

Logical Modelling and Analysis of the Budding Yeast Cell Cycle

Plugging the Morphogenesis Checkpoint Module

Adrien Fauré, Ph. D. student

Bioinformatics, Structural Biochemistry and Genomics (Marseille)
Complexity in Post-Genomic Biology (Torino)

Denis Thieffry



Marseille - FRANCE

Andrea Ciliberto



Milano - ITALY

Outline

The logical formalism:

Logical modelling
Circuit functionality

Our models:

The morphogenesis checkpoint
The core engine of the cell cycle

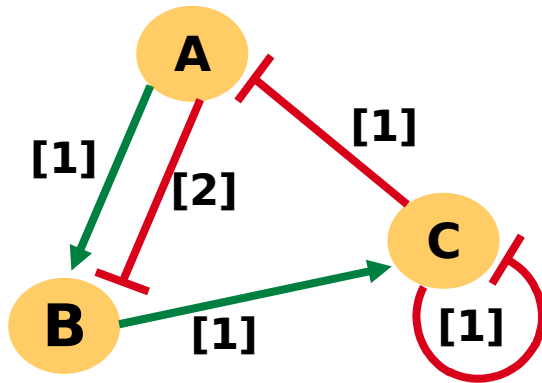
Plugging the module:

The method: Clb2 example
Behaviour of the coupled model

Conclusion and prospects

The Logical Formalism

Logical Modelling



A **graph** describes the interactions between genes or regulatory products

Discrete levels of expression associated to each gene (**logical variables**) and interaction

Logical parameters

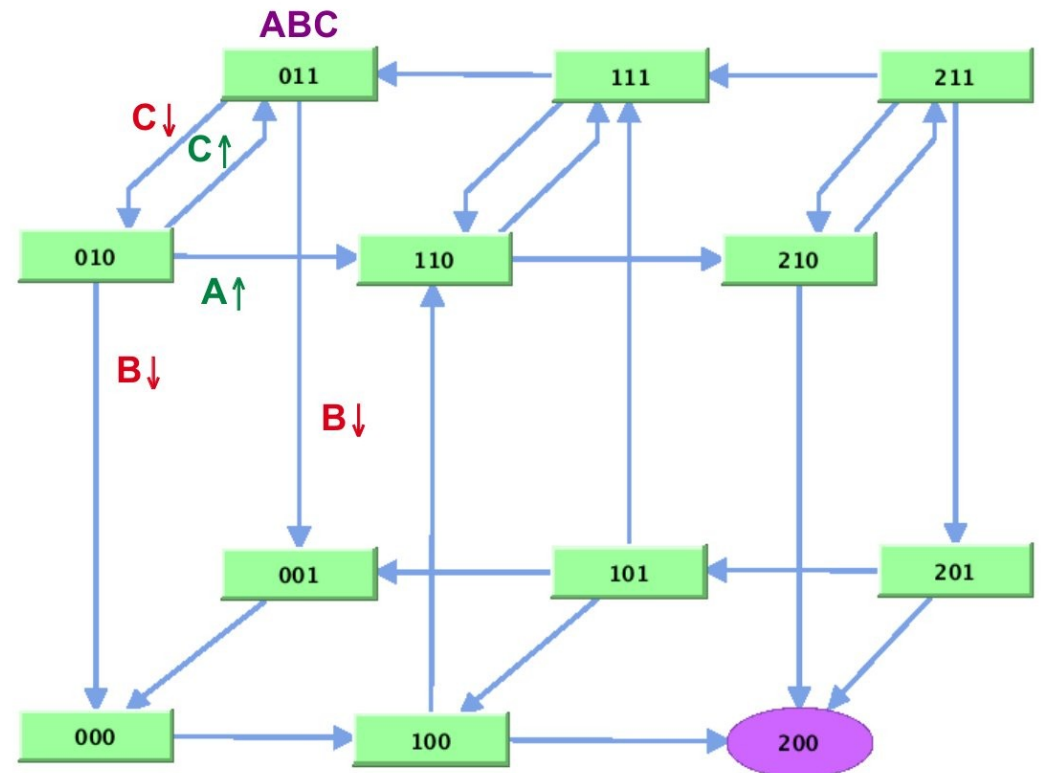
define the effect of combinations of incoming interactions

