

# Systems Biology: A Mathematical Perspective on Biological Networks

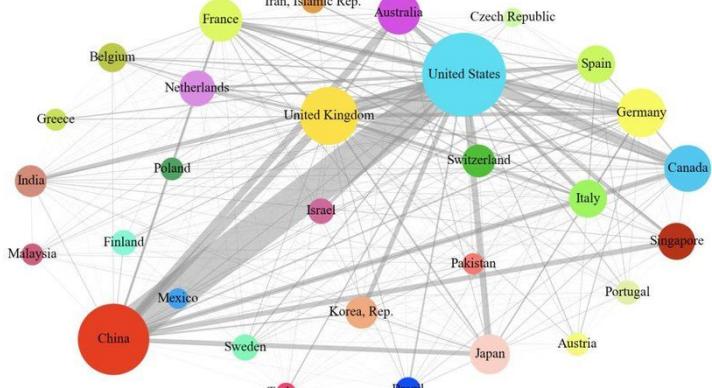
Aryan Bora  
Julia Westwater Brodsky

Mentor: Karol Bacik

Directed Reading Program 2025

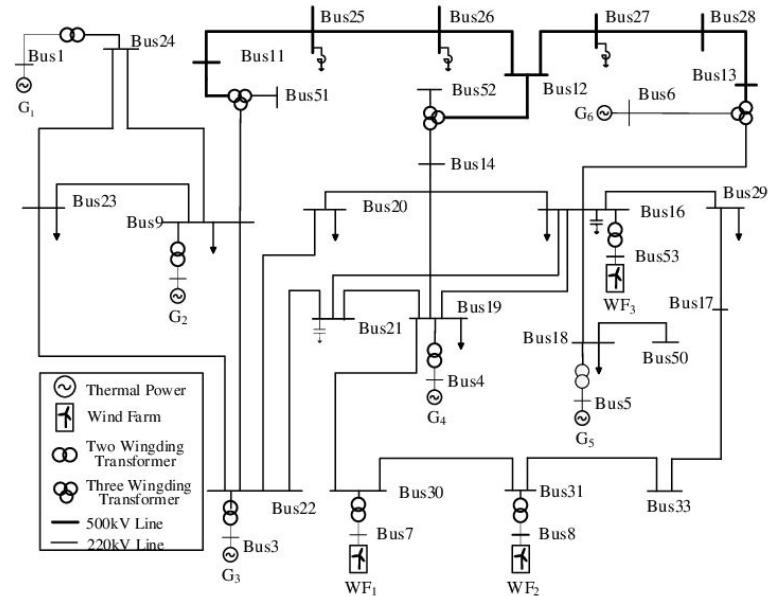
# What is Systems Biology?

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International collaboration in AI research

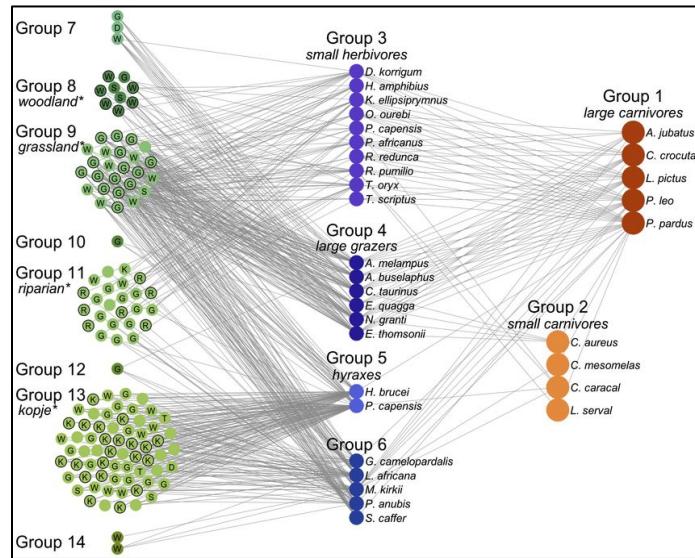
Tang et al. 2021



Network wiring for wind-thermal power coordination

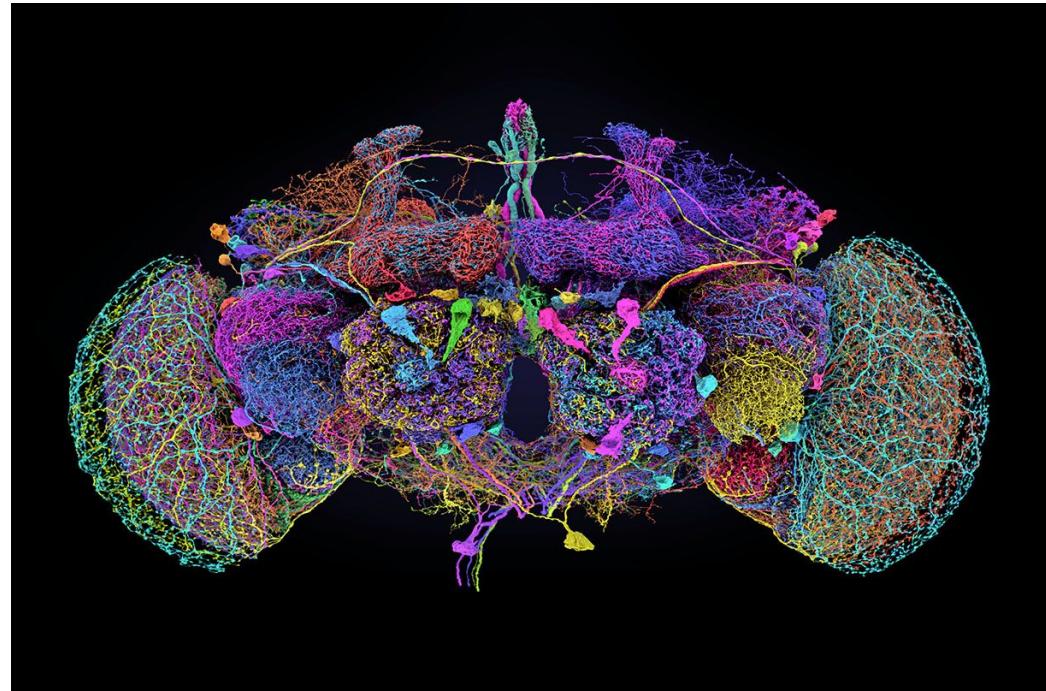
Yang et al. 2019

# What is Systems Biology?



# The Serengeti food web

Dobson 2023



## The first complete neural network of a fruit fly

FlyWire, 2024

# What is Systems Biology?



Protein-protein interactions in yeast

Jeong et al. 2001

# Talk Overview

Transcription Networks

Network Motifs

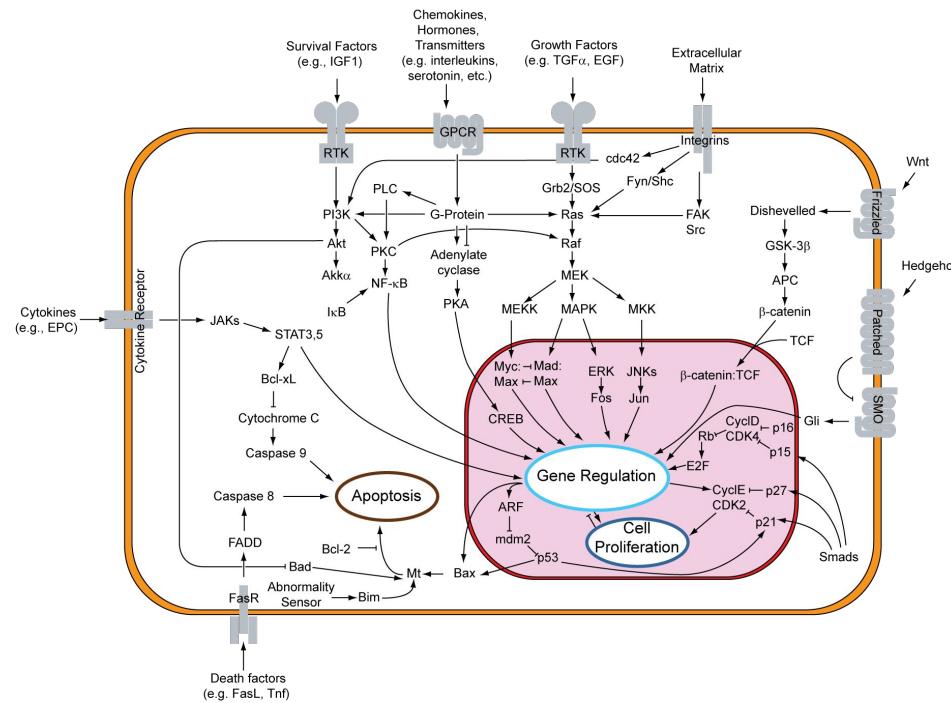
Molecular Interactions

Example 1: Feedforward Loops

Example 2: Feedback Loops

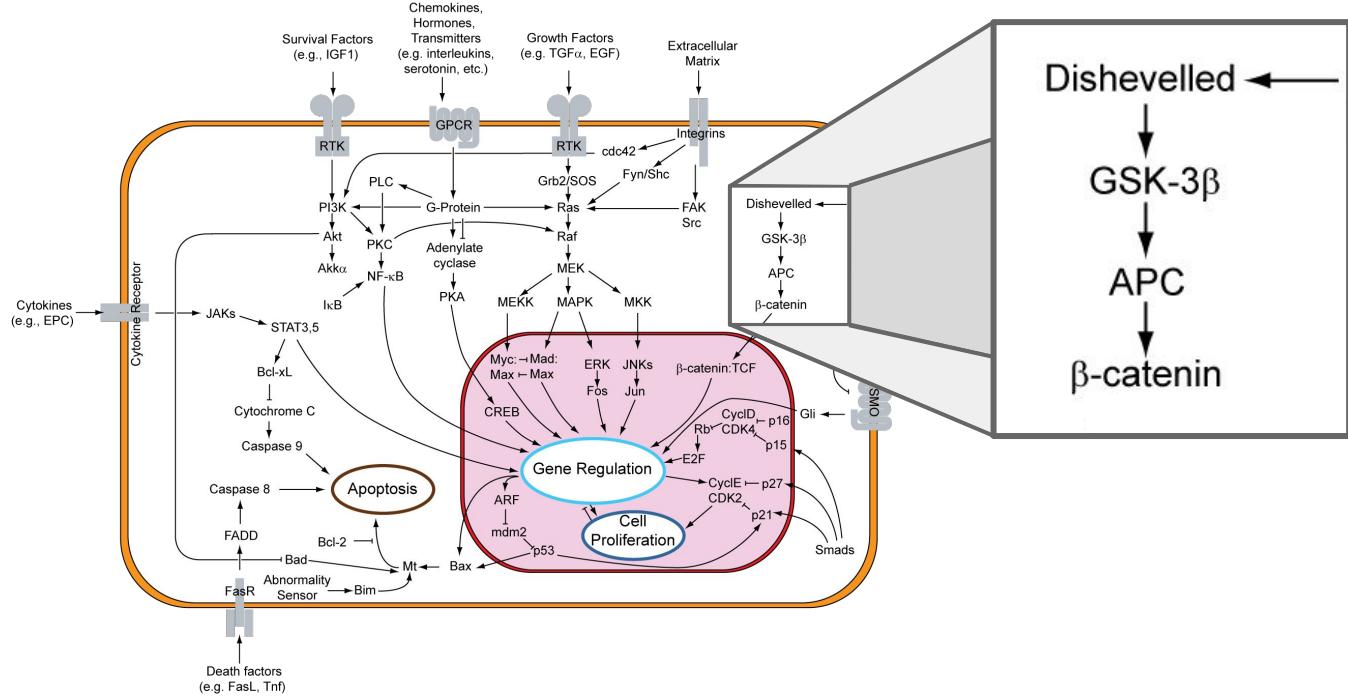
# Transcription Networks

- “transcription factors” regulate the production of other proteins



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- “transcription factors” regulate the production of other proteins
- interactions mapped in directed graphs: “transcription networks”



# Transcription Networks

Two types of relationships:

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## Activation

- Presence of protein X *increases* the production rate of protein Y



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## Repression

- Presence of protein X *decreases* the production rate of protein Y



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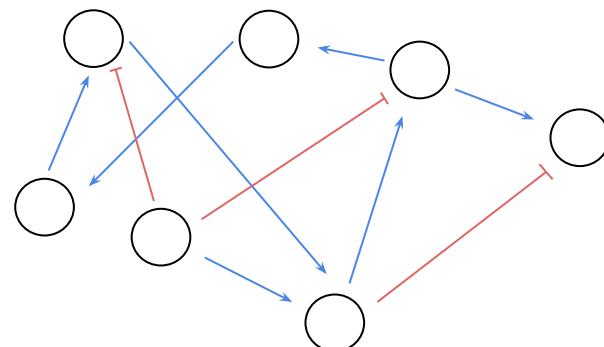
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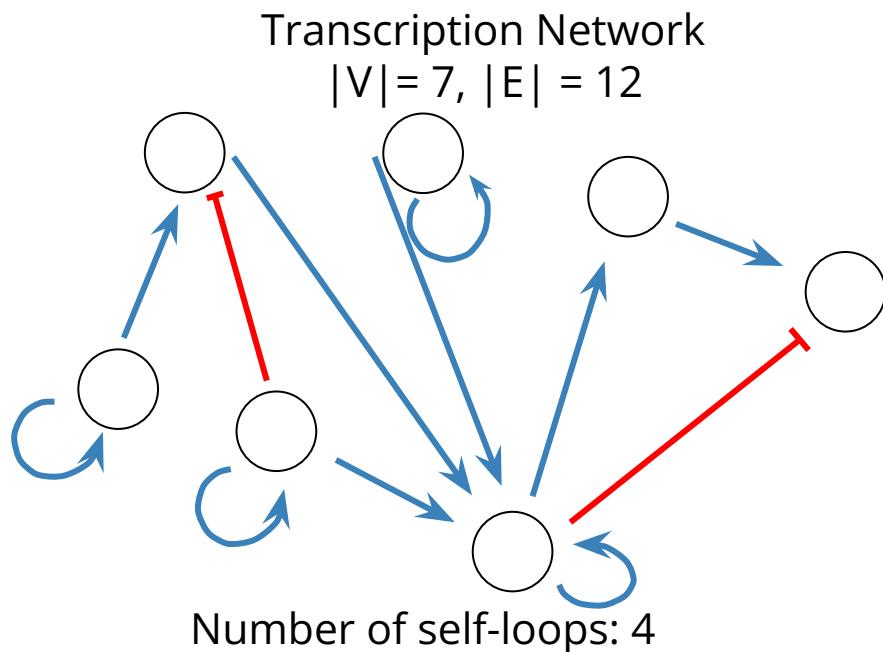


# Motifs

*Motifs* are subgraphs that appear more frequently in biological networks than random networks.

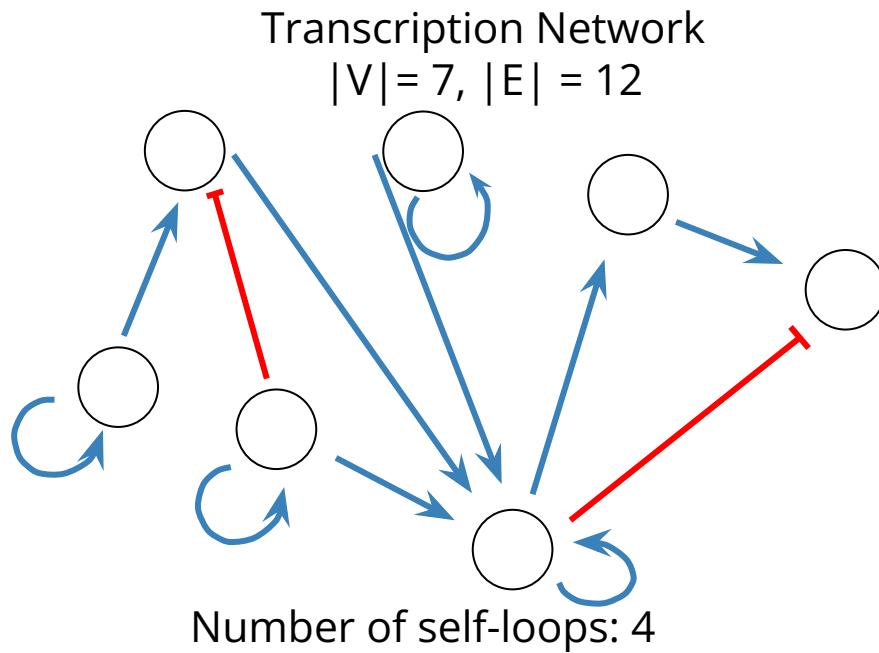
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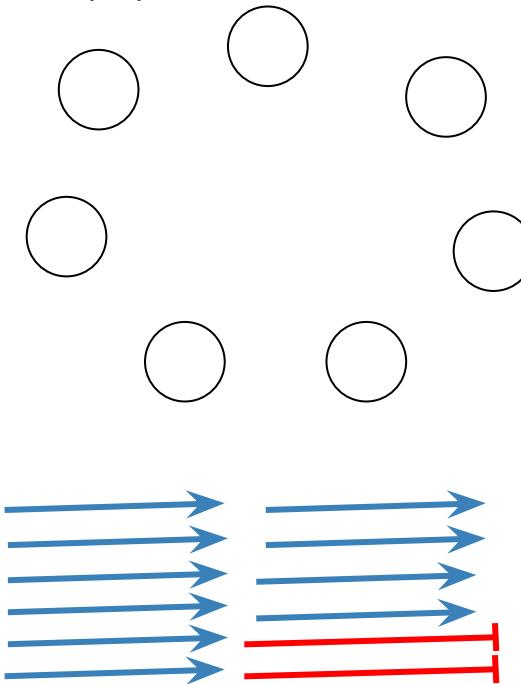


