Application of Differential Algebra to the Quasi-Steady State Approximation in Biology and Physics

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Plan

1 Background
   - Differential elimination
   - Slow/fast dynamics
   - Tikhonov theorem

2 Slow/fast chemical reaction systems reduction
   - Michaelis Menten example
   - General method

3 Application to physics
   - Communicating vessels
   - Diffusion
   - Pendulum
   - Other examples ...

4 MABSys

5 Conclusion
Summary

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founders of differential algebra: Ritt (50), Kolchin (73)
many people in this room have contributed to differential algebra
key notions:
  - ranking
    → an ordering on the derivatives
  - characteristic sets
    (regular differential chains, characterizable sets)
    → membership test to an ideal
package for computing the characteristic sets: diffalg package (Boulier, Hubert, Lemaire)
evolution of diffalg:
  → Differential Algebra (Boulier, Maple 14), based on BLAD (Boulier, C library, GPL)
Differential elimination

System (diff notation)

\[
\begin{align*}
\frac{dC(t)}{dt} &= F_1(t) - k_2 C(t) \\
\frac{dS(t)}{dt} &= -F_1(t) \\
\frac{dE(t)}{dt} &= -F_1(t) + k_2 C(t) \\
\frac{dP(t)}{dt} &= k_2 C(t) \\
k_1 E(t) S(t) &= k_{-1} C(t)
\end{align*}
\]

Symbols

- differential indeterminates: \( C(t), S(t), E(t), P(t), F_1(t) \)
- parameters (=constants): \( k_1, k_{-1}, k_2 \)
Differential elimination

### System (dotted notation)

\[
\begin{align*}
\dot{C} &= F_1 - k_2 C \\
\dot{S} &= -F_1 \\
\dot{E} &= -F_1 + k_2 C \\
\dot{P} &= k_2 C \\
k_1 E S &= k_{-1} C
\end{align*}
\]

### Symbols

- differential indeterminates: \( C, S, E, P, F_1 \)
- derivatives: \( C, \dot{C}, S, \dot{S}, E, \dot{E}, P, \dot{P}, F_1 \)
- ranking \([F_1] \gg [C, E, P, S]\):
  - any derivative of \( F_1 \) is greater than any derivative of \( C, S, E, P \).
  - \( \rightarrow \) elimination ranking (which eliminates \( F_1 \))
- parameters (=constants): \( k_1, k_{-1}, k_2 \)

In this talk, all equations are ordinary (i.e. no partial derivatives)
Rosenfeld-Gröbner algorithm

- compute a list of r.d.c. $C_1, \ldots, C_s$ from a input system $\Sigma$
- $\sqrt{[\Sigma]} = \cap_{i=1}^{s} \text{Sat}(C_i)$ with $\text{Sat}(C_i) = [C_i] : H_{C_i}^\infty$
- each r.d.c. yields a rewritting system such that $p \in \text{Sat}(C_i) \iff p \xrightarrow{c_i}^* 0$

\[
\begin{align*}
C & \rightarrow \frac{E S k_1}{k_1} \\
\dot{S} & \rightarrow -\frac{k_2 k_1 ES(k_1 S + k_1)}{k_1 S + k_1 S + k_1 E} \\
\dot{P} & \rightarrow \ldots \\
\dot{E} & \rightarrow \ldots \\
F_1 & \rightarrow \frac{k_2 k_1 ES(k_1 S + k_1)}{k_1 S + k_1 S + k_1 E}
\end{align*}
\]

ranking: $\ldots > \dot{F}_1 > F_1 > \ldots > \dot{C} > \dot{E} > \dot{P} > \dot{S} > C > E > P > S$
one has a normal form for polynomials (BL Issac01):
\[ p = q \mod \text{Sat}(C_i) \iff \text{NF}(p, C_i) = \text{NF}(q, C_i) \]

the normal form of a polynomial is a rational fractions \( f/g \)

recent paper: *A Normal Form Algorithm For Regular Differential Chains*,
→ Boulier Lemaire, AADIOS09MCS

one can also consider normal forms of a rational fraction (provided its denominator
is not a zero divisor).
Different timescales

