

DISCRETE NETWORK DYNAMICS ANALYSIS USING NETWORK WORKBENCH

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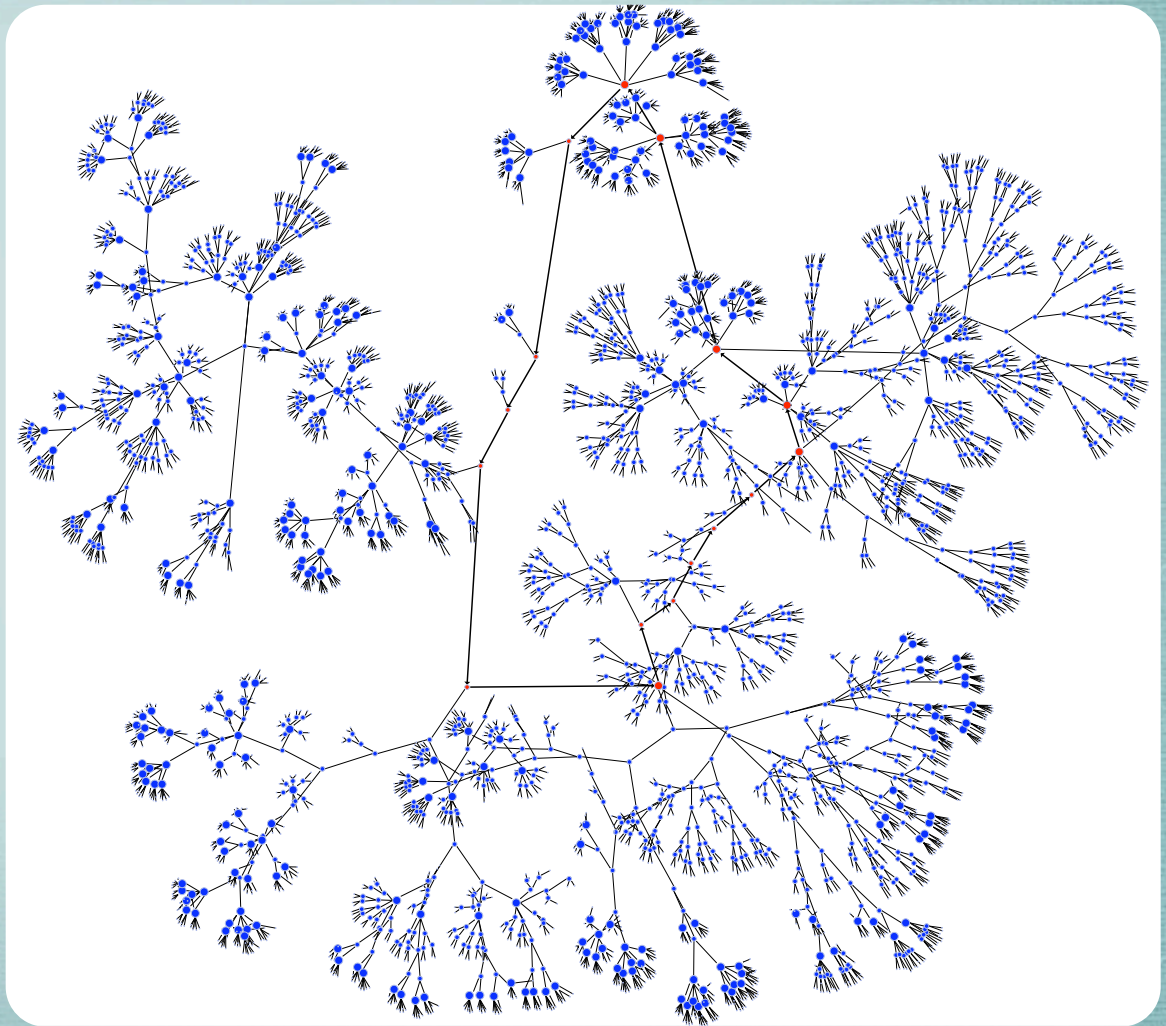
Bioinformatics

School of Informatics

Indiana University

Network Workbench

<http://nwb.slis.indiana.edu/>



The lack of widely available tools for discrete network analysis limits the usefulness of a powerful analytical technique.

- * What is a discrete network model?
 - * How might it be applied to Bioinformatics?
- * Building a tool for analyzing discrete networks
 - * How does one analyze and construct a discrete network model for biological data?
 - * Sample application as applied to the segmentation clock

A Boolean network model is an abstract way of viewing interactions.

