Abstract

Treating a realistic problem in any field of reaction kinetics raises a series of problems: we review these illustrated with examples using ReactionKinetics, a Mathematica based package.

Keywords: kinetics, numerical analysis, simulation, parameter identification, decomposition of overall reactions, combustion

1. Introduction

In Part I of our paper Tóth et al. [2011] we have formulated the requirements for a reaction kinetics package to be useful for a wide circle of users.

In the present Part II we enumerate the major problems arising when writing and using such a package. It turns out that the solution of some problems is far from being trivial.

2. Parsing

As we mentioned in the first part of our paper, at the very beginning of application of computers to chemical kinetics the problem arouse how to construct the induced kinetic differential equation of a reaction without making to much errors. The best thing is if the chemist provides the reaction steps, and the program creates the induced kinetic differential equations automatically, if the kinetics is supposed to be of the mass action type. If it is not then reaction rates should also be provided by the user.

As our program is based on a modern mathematical program package (often called by the misnomer computer algebra system) there is no limitation as to the size of the reaction to be handled, see the Lendvay example in our previous paper. Confer this with the quite typical restriction "...has the capabilities for handling up to 590 differential equations."

It may be instructive to cite the code building the right hand side of the induced kinetic differential equation of the reaction (note that reversibility is not assumed)

$$\sum_{m=1}^{M} \alpha(m, r)X(m) \xrightarrow{k_r} \sum_{m=1}^{M} \beta(m, r)X(m) \quad (r = 1, 2, \ldots, R)$$

given the matrices ($\alpha, \beta$) of molecularities, the vector of reaction rate coefficients ($k = (k_r)_{r=1}^R$) and the concentration vector ($c$) the right-hand side of the kinetic ODE gets an exceedingly transparent form (in coding as well):

$$(\beta - \alpha). (k \text{ Times} @@ c^\alpha),$$

where notice that both dot and componentwise products are...
used. The reaction step vector \( \gamma(\cdot, r) \), where \( \gamma = \beta - \alpha \) expresses as the effect of the \( r^{th} \) reaction step.

3. Combinatorics

In reaction kinetics graphs of many types are useful and used, though it is not quite obvious how to visualize them to be the most informative for users, especially concerning to large mechanisms. Hence we accept the representations offered by Mathematica.

The Volpert graph is one of the widely applied graphs in reaction kinetics which proved to be a good tool to investigate problems emerging e.g. in the theory of kinetic ordinary differential equations. It is a directed bipartite graph with species and reaction steps as its vertices and with \( \alpha(m, r) \) edges from the vertex representing species \( X(m) \) into the vertex representing reaction step \( r \) and with \( \beta(m, r) \) edges from the vertex representing reaction step \( r \), into the vertex representing species \( X(m) \) [Erdi and Tóth, 1989]. At the same time this is the graph one can see in textbooks on biochemistry, in metabolic maps or at MaCKiE Workshops. Without any additional advantage they can also be called Petri nets [Martínez and Silva, 1982]. A model of glycolysis is a built-in reaction of our program package therefore having got it we can easily draw its Volpert graph which turns out to be not so much different from the one used in textbooks on biochemistry (see Figure 3).

4. Linear (Diophantine) equations

Complex reactions occur via pathways of simple “elementary” reaction steps. It is a common problem that the overall (or global) reaction is measured, and one would like to reconstruct the underlying network of simple reaction steps. By simple here one may mean reaction steps of order not higher than two. Let us consider an example [Kovács et al., 2004]. We start form the overall description of the permanganate/oxalate reaction

\[
2\text{MnO}^{4-} + 6\text{H}^+ + 5\text{C}_2\text{H}_2\text{O}_4 \rightleftharpoons 2\text{Mn}^{2+} + 8\text{H}_2\text{O} + 10\text{CO}_2.
\]

The following steps lead to its the decompositions to elementary steps:

![Volpert graph or Petri net](image-url)
To generate all combinatorially feasible elementary reactions,

$$\text{H}_2\text{C}_2\text{O}_4 \quad \text{HC}_2\text{O}_4^- \quad \text{H}^+ \quad \text{C}_2\text{O}_4^{2-} \quad \text{Mn}^{2+} \quad \text{MnC}_2\text{O}_4^-$$

$$\text{MnO}_4^- \quad \text{MnO}_2^- \quad \text{Mn}^{3+} \quad \text{CO}_2 \quad \text{H}_2\text{O} \quad \text{CO}_3^{2-}$$

$$[\text{MnO}_4^-, \text{H}_2\text{C}_2\text{O}_4^-] \quad [\text{Mn}^{3+}, \text{HC}_2\text{O}_4^-] \quad [\text{MnC}_2\text{O}_4^-, \text{Mn}^{2+} \text{C}_2\text{O}_4^-]$$

Table 1: Species of the permanganate/oxalic acid reaction according to Kovács et al. [2004]. Species with initially positive concentration are typeset bold.

| Position | Species |
|----------|---------|
| 1 | $\text{H}_2\text{C}_2\text{O}_4$ |
| 2 | $\text{HC}_2\text{O}_4^-$ |
| 3 | $\text{H}^+$ |
| 4 | $\text{C}_2\text{O}_4^{2-}$ |
| 5 | $\text{Mn}^{2+}$ |
| 6 | $\text{MnC}_2\text{O}_4^-$ |
| 7 | $\text{MnO}_4^-$ |
| 8 | $\text{MnO}_2^-$ |
| 9 | $\text{Mn}^{3+}$ |
| 10 | $\text{CO}_2$ |
| 11 | $\text{H}_2\text{O}$ |
| 12 | $\text{CO}_3^{2-}$ |

1. determine the combinatorially possible species and select from those the chemically acceptable ones,

2. determine the combinatorially possible reaction steps which are simple in the above sense and select from those the chemically acceptable ones,

3. find those representations of the given overall reaction which are chemically acceptable.

As we have seen in Part I of our paper, the second and third steps reduce to the solution of linear Diophantine equations. The authors of Kovács et al. [2004] worked with 19 species, including four hypothetical transient species, made up of four atomic constituents (and charge); these are listed in Table 1. The corresponding atomic matrix (see part I) is a $5 \times 19$ matrix.

To generate all combinatorially feasible elementary reactions, $2 \cdot 19 + \binom{19}{3} = 209$ systems need to be solved. The results give 1022 combinatorially feasible elementary steps. Based on chemical evidence a large number of them were eliminated, leaving 673 elementary reactions.

The same computational results were reproduced in Papp and Vizvári [2006], where further combinatorial analysis revealed that only 297 of the previously generated elementary reactions may be part of decompositions, and that 3 of the species cannot be generated during the reaction. This analysis takes into account which five species are present initially in the reaction (based on experiments), and is an adaptation of the indexing process by Volpert [1972]. It is perhaps worth mentioning that the result (in this specific example) is not sensitive to the assumption on the initial species; the same elementary steps and species remain if every non-complex species is assumed to be present initially in the vessel.

Decompositions of the overall reaction can be obtained via the solution of another linear Diophantine system of equations. With the above analysis the dimensions of this system are reduced to $16 \times 297$. The generation of decompositions can be further accelerated by preprocessing: simple analysis, using linear programming, shows that every decomposition consists of at least 15 steps, and that two elementary steps take part in every decomposition, one of them with a coefficient of at least four. After this preprocessing, it is possible to find all decompositions of 15–17 steps, and thousands of more complex decompositions, from which chemically acceptable ones can be selected.

We refer the reader to the two papers cited above for details of these computations, and a review of a number of algorithms for the solution of linear Diophantine equations. All of these algorithms and the various methods of combinatorial analysis mentioned above are now built in to our program.

5. Numerics

5.1. Stiffness

One of the major problems when solving initial value problems describing chemical reactions is—as in general—stiffness: the situation when the reaction proceeds along more than one time scales, reaction rates of different steps are of different magnitude. Then the codes meet the dilemma: if they choose a small step size, then the numerical solution will need much time, if they take a too long step size, then interesting phenomena occurring in the time evolution of the fast species will be lost. Starting with Gear [1992] and Butcher [1990], many methods fulfilling the requirements of the chemist have been elaborated and built in into program packages. The following example show that such an insertion has been carried out especially successfully in the case of Mathematica.

