

# Piece-wise linear differential equations

When quantitative data are not known, the dynamics of genetic regulatory network can be modeled by a class of piece-wise linear (PL) differential equations originally proposed by Glass and Kauffman (1973) and generalized by Mestl *et al.* (1995).

The model have mathematical properties that favour qualitative analyses of:

- the steady state
- transient behavior of regulatory systems.

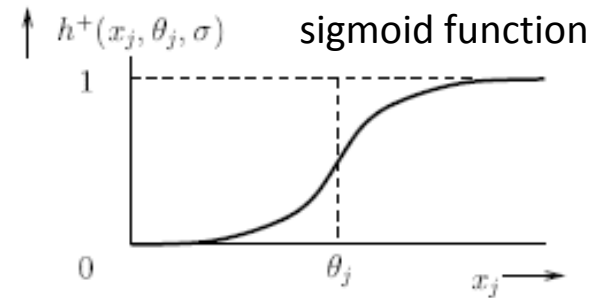
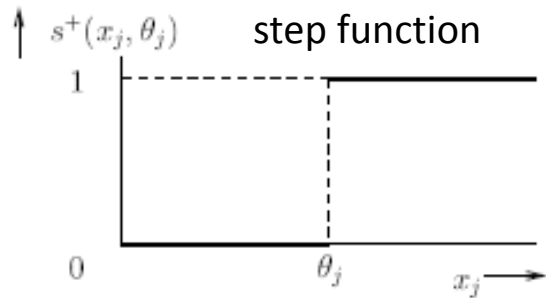
In PL model:

- state variables correspond to concentrations of proteins encoded by genes in the network
- differential equations represent the interactions arising from the regulatory influence of some proteins on the synthesis or degradation of others
- discontinuous step functions modeled the regulatory interactions ( approximation of the switch-like behavior of genes whose expression is regulated by continuous sigmoid curves)



Resulting differential equations are piecewise linear

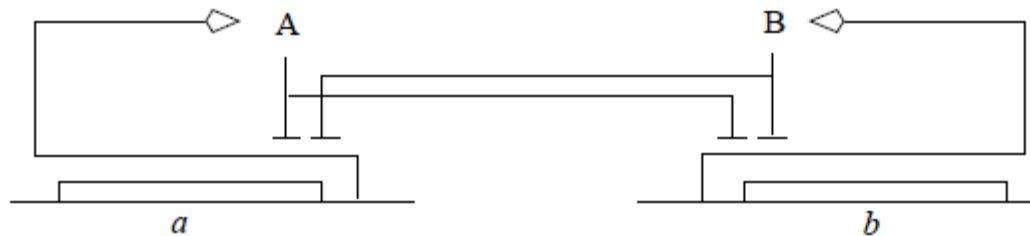
# Piece-wise linear differential equations



When  $\sigma \rightarrow \infty$ , the sigmoid functions (also called Hill functions) can be approach by a step function.

# Piece-wise linear differential equations

Simple example : two genes  $a$  and  $b$ , transcribed from separate promoters, encode proteins A and B. Proteins A and B repress gene  $a$  and  $b$  at different concentrations. Repressions of the genes is achieved through the binding of the proteins to regulatory sites overlapping the promoters. One positive and two negative feedback loops.



concentration of  $A > \theta_{a_2}$  inhibition of gene  $a$  expression

concentration of  $A > \theta_{a_1}$  inhibition of gene  $b$  expression

concentration of  $B > \theta_{b_1}$  inhibition of gene  $a$  expression

concentration of  $B > \theta_{b_2}$  inhibition of gene  $b$  expression

General form of the state equation represents the difference of the rate of synthesis of protein  $x$  and the rate of degradation of protein  $x$ :

$$\frac{dx}{dt} = \text{synthesis}(x) - \text{degradation}(x)$$

# Piece-wise linear differential equations

State equation:  $\frac{dx_i}{dt} = f_i(x) - g_i(x)x_i$  (1) with  $f_i(x)$  = rate of synthesis  
 $g_i(x)x_i$  = rate of degradation  $x_i \geq 0, 1 \leq i \leq n$

$x = (x_1, \dots, x_n)'$  is a vector of cellular concentrations.

The function  $f_i: \mathbb{R}_{\geq 0}^n \rightarrow \mathbb{R}_{\geq 0}$  is defined as:

$$f_i(x) = \sum_{l \in L} \kappa_{il} b_{il}(x)$$

Where  $\kappa_{il} > 0$  is a rate parameter and  $b_{il}: \mathbb{R}_{\geq 0}^n \rightarrow \{0,1\}$  is a regulation function defined in terms of step function. In the simplest case, the step function  $s^+ : \mathbb{R}^2 \rightarrow \{0,1\}$  is defined as follow:

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

**In the simple case:**

$$f_i(x) = \kappa_i s^+(x_j, \theta_j)$$

gene  $i$  is not expressed if the concentration of protein  $J$  is below the threshold  $\theta_j$  and above this threshold it is expressed at the rate  $\kappa_i$

If protein  $J$  is a negative regulator of gene  $i$ :

$$f_i(x) = \kappa_i s^-(x_j, \theta_j)$$

$$\text{with } s^-(x_j, \theta_j) = 1 - s^+(x_j, \theta_j)$$

The degradation function  $g_i$  is expressed analogously with degradation rates note  $\gamma$  instead of  $\kappa$

# Piece-wise linear differential equations

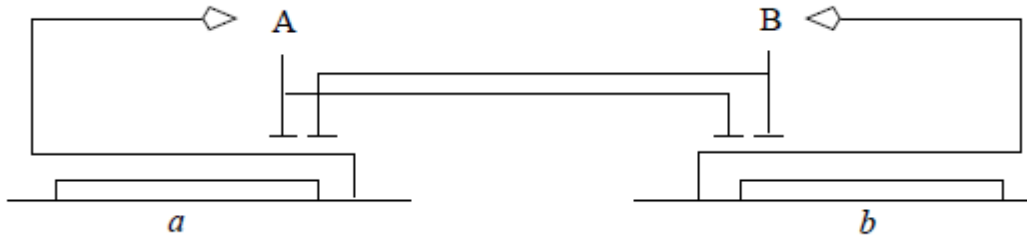
The PL models can be extended to take into account **input variable**  $u = (u_1, \dots, u_m)$ , representing the concentration of proteins and small molecules whose synthesis and degradation are regulated outside the system.

