Network Science applied to Epilepsy

BioBytes Group

MO413 · 1º semester of 2024 · Institute of Computing · UNICAMP

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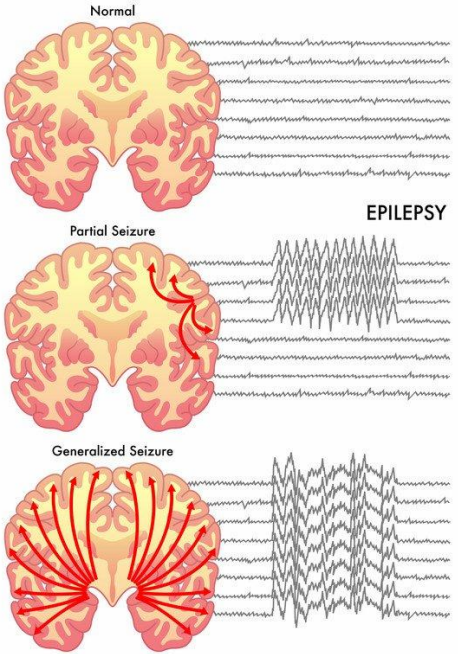
16/04/2024

Introduction

What is **epilepsy**[1]?

- Epilepsy is a disease caused by the **synchronous**, **excessive** or **abnormal** activity of neuronal cells in the brain.
- Multiple causes.
- 50 million people/Brazil = 2% [2]

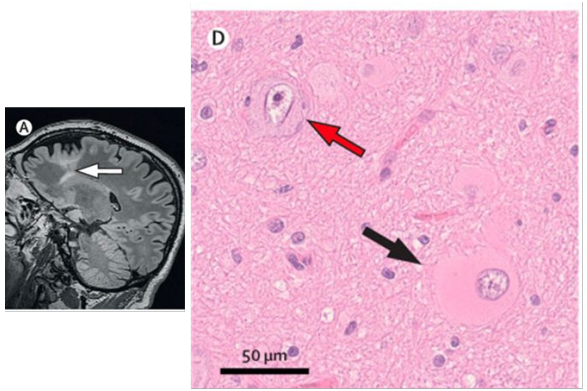


Normal Brain (on top) and Brain with epilepsy (below) [2]

[2] - World Health Organization

Introduction

- Focal Cortical Dysplasia
  - Pediatric epilepsy
  - Malformation of cortical development
  - Cortical and cellular abnormalities