$$K_B(\emptyset) = 0$$

$$K_B(\{A, 1\}) = 1$$

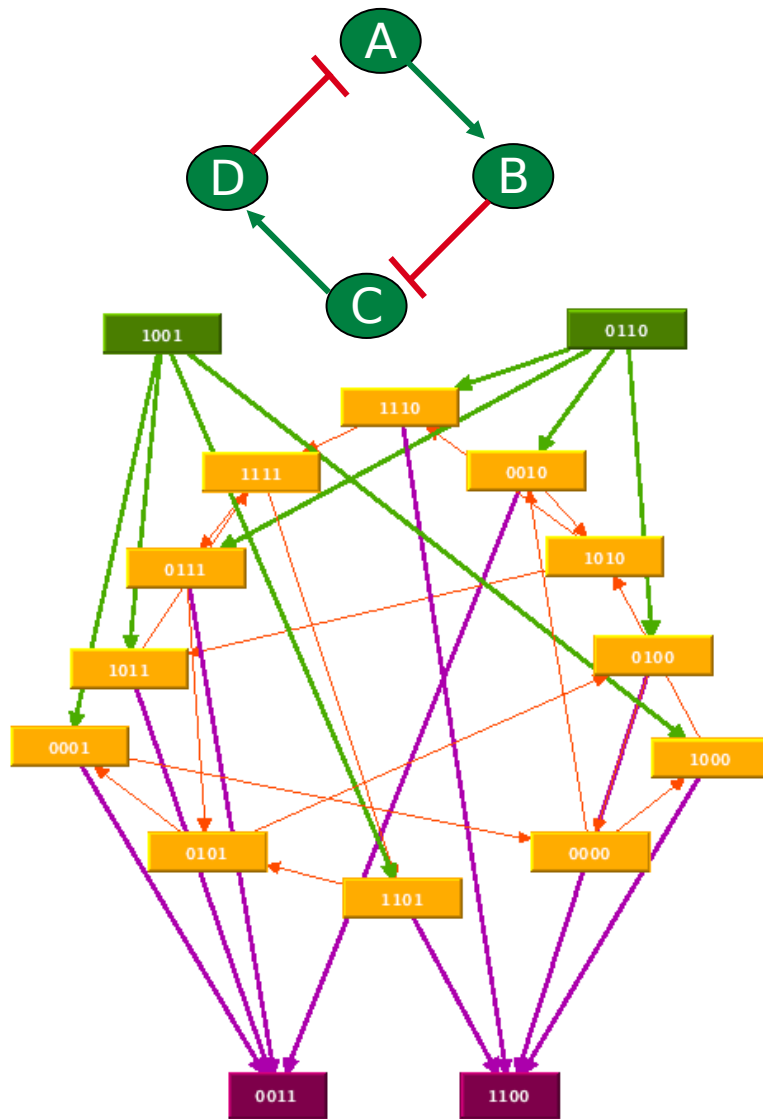
$$K_B(\{A, 2\}) = 0$$

The dynamics is represented by a **State Transition Graph** (here, all possible trajectories)



