

The FreeMABSys Project and the BLAD Libraries

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(work supported by the French ANR LEDA)

September 26, 2011

FreeMABSys

- **FreeMABSys** is a software (library ?) dedicated to **systems biology**, involving **computer algebra** methods.
- It is open source.
- It is supported by the French ANR LEDA project.
- Scientific leader: François Lemaire.
- It evolves from the MAPLE **MABSys** software.

BLAD

The **Bibliothèques Lilloises d'Algèbre Différentielle** are C libraries dedicated to the symbolic processing of polynomial differential equations.

They are open source (LGPL).

They are available through the **MAPLE DifferentialAlgebra** package.



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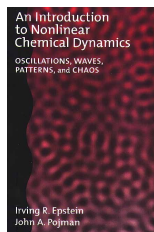
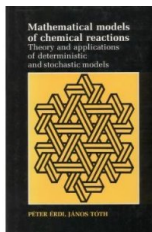
Relationship with MATHEMAGIX

It is planned to connect the BLAD libraries (and FreeMABSys ?) to **MATHEMAGIX**. We need some **help** for

- **promoting** the project to computer science students
- setting up **use cases**

- 1 Introduction
- 2 Chemical Reaction Systems**
- 3 Deterministic modeling
- 4 Stochastic modeling

Books

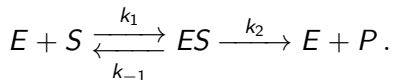


- Mathematical models of chemical reactions. Érdi and Tóth. 1989
- An Introduction to Nonlinear Chemical Dynamics. Epstein and Pojman. 1998
- Theoretical Systems Biology of Metabolism. Schuster. 2012

▶ pathway

Basic definitions

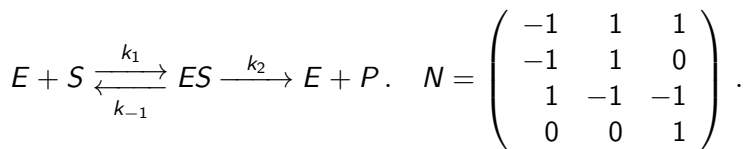
This system describes the transformation of a substrate S into a product P , in the presence of some enzyme E . It involves four chemical **species** E , S , ES and P and three **reactions**. E and S are the **reactants** of the first reaction.



The **stoichiometry matrix** N involves one row per species and one column per reaction. Its coefficient, row r and column c , is equal to the number of molecules of species r produced by the reaction c .

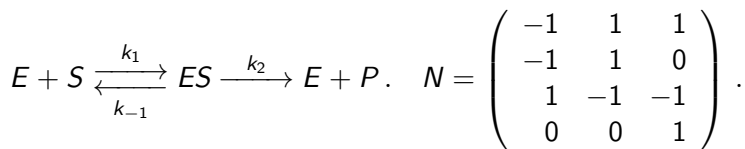
$$N = \begin{pmatrix} -1 & 1 & 1 \\ -1 & 1 & 0 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix}.$$

The stoichiometry matrix



The stoichiometry matrix N depends on the chemical reaction system. It **does not depend** on any assumption on the dynamics of the system.

The stoichiometry matrix



The nullspace of N provides **linear conservation laws**:

$$-E(t) + S(t) + P(t) = \text{cst}_1, \quad E(t) + ES(t) = \text{cst}_2.$$

The nullspace of its transpose provides very interesting informations too. See [Schuster et al, Nature, 2000].

Mathematical models

At least 8 different kinetic models

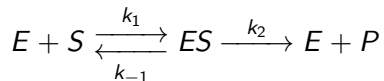
- **time** may be **C**ontinuous or **D**iscrete.
- **state space** may be **C**ontinuous ($A(t) \in \mathbb{R}$ is the concentration of species A) or **D**iscrete ($A(t) \in \mathbb{N}$ is the number of molecules of A).
- **determination** may be **D**eterministic or **S**tochastic.

Focus:

- 1 Continuous time, continuous state-space, deterministic determination derived from the **mass-action law**.
- 2 Continuous time, discrete state-space, stochastic determination.

