Approximation au premier ordre des variétés lentes dans les systèmes de réactions chimiques
First Order Approximation of Slow Manifolds in Chemical Reactions Systems

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Plan

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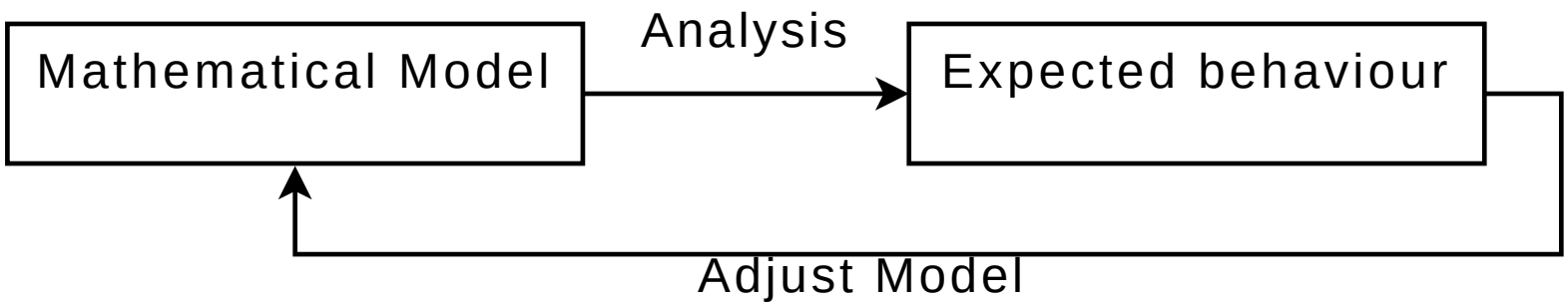
Model analysis and validation



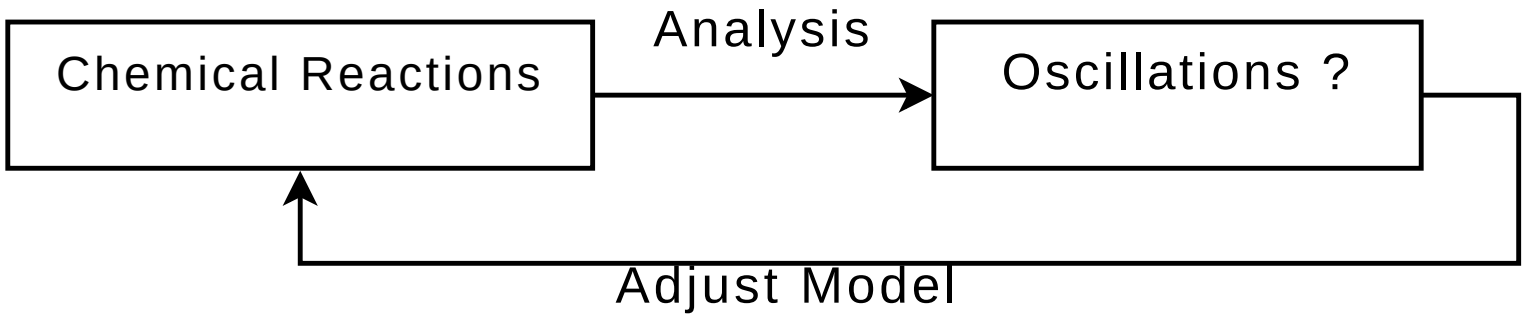
Steps

- Adjust model: done by human
- Analysis: done by human/computer

Goal

- Adjust the model until it correctly predicts a specific behaviour of the organism
- Make the analysis completely algorithmic

Looking for oscillating models



Analysis

- Based on **non linear** differential equations with **parameters** (our speciality/Équipe Calcul Formel Lille)
- Other possible techniques: boolean networks, (piecewise) linear differential equations,. . .

Objective

- Find values for parameters which make the model oscillate
- Make the analysis part fully **algorithmic** (one click !)

