

# Finding intervention strategies for gene regulatory networks

Bachelor thesis seminar

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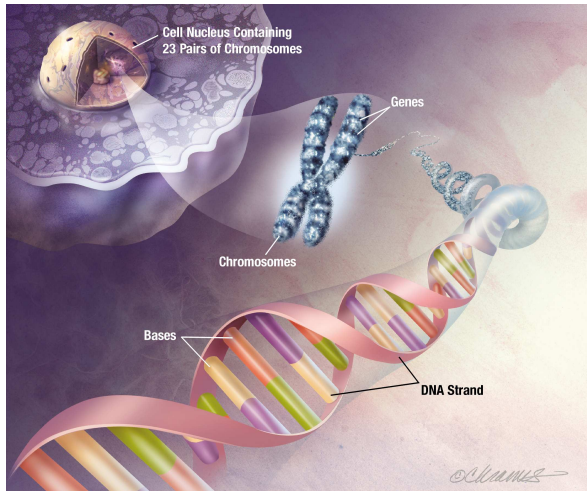
# Outline

- 1 Aim
- 2 Background
- 3 Preliminary results
- 4 Future directions

# Aim of the Bachelor thesis

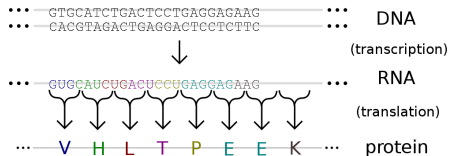
- Implement software to calculate strategies to affect gene regulatory networks.
- More specifically: Make a component for work-flow framework Anduril using CellNetAnalyzer.

# Genes (1)

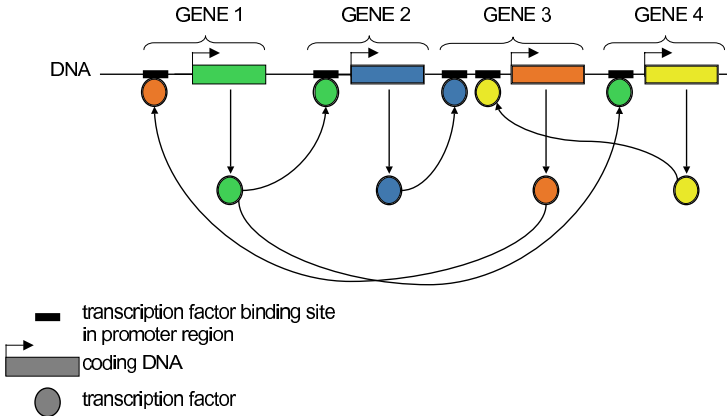


# Genes (2)

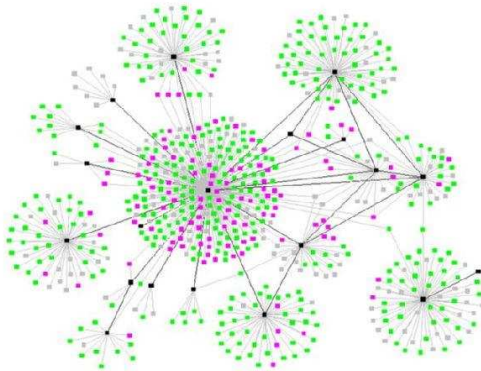
- DNA consists of bases A,C,G and T
- DNA → RNA → Protein



# Gene networks (1)



# Gene networks (2)



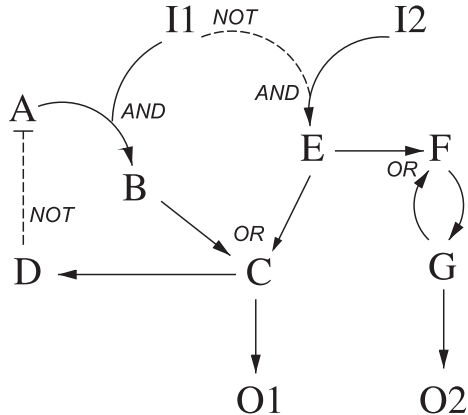
# Modelling gene regulatory networks within Boolean framework

- Genes are represented by nodes, which can be either in active state (1), or in inactive state (0).
- Regulatory interactions are coded as Boolean operations on the nodes.



