A.I. Applied to Simulation

Eds E.J.H. KERCKHOFFS, G.C. VANSTEENKISTE, B.P. ZEIGLER

S.C.S. Simul. Series (18), 1, 1986.

COMPUTER AIDED MODELLING IN BIOLOGY : AN ARTIFICIAL INTELLIGENCE APPROACH

Pavé Alain
Laboratoire de Biométrie et de Biologie des Populations. Université Cl. Bernard
69622 Villeurbanne Cedex, France

Rechenmann François
INRIA. Laboratoire ARTEMIS-IMAG BP 68
38402 Saint Martin d'Hères Cedex
France

SUMMARY

The large scope of tools and competences to achieve a modelling approach in biology leads to note that classical simulation software products give only partial solutions to this problem. The recent developments of software designs lead to a new conception of computer aided modelling systems. It is proposed to develop a computer system based on these ideas. This system would include knowledge about models and their handling (mathematical properties, numerical and formal calculus tools...), and also knowledge related to the domain of application and to the modelling approach itself.

In this paper, we examine possible knowledge representations and the choice of an object-centered one based on frames concept. We discuss the use of schematic descriptions to aid both model building and model interpretation, an example related to population dynamics is presented. One notes a possible organization of the knowledge based on schemes associated to models of this application field.

INTRODUCTION

Mathematical representations of biological phenomena have been for a long time essentially devoted to theoretical studies, and thus reserved to specialists: some biologists and some mathematicians (or "biomathematicians"). These last years a wide diffusion of modelling approaches and uses of practical models have been noted (1). Models are now considered as efficient means to solve biological problems. These developments have been strongly dependent on the extension of computer tools (2), especially numerical ones.

However, mathematical modelling in biology is not a simple task. It requieres competences in many domains, from mathematics and computer sciences to biology, which are difficult to gain for a scientist, or even to gather in a staff. Therefore a possible solution to facilitate modelling approaches in life sciences might be the use of adapted computer systems.

State Of The Art Solution : Classical Simulation Software Products

If we consider dynamics problems (for example, biochemical kinetics, population dynamics...), it is well known that a large number of computer systems have been especially developed to assist the elaboration of models based on differential or difference equations. The trend in this field is to increase the capabilities of these products through the introduction of various methods, generally numerical ones such as identification, numerical integration or tools for optimal control design. Thus the number of available methods is becoming a fundamental evaluation criterion to compare these systems : "the best has the greatest number of methods".

Because of their high costs of conception, these computer systems are designed to be used by a large set of potential users :

- then great advance are made in order to make the system easily to operate :

- they do not have specific application domains. CSMP or ACSL, for instance, can be operated as soon as differential equations are implied in a modelling problem in any domain of application. There are some exceptions when specific description languages enable to write a model in a symbolic form different from mathematical expression (graphs, chemical like reactions, compartmental diagrams...) (3)(4)(5). Often, such representations can only be considered as "syntactic sugar" in so far as, when the mathematical representation is obtained, the first formalism and the associated semantics disappear.

The consequences of this evolution are paradoxical. They become more easily accessible by users who do not always possess the requested mathematical knowledge and expertise. These users tend either to operate systematically the same general-purpose costly method for a given task (for example, a sophisticated integration algorithm when a simple RK4 method is sufficient), either to operate the same method among those available in the system even it is not adapted to the problem (for example, an ordinary least squares method for identification when a weighted one would be more adapted). Thus, at the best, the software is underemployed; but more often it is ill employed leading to some erroneous results which remain undectected by a user who is unable to interpret these results.

In summary, today, simulation and associated software concern numerical approaches of phenomena and need :

(i) a formal representation of the phenomenon under study : i.e. a mathematical model (for example a set of differential equations),

(ii) procedures adapted to the numerical solving of a problem related to this mathematical model (e.g. numerical integration, parameter estimation from experimental data...),

(iii) user interfaces (command language, description language, graphical capabilities...),

but most of available software products do not take into account :

(iv) the "good choice" of an algorithm,

(v) formal manipulations, such as symbolic differentiation or symbolic solving of equations (to calculate stationnary solutions, sensitivity functions...),

(vi) the known mathematical properties of a model,

(vii) the connection with the application domain, particularly

- for a given situation : to aid the choice and/or the elaboration of a mathematical representation,

- conversely the interpretation of a mathematical expression.

Finally, classical simulation systems are often voluminous, difficult to extend, adapt and modify.

Toward A Solution : Expert System

It seems therefore opportune to develop a new generation of computer aided modelling systems which would incorporate knowledge on the available methods, the manipulated objects such as equations, coefficients, variables or time series and on the modelling process itself. Part of this knowledge is domain specific and cannot be frozen in one system. Moreover, new objects and methods are to be added in a system as advances are made, for instance in numerical or statistical analysis. The necessity to incorporate an extensible knowledge base appears clearly (6). Such needs were well felt by Zeigler (7), who proposed an "organization of questions and models", and also by Klir (8) and Sitharama Iyengar (9) who discussed about "computer systems aided modelling".

Several knowledge representation methods exist, among them production rules have been extensively used in the so-called expert systems. However, production rules are not adapted to the development of intelligent systems where an important part of the knowledge implied can exist only in procedural form. This is the case of most scientific, numerical or non numerical, and representation algorithms.

In the framework of the EDORA Club which gathers various research laboratories in computer science, mathematics and biology, a new computer-aided modelling system is being developed using ordinary differential and recurrence equations with applications in biology (in a first time essentially population dynamics). A specific knowledge representation based on frames (10) has been retained and refined. In the second section the problems related to knowledge representation, particularly frames, are discussed together with the qualities and performances of this last representation.

Now as mentioned above, specific interface languages (i.e. description languages) may be defined to aid both elaboration and interpretation of models. However the "syntactic sugar" aspect can be expanded to maintain relations of the mathematical representations with the domain of application thus to ensure some semantic support. This can be done by defining the direct translation algorithm (from schematic representation to mathematical formula), but also by proposing a converse approach for translation, if possible, of a mathematical formula in a schematic representation,in order to assist the model interpretation. Both translation procedures and heuristics can ensure the connection between the "neutral" mathematical formalism and the "oriented" schematic representation. In the third section we present an example of such a description tool, specifically a chemical like language associated to models of population dynamics where a mathematical expression can be associated with a "functional scheme" (i.e. a pseudo-chemical reaction). Translation of schemes in mathematical equations is presented, and the converse process is discussed as an aid to biological interpretation of some models. Then we show that thinking about the relations between schemes and models leads to propose a hierarchical organization of this class of models, namely Lotka-Volterra and related equations, organization which can be examined in the framework of a structured knowledge base.

KNOWLEDGE REPRESENTATION

A computer aided modelling system would be able to manage simultaneously three kind of bases :

(i) a data and object base (for example, time series obtained from experimental data, intermediate or final results of computation, mathematical models...);

(ii) an algorithm base (e.g. integration procedures for simulation, identification algorithms for parameter estimation, formal manipulation capabilities such as formal differentiation, ...) ;

(iii) a knowledge base : this base should contain knowledge about the conditions of application of methods, mathematical knowledge about formal objects, elements on the interpretation in the domain of application (for instance, population biology), and knowledge on the modelling-analysis process itself.

Complete computer-aided modelling leads to multiple inference processes operating on these bases. So an appropriate representation is needed to facilitate system management and the design of these inference processes. Just two possible solutions are examined: production rules and frames, the choice of the last representation is explained and some ideas are given about inference possibilities from these representations.

Production Rules

Remember that a production rule may be written (11) :

IF condition THEN action

The first part (i.e. condition) is one or a list of premises linked to facts. Truth of these facts is a priori assumed as hypothesis or infered by using other rules of the knowledge base.

In the right hand side, the most frequently encountered action is to add new facts when the rule is selected, that is when premises in the left hand side are all verified.

Classically there are three exploitation modes (or control strategies) of these rules : data driven, goals driven and mixed strategies according to the context. Either one starts from known facts in order to infer new ones, or goals are given and verification is desired by searching corresponding facts. In all cases an inference engine is run, its algorithm consists principally in examining the state of the facts data base and to select appropriate rules.

The advantages of this representation are today well known, and are related to modularity of relevant systems :

- a rule incorporates a small chunk of knowledge,
- it is theoretically independent of the others,
- communications between rules are ensured only through the fact base.