Difficulties and Techniques

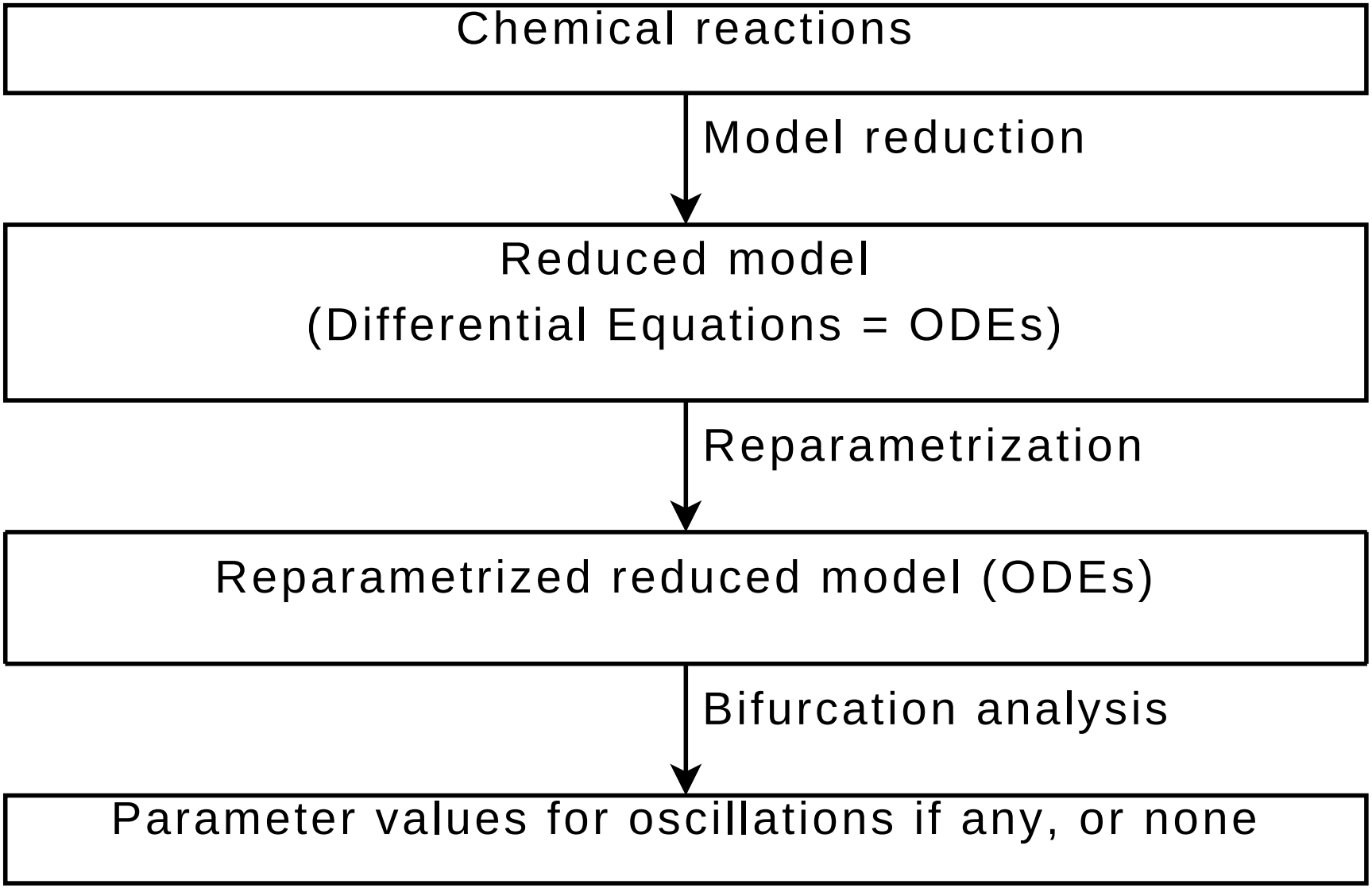
Main difficulty: number of parameters/variables

number params/vars	technique
2	nullclines, phase portrait
$2 < \cdots < 10$	algebraic methods (what we do)
> 10	?

Techniques

- model reduction (computer algebra, and differential elimination)
- symmetries
- real algebraic geometry

Different steps of the analysis



The algorithm DIFFERENTIALMODELREDUCTION

Input:

List of chemical reactions ($E + S \xrightarrow{k1} C, \ldots$) tagged slow or fast.

Output:

A dynamical system with less parameters or less variables.

- category: approximate reduction of chemical reactions
- tools: slow/fast systems, Thikonov theorem, slow/fast manifold, differential elimination
- interest : it is easier to study systems with less variables or less parameters

Our algorithm DIFFERENTIALMODELREDUCTION

- completely algorithmic (based on differential elimination)
- available in MABSys (Maple package, Lemaire/Ürgüplü)
- makes algorithmic ideas from [1, 2, 3].


[1] V. Van Breusegem and G. Bastin.
Reduced order dynamical modelling of reaction systems: a singular perturbation approach
30th IEEE Conf. on Decision and Control. pp. 1049-1054, 1991.


[2] N. Vora and P. Daoutidis.
Nonlinear model reduction of chemical reaction systems.
AIChE Journal vol. 47, pp. 2320-2332, 2001.


[3] M. Bennet, D. Volfson, L. Tsimring and J. Hasty.
Transient Dynamics of Genetic Regulatory Networks
Biophysical Journal vol. 92, pp. 3501-3512, 2007


[4] F. Boulier, M. Lefranc, F. Lemaire and P.-E. Morant.
Model Reduction of Chemical Reaction Systems using Elimination.
MACIS, http://hal.archives-ouvertes.fr/hal-00184558, 2007.