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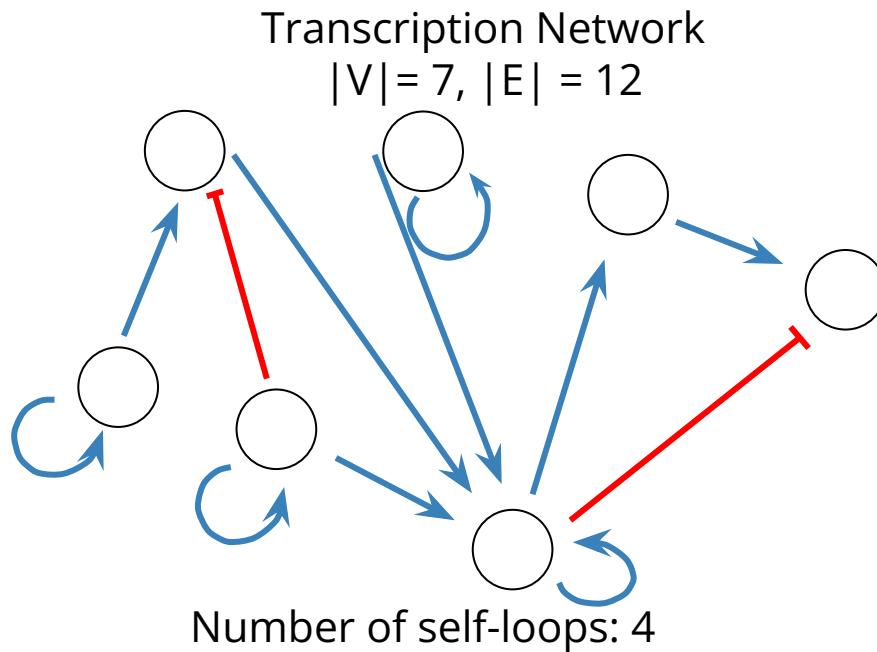


Erdős-Rényi Random Graph  
All  $|E|$  edges randomly chosen

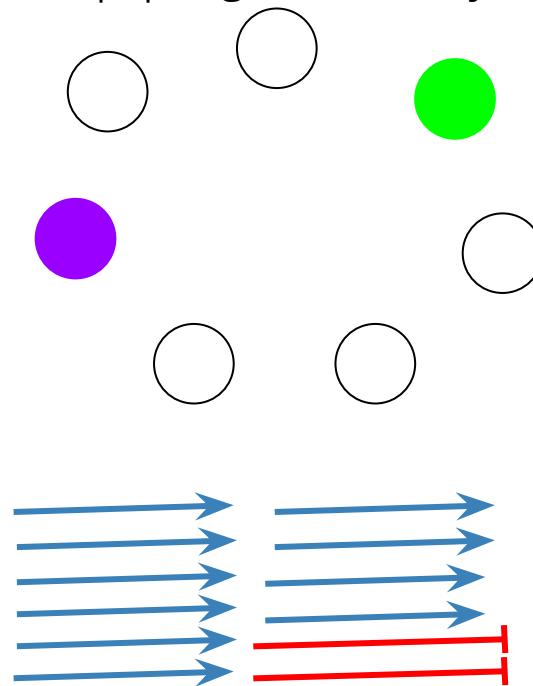


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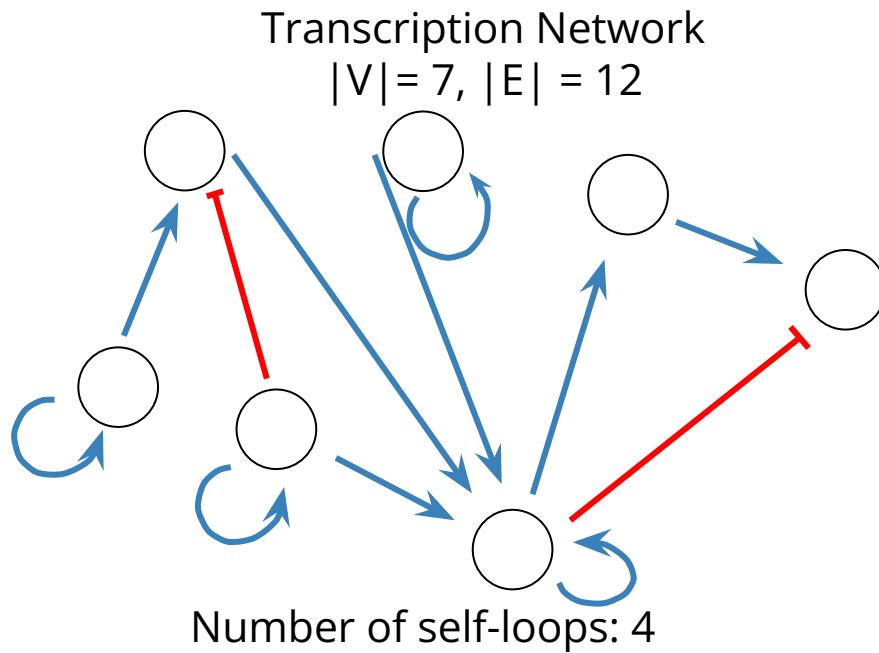


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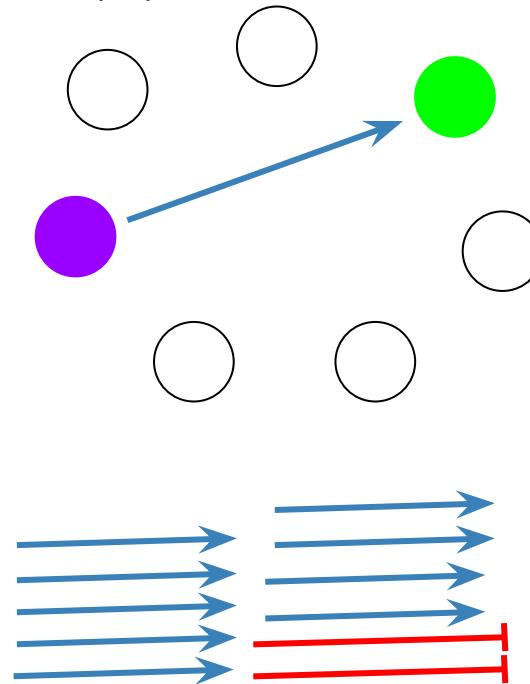


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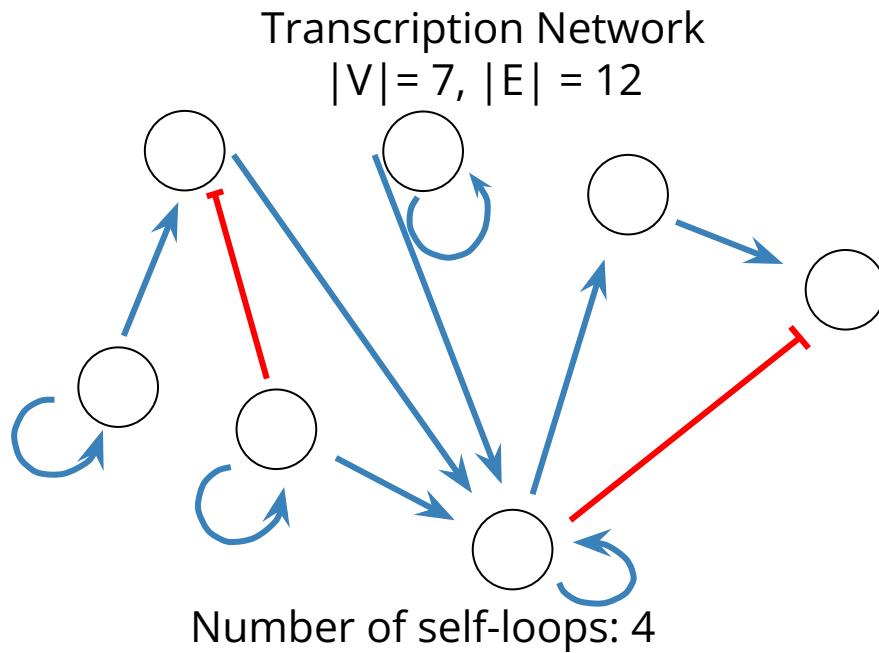


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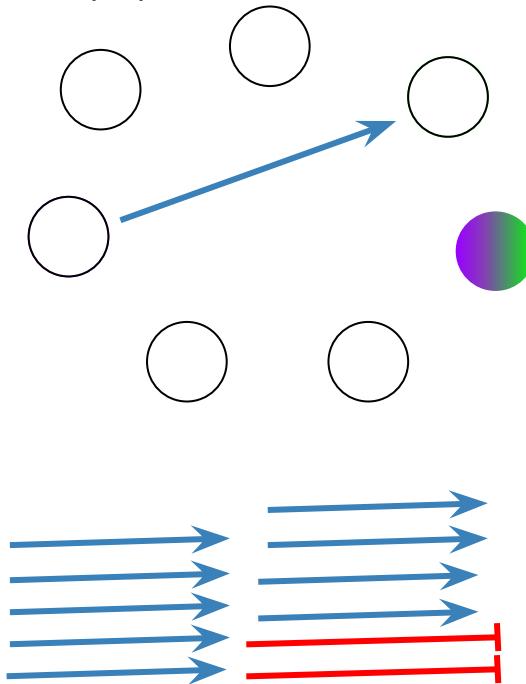


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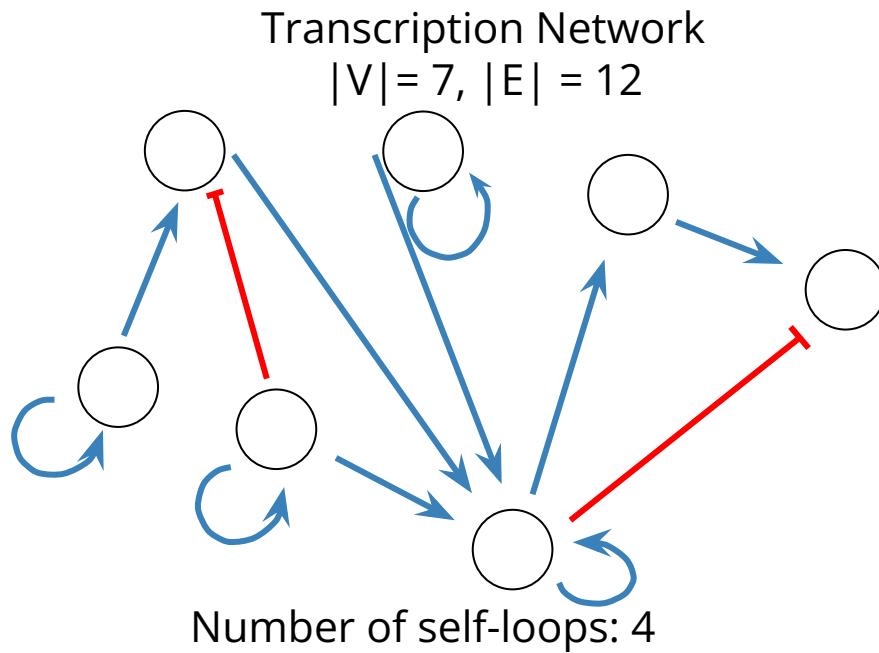


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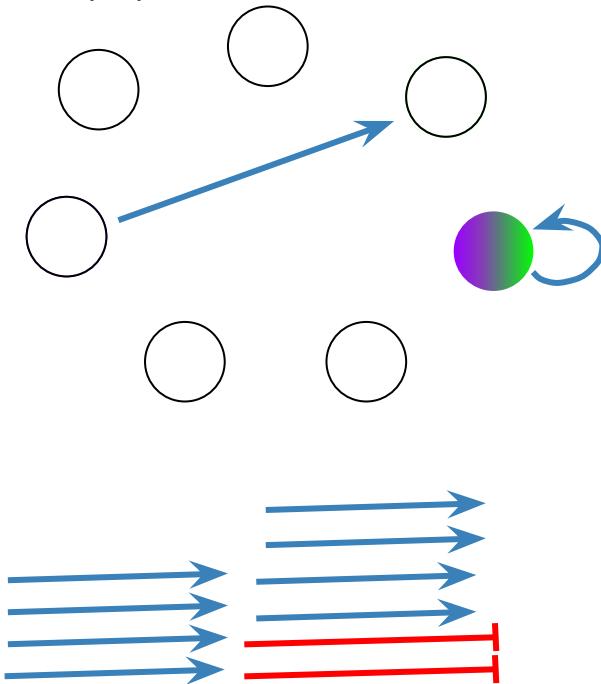


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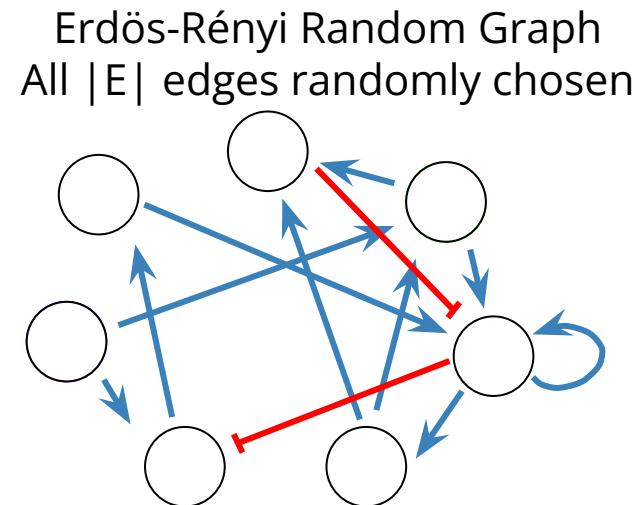
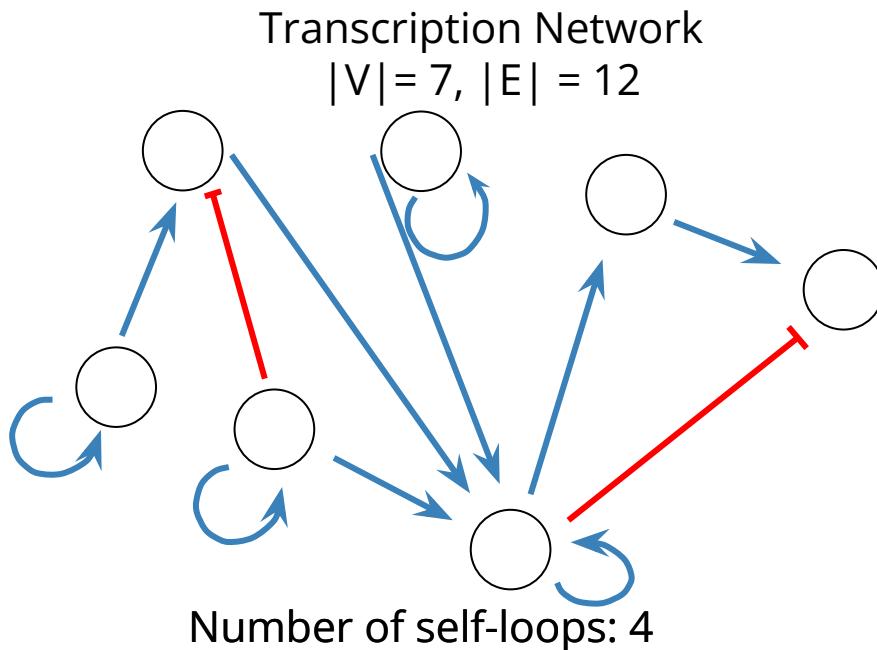