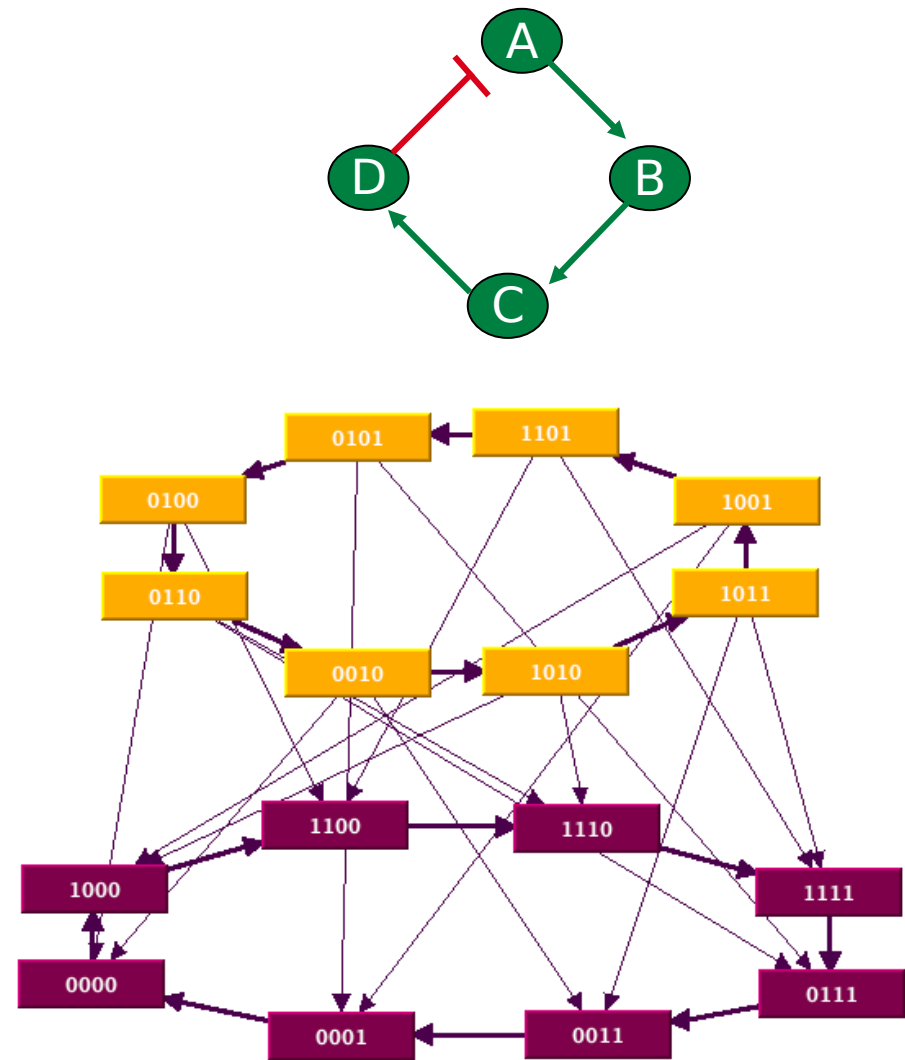
Circuit Functionality

Positive circuit



stable states

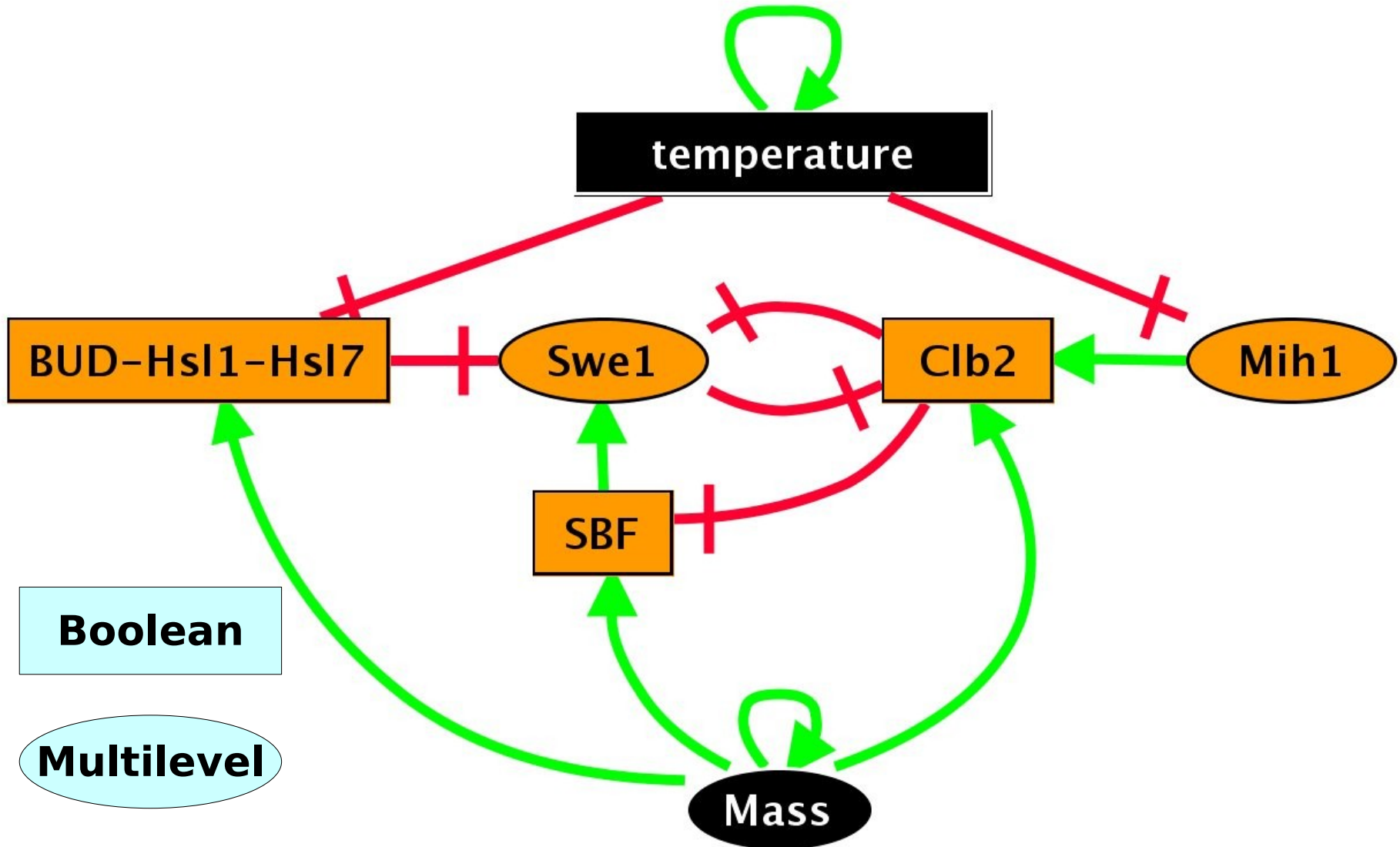
Negative circuit



attracting cycle

The models

The Morphogenesis Checkpoint Regulatory graph



Reference: Ciliberto et al., J Cell Biol. 163(6):1243-54, 2003.

The Morphogenesis Checkpoint

Dynamics: permissive temp.

