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DYNAMIC OPTIMIZATION OF BIOREACTORS: A REVIEW

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Model based optimization can be successfully used to improve the design and operation of bioreactors. In this contribution, we present a review of this area, especially focusing on the dynamic optimization of fed-batch bioreactors, a class of problems, which has attracted (and continues to receive) huge attention. Both classical and more novel approaches, like those using bio-inspired optimization methods, are discussed. Finally, future research trends and needs are outlined.

Key Words: Bioreactor Optimization; Dynamic Optimization; Optimal Control; Fed-batch Bioreactors

Introduction

In order to increase the productivity and profitability of bioprocesses, many research efforts have been devoted to their improvement via process systems engineering approaches. In this way, mathematical modelling, optimization and control have become fundamental tools to optimally design and operate production facilities in the bioprocess industries[1-5].

Fermentation processes play a key role in the pharmaceutical, biotechnology and food industries. Fermentation can be carried in continuous, batch and fed-batch modes. In fed-batch fermentation, cells or micro-organisms are grown in a bioreactor where nutrient(s) are provided along the process using a controlled (time-varying) feed. Fed-batch bioreactors have a number of well known advantages over batch or continuous fermentors. For example, fed-batch can be the best (or even the only) alternative due to its effectiveness in overcoming undesired effects like substrate inhibition and catabolite repression. Besides, it provides better control of deviations in the organism's growth pattern, and production of high cell densities can be possible due to extension of process time, which is useful for the production of substances associated with growth. An illustrative example of the importance of fed-batch culture is the large scale production of monoclonal antibodies, with product revenues in the USA of several billions of USD[6].

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Not surprisingly, the dynamic optimization of fed-batch bioreactors is a class of problems that has received major attention during the last decades. Basically, dynamic optimization allows the computation of the optimal operating policies for these units, i.e. the best time-varying feed rate(s) which ensure the maximization of a pre-defined performance index (usually, a productivity, or an economical index derived from the operation profile and the final concentrations). Dynamic optimization is also usually called optimal control. However, more rigorously speaking, it should be called open loop optimal control, in order to avoid the confusion with closed loop (feedback) control. Good introductions to dynamic optimization are given in refs. [7] and [8].

The aim of this article is to review the field of dynamic optimization of bioreactors, and especially fed-batch bioreactors, making special emphasis on the available solution methods and their computational performance. A quick search on relevant electronic databases reveals over 300 related papers during the last decade, a good indication of the many efforts devoted to the topic. Obviously, once the optimal operating policies have been derived by dynamic optimization, then the problem of implementing them must be faced, i.e. the closed loop control problem. In this review, we will restrict ourselves to dynamic optimization, not covering the related important problems of fermentation process control, state estimation and robust operation. Regarding control and estimation, the interested reader will find useful the reviews of Johnson[9] and Rani and Rao[10], and the book of Bastin and Dochain[11]. Regarding robust operation, refs. [12] and [13] and the works cited therein will be helpful.

This article is structured as follows: next, we present a general statement of the class of dynamic optimization problems considered, followed by a selection of interesting case studies taken from the open literature, which can be used as benchmark problems. In the following sections, a review and discussion on the different techniques which have been applied to the optimization of fed-batch fermentation is given, with emphasis on stochastic methods, which are becoming rather popular. The comparative performance of these methods is discussed next, focusing on efficiency and robustness issues, and highlighting the potential of hybrid methods. Finally, a set of conclusions and trends for future research are outlined.

Statement of the Dynamic Optimization Problem

Fermentation processes are usually subject to substrate and/or product inhibition. In fed-batch fermentors, a certain amount of biomass is initially present, and the substrate feed rate (or its concentration) is changed during the process, with no product removed until the end of the process. This kind of operation can avoid some of the drawbacks originated by inhibition in batch fermentations, thus leading to significantly improved performance. As already mentioned, the optimal operation and control of these processes has received (and continues to receive) a huge amount of attention.

Most fed-batch fermentation models have highly nonlinear dynamics, and constraints are also frequently present on both the state and the control variables. Thus, efficient and robust dynamic optimization methods are needed in order to successfully obtain their optimal operating policies.