Then developments and modifications of the knowledge base are easy. But, practically this modularity is far from complete. Most often, to be efficient the inference mechanism is governed by meta-rules (i.e. rules describing the use of basic rules) or by some artificial means. Then the independence of rules is reduced and it is no longer possible to modify or to add rules without considering the entire knowledge base.

Computer Aided Modelling Systems And Production Rules Representation

An illustration of this approach can be found in the paper of Swaan Arons (12). The chosen example consists to aid in model definition of a simple physical situation : a mass coupled to a spiral spring. A priori different hypotheses can be considered (for instance, the relative importance of the mass relatively to that of the spring one, existence, or not, of a friction strength, etc...). Among the twenty rules of the base, twelve have in their right hand side the expression of the selected model. In fact, these rules define a hierarchic classification of all known models of this simple system which are specializations of a general model. At a given level a model includes implicitely hypotheses of a less specific one.

It appears particularly in this example, that these notions of hierarchic classification and of context disappear, by dispersion, in a production rules representation. In addition this knowledge representation does not ensure easily the representation of objects, i.e. models or methods, the management and the coherence keeping of the base.

Finally the important problem of integration of a set of rules in a real computer aided modelling system is not obvious to solve. When a model is specified it is desirable to manipulate it (e.g. identification, numerical simulation...), therefore to access on the one hand to representations which enable numerical and symbolical manipulations, on the other hand to its mathematical properties. If we consider this last problem, the properties could be infered with rules, but if we examine the example of the mass-spring coupling, a model can be written following the differential form :

$$\ddot{x} + g M \dot{x} + \frac{1}{M} f(x) = \frac{F(t)}{M}$$

where F(t) describes the action of an external force.

The following rules distinguish two cases :

IF F(t) = 0 THEN the equation is homogeneous

IF F(t) $\neq$ 0 THEN the equation is non-homogeneous

from which mathematical properties could be deduced.

However, such information are not new in so far as they appear implicitly when a problem is formulated in physical terms. In the example above, the fact that the differential equation is homogeneous (resp. non-homogeneous) can be deduced immediately from the description of the physical system, which is autonomous (resp. non-autonomous). This description is obviously a previous step before the choice of a mathematical model. This example shows that a same object, i.e. a model, can be considered following several points of view, here a physical one and a mathematical one. Generally, different views are not independent (for example the description of the physical system leads to the choice of a particular mathematical expression). Rules are not adapted to describe such situations.

In conclusion, an other type of knowledge representation which could take into account structured knowledge, different contexts and multiple points of view would be a more adapted solution than production rules representation in a computer aided modelling approach. Among the actual representations it seems that an object centered one could provide a good framework.

Objects-Centered Knowledge Representations

The concept of objects-centered representation comes from two origins, independent at the beginning:

- the Minsky's work on a model of knowledge representation of human perception system (13). He defined the concept of frame, which is a data structure representing a typical situation.

- the introduction by computer scientists, in their own field, of the notion of object through the definition and the development of "object oriented languages", and of corresponding programming environments (for instance, SIMULA and especially SMALLTALK (14)).

It is important to mention that, besides common ideas, object-centered knowledge representation and objet-centered programming are, in fact, distinct domains of computer science. So, only the first aspect, related to our problem, is examined in this paper.

The common characteristics of objects-centered knowledge representation systems are the following:

(i) each object is an instance (i.e. a particular individual) of a class or a family of objects. For example, in population dynamics, the expression :

$$\frac{dx}{dt} = 1.1\, x\, (1 - \frac{x}{100}) \quad ; \quad x(0) = 10$$

is an instance of the general logistic model which can be written

$$\frac{dx}{dt} = r\, x\, (1 - \frac{x}{K}) \quad ; \quad x(0) = x_o$$

(ii) A class of objects is defined by its name and the list of its slots. Knowledge is attached to each slot, such as its value, or how to obtain this value if it is not a priori known, or yet a default value. For example, parameter values for the logistic model can be obtained from experimental data, or default values can be assigned to show a typical case (cf. table 2).

These classes are hierarchically organized, each class in the hierarchy inherits knowledge attached to the upper classes. The own knowledge attached to an object is transmitted to lower classes in the hierarchy.

For example, in the hierarchy proposed in the table 3 which attempts to describe relations between some models of population dynamics, a common property of these models is that the domain of values of state variables is a domain of R^+, because their biological significances are populations sizes or densities. But the corresponding mathematical objects defined in a mathematical hierarchy will have generally a larger definition domain.

(iii) Procedures can be attached to a slot (i.e. procedural knowledge). Such procedures are called when an action is wanted. For instance, the value of a slot can be computed if it is not available. In the above example, values of the parameters of the logistic model can be obtained by calling an identification procedure which operates on experimental time series (cf. table 2).

The procedural attachment possibilities offered in such representation systems are essential as they reduce the opposition between declarative and procedural knowledge.

These general ideas has been applied in various contexts, for instance :

- for languages development such as KRL (16),

- for knowledge processing control by frames in some expert systems based on production rules (e.g. CENTAUR (17) or WEEZE (18)),

- as elementary tools, generally immersed in a LISP environment and devoted to the building of expert systems based on hybrid representations (often frames and production rules, (19)(20)(21)(22)). Only inheritance and procedural attachment are used for inference.

Finally, note that the advantage of frames over production rules lies in the uniformity of representation. A frame base fills the three roles of data base, algorithm base and knowledge base.

Frames

Elementary Definitions. A frame is basically a three level nested list. The first level corresponds to the frame name, the second one to slots, the third to facets. Facets completely describe a slot, each of then has one or more values. In LISP formalism one can write a frame as shown in figure 1.

In a computer aided modelling system, a frame may describe a process (e.g. numerical integration, parameter estimation, for a given model), an object such as a model, an equation or a parameter or still a state variable, a set of experimental data. It can also define objects of the modelling application domain, for instance species in population dynamics or relations between species (e.g. predation, competition...).

Classes And Instances. We have seen in a previous section that a frame defines a class of objects (a class frame), a particular object is also described by a frame (an instance). A simple frame can be associated to the logistic model (cf. table 2), a particular case (i.e. an instance) is obtained when parameter values are computed. Then the instance may be written :

```
(logistic_model_#1
      (is_a ($value logistic_model))
      (parameter ($value 1.1 100 10))
       ...        ...          )))
```

An instance may be a full or a partial instantiation of a frame. It inherits properties directly from this frame which defines the corresponding class by the slot "is_a".

Hierarchical Organization, Inheritance. Each frame is at a level of a hierarchy. It is dominated by less specific frames specified in the slot "a_kind_of", and inherits slot values of these frames. It can also inherit from frames at the same level if they are specified in the facet "$value" associated to the "a_kind_of" slot. This inheritance is ensured in the order of appearance of the corresponding frame after this facet. The involved algebraic structure is a semi-lattice. The figure 2 shows an example of a hierarchy defined on Ordinary Differential Systems, for instance the structure of O.D.S. Then the structure of an O.D. Equation can be defined at the top level, each lower class inherits this structure.

```
(frame_name
    (slot_1  ($facet_11 value_11)
           .
           .
           ($facet_1n value_1n))
    .      .
    .      .
    (slot_p ($facet_pn_1  value_pn_1)
           .
           .
           ($facet_pn_p  value_pn_p)))
```

Figure 1 : frame, general notation in LISP formalism: frame and slot names are user defined, facets are built-in (a predefined set of directives, cf. table 1).

---

1) Facets for type defining

$one followed by an elementary type or by the name of a frame ;
$list_of followed by an elementary type or by the name of a frame ;

Where an elementary type is integer, real, boolean or string. A frame describes a more complex object or data structure, for example an array.

2) Facets for slot values determination

$value defined the value of a slot in a frame common to all objects of the corresponding class, or a description which can be used to obtain this value by pattern matching ;
$if_necessary permits the association of computation and make possible the procedural attachment. The corresponding methods are also described by frames, they are generally written in an algorithmic language ;
$default value is assigned to a slot if all other ways failed.

3) Facets for restrictive conditions

$domain followed by a list of admissible values for the corresponding slot ;
$interval enables the definition of intervals for correct values for elementary types ;
$verify for attachment of a predicate, which must be verified for all values of the slot.

Other facets enable coherence keeping of the base, control of reasonning and passage from external to internal representation and conversely.

