Modeling gene regulatory networks by means of piecewise-linear models

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INRIA Grenoble - Rhône-Alpes and IBIS

- IBIS: systems biology group at INRIA/Université Joseph Fourier/CNRS
  - Analysis of bacterial regulatory networks by means of models and experiments
  - Biologists, computer scientists, mathematicians, physicists, …

http://ibis.inrialpes.fr

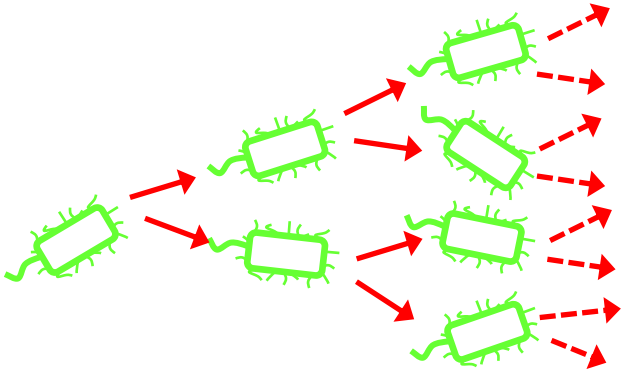
Course overview

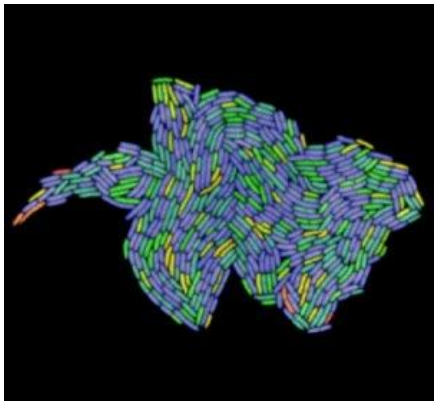
- **Gene regulatory networks**
- Piecewise-linear models of gene regulatory networks
- Solutions of piecewise-linear models
- Qualitative analysis of gene regulatory networks
- Numerical simulation of gene regulatory networks
- Conclusions

Bacterial growth

- **Bacteria** are unicellular organisms geared towards growth and division

  Escherichia coli cells have doubling times up to 20 min



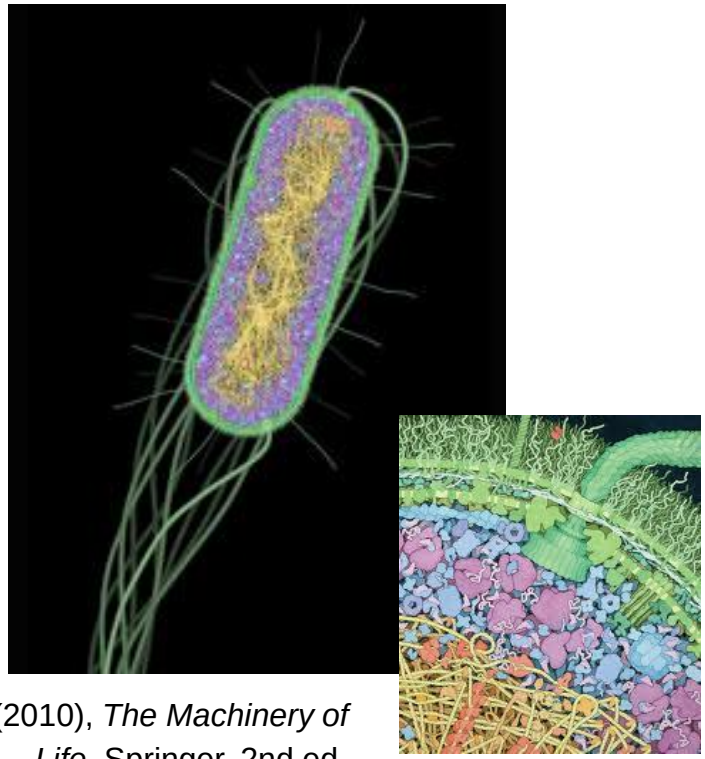


Stewart *et al.* (2005), *PLoS Biol.*, 3(2): e45

Bacterial growth

- **Bacteria** are unicellular organisms geared towards growth and division
- Growth and division require replication of cellular contents
- Cell composition (% total cell mass):
  - Proteins (~60%)
  - RNA (~15%)
  - DNA (~3%)
  - Other

Bremer and Dennis (1996), *Escherichia Coli and Salmonella*, ASM Press, 1553-69



Goodsell (2010), *The Machinery of Life*, Springer, 2nd ed.

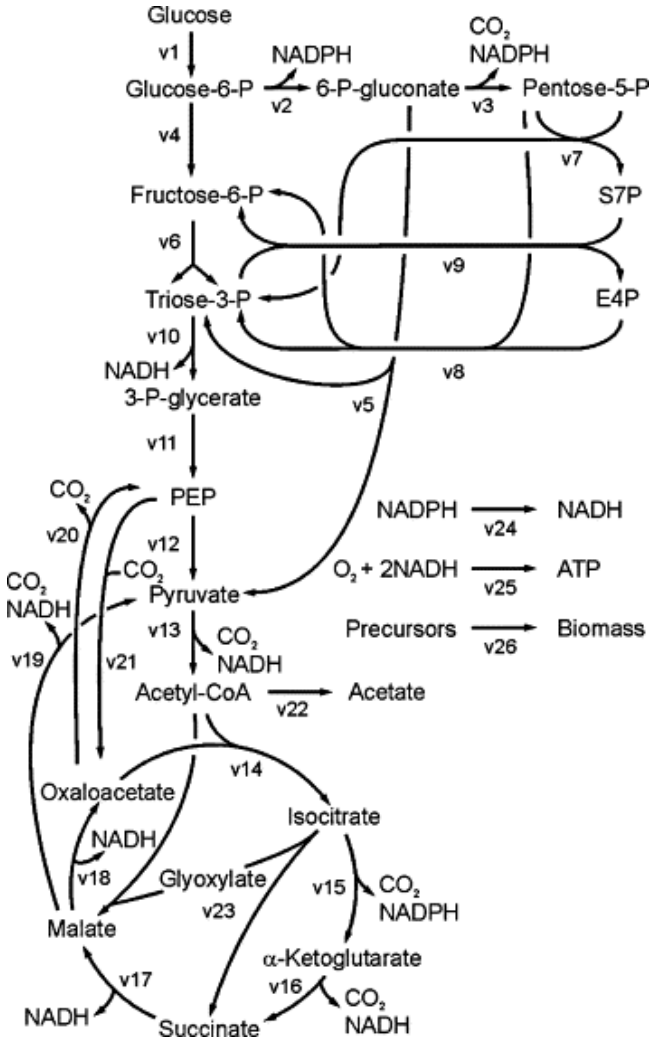
Proteins

- **Proteins** are essential for cellular functioning
  - Single *E. coli* cell contains1900 different kinds of protein and $2.4 \cdot 10^6$ protein molecules

Proteins and metabolism

- **Proteins** are essential for cellular functioning
- Proteins catalyze **metabolic reactions** that convert nutrients into energy and building blocks necessary for growth

  Enzymes

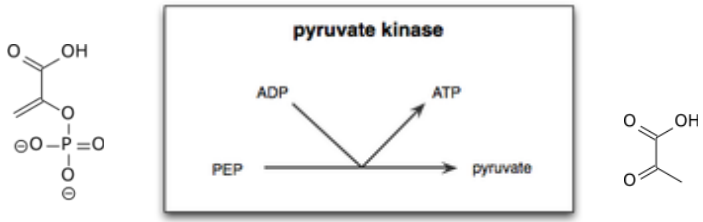


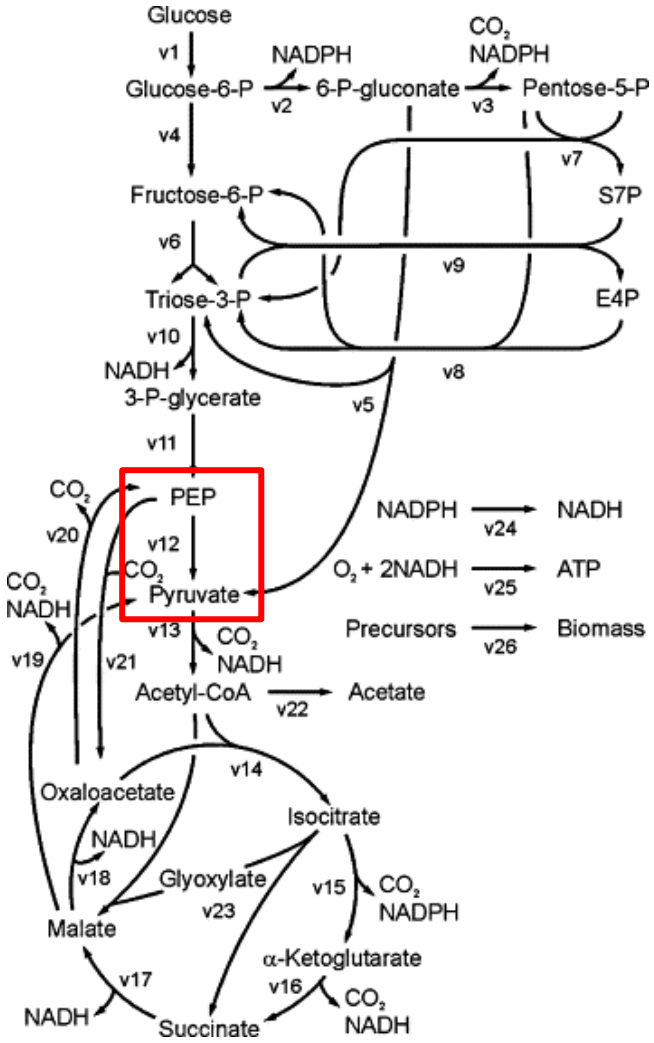
Fischer *et al.* (2004), *Anal. Biochem.*, 325(2):308–16

Proteins and metabolism

- **Proteins** are essential for cellular functioning
- Proteins catalyze **metabolic reactions** that convert nutrients into energy and precursors necessary for growth

  Enzymes

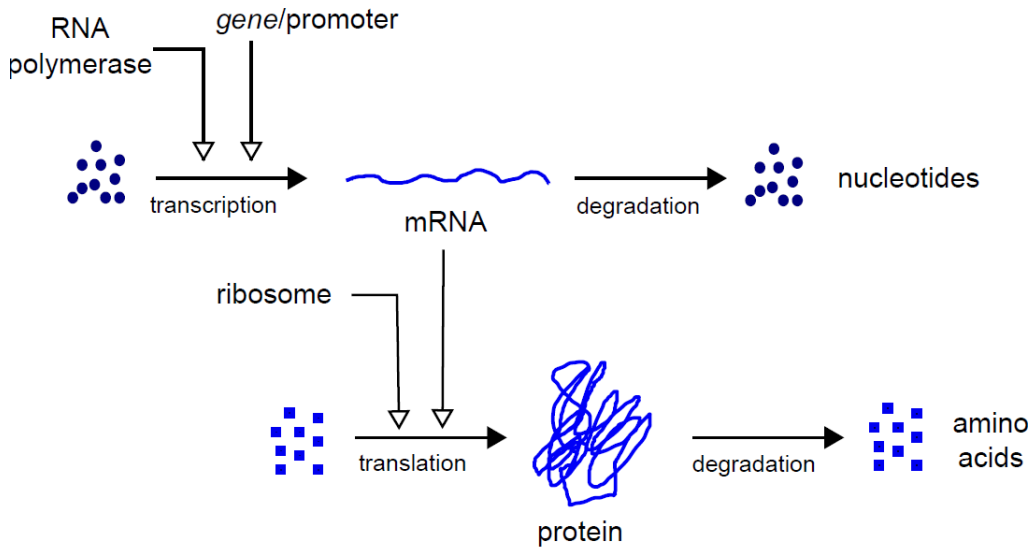




Fischer *et al.* (2004), *Anal. Biochem.*, 325(2):308–16

Proteins and gene expression

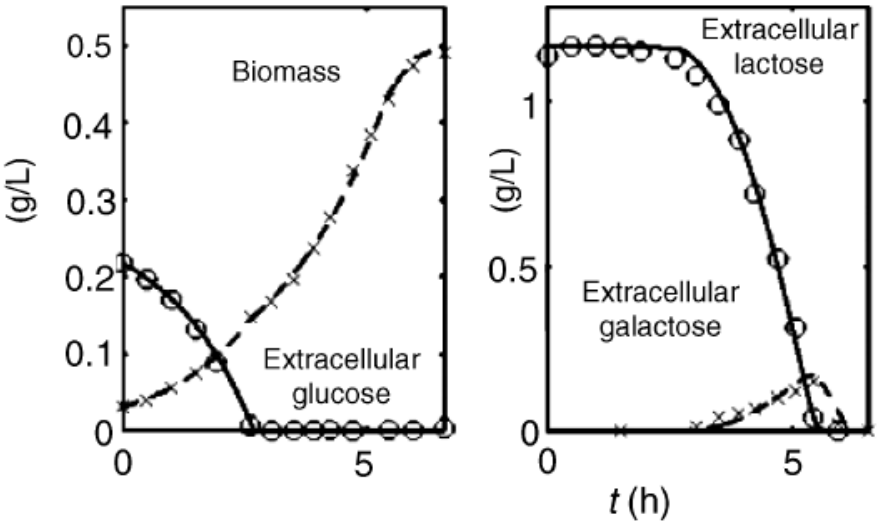
- **Proteins** are essential for cellular functioning
- Proteins compose molecular machines that **synthesize new proteins** from genetic information (DNA)
  - RNA polymerase and ribosome



Changes in protein contents of cell

- Cells need to be able to adapt protein contents to changes in environment
- Bacterial cells are able to grow on different carbon sources

  Preferential utilisation: **diauxic growth** on glucose and lactose



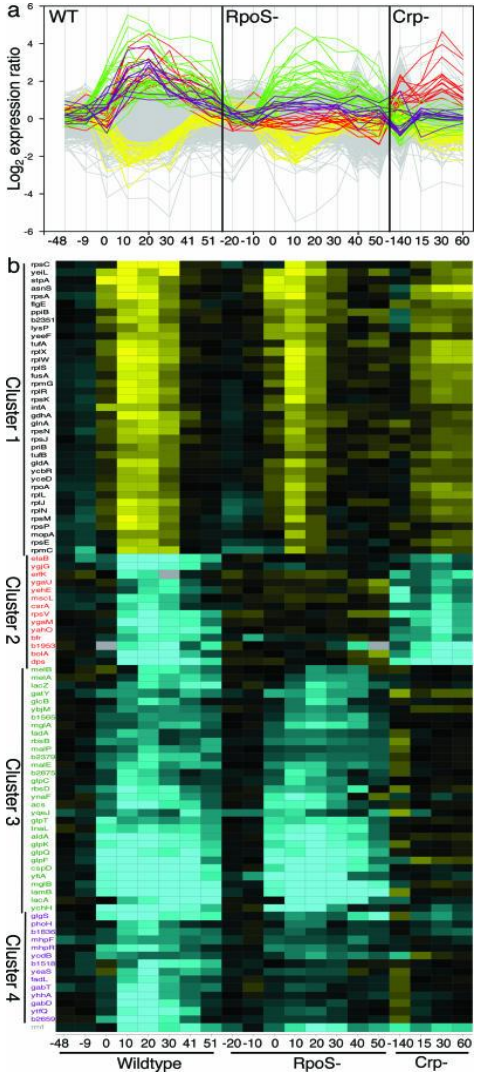
Bettenbrock *et al.* (2006), *J. Biol. Chem.*, 281(5):2578-84

- Uptake and utilization of different carbon sources requires specific proteins (enzymes)

Changes in protein contents of cell

- **Global reorganisation of gene expression** upon adaptation to different carbon source

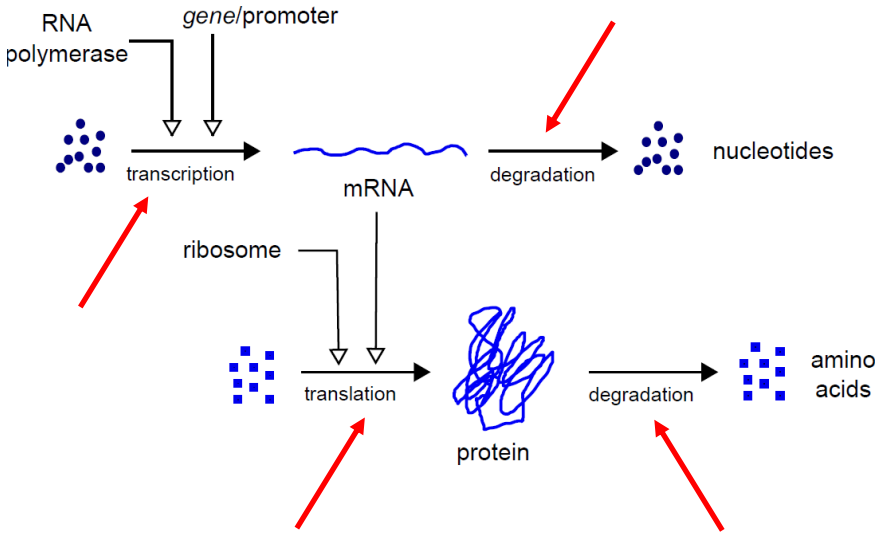
  mRNA levels during glucose-lactose shift in *E. coli*



Traxler *et al.* (2006), *Proc. Natl. Acad. Sci. USA*, 103(7):2374–9

Regulation of gene expression

- Bacterial cell controls protein contents through **regulation of gene expression**
  - Transcription regulation by transcription factors
  - Translation regulation by translation inhibitors
  - Regulation of degradation by proteases



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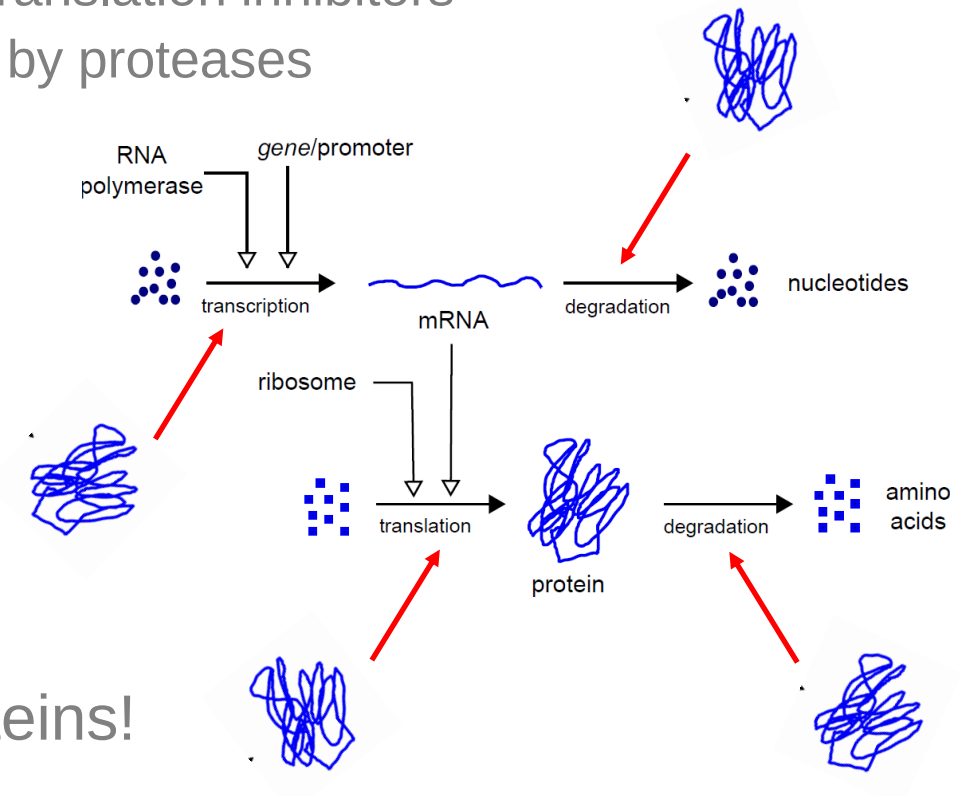
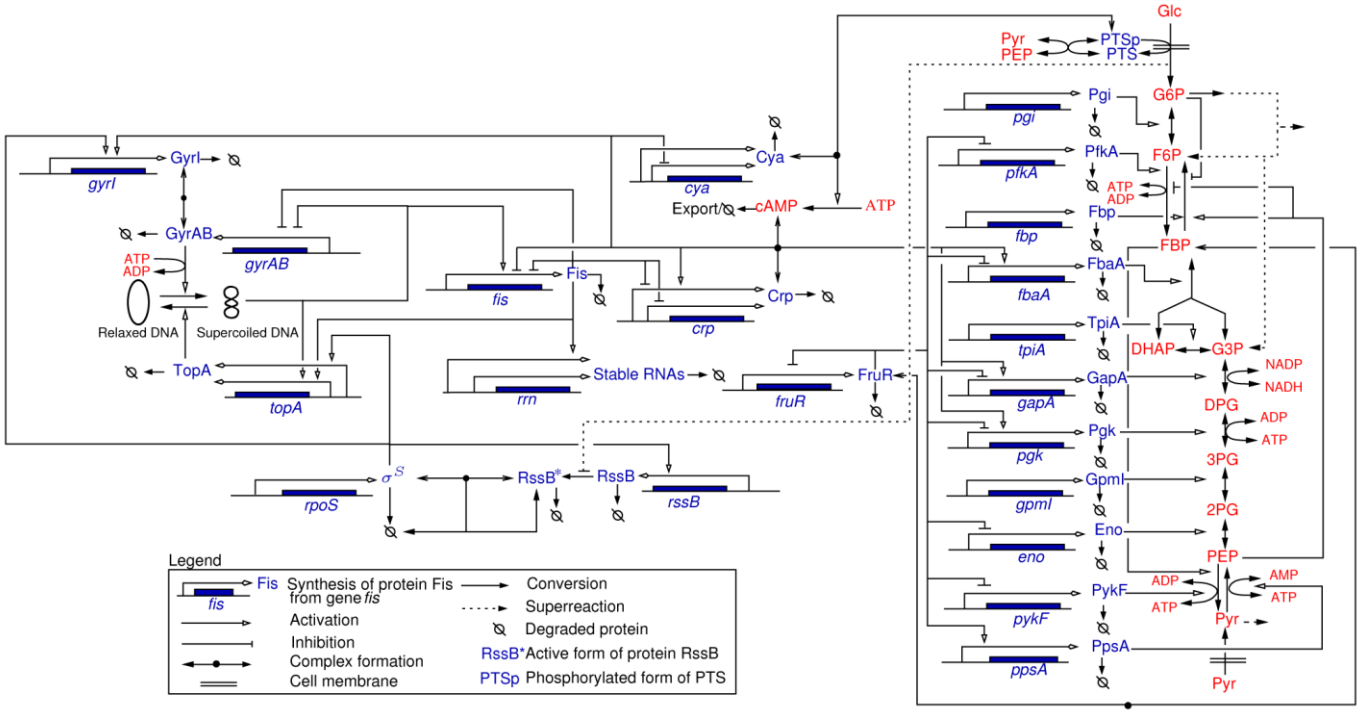


- Many regulators are proteins!