Mass=0

0000000



0000100



0000200

Mass=1

0000201



0100201



0100211

Order:

Temp.

BUD

SBF

Swe1

Mih1

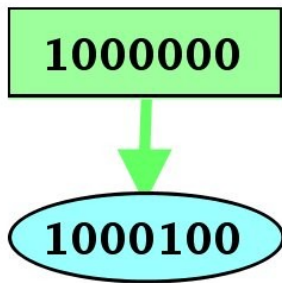
Clb2

Mass

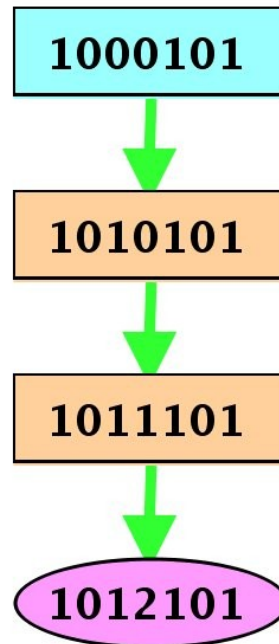
The Morphogenesis Checkpoint

Dynamics: restrictive temp.

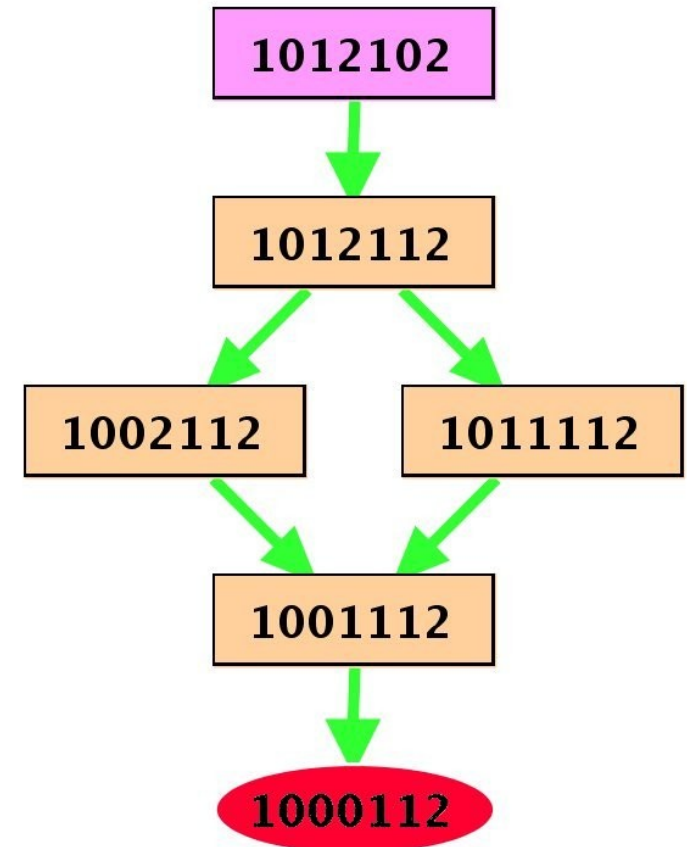
Mass=0



Mass=1



Mass=2



Order:

Temp.

