Deep Learing and its Application to Predicting Quantitative Phenotypes from Genomic Data

TFG by **Víctor Fernández Oliveras** / Bibliographic review / Genetics Degree

INTRODUCTION

Inside artificial intelligence (AI), **machine learning** (ML) methods are desiged to **mimic the human brain function**. The **data quantity and complexity** these methods can process is limited, so **deep learning** (DL), the core framework of which are **neural networks** (NN) formed of neurons or nodes, emerged as a powerfool tool to handle these datasets, such as **nonlinear genotype-phenotype relations**. These predictive models rely on **supervised learning**, as they are trained with labeled samples to predict unseen data.

Not intherently superior to ML. ⇒ **ML outperforms** in predicting **phenotypes** based on **purely additive** effects.

OBJECTIVES

- **Describe** model architecture, training, interpretability and main challenges in DL.
- **Contextualize** DL in genomics predictions.
- **Critically review** current situation and **propose** future research.
- **Create** a naive model to exemplify the concepts discussed.

METHODOLOGY

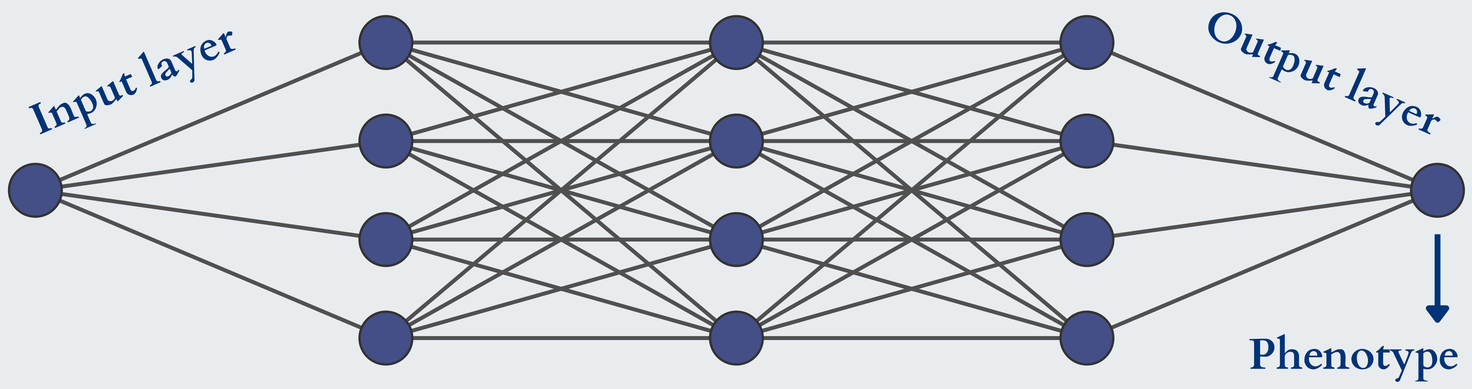
mainly → 2020-2025

Keywords: "deep learning", "neural network", "genomics", "phenotype prediction", "complex trait"...

RESULTS

A	G	C	T	A		G
1	0	0	0	1		0
0	0	1	0	0	...	0
0	0	0	1	0		0
0	1	0	0	0		1

Fig 1. One-hot encoded sequence. Modified from Liu et al. (2022).



Convolutional NNs

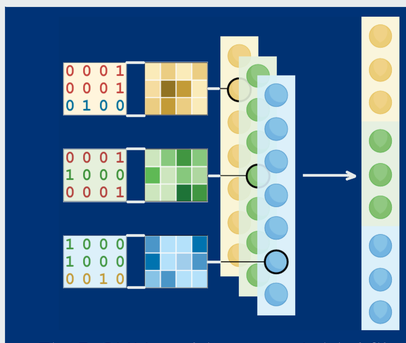


Fig 5. CNN architecture. Initial filters generate activation maps. Posterior pooling (parameter reduction) and flatten (information coupling). Modified from Novakovski et al. (2023).

