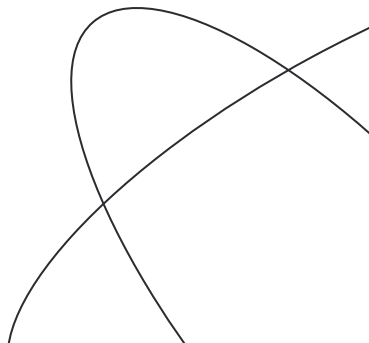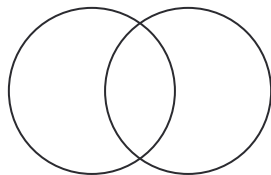# Resilience of Gene Network Cores to Perturbations in the Periphery
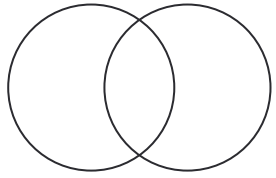
-Group D Sanjana, Gia, Sameekshya, Manav, Sai Shyam

-Physics of Life Monsoon School 2023

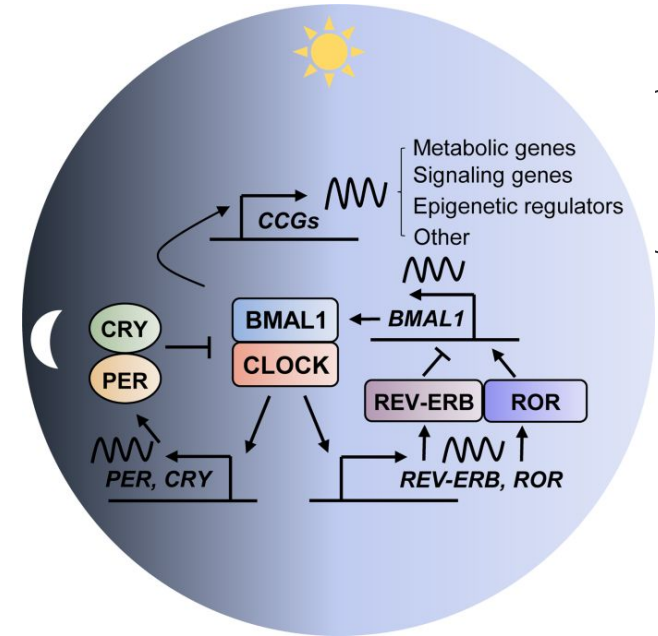-National Centre for Biological Sciences

01

Introduction

Gene Networks

A gene regulatory network (GRN) is a system of genes and proteins that control the expression of other genes in a cell.

A GRN can involve genes that produce proteins that activate or inhibit other genes.

A GRN can also respond to signals from inside or outside the cell, such as hormones or nutrients

Lee, Yool. "Roles of circadian clocks in cancer pathogenesis and treatment." *Experimental & molecular medicine* vol. 53,10 (2021): 1529-1538. doi:10.1038/s12276-021-00681-0

Stability in Gene Networks

Our Question

- Core Gene Networks are mostly observed to remain stable in spite of minor perturbations that occur due to various reasons

- Biologists mostly focus on a particular network while studying genetic networks

Do core gene networks remain stable under external perturbations?

02

Methodology

Mathematical Model: Hill's Equation

n_{AB} Hills coefficient of A acting on B

g_{B} - Production rate of gene B

k_{B} - Degradation rate of gene B
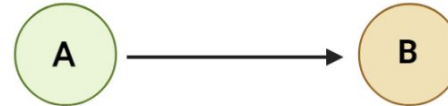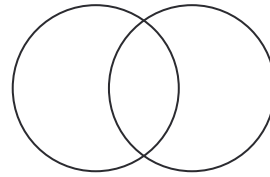
λ_{AB} - Maximum fold change in the expression level of gene B due to gene A