The state equation becomes:

$$\frac{dx}{dt} = f(x, u) - g(x, u)x$$

If the input variables are assumed to be constant  $\frac{du}{dt} = 0$  and the state equation are reduced to (1)

# Piece-wise linear differential equations



concentration of  $A > \theta a_2$  inhibition of gene  $a$  expression  
concentration of  $A > \theta a_1$  inhibition of gene  $b$  expression  
concentration of  $B > \theta b_1$  inhibition of gene  $a$  expression  
concentration of  $B > \theta b_2$  inhibition of gene  $b$  expression

State equation for gene  $a$ :

$$\frac{dx_a}{dt} = \kappa_a s^-(x_a, \theta a_2) s^-(x_b, \theta b_1) - \gamma_a x_a$$

State equation for gene  $b$ :

$$\frac{dx_b}{dt} = \kappa_b s^-(x_a, \theta a_1) s^-(x_b, \theta b_2) - \gamma_b x_b$$

# Piece-wise linear differential equations

Dynamical properties of PL of the form (1) could be analyzed in the  $n$ -dimensional phase space box  $\Omega$ .

$\Omega = \Omega_1 \times \dots \times \Omega_n$  where every  $\Omega_i$   $1 \leq i \leq n$  is defined as:

$$\Omega_i = \{x_i \in \mathbb{R}_{\geq 0} \mid 0 \leq x_i \leq \max_i\} \text{ with } \max_i \text{ a parameter corresponding to a maximum concentration for the protein}$$

In general, a protein encoded by a gene will be involved in different interactions at different threshold concentrations. Thus the phase space  $\Omega$  will be divided into hyper-rectangular regions that are called **regulatory domains**.

A regulatory domain  $D \subseteq \Omega$  is defined by  $D = D_1 \times \dots \times D_n$  where every  $D_i$   $1 \leq i \leq n$  is defined by one of the following equations:

$$D_i = \{x_i \mid 0 \leq x_i < \theta_i^1\},$$

$$D_i = \{x_i \mid \theta_i^1 < x_i < \theta_i^2\},$$

...

$$D_i = \{x_i \mid \theta_i^{p_i} < x_i \leq \max_i\}$$

If for a domain  $D$ , there are some  $i, j$ ,  $1 \leq i \leq n$  and  $1 \leq j \leq p_i$  such as

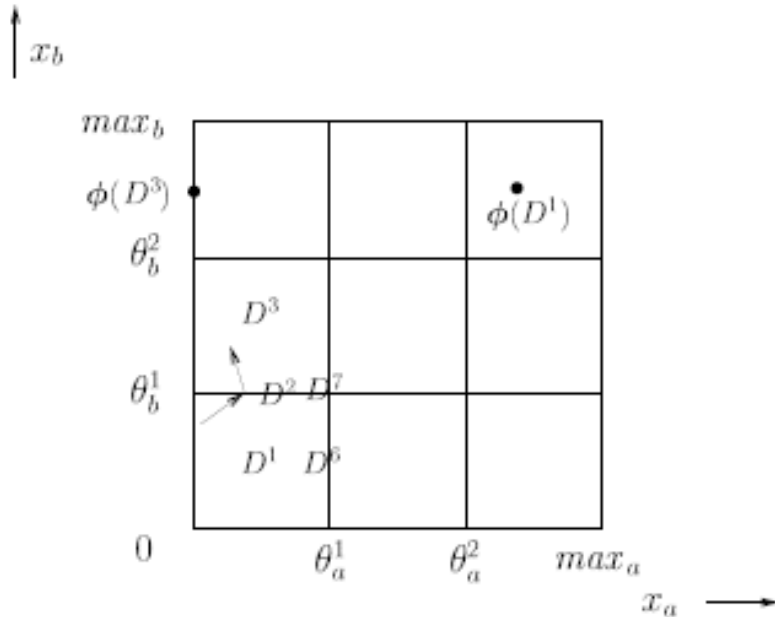
$$D_i = \{x_i \mid x_i = \theta_i^j\}$$

Then  $D$  is called a **switching domain**

With protein  $i$  having  $p_i$  thresholds

# Piece-wise linear differential equations

In our simple example, proteins A and B have two concentration thresholds. Thus,  $\Omega$  is divided into 9 regulatory domains.



$$D^1 \text{ is defined by: } 0 \leq x_a < \theta_a^1 \\ 0 \leq x_b < \theta_b^1$$

$$D^2 \text{ is defined by: } 0 \leq x_a < \theta_a^1 \\ x_b = \theta_b^1$$

$$D^3 \text{ is defined by: } 0 \leq x_a < \theta_a^1 \\ \theta_b^1 < x_b < \theta_b^2$$

$$D^6 \text{ is defined by: } x_a = \theta_a^1 \\ 0 \leq x_b < \theta_b^1$$

If  $max_i$  is chosen as  $max_i = \max_{x \geq 0} \frac{f_i(x)}{g_i(x)}$ , it can be shown that all trajectories starting in  $\Omega$  will stay in it.

Trajectories starting outside will enter  $\Omega$  at some point.



# Piece-wise linear differential equations

When the expression of the step functions are evaluated in a regulatory domain,  $f_i$  and  $g_i$  reduce to the sum of rate constants.

More precisely, in every regulatory domain  $D$   $f_i$  reduces to some  $\mu_i^D \in M_i \equiv \{f_i(x) \mid 0 \leq x \leq \max\}$  and  $g_i$  to some  $\nu_i^D \in N_i \equiv \{g_i(x) \mid 0 \leq x \leq \max\}$

$M_i$  and  $N_i$  collect the synthesis and degradation rates of the protein in different domains of  $\Omega$ .

It can be shown that all trajectories in  $D$  monotonically tend towards a stable steady state  $x = \mu^D/\nu^D$ , the **target equilibrium** lying at the intersection of the  $n$  hyperplans  $x_i = \mu_i^D/\nu_i^D$ . The target equilibrium of the protein concentration  $x_i$  gives an indication of the strength of gene expression in  $D$ .

