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AN APPROACH TO COMPUTER-AIDED DESIGN: A TOOL FOR MATHEMATICAL MODELLING IN BIOLOGY AND ECOLOGY

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Abstract—A matricial formulation of like chemical systems is proposed. This representation permits us to draw up easily a generation algorithm of rate equation, and reversively an algorithm which gives, if it is possible, a descriptive chemical system from a set of differential equations. The problem of numerical simulation is also studied. All these levels have been integrated in a general computer program which can be considered as a tool for modelling. A biological example illustrates the use of this program in the study of a model: the evolution of RNA in the silkgland of the silkworm.

Algorithm Chemical reactions Computer-aided design Ecology Enzymes Models Simulation

INTRODUCTION

Kinetics analysis of chemical systems can be considered as a particular case of systems analysis. With extensions, analogue studies have a great interest in other fields than chemistry, such as biochemistry, molecular biology (for example: compartmental models), and ecology (determinist models of populations dynamics; Garfinkel [5], and Lotka [9]). we call these types of systems: "like chemical systems".

Mathematical kinetics models of chemical systems are obtained from hypotheses derived from general theories. We assume that like chemical systems can be analysed in the same way, with eventually complementary hypotheses. We are interested in the set of hypotheses which permits mathematical modelling in terms of differential equations.

However, before modelling, a particular system must be described specifically. This description (i.e. list of particles of the system, interaction between particles, etc) can be made discursively or formally. In fact, it is well known that for this purpose chemists use a symbolic language which facilitates the derivation of the associated mathematical model [7, 12]†. Such a description may be seen as a complementary set of hypotheses applied in a particular case. Consequently we consider that a formal description is also a *model* of the studied system. The problem of modelling thus takes on two complementary aspects:

(i). That of a formal description with a goal of finding the mathematical model of a system. This corresponds to the translation problem of a phrase of a symbolic language in a mathematical expression‡. This translation makes possible the numerical simulation of the system, and the comparison with experimental data (by using an optimisation method for the estimation of model parameters).

(ii). In some cases, it is possible to infer directly a mathematical model. So one may be asked: if we assume true the general hypothesis of kinetics of like chemical systems, is it possible to find a formal description of the system studied?

This first aspect has appeared in the literature: see Garfinkel [5–7]. To our knowledge a solution for the second one has not appeared. The present parallel approach to the

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† This formal description approach can be used in other fields of system analysis.

‡ Eventually if the usual form of the mathematical expression is not necessary, it can be obtained in a convenient form for computing (for example, post-fixed form).

two problems permits a new and simple formulation. In fact, it becomes possible with such an approach to work at three interdependent levels:

(i). Conceptualisation of the system (formal description) directly, or solution of a mathematical model.

(ii). The mathematical model itself possibly obtained from a previous formal description.

(iii). Numerical simulation.

These levels have been integrated in a study using a computer as a modelling aid.

MATRICIAL EXPRESSION OF LIKE CHEMICAL SYSTEMS

Using chemists' formalism, we can consider that the general representation of like chemical systems is the following:

$$\begin{array}{l} n_{11}X^{(g)}_{11} + \cdots + n_{1g_1}X^{(g)}_{1g_1} \xrightarrow{k_1} m_{11}X^{(d)}_{11} + \cdots + m_{1d_1}X^{(d)}_{1d_1} \\ \vdots \\ n_{21}X^{(g)}_{21} + \cdots + n_{2g_2}X^{(g)}_{2g_2} \xrightarrow{k_2} m_{i1}X^{(d)}_{i1} + \cdots + m_{2d_2}X^{(d)}_{2d_2} \\ \vdots \\ n_{i1}X^{(g)}_{i1} + \cdots + n_{ig_i}X^{(g)}_{ig_i} \xrightarrow{k_i} m_{i1}X^{(d)}_{i1} + \cdots + m_{id_i}X^{(d)}_{id_i} \\ \vdots \\ n_{r1}X^{(g)}_{r1} + \cdots + n_{rg_r}X^{(g)}_{rg_r} \xrightarrow{k_r} m_{r1}X^{(d)}_{r1} + \cdots + m_{rd_r}X^{(d)}_{rd_r}. \end{array} \tag{1}$$

$X^{(g)}_{ij}$ is the species of particles in the left hand side of the i^{th} reaction ($1 \leqslant i \leqslant r$, $1 \leqslant j \leqslant g_r$)

$X^{(d)}_{ij}$ is the species of particles in the right hand side of the i^{th} reaction ($1 \leqslant i \leqslant r$, $1 \leqslant j \leqslant d_r$).

n_{ij}, a positive integer, is the number of particles of species X_{ij} in the right hand side of the i^{th} reaction.

m_{ij}, also a positive integer, is the number of particles of species X_{ij} in the left hand side of the i^{th} reaction.

