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ON THE ROLE OF DIFFERENTIAL ALGEBRA IN BIOLOGICAL MODELING

FRANÇOIS BOULIER

Differential algebra is an algebraic theory for studying systems of polynomial ordinary differential equations (ODE). Among all the methods developed for system modeling in cellular biology, it is particularly related to the well-established approach based on nonlinear ODE. A subtheory of the differential algebra, the differential elimination, has proved to be useful in the parameters estimation problem. It seems however still more promising in the quasi-steady state approximation theory, recent results show.

1. Background

Differential algebra [15, 19] is an algebraic theory for studying systems of polynomial ordinary differential equations (ODE). Among all the methods developed for system modeling in cellular biology, it is particularly related to the well-established approach based on nonlinear differential equations [10, 16]. A very classical way for deriving a system of polynomial ODE from a genetic circuit consists in first, translating the circuit as a system of generalized chemical reactions, second translating the chemical system as a system of polynomial ODE by means of the mass-action law.

The parametric ODE systems derived from these generalized chemical reaction systems are often too complicated for further analysis and need to be

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reduced. They are often overparameterized, which makes fitting methods to determine the parameters values heavy to carry out and unreliable: the parameters values which reproduce a behaviour of interest are usually far from unique. See the impressive analysis of [23] about their own outstanding work on the Segment Polarity Network. Moreover, the large number of parameters and variables makes their qualitative analysis difficult to achieve: many important dynamical properties of polynomial ODE systems do not depend on precise values of the parameters [11]. Discussing the presence of these properties in terms of the parameters values becomes dramatically difficult as the number of parameters and variables increases.

For the important purpose of understanding which parts of the system contribute the most to some property of interest [14], it is preferable to deal with smaller systems. More conceptually, reducing the size of a model is one way to achieve the important goal: a model should not involve more information than the biological data it comes from.

2. Applications to the model reduction problem

The model reduction problem is well-known in biological modeling. Though not formulated in these terms, all the approaches listed in [11] address this issue. Even in the particular case of polynomial ODE models derived from generalized chemical reactions systems, many methods [18] exist (lumpings, sensitivity analysis, multiple time-scales analysis, ...).

Among all these ones, the quasi-steady state approximation (QSSA) theory relies on the assumption that some of the chemical reactions are much faster than the other ones. The idea of quasi-steady state approximation is simple: study the dynamics of the slow reactions, assuming that the fast ones are at quasi-equilibrium, thereby removing from the ODE system, the differential equations which describe the evolution of the variables at quasi-equilibrium. Quasi-steady state approximation has two advantages:

1. it reduces the number of ODE occuring in the system under study ;
2. it transforms stiff ODE systems as nonstiff ones.

It was extensively studied [18, 22, 24] and references therein. All these approaches turn out to be equivalent. All amount to a two time-scales analysis. None of them is formulated in algorithmic terms.

The differential algebra [15, 19] theory makes the quasi-steady state approximation algorithmic, in the particular setting of ODE systems derived from generalized chemical reactions systems, as shown for the first time by [6]. Observe that, for general systems of ODE, the QSSA is not algorithmic. The

method over which this new algorithm relies is the differential elimination theory [4, 5, 13, 21], pioneered by Prof. G. Carrà-Ferro [9]. After the quasi-steady state approximation step, the reduced model is still overparameterized (it is a raw reduced model). The differential algebra theory then permits to reduce the set of parameters of the raw reduced model, leading to a reduced model. This exact simplification can be algorithmically performed by determining Lie symmetries of the system [20].

The sketched above method (model reduction by QSSA followed by reduction of the parameter set) was recently applied over a family of models [7, 8], giving conditions for the presence of oscillations.

3. Applications to the optimisation theory

Differential elimination helps solving the following problem [2, 3, 17]: given a parametric ODE system and experimental data for *some* of the variables, how to estimate the parameters values ?

The idea consists in eliminating the variables for which no experimental data are available (non observed variables) then in applying linear least squares to compute a first estimate of the observed variables. This first estimate can be used as a starting point for a nonlinear least squares methods such as the Levenberg-Marquardt algorithm [12]. The first estimate is usually not very precise because it requires the numerical computation of derivatives of the observed variables from the experimental data.

Put in a nutshell, differential elimination transforms nonlinear least squares problems into linear ones. It is not practical in cellular biology because it requires too accurate experimental data. However, whenever it applies, it improves the classical Newton-like methods by guessing a starting point.

In the particular case of generalized chemical reactions systems, another improvement can be imagined using the algorithm obtained in the quasi-steady state approximation theory. In the nonlinear fitting methods, the parameters are the variables. The sets of large and small parameters have to change during the process. Because of these changes of parameters, the ODE systems to numerically integrate, in order to compute the error, often get stiff at runtime: stiffness is often caused by the presence of different time scales in the ODE systems. Stiffness considerably slows down the whole optimisation problem. The algorithm for performing the quasi-steady state approximation could then be applied in order to replace at runtime the stiff ODE systems by nonstiff ones. The error computation of the nonlinear fitting methods could then be performed over the reduced system, speeding up the overall process.

4. Conclusion

Differential algebra has indeed a role to play for system modeling in cellular biology. However, this role is local: differential algebra tools must be used in connection with many other tools. This motivates the development of standalone, easy to plug-in software. The BLAD libraries [1], developed by the author, are an attempt in that direction.

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