In our example, we have the following state equations and the sets  $M_a, N_a, M_b$  and  $N_b$  :

$$\frac{dx_a}{dt} = \kappa_a s^-(x_a, \theta a_2) s^-(x_b, \theta b_1) - \gamma_a x_a \quad M_a = \{0, \kappa_a\} \text{ and } N_a = \{\gamma_a\}$$

$$\frac{dx_b}{dt} = \kappa_b s^-(x_a, \theta a_1) s^-(x_b, \theta b_2) - \gamma_b x_b \quad M_b = \{0, \kappa_b\} \text{ and } N_b = \{\gamma_b\}$$

In domain  $D^1$ :  $0 \leq x_a < \theta_a^1$       Then, protein A does not inhibits either gene  $a$  or  $b$ , and  
 $0 \leq x_b < \theta_b^1$       protein B does not inhibits either gene  $a$  or  $b$ .

In  $D^1$ , the state equations become:  $\frac{dx_a}{dt} = \kappa_a - \gamma_a x_a$       Target equilibrium =  $(\kappa_a/\gamma_a, \kappa_b/\gamma_b)$   
 $\frac{dx_b}{dt} = \kappa_b - \gamma_b x_b$       lies outside  $D^1$

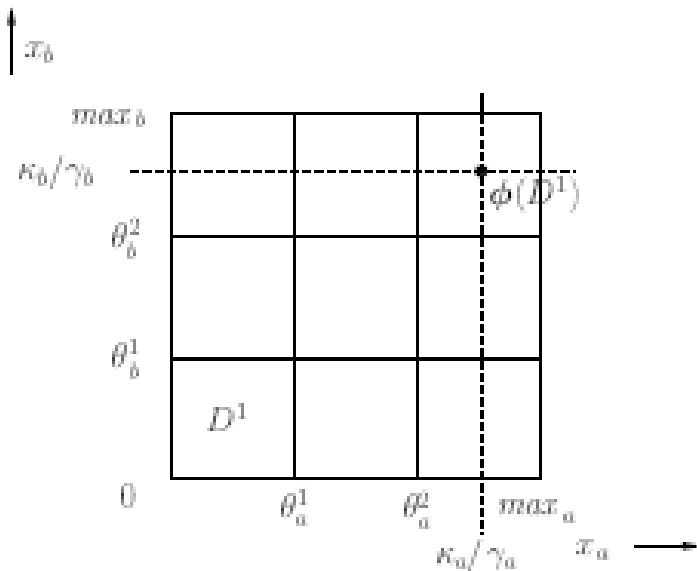
# Piece-wise linear differential equations

In domain  $D^3$ :  $0 \leq x_a < \theta_a^1$       Then, protein A does not inhibit either gene  $a$  or  $b$ , and  
 $\theta_b^1 < x_b < \theta_b^2$       protein B inhibits gene  $a$  but not gene  $b$ .

In  $D^3$ , the state equations become:       $\frac{dx_a}{dt} = -\gamma_a x_a$       Target equilibrium =  $(0, \kappa_b/\gamma_b)$   
lies outside  $D^3$   
 $\frac{dx_b}{dt} = \kappa_b - \gamma_b x_b$

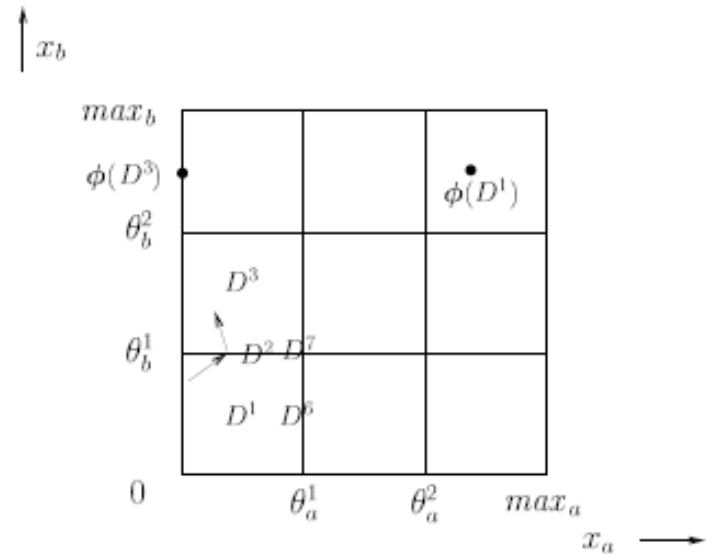
Thus, different regulatory domains have different target equilibriums

# Piece-wise linear differential equations



Target equilibrium  $\phi(D^1) = (\kappa_a/\gamma_a, \kappa_b/\gamma_b)$   
lies outside  $D^1$

Below the threshold  $\theta_{a2}$  the protein A is not synthesized and below the threshold  $\theta_{b2}$  the protein B is not synthesized. Therefore, the coordinates of the target equilibrium should be in  $D^9$



Target equilibrium  $\phi(D^3) = (0, \kappa_b/\gamma_b)$   
lies outside  $D^3$

A is only degraded, thus at the equilibrium the concentration of A is equal to 0. To be synthesized, the concentration of B must be higher than  $\theta_{b2}$ .

# Piece-wise linear differential equations

Qualitative constraints on parameter values that can be inferred from biological data:

- threshold inequalities
- equilibrium inequalities

**Threshold inequalities:** they are obtained by ordering the  $p_i$  concentration thresholds of the protein encoded by the gene  $i$ .

$$0 < \theta_i^1 < \theta_i^2 < \dots < \theta_i^{p_i} < \max_i$$

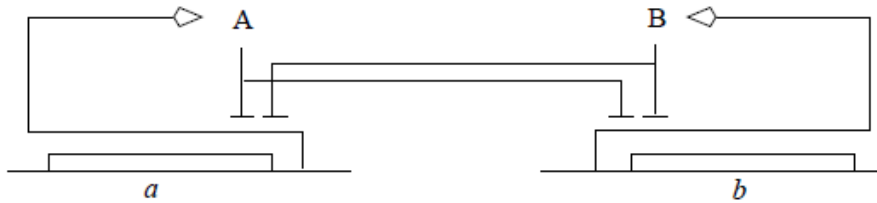
The threshold inequalities determine the partitioning of  $\Omega$  into regulatory and switching domains

**Equilibrium inequalities:** they order the possible target equilibrium levels of  $x_i$  in different regulatory domains  $D \subseteq \Omega$  with respect to the threshold values. They define the strength of gene expression in the domain in a qualitative way, on the scale of ordered concentration thresholds.