Plan

Thikonov theorem

Singularly perturbated system

$$\Sigma \begin{cases} \dot{x}(t) &= f(x(t), y(t), \varepsilon) \\ \dot{y}(t) &= \dfrac{1}{\varepsilon} g(x(t), y(t), \varepsilon) \end{cases}$$

- $x(t)$ is a slow variable, $y(t)$ is a fast variable

Theorem (informal)

If ε is small enough (plus other conditions), then the solutions of Σ can be approximated by the solutions of:

$$\begin{cases} \dot{x}(t) &= f(x(t), y(t), 0) \\ y(t) &= \psi(x(t)) \end{cases}$$

- ψ satisfies $g(x, \psi(x), 0) = 0$.
- $y = \psi(x)$ defines “the slow manifold”

Thikonov theorem (references)

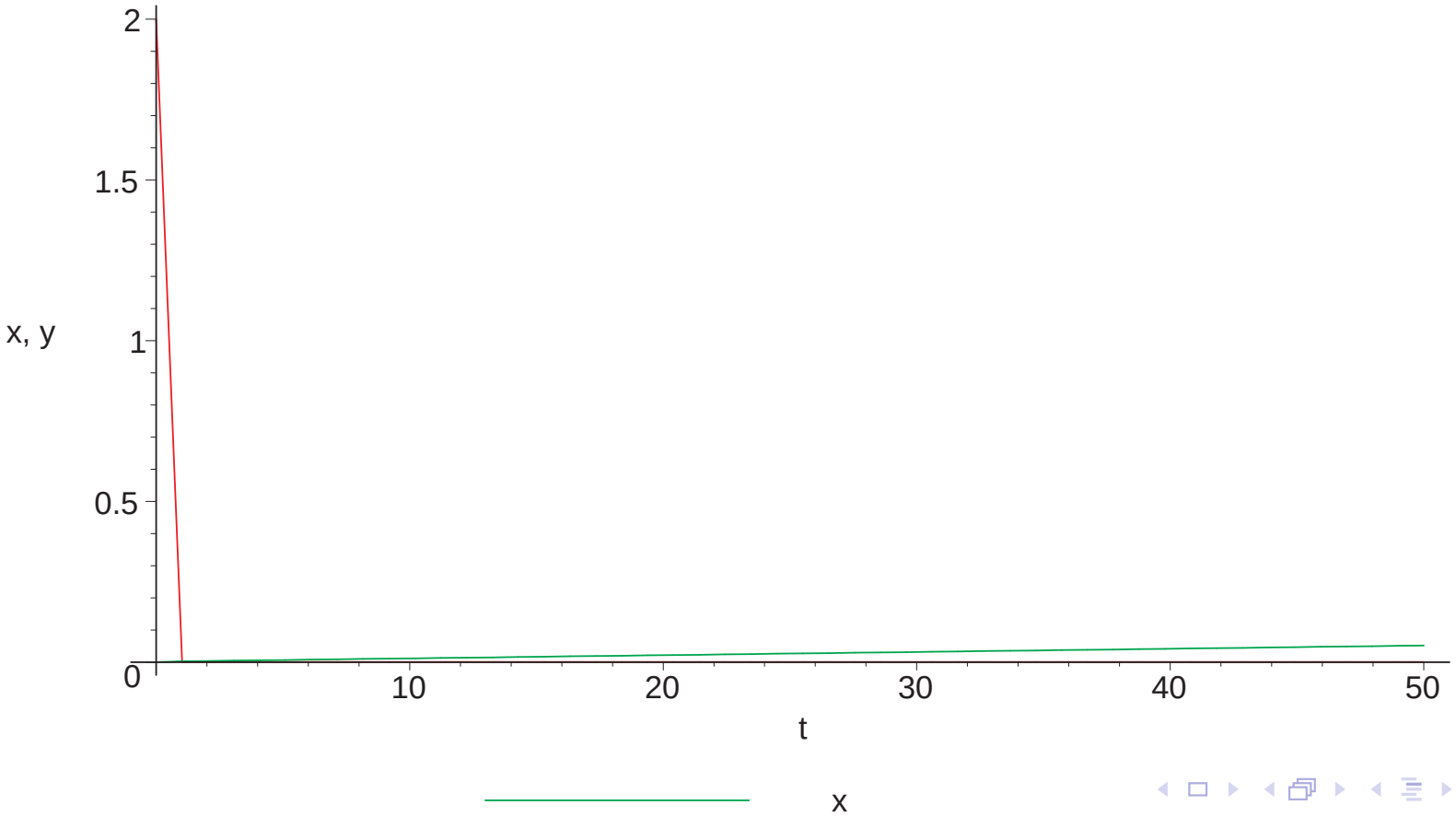
[1] Pierre Rouchon.
Analyse et commande de systèmes dynamiques.
Majeure de mathématiques appliquées (2003-2004), École Polytechnique.

[2] Peter V. Kokotovic and John O'Reilly and Hassan K. Khalil.
Singular Perturbation Methods in Control: Analysis and Design (1986).
Academic Press, Inc.

[3] B. Rosseto
Singular approximation of chaotic slow-fast dynamical systems

Thikonov theorem (example 1/2)

