



Transcriptomic landscape, gene signatures and regulatory profile of aging in the human brain

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[Bioinformatics and functional genomics]

Aging on the Human Brain

[Lab19 - Óscar G. Velasco]



COHORTS!



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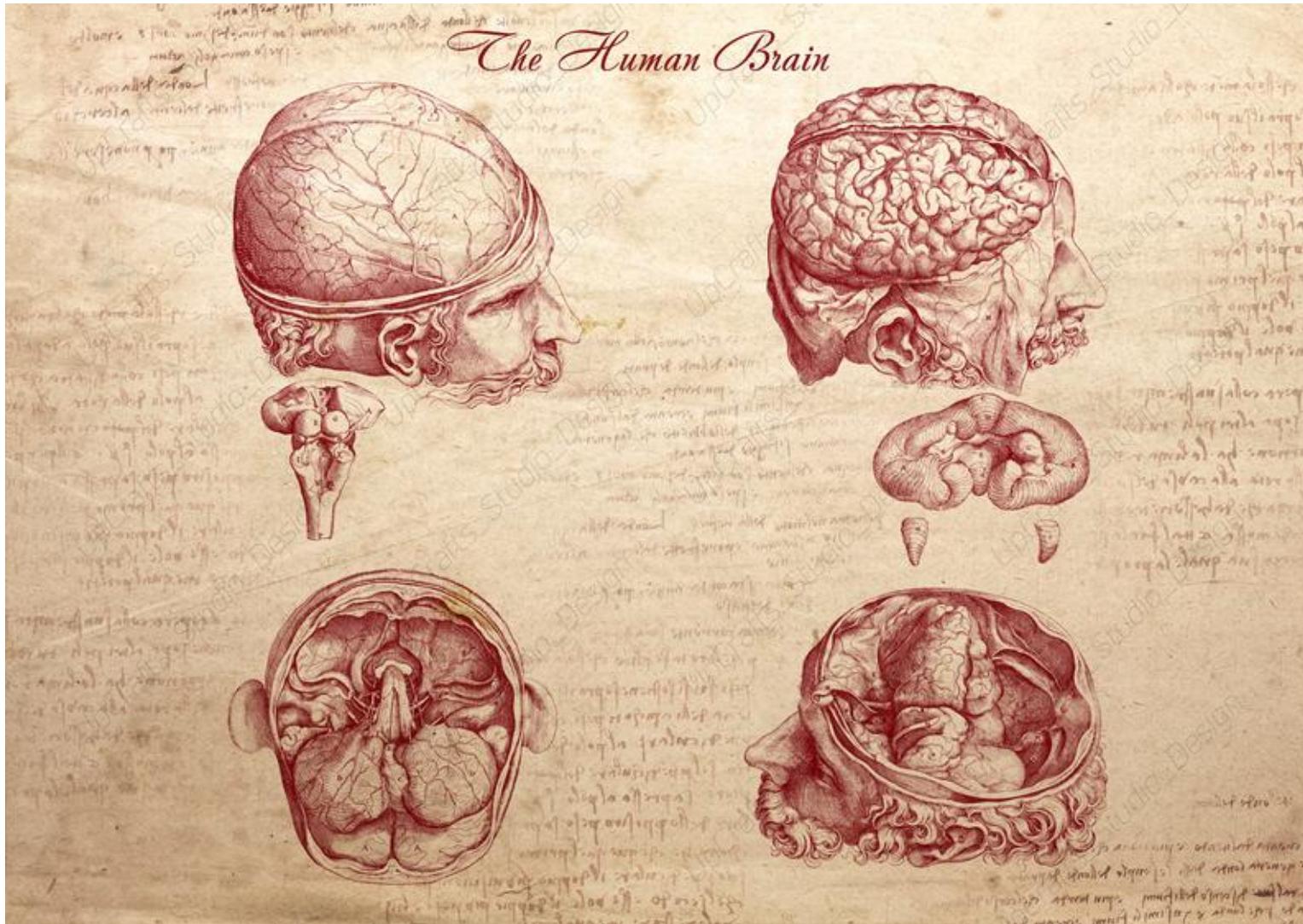
Age Stages

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Spatial Transcriptomic Signature



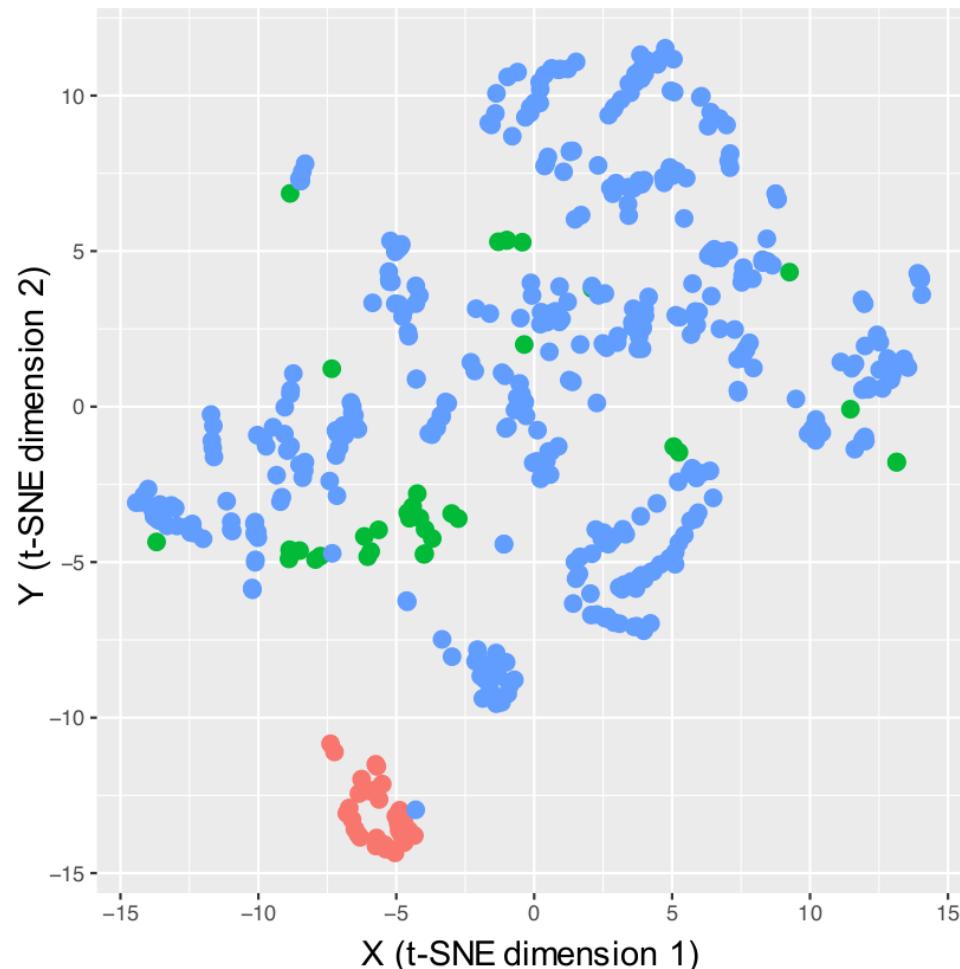
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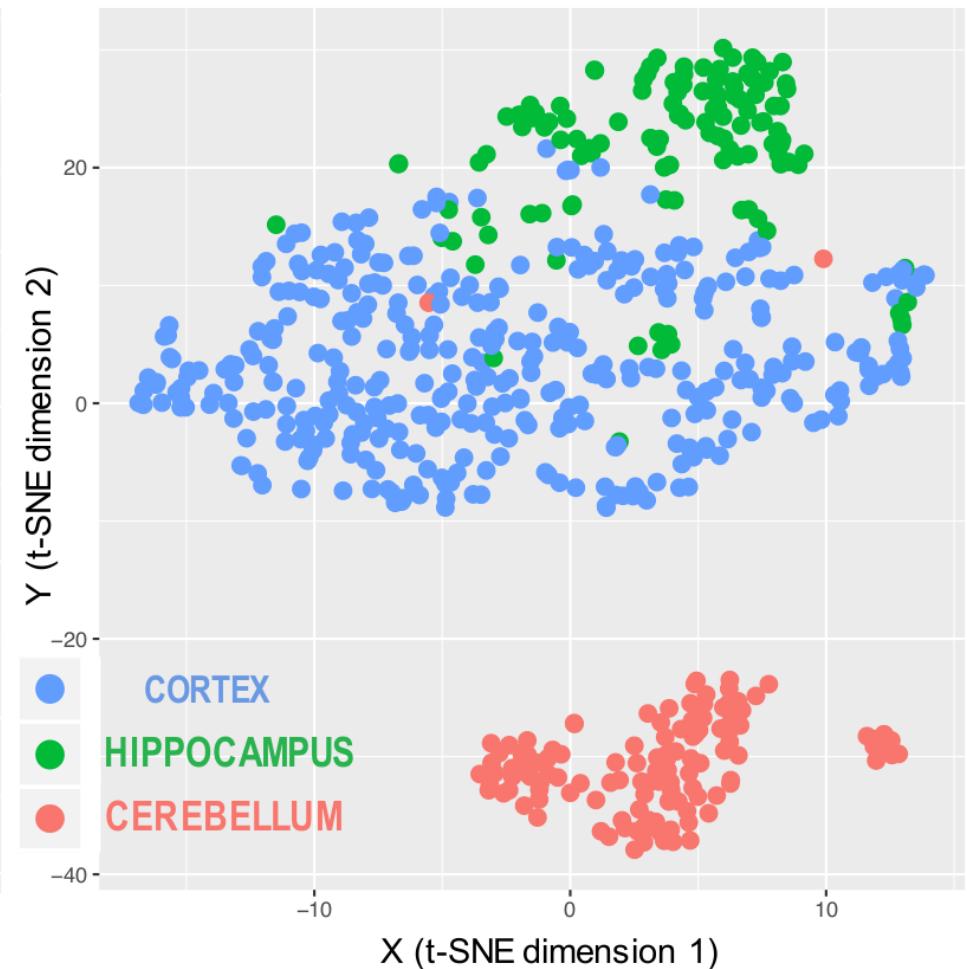