For  $\mu_i \in M_i$ ,  $\nu_i \in N_i$  and  $\mu_i \nu_i \neq 0$ , we can specify:

$$\begin{aligned} 0 &< \mu_i / \nu_i < \theta_i^1, \\ \theta_i^1 &< \mu_i / \nu_i < \theta_i^2, \\ &\dots \\ \theta_i^{p_i} &< \mu_i / \nu_i < \max_i. \end{aligned}$$

# Piece-wise linear differential equations



concentration of A  $> \theta a_2$  inhibition of gene *a* expression  
 concentration of A  $> \theta a_1$  inhibition of gene *b* expression  
 concentration of B  $> \theta b_1$  inhibition of gene *a* expression  
 concentration of B  $> \theta b_2$  inhibition of gene *b* expression

Equilibrium inequalities for this example :

In the absence of protein B ( $s^-(x_b, \theta_b^1) = 1$ ), while protein A has not reached its highest level ( $s^-(x_a, \theta_a^2) = 1$ ) gene *a* is expressed at rate  $\kappa_a$ . The corresponding target equilibrium  $\kappa_a / \gamma_a$  must be above the threshold  $\theta_a^2$ , Otherwise, the protein A would not be able to reach or maintain a concentration at which the observed negative autoregulation of gene *a* occurs. The same pertains for protein B.

For gene *a*:

State equation:

$$\frac{dx_a}{dt} = \kappa_a s^-(x_a, \theta a_2) s^-(x_b, \theta b_1) - \gamma_a x_a$$

Threshold inequalities:

$$0 < \theta_a^1 < \theta_a^2 < \max_a$$

Equilibrium inequalities:

$$\theta_a^2 < \frac{\kappa_a}{\gamma_a} < \max_a$$

For gene *b*:

State equation:

$$\frac{dx_b}{dt} = \kappa_b s^-(x_a, \theta a_1) s^-(x_b, \theta b_2) - \gamma_b x_b$$

Threshold inequalities:

$$0 < \theta_b^1 < \theta_b^2 < \max_b$$

Equilibrium inequalities:

$$\theta_b^2 < \frac{\kappa_b}{\gamma_b} < \max_b$$

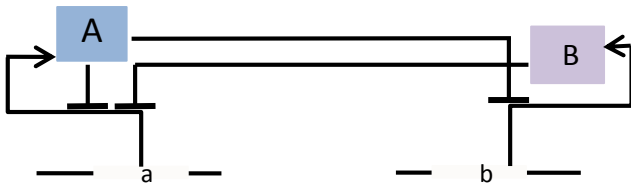
# Piece-wise linear differential equations

## Qualitative simulation:

Given a qualitative PL model and initial conditions, the aim of qualitative simulation is to determine the possible qualitative behaviors of the system.

The simulation algorithm included in the Genetic Network Analyzer (GNA) developed by Hidde de Jong and collaborators results in a transition graph, a directed graph of qualitative states and transitions between qualitative states. This graph contains qualitative equilibrium states of qualitative cycles.

A sequence of qualitative states in the transition graph represents a predicted qualitative behavior of the system.



concentration of A >  $t\_xa2$  inhibition of gene a expression  
 Concentration of B >  $t\_xb$  inhibition of gene a expression  
 Concentration of A >  $t\_xa1$  inhibition of gene b expression

GNA

File Edit Analysis Results Window

Model (xaxb)

- Variables
  - xa
  - xb
- Initial conditions
  - xaxb1
  - xaxb27
- Atomic propositions
- Properties

**Variable xa**

Variable name: xa    Variable type:  State variable     Input variable

State equation:

$$\frac{dxa}{dt} = kxa * s^-(xa, t\_xa2) * s^-(xb, t\_xb) - g\_xa * xa$$

**Variable xb**

Variable name: xb    Variable type:  State variable     Input variable

State equation:

$$\frac{dxb}{dt} = kxb * s^-(xa, t\_xa1) - g\_xb * xb$$

Parameter ordering:  $z\_xa$   $t\_xb$   $k\_xb/g\_xb$   $max\_xb$

**Simulation graph window - Graph3**

**State variables in path of selected states Graph3**

# Exemple : modélisation de la régulation de l'initiation de la sporulation chez *B. subtilis*

Adaptation de l'organisme à son environnement de manière à survivre aussi bien sur une courte période de temps qu'à l'échelle de l'évolution.

