

Steady state analysis of Boolean network models

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Modeling paradigm:
state-discrete, time-discrete models

Special case: Boolean networks

$$f = (f_1, \dots, f_n): \{0, 1\}^n \rightarrow \{0, 1\}^n$$

which each

$$f_i: \{0, 1\}^n \rightarrow \{0, 1\}$$

a Boolean function.

Polynomial dynamical systems

View $\{0, 1\}$ as a field \mathbf{F}_2 , with addition and multiplication modulo 2.

Then each f_i can be represented as a polynomial function with coefficients in \mathbf{F}_2 .

Furthermore, each variable in f_i appears with exponent 1.

Steady state analysis for BN

Find all \mathbf{x} such that

$$f(\mathbf{x}) = (f_1(\mathbf{x}), \dots, f_n(\mathbf{x})) = \mathbf{x}.$$

Equivalently: $f_i(\mathbf{x}) = x_i$ for all i

Existing methods

- Model reduction (“steady state approximation”)
- Graph-theoretic reduction (minimal feedback vertex sets)
- SAT methods
- Integer programming methods
- Strategic sampling
- Binary decision diagrams

Steady state analysis of Boolean molecular network models via model reduction and computational algebra

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Algorithm:

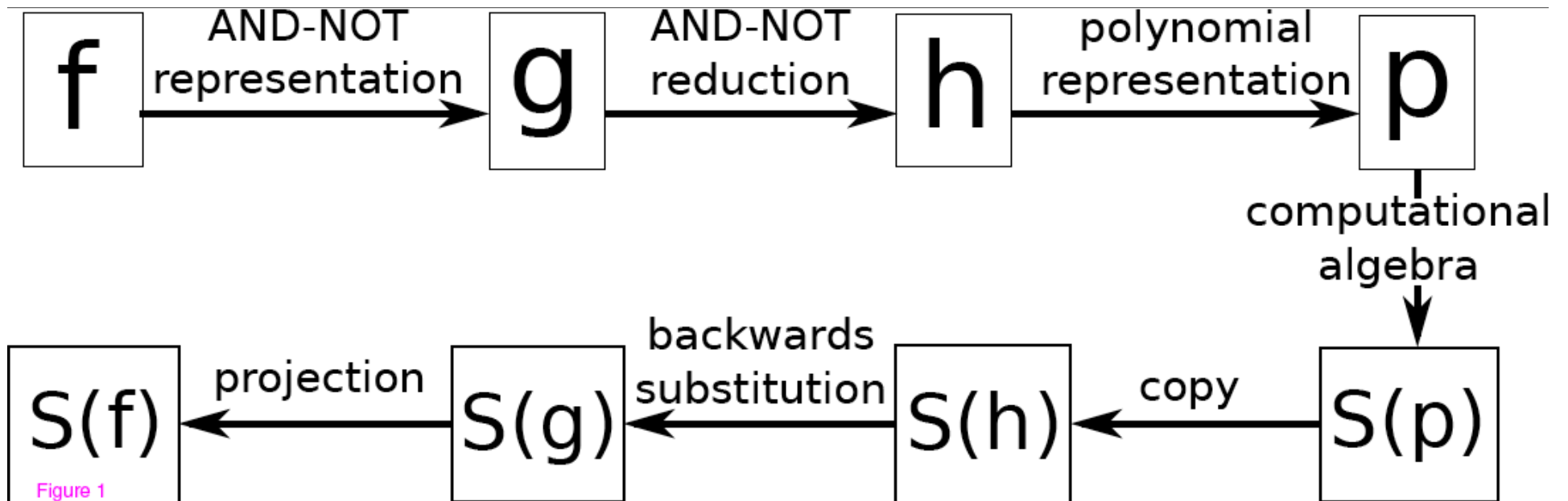


Figure 1

Step 1: Transformation to AND-NOT logic

Theorem. Let $f = (f_1, \dots, f_n): \{0, 1\}^n \rightarrow \{0, 1\}^n$ be a general BN. Then there exists an AND-NOT BN $g: \{0, 1\}^m \rightarrow \{0, 1\}^m$ for some $m \geq n$, such that there is a constructive one-to-one correspondence between the steady states of f and g .

Furthermore, m is “not much bigger than” n .

Example

Let $f = x \vee -y$.

