

# Qualitative Analysis of Dynamical Systems: Application to Biology

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I'm working on:

- computational methods for the quantitative analysis of dynamical systems;
- their application to biological context in order to understand living organism' functioning;
- models of genetic regulatory networks based on first-order nonlinear ordinary differential equations (ODEs).

## Why computer algebra?

- Unlike numerical methods, one does not need to specify initial conditions and parameters values;
- In practice, it allows to predict qualitative behaviours for medium size systems of ODEs (see [BLLMU2007, BLSU2008] for a system of  $n + 2$  equations and  $2n + 5$  parameters)
- It relies on well-established theory: Lie algebra.



F. Boulier, M. Lefranc, F. Lemaire, and P.-E. Morant and A. Ü. *On proving the absence of oscillations in models of genetic circuits*, Algebraic Biology, 2007, 4545: 66-80, [www.lifl.fr/~urguplu](http://www.lifl.fr/~urguplu)



F. Boulier, F. Lemaire, A. Sedoglavic and A. Ü. *Towards an automated reduction method for polynomial ODE models in cellular biology* Submitted to the Journal Mathematics in Computer Science, Special Issue Symbolic Computation in Biology, 2008, [www.lifl.fr/~urguplu](http://www.lifl.fr/~urguplu)

Two Maple packages:

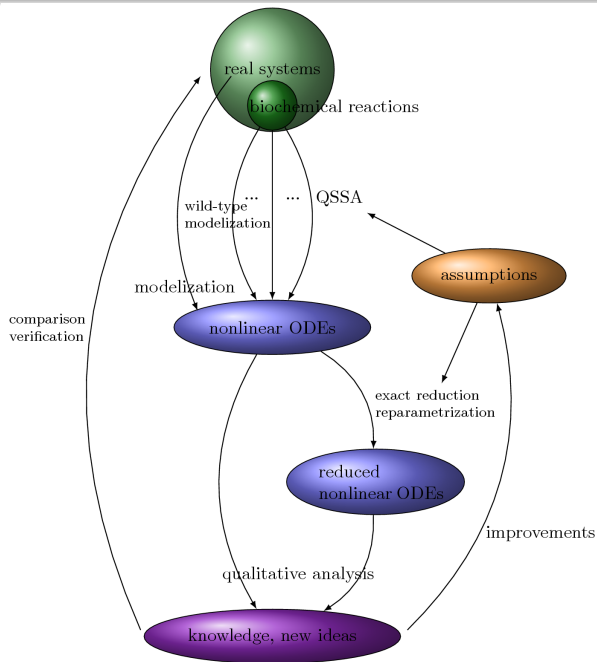
MABSys (Modelization and Analysis of Biological Systems)

- Lemaire and Ü., 2008;
- offers routines for qualitative analysis of dynamical systems, especially in the context of biochemical networks;
- uses some functionalities of `ExpandedLiePointSymmetry` package.

`ExpandedLiePointSymmetry`

- Sedoglavic and Ü., 2007;
- offers routines to “reduce” the number of parameters and/or to “reparametrize” algebraic/ordinary differential/recurrence systems by using Lie symmetries.

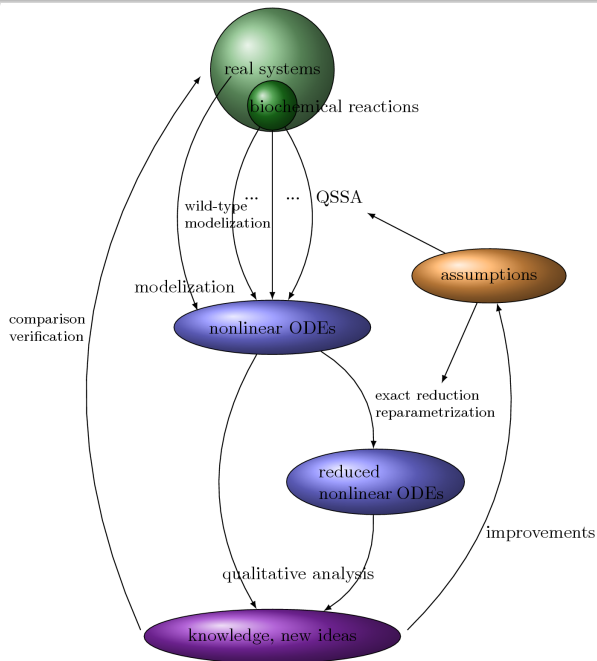
# Main Structure of MABSys



- 1 Modelization of the Network by Means of Nonlinear ODEs
- 2 Reduction and Reparametrization of the Model
- 3 Qualitative Analysis

