On *DifferentialAlgebra*

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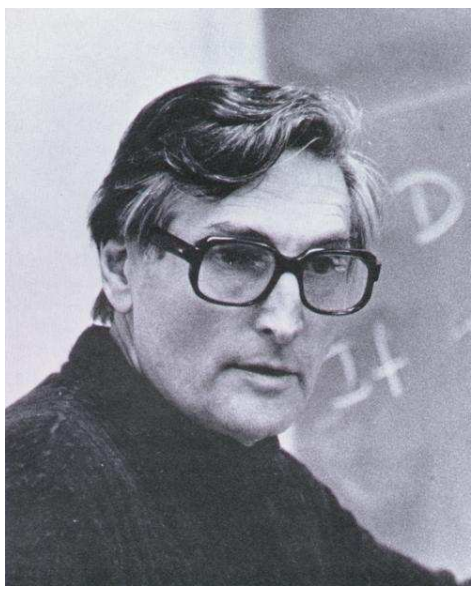
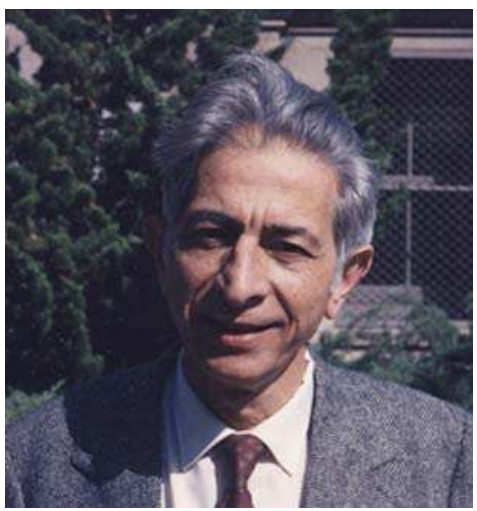
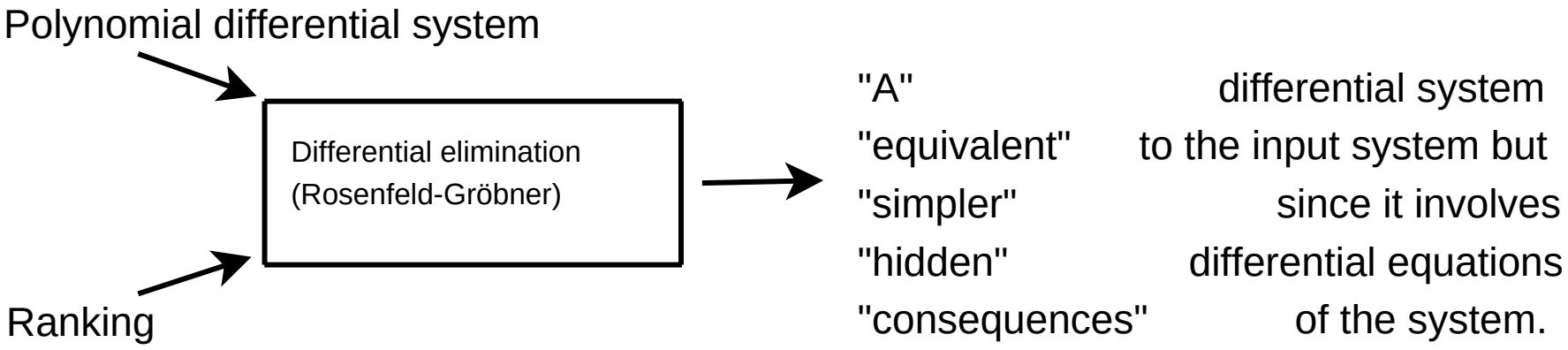
8 décembre 2008

Differential algebra

- A mathematical theory (Ritt, Kolchin) which permits to process systems of differential equations symbolically, e.g. in computer algebra systems.
- A subtheory : the differential elimination (Ritt, Seidenberg).

Differential elimination



"The" output system is a regular differential chain.

Rankings indicate the sort of sought differential equations.

Technically, a ranking is an "admissible" total ordering on the derivatives of the dependent variables.
In the case of ODE in two dep. vars. $u(t)$ and $v(t)$ it might be :

$$\cdots > \ddot{u} > \dot{v} > \dot{u} > v > u.$$

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Example : a DAE (Hairer, Wanner)

The unknowns are three functions $x(t)$, $y(t)$ and $z(t)$.

$$\begin{cases} \dot{x}(t) &= 0.7 \cdot y(t) + \sin(2.5 \cdot z(t)) \\ \dot{y}(t) &= 1.4 \cdot x(t) + \cos(2.5 \cdot z(t)) \\ 1 &= x^2(t) + y^2(t). \end{cases}$$

Equivalent polynomial DAE

$$\begin{cases} \dot{x}(t) &= 0.7 \cdot y(t) + s(t) & \dot{s}(t) &= 2.5 \cdot \dot{z}(t) \cdot c(t) \\ \dot{y}(t) &= 1.4 \cdot x(t) + c(t) & \dot{c}(t) &= -2.5 \cdot \dot{z}(t) \cdot s(t) \\ 1 &= x^2(t) + y^2(t) & 1 &= s^2(t) + c^2(t). \end{cases}$$

Differential elimination helps integrating the DAE by computing

- the underlying ODE $\dot{z}(t) = \textit{something}$
- a complete set of constraints on initial values

Synthesis

DifferentialAlgebra

- A MAPLE package still under development which implements differential elimination methods.
- It improves the MAPLE *diffalg* package (1996).
- It is just an interface for the *BLAD* libraries.