BUD

SBF

Swe1

Mih1

Clb2

Mass

The Morphogenesis Checkpoint Mutants

Wild Type

At temperature:

Clb2 is activated for **mass=**

T=0		T=1
1		2

swe1Δ

T=0		T=1
1		1

mih1Δ

T=0		T=1
2		NO

hsl1Δ

T=0		T=1
1		2

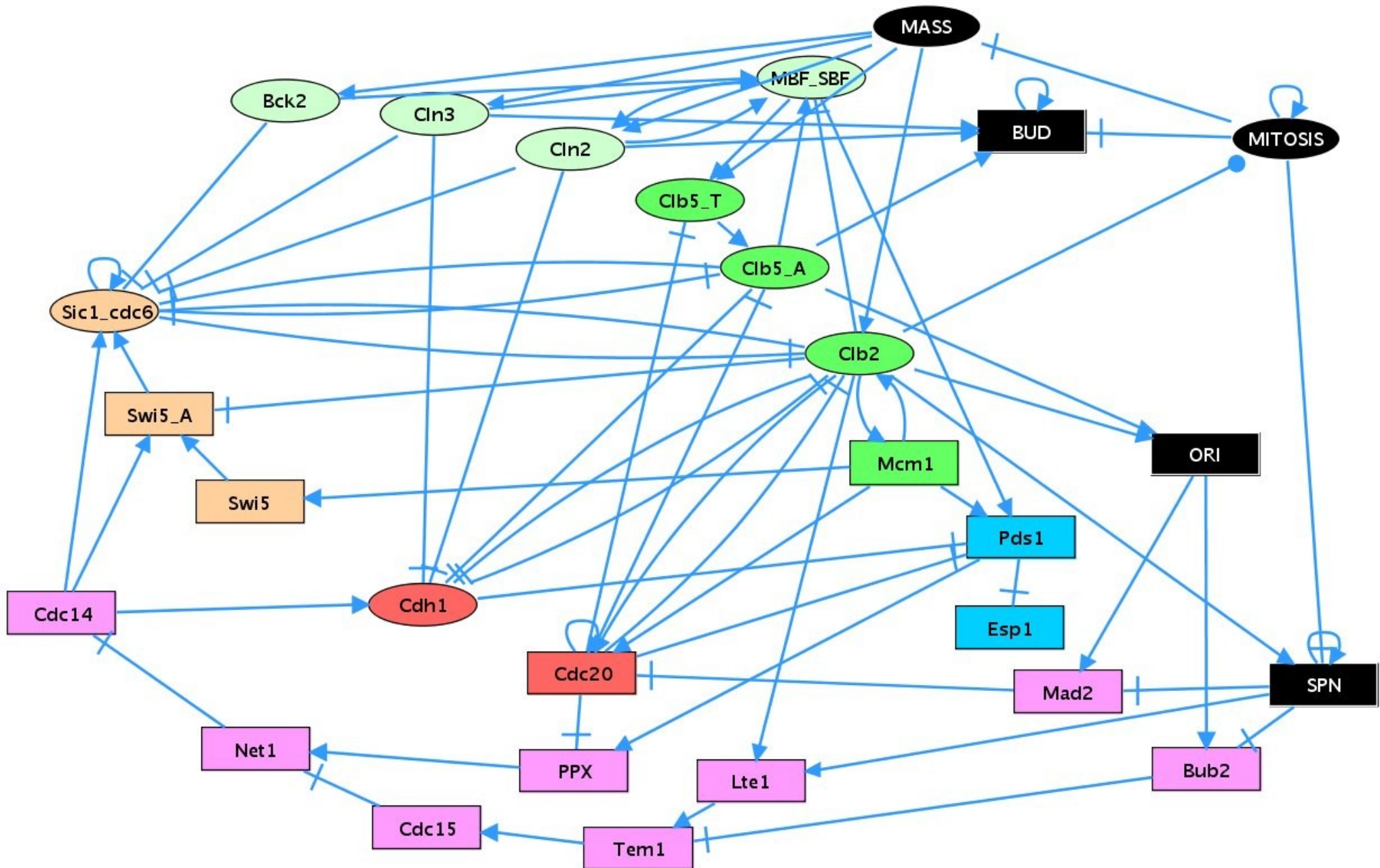