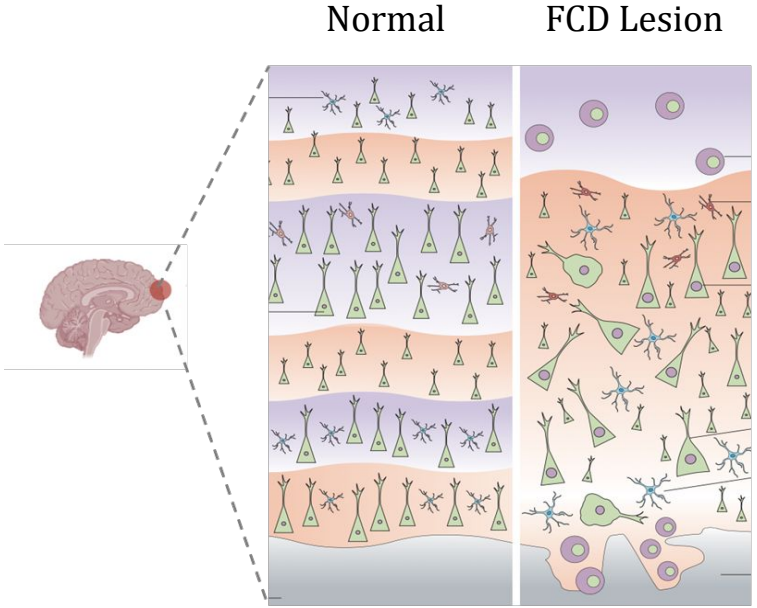


Baulac et al, Lancet Neur., 2021

Dysmorphic Neurons

+

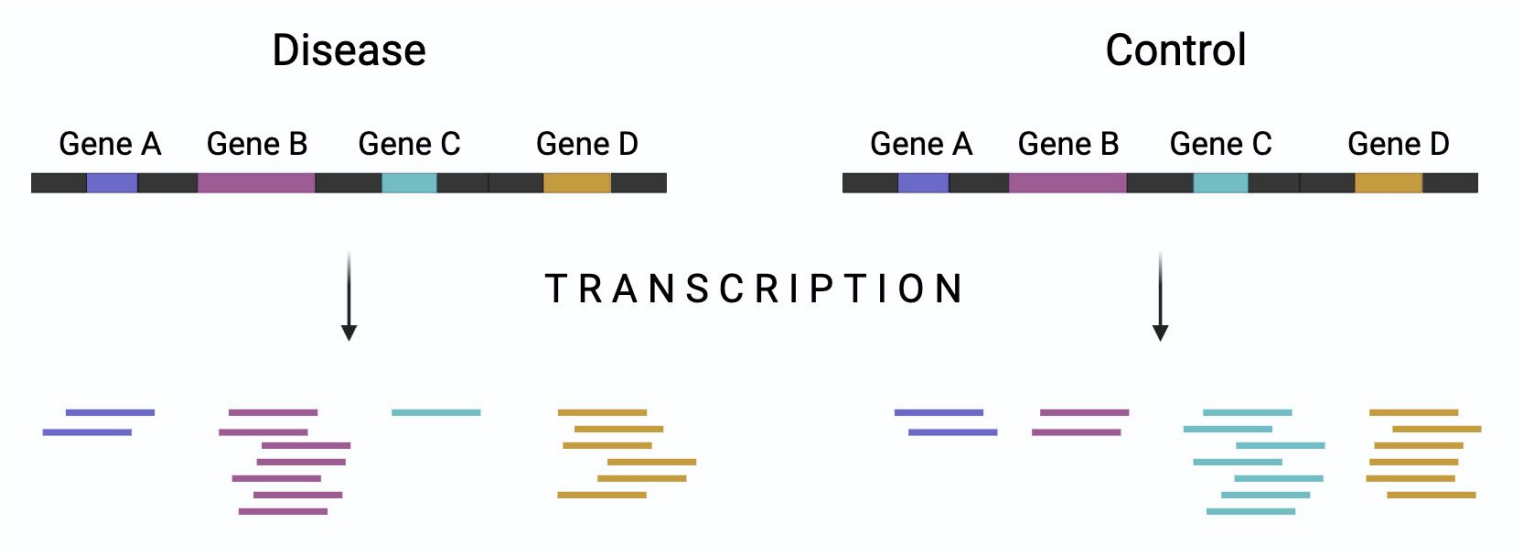
Balloon Cells



Sisodiya et al., Lancet Neur., 2009

Transcriptomics

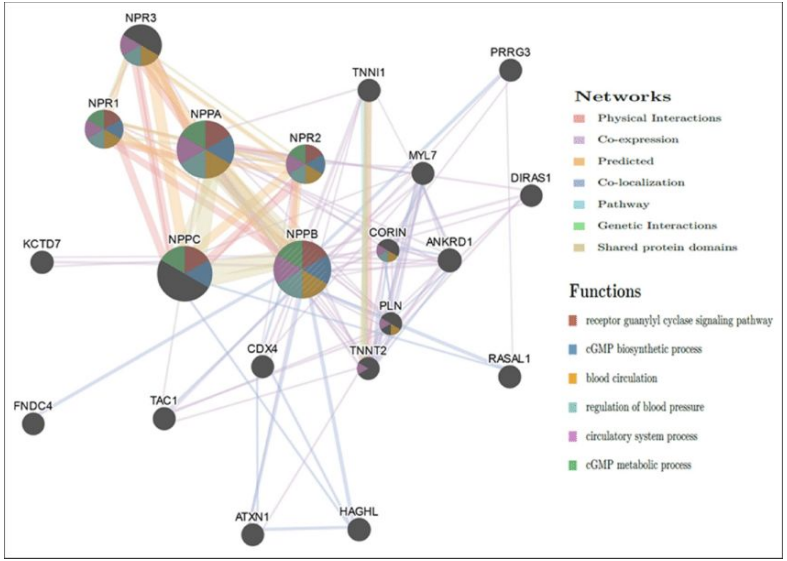
- Quantifies RNA expression by number of transcript counts



Genes B and C = Differentially Expressed Genes (DEGs)

Proposal

- Apply **network science methods** in the analysis of differentially expressed genes in patients diagnosed with **epilepsy** caused by Focal Cortical Dysplasia type 2b (FCD 2b)
- Analyze the correlation between **genes** and **biological functions**



Schematic illustration of the gene network and biological functions involving the NPPB gene[4]

Research Questions

- What are the differentially expressed genes between **disease** and **control group**?
- Which **biological functions** are most represented in the disease? → **functional networks**
- How are these genes being regulated? → **regulation networks**