Bibliothèques Lilloises d'Algèbre Différentielle

- *BLAD* is a tower of five open source C libraries.
- The LGPL license permits anybody to use freely *BLAD*, even for commercial purposes.

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Differential algebra

A derivation over a ring R is an operation $R \to R$ such that

$$\delta(a+b) = \delta a + \delta b, \quad \delta(a\,b) = (\delta a)\,b + a\,\delta b.$$

A differential ring is a ring equipped with finitely many derivations which commute pairwise.

A set of polynomial differential equations is a subset of a differential polynomial ring $R = K\{U\}$ (K field of coefficients, U finite set of differential indeterminates = dependent variables).

Example : $R = \mathbb{Q}\{x, y, z, s, c\}$ endowed with $\delta = \mathrm{d}/\mathrm{d}t$.

Solutions compatible with differential elimination

Inference rules applied by the algorithms

Let a, b be two differential polynomials of R

1. $a = 0$ and $b = 0 \Rightarrow a + b = 0$
2. $a = 0$ and $b =? \Rightarrow a\,b = 0$
3. $a = 0 \Rightarrow \delta a = 0$
4. $a\,b = 0 \Rightarrow a = 0$ or $b = 0$

The set of the differential polynomial equations which are consequences of a given input system is a radical differential ideal of R.

Solutions need : C^∞ + domain

- Formal power series
- Functions analytical over some domain

RosenfeldGroebner (ODE)

RosenfeldGroebner represents the radical differential ideal J generated by a given system as an intersection of radical differential ideals I_k :

$$J = I_1 \cap \cdots \cap I_n.$$

Each I_k is presented by a regular differential chain C_k.

A regular chain is a rewrite system with "good" properties.
The ranking fixes the lefthand sides of the rewrite rules.

Fix the ranking $\cdots \dot{u} > \dot{v} > u > v$. Then

$$\dot{v}\,\dot{u} - v = 0, \quad \dot{v}^2 - 2 = 0$$

is a regular chain, and is viewed as

$$\dot{u} \to v/\dot{v}\,, \quad \dot{v}^2 \to 2.$$

Regular chains permit to compute *NormalForm*

Normal forms are normalized notations for expressions, assuming that variables satisfy the regular chain equations.

Assume the regular chain C is

$$\dot{u} \to v/\dot{v}\,, \quad \dot{v}^2 \to 2.$$

Then

$$\mathrm{NF}(2\,\dot{u}, C) = \mathrm{NF}(2\,v/\dot{v}, C) = v\,\dot{v}$$

- substitution of the lefthand sides by righthand sides
- algebraic inverses computation

- $a \equiv b \mod I$ iff $\mathrm{NF}(a, C) = \mathrm{NF}(b, C)$.
- $\mathrm{NF}(a, C) = 0$ iff $a \in I$.
- Every linear combination of normal forms is a normal form.

RosenfeldGroebner (PDE)

RosenfeldGroebner "computes all" the integrability conditions (the coherence property of Rosenfeld and Seidenberg).

The following rewrite system C is not a regular chain.

$$u_x \longrightarrow v, \quad u_y \longrightarrow 0.$$

Indeed normal forms are not unique :

$$\mathrm{NF}(u_{xy}, C) = v_y ? = 0 ?$$

RosenfeldGroebner completes (in the Knuth-Bendix sense) the rewrite system by inserting new equations :

$$u_x \longrightarrow v, \quad u_y \longrightarrow 0, \quad v_y \longrightarrow 0.$$

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The idea

- A polynomial ring R
- A polynomial system C of R (it is a regular chain – to be defined)
- An ideal I associated to C (in a sense to be defined)

In *DifferentialAlgebra*

Let C be a regular chain and a be a polynomial of R. Then

$$\mathrm{NF}(a, C) = \frac{p}{q}$$

is a rational fraction such that q is regular and $p/q = a$ in R/I.

Non differential : $|X| = |C|$

Point : C is triangular

$$f_1(x_1) = 0,\ f_2(x_2, x_1) = 0, \ldots, f_n(x_n, \ldots, x_1) = 0$$

- Euclidean division. Bézout.
- I is the ideal generated by C.
- One can decide zero and regularity in R/I.
- One can try to make C monic (*idéaux premiers à usage commercial*).
- If monic, C is a Gröbner basis. Use the Gröbner normal form, which is a polynomial.

Non differential : $|X| \geq |C|$

Denote $T = \{t_1, \ldots, t_p\}$.

$$f_1(x_1, T) = 0,\ f_2(x_2, x_1, T) = 0, \ldots, f_n(x_n, \ldots, x_1, T) = 0$$

Point : the ideal

$I = M^{-1}(C) \cap R$, where M denotes the multiplicative family generated by the leading coefficients of C.