tSNE: Stochastic Neighbor Embedding (*t*-Distributed ;))

A Dataset 1 (Kang et al. 2011): 498 samples
CORTEX 429 ; HIPPOCAMPUS 35 ; CEREBELLUM 34



B Dataset 3 (Trabzuni et al. 2013): 625 samples
CORTEX 374 ; HIPPOCAMPUS 121 ; CEREBELLUM 130



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Spatial Transcriptomic Signature ✓✓

Temporal Transcriptomic Signature ✓✓ ??

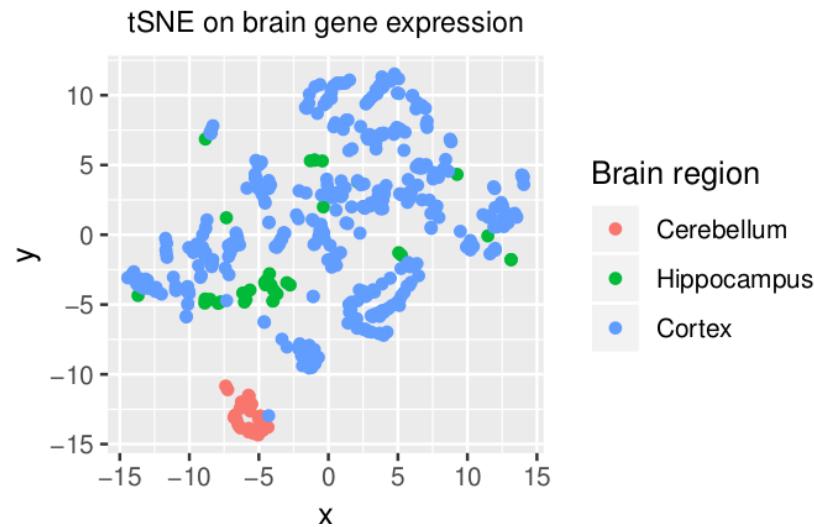


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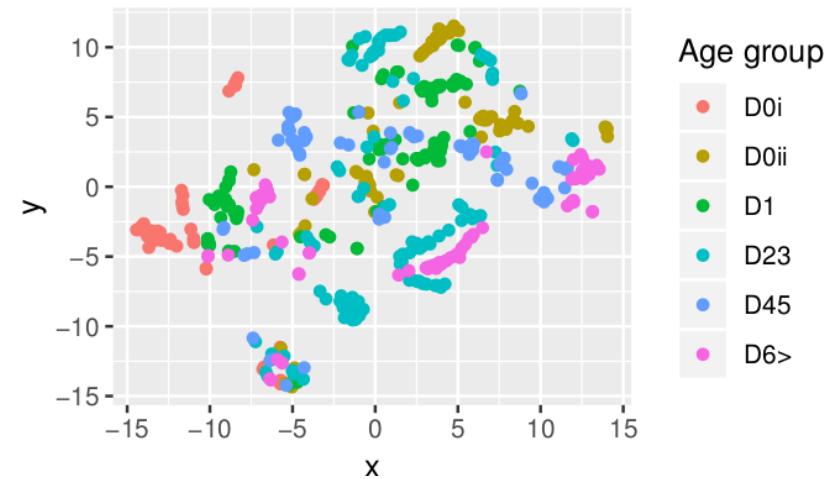
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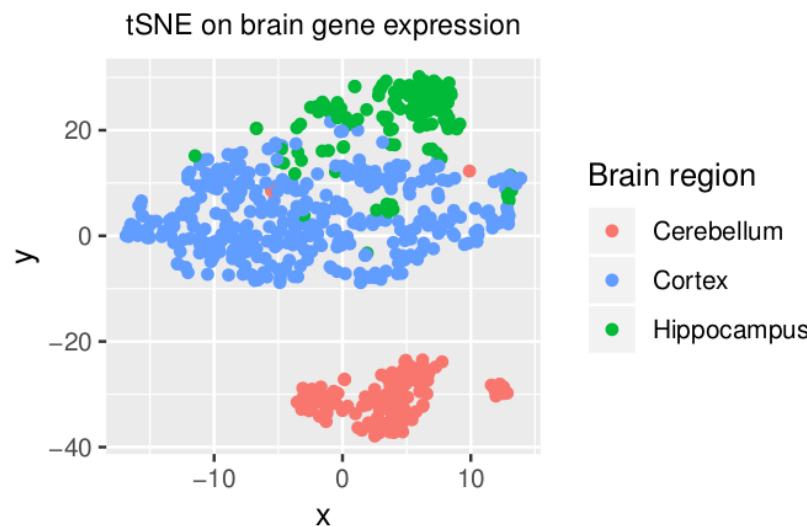
Dataset 1 – GSE25219 Kang et al.



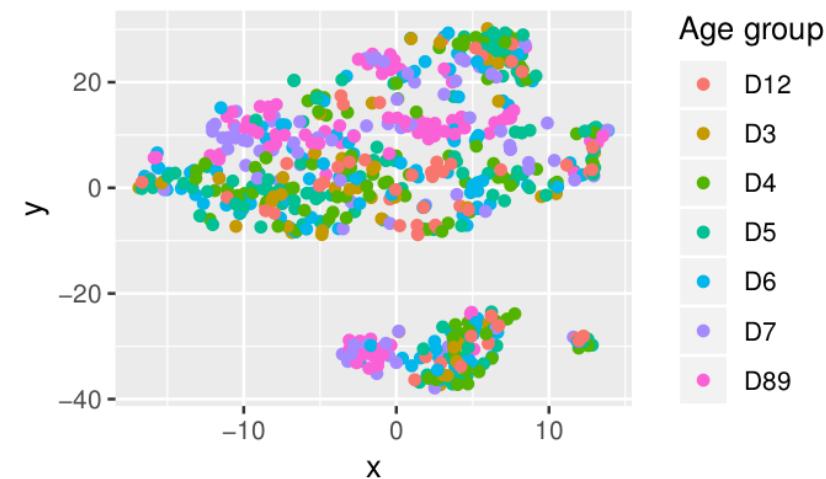
tSNE on brain gene expression



Dataset 3 – GSE46706 Trabzuni et al.



tSNE on brain gene expression



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How to measure differential expression across multiple time-stages?