In this work, the general formulation of dynamic optimization of fed-batch bioreactors with unspecified final time and possible free initial conditions is considered. Considering a lumped parameter system (no spatial distributions), the statement is:

Find $\mathbf{u}(t)$ and t_f over $t \in \lfloor t_o, t_f \rfloor$ to minimize (or maximize):

$$J[x,u] = \tilde{\theta}[x\{t_f\}] + \int_{t_0}^{t_f} \tilde{\phi}[x\{t\},u\{t\},t]dt \qquad ...(1)$$

subject to:

$$\frac{dx}{dt} = \psi[x\{t\},u\{t\},t],\ \mathbf{x}(t_0) = \mathbf{x}_0 \qquad ...(2)$$

$$\mathbf{h}[\mathbf{x}(t),\mathbf{u}(t)] = 0 \qquad ...(3)$$

$$\mathbf{g}[\mathbf{x}(t),\mathbf{u}(t)] \leq 0 \qquad ...(4)$$

$$\mathbf{g}[\mathbf{x}(t),\mathbf{u}(t)] \leq 0 \qquad ...(5)$$

$$\mathbf{u}^L \leq \mathbf{u}(t) \leq \mathbf{u}^U \qquad ...(6)$$

where J is the performance index (usually, a measure of productivity or profitability), x is the vector of state variables (concentrations, volume, etc.), u the vector of control variables (e.g. input feed rates), eqs. (2) are the system of ordinary differential equality constraints (i.e. the dynamic model) with their initial conditions, eqs. (3) and (4) are the equality and inequality algebraic constraints (e.g. safety or quality constraints) and eqs. (5) and (6) are the upper and lower bounds on the state and control variables. It should be noted that free final time problems are easily incorporated into the form of a fixed terminal time optimal control problem. The idea is to specify a nominal time interval for the problem and to use a scale factor, adjustable by the optimization procedure, to scale the system dynamics and hence, in effect, scale the duration of the time interval.

The above formulation assumes that the process is modelled as a lumped system (i.e., described by ordinary differential equations), which is valid for most fed-batch bioreactors. If the process is modelled as a distributed system (e.g., a bioreactor where state variables are function of both time and spatial position), the corresponding governing partial differential equations (PDEs) are introduced as an additional set of equality constraints, and they can be transformed to an additional set of differential-algebraic equations (which fits directly in the previous formulation) using a suitable discretization method (e.g., finite elements, method of lines[14-15]).

Selected Case Studies (Benchmarks)

In order to assess the performance of different solution methods in a fair way, it is advisable to use a set of case studies as benchmark problems. In this section, we suggest a set of four problems which have been well documented in the literature. Furthermore, these selected problems have been already solved by a number of researches using widely different techniques, so the available data can be used as an excellent test bed in order to asses other methods or implementations.

- *Fed-batch Reactor for Ethanol Production:* this case study considers the dynamic optimization of a fed-batch reactor involving the production of ethanol by *Saccharomyces cerevisiae*, as studied by Chen and Hwang[16-17], Luus[18], Banga *et al.*[19-21], Balsa-Canto *et al.*[22] and Jayaraman *et al.*[23]. The (free terminal time) optimal control problem is to maximize the yield of ethanol using the feed rate as the control variable.
- *Fed-batch Reactor for Penicillin Production:* this problem considers the dynamic optimization of a fed-batch reactor for the production of penicillin. It was studied by Lim *et al.*[24] and revised by Cuthrell and Biegler[25]. The same problem was also studied by Luus[26,27] using Iterative Dynamic Programming, and by Banga and co-workers[19, 20, 22, 28] using a CVP scheme and stochastic optimization methods. The optimal control problem is to maximize the total amount of penicillin produced (performance index) using the feed rate of substrate as the control variable.
- *Park-Ramirez Fed-batch Bioreactor:* this problem deals with the optimal production of secreted protein in a fed-batch reactor, as originally formulated by Park and Ramirez[29]. It has also been considered by other researchers as an example of a challenging singular optimal control problem[30-36]. The objective is to maximize the secreted heterologous protein by a yeast strain in a fed-batch culture. The dynamic model accounts for host-cell growth, gene expression, and the secretion of expressed polypeptides.
- *Lee-Ramirez Fed-batch Bioreactor:* this problem was first presented by Lee and Ramirez[37] and deals with the optimal fed-batch control of induced foreign protein production by recombinant bacteria. The nutrient and inducer feeding rates to the fed-batch bioreactor are the control variables. The objective is to maximize the profitability of the process (i.e. the difference between the value of the product and the cost of the inducer) for a specified final time of fed-batch operation. The same problem was studied by Tholudur and Ramirez[38] using neural network parameter function models, and by Carrasco and Banga[39], who used adaptive stochastic algorithms to obtain better results. These authors indicated that in the original formulation the performance index exhibited a very low sensitivity with respect to the controls. Recently, Tholudur and Ramirez[35] presented a modified parameter function set for this problem in order to increase the sensitivity to the controls. Other references where this case study has been considered are given in refs.[23] and[26].