- * Many events can be seen as occurring or not occurring. Whether or not those events occur or do not occur influence other events.
- * I present at the McGill Summer Sessions
 - * People listened to my presentation
 - * People were bored
 - * People found my presentation helpful or relevant
- * This same abstraction can be applied to interactions between genes, mRNAs, and proteins.

Interaction between cellular entities is complex, but we want to understand the dynamics.

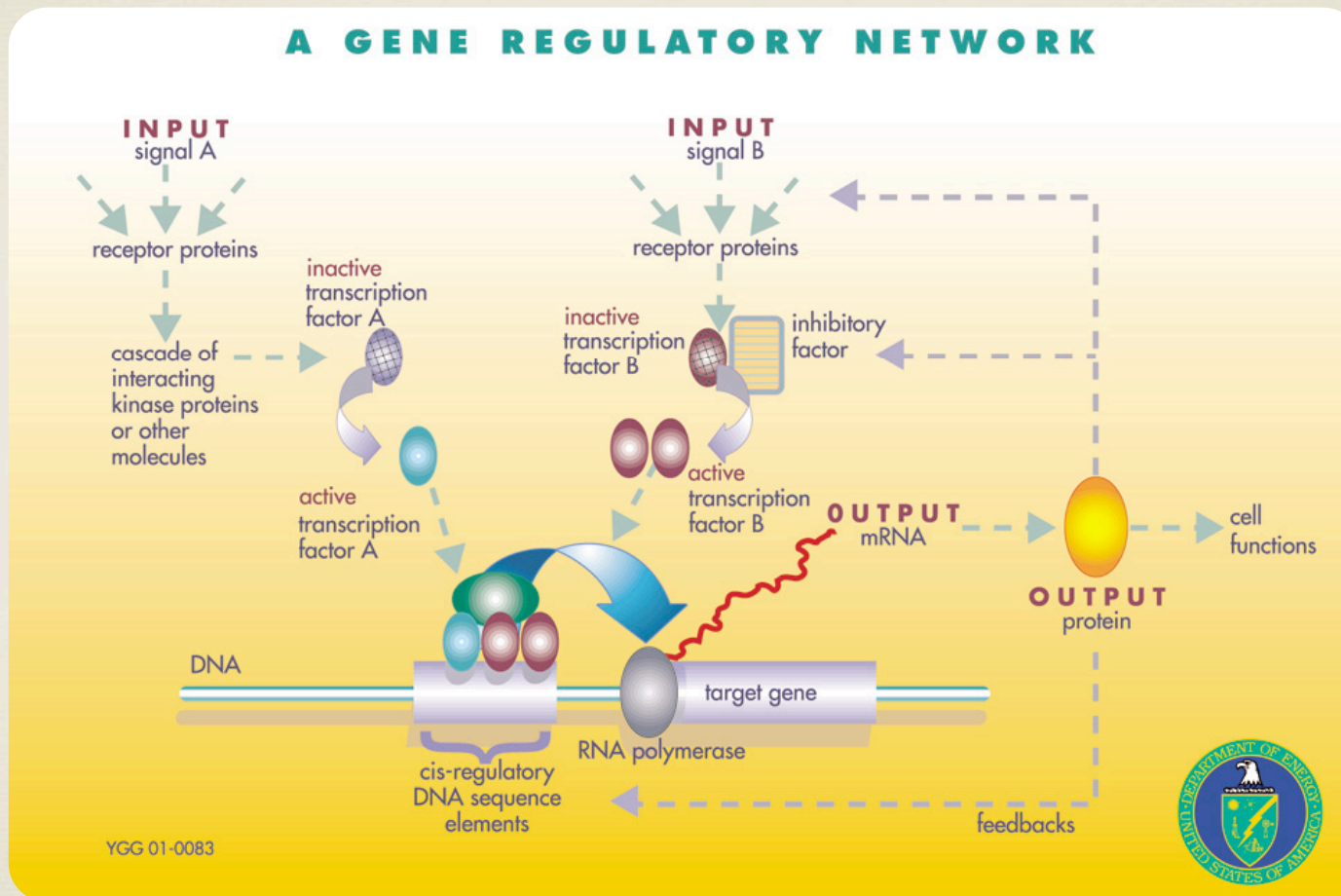


Image from http://genomics.energy.gov/gallery/systems_biology/detail.np/HGPI_HiRes/REGNET.jpg

Boolean network models are powerful analysis tools.

