

UNIVERSITY OF SANNIO
Department of Engineering



Infer Gene Regulatory Networks from Time Series Data with Probabilistic Model Checking

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BIOLOGICAL BACKGROUND

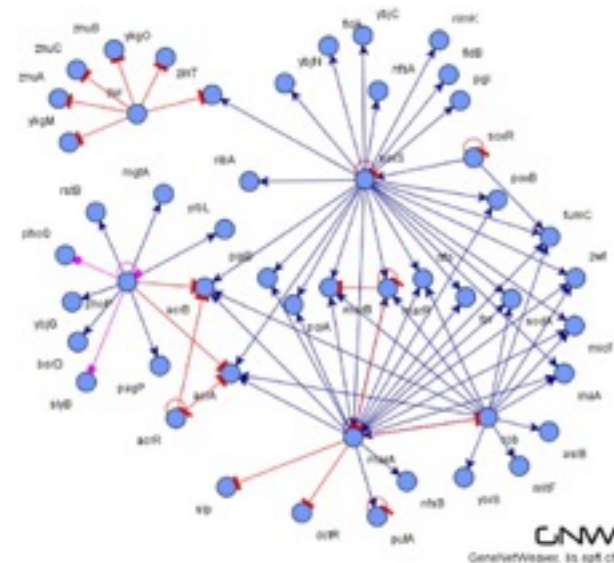
GENE EXPRESSION: specifies the nature and the properties of proteins and functional molecules that the organism is able to produce

Create a global picture of cellular function



Gene Expression Profiling

Genetic Regulatory Networks (GRN) describe the complex interactions that influence gene expression



GOAL & REASON

The dynamics of biological systems are not completely known



Identify mathematical models to derive the structure and/or unknown parameters from experimental data

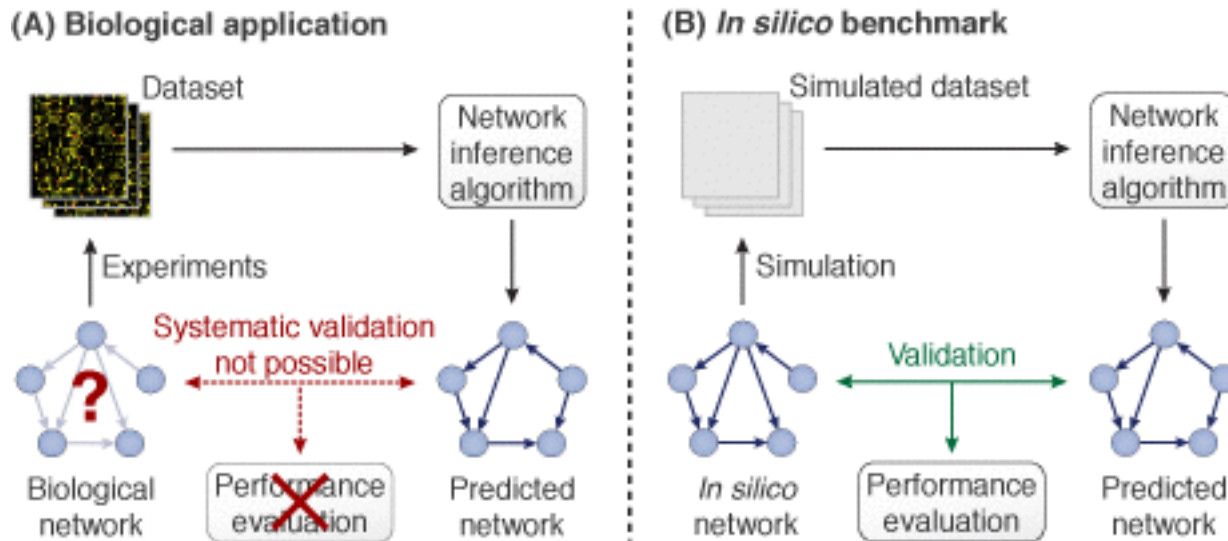
*Definition of a methodology for the **inference** of genetic networks*

Formal Methods (Model Checking)

PRISM



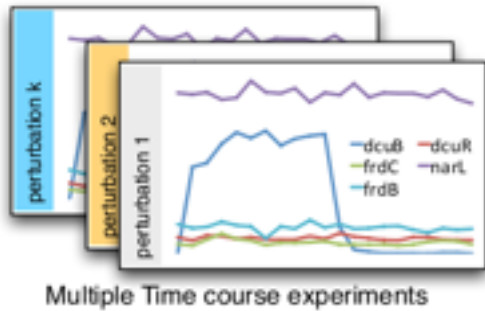
BIOLOGICAL AND IN SILICO NETWORKS



In Silico Network: networks obtained by a process of reverse engineering which obtains possible expression data from a given network.



APPROACH



Discretized
Data

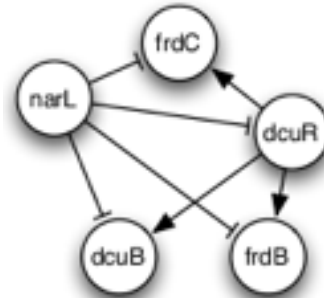
PRISM
Model

Biological Properties
expressed in PRISM
logic (PCTL*)