Table 1 : Example of facets in SHIRKA

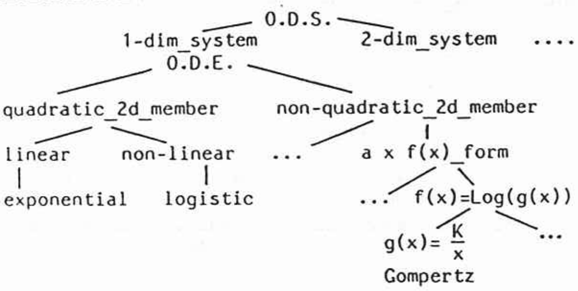


Figure 2 : Example of a hierarchy for O.D.S. oriented to models of population dynamics.

Inference Mechanisms. The basic inference mechanisms attached to an object-centered representation are : instantiation, inheritance, pattern-matching and procedural inference.

These mechanisms are not examined in details, just principles are presented. One can find more complete expositions in (10).

(i) Instantiation

This is the fundamental inference mechanism. It corresponds to the completion of a frame, by obtaining values of slots of the corresponding class frame and also values of slots inherited from other class frames. At each level one can identify a particular view of the situation to be instantiated, the instance is the union of these particular views. Figure 3 illustrates the instantiation on a simple example.

frames	instances one_species_#1	instances one_species_#2
one_species	one species situation	one species situation
dynamics	dynamical view of problem	dynamical view of problem
spatial		spatial view of the problem

↑ spatio-temporal situation

Figure 3 : Example of instances and views from population biology situations : each level specifies views of the study of one species cases. This study can be only dynamical, then one_species_#1 instance is created. If special constraints are introduced then the instance one_species_#2 is created.

(ii) Inheritance

If the value of a slot is defined at a level, all the instances of this class and of more specific classes inherit this value.

(iii) Pattern-matching

The facet $value can be followed, in a class frame, by a list of patterns which are frame specialisations of existing frames : they are descriptions of instances which can be assigned to slot value. The pattern-matching consists of finding this slot value. The figure 4 is an example of the use of pattern to find candidate models which could describe a particular biological situation: the growth of a population or of an organism.

```
(growth_curve
     (inflection_point
       ($variable ?inflection_point))
     ...
     (model_of_growth
       ($list_of model)
       ($value
        (model
         (has_inflection_point
            ($value !inflection_point))
         (model_name
            ($value ?model_name)))))
```

Figure 4 : The slot model_of_growth has its value assigned after pattern-matching. They are the models names for which inflection points verify the desired value. Note the use of the facet $variable and of symbols "?" and "!" : a variable name preceded by ? means that the value is assigned after matching (side effect), a variable name preceded by ! means that the value of the variable must be known at this level, particularly before matching.

(iv) Procedural inference

The values of a slot can be computed by an external algorithmic routine. These routines are themselves described by frames. Their slots are input and output parameters. Syntactically, the need of a routine is specified by a pattern following the facet $if_necessary. In this case, the first step consists of matching the set of instances of the treatment frame. If no correct instance is found (i.e. corresponding values have not been previously computed by a preceding call), then the associated algorithm is executed and values are assigned to parameters. If their values satisfy the constraints then an instance is created. Finally, by a side effect, the slot associated to the facet $if_necessary receive values. Note that if values can be computed in different ways (i.e. methods) sequentially denoted after the facet $if_necessary they are tried also sequentially until a success has been obtained. The table 2 shows an example of a frame where treatments are needed.

Conclusion

The theoretical equivalence between object-centered representations and first order logic must not lead to consider only the choice of a representations as an implementation one, or a suggestion for large bases organization (23). Besides implementation facilities, the detailed information, equivalent to a complex assertion, contained in a frame and in the semi-lattice organization, make their use more efficient than a set of rules where knowledge is dispersed in the base (24).

In addition the objects exist in the base and can be handled as whole individuals. They do not need for this an associated structure to link their properties. Then it is not a surprise to observe that the object-centered representation are more and more employed for application developments (for example in C.A.D. (25)). In such applications frames are used to represent in a unique way data, objects, treatments and knowledge.

We have chosen such a representation for the elaboration of the EDORA system : a computer aided modelling system in biology.

- -

```
(logistic_model
   ┌ (a_kind_of
 (1)   ($value one_species_model one_dim_ODS
   └       one_scheme))
     (parameter ($list_of real)
       ($variable ?parameter)
       ($interval (0 inf))
   ┌   ($if_necessary
   │    ┌ (MAP
   │    │   (exp_data ($variable !exp_data))
   │    │   (mat_cov ($one array)
   │    │            ($variable !mat_cov))
   │    │   (parameter  ($variable  ?parameter)))
   │    │ (WLS
   │    │   (exp_data ($variable !exp_data))
   │ (3)│   (var_data ($one time_series)
  (2)   │            ($variable !var_data))
   │    │   (parameter  ($variable  ?parameter)))
   │    │ (OLS
   │    │   (exp_data ($variable !exp_data))
   │    └   (parameter  ($variable  ?parameter)))
   │      (ask
   │        (question ($one string)
   │                  ($value "parameter value ?"))
   └        (answer   ($variable  ?parameter))))
       ($default
         (logistic_example ($variable ?parameter)))

                                                ...)
```

Table 2 : Example of a frame defining the logistic model.
(1) Multiple inheritance : the object logistic_model inherits properties of corresponding objects in mentioned classification.

(2) Example of procedural inference : values (estimates) of parameters can be obtained from an identification method. If there is either no experimental data available, or the identification process fails then the system asks the user for values. If the user does not answer then default values are given (i.e. a typical example is retained).

(3) Example of a procedural classification : if an a priori covariance matrix of parameters is known then a Maximum A Posteriori method is chosen, else if variances of measures are known then a Weighted Least Squares method is actived, else an Ordinary Least Squares method is chosen. The corresponding procedural classification is the following :

```
                         Identification_methods
                          /                 \
        Ordinary Least Squares               ...
               (OLS)
             /       \
Max. A Posteriori    Weighted Least Squares
     (MAP)                  (WLS)
```

(ref. for identification methods : BECK & ARNOLD, (15)).

- -

PROBLEM ORIENTED SCHEMATIC DESCRIPTIONS. EXAMPLE OF CHEMICAL LIKE REPRESENTATION AND MODELS OF POPULATION DYNAMICS

Schematic Descriptions

The aim of this section is to examine a part of the works related to the above mentioned project. That is the use of symbolic or schematic representations to aid both mathematical modelling and model interpretation. These are representations mediate between a set of discursive hypotheses and a mathematical formulation.

In many domains such schematic representations are well known. Some examples can be cited :

- "box-arrows" flow diagrams used in compartmental analysis,
- symbolic notation of chemical reactions,
- block diagrams used in engineering,
- bond graphs.

They are characterized by

- the use of a limited set of symbols. Each of them has a precise significance (for example, in compartmental analysis, boxes are compartments and arrows symbolize flows of matter between compartments); schematic representations (schemes or diagrams) can be considered as elements of a description language;
- the association with a class of mathematical models (for instance, linear differential systems for linear compartmental analysis) ;
- the translation process of a schematic representation in the mathematical language : it is known and can be executed by an appropriate computer procedure which works like a compiler (the input is the description language, the produced code is a mathematical expression). Some simulation systems include such features (see, for example COSMOS for compartmental analysis (3)).

It was mentioned above that symbols used in schematic representations have precise significances, they are more suggestive and more connected to the corresponding application domain than mathematical models (equations are semantically disconnected from the application domain : a mathematical object can "live its own life" without regarding to any significance out of mathematical world).

Althoug the translation process (scheme to mathematical expression) is generally well known, and can be integrated into the classical deductive approach, the inductive process (mathematical model to scheme) has not been widely studied. Indeed the litterature swarms with mathematical models not related to schemes, and it is sometimes convenient to choose or to write directly a mathematical expression. So the question arises : is it possible to associate a scheme to a model, and then to aid in its biological interpretation ?

In fact, we are mainly interested by this last question, and thus

- to study some "classical" models for elaboration of a structured model base (a part of the knowledge of the EDORA system) ;
- to analyse the inference process for computer implementation.

The problem is studied in a particular case : the class of models related to Lotka-Volterra equations in population dynamics modelling and a chemical like representation for associated schemes. Then

- we discuss about the different computer tools whose conception is necessary to aid both the deductive and inductive approaches,

- we propose a new classification of classical models of population dynamics, based on implicit hypotheses to be considered for scheme generation. It is a contribution to a knowledge base conception and organization for EDORA system.

Finally, to make our approach clearer the figure 5 summarizes relations beween objects introduced in this section : "natural/real" system (in our case a biological one), schematic and mathematical representations.