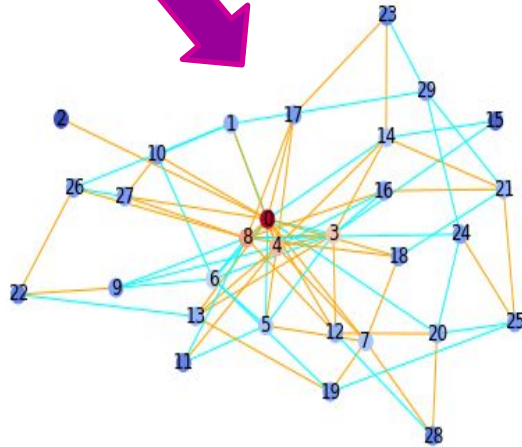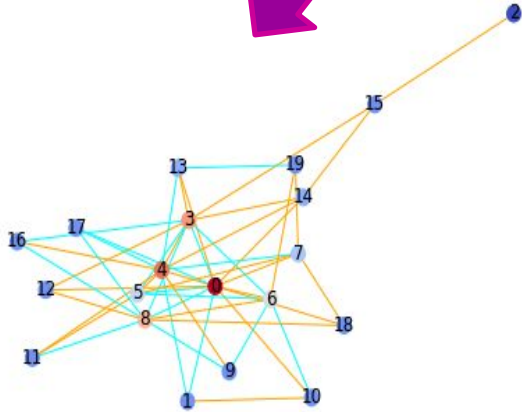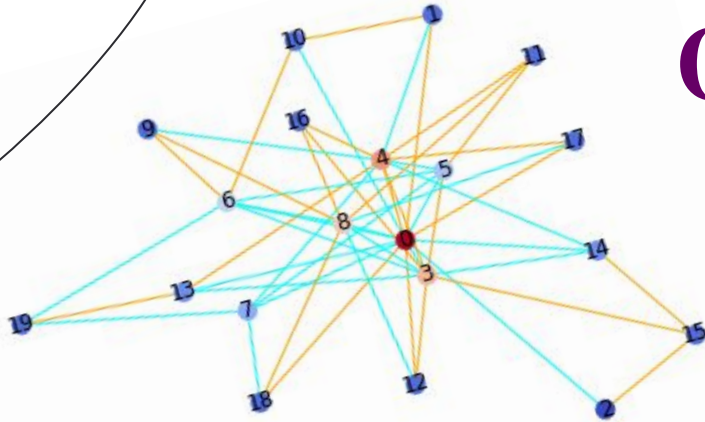A^{0}_{B} Threshold level for the regulation of gene B by A

$$\frac{dB}{dt} = g_B H^S(A, A^0_B, n_{AB}, \lambda^-_{AB}) - k_B B$$

Hill inihibtion function H^- for A inhibiting $B = \dfrac{1}{1 + (A/A^0_B)^{n_{AB}}}$

Hill activation function H^+ for A activating $B = \dfrac{A^{n_{AB}}}{(A^0_B)^{n_{AB}} + A^{n_{AB}}}$

Creating the Network

Framework for the network

Enter n nodes and m edges per new node to create a base network

Assign the edges interaction

Inhibition and Activation

Establish a core

The nodes with the highest degree

"Perturb" the network

- Delete an edge from one of the least connected nodes
- Add 10 new nodes, connected to the base network
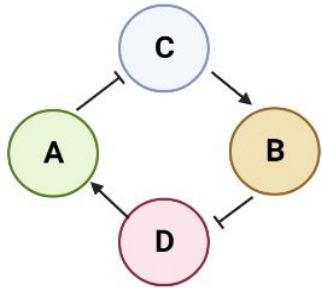
Creating the Input Data

B Node

→ Activation is indicated by 1 (Cyan edge)

⊣ Inhibition is indicated by 2 (Orange edge)

