Remarks

- The actual transitions depend on the time delays, e.g.

$$\begin{tikzcd}
 & 10 \quad \text{if } t_x < t_y \\
00 \arrow[ur, "x"] \arrow[dr, "y"'] & \\
 & 01 \quad \text{if } t_y < t_x
\end{tikzcd}$$

- The transitions $00 \longrightarrow 11$, with $t_x = t_y$, and $00 \longleftarrow 11$, with $t_{\bar{x}} = t_{\bar{y}}$, are not included.

States

- State of the system

$$(x_1, \dots, x_n) \in \{0,1\}^n$$

- Extended state

$$(x_1, \dots, x_n, X_1, \dots, X_n) \in \{0,1\}^{2n}$$

- $X_i = \Phi_i(x_1, \dots, x_n)$: Effect of $x_1, \dots, x_n$ on the gene X_i that produces x_i.

Simplified notation (in the Boolean case)

$$(\tilde{x}_1, \dots, \tilde{x}_n),$$

where $\tilde{x}_i$ means that we put a dash over x_i iff

$$x_i \neq \Phi_i(x_1, \dots, x_n)$$

State transition graph

- Nodes States

$$(x_1, \dots, x_n) \in \{0,1\}^n$$

- Arcs State transitions

$$(x_1, \dots, x_{i-1}, \quad x_i, \quad x_{i+1}, \dots, x_n)$$
$$\downarrow$$
$$(x_1, \dots, x_{i-1}, \quad \Phi_i(x_1, \dots, x_n), \quad x_{i+1}, \dots, x_n),$$

if $x_i \neq \Phi_i(x_1, \dots, x_n)$ (update only 1 variable)

⇨ non-deterministic dynamics

Stable states

A state

$$(x_1, \dots, x_n) \in \{0,1\}^n$$

is stable

iff there is no transition to another state

$$(x'_1, \dots, x'_n) \in \{0,1\}^n,$$

i.e.,

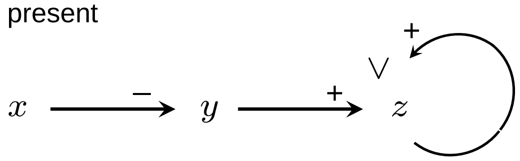
$$x_i = \Phi_i(x_1, \dots, x_n),$$

for all i = 1,…,n.

3. Kinetic logic (II)
Selecting pathways

Three variable example

- Gene X expressed constitutively
- Gene Y expressed only in absence of product x
- Gene Z expressed if product y or z is present

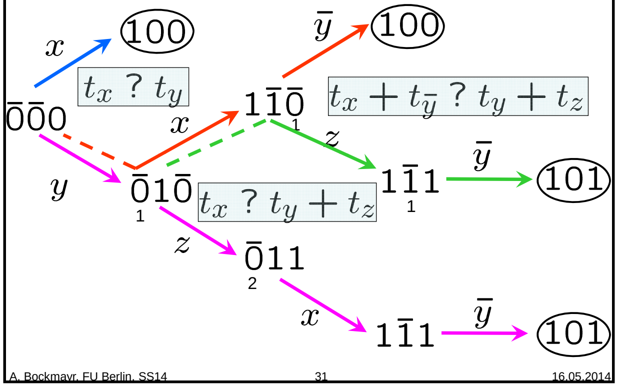


Logical description

$$X = 1$$
$$Y = \bar{x}$$
$$Z = y \vee z$$

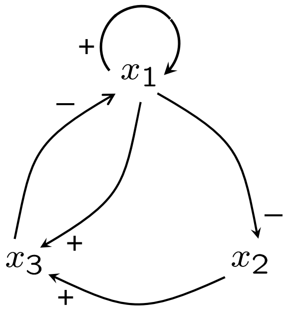
x	y	z	X	Y	Z
0	0	0	1	1	0
0	0	1	1	1	1
0	1	0	1	1	1
0	1	1	1	1	1
1	0	0	1	0	0
1	0	1	1	0	1
1	1	0	1	0	1
1	1	1	1	0	1

Pathways



4. Continuous and discrete models of gene regulation

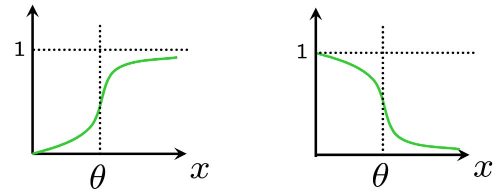
Interaction graph



Continuous model

- Real variables $x_1,\ldots,x_n$:
  x_i gives the concentration of the product of gene i.
- Regulatory interaction: Activation/inhibition of x_i by x_j is effective only if x_j lies above a certain threshold θ_{ij}.