Data curation

Genomic data usually contains **biases** that should be minimized, as they **impede correct training**.

Distributional differences between genotypes, phenotypes or subsets.

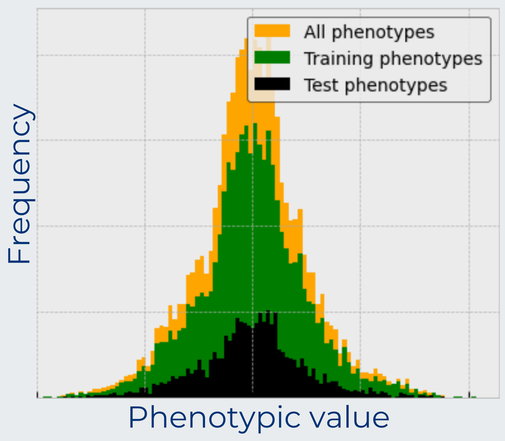


Fig 2. Distribution of phenotypic values through subdatasets.

Correlated samples

AGCTAAG
AGCTAAG
ACCTAAG
→ Familiar relation?

Model training

Training subset → Model preditcts a **phenotype** (Y_i') for each **genotype** (X_i). ← **Validation** subset

back-propagation → **Parameter update**

Calculates the **error** with the **Loss function** → $L(Y_i, Y_i')$.

Performance in the training set. / **Performance** in the validation set. → **Evaluation**

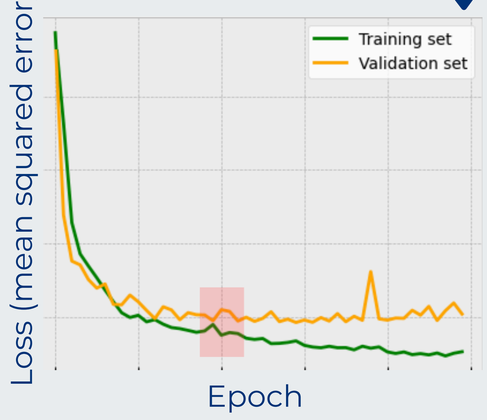


Fig 3. Loss change in subsets during training. Overfitting marked with a red square.

Overfitting: too many iterations can cause the model to **excessively adapt** its predictions to the **training set**.

Hyperparameters = elements decided by the modeller. → **AutoML** to perform **hyperparameter tunning**.

Interpretability

DL is considered a "**Black-box**"... → explainable AI (**xAI**)

Relative **importance** of dataset/model's **elements** to **prediction**-making.

Back-propagation → Self-attention (epistasis)

Perturbation-based methods.

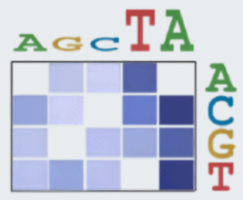


Fig 4. Attribution map. Modified from Novakovski et al. (2023)

Others:

- **Position Weighted Matrices** (**PWMs**) → motif detection.
- **Visible Neural Networks** (**VNNs**): assign genes/pathways to nodes/layers.

DOWNSIDE

- Data is not representative of all populations.
- Models reach local extrema, not optima.
- Interpretability requires validation.
- No-free-lunch theorem → each task needs an own model → domain expertise required.

CONCLUSIONS & FUTURE RESEARCH

- **Descriptive objectives accomplished** and **contextualized in genomics prediction**: addressed architecture, training process and overfitting, interpretability, curation of the data...
- DL is a **useeful and promising tool**, but it has **several downsides**: skewed data, sub-optimal models, difficult interpretability, needed domain knowledge...
- **In the future**, more **comparisons** between models' elements are expected **to reduce search space** in model making, as well as more **user-friendly tools** to enable the field's growth.

GitHub

Simple **model** available here to **put in practice** all this theory!

MAIN REFERENCES

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UAB Universitat Autònoma de Barcelona