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APPLICATION OF ALGEBRAIC METHODS TO THE CALCULATION OF STEADY STATES IN CONTINUOUS CULTURE

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Abstract: For the calculation of steady states in continuous culture and the application to optimization, numerical methods for solving the related nonlinear system of equations are usually employed. Such a system may have more than one solution but numerical algorithms find - at best - one solution per computational run depending on the starting point. There is no proof that all the solutions are actually found. To overcome these problems algebraic methods can be employed. Many biotechnological models can be transformed into a polynomial form. In contrast to nonlinear systems in general, polynomial systems are well investigated and all solutions can be calculated with given accuracy for example by using the Gröbner Bases representation. This allows even for sensitivity studies which are difficult to handle with numerical methods. The process of transforming and solving the system of equations is automated with the computer algebra system REDUCE. In this contribution the approach is presented and examples are shown.

Keywords: Computer algebra system, Gröbner Bases, continuous culture, plant optimization, biotechnology

1. INTRODUCTION

Computer algebra systems are now well-established tools to make many calculation problems in science and engineering easier, eg. (Atkinson *et al.*, 1982). For numerical optimization problems for example, derivatives of the system equations are needed which can be calculated comfortably, employing such tools.

In biotechnology the calculation of steady states in continuous culture is one problem that in many cases cannot be solved satisfactorily. Since many bioprocesses show a remarkable variance in the biological parameters, the dependencies of operating points from these parameters are also of interest. The numerical situation gets even worse if such sensitivity or optimization studies are required. In this contribution an approach is presented to overcome such problems by employing algebraic methods.

2. STATEMENT OF THE PROBLEM

In biology, mathematical modelling has become a useful tool for analyzing and understanding intracellular metabolism and regulation. In biotechnology, adequate process descriptions are needed as a basis for plant optimization, filter and controller design.

2.1 Biotechnological Models

One of the most famous models is the observation of Monod (1942) that the specific growth rate μ of a bacterial culture depends on the substrate concentration S in form of the saturation curve

$$\mu = \mu_{max} \cdot S / (k_m + S) \qquad (1a)$$

with k_m called the "Monod constant". Pirt (1965) introduced the concept of maintenance to biological modelling, resulting in equations like

$$r_S = r_{S,max} \cdot S / (k_S + S) \text{ and} \qquad (1b)$$
$$\mu = y_{X,S} \cdot r_S - \mu_e, \qquad (1c)$$

where the specific substrate uptake rate r_S is assumed to be properly described by an enzymatic Michaelis-Menten type step for substrate uptake. Several product or substrate inhibition terms have been mentioned, most of them being motivated by enzymatic kinetics. In structured models similar terms are employed. A collection of such mechanistic models is given in (Bellgardt, 1992) and (Nielsen, Villadsen, 1992). Beside kinetics for the description of rate limiting steps, biotechnological models often consist of a set of linear balance equations to describe intracellular mass, energy and redox flows as well as

stoichiometry (Noorman *et al.*, 1991). These sets of linear balance equations have to be solved, e.g. for numerical simulation, which is convenient by using computer algebra systems.

2.2 Example Model

For the following examinations the simplified model equations

$$r_S = r_{S,max} \cdot S / (k_S + S + k_{i,S} \cdot S^2) - k_{i,P} \cdot P, \quad (2a)$$

for ethanol and substrate inhibited substrate uptake

$$\mu = y_{X,S} \cdot r_S - \mu_e, \quad (2b)$$

for energy-dependent growth and

$$r_P = y_{P,S} \cdot r_S \quad (2c)$$

for product formation of an ethanol fermentation with *Zymomonas mobilis* (Posten, 1989) is used.

The complete process description contains the physiological model as well as the reactor model

$$\mu \cdot X - D \cdot X = 0, \quad (3a)$$
$$D \cdot S_0 - r_S \cdot X - D \cdot S = 0 \text{ and} \quad (3b)$$
$$r_P \cdot X - D \cdot P = 0 \quad (3c)$$

in the form of balance equations that are valid at stationary working conditions during continuous culture. The meanings and nominal values of the parameters are listed in Table 1.