Solution of the Dynamic Optimization Problems

The dynamic optimization of fed-batch bioreactors is a very challenging problem due to several reasons. First, the control variable (feed rate) appears linearly in the system differential equations, so the problem is singular, creating additional difficulties for its solution (especially using indirect methods). For this type of problems, the optimal operating policy will be either bang-bang, or singular, or a combination of both. Second, most bioprocesses have highly nonlinear dynamics, and constraints are also frequently present on both the state and the control variables. These characteristics introduce new challenges to the existing solution techniques, as it will be discussed below.

Therefore, efficient and robust methods are needed in order to obtain the optimal operating policies. Numerical methods for the solution of dynamic optimization (open loop optimal control) problems are usually classified under two categories: indirect approaches, dynamic programming, and direct approaches.

Indirect Approaches

Indirect (classical) approaches are based on the transformation of the original optimal control problem into a two point boundary value problem using the necessary conditions of Pontryagin[40]. Many researches have followed this approach, or related variational techniques, for the optimization of fed-batch reactors (see refs.[24],[29],[41-63]). Indirect approaches can be used to extract generic properties of the solution[64, 65].

However, the resulting boundary value problems (BVPs) are usually difficult to solve, especially when state constraints are present. The use of transformations have been suggested in order to facilitate the numerical solution of the BVPs[66-68].

Dynamic Programming

The original dynamic programming method of Bellman[69] suffers from the so called "curse of dimensionality", which precludes its application to problems of realistic size. De Tremblay *et al.*[70] and Luus[30] have proposed the use of Iterative Dynamic Programming (IDP), but this method seems to be computationally too expensive[67-71], especially for systems involving a large number of differential and algebraic equations (DAEs). Further, several search parameters of IDP must be adjusted by the user in order to ensure suitable convergence, so a number of exploratory runs are necessary. Several studies have dealt with the enhancement of the convergence of IDP[72,35], but other methods based on the direct approach (explained below) seem to be much more efficient[36].

Direct Approaches

Alternatively, direct approaches transform the original dynamic optimization problem into a non-linear programming (NLP) problem. Direct approaches seem to be the currently preferred way of solving dynamic optimization problems. Basically, there are two strategies:

- *Control Vector Parameterization (CVP):* only the control variables are parameterized, resulting in an outer NLP problem and an inner initial value problem, IVP. The dimensionality of the NLP is relatively small (and directly related with the discretization chosen for the controls), but the IVP must be solved for each function evaluation, which can be expensive. Gradients are usually estimated using sensitivities. Detailed description of CVP and the theory behind can be found in refs.[73-75], [31],[76,77].
- *Complete Parameterization (CP):* both the controls and the states are parameterized, resulting in a larger NLP, but which does not require the solution of any IVP, as in CVP. It is also called simultaneous strategy. The application of this method for the optimization of a fed-batch bioreactor was illustrated in ref.[78]. The state of the art of CP has been recently reviewed in ref.[79].

Regarding the dynamic optimisation of bioreactors, the control vector parameterization (CVP) approach has been the one more frequently used. The solution of the master NLPs arising from this approach can be quite challenging, and a large number of different methods have been proposed. We will review and discuss CVP in the next section.

The Control Vector Parameterization (CVP) Approach

As already mentioned, the CVP approach transforms the original dynamic optimisation problem into a NLP. Gradient-based local methods are the best option for solving NLPs, provided that these problems are unimodal (i.e. single optimum) and smooth. Sequential Quadratic Programming (SQP) methods are usually recognized as the state of the art in this domain, and a number of authors have successfully solved bioreactor optimisation problems using SQP within the CVP framework[31, 80].

In this scheme, gradients are usually estimated using either finite differences, adjoints or first order sensitivities, the latter being the preferred approach[31]. The simultaneous integration of the system's dynamics with the first order sensitivities provides both the states and the needed gradients accurately and with a low computational cost.

Recently, this approach has been extended using second order sensitivities[81], so the estimation of the Hessian can be done efficiently. Using second order information of high quality, SQP methods can solve the master NLP more efficiently. Following these ideas, Balsa-Canto *et al.*[36] have presented a CVP method which makes use of restricted second order information and a mesh refinement procedure in order to solve these problems in a very efficient way, even for high levels of control discretization. These authors have demonstrated how this new method allows a rapid and robust solution of several challenging bioreactor optimization problems. For example, very good solutions for the Park-Ramirez and Lee-Ramirez fed-batch bioreactors (reviewed above) were obtained in just a few seconds of computation time, greatly improving previously reported performances.