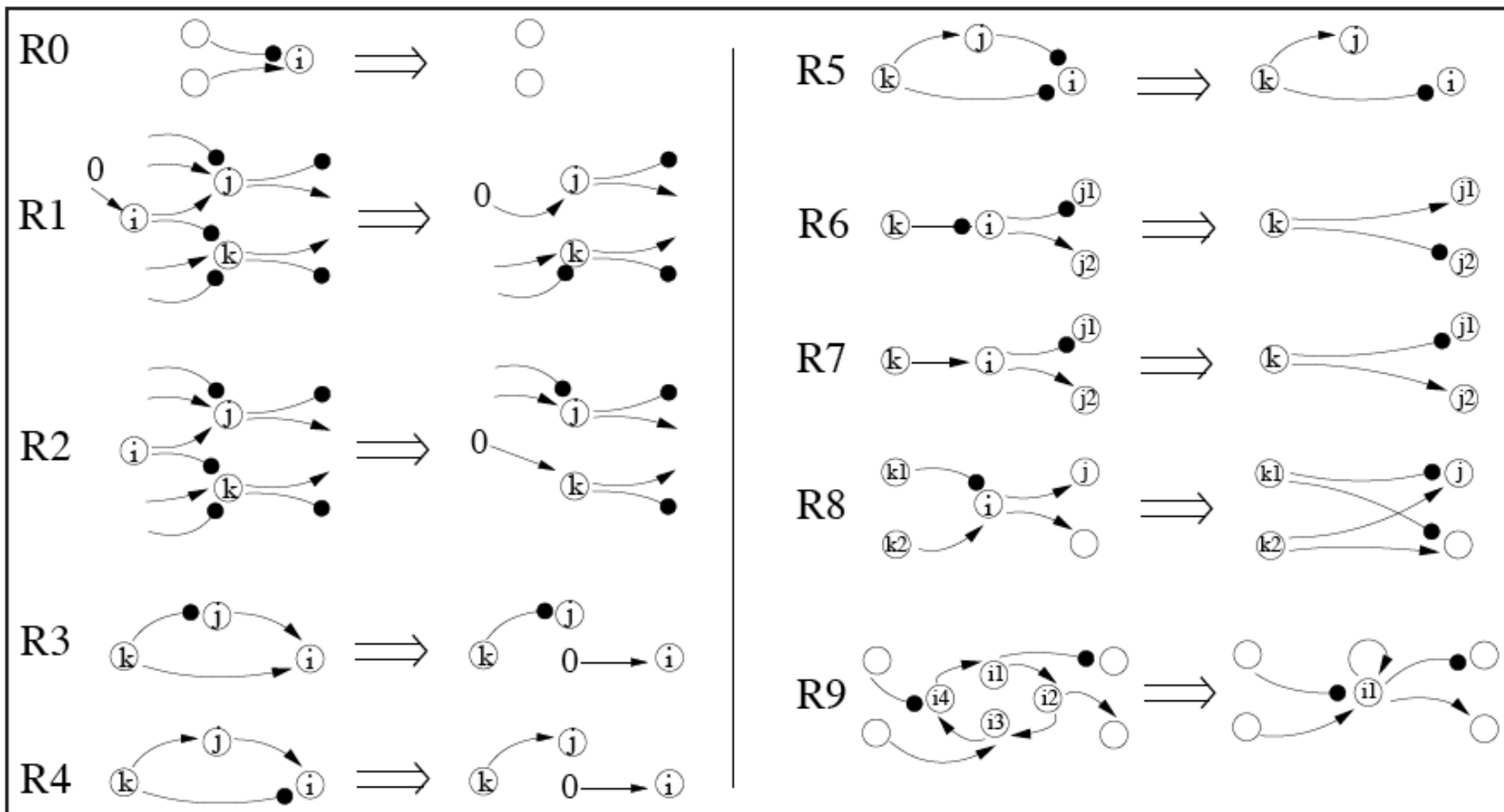
Introduce a new variable z with function