Regulatory networks

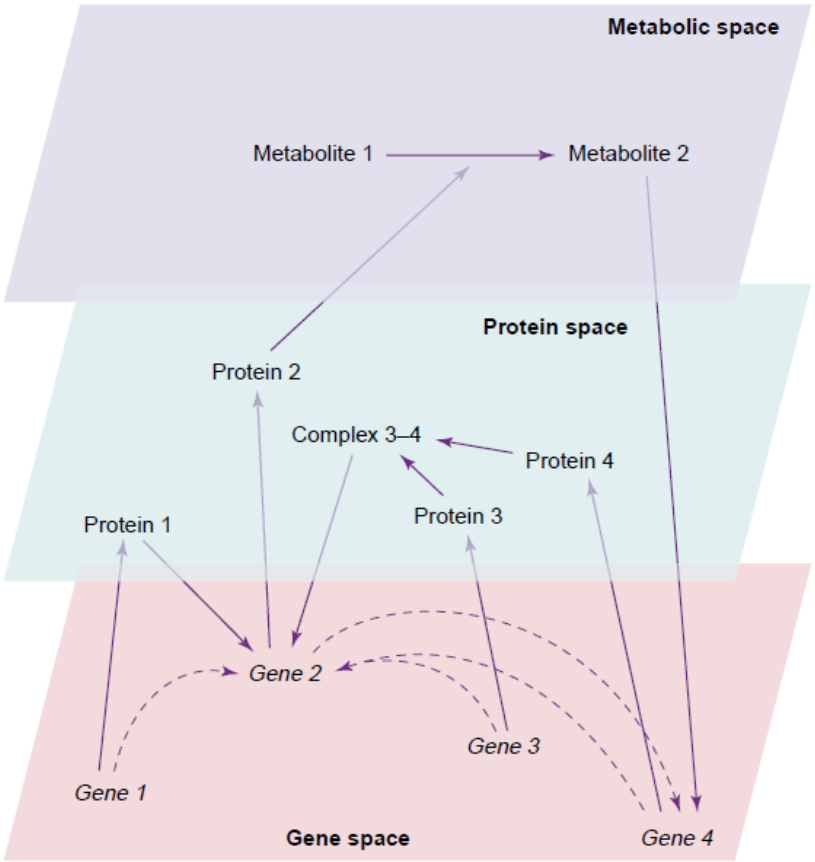
- Cellular response to external perturbations controlled by complex **regulatory networks**
  - Variety of molecular mechanisms…
  - … operating on different time-scales…
  - … involving numerous feedback loops across levels



Baldazzi *et al.* (2010), *PLoS Comput. Biol.*, 6(6):e1000812

Gene regulatory networks

- **Gene regulatory network** is abstraction of regulatory network, focusing on interactions between genes and their products (proteins)
- Gene regulatory networks include both **direct** and **indirect** interactions



Brazhnik et al. (2002), Trends Biotechnol., 20(11):467-72

Gene regulatory networks

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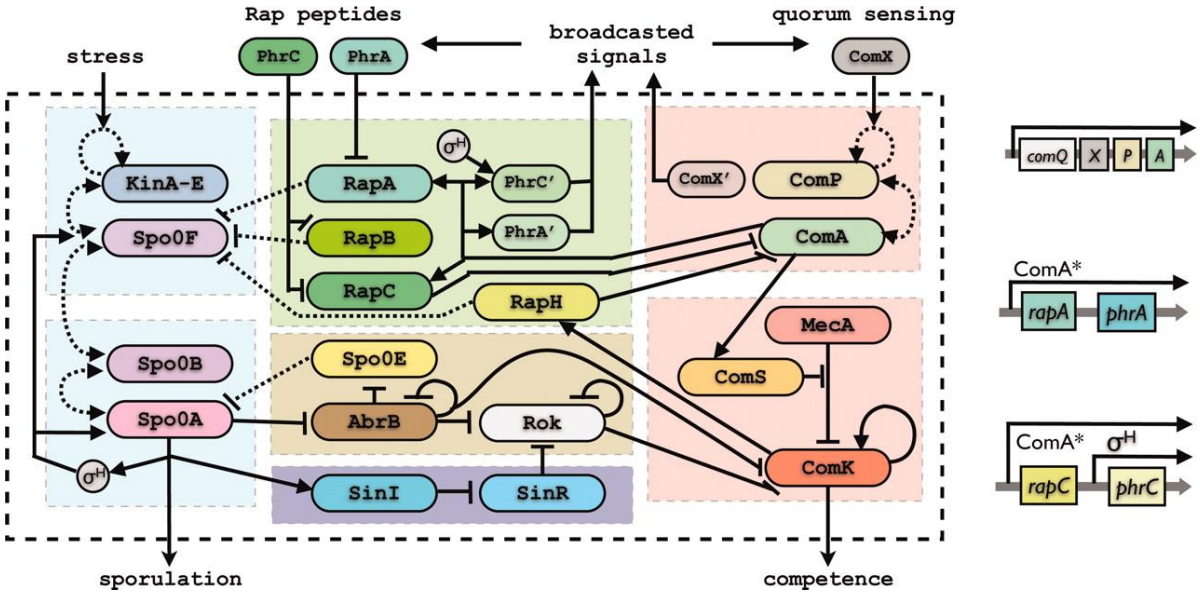
  Sporulation and competence in *B. subtilis*



Schultz *et al.* (2000), *Proc. Natl. Acad. Sci.*, 106(50):21027-34

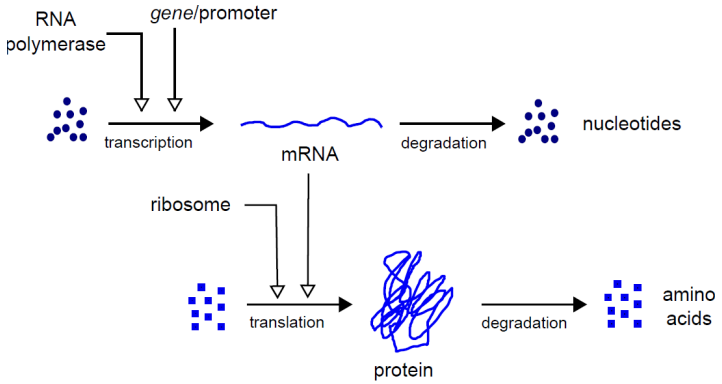
Systems biology

- Most gene regulatory networks of biological interest are large and complex
- **No global view of functioning** of network available, despite abundant knowledge on network components
  - Understanding of dynamics requires **experimental tools** for monitoring gene expression over time
  - Understanding of dynamics requires **mathematical modeling** and **computer analysis and simulation**
  - Discipline now often referred to as **systems biology**

Alon (2007), *An Introduction to Systems Biology,* Chapman & Hall/CRC Press

Modeling of gene regulatory networks

- Modeling of gene regulatory networks amount to modeling of gene expression and regulation of gene expression



- **Aims** of modeling gene regulatory networks:
  - Understanding role of individual components and interactions
  - Suggesting missing components and interactions
- Advantages of **mathematical and computer tools**:
  - Precise and unambiguous description of network
  - Systematic derivation of predictions of network behavior

Modeling of gene regulatory networks

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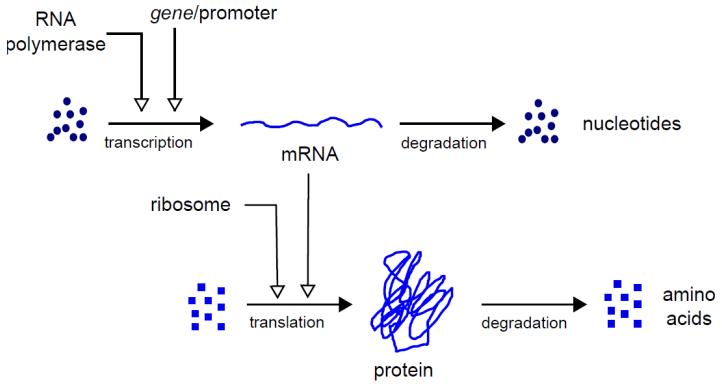
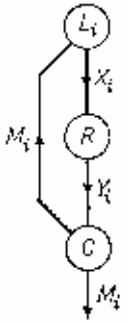


- First models of gene regulatory networks date back to early days of molecular biology

  Feedback circuits and oscillators



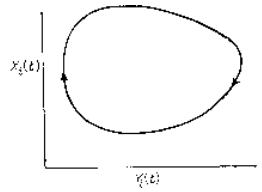
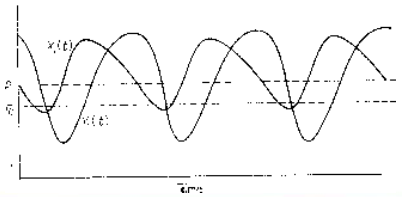


FIGURE 3.



Goodwin (1963), *Temporal Organization in Cells*

Modeling of gene regulatory networks

- Different modeling formalisms exist, describing gene expression on different levels of detail

Stochastic master equations

Ordinary differential equations (ODEs)

Boolean networks

Smolen *et al.* (2000), *Bull. Math. Biol.*, 62(2):247-292

Hasty *et al.* (2001), *Nat. Rev. Genet.*, 2(4):268-279

de Jong (2002), *J. Comput. Biol.*, 9(1): 69-105

Szallassi *et al.* (2006), *System Modeling in Cellular Biology*, MIT Press

Bolouri (2008), *Computational Modeling of Gene Regulatory Networks*, Imperial College Press

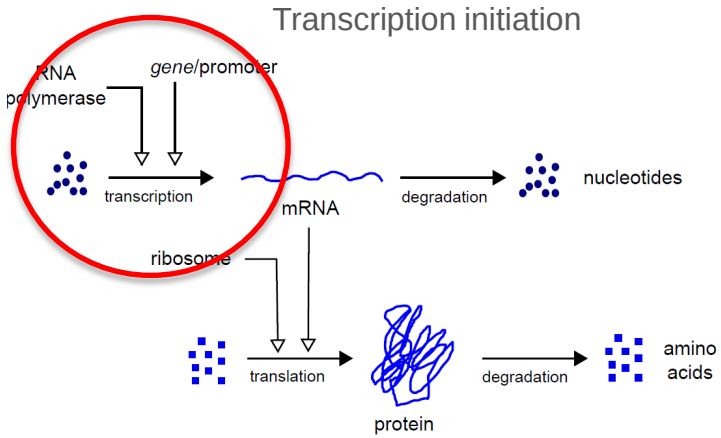
Karleback and Shamir (2008), *Nat. Rev. Mol. Cell Biol.*, 9(10):770-80

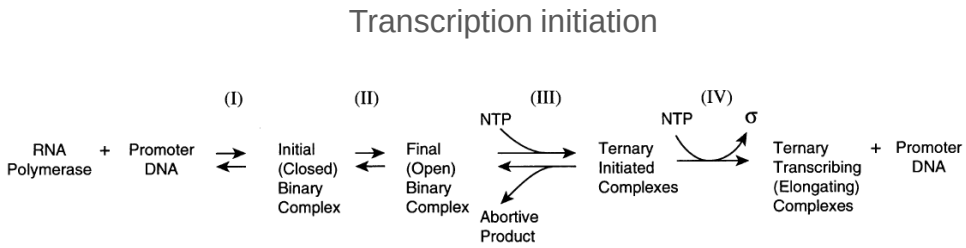
Course overview

- Gene regulatory networks
- **Piecewise-linear models of gene regulatory networks**
- Solutions of piecewise-linear models
- Qualitative analysis of gene regulatory networks
- Numerical simulation of gene regulatory networks
- Conclusions

Modeling of gene regulatory networks

- Well-established theory for modeling gene regulatory networks using **ordinary differential equation (ODE)** models
- Gene expression involves large number of individual reactions





Record Jr *et al.* (1996), *Escherichia Coli and Salmonella*, ASM Press, 792-821

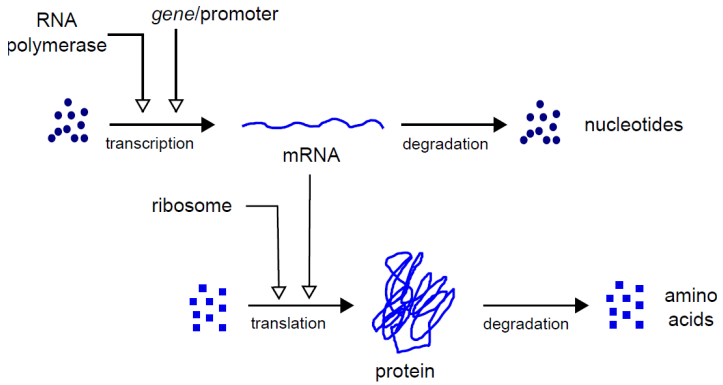
- In principle possible to model gene expression by biochemical reaction rate equations, but not convenient in practice

Modeling of gene regulatory networks

- **Practical problems** encountered by modelers:
  - Knowledge on molecular mechanisms rare
  - Quantitative information on kinetic parameters and molecular concentrations absent
  - Large models
- Intuition: essential properties of network dynamics **robust** against reasonable model simplifications

Simplifying assumptions

- Assume that gene expression machinery and precursor pools remain constantly available



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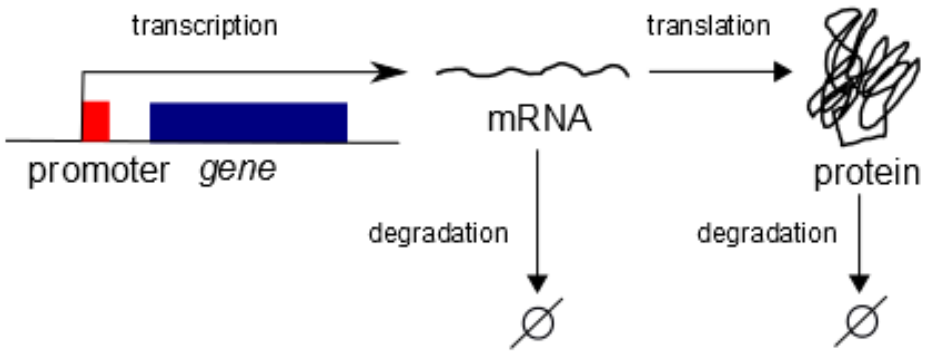
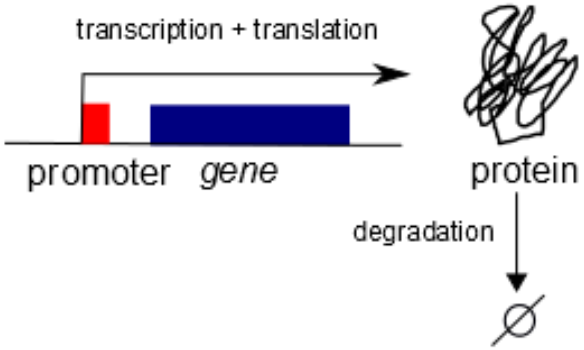


Simplifying assumptions

- Assume that gene expression machinery and precursor pools remain constantly available
- Assume that transcription and translation can be lumped into a single step



Simplifying assumptions

- Assume that gene expression machinery and precursor pools remain constantly available
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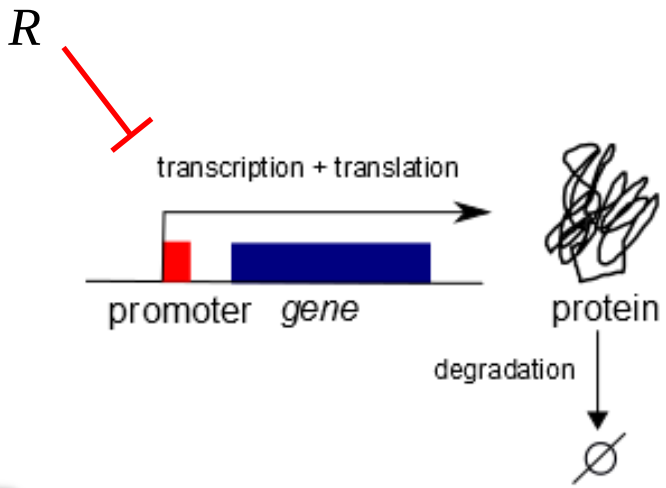
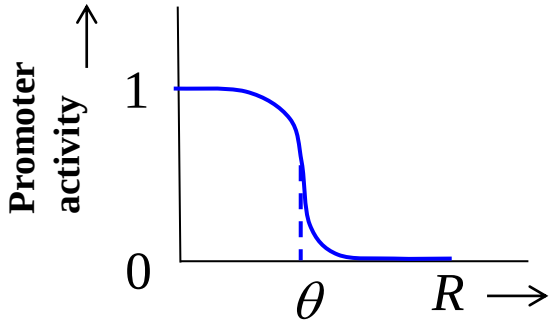
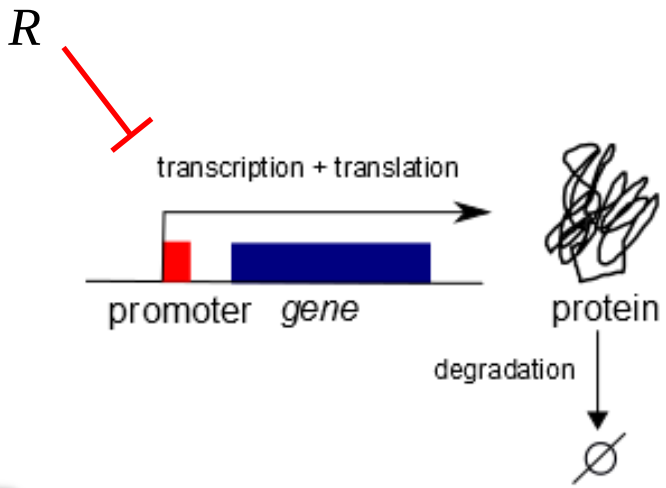
- Describe regulatory effect by sigmoidal response curve

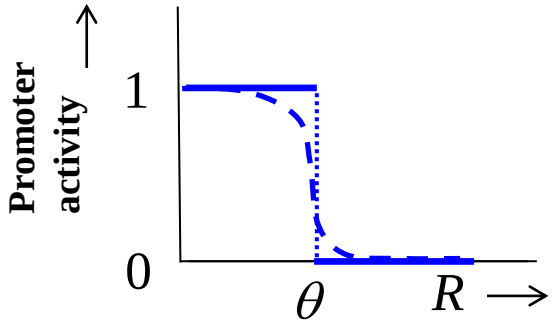




Simplifying assumptions

- Assume that gene expression machinery and precursor pools remain constantly available
- Assume that transcription and translation can be lumped into a single step
- Describe regulatory effect by sigmoidal response curve
- Approximate sigmoidal response by step response





Piecewise-linear models

- **Piecewise-linear models** of gene regulatory networks

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

$$\dot{x}_i = f_i(x) - \gamma_i x_i, \qquad 1 \leq i \leq n$$

$$f_i(x) = \sum_{i \in I} \kappa_{il} b_{il}(x)$$

$x = (x_1, \ldots, x_n)^t$ Protein concentrations

κ_{il}, γ_i Synthesis, degradation parameters (positive)