However, solving the NLPs arising from direct approaches like CVP is not always trivial, due to at least two main reasons:

- *Non-convexity:* these NLPs are frequently multimodal (nonconvex, i.e. presenting multiple local optima), due to the highly nonlinear and constrained nature of the dynamics, and/or to the presence of discontinuities[28,82].
- *Non-smoothness:* as already mentioned, an inner initial value problem (IVP) must be solved iteratively within the master NLP. If the integration tolerances are not tight enough (or are similar to the optimisation ones), then the resulting "numerical

noise" will make the NLP non-smooth, leading the NLP solver to bad convergence and/or early stops.

Therefore, deterministic (gradient based) local optimization techniques may converge to local optima, especially if they are started far away from the global solution. In order to surmount these difficulties, we need non-convex (i.e. global) optimization methods.

Direct Methods Using Global Optimization

In order to ensure a globally optimal solution, direct methods (including CVP) should use *global optimization (GO)* methods. However, the state of the art in GO is far from satisfactory. Essentially, GO methods can be classified as *deterministic*[83-85] and stochastic strategies[86-87]. It should be noted that, although deterministic methods can guarantee global optimality for certain GO problems, no algorithm can solve general GO problems with certainty in finite time. In fact, although several classes of deterministic methods have sound theoretical convergence properties, the associated computational effort increases very rapidly with the dimensionality of the problem. Also, most of these methods have a number of requirements (e.g. smoothness, differentiability) which are not met by many of the NLPs resulting from direct methods.

In the domain of *deterministic GO methods*, Esposito and Floudas[88] have recently presented a deterministic global optimization approach which can solve nonlinear optimal control (dynamic optimization) problems. This is indeed a very promising and powerful approach, but so far the objective function and the dynamics of the system must be twice continuously differentiable, and restrictions may also apply for the type of path constraints which can be handled. Other researches[89-90] are also making good progress in deterministic global optimization of dynamic systems, yet several barriers regarding requirements and computational effort are still present.

In contrast, many *stochastic GO methods* can locate the vicinity of global solutions with relative efficiency, but the cost to pay is that global optimality can not be guaranteed. However, in practice we can be satisfied if these methods provide us with a very good (often, the best available) solution in modest computation times. Furthermore, stochastic methods are usually quite simple to implement and use, and they do not require transformation of the original problem, which can be treated as a black box. A rough classification of stochastic GO algorithms is as follows:

- *Random Search and Adaptive Stochastic Methods*: these methods have their origins in the works 1950s and 1960s[91-94], but much more refined and efficient methods of this type have been developed during the last decades[28,95,96].
- *Evolutionary Computation (or Bio-inspired Methods)*: these algorithms were created following the ideas of biological evolution, but in fact, they can be regarded as population-based adaptive stochastic methods. At least three different types were developed independently in the late 1960s and early 1970s:
  - * Genetic Algorithms (GAs)[97-99]
  - * Evolutionary Programming (EP)[100, 101]
  - * Evolution Strategies (ES)[102-104]
- *Simulated Annealing (SA), and Variants:* these methods were created by simulating certain natural phenomena taking place at the atomic level in the cooling of metals[105-106]
- *Other Metaheuristics:* recently, a number of (so called) meta-heuristics have been presented, mostly based on other biological or physical phenomena, and with combinatorial optimization as their original domain of application. Examples of these more recent methods are Taboo Search (TS), Ant Colony Optimization (ACO)[107,108] and particle swarm methods[109]. A review of these and other recent techniques can be found in ref.[110].

Genetic algorithms (GAs) and simulated annealing are, so far, the most popular types of methods, but, as many authors have reported during recent years, they are usually not the most efficient and robust algorithms for GO. In fact, for GO in real variables, many other simple techniques outperform both GAs and SA, which were originally developed with combinatorial problems (integer variables) in mind. In any case, the literature is very fragmented, and there is a lack of sound comparative studies. This complicates the selection of methods for a given type of GO problem. Furthermore, although the topic is still the subject of great debate, it should be noted that for the general GO problem with no known structure a priori, there is no best method[111]. Yet, for the case of GO of nonlinear dynamic processes, different recent experiences indicate that certain simple stochastic methods and ES might present the best performance[22,28,112].

Considering the main topic of this review, the dynamic optimization of bioreactors, adaptive stochastic methods have been proposed as robust alternatives by

Banga and co-worker[19,20,21,28]. Other researches have used other types of stochastic algorithms, including different random search algorithms, arriving to similar conclusions[113-115]. Genetic algorithms and related evolutionary algorithms, which were suggested for solving general optimal control problems by several authors[116-118], have also been extensively used for the optimization of fed-batch fermentation in the last decade[22,119-128]. Other metaheuristics, like Ant Colony Optimization, have also been successfully employed[23].

