On the Use of Computer Algebra Systems and Enclosure Methods in the Modelling and Optimization of Biotechnological Processes

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Abstract: This survey paper aims to promote certain novel mathematical tools, such as computer algebra systems, enclosure methods and interval analysis, to the mathematical modelling and optimization of biotechnological processes.

Key words: Computer algebra systems, Enclosure methods, Interval analysis, Mathematical modelling, Optimization, Biotechnological processes.

Introduction

Rapid interaction between mathematics and biology is widely recognized in the past decades. This interaction goes in two opposite directions: i) novel mathematical tools and models are increasingly introduced in life sciences, and ii) biological problems require and generate new mathematical results and stimulate the development of novel mathematical theories and programming tools. Recently a number of textbooks devoted to the mathematical modelling in life sciences appeared, e. g. [14, 15, 34, 38, 66, 77, 78, 80, 84].

The two most popular in life sciences **computer algebra systems** (CAS) are MAPLE and MATHEMATICA [28, 45, 83]. MAPLE can be accessed through the familiar system MATLAB. Other CAS that can be used for modelling in life science include AXIOM, MACSYMA, REDUCE, FORM and SACLIB [33, 30, 29, 79, 19].

CAS are mainly used to simplify algebraic expressions and perform symbolic operations such as integration and differentiation. The symbolic results of CAS can be used by procedures that evaluate formulas and solve equations numerically. Symbolic calculations are combined with statistical operations and data analysis. CAS are used increasingly for numerical calculations. They are computationally less efficient than programming languages such as FORTRAN and C, however they are easier to use for investigations in biology which usually do not require highly repetitive computations.

In this paper we discuss the use of CAS in the modelling, optimization and control of biotechnological processes emphasizing the role of enclosure methods in dealing with problems of uncertainty. When talking of uncertainty we usually presume that no knowledge about probability distributions is available. That is why applications of probability and stochastic CAS tools have been omited in this work. For such applications we recommend the survey paper [9]; there the interested reader may find information about CAS applications to all branches of life sciences.

Uncertainty in bioprocesses

A main characteristic of biological systems is ***uncertainty***, due to the use of simplified models, variation with time of parameters, unpredictable phenomena, inexact measurements, intrinsic sensitivity of the system, etc. Characterisation of uncertainty and its consideration in subsequent analysis is important for understanding bioprocesses, the identification of state variables and the design of effective control strategies. Researchers in life sciences often underestimate uncertainty. Although formal methods for dealing with uncertainty have been developed over the last decades, little effort has been invested so far to produce results concerning *guaranteed characterisation of uncertainty, guaranteed modelling and simulation, guaranteed optimization, experiment design, robust control*, etc.

For model identification of biological processes involving short uncertain records and unstable solutions (as is often the case whenever enzyme reactions are present) it seems that novel mathematical tools, such as differential inclusions, set-valued analysis, viability analysis, enclosure methods, interval analysis, numerical methods with automatic result verification, will play a major roles in the future. Such methods may require some additional effort from experimental scientists in providing bounds for the measured quantities.

The *management of uncertainty in biological systems* requires an *interaction* and *transfer of knowledge* between different fields involved, such as biological modelling, bioprocess applications, CAS, enclosure methods, interval analysis, validated numerical analysis, robust control. The integration of experimental and computational research is helpful for the understanding of complex biological systems. Global optimization is a fundamental prerequisite for model identification [81]. Identifiability studies are important in qualitative experiment design. Various methods have been proposed for linear systems and some novel methods are available for nonlinear ones [81, 17, 18, 7, 8]. Most identification methods require the solution to systems of highly nonlinear algebraic equations.

As far as a model is specified, the problem of estimating its parameters arises, leading usually to an optimization problem [82]. Characterisation of the uncertainty in the subsequent analysis is important for the understanding of the underlying processes. Novel developments and tools to manage uncertainty are now available for biological researches; amongst them enclosure methods and interval analysis plays important roles.