$f_i : \mathbb{R}_+^n \to \mathbb{R}_+$

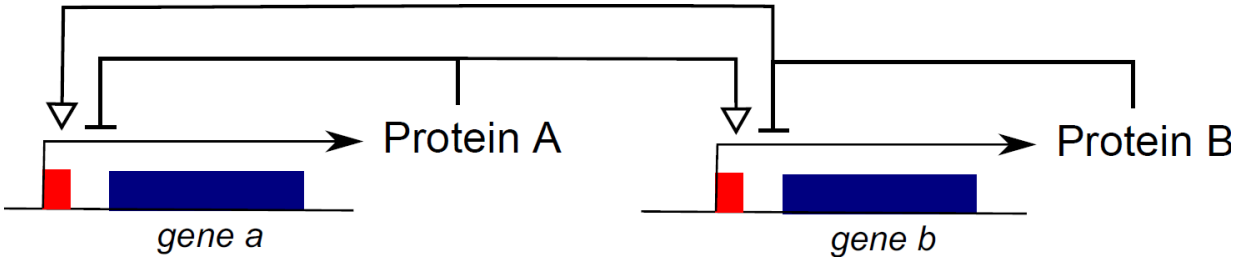
$b_{il} : \mathbb{R}_+^n \to \{0, 1\}$ Regulation function, affine w.r.t. step functions:

$$s^+(x_i, \theta_i^j) = \begin{cases} 1, & x_i > \theta_i^j, \\ 0, & x_i < \theta_i^j, \end{cases} \qquad \text{and} \qquad s^-(x_i, \theta_i^j) = 1 - s^+(x_i, \theta_i^j)$$

θ_i^j Threshold parameter (positive)

Piecewise-linear models

- Piecewise-linear model of simple **cross-activation network**



$$\dot{x}_a = \kappa_a \, s^+(x_b, \theta_b^1) \, s^-(x_a, \theta_a^2) - \gamma_a \, x_a,$$
$$\dot{x}_b = \kappa_b \, s^+(x_a, \theta_a^1) \, s^-(x_b, \theta_b^2) - \gamma_b \, x_b.$$

- Combinatorial regulation of gene expression (AND, OR, …)

  Relation with **discrete, logical models**

Thomas and d'Ari (1990), *Biological Feedback*, CRC Press

Kauffman (1993), *The Origins of Order*, Oxford University Press

Course overview

- Gene regulatory networks
- Piecewise-linear models of gene regulatory networks
- **Solutions of piecewise-linear models**
- Qualitative analysis of gene regulatory networks
- Numerical simulation of gene regulatory networks
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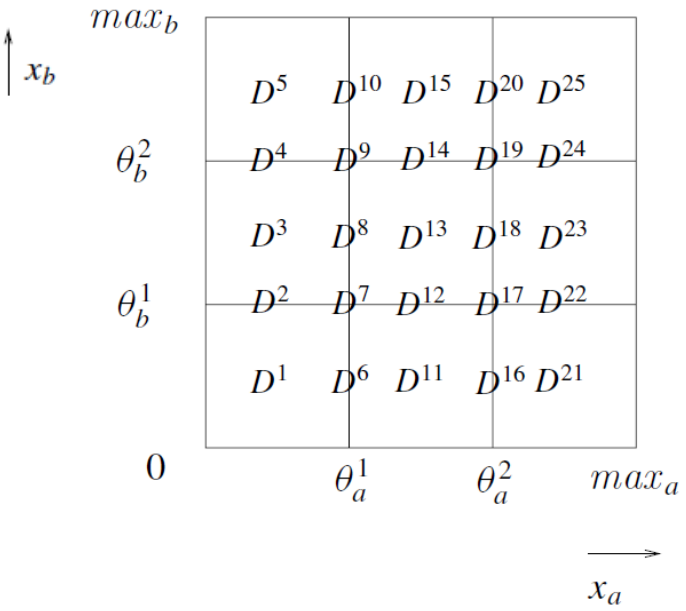
Decomposition of phase space

- Dynamics studied in *n*-dimensional phase space

$$\Omega = \Omega_1 \times \ldots \times \Omega_n$$

- Thresholds decompose phase space into set of hyperrectangular **domains** $D \in \mathcal{D}$
  - **Switching variables**
  - **Regulatory** domains $\mathcal{D}_r$
  - **Switching** domains $\mathcal{D}_s$



$$D^1 = \{(x_a, x_b) \in \Omega \mid 0 \leq x_a < \theta_a^1,\ 0 \leq x_b < \theta_b^1\}$$
$$D^2 = \{(x_a, x_b) \in \Omega \mid 0 \leq x_a < \theta_a^1,\ x_b = \theta_b^1\}$$

de Jong *et al*. (2004), *Bull. Math. Biol*., 66(2):301-40

Decomposition of phase space

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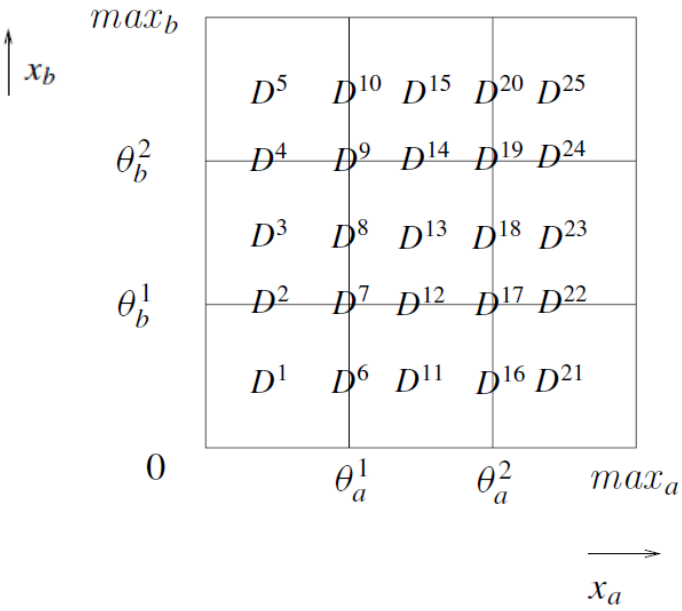
  - **Switching variables**
  - **Regulatory** domains $\mathcal{D}_r$
  - **Switching** domains $\mathcal{D}_s$
- Domains in **boundary** of D

$$A(D) = \{D' \in \mathcal{D} \mid D' \subseteq \partial D\}$$

- Regulatory domains with D in boundary

$$R(D) = \{D' \in \mathcal{D}_r \mid D \subseteq \partial D'\}$$



de Jong *et al*. (2004), *Bull. Math. Biol*., 66(2):301-40

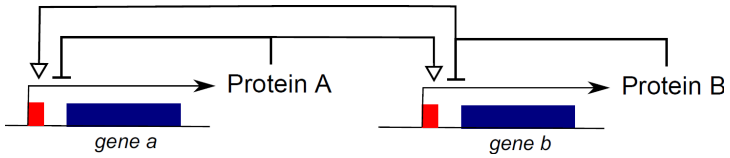
Focal points

- Rewrite system in vector form: $\dot{x} = f(x) - \gamma x$

$$f(x) = (f_1(x), \ldots, f_n(x))^t$$
$$\gamma = \mathrm{diag}(\gamma_1, \ldots, \gamma_n)$$

- For every regulatory domain $D \in \mathcal{D}_r$, $f(x)$ is constant for all $x \in D$

$$\dot{x} = f^D - \gamma x, \quad x \in D$$



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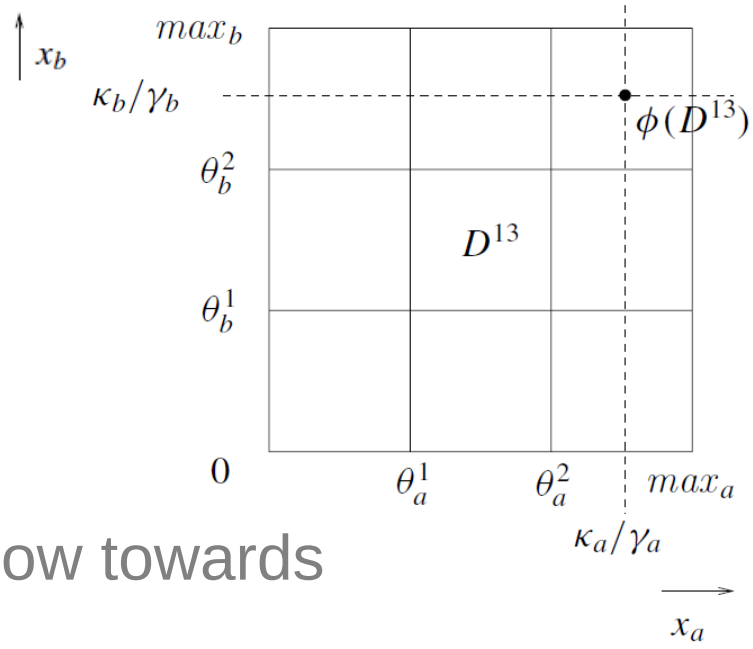

- Solutions in regulatory domains flow towards **focal point**

Definition 3. *Given a regulatory domain* $D \in \mathcal{D}_r$, *the point* $\phi(D) = \gamma^{-1} f^D \in \Omega$ *is called the* focal point *for the flow in* D.

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal points

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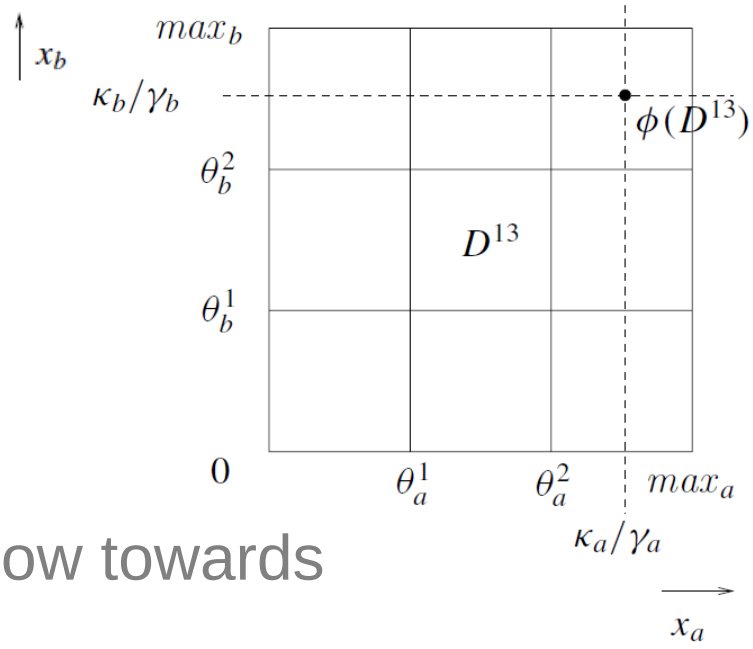
$$\dot{x} = f^D - \gamma x, \quad x \in D$$



- Solutions in regulatory domains flow towards **focal point**

$$x(t) = \phi(D) + e^{\gamma(t_0 - t)}(x(t_0) - \phi(D))$$

Glass and Kauffman (1973), *J. Theor. Biol.*, 39(1):103-29

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

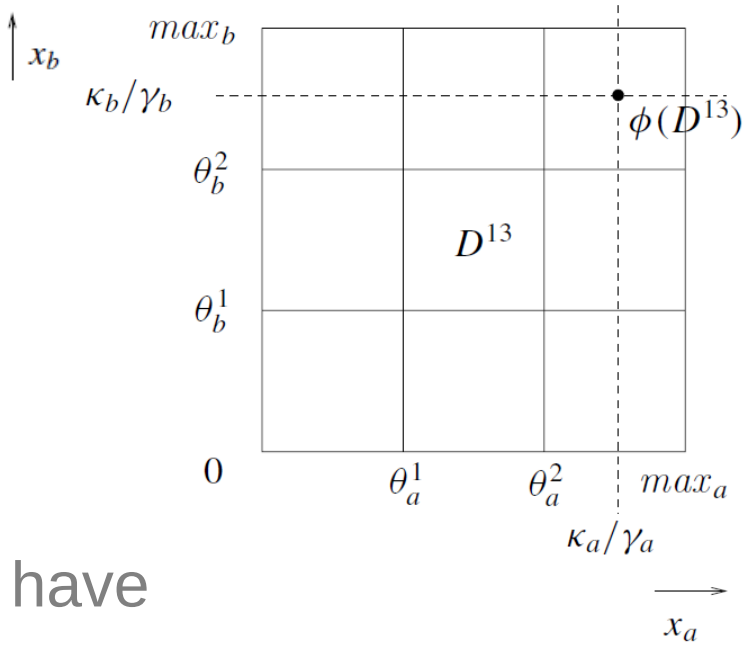
Focal points

- Rewrite system in vector form: $\dot{x} = f(x) - \gamma x$

$$f(x) = (f_1(x), \ldots, f_n(x))^t$$
$$\gamma = \mathrm{diag}(\gamma_1, \ldots, \gamma_n)$$

- For every regulatory domain $D \in \mathcal{D}_r$, $f(x)$ is constant for all $x \in D$

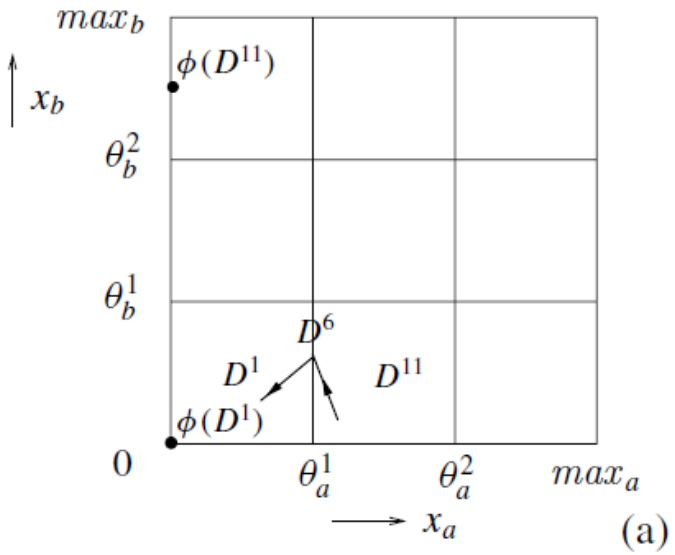
$$\dot{x} = f^D - \gamma x, \quad x \in D$$

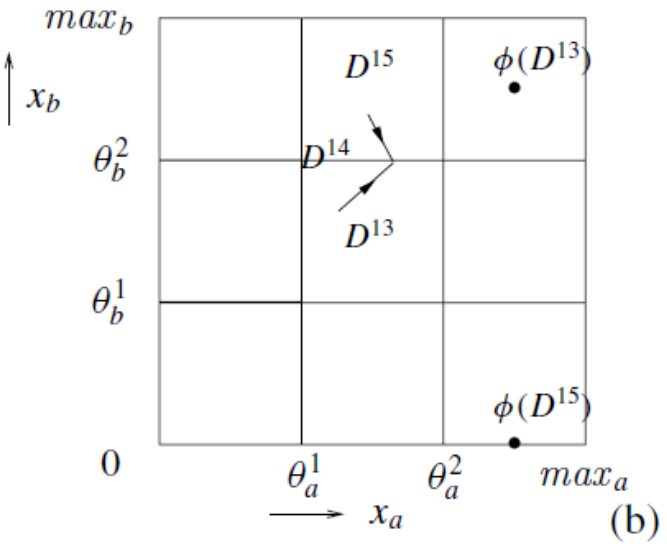


- Different regulatory domains may have different focal points
- Change of dynamics when crossing threshold

Filippov solutions

- System is not well-defined at threshold hyperplanes, where discontinuities occur





Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Filippov solutions

- System is not well-defined at threshold hyperplanes, where discontinuities occur
- **Filippov extension** of piecewise-linear model to differential inclusion

$$\dot{x} \in H(x) \qquad (1)$$

where in regulatory domains

and in switching domains

$$H(x) = \{f^D - \gamma x\}$$

$$H(x) = \overline{co}(\{f^{D'} - \gamma x \mid D' \in R(D)\})$$

Definition 4. *A solution of* (1) *on* $[0, T]$ in the sense of Filippov *is an absolutely continuous function (w.r.t. t)* $\xi_t(x_0)$ *such that* $\xi_0(x_0) = x_0$ *and* $\dot{\xi}_t \in H(\xi_t)$, *for almost all* $t \in [0, T]$.

Gouzé and Sari (2002), *Dyn. Syst.*, 17(4):299-316

Filippov (1988), *Differential Equations with Discontinuous Right Hand Sides*, Kluwer

Filippov solutions

- System is not well-defined at threshold hyperplanes, where discontinuities occur
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$$H(x) = \overline{co}(\{f^{D'} - \gamma x \mid D' \in R(D)\})$$

- Existence of solutions guaranteed, but not uniqueness!

Gouzé and Sari (2002), *Dyn. Syst.*, 17(4):299-316

Filippov (1988), *Differential Equations with Discontinuous Right Hand Sides*, Kluwer

Filippov solutions

- System is not well-defined at threshold hyperplanes, where discontinuities occur
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- Other extensions have been proposed in the literature, *e.g.*, **Aizerman–Pyatnitskii extensions**

  Equivalent for piecewise-linear systems considered here under mild modeling assumption

Machina and Posonov (2011), *Nonlinear. Anal.*, 74(3):882-900

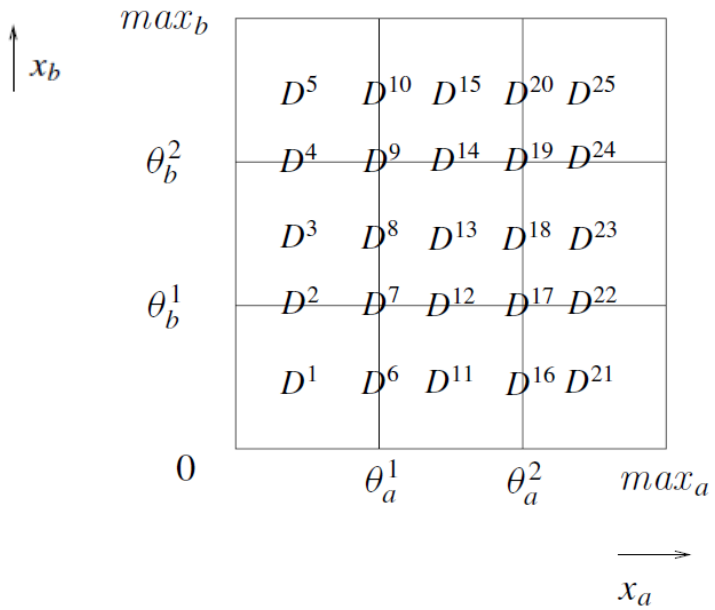
Acary *et al.*(2014), *Physica D*, 269:103-19

Focal sets

- Generalization of focal points to **focal sets**

Definition 1. *The* order *of a domain* $D \in \mathcal{D}$ *is the number* $k \in \mathbb{N}$, $0 \leq k \leq n$, *equal to the number of switching variables in* D, *denoted* order(D).

Definition 2. *For every domain* $D \in \mathcal{D}_s$ *of order* $k \geq 1$, *define* supp$(D) \subset \Omega$ *to be the* $(n-k)$*-dimensional hyperplane containing* D. *If* $D \in D_r$ *then we define* supp(D) *to be equal to* Ω.



Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal sets

- Generalization of focal points to **focal sets**

Definition 5. *Let $D \in \mathcal{D}$ be a domain. If D is a regulatory domain then its focal set $\Phi(D)$ is given by*

$$\Phi(D) = \{\phi(D)\}, \tag{12}$$

where $\phi(D)$ is the focal point of $D \in \mathcal{D}_r$ as in Definition 3. If D is a switching domain of order k, and $\mathrm{supp}(D)$ is the $(n-k)$-dimensional hyperplane supporting D, then its focal set $\Phi(D)$ is

$$\Phi(D) = \mathrm{supp}(D) \cap \overline{co}(\{\phi(D') \mid D' \in R(D)\}). \tag{13}$$

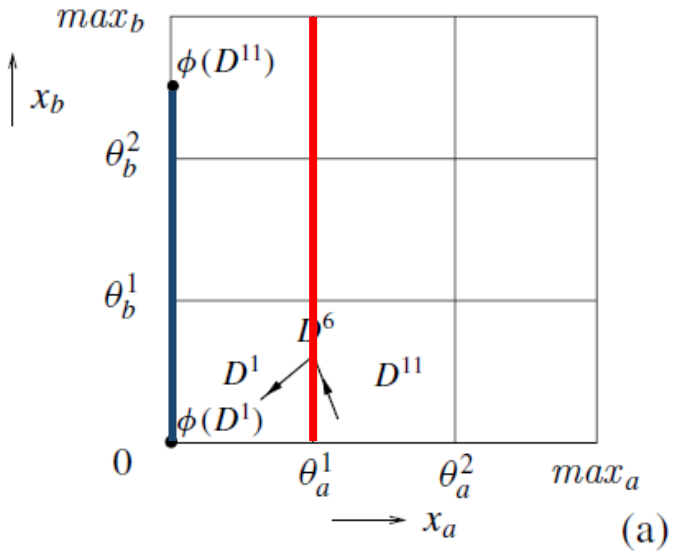
- **Sliding modes** in switching domains occur under the condition that

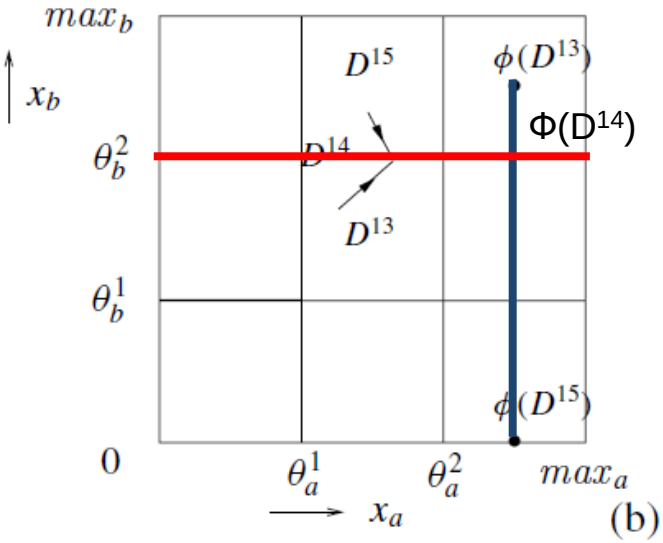
$$\Phi(D) \neq \{\}$$

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal sets

- Examples of focal sets





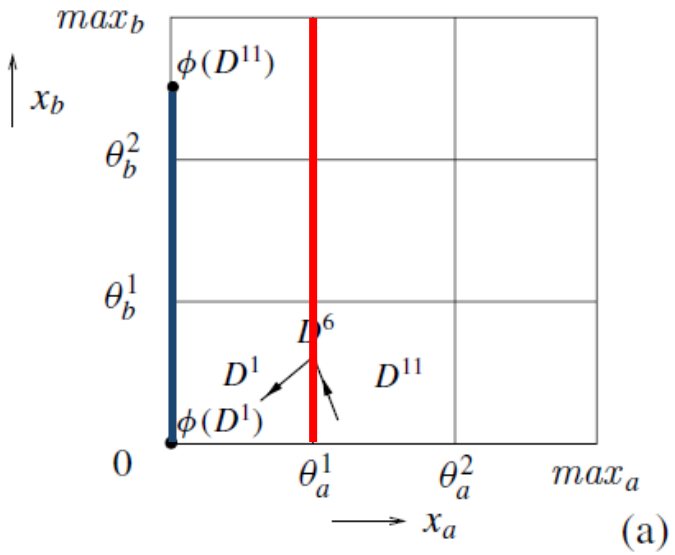
$\Phi(D^6) = \{\}$

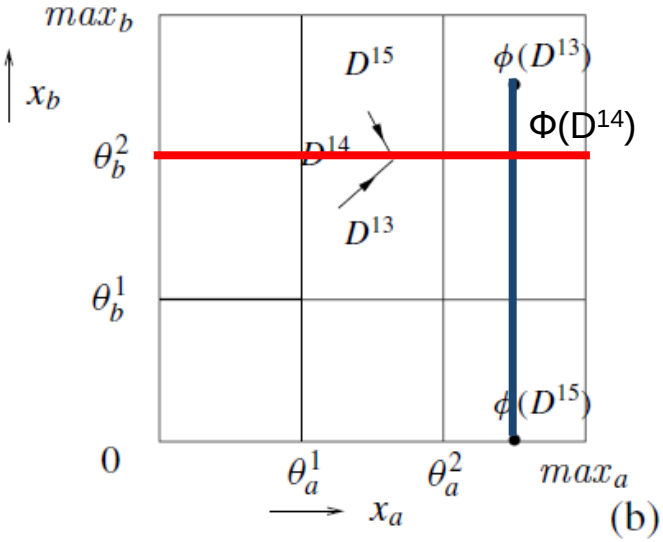
- Focal set not necessarily a point!

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal sets

- Examples of focal sets





$\Phi(D^6) = \{\}$

- Technical assumption: focal set of domain not located in support of boundary

Assumption 1. *For all domains* $D \in \mathcal{D}$,

$$\Phi(D) \cap \text{supp}(D') = \{\}, \ \forall D' \subseteq \partial D.$$

Focal sets and convergence

- **Monotonic convergence** of solutions towards focal set

> **Corollary 2.** *If* $\Phi(D)$ *is a point, all solutions* ξ_t *in* D *converge monotonically towards* $\Phi(D)$.

- Weaker convergence result if focal set is not a point (D a switching domain)

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal sets and equilibrium points

- Some focal sets correspond to « equilibria » of the system

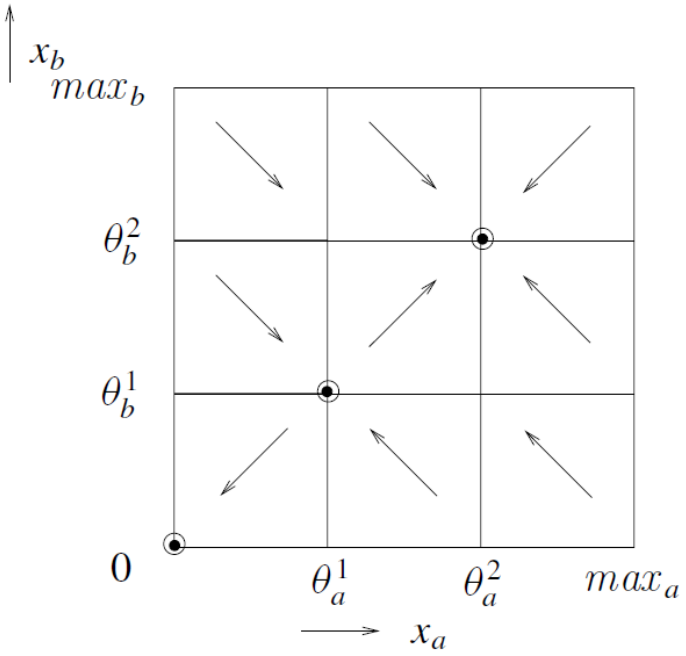
Theorem 3.1. *Let D be a regulatory domain with focal point $\phi(D)$. If $\phi(D) \in D$ then $x = \phi(D)$ is an asymptotically stable equilibrium point of (2).*

- If D is a switching domain, generalization of notions of equilibrium point and stability required
  - $y \in \Omega$ is an equilibrium point if $0 \in H(y)$
  - If $\Phi(D) \subseteq D$, then every $\phi \in \Phi(D)$ is an equilibrium point and $\Phi(D)$ an **equilibrium set**
  - Stable and weakly (asymptotically) stable equilibrium sets

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Focal sets and equilibrium points

- Examples of equilibrium points
  - Cross-activation network is bistable



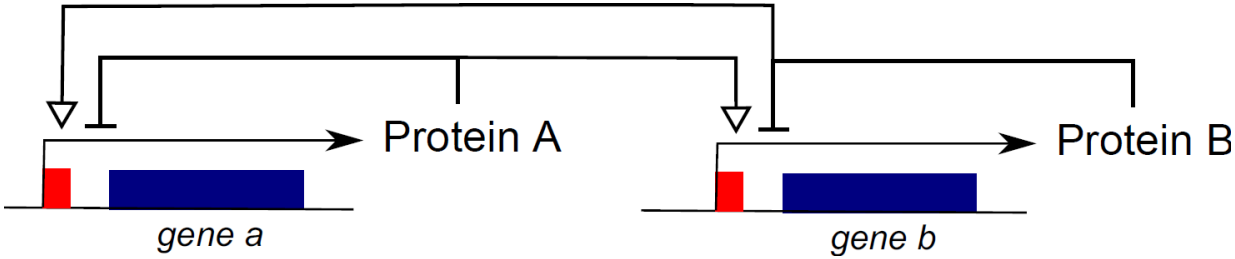
Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Course overview

- Gene regulatory networks
- Piecewise-linear models of gene regulatory networks
- Solutions of piecewise-linear models
- **Qualitative analysis of gene regulatory networks**
- Numerical simulation of gene regulatory networks
- Conclusions

Recap

- Piecewise-linear models can be used to model dynamics of gene regulatory networks

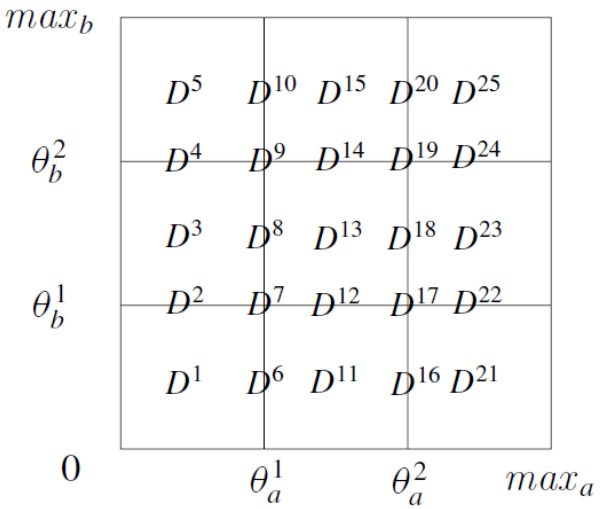


$$\dot{x}_a = \kappa_a \, s^+(x_b, \theta_b^1) \, s^-(x_a, \theta_a^2) - \gamma_a \, x_a,$$
$$\dot{x}_b = \kappa_b \, s^+(x_a, \theta_a^1) \, s^-(x_b, \theta_b^2) - \gamma_b \, x_b.$$

Recap

- Piecewise-linear models can be used to model dynamics of gene regulatory networks
- Piecewise-linear models studied by partitioning of phase space into regions
  - Regulatory domains and switching domains

$$D^1 = \{(x_a, x_b) \in \Omega \mid 0 \leq x_a < \theta_a^1,\ 0 \leq x_b < \theta_b^1\}$$
$$D^2 = \{(x_a, x_b) \in \Omega \mid 0 \leq x_a < \theta_a^1,\ x_b = \theta_b^1\}$$

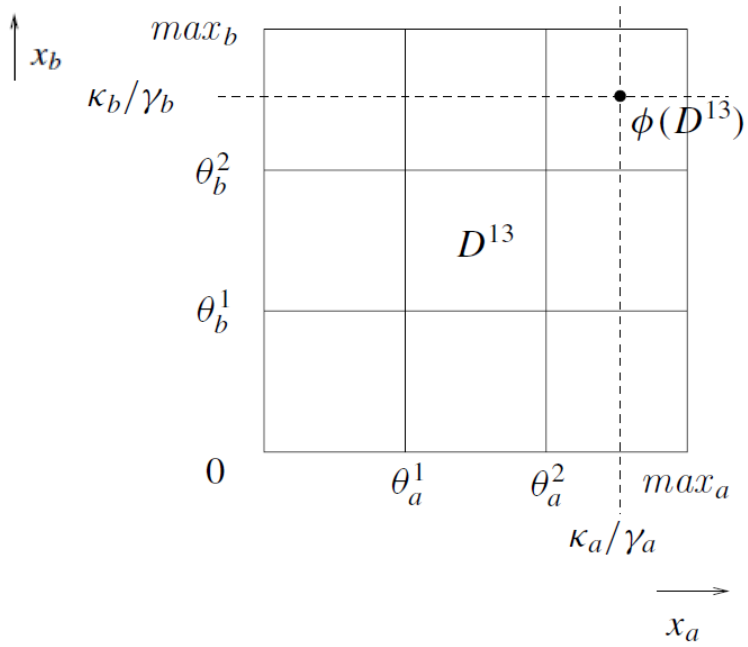


Recap

- Study of dynamics in regulatory domains straightforward
  - Monotonic convergence towards focal point

$$\dot{x} = f^D - \gamma x, \quad x \in D$$

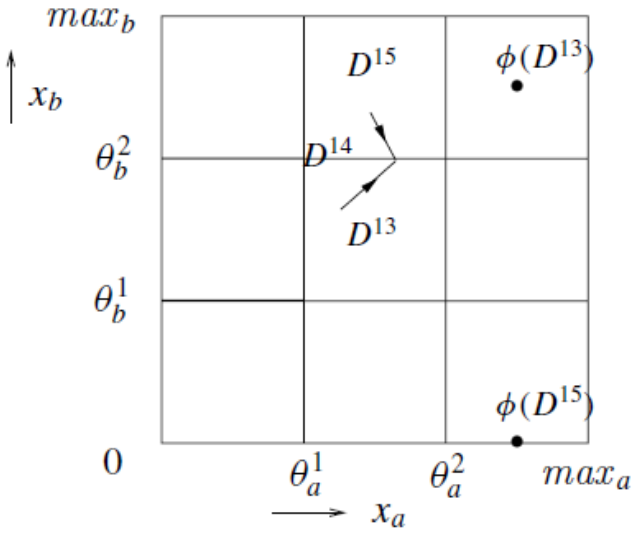
$$\phi(D) = \gamma^{-1} f^D \in \Omega$$



Recap

- Study of dynamics in regulatory domains straightforward
  - Monotonic convergence towards focal state
- Study of dynamics in switching domains requires extension of differential equations to differential inclusions (Filippov)

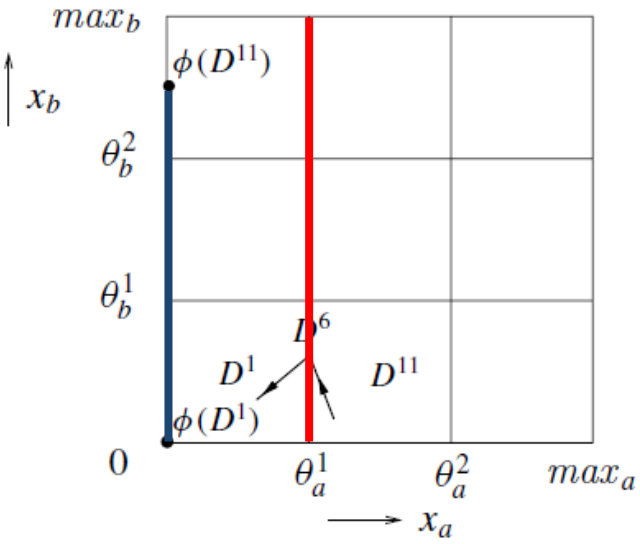
$$\dot{x} \in H(x)$$
$$H(x) = \overline{co}(\{f^{D'} - \gamma x \mid D' \in R(D)\})$$

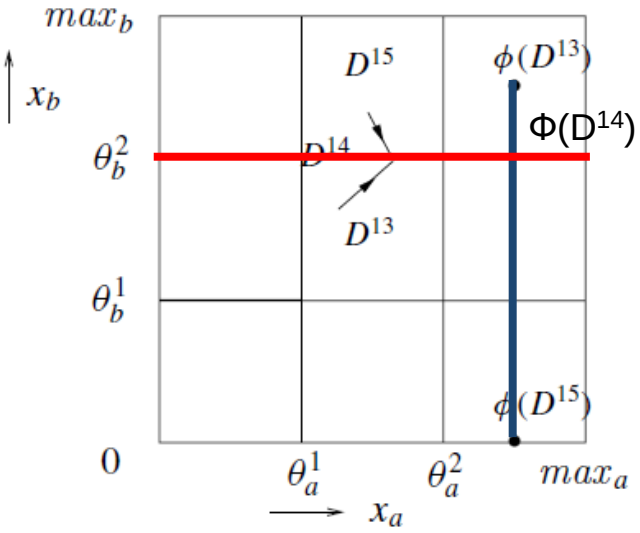


Recap

- Dynamics in switching domains determined by focal sets

$$\Phi(D) = \text{supp}(D) \cap \overline{co}(\{\phi(D') \mid D' \in R(D)\}).$$

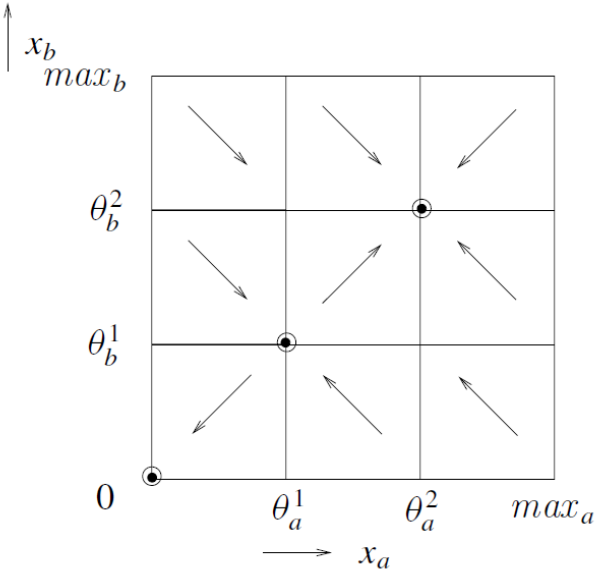




$\Phi(D^6) = \{\}$

Recap

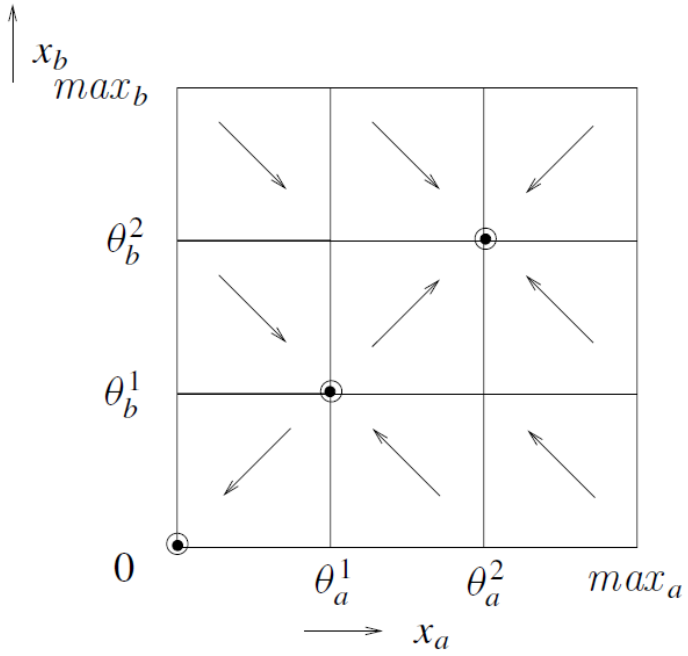
- Sliding modes in switching domains occur if $\Phi(D) \neq \{\}$
- In case of sliding modes, (weak) monotonic convergence towards focal sets in switching domains
- If $\Phi(D) \subseteq D$, then every $\phi \in \Phi(D)$ is an equilibrium point and $\Phi(D)$ the **equilibrium set**



Transitions between domains

- Set of domains $\mathcal{D}$ can be thought of as qualitative states

  System behaves in qualitatively homogeneous manner in each domain: (quasi-)monotonic convergence towards focal set



Transitions between domains

- Set of domains $\mathcal{D}$ can be thought of as qualitative states

  System behaves in qualitatively homogeneous manner in each domain: (quasi-)monotonic convergence towards focal set

- **Transition** from domain D to D', if there is a solution (in the sense of Filippov) starting in D and reaching D'

  $A(D)$ is set of switching domains in boundary of D

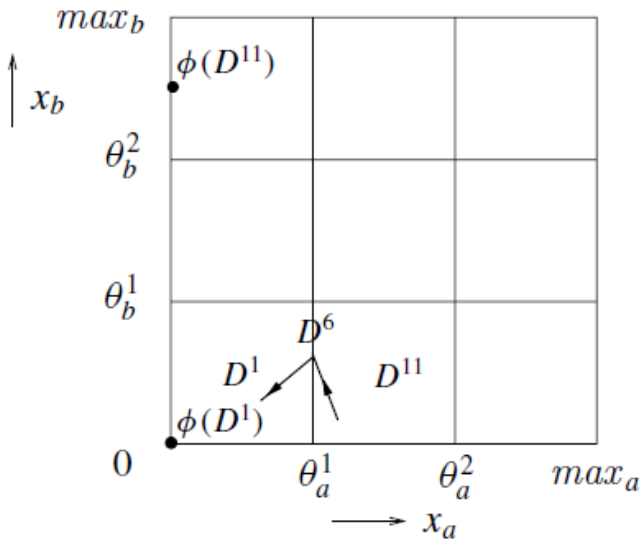
Definition 12. *Let $D, D' \in \mathcal{D}$ be two contiguous domains. We say that there exists a* transition *from D to D' if one of the following two properties holds:*

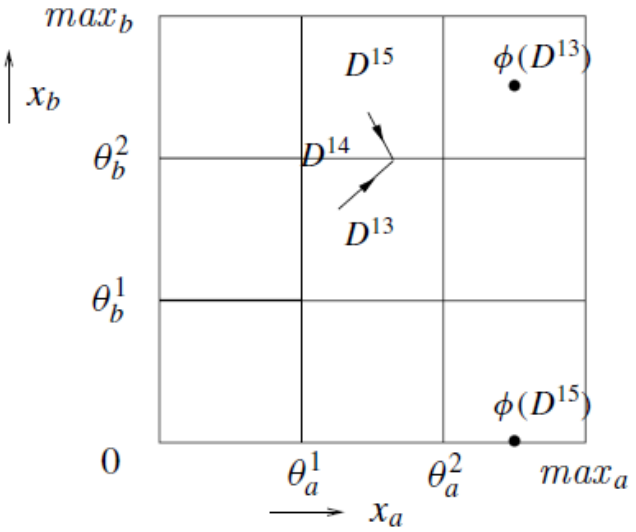
1. *If $D' \in A(D)$, then there exists $x_0 \in D$ and a Filippov solution $\xi_t(x_0)$ defined on a finite time interval $[0, \tau]$ such that*
   (a) $\xi_t(x_0) \in D$ for all $t \in [0, \tau)$, and
   (b) $\xi_\tau(x_0) \in D'$.
2. *If $D \in A(D')$, then there exists $x_0 \in D$ and a Filippov solution $\xi_t(x_0)$ defined on a finite time interval $[0, \tau]$ such that*
   (a) $\xi_0(x_0) = x_0 \in D$, and
   (b) $\xi_t(x_0) \in D'$ for all $t \in (0, \tau]$.