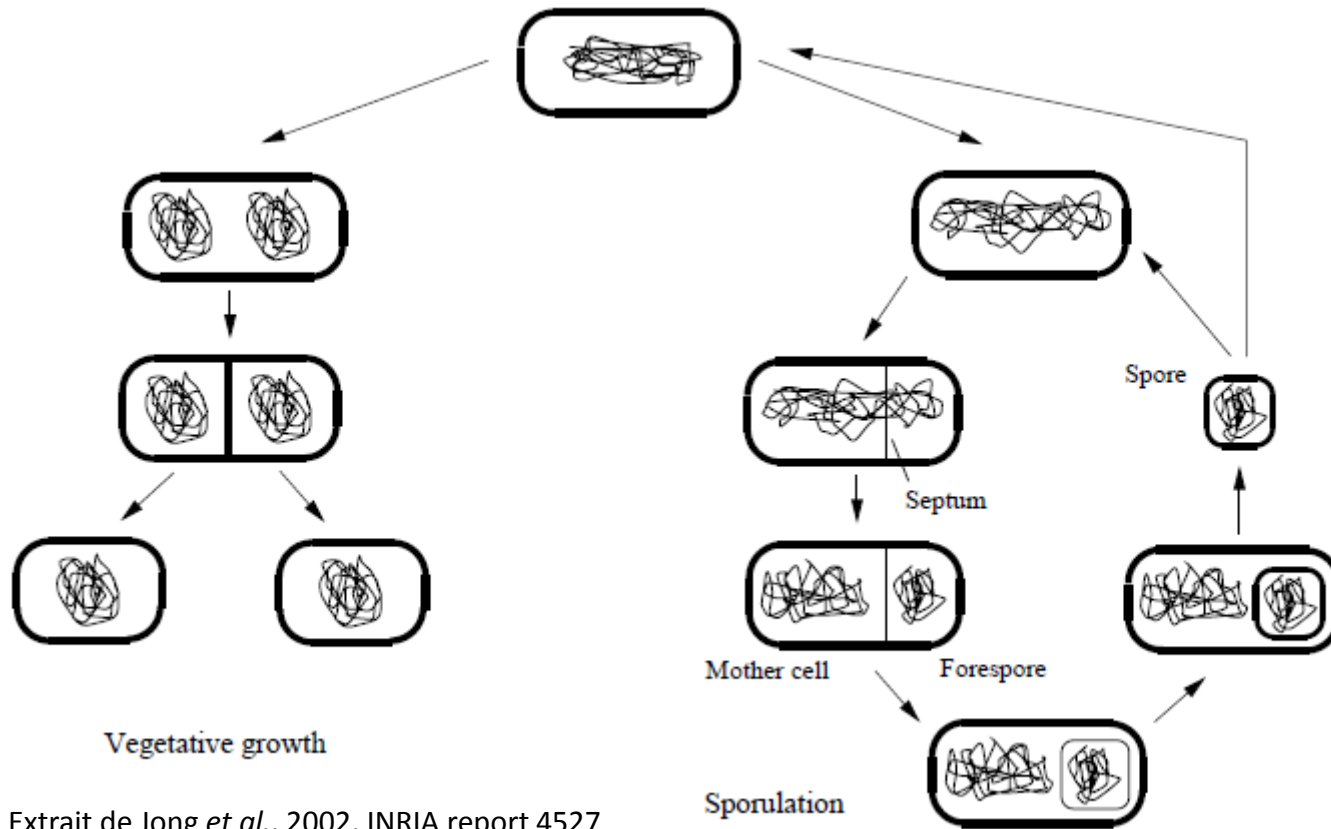
Les clefs de l'adaptation consistent à répondre aux changements environnementaux, comme la disponibilité de nutriments, la densité de cellules, la température etc. en ajustant la synthèse et la dégradation de protéines régulatrices contrôlant la croissance, le métabolisme et le développement.

Quand les conditions environnementales se détériorent, la bactérie *Bacillus subtilis* stoppe sa croissance exponentielle et entre dans la phase stationnaire. Durant la transition en phase stationnaire la cellule initie tout un tas de réponses en vue de survivre dans un environnement de plus en plus hostile. La réponse ultime de la cellule est la sporulation, c'est-à-dire la formation d'une spore remarquablement résistante. La spore peut rester en dormance plusieurs années. Quand les conditions deviennent favorables, la spore germe et la bactérie reprend sa croissance végétative.

Le changement de programme, passage de la croissance végétative à la sporulation implique un changement radical du programme génétique de la cellule. Le switch est contrôlé par un réseau complexe de régulation génétique impliquant plus de 125 gènes.



# Exemple : modélisation de la régulation de l'initiation de la sporulation chez *B. subtilis*



Extrait de Jong *et al.*, 2002, INRIA report 4527

Cycle cellulaire en phase végétative : division symétrique, génération de deux cellules identiques  
Sporulation : division asymétrique résultant en deux types cellulaires différents, la « forespore » qui formera la spore et la « mother cell » qui aide à dépôt d'une enveloppe résistante autour de la spore et ensuite se désintègre.

# Exemple : modélisation de la régulation de l'initiation de la sporulation chez *B. subtilis*

Facteur crucial pour la décision de passer en sporulation : l'état de phosphorylation du facteur de transcription Spo0A en réponse à différents signaux de l'environnement, du cycle cellulaire et de signaux provenant du métabolisme.

Au dessus d'un certain seuil de concentration, Spo0A~P active une cascade de facteur  $\sigma$  dirigeant la transcription de gènes initiant les changements morphologiques ayant lieu pendant la sporulation.

Spo0A~P active la transcription du gène  $\sigma^H$  dont le produit est impliqué dans la formation du septum, dans une boucle de rétroaction négative contrôlant l'accumulation de Spo0A~P et dans l'activation de la transcription des gènes de deux autres facteurs sigma  $\sigma^E$  et  $\sigma^F$ , dont les produits sont respectivement impliqués dans le développement de la « mother cell » et de la « forespore ». Ils activent, entre autre, l'expression des gènes de deux autres facteurs sigma  $\sigma^G$  et  $\sigma^K$  dont les produits contrôlent les étapes tardives de la sporulation.

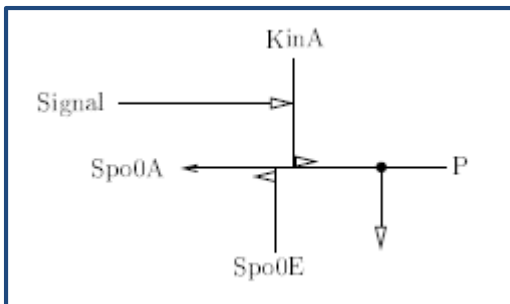
Modélisation de l'étape initiale seulement!

# Exemple : modélisation de la régulation de l'initiation de la sporulation chez *B. subtilis*

## Initiation :

Centrée sur un phospho-relai. Il transfère un phosphate à partir d'une kinase, KinA, KinB ou KinC à un régulateur de réponse Spo0F qui à son tour transfère le phosphate à Spo0A par le biais de la phosphotransférase Spo0B. Les phosphatases Spo0E, RapA et RapB, agissant sur Spo0A~P ou Spo0F~P peuvent inverser le flux de phosphate au travers du phospho-relai, inactivant ainsi *spo0A*. L'activation des kinases et phosphatases est réalisée par des signaux informant entre autre sur la disponibilité de nutriment, la densité cellulaire, la progression du cycle cellulaire et l'activité des réseaux métaboliques.