- Key theorem : The nonzero elements of $\mathbb{Q}[T]$ are regular in R/I (holds also if M is generated by the separants).
- Back to the former case. The normal form is a rational fraction p/q with $p \in \mathbb{Q}[T, X]$ and $q \in \mathbb{Q}[T]$.

C is a regular chain if C can be transformed as a monic triangular set C_0, in the ring $R_0 = \mathbb{Q}(T)[X]$.

Non differential : squarefreeness

If the separants of a regular chain C are regular in R/I then the chain is said to be squarefree.

Point : Lazard's lemma

If C is a squarefree regular chain then I is radical.

Differential : ODE

$R = \mathbb{Q}\{U\}$ where $U = \{u_1, \ldots, u_n\}$.
The x_i and t_j are derivatives of elements of U.

$$f_1(x_1, T) = 0,\ f_2(x_2, x_1, T) = 0, \ldots, f_n(x_n, \ldots, x_1, T) = 0$$

Point : C is differentially triangular

The x_i and t_j must not be derivatives of any x_k.

C is a differential regular chain if

- C is a squarefree regular chain (in the non differential sense).
- C is differentially triangular.

Not completely straightforward since the key theorem relies on Macaulay's unmixedness theorem which applies in (some) Nötherian rings.

Differential : PDE

There are finitely many derivations which commute pairwise.

Point : the coherence property

A finite condition on cross-derivatives.

C is a differential regular chain if

- C is a squarefree regular chain (in the non differential sense).
- C is differentially triangular.
- C is coherent.

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The goal

Integrating differential elimination methods within scientific computation libraries (MINPACK, GSL).

Applications

- Index reduction for DAE
- QSSA for chemical systems
- Parameters estimation

Applications of applications

- Model reduction in cellular biology

BLAD structure

A tower of five libraries

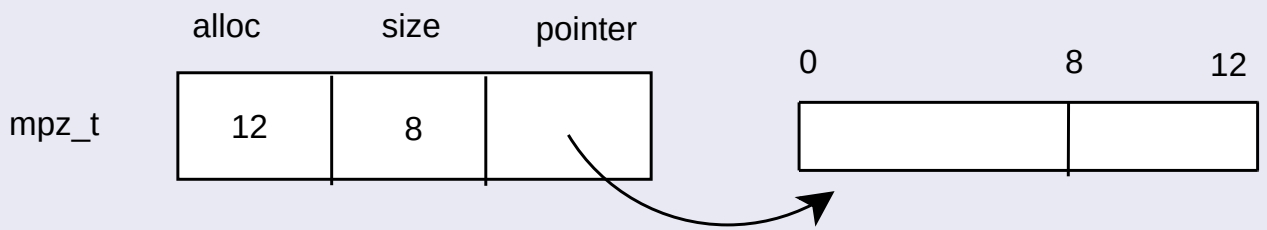
- **ba0** Memory management. Parsers. Exceptions.
- **bav** Variables. Rankings.
- **bap** Differential polynomials. A multivariate gcd algorithm close to that of MAPLE.
- **bad** Differential systems. Regular chains. Rosenfeld-Gröbner. Normal Forms. Change of ranking.
- **bai** Numerical integrators for regular chains. C code generation. DOP853.

First choices

C language (POSIX)

- One chooses the language and its standard libraries.
- Basic features. Rather precise specifications. Portability.
- The language imposes restrictions on memory management, which in turn imposes restrictions on the data structures.

The GMP programming scheme




```
mpz_init (n);
mpz_init_set (p, 1);
mpz_add (n, n, p);
```