- in physics, biology, ...: phenomena can have very different timescales
- exemple: communicating vessels with an input

Two phenomena:
- input: $u(t) \ (m^3/s)$
- exchange between 1 and 2

Variables:
- volumes: $V_1(t), V_2(t) \ (in \ m^3)$
- sections: $S_1, S_2 \ (in \ m^2)$
- water heights: $x_1(t), x_2(t) \ (in \ m)$

Objective

Get rid of the fast timescale
First case: assume the input is much slower than the exchange

- the two vessels balance instantly
- one can assume $x_1(t) = x_2(t)$ (after some transient time)
- the input is split between the two vessels w.r.t. their surfaces

If one assumes it starts balanced:

$$\dot{x}_1 = \frac{1}{S_1 + S_2} u$$

$$\dot{x}_2 = \frac{1}{S_1 + S_2} u$$

$x_1(0) = x_2(0)$
Second case: assume the input is much faster than the exchange

- the two vessels have no time for balancing
- the input only goes in vessel 1

the vessel 1 will be full in a very short time
removing the fast timescale here makes no sense
indeed, the fast phenomena does not reach a equilibrium
one expects the fast phenomena to balance

Remark
One can easily remove the slow timescale: $\dot{x}_1 = u/S_1$, $\dot{x}_2 = 0$
Intuition of the Tikhonov theorem

\[
\sum \begin{aligned}
\dot{x} &= f(x, y) \\
\dot{y} &= \frac{1}{\varepsilon} g(x, y)
\end{aligned}
\]

- \(\varepsilon\) is small
- \(x\) is the slow variable
- \(y\) is the fast variable (because of \(1/\varepsilon\))
- a solution starting from \((x_0, y_0)\) behaves in two steps:
  - **fast transient** \(x(t)\) does not change
  - \(y(t)\) quickly reaches the curve \(g(x_0, y) = 0\)
  - **slow** the solution slowly drifts on \(g(x, y) = 0\)
    following \(\dot{x} = f(x, y)\).

The variety \(g(x, y) = 0\) is called the *slow variety*
Example of the Tikhonov theorem

\[
\begin{align*}
\dot{x} &= x + y \\
\dot{y} &= \frac{1}{\varepsilon}(1 - xy)
\end{align*}
\]

for \( \varepsilon = 0.01 \) and three different initial conditions \((x_0, y_0) = (2, 3), (3, 1)\) and \((1, 0.5)\). The transient is (almost) vertical, and solutions slides along \( y = 1/x \).
Tikhonov theorem

Idea of the theorem
- it is a limit theorem: the limits of the solutions (when $\varepsilon \to 0$) are the solutions when $\varepsilon = 0$ in the system.

Theorem (rough version)

\[
\Sigma \begin{cases} 
\dot{x} &= f(x, y) \\
\dot{y} &= \frac{1}{\varepsilon} g(x, y)
\end{cases}
\]

If for any $(x_0, y_0)$, the solution of $\dot{y} = \frac{1}{\varepsilon} g(x_0, y)$, $y(0) = y_0$ converges to $\bar{y}$ with $g(x_0, \bar{y}) = 0$, then there exist $\alpha$, $T > 0$ such that the solution of $\Sigma$ uniformly tends (for $t \in [\alpha, T]$) towards the solution of the reduced system

\[
\bar{\Sigma} \begin{cases} 
\dot{x} &= f(x, y) \\
0 &= g(x, y)
\end{cases}
\]

$\bar{\Sigma}$ is the quasi steady-state approximation of $\Sigma$. 
the exchange satisfies: $F(x_1, x_2) = 0 \iff x_1 = x_2$
if you assume that $x_1 = x_2$, you get: $\dot{x}_1 = u/S_1$ and $\dot{x}_2 = 0$
pb: $1/\varepsilon$ times something small is not zero
exact algorithms do not like $\approx 0$
The theorem does not apply (not in Tikhonov form).

$x_1$ and $x_2$ are both "fast".