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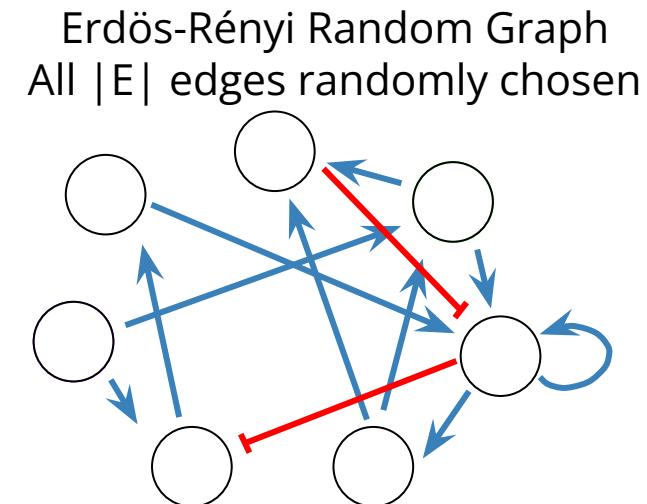
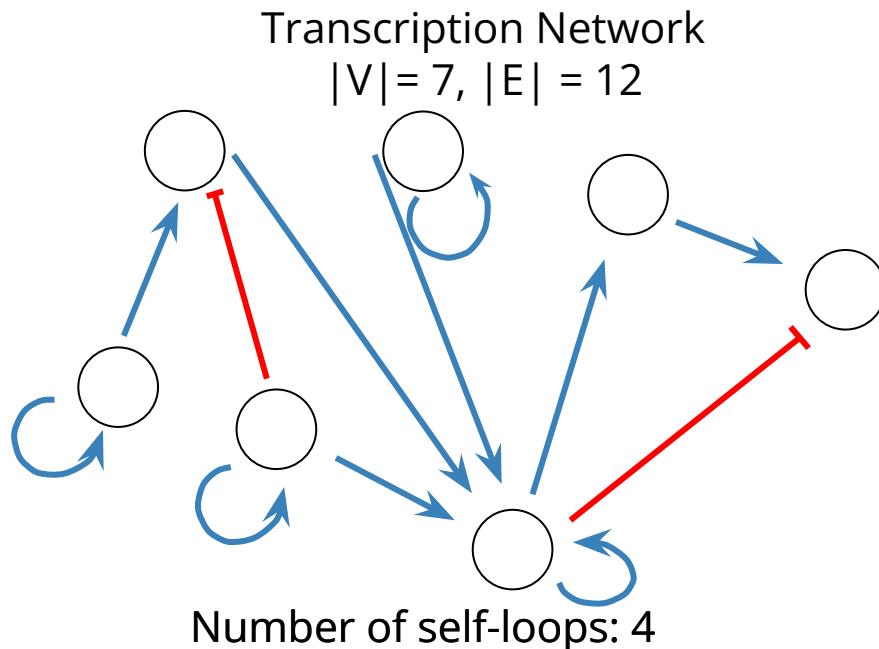
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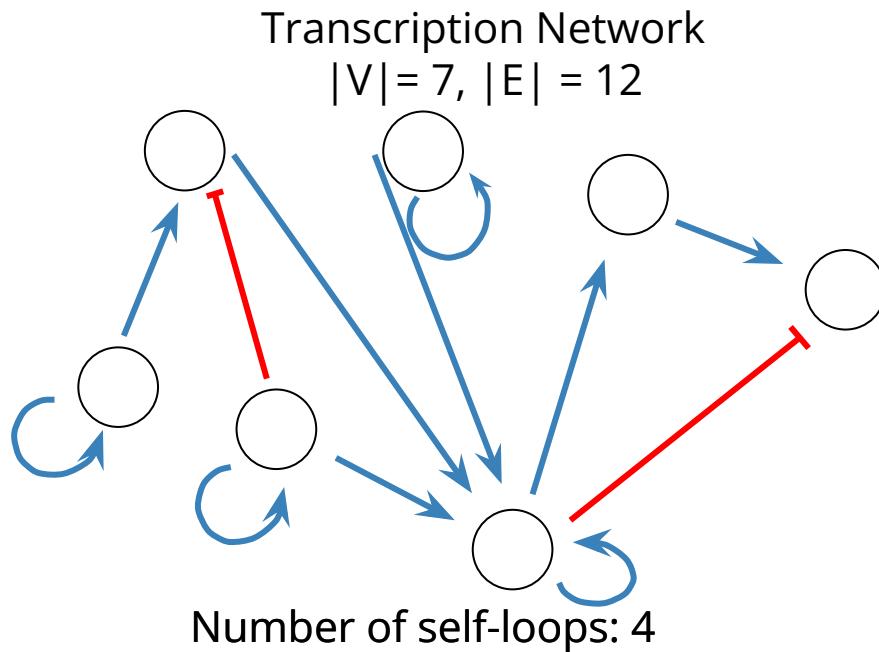
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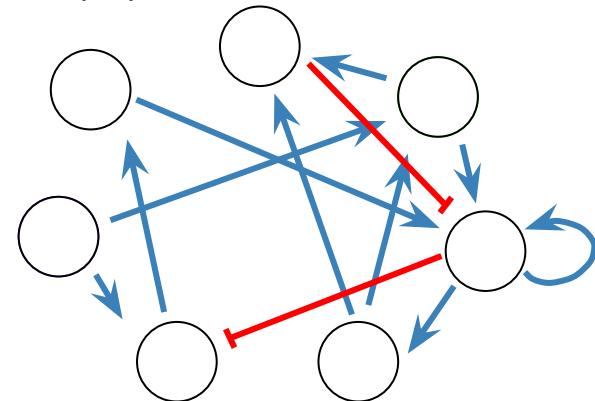
Chance of self loop:  $1/|V| = 0.14$

# Motifs

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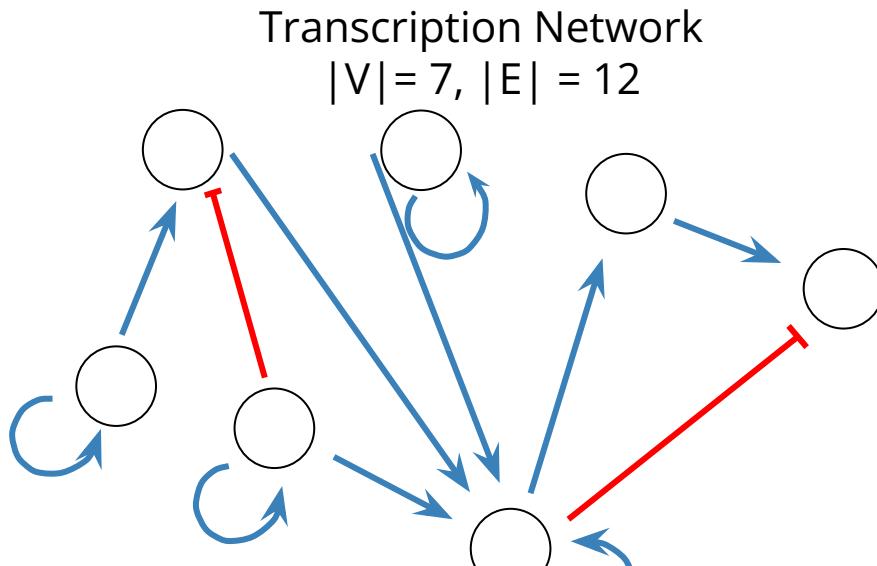


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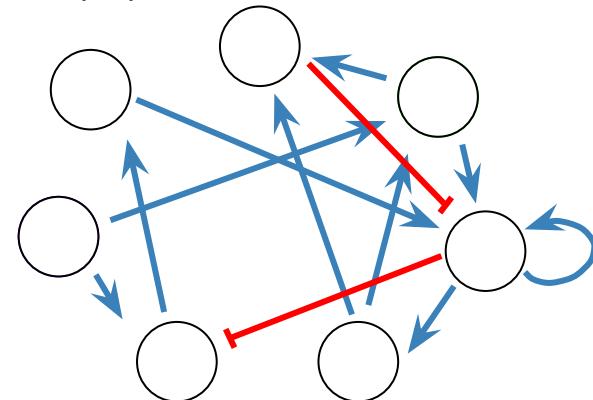
# Motifs

*Motifs* are subgraphs that appear more frequently in biological networks than random networks.



Number of self-loops: 4  
Self-loops are a network motif!  
 $p = 0.028$

Erdős-Rényi Random Graph  
All  $|E|$  edges randomly chosen



Chance of self loop:  $1/|V| = 0.14$   
 $E[\# \text{ of self loops}] = |E|/|V| = 1.7$   
 $\sigma[\# \text{ of self loops}] \approx 1.2$

# Network Dynamics

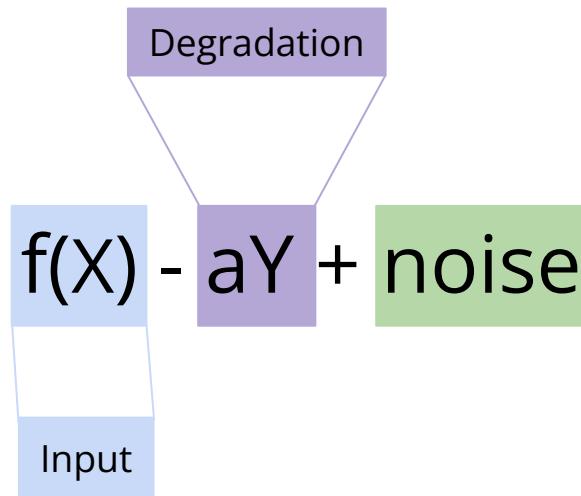
# Network Dynamics



“ X activates Y ”

$$\frac{dX}{dt} = 0$$

$$\frac{dY}{dt} = f(X) - aY + \text{noise}$$



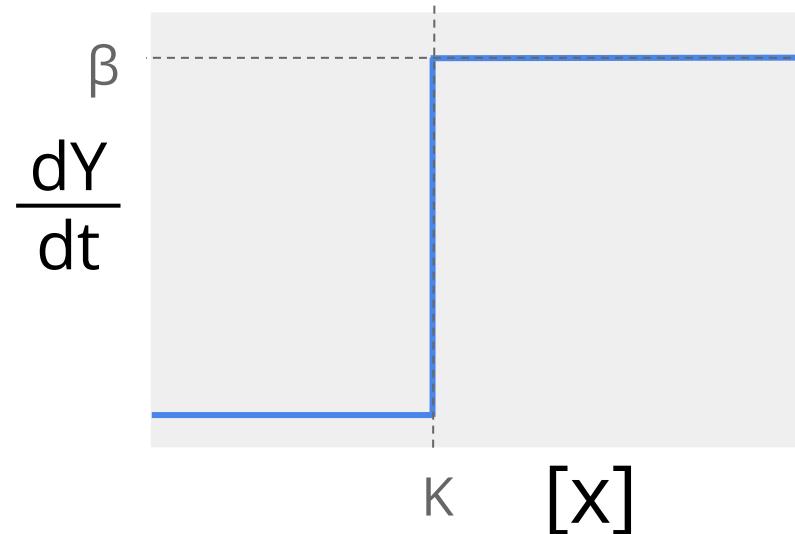
# Input Functions



“ X activates Y ”

## Step function

$$f(X) = \beta \Theta(X > K)$$



# Input Functions

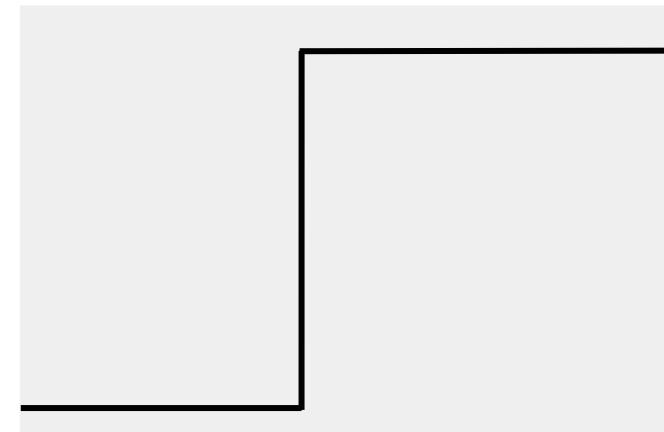


“ X activates Y ”

**Step function**

$$f(X) = \beta \Theta(X > K)$$

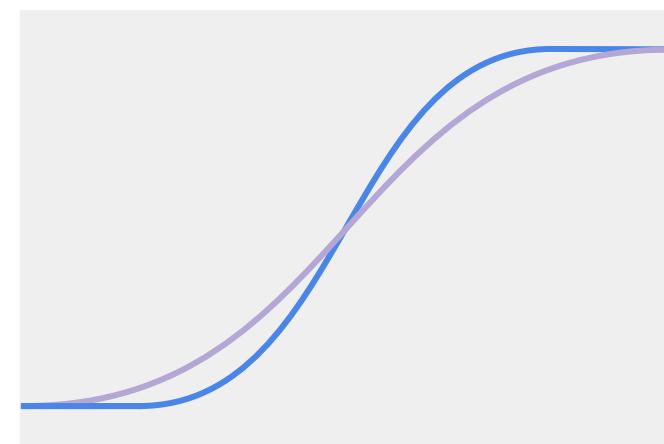
$$\frac{dY}{dt}$$



**Hill function**

$$f(X) = \beta \frac{(X)^n}{K^n + (X)^n}$$

$$\frac{dY}{dt}$$

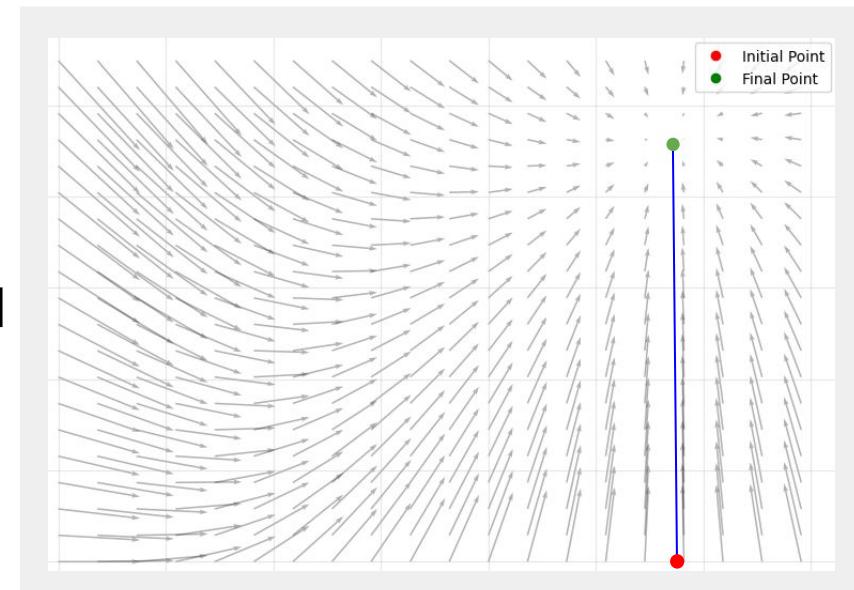
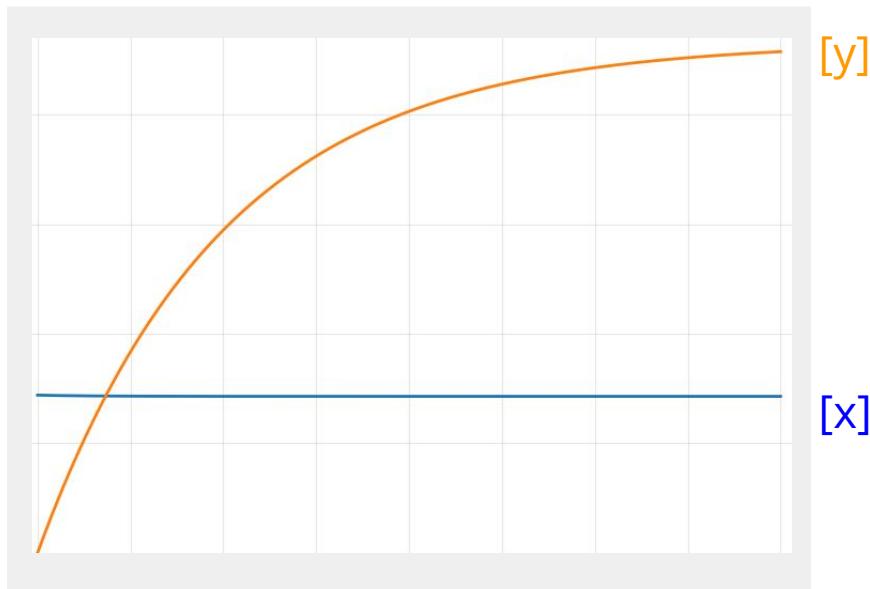