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Modeling using the Mass Action Law



The mathematical model is

$$\frac{dX}{dt} = N \cdot V$$

where X is the vector of the **species concentrations** and V is the vector of the **reaction laws**. The law of the first reaction is $k_1 E(t) S(t)$. The model is a polynomial ODE system depending on parameters: the **kinetic constants**.

$$\frac{d}{dt} E(t) = k_2 ES(t) - k_1 E(t) S(t) + k_{-1} ES(t), \quad \frac{d}{dt} P(t) = k_2 ES(t),$$

$$\frac{d}{dt} ES(t) = -k_2 ES(t) + k_1 E(t) S(t) - k_{-1} ES(t),$$

$$\frac{d}{dt} S(t) = -k_1 E(t) S(t) + k_{-1} ES(t).$$

Mass Action based models have striking properties

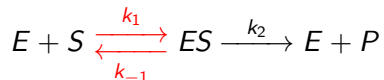
- An ODE system is the mathematical model of a chemical reaction system if, and only if, in the right hand side of the ODE which gives the evolution of any concentration $A(t)$, every monomial endowed with a **minus sign**, actually **depends on $A(t)$** .
- The **zero deficiency theorem** gives a sufficient condition for a system to admit a unique attractive **steady state** with **strictly positive** coordinates. The algorithmic test is very **cheap**.

Generalizations by [Feinberg, 1995], [Chaves and Sontag, 2002], [Gatermann et al, 2003].

Model reduction 1: approximation

The quasi-steady state approximation method permits to approximate the mathematical model derived from the mass-action law, under the assumption that reactions are split in two sets: the **slow reactions** and the **fast reactions**.

The approximated model can be obtained by differential elimination. In particular, the Henri (1903), Michaelis and Menten (1913) formula is the solution of a differential elimination problem [Boulier, Lemaire, Lefranc, Morant 2007].



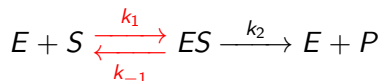
Red reactions are **fast**.

$$\frac{d}{dt} S(t) = -\frac{V_{\max} S(t)}{K + S(t)}$$

A note on the quasi-steady state approximation

- In general, the QSSA is an approximation method for ODE systems, which relies on the **Tikhonov theorem**.
- In general, there is **no algorithm** to find the change of coordinates which rewrites the ODE system into the standard form, needed by this theorem.
- In the particular case of chemical reaction systems, the change of coordinates can be obtained algorithmically [Van Breuseghem and Bastin, 1991].
- Our contribution: a very simple formulation relying on differential elimination.

The Henri, Michaelis, Menten reduction, revisited



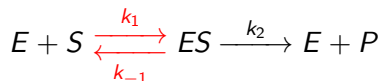
Red terms are the contributions of the fast reactions in the mathematical model derived from the mass-action law.

$$\begin{aligned} d/dt E(t) &= k_2 ES(t) - (k_1 E(t) S(t) - k_{-1} ES(t)), \\ d/dt S(t) &= -(k_1 E(t) S(t) - k_{-1} ES(t)), \\ d/dt ES(t) &= -k_2 ES(t) + k_1 E(t) S(t) - k_{-1} ES(t), \\ d/dt P(t) &= k_2 ES(t). \end{aligned}$$

- The sought approximation, mainly assuming $k_1, k_{-1} \gg k_2$

$$\frac{d}{dt} S(t) = -\frac{V_{\max} S(t)}{K + S(t)}.$$

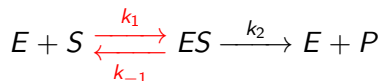
The Henri, Michaelis, Menten reduction, revisited



- Encode the **conservation of the flow** by replacing the contribution of the fast reaction by a new symbol $F_1(t)$.

$$\begin{aligned}d/dt E(t) &= k_2 ES(t) - F_1(t), \\d/dt S(t) &= -F_1(t), \\d/dt ES(t) &= -k_2 ES(t) + F_1(t), \\d/dt P(t) &= k_2 ES(t).\end{aligned}$$

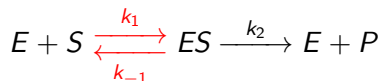
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- Encode the **conservation of the flow** by replacing the contribution of the fast reaction by a new symbol $F_1(t)$.
- Encode the **speed** by adding the equilibrium equation.

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- Raw formula by eliminating $F_1(t)$ from Lemaire's DAE.

$$\frac{d}{dt} S(t) = -\frac{ES(t) S(t)^2 k_1 k_2 + ES(t) S(t) k_{-1} k_2}{k_{-1} ES(t) + S(t)^2 k_1 + S(t) k_{-1}}.$$

Software demonstration

The MAPLE **DifferentialAlgebra** package is a general purpose package for performing differential elimination. Computations are performed by the open source **BLAD** libraries, written in the C programming language.