Memory management

Two different/compatible mechanisms are available

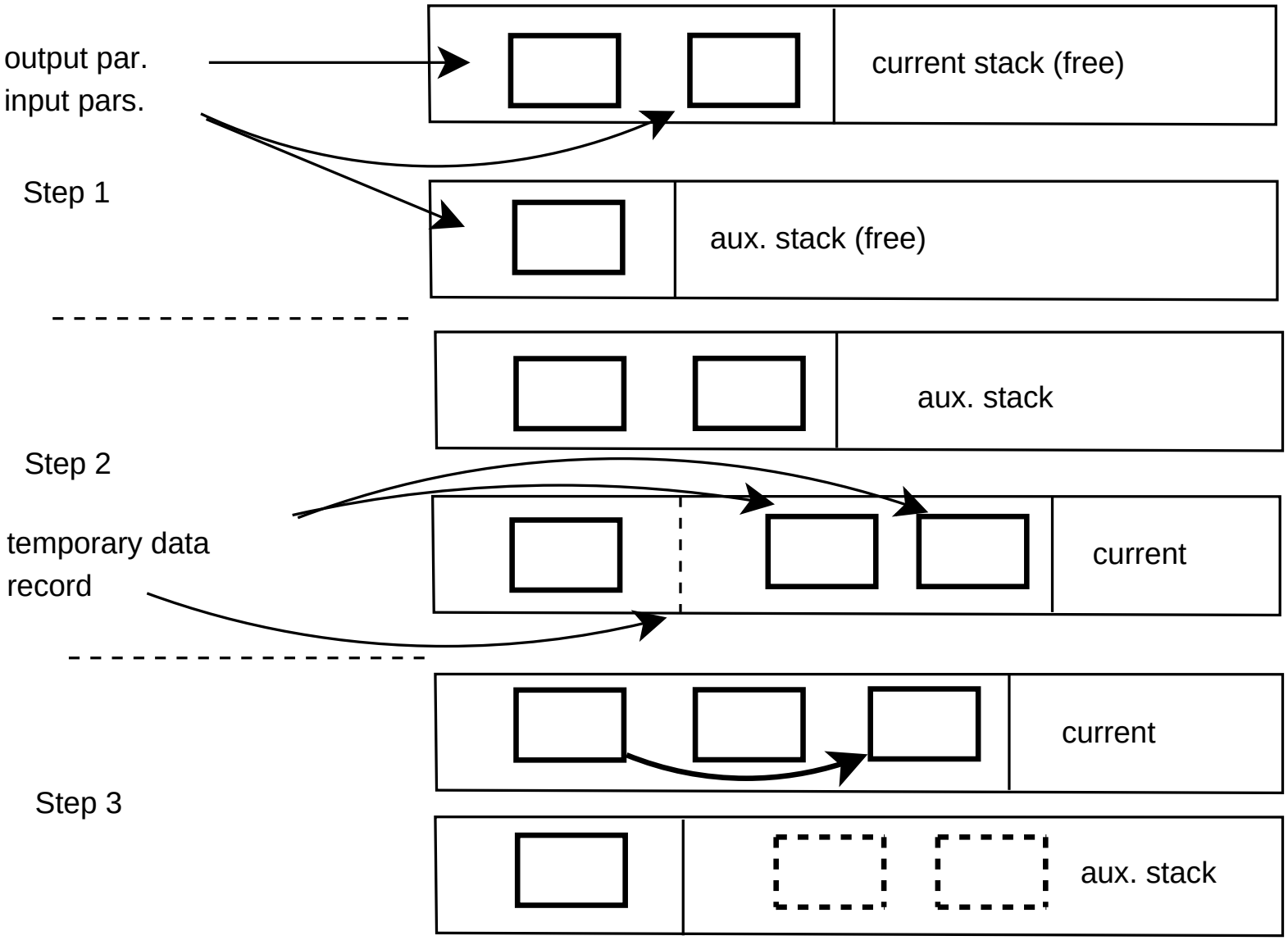
Concerns taken into account

- Garbage collection must be incorporated in the mathematical algorithms.
- It imposes restrictions on the code and the data structures.
- It must permit a powerful exception handling mechanism (catching errors ; timeout/memout ; inversion of a zero divisor)