Introducing $y = S_1 x_1 + S_2 x_2$, the system is under Tikhonov form ($y$ is slow . . .)

Indeed, $y$ is the total volume of liquid, so it is not affected by the exchange phenomenon

\[
\begin{align*}
\dot{y} &= u \\
\dot{x}_2 &= \frac{1}{\varepsilon} F((y - S_2 x_2)/S_1, x_2)/S_2
\end{align*}
\]

Since $x_1 = (y - S_2 x_2)/S_1$

Applying the Tikhonov theorem . . .
The theorem does not apply (not in Tikhonov form).

\( x_1 \) and \( x_2 \) are both "fast".

Introducing \( y = S_1 x_1 + S_2 x_2 \), the system is under Tikhonov form (\( y \) is slow . . .)

Indeed, \( y \) is the total volume of liquid, so it is not affected by the exchange phenomenon.

\[
\begin{align*}
\dot{y} &= u \\
0 &= F((y - S_2 x_2)/S_1, x_2)/S_2
\end{align*}
\]

Since \( F(x_1, x_2) = 0 \iff x_1 = x_2 \), and replacing \( y \) by its value
The theorem does not apply (not in Tikhonov form).

\( x_1 \) and \( x_2 \) are both "fast".

Introducing \( y = S_1 x_1 + S_2 x_2 \), the system is under Tikhonov form (\( y \) is slow . . .)

Indeed, \( y \) is the total volume of liquid, so it is not affected by the exchange phenomenon.

\[
S_1 \dot{x}_1 + S_2 \dot{x}_2 = u \\
\dot{x}_1 = \dot{x}_2
\]
Tikhonov for the vessels

\[ \begin{align*}
\dot{x}_1 &= \frac{1}{S_1 + S_2} u \\
\dot{x}_2 &= \frac{1}{S_1 + S_2} u 
\end{align*} \]

- The theorem does not apply (not in Tikhonov form).
- \(x_1\) and \(x_2\) are both "fast".
- Introducing \(y = S_1 x_1 + S_2 x_2\), the system is under Tikhonov form (\(y\) is slow . . .)
- Indeed, \(y\) is the total volume of liquid, so it is not affected by the exchange phenomenon.

\[ \begin{align*}
\dot{x}_1 &= \frac{u}{S_1} - \frac{1}{\varepsilon} F(x_1, x_2)/S_1 \\
\dot{x}_2 &= \frac{1}{\varepsilon} F(x_1, x_2)/S_2 \\
x_1(0) &= x_2(0)
\end{align*} \]
Elimination can help you

- if you do not want to find the change of variables
  → differential elimination is for you:

\[ \begin{align*}
\dot{x}_1 &= u/S_1 - F_1/S_1 \\
\dot{x}_2 &= F_1/S_2 \\
x_1 &= x_2
\end{align*} \]

- we do as if we don’t know the law for balancing, but only the law describing the balanced state \((x_1 = x_2)\)
  → indeed, the slow system does not depend on the balancing law

- the elimination of \(F_1\) combines the three steps:
  - finding the change of variables
  - applying the tikhonov theorem in the new variables
  - express the system in the original variables
Elimination can help you if you do not want to find the change of variables → differential elimination is for you:

\[ \begin{align*}
\dot{x}_1 &= \frac{u}{S_1} - \frac{F_1}{S_1} \\
\dot{x}_2 &= \frac{F_1}{S_2} \\
x_1 &= x_2
\end{align*} \]

\[ \begin{align*}
\dot{x}_1 &\rightarrow \frac{u}{S_1 + S_2} \\
x_2 &\rightarrow \frac{x_1}{S_1 + S_2} \\
F_1 &\rightarrow \frac{u S_2}{S_1 + S_2}
\end{align*} \]

ranking: \( \cdots > \dot{F}_1 > F_1 > \cdots > \dot{x}_2 > \dot{x}_1 > x_2 > x_1 \)
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Statement of the problem

**Input**
- a set of chemical reactions
- some are really fast, the others are slow

**Consequence**
- the fast reactions tend to be (almost) at equilibria
- two timescales: a fast one for the fast reactions, a slow one for the slow ones
- the fast timescale yields stiff ode systems which are hard to integrate (the integrator tends to oscillate around the correct solution)
- some variables are not needed

**Objective**
- Eliminate the fast timescale
Our algorithm ModelReduce

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

Reduced order dynamical modelling of reaction systems: a singular perturbation approach

Nonlinear model reduction of chemical reaction systems.