Network to Topology File →

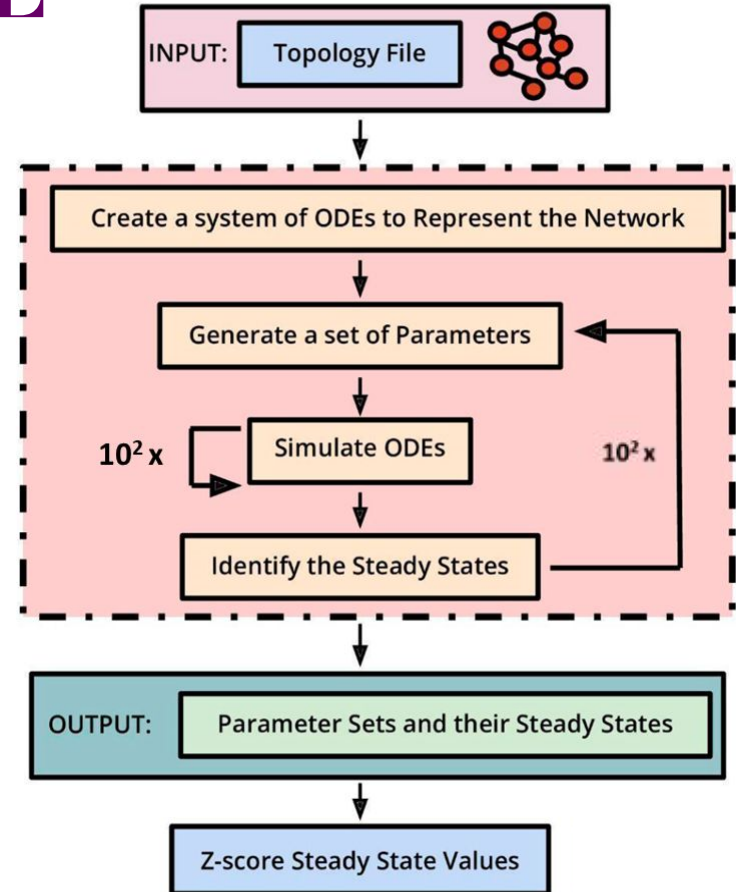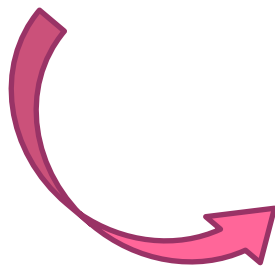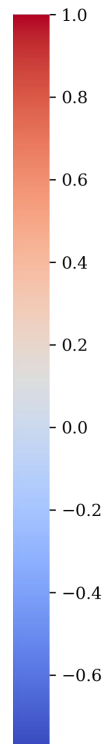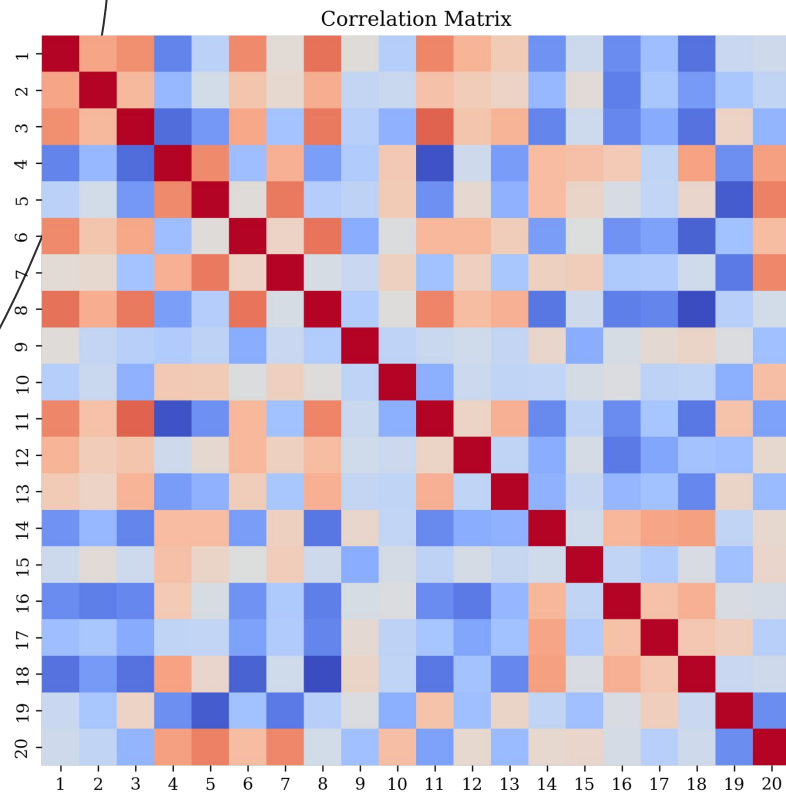| Source	Target	Interaction
A	C	2
C	B	1
B	D	2
D	A	1

The Network is converted to a Topology File(.topo)

The Topology file is used as input for RACIPE software

Python Code used: https://drive.google.com/file/d/1ZjPsjG4f4FeLs8dFbccFQYxYCXkVIT6B/view?usp=drive_link

RACIPE

- RACIPE (Random Circuit Perturbation) tool used for simulating and analyzing gene regulatory networks (GRNs) in biology.

- The behavior of genes and gene products part of GRN can be investigated by considering the interactions between genes and their regulatory elements.

Schematic: Harlapur et al., *Biomolecules* 12, no. 12: 1842 (2022)