Model
Checker

ProFoGRN

Genetic Regulatory
Network



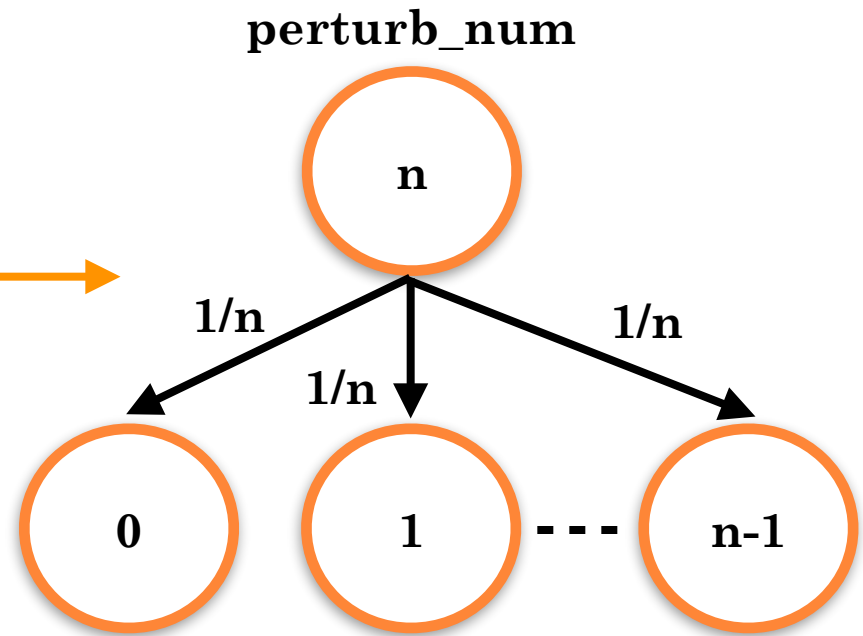
MODEL

Gene	Pert. 0	Pert. 1	Pert. 2
A	B	D	B
B	B	D	B
C	B	B	U

```
[ ] perturb_num=n -> 1/n:(perturb_num'=0)  
+ 1/n:(perturb_num'=1)  
+ ...  
+ 1/n:(perturb_num'=n-1);
```

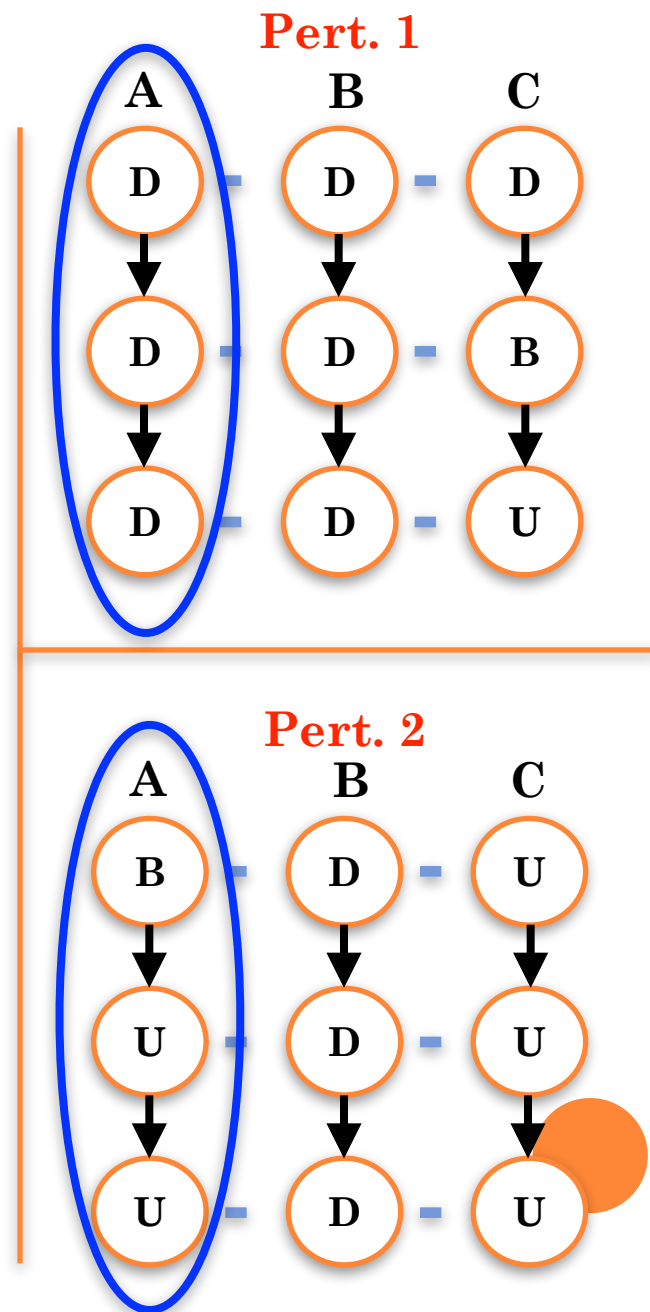
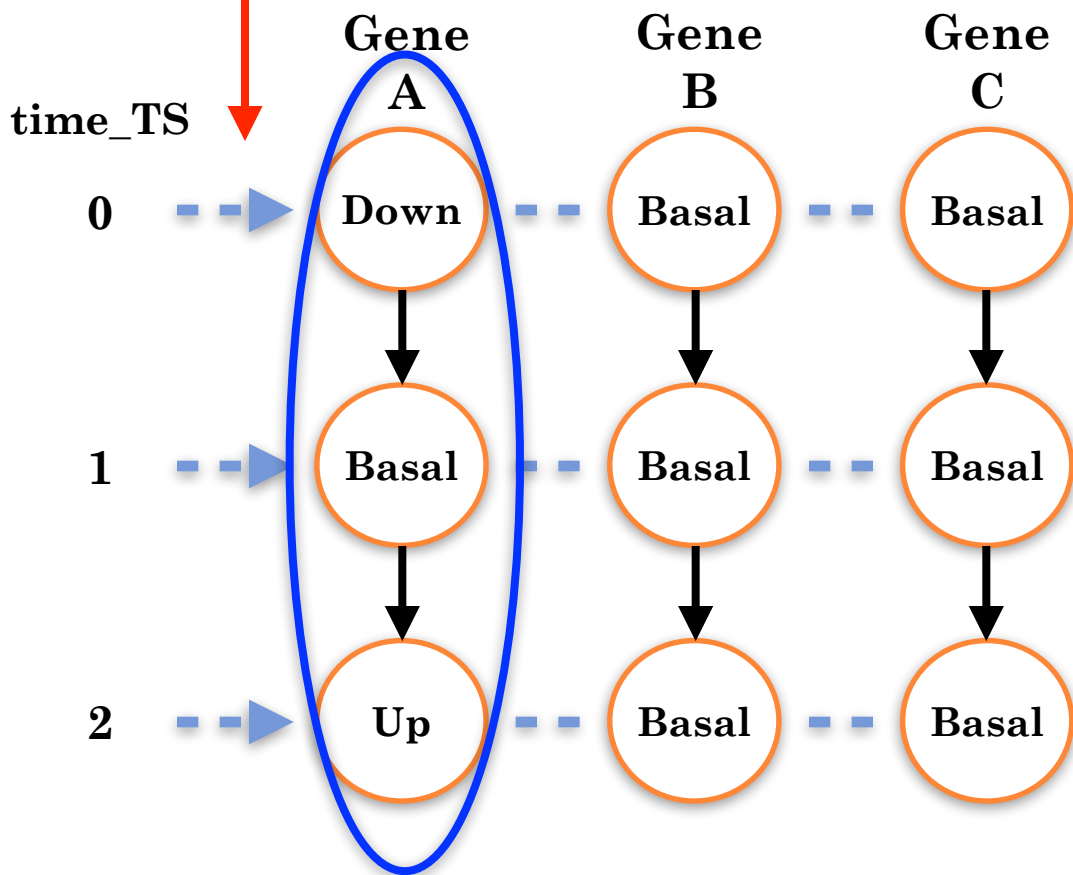


```
[st0] perturb_num=0 -> (A_state_p'=Basal)  
& (B_state_p'=Basal)  
& (C_state_p'=Basal);
```