Table 1. Physiological model parameters

$r_{S,max}$	maximum specific substrate uptake rate	10 [g/(gh)]
k_S	substrate limitation constant	0.2 [g/L]
$k_{i,S}$	substrate inhibition constant	0.001,0.01,0.05 L/g
$k_{i,P}$	product inhibition constant	0.1 [L/(gh)]
$y_{X,S}$	biomass yield from substrate	0.05 [g/g]
$y_{P,S}$	product yield from substrate	92/180 [g/g]
μ_e	maintenance part of growth	0.05 [1/h]

2.3 Problems

Since the biological models are nonlinear in nature, numerical methods are usually used for their calculation and their application to optimization and control. This results in several difficulties:

The nonlinear equation system may have more than one solution, characterized for example by product- and substrate inhibition or as the trivial case by wash-out conditions. Numerical algorithms for solving the equations find - at best - one solution per computation run depending on the starting point. Unfortunately, there is no proof that all the solutions are actually found. On the other hand the algorithms may suggest pseudo-solutions with a very small (but definitely not zero) residuum.

During plant optimization the calculation of stationary working points has to be done repeatedly as a function of the inputs that have to be optimized. Here the general problems of finding global minima of cost functions in a numerical way compound the problems of solving the corresponding process equations. In addition, often not only one special working point is required, but also the course of the optimum as a function of some parameters. These problems give the reason for the demand for more stable and powerful algorithms (Seader et al., 1990).

2.4 Employment of Algebraic Methods

The use of algebraic methods is a way to avoid the disadvantages of numerical methods. Polynomial equations are especially well investigated and allow for the nearly exact determination of all zero points, derivatives and minima. Algebraic computer languages like REDUCE (Hearn, 1991) make it relatively easy to handle such algebraic systems. However, other computer algebra systems like MAPLE (Char *et al.*, 1988), or AXIOM (Jenks and Sutor, 1992) allow for the handling of such problems with convenient user interfaces.

All of the model equations mentioned above are rational functions of the system variables like the hyperbolic term in the Monod model.

Now the rational functions which are themselves not easy to handle can be transformed into polynomial equations and so the set of well- known theorems about polynomials can be employed to deal with the biotechnological problems. The following paragraphs show a way to carry out this transformation, and to make use of the polynomials by the computer algebra system REDUCE. Also, some example results concerning the calculation and optimization of stationary working points are given.

3. STATIONARY POINTS

3.1 Deduction of Polynomials from Model Equations

In order to transform the set of rational equations into a set of polynomial equations, first the numerators are taken and set to zero. When solving this the solution set of the system of numerators may contain points where the denominators of one or more of the rational equations vanishes. In order to exclude these solutions the following trick is employed. Let

$$f_1(x_1,\ldots,x_n) = 0$$
$$\ldots$$
$$f_n(x_1,\ldots,x_n) = 0 \qquad (4)$$

be given with $f_i(x_1,\ldots,x_n) = Z_i(x_1,\ldots,x_n)\, N_i(x_1,\ldots x_n)$, $i=1,\ldots$, where Z_i and N_i are polynomials in the variables $x_1,\ldots x_n$.
Then the naive approach would be to solve

$$Z_1(x_1,\ldots,x_n) = 0$$
$$\ldots \qquad (5)$$
$$Z_n(x_1,\ldots,x_n) = 0\ .$$

In order to exclude solutions with vanishing denominators further variables $x_{n+1},\ldots,x_{2n}$ with

$$N_1(x_1,\ldots,x_n)\cdot x_{n+1} - 1 = 0$$
$$\ldots \qquad (6)$$
$$N_n(x_1,\ldots,x_n)\cdot x_{2n} - 1 = 0$$

are introduced and the system (5,6) is solved for $x_1,\ldots,x_n,x_{n+1},\ldots,x_{2n}$. Due to the definition of $x_{n+1},\ldots,x_{2n}$ the denominators N_i are finite at every solution point. The transformation from the system (4) to the polynomial system (5,6) can be carried out completely by REDUCE.

4. SYSTEMS OF POLYNOMIAL EQUATIONS

In the previous section the determination of the operating point for the biological model is transferred to the solution of a set of polynomial equations in more than one variable. The exact solution without numerical difficulties will be the aim of this section.