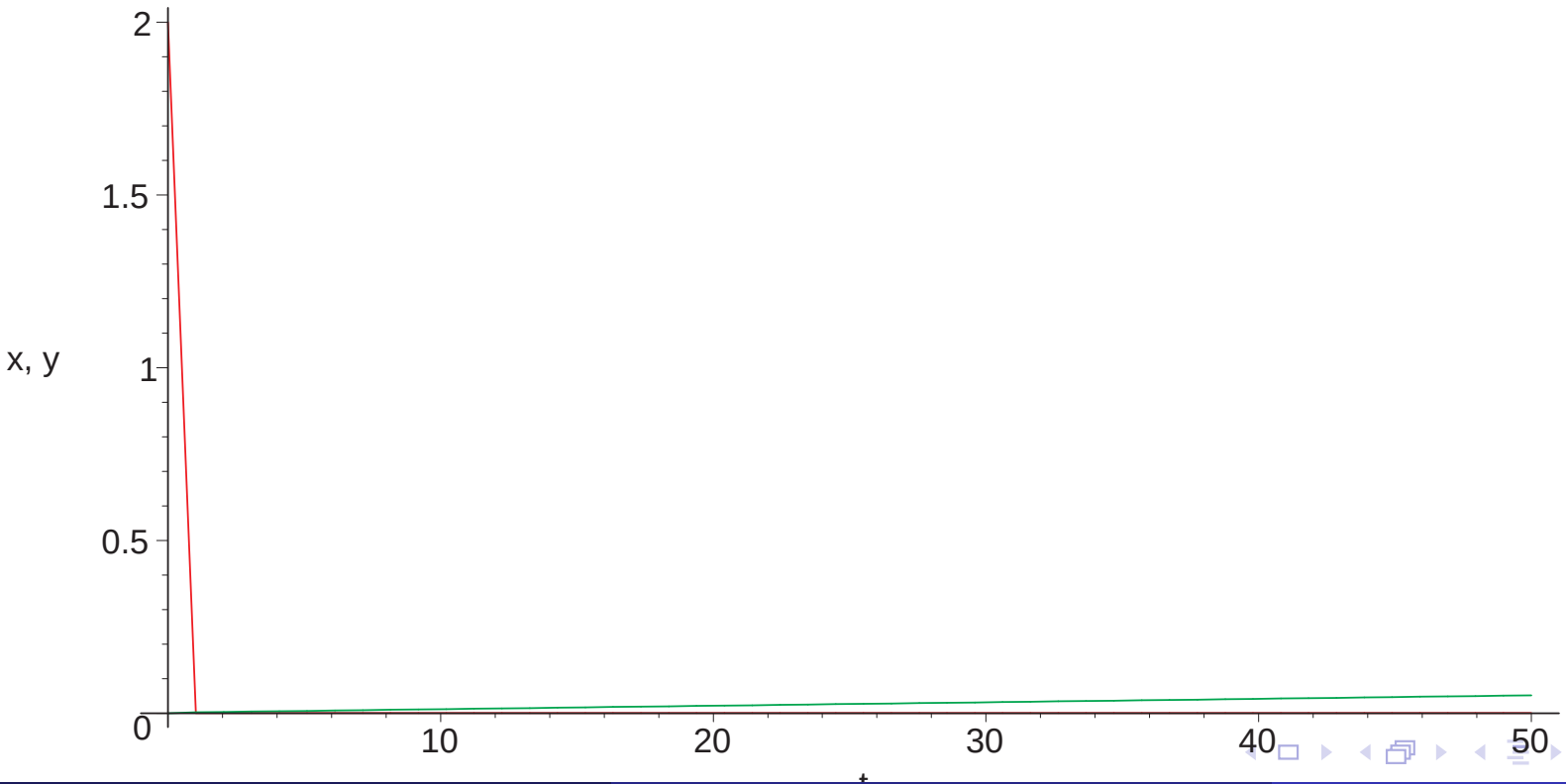
$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & y(t) \\ \dot{y}(t) & = & \frac{1}{\varepsilon}(-y(t)+\varepsilon) \\ y(0) & = & 100, x(0) = 0, \varepsilon = 10^{-3} \end{array} \right.$$



Thikonov theorem (example 2/2)

$$\begin{cases} \dot{x}(t) &= y(t) \\ \dot{y}(t) &= \frac{1}{\varepsilon}(-y(t)+\varepsilon) \end{cases} \rightarrow \begin{cases} \dot{x}(t) &= 0 \\ 0 &= y(t) \end{cases}$$

Problem: $x(t)$ does not deviate in the reduced system
Reason: the slow manifold is not accurate enough



Thikonov theorem

Singularly perturbated system

$$\Sigma \begin{cases} \dot{x}(t) &= f(x(t), y(t), \varepsilon) \\ \dot{y}(t) &= \dfrac{1}{\varepsilon} g(x(t), y(t), \varepsilon) \end{cases}$$

Theorem (a bit less informal)

If ε is small enough (plus other conditions), then the solutions of Σ can be approximated by the solutions of:

$$\begin{cases} \dot{x}(t) &= f(x(t), y(t), \varepsilon) \\ y(t) &= \phi(x(t), \varepsilon) \end{cases}$$

where $y = \phi(x, \varepsilon)$ is the so-called (unique) slow manifold

Approximations of the slow manifold

Singularly perturbated system

$$\Sigma \begin{cases} \dot{x}(t) &= f(x(t), y(t), \varepsilon) \\ \dot{y}(t) &= \dfrac{1}{\varepsilon} g(x(t), y(t), \varepsilon) \end{cases}$$

Examples of approximations of the slow manifold $y = \phi(x, \varepsilon)$

- order 0 in ε: $y = \psi(x)$ with $g_0(x, \psi(x)) = 0$.
- order 1 in ε: $y = \psi(x) + \varepsilon y_1(x)$ where $y_1 = \ldots$.