MODEL (2)

Gene	Pert. 0			Pert. 1			Pert. 2		
	0	1	2	0	1	2	0	1	2
A	D	B	U	D	D	D	B	U	U
B	B	B	B	D	D	D	D	D	D
C	B	B	B	D	B	U	U	U	U



MODEL (3)

Gene	Pert. 0			Pert. 1			Pert. 2		
	0	1	2	0	1	2	0	1	2
A	D	B	U	D	D	D	B	U	U
B	B	B	B	D	D	D	D	D	D
C	B	B	B	D	B	U	U	U	U

module GENE_A

```
A_state : int;
time_TS : [0..3] init 0;
```

// PERT. -> 0

// initial state PERTURBATION 0

```
[st0] A_state=Init & perturb_num=0 -> (A_state'=Down) & (time_TS'=1);
```

```
[st1] A_state=Down & time_TS=1 & perturb_num=0 -> (A_state'=Basal) & (time_TS'=2);
```

```
[st2] A_state=Basal & time_TS=2 & perturb_num=0 -> (A_state'=Up) & (time_TS'=3);
```

// PERT. -> 1

// initial state PERTURBATION 1

```
[st0] A_state=Init & perturb_num=1 -> (A_state'=Down) & (time_TS'=1);
```

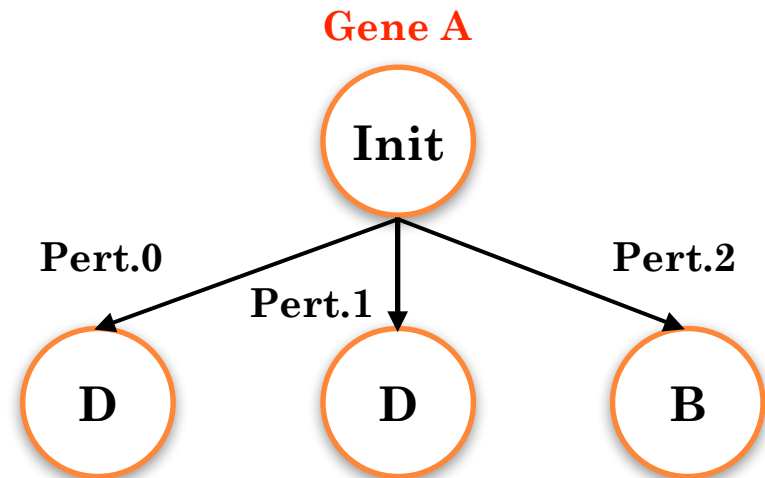
```
[st1] A_state=Down & time_TS=1 & perturb_num=1 -> (A_state'=Down) & (time_TS'=2);
```

```
[st2] A_state=Down & time_TS=2 & perturb_num=1 -> (A_state'=Down) & (time_TS'=3);
```