Robust Gamma Rank Correlation:

We calculate:

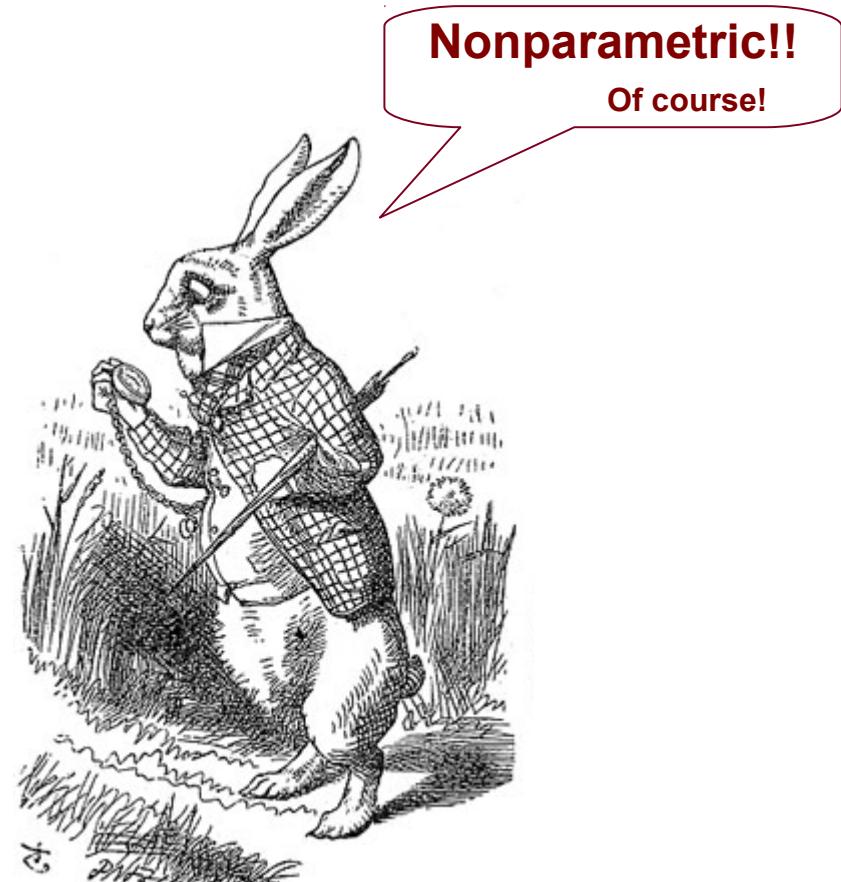
Number of **concordant pairs C** and the number of **discordant pairs D**:

$$\tilde{C} = \sum_{i=1}^n \sum_{j \neq i} \bar{T}(R_X(x_i, x_j), R_Y(y_i, y_j))$$

$$\tilde{D} = \sum_{i=1}^n \sum_{j \neq i} \bar{T}(R_X(x_i, x_j), R_Y(y_j, y_i))$$

Goodman & Kruskal's Gamma

$$\gamma = \frac{C - D}{C + D}$$



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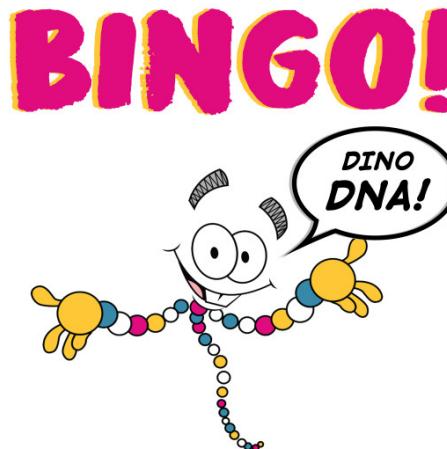
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Robust Gamma Rank Correlation

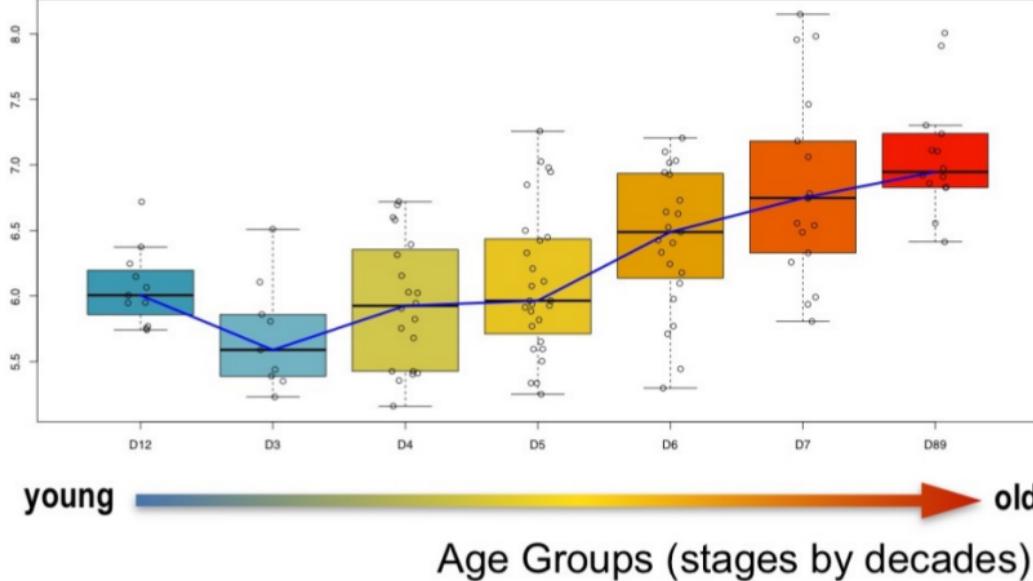
HLA-DPA1: major histocompatibility complex DP alpha 1

- Central role in the immune system by presenting peptides derived from extracellular proteins.
- Expressed in antigen presenting cells (APC: B lymphocytes, dendritic cells, macrophages).



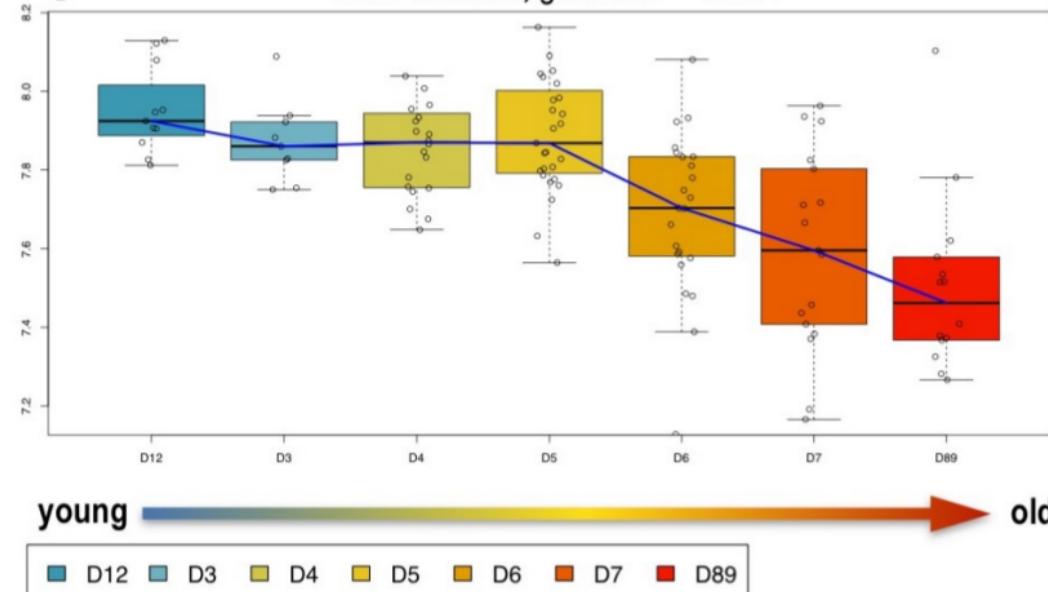
C

Gene HLA-DPA1 , gamma.r = 0.473



F

Gene NRXN2 , gamma.r = -0.492

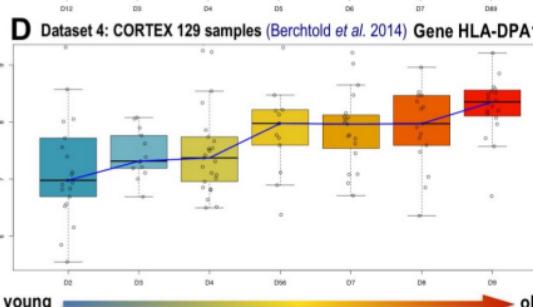
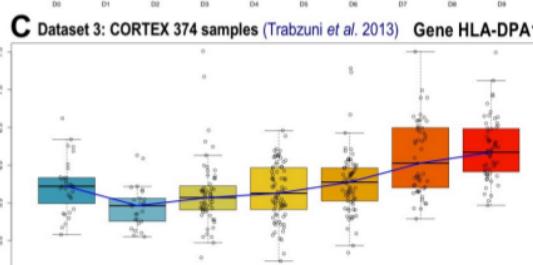
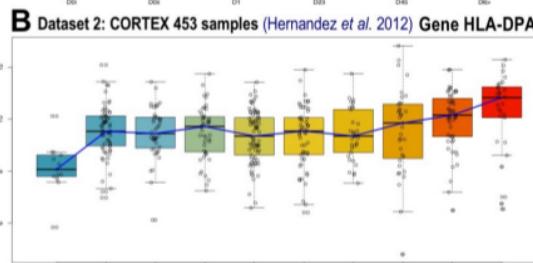
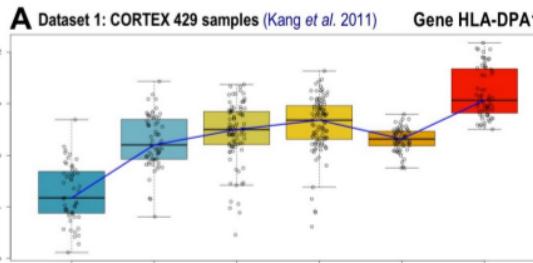