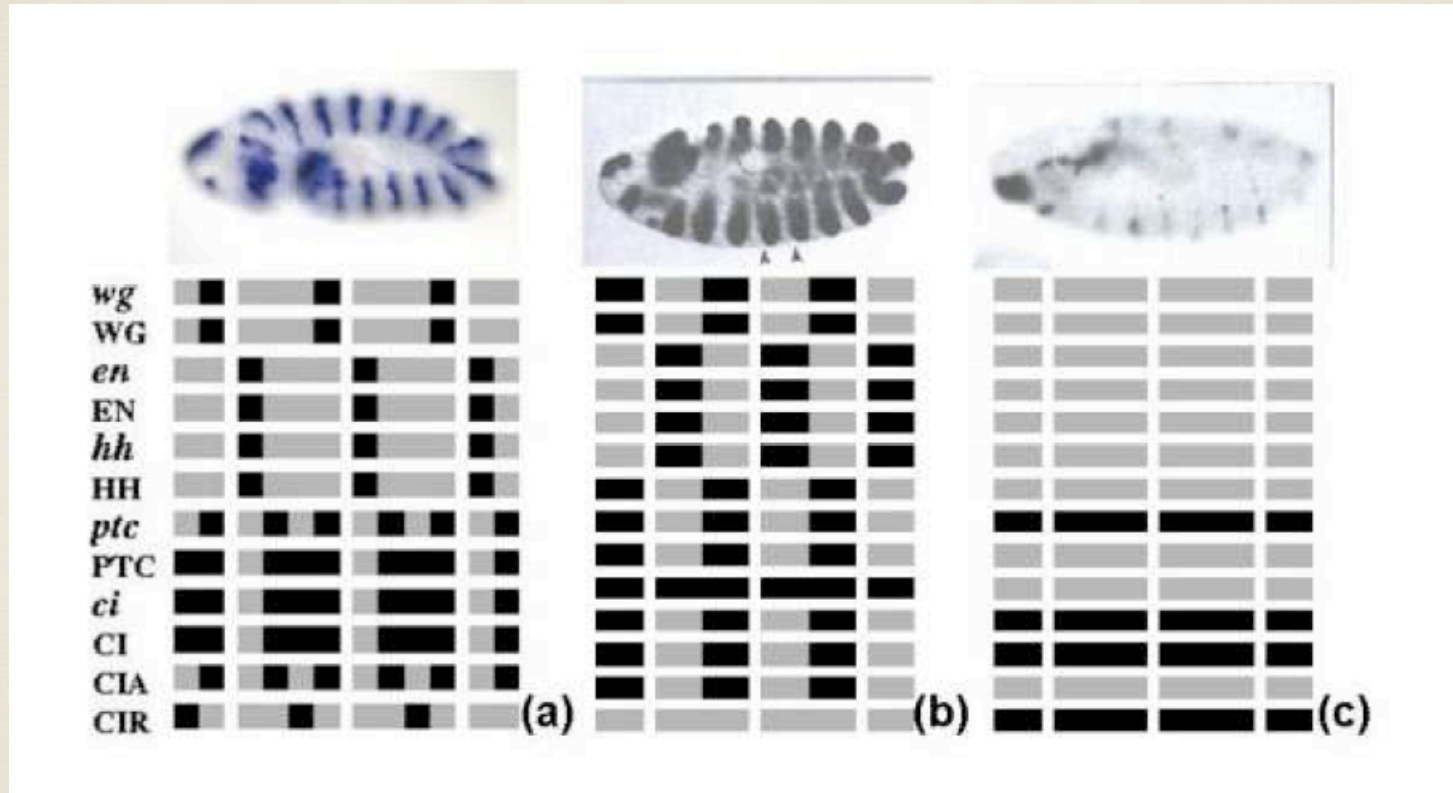


Image from M. Chaves, R. Albert, and E.D. Sontag. *Robustness and fragility of Boolean models for genetic regulatory networks*.
Journal of Theoretical Biology, 2005. Vol 235.

Analyzing large networks is computationally intractable and there are few tools for analyzing smaller networks.

Analyzing the displayed network of 401 proteins on a 3.0 GHz computer would take 5.458×10^{103} years, approximately 10^{94} times longer than the age of the Earth and 4×10^{93} times longer than the age of the universe.