Several works have performed partial comparisons of different types of methods[27,71,121,129], but more work is needed in order to arrive to meaningful conclusions. In particular, a uniform set of benchmark problems should be used. Moreover, simple comparison of computation times and final performance index values are not adequate. Rather, standard convergence curves (i.e. performance index versus computation time) should be used, together with a systematic approach (e.g. the use of function evaluations for measuring computational effort should be avoided, since different methods can have other very different overheads due to their structure).

Hybrid Stochastic-Deterministic Methods

Using the above- mentioned stochastic methods, refined solutions are usually obtained at a very large computational cost. Although there is always a trade-off between convergence speed and robustness in both stochastic and deterministic (local) methods, the latter usually have the opposite behaviour, i.e. they converge very fast if they are started close to the global solution. Clearly, a convenient approach would be to combine both methodologies in order to compensate for their weaknesses while enhancing their strengths. A hybrid (stochastic-deterministic) approach was suggested by Banga and Seider[28], and later considered by Balsa-Canto *et al.*[22] and Carrasco and Banga[130] with very good results. This approach was developed by adequately combining the key elements of a stochastic and a deterministic method, taking advantage of their complementary features. Other authors have also used hybrid approaches, confirming their usefulness[121,131].

Recently, Banga *et al.*[21] considered the general problem of dynamic optimization of bioprocesses with unspecified final time. Several solution strategies, both deterministic and stochastic, were compared based on their results for a set of case studies. These strategies included two types of gradient-based CVP methods, one complete parameterization (CP) method, four different stochastic methods (using CVP) and a two-phase hybrid method. The comparative evaluation of their efficiency and robustness indicated the superiority of the hybrid approach, presenting the best compromise between robustness and efficiency.

Conclusions

The dynamic optimization (open loop optimal control) of fed-batch bioreactors was considered in this contribution. A review of the available solution techniques for this class of problems was presented, with particular attention to the control vector parameterization (CVP) approach. The CVP approach is a direct method, which transforms the original problem into a non-linear programming (NLP) problem, which must be solved by a suitable (efficient and robust) solver. In this regard, the numerical difficulties arising from the non-linear, constrained and often discontinuous nature of these systems were highlighted.

In order to surmount these difficulties, special emphasis was placed on reporting several alternative stochastic and hybrid techniques based on the CVP approach. In particular, recent results considering hybrid techniques, which use combinations of global optimization methods followed by fast local deterministic method, suggest they can adequately handle the nonconvexity of many of these NLPs.

Research Trends And Needs

Finally, several research trends and needs are outlined. In the first place, a very promising numerical approach is based on the flatness of dynamic systems: a dynamic optimization problem can be transformed into a lower dimensional nonlinear programming problem through the use of flat outputs[132,133].

Second, fed-batch bioreactors are not isolated units in bioprocess plants. There is a need of methods for obtaining the optimal operating policies for full biochemical plants, which means taking into account their discrete-continuous nature[134, 135].

Third, apart from the computation of the optimal operating policies for fed-batch bioreactors, dynamic optimization can be used to solve other important problems in bioprocess engineering. For example, Conejeros and Vassiliadis[136-138] have recently used a dynamic optimization framework to identify reaction bottlenecks for dynamic fermentation processes. This procedure facilitates the identification of enzymatic reactions for possible genetic manipulation by considering the impact of process time and operating conditions simultaneously. Other researches[139-141] have used dynamic optimization to design optimal identification experiments for nonlinear dynamic bioprocesses.

Therefore, it is clear that dynamic optimization already plays a very significant role in bioprocess systems engineering, and this situation can only increase during the coming years.