// PERT. -> 2

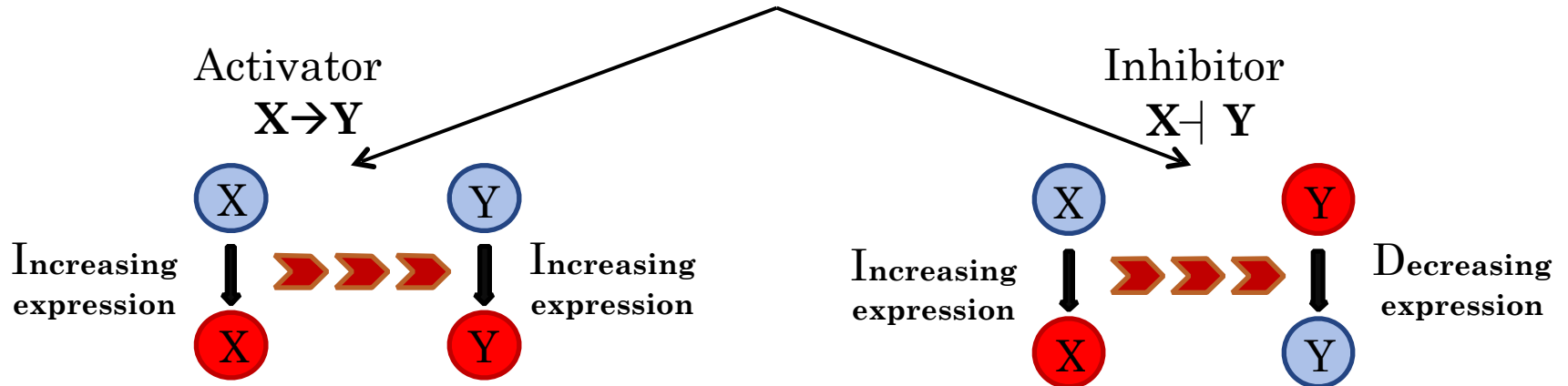
// ...

endmodule



PROPERTIES

Edges of a gene regulatory network

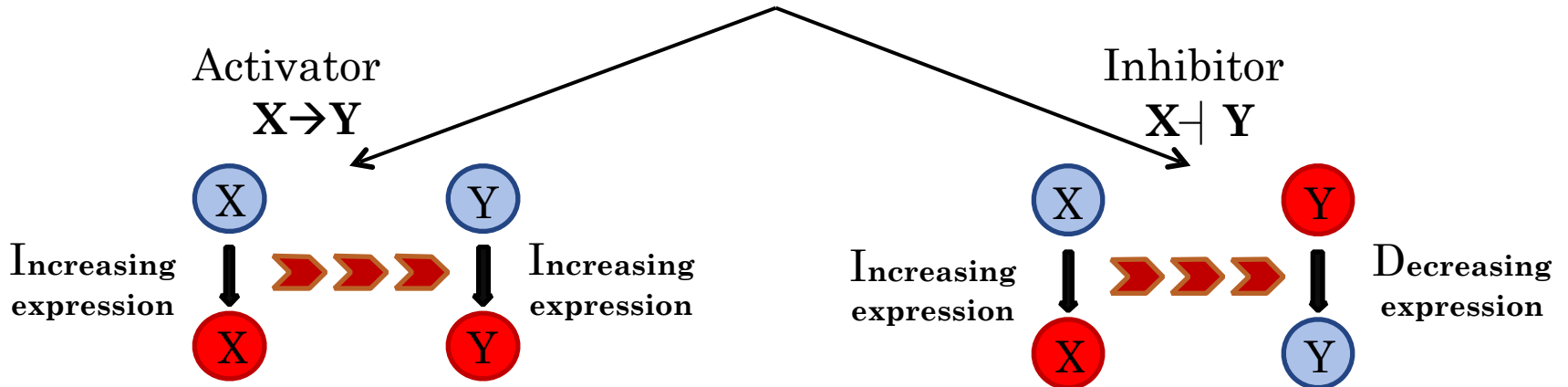


Edges Properties

- **Activator Edge:** given two genes X and Y, whenever X becomes high also Y becomes high and does not return low;
- **Inhibitor Edge:** given two genes X and Y, whenever X becomes high Y becomes low and does not return high.

PROPERTIES

Edges of a gene regulatory network



Edges Properties

- **Activator Edge:** $P=? [(A_state \leq Init \cup (A_state = Up)) \cup (A_state = Up \ \& \ (F \ (G \ C_state = Up)))]$
- **Inhibitor Edge:** $P=? [(A_state \leq Init \cup (A_state = Up)) \cup (A_state = Up \ \& \ (F \ (G \ C_state = Down)))]$



PROPERTIES (2)

Edge Properties **WEAK**

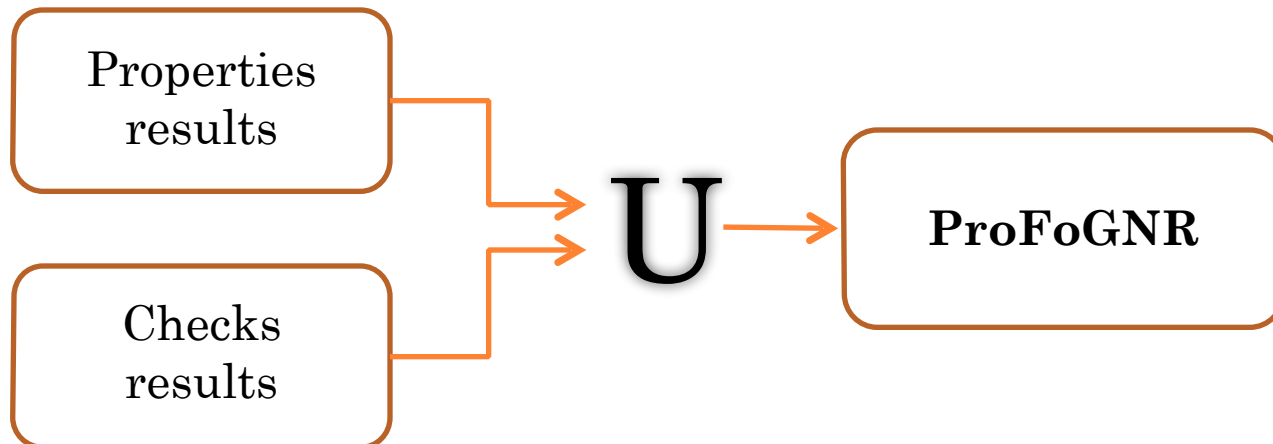
- **Activator Edge:** given two genes X and Y, whenever X becomes high also Y becomes ~~high and does not return low~~;
- **Inhibitor Edge:** given two genes X and Y, whenever X becomes high Y becomes ~~low and does not return high~~.