The X_{ij} terms are not all necessarily different (generally not).

A "reversible" reaction can be represented as two parallel reactions where the left hand member of the first one becomes the right hand member of the second one and vice versa.

Now, consider the vector of all differents names (i.e. different species) in the system:

$$X = \begin{bmatrix} X_1 \\ \vdots \\ X_j \\ \vdots \\ X_q \end{bmatrix},$$

and the matrix

$$D_g = \begin{bmatrix} n_{11} \ldots n_{1j} \ldots n_{1q} \\ \vdots \quad\quad \vdots \quad\quad \vdots \\ n_{i1} \ldots n_{ij} \ldots n_{iq} \\ \vdots \quad\quad \vdots \quad\quad \vdots \\ n_{r1} \ldots n_{rj} \ldots n_{rq} \end{bmatrix} = \|n_{ij}\|.$$

Where n_{ij} is a positive integer if X_j is present in the left hand of the i^{th} reaction, or 0 if X_j is absent.

With the rule

$$s_{ij} ::= \text{if } n_{ij} \neq 0 \text{ then } n_{ij} \times X_j \text{ else } \lambda. \tag{2}$$

Where λ is the empty string.

The left hand term of system (1) can be denoted as a matricial product on strings, applying the rule (2):

$$R_g = D_g . X, \tag{3}$$

where $D_g = \|n_{ij}\|$, and by adding between all the non-empty strings s_{ij} the separator $+$. For the right hand terms, we have the same result:

$$R_d = D_d . X \tag{4}$$

where $D_d = \|m_{ij}\|$, if

$$K = \begin{bmatrix} K_1 \\ \vdots \\ K_i \\ \vdots \\ K_r \end{bmatrix},$$

is the vector of the rate constants of the reactions, then the system (1) can be denoted, using a matricial representation:

$$D_g X \xrightarrow{K} D_d X \tag{5}$$

example:

Consider the system

$$\begin{aligned} A + 2B &\xrightarrow{k_1} C \\ A + D &\xrightarrow{k_2} E \end{aligned} \tag{6}$$

then

$$X = \begin{bmatrix} A \\ B \\ C \\ D \\ E \end{bmatrix}; \quad K = \begin{bmatrix} k_1 \\ k_2 \end{bmatrix}$$

$$D_g = \begin{bmatrix} 1 & 2 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 \end{bmatrix} \quad \text{and} \quad D_d = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

HYPOTHESIS, MATRICIAL EXPRESSION OF A DIFFERENTIAL SYSTEM RELATED TO A LIKE CHEMICAL SYSTEM

We use the results of chemical kinetics theory (essentially the Van't Hoff rule, and theory of molecular shocks). These results are very general and can be applied to many systems which consider populations of particles, such as bacterial populations and some animal populations, particularly if we accept "autoreproduction" of particles: (Garfinkel [5, 7]).

General hypothesis

One can formalize the results of chemical kinetics theory as follows:

(i). Consider the elementary reaction

$$n_1X_1^{(g)} + \cdots + n_pX_p^{(g)} \xrightarrow{k} m_1X_1^{(d)} + \cdots + m_{p'}X_{p'}^{(d)}$$

We are interested in the variation of concentration (or number of particles) of the "compounds" $X_1^{(g)}, \ldots, X_{p'}^{(d)}$. To simplify, we use the same notation for the name of the compound and the quantities related to it (concentration, number of particles . . .)*

(ii). The rate of the reaction can be denoted:

$$V = k \times X_1^{(g)} \uparrow n_1 \times X_2^{(g)} \uparrow n_2 \times \cdots \times X_p^{(g)} \uparrow n_p. \tag{7}$$

To clarify the notation we have used the following symbols: ↑ for the exponentiation; × for the multiplication.