Transient Dynamics of Genetic Regulatory Networks
Biophysical Journal vol. 92, pp. 3501-3512, 2007

Model Reduction of Chemical Reaction Systems using Elimination.
A classical enzymatic degradation

The reactions

\[ E + S \stackrel{k_1}{\leftrightarrow} C \quad \text{(supposed fast)} \]
\[ C \stackrel{k_2}{\rightarrow} E + P \quad \text{(supposed slow)} \]

substrate S, product P, complex C, enzyme E

Consequence

- \( E + S \rightleftharpoons C \) is always (almost) at equilibria
- by “ignoring” \( E \) and \( C \), can the system be viewed as \( S \rightarrow P \)?
A classical enzymatic degradation

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

\[ \dot{S} = -\frac{V_m S (K + S)}{K E_0 + (K + S)^2} \]
seems valid even if \( S < E_0 \)

- \( V_m = k_2 E_0 \)
- \( K = \frac{k_{-1}}{k_1} \)
A classical enzymatic degradation

The usual reduction

\[ \dot{S}(t) = -\frac{V_m S(t)}{K + S(t)} \]

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Our reduction

\[ \dot{S} = -\frac{V_m S (K + S)}{K E_0 + (K + S)^2} \]

seems valid even if \( S < E_0 \)

\[ V_m = k_2 E_0 \]

\[ K = \frac{k_{-1}}{k_1} \]
From the reactions to a dynamical system

\[ R_1 : \quad E + S \xrightarrow{k_1} C \]
\[ R_2 : \quad C \xrightarrow{k_{-1}} E + S \]
\[ R_3 : \quad C \xrightarrow{k_2} E + P \]

Dynamical system: \( \dot{X} = MV \)

Vector of concentrations: \( X = \begin{pmatrix} C \\ E \\ P \\ S \end{pmatrix} \)

Reaction rate (following mass action law): \( V = \begin{pmatrix} k_1 E S \\ k_{-1} C \\ k_2 C \end{pmatrix} \)

Stoichiometric matrix: \( M = \begin{pmatrix} 1 & -1 & -1 \\ -1 & 1 & 1 \\ 0 & 0 & 1 \\ -1 & 1 & 0 \end{pmatrix} \)
**Detail of the reduction**

\[ E + S \xrightleftharpoons[k_{-1}]{k_1} C \quad \text{(supposed fast)} \]

\[ C \xrightarrow{k_2} E + P \quad \text{(supposed slow)} \]

**Step 1: build the system**

\[
\begin{align*}
\dot{C} &= F_1 - k_2 C \\
\dot{S} &= -F_1 \\
\dot{E} &= -F_1 + k_2 C \\
\dot{P} &= k_2 C \\
k_1 ES &= k_{-1} C
\end{align*}
\]

- \( F_1 \): contribution of the fast reaction (unknown for the moment)
- \( (eq) \) implies that \( E + S \rightleftharpoons C \) is at equilibria
Detail of the reduction

\[ E + S \xrightleftharpoons[k_1]{k_{-1}} C \quad \text{(supposed fast)} \]
\[ C \xrightarrow{k_2} E + P \quad \text{(supposed slow)} \]

Step 2: eliminate the \( F_1 \) with Rosenfeld–Gröbner

\[
\begin{align*}
\dot{S} &= -\frac{k_2 k_1 ES(k_1 S + k_{-1})}{k_{-1}(k_{-1} + k_1 S + k_1 E)} \\
\dot{C} &= \ldots \\
\dot{E} &= \ldots \\
F_1 &= \ldots
\end{align*}
\]
Detail of the reduction

\[ E + S \xrightleftharpoons[k_1]{k_{-1}} C \]  
\[ C \xrightarrow{k_2} E + P \]  
(supposed fast)  
(supposed slow)