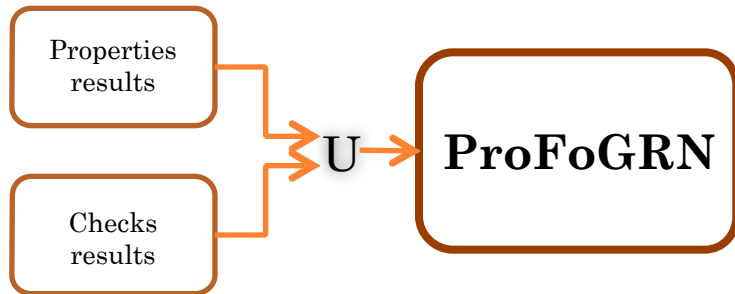
PROPERTIES (3)

Other Checks

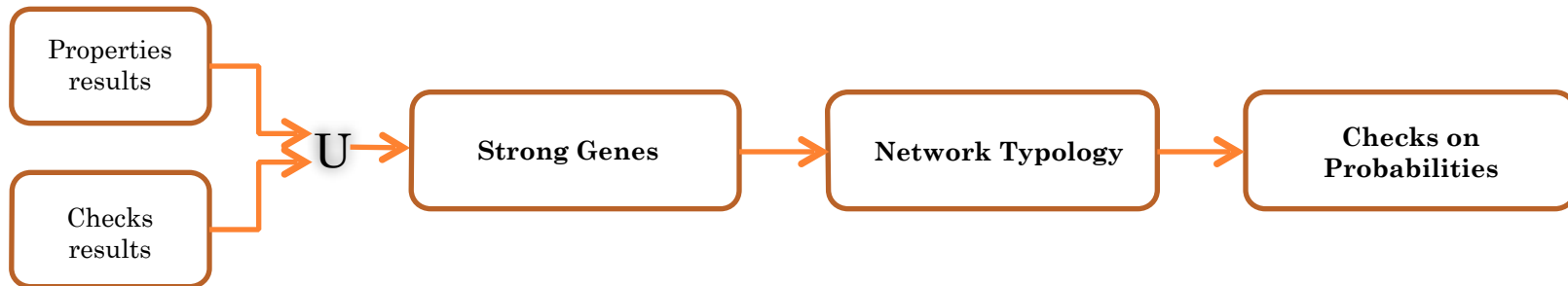
- A gene becomes high and then does not return low;
- A gene is always at the high logic level;
- The initial state of a gene is at high logic value.