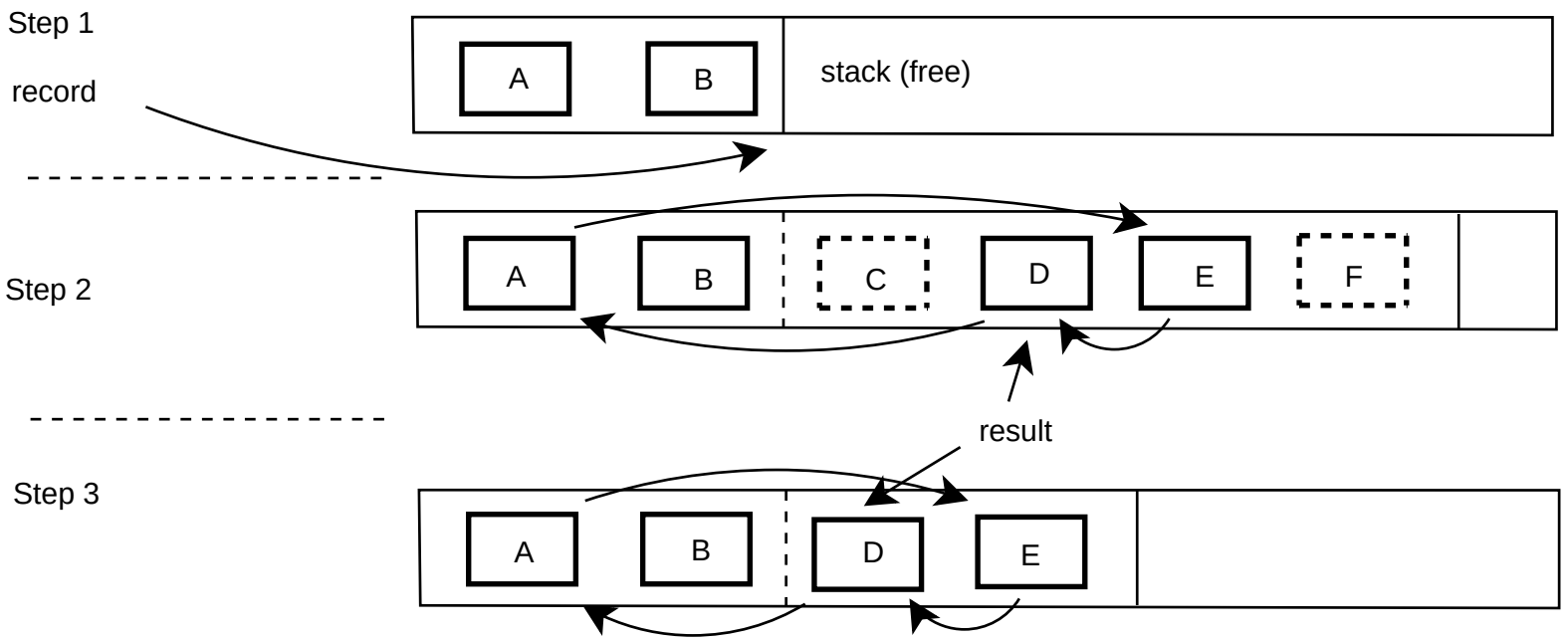
Other concerns

- Thread-safety
- Multi-core processors

The two stacks mechanism



Faugère's mechanism



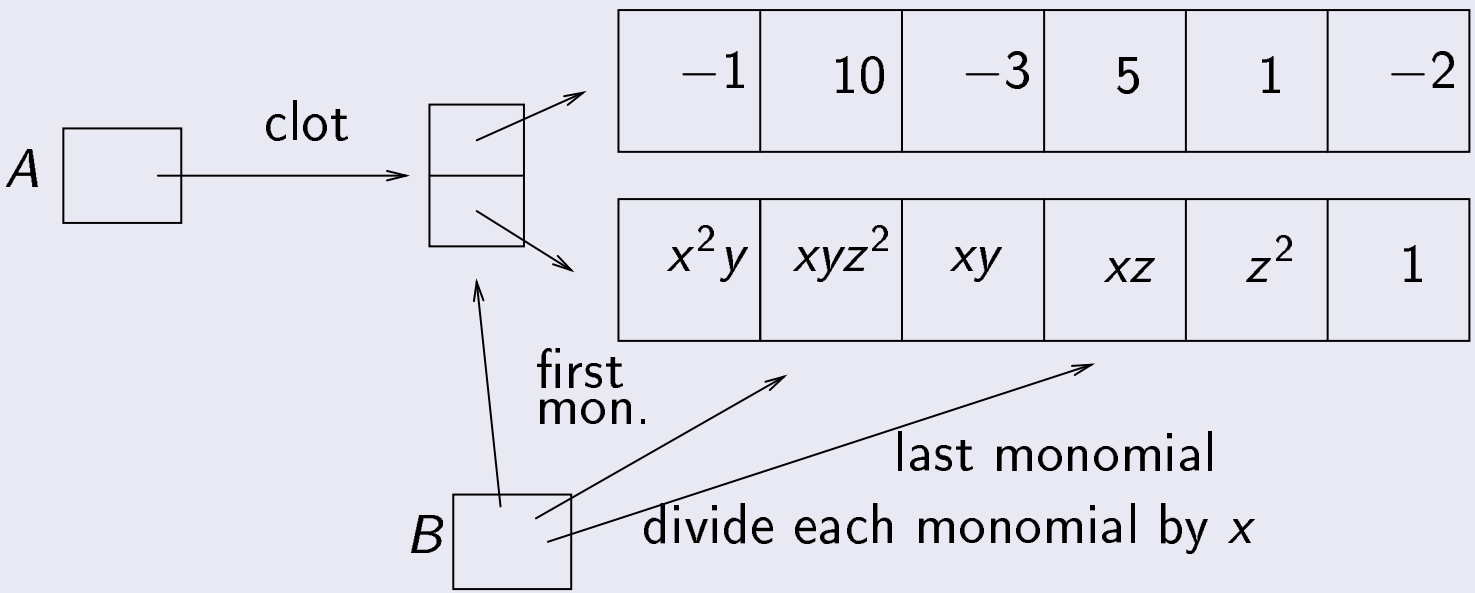
Variables and rankings

- One global table of all BLAD variables :
  independent variables, derivatives of dependent variables.
- To each variable is associated one positive integer per ranking.
  The greater the number, the greater the variable.
  Numbers are recomputed each time a variable is created.

Polynomials

Variant of the distributed representation.
Change of rankings + access to coefficients not too costly.
GMP integers + rational ; GMP + machine modular numbers.

$A := -x^2\,y + 10\,x\,y\,z^2 - 3\,x\,y + 5\,x\,z + z^2 - 2$
$B := \mathrm{coeff}\,(A, x, 1)$



Regular chains

A regular chain is endowed with structural properties :

- prime ideal ?
- differential ideal ?

and with desired properties :

- autoreduced chain ?
- primitive chain ?
- squarefree chain ?
- normalized chain ?
- coherent chain ?