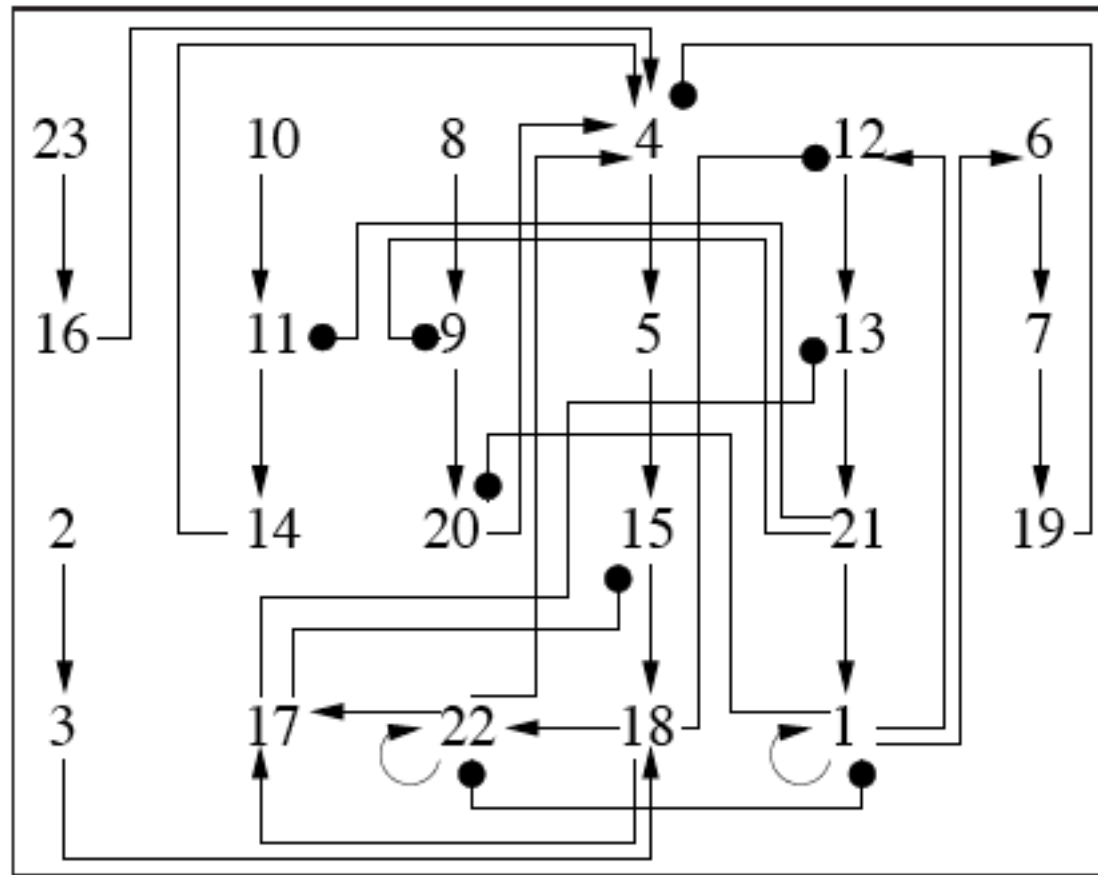
$g = -x \wedge y$.

Then $f = -z$.

Step 2: Model reduction

Theorem. Let f be an AND-NOT network. Then there is an AND-NOT network g , obtained from f by applying the reduction rules R0-R9 below, and a one-to-one correspondence between the steady states of f and g .