$n = 4$   
 $n = 2$

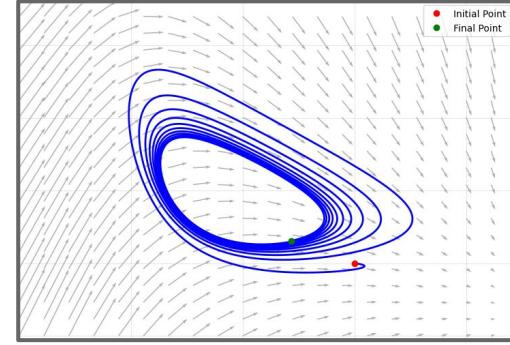
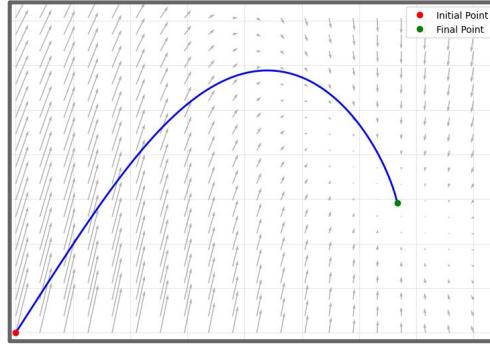
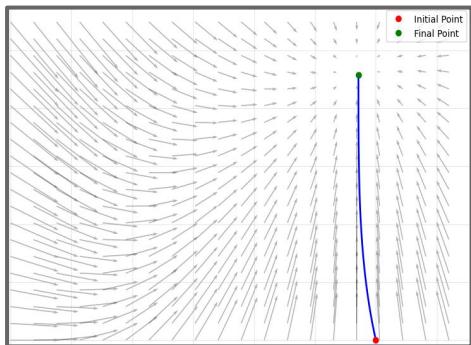
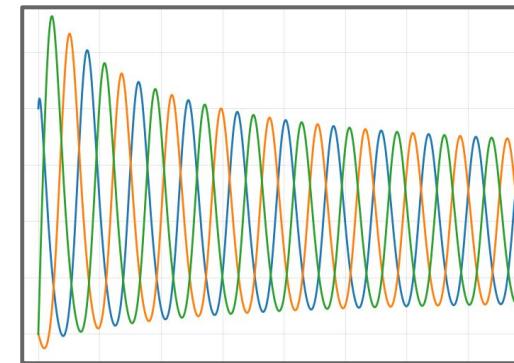
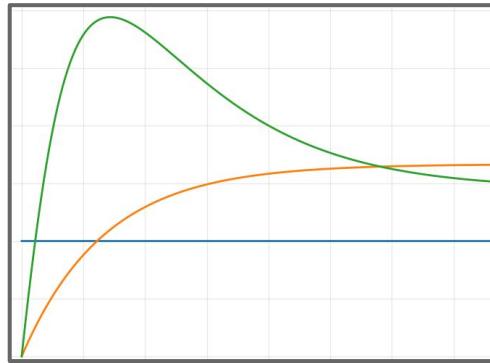
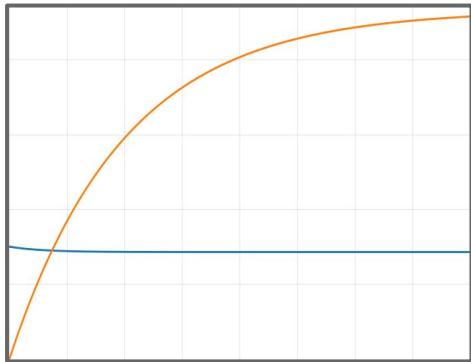
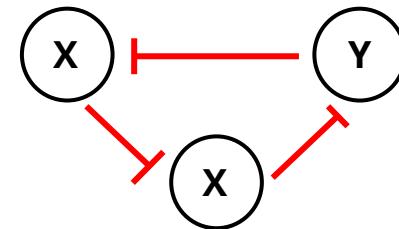
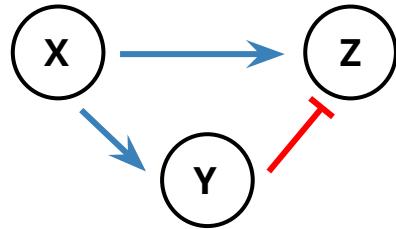
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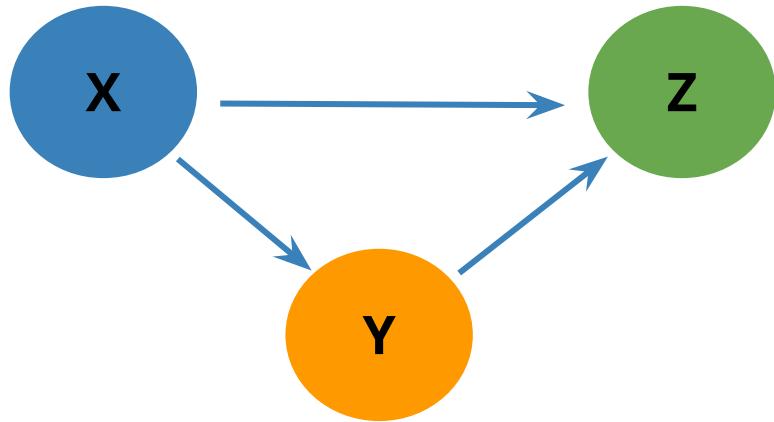
“ X activates Y ”



# Math Modeling

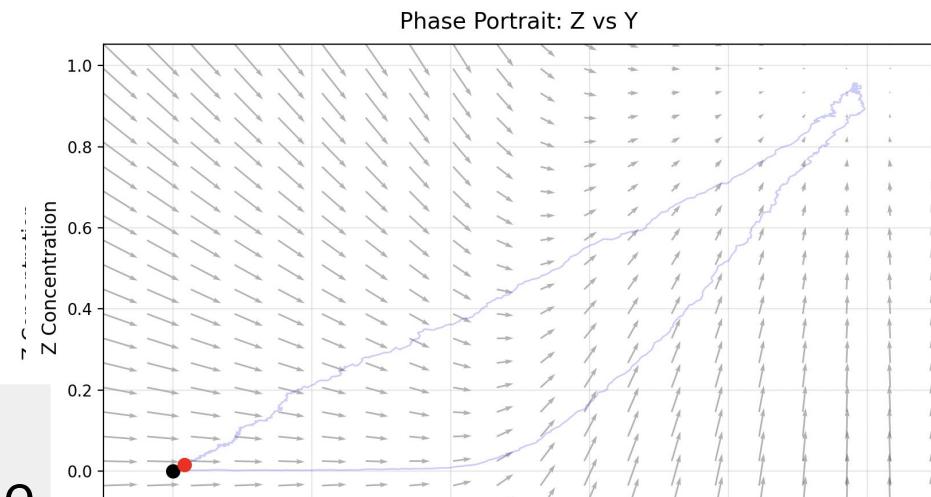
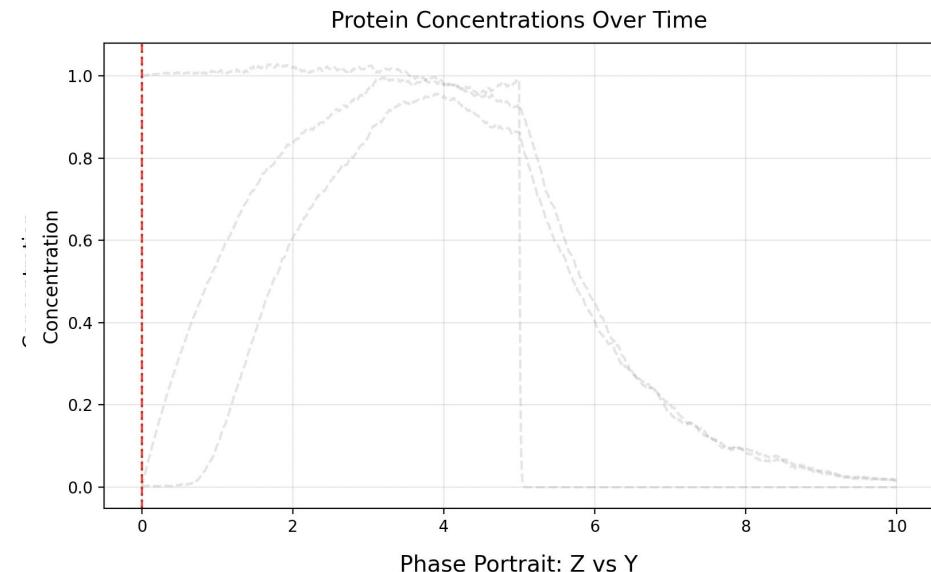


# The Feedforward Loop Motif

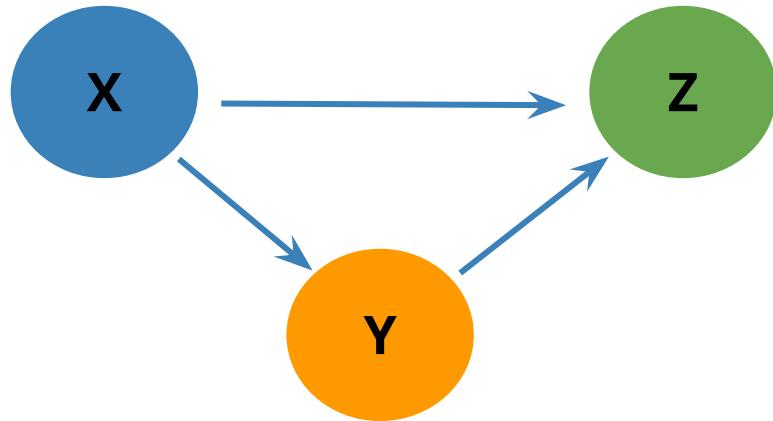


$$\frac{dY}{dt} = \beta \frac{X^n}{K^n + X^n} - \alpha Y + \text{noise}$$

$$\frac{dZ}{dt} = \beta \frac{X^n}{K^n + X^n} \frac{Y^n}{K^n + Y^n} - \alpha Z + \text{noise}$$

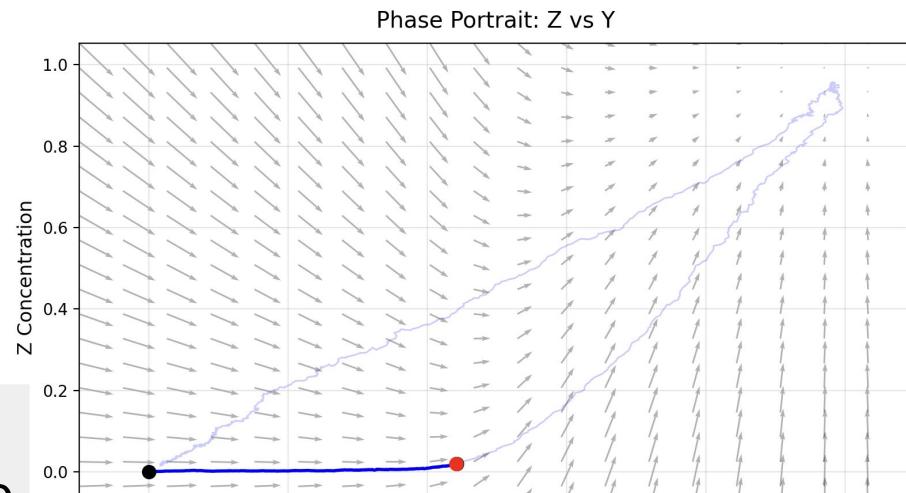
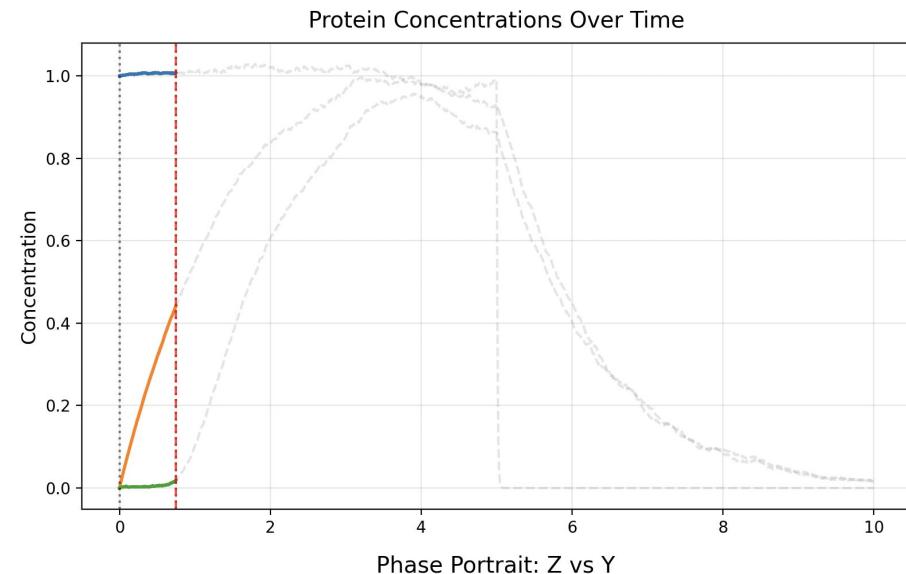


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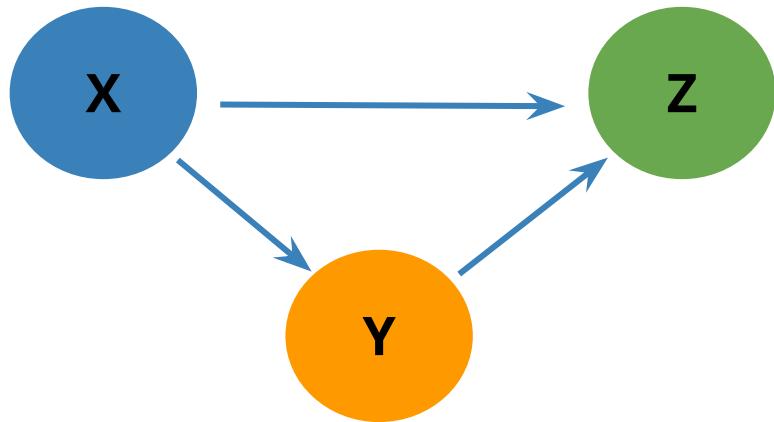


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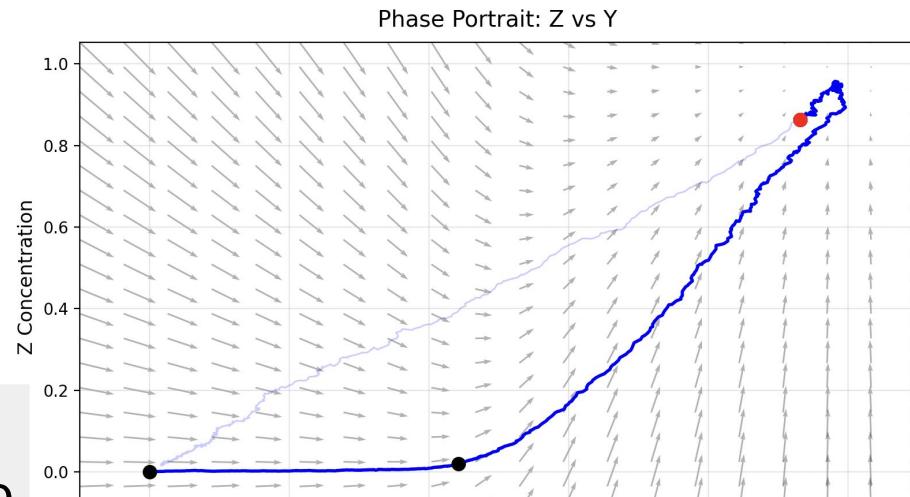
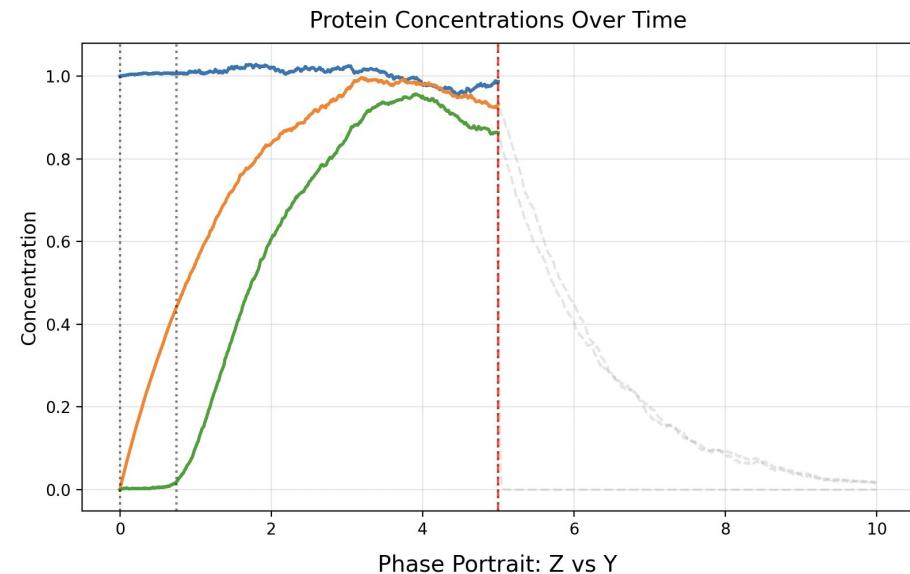


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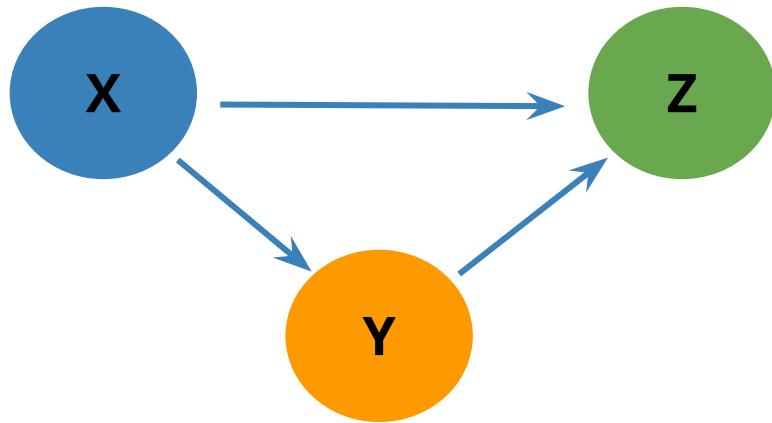


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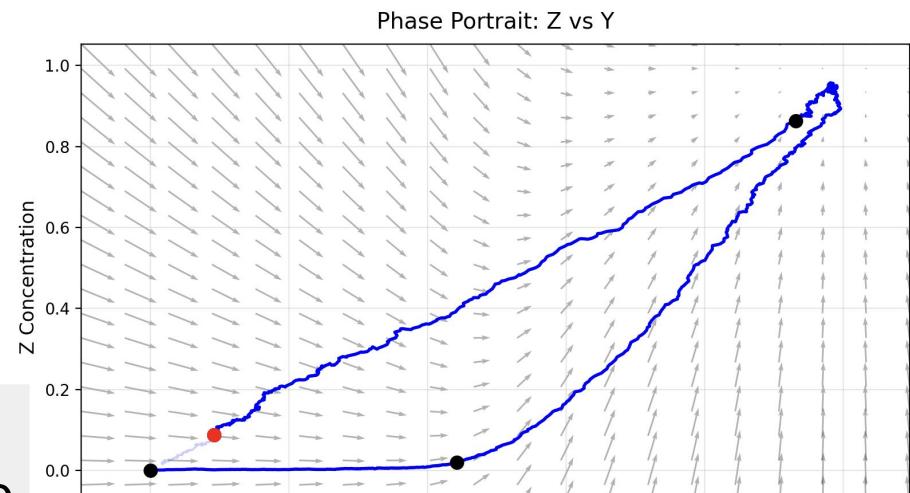
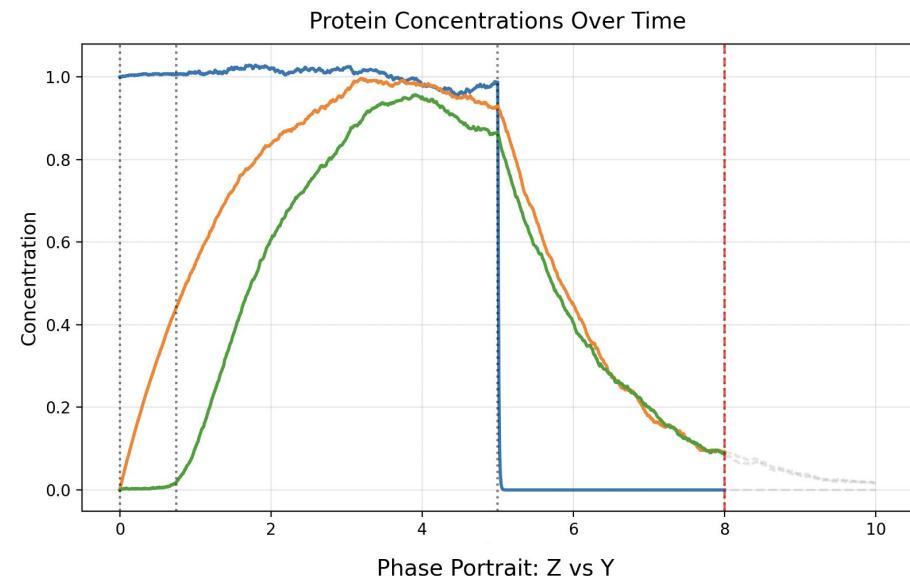