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The principle of the QSSA

The two-time-scales standard form : fast and slow variables

Assuming ε is small, approximate

$$\dot{x} = f(x, y, \varepsilon), \quad \varepsilon \dot{y} = g(x, y, \varepsilon)$$

by

$$\dot{x} = f(x, y, 0), \quad 0 = g(x, y, 0).$$

The problem

There is no general method to find out if a given system can be transformed into the above form. In general, fast and slow variables are obtained by a change of coordinates.

For chemical reaction systems

Given fast and slow reactions, the transformation is algorithmic. A difficult step of the process just amounts to differential elimination.

The Henri-Michaelis-Menten approximation

The basic enzymatic reaction system

$$E + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_3} E + P$$

The initial ODE model :

$$\begin{aligned} \dot{E} &= -k_1\, E\, S + (k_2 + k_3)\, C, \\ \dot{S} &= -k_1\, E\, S + k_2\, C, \\ \dot{C} &= k_1\, E\, S - (k_2 + k_3)\, C, \\ \dot{P} &= k_3\, C. \end{aligned}$$

The approximation, assuming $k_1,\ k_2 \gg k_3$

$$\dot{S} = -\frac{V_{\max}\, S}{K + S}$$

$V_{\max}$ and K being constants

The Henri-Michaelis-Menten approximation

$$
\begin{array}{lrcl}
 & \dot{E} & = & -k_1\,E\,S + k_2\,C + k_3\,C, \\
\textit{initial} & \dot{S} & = & -k_1\,E\,S + k_2\,C, \\
\textit{model} & \dot{C} & = & k_1\,E\,S - k_2\,C - k_3\,C, \\
 & \dot{P} & = & k_3\,C.
\end{array}
$$

Red terms are the contributions of the fast reaction.

$$
\begin{array}{lrcl}
 & \dot{E} & = & -F_1 + k_3\,C, \\
 & \dot{S} & = & -F_1, \\
\textit{F. Lemaire's DAE} & \dot{C} & = & F_1 - k_3\,C, \\
 & \dot{P} & = & k_3\,C, \\
 & 0 & = & k_1\,E\,S - k_2\,C.
\end{array}
$$

The fast reaction is assumed to be at equilibrium.
The contribution of the fast reaction is an unknown function F_1.
The reduced model is the result of the elimination of F_1 in the DAE.

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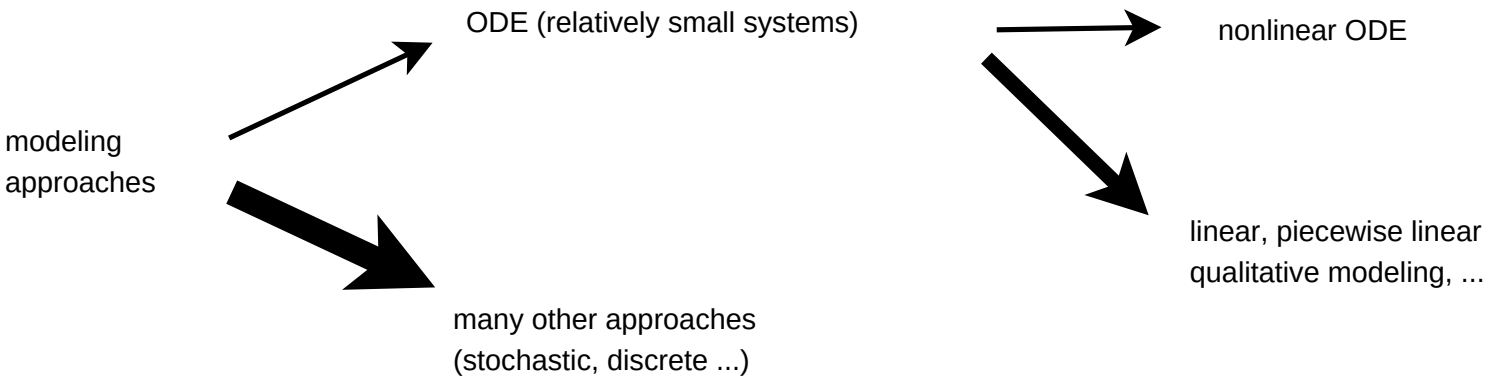
Cellular modeling by generalized chemical reaction systems