Phospho-relai : système intégrant des paramètres environnementaux et physiologique pour prendre sa décision. Décision importante, la cellule doit balancer le risque d'entrer sans nécessité en sporulation créant ainsi un désavantage sérieux de croissance contre le risque d'une entrée trop tardive en sporulation. Ceci explique la complexité du phospho-relai.

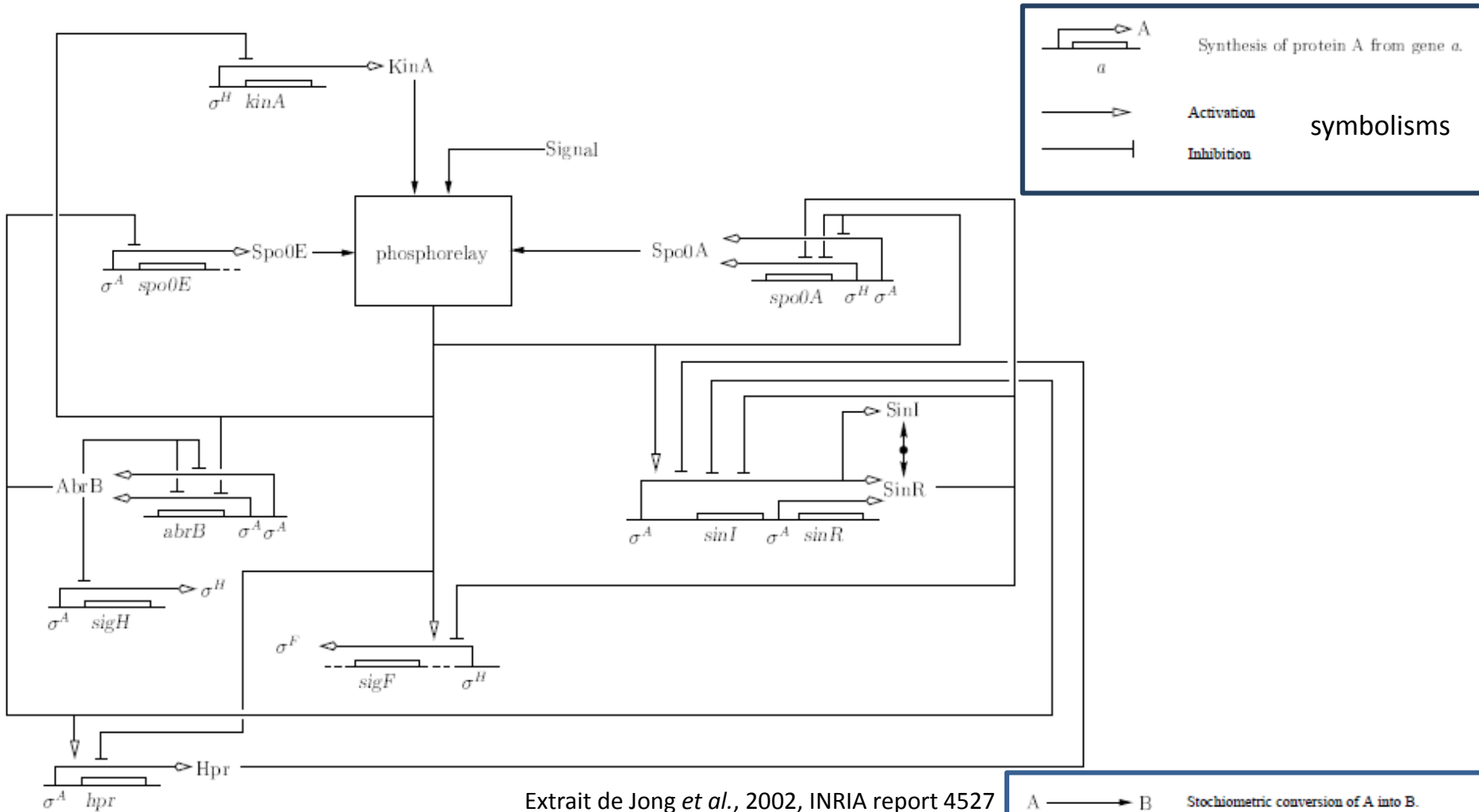


## Modélisation simplifiée :

-n'affecte pas la fonction du phospho-relai (modulation du flux de phosphate au travers de la compétition kinase- phosphatase).

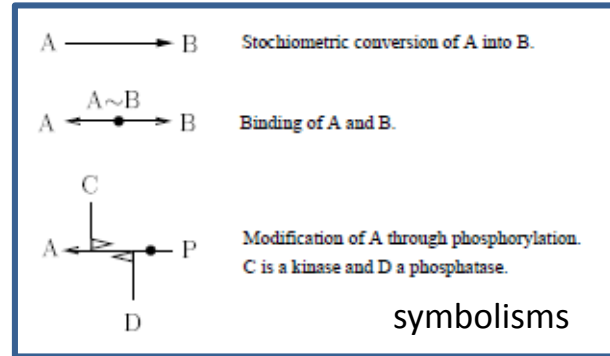
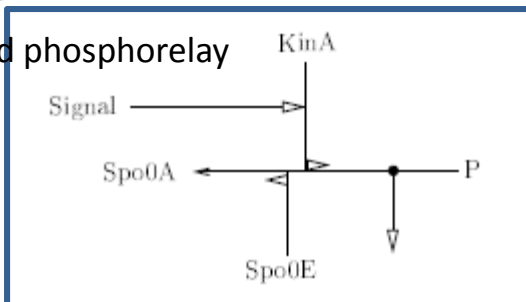
- une seule kinase KinA
- une seule phosphatase Spo0E
- signal environnemental agissant sur KinA
- éléments du phospho-relai sont régulés au niveau transcriptionnel par Spo0A~P et par un nombre de protéines dont les gènes sont directement ou indirectement contrôlés par Spo0A~P

# Simplified regulatory network of initiation of sporulation in *B. subtilis*



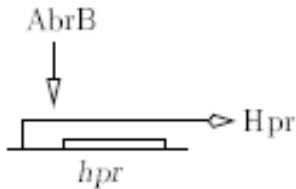
Extrait de Jong *et al.*, 2002, INRIA report 4527