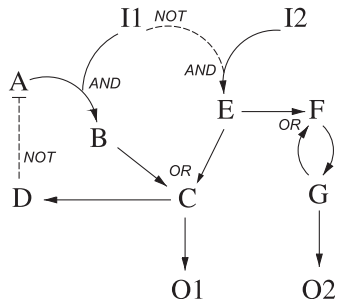
# Example network

I1 (Input)  
I2 (Input)  
 $A = \neg D$   
 $B = A \cdot I1$   
 $C = B + E$   
 $D = C$   
 $E = \neg I1 \cdot I2$   
 $F = E + G$   
 $G = F$   
 $O1 = C$   
 $O2 = G$



# Minimal intervention set (MIS)

- A support-minimal sets of Boolean interventions that fulfill a given intervention goal.
- How to accomplish inactivation of O1 ( $O1 = 0$ ) and activation of O2 ( $O2 = 1$ )?



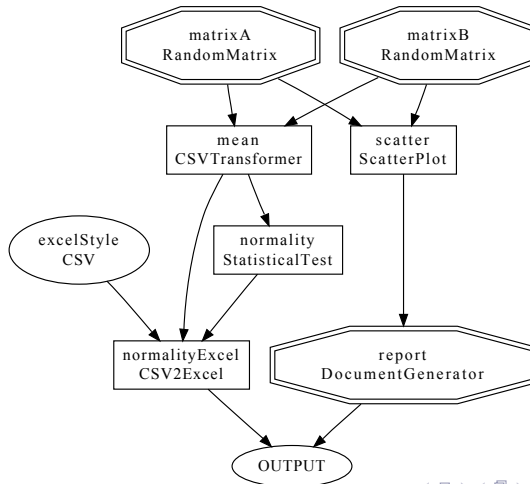
# CellNetAnalyzer

- MATLAB package for structural and functional analysis of biochemical networks.
- Includes API functionalities to enable use in external programs.
- Klamt et al. Structural and functional analysis of cellular networks with CellNetAnalyzer, BMC Systems Biology 2007.

# Anduril

- A open source component-based workflow framework.
- A workflow is series of processing steps connected together
- Steps are implemented as components which can be implemented in any programing language
- Ovaska et al. Large-scale data integration framework provides a comprehensive view on glioblastoma multiforme, Genome Medicine 2010.


# Anduril - a workflow example



# The component


- Anduril component CNACComputeMIS.
- Input: Genes regulating each other, type of regulations and the desired state of target genes.
- Output: The MISs leading to the desired state of the target genes.

Component ↑ Up: [Component summary](#)


 **CNACComputeMIS**

Computes minimal intervention sets (MISs) for a given network fulfilling a given intervention goal.


**Version** 0.1  
**Categories** [Graph](#)  
**Authors** [Erkka Valo \(erkka.valo@helsinki.fi\)](#)  
**Requires** Matlab  
**Source files** [component.xml](#) [computeMIS.m](#) [execute.m](#)  
**Usage** [Example with default values](#)

 **Inputs**

Name	Type	Mandatory	Description
Incidence	<a href="#">CSV</a>	Mandatory	Incidence matrix of the network.
InteractionType	<a href="#">CSV</a>	Mandatory	Interaction type of the edges.
InterventionGoal	<a href="#">CSV</a>	Mandatory	Intervention goal. Two columns ID and STATE are required. ID contains the node IDs and STATE the desired state of the nodes after intervention (1 active, 0 inactive and NA no goal).

 **Outputs**

Name	Type	Description
mis	<a href="#">CSV</a>	Minimal intervention sets found for the network for the given intervention goal.

