Discrete modeling of regulatory networks

Alexander Bockmayr
FU Berlin
SS 2014

1. Introduction

Mathematical modeling approaches

- Continuous
  - Ordinary differential equations
  - Partial differential equations
- Discrete
  - Logical networks
  - Petri nets
  - Process calculi
- Hybrid discrete/continuous
- Stochastic

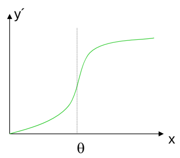
Differential vs. logical descriptions

- Differential
  - Continuous variables
  - State as a function of time
  - (Nonlinear) differential equations
- Logical
  - Discrete variables (small number of distinct levels)
  - Finitely many states, discrete switch
  - Logical equations, time delays

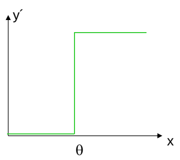
⇒ quantitative vs. qualitative modeling

Regulatory interactions

- Sigmoid function
  - x activates synthesis of y
  - threshold θ



- Approximation by a step function



- Idealization

Logical modeling

- Boolean vs. multi-valued logic
- Synchronous vs. asynchronous dynamics
- deterministic vs. non-deterministic

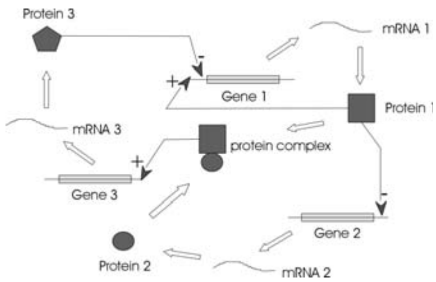
Early history (1960s, 1970s):

Sugita, Kauffman, Glass, Thomas, …

2. Kinetic logic

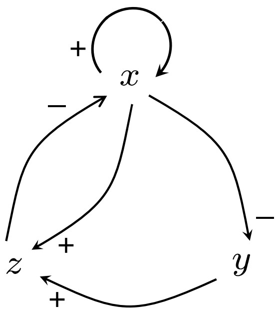
R. Thomas: Boolean formalization of genetic control circuits. J. Theor. Biol. 42, 565 – 583, 1973

Gene regulatory network



http://www.zaik.uni-koeln.de/AFS/

Interaction graph



Logical variables

- Genes X, Y, …
- Logical Variables X , Y, …
  - X = 0 : gene X off
  - X = 1 : gene X on
- Gene products x, y, …
- Logical variables x , y , …
  - x = 0 : gene product x absent
  - x = 1: gene product x present

Logical functions

State of a gene depends on presence or absence of gene products

$$X = \Phi(x, y, z, \ldots)$$
$$Y = \Psi(x, y, z, \ldots)$$

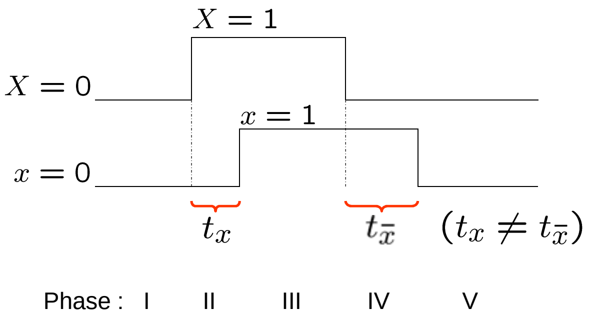
where Φ and Ψ are logical (Boolean) functions.

Examples

$$X = \bar{z}$$
$$Y = \bar{z} \wedge u$$

- Gene X is on iff product z is absent
- Gene Y is on iff product z is absent and product u is present

Time delays

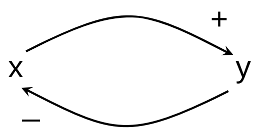


Logical network

- N = (V, F)
- V = {x_1, …, x_n} a set of n Boolean variables $x_i \in$ {0,1}
- F = {ϕ_1, …, ϕ_n} a set of Boolean functions ϕ_i : $\{0,1\}^n \rightarrow \{0,1\}$

Two-element negative circuit

- Suppose product x activates gene Y, and product y represses gene X.
- Interaction graph



Formalization

- N = (V,F)
- V = {x, y}
- F = {Φ, Ψ} with

$$X = \Phi(x, y) = \bar{y}$$
$$Y = \Psi(x, y) = x$$

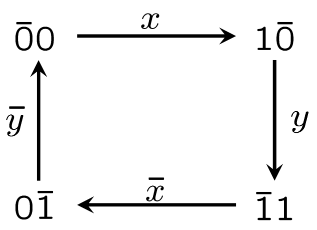
State table

x	y	X	Y
0	0	1	0
0	1	0	0
1	0	1	1
1	1	0	1

or

x	y
$\bar{0}$	0
0	$\bar{1}$
1	$\bar{0}$
$\bar{1}$	1

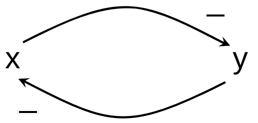
State transition graph



Periodic behavior

Two-element positive circuit

- Two genes each of which is repressed by the product of the other
- Interaction graph



Formalization

- N = (V,F)
- V = $\{x, y\}$
- F = $\{\Phi, \Psi\}$ with

$$X = \Phi(x,y) = \bar{y}$$
$$Y = \Psi(x,y) = \bar{x}$$

State table

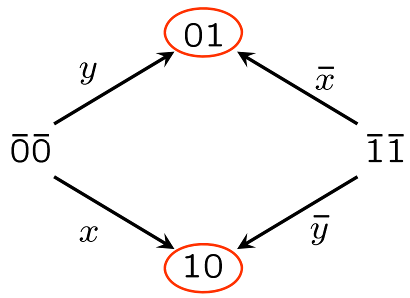
x	y	X	Y
0	0	1	1
0	1	0	1
1	0	1	0
1	1	0	0

or

x	y
$\bar{0}$	$\bar{0}$
0	1
1	0
$\bar{1}$	$\bar{1}$

Two stable states

State transition graph



Multiple stable states