Chemical Like Representations And Differential Models Of Population Dynamics

Relations between multilinear differential systems and formalism used by chemists to represent kinetics of chemical reactions are well known. The relevance of this representation for mathematical model elaboration has been studied since 1962, essentially by Garfinkel (4), (26). This author has also defined an algorithm for automatic translation of chemical like diagrams in diffeential systems. Another presentation of the translation, based on matrix notation, facilitates the design of the associated algorithm, but also, and mainly, the definition of the reciprocal procedure : the generation of a schematic representation from a differential system (27)(28).

However, the mathematical model need to be written in a form (i.e. a multilinear differential system) facilitating the search for an associated chemical like representation. Conversely, it is sometimes possible to simplify a differential system obtained from a functional scheme, and perhaps thereby to obtain an explicit solution x=f(t).

Apart of a general presentation (cf. appendix), some cases have been studied to identify steps of symbolic manipulations which can be automated and offered to users in a computer system (for this MACSYMA (29) possibilities have been widely used).

To make our approach clearer, just an example is presented in detail, and complete results are just summarized.

Example Of The Logistic Model. The logistic model can be considered as a basic model in population dynamics.

a) Scheme inference

x is a state variable which represents the density or the size of a population (obviously $x > 0$) then the logistic equation can be written :

$$\frac{dx}{dt} = a\,x\,(1 - \frac{x}{K}) \qquad (a1)$$

or

$$\frac{dx}{dt} = a\,x - b\,x^2 \qquad (a2)$$

the initial condition is $x(t=0) = x_0$, it is possible to find

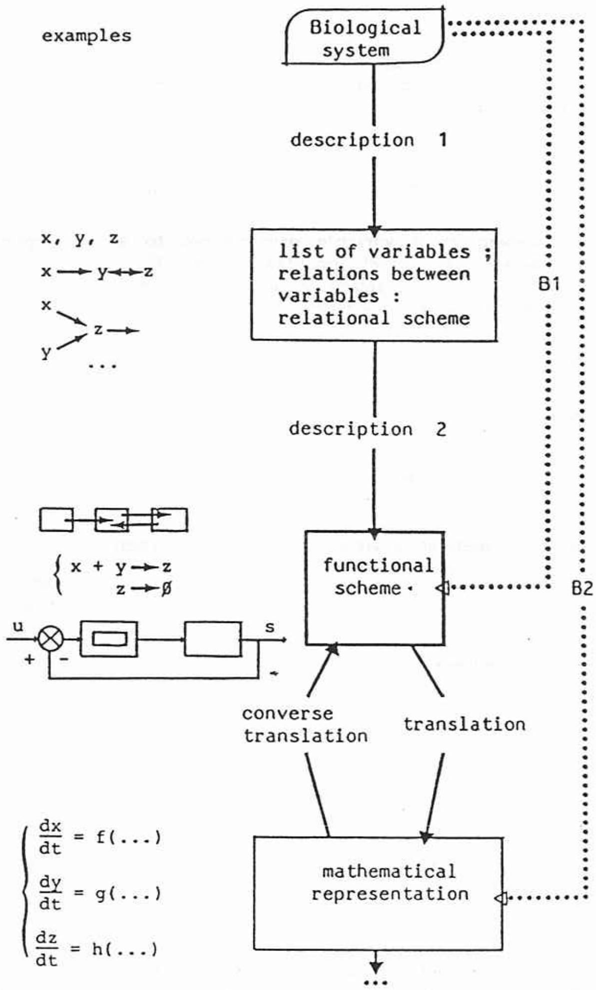


Figure 5 : Schematic representations and mathematical models. One can distinguish between two levels of intermediate representations before writing the mathematical expression.

level 1 : relational scheme, for which no hypotheses are expressed about mathematical expressions linking the variables.

level 2 : functional scheme, where the type of mathematical expressions is defined for each relation. In some cases, the most interesting one, there is a general relation between a set of schemes and a set of mathematical representations (for example, in classical compartmental analysis between the box-arrows diagrams and the set of linear differential system).

level 3 : finally a translation permits to write the mathematical model associated to a scheme.

Obviously, one can by-pass some of these steps. For example one can write directly the functionnal scheme (B1) or the mathematical model (B2). In this last case, the most frequent encountered in the literature, one could examine if some functional scheme exists which can be associated to this mathematical expression (converse translation).

an explicit solution

$$x = \frac{K}{1 + C e^{-a t}} \quad ; \quad c = \frac{K - x_o}{x_o} \qquad (a3)$$

We just try to find at least an associated functional scheme. From (a2), which is a simple multilinear differential equation one can obtain directly the scheme (28) :

$$x \underset{b}{\overset{a}{\rightleftarrows}} 2x \qquad (a4)$$

Which can be interpreted as an autoreproduction of the species x limited by an intraspecific competition (e.g. spatial competition).

Now, from (a1), let

$$s = (1 - \frac{x}{K}) \qquad (a5)$$

s can be viewed as a variable proportional to a substrate, the medium on which population growth is limited in substrate. This substrate is consumed when the population increases, at t=0 we have $s=s_o$.

From (a5) and (a1) it comes

$$\frac{dx}{dt} = b K x s$$
$$\frac{ds}{dt} = - b x s \quad ; \quad b = \frac{a}{K} \qquad (a6)$$

note that K can be seen as a yield of the growth. Then a scheme can be associated to (a6) :

$$x + s \xrightarrow{b} (1 + K) x \qquad (a7)$$

it is often more convenient to write

$$s = c (1 - \frac{x}{K}) \quad \text{and} \quad R = \frac{K}{c}$$

then

$$K = R s_o + x_o$$

and (a7) becomes

$$x + s \xrightarrow{b} (1 + R) x \qquad (a8)$$

This example shows the non-uniqueness of the solution. The solution depends on implicit hypotheses concerning the involved mechanisms or conditions compare (a5) and (a8). One of the interests of this approach is to oblige the modeller to specify his hypotheses.

b) Mathematical model generation

The above scheme describes the growth of a population on a limited, isolated, medium. This scheme does not include a death process for biomass x. Assuming an exponential death process, the scheme (a7) is completed by the corresponding pseudo-reaction :

$$x + s \xrightarrow{b} (1 + R) x \ ; \text{(logistic growth)}$$

$$x \xrightarrow{d} r s \quad ; \text{(exponential death process with a substrate release).} \qquad (b1)$$

On this example the main steps of the mathematical model generation from a functional scheme are briefly presented (cf. appendix for details). The ordinary differential system (ODS) can be written (appendix : A5) :

$$\frac{dX}{dt} = D V \qquad (b2)$$

here

$$X = \begin{pmatrix} x \\ s \end{pmatrix} \quad ; \quad D = \begin{pmatrix} R & -1 \\ -1 & r \end{pmatrix} \text{and} \quad V = \begin{pmatrix} b x s \\ d x \end{pmatrix}$$

then the differential system corresponding to (b1) is

$$\frac{dx}{dt} = b R x s - d x$$
$$\frac{ds}{dt} = - b x s + d r x \qquad (b3)$$

- if r=1/R, as above, then s and x are linearly dependent and this leads to the logistic model (a1) with

$$K = \frac{R s_o + x_o}{1 + \frac{d}{a}}$$

- if $r \neq 1/R$, it leads to the Kostitzin integro-differential equation (31).

c) Discussion

From a scheme a mathematical model can be generated uniquely. Conversely the same mathematical expression can be obtained from different schemes, and different hypothesis on involved mechanisms. Thus the mathematical formulation appears not to be as unambiguous that we generally believe. Thus it is important to consider such difficulties and to caution the basic user, event the modeller himself, about model interpretation.

Consequently, although automatic formal manipulations are sufficient to generate a mathematical model from a scheme, additional knowledge is necessary to infer a precise scheme from a mathematical expression.

Computer Implementation

a) Scheme to ODS translation, simplifications

Consider the last example (b1), the first step of which (i.e. translation) gives the ODS (b3). But in some cases state variables are linearly dependent (for our example if r=1/R, s and x are linearly dependent), then it is possible to simplify the differential system :

- the simplified system may be easier to handle than the original one, for example the number of equations is lesser, which leads to faster numerical computing;

- at the experimental level, only independent variables have to be measured.

Thus it will be convenient that a computer aided-modelling system oriented to such problems solving has these capabilities. The following steps can be proposed :

- generation of matrix D,
- test of linear dependencies,
- generation of complete and/or simplified system.

b) ODS to scheme inference

Scheme generation from a mathematical model written in ODS form needs :

(i) to verify some formal constraints (cf. appendix and logistic example presented above). Principally the ODS must have multilinear right hand sides, and the DR matrix, computed from D and DL matrices, must have positive or null components.