where:

$$f(x, y, \varepsilon) = f_0(x, y) + \varepsilon f_1(x, y) + \cdots$$

$$g(x, y, \varepsilon) = g_0(x, y) + \varepsilon g_1(x, y) + \cdots .$$

Implicit formulation

$$(D_y g_0)(g_0 + \varepsilon g_1) + (D_x g_0)(\varepsilon f_0) = 0$$

Approximations of the slow manifold (example)

Order 0: $y = 0$

$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & y(t) \\ \dot{y}(t) & = & \frac{1}{\varepsilon}(-y(t) + \varepsilon) \end{array} \right. \rightarrow \left\{ \begin{array}{rcl} \dot{x}(t) & = & 0 \\ 0 & = & y(t) \end{array} \right.$$

Order 1: $y = \varepsilon$

$$\left\{ \begin{array}{rcl} \dot{x}(t) & = & y(t) \\ \dot{y}(t) & = & \frac{1}{\varepsilon}(-y(t) + \varepsilon) \end{array} \right. \rightarrow \left\{ \begin{array}{rcl} \dot{x}(t) & = & \varepsilon \\ 0 & = & y(t) - \varepsilon \end{array} \right.$$

Plan

Reduction process example (1/2)

chemical reactions

Fast: $A \xrightarrow{k_1/\varepsilon} \emptyset$ Slow : $\emptyset \xrightarrow{c} A$, $A \xrightarrow{k_2} B$

Interpretation

A decreases very quickly, A is produced slowly and B is produced at a rate proportional to A.

Building ODEs

$$\dot{X} = \frac{1}{\varepsilon} M_f V_f + M_s V_s$$

$$\begin{pmatrix} \dot{A} \\ \dot{B} \end{pmatrix} = \frac{1}{\varepsilon} \begin{pmatrix} -1 \\ 0 \end{pmatrix} (k_1 A) + \begin{pmatrix} 1 & 1 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} c \\ k_2 A \end{pmatrix}$$

Reduction process example (2/2)

chemical reactions

Fast: $A \xrightarrow{k_1/\varepsilon} \emptyset$ Slow : $\emptyset \xrightarrow{c} A$, $A \xrightarrow{k_2} B$

Assumptions

The fast reactions are at equilibrium (QSSA). This implies the variables A and B are constrained on the “slow manifold” of the system.

Reduction method

$$\begin{array}{rcl} \dot{X} & = & \frac{1}{\varepsilon} M_f F + M_s V_s \\ 0 & = & M_f V_f \end{array} \xrightarrow{\text{diff. elim.}} \dot{X} = G(X)$$

Reduction process example (2/2)

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$$\begin{pmatrix} \dot{A} \\ \dot{B} \end{pmatrix} = \frac{1}{\varepsilon} \begin{pmatrix} -1 \\ 0 \end{pmatrix} (F) + \begin{pmatrix} 1 & 1 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} c \\ k_2 A \end{pmatrix} \xrightarrow{\text{diff. elim.}} \dot{X} = G(X)$$

$$0 = k_1 A$$

Reduction process example (2/2)

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Reduction method

$$\begin{pmatrix} \dot{A} \\ \dot{B} \end{pmatrix} = \frac{1}{\varepsilon} \begin{pmatrix} -1 \\ 0 \end{pmatrix} (F) + \begin{pmatrix} 1 & 1 \\ 0 & -1 \end{pmatrix} \begin{pmatrix} c \\ k_2 A \end{pmatrix} \xrightarrow{\text{diff. elim.}} \begin{cases} \dot{B} = 0 \\ A = 0 \end{cases}$$

$$0 = k_1 A$$

- wrong, since B should grow slowly
- reason: the slow manifold $A = 0$ is not accurate enough

First Order Approximation

Lemma (new)

$\dot{X} = \frac{1}{\varepsilon} M_f V_f + M_s V_s$ with extra conditions (M_f full column rank, ...).
A first approximation of the slow manifold is given by :