Hill functions



$$F_m^+(x,\theta) = \frac{x^m}{\theta^m + x^m}, \quad F_m^-(x,\theta) = \frac{\theta^m}{\theta^m + x^m}$$

Kinetics

- Effect of activation/inhibition of x_i by x_j described by kinetic parameter k_{ij}
- Degradation rate: k_{-i}

ODE model

For i = 1,…,n:

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} k_{ij} F_m^{\alpha_{ij}}(x_j, \theta_{ij}) - k_{-i} x_i$$

where

$$k_{ij} \geq 0, \alpha_{ij} \in \{+,-\}, k_{-i} > 0, m \geq 1.$$

Piecewise linear ODE model

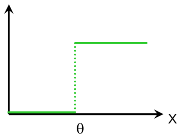
For m → ∞:

$$\frac{dx_i}{dt} = \sum_{j=1}^{n} k_{ij} F^{\alpha_{ij}}(x_j, \theta_{ij}) - k_{-i} x_i$$

where $k_{ij} \geq 0, \alpha_{ij} \in \{+,-\}, k_{-i} > 0,$

$$F^+(X,\theta) = \begin{cases} 1, & \text{if } X > \theta \\ 0, & \text{if } X < \theta \end{cases}$$

$$F^-(X,\theta) = 1 - F^+(X,\theta)$$



Discretization

Thomas 73, Snoussi 89

- Suppose gene i acts on n_i other genes

  ⇨ n_i thresholds

  $$0 < \theta^1 < \theta^2 < \ldots < \theta^{n_i}$$

- Discretization operation

$$d_i : \mathbb{R}^+ \rightarrow \{0, \ldots, n_i\}$$

$$d_i(x) = \begin{cases} 0, & \text{if } 0 < x < \theta^1 \\ 1, & \text{if } \theta^1 < x < \theta^2 \\ \vdots & \\ n_i, & \text{if } \theta^{n_i} < x \end{cases}$$

Discrete model

$$X_i' = d_i\left(\sum_{j=1}^{n} K_{ij} F^{\alpha_{ij}}(X_j, \Theta_{ij})\right)$$

where

• $X_i, X_i' \in \{0, \ldots, n_i\}$	discrete variables
• X_i' new value for X_i	discrete “derivative”
• $K_{ij} = k_{ij}/k_{-i} \geq 0$	
• $\Theta_{ij} \in \{0.5, 1.5, 2.5, \ldots\}$	discrete thresholds

Discrete dynamics

- State

$$X = (X_1, \dots, X_n),\ X_i \in \{0, \dots, n_i\}$$

- State transitions

$$(X_1, \dots, X_n) \longrightarrow (X_1, \dots, X_i \pm 1, \dots, X_n)$$

if $X_i' > X_i$ resp. $X_i' < X_i$.

- Only one variable is updated at a time.
- Several successor states are possible.

➡ Generalized kinetic logic

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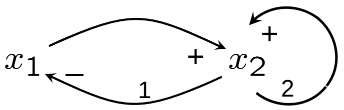
5. An illustrating example

Example



- $X_1 \in \{0,1\}$
- $X_2 \in \{0,1,2\}$
- Assume $\theta_{12} < \theta_{22}$, i.e., upon activation, X_2 acts first on X_1, then on itself.