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Another demonstration, relying on the specialized MAPLE **MABSys** package might be given in the next talk.

Model reduction 2: exact reduction and reparametrization

Positivity constraints are very important in mathematical models of chemical reaction systems. **Scalings** preserve them.

- The scalings of the ODE system permit to remove parameters.
- The scalings of the associated steady point system permit to make some parameters act on the stabilities of the steady points only [Lemaire and Ürgüplü, 2010].

The circadian clock of a green algae

The ▶ autoregulated gene of [Boulhier, Lemaire et al. 2007, 2008].

The mathematical model derived from the mass-action law involves $n + 3$ ODE depending on $2n + 5$ parameters.

Assuming polymerisation of P is **fast**, the reduced model (QSSA plus exact reduction and reparametrization) involves 3 ODE only.

It involves a Hopf bifurcation if, and only if, $n \geq 9$.

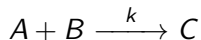
$$\begin{aligned} \dot{G} &= \theta (\gamma_0 - G - G P^n), \\ \dot{M} &= \lambda G + \gamma_0 \mu - M, \\ \dot{P} &= \frac{n \alpha (\gamma_0 - G - G P^n) + \delta (M - P)}{\sum_{i=0}^{n-1} (i+1)^2 K_i P^i}. \end{aligned}$$

For a qualitative analysis of this system, see [Sturm and Weber, 2008]. For a recent review of other tools, see [Niu, 2011].

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Stochastic modeling

Continuous time, Discrete state-space, Stochastic determination.

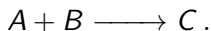


The probability that the reaction gets fired in the next time interval depends on the **stochastic constant** k . The variables $A(t)$, $B(t)$ and $C(t)$ are **random variables** which count the numbers of molecules of species A , B and C . **Numerical** simulations by the [Gillespie, 1977] algorithm.

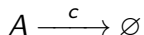
- The same average deterministic behaviour may correspond to many different stochastic behaviours. [▶ Example](#)
- Stochastic simulations help taking into account the surprising effects of the noise in gene expression [Vilar et al, 2002].

Symbolic contributions to stochastic modeling

- The **statistical moments** of the random variables which count the numbers of molecules are solutions of a system of **ODE**. See [Paulsson, 2005].
- Rewriting techniques are useful for **truncating** this ODE system, which is **infinite**, whenever a reaction involves two reactants or more



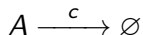
Generation of the ODE system in the order 1 case



Introduce a formal variable z for the species A ; for each $\nu \in \mathbb{N}$, define $\pi_\nu(t)$ as the probability that $A(t) = \nu$; define

$$\phi(z, t) \stackrel{\text{def}}{=} \sum_{\nu=0}^{\infty} \pi_\nu(t) z^\nu .$$

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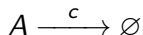
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Differentiate w.r.t. z

$$\frac{\partial}{\partial z} \phi(z, t) = \sum_{\nu=0}^{\infty} \nu \pi_\nu(t) z^{\nu-1} .$$

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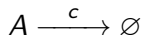
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$$\frac{\partial}{\partial z} \phi(z, t) = \sum_{\nu=0}^{\infty} \nu \pi_\nu(t) z^{\nu-1} .$$

Evaluate at $z = 1$. One gets the **mean** $EA(t)$ of $A(t)$:

$$\frac{\partial}{\partial z} \phi(z, t) \Big|_{z=1} = EA(t) = \sum_{\nu=0}^{\infty} \nu \pi_\nu(t) .$$

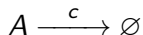
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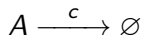
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Now, by a “well-known” method one gets a PDE

$$\frac{\partial}{\partial t} \phi(z, t) = c(1 - z) \frac{\partial}{\partial z} \phi(z, t) .$$

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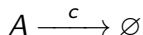
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Differentiate w.r.t. z

$$\frac{\partial^2}{\partial z \partial t} \phi(z, t) = -c \frac{\partial}{\partial z} \phi(z, t) + c(1-z) \frac{\partial^2}{\partial z^2} \phi(z, t).$$