(iii). The rates of variation of related quantities (concentrations, numbers of particles . . .) are:

$$-\frac{1}{n_1}\frac{\mathrm{d}X_1^{(g)}}{\mathrm{d}t} = \cdots = -\frac{1}{n_p}\frac{\mathrm{d}X_p^{(g)}}{\mathrm{d}t} = \frac{1}{m_1}\frac{\mathrm{d}X_1^{(d)}}{\mathrm{d}t} = \cdots = \frac{1}{m_{p'}}\frac{\mathrm{d}X_{p'}^{(d)}}{\mathrm{d}t} = V. \tag{8}$$

(iv). If a compound X_i is present on both sides of the reaction then

$$V = \frac{1}{m_i - n_i}\frac{\mathrm{d}X_i}{\mathrm{d}t},$$

or

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = (m_i - n_i) \times V. \tag{9}$$

If X_i is absent on the right (or left) side of the reaction we have:

$$m_i = 0 \text{ (resp. } n_i = 0).$$

This equality can be considered as the general formulation of the variation rate of the quantity related to the compound X_i; it also permits us to introduce "autoreproduction".

(v). For r parallel simultaneous reactions, the variation rate of X_i is

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = \sum_{k=1}^{r}\left(\frac{\mathrm{d}X_i}{\mathrm{d}t}\right)_k,$$

where $(\mathrm{d}X_i/\mathrm{d}t)_k$ is the variation rate of X_i in the k^{th} reaction.

Matricial expression of the variation rates of compounds in an r *parallel reactions system*

Suppose $V_1, V_2, \ldots, V_r$ are the rates of the reactions of the system. For the reaction k, from equation (9).

$$\left(\frac{\mathrm{d}X_i}{\mathrm{d}t}\right)_k = d_{ik} \times V_k,$$

where $d_{ik} = m_{ik} - n_{ik}$. Thus (9) becomes

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = \sum_{k=1}^{r} d_{ik} \times V_k,$$

this expression is the scalar product of the vectors, in matricial notation:

$$D_i = \begin{bmatrix} d_{i1} \\ \vdots \\ d_{ir} \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} V_1 \\ \vdots \\ V_r \end{bmatrix}.$$

Note: * In this sense, $X_1^{(g)} \ldots X_{p'}^{(d)}$ are identifiers of variables, as in programmation languages.

For all compounds, we can denote

$$\frac{\mathrm{d}X}{\mathrm{d}t} = D.V, \tag{10}$$

where X is the vector of the compounds: $X_1, \ldots, X_i, \ldots, X_q$. D is the $q \times r$ matrix

$$\begin{bmatrix} {}^tD_1 \\ \vdots \\ {}^tD_i \\ \vdots \\ {}^tD_q \end{bmatrix}$$

(${}^tD_i$ is the transposed matrix of D_i).

Now, consider the definition of the matrix D and the definitions of the matrix D_g and D_d; we find that

$$D = {}^tD_d - {}^tD_g. \tag{11}$$

Further, the vector V can be obtained by the multiplication of the diagonal matrix K', times the vector of kinetic terms:*

$$T = \begin{bmatrix} X_{11}^{(\mathrm{g})} \uparrow n_{11} \times \cdots \times X_{1p}^{(\mathrm{g})} \uparrow n_{1p} \\ X_{rl}^{(\mathrm{g})} \uparrow n_{r_1} \times \cdots \times X_{rp}^{(\mathrm{g})} \uparrow n_{rp} \end{bmatrix}. \tag{12}$$

Then, (10) becomes

$$\frac{\mathrm{d}X}{\mathrm{d}t} = ({}^tD_d - {}^tD_g) \cdot K' \cdot T. \tag{13}$$

Note that a such representation of kinetics equations is customarily used for linear differential systems; in these cases T is equal to X and D is a square matrix $q \times q$. In fact, as shown above, a matricial expression is also available for non-linear systems. For a computer program design, such a representation is very convenient.

GENERATION OF RATE EQUATIONS FROM A LIKE CHEMICAL SYSTEM. ALGORITHM A1

The matricial equations (10) or (13) may be used in two complementary directions:

(i). To obtain a numerical evaluation of $\mathrm{d}X/\mathrm{d}t$. The numerical integration of the differential system then becomes possible.