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Transitions between domains

- Examples of transitions





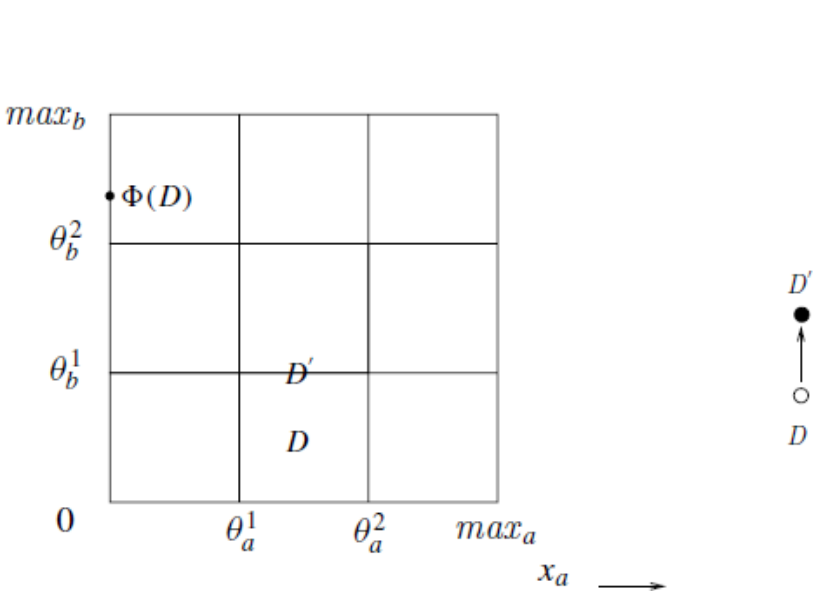
Transitions between domains

- Transition follows from relative position of focal set

Proposition 4.1. *Let $D, D' \in \mathcal{D}$ be two contiguous domains such that $D' \in A(D)$. Under Assumption 1, there exists a transition from D to D' iff*

1. $\Phi(D) \neq \{\}$.
2. *For all $i \in \{1, \ldots, n\}$ such that x_i is switching in D' but not in D,*

$$(d'_i - d_i)(\phi_i - d'_i) > 0, \ \forall d \in D, \forall d' \in D', \forall \phi \in \Phi(D). \qquad (19)$$



Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

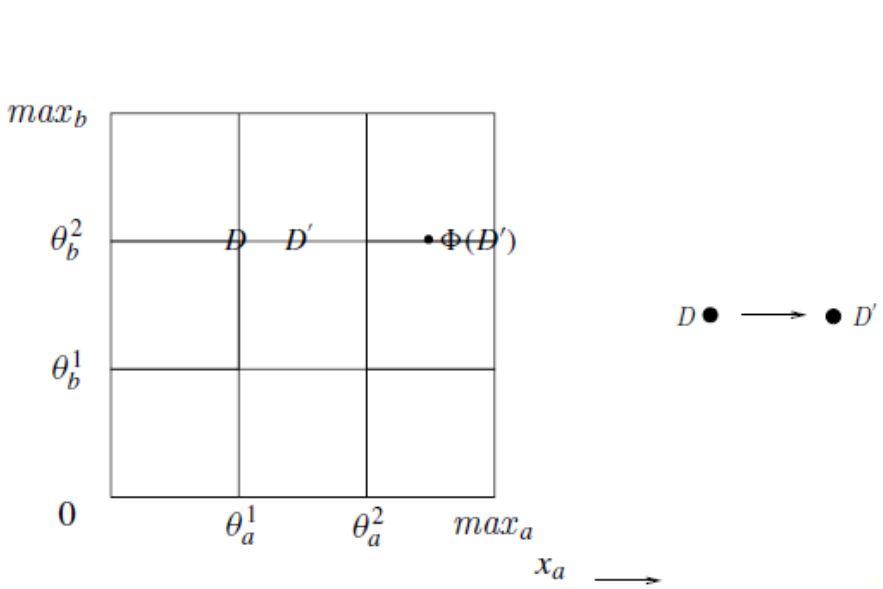
Transitions between domains

- Transition follows from relative position of focal set

Proposition 4.2. *Let $D, D' \in \mathcal{D}$ be two contiguous domains such that $D \in A(D')$. Under Assumption 1, there exists a transition from D to D' iff*

1. $\Phi(D') \neq \{\}$.
2. *For all $i \in \{1, \ldots, n\}$ such that x_i is switching in D but not in D',*

$$(d'_i - d_i)(\phi'_i - d_i) > 0, \ \forall d \in D, \forall d' \in D', \forall \phi' \in \Phi(D'). \qquad (21)$$

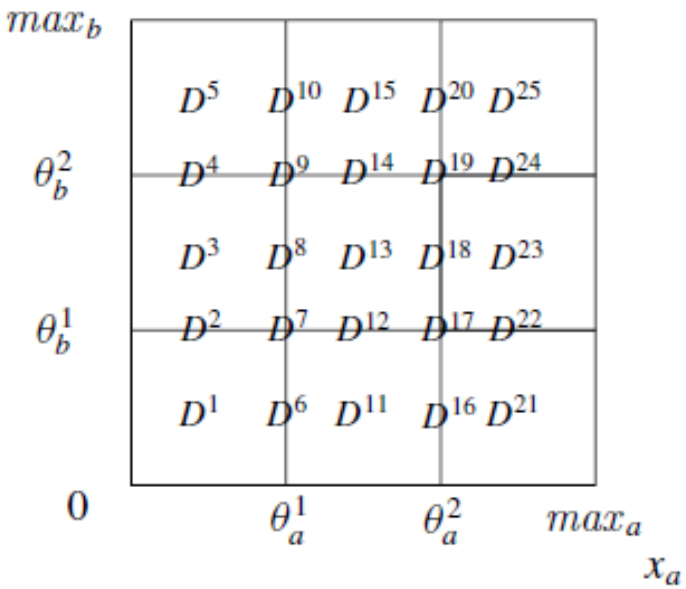


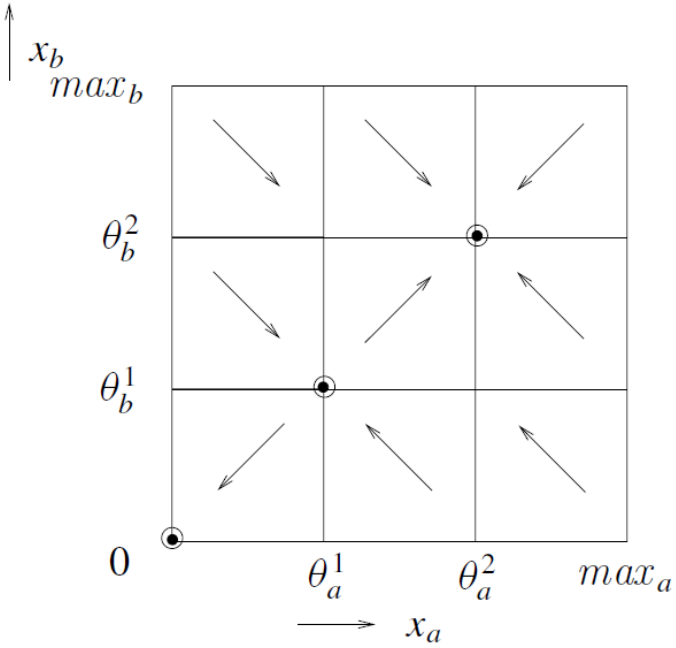
Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

State transition graph

- **State transition graph**: directed graph with nodes that are domains and edges that are transitions between domains

  Discrete representation of qualitative dynamics of piecewise-linear system





- **Paths**, **cycles**, and **attractors** in graph

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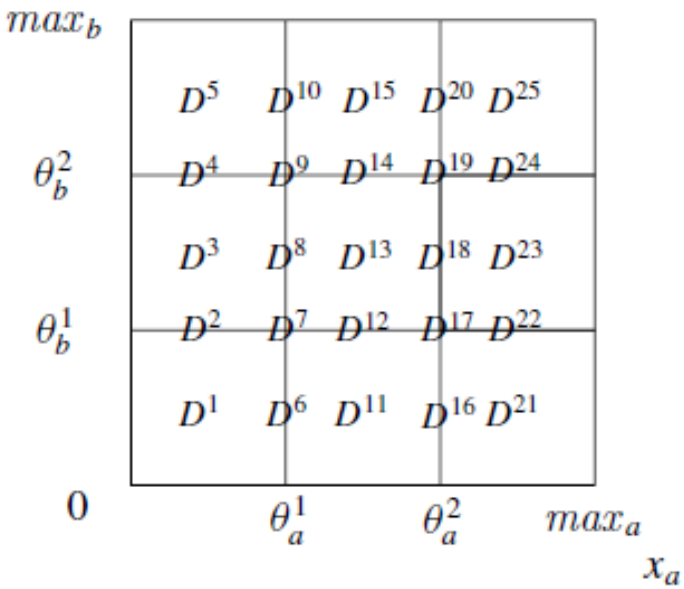
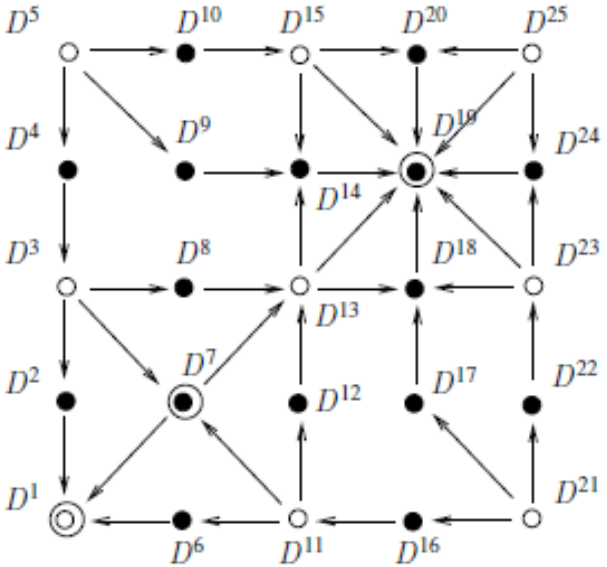




- **Paths**, **cycles**, and **attractors** in graph

State transition graph as discrete abstaction

- Formal definition of state transition graph as discrete abstraction
  - Definition of piecewise-linear system as **continuous transition system** having same reachability properties
  - Definition of **equivalence relation**
  - Definition of discrete abstraction as **quotient** of continuous transition system
  - Resulting **discrete transition system** is state transition graph

Alur *et al.* (2000), *Proc. IEEE*, 88(7):971-84

- State transition graph gives **conservative approximation** of continuous dynamics
  - Every Filippov solution of piecewise-linear model corresponds to path in state transition graph
  - Converse is not generally true!

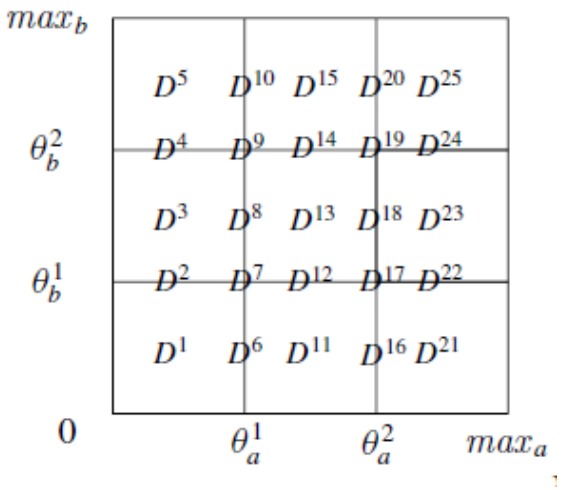
de Jong *et al*. (2004), *Bull. Math. Biol*., 66(2):301-40

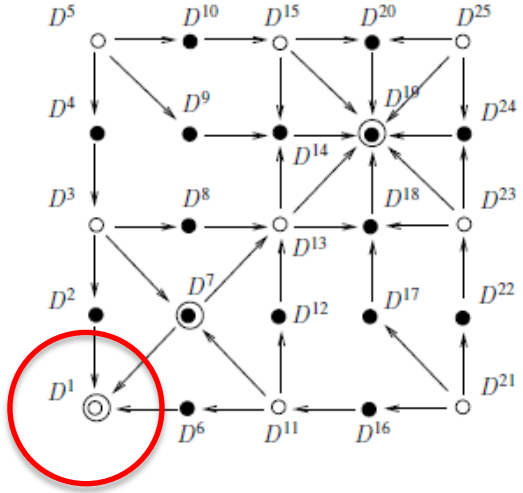
Batt *et al.* (2008), *Automatica*, 44(4):982-9

Analysis of state transition graph

- Under certain conditions, the attractors of the graph correspond to **stable equilibrium sets**

Theorem 3.1. *Let D be a regulatory domain with focal point $\phi(D)$. If $\phi(D) \in D$ then $x = \phi(D)$ is an asymptotically stable equilibrium point of (2).*





Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

Analysis of state transition graph

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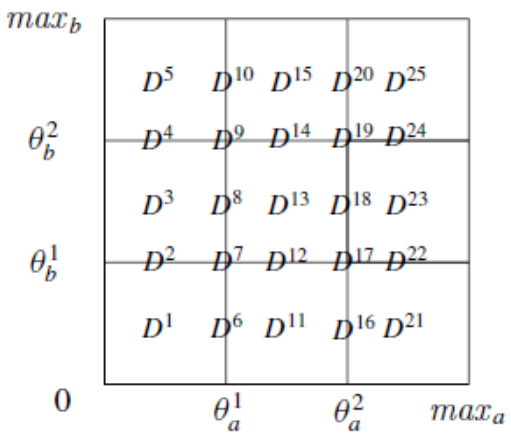
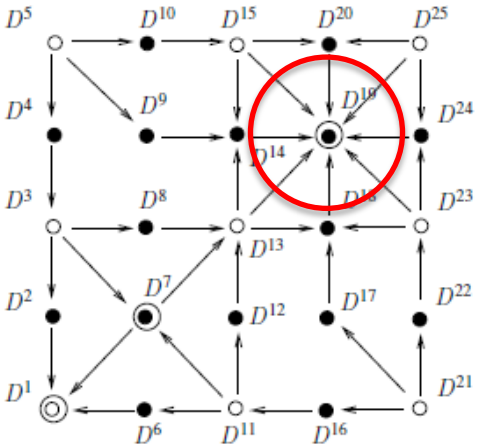
Assumption 1. *For all domains* $D \in \mathcal{D}$,

$$\Phi(D) \cap \text{supp}(D') = \{\}, \ \forall D' \subseteq \partial D.$$

Theorem 5.2. *Assume* $\Omega \subset \mathbb{R}^n$. *Let* $D \in \mathcal{D}_s$ *be a switching domain of order* $p \geq 1$ *containing a singular equilibrium set* $\Phi(D)$ *that satisfies Assumption 1. If for all* $D' \in R(D)$, *there is a transition from* D' *to* D *in the state transition graph, then* $\Phi(D)$ *is weakly asymptotically stable*





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Assumption 1. *For all domains* $D \in \mathcal{D}$,

$$\Phi(D) \cap \text{supp}(D') = \{\}, \ \forall D' \subseteq \partial D.$$

Theorem 5.2. *Assume* $\Omega \subset \mathbb{R}^n$. *Let* $D \in \mathcal{D}_s$ *be a switching domain of order* $p \geq 1$ *containing a singular equilibrium set* $\Phi(D)$ *that satisfies Assumption 1. If for all* $D' \in R(D)$, *there is a transition from* D' *to* D *in the state transition graph, then* $\Phi(D)$ *is weakly asymptotically stable*

Corollary 4. *Under the conditions of Theorem 5.2, if, moreover,* $\Phi(D)$ *is a single point, it is asymptotically stable.*

Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

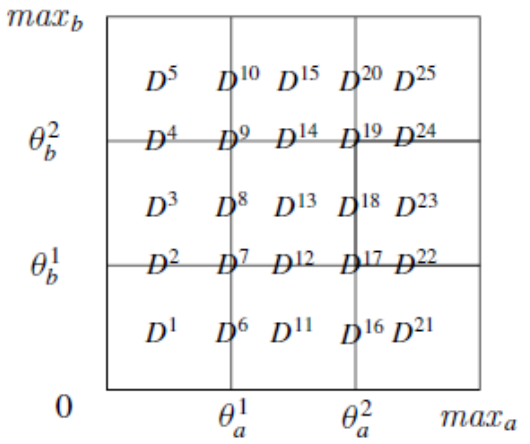
- Other conjecture of graph-based stability criteria, recently proven

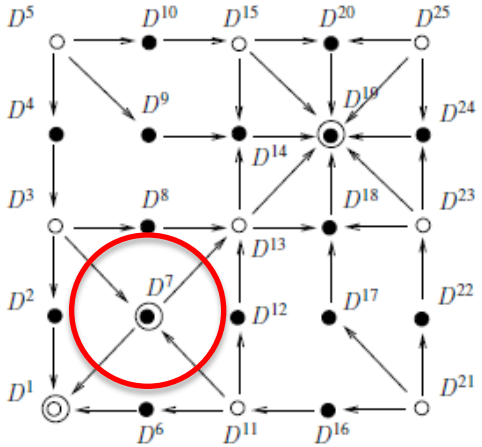
Wang (2012), *Physica D*, 246(1):39-49

Analysis of state transition graph

- Under certain conditions, the attractors of the graph correspond to **unstable equilibrium sets**

Theorem 5.3. *Let $\Omega \subset \mathbb{R}^n$ and $D \in \mathcal{D}_s$ be a switching domain containing a singular equilibrium set $\Phi(D) \subseteq D$ that satisfies Assumption 1. If there exists $D' \in R(D)$ with a transition from D to D', then $\Phi(D)$ is unstable.*





Casey *et al.* (2006), *J. Math. Biol.*, 52(1):27-56

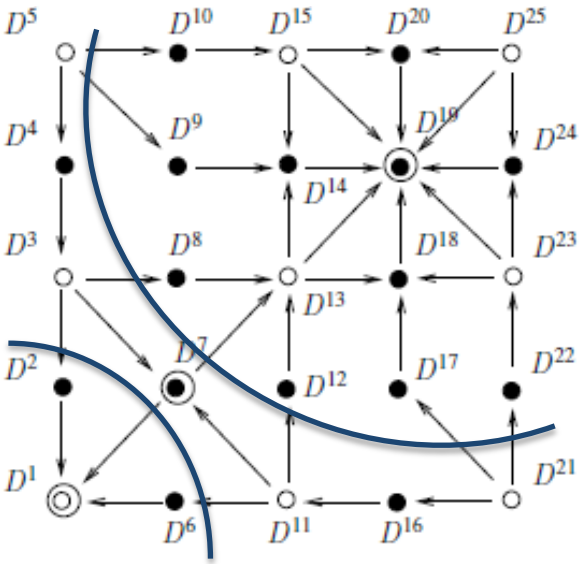
Analysis of state transition graph

- Under certain conditions, cycles in the graph correspond to **limit cycles** in the piecewise-linear systems

Glass and Pasternack (1978), *J. Math Biol*., 6(2):207-23
Edwards (2000), *Physica D*, 146(1-4):165-99

Analysis of state transition graph

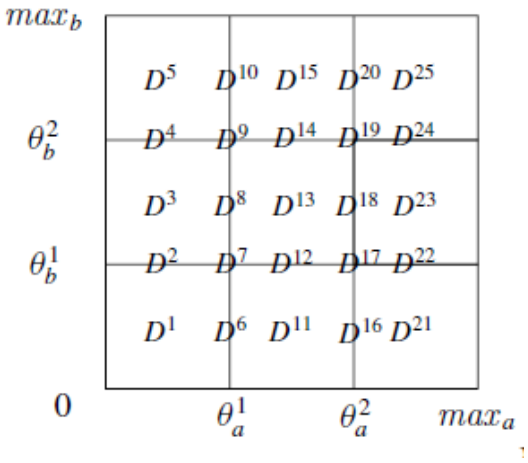
- Paths in state transition graph provide information on **basins of attraction**

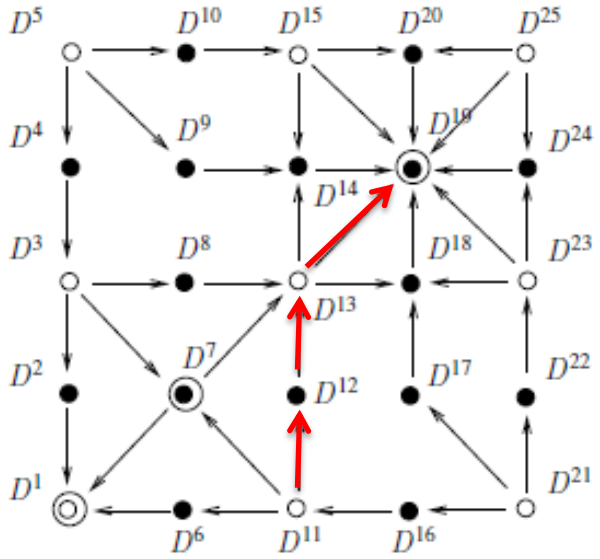


Analysis of state transition graph

- Paths in state transition graph provide information on **basins of attraction**
- Paths in state transition graph provide information on possible **sequences of qualitative events** from initial state

