Invited Paper

Analyses of Methods and Algorithms for Modelling and Optimization of Biotechnological Processes

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Abstract: *A review of the problems in modeling, optimization and control of biotechnological processes and systems is given in this paper. An analysis of existing and some new practical optimization methods for searching global optimum based on various advanced strategies – heuristic, stochastic, genetic and combined are presented in the paper. Methods based on the sensitivity theory, stochastic and mix strategies for optimization with partial knowledge about kinetic, technical and economic parameters in optimization problems are discussed. Several approaches for the multi-criteria optimization tasks are analyzed. The problems concerning optimal controls of biotechnological systems are also discussed.*

Keywords: *Modeling, Optimization, Uncertainty, Global optimization, Weight coefficients, Decision making, Data filtering, Optimal control, Dynamic programming, Iterative dynamic programming, Neuro-dynamic programming.*

Introduction

The optimization problems vary largely depending on the task formulation and the specific features of the process or system. For biotechnological processes in particular very often it is necessary to adapt mathematical models or to select a model from several ones competitive to each other. In such cases it is necessary to estimate parameters in strongly non linear mathematical models with some uncertainties. The created functional to be minimized in parameter estimation is very often multimodal. Occasionally the obtained optimal solution is "compromised" if the classical gradient or direct optimization methods are used for multimodal objective functions. The significant nonlinearities and uncertainties in mathematical models create also difficulties when optimal control strategies in biotechnological processes and systems are applied.

Main problems in modeling, optimization and control of biotechnological systems

The optimization problems in biotechnological processes and systems differ in the following signs:

- The objective function is complex and requires a lot of time for evaluation even when using up-to-date computing systems;
- The objective function is multimodal or/and of a ridge type;
- The number of local minimums (or maximums) of the objective function can be small or very large (some times several hundreds or thousands);
- The number of estimated parameters in the mathematical model is very large;

- The number of control variables is very large;
- The optimization task is with mix – integer control variables;
- The number of objective functions is more then one;
- The experimental data used for process identification are highly noised.

An attempt to review and to compare some of the up-to-date tendencies in optimization technique used for biotechnological systems is presented in this article.

The peculiarities of problems in mathematical modeling of biotechnological processes are well presented in many studies [8, 9, 10, 11, 12, 18, 21, 32, 65, 84]. Let us examine as an example the mathematical model of the bioprocess for production of *L-lysine* in a bioreactor [31, 32, 60, 61]:

$$\begin{aligned}
&\frac{dX}{dt} = \mu X - \frac{F}{V}X \\
&\frac{dS}{dt} = \frac{F}{V}(S_{in} - S) - k_5\mu X - k_6 X - k_7\eta X \\
&\frac{dTr}{dt} = \frac{F}{V}(Tr_{in} - Tr) - k_{13}\mu X - \frac{F}{V}Tr \\
&\frac{dC_L}{dt} = k_l a(C^* - C_L) - k_{14}\mu X - k_{15}X - k_{16}\eta X - \frac{F}{V}C_L \\
&\frac{dL}{dt} = \eta X \\
&\frac{dV}{dt} = F
\end{aligned} \tag{1}$$

$$\mu = \frac{k_1 Tr C_L}{(k_2 + Tr)(k_3 + S_0 - S)(k_4 + C_L)}, \quad \eta = \frac{k_8 S C_L}{(k_9 + S)(k_{10} + S)(k_{11} + C_L)(k_{12} + C_L)},$$

where:

μ – specific growth rate of *L-lysine* synthesis, h^{-1}; η – specific consummation rate of *L-lysine*, h^{-1}; t – process time, h; Tr – *Threonine* concentration, $mg\cdot l^{-1}$; Tr_{in} – initial *Threonine* concentration, mgl^{-1}; F – feed flow rate, lh^{-1}; S – glucose concentration, $g\cdot l^{-1}$; S_0 – feed substrate concentration, $g\cdot l^{-1}$; S_{in} – input feed substrate concentration, $g\cdot l^{-1}$; C^* – equilibrium dissolved oxygen concentration, $g\cdot l^{-1}$; C_L – dissolved oxygen concentration, $g\cdot l^{-1}$; L – *L-lysine* concentration, $g\cdot l^{-1}$; X – biomass concentration, $g\cdot l^{-1}$; V – working liquid volume, l; $k_l a$ – volumetric oxygen mass-transfer coefficient, h^{-1}; $k_1 \div k_{16}$ – process model constants.