(ii). To generate the differential system of a like chemical system. This set of differential equations is generally called the "rate equations". So, this formal expression permits analytical or heuristic studies on the mathematical model.

For any of these purposes, it is necessary to obtain all the components of the equation (13) from a like chemical system written with the *implicit syntax* (1), or any equivalent syntax. As the problem is defined, the generation of matrix D_g, D_d and K' is easy from a string of type (1). In the same way, the generation of the components of the vector T is possible using an algorithm F applied on the left side of the reaction:

$$n_1 X_1^{(\mathrm{g})} + \cdots + n_p X_p^{(\mathrm{g})} \xrightarrow{F} X_1^{(\mathrm{g})} \uparrow n_1 \times \cdots \times X_p^{(\mathrm{g})} \uparrow n_p. \tag{14}$$

F can be seen as a bijection of the sets of strings, implicitly defined in (14) (i.e. a bijection of a language L_1, describing the left hand side of the reaction, on a language L_2 which can be considered as a subset of mathematical language or, in the present case, as a subset of arithmetic expressions in the sense of a programmation language, ALGOL 60 for example).

Note: * Diagonal terms of K' are k_1, $k_2 \ldots k_r$. It is obvious that in practice in a computer program, we shall use only vector K as it is defined in Section 2.

Finally, we must specify that, in the way of formal generation, the symbolic matricial multiplication $D.V$ is done using the rule (2) (substitute d_{ij} to n_{ij}).

GENERATION OF A LIKE CHEMICAL SYSTEM FROM A DIFFERENTIAL SYSTEM. ALGORITHM A2

Let us consider a differential system. If it can be considered as derived from a chemical system, then it must have a syntax equivalent to the following formula:

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = \sum_{l=1}^{s} n_{il} \times k_l \times \prod_{j \in I} X_j \uparrow n'_j$$

$1 \leqslant i \leqslant q$, $I = \{1, 2, \ldots, q\}$. n_{il} is an integer (signed or not); k_l is an identifier (rate constant); n'_j is an unsigned integer. All the terms

$$\prod_{j \in I} X_j \uparrow n'_j$$

are kinetics terms, as they are defined in (12).

From such a set of formulas it is obviously possible to obtain:

(i). The vector X
(ii). The vector T
(iii). The vector K
(iv). The matrix D.

And from the vector T, one easily finds the vector X' of compounds in the supposed left side of the reaction, and the matrix D' of the exponents of each compound in T. Hence, D_g is obtained by completing D' by nul columns corresponding to each compound present in X and absent in X' (in the same order). Then, in respect to (11), we have

$${}^tD_d = D + {}^tD_g.$$

If, simultaneously, all terms of D_g and D are positive integers or zeros, and the lines of these matrix contain one more non nul term (a reaction has a left and a right hand side !), then applying the symbolic multiplications (3) and (4), we have finally the right and the left hand sides of the reactions of the desired like chemical system.

NUMERICAL SIMULATION

Second members of equation (13) are generally continuous, derivable in terms of $X_1, \ldots, X_q$, and the concentrations (or rates or number of particles) are bounded. Thus, equation (13) has one, and only one, solution depending on the initial conditions (generally values of $X_1 \ldots X_q$ at $t = 0$). However, in most cases, analytical solutions of (13) are impossible to find. So we must use simulation methods.

Today, it is well known that there are few methods of simulation: electrical analogy, analog computation, numerical computation with, or without, automatic generation of equations.

To explain our choice we examine an example of like chemical system: the study of enzymes action in biochemistry.

An enzyme can be considered as a "black box" whose inputs are substrates $S_1, \ldots S_m$ and outputs are products $P_1, \ldots P_n$. So, the cellular metabolism may be represented by a complete network of such boxes. This model suggests an electrical analogy (as proposed by Atkinson [1])

enzyme ↔ transistor
reaction rate ↔ current
concentration ↔ voltage.

This analogy is not devoided of interest [3]; but it cannot be used very far:

If a capacitance can represent the volume of the solvent, it is difficult to find out the analogue of a resistance or inductance.

Ohm's law can only be obtained in particular cases. Beside many authors have built computers to solve equation (13) [3, 10, 13].