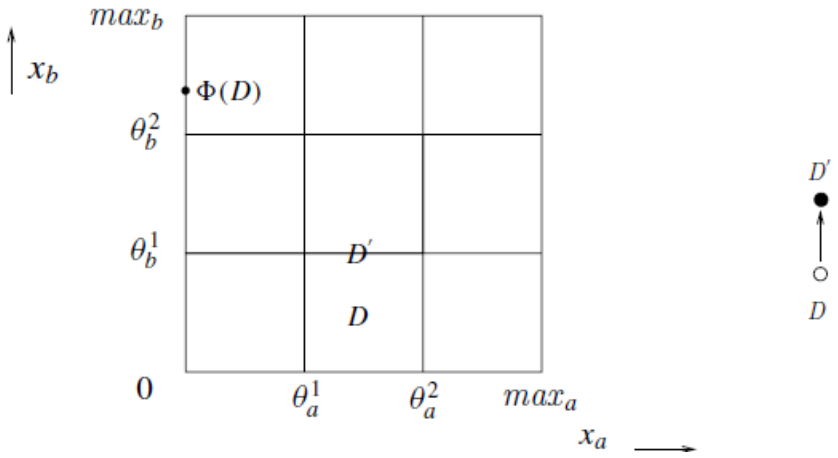
  Threshold crossings





Robustness of state transition graph

- Intuition: state transition graph provides **robust** picture of qualitative dynamics
  - Transitions defined by relative position of focal set, not specific parameter values



Robustness of state transition graph

- Intuition: state transition graph provides **robust** picture of qualitative dynamics
- If $H(x)$ is hyperrectangular, then the state transition graphs are isomorphic for given set of parameter inequalities

  Total strict ordering of threshold parameters and focal point coordinates for each variable fixes state transition graph

$$\{\theta_i^1, \ldots, \theta_i^{p_i}\} \cup \{\phi(D)_i \mid D \in \mathcal{D}_r\} \qquad 1 \leq i \leq n$$

de Jong *et al*. (2004), *Bull. Math. Biol*., 66(2):301-40

Batt *et al.* (2008), *Automatica*, 44(4):982-9

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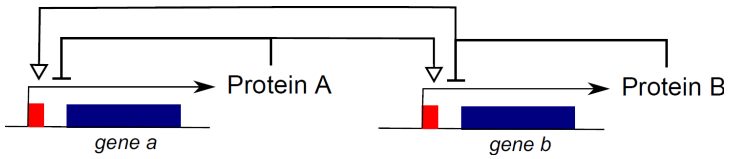
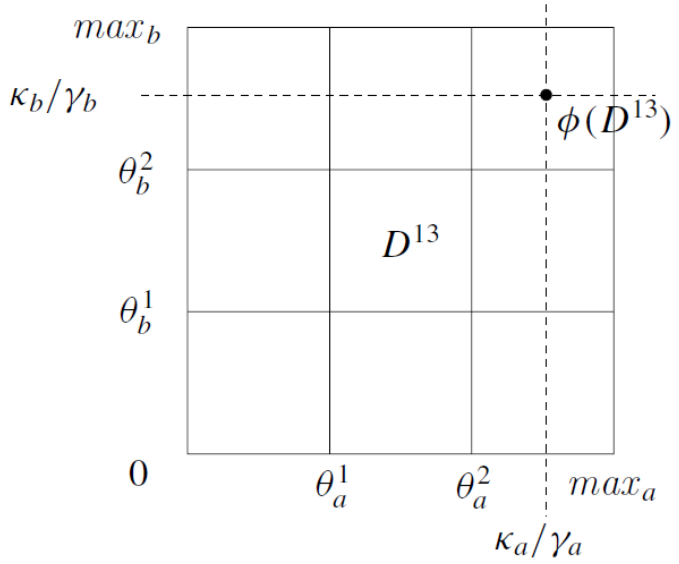


$$\dot{x}_a = \kappa_a \, s^+(x_b, \theta_b^1) \, s^-(x_a, \theta_a^2) - \gamma_a \, x_a,$$
$$\dot{x}_b = \kappa_b \, s^+(x_a, \theta_a^1) \, s^-(x_b, \theta_b^2) - \gamma_b \, x_b.$$



Robustness of state transition graph

- Intuition: state transition graph provides **robust** picture of qualitative dynamics
- If $H(x)$ is hyperrectangular, then the state transition graphs are isomorphic for given set of parameter inequalities

  Total strict ordering of threshold parameters and focal point coordinates for each variable fixes state transition graph
- Exact parameter values difficult to obtain, but parameter inequalities can be inferred from data!

Robustness of state transition graph

- Intuition: state transition graph provides **robust** picture of qualitative dynamics
- If $H(x)$ is hyperrectangular, then the state transition graphs are isomorphic for given set of parameter inequalities
- $H(x)$ is hyperrectangular under mild modeling assumptions for piecewise-linear models considered here

Assumption 2. The regulation functions $b_i^l(\cdot)$ are multi-affine functions, that is, they are affine with respect to each $s^+(x_j, \theta_j^k)$, for $j \in \{1, \ldots, n\}$ and $k \in \{1, \ldots, p_j\}$.

Assumption 4. Every step function $s^+(x_j, \theta_j^k)$, with $j \in \{1, \ldots, n\}$ and $k \in \{1, \ldots, p_j\}$, occurs in at most one $b_i(\cdot)$, $i \in \{1, \ldots, n\}$. As a consequence, for a given j, k, every vector $[\partial b_i(x)/\partial s_{jk}^+]_{i \in \{1,\ldots,n\}}$, with $s_{jk}^+ \equiv s^+(x_j, \theta_j^k)$, has at most one non-zero element.

Acary *et al.*(2014), *Physica D*, 269:103-19

Robustness of state transition graph

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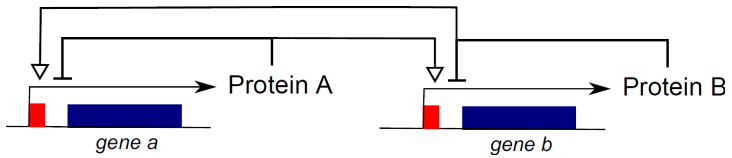

$$\dot{x}_a = \kappa_a \, s^+(x_b, \theta_b^1) \, s^-(x_a, \theta_a^2) - \gamma_a \, x_a,$$
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Acary *et al.*(2014), *Physica D*, 269:103-19

Genetic Network Analyzer

- **Genetic Network Analyzer** is computer tool for qualitative analysis of piecewise-linear models of gene networks:
  - Formulation of gene regulatory network structure
  - Definition of piecewise-linear models and parameter inequalities
  - Generation of (implicit and explicit) state transition graphs using symbolic algorithms (applicable when $H(x)$ is hyperrectangular)
  - Visual analysis of state transition graphs
  - Analysis of graph properties by means of model-checking tools
  - Export of models to numerical simulation tools

de Jong *et al*. (2003), *Bioinformatics*, 19(3):336-44

Batt *et al.* (2005), *Bioinformatics*, 21(supp. 1): i19-i28

Monteiro *et al.* (2008), *Bioinformatics*, 24(16):i227-33

Monteiro *et al.*, (2009), *BMC Bioinform.*, 10:450

Genetic Network Analyzer

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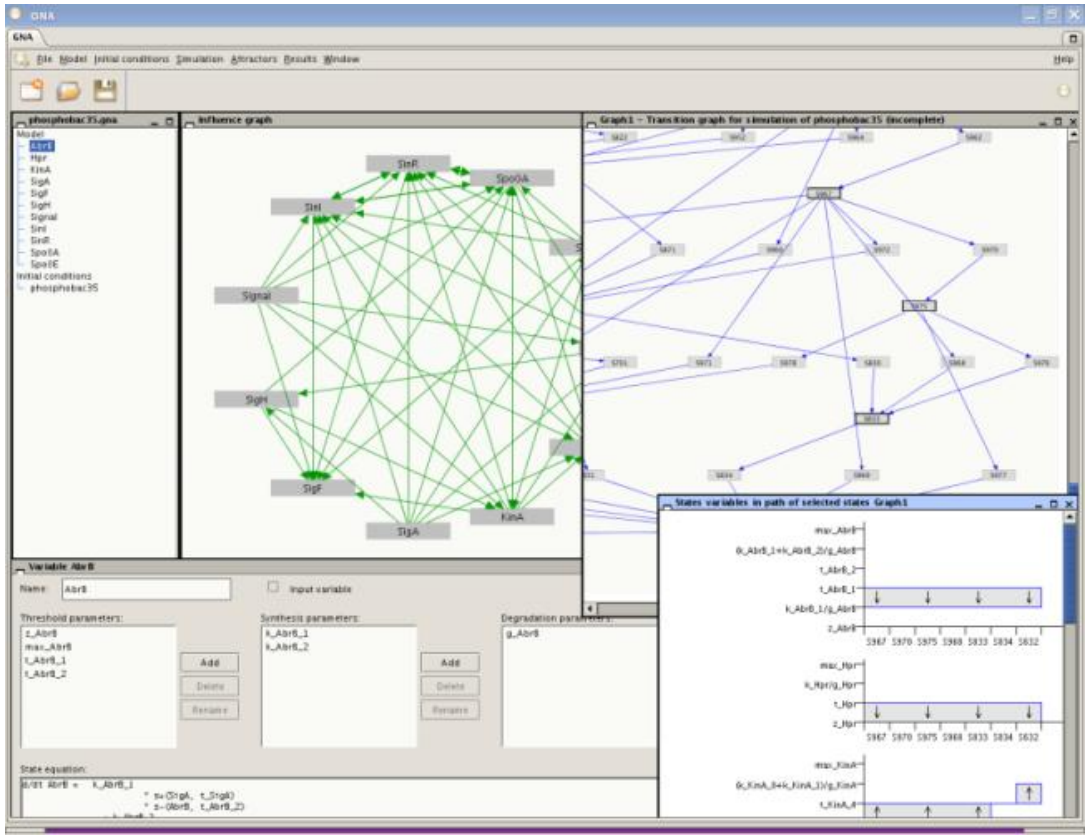


http://www-helix.inrialpes.fr/gna

Analysis of bacterial regulatory networks

- Applications of qualitative analysis in bacteria:
  - Initiation of sporulation in *Bacillus subtilis*

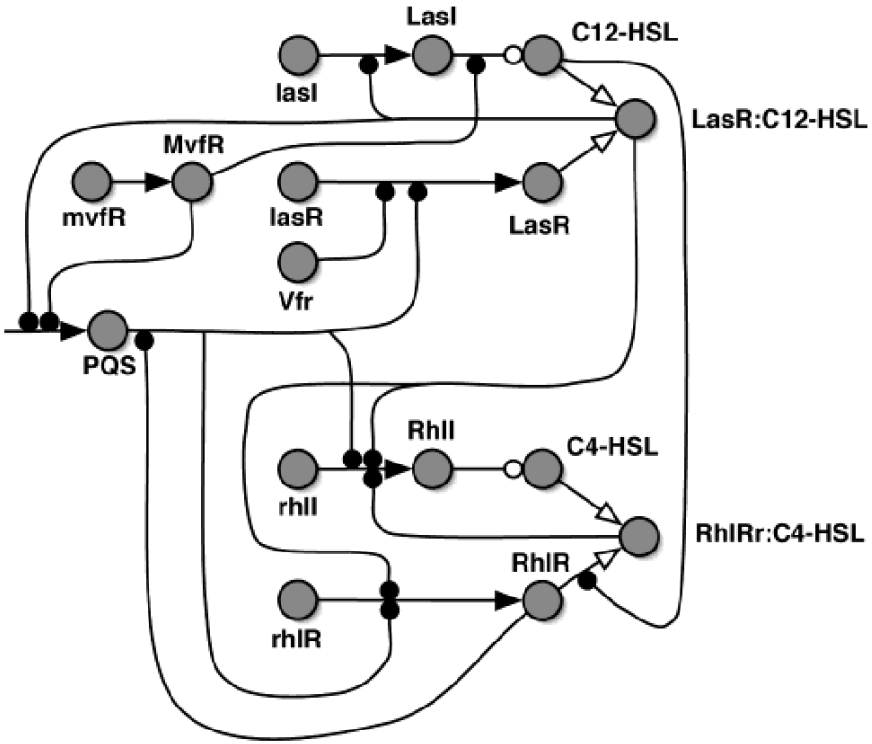
    de Jong, Geiselmann *et al.* (2004), *Bull. Math. Biol.*, 66(2):261-300

  - Quorum sensing in *Pseudomonas aeruginosa*

    Viretta and Fussenegger (2004), *Biotechnol. Prog.*, 20(3):670-8

  - Onset of virulence in *Erwinia chrysanthemi*

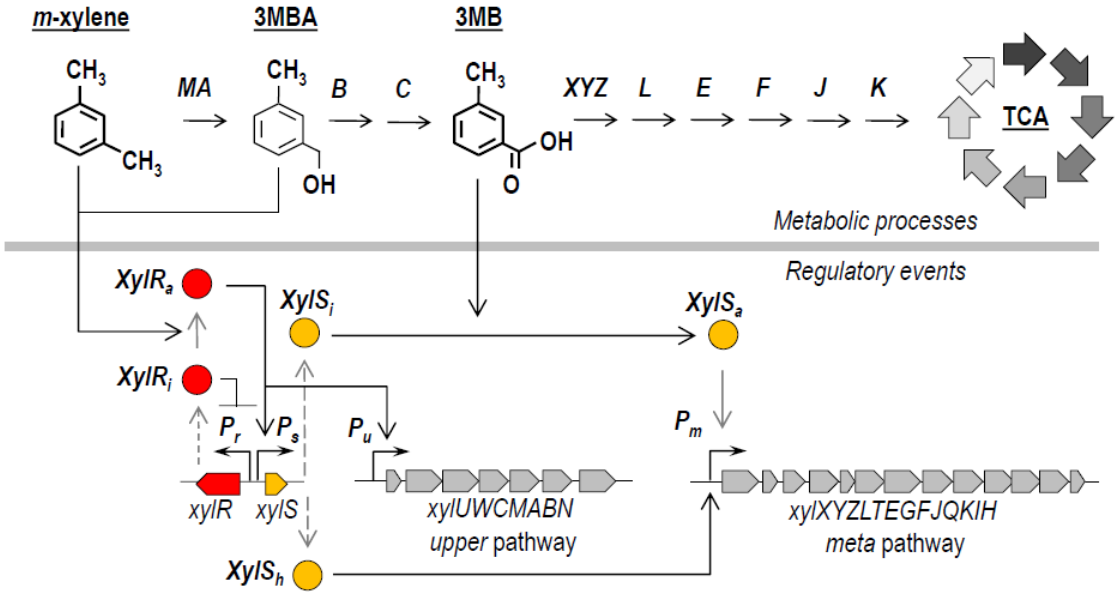
    Sepulchre *et al.* (2007), *J. Theor. Biol.*, 244(2):239-57



Biodegradation of polluants by *P. putida*

- Soil bacterium *Pseudomonas putida* mt-2 is archetypal model for environmental biodegradation of aromatic pollutants

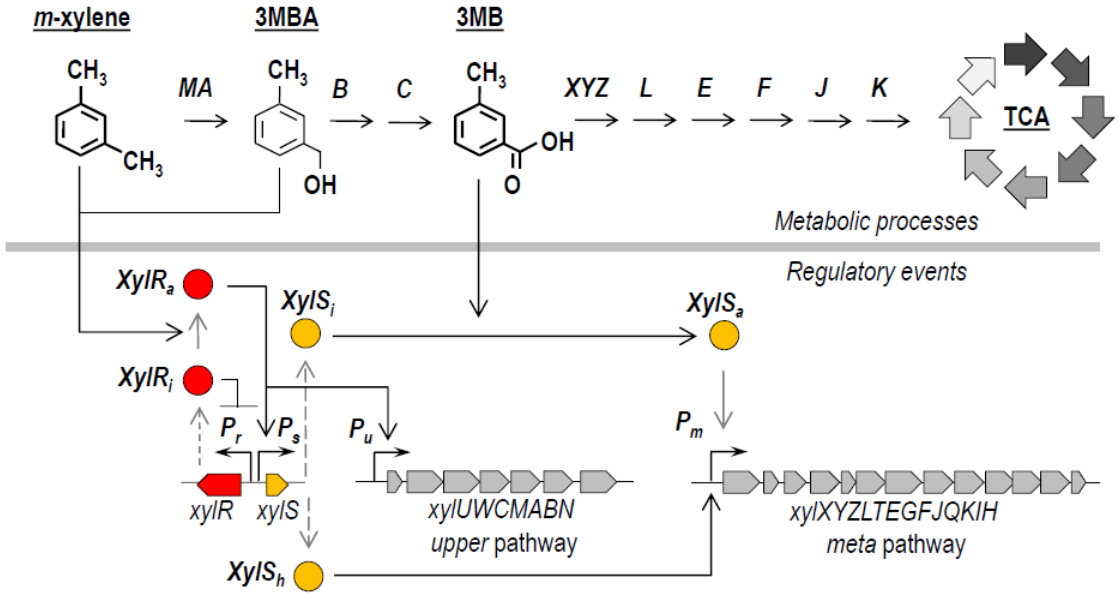
  TOL network involved in degradation of *m*-xylene to intermediates for central carbon metabolism



Rocha-Silva *et al.* (2011), *Environ. Microbiol.*, 13(9):2389-402

Role of regulators of TOL network

- **Question**: what is the role of the central, plasmid-encoded regulators XylR and XylS?



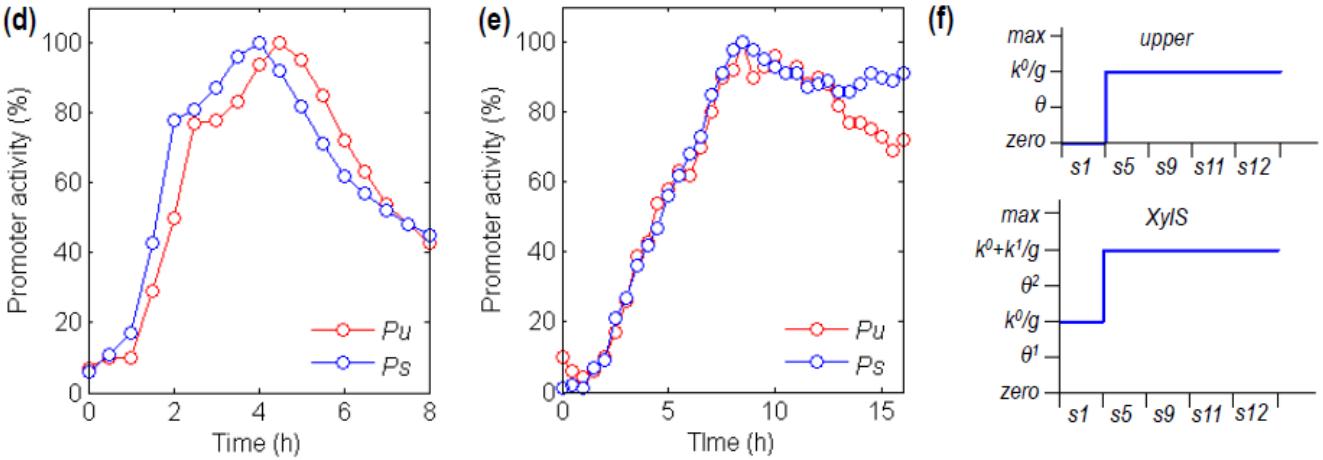
- Development of piecewise-linear model of TOL network

  Translation of network diagram into regulatory logic and model

Rocha-Silva *et al.* (2011), *BMC Syst. Biol.*, 5:191

Role of regulators of TOL network

- Validation of model by testing predictions under different perturbation conditions (mutants, metabolic inducers, …)