(ii) generally additional knowledge about biological problems under study has to be considered to distinguish between different schemes. For instance, for the logistic case if the studied population grows on a medium limited for substrate, without significant mortality then the solution (a8) has to be chosen.

It is also interesting to look to the possibility of interpretation of models written in integrated form x=f(t). Then a first step in scheme inference consists in finding, if possible, a multilinear ODS which analytical solution is x=f(t).

Thus the following solutions could be proposed

- to define procedures for the passage from ODS to a scheme, on the basis of remark (i) ;
- to freeze a part of knowledge in a scheme base associated to a model base ;
- to envisage formal manipulations to handle the last case for analytical model aided interpretation. For this we have used MACSYMA (29) capabilities on some models to select formal calculus procedures necessary to solve this problem.

Finally, figure 6 depicts principal steps and associated operations to make possible both approaches.

Toward a Knowledge Base in Population dynamics

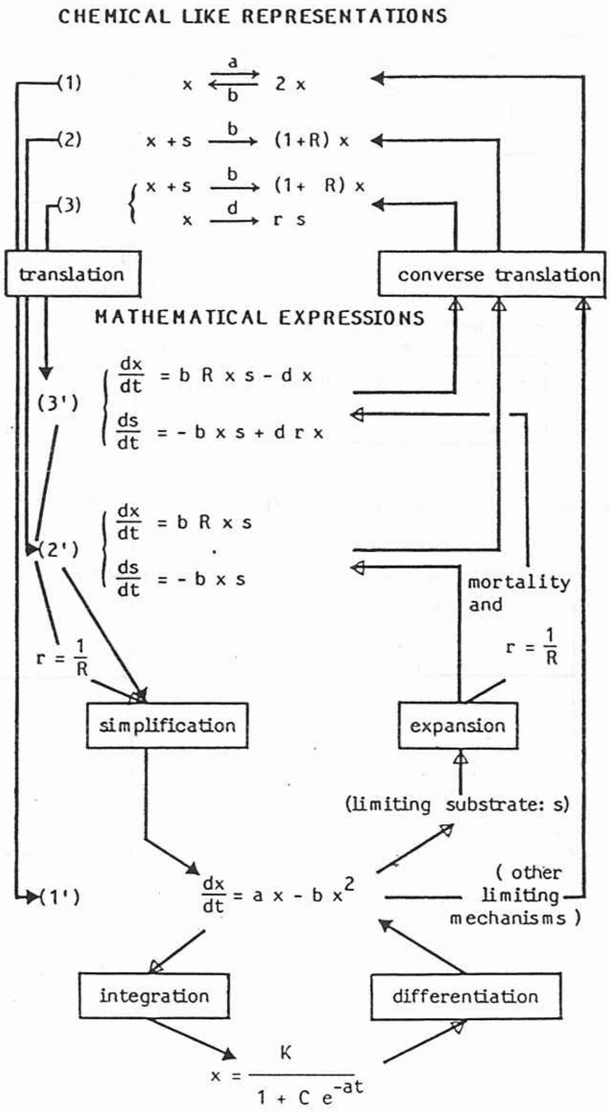
Models of population dynamics have been developed for a long time (Fibonnaci's work, 1228 (32), and more recently Malthus, 1798 (33), and Verhulst, 1848 (30), Volterra, 1931 (34)...). Most of them are written in differential equation terms. As already mentioned these models were essentially devoted to theoretical studies. Apart from mathematical difficulties, technical aspects can explain the lack of interest in differential equations in practical use :

- for a long time the difficulties to access to numerical tools and means has not permitted large developments of their quantitative use (numerical integration, parameter estimation...),

- the biological interpretation is not always obvious and not easily accessible to the biologist. It is generally proposed by the mathematician, a paradoxical situation.

Today numerical procedures and powerful low cost computers enable practical uses in relation with experiments or observations and measurements in nature. We have contributed in some degree to this development (35)(36).

For biological interpretation some indications can be found in the literature. However they are essentially based on considerations about the mathematical expression of models. Now we have seen about the logistic model example that the same mathematical expression may have different interpretations and schemes appear more adapted than equations, at least for this purpose. We propose therefore to use such schematic representa-



$(K = R\, s_o + x_o\ ;\ a = b\, K \text{ and } C = (K - x_o)/x_o)$

Figure 6 : Illustration of different steps permitting the translation from schemes to ODS and conversely (on logistic model example). Note that it is possible to associate to the expression (1') three different schemes following hypotheses about the studied problem : (1) no explicit limiting substrate (the limitation is explained by other mechanisms), (2) limiting substrate, (3) id. (2) plus mortality of x with regeneration of substrate r = 1/R.

tions not only as an interface computer language, but also as a tool for model base organization.

Procedural Knowledge. Clearly a computer aided-modelling system has to offer to users numerical and formal procedures permitting model manipulations, simulation and identification (i.e. parameter estimation

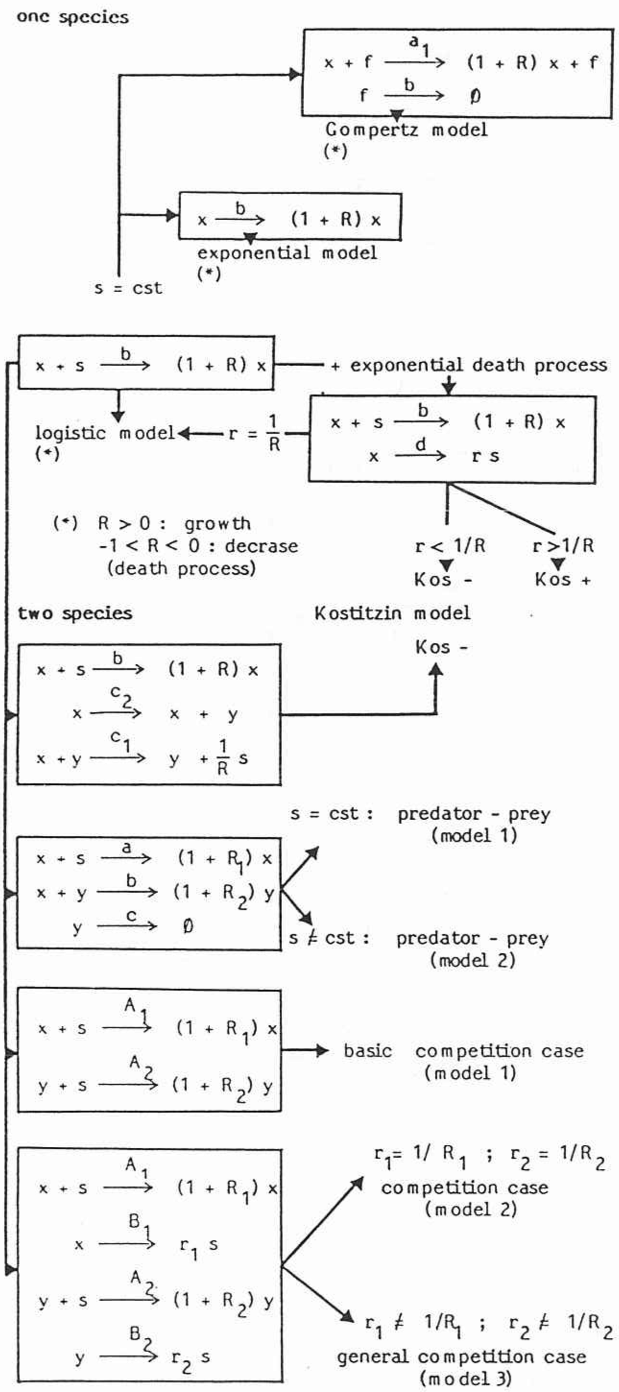


Table 3A : classification based on functional schemes representation.

Table 3 : example of knowledge organisation for some classical models of population dynamics.

It is supposed that populations are in a medium limited (or not) in substrate (s) or factor (f) and at t = 0 :

$x(0) = x_o$, $y(0) = y_o$, $s(0) = s_o$ and $f(0) = f_o$

for details about the relations between schemes and equations see the text, the figure 6 and the appendix.