## Simplified phosphorelay

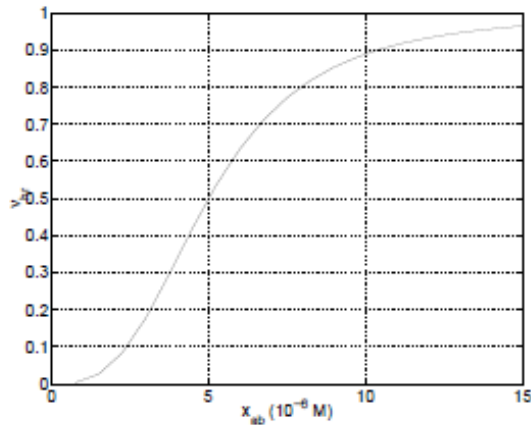


# Modélisation simple pour commencer

Régulateur de transcription:

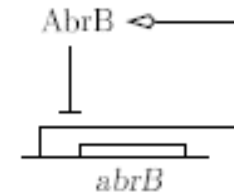


AbrB présent en concentration  $x_{ab}$  active le gène *hpr*  
Modélisation par une courbe de Hill

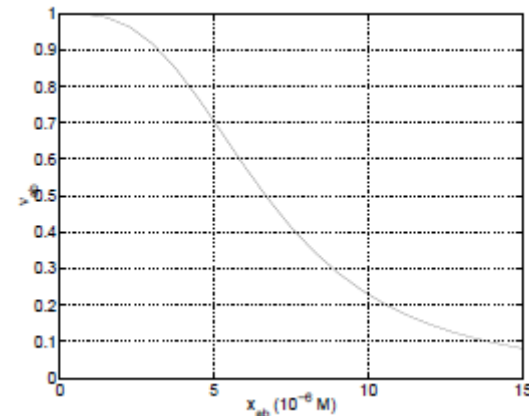


Extrait de Jong *et al.*, 2002, INRIA report 4527

$x_{ab} > \theta_{ab}^1$  : activation du gène *hpr*



AbrB présent en concentration  $x_{ab}$  réprime son propre gène  
Modélisation par une courbe sigmoïde mais fonction décroissante en fonction de la concentration  $x_{ab}$

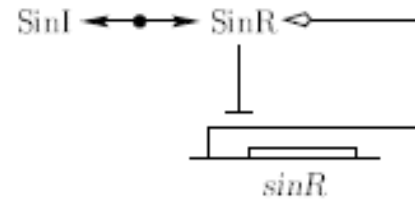
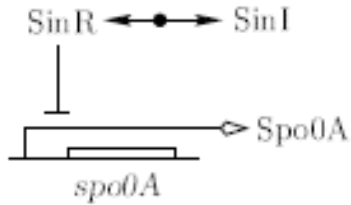


$x_{ab} > \theta_{ab}^2$  : répression du gène *abrB*

avec  $0 < \theta_{ab}^1 < \theta_{ab}^2 < \max_{ab}$

# Modélisation simple pour commencer

Régulateur de transcription inactivé par un anti-répresseur:



SinR réprime l'expression de *spo0A* et de son propre gène. Liaison avec SinI inhibe la répression.

SinR existe sous deux formes :

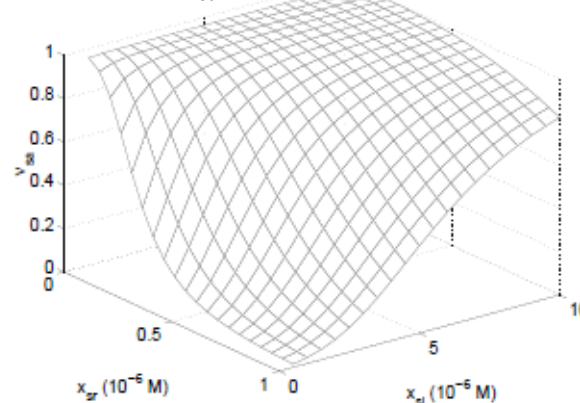
- libre → active
- complexée → inactive

Association/dissociation SinI-SinR se réalisant à une échelle de temps bien inférieure à celle de la synthèse/dégradation des protéines, on peut supposer que le premier processus est quasiment à l'équilibre par rapport au second. Simplifie le modèle.

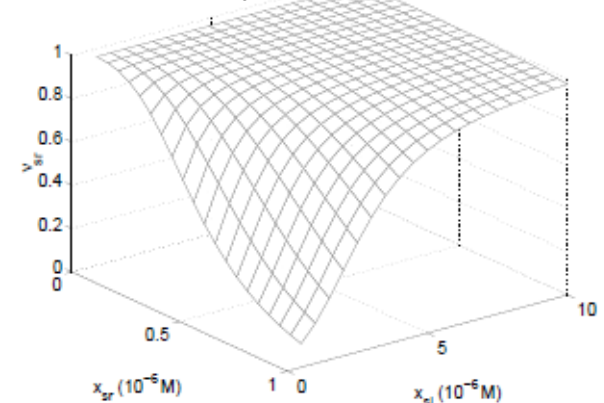
On peut donc calculer l'activité de *spo0A* en fonction des concentrations de SinI et SinR

Modélisation : surface sigmoïdale

Gène *spo0A* ( $v_{sa}$ )



Gène *sinR* ( $v_{sr}$ )