Enclosure methods and interval analysis

The main idea of enclosure methods is to enclose uncertain/inexact data by means of simple representable sets such as interval boxes, ellipsoids, polytopes, zonotopes, etc. In the case of interval boxes such methods are known as interval methods and the corresponding fundamental theory is known as interval analysis [65]. Interval analysis is a branch of numerical analysis aiming to bound the error propagation in computations and to take into account uncertainties in data measurements. At present, interval analysis is being successfully applied in a number of fields, other than numerical analysis, such as global optimization, systems theory, control, robotics, diagnosis, economy, etc. [31, 32]. Applications with a direct impact in biological modelling are for instance guaranteed parameter estimation, identifiability studies and guaranteed simulation. Several approaches have been suggested in the literature for the solution of uncertain differential equations. The most widely used is the application of interval methods to guaranteed numerical integration. Typically these methods use Taylor series, automatic differentiation and CAS. A survey of these techniques can be found in [76].

Techniques of guaranteed integration and guaranteed optimization enable a global analysis to be carried out in parameter estimation, as opposed to local methods. When only bounds are available for the measurement noise and state perturbations, bounded-error techniques may be used [61, 64]. One has then to characterize the set of all parameter or state vectors that are consistent with the data. The characterization should be guaranteed in the sense that outer (and sometimes inner) bounds are provided. When the model output depends nonlinearly on uncertain parameters, this is a challenging task. The promising results recently obtained in this rapidly evolving domain with interval analysis, guaranteed integration and constraint propagation should find their way into the modelling and optimization of bioprocesses.

The application of contemporary mathematical methods in biotechnological processes (BTP) is characterized by the following: BTP involve living microorganisms, their dynamics is often badly understood and strongly nonlinear. The reproducibility of the experiments is uncertain. BTP are typically characterized by the impossibility of repeating of the experimental data even by strictly keeping equal conditions for cultivating of microorganisms. Small variations in the physico-chemical conditions of cultivation (temperature, dissolved oxygen, pH and etc.), or internal factors (genetic, biochemical, etc) influence the enzyme and physiological activity of microorganisms. The model parameters do not remain constant over long periods due to methabolic variations and physiological modifications. There are no reliable tools capable of providing direct on-line measurements of the biological variables (such as biomass or metabolite concentration) required to implement efficient control strategies.

BTP are described by systems of ordinary differential equations involving uncertainties in the model parameters (yield and kinetic coefficients) and unknown functional relations (specific growth rate and productivity functions) [77]. The uncertainties in the experimental data reflect on the values of the model parameters, i.e. they are unknown but bounded. These peculiarities lead to the necessity of applying contemporary mathematical approaches for modelling and control, taking into account all influent factors [43, 23, 16].

Enclosure methods are tightly connected to specific approaches of collecting and reading off experimental quantitative data in the form of intervals or other bounding volumes. The experimental scientist should make some additional effort in the process of collecting data from biological experiment/observation by providing bounds (e. g. intervals) that contain the true values of the measured/observed quantities. A careful consideration of the measured quantities and of the physical construction of the measurment tools is of immense importance for the new methodology. We recommend the assignment of three types of bounds to each measured/observed quantity: i) bounds which contain the true values with absolute guarranty; ii) bounds that contain the true values with "almost full guaranty", and, iii) bounds that contain the true values with "some guaranty" [48]. After specifying or constructing an enclosure numerical algorithm for the solution of the problem, one can easily obtain bounds for the solutions corresponding to these three sets of input data. The experimental scientist should trust the resulting bounds corresponding to the absolute guaranteed input bounds. If these resulting bounds are too large, then the remaining results can be used with a degree of trust corresponding to the degree of guarancy assigned to the input bounds. The comparisson of the three different types of resulting bounds for the solutions of model identification problems can be valueable for the final interpretation and the global study of the particular biological process.

The use of CAS in the study of BTP

The use of computer algebra systems, such as MAPLE and MATHEMATICA, is increasing rapidly and impacts research on biotechnological processes and related topics, such as enzyme kinetics and population dynamics. The following topics within the scope of biotechnological processes have been discussed in research papers applying CAS.