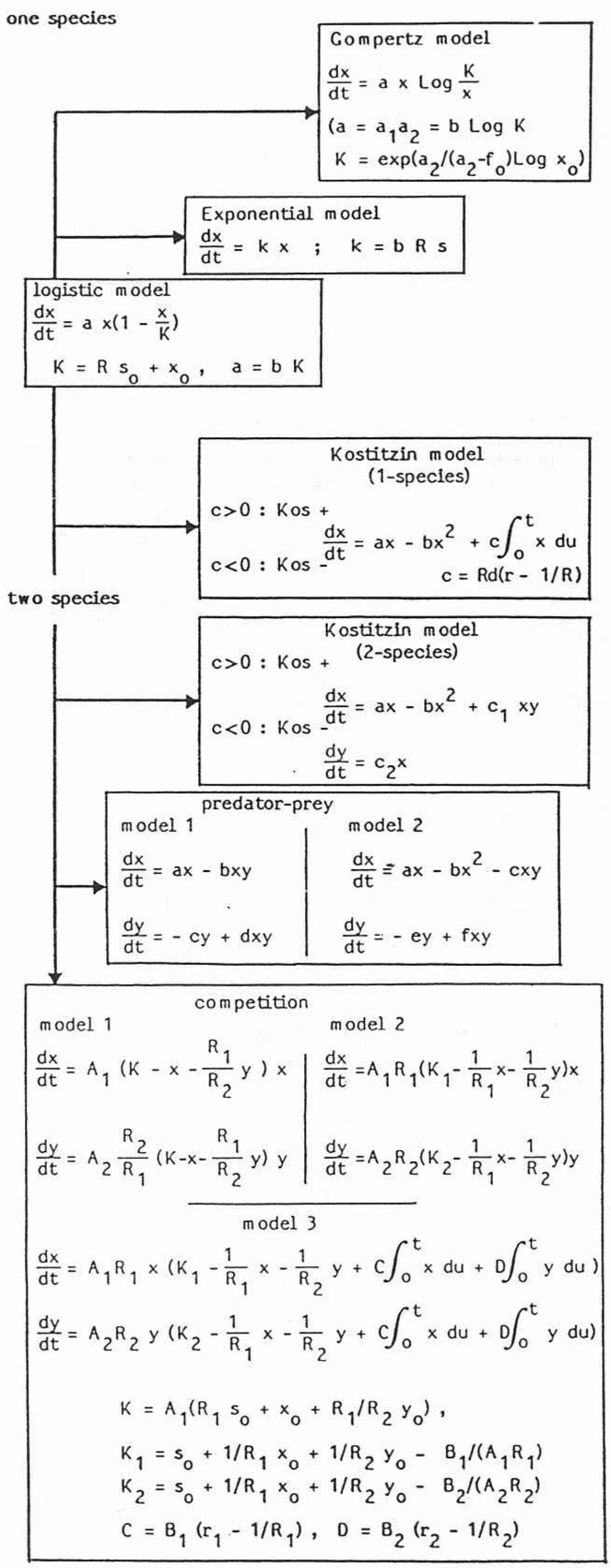


Table 3 B : classification based on mathematical representation.

from experimental data). We have seen that procedural attachment enables the call of such procedures from a frame and procedural inference, by pattern-matching, permits using a method adapted to the problem under study (cf. table 2). More generally, apart from the algorithm itself, the procedural knowledge itself can be augmented by informations on its good use. This enables the system, or the user, to choose the most appropriate method if it is available, to solve a given problem.

At first it is envisaged to furnish recent algorithms for ODS handling, particularly for multilinear ones. One of our principal goals is the connection with the experimental domain, thus parameter estimation and experiment aided design methods will be considered with great attention.

Models of Population dynamics : Knowledge Organization. Schemes seem to be powerful tools for model design and interpretation. Relations between classical models of population dynamics and the proposed chemical like representation have been studied in similar way to that of logistic model example. In this section results concerning isolated populations are presented. These populations are assumed to growth in isolated media limited, or not, for substrate, factors (toxic or conversely, growth factors) may have an influence on studied populations.

The proposed organization is summarized in table 3. This approach has permitted, as a side effect, to find some original results, briefly :

- the Gompertz model (37), often considered as an "exotic" one, is presented in the same framework with other models of population dynamics ; it describes growth on a limited medium controlled by a growth factor ;

- the Kostitzin model generally interpreted as a growth with a simultaneous generation of a toxic factor (31)(35) can be viewed as a simple model of growth on a limited medium with a "natural" death process ;

- the basic competitive case leads to a singular system (i.e. the equilibrium points are on a straight line) then the reached equilibrium point depends on initial conditions ;

- a general integro-differential model of competition (i.e. a two dimensional Kostitzin model) is given.

We propose, in a first attempt, to use this organization as a basis for a knowledge model base in population dynamics. This base will be extended to integrate other problems and other formalisms, such as difference equations.

CONCLUSION

Some aspects of the development of a computer system to aid modelling approaches have been presented.

The goal of the EDORA project is to propose an "intelligent" tool for model building, study, manipulations and using in Biology, particularly to guide modellers and experimentalists in problem solving related to analysis and/or control of biological systems, and to aid them for "optimal" design of experiments. At first, the biological ability of the system will be in population dynamics, further developments will be in biochemical kinetics, and dynamics of biotechnical processes. The choice of a knowledge-based conception enables to extend easily the application domain.

Our approach is justified by the present (and future) need for modelling competence in Biology and Biotechnology and by the extensive knowledge necessary to complete a modelling work (from mathematics, statistics, to a good understanding of biological problems) which is difficult to gather for one individual and also for a staff.

This system will be a knowledge Management System handling :

- procedural knowledge (numerical and formal algorithms and their choice);

- application field knowledge (e.g. interpretation of equations, meaning of variables, effective domain of validity, ...) ;

- knowledge about the modelling approach itself (how to choose and/or to build a model, how to use it : identification, validation, optimisation of experiments, simulations, ...) ;

- data and model bases ;

- elaborate tools for interaction with users (for instance, adapted description languages to aid model building and interpretation).

The object-centered representation facilitates encoding naturally structured knowledge in an easier, and certainly more efficient, way than do production rules. Moreover, we have seen, through the study of classical models of population dynamics, that if a domain appears to be structured, thinking about this structure for the particular objective of acheving a computer knowledge representation is desirable. It may lead to new considerations about the knowledge and the relations between objects, for example between existing models. Finally, apart from technical facilities in model building, the use of intermediate representations such as functional schemes presents some interest in model organization, in so far as it requires more precision about involved mechanisms than mathematical expressions.

APPENDIX

In this section the principles of the translation algorithms are briefly presented, they enable to write a differential systems from a scheme and reciprocally. Informations about computer applications can be found in a previous paper (27) and a discussion of these algorithms in our work (28). We must note that we did not try to forecast the mathematical behaviour of the system of equations associated to a scheme, it is certainly an interesting way, difficult in non linear cases, however we can retain the work of Beretta et al. (38), which is a promising attempt in this direction.

Definitions and notations

A set of chemical, or "chemical like", reactions can be written :

$$\mathcal{A} = \{ n_{i1} X_{i1}^{(L)} + \ldots + n_{ij} X_{ij}^{(L)} + \ldots + n_{iL_i} X_{iL_i}^{(L)} \xrightarrow{K_i} \quad \text{(A1)}$$

$$m_{i1} X_{i1}^{(R)} + \ldots + m_{ik} X_{ik}^{(R)} + \ldots + m_{iR_i} X_{iR_i}^{(R)} \}$$

$$\text{for } 1 \leqslant i \leqslant r$$

where r is the number of reactions and $\mathcal{A}$ is a scheme (a functional scheme) in the sense that it describes interactions between species denoted in the left hand sides (i.e. for the ith reaction: $X_{ij}^{(L)}$, $1 \leqslant j \leqslant L_i$, in the corresponding proportions n_{ij}) which product species denoted in the right hand side (i.e. for the ith reaction : $X_{ik}^{(R)}$, $1 \leqslant k \leqslant R_i$ in the proportions m_{ik}).

We suppose that the n_{ij} are positive integers and the m_{ij} are reals positive. Practically, in the most cases we have : $L_i \leqslant 3$ and $n_{ij} \leqslant 2$ (i.e. the elementary reactions are very simple).

The sign + has no arithmetical significance, it just means that species are all together involved in the corresponding reaction.

Matricial notation

We have proposed to give a matricial representation of the set of reactions $\mathcal{A}$

$$D_L \quad X \xrightarrow{K} D_R \quad X \qquad \text{(A2)}$$

where D_L is the r x N matrix : $D_L = [n_{ij}]$,

D_R is the r x N matrix : $D_R = [m_{ij}]$,

X is the N x 1 matrix of species, and K is the r x 1 matrix of kinetics parameters K_i.