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# MABSys - Modelization by Means of Nonlinear ODEs





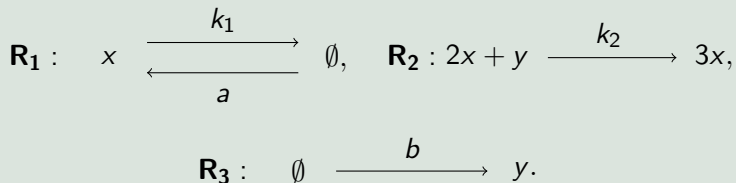
“Transformation” into a system of ODEs:

- Basic modelization (mass-action law);  
ReactionSystem20DS;
- Quasi-steady state approximation (see [BLLM2007]);  
Decreases considerably the number of ODEs;  
ModelReduce
- ...



F. Boulhier, M. Lefranc, F. Lemaire and P.-E. Morant *Model Reduction of Chemical Reaction Systems using Elimination*, MACIS, 2007,  
<http://hal.archives-ouvertes.fr/hal-00184558/fr>

## Simple Two-Species Oscillator (Schnackenberg, 1979)



## MABSys code

```

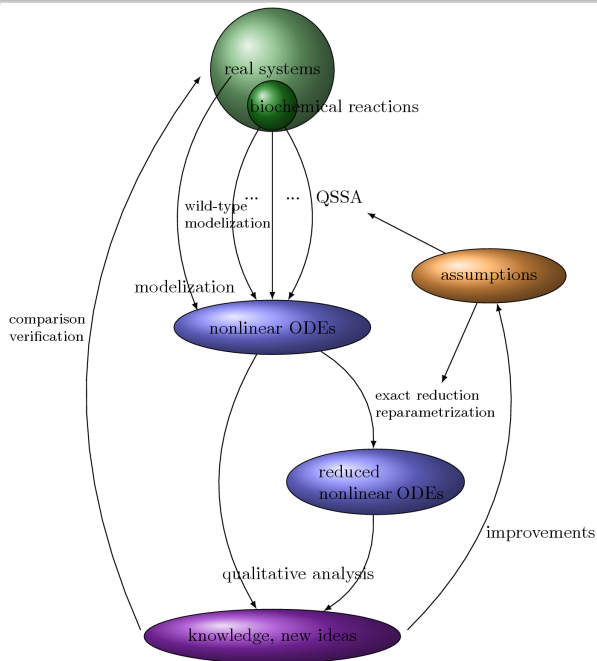
> RS := [R1,R1bis,R2,R3]:
> ODS := ReactionSystem20DS(RS, [x,y]):
    
```

## Initial model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

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# MABSys - Reduction and Reparametrization of the Model



## Initial model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

$$\begin{cases} a - k_1 x + k_2 x^2 y = 0, \\ b - k_2 x^2 y = 0, \end{cases} \quad \Rightarrow \quad \begin{cases} x = \frac{a+b}{k_1}, \\ y = \frac{b k_1^2}{k_2 (a+b)^2}. \end{cases}$$

## Initial model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

$$\begin{cases} a - k_1 x + k_2 x^2 y = 0, \\ b - k_2 x^2 y = 0, \end{cases} \quad \Rightarrow \quad \begin{cases} x = \frac{a+b}{k_1}, \\ y = \frac{b k_1^2}{k_2 (a+b)^2}. \end{cases}$$

## Reduced model

$$\frac{dx(t)}{dt} = k_1 (a - x(t) + x(t)^2 y(t)), \quad \frac{dy(t)}{dt} = \frac{k_2}{k_1^2} (1 - x(t)^2 y(t)).$$

$$\begin{cases} a - x + x^2 y = 0, \\ 1 - x^2 y = 0, \end{cases} \quad \Rightarrow \quad \begin{cases} x = a + 1, \\ y = \frac{1}{(a+1)^2}. \end{cases}$$

Goal (when it's possible):

- Decrease the number of freedom for quantitative analysis;
- Eliminate “useless” parameters;
- Reparametrize the system in order to distinguish the role of parameters:
  - the position of the fixed point;
  - the nature of fixed point.