The use of CAS in the BIOESTIM system for on-line estimation in bioprocess engineering from minimal knowledge of process kinetics is presented in [24]. Global identifier linear and nonlinear problems in enzyme kinetics using CAS are discussed in [7, 8]. The papers [75], [17] and [44] are devoted to enzyme kinetics and make use of compartmental analysis and CAS. Related studies have been conducted in [10-13, 74, 85-87]. A model of animal digestion using MATHEMATICA to study the kinetic equations for hydrolysis and absorption in three kinds of chemical reactor, and to find the optimal ingestion rate is considered in [35]. A pharmacokinetics problem using compartmental analysis and identifiability methods is studied in [46].

In the Biomathematics department of the Institute of Mathematics and Informatics (IMI) at the Bulgarian Academy of Sciences (BAS) investigations using MAPLE and MATHEMATICA, enclosure methods, interval analysis and other novel tools (such as stochastic arithmetic [5, 6, 56, 57], zonotopes [4, 51, 55], etc.) have been performed in the following directions related to biotechnological processes:

i)   steady states analysis (stability and bifurcations), sensitivity analysis of input-output static characteristics under uncertainty, with numerical simulations in MAPLE [37, 39-42, 88, 89];

ii)   feedback design for asymptotic stabilization of the dynamic systems with respect to on-line measurable state variables; robustness with respect to uncertainties in the model parameters, with numerical simulations in MAPLE [20-22, 40-41];

iii)   numerical study of enzyme-kinetic and metabolic processes using MATHEMATICA [25-27, 53, 63, 49];

iv)   interpolation/approximation linear problems under uncertainties and nonlinear case studies with numerical simulations [1, 2, 47, 58–62, 73]; a corresponding MATHEMATICA package has been developed [54, 61, 62];

v)   theoretical fundamentals of "interval computer algebra" [50, 51] and relevant implementations in MATHEMATICA [3, 67-70];

vi)   development of enclosure and interval methods and algorithms with relevant fundamentals [50, 51, 55, 57, 71-72].

The Biomathematics department of IMI-BAS collaborates with other BAS units working in the field of bioprocess modelling, such as the Research Group for Knowledge-Based Control Systems at the Institute of Control and System Research (http://www.icsr.bas.bg/), the Research Group for Mathematical Modelling and Computer Sciences at the Institute of Microbiology (http://www.microbio.bas.bg/), and the Research Group for Modelling and Optimization of BioProcesses Systems at the Centre of Biomedical Engineering

(http://www.clbme.bas.bg/). More about the activity of the Biomathematics department of IMI-BAS can be found at the web site: http://www.math.bas.bg/~bio/.

Concluding remarks

The modeling, optimization and control of BTP involving uncertain data requires new mathematical tools for efficient solving of set-valued problems. Computer algebra systems such as MAPLE and MATHEMATICA provide suitable software platforms for the development of   relevant simulation experiments. Extensive graphics capabilities allow the user to generate two- and three-dimensional graphics, which can be used in the process of mathematical modelling and control.

There is an obvious tendency of hybridization between CAS and tools for treating uncertainties such as interval analysis. The computer algebra systems MAPLE and MATHEMATICA possess packages for interval arithmetic that can deal with interval-arithmetic expressions and are suitable environments for the development of specialized tools. However, these packages are still not very effective in performing symbolic computations involving interval variables and interval arithmetic expressions. The implemented interval arithmetic is restricted to the classical theory based on the additive semigroup of proper intervals [65]. Clearly computations within this semigroup are not as efficient as ones using the induced additive group, known as Kaucher interval arithmetic [36]. The latter arithmetic is extremely suitable for CAS implementations. We believe that such implementations will lead to a new branch of computer algebra, an "interval computer algebra". Some work related both to the theoretical fundamentals of this novel direction [50, 51], as well as to relevant MATHEMATICA implementations is in progress [67-70].

Acknowledgments

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