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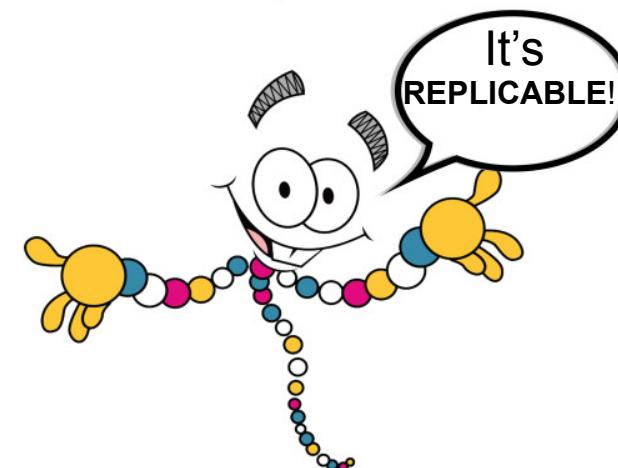


Robust Gamma Rank Correlation:

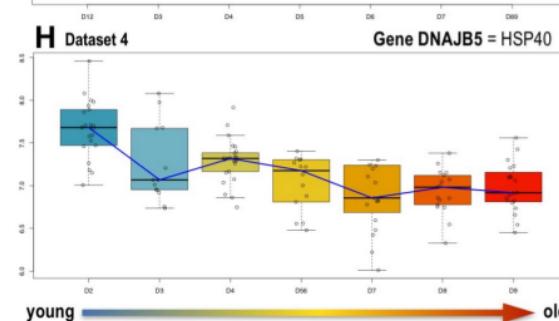
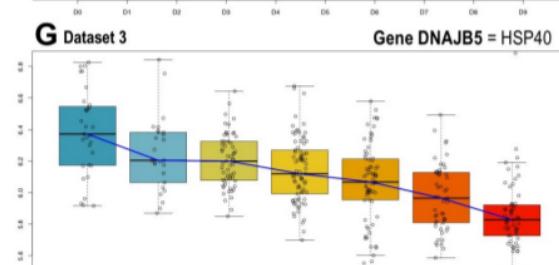
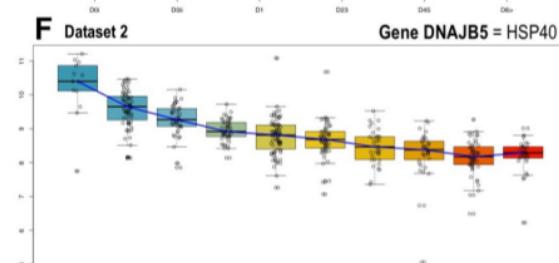
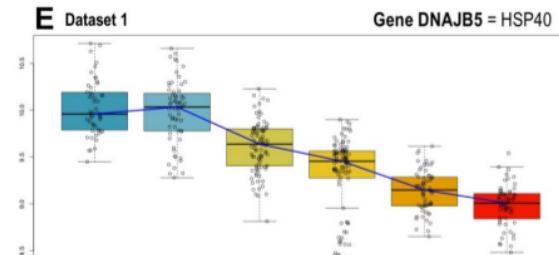


Gene HLA-DPA1
Upregulated

BINGO!



Gene HSP40 (DNAJB5)
Downregulated

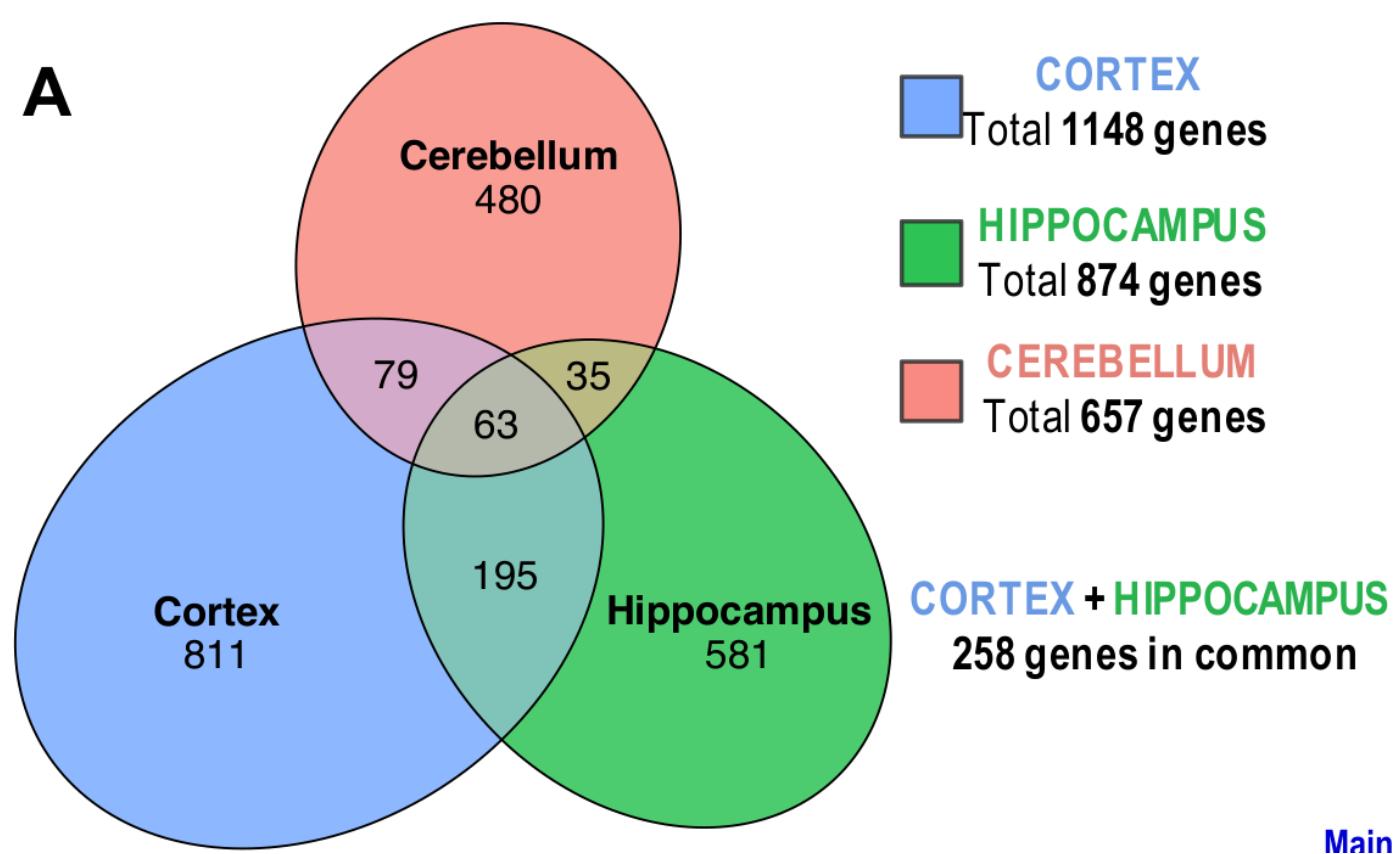


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Robust Gamma Rank Correlation: – RESULTS