The problems that might appear in modeling, optimization and optimal control in a similar to the above given object as in many other biological systems are as follows:

(a) Selection of the best model if a number of competitive models exist [31].

(b) Estimation of the process constants $k_1 \div k_{16}$ and $k_l a$ in the accepted mathematical model using experimental data through minimization of the created functional for the nonlinear parametrical identification of the model:

$$\Phi = \sum_{i=1}^{N}\left[L_{i,\exp.} - L_{i,calc.}(k_1, k_2, \ldots, k_{16}, k_l a)\right]^2 \to \min_{k_j} \tag{2}$$

Most often the functional (2) is multimodal and a reliable method for global minimization is needed [9, 16, 52, 54, 68, 69, 70, 80, 79, 83].

(c) Selection of a method for smoothing the noised experimental data [1, 71].

(d) To find the optimal control $u_{opt}(t)$ (for example optimal profile of the feed flow rate $F(t)$ of a fed-batch process, the stirrer rotation speed $n(t)$, gas flow rate $Q(t)$, etc.) over the certain period from initial time t_0 to the final time of fermentation t_f in order to obtain maximum quantity of useful product (for example *L-lysine*). For this purpose it is necessary to maximize the functional:

$$J = \int_{t_0}^{t_f} f[L(t), V(t), F(t), Q(t), n(t)]dt \;\rightarrow \max_{u(t)\in U} \tag{3}$$

When solving the task for optimal control, the following problems could appear:

- Estimation of the optimal number of discrete intervals during the time $t_0 \div t_f$;
- Selection of en effective method for solving the task of dynamic programming:
  - Classical algorithm of Bellman [2];
  - Iterative dynamic programming [46, 47, 48, 49, 50, 51];
  - Neuro-dynamic programming [3, 30, 31, 32, 35, 37];
  - Combined methods of dynamic programming [28, 29, 33, 34, 36], etc.
- Selection of a method for global optimization in the cases of multiple times maximization of the functional (3);
- Selection of a strategy for optimization under uncertainty regarding the precise values of some parameters in the mathematical model (kinetic constants, heat transfer coefficients, etc);

(e) Selection of a strategy for multicriteria optimization when several objective criteria are formulated (maximum quantity of useful product, maximum biological activity of the product, maximum degree of consumption of the substrate in the feeding solution, minimum time for conversion, etc.).

Optimization tasks for searching global optimum

Problem formulation for global optimization

Searching the global optimum is necessary very often in modeling and control of biological processes and systems, because of the high nonlinearity of the system. The optimization problem considered is the determination of a vector of n control variables (or estimated model parameters) $\mathbf{x}^* = (x_1^*, x_2^*, ..., x_n^*)$, which will maximize (or minimize) a given multimodal objective continuous function (4) subject to constraints of control variables $\mathbf{x} \in X$, equality $\mathbf{h(x)} = 0$ and/or inequality $\mathbf{g(x)} \leq 0$ constraints, where X is the feasible region of the control variables:

$$\max_{\mathbf{x}\in X} Q(\mathbf{x}) = f(x_1, x_2, ..., x_n) \tag{4}$$

Problems in selection of global search algorithms

A large number of methods for searching of a global optimum have been proposed during the last years [17, 19, 23, 27, 38, 39, 43, 44, 45, 52, 54, 63, 75, 80, 87], however no effective method for solving complex practical problems with a large number of local optimums and for objective functions requiring a lot of computational time has been found to date. The probability to find the global optimum by use of classical gradient and non gradient methods is rather low. Because of the effort to identify a reliable algorithm, many new methods for global search have been introduced in the last 40 years. The methods of random search or combinations of positive features of different methods using different heuristic ideas seem to be relatively more effective. The so called “genetic algorithms” are widely discussed recently

[16, 44, 70, 75]. In spite of the fact that the genetic algorithms are introduced as new methods the earliest ideas are given by M. Box [5] and developed later by including new heuristic, clusters and genetic elements [39, 52, 54, 63, 80]. The controlled random search method proposed by Price [63] as a base of genetic algorithms is very promising. The method of Price has undergone many modifications towards its further perfection [6, 38, 39].

Genetic algorithms as up-to-date strategies for global optimization in biotechnological systems

The genetic algorithms are largely used during the last years for optimization and mathematical models parameter estimation in biotechnological processes. They are highly interconnected with many other optimization methods and algorithms as heuristic, stochastic, adaptive and are using a lot of heuristic rules. This is the reason that many of the algorithms having genetic character are not defined as “genetic”.

