GenNet Framework: Interpretable Neural Networks for Predicting Phenotype from Genotype

Arno van Hilten [1], Steven A. Kushner [2], Hieab H.H. Adams[1,3], Wiro J. Niessen [1,4], Gennady V. Roshchupkin [1,5]

[1] Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands; [2] Department of Psychiatry, Erasmus MC, Rotterdam, The Netherlands; [3] Department of Clinical Genetics, Erasmus MC, Rotterdam, Netherlands. ; [4] Department of Imaging Physics, Delft University of Technology, Delft, The Netherlands; [5] Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands

Introduction

Neural networks are currently the state of the art in many areas of scientific research and applications but are seldom applied in population genomics and **predictive genetics** due to the computational burden and lack of **interpretability**. Here, we propose a novel **open-source** deep learning framework, **GenNet**, for interpretable predictions of phenotypes from genotypes. In this framework, public prior **biological knowledge** (e.g. DNA and pathway annotations) is used to define a sparse, **memory-efficient networks**.

Methods

In the framework, **prior knowledge** is used to create groups of connected nodes to reduce the number of learnable parameters in comparison to a fully connected neural network. For example in the first layer, where **millions** of single nucleotide polymorphisms (**SNPs**) inputs are only connected to their corresponding **genes**, creating **meaningful** and **interpretable connections** while significantly **reducing** the total number of **parameters**.

