On Differential Algebra

François Boulier
University Lille I
LIFL – Computer Algebra

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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).
Polynomial differential system

Differential elimination
(Rosenfeld-Gröbner)

Ranking

"A" differential system equivalent to the input system but simpler since it involves hidden differential equations consequences of the system.

"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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A. Seidenberg.
An elimination theory for differential algebra.
Example: a DAE (Hairer, Wanner)

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

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

Equivalent polynomial DAE

$$
\begin{aligned}
\dot{x}(t) &= 0.7 \cdot y(t) + s(t) \\
\dot{y}(t) &= 1.4 \cdot x(t) + c(t) \\
1 &= x^2(t) + y^2(t)
\end{aligned}
$$

$$
\begin{aligned}
\dot{s}(t) &= 2.5 \cdot \dot{z}(t) \cdot c(t) \\
\dot{c}(t) &= -2.5 \cdot \dot{z}(t) \cdot s(t) \\
1 &= s^2(t) + c^2(t).
\end{aligned}
$$

Differential elimination helps integrating the DAE by computing
- the underlying ODE $\dot{z}(t) = \text{something}$
- a complete set of constraints on initial values
Synthesis

**Differential Algebra**
- 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.
Bibliography

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http://www.lifl.fr/~boulier/BLAD

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Springer-Verlag. 1996.
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 $\delta = \frac{d}{dt}$. 
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 : \( C^\infty \) + 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

$$\dot{u} \rightarrow v/\dot{v}, \quad \dot{v}^2 \rightarrow 2.$$
Regular chains permit to compute *Normal Form*

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

\[ \text{NF}(2\,\dot{u}, C) = \text{NF}(2\,v/\dot{v}, C) = v\,\dot{v} \]

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

\[ a \equiv b \mod l \text{ iff } \text{NF}(a, C) = \text{NF}(b, C). \]
\[ \text{NF}(a, C) = 0 \text{ iff } a \in l. \]
\[ \text{Every linear combination of normal forms is a normal form.} \]
Rosenfeld-Groebner (PDE)

Rosenfeld-Groebner “computes all” the integrability conditions (the coherence property of Rosenfeld and Seidenberg).

The following rewrite system C is not a regular chain.

\[ u_x \to v, \quad u_y \to 0. \]

Indeed normal forms are not unique:

\[ \text{NF}(u_{xy}, C) = v_y? = 0? \]

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

\[ u_x \to v, \quad u_y \to 0, \quad v_y \to 0. \]
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1 Index reduction
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6 Biological modeling
7 Parameters estimation
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 *Differential Algebra*

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

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

is a rational fraction such that $q$ is regular and $p/q = a$ in $R/I$. 
Non differential: $|X| = |C|$

**Point: $C$ is triangular**

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

- 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 \( T = \{t_1, \ldots, t_p\} \).

\[
\begin{align*}
f_1(x_1, T) &= 0, \\
f_2(x_2, x_1, T) &= 0, \\
&\vdots \\
f_n(x_n, \ldots, x_1, T) &= 0
\end{align*}
\]

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

\[ R = \mathbb{Q}\{U\} \text{ where } U = \{u_1, \ldots, u_n\}. \]
The \( x_i \) and \( t_j \) are derivatives of elements of \( U \).

\[ f_1(x_1, T) = 0, \quad f_2(x_2, x_1, T) = 0, \ldots, f_n(x_n, \ldots, x_1, T) = 0 \]

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) Noetherian rings.
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 Differential Ideal \([P] : M^\infty\)

F. Boulier, F. Lemaire, M. Moreno Maza
Well known theorems on triangular systems and the \(D^5\) principle
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1. Index reduction
2. Theory
3. Normal forms
4. BLAD internals
5. QSSA
6. Biological modeling
7. Parameters estimation
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

\texttt{ba0} Memory management. Parsers. Exceptions.

\texttt{bav} Variables. Rankings.

\texttt{bap} Differential polynomials. A multivariate gcd algorithm close to that of MAPLE.