These procedures use Lie symmetries (see `ExpandedLiePointSymmetry`).

Idea: Elimination of as many parameters as possible.

- Moving frame based exact reduction method (see [C35, OF98, OF99]);
- Lie symmetries of the associated ODEs;
- Here only scalings for positivity assumption of the parameters but may be generalized (implemented in ExpandedLiePointSymmetry package);
- Interface function in MABSys for an easier utilization: `RemoveParameterByScalings`.



E. Cartan *La Méthode du Repère Mobile, la Théorie des Groupes Continus, et les Espaces Généralisés*, 1935, Exposés de Géométrie No. 5, Hermann, Paris.



M. Fels and P. J. Olver *Moving coframes I. A practical algorithm*, 1998, Acta Appl. Math. 51: 161-213.



M. Fels and P. J. Olver *Moving coframes II. Regularization and theoretical foundations*, 1999, Acta Appl. Math. 55: 127-208.



## Initial model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

## MABSys code

```
> tmp := RemoveParameterByScalings(ODS, [b], [], false):  
> Inter_ODS := tmp[1]: ChangeOfCoord1 := tmp[2]:
```

## Intermediaire model (b is eliminated !)

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = 1 - k_2 x(t)^2 y(t).$$

## Change of Coordinates - 1

$$x = b \mathbf{x}, \quad y = b \mathbf{y}, \quad a = b \mathbf{a}, \quad k_2 = \frac{k_2}{b^2}$$

Idea: Reorganisation of the variables so that the solutions of the system of fixed points do not depend anymore on some parameters.

- Lie symmetries of the associated algebraic system (which defines fixed points);
- Here only scalings are used for positivity assumption of the parameters but may be generalized (implemented in `ExpandedLiePointSymmetry` package);

# MABSys - Reparametrization of the Model

## Intermediaire model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = 1 - k_2 x(t)^2 y(t).$$

## MABSys code

```
> tmp := CylindrifySteadyPoints(Inter_ODS, [a,k1,k2], [x,y]):  
> Reduced_ODS := tmp[1,1]; ChangeOfCoord2 := tmp[1,3];
```

## Reduced model (The fixed points depend on 1 parameter $a$ .)

$$\frac{dx(t)}{dt} = k_1 (a - x(t) + x(t)^2 y(t)), \quad \frac{dy(t)}{dt} = \frac{k_2}{k_1^2} (1 - x(t)^2 y(t)).$$

## Change of Coordinates - 2

$$x = \frac{x}{k_1}, \quad y = \frac{k_1^2 y}{k_2}$$

# Summary

## Initial model

The fixed points depend on 4 parameters.

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

## Reduced model

The fixed points depend on 1 parameter.

$$\frac{dx(t)}{dt} = k_1 (a - x(t) + x(t)^2 y(t)), \quad \frac{dy(t)}{dt} = \frac{k_2}{k_1^2} (1 - x(t)^2 y(t)).$$

## Final Change of Coordinates

```
> ChangeOfCoord := ComposeChangeOfCoord(ChangeOfCoord1,  
                                         ChangeOfCoord2);
```

$$x = \frac{bx}{k_1}, \quad y = \frac{bk_1^2 y}{k_2}, \quad a = ba, \quad k_2 = \frac{k_2}{b^2}$$