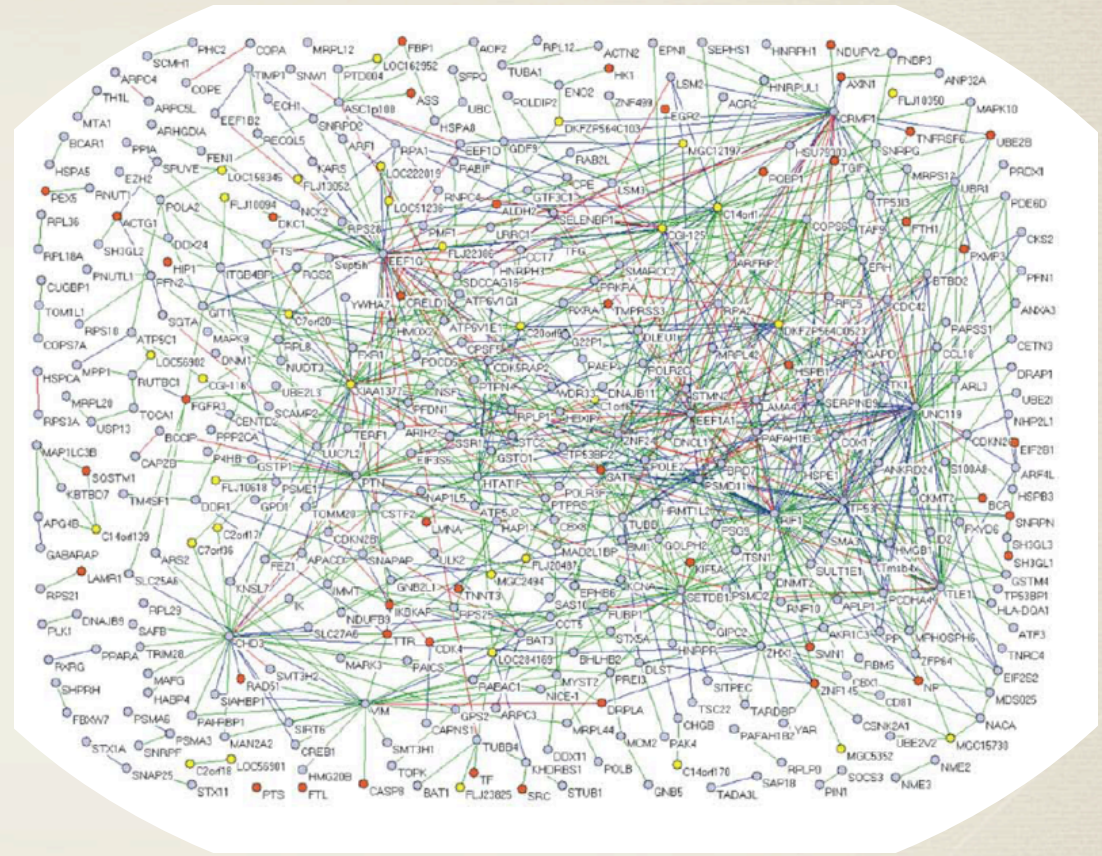


Image from *A human protein-protein interaction network: a resource for annotating the proteome*. Cell, 2005. Vol 122:6.

Network Workbench is a widely available tool for network analysis built on the OSGi framework.

The screenshot displays the Network Workbench Tool interface. The main window shows a network graph visualization with blue nodes and edges. A console window is open, displaying the following text:

```
GUESS was selected.  
Author(s): Eytan Adar  
Implementer(s): Eytan Adar (GUESS), Bernie Hogan (GraphModifier front-end), Jeffrey Wong (GraphModifier front-end), Russell Duhon (resizeLinear fix)  
Integrator(s): Russell Duhon  
Reference: Adar, Eytan, "GUESS: A Language and Interface for Graph Exploration," CHI 2006 (http://graphexploration.cond.org/)  
Documentation: https://nwb.slis.indiana.edu/community/?n=VisualizeData.GUESS  
GUESS Version: 1.0.3beta (20070813-1150)
```

Below the console, a table lists various fields and their values:

Field	Value
0 1 0 0 1 0 0 1 1 ...	
attractor	2
color	0,0,255,...
fixed	false
height	29.1547...
image	
indegree	2
label	0 1 0 0 1 ...
labelcolor	
labelvisible	false
name	n3184
outdegree	1
strokecolor	cadetblue
style	2
totaldegree	3
visible	true
width	29.1547...
x	3203.5
y	230.25

The Scheduler window shows a list of tasks with checkboxes and a "Remove From List" button. The Data Manager window shows a tree view of data files and graphs. The Interpreter window shows the following code:

```
>>> n0.indegree  
0  
>>> resizeLinear(indegree,5,50)  
>>>
```

The Graph Modifier window is also visible at the bottom of the main window.