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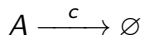
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$$\frac{\partial}{\partial t} \phi(z, t) = c(1-z) \frac{\partial}{\partial z} \phi(z, t) .$$

which gives

$$\frac{d}{dt} EA(t) = -c EA(t) .$$

Generation of the ODE system in the order 2 case



Introduce a formal variable z for the species A ; for each $\nu \in \mathbb{N}$, define $\pi_\nu(t)$ as the probability that $A(t) = \nu$; define

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The rhs of the PDE now has **order 2**

$$\frac{\partial}{\partial t} \phi(z, t) = \frac{c}{2} (1 - z^2) \frac{\partial^2}{\partial z^2} \phi(z, t).$$

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Differentiate w.r.t. z

$$\frac{\partial^2}{\partial z \partial t} \phi(z, t) = -c z \frac{\partial^2}{\partial z^2} \phi(z, t) + \frac{c}{2} (1 - z^2) \frac{\partial^3}{\partial z^3} \phi(z, t).$$

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We are led to an **infinite cascade unless we rewrite** the rhs term

$$\frac{d}{dt} EA(t) = -c \frac{\partial^2}{\partial z^2} \phi(z, t) \Big|_{z=1}.$$

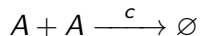
Breaking the infinite CAScade

Fortunately, or
unfortunately, it is not
always possible to break
the infinite cascade

However, under some
assumptions . . .



Breaking the infinite CAScADE



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$$\phi(z, t) \stackrel{\text{def}}{=} \sum_{\nu=0}^{\infty} \pi_\nu(t) z^\nu \quad \left(\text{we are bothered by } \frac{\partial^2}{\partial z^2} \phi(z, t) \right)$$

Breaking the infinite CAScADE



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Assume $A(t)$ is either 0 or 2. Then

$$\psi(z, t) \stackrel{\text{def}}{=} \sum_{\nu=0}^{\infty} \nu(\nu - 2) \pi_\nu(t) z^\nu = 0.$$

Breaking the infinite CAScAde



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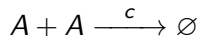
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$$\psi(z, t) \stackrel{\text{def}}{=} \sum_{\nu=0}^{\infty} \nu(\nu - 2) \pi_\nu(t) z^\nu = 0.$$

One easily deduces:

$$\psi(z, t) = z \left(z \frac{\partial^2}{\partial z^2} \phi(z, t) - \frac{\partial}{\partial z} \phi(z, t) \right).$$

Breaking the infinite CAScAde



Introduce a formal variable z for the species A ; for each $\nu \in \mathbb{N}$, define $\pi_\nu(t)$ as the probability that $A(t) = \nu$; define

$$\phi(z, t) \stackrel{\text{def}}{=} \sum_{\nu=0}^{\infty} \pi_\nu(t) z^\nu \quad \left(\text{we were bothered by } \frac{\partial^2}{\partial z^2} \phi(z, t) \right)$$

Assume $A(t)$ is either 0 or 2. Then

$$z \frac{\partial^2}{\partial z^2} \phi(z, t) = \frac{\partial}{\partial z} \phi(z, t)$$

hence

$$\frac{d}{dt} EA(t) = -c EA(t).$$

Further methods

- The use of Euler operators and Weyl algebra rather than partial derivatives makes proofs simpler.
- Other reduction methods as well as efficient formulas are given in [Vidal, Petitot, Boulier, Lemaire, Kuttler, 2010]
- A prototype software has been developed by M. Petitot.

Metabolic Pathways (borrowed from a slide of S. Schuster)

[Picture removed]

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A gene regulated by a polymer of its own protein

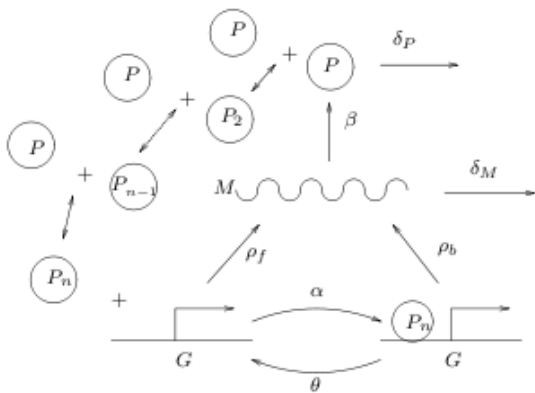


Fig. 1. A gene regulated by a polymer of its protein

Stochasticity in gene expression

Borrowed from [Koern et al, Nature Reviews, 2005]
[two pictures removed]

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