mih1Δ swe1Δ

T=0		T=1
1		1

mih1Δ hsl1Δ

T=0		T=1
NO		NO

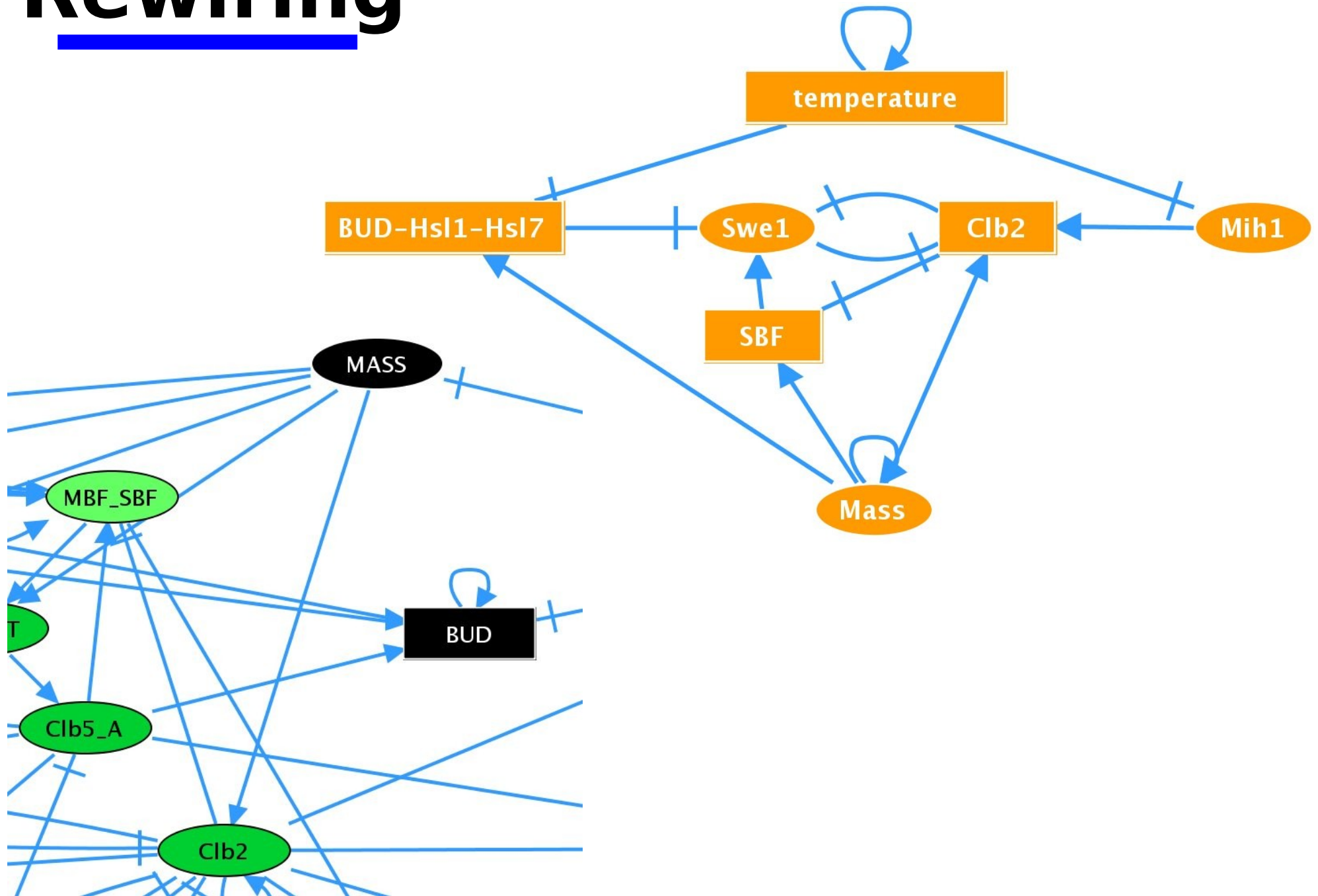
The Core Model



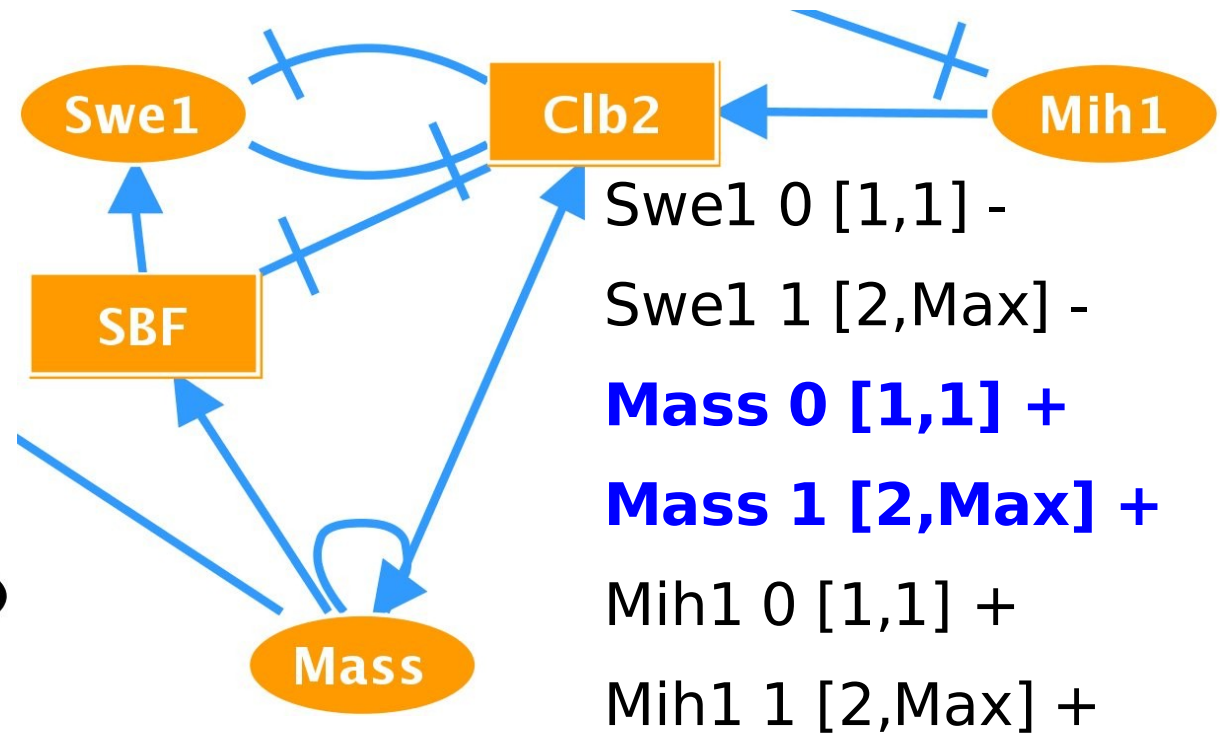
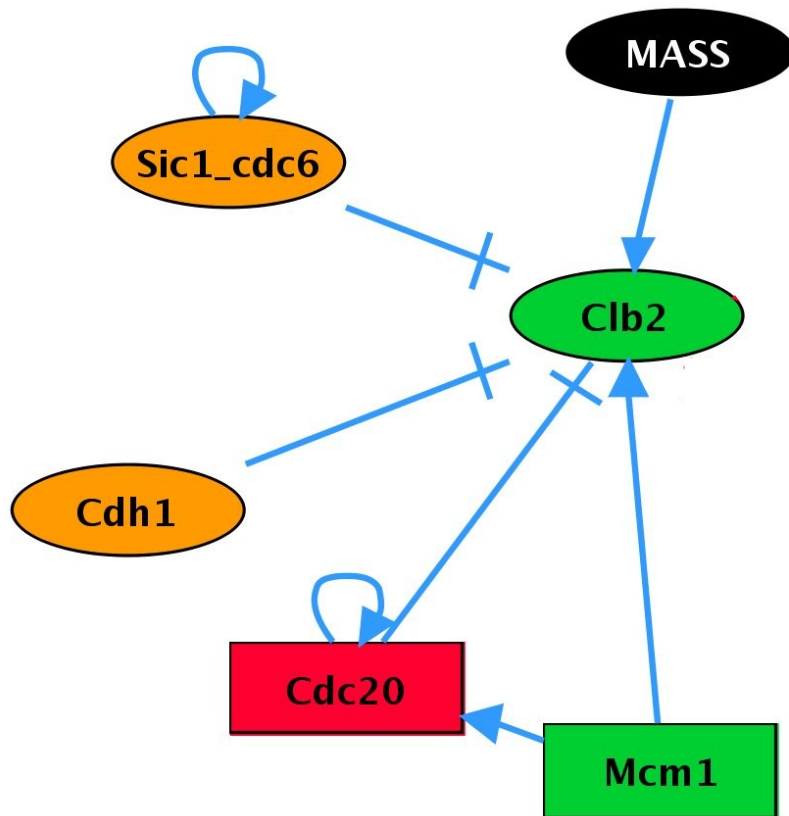
Reference: Chen et al., Mol. Biol. Cell, 15:3841-62, 2004.