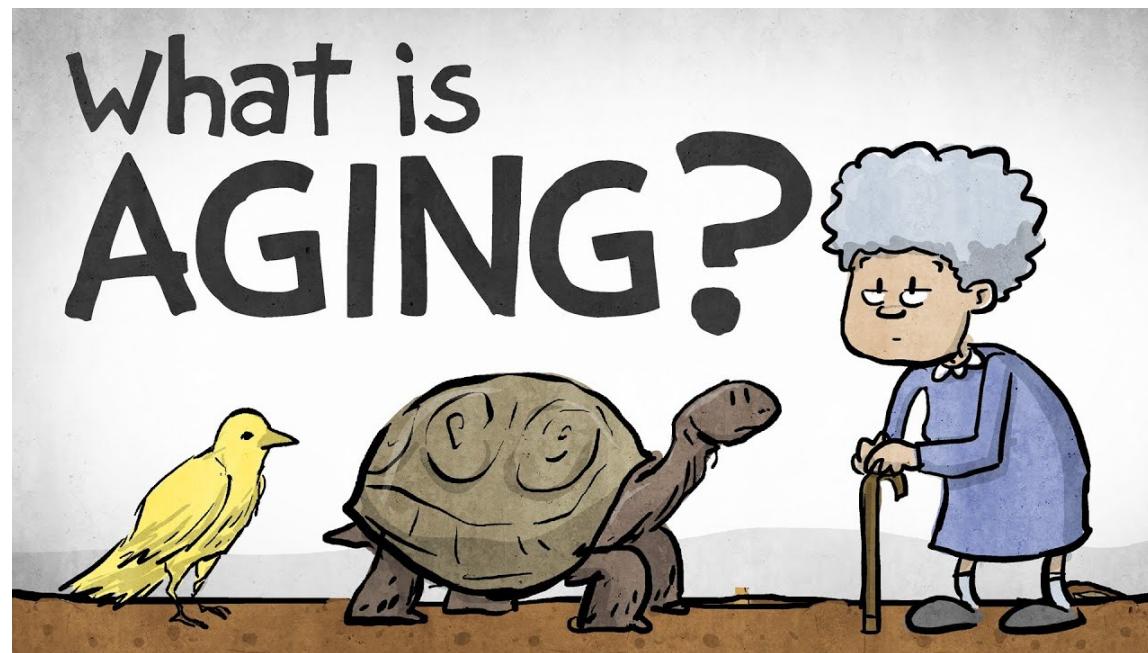


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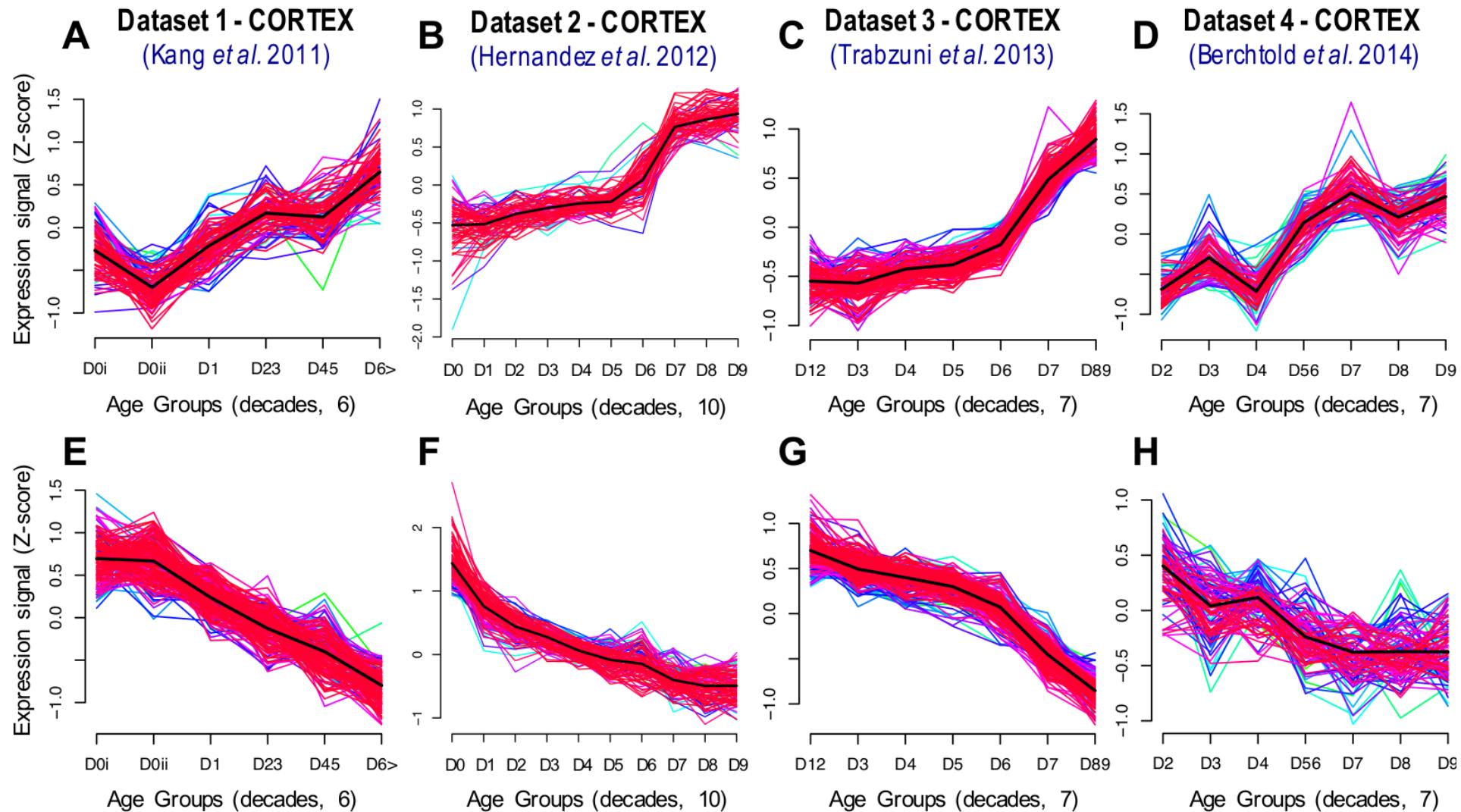


The complexity of the aging process at molecular level



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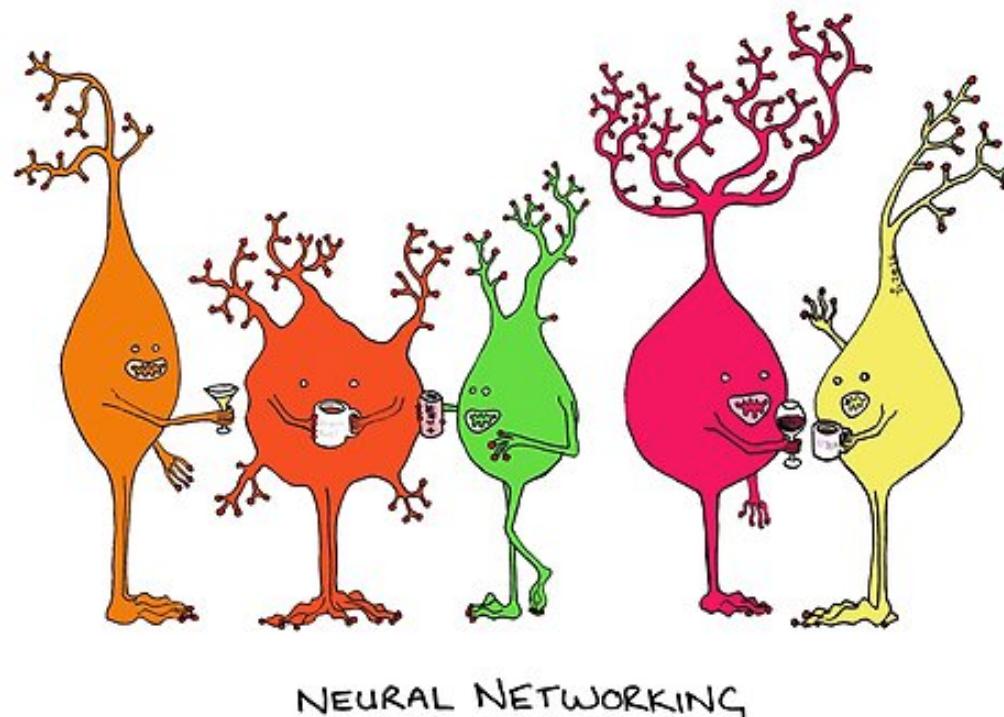