4.1 Solution Methods

In the mathematical literature very much has been published about the solution sets of polynomial equations. The corresponding discipline is algebraic geometry. The simplest algorithm for the solution of poylnomial systems is by so-called "resultants" and is in some sense the classical approach. The resultant approach suffers from some disadvantages, firstly the required number of computations explodes and secondly some special cases have to be taken into account and the process of solution is not entirely straightforward.

In recent years the so-called Gröbner Bases (Geddes, 1992) have been described in the literature. This tool is suitable for investigating the properties of systems of polynomial equations especially for determining the number of solutions and actually computing them.

In the experience of the authors the solution method via Gröbner Bases is the fastest and most easy to use method among all other methods for solving polynomial equations (Tibken, Posten, 1993).

The Gröbner Bases algorithm in the version used in this paper transforms a set of polynomials

$$p_1(x_1,\ldots,x_n)$$
$$\ldots \qquad (7)$$
$$p_k(x_1,\ldots,x_n)$$

into a set of polynomials

$$q_1^{(n)}(x_1,\ldots,x_n),\ldots,q_{rn}^{(n)}(x_1,\ldots,x_n),$$
$$q_1^{(n-1)}(x_1,\ldots,x_n),\ldots,q_{rn-1}^{(n-1)}(x_1,\ldots,x_{n-1}), \qquad (8)$$
$$q_1^{(1)}(x_1),\ldots,q_{r1}^{(1)}(x_1)$$

such that the zero sets of both polynomial sets coincide. By a simple inspection of the second set the validity of the solution set can be verified.

Another remarkable feature is the fact that the second polynomial set has in some sense a triangular structure, i.e. some polynomials depend only on one variable, namely x_1, some polynomials depend on two variables, and so on. These dependencies lead immediately to a solution by solving the polynomial in one variable of least degree for this variable, substituting this value for x_1 into all other polynomials, then solving the polynomial of least degree in x_2 for x_2, and so on. In this way all solutions of the second set of polynomials can be computed and because of the fact that the solutions on zero sets of both polynomial sets coincide, all solutions to the original first set of polynomials have been found. The process of solution involves only the solution of a polynomial equation in one variable at each stage. This is a numerically as well as an algebraically well-investigated problem and can be done by the methods given in the literature. For the example given here only the numerical approach is used, because the numerical results were highly correct in the examples. In some complicated situations it may well be necessary to use algebraic methods; in that case the use of algorithms for algebraic numbers given in (Buchberger, 1970; Buchberger *et al.*, 1983) is proposed. This was implemented in REDUCE and very good results were obtained with moderate calculation time.

4.2 Application to Example

Using the indentifications

$$x_1 = X,\ x_2 = S,\ x_3 = P \qquad (9a,b,c)$$

and introducing as shown in 3.1 an auxiliary variable x_4 by

$$x_4 = S/(k_S+S+k_{i,S}\cdot S^2) = x_2/(k_s+x_2+k_{i,S}\cdot x_2^2) \quad (9d)$$

the following equations have to be solved for the operating point.

$$r_S = r_{S,max}\cdot x_4 - k_P\cdot x_3, \quad (10a)$$
$$\mu = y_{X,S}\cdot r_S - \mu_m, \quad (10b)$$
$$r_p = y_{P,S}\cdot r_S, \quad (10c)$$
$$x_4\cdot(k_S+x_2+k_{i,S}\cdot x_2^2) - x_2 = 0, \quad (10d)$$
$$my\cdot x_1 - D\cdot x_1 = 0, \quad (10e)$$
$$D\cdot S_0 - r_S\cdot x_1 - D\cdot x_2 = 0 \text{ and} \quad (10f)$$
$$r_p\cdot x_1 - D\cdot x_3 = 0. \quad (10g)$$

From these equations the Gröbner Bases are obtained from the REDUCE program.