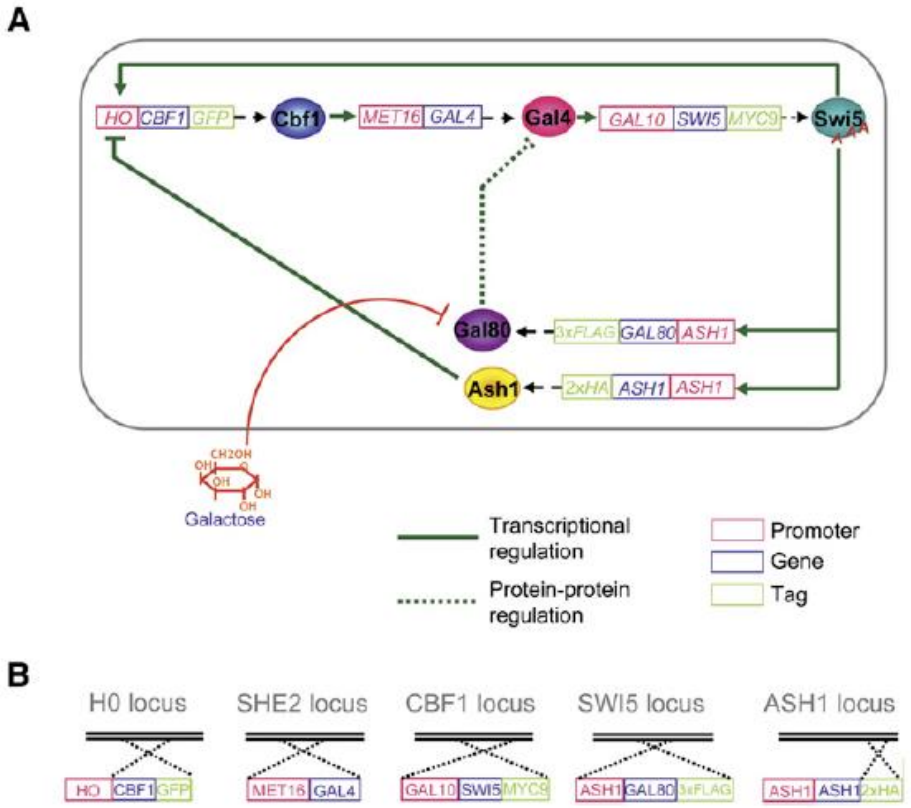
- Plasmid-encoded regulators of TOL network act as **regulatory firewall**

  Prevent toxic *m*-xylene and its biodegradation intermediates from intervening with indigenous metabolic pathways

Rocha-Silva *et al.* (2011), *BMC Syst. Biol.*, 5:191

IRMA: synthetic network in yeast

- **IRMA**: synthetic network in yeast consisting of interlocked positive and negative feedback loops
  - Network functions independently from host cell
- Network can be externally controlled by growing cells in glucose or galactose

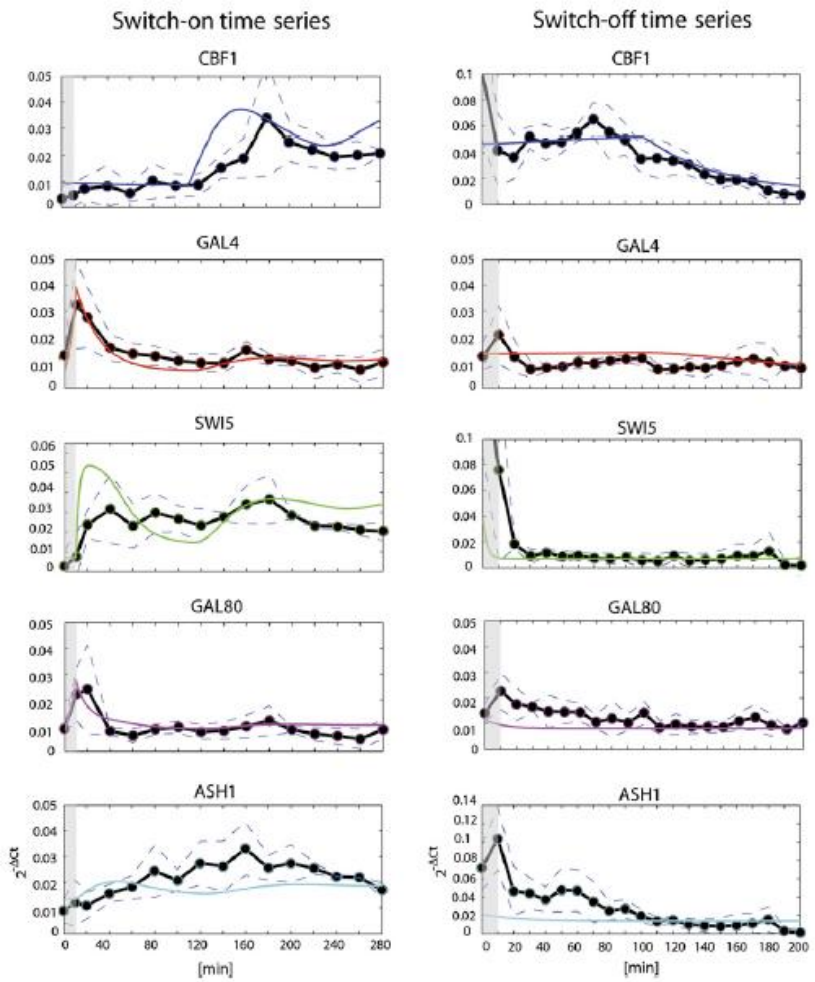


Cantone *et al.* (2009), *Cell*, 137(1):172-81

IRMA: synthetic network in yeast

- IRMA proposed as a benchmark for modeling and identification approaches
- IRMA dynamics measured over time in galactose (switch-on) and glucose (switch-off)

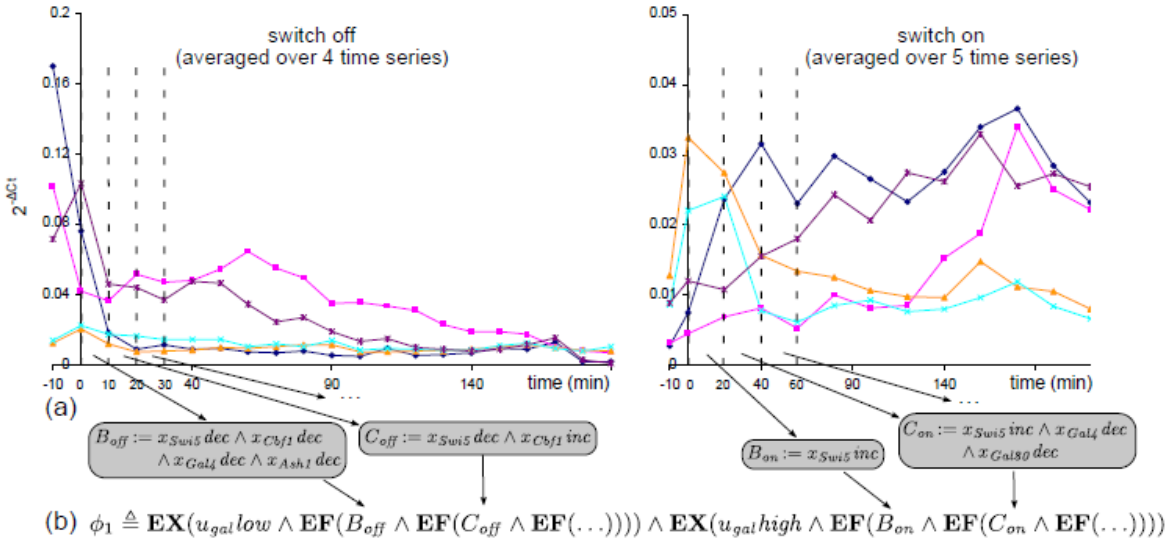
  Quantitative RT-PCR
- **Question**: are measured dynamics consistent with constructed network structure?



Cantone *et al.* (2009), *Cell*, 137(1):172-81

Test of consistency structure-dynamics

- Development of (unparametrized) piecewise-linear model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics



Batt *et al.* (2010), *Bioinformatics*, 26(18):i603-10

Test of consistency structure-dynamics

- Development of (unparametrized) piecewise-linear model representing network structure
- Approach to test consistency between network structure and data based on automated parameter constraint search:
  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of piecewise-linear model satisfying temporal logic formulae

	Symbolic state space and symbolic parameter space		Symbolic state space and explicit parameter space	
Property	Existence of parametrization	Parametrization*	Number of parametrizations	Parametrization*
ϕ_1: averaged time-series	Yes (49 s)	$\frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} < \theta^c_{Swi5} < \theta^a_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \wedge \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} < \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80}$	12 (925 s)	$\frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^c_{Swi5} < \theta^a_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \wedge (\theta_{Gal80} < \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} \wedge \frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} < \frac{\kappa^0_{Swi5}+\kappa_{Swi5}}{\gamma_{Swi5}} \vee \frac{\kappa^0_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80} < \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} \wedge \frac{\kappa^0_{Swi5}}{\gamma_{Swi5}} < \theta^g_{Swi5} \vee \frac{\kappa^0_{Gal80}+\kappa_{Gal80}}{\gamma_{Gal80}} < \theta_{Gal80})$

*All parametrizations additionally include $\kappa^1_{Cbf1}/\gamma_{Cbf1} < \theta_{Cbf1} < (\kappa^1_{Cbf1}+\kappa^2_{Cbf1})/\gamma_{Cbf1} \wedge \kappa^0_{Gal4}/\gamma_{Gal4} < \theta_{Gal4} < (\kappa^0_{Gal4}+\kappa_{Gal4})/\gamma_{Gal4} \wedge \kappa^0_{Ash1}/\gamma_{Ash1} < \theta_{Ash1} < (\kappa^0_{Ash1}+\kappa_{Ash1})/\gamma_{Ash1}$.

Test of consistency structure-dynamics

- Development of (unparametrized) piecewise-linear model representing network structure
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  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of piecewise-linear model satisfying temporal logic formulae
  - Analyze parametrizations for biological plausibility

« Activation threshold of CBF1 by Swi5 higher than activation threshold of ASH1 »: confirmed by independent experimental data

Batt *et al.* (2010), *Bioinformatics*, 26(18):i603-10

Test of consistency structure-dynamics

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  - Generate temporal logic formulae encoding observed network dynamics
  - Test if there are any parametrizations of piecewise-linear model satisfying temporal logic formulae
  - Analyze parametrizations for biological plausibility
- Automated approach for testing consistency based on model-checking techniques

  Symbolic encoding of model, dynamics and properties to make problem feasible

Course overview

- Gene regulatory networks
- Piecewise-linear models of gene regulatory networks
- Solutions of piecewise-linear models
- Qualitative analysis of gene regulatory networks
- **Numerical simulation of gene regulatory networks**
- Conclusions

Qualitative analysis vs numerical simulation

- GNA is qualitative simulation tool allowing coarse-grained dynamics of piecewise-linear (PWL) models to be analyzed
- However, for many purposes qualitative analysis is not adequate
  - Analysis of limit cycle
  - Design of synthetic controller network
- Demand for appropriate **numerical tools**, capable of dealing with differential inclusions

F-extensions of piecewise-linear models

- Extension of PWL model using classical Filippov approach: **F-extensions**

Gouzé and Sari (2002), *Dyn. Syst.*, 17(4):299-316

Definition 5 (*F-extension of PWL Models*)**.** The F-extension of the PWL model (1) is defined by the differential inclusion

$$\dot{x} \in \mathbf{F}(x), \quad \text{with } \mathbf{F}(x) = \overline{co}\left(\left\{\lim_{y \to x,\, y \notin \Theta} f(y)\right\}\right), \quad x \in \Omega, \qquad (13)$$

where $\overline{co}(P)$ denotes the closed convex hull of the set P, and $\{\lim_{y \to x,\, y \notin \Theta} f(y)\}$ the set of all limit values of $f(y)$, for $y \notin \Theta$ and $y \to x$.

Definition 6. A solution of an F-PWL system Σ on a time interval I is a solution of the differential inclusion (13) on I, that is, an absolutely-continuous vector-valued function $\xi(\cdot)$ such that $\dot{\xi}(t) \in \mathbf{F}(\xi(t))$ almost everywhere on I.

PA-extensions of piecewise-linear models

- Extension of PWL model using alternative **Aizermann-Pyatnitskii (PA)-extensions**

Machina and Posonov (2011), *Nonlinear. Anal.*, 74(3):882-900

Definition 8 (*AP-extension of PWL Models*). The AP-extension of a PWL model (1) is defined by the following differential inclusion

$$\dot{x} \in \begin{bmatrix} \mathbf{G}_1(x) \\ \vdots \\ \mathbf{G}_n(x) \end{bmatrix} = \left\{ \begin{bmatrix} -\gamma_1 x_1 + g_1(\sigma) \\ \vdots \\ -\gamma_n x_n + g_n(\sigma) \end{bmatrix} \middle| \sigma_j^k \in S^+(x_j, \theta_j^k), \right.$$

$$\left. j \in \{1, \ldots, n\},\ k \in \{1, \ldots, p_j\} \right\}. \qquad (17)$$

$$S^+(x_j, \theta_j^k) = \begin{cases} 1 & x_j > \theta_j^k \\ [0, 1] & x_j = \theta_j^k \\ 0 & x_j < \theta_j^k \end{cases}$$

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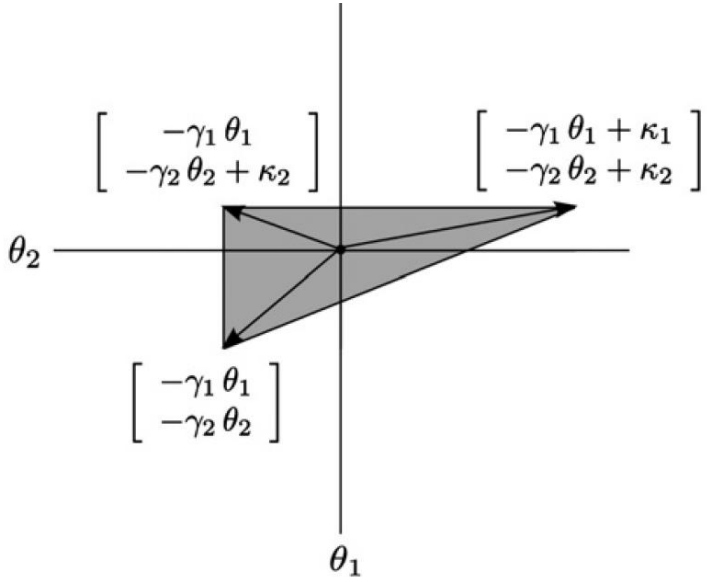
Comparison of F and PA-extensions

- In general, the two extensions are **not equivalent**
  - PA-extensions are not generally convex
  - PA-extensions do not guarantee existence of solutions
  - F-extensions contain PA-extensions

$$\begin{cases} \dot{x}_1 = -\gamma_1 x_1 + \kappa_1 \left[s^+(x_1, \theta_1) + s^+(x_2, \theta_2) \right. \\ \qquad\qquad \left. - 2\, s^+(x_1, \theta_1)\, s^+(x_2, \theta_2) \right] \\ \dot{x}_2 = -\gamma_2 x_2 + \kappa_2 \left[1 - s^+(x_1, \theta_1)\, s^+(x_2, \theta_2) \right] \end{cases}$$



$$\mathbf{F}(x) = \begin{bmatrix} -\gamma_1 x_1 \\ -\gamma_2 x_2 \end{bmatrix} + \overline{co} \left\{ \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ \kappa_2 \end{bmatrix}, \begin{bmatrix} \kappa_1 \\ \kappa_2 \end{bmatrix} \right\}$$

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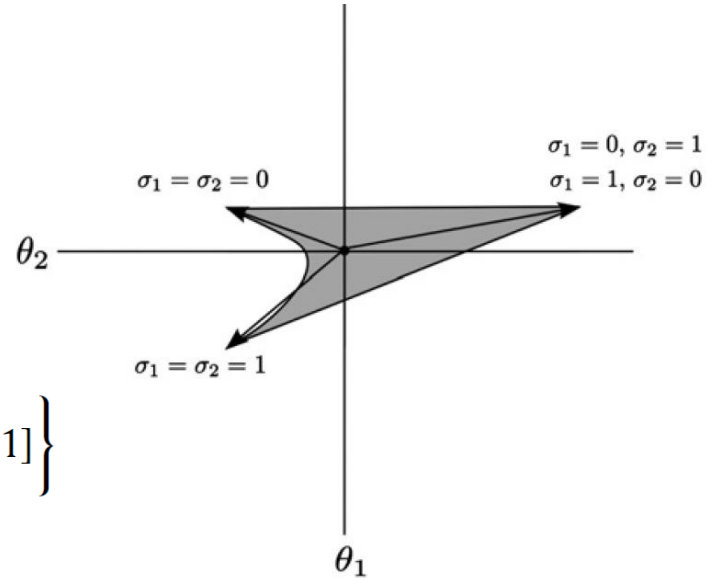

$$\mathbf{G}(x) = \left\{ \begin{bmatrix} -\gamma_1 x_1 + \kappa_1 \left[\sigma_1 + \sigma_2 - 2\sigma_1 \sigma_2 \right] \\ -\gamma_2 x_2 + \kappa_2 \left[1 - \sigma_1 \sigma_2 \right] \end{bmatrix} \middle| \, \sigma_1, \sigma_2 \in [0, 1] \right\}$$

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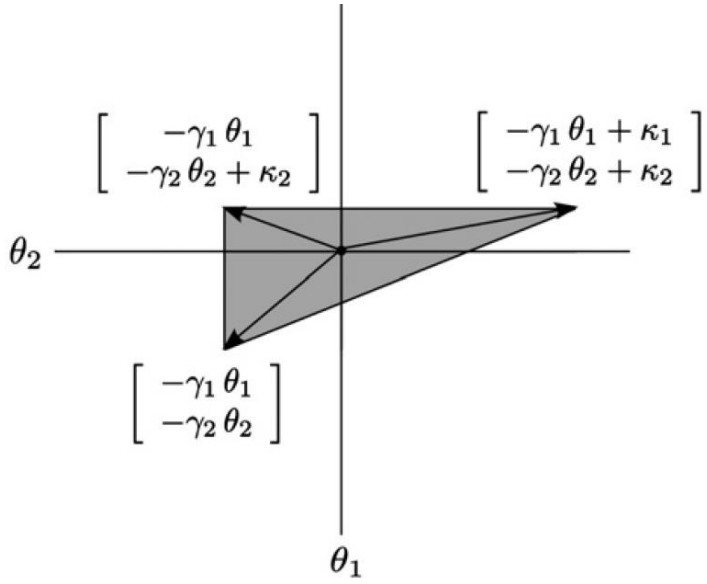
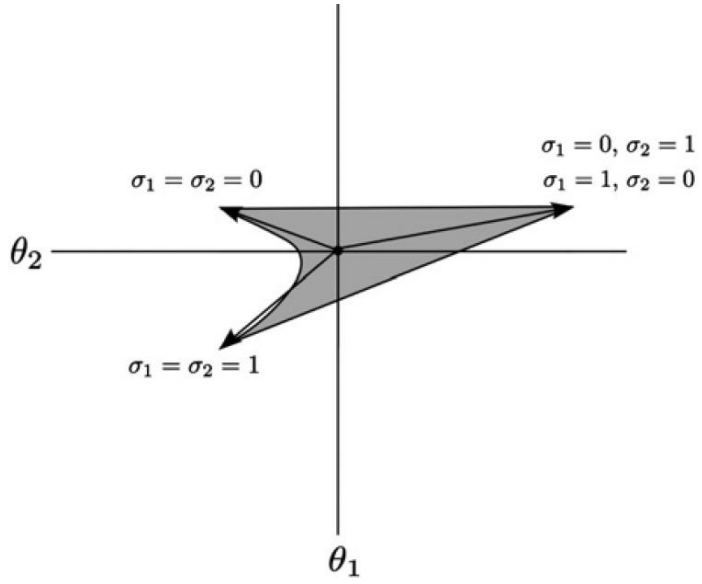




Comparison of F and PA-extensions

- In general, the two extensions are not equivalent
- But: **equivalency** obtained under the two assumptions

> **Assumption 2.** The regulation functions $b_i^l(\cdot)$ are multi-affine functions, that is, they are affine with respect to each $s^+(x_j, \theta_j^k)$, for $j \in \{1, \ldots, n\}$ and $k \in \{1, \ldots, p_j\}$.

  - Satisfied for regulation functions equivalent to Boolean functions

> **Assumption 4.** Every step function $s^+(x_j, \theta_j^k)$, with $j \in \{1, \ldots, n\}$ and $k \in \{1, \ldots, p_j\}$, occurs in at most one $b_i(\cdot)$, $i \in \{1, \ldots, n\}$. As

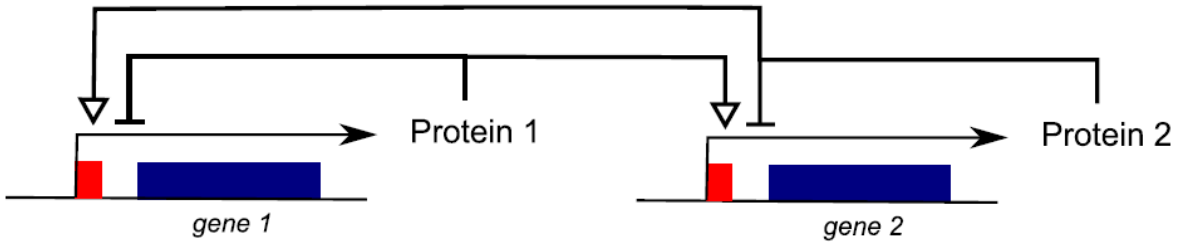
  - Weak modeling assumption, not constraining in practice

Comparison of F and PA-extensions

- In general, the two extensions are not equivalent
- But: **equivalency** obtained under the two assumptions

Proposition 12. *Under Assumptions 2 and 4,* $\mathbf{F}(x) = \mathbf{G}(x)$ *for all* $x \in \Omega$.