Mendoza, Xenarios, Theor. Biol. And Med., 2006

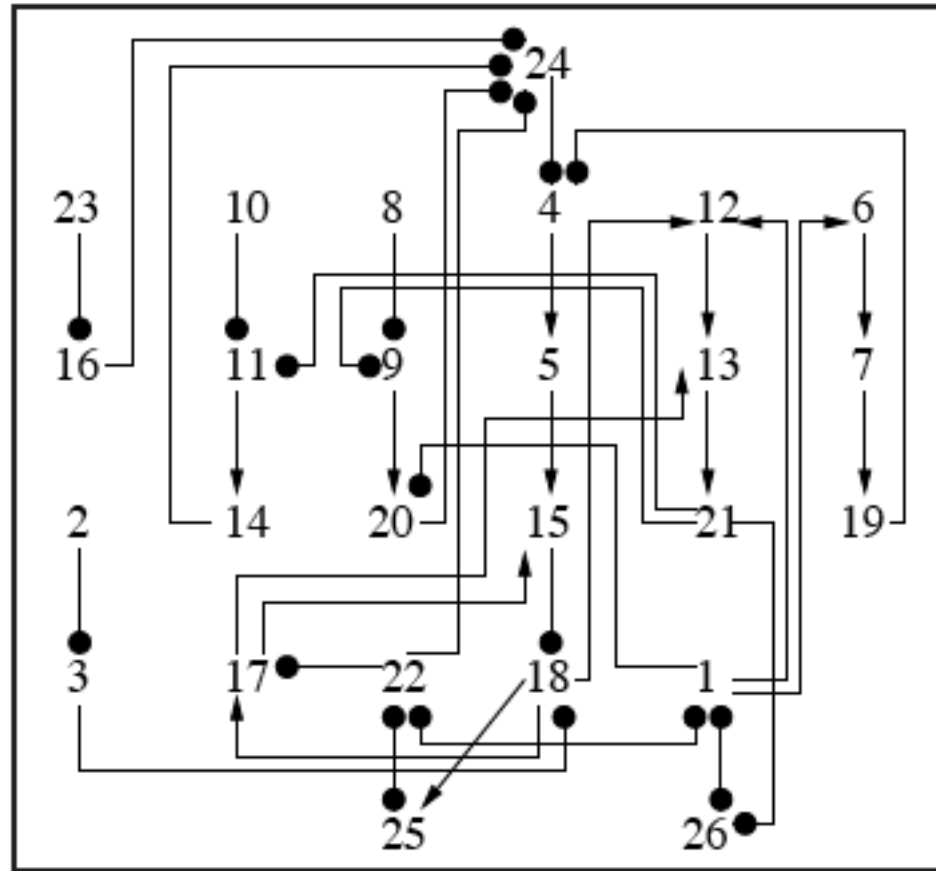


FIGURE 11. AND-NOT model of Th-cell differentiation.

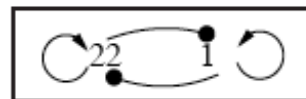


FIGURE 12. Reduced AND-NOT network for Th-cell differentiation obtained by our algorithm.

Step 3: polynomial system solving

- For a BN f , view f as described by polynomial functions f_i .
- To find all \mathbf{x} such that $f_i(\mathbf{x}) = x_i$ for all i is equivalent to solving the system of polynomial equations

$$f_i(\mathbf{x}) - x_i = 0 \text{ for all } i.$$

This can be done using standard computer algebra algorithms.

Performance

Timing in seconds for Kauffman networks with $K = 2$.

n	mean	stdev.
2000	0.490	0.023
4000	1.123	0.049
6000	2.172	0.114
8000	3.642	0.212
10000	5.218	0.235

Timing in seconds for Kauffman networks with $K = 3$.

n	mean	stdev.
20	0.273	0.040
40	0.300	0.126
60	0.415	0.552
80	1.143	8.414
100	2.878	16.74
120	9.278	51.79

Table 3 Timing in seconds for power-law networks with average connectivity $\langle k \rangle = 2$.

n	mean	stdev.
25	0.254	0.011
50	0.257	0.018
100	0.260	0.022
250	0.271	0.046
500	0.358	1.429
1000	6.798	65.39

Table 4 Timing in seconds for power-law networks with average connectivity $\langle k \rangle = 3$.

n	mean	stdev.
20	0.251	0.029
40	0.259	0.055
60	0.288	0.222
80	0.543	4.724
100	1.331	7.752
120	3.033	25.94
140	7.185	57.23

Table 5 Timing in seconds for published models. *=49% of simulations reported, 51% of simulations were stopped because they did not finish in a day or had a large memory consumption.

n	$\langle k \rangle$	mean	stdev.
62	1.62	0.231	0.010
94	1.65	0.234	0.012
302	1.71	0.236	0.011
60	2.10	0.239	0.013
120	2.45	0.312	0.141
54	2.59	0.256	0.030
54	3.62	0.492	0.247
76	4.01	0.242	0.013
130	5.00	23.19	98.42
225	5.16	4186*	12284

Discussion

- Can be extended to multi-state models using work of Chaouyia et al.
- Computing steady states of large models is feasible.
- Obtain better performance by combining different methods.
- Method cannot be generalized to finding periodic attractors.

“A Model in Every Lab”