\texttt{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_t alloc size pointer

12 8

0 8 12
```

- `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

- **Step 1**: current stack (free) → aux. stack (free)
- **Step 2**: temporary data record
- **Step 3**: current → current → current → aux. stack
Faugère’s mechanism

Step 1
record

Step 2

Step 3
result

stack (free)
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.

\[
A := -x^2 y + 10 x y z^2 - 3 x y + 5 x z + z^2 - 2
\]

\[
B := \text{coeff} \left( A, x, 1 \right)
\]

\[
\begin{array}{ccccccc}
-1 & 10 & -3 & 5 & 1 & -2 \\
x^2 y & xyz^2 & xy & xz & z^2 & 1
\end{array}
\]

- Clot
- First monomial
- Divide each monomial by \( x \)
- Last monomial
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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Private communication (1998)
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The principle of the QSSA

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

Assuming \( \varepsilon \) 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

\[ E + S \xrightleftharpoons[k_2]{k_1} C \xrightarrow{k_3} E + P \]

The initial ODE model:

\[
\begin{align*}
\dot{E} &= -k_1 E S + (k_2 + k_3) C, \\
\dot{S} &= -k_1 E S + k_2 C, \\
\dot{C} &= k_1 E S - (k_2 + k_3) C, \\
\dot{P} &= k_3 C.
\end{align*}
\]

The approximation, assuming \( k_1, k_2 \gg k_3 \)

\[
\dot{S} = -\frac{V_{\text{max}} S}{K + S}
\]

\( V_{\text{max}} \) and \( K \) being constants
The Henri-Michaelis-Menten approximation

\[\begin{align*}
\dot{E} &= -k_1 E S + k_2 C + k_3 C, \\
\dot{S} &= -k_1 E S + k_2 C, \\
\dot{C} &= k_1 E S - k_2 C - k_3 C, \\
\dot{P} &= k_3 C.
\end{align*}\]

Red terms are the contributions of the fast reaction.

**F. Lemaire’s DAE**

\[\begin{align*}
\dot{E} &= -F_1 + k_3 C, \\
\dot{S} &= -F_1, \\
\dot{C} &= F_1 - k_3 C, \\
\dot{P} &= k_3 C, \\
0 &= k_1 E S - k_2 C.
\end{align*}\]

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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Nonlinear model reduction of chemical reaction systems.

M. Bennet, D. Volfson, L. Tsimring, J. Hasty.
Transient Dynamics of Genetic Regulatory Networks

Model Reduction of Chemical Reaction Systems using Elimination.
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http://hal.archives-ouvertes.fr/hal-00184558
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

\[
\begin{align*}
G + P_n & \xrightarrow{\alpha} H, \\
G & \xrightarrow{\rho_f} G + M, \\
H & \xrightarrow{\rho_b} H + M, \\
M & \xrightarrow{\beta} M + P, \\
M & \xrightarrow{\delta_M} \emptyset, \\
P & \xrightarrow{\delta_P} \emptyset,
\end{align*}
\]

\[
P_i + P \xleftrightarrow{\frac{k_i^+}{k_i^-}} P_{i+1} \quad (1 \leq i \leq n - 1).
\]

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

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

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

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

- 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 \( n \geq 9 \).
G. Von Dassow, E. Meir
Exploring modularity with dynamical models of gene networks

On proving the absence of oscillations in models of genetic circuits

Towards an automated reduction method for polynomial ODE models in
cellular biology
Mathematics in Computer Science (to appear).
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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 $k_e$, $V_e$, $k_{12}$, $k_{21}$):

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

- some measures:

<table>
<thead>
<tr>
<th>$t$</th>
<th>$x_1(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000000e − 01</td>
<td>5.000000e + 01</td>
</tr>
<tr>
<td>0.500000e − 01</td>
<td>4.45078e + 01</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1.500000e + 00</td>
<td>4.95270e − 02</td>
</tr>
</tbody>
</table>

- 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 $x_1(t)$.

![Graph showing observed and simulated curves of $x_1$.]

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

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

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:

\[ k_{12} + k_{21} = \text{value}_1, \quad V_e = \text{value}_2, \quad k_{21} V_e = \text{value}_3. \]
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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Utilisation du calcul formel pour l’identifiabilité de modèles paramétriques et nouveaux algorithmes en estimation de paramètres.

F. Boulier, F. Lemaire, M. Moreno Maza.
PARDI!

System identifiability (symbolic computation) and parameter estimation (numerical computation).

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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.