Acary *et al.*(2014), *Physica D*, 269:103-19



$$\begin{cases} \dot{x}_1 = -\gamma_1\, x_1 + \kappa_1\, s^+(x_2, \theta_2^1)\, s^-(x_1, \theta_1^2) \\ \dot{x}_2 = -\gamma_2\, x_2 + \kappa_2\, s^+(x_1, \theta_1^1)\, s^-(x_2, \theta_2^2) \end{cases}$$

Comparison of F and PA-extensions

- In general, the two extensions are not equivalent
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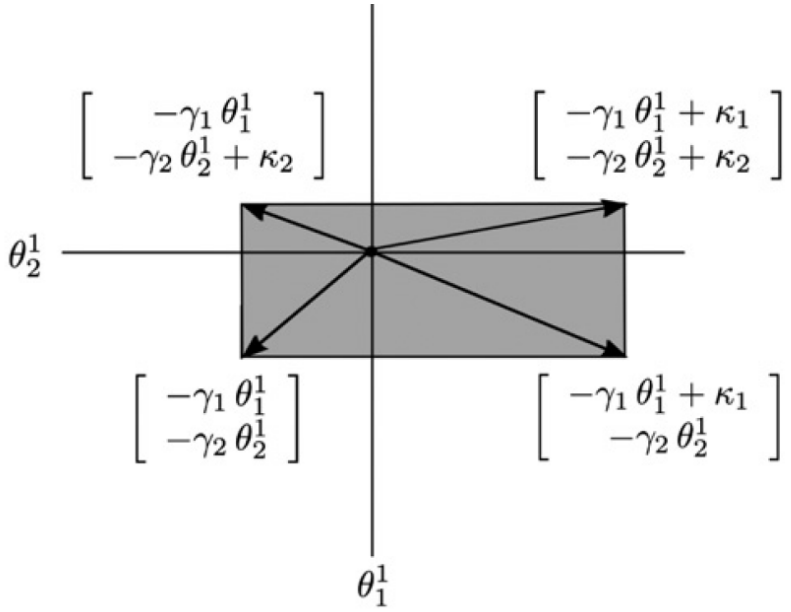
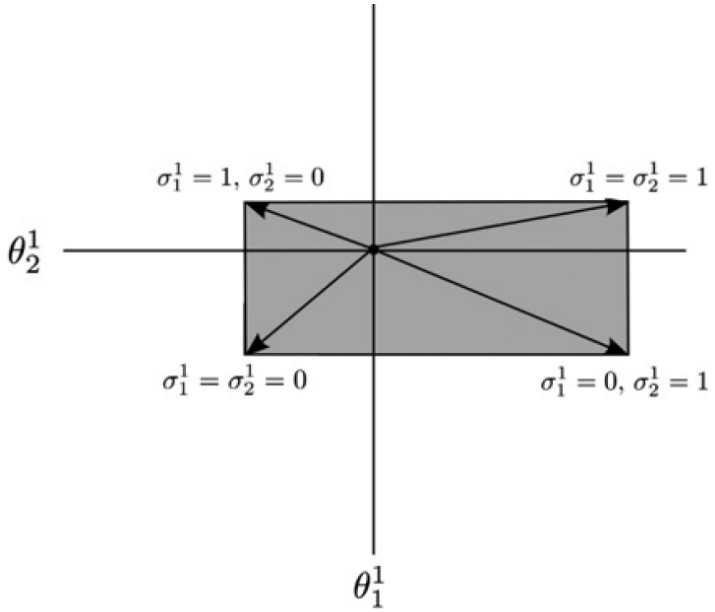




PWL models and complementarity systems

- Transformation of PA-extension to mixed **complementarity system** allows application of powerful numerical tools

  Acary and Brogliato (2008), *Numerical Methods for Nonsmooth Dynamical Systems*, Springer, Berlin

- **Principle of approach**:
  1. Reformulation of set-valued relation

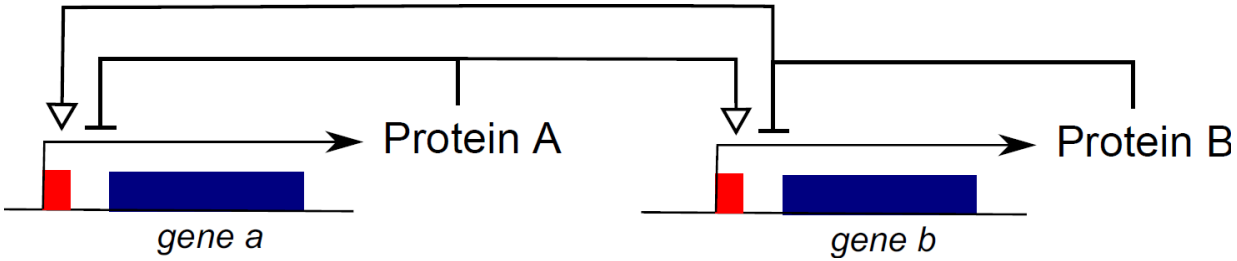
     $$\sigma \in S^{+}(x, \theta)$$

     as inclusion into normal cone, complementarity problem (CP) and variational inequalities (VI)
  2. Definition of implicit event-capturing time-stepping scheme (backward Euler scheme), capable of dealing with switches and sliding motion
  3. Use of numerical solver for one-step problem, resulting from CP/VI formulation. Efficient enumeration of possible solutions.
  4. Use of solvers in Siconos platform (http://siconos.gforge.inria.fr)

Acary *et al.*(2014), *Physica D*, 269:103-19

Simulation of example network

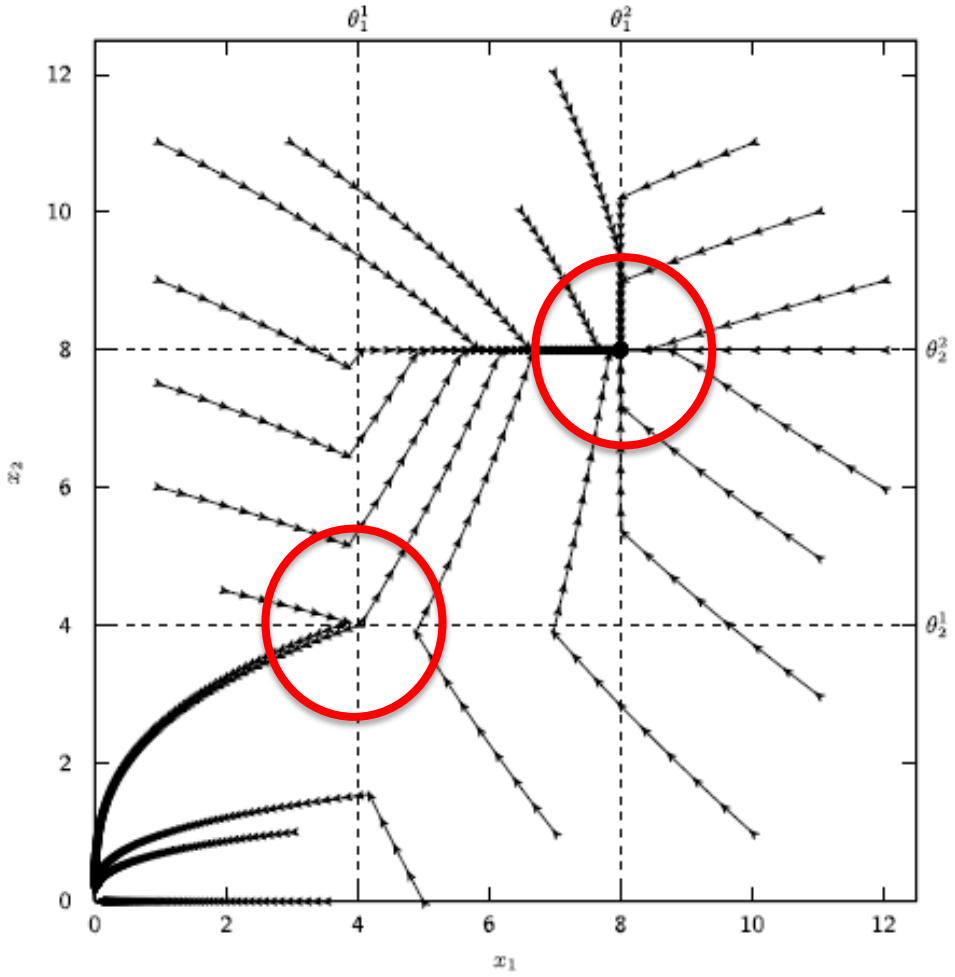
- Piecewise-linear model of simple **cross-activation network**



$$\dot{x}_a = \kappa_a \, s^+(x_b, \theta_b^1) \, s^-(x_a, \theta_a^2) - \gamma_a \, x_a,$$
$$\dot{x}_b = \kappa_b \, s^+(x_a, \theta_a^1) \, s^-(x_b, \theta_b^2) - \gamma_b \, x_b.$$

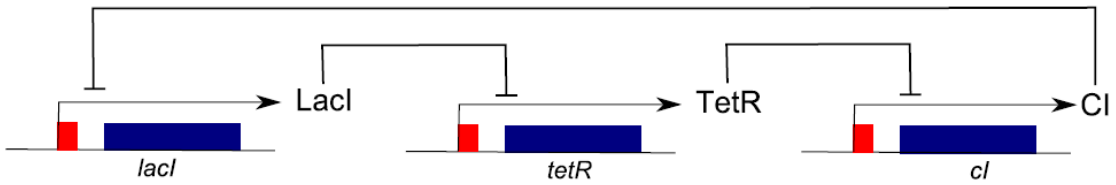
Simulation of example network

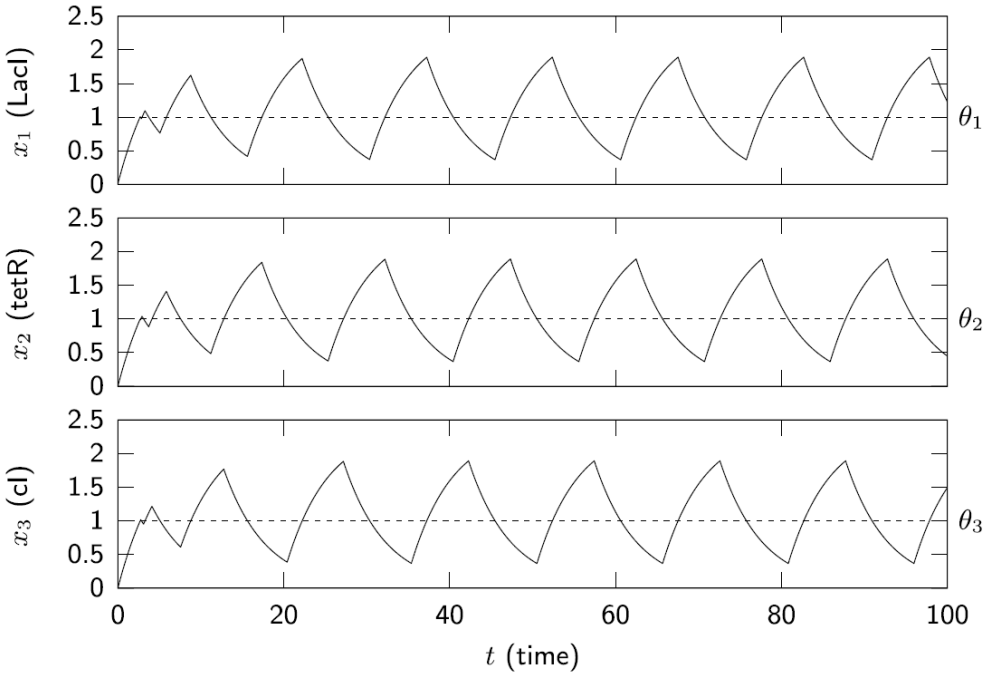
- Equilibrium points on threshold hyperplanes reproduced
- Sliding mode on threshold hyperplanes without chattering
- Finite-time stability of equilibrium points on threshold hyperplanes
- Rapid and easy-to-use simulation tool

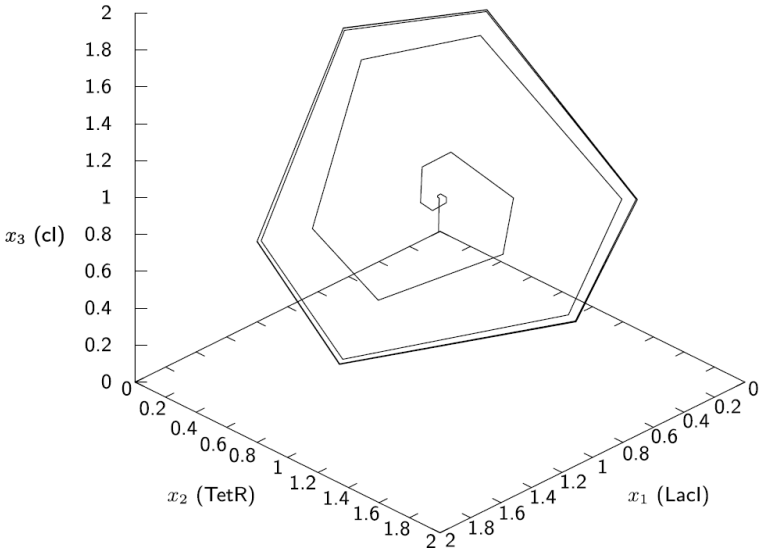


Simulation of synthetic network

- Repressilator



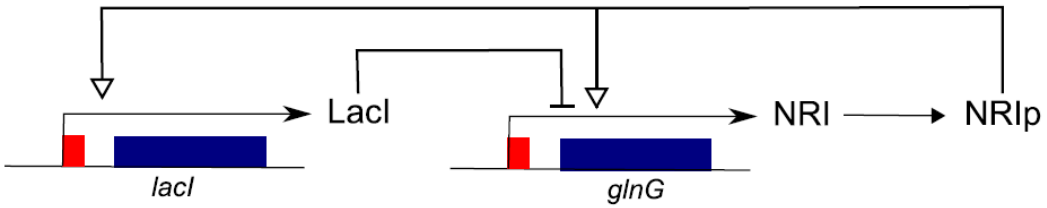


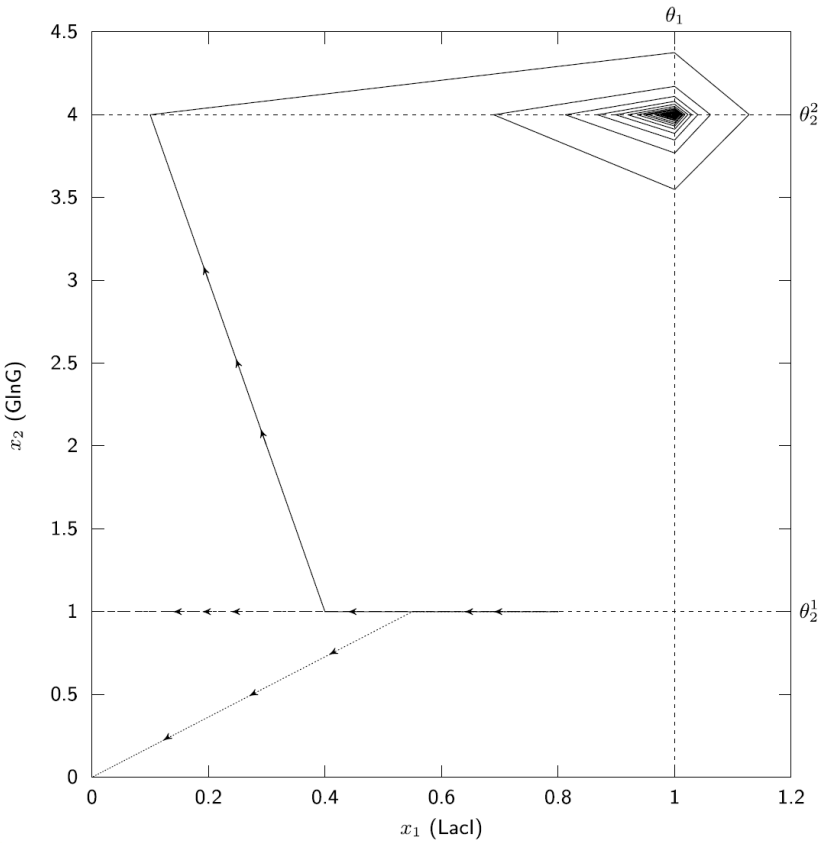


Elowitz and Leibler (2000), *Nature*, 403(6767):335-8

Simulation of synthetic network

- Oscillator with positive feedback

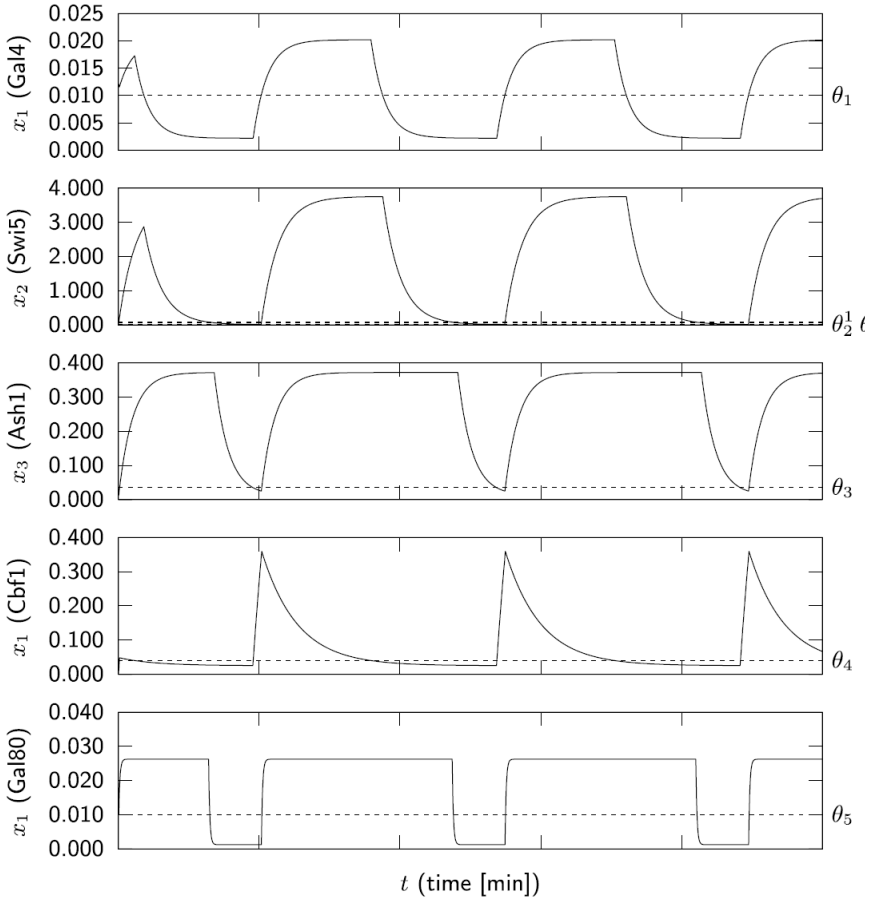


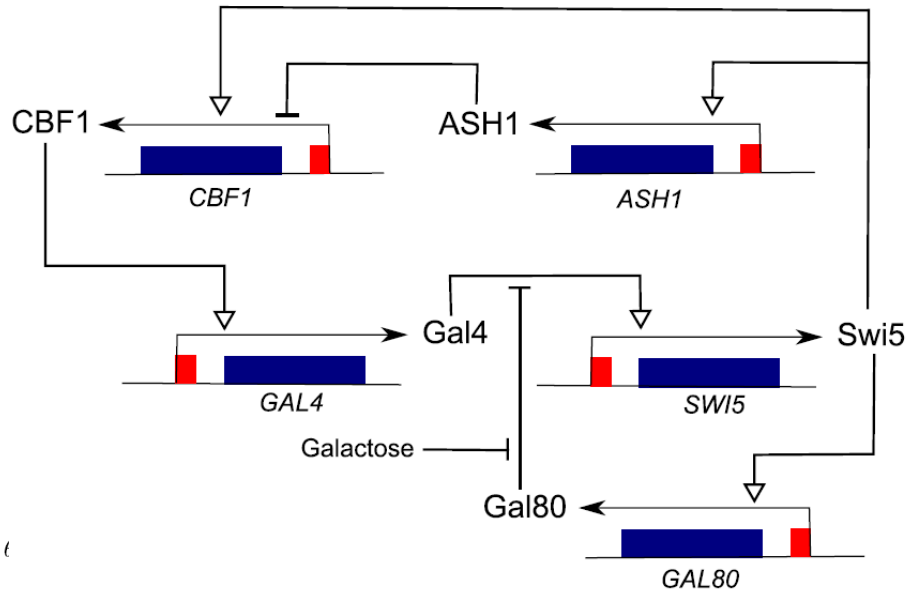


Atkinson *et al.* (2003), *Cell*, 113(5):597-608

Simulation of synthetic network

- IRMA network





Cantone *et al.* (2009), *Cell*, 137(1):172-81

Conclusions

- Gene regulatory networks can be modeled by piecewise-linear models
- Analysis of piecewise-linear model requires extension of differential equations to differential inclusions
- Piecewise-linear models are simple enough to allow robust, qualitative analysis of dynamics
- Numerical tools can be used to provide higher quantitative precision and resolve ambiguities in qualitative analysis
- Piecewise-linear models are tools, appropriate for certain kind of questions but not for others

Contributors

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Merci !

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