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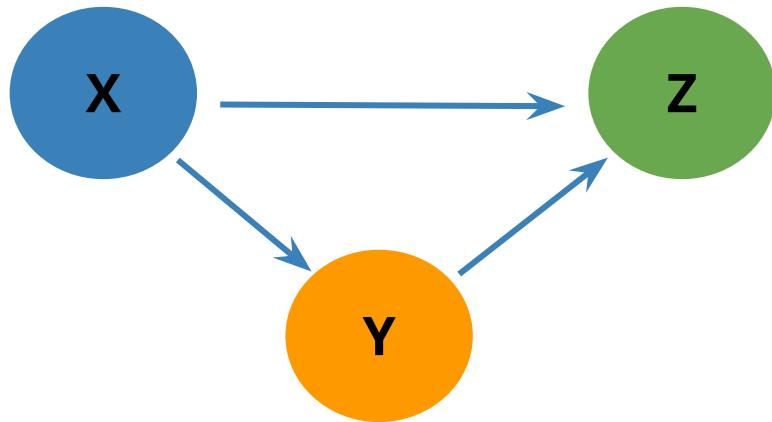


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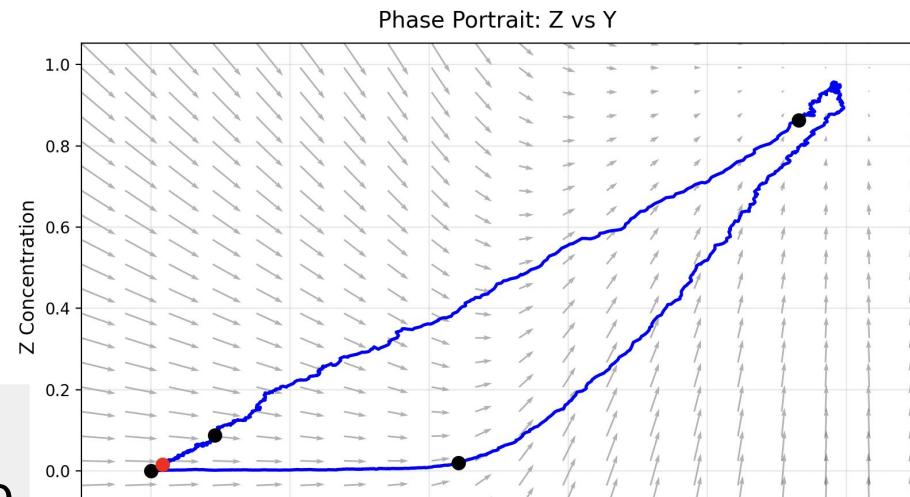
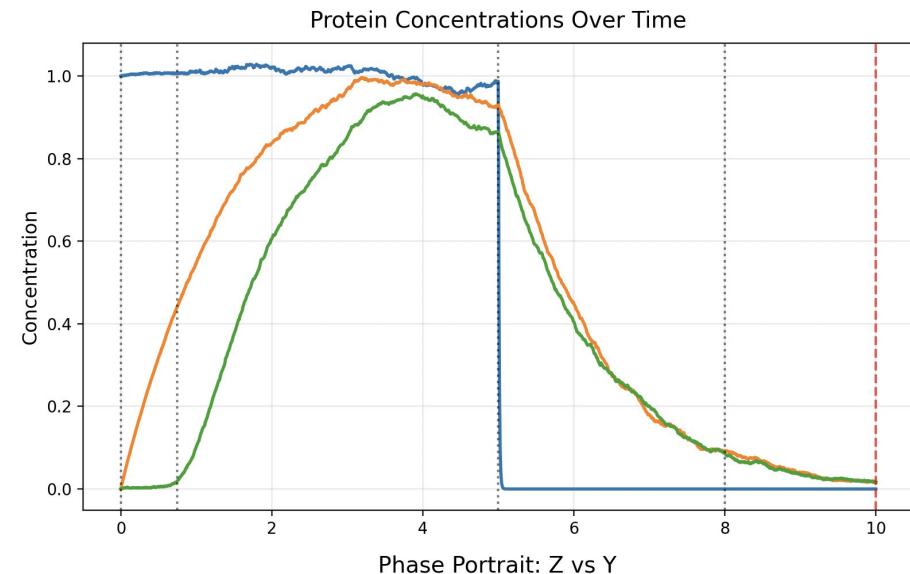


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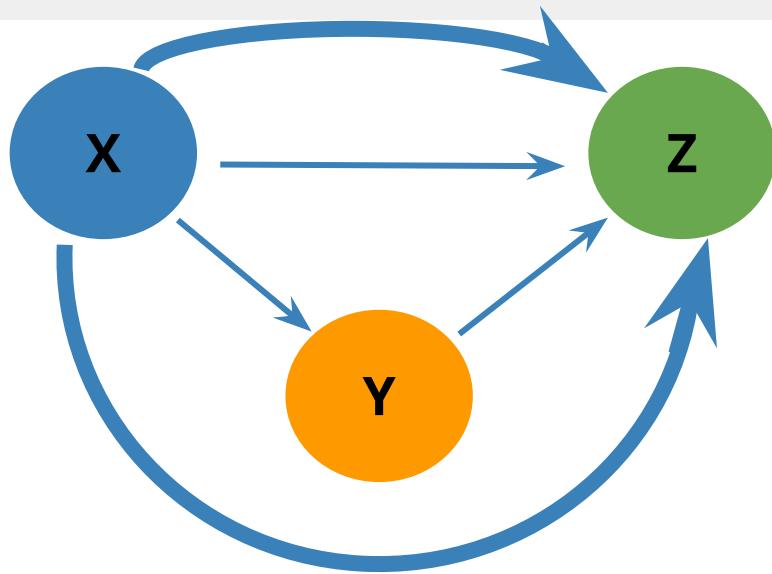


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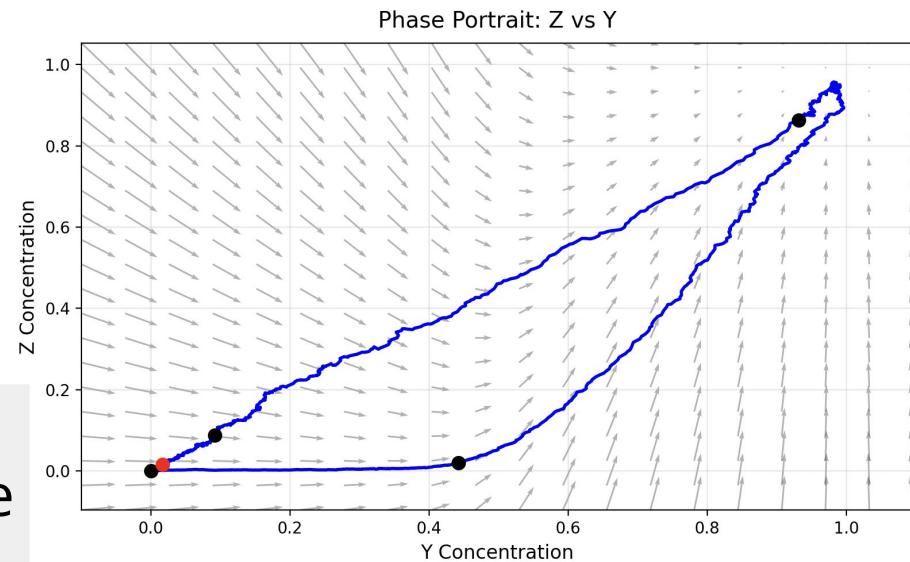
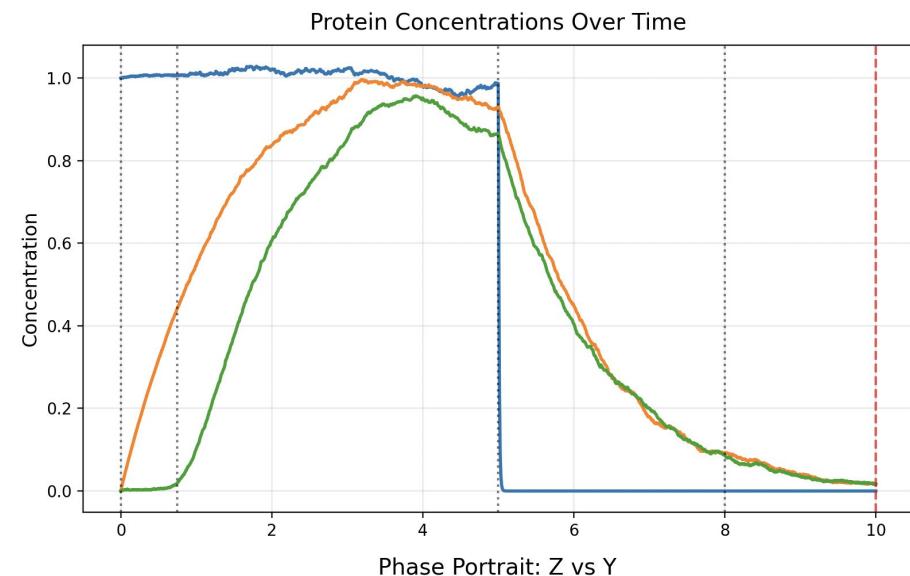
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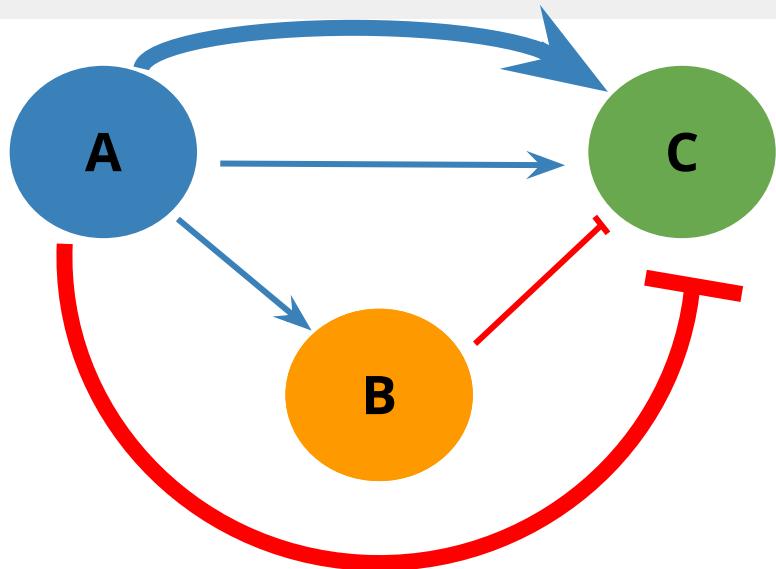
Coherent FFL