Table 2. Excerpt from the REDUCE program

```
% physiological model equations
rs := rsmax * s / (ks+s+kis*s**2) - kip*p;
mu := yxs * rs - mue;
rp := yps * (rs - mu);

% reactor equations
gls := -rs * x + d * (s0-s);
glx := mu * x - d * x;
glp := rp * x - d * p;

% numerators and denumerators
glsn := num(gls)$
glxn := num(glx)$
glpn := num(glp)$
        % z is additional variable
glsd := den(gls) *z - 1$
        % other denumerators are identical

% groebner basis and extraction of polynomials
grob := groebner({glsd,glsn,glxn,glpn},
        {z,s,x,p})$
polp := part(grob,4);
polx := part(grob,3);
pols := part(grob,2);

% numerical evaluation of polynomials
ON ROUNDED;
rsmax = 10; ...
plist := SOLVE(polp,p);
...
```

Some results are shown in Fig. 1. The substrate concentration is calculated as a function of the dilution rate for three different substrate inhibition constants. Beside non-physiological solutions (e.g. negative concentrations, not shown) in the three cases substrate limited growth occurs. This is the state that is usually pursued in bioprocesses. If substrate inhibition is very high a second stable state called substrate inhibited growth can be achieved. This situation may be caused by insufficient inocculation. In real fermentations experimentors try to overcome this problem by reducing the dilution rate, but as can be seen from the results this may be successful only if the substrate inhibition constant is not too high (0.01, e.g.). In all three cases of course wash-out is one possible solution.

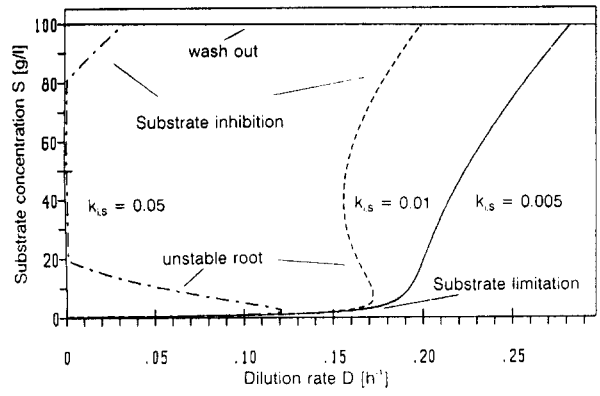

Fig. 1. Substrate concentration as a function of dilution rate for three different substrate inhibition constants

5. OPTIMIZATION

One important application of biotechnological models is the optimization of reactor design and operation parameters with respect to a given cost function. Although these functions are normally the results of complex economic considerations, they often consist of rational or polynomial equations. Many of them even have a quadratic or bilinear structure.

Sometimes not all parameters that influence the criterion are known exactly at the time of optimization. In these cases one wants to know the effect of parameter changes on the optimal working points. The solution of the optimization and sensitivity problem is dealt with in the next section.

5.1 Formulation of the Problem

To solve the optimization problem, a cost function $J(\underline{u},\underline{x},\underline{p})$ has to be minimized with the reactor model equations being constraints. In the case of stationary working conditions this means

$$J^*(\underline{u}^*,\underline{x}^*,\underline{p}) = \min_{\underline{u}}(\underline{u},\underline{x},\underline{p}) \quad (11a)$$

subject to

$$\underline{g}(\underline{u},\underline{x},\underline{p}) = \underline{0} \; . \qquad (11b)$$

The constraints can be considered by using Lagrange-multipliers which leads to

$$J^*(\underline{u}^*,\underline{x}^*,\underline{p}) = \min_{\underline{u}} J(\underline{u},\underline{x},\underline{p}) \max_{\underline{\lambda}} L(\underline{u},\underline{x},\underline{\lambda},\underline{p}) \qquad (12a)$$

with

$$L(\underline{u},\underline{x},\underline{\lambda}) = J(\underline{u},\underline{x},\underline{p}) - \underline{\lambda}^T \cdot \underline{g}(\underline{u},\underline{x},\underline{p}) \qquad (12b)$$

as an unconstrained problem.

The optimal working point is characterized by a saddle-point of the Lagrangian and can be found by solving the system of equations

$$\partial L/\partial \underline{u} = 0, \; \partial L/\partial \underline{x} = 0, \; \partial L/\partial \underline{\lambda} = 0. \qquad (13a,b,c)$$

This task needs two different steps. Firstly, the formal deduction of the derivatives of the Lagrangian has to be carried out.