A nul term in D_L (resp. in D_R) means that the corresponding species doesn't intervene in the i^{th} reaction.

Example : for the scheme describing the competition case (1) (cf. table 3).

$$x + s \xrightarrow{A_1} (1 + R_1)\, x$$

$$y + s \xrightarrow{A_2} (1 + R_2)\, y$$

we have

$$x = \begin{pmatrix} x \\ y \\ s \end{pmatrix} ; \quad D_L = \begin{pmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix} ; \quad D_R = \begin{pmatrix} 1+R_1 & 0 & 0 \\ 0 & 1+R_2 & 0 \end{pmatrix}$$

$$\text{and} \quad K = \begin{pmatrix} A_1 \\ A_2 \end{pmatrix}$$

Mathematical model

If the kinetics are governed by the mass action law, they can be formalized as in classical chemical kinetics, by a set of differential equations :

$$\frac{dX_k}{dt} = \sum_{i=1}^{r} d_{ki} K_i \prod_{j=1}^{L_i} (X_{ij}^{(L)})^{n_{ij}} \qquad \text{(A3)}$$

$1 \leqslant k \leqslant N$

d_{ki} is the general term of the N x r matrix D

$$D = D_R^T - D_L^T \qquad \text{(A4)}$$

$$(d_{ki} = m_{ki} - n_{ki})$$

d_{ki} is the difference between the quantity of X_k in the left hand side, which is supposed to "disappear", and the quantity of X_k in the right hand side, which is suppose to "appear", in the i^{th} reaction.

Then (A3) can be written

$$\frac{dX}{dt} = DV \qquad \text{(A5)}$$

where V is the r x 1 matrix

$$V = \Big[K_i \prod_{j=1}^{L_i} (X_{ij}^{(L)})^{n_{ij}} \Big] = K_1 \, T$$

K_1 is the r x r matrix of kinetics parameters (diagonal), and T the matrix of products of species.

Practically, the most interesting equations are linear or bilinear, then the effective expressions are more simple than (A3).

For example, for the competitive case (1) we have

$$D = \begin{pmatrix} R_1 & 0 \\ 0 & R_2 \\ -1 & -1 \end{pmatrix} ; \quad K = \begin{pmatrix} A_1 & 0 \\ 0 & A_2 \end{pmatrix} \text{ and } \quad T = \begin{pmatrix} x.s \\ y.s \end{pmatrix}$$

Writting the differential system

The following algorithm can be proposed : from a set of chemical reactions $\mathcal{A}$ one can generate :

(i) the vectors T and V from left hand sides of reactions, and kinetics parameters.

(ii) the matrix D_L and D_R and

$$D = D_R^T - D_L^T$$

(iii) then the differential system (A3)

(iv) simplifications

- for a reaction or a set of reactions, the dynamics are completely determined by the left hand sides of reactions, then by compounds which appear in these sides. In the other hand products which can be measured during an experiment are important to be considered even if they appear only in right hand sides. These sets of compounds may be called <u>determinant</u> compounds (or species): they must be considered for formal and/or experi-

mental reasons. Other products (or species) give no complementary information, we call them non-determinant products (or species), they can be omitted in the differential system, even in the reactional scheme itself.

- some other simplifications can be done, for example by considering the rank of matrix D, and then the analysis of linear dependance:

The rank of matrix D is at most equal to the lower dimension of D (i.e. min (N,r)). It is particularly interesting if r<N : in this case rank (D)<r. It means that the rank of the system is at most equal to the number of reactions, then some variables associated to species (i.e. state variables) are linearly dependent of the others.

Example : we have seen that it is possible to reduce the number of equations, for the competitive model where

$$D = \begin{pmatrix} R_1 & 0 \\ 0 & R_2 \\ -1 & -1 \end{pmatrix}$$

Obviously rank (D) = 2, then we can choose two independant variables for which lines of D correspond to orthogonal vectors (in our case we have chosen x and y).

Scheme inference

From a differential system written as (A3) one can build :

(i) the matrix T, then the left hand sides of reactions and matrix D_L with exponents of species variables,

(ii) the diagonal matrix K_1, or the matrix K

(iii) the matrix D

(iv) the matrix $D_R = D^T + D_L$

the following conditions must be verified

$$n_{ij} \in \mathbf{N}$$

$$m_{ij} \in \mathbf{R}^+$$

(v) If all elements of a line of D_R (resp. D_L) are null then the right hand side (resp. the left hand side) of the corresponding reaction doesn't exist. Such a situation can occur if non determinant products are omitted, then

- to represent a death, or an emigration, process one can write

$$X \xrightarrow{k} \quad \text{or} \quad X \xrightarrow{k} \emptyset$$

- a mutually toxical or degenerational effect for two species

$$X + Y \xrightarrow{k} \emptyset$$

- an immigration process with a constant rate

$$1 \xrightarrow{k} X$$

or $\quad \xrightarrow{k} X$

or $\quad \xrightarrow{k} m_1 X_1 + m_2 X_2 + \ldots$ for several species.

Discussion about automatic generation of differential equations and scheme inference

a) strings obtained by permutations of species variables with their exponent or with their coefficient in reactional notation) are equivalent.

For example, x + y is equivalent to y + x in a reaction, and the corresponding terms x.y and y.x are equivalent in a differential equation.

To have a minimal representation it is convenient to write the matrix T, formally, by defining the generic element of the class of equivalence.

b) The case of reversible reactions can be solved by considering that such a reaction is equivalent to a set of two reactions where the right hand side of the first one is the left hand side of the second one.

c) scheme inference : the unicity of the infered scheme is ensured if d_{ki} and K_i are known, it is obviously a consequence of the unicity of matricial operation. In the case of reversible reactions, it depends of an a priori convention of its representation with one reaction with two arrows or two reactions.

However in most cases d_{ki} and K_i are not individually known, so the unicity of a scheme deduced from a given differential system is not ensured. But in such a case n_{ij} are always known (i.e. exponents in differential equations), then left hand sides of scheme are uniquely determined. Then, the problem of inference is reduced to the right hand sides of the scheme.

Suppose a multiplicative term in the k^{th} differential equation :

$$\frac{dX_k}{dt} = \ldots + w_{ki} \prod_j (X_{ij}^{(L)})^{n_{ij}} + \ldots$$

we have $w_{ki} = d_{ki} K_i$

but d_{ki} and K_i are not known individually.

Obviously $w_{ki} \neq 0$, else this term wouldn't appear in the right hand side of the differential equation

(i) the sign of w_{ki} is determined by the sign of d_{ki} (K_i is always positive) then

- if $w_{ki} > 0$ it means that $d_{ki} > 0$ and $m_{ki} > n_{ki}$: there is a positive contribution of the term corresponding to the i^{th} reaction in the differential equation, that is a production of X_k from the set od species which appear in this multiplicative term (i.e. in the right hand side of the associated reaction).

- if $w_{ki} < 0$, $d_{ki} < 0$ and $n_{ki} < m_k i$: there is a negative contribution of the term corresponding to the i^{th} reaction in the differential equation, it can be seen as a degradative effect of the set of species appearing in the multiplicative term (i.e. in the right hand side of the associated reaction).

(ii) It is interesting to discuss the cases $n_{ki} \neq 0$ and $n_{ki} = 0$.

Remember that n_{ki} is the k^{th} element of the i^{th} column of D_L^T (or of the i^{th} line of D_L).

Let $\{X_{ij}\}$ be the set of variables appearing in the multiplicative term above mentionned, their exponents are non null.

- if $n_{ki} \neq 0$ then X_k $\{X_{ij}\}$ (i.e. X_k appears in the right hand side of the reaction) and

$$m_{ki} = n_{ki} + \frac{w_{ki}}{K_i}$$

as K_i is unknown, any real positive value can be chosen such that $m_{ki} > 0$. for example :

$K_i = 1$ then $m_{ki} = w_{ki} + n_{ki}$ (always verified if $w_{ki} > 0$ or if $w_{ki} < n_{ki}$)

or yet

$K_i = w_{ki}$ then $m_{ki} = 1 + n_{ki}$, if $w_{ki} > 0$

$K_i = -w_{ki}$ then $m_{ki} = n_{ki} - 1$, if $w_{ki} < 0$

Note that the choice of K_i must be compatible with analog constraints for other implied variables.