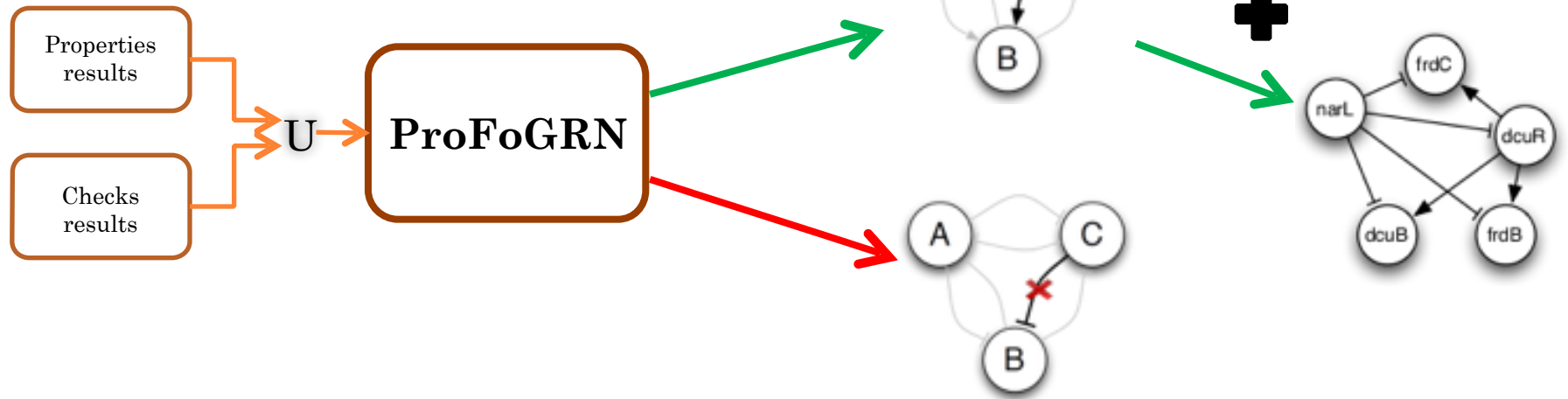
PROPOSED METHODOLOGY



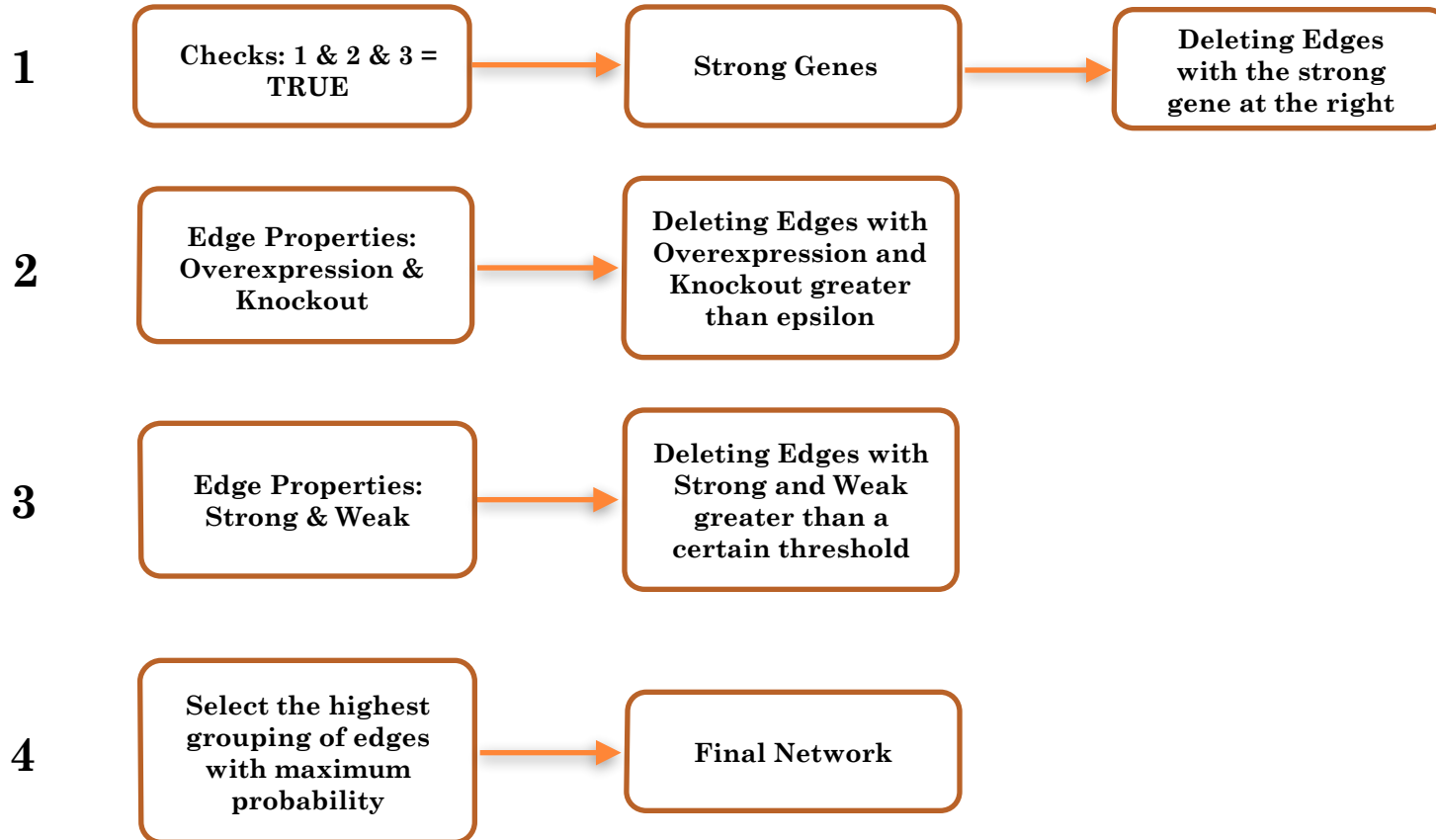
PROPOSED METHODOLOGY



PROPOSED METHODOLOGY

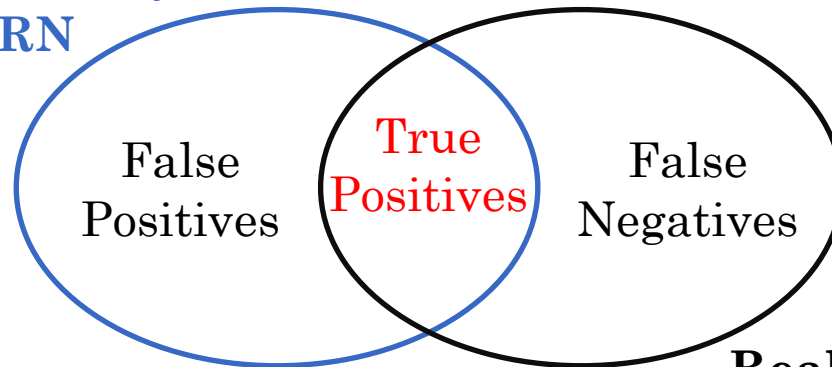


STEPS OF THE ALGORITHM



EXPERIMENTAL RESULTS

Edges identified by
ProFoGRN



Real Network's
Edges

$$\textit{Precision} = \frac{\textit{True_Positives}}{\textit{True_Positives} + \textit{False_Positives}} \quad \textit{Recall} = \frac{\textit{True_Positives}}{\textit{True_Positives} + \textit{False_Negatives}}$$