Step 3: use conservation laws

\[
\dot{S} = -\frac{k_1 k_2 E_0 S (k_1 S + k_{-1})}{k_1 k_{-1} E_0 + (k_1 S + k_{-1})^2}
\]
\[
\dot{C} = \ldots
\]
\[
\dot{S} = \ldots
\]
\[
\dot{E} = \ldots
\]

using the conservation laws:

- \[ C + P + S = C_0 + P_0 + S_0 \]
- \[ C + E = C_0 + E_0 \]
- and assuming \( C_0 = 0 \).
Detail of the reduction

\[
E + S \xrightarrow{k_1}{k_{-1}} C \quad \text{(supposed fast)}
\]

\[
C \xrightarrow{k_2} E + P \quad \text{(supposed slow)}
\]

Step 4: use symmetries

\[
\dot{S} = -\frac{k_1 k_2 E_0 S (k_1 S + k_{-1})}{k_1 k_{-1} E_0 + (k_1 S + k_{-1})^2}
\]

is reformulated to

\[
\dot{S} = -\frac{V_m S (K + S)}{K E_0 + (K + S)^2}
\]

with \( V_m = k_2 E_0 \) and \( K = \frac{k_{-1}}{k_1} \)
ModelReduce algorithm

**Input**
- a set of chemical reactions tagged slow and fast
- some options (conservation laws, ordering, ...)

**Output**
- a list of dynamical systems (i.e. $\dot{X} = \cdots$)
- multiple output occurs when the slow variety is split
ModelReduce algorithm

**Steps**

- Introduce a new symbol $F_i \in F$ for each fast reaction.
- Build the stoichiometric matrix $M_f$ and the vector rate $V_f$ for the fast reactions.
- Do the same for the slow reactions (yields $M_s$ and $V_s$).
- Build $\Sigma$:
  \[
  \begin{align*}
  \dot{X} &= M_s V_s + M_f F \\
  M_f V_f &= 0
  \end{align*}
  \]
  (Dynamical system)
  (Fast reactions at equilibria)
- Eliminate all the $F_i$'s and obtain one or several r.d.c. $C_1, C_2, \ldots$
- For each $C_i$, output the dynamical system $[\ldots, \dot{x}_j = NF(\dot{x}_j, C_i), \ldots]$.

When the Tikhonov theorem does not apply, the output is not correct (in that case $NF(\dot{x}_j, C_i)$ might involve 1st-order derivatives, or some $F_i$).
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Communicating vessels: the system

Variables

- Volumes: $V_1(t)$, $V_2(t)$ (in $m^3$)
- Sections: $S_1$, $S_2$ (in $m^2$)
- Water heights: $x_1(t)$, $x_2(t)$ (in $m$)
- Input in the vessel 1: $u(t)$ (in $m^3/s$)
Communicating vessels: the system

Hypothesis

- the filling is much slower than the balancing between the two vessels
- the dynamics of the balancing law needs to be known
- one just assumes the balancing is done when $x_1 = x_2$
Communicating vessels: the reduction

Equations

\[
\begin{align*}
\dot{V}_1(t) &= u(t) + F_1(t) \\
\dot{V}_2(t) &= -F_1(t) \\
V_1(t) &= S_1 x_1(t) \\
V_2(t) &= S_2 x_2(t) \\
x_1(t) &= x_2(t)
\end{align*}
\]

After eliminating \( F_1 \)

\[
\dot{x}_1 = \frac{u}{S_1 + S_2}
\]

For information: \( F_1 = -\frac{S_2 u}{S_1 + S_2} \)
Fast diffusion: system

Variables
- Volumes: $V_1$, $V_2$ (in l)
- Number of moles of a species $X$: $n_1(t)$, $n_2(t)$ (in mol)
- Concentration of $X$: $x_1(t)$, $x_2(t)$ (in mol/l)
- Addition of $X$ in compartment 1: $u(t)$ (in mol/s)
Hypothesis