The associated chemical like reactions have the following forms

$K_i = 1$:

$$\ldots + n_{ki} X_k + \ldots \overset{1}{\rightarrow} \ldots + (n_{ki} + w_{ki}) X_k + \ldots$$

$K_i = w_{ki}$, ($w_{ki} > 0$) :

$$\ldots + n_{ki} X_k + \ldots \overset{-w_{ki}}{\rightarrow} \ldots + (1 + n_{ki}) X_k + \ldots$$

$K_i = - w_{ki}$, $w_{ki} < 0$; by adjusting K_i such that $m_{ki} = 0$ the following scheme can be obtained

$$\ldots + n_{ki} X_k + \ldots \overset{-w_{ki}}{\rightarrow} \ldots$$

which is particularly suggestive to show a degradative effect on K_k.

- if $n_{ki} = 0$ then X_k / $\{X_{ij}\}$, X_k does not appear in the left hand side of the reaction.

$w_{ki} > 0$ then

$$m_{ki} = \frac{w_{ki}}{K_i}$$

and the following scheme can be proposed

$$\ldots \overset{K_i}{\rightarrow} \ldots + m_{ki} X_k + \ldots$$

production of X_k in proportion m_{ki}

$w_{ki} < 0$ then as K_i and m_{ki} must be positive (or null) it is not possible to find a corresponding reaction.

To conclude, if only w_{ki} are known there is for the left hand side of associated chemical like reaction at most one solution, but more than one solution for right and sides (it depends of the choice of K_i) but the significance of the reaction is not modified by alternative possible right hand sides.

d) variables can be omitted in the differential system if there is known functional relations, for example linear ones, with other variables, then they can be replaced by these functions. Such simplification can give a more simple system with less equations than the former one. It is particularly interesting if numerical integration is needed.

However the inverse problem, i.e. to find a scheme associated to a such "simplified" differential system, may be not obvious to solve if the relations are not explicitely specified. To associate possible schemes with some classical differential equations and to show such an approach is an aid to biological interpretation of these models is precisely one of our goals.

LITERATURE

(1) Lebreton J.D., Millier C., Modèles dynamiques déterministes en Biologie. Masson, Paris, 1982, 207.

(2) Spriet J.A., Vansteenkiste G.C., Computer-Aided modelling and Simulation. Acad. Press, London, 1982, 490.

(3) Hamrouni M.K., Etude et développement d'un système informatique d'aide à l'élaboration de modèles en biologie. Dr 3ème cycle thesis, Université Pierre et Marie Curie, Paris, 1979.

(4) Garfinkel D., Rutledge J.D., Higgins J.J., Simulation and Analysis of Biochemical Systems : I. Representation of Chemical Kinetics. Comm. of the ACM, 1961, 559-562.

(5) Edelson D., A Simulation Language and Compiler to aid Computer Solution of Chemical Kinetics Problems. Comput. in Chem., 1, 1976, 29-33.

(6) Vansteenkiste G.C., de Wael L., Kerckhoffs E.J.H., Artificial Intelligence in Large Scale System Modelling. Proceed. Intelligence Artificielle et Productique, Paris, 1983, 30-32.

(7) Zeigler B.P., Multilevel Multiformalism Modeling: an Ecosystem Example. in "Theoretical System Ecology", ed. Halfon E., Acad. Press, New-York, 1979, 18-54.

(8) Klir G.J., Computer-Aided System Modeling. in "Theoretical System Ecology", ed. Halfon E., Acad. Press, New-York, 1979, 292-323.

(9) Sitharama Iyengar S., Computer Modeling of complex Biological Systems. CRC Press, 1984, 142.

(10) Rechenmann F., SHIRKA : mécanisme d'inférence sur une base de connaissances centrée-objet. Proceed. of "reconnaissance des formes et I.A.", Grenoble, Nov. 1985.

(11) Davis R., King J., An Overview of Production Systems. In "Machine Intelligence 8", Eds. Elcock E.W. & Michie D., Halsted Press, 1977, 300-332.

(12) de Swaan Arons H., Expert System in the Simulation Domain. Math. and Comp. in Simul., XXV, 1983, 10-16.

(13) Minsky M., A Framework for Representing Knowledge. in "The Psychology of Computer Vision", Ed. Winston P.H., Mc Graw-Hill, 1975, 211-277.

(14) The Smalltalk 80 System. Xerox Learning Research Group, Byte, Aug. 1981.

(15) Beck J.V., Arnold K.J., Parameter Estimation in Engineering and Science, J. Wiley & Sons, New-York, 1977, 540.

(16) Bobrow D.G., Winograd T., An Overview of KRL, a Knowledge Representation Language. Cognitive Science, 1, 1, 1977, 2-46.

(17) Aikins J., Prototypical Knowledge For Expert Systems. Artificial Intelligence, 20, 1983, 163-211.

(18) Smith D.E., Clayton J.E., A Frame-based Production System Architecture. 1st Annual Nat. Conf. on Artificial Intelligence, 1980, 154-156.

(19) Brachman R.J., Fikes R.E., Levesques H.J., Krypton : a Functionnal Approach to Knowledge Representation. IEEE Computers, 1983.

(20) Allen B.P., Wright J.M., Integrated Logic Programs and Schemata. IJCAI, 1983, 340-342.

(21) Albert P., KOOL : Représentation des connaissances. Journees Bigres, 1983, 88-91.

(22) Allen E., YAPS : a Production Rule System Meets Objects. AAAI, Washington D.C., Aug. 1983, 5-7.

(23) Hayes P.J., The Logic of Frames. Readings in Artificial Intelligence. Webber B.L. & Nilson Eds. Tioga pub. Cie, Palo Alto, Calif., 1981, 451-458.

(24) Niwa K., Sasaki K., Ihara H., An Experimental Comparison of Knowledge Representation Schemes. The A. I. Mag., 5, 2, 1984, 29-36.

(25) Barbuceanu M., Object-Centered Representation and Reasonning : an Application to Computer Aided Design. Sigart Newsletter, 87, Juan. 1984, 33-39.

(26) Garfinkel D., A Machine-Independent Language for the Simulation of Complex Chemical and Biochemical Systems. Comp. & Biomed. Res., 2, 1968, 31-44.

(27) Pavé A. & Pagnotte Y., An Approach to Computer Aided Design, a Tool for Mathematical Modelling in Biology and Ecology. Comp. in Biol. & Med., 7, 1977, 300-310.

(28) Pavé A., Contribution à la théorie et à la pratique des modèles mathématiques pour l'analyse dynamique de systèmes biologiques. Etude de quelques cas typiques en biologie cellulaire et moléculaire. Dr. es Sciences Thesis, Université Claude Bernard, Lyon, 1980, (Réed. 1985).

(29) MACSYMA. Ref. Manual, The Mathlab Group, Lab. for Computer Science, MIT, 1982.

(30) Verhults P.F., Notice sur la loi que la population suit dans son accroissement. Corr. Math. Phys., 10, 1938. English trans. : A note on The Law of Population Growth. in Smith D. & Keifitz N. : Mathematical Demography. Biomath., Vol. 6, Springer-Verlag, Berlin, 1977, 113-121.

(31) Kostitzin V.A., Biologie mathématique. Armand Colin, Paris, 1937, 120.

(32) Fibonnacci (Léonard de Pise), Liber Abaci. 1228. in Collette J.P. : "Hist des Mathématiques", Edit. du Renouveau Pédagogique, Montréal, 1978, 143-145.

(33) Malthus R.T., An Essay on the Principle of population. 1978. in Hardin G. : Population, evolution and Birth Control : a Collage of Controversial Ideas. Freedman, San Francisco, 1969.

(34) Volterra L., Leçons sur la théorie mathématique de la lutte pour la vie. Gauthier-Villars, Paris, 1931, 210.

(35) Pavé A., Dynamics of Macromolecular Populations: a Mathematical Model of the Quantitative Change of RNA in the Silkgland during the Last Larval Instar. Biochim., 61, 1979, 263-273.

(36) Corman A., Pavé A., On Parameters Estimation of Monod's Bacterial Growth Model from Batch Culture Data. J. Gen. Appl. Microbio., 29, 1983, 91-101.

(37) Gompertz B., On the Nature of the Function Expressive of the Law of Human Mortality. Philosoph. Transac. 27, 1825. in Smith D. & Keifitz N. : Mathematical Demography. Biomath. Vol. 6, Springer-Verlag, Berlin, 1977, 279-282.

(38) Beretta E., Vetrano F., Solimani F. & Lazzari C., Some Results about Nonlinear Chemical Systems Represented by Trees and Cycles. Bull. of Math. Biol., 41, 1979, 641-664.