References

1 K Shimizu *Comput Chem Eng* **20** (1996) 915

2 J E Bailey *Biotechnol Prog* **14** (1998) 8

3 R Simutis, R Oliveira, M Manikowski, S F d Azevedo and A Lubbert *J Biotechnol* **59** (1997) 73

4 A Lubbert and S Bay Jorgensen *J Biotechnol* **85** (2001) 187

5 K Schugerl *J Biotechnol* **85** (2001) 149

6 T A Bibila and D K Robinson *Biotech Prog* **11** (1995) 1

7 A E Bryson *Dynamic Optimization* Addison Wesley Longman Menlo Park CA (1999)

8 S K Agrawal and B C Fabien *Optimization of Dynamic Systems* Kluwer Academic Publishers Dordrecht Boston (1999)

9 A Johnson *Automatica* **23** (1987) 691

10 K Y Rani and V S R Rao *Bioproc Eng* **21** (1999) 77

11 G Bastin and D Dochain *On-line Estimation and Adaptive Control Bioreactors* Elsevier Amsterdam (1990)

12 F Uesbeck, N J Samsatli, L G Papageorgiou and N Shah *Comput Chem Eng* **22** (1998) S167

13 C Kuhlmann, I D L Bogle and Z S Chalabi *Bioprocess Engineering* **19** (1998) 53

14 W E Schiesser *The Numerical Method of Lines* Academic Press New York (1991)

15 W E Schiesser *Computational Mathematics in Engineering and Applied Science* ODEs, DAEs and PDEs CRC Press Inc (1994)

16 C T Chen and C Hwang *Ind Eng Chem Res* **29** (1990) 1869

17 C T Cheng and C Hwang *Chem Eng Commun* **97** (1990) 9

18 R Luus *Comput Chem Eng* **17** (1993) 373

19 J R Banga, A A Alonso and R P Singh *AIChE Annual Meeting* San Francisco (1994)

20 J R Banga, A A Alonso and R P Singh *Biotech Prog* **13** (1997) 326

21 J R Banga, A A Alonso, C G Moles and E Balsa-Canto *Proc Mediterranean Conference on Control and Automation (MED2002)* Lisbon Portugal (2002)

22 E Balsa-Canto, A A Alonso and J R Banga *Presented at, ACoFop IV (Automatic Control of Food and Biological Processes)* Göteborg Sweden (1998)

23 V K Jayaraman, B D Kulkarni, K Gupta, J Rajesh and H S Kusumaker *Biotech Prog* **17** (2001) 81

24 H C Lim, Y J Tayeb, J M Modak and P Bonte *Biotechnol Bioeng* **28** (1986) 1408

25 J E Cuthrell and L T Biegler *Comput Chem Eng* **13** (1989) 49

26 R Luus *Biotech Bioeng* **41** (1993) 599

27 S A Dadebo and K B McAuley *Comput Chem Eng* **19** (1995) 513

28 J R Banga and W D Seider *State of the Art in Global Optimization* (Eds. C A Floudas and P M Pardalos) *Kluwer Academic Pub Dordrecht The Netherlands* (1996)

29 S Park and W F Ramirez *AIChE J* **34(9)** (1988) 1550

30 R Luus *IEEE Trans Autom Control* **37(11)** (1992) 1802

31 V S Vassiliadis *Computational Solution of Dynamic Optimization Problems with General Differential-Algebraic Constraints* Imperial College University of London London (1993)