Plugging the Module

Rewiring



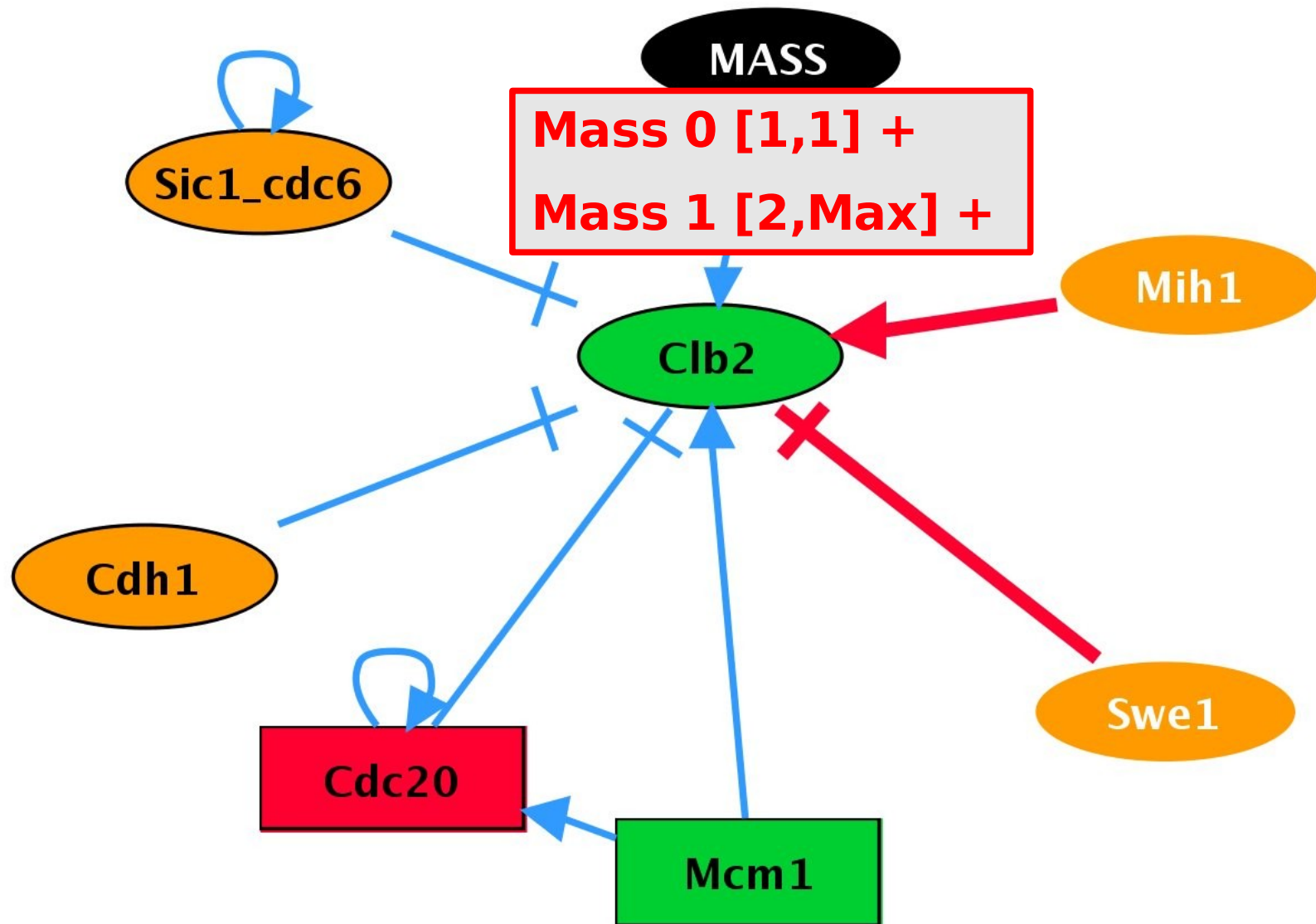
Rewiring: Clb2 Input



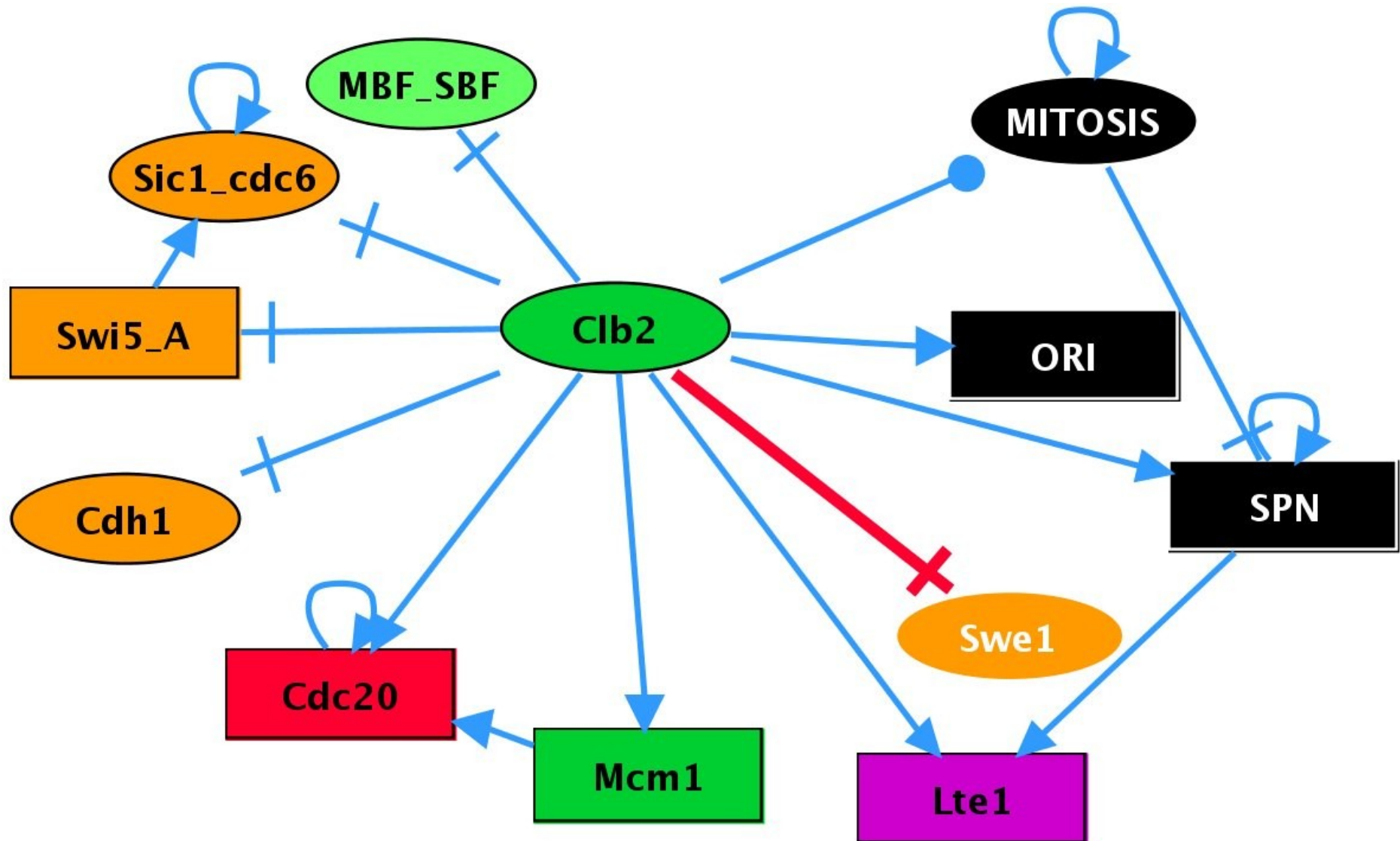
Swe1 0 [1,1] -
 Swe1 1 [2,Max] -
Mass 0 [1,1] +
Mass 1 [2,Max] +
 Mih1 0 [1,1] +
 Mih1 1 [2,Max] +

Mcm1 0 [1,Max] +
 Sic1_cdc6 0 [1,Max] -
 Cdh1 0 [1,Max] -
MASS 0 [1,Max] +
 Cdc20 0 [1,Max] -

Rewiring: Clb2 Input



Rewiring: Clb2 Output



Rewiring: Clb2 Output: Thresholds

Interactions from Clb2:

Core model

[1,1]

[2,2]

[2,max]

[3,max]

Morphogenesis

[1,max]