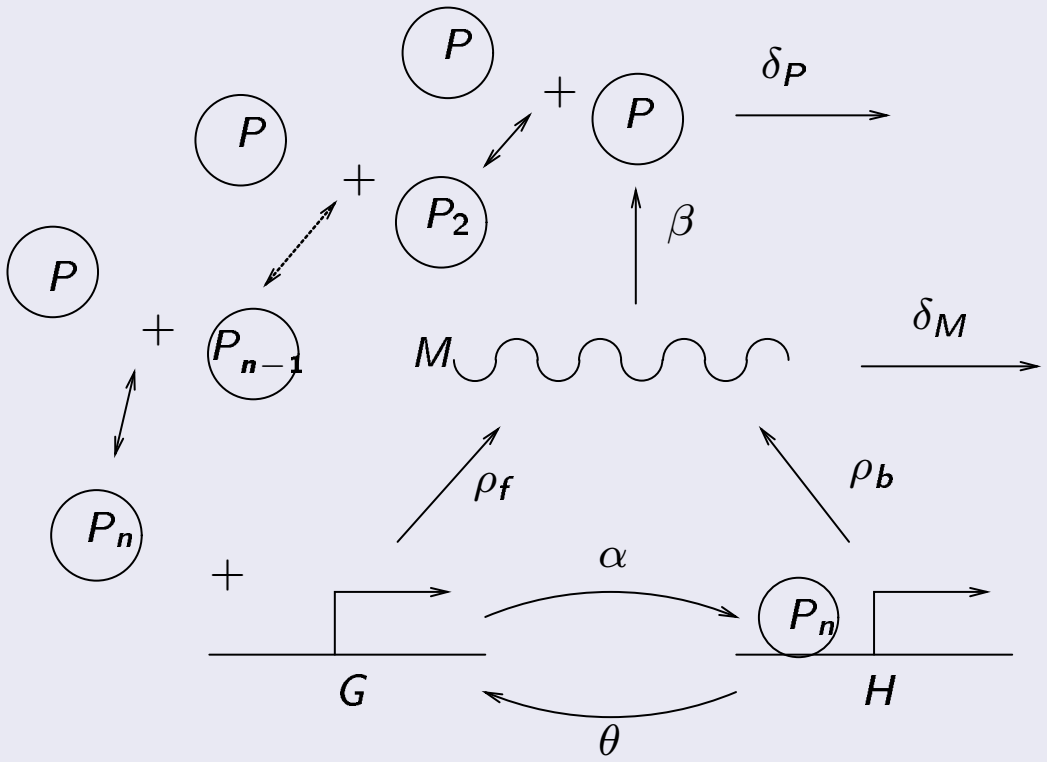


Difficulties : need for model reduction

ODE systems quickly get very large, overparameterized.
ODE systems are very accurate but a model should not involve more information than the data it comes from.

A single autoregulated gene

Is there a clock in this model ? Where ?



The generalized chemical reactions system

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

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

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

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.

The initial ODE system

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

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

The right handside of some ODE depend on mixtures of fast and slow terms : these variables should not be considered as fast.

QSSA : replace the A_i by variables, add equilibrium conditions and eliminate.

The reduced model

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

- Numerically, the integral curves of the reduced model fit with the ones of the initial model.
- The reduced model is simple enough : a symbolic qualitative analysis could be carried out to prove that a Hopf bifurcation (i.e. an oscillating behaviour) occurs if and only if $n \geq 9$.

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Parameters estimation

Differential elimination transforms nonlinear least squares problems into linear ones by guessing a starting point for a Newton like method.

Statement of the problem

Given

- a parametric ODE system (four parameters k_e, V_e, k_{12}, k_{21}) :

$$\begin{aligned} \dot{x}_1(t) &= -k_{12}\, x_1(t) + k_{21}\, x_2(t) - \frac{V_e\, x_1(t)}{k_e + x_1(t)}, \\ \dot{x}_2(t) &= k_{12}\, x_1(t) - k_{21}\, x_2(t). \end{aligned}$$

- some measures :
  $x_1(t)$ is observed ;
  $x_2(t)$ is not observed

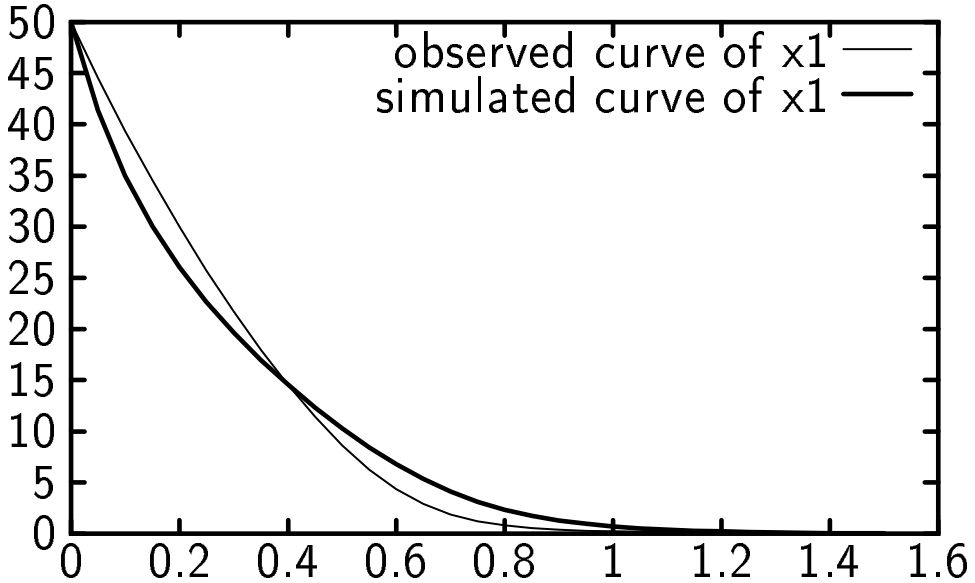
t	$x_1(t)$
$0.00000e-01$	$5.00000e+01$
$0.50000e-01$	$4.45078e+01$
...	
$1.50000e+00$	$4.95270e-02$

- possibly some extra information : $x_2(0) = 0$; $k_e = 7$.