Methodology

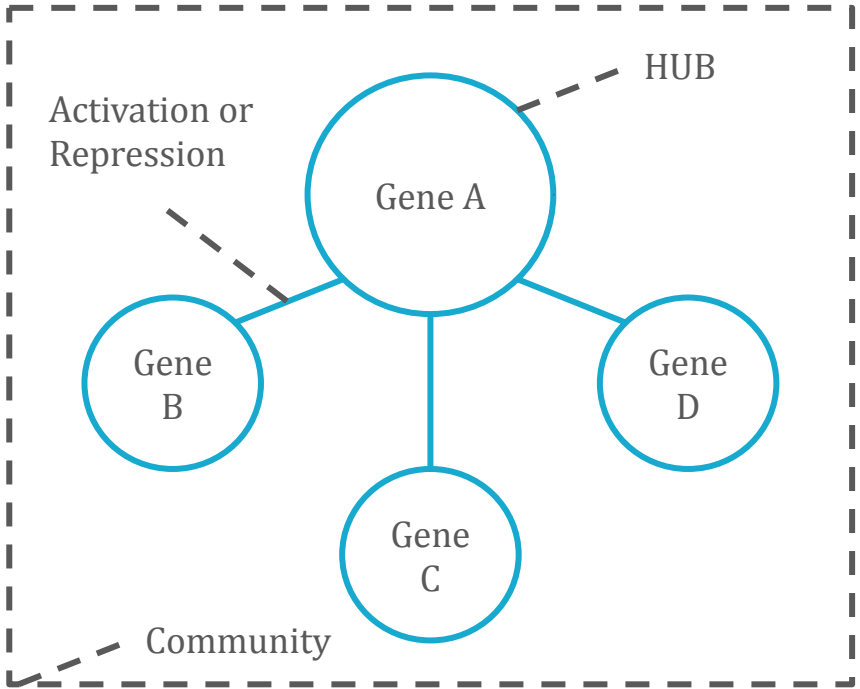
- Determine gene expression difference using statistical methods of **DESeq2**[5] package of *Bioconductor Software*
  - Models read counts using a negative binomial distribution
- Create a network of interactions with the identified **differentially expressed genes**
- Integrate the network with functional annotation information, using *Gene Ontology*[6], and relate them to their respective **biological functions** and **signaling pathways** that are involved, resulting in a functional enrichment analysis

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

GENEONTOLOGY
Unifying Biology

Methodology

- Use Network Science techniques to explore the organization and dynamics of genes in the network:
  - **Centrality analysis**: identify genes that play important roles in the functioning of epilepsy
  - **Community detection**: revealing groups of genes that strongly interact with each other
  - **Perturbation and robustness analysis**: assess how the removal or perturbation of specific genes affects network structure and function



Softwares and Tools

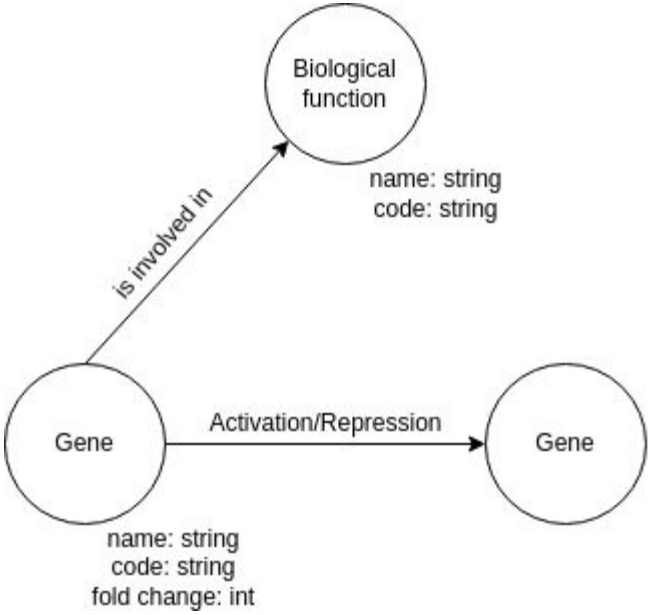
- **DESeq2**[5]: Differential expression tests

- **Cytoscape**[7]:
  - Generation of a network of differentially expressed genes with associated biological functions
  - Analysis using Network Science techniques

Data Base

- Transcriptomes distinguish human FCD subtypes (NCBI)[8]:
  - Format: CSV (data) and XLSX (metadata)
  - Size: 5.5 Mb (data) and 5 Mb (metadata)
  - Row represents genes and columns represent samples
- Gene Ontology[6]:
  - Formats: OBO and OWL
  - Computational representation of the current scientific knowledge about the functions of genes from many different organisms
    - Functions of genes: the protein and non-coding RNA molecules produced by genes

Logic Model


Biological function
name: string
code: string
is involved in
Gene
Activation/Repression
Gene
name: string
code: string
fold change: int


Thank You!
Questions?

References

[1] - Patel P, Moshé SL. The evolution of the concepts of seizures and epilepsy: What's in a name? Epilepsia Open. 2020 Jan 10;5(1):22-35. doi: 10.1002/epi4.12375. PMID: 32140641; PMCID: PMC7049807.

[2] - World Health Organization: https://www.who.int/news-room/fact-sheets/detail/epilepsy/

[3] - Drugs.com: https://www.drugs.com/health-guide/seizure.html

[4] - Associations of B-Type Natriuretic Peptide and Its Coding Gene Promoter Methylation With Functional Outcome of Acute Ischemic Stroke: A Mediation Analysis - DOI:10.1161/JAHA.120.017499

[5] - DESeq2 (Bioconductor Software Package): https://bioconductor.org/packages/release/bioc/html/DESeq2.html

References

[6] - Gene Ontology: https://geneontology.org/

[7] - Cytoscape: https://cytoscape.org/

[8] - Transcriptomes distinguish human FCD subtypes: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE128300

[9] - Brain image theme: Getty Images (Yuichiro Chino)

[10] - DNA image theme: iStock (Shutter2U)