- More general Lie symmetries of the form

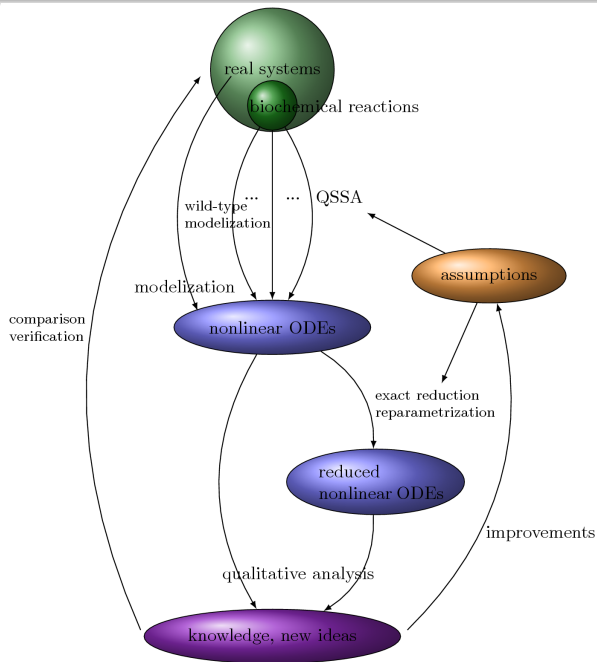
$$\delta = \sum_{i=1}^n \xi_i \frac{\partial}{\partial z_i}$$

where  $Z = (z_1, \dots, z_n)$ ,  $\xi_i \in \mathbb{Q}[Z]$  and  $\deg(\xi_i) = d$ :  $O(n^{d\omega})$ ;

- Reduction:  $O(1)$ ;
- Reparametrization:  $O(n^\omega)$ .

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# MABSys - Qualitative Analysis



### Initial model

$$\frac{dx(t)}{dt} = a - k_1 x(t) + k_2 x(t)^2 y(t), \quad \frac{dy(t)}{dt} = b - k_2 x(t)^2 y(t).$$

$$\text{Fixed point: } x = \frac{a+b}{k_1}, \quad y = \frac{b k_1^2}{k_2 (a+b)^2}$$

### Reduced model

$$\frac{dx(t)}{dt} = k_1 (\mathbf{a} - \mathbf{x}(t) + \mathbf{x}(t)^2 \mathbf{y}(t)), \quad \frac{dy(t)}{dt} = \frac{k_2}{k_1^2} (1 - \mathbf{x}(t)^2 \mathbf{y}(t)).$$

$$\text{Fixed point: } \mathbf{x} = \mathbf{a} + 1, \quad \mathbf{y} = \frac{1}{(\mathbf{a}+1)^2}$$



Necessary conditions, so that a Hopf bifurcation arises on a fixed point, are given by HopfBifurcationConditions function of MABSys (uses Routh-Hurwitz theorem):

- $k_1 = \left( \frac{k_2 (a+1)^3}{1-a} \right)^{\frac{1}{3}}$ ,
- $k_1^2 (a + 1) > 0$  (always true),
- $-k_2 k_1 (a + 1)^3 < 0$  (always true).

## How about the initial model?

One can carry on the information by the inverse of the change of coordinates:  $\mathbf{x} = \frac{x k_1}{b}$ ,  $\mathbf{y} = \frac{y k_2}{b k_1^2}$ ,  $\mathbf{a} = \frac{a}{b}$ ,  $\mathbf{k}_2 = k_2 b^2$

Hopf bifurcation conditions for the reduced and initial model:

$$\left\{ \begin{array}{l} k_1 = \left( \frac{\mathbf{k}_2 (\mathbf{a} + 1)^3}{1 - \mathbf{a}} \right)^{\frac{1}{3}} \\ k_1^2 (\mathbf{a} + 1) > 0 \\ -\mathbf{k}_2 k_1 (\mathbf{a} + 1)^3 < 0 \end{array} \right. \rightsquigarrow \left\{ \begin{array}{l} k_1 = \left( \frac{k_2 (a+b)^3}{b-a} \right)^{\frac{1}{3}} \\ \frac{k_1^2 (a+b)}{b} > 0 \\ -\frac{k_2 k_1 (a+b)^3}{b} < 0 \end{array} \right.$$

- Generalization of the reduction and the reparametrization method with more complicated Lie symmetries.
- Finding the most appropriate **modelization and simplification** automatically for qualitative analysis of the biochemical networks.
- New algorithms ?
- Improvement of Maple packages MABSys and ExpandedLiePointSymmetry.

Thank you !

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