The Discrete Network Dynamics plugin allows for a large range of model analysis techniques while minimizing the computational time costs.

Network Description

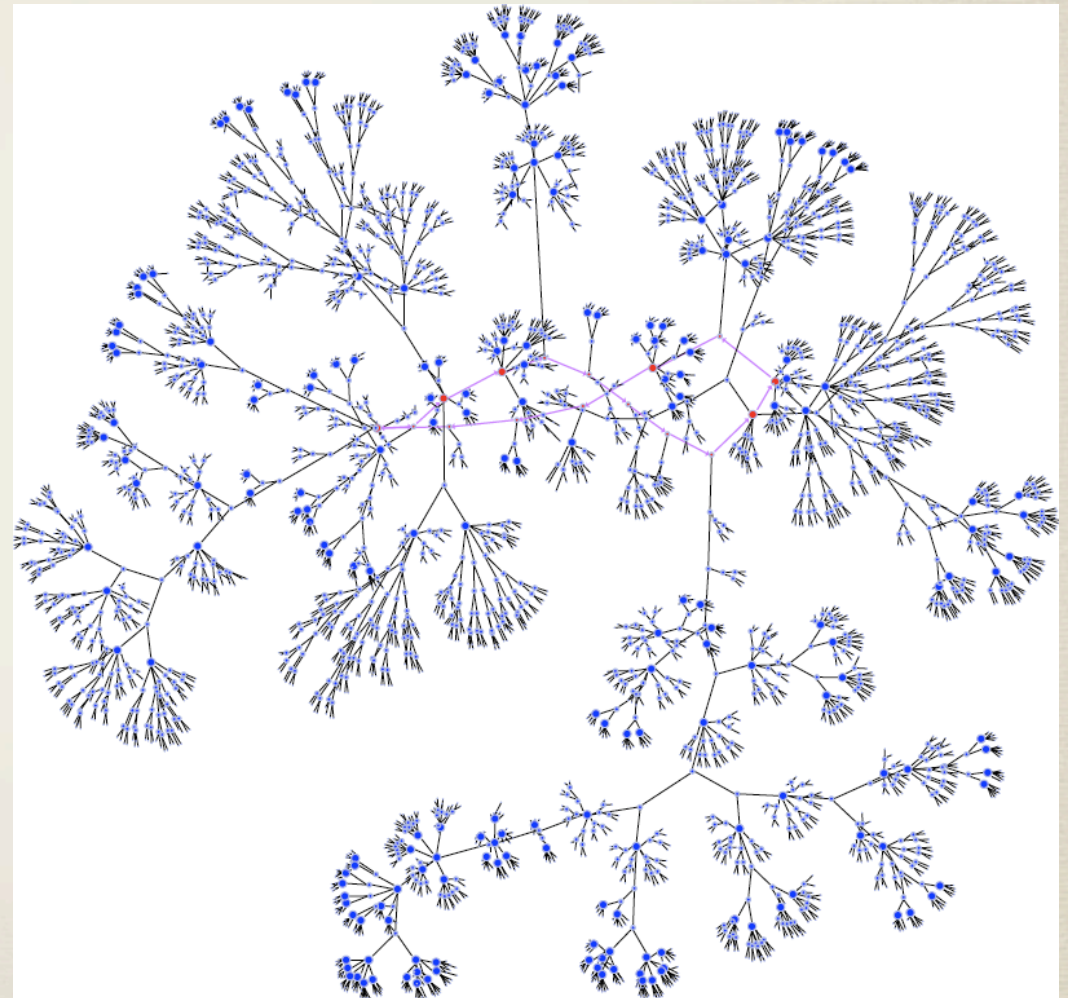
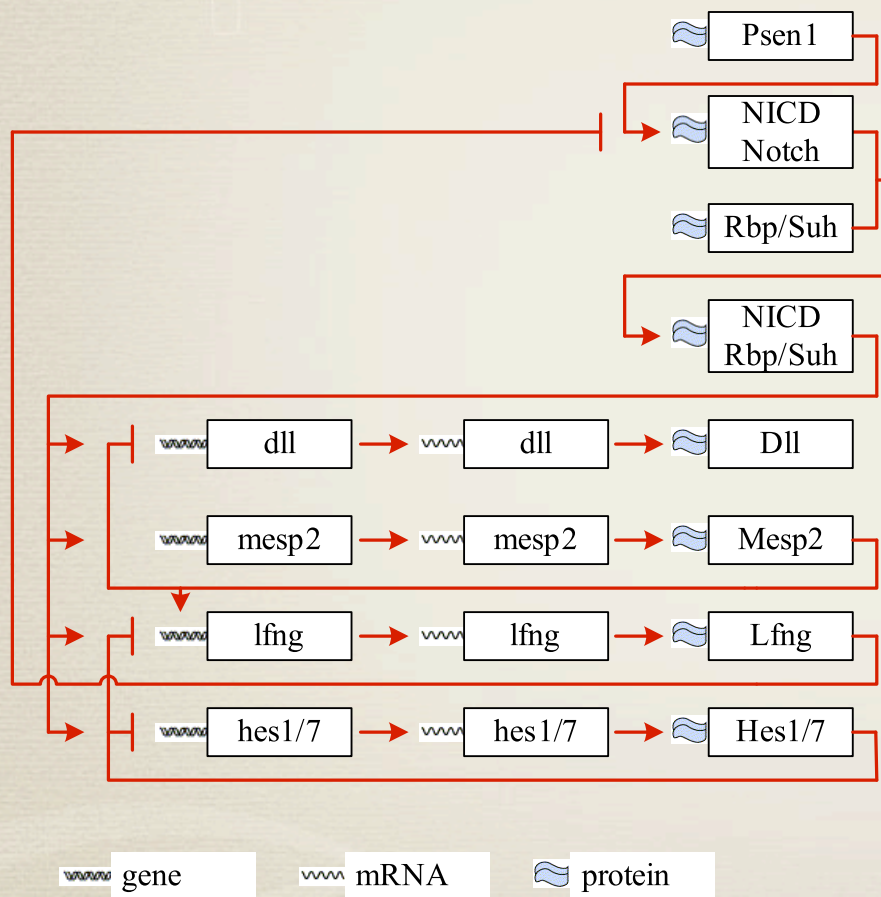
Blah