These devices have the disadvantage to be adapted to a given reaction; and since the initial conditions are altered, certain components have to be changed, or if the whole of the studied reactions are modified, the structure of the computers has to be adapted.

Therefore, it seems more flexible and more general to solve this problem with numerical methods on a computer. However, to have an available solution in all cases it is necessary to use a good procedure for numerical integration. So, we don't use all separated step methods in order to obtain a better convergence and a greater precision of the results. Hence, we have chosen a set of variable step methods proposed by Gear [8]: Adams' predictor–corrector methods; Gear's variable step method with numerical derivation which is also good for non stiff problem; Gear's variable step method but with a formal derivation, a more accurate method, but slower than the previous one, its use is necessary for stiff problems:

In order to have a fast calculation right hand sides of differential equations are converted in a post-fixed mode.

The integration methods require the derivatives of the second member of these equations to be known. In order to have accurate calculations, the derivation is formally carried out and not numerically.

The description language and resolution program are machine independants as proposed by Garfinkel [4].

PROGRAM DESCRIPTION

The program has been drawn up in the goal of a conversational use, and organized around two principal subsets:

(i). The first one is a processor working on strings as inputs and outputs; this subset has two functions:

To analyze a set of chemical reactions written in a similar chemist's language. Rate coefficients can be constants or functions of external and/or internal parameters to take in account the outside influence on kinetics. After syntaxical analysis, the compilation gives the rate equations associated to the input like chemical system (application of the algorithm A1). Conversely, this subset can propose the associated like chemical system of an input set of differential equations, if it is possible (Algorithm A2).

Using two distinct buffers to store chemical system and differential equations, all change of a part, or of the totality, of one buffer is possible. Then the changed system can be, a new time, analyzed by the processor for differential or chemical system generation, and so on.

(ii). The second one is usable to obtain the numerical solution of a differential system with given initial conditions, the method of integration is chosen by the user. Post fixed forms of the right hand sides of the differential equations are used for the computation, they are automatically generated when this subset is called.

Bounded methods used need the knowledge of partial derivatives of right hand sides of the equations, we have chosen to use a formal derivator subroutine for this purpose. Hence, the evaluation of Jacobian matrix is easy with a good precision.

The subsets, all the functions of these subsets, and input output functions need at any level of an analyze are called using a simple command language.

The program is written FORTRAN IV, so it can be used on many computers.

DISCUSSION

In order to present a practical discussion on the use of such a procedure in model analysis, we shall present a simple example of a biological process.

Experimental data of Prudhomme [11] are considered. They concern RNA populations in the silk gland of the silkworm.

During the last larval instar, the gland activity is principally oriented to produce silk proteins. However, it is well known that proteins synthesis is intracellular RNA-dependent. So this author has studied the evolution of the rate of RNA, in the gland cells during the last instar of the worm. Experimental results are plotted in Fig. 1.

The curve shape seems to a graphical representation of a solution of Kostitzin–Volterra equation [2], whose analytical expression is:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = aq - bq^2 - cq \int_0^t q(u)\,\mathrm{d}u, \tag{16}$$

where q represents RNA rate; a, b, c, are positive constants.

Using an original optimization procedure, [2] estimations of parameters was found:

$$a = 0.68 \quad b = 2.99\ 10^{-2} \quad c = 1.36\ 10^{-2}.$$

The computer simulation performed with the numerical subset of our program has given the results plotted in Fig. 1. Comparing the experimental results we may consider that the Kostitzin–Volterra model is a good description of the experiments.

In reality, this model had been proposed after speculative assumptions on growth mechanisms occurring in a population. But the field of original applications (ecology) and the discursive expression of the hypotheses don't give a synthetic picture of the mechanisms, especially for the non mathematician. Observing that equation (16) can be set into the following differential form:

$$\frac{\mathrm{d}q}{\mathrm{d}t} = aq - bq^2 - c_1qf$$

$$\frac{\mathrm{d}f}{\mathrm{d}t} = c_2q, \tag{13}$$

with $c = c_1 \cdot c_2$.

Using algorithm A_2 we have found the like chemical system:

$$q \underset{b}{\overset{a}{\rightleftarrows}} 2q \tag{i}$$

$$q \xrightarrow{c_2} f + q \tag{ii}$$

$$q + f \xrightarrow{c_1} f. \tag{iii}$$

This result allows to suggest a mechanism explaining the experimental results.

