POLITECNICO DI MILANO

Discovering Gene Interactions from Gene Expression Data using Neural Networks

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ABSTRACT

Search for genetic factors influencing complex traits:

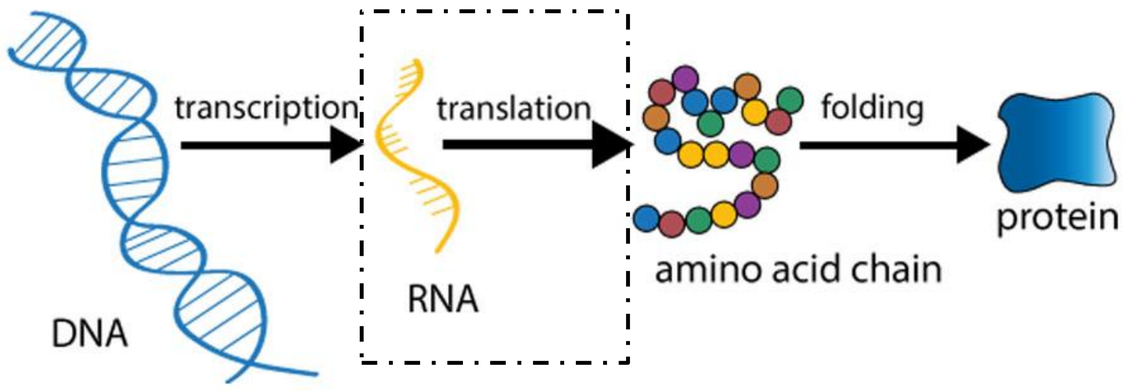
- A challenge and goal for genetics
- Standard methods not able to detect high level interactions and no correlation with phenotype [2].

We propose a methodology relying on **neural networks**:

- Works on RNA-seq data
- Identify interacting gene subsets
- Cooperative interaction between genes

DATA

THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute



We use RNA-seq data, which can be seen as a matrix:

		Genes: G1	Genes: G2	Genes: …	Label: Cancer
Patients	P1	300	0	…	Yes
	P2	0	23	…	No
	…	…	…	…	…

- # features: **20530**
- # patients: **1000**

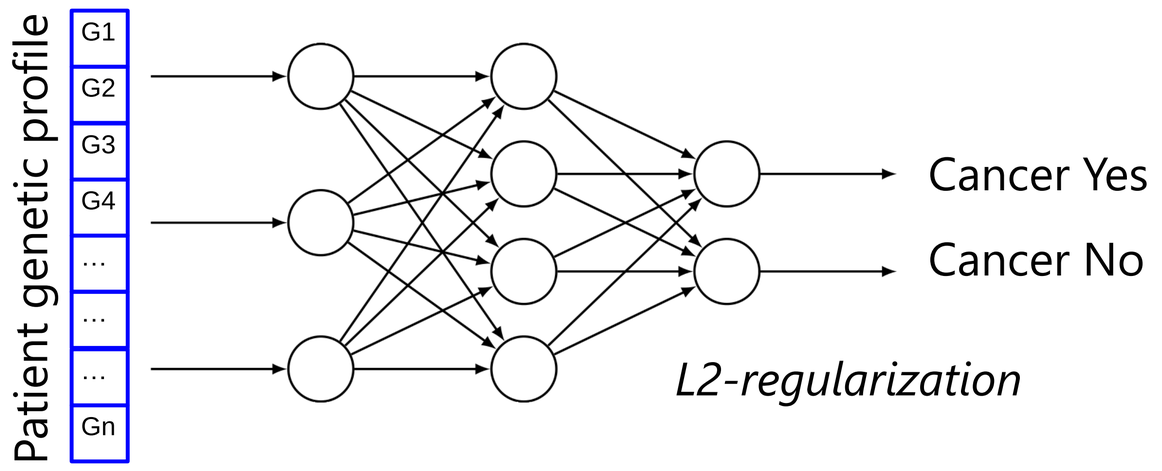
} **Dimensionality curse**

RESULTS

- Ontological analysis of the results (GO ontology)
- We are able to identify known interactions related to presence of cancer, but results are unstable!!
- We have an overlapping of the top interacting genes of 25% between different runs.

METHODOLOGY

We train a neural network for the classification of patients on the basis of presence or absence of cancer.



We use a method described in [1] to extract knowledge from the trained neural network weights.

Backpropagate the weight influence w.r.t. output:

$$\mathbf{z}^{(l)} = |\mathbf{w}^{y}|^{T} \cdot \left|\mathbf{W}^{(L)}\right| \cdot \left|\mathbf{W}^{(L-1)}\right| \dots \left|\mathbf{W}^{(l+1)}\right|$$

We assign a score to each candidate interaction:

$$\omega_i(\mathcal{I}) = z_i^{(1)} \mu\left(\left|\mathbf{W}_{i,\mathcal{I}}^{(1)}\right|\right) \qquad \mathcal{I} = \{g_{i_1}, g_{i_2}, \dots, g_{i_k}\}$$

Finally we rank interactions based on the score.

The subsets of features which are found represent genes which are jointly correlated with the output, ranked on the basis of their influence.

PROBLEMS

- Class unbalance (tumor cases are much more than normal ones) → up-sampling
- Dimensionality curse → prefiltering on the genes
- Instability of the results (multiple local minima) → using *multiple regularized neural networks*

REFERENCES

1. Tsang, M., Cheng, D., Liu, Y.: Detecting Statistical Interactions from Neural Network Weights (2017). http://arxiv.org/abs/1705.049771705.04977
2. Pepke, S., Ver Steeg, G.: Comprehensive discovery of subsample gene expression components by informationexplanation: therapeutic implications in cancer. BMC Medical Genomics (2017)