- the addition of $X$ is much slower than the balancing between the two compartments
- the diffusion law needs not to be known
- one just assumes that the diffusion preserves the total number of $X$ and satisfies $x_1 = x_2$
Fast diffusion: reduction

Equations

\[
\begin{align*}
\dot{n}_1(t) &= u(t) + F_1(t) \\
\dot{n}_2(t) &= -F_1(t) \\
n_1(t) &= V_1 x_1(t) \\
n_2(t) &= V_2 x_2(t) \\
x_1(t) &= x_2(t)
\end{align*}
\]

After eliminating \( F_1 \)

\[
\dot{x}_1 = \frac{u}{V_1 + V_2}
\]

For information: \( F_1 = -\frac{V_2 u}{V_1 + V_2} \)
The spring pendulum: system

Variables

- coordinates: $x(t)$, $y(t)$ (in m)
- mass: $m$ (in kg)
- spring constant: $k$ (in kg/s$^2$)
- gravitation: $g$ (in m/s$^2$)
- free length of the spring: $l_0$
Hypothesis: the spring has an infinite spring constant

- its length equals the free length (the gravitation and the motion do not stretch it)
- the spring applies a force \((T_x, T_y)\) (supposed unknown) collinear to the spring direction
- caution: \(T_x\) and \(T_y\) are two different functions (no partial derivatives here)
Spring pendulum: reduction

**Equations**

\[
\begin{align*}
    m\ddot{x}(t) & = -T_x(t) \\
    m\ddot{y}(t) & = mg - T_y(t) \\
    x(t)^2 + y(t)^2 & = l_0^2 \\
    x(t)T_y(t) & = y(t)T_x(t)
\end{align*}
\]

**After eliminating** $T_x$ and $T_y$

\[
\begin{align*}
    y^2 + x^2 & = l_0^2 \\
    \ddot{x} & = \frac{\dot{x}^2}{2} \left( \frac{1}{l_0 + x} - \frac{1}{l_0 - x} \right) - \frac{yxg}{l_0^2}
\end{align*}
\]
Singularities

**Horizontal position**

The following system has a singularity when \( x(t) = l_0 \) or \( x(t) = -l_0 \)

\[
\begin{align*}
y^2 + x^2 &= l_0^2 \\
\ddot{x} &= \frac{\dot{x}^2}{2} \left( \frac{1}{l_0 + x} - \frac{1}{l_0 - x} \right) - \frac{y x g}{l_0^2}
\end{align*}
\]

**Vertical position**

The following system has a singularity when \( y(t) = l_0 \) or \( y(t) = -l_0 \)

\[
\begin{align*}
y^2 + x^2 &= l_0^2 \\
\ddot{y} &= g - \frac{g y^2}{l_0^2} - \frac{\dot{y}^2}{2} \left( \frac{1}{l_0 + y} - \frac{1}{l_0 - y} \right)
\end{align*}
\]

**Numerical considerations**

- numerical consequence: how to integrate? By switching model?
- linked to our project LEDA (ANR=french research agency), which deals with the treatment of DAE
Communicating vessels with varying section

The section is a function of the height $x$: $V_1(x_1) = \int_0^{x_1} S(x)\,dx$. One needs to solve the problem with compositions of functions.

**System**

\[
\begin{align*}
\dot{V}_1(x_1(t)) &= u(t) + F_1(t) \\
\dot{V}_2(x_2(t)) &= -F_1(t) \\
V_1(x_1(t)) &= \int_0^{x_1(t)} S(x)\,dx \\
V_2(x_2(t)) &= \int_0^{x_2(t)} S(x)\,dx \\
x_1(t) &= x_2(t)
\end{align*}
\]

Hard to do because of composition of unknown functions. Easy by hand, not in diffalg or DifferentialAlgebra.
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Presentation

Implementation

- Authors: François Lemaire and Aslı Ürgüplü (2008-)
- Coded in Maple
- Download: www.lifl.fr/~urguplu

Description

- handles: models described by chemical reactions
- provides: routines for reducing/simplifying the model (ODEs)
- goal:
  - make algorithmic the reductions usually made by hand
  - help the analysis of the model
- spirit: accessible to non specialists, inspired by collaboration with modelers
Typical use of MABSys

System of chemical reactions

Rate laws or QSSA (App. Reduction)

user

system of ODEs

Exact Reduction (parameter reduction/semi-rectification)

user

system of ODEs

Outside MABSys (User, Extensive computations, Bifurcation Analysis, …)

Qualitative/quantitative Information
Underlying techniques

Techniques

- **differential elimination for the QSSA**
  
  Model Reduction of Chemical Reaction Systems using Elimination.
  http://hal.archives-ouvertes.fr/hal-00184558/fr.