To figure out the derivatives by hand needs a high sacrifice of time and often leads to mistakes, but it can be automated by using computer algebra systems. This step of solving the optimization problem is possible for many classes of non-linearities in the cost function or in the reactor equations without any assumption about the values of the model parameters. The basic difficulties of the second step are, for example, during the determination of the stationary working conditions finding all the solutions and being sure of the accuracy of the numerical results. Especially in the case of $L(\underline{u},\underline{x},\underline{\lambda})$ being a rational or polynomial expression the system (13) can be transformed into a polynomial form and the zeroes can be calculated as described above.

5.2 Application to example

In the example process a cost function

$$J = D \cdot P + w \cdot P \qquad (14)$$

is set up that considers volumetric productivity as well as product quality in terms of the weighted product concentration. Since the reactor equations (eq. 10) act as constraints and the dilution rate D as sole input variable, the optimization problem (eq. 13) is given in the representation of a set of polynomial equations and can be solved following the procedure given in Section 4.1, in principle.

Unfortunately, the size of the problem becomes too big to be handled on a PC by a reasonable amount of calculation time and storage. The complete Gröbner basis of one steady state already includes more than three hundred terms and needs about 10 min computing time on a PC. With increasing complexity of the problem there is a more than exponential increase in computing time and storage demand. The result file of the complete optimization example was about 2 MByte and made numerical evaluation questionable. In such a case it is necessary to assign numerical values to most of the model parameters before calculating the Gröbner basis. In some cases another reduction of the size of the optimization problem can be undertaken, firstly by calculating the Gröbner basis of the reactor equations, and secondly by including only the necessary equations, in the example $\underline{g}(\underline{u},\underline{x},\underline{p}) = q(D,P)$, as constraints into the Lagrangian.

Figure 2 shows results of the optimization problem, where the optimum dilution rate D^* with respect to the cost function J (equ. 14) is given as a function of two formal parameters, namely the substrate feeding concentration S_0 and the quality index w. As expected, the optimum dilution rate decreases with increasing substrate feeding concentration, reflecting the linear inhibition of substrate turnover by ethanol. Substrate turnover is nearly completely independent from the quality index, because a further increase of the dilution rate results in less product but not in a remarkable increase of productivity. For lower dilution rates ethanol increases slightly but with a remarkable loss in productivity, because the concentration of residual substrate comes into the range of k_S. For high feeding concentrations this structure of optimal working points changes. Now substrate turnover is incomplete and the process operates at a point of mixed product and substrate inhibition.

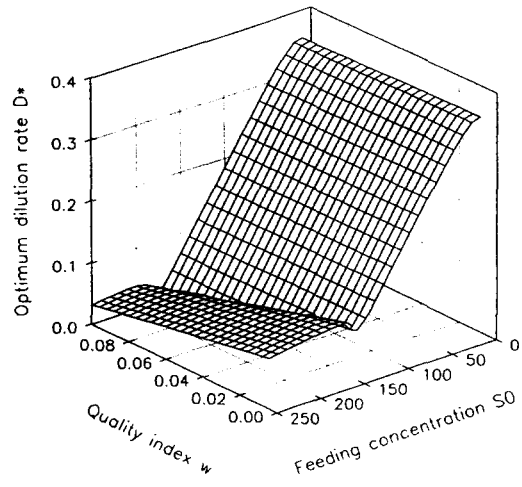

Fig. 2. Optimum dilution rate for the process of continuous production of ethanol as a function of two parameters, namely substrate feeding concentration and a quality index for product concentration

The problem of optimization becomes even more difficult for plants with several stages. Here hierarchical optimization is usually used. In an outer optimization loop several subproblems have to be solved. Each of these subproblems is again an optimization which requires solving a nonlinear system of equations iteratively. In this situation numerical methods need high computation time, or even fail.