Genetic algorithms start from a great number of initial points (named “*population*”) in which the objective function is estimated. The solutions from one population are used in the next population. This is grounded on the expectation that the new population will be better than the old one. The points of the new population are chosen according to their “capacity for living” i.e. improved values of the objective function. Search for “better points” for the objective function and consecutively rejection of the “worst points” continues until certain accepted stop criterion of the algorithm has been fulfilled. For example: total number of iterations, the precision of the found solution, etc. The algorithms differ from each other in accepted heuristic constants, way of analysis of the set of solutions and the strategy to refuse worst solutions and to keep the better ones in each iteration of the search process.

Genetic algorithms have been applied to a wide range of bioprocess engineering problems, such as parameter identification [43, 64, 65, 69, 71, 72, 75], feeding trajectory optimization [8, 9, 53, 74], etc. The presented solutions of the off-line parameter estimation problems of fermentation processes models are a stimulated sign of the very challenging nature of the bioprocess optimization problems [71, 73, 75].

However, the optimization technique using genetic algorithms is not a panacea, despite its apparent robustness. There are a lot of parameters involved in the algorithm. In general, some form of trial-and-error tuning is necessary for each particular instance of optimization problem. The appropriate setting of these parameters is a key point for success [65, 66, 67, 71]. The main disadvantage of genetic algorithms is the large number of necessary computations of the objective function and slow convergence which could create difficulties in on-line process identifications and process control. This is the reason for continuous searching effective methods, which will satisfy the requirements for high convergence to the global optimum and minimum number of function evaluation.

Many variations of the genetic algorithms can be found in the literature [13, 23, 42]. A modifications that aims to adapt the algorithm to particular problem domain – parameter identification of fermentation processes models are presented in [70, 73].

Analysis of the efficiency of global optimization strategies

Surveys on convergence and efficiency of different algorithms with regards to global search [27, 54, 79, 80, 83] demonstrate that the combinations of different algorithms may lead to improvement the effectiveness of the global search. A number of algorithms for global optimization have been investigated with real practical and test multimodal objective functions with small and very large (up to several hundreds) local optimums [20, 39, 54, 83] comparing the convergence and the average number of objective function evaluations only for solved tasks. The results are shown on Fig. 1 and Fig. 2. The investigated algorithms are the following:

(1) Multi random search [80];
(2) Modified method of Gelfand and Tcetlin for global optimization [22, 83];
(3) Multi-complex method – genetic algorithm [5, 80];
(4) Random search – interval metrics [83];
(5) Random search – directed cones [83];
(6) Modified Luus – Jaacola method [45, 83];
(7) Modified Wang – Luus method [83, 87];
(8) Shifting constraints with complex method [80];
(9) Modified genetic algorithm of Price [63, 80];
(10) Tunneling method [43].