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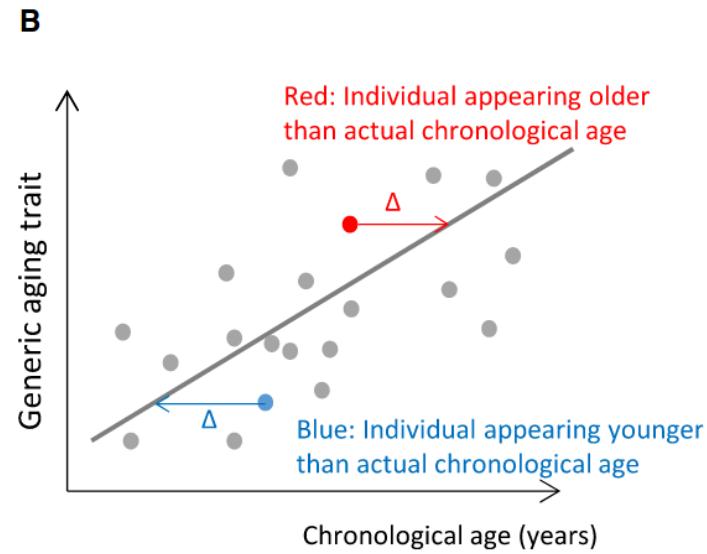
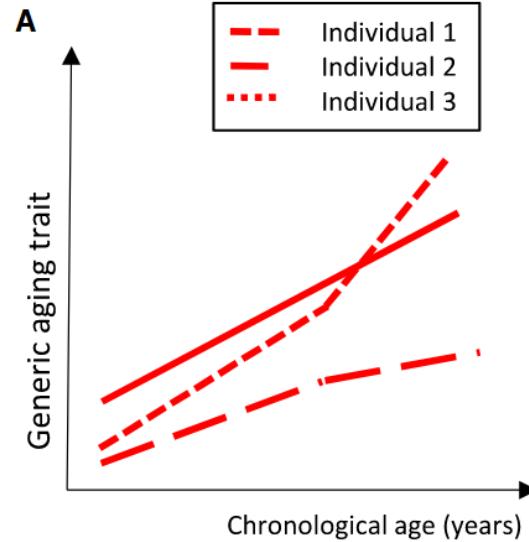
Deep Learning Neural Network as a Biological Age Predictor



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Bioage vs Physical Age and Deep Learning



The **Delta-aging** coefficient trait for a given individual within a cohort is a **theoretical value defined as the difference between the age as evaluated on the basis of the phenotypic measurements and the true chronological age** of the individual, and thus with the dimension of time.

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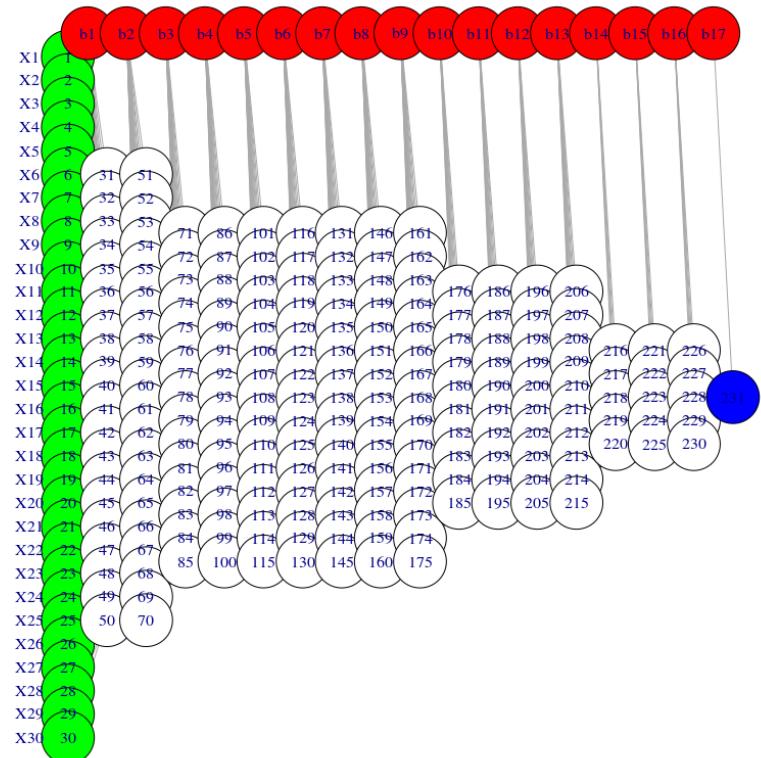
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Deep Neural Network Parameters:

Input Data: 1077 genes * 4 (median z-score + 3 gene-centered-z-score)

- Input layer 4308 neurons
- Intermediate Layers: 16
- Output Layer: 1 neuron



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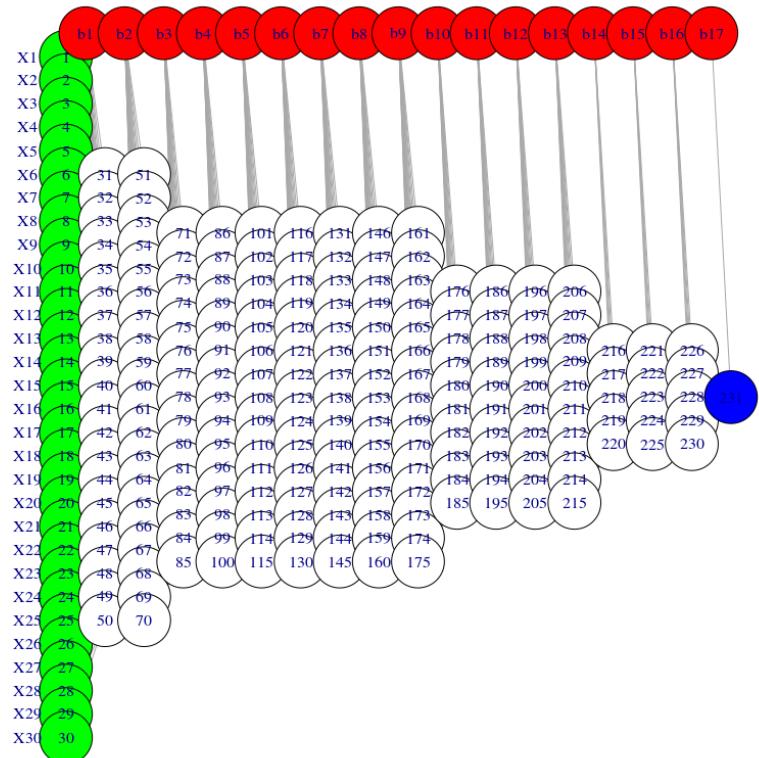
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$$\text{Robust Z-score} = \frac{X_{\text{indiv}} - \text{MEDIAN}(X_{\text{population}})}{\text{MAD}(X_{\text{population}})}$$



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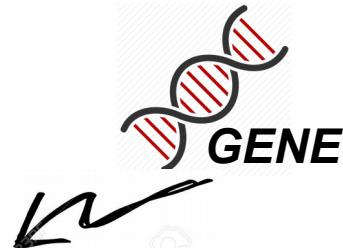
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Deep Neural Network Parameters:

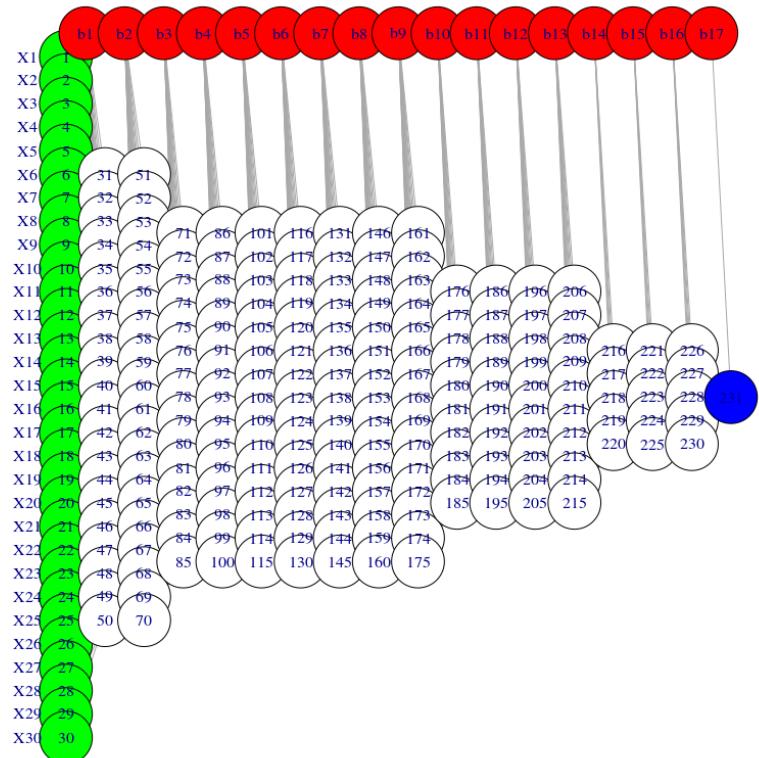
Input Data: 1077 genes * 4 (median z-score + 3 gene-centered-z-score)

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CENSORED Z-score =
$$\frac{x_{\text{indiv}} - \text{CENSORED}}{\text{MAD } (x_{\text{population}})}$$