$$J(V_f)(M_f V_f + \varepsilon M_s V_s) = 0$$

On the example

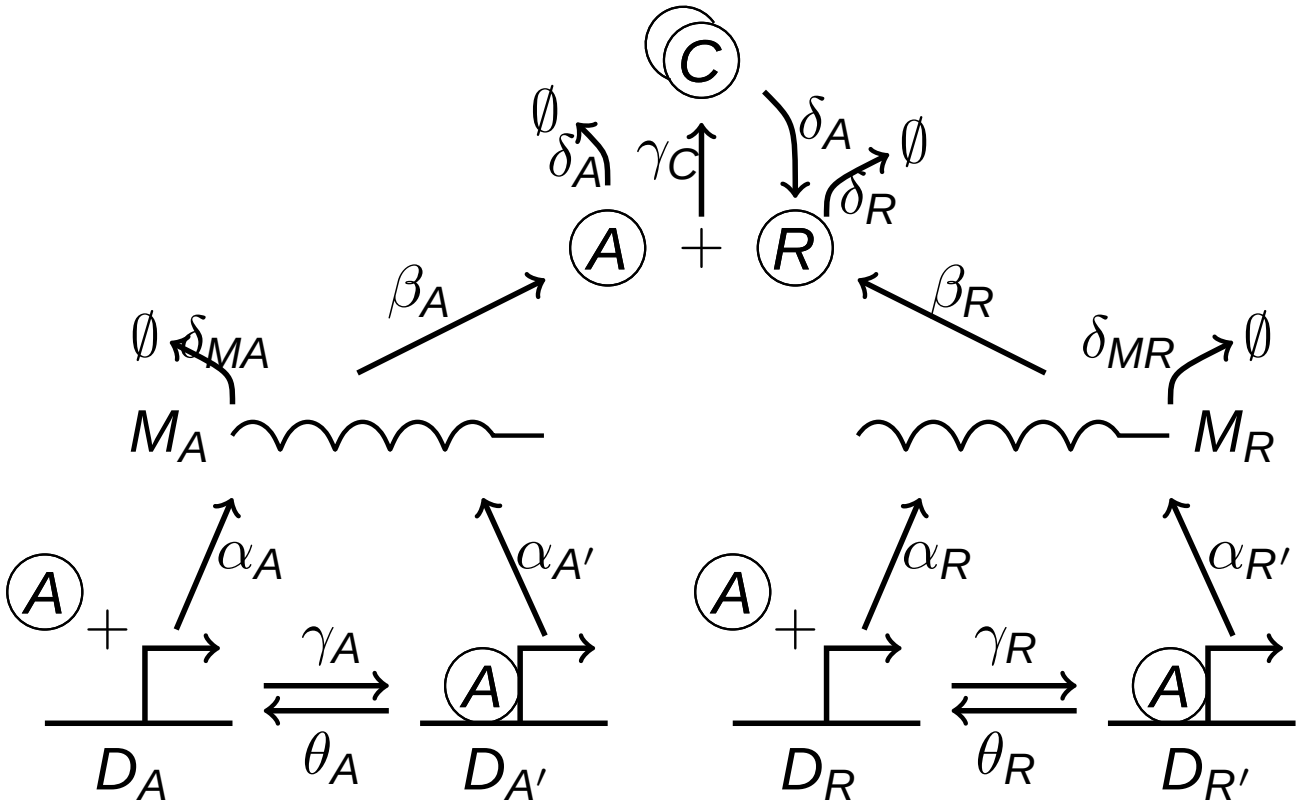
$$A = \frac{c}{k_1/\varepsilon + k_2}$$

Reduction using the first order approximation

$$\begin{cases} \dot{B} &= \frac{ck_2}{k_1/\varepsilon + k_2} \\ A &= \frac{c}{k_1/\varepsilon + k_2} \end{cases}$$

Interest of the first order approximation

- more accurate (but larger) reduced model
- needed in some systems which commute between two states (like the Leibler example)



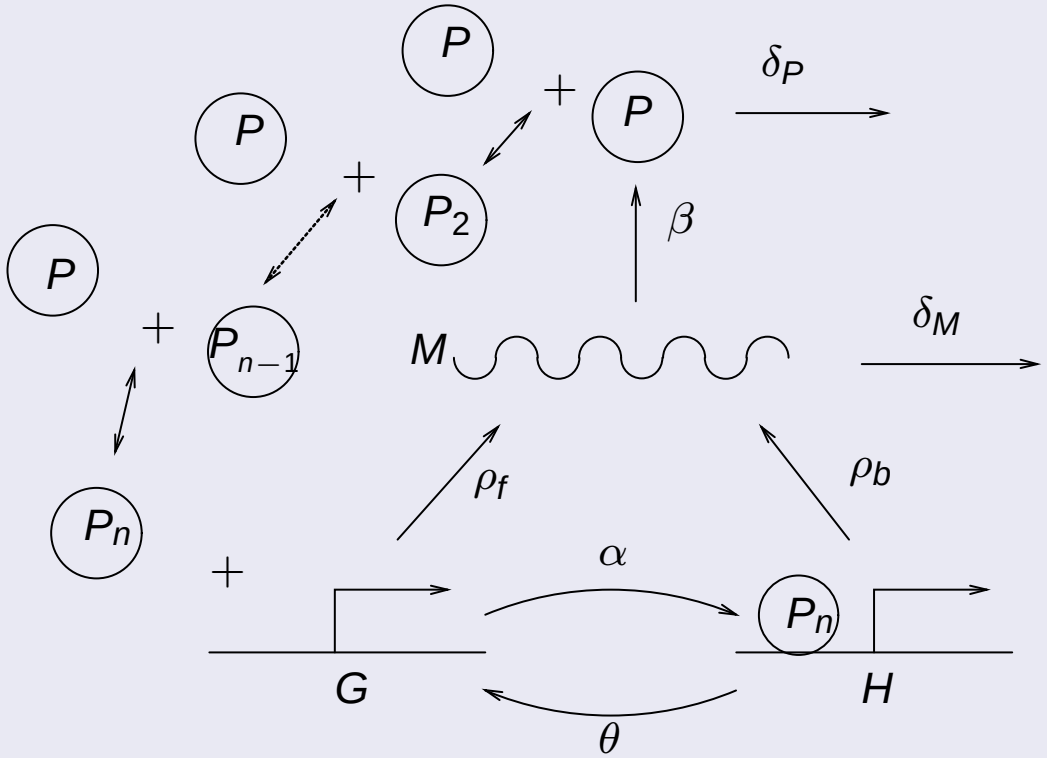
Plan

Further work

- smart numerical integration: automatically find the fast reactions and reduce the model accordingly
- apply the reduction method to bigger biological systems
- make advertisement for MABSys and get feedback from biologists
- integrate software in Biological Software (SBML format, . . .)
  $\longrightarrow$ Master II training in Lille, February 2009.