Discrete and ODE model

$$\begin{aligned} X_1' &= d_1(K_{12}F^-(X_2, \Theta_{12})) \\ X_2' &= d_2(K_{21}F^+(X_1, \Theta_{21}) \\ &\quad +K_{22}F^+(X_2, \Theta_{22})) \end{aligned}$$

$$\begin{aligned} \frac{dx_1}{dt} &= k_{12}F_m^-(x_2, \theta_{12}) - k_{-1}x_1 \\ \frac{dx_2}{dt} &= k_{21}F_m^+(x_1, \theta_{21}) \\ &\quad +k_{22}F_m^+(x_2, \theta_{22}) - k_{-2}x_2 \end{aligned}$$

Logical parameters

$$\begin{aligned} \mathbf{K}_{ij} &\overset{\text{def}}{=} d_i(K_{ij}) \in \{0, \dots, n_i\} \\ \mathbf{K}_{ij+ij'} &\overset{\text{def}}{=} d_i(K_{ij} + K_{ij'}) \in \{0, \dots, n_i\} \end{aligned}$$

(only finitely many possible values)

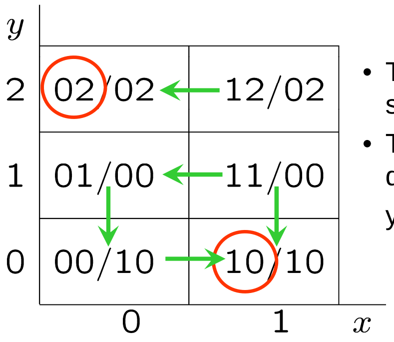
State table

X_1	X_2	X_1'	X_2'
0	0	$\mathbf{K}_{12}$	0
0	1	0	0
0	2	0	$\mathbf{K}_{22}$
1	0	$\mathbf{K}_{12}$	$\mathbf{K}_{21}$
1	1	0	$\mathbf{K}_{21}$
1	2	0	$\mathbf{K}_{21+22}$

States in phase space

X_2			
2	$02/0\mathbf{K}_{22}$	$12/0\mathbf{K}_{21+22}$	
1	$01/00$	$11/0\mathbf{K}_{21}$	
0	$00/\mathbf{K}_{12}0$	$10/\mathbf{K}_{12}\mathbf{K}_{21}$	
	0	1	X_1

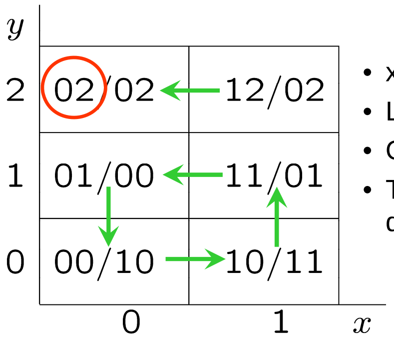
K_{12} = 1, ***K_{21} = 0***, K_{22} = 2, K_{21+22} = 2



y			
2	02/02	12/02	
1	01/00	11/00	
0	00/10	10/10	
	0	1	x

- Two stable states
- Two separate domains for y > 1 and y ≤ 1

K_{12} = 1, ***K_{21} = 1,*** K_{22} = 2, K_{21+22} = 2



y			
2	02/02	12/02	
1	01/00	11/01	
0	00/10	10/11	
	0	1	x

- x acts on y
- Logical cycle
- One stable state
- Two separate domains

Stable state

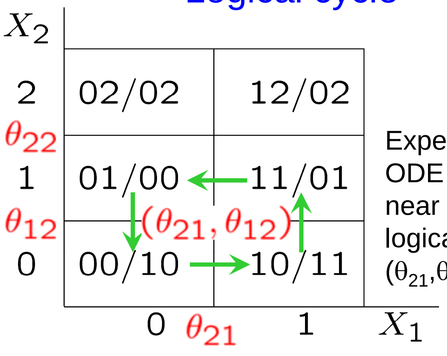
- Stable logical state : 02
- Corresponds to the region $0 < x_1 < \theta_{21}$ and $\theta_{22} < x_2$ in the phase plane, i.e., $F^+(x_1,\theta_{21}) = 0$, $F^+(x_2,\theta_{12}) = F^+(x_2,\theta_{22}) = 1$.
- Steady state equations

$$\frac{dx_1}{dt} = k_{-1}x_1 = 0, \quad \frac{dx_2}{dt} = k_{22} - k_{-2}x_2 = 0$$

- Steady state

$$x_1 = 0, \quad x_2 = k_{22}/k_{-2} = K_{22}$$

Logical cycle



X_2			
2	02/02	12/02	
θ_{22}			
1	01/00	11/01	
θ_{12}	$(\theta_{21},\theta_{12})$		
0	00/10	10/11	
	0 θ_{21}	1	X_1