- **Lie Symmetries (parameter reduction, semi-rectification)**

  F. Lemaire and A. Ürgüplü.

  P. J. Olver.
  *Applications of Lie groups to differential equations*, second ed., vol. 107 of *Graduate Texts in Mathematics*.
  Springer Verlag, 1993.

  A. Sedoglavic.
  Reduction of Algebraic Parametric Systems by Rectification of their Affine Expanded Lie Symmetries.

Techniques are hidden to the user! We want a friendly interface.
Model definition

Basic enzymatic degradation

\[ E + S \xrightleftharpoons[k_{-1}]{k_1} C \quad \text{(supposed fast)} \]

\[ C \xrightarrow{k_2} E + P \quad \text{(supposed slow)} \]

substrate $S$, product $P$, complex $C$, enzyme $E$

```plaintext
> R2 := NewReaction(C,E+S,MassActionLaw(km1),fast=true):
> R3 := NewReaction(C,E+P,MassActionLaw(k2)):
> RS := [R1,R2,R3]:
```

Remark: one can use `CustomizedLaw` for arbitrary rates
Basic operations

\[
E + S \xrightleftharpoons[k_1]{k_{-1}} C \quad \text{(supposed fast)}
\]

\[
C \xrightarrow[k_2]{\quad} E + P \quad \text{(supposed slow)}
\]

Vector of rates

\[
\text{RateVector(RS);} \\
[k_1 \ E \ S] \\
[\ ] \\
[k_{m1} \ C] \\
[\ ] \\
[k_2 \ C]
\]

Stoichiometry matrix

\[
\text{StoichiometricMatrix(RS, \ [E,S,C,P]);} \\
[-1 \ 1 \ 1] \\
[\ ] \\
[-1 \ 1 \ 0] \\
[\ ] \\
[1 \ -1 \ -1] \\
[\ ] \\
[0 \ 0 \ 1]
\]
Basic operations

Conversion to an ODE system

```maple
> ReactionSystem2ODEs(RS, [E,S,C,P]);

\[
\begin{align*}
\frac{d}{dt}E(t) &= -k_1 E(t) S(t) + k_{m1} C(t) + k_2 C(t), \\
\frac{d}{dt}S(t) &= -k_1 E(t) S(t) + k_{m1} C(t), \\
\frac{d}{dt}C(t) &= k_1 E(t) S(t) - k_{m1} C(t) - k_2 C(t), \\
\frac{d}{dt}P(t) &= k_2 C(t)
\end{align*}
\]
```

Steady points equations

```maple
> Equilibria(RS);

[k_1 E S - k_{m1} C - k_2 C, k_2 C]
```

Other basic routines: access reactions information, ODE simulation and plottings,…
no conservation laws

> output := ModelReduce(RS, [E,C,P,S]): # only one output
> output[1][1];

\[
\frac{d}{dt} E(t) = \frac{k_{m1} C(t) k_2}{2}, \\
\frac{d}{dt} C(t) = -\frac{k_{m1} S(t) + k_1 S(t) + k_{m1} C(t)}{2}, \\
\frac{d}{dt} P(t) = k_2 C(t), \\
\frac{d}{dt} S(t) = -\frac{k_{m1} S(t) + k_1 S(t) + k_{m1} C(t)}{2}
\]