The Robertson problem [Robertson, 1966]

$$A \xrightarrow{0.04} B, \quad 2B \xrightarrow{3 \times 10^7} C, \quad B + C \xrightarrow{10^9} A + C$$
Figure 2: The Volpert graph of the Robertson model

is a popular benchmark problem of stiff type, because there is a nine order of magnitude difference between the reaction rate coefficients. To make matters worse, the solution is required on the time interval $[0, 10^{11}]$. Figure 5.1 shows its Volpert graph.

No matter what the values of the reaction rate coefficients are, the derivatives of the concentrations sum up to zero, meaning that total mass is conserved. One way to verify this fact is to execute the following:

$$\text{Total[RightHandSide["Robertson", k_1, k_2, k_3]]},$$

which gives 0, cf. [?]. The concentrations are calculated numerically as simply as usual (with our built-in function `Concentrations`):

$$\text{Concentrations[{"Robertson"}, {0.04, 3 \times 10^7, 10^4}, {1, 0, 0}, {0, 10^{11}}]}$$

Also the numerical method is good enough to conserve mass (Figure 5.1).

Let us see the individual concentrations of species A and C using the logarithmic time scale (Figure 5.1). But what about the species B? See Figure 5.1.

One of our colleagues, Dr. R. Horváth, was so kind as to solve the same problem using MATLAB; the same results were obtained within the same CPU time, but much less automatically.

Finally, we remark that a symbolic approach to unveil stiffness when it does not manifest itself on the surface has been given by Prof. Goldshtein at the conference, and see also [Bykov et al., 2008].

Figure 3: The total mass in the Robertson model

Figure 4: Species A and C in the Robertson model

5.2. Bifurcations

A usual method to show that oscillatory solutions exist in the induced kinetic differential equation of a reaction is to apply the well-known Andronov–Hopf bifurcation theorem. Visualizing
The quantity of the intermediate \( b \) is so small that we were unable to see it in the previous figures.

Figure 5: Species B in the Robertson model

the effect of the change of the parameters is really simple using the `Manipulate` command of *Mathematica* see also the last example in the first part of our paper. If you are interested how easily this can be done you might have a look at the demonstration by Váradi and Tóth. In fact the method used there is based on particular ideas and has not as yet been built in into our program package handling general models.

6. Symbolic methods

Symbolic solutions are easier to find nowadays, still it is a hard problem even in the case of stationary points, see our previous paper. The most interesting developments are expected in these fields, e.g. how to find automatically the equivalence (of some kind) of different kinetic models [Mendez and Femat, 2011], how to show the possibility or impossibility of transforming one dynamics into another by (say, orthogonal) transformations [Tóth and Hárás, 1986a] using perhaps the theory of algebraic invariants of differential equations [Halschlag et al., 2004], how to find a minimal model with given properties within a class of reactions [Wilhelm, 2009; Tóth and Hárás, 1986b], given an induced kinetic differential equation how to find a reaction with a given structure [Szederkényi, 2010; Szederkényi and Hangos, 2011], etc.

7. Stochastic simulation

In reaction kinetics, it has always been obvious from the theoretical point of view that in the case of small systems (see e.g. Arányi and Tóth [1977]), and systems operating around an unstable stationary state (e.g. models of chirality, see e.g. Barabás et al. [2010]) are better described with the standard continuous time discrete state stochastic model of chemical reactions, see e. g. [Érdi and Tóth, 1989, Chaptr 5]. However, it turned out to be much more relevant only recently as with the development of analytical techniques it became possible to measure individual molecules. That is the reason why simulation of the stochastic model forms a relevant part of our program package.

Here we are considering only the usual continuous time discrete state model which is a Markovian jump process. Denote by \( \mathbf{X}(t) \) the number of species present in the system at time \( t \). Now, our investigated process is defined to evolve in time so that the law

\[
P(R_t \text{ takes place in } [t, t+h) | \mathbf{X}(t)) = \kappa_r(\mathbf{X}(t)) h + \epsilon(h) h \quad (1)
\]

is fulfilled where \( \epsilon(h) \to 0 \) if \( h \to 0 \) and \( \kappa_j \)'s (\( r = 1, 2, \ldots, R \)) are a kind of combinatorial functions of the vector of numbers of species similar to but slightly different from the product of powers (Kurtz kinetics) involving also the reaction rate coefficients. From this assumption one can easily determine the infinitesimal generator of this Markov process from which the Kolmogorov forward and backward equations as well as the master equation are obtained. However, our formulation is equivalent to the following explicit representation:

\[
\mathbf{X}(t) = \mathbf{X}(0) + \sum_{r=1}^R Z_r \left( \int_0^t \kappa_r(\mathbf{X}(s)) \, ds \right) \gamma(\cdot, r) \quad (2)
\]

where the \( Z_r \)'s are independent, unit-rate Poisson processes. Note that there are many known stochastic simulation algorithms for the presented problem, but we intend to summarize only a few of them, namely: the direct method [Sipos et al., 1974a,b]: let \( \mathbf{X}(x) := \sum_{r=1}^R k_r(x) \) and suppose \( T > 0 \) is given, then the initialization step is: \( \mathbf{x}(0) := \mathbf{x}_0 \in \mathbb{R}^M, t := 0 \) then the algorithm works as follows:
While \([t < T]\),
\[\gamma := \text{RandomChoice}[\{\frac{r_i}{\sum r_i}; r = 1, 2, \ldots, R\} \rightarrow \{R_i; r = 1, 2, \ldots, R\}];\]
\[s := \text{RandomVariate}[\text{ExponentialDistribution}[r(t)]];\]
\[x(t + s) := x(t) + \gamma; t = t + s\]

Notice that the idea of the direct method relies on the definition \([1]\). Also there exists several variants (e.g. first reaction method) and improvements of this early method (see e.g. Gibson and Bruck [2000]). In what follows we briefly present the approximation methods, which have their roots in formula \([2]\). At the heart of these kinds of methods is the leap condition, that is choose \(\tau\) to be small enough so that the change in the state in \([t, t + \tau]\) causes no relevant change for the \(k_i's\).

Again, the initialization step is \(x(0) := x_0 \in \mathbb{R}^M, t := 0\) then the algorithm works as follows:

While \([t < T]\),

Choose \(\tau\) so as to satisfy the leap condition;

Do[\(p_r := \text{RandomVariate}[\text{PoissonDistribution}[k_r(x(t)) \tau], \{r, 1, R\}];\),
\(x(t + s) := x(t) + \sum_{r=1}^{R} P_r(x(t), x(t + \tau), p_r);\),
\(t = t + \tau\]

- If we take \(P_r(x(t), x(t + \tau), p_r) := p_r\), then we get the explicit \(\tau\)-leaping method.
- If \(P_r(x(t), x(t + \tau), p_r) := p_r - \sum_{r=1}^{R} k_r(x(t)) + k_r(x(t + \tau))\), we are led to the implicit \(\tau\)-leaping method.
- If we set \(P_r(x(t), x(t + \tau), p_r) := p_r - \frac{1}{\tau}k_r(x(t)) + \frac{1}{2}k_r(x(t + \tau))\) then what we get is the trapezoidal \(\tau\)-leaping method (Cao and Petzold [2005]; Rathinam et al. [2003]).

However, these methods may also be considered as the stochastic analogues of certain numerical schemes applied for ordinary differential equations. Choosing the appropriate \(\tau\) has turned out to be a non-trivial task. It is also a challenging problem to avoid negative population for \(x(t)\) in the simulation process, see Cao et al. [2005]. Especially these last methods are used to handle stiff problems, where typically implicit approaches give the most appropriate results. These and several other algorithms have also been implemented into our program package. We also included conversion of units functions which provide an elegant way to compare the solution of the induced kinetic differential equation with the results of the stochastic simulation process which is considered to be taking place in a certain volume. In Figure 7, we can see this comparison on the example of Brusselator model:

\[
A \overset{k_1}{\rightarrow} X, X \overset{k_2}{\rightarrow} Y, 2X + Y \overset{k_3}{\rightarrow} 3X, X \overset{k_4}{\rightarrow} P
\]

where A and P are external species.