Gene-centered



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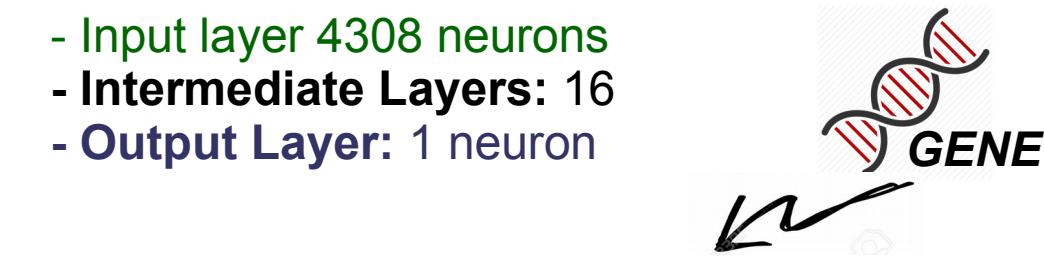
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Deep Neural Network Parameters:

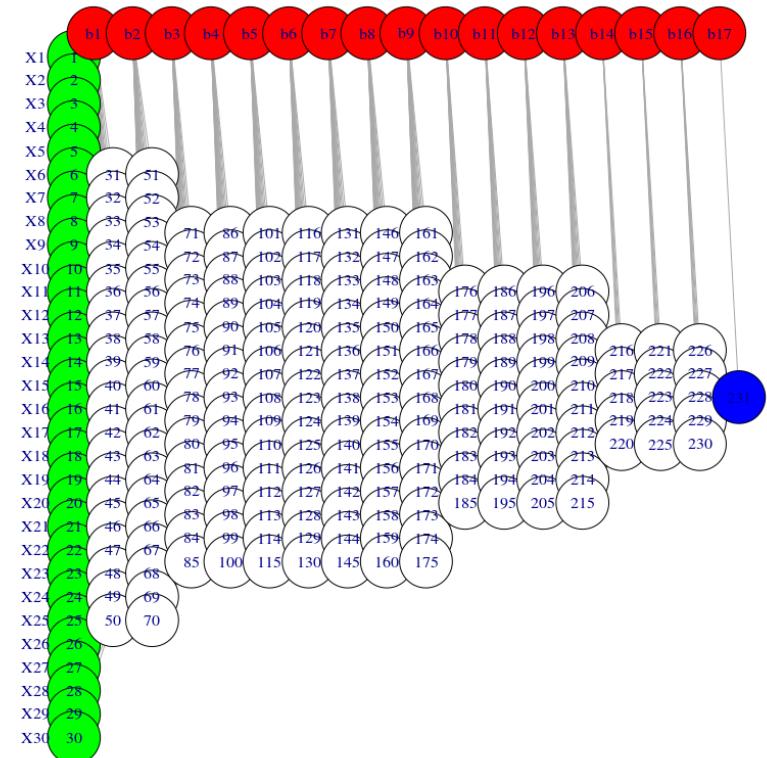
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CENSORED Z-score =
$$\frac{x_{\text{indiv}} - \text{CENSORED}}{\text{MAD } (x_{\text{population}})}$$

Gene-centered



Samples mixed from 3 cortex datasets:

652 samples for training [70%]

280 samples for validation [30%]

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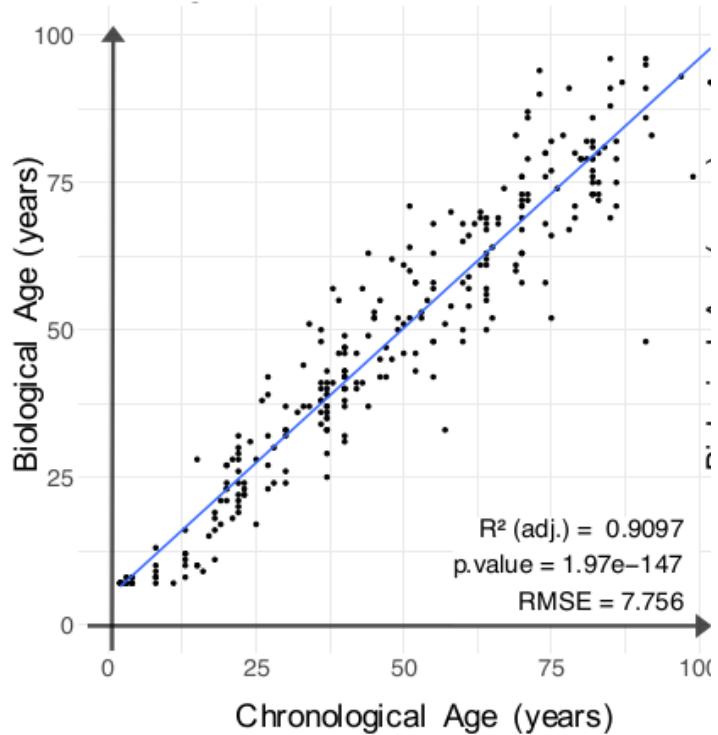
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Deep Learning Neural Network Results

A

Deep-Learning NN



DEEP NN metrics:

- 85.3% epsilon-accuracy within a 10-year frame
- $r = 0.954$
- adjusted $R^2 = 0.91$
- MAE = 5.78 years



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Deep Learning Neural Network as a Biological Age Predictor

A

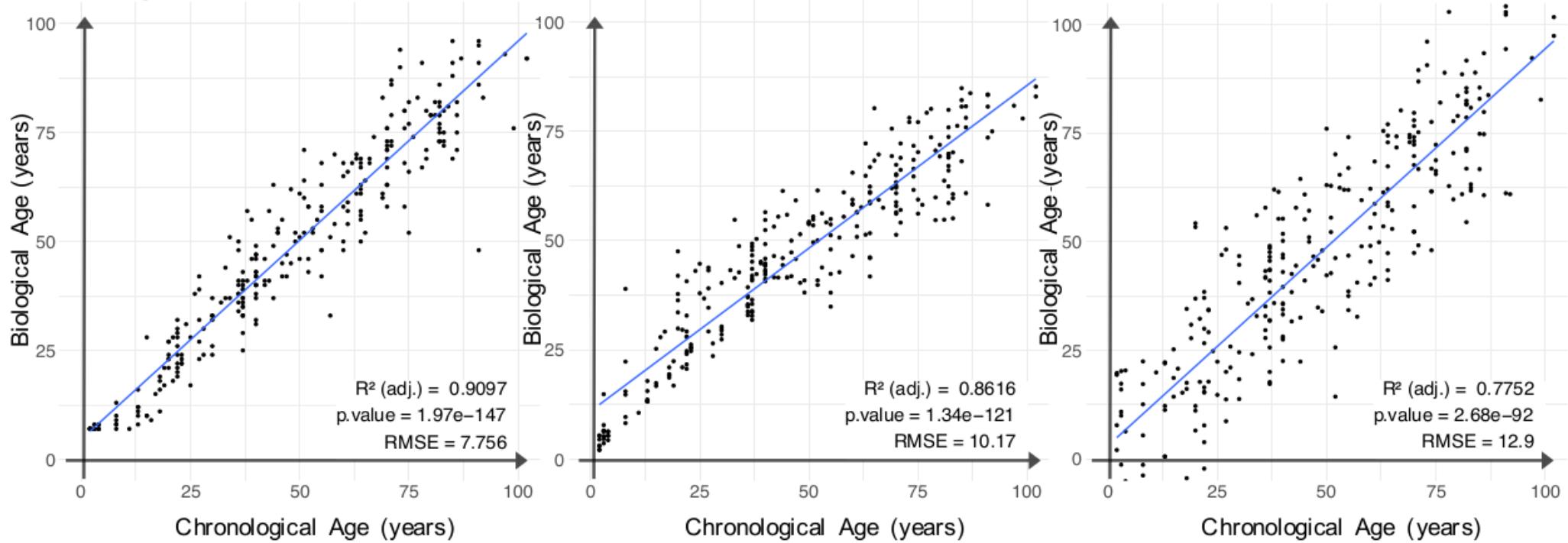
Deep-Learning NN

B

Random-Forest

C

SVM



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Deep Learning Neural Network as a Biological Age Predictor

Correlation of gene expression with inferred bioage performs better in some aging-related genes:

D Top 20 genes of best **positive Spearman correlation** with **Biological Age**

Gene Symbol ID	Mean Corr with BioAge	Gene Description
C2CD2	0.60574	C2 calcium dependent domain containing 2 [HGNC:1266]
CD74	0.56796	CD74 molecule [HGNC:1697]
CHI3L1	0.65504	chitinase 3 like 1 [HGNC:1932]
CLU	0.55673	clusterin [HGNC:2095]
DYSF	0.54747	dysferlin [HGNC:3097]
FKBP5	0.64142	FKBP prolyl isomerase 5 [HGNC:3721]
GFAP	0.55495	glial fibrillary acidic protein [HGNC:4235]
GMPR	0.68672	guanosine monophosphate reductase [HGNC:4376]
HLA-DPA1	0.60533	major histocompatibility complex, class II, DPalpha 1 [HGNC:4938]
HLA-DPB1	0.58213	major histocompatibility complex, class II, DPbeta 1 [HGNC:4940]
HLA-DRA	0.62844	major histocompatibility complex, class II, DRalpha [HGNC:4947]
ITGB4	0.58707	integrin subunit beta 4 [HGNC:6158]
ITPKB	0.54751	inositol-trisphosphate 3-kinase B [HGNC:6179]
LPIN1	0.58197	lipin 1 [HGNC:13345]
MAOB	0.56587	monoamine oxidase B [HGNC:6834]
PLPP5	0.55346	phospholipid phosphatase 5 [HGNC:25026]
RCL1	0.54645	RNA terminal phosphate cyclase like 1 [HGNC:17687]
RPS6KA5	0.58891	ribosomal protein S6 kinase A5 [HGNC:10434]
SLC14A1	0.58430	solute carrier fam. 14 member 1 (kidd blood group) [HGNC:10918]
TPP1	0.59927	tripeptidyl peptidase 1 [HGNC:2073]

E Top 20 genes of best **negative Spearman correlation** with **Biological Age**

Gene Symbol ID	Mean Corr with BioAge	Gene Description
ADGRB2	-0.58784	adhesion G protein-coupled receptor B2 [HGNC:944]
B4GALT2	-0.58908	beta-1,4-galactosyltransferase 2 [HGNC:925]
CACNA1G	-0.59276	calcium voltage-gated channel subunit alpha1 G [HGNC:1394]
CX3CL1	-0.60234	C-X3-C motif chemokine ligand 1 [HGNC:10647]
DNAJB5	-0.70282	DnaJ heat shock protein fam. (Hsp40) member B5 [HGNC:14887]
DPYSL4	-0.58685	dihydropyrimidinase like 4 [HGNC:3016]
EPHB3	-0.59838	EPH receptor B3 [HGNC:3394]
GPR26	-0.60415	G protein-coupled receptor 26 [HGNC:4481]
KIF21B	-0.59067	kinesin family member 21B [HGNC:29442]
MARCH4	-0.66160	membrane associated ring-CH-type finger 4 [HGNC:29269]
NREP	-0.58812	neuronal regeneration related protein [HGNC:16834]
OLFM1	-0.60750	olfactomedin 1 [HGNC:17187]
PNOC	-0.51468	pronociceptin [HGNC:9163]
RAB11FIP4	-0.62334	RAB11 family interacting protein 4 [HGNC:30267]
RNF165	-0.59137	ring finger protein 165 [HGNC:31696]
SEMA6B	-0.58579	semaphorin 6B [HGNC:10739]
SMPD3	-0.68615	sphingomyelin phosphodiesterase 3 [HGNC:14240]
TMEM8B	-0.60885	transmembrane protein 8B [HGNC:21427]
TRIB2	-0.63471	tribbles pseudokinase 2 [HGNC:30809]
TTC9B	-0.59174	tetratricopeptide repeat domain 9B [HGNC:26395]



Transcriptomic landscape, gene signatures and regulatory profile of aging in the human brain

Laboratory 19 CIC-IBMCC are:

Javier De Las Rivas

Diego Alonso

Óscar González

Santiago Bueno

Elena Sánchez

Alberto Berral

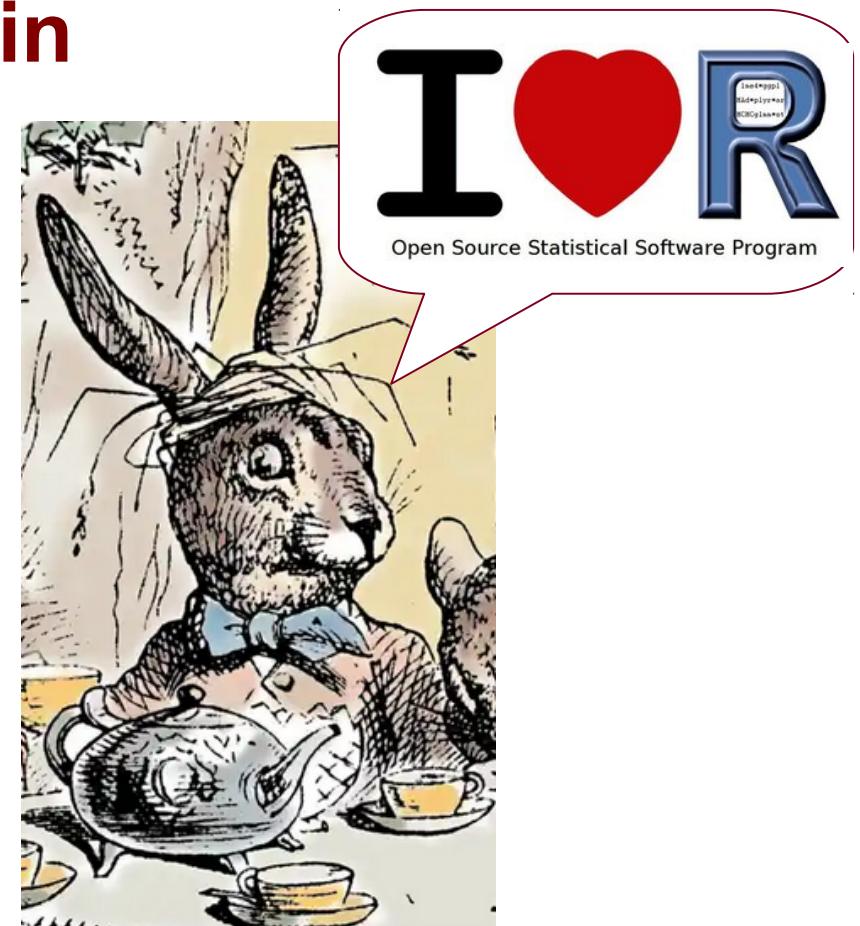
Fernando Bueno

Departamento Estadística – USAL

José Manuel Sánchez Santos



CENTRO DE INVESTIGACIÓN
DEL CÁNCER



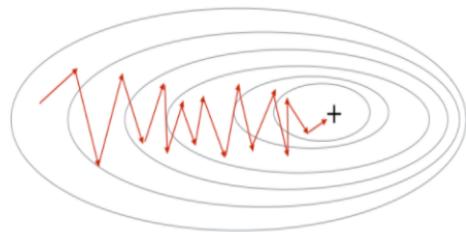
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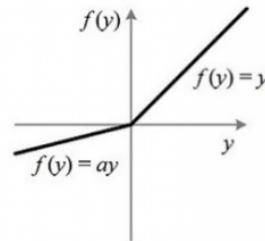


Optimization algorithm:

Stochastic Gradient Descent



Neuron function:

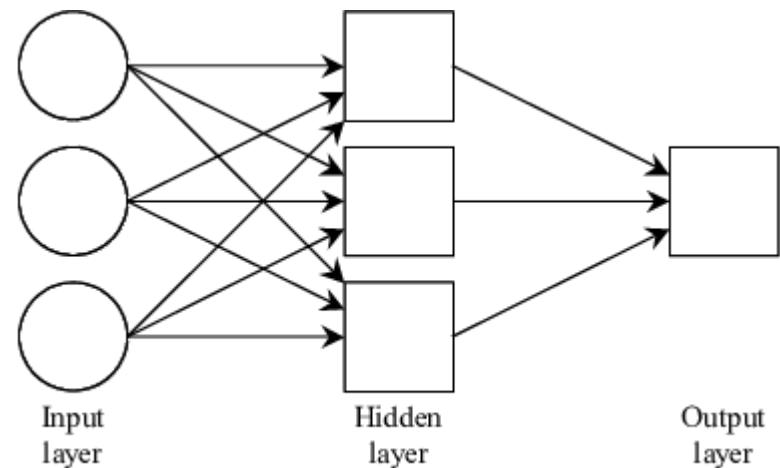


$$PReLU(x_i) = \begin{cases} x_i & \text{if } x_i > 0 \\ a_i x_i & \text{if } x_i \leq 0 \end{cases}$$

Error function/Cost function:

The cost function J for a particular choice of parameters θ is the mean squared error (MSE):

$$J(\theta) = \frac{1}{m} \sum_{i=1}^m (h_\theta(x^{(i)}) - y^{(i)})^2$$



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Backpropagation
Stochastic Gradient Descent
SoftMax
RMSE
Adagrad