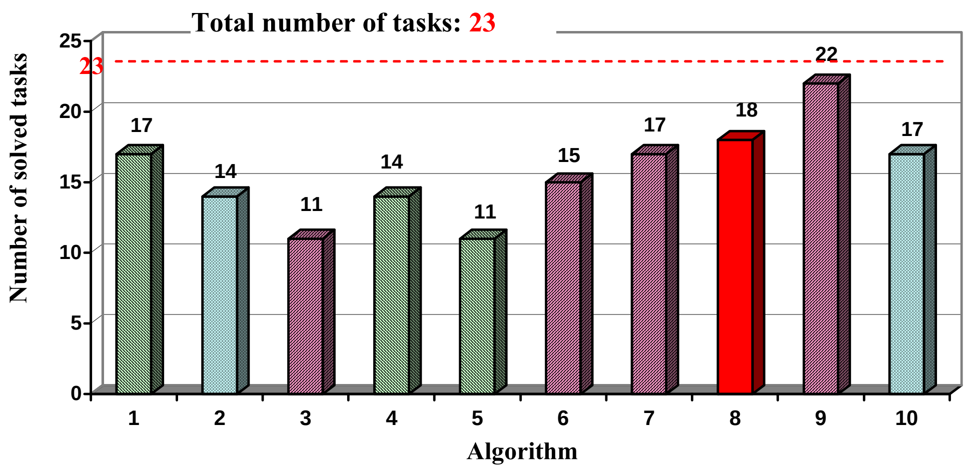

Fig. 1 Number of solved global optimization problems

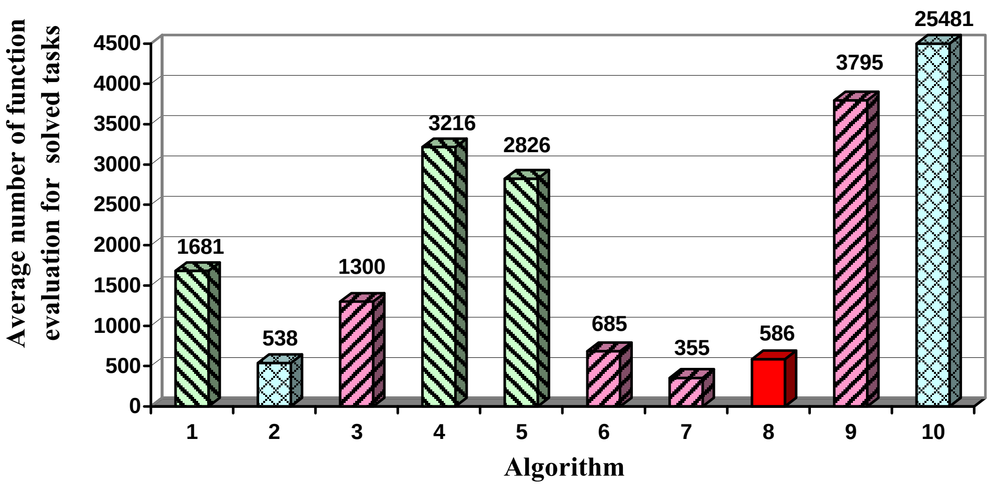

Fig. 2 Average number of function evaluation for solved tasks

The genetic algorithm of Price modified with new heuristic rules has the best convergence (96%) (Fig. 1). The method of shifting constraints combined with complex method also demonstrates good convergence (78%). This algorithm uses every better local optimum found by complex – method as an inequality constraint in order to avoid unnecessary search in the domains without expectation. This combination reduces the number of objective function evaluations about six times in comparison to the Price method (Fig. 2).

The very well theoretically grounded tunneling method shows 74% convergence, but it has about 7 times lower efficiency concerning the number of required computations in comparison to the Price method.

Optimization problems under uncertainty

Another significant optimization problem in design and control of biotechnological systems is the existence of uncertainty from various kinds:

- Structural and parametric;
- Internal and external;
- Quantitative and qualitative;
- Total or partial uncertainty.

The most common optimization cases comprise external quantitative and qualitative uncertainties and process coefficients and other parameters. It is presumed that there is partial knowledge for at least one of the following characteristics: nominal value, the expected value, the interval of expectance, dispersion (standard deviation) or the distribution function.

The uncertainties can be involved in the objective function and (or) in the constraints. The uncertainties are related mainly to imperfect knowledge of the values of kinetic, heat transfer catalytic or other constants (for example the constants $k_1 \div k_{16}$ and k_la in mathematical model (1)) or external changes of the quality and property of feeding flows, raw materials and energy supply. The quality requirements, the prices of raw materials or energy, also the trade policies are always potential uncertainties in searching of optimal solutions.

A variety of aspects on optimization tasks under uncertainties problem have been examined and different approaches for overcoming the problem have been published [4, 59, 76, 78, 80, 82].

- Maximum determination of the uncertainty;
- Synthesis of robust systems;
- Synthesis of adaptive systems;
- Applying different optimization strategies in cases of partial knowledge.

Three different strategies for optimal design and optimal operations are mostly applied in the case of uncertainty:

- Strategies based on the minimization of the sensitivity of the optimal solution in the presence of uncertainty [7];
- Strategies based on the probability characteristics of the uncertain parameters [4, 24];
- Mixed strategies [56].

Formulation of the optimization task under uncertainty

Since optimization under uncertain parameters **p** appears most often at design stage, let us divide the searched optimal variables into design **d** and control **x** variables, despite that the design variables **d** can be added to the control variables **x**. Let us assume searching the maximum of the objective function:

$$\max_{\mathbf{x}\in X,\mathbf{d}\in D} Q(\mathbf{x},\mathbf{d},\mathbf{p}) \tag{5}$$

in the feasible domain of control and design variables $\mathbf{x}\in X, \mathbf{d}\in D$ subject to equality and/or inequality constraints

$$\mathbf{h}(\mathbf{x},\mathbf{d},\mathbf{p}) = 0 \tag{6}$$

$$\mathbf{g}(\mathbf{x},\mathbf{d},\mathbf{p}) \le 0 \tag{7}$$

Basic strategies for