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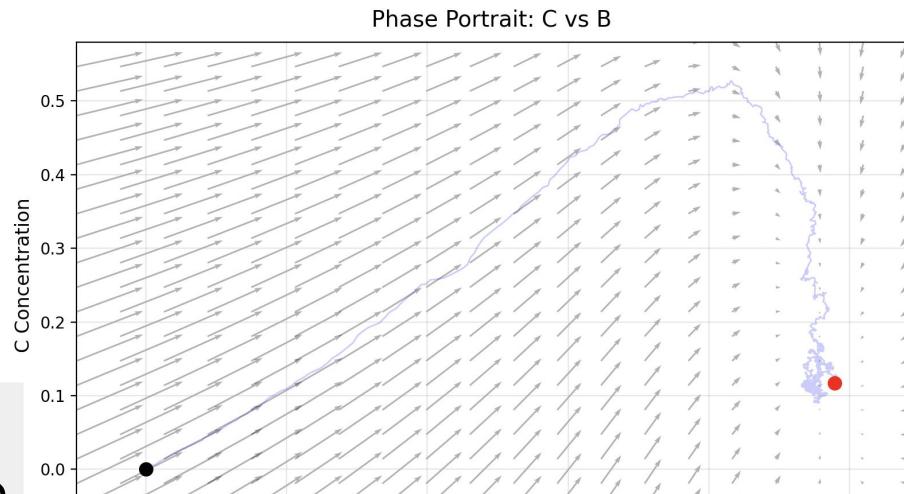
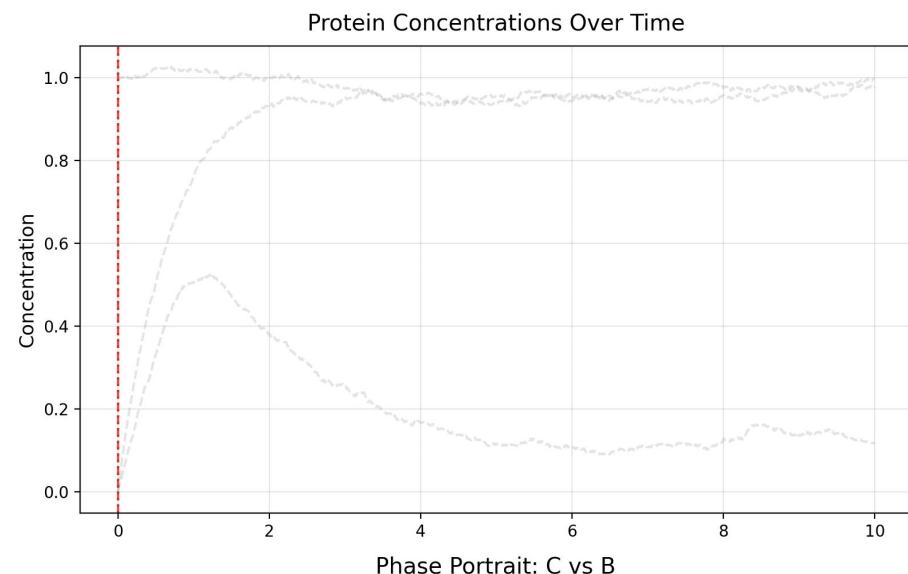
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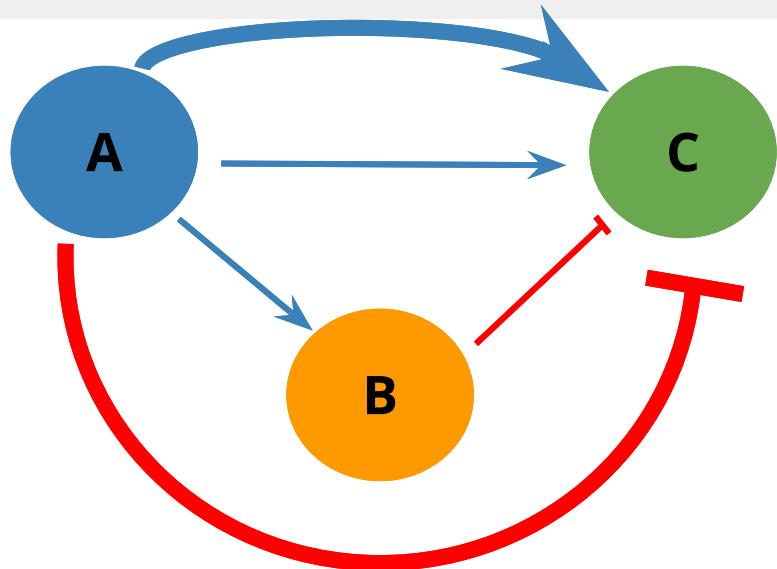
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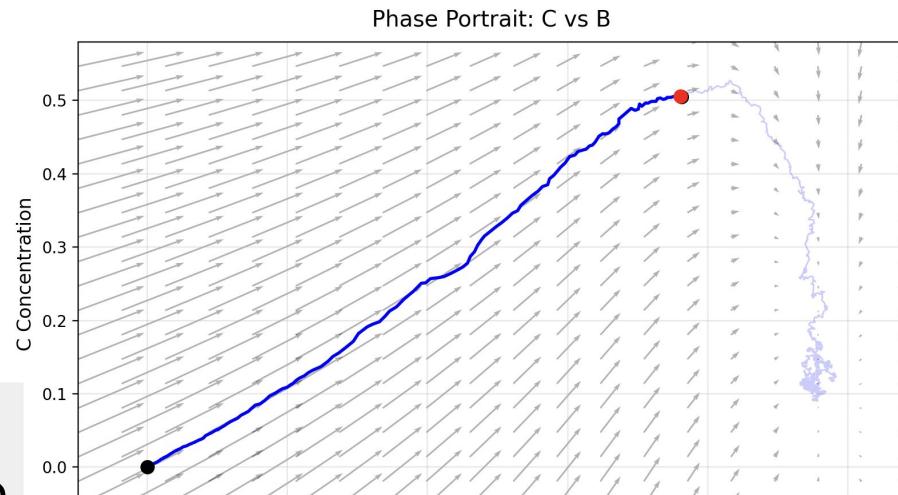
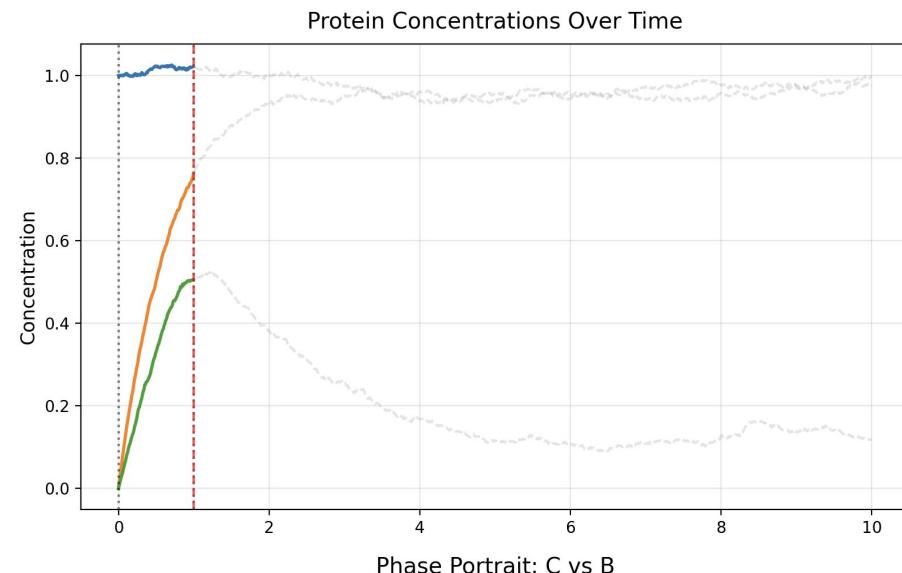
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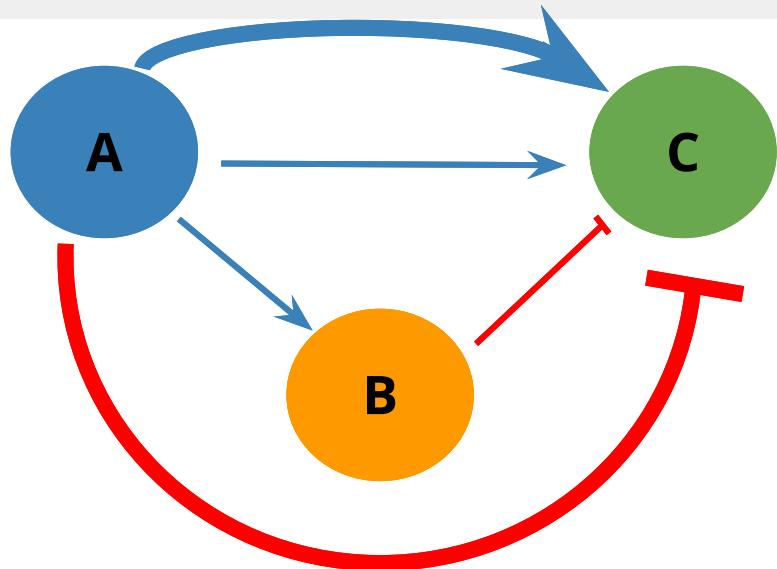
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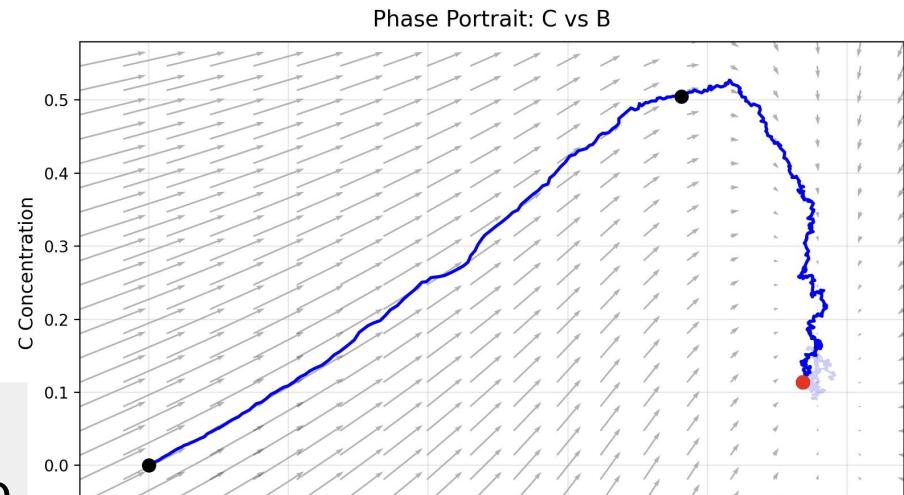
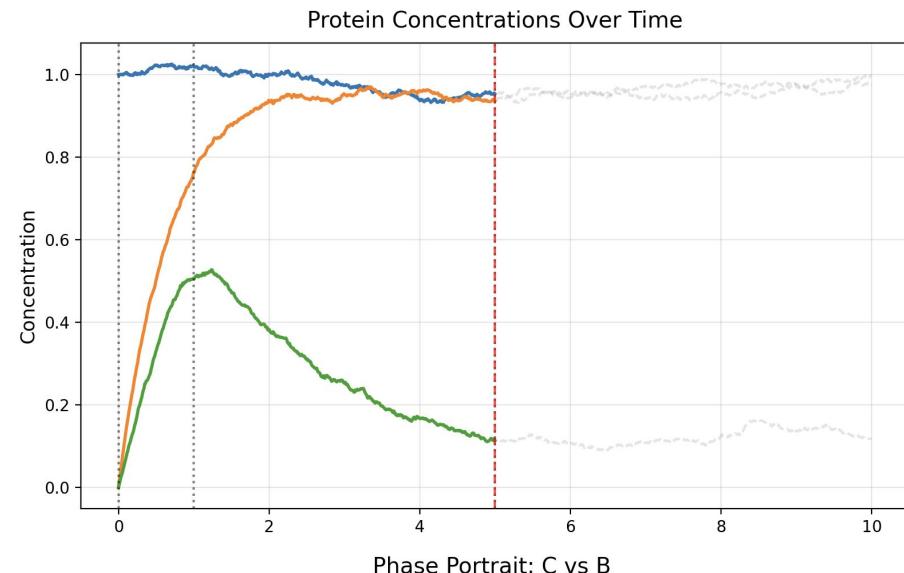
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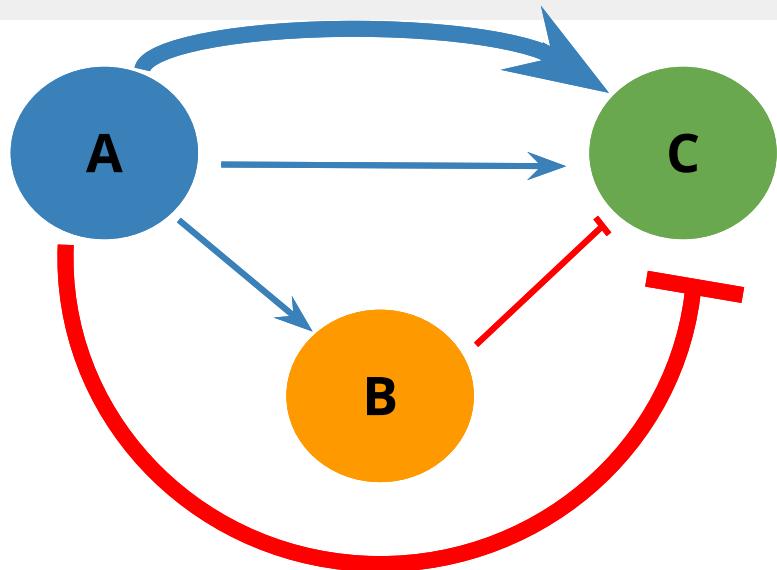
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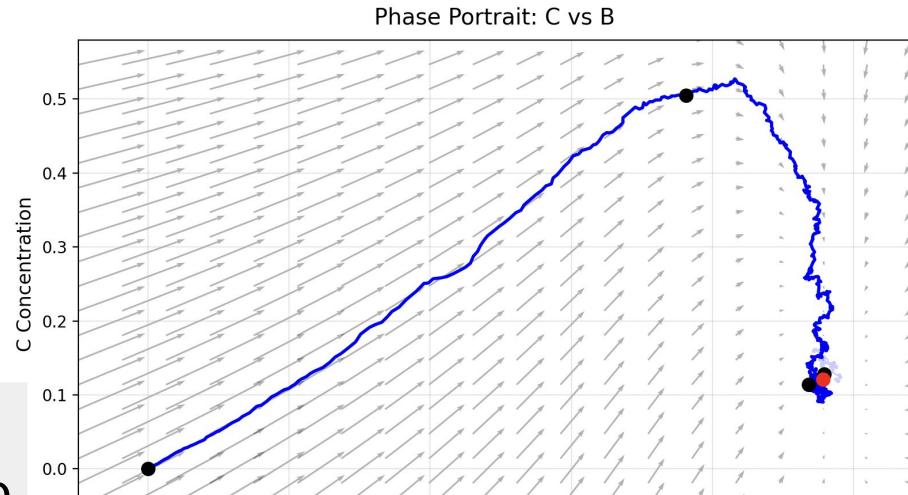
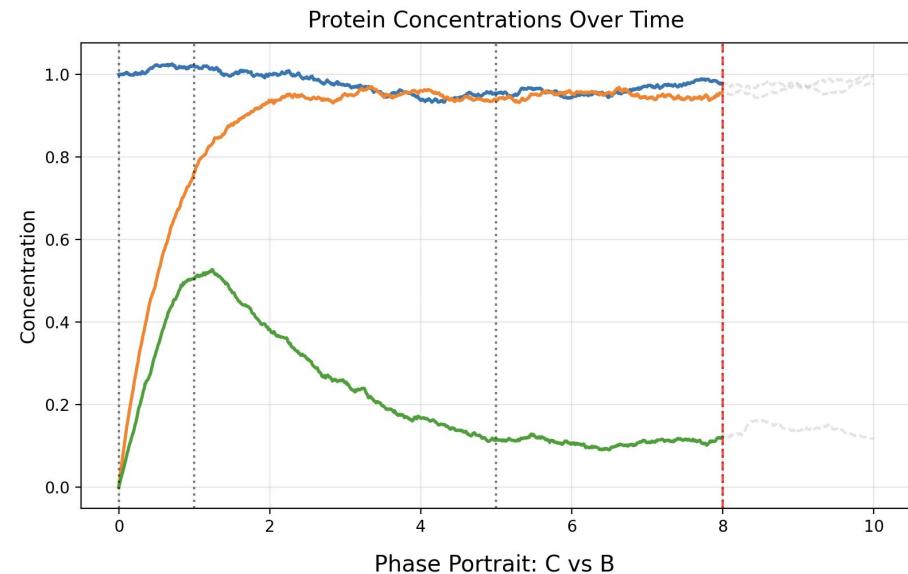
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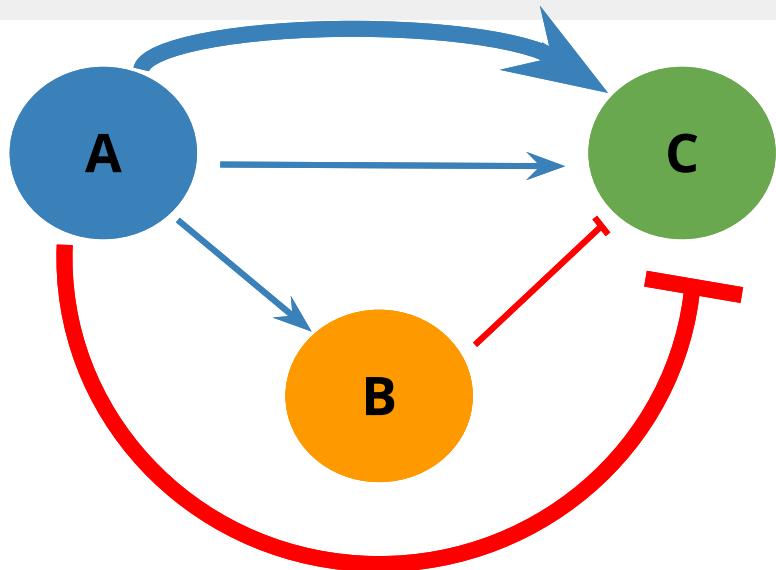
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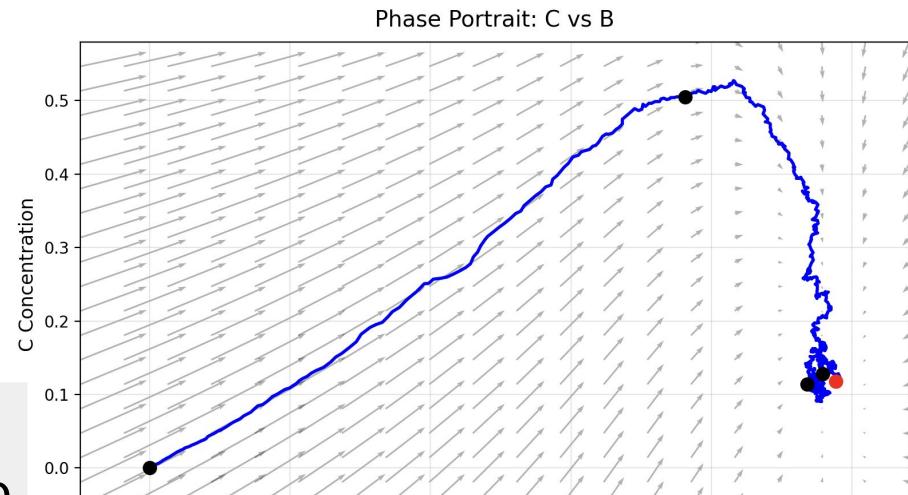
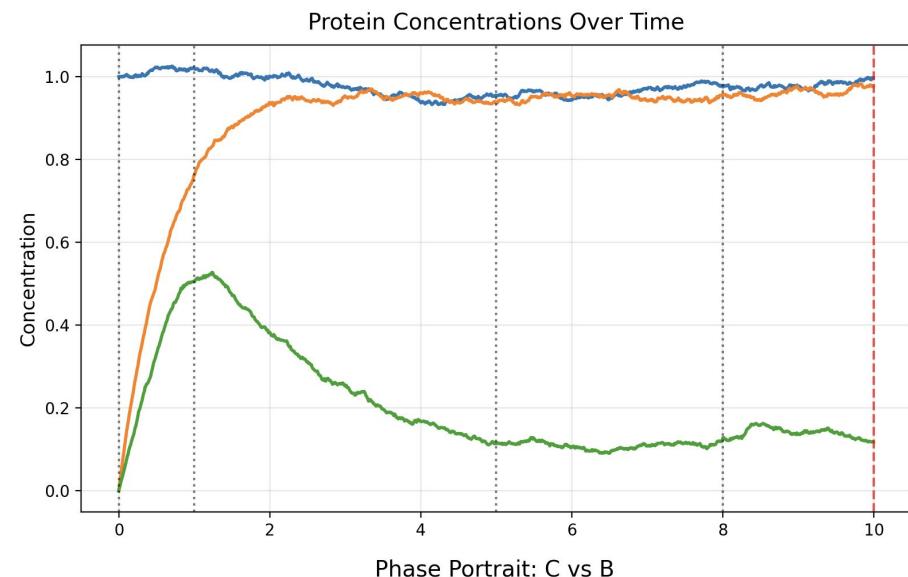
# The Feedforward Loop Motif