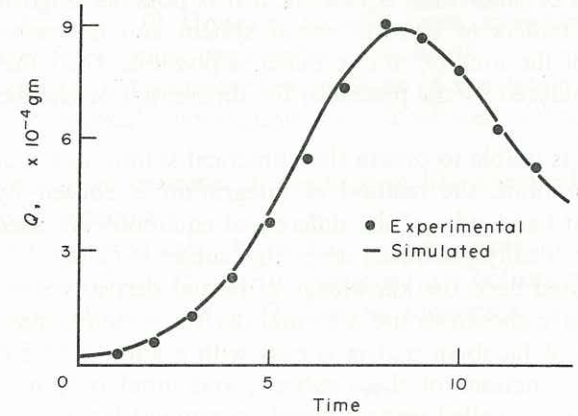

Fig. 1.

Reaction (i) looks an autoreproductive limited mechanism for the RNA. But it is well known that the RNA is not autoreproductive. In fact, the RNA is copied on an autoreproductive molecule: the DNA. And this reaction summarizes these two mechanisms.

Reaction (ii) represents the production of a compound f which in (iii) interacts with q to degrade it. Other experimental results suggest that f represents an RNA degradative enzyme called RNAase.

So the complete study of this model allows to say that a continuous evolution of all involved components can explain the experimental results (i.e. it is not necessary to introduce discrete regulation mechanisms as it is often proposed, particularly for the production of RNAase).

We have proposed a relatively simple model which summarizes correctly the experimental data. The analysis in terms of like chemical system gives us explicable mechanism of the RNA evolution in the silkgland. In fact, we must note that, on speculative assumptions and with the known biochemical mechanisms, it could be possible to propose more elaborate models of this situation. But, such models are generally so complex that their practical use is difficult (for example, it is not easy to have estimations of parameters from necessary limited data). Now it is obvious that such a program permits to work on complex forms. Such an easiness may induce the user to complicate his model perhaps too much in respect with the experimental results. So, a computer aided design program must be used with a good comprehension of model analysis or model building.

This observation is generally available for many situations in systems analysis. Observing a "natural" system we are interested on some aspects of this system. Hence the level of analysis of a system is defined on speculative choices or determined by experimental approach. Then the level of modelisation must be chosen in the same order of the defined system (for example kinetics models in chemistry use a particular set of models, they do not integrate explicitly complex models of ondulatory mechanics). So, one must distinguish the "natural" system, the effectively studied system after integration, the discursive or formal description of the system (description model) and the mathematical model.

Finally, always in the goal of an aid for modelling, future developments of our work may be forecasted:

a subset of optimization, as a generalization of that used in our example;
an heuristic routine, which can propose one, or more than one, model from experimental results, under defined constraints.

So, we think that such a program can be seen not only as an aid for modelling in a necessary limited field, but also as an approach for a methodology to be developed in the future, eventually using the results of the studies in the field of artificial intelligence.

SUMMARY

With some extensions, kinetics models of chemical systems have a great interest in other fields than chemistry, particullary in ecology and biology.

If we assume that general hypothesis of chemical kinetics models can be accepted for a particular system, at first we must describe the particles interaction; for this purpose we can use a description language which can be considered as a representation of the system behaviour, since the mathematical expressions of the rate equations are available. Conversely it is possible to suggest a mechanism of interactions from a mathematical model (i.e. differential equations).

We show that a mathematical expression of like chemical systems permits to draw up easily a generation algorithm (A1) of the associated rate equations, and a descriptive chemical system can be obtained from a set of differential equations with a converse algorithm (A2).

Using the example of enzyme action, the problem of numerical simulation is studied. All these levels have been integrated in a general computer program which can be seen as a tool for modelling.

Around a biological example, we discuss of the use of such a procedure for models study. For this purpose experimental data of the evolution of RNA in the silk gland of the silkworm are considered. Such an evolution can be described by the Kostitzin–Volterra model. Parameters estimation and numerical simulation is possible with the algorithm (A1), and also a mechanism of this phenomenon is proposed by the algorithm (A2).

So we think that such an analyze of an experimental situation can be generalized, not only in the field of kinetics determinist models, but also in systems analysis, using other ways for mathematical modelling.

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