 **Test cases**

Test case	Parameters	IN incidence	IN interactionType	IN interventionGoal	OUT mis
case1	(missing)	<a href="#">incidence</a>	<a href="#">interactionType</a>	<a href="#">interventionGoal</a>	<a href="#">mis</a>

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# Testcase: Example network (1)

- How to accomplish inactivation of O1 ( $O1 = 0$ ) and activation of O2 ( $O2 = 1$ )?
- INPUT:

$$\text{incidence} = \begin{pmatrix} \text{NODES} & \text{EDGE\_1} & \dots & \text{EDGE\_13} \\ I1 & -1 & \dots & 0 \\ I2 & 0 & \dots & 0 \\ A & 0 & \dots & 0 \\ B & 1 & \dots & 0 \\ C & 0 & \dots & 0 \\ D & 0 & \dots & 0 \\ E & 0 & \dots & 0 \\ F & 0 & \dots & 0 \\ G & 0 & \dots & -1 \\ O1 & 0 & \dots & 0 \\ O2 & 0 & \dots & 1 \end{pmatrix} \quad \text{type} = \begin{pmatrix} \text{ID} & \text{SIGN} \\ \text{EDGE\_1} & 1 \\ \text{EDGE\_2} & -1 \\ \text{EDGE\_3} & 1 \\ \text{EDGE\_4} & 1 \\ \text{EDGE\_5} & 1 \\ \text{EDGE\_6} & 1 \\ \text{EDGE\_7} & 1 \\ \text{EDGE\_8} & -1 \\ \text{EDGE\_9} & 1 \\ \text{EDGE\_10} & 1 \\ \text{EDGE\_11} & 1 \\ \text{EDGE\_12} & 1 \\ \text{EDGE\_13} & 1 \end{pmatrix} \quad \text{goal} = \begin{pmatrix} \text{ID} & \text{STATE} \\ I1 & \text{NA} \\ I2 & \text{NA} \\ A & \text{NA} \\ B & \text{NA} \\ C & \text{NA} \\ D & \text{NA} \\ E & \text{NA} \\ F & \text{NA} \\ G & \text{NA} \\ O1 & 0 \\ O2 & 1 \end{pmatrix}$$

# Testcase: Example network (2)

## ● OUTPUT:

"I1"	"I2"	"A"	"B"	"C"	"D"	"E"	"F"	"G"	"O1"	"O2"
-1	0	0	0	-1	0	0	0	0	0	
-1	0	0	0	0	0	0	0	-1	0	
0	1	0	0	-1	0	0	0	0	0	
0	0	0	0	-1	0	0	1	0	0	
0	0	0	0	-1	0	0	0	0	0	1
0	1	0	0	0	0	0	0	-1	0	
0	0	0	0	0	0	0	1	0	-1	0
0	0	0	0	0	0	0	0	-1	1	
0	0	0	0	-1	0	1	0	0	0	0
0	0	0	0	0	0	1	0	0	-1	0
0	0	0	0	-1	0	0	0	1	0	0
0	0	0	0	0	0	0	0	1	-1	0
0	0	0	-1	0	0	-1	1	0	0	0
0	0	0	-1	0	0	-1	0	0	0	1
0	0	0	-1	0	0	-1	0	1	0	0
-1	0	-1	0	0	0	-1	1	0	0	0
-1	0	-1	0	0	0	-1	0	0	0	1
1	-1	0	-1	0	0	0	1	0	0	0
1	-1	0	-1	0	0	0	0	0	0	1
-1	0	0	0	0	1	-1	1	0	0	0
-1	0	0	0	0	1	-1	0	0	0	1
-1	0	-1	0	0	0	-1	0	1	0	0
1	-1	0	-1	0	0	0	0	1	0	0
-1	0	0	0	0	1	-1	0	0	0	



# Future directions

- In a disease such as cancer certain genes are misregulated.
- Find genes to activate or inactivate to return the cancer driving genes to normal state.
- These genes are possible drug targets.

# Acknowledgements

- Work was done in Computational Systems Biology Lab, Faculty of Medicine, University of Helsinki
- Dr. Vladimir Rogojin
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# Thank you!