Incoherent FFL

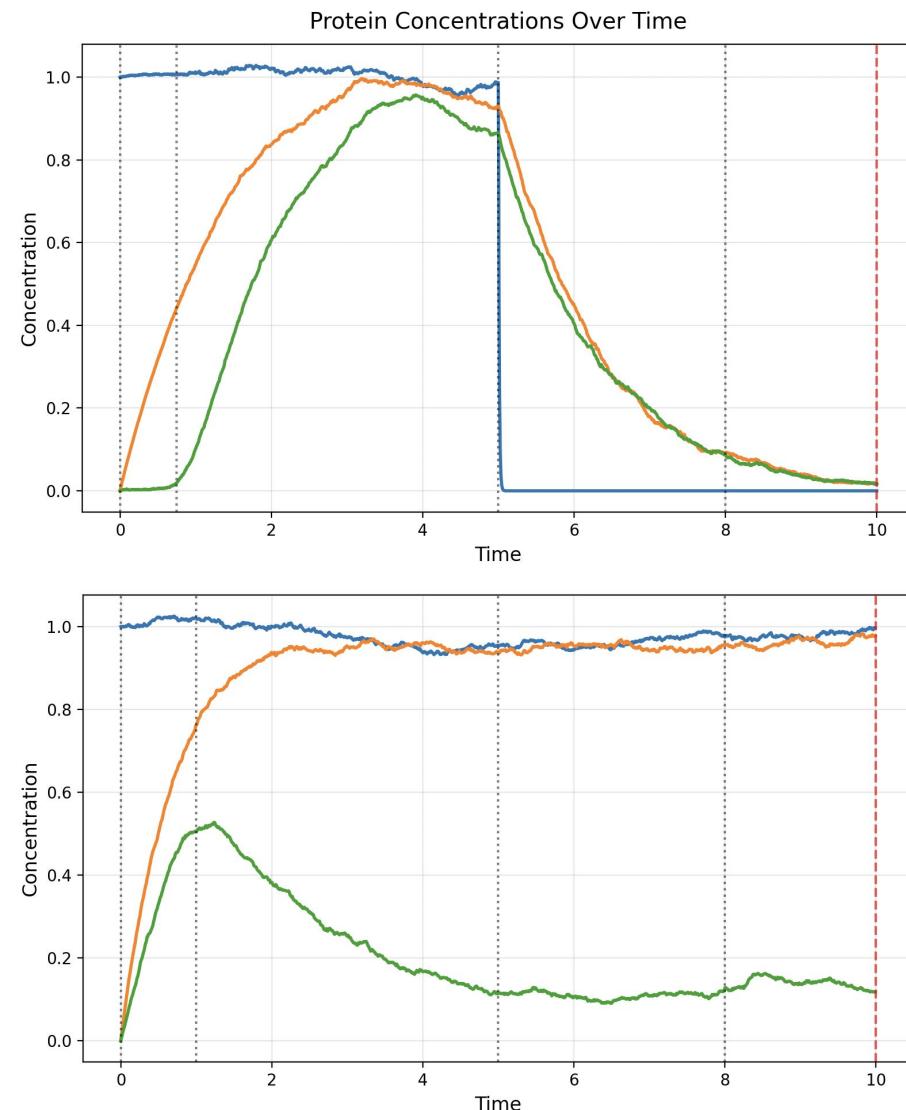
$$\frac{dY}{dt} = \beta \frac{X^n}{K^n + X^n} - \alpha Y + \text{noise}$$

$$\frac{dZ}{dt} = \beta \frac{X^n}{K^n + X^n} \frac{K^n}{K^n + Y^n} - \alpha Z + \text{noise}$$



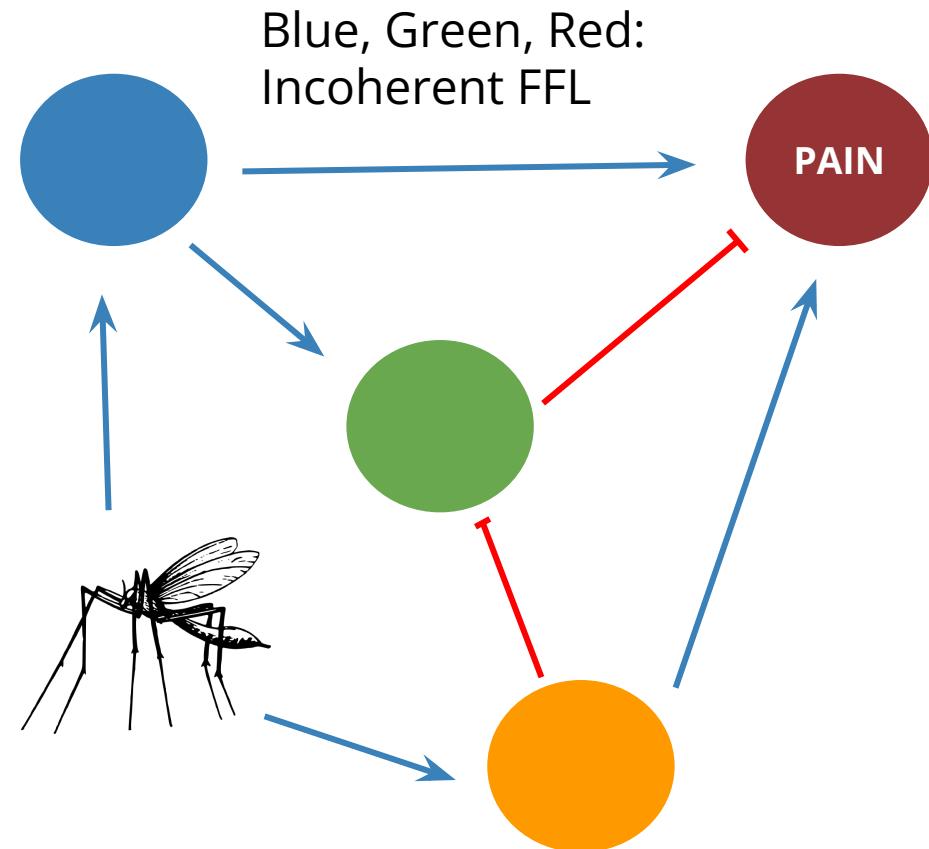
# Summary of FFLs

Coherent	Incoherent
Delay	Pulse
Slows response	Speeds response
Differential On/Off	Biphasic Response



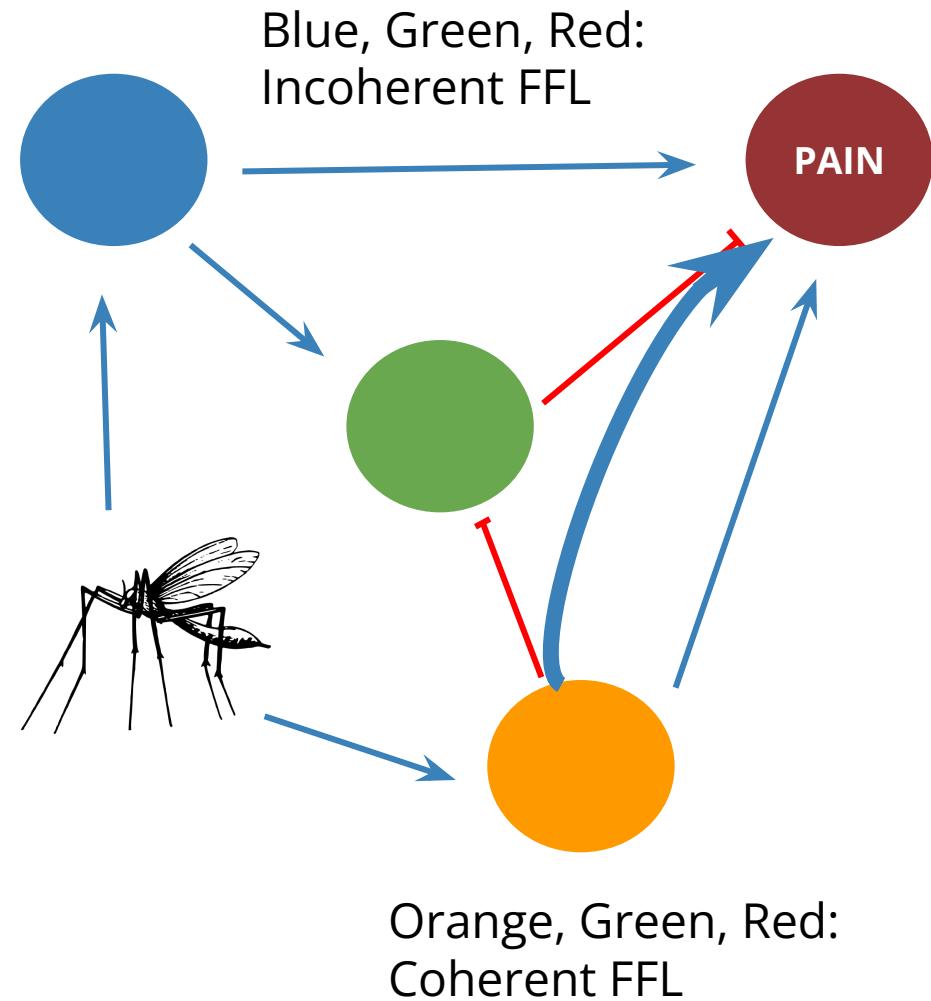
# Pain Sensation with FFLs

Coherent	Incoherent
Delay	Pulse
Slows response	Speeds response
Differential On/Off	Biphasic Response



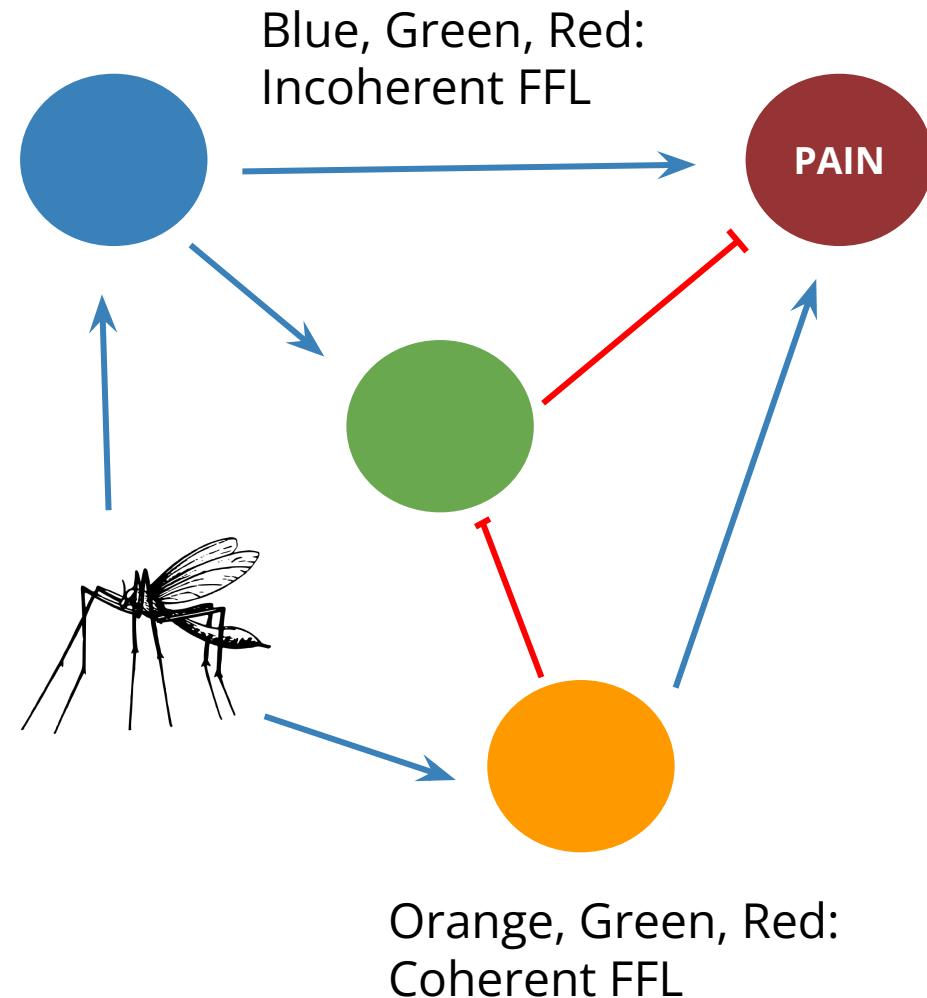
# Pain Sensation with FFLs

Coherent	Incoherent
Delay	Pulse
Slows response	Speeds response
Differential On/Off	Biphasic Response

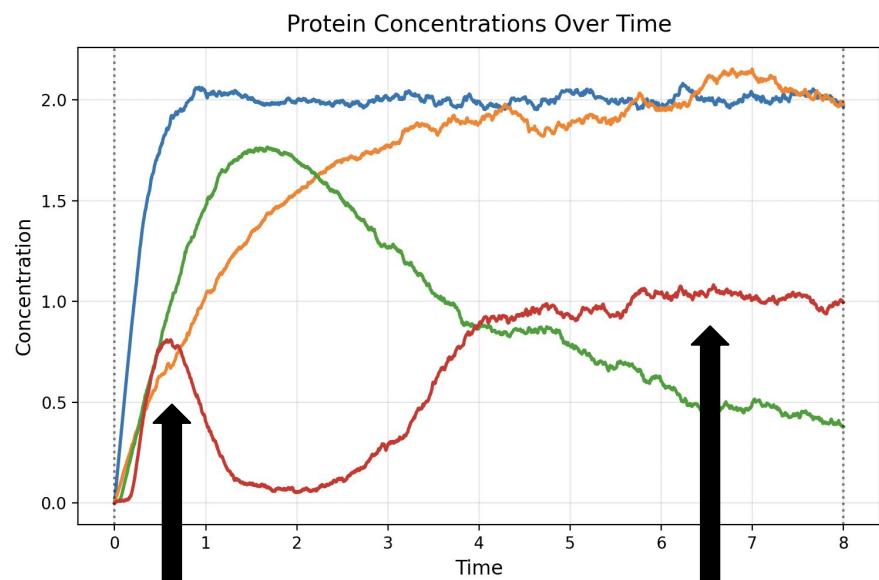


# Pain Sensation with FFLs

Coherent	Incoherent
Delay	Pulse
Slows response	Speeds response
Differential On/Off	Biphasic Response

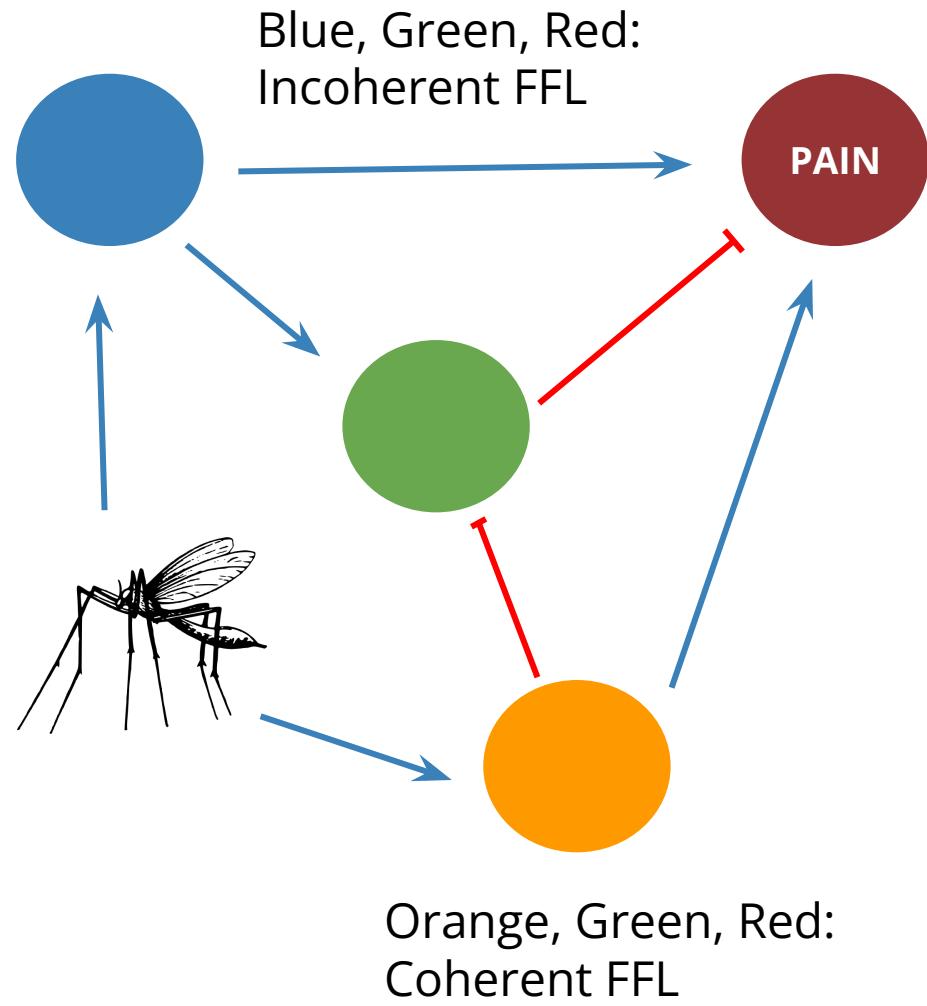


# Pain Sensation with FFLs



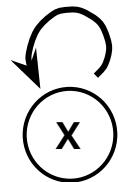
Initial Pulse:  
Temporary,  
Sharp Pain

# Equilibrium: Dull, Throbbing Pain



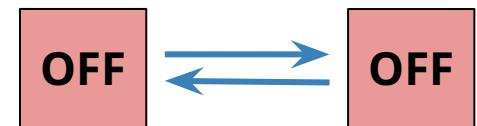
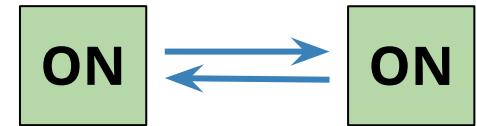
# Feedback Loops