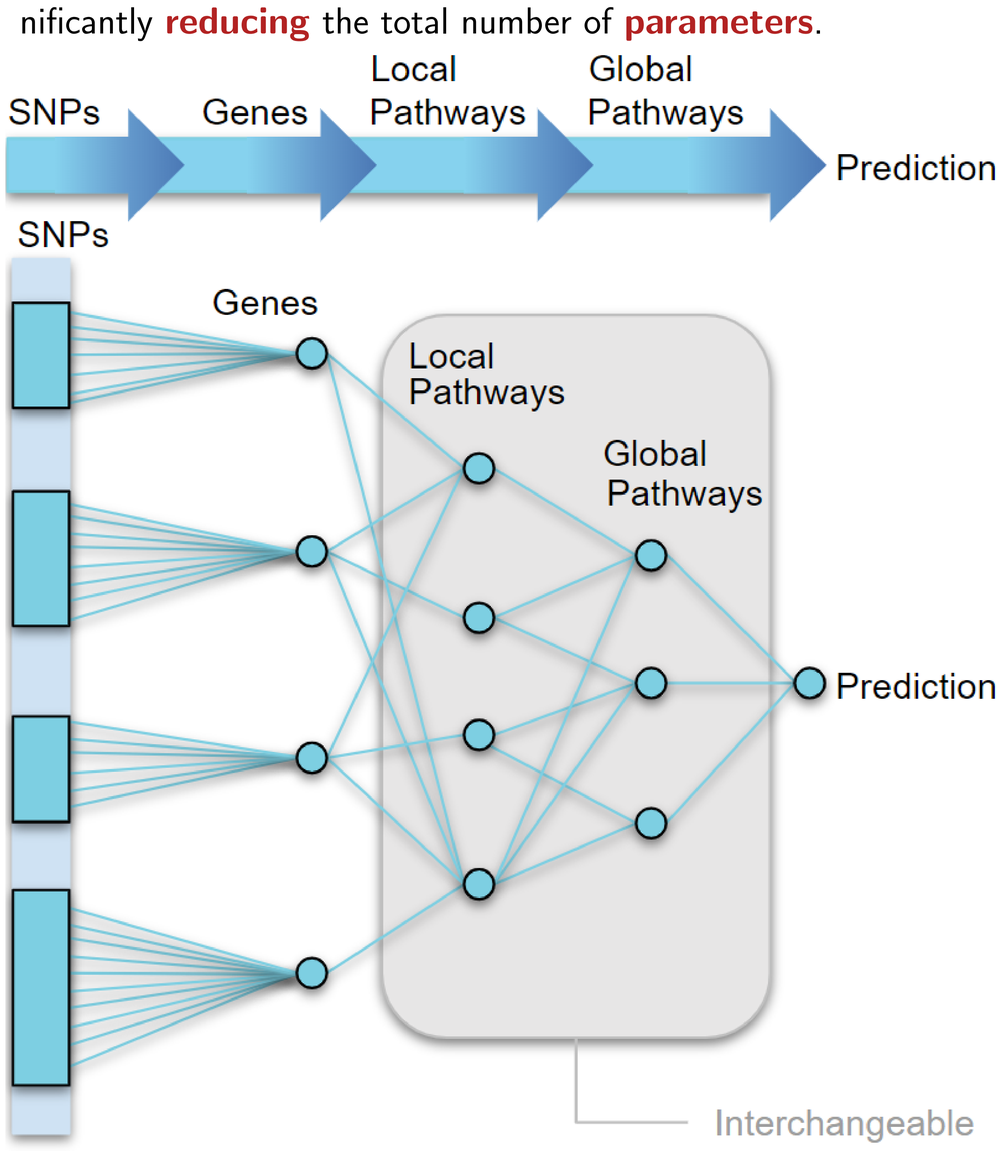

Figure 1: *Overview of neural networks in the* **GenNet framework**. *Different types of prior biological knowledge can be used to* **define** *the* **connections**. *In the shown network* **gene annotations** *were used to define the connections to the first layer and* **pathway annotations** *to group the genes from the first layer. Aside from gene and pathway annotations, our framework provides layers built from exon annotations, chromosome annotations and cell and tissue type expressions.*

GenNet is an open-source framework written in **Keras and Tensorflow**, code and tutorials are available on `https://github.com/arnovanhilten/GenNet/`.

Conclusion

- We developed a framework with **memory-efficient** and **interpretable neural networks** by using publicly available **biological** knowledge.
- These networks obtain **good predictive performance** even while only using **exomic variants**.
- We anticipate this approach as having the potential for uncovering **novel insights** into the genetic architecture of complex diseases

Results

The framework is validated in linear and non-linear simulations (see figure 2) and applied to **the Rotterdam study** (exonic variants) the **UK Biobank** and the **Schizophrenia WES Data** (see table 1). Identifying commonly associated genes for identifying hair and eye color such as *OCA2* and *HERC2*, validating the interpretabilty of the network.

Trait	Dataset (type)	Subjects & Phenotype Class I	Class II	Heritability	AUC Lasso	AUC GenNet	GenNet: top 3 genes
Eye color	Rotterdam genotype array	4041 Blue	2250 Other	0.80-0.98	0.68	0.75	*HERC2, OCA2, LAMC1*
Hair color	UK Biobank WES data	1648 Blond	1656 Red	0.70-0.97	0.78	0.83	*MC1R*, OCA2, TC2N*
	UK Biobank WES data	1672 Dark brown	1664 Red	0.70-0.97	0.79	0.88	*MC1R*, OCA2, ZCCHC4*
	UK Biobank WES data	4352 Blond	4343 Dark brown	0.70-0.97	0.64	0.75	*OCA2, TC2N, EXOC2*
Male baldness	UK Biobank WES data	3454 No balding	3454 Severe balding	0.60-0.70	0.57	0.57	*NGEF, NKRD18B, SYNJ2*
Bipolar	UK Biobank WES data	343 Cases	347 Controls	0.73-0.93	0.59	0.60	*LINC00266-1, CSMD1, TCERG1L*
Schizophrenia	Sweden WES data	4969 Cases	6245 Controls	0.80-0.85	0.65	0.74	*ZNF773, PCNT, DYSF*

Table 1: Summary of the experiments and results in this study for the simplest network in our framework that contains the input SNPs, the gene layer and the output layer. *MC1R was not present in gene annotations but identified by linkage disequilibrium.