# QSSA Assumptions:
> output[1][2];

\[
[k_1 E(t) S(t) - k_{m1} C(t)]
\]
ModelReduce

with conservation laws

\[
\text{output} := \text{ModelReduce}(\text{RS, [E,C,P,S]}, \text{useConservationLaws=true}): \\
\text{red_sys} := \text{output}[1][1]: \\
\text{red_sys} := \text{subs(C_0=0, red_sys)}: \\
\text{red_sys}[4];
\]

\[
\frac{d}{dt} S(t) = - \frac{E_0 k_2 k_1 S(t) (k m_1 + k_1 S(t))}{2 k_1 S(t)^2 + 2 S(t) k m_1 k_1 + k m_1 k_1 E_0 + k m_1}
\]

- one has a diff. equation in \( S(t) \) only, but still many parameters.
- we are far from:

\[
\dot{S}(t) = - \frac{V_m S(t)}{K + S(t)}
\]

with \( V_m = k_2 E_0 \) and \( K = \frac{k_{-1}}{k_1} \) (or \( \frac{k_{-1}+k_2}{k_1} \))
Exact Reductions

Idea
- obtain an **equivalent** system which is "easier" to study

Two routines
- **InvariantizeByScalings**: reduce the number of parameters
  - reduce the complexity of parameter value exploration
  - helps hand analysis
  - (shown on the enzymatic degradation)
- **SemiRectifySteadyPoints**: reduce the number of parameters on which the steady points depend
  - some parameters only affect the dynamic

Based on change of coordinates
- one imposes monomial maps \((x_i \rightarrow x_1^{\alpha_1} \cdots x_n^{\alpha_n})\). Ex: \(V_m \rightarrow V_m/k_1\)
- ensures equivalence of systems, and positivity of parameters
InvariantizeByScalings

- **Input:** a dynamical system, list of positive variables, list of remaining variables.
- **Output:** a reduced system, a change of variables, list of parameters removed

```
> red_sys[4];
  d
  -- S(t) = - -----------------------------------------------
  dt 2 2 2
  k1 S(t) + 2 S(t) km1 k1 + km1 k1 E_0 + km1

> output := InvariantizeByScalings(red_sys, [k1,km1,k2], [],
  fixedvars=[E,C,P,S],
  scaletime=false):
>
> red_sys2 := output[1];
> red_sys2[4];
  d
  -- S(t) = - -----------------------------------------------
  dt 2
  S(t) + 2 km1 S(t) + E_0 km1 + km1

> output[2], output[3];
  km1
  [km1 = ---], [k1]
  k1
```
A last hypothesis

If one assumes $S \gg E_0$, one retrieves a simpler formula (classical hypothesis)

```plaintext
> red_sys2[4];

\[
\frac{d}{dt} S(t) = - \frac{k_2 E_0 (S(t) + k m_1)}{2 km_1 S(t) + S(t) + E_0 k m_1 + k m_1}
\]

> ApproximateSmallQuantity(red_sys2[4], E_0<S(t));

\[
\frac{d}{dt} S(t) = - \frac{k_2 E_0}{S(t) + k m_1}
\]

Better simplification ?

- Another step can automatically rename $k_2 E_0$ into $k_2$.
- We simplify by reducing the **number** of parameters.
- Further work: find changes of variables which reduce the **size** of the equations ($\dot{x}(t) = 1 + a + a b x(t)$ into $\dot{x}(t) = 1 + a + b x(t)$)
Summary

1 Background
- Differential elimination
- Slow/fast dynamics
- Tikhonov theorem

2 Slow/fast chemical reaction systems reduction
- Michaelis Menten example
- General method

3 Application to physics
- Communicating vessels
- Diffusion
- Pendulum
- Other examples ...

4 MABSys

5 Conclusion
Conclusion

Main idea

- many systems with constraints are limit case of systems with slow/fast timescales
- differential elimination can help to remove the fast timescale
- the dynamics of the fast phenomena is not important, only the equilibria of the fast phenomena is important,

Further work

- convince people to use differential elimination for QSSA problems
- convince physicists/biologists to use packages for reduction (QSSA, parameter reduction, . . . )
- write a C version of MABSys with a GPL licence (ModelReduce is done, parameter reduction is not, . . . )
  → ANR LEDA