# Feedback Loops



# Feedback Loops

Double-positive feedback loop

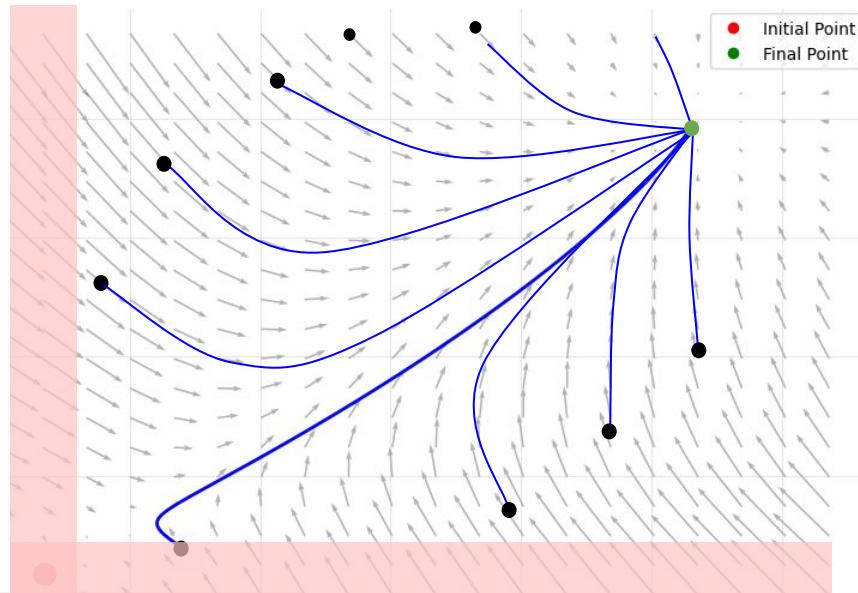


$$\frac{dX}{dt} = \beta \frac{(Y)^n}{K^n + (Y)^n} - \alpha X$$

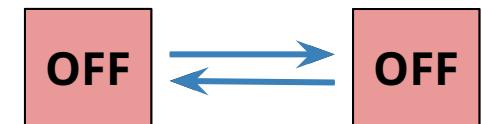
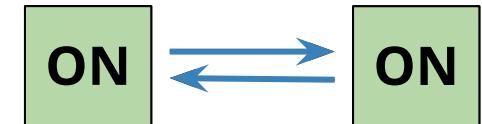
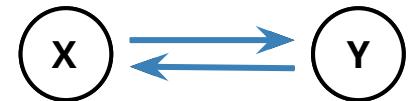
$$\frac{dY}{dt} = \beta \frac{(X)^n}{K^n + (X)^n} - \alpha Y$$

# Feedback Loops

## Double-positive feedback loop



stable point :  
 $[x]=[y]=\text{OFF}$

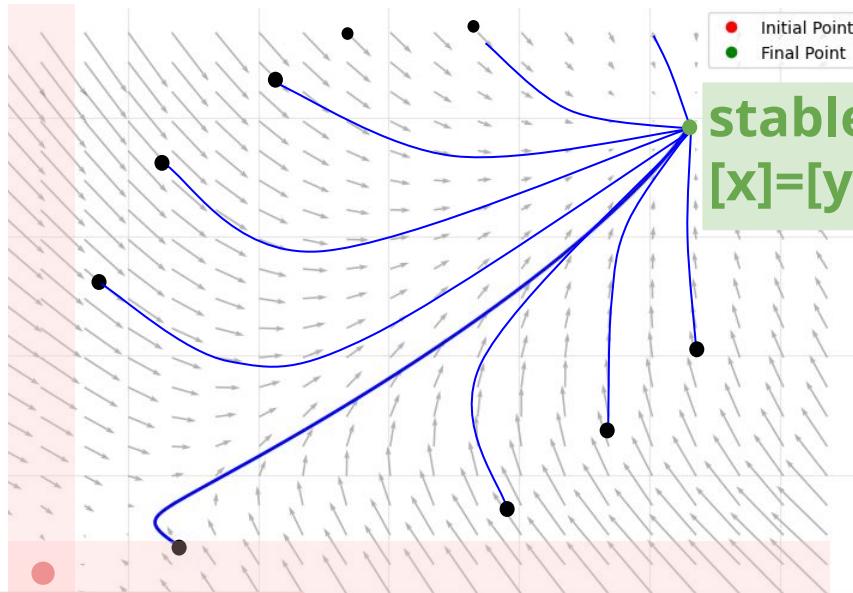


$$\frac{dX}{dt} = \beta \frac{(Y)^n}{K^n + (Y)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(X)^n}{K^n + (X)^n} - \alpha Y$$

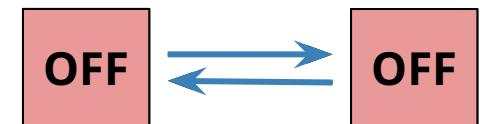
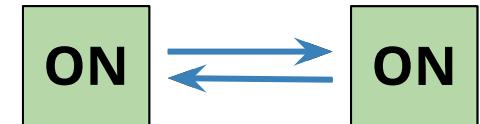
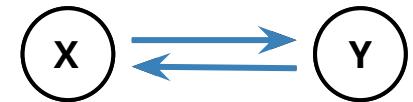
# Feedback Loops

## Double-positive feedback loop



stable point :  
[x]=[y]=OFF

stable point :  
[x]=[y]=ON



$$\frac{dX}{dt} = \beta \frac{(Y)^n}{K^n + (Y)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(X)^n}{K^n + (X)^n} - \alpha Y$$

# Feedback Loops

Double-negative feedback loop



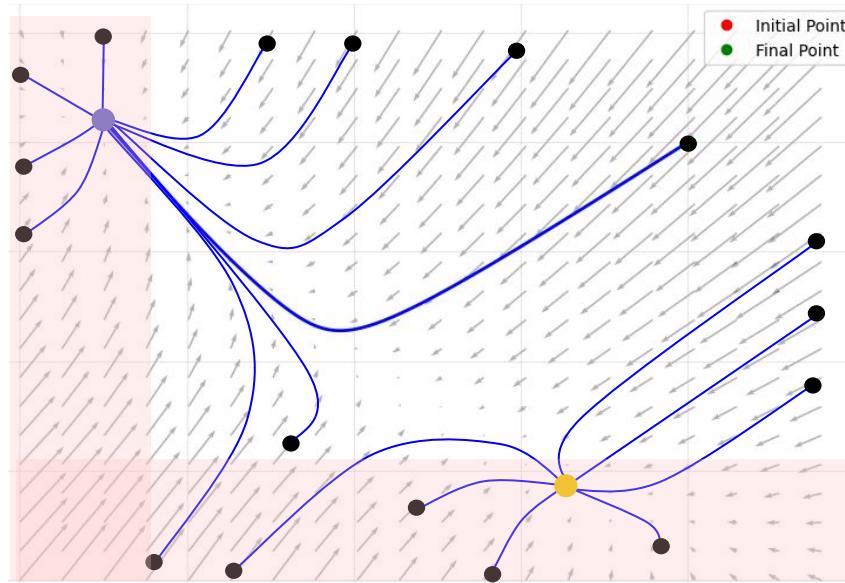
$$\frac{dX}{dt} = \beta \frac{(K)^n}{K^n + (Y)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(K)^n}{K^n + (X)^n} - \alpha Y$$

# Feedback Loops

## Double-negative feedback loop

[X]=OFF  
[Y] =ON

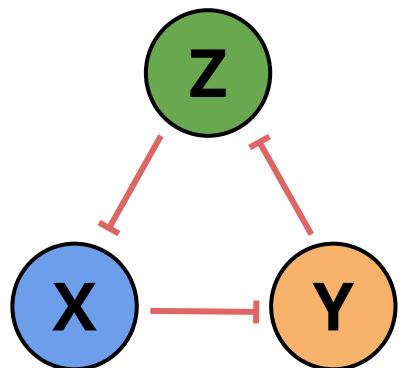


$$\frac{dX}{dt} = \beta \frac{(K)^n}{K^n + (Y)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(K)^n}{K^n + (X)^n} - \alpha Y$$

# Oscillation

# The Repressilator

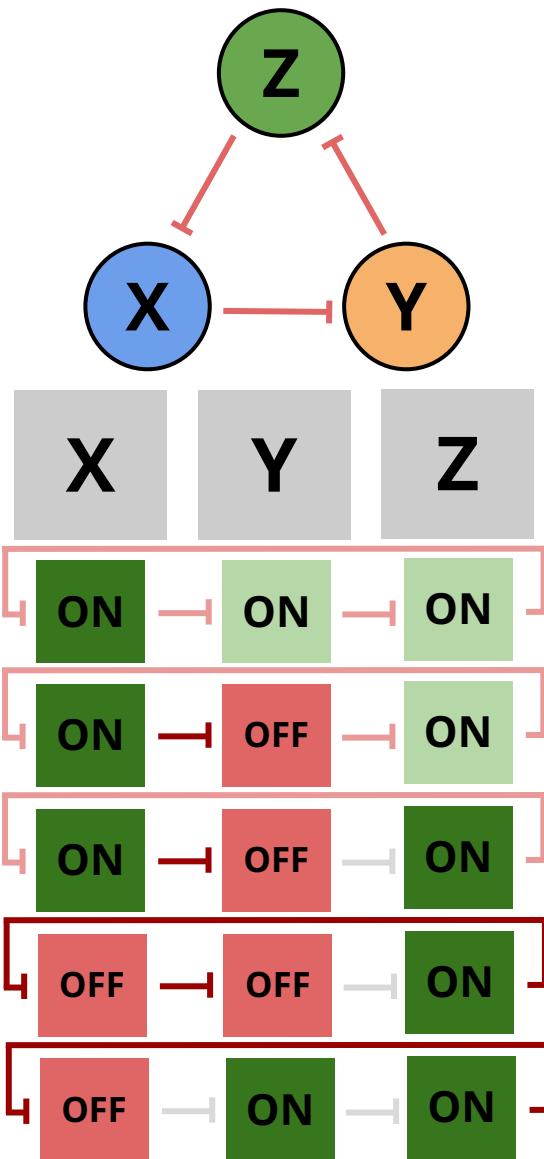


$$\frac{dX}{dt} = \beta \frac{(K)^n}{K^n + (Z)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(K)^n}{K^n + (X)^n} - \alpha Y$$

$$\frac{dZ}{dt} = \beta \frac{(K)^n}{K^n + (Y)^n} - \alpha Z$$

# The Repressilator

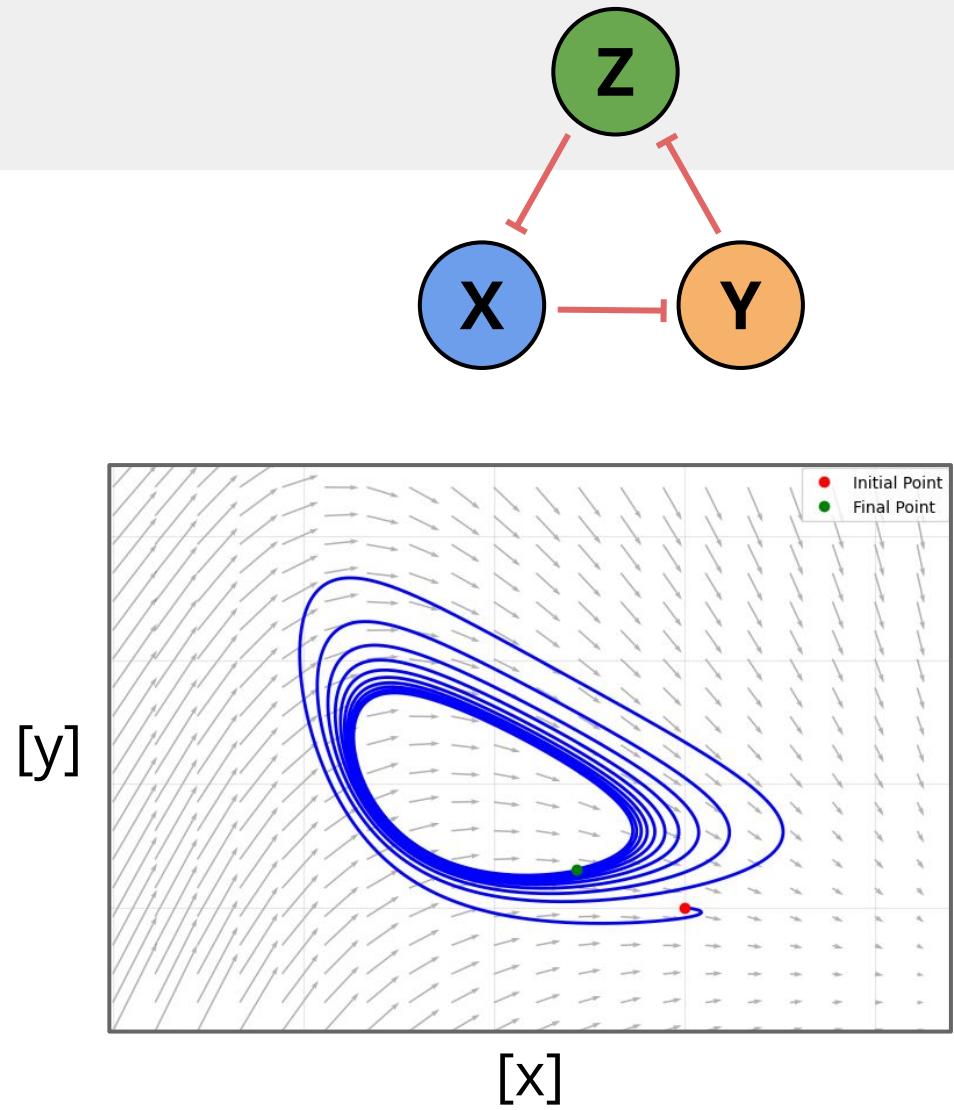
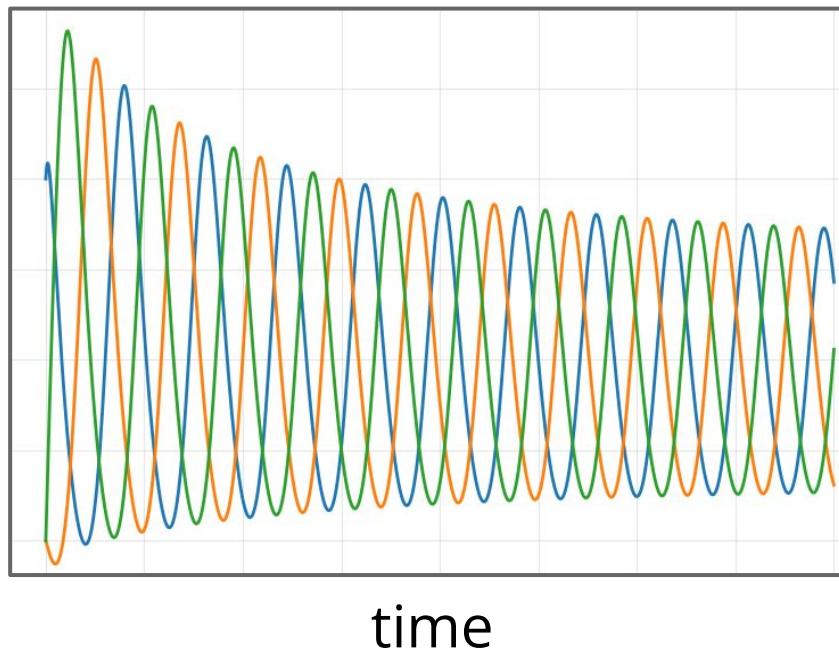


$$\frac{dX}{dt} = \beta \frac{(K)^n}{K^n + (Z)^n} - \alpha X$$

$$\frac{dY}{dt} = \beta \frac{(K)^n}{K^n + (X)^n} - \alpha Y$$

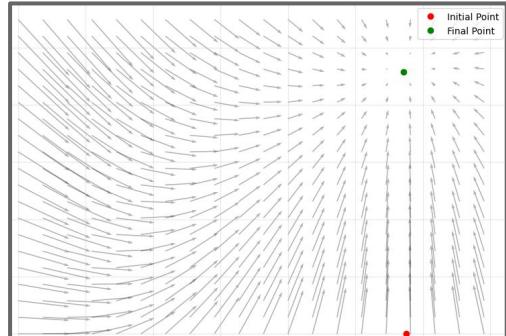
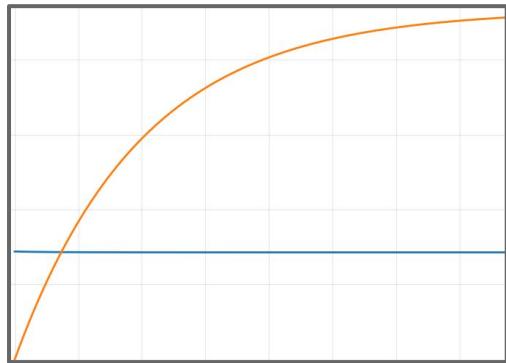
$$\frac{dZ}{dt} = \beta \frac{(K)^n}{K^n + (Y)^n} - \alpha Z$$

# The Repressilator

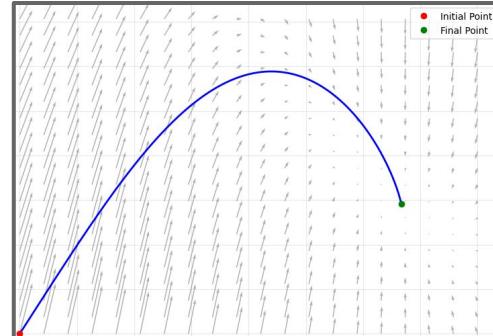
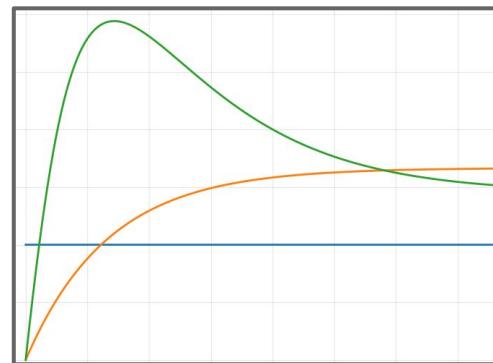
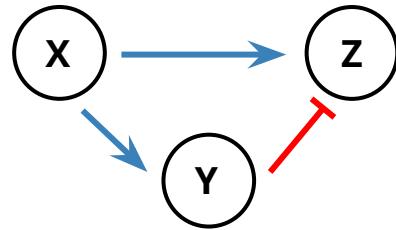


# Simple Activation   Feedforward Loop   Feedback Loop

- Not a motif



- Signal processing



- Bistability
- Oscillations