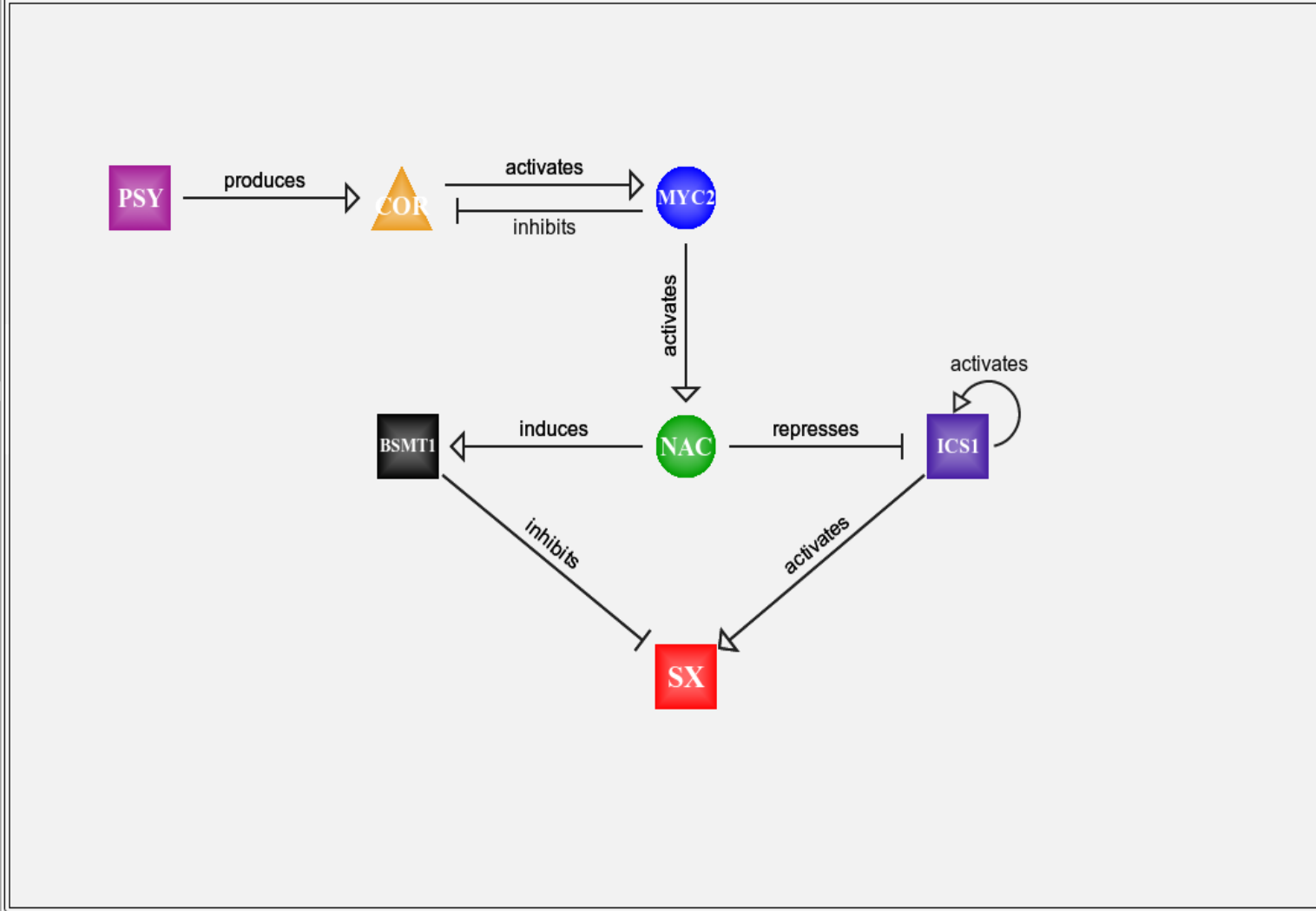
Discrete models can be intuitive, flexible, and accessible to experimentalists.

Mathematical back end of a modeling software, *PlantSimLab*.

Model Editor Experimental Setup Analysis Results Viewer

Save Hand Pointer Zoom In Zoom Out Camera Mute Play Pause Stop Reset Go

- Model: Demo1
 - Model
 - Experiments
 - Default
 - Setup
 - Results
 - Cyclone
 - Control
 - Network Reduction
 - Reverse Engineering
 - Experiment_1
 - Setup
 - Results
 - Cyclone
 - Control
 - Network Reduction
 - Reverse Engineering



Model=Demo1 Saved successfully

Node Specification

Short Name:

Full Name:

Number of States:

Color:

Shape:

Edge Specification

Edge Name:

Timescale:

Input(t)		Output(t+Δt)
COR	MYC2	MYC2
low	low	<input type="text" value="low"/>
low	high	<input type="text" value="high"/>
high	low	<input type="text" value="high"/>
high	high	<input type="text" value="high"/>

Node States Specifications

State 1	<input type="text" value="low"/>
State 2	<input type="text" value="high"/>

State Transition Table

Timescale:

	Input(t)		Output(t+Δt)
	NAC	ICS1	ICS1
NAC	low	low	<input type="text" value="low"/>
	low	high	<input type="text" value="high"/>
	low	low	<input type="text" value="high"/>
	low	high	<input type="text" value="high"/>
	high	low	<input type="text" value="low"/>
	high	low	<input type="text" value="low"/>
	high	high	<input type="text" value="low"/>
	high	high	<input type="text" value="high"/>

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Several postdoc positions available at the
UConn Center for Quantitative Medicine
in the groups of

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Mendes

Vera-Licona

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