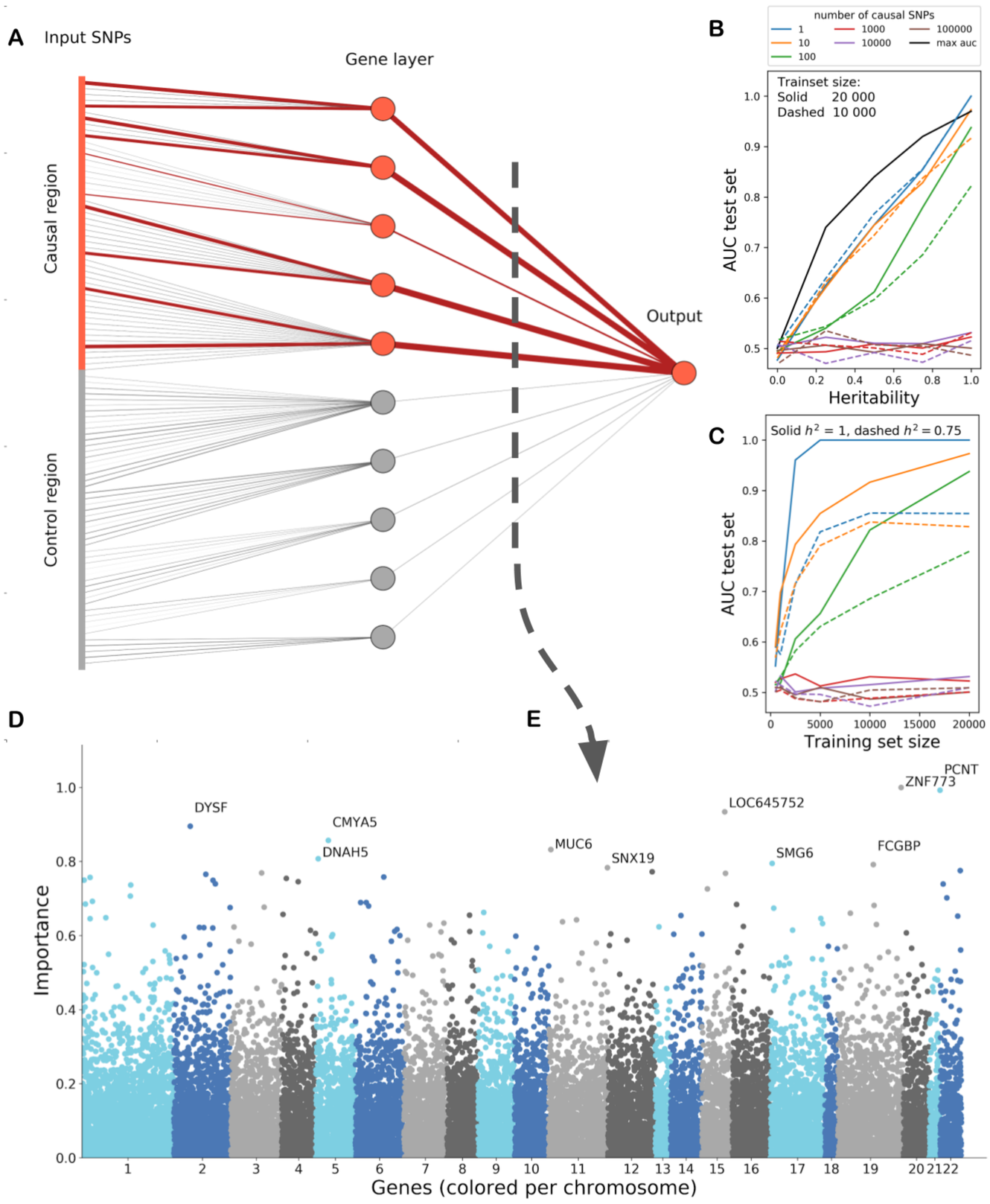

Figure 2: **A)** *Non-linear simulation showing the basic principle of the network, thickness of the connections represents the learned weight (causal in red).* **Run online** *`https://tinyurl.com/y8hh8rul`.* **B)** *Simulations with synthetic data showing the performance of GenNet expressed in the area under the curve for increasing levels of heritability and training set size* **(C)**. *In black the theoretical maximum of the AUC versus heritability.* **D)** *Manhattan plot of the importance of the genes according to the network for distinguishing between* **schizophrenia** *cases and controls.* **E)** *This manhattan plot is a cross section of the trained network between the gene layer and the outcome.*