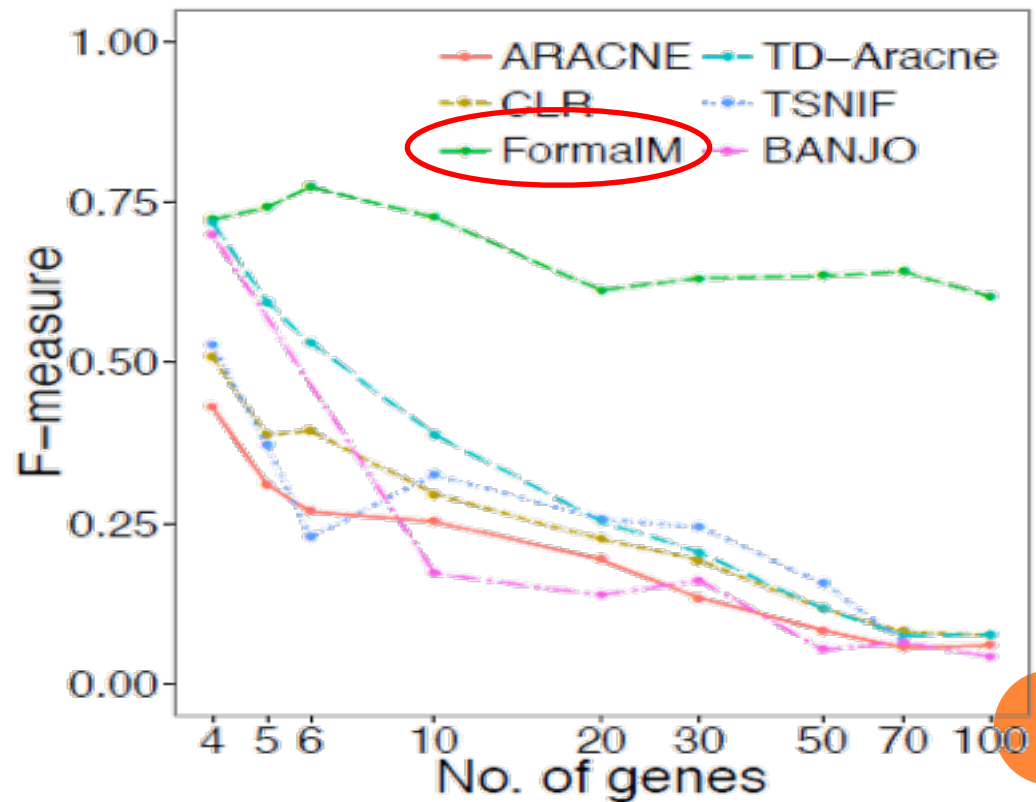
$$\textit{F-measure} = 2 \cdot \frac{\textit{Precision} \cdot \textit{Recall}}{\textit{Precision} + \textit{Recall}}$$



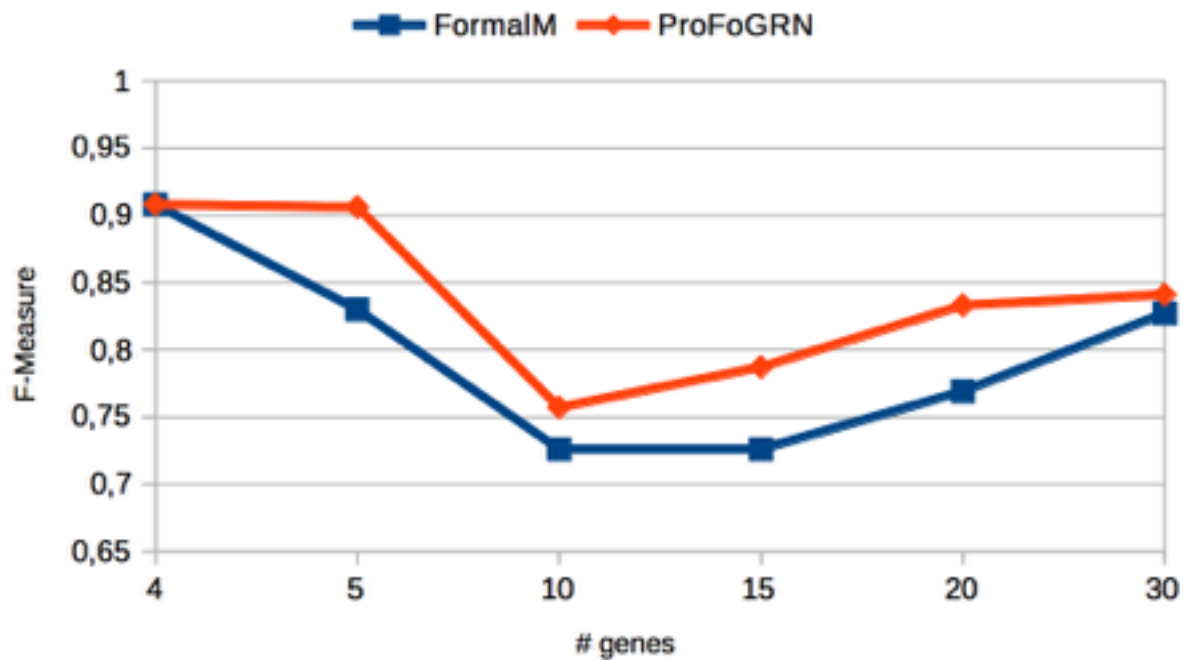
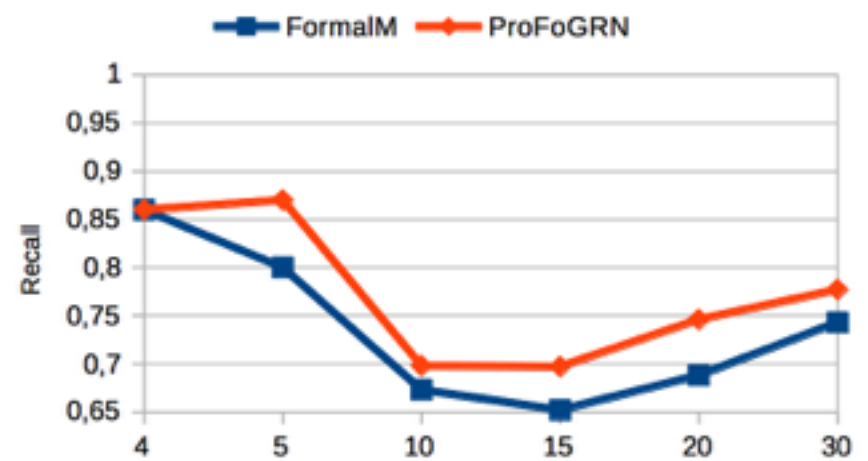
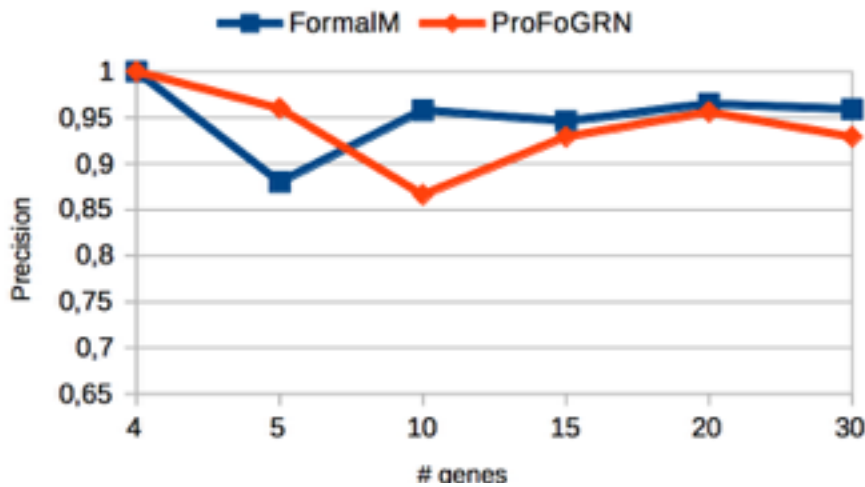
EXPERIMENTAL RESULTS (2)