Function Label	clockFunctions	!
Number of States per Node	2	!
Input Function Format	Polynomial	!
State Space Specification	All trajectories	!
Updating Scheme	Synchronous	!
Node Label	Names	!
Enter update schedule separated by space		!
Enter Initial Condition to Evaluate		!

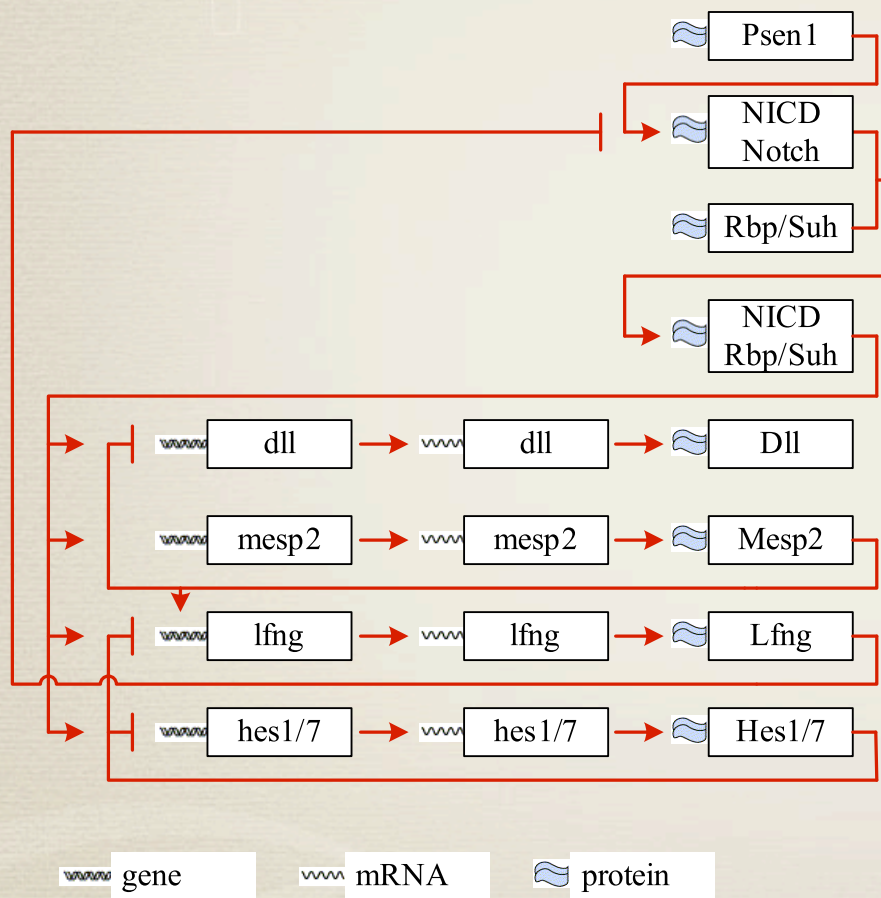
OK Cancel

```
segmentationClockDelays.csv
"originalModel","Names","clockFunctions"
"f1=x11+~x13","g_dll","f1=x11*~x13"
"f2=x11","g_mesp2","f2=x11"
"f3=x11+x13+~x15","g_lfng","f3=x11+x13*~x15"
"f4=x11+~x15","g_hes1/7","f4=x11*~x15"
"f5=x1","m_dll","f5=x1"
"f6=x2","m_mesp2","f6=x2"
"f7=x3","m_lfng","f7=x3"
"f8=x4","m_hes1/7","f8=x4"
"f9=x9","P_sen1","f9=x9"
"f10=x9+~x14","p_Notch/NICD","f10=x9*~x14"
"f11=x10","p_NICD/Rbp/Suh","f11=x10"
"f12=x5","p_dll","f12=x5"
"f13=x6","p_mesp2","f13=x6"
"f14=x7","p_lfng","f14=x7"
"f15=x8","p_hes1/7","f15=x8"
```