32 R L Yang and C P Wu *Presented at the First Asian Control Confence* Tokyo Japan (1994)

33 R Luus *Presented at the IASTED Int Conf on Modelling and Simulation* Pittsburg PA USA (1995)

34 J R Banga, R Irizarry Rivera and W D Seider *Comput Chem Eng* **22** (1998) 603

35 A Tholudur and W F Ramirez *Int J Control* **68(5)** (1997) 1115

36 E BalsaCanto, J R Banga, A A Alonso and V S *Vassiliadis Ind Eng Chem Res* **39** (2000) 4287

37 J Lee and W F Ramirez *AIChE J* **40(5)** (1994) 899

38 A Tholudur and W F Ramirez *Biotech Prog* **12** (1996) 302

39 E F Carrasco and J R Banga *Ind Eng Chem Res* **36(6)** (1997) 2252

40 A Bryson and Y-C Ho *Applied Optimal Control* New York Hemisphere Publishing Corporation (1975)

41 H Ohno and E Nakanishi *Biotechnol and Bioeng* **18** (1976) 847

42 S Y San and G Stephanopoulos *Biotechnol and Bioeng* **26** (1984) 1261

43 J Hong *Biotechnol and Bioeng* **28** (1986) 1421

44 J M Modak, H C Lim and Y J Tayeb *Biotech Bioeng* **28** (1986) 1396

45 L Cazzador *Biotechnol and Bioeng* **31** (1988) 670

46 A Menawat, R Mutharasan and D R Coughanowr *AIChE J* **33** (1987) 776

47 J M Modak and H C Lim *Biotech Bioeng* **33** (1989) 11

48 J M Modak and H C Lim *Chem Eng J* **42** (1989) B15

49 Y R Pyun, J M Modak and Y K Chang *Biotech Bioeng* **33** (1989) 1

50 K Y San and G Stephanopoulos *Biotech Bioeng* **34** (1989) 72

51 K San and G Stepahnopoulos **34** (1989) 72

52 I Queinnec, B Dahhou and Y Sevely *J Syst Eng* **1** (1991) 31

53 A Meszaros and V Bales *Bioproc Eng* **7** (1992) 363

54 J M Modak and H C Lim *Chem Eng Sci* **47** (1992) 3869

55 J M Modak *Chem Eng J* **52** (1993) B59

56 S J Parulekar *Chem Eng Sci* **47** (1992) 4077

57 S Shioya *Adv Biochem Eng Biotechnol* **46** (1992) 111

58 J F VanImpe, B M Nicolai and P A Vanrolleghem *Chem Eng Comm* **117** (1992) 337

59 J M Hansen and H C Lim *Jour Chem Eng Sci* **48** (1993) 2375

60 J M Modak *Chem Eng J* **52** (1993) B59

61 J Lee and W F Ramirez *AIChE J* **40** (1994) 899

62 I Queinnec and B Dahhou *Opt Control Appl Meth* **15** (1994) 175

63 B Tartakovsky, S Ulitzur and M Sheintuch *Biotech Prog* **11** (1995) 80

64 J F VanImpe, B M Nicolai and J Vandewalle *Optimal Control Applications and Methods* **15** (1994) 13

65 I Y Smets and J F Van Impe *Math Comput Simul* (2002) (In Press)

66 A Jayant and S Pushpavanam *Ind Eng Chem Res* **37** (1998) 4314

67 J-H Lee, H C Lim, Y J Yoo and Y H Park *Bioproc Eng* **20** (1999) 137

68 H J Oberle and B Sothmann *J Optim Theory Appl* **100** (1999) 1

69 R Bellman *Dynamic Programming* Princeton University Press Princeton New Jersey (1959)

70 M De Tremblay, M Perrier, C Chavarie and J Archambault *Bioprocess Eng* (1992) 229

71 J A Roubos, C D d Gooijer, G V Straten and A J B V Boxtel *Bioprocess Engg* **17** (1997) 99

72 J S Lin and C Hwang *Ind Eng Chem Res* **37** (1998) 2469

73 C J Goh and K L Teo *Automatica* **24** (1988) 3

74 K L Teo, C J Goh, K H Wong *A Unified Computational Approach to Optimal Control Problems* Longman Scientific and Technical Harlow UK (1991)

75 R W H Sargent and G R Sullivan *8th IFIP Conf Optimization Tech* **Pt 2** (1977)

76 V S Vassiliadis, C C Pantelides and R W H Sargent *Ind Eng Chem Res* **33** (1994) 2111

77 V S Vassiliadis, C C Pantelides and R W H Sargent *Ind Eng Chem Res* **33** (1994) 2123

78 J E Cuthrell and L T Biegler *Comput Chem Eng* **13** (1989) 49

79 L T Biegler, A M Cervantes and A Wachter *Chem Eng Sci* **57** (2002) 575

80 S Pushpavanam S Rao and I Khan *Ind Eng Chem Res* **38** (1999) 1998

81 V S Vassiliadis, E Balsa-Canto and J R Banga *Chem Eng Sci* **54** (1999) 3851

82 P I Barton, R J Allgor and S Galan *Ind Eng Chem Res* **37** (1998) 966

83 R Horst and H Tuy *Global Optimization: Deterministic Approaches* Springer-Verlag Berlin Germany (1990)

84 I E Grossmann *Global Optimization in Engineering Design* Kluwer Academic Dordrecht Boston (1996)

85 C A Floudas *Deterministic Global Optimization: Theory, Methods and Applications* Kluwer Academic Publishers Dordrecht (2000)

86 A Törn, M Ali and S Viitanen *J Global Optim* **14** (1999) 437

87 C Guus, E Boender and H E Romeijn *Handbook of Global Optimization* Kluwer (1995)

88 W R Esposito and C A Floudas *J Global Optim* **17** (2000) 97

89 A B Singer, J K Bok and P I Barton *Computer Aided Chemical Engineering* **9** (2001) 767

90 I Papamichail and C S Adjiman *J Global Optim* **24** (2002)1

91 S H Brooks *Operations Research* **6** (1958) 244

92 J Matyas *Automat Remote Contr* **26** (1965) 246

93 L A Rastrigin and Y Rubinstein *Automat Control* **2** (1969) 23

94 M A Schumer and K Steiglitz *IEEE Trans Automatic Control* **13** (1968) 270

95 Z B Zabinsky and R L Smith *Math Programm* **53** (1992) 323

96 M M Ali, C Storey and A Törn *J Optim Theory Appl* **95** (1997) 545

97 J H Holland *Adaptation in Natural and Artificial Systems: An Introductory Analysis with Applications to Biology, Control, and Artificial Intelligence* University of Michigan Press Ann Arbor (1975)