State of
the Art

TOOL
<i>ARACNE</i>
<i>CLR</i>
<i>TD-Aracne</i>
<i>TSNIF</i>
<i>BANJO</i>
<i>FormalM</i>



IN SILICO RESULTS



E. COLI SOS RESULTS

Method	Graph	Pr	Rc	Fm
ARACNE	Undirected	0.44	0.57	0.50
CLR	Undirected	0.35	1.00	0.52
TD-Aracne	Undirected	0.22	1.00	0.36
FormalM	Undirected	0.25	1.00	0.40
TSNIF	Undirected	0.21	0.43	0.29
BANJO	Undirected	0.36	0.71	0.48
ProFoGRN	Undirected	1.00	1.00	1.00
TD-Aracne	Directed	0.12	0.88	0.22
FormalM	Directed	0.14	1.00	0.25
TSNIF	Directed	0.12	0.25	0.17
BANJO	Directed	0.26	0.62	0.37
ProFoGRN	Directed	1.00	1.00	1.00
FormalM	Signed	0.04	0.25	0.06
TSNIF	Signed	0.12	0.25	0.17
BANJO	Signed	0.05	0.12	0.07
ProFoGRN	Signed	0.14	0.13	0.14



IRMA RESULTS

Method	Graph	Pr	Rc	Fm
ARACNE	Undirected	0.60	0.43	0.50
CLR	Undirected	0.75	0.86	0.80
TD-Aracne	Undirected	0.61	1.00	0.76
FormalM	Undirected	0.70	1.00	0.82
TSNIF	Undirected	1.00	0.86	0.92
BANJO	Undirected	0.67	0.86	0.75
ProFoGRN	Undirected	0.86	0.86	0.86
TD-Aracne	Directed	0.32	0.75	0.44
FormalM	Directed	0.40	1.00	0.57
TSNIF	Directed	0.71	0.62	0.67
BANJO	Directed	0.45	0.62	0.53
ProFoGRN	Directed	0.71	0.86	0.78
FormalM	Signed	0.25	0.62	0.36
TSNIF	Signed	0.43	0.38	0.40
BANJO	Signed	0.36	0.50	0.42
ProFoGRN	Signed	0.50	0.50	0.50



S. CERVISIAE RESULTS

Method	Graph	Pr	Rc	Fm
ARACNE	Undirected	0.24	0.20	0.22
CLR	Undirected	0.26	0.45	0.33
TD-Aracne	Undirected	0.36	0.85	0.51
FormalM	Undirected	0.36	1.00	0.53
TSNIF	Undirected	0.23	0.25	0.24
BANJO	Undirected	0.32	0.35	0.33
ProFoGRN	Undirected	0.30	0.18	0.23
TD-Aracne	Directed	0.21	0.61	0.31
FormalM	Directed	0.21	1.00	0.35
TSNIF	Directed	0.16	0.17	0.17
BANJO	Directed	0.21	0.26	0.23
ProFoGRN	Directed	0.20	0.09	0.12
FormalM	Signed	0.18	0.87	0.30
TSNIF	Signed	0.08	0.09	0.08
BANJO	Signed	0.17	0.22	0.19
ProFoGRN	Signed	0.20	0.09	0.12



CONCLUSION & FUTURE WORK

- We have introduced a novel Methodology
 - Model & Properties
 - Model Checking
 - Performance Analysis



- Speed Performance Improvement
- Scalability
- Other regulatory pattern investigation
- Integration of our tool into existing bioinformatics frameworks