AB07: gene regulated by a polymer of its own protein

Is there a clock in this model ? Where ?



F. Boulier, M. Lefranc, F. Lemaire, P.-E. Morant and A. Ürgüplü.
On proving the absence of oscillations in models of genetic circuits
Algebraic Biology, LNCS vol. 45, pp. 66-80, 2007.

AB07: the generalized chemical reactions system

$$G + P_n \underset{\theta}{\overset{\alpha}{\rightleftarrows}} H, \quad G \xrightarrow{\rho_f} G + M, \quad H \xrightarrow{\rho_b} H + M,$$

$$M \xrightarrow{\beta} M + P, \quad M \xrightarrow{\delta_M} \emptyset, \quad P \xrightarrow{\delta_P} \emptyset,$$

$$P_i + P \underset{k_i^-}{\overset{k_i^+}{\rightleftarrows}} P_{i+1} \quad (1 \leq i \leq n-1).$$

Polymerisation reactions are assumed to be fast.
Random variables G and H are the two states of the gene.
Other variables are concentrations:

- M for the mRNA,
- P_i for the polymer of order i.

AB07: the initial ODE system

$$
\begin{aligned}
\dot{G} &= \theta H - \alpha G P_n, \\
\dot{H} &= -\theta H + \alpha G P_n, \\
\dot{M} &= \rho_f G + \rho_b H - \delta_M M, \\
\dot{P} &= \beta M - \delta_P P + 2A_1 + A_2 + \cdots + A_{n-1}, \\
\dot{P}_i &= -A_{i-1} + A_i \qquad (2 \leq i \leq n-1), \\
\dot{P}_n &= -A_{n-1} + \theta H - \alpha G P_n
\end{aligned}
$$

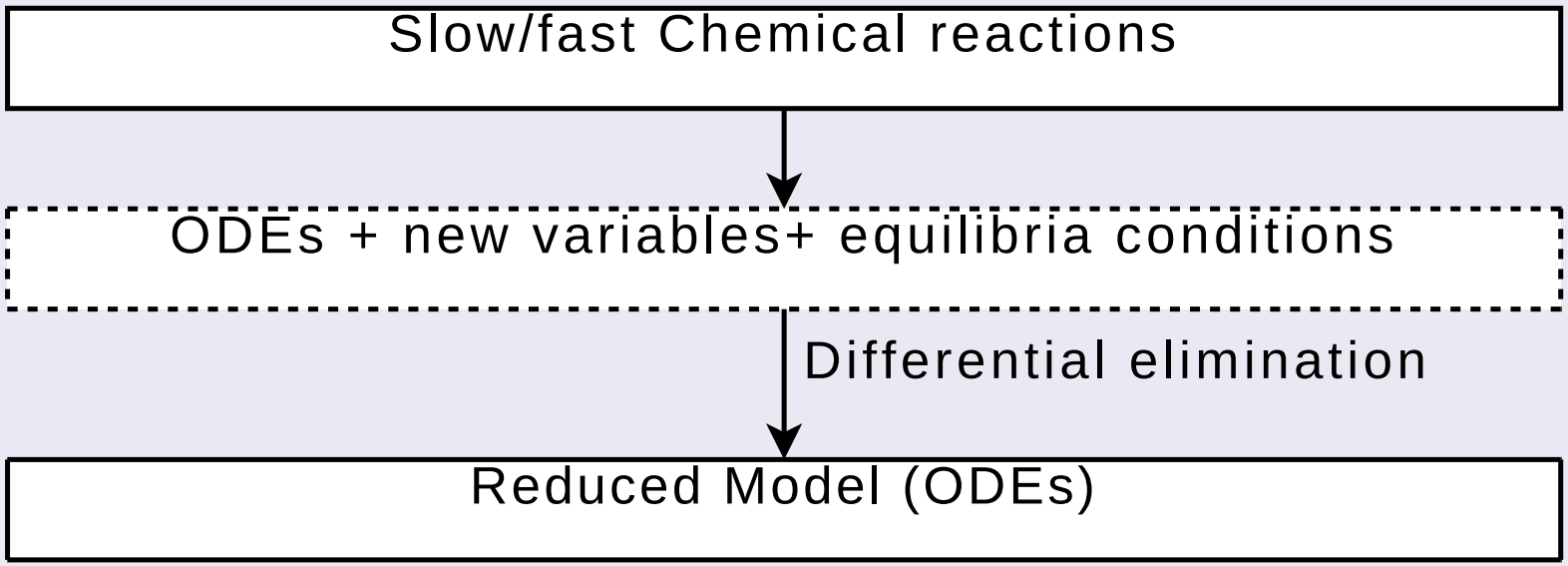
where $A_i = (k_i^- P_{i+1} - k_i^+ P_i P)$.