Correlation Matrix

Analysis

Correlation Matrix for the Base Core

Correlation Matrix for the Core in -Edge Graph 10

Correlation Matrix for all the nodes
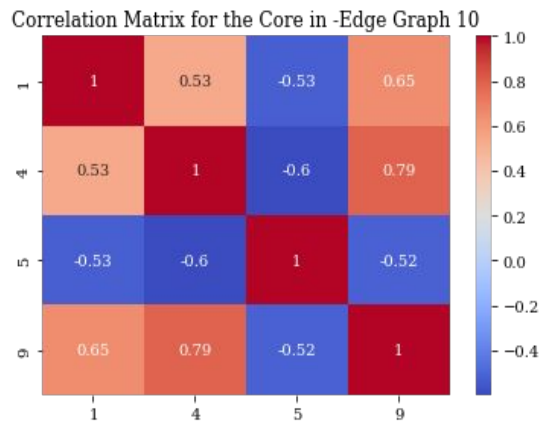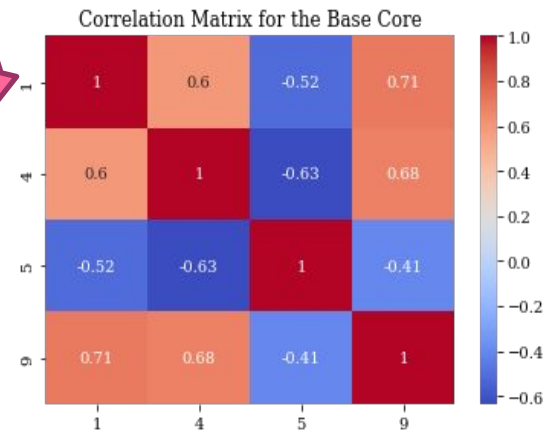
Metric to measure Resilience

Root Mean Square Deviation

$$\text{RMSD} = \sqrt{\frac{\sum_{i=1}^{n} \sum_{j=1}^{m} (A_{ij} - B_{ij})^2}{n \cdot m}}$$

- A_{ij} represents the element at the i-th row and j-th column of matrix A
- B_{ij} represents the element at the i-th row and j-th column of matrix B
- n represents the number of rows in the matrices
- m represents the number of columns in the matrices.

03

Results

Core-Core Comparison

<u>For Edge Deletion:</u>

RMSD values are have a mean of 2.22 and a standard deviation of 1.03
Constant RMSD indicates that the core is not being affected by random edge deletion

<u>For Node Addition:</u>

Mean RMSD is 2.52 with a standard deviation of 0.81 which again indicates that the core is remaining unaffected by the perturbations in spite of the nature of perturbation being very different and to a much larger extent

Periphery-Periphery Comparison

<u>For Edge Deletion:</u>

Mean RMSD values is 6.55 with a standard deviation of 0.65
In spite of perturbation in the periphery, RMSD in the periphery is higher than the perturbation in the core indicating that the core is stable

<u>For Node Addition:</u>

Mean RMSD is 6.44 with a standard deviation of 0.25 which again indicates that the core is remaining unaffected by the peripheral perturbations
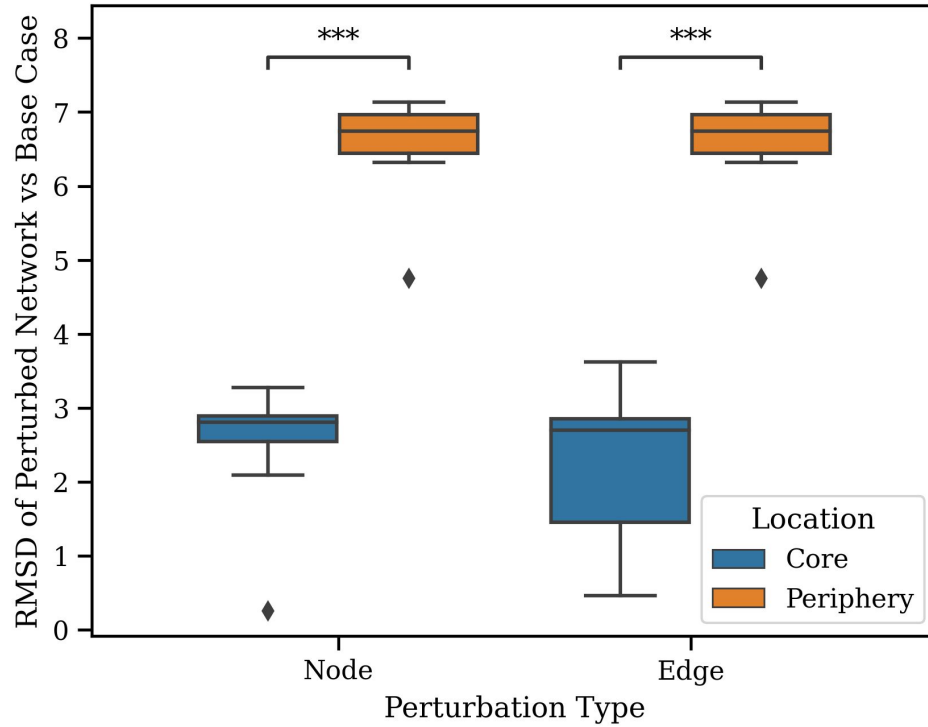
The Root Mean Square deviation in the correlation of the Perturbed Network from the Wild Type Network (Base). *** indicates p-value < 0.001

Acknowledgements

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