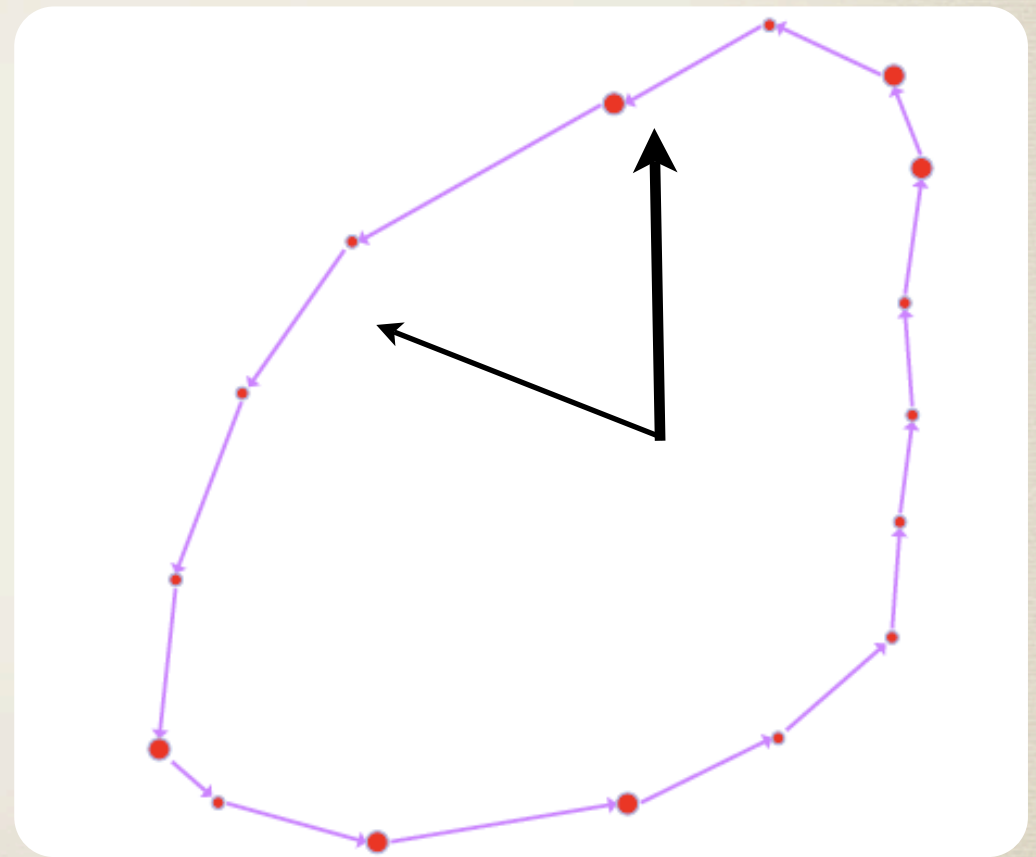
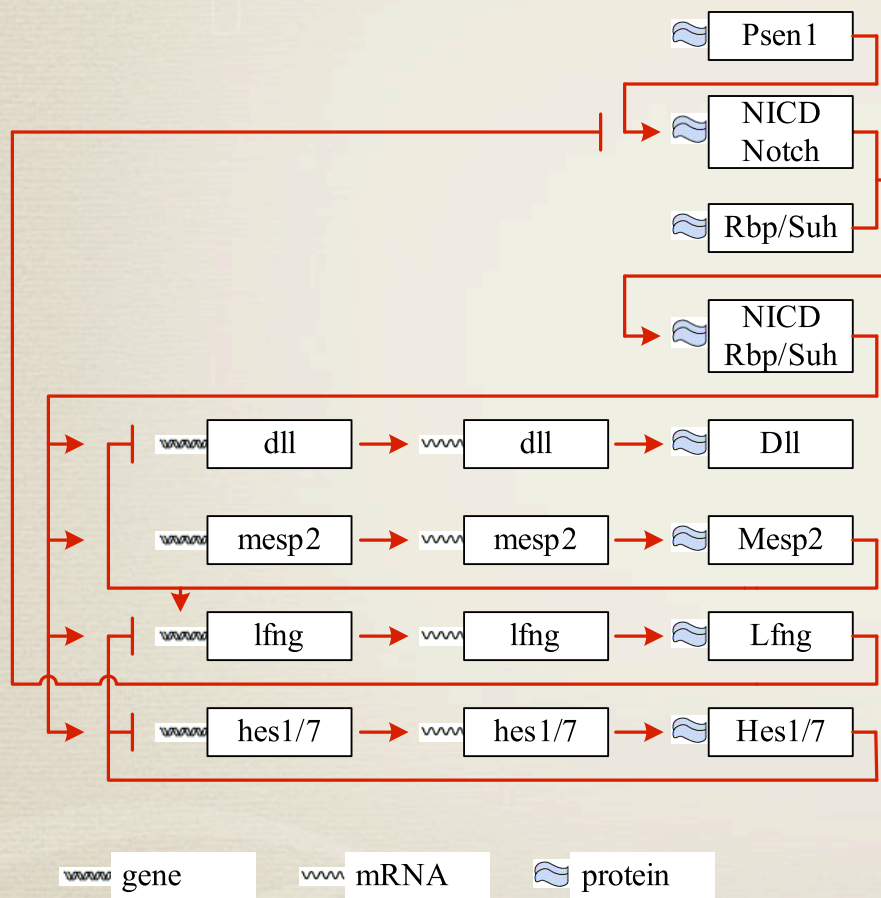

