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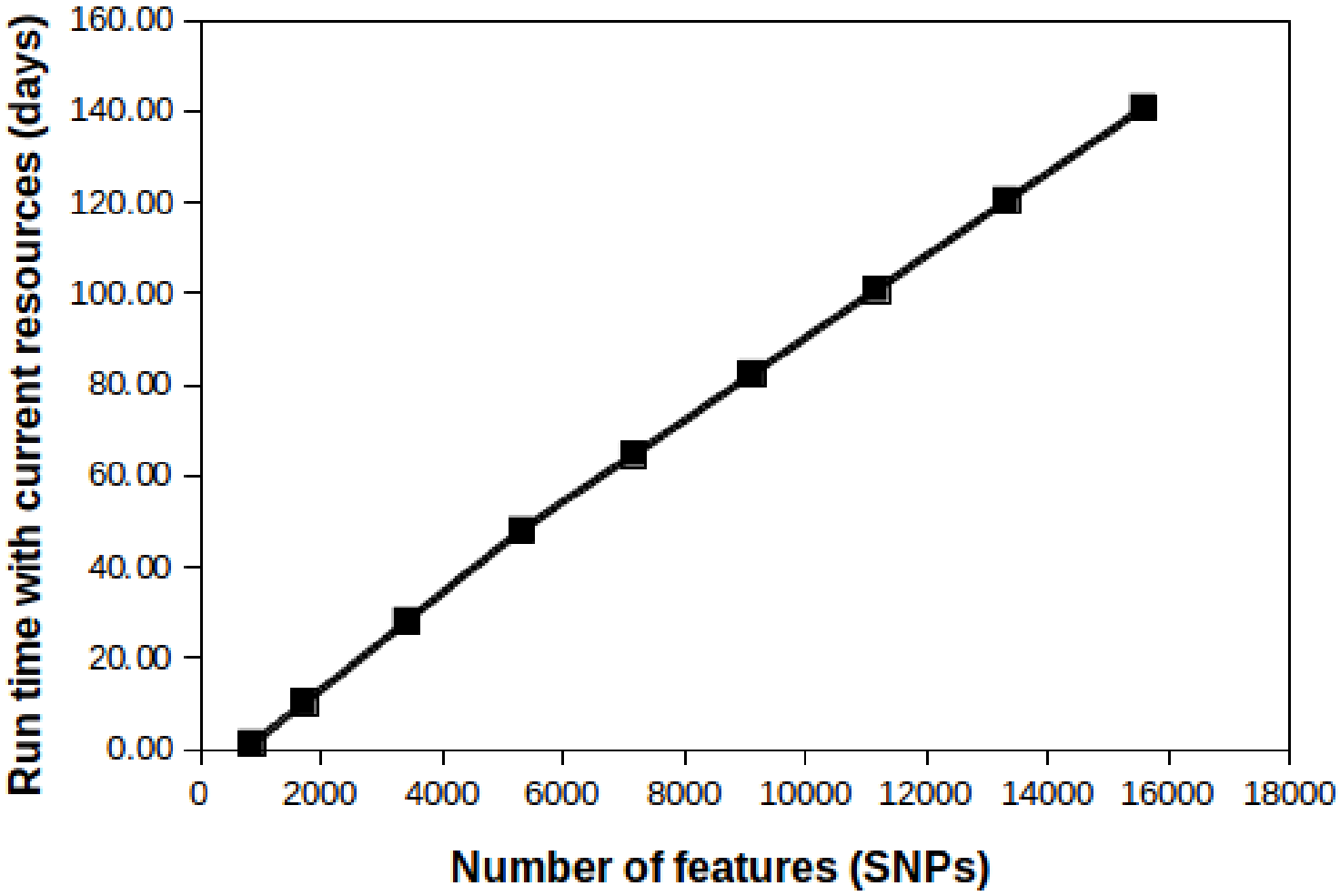
Lin, Tsung-Yi, et al. **"Focal loss for dense object detection."** *Proceedings of the IEEE international conference on computer vision*. 2017.

Limitations: expanding the methodology to other genomic regions



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Acknowledgements

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Ali Torkamani PhD
Shang-Fu Chen
Elias Salfati PhD
Doug Evans
Shuchen Liu
Alex Lippman
Nathan W. PhD
Emily Spencer PhD
Eric Topol MD

NVIDIA collaborators

Johnny Israeli
Carla Leibowitz
Fernanda Foertter
Brian Welker
David Nola

NIH National Institutes of Health

Funding

NIH/NCRR flagship CTSA Grant

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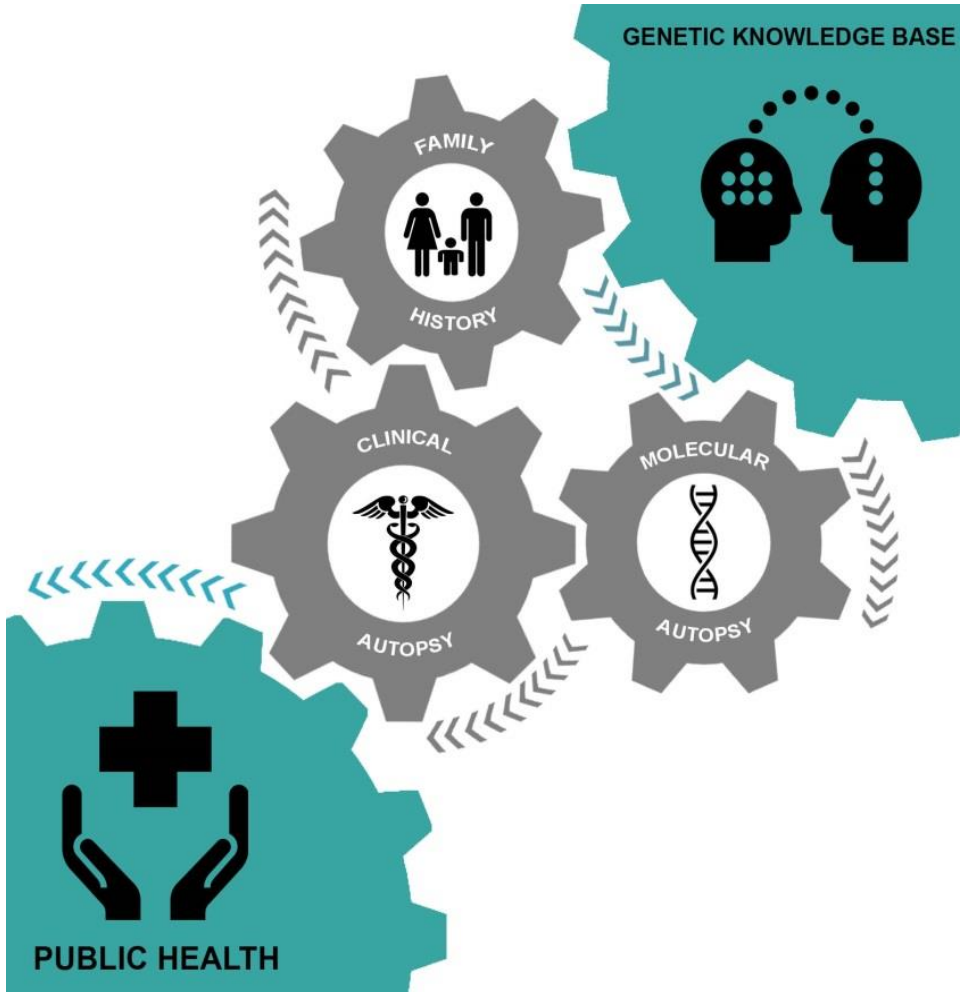

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