Expect focus in ODE description near singular logical state (θ_{21},θ_{12})

Parameter inference

$$\mathbf{K}_{ij} = d_i(K_{ij}) = d_i(k_{ij}/k_{-i})$$

➡ logical parameters yield inequalities to be satisfied by ODE parameters

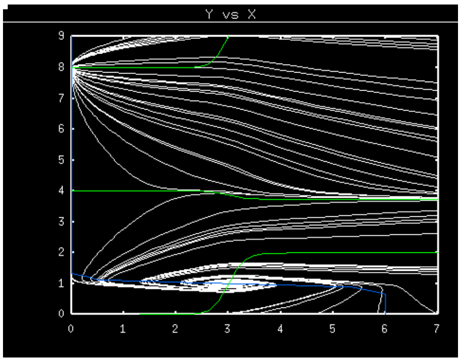
Example

- Suppose $k_{-1} = 2$, $k_{-2} = 1$
- Suppose $\theta_{12} = 1$, $\theta_{21} = 3$, $\theta_{22} = 4$
- From $\mathbf{K}_{12} = 1$, derive $K_{12} = k_{12}/k_{-1} > \theta_{21} = 3$
  Choose $K_{12} = 6$, i.e., $k_{12} = 12$
- From $\mathbf{K}_{22} = 2$, derive $K_{22} = k_{22}/k_{-2} > \theta_{22} = 4$
  Choose $K_{22} = 8$, i.e., $k_{22} = 8$
- From $\mathbf{K}_{21} = 1$, derive $1 = \theta_{21} < K_{21} < \theta_{22} = 4$,
  Choose $K_{21} = 2$, i.e., $k_{22} = 2$.

ODE model

- Stable logical state : 02
  Expected location for steady state:
  $(0, k_{22}/k_{-2}) = (0, 8)$
- Logical cycle 00 → 10 → 11 → 01 → 00
  Expected focus near
  $(\theta_{21}, \theta_{12}) = (3, 1)$
- Separatrix close to $y = \theta_{22} = 4$

Illustration



6. Multistationarity and stable periodicity

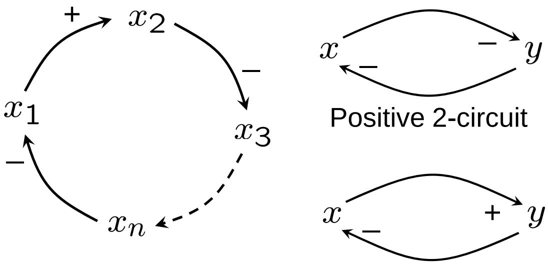
Biological properties

- Multistationarity (Differentiation)
- Stable periodic behavior (Homeostasis)
- Three models
  - ODE
  - piecewise linear ODE
  - discrete
- What information on the ODE/PL model can be obtained from the PL/discrete one ?

Steady states and periodicity

- Asymptotically stable steady states in ODE model are related to stable logical states in the discrete model (Snoussi 89).
- Stable periodicity in ODE model is related to cycles in the discrete model (Snoussi/Thomas 93).
- In a logical cycle, the equivalent of the focus in the ODE description is located at the junction of logical states, i.e., at threshold values.
- Logical description should take into account threshold values ⇨ singular logical states

Positive and negative circuits



Positive 2-circuit

Negative 2-circuit

Sign of circuit =
Product of signs of arcs

Thomas´ conjectures

Thomas´81

1. A positive circuit in the interaction graph is a necessary condition for multistationarity.
2. A negative circuit in the interaction graph is a necessary condition for stable periodic behavior.

Proofs exist in various particular cases.

Conclusion

- Modeling levels
  - ODE
  - piecewise linear ODE
  - discrete
- Biological properties
  - Multistationarity
  - Stable periodicity

Conclusion II

- Logical parameters (only finitely many combinations) ⇨ inequalities to be satisfied by kinetic parameters
- Stable logical state ⇨ asymptotically stable steady state
- Logical cycle ⇨ periodic behavior (stable/unstable focus, limit cycles)

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