![Figure 6: Stochastic Brusselator model is considered with reaction rate coefficients: k_1 = 1.92, k_2 = 5.76, k_3 = 5.6, k_4 = 4.8 and initial conditions x_0 = 500, y_0 = 720. The "noisy" curve describes the evolution of the stochastic model, where the volume is 10^{-21} \text{dm}^3.](image)

In Figure 7, one can see the behaviour of the Autocatalator model:

\[
A \overset{k_1}{\rightarrow} X, X \overset{k_2}{\rightarrow} Y, X + 2Y \overset{k_3}{\rightarrow} 3Y, Y \overset{k_4}{\rightarrow} P,
\]

where again A and P are external species.
Then, the model needed by the function FindFit

\[
\text{FindFit}[\text{data, model}[a, b][x], \\
\{a, 0.7\}, \{b, 0.2\}, x]
\]

is defined in the following way.

\[
\text{model}[a, b] := (\text{model}[a, b] = \text{First}[x /.
\text{NDSolve}[x'[t] == b x[t] - a x[t]^2, x[0] == 2], \\
x, \{t, \text{end}\}])
\]

As a result we get \((0.344129, 0.75174)\) instead of \((0.33, 0.72)\), not a bad result, but certainly this is only a toy example. The agreement between the “measurements” and the fitted model is quite good, see Figure 8. A systematic investigation of similar (and further) estimation procedures for more complicated models is in progress.

We also mention that a method similar to simulated annealing applied to the determination of Arrhenius parameters of reaction rate coefficients has also been elaborated \cite{Nagy et al., 2011}.

8.2. Based on the stochastic model

Based on the stochastic model one can obtain estimates in different ways. If we are able to collect data on the individual changes of the molecules what is not so impossible in these days, then we can have maximum likelihood estimates. What is more even equilibrium fluctuations might be enough to estimate the parameters. \cite[Subsection 5.8.7]{Erdi and Toth, 1989}. 

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Figure 7: Stochastic Autocatalator model with reaction rate coefficients: \(k_1 = 110.2, k_2 = 0.094, k_3 = 0.011, k_4 = 90.34\), where the initial conditions \(x_0 = 15, y_0 = 80\) were considered.

8. Estimation methods

8.1. Based on the deterministic model

Estimating the reaction rate coefficients (or even the Arrhenius parameters \(k_0, n\) and \(A\) in the formula

\[
k(T) = k_0 T^n \exp(-A/(RT)),
\]

see \cite{Nagy and T., 2011}) based on measurements is a kind of art. Here we only make a few remarks.

First of all, *Mathematica* gives the possibility to obtain estimates (seemingly) without any kind of iteration: it is capable using the numerical solution of a differential equation in the same way as an explicitly given function. Let us start from the deterministic model of the reaction

\[
2X \xrightarrow{k_1} k_2 X,
\]

where \(k_1 = 0.33\) and \(k_2 = 0.72\) with the following initial concentration of \(X\): \(x(0) = 2\). Let us generate experimental data from the numerical solution and add a small amount of error.

\[
\text{end} = 7; \text{sol} = \text{First}[x /.
\text{NDSolve}[x'[t] == -0.33 x[t]^2 + 0.72 x[t], \\
x[0] == 2, x, \{t, \text{end}\}]]; \\
\text{times} = \text{N}[	ext{Range}[0, 5 \text{ end}]/5]; \\
\text{data} = \text{Transpose}[\{\text{times}, \text{sol}[\text{times}] + \\
\text{RandomReal}[.01, 5 \text{ end} + 1]\}];
\]

No worse fitting ever!

Figure 8: Fitted model and data
Another approach is to use a kind of implicit linear regression: \cite{Hangos2018}. Methods elaborated to estimate parameters of mass communication can also be adapted to the goals of reaction kinetics, see \cite{Kovacs2022}.

9. Visualization

No external package is needed to provide camera ready figures for papers in any of the following forms: eps, jpg, pdf, bmp, gif, wmf etc. (see a delicate example on Figure 9).

![Figure 9: The deterministic Brusselator model plotting in 2D using Manipulate in which one can change the initial conditions in real time (using the “locator” object)](image)

10. Discussion, further plans

We allow non mass action type kinetics even now, therefore it does not seem to be a hard task to include temperature dependence, so important in the case of modelling e.g. atmospheric chemistry and combustion. Surely, reaction diffusion equations should also be treated in full generality including symbolic treatment, as well. The reduction of the number of variables is also a very important topic, see e.g. \cite{Toth1997}.

Finally, please visit the website: \url{demonstrations.wolfram.com} and look for the demonstrations of Attila László Nagy and Judit Várdai.

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