- $n + 3$ variables
- $2n + 5$ parameters

Reduction based on QSSA

$$P_i + P \underset{k_i^-}{\overset{k_i^+}{\rightleftarrows}} P_{i+1} \quad (1 \leq i \leq n-1)$$

- QSSA: quasi-steady state approximation
- Fast reactions are at equilibria: $k_i^- P_{i+1} - k_i^+ P_i P = 0$



AB07,08: the reduced models

AB07: the handmade reduction

$$\begin{aligned}
\dot{G} &= \theta H - \alpha K_{n-1} P^n G, \qquad \dot{H} = -\dot{G} \\
\dot{M} &= \rho_b H + \rho_f G - \delta_M M, \\
\dot{P} &= n(\theta H - \alpha K_{n-1} P^n G) - \delta_P P + \beta M.
\end{aligned}$$

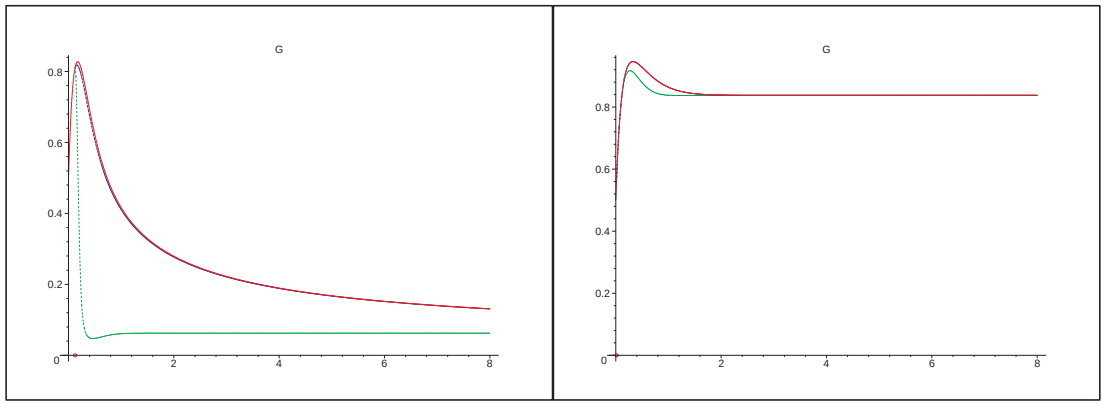


Figure: $G(t)$; green (AB07), blue (AB08), red (non reduced)

AB07,08: the reduced models

AB08: the automatic reduction

$$
\begin{aligned}
\dot{G} &= \theta H - \alpha K_{n-1} P^n G, \qquad \dot{H} = -\dot{G} \\
\dot{M} &= \rho_b H + \rho_f G - \delta_M M, \\
\dot{P} &= \frac{n(\theta H - \alpha K_{n-1} P^n G) - \delta_P P + \beta M}{\sum_i (i+1)^2 K_i P^i}.
\end{aligned}
$$

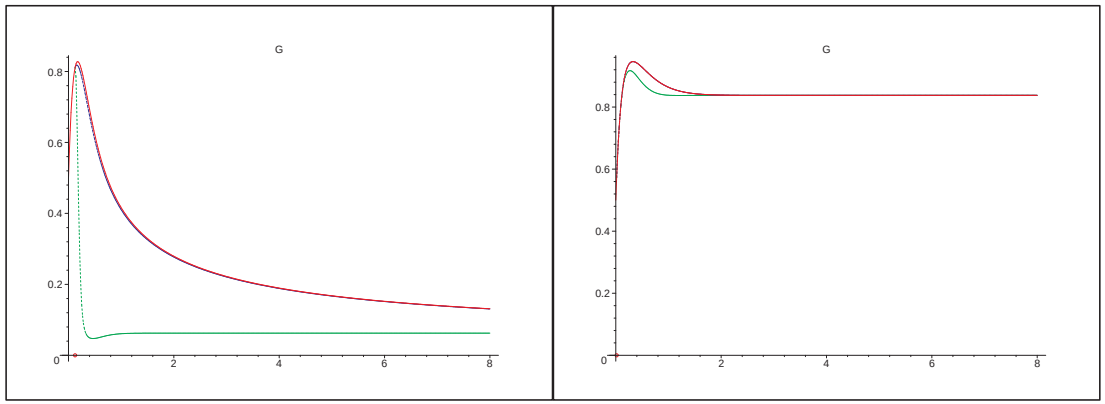


Figure: $G(t)$; green (AB07), blue (AB08), red (non reduced)

The Michaelis-Menten example

The reactions

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$C \xrightarrow{k_2} E + P$$

substrate S, product P, complex C, enzyme E

Assumption

First equation much faster than the second one

The Michaelis-Menten example (2)

The usual reduction

- $\dot{S}(t) = -\frac{V_m\, S(t)}{K + S(t)}$ assuming $S \gg E_0$
- $V_m = k_2\, E_0$
- Briggs-Haldane: $K = \frac{k_{-1}}{k_1}$
- Henri-Michaëlis-Menten: $K = \frac{k_{-1} + k_2}{k_1}$

Our reduction

- $\dot{S} = -\frac{V_m\, S\,(K + S)}{K\, E_0 + (K + S)^2}$ valid even if $S < E_0$
- $V_m = k_2\, E_0$
- $K = \frac{k_{-1}}{k_1}$