98 D E Goldberg *Genetic Algorithms in Search, Optimization Machine Learning* Addison Wesley Longman (1989)

99 Z Michalewicz Genetic Algorithms + Data Structures = Evolution Programs Springler-Verlag (1996)

100 L J Fogel, A J Owens and M J Walsh *Artificial Intelligence through Simulated Evolution* Wiley New York (1966)

101 D B Fogel *Evolutionary Computation: the Fossil Record* IEEE Press New York (1998)

102 H-P Schwefel *Evolution and Optimum Seeking* Wiley New York (1995)

103 H G Beyer *Evolut Comp* **3 (3)** (1996) 311

104 H G Beyer and H P Schwefel *Natural Computing* **1** (2002) 3

105 S Kirkpatrick, C D Gellatt and M P Vecchi *Science* **220** (1983) 671

106 P J M v Laarhoven and E H L *Aarts Simulated Annealing: Theory and Applications* Reidel Publishing Company Dordrecht (1987)

107 M Dorigo, V Maniezzo and A Colorni *IEEE Trans Syst Man Cyb B* **26** (1996) 29

108 E Bonabeau, M Dorigo and G Theraulaz *Nature* **406** (2000) 39

109 E Bonabeau, M Dorigo and G Theraulaz *Swarm Intelligence: From Natural to Artificial Systems* Oxford University Press New York (1999)

110 D Corne, M Dorigo and F Glover *New Ideas in Optimization* McGraw-Hill (1999)

111 D H Wolpert and W G Macready *IEEE Trans Evolut Comp* **1** (1997) 67

112 L Costa and P Oliveira *Comput Chem Eng* **25** (2001) 257

113 R Simutis and A Lubbert *J Biotechnol* **52** (1997) 245

114 R Luus and D Hennessy *Ind Eng Chem Res* **38** (1999) 1948

115 F Rodriguez-Acosta, C M Regalado and N V Torres *J Biotechnol* **68** (1999) 15

116 Z Michalewicz, C Z Janikow and J B Krawkczyk *Comput Math Appl* **23** (1992) 83

117 H Seywald, R R Kumar and S M Deshpande *J Guid Contr Dyn* **18** (1995) 177

118 Y Yamashita and M Shima *Nonlinear Anal-Theory Meth Appl* **30** (1997) 2285

119 K Matsuura, H Shiba, Y Nunokawa and H Shimizu *Sebutsu-Kogaku Kaishi – J Soc Ferm Bioeng* **71** (1993) 171

120 J A Roubos, G van Straten and A J B van Boxtel *J Biotechnol* **67** (1999) 173

121 J-P Chiou and F-S Wang *Comput Chem Eng* **23** (1999) 1277

122 F-S Wang and J-W Sheu *Chem Eng Sci* **55** (2000) 3685

123 K Zuo and W T Wu *Comput Chem Eng* **24** (2000) 1105

124 I L Lopez Cruz, L G van Willigenburg and G van Straten *Proc IASTED International Conf on Control Applications* 2000 Cancun (Mexico)

125 L Z Chen, S K Nguang and X D Chen *Proc American Control Conf* **5** (2001) 3811

126 S K Nguang, L Chen and X D Chen *ISA Transac* **40** (2001) 381

127 J G Na, Y K Chang, B H Chung and H C Lim *Bioproc Biosyst Eng* **24** (2002) 299

128 M Ronen, Y Shabtai and H Guterman *J Biotechnol* **97** (2002) 253

129 J H Lee *Appl Biochem Biotech* **81** (1999) 91

130 E F Carrasco and J R Banga *IEE Conference Publication (The Institution of Electrical Engineers)* **2** (1998) 925

131 Y J Shimizu *J Chem Eng Jap* **32** (1999) 51

132 R Mahadevan, S K Agrawal and F J Doyle *Control Eng Practice* **9** (2001) 889

133 J Oldenburg and W Marquardt *Comp Chem Eng* **26** (2002) 385

134 P I Barton, J R Banga and S Galan *Comp Chem Eng* **24** (2000) 2171

135 E Chekhova, P I Barton and A Gorak *Comput Chem Eng* **24** (2000) 1167

136 R Conejeros and V S Vassiliadis *Ind Eng Chem Res* **37** (1998a) 4699

137 R Conejeros and V S Vassiliadis *Ind Eng Chem Res* **37** (1998b) 4709

138 R Conejeros and V S Vassiliadis *Biotechnol Bioeng* **68** (2000) 285

139 K J Versyck, J E Claes and J F Van Impe *Math Comput Simul* **46** (1998) 621

140 J R Banga, K J Versyck and J F V Impe *European Symposium on Computer Aided Process Engineering-10* (Ed. S Pierucci) (2000) 37

141 J R Banga, K J Versyck and J F VanImpe *Ind Eng Chem Res* **41** (2002) 2425