Analyzing the state space of the segmentation clock using the Discrete Network Dynamics plugin reveals that the network topology drives oscillations.



Analyzing the state space of the segmentation clock using the Discrete Network Dynamics plugin reveals that the network topology drives oscillations.



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Genes				mRNAs				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
Black	Black	Black	Black	White	White	White	White	Black	Black	White	Black	Black	Black	Black
White	White	White	White	Black	Black	Black	Black	Black	White	Black	White	White	White	White
Black	Black	Black	Black	White	White	White	White	Black	Black	White	Black	Black	Black	Black

Genes				mRNAs				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
								■						
								■	■					
								■	■	■				
■	■	■	■					■	■	■				
■	■	■	■	■	■	■	■	■	■	■		■	■	■
	■			■	■	■	■	■		■	■	■	■	■
	■				■			■				■	■	■
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■	■	■	■	■	■	■	■	■			■	■	■	■
				■	■	■	■	■			■	■	■	■
								■						

Genes				mRNAs				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
								■				■		
		■						■	■					
						■		■	■	■				
■	■	■	■					■	■	■			■	
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								■				■		

Genes				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
				■		■				
■	■	■	■	■	■					
				■		■	■	■	■	■
	■			■		■				
■	■	■	■	■	■			■		
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		■		■	■		■	■	■	■
				■		■			■	
■	■	■	■	■						
				■	■		■	■	■	■
				■		■				

Genes				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
				■						
				■	■					
				■	■	■				
■	■	■	■	■	■	■				
■	■	■	■	■	■	■	■	■	■	■
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				■						

Genes				Proteins						
Dll	Mesp2	Lfng	Hes1/7	Psen1	Notch	NICD	Dll	Mesp2	Lfng	Hes1/7
	■			■						
				■	■			■		
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