=> [1,max](Morpho) -----> **[2,max]**

Rewiring: Cib2 Parameters

Core model

```
2 MASS_0
3 MASS_0 Mcm1_0
2 Cdc20_0 MASS_0 Mcm1_0
```

Morphogenesis module

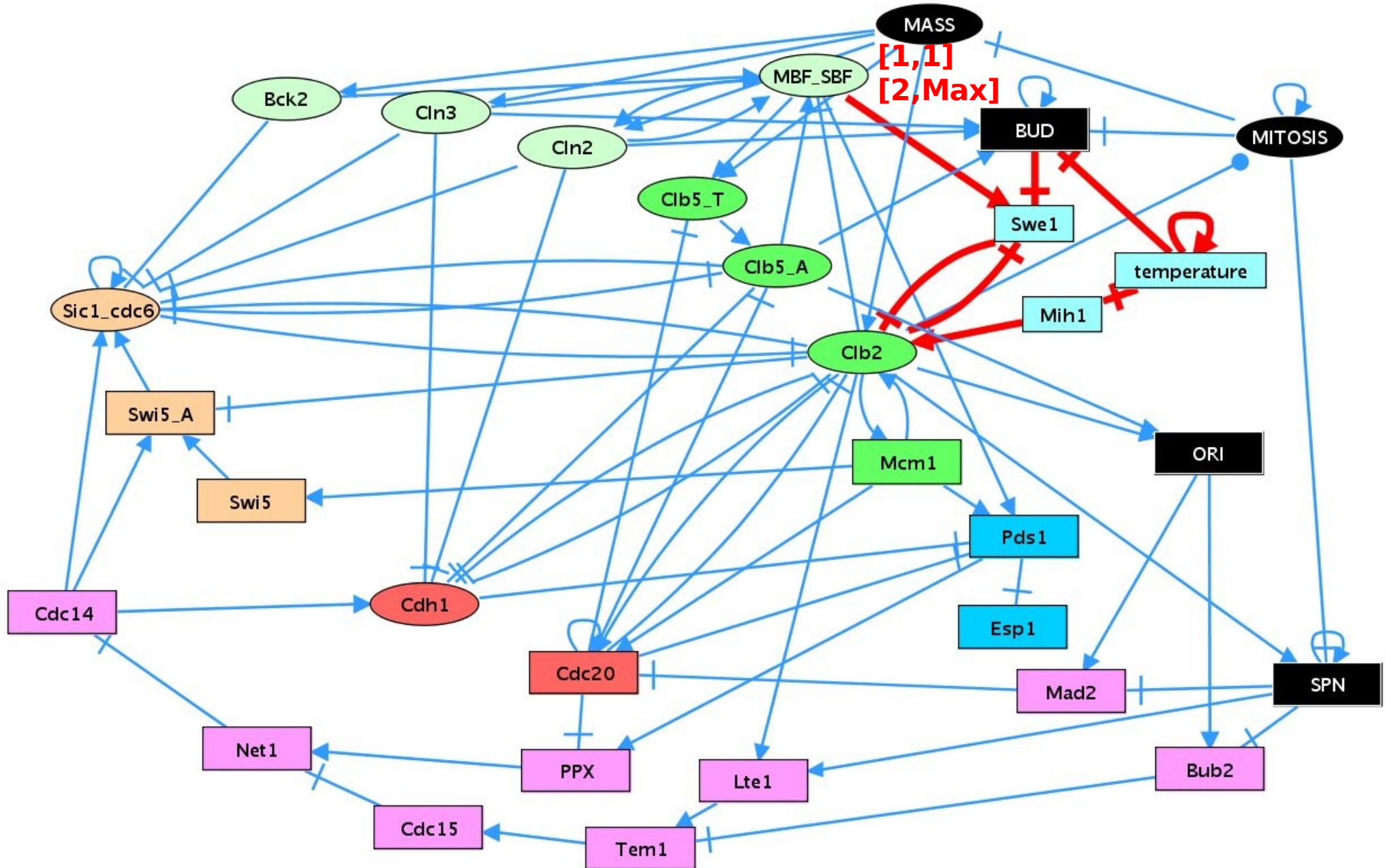
```
1 Mass_0
1 Mih1_0 Mass_0
1 Mih1_1 Mass_0
0 Swe1_0 Mass_0
0 Swe1_1 Mass_0
0 Swe1_0 Mih1_0 Mass_0
1 Swe1_0 Mih1_1 Mass_0
0 Swe1_1 Mih1_0 Mass_0
1 Swe1_1 Mih1_1 Mass_0
1 Mass_1
1 Mih1_0 Mass_1
1 Mih1_1 Mass_1
1 Swe1_0 Mass_1
0 Swe1_1 Mass_1
1 Swe1_0 Mih1_0 Mass_1
1 Swe1_0 Mih1_1 Mass_1
1 Swe1_1 Mih1_0 Mass_1
1 Swe1_1 Mih1_1 Mass_1
```

Coupled model

```
2 MASS_0
3 Mcm1_0 MASS_0
2 Mcm1_0 MASS_0 Cdc20_0
2 MASS_0 Mih1_0
3 Mcm1_0 MASS_0 Mih1_0
2 Mcm1_0 MASS_0 Cdc20_0 Mih1_0
2 MASS_0 Mih1_1
3 Mcm1_0 MASS_0 Mih1_1
2 Mcm1_0 MASS_0 Cdc20_0 Mih1_1
```

...

Resulting Model



Results: Behaviour

Wild type, permissive temp.:

Sequence of **activations** and **inhibitions**:
expected behaviour.

Mutants:

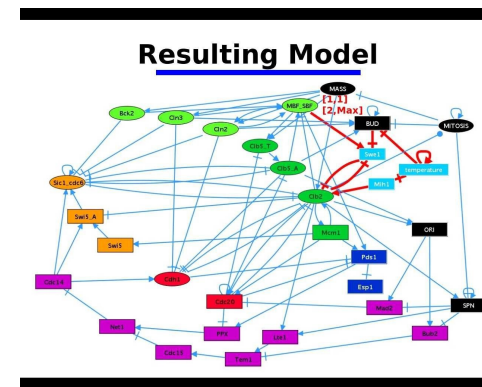
Analysis in terms of **stable states**:
the properties of individual modules are
conserved in the coupled model.

Conclusion and prospects

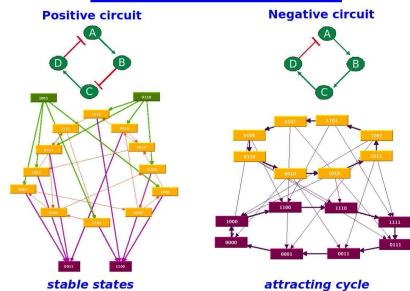
Conclusion and prospects

Results

coupling of the two models
simple method
preserves behaviour



Circuit functionality



Work in progress

mutants analysis
circuit analysis

Further prospects

coupling of other modules
model checking
automation?

Acknowledgements



Marseille, France:

Denis Thieffry

Claudine Chaouiya

Aurélien Naldi

Fabrice Lopez



IFOM FONDAZIONE
ISTITUTO FIRG
DI ONCOLOGIA MOLECOLARE

Milano, Italy

Andrea Ciliberto

Financial support:

EU STREP-DIAMONDS

<http://www.sbcellcycle.org/index.htm>



Download GINsim:

<http://gin.univ-mrs.fr/>