6. STABILITY ANALYSIS

The determined working points are not necessarily stable. To assess the stability of a given working point P_0, the characteristic polynomial

$$P(\lambda) := \det(\lambda \cdot \mathbf{I} - \mathbf{A}) = 0 , \qquad (15)$$

where **A** is the Jacobian matrix of the the model equations at P_0, has to be evaluated. Besides the evaluation of a polynomial only the formal computation of derivatives of polynomials and the formation of the determinant is required. All these steps can be completely carried out by computer algebra systems.

However, it is not easy to view the stability of a whole branch of a set of solutions for a range of dilution rates (e.g. Fig. 1) or for other formal parameters. In the general case the unknown states cannot be given explicitly as a function of these parameters. In such cases the Jacobian matrix depends not only on these parameters but also on the unknown states. The solutions of the characteristic polynomial $P(\lambda)$ have to be discussed respectively. In simple cases the Hurwitz criterion can be employed succesfully. Since only the signs of the real parts of λ_i are required, methods from interval mathematics included in computer algebra are recommended to solve such problems.

In the example the substrate limited operation points show three stable poles. Substrate inhibition results in one negative real pole and a conjugate complex pair of poles. Corresponding damped oscillations have often been described in the literature for substrate inhibited fermentations. The wash-out case exhibits three stable poles for $D > D_{max}(S_0, k_{i,S})$ (e.g. $D > 0.2$ for $S_0 = 100$, $k_{i,S} = 0.01$, see Fig. 1) as expected, because definitely no growth (and therefore no dynamics) is possible under these conditions. But in cases where the dilution rate allows for substrate limited growth but is too high for substrate inhibited growth (e.g. $0.03 < D < 0.12$, $k_{i,S} = 0.05$, see Fig. 1) the wash-out case is also stable. A cell population from a probably small amount of inoculum would suffer from substrate inhibition, allowing only for $\mu <$ D, and would finally die out. In all other cases the wash-out state exhibits one unstable pole, representing the well-known (and sometimes unpalatable) fact that one bacterium is enough to make a fermenter insterile. Beside these working points, which can be interpreted physiologically, an additional unstable pole exists (Fig. 1) with two negative and one positive real solutions of the characteristic polynomial. Although such states can be obtained in experiments only by employing controllers, they may be useful for studying different environmental conditions in cells at the same growth rate.

7. CONCLUSIONS AND PROSPECTS

It has been shown that algebraic methods can be employed with advantage to facilitate or even make possible calculations for modelling and simulation of continuous cultivations in biotechnology. Many models consist of linear and rational functions. These special properties have been used to make model development more convenient and to find all solutions of the resulting nonlinear system of equations with guaranteed accuracy. Therefore, the rational functions are transformed into a system of polynomials which is then transformed into a triangular representation to allow for the successive calculation of the state variables. So the problems of numerical simulation of steady states have been overcome. For many practical cost functions plant optimization is also possible using the approach proposed here.

One disadvantage of the approach proposed here is the high demand of memory and computing time for calculation of the Gröbner bases. Moresophisticated algorithms are under development and will solve this problem.

Many other problems can be solved by employing computer algebra systems. These include stability analysis with respect to sometimes observed oscillating cultures, or solving the inverse steady-state problem. Here the inputs for achieving a given state of the bioprocess are investigated. Usually, it is not enough to calculate one optimum value for a cost function with a given parameter set, but it is necessary to give sensitivity curves with respect to inputs or design parameters. Here again, computer algebra systems may be employed with advantage.

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Nomenclature

$\mathbf{A}$	Jacobian matrix
f(x)	rational function
$\underline{g}$	Constraint
J	Cost function
$\underline{k}$	Vector of model parameters
L	Lagrangian
N(x)	Denominator polynomial
P	Product concentration
$\underline{p}$	Parameter vector
p(x)	Polynomials
q(x)	Gröbner Bases
S	Substrate concentration
$\underline{r}$	Vector of specific turn over rates
$\underline{u}$	Input functions
w	quality parameter
x	Independent variable
X	Biomass dry weight concentration
$\underline{y}$	Vector of yield coefficients
Z(x)	Numerator polynomial
$\underline{\lambda}$	Lagrange-multipliers
μ	Specific growth rate
μ_{max}	Maximum specific growth rate