Estimate the values of the unknown parameters V_e, k_{12}, k_{21}.

There exists a purely numerical method

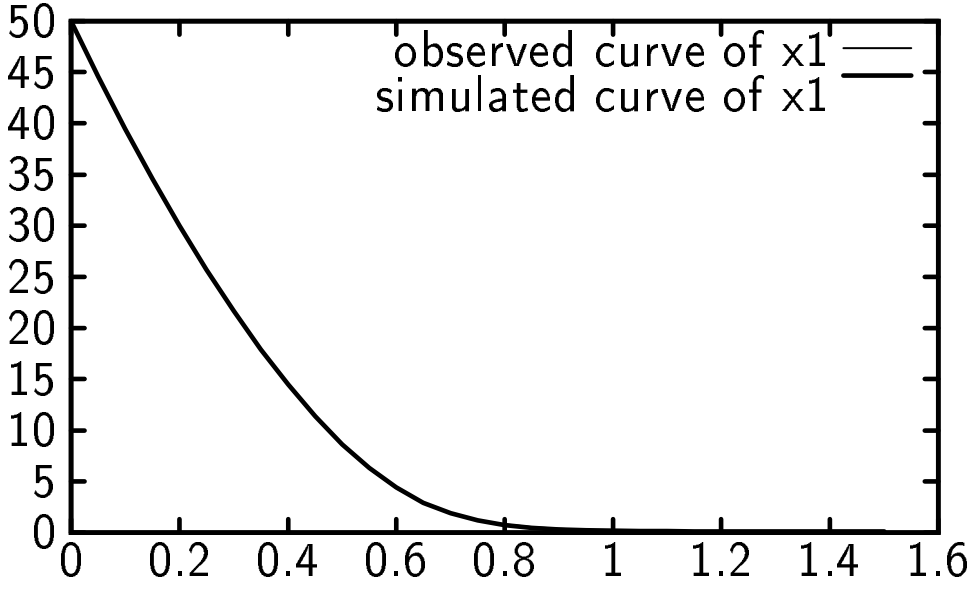
1. Give random values to k_{12}, k_{21}, V_e.
2. Integrate numerically the ODE and get a graph for $x_1(t)$.



3. If the error is too large, update k_{12}, k_{21}, V_e by the Levenberg-Marquardt method and goto step 2.

There exists a purely numerical method

1. Give random values to k_{12}, k_{21}, V_e.
2. Integrate numerically the ODE and get a graph for $x_1(t)$.



The Levenberg-Marquardt method ends in a wrong local minimum

$$k_{21} = .16, \quad k_{12} = .76, \quad V_e = 82.8.$$

Should be

$$k_{21} = .5, \quad k_{12} = 3, \quad V_e = 101.$$

Differential elimination for guessing good initial values

$$\begin{aligned}\dot{x}_1(t) &= -k_{12}\,x_1(t) + k_{21}\,x_2(t) - \frac{V_e\,x_1(t)}{k_e + x_1(t)},\\ \dot{x}_2(t) &= k_{12}\,x_1(t) - k_{21}\,x_2(t).\end{aligned}$$

1. Eliminate the non observed variable $x_2(t)$ using *RosenfeldGroebner* or, better, *PARDI*.

$$\ddot{x}_1\,(x_1+k_e)^2+[k_{12}+k_{21}]\,\dot{x}_1\,(x_1+k_e)^2+[V_e]\,\dot{x}_1\,k_e+[k_{21}\;V_e]\,x_1\,(x_1+k_e).$$

2. Evaluate the ODE for many different values of t.
   By linear least squares, estimate the [parameters blocks].
3. Solve the parameters blocks w.r.t. parameters :

$$k_{12} = 0.45, \quad k_{21} = 1.65, \quad V_e = 87.29.$$

4. Run the optimization method starting from these values.

There are (numerical !) difficulties

The parameters change during the optimisation process, leading to stiffness. However, in the context of chemical reactions systems, QSSA could be performed at runtime.

Difficulty to numerically evaluate the derivatives.

Getting the parameters from the [blocks] may be difficult.
Over the example, this is easy :

$$k_{12} + k_{21} = value_1, \quad V_e = value_2, \quad k_{21}\, V_e = value_3.$$

There are (numerical !) difficulties

The parameters change during the optimisation process, leading to stiffness. However, in the context of chemical reactions systems, QSSA could be performed at runtime.

Difficulty to numerically evaluate the derivatives.

Getting the parameters from the [blocks] may be difficult.
In general, beware algebraic relations amongs blocks :

$$k_{12} + k_{21} = value_1, \quad V_e = value_2, \quad k_{21}\, V_e = value_3.$$

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Conclusion

Differential elimination is a tool that could be embedded in the main numerical libraries (say, MINPACK).

However

1. One needs to provide software : easy to use MAPLE packages, libraries easy to plug in existing software.
2. One needs also to prove the usefulness of these methods on convincing applications.