$\dot{u}_a = 0$ $0 < \theta_a < \max_a$
$\dot{x}_h = \kappa_h^0 s^+(x_a, \theta_a) + \kappa_h^1 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}^1) - \gamma_h x_h$ $0 < \theta_h < \max_h$ $0 < \kappa_h^0 / \gamma_h < \theta_h, \quad \theta_h < (\kappa_h^0 + \kappa_h^1) / \gamma_h < \max_h$
$\dot{x}_f = \kappa_f s^+(x_h, \theta_h) (1 - s^+(x_{sr}, \theta_{sr}^1) s^-(x_{si}, \theta_{si}^2)) \cdot$ $s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^3) s^+(x_{ka}, \theta_{ka}^3) s^-(x_{sc}, \theta_{sc}^2) - \gamma_f x_f$ $0 < \theta_f < \max_f$ $\theta_f < \kappa_f / \gamma_f < \max_f$
$\dot{x}_{sa} = \kappa_{sa}^1 s^+(x_a, \theta_a) (1 - s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^3) s^+(x_{ka}, \theta_{ka}^3) s^-(x_{sc}, \theta_{sc}^2)) +$ $\kappa_{sa}^2 s^+(x_h, \theta_h) (1 - s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^4) s^+(x_{ka}, \theta_{ka}^4) s^-(x_{sc}, \theta_{sc}^1)) \cdot$ $(1 - s^+(x_{sr}, \theta_{sr}^1) s^-(x_{si}, \theta_{si}^2)) - \gamma_{sa} x_{sa}$ $0 < \theta_{sa}^1 < \theta_{sa}^2 < \theta_{sa}^3 < \theta_{sa}^4 < \max_{sa}$ $\theta_{sa}^2 < \kappa_{sa}^1 / \gamma_{sa} < \theta_{sa}^3, \quad \theta_{sa}^4 < \kappa_{sa}^2 / \gamma_{sa} < \max_{sa}, \quad \theta_{sa}^4 < (\kappa_{sa}^1 + \kappa_{sa}^2) / \gamma_{sa} < \max_{sa}$
$\dot{x}_{ka} = \kappa_{ka}^0 s^+(x_a, \theta_a) + \kappa_{ka}^1 s^+(x_h, \theta_h) (1 - s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^4) s^+(x_{ka}, \theta_{ka}^4) s^-(x_{sc}, \theta_{sc}^1)) - \gamma_{ka} x_{ka}$ $0 < \theta_{ka}^1 < \theta_{ka}^2 < \theta_{ka}^3 < \theta_{ka}^4 < \max_{ka}$ $\theta_{ka}^2 < \kappa_{ka}^0 / \gamma_{ka} < \theta_{ka}^3, \quad \theta_{ka}^4 < \kappa_{ka}^1 / \gamma_{ka} < \max_{ka}, \quad \theta_{ka}^4 < (\kappa_{ka}^0 + \kappa_{ka}^1) / \gamma_{ka} < \max_{ka}$
$\dot{x}_{sc} = \kappa_{sc}^0 s^+(x_a, \theta_a) + \kappa_{sc}^1 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}) - \gamma_{sc} x_{sc}$ $0 < \theta_{sc}^1 < \theta_{sc}^2 < \theta_{sc}^3 < \theta_{sc}^4 < \max_{sc}$ $\theta_{sc}^1 < \kappa_{sc}^0 / \gamma_{sc} < \theta_{sc}^2, \quad \theta_{sc}^3 < (\kappa_{sc}^0 + \kappa_{sc}^1) / \gamma_{sc} < \theta_{sc}^4$
$\dot{x}_{ab} = \kappa_{ab}^1 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}^2) + \kappa_{ab}^2 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}^2) \cdot$ $(1 - s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^1) s^+(x_{ka}, \theta_{ka}^1) s^-(x_{sc}, \theta_{sc}^1)) - \gamma_{ab} x_{ab}$ $0 < \theta_{ab}^1 < \theta_{ab}^2 < \max_{ab}$ $0 < \kappa_{ab}^1 / \gamma_{ab} < \theta_{ab}^1, \quad \theta_{ab}^2 < (\kappa_{ab}^1 + \kappa_{ab}^2) / \gamma_{ab} < \max_{ab}$
$\dot{x}_{sr} = \kappa_{sr}^0 s^+(x_a, \theta_a) + \kappa_{sr}^1 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}^1) s^-(x_{hr}, \theta_{hr}) (1 - s^+(x_{sr}, \theta_{sr}^2) s^-(x_{si}, \theta_{si}^1)) \cdot$ $s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^2) s^+(x_{ka}, \theta_{ka}^2) s^-(x_{sc}, \theta_{sc}^1) - \gamma_{sr} x_{sr}$ $0 < \theta_{sr}^1 < \theta_{sr}^2 < \max_{sr}$ $\theta_{sr}^2 < \kappa_{sr}^0 / \gamma_{sr} < \max_{sr}, \quad \theta_{sr}^2 < (\kappa_{sr}^0 + \kappa_{sr}^1) / \gamma_{sr} < \max_{sr}$

Equations d'état et inégalités pour chacune des variables du modèle de régulation de la sporulation chez *B. subtilis*.

Extrait de Jong *et al.*, 2002, INRIA report 4527

Equations d'état et inégalités pour chacune des variables du modèle de régulation de la sporulation chez *B. subtilis* (suite).

$$\dot{x}_{si} = \kappa_{si}^0 s^+(x_a, \theta_a) + \kappa_{si}^1 s^+(x_a, \theta_a) s^-(x_{ab}, \theta_{ab}^1) s^-(x_{hr}, \theta_{hr}) (1 - s^+(x_{sr}, \theta_{sr}^2) s^-(x_{si}, \theta_{si}^1)) \cdot s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^2) s^+(x_{ka}, \theta_{ka}^2) s^-(x_{se}, \theta_{se}^3) - \gamma_{si} x_{si}$$

$$0 < \theta_{si}^1 < \theta_{si}^2 < \max_{si}$$

$$\theta_{si}^1 < \kappa_{si}^0 / \gamma_{si} < \theta_{si}^2, \quad \theta_{si}^2 < (\kappa_{si}^0 + \kappa_{si}^1) / \gamma_{si} < \max_{si}$$

$$\frac{dx_{hr}}{dt} = k_{hr} s^+(x_a, \theta_a) s^+(x_{ab}, \theta_{ab}^1) [1 - (s^+(u_s, \theta_s) s^+(x_{sa}, \theta_{sa}^2) s^+(x_{ka}, \theta_{ka}^2) s^-(x_{se}, \theta_{se}^3))] - \gamma_{hr} x_{hr}$$

$$0 < \theta_{hr} < \max_{hr}$$

$$\theta_{hr} < \kappa_{hr} / \gamma_{hr} < \max_{hr}$$

$$\dot{u}_s = 0$$

$$0 < \theta_s < \max_s$$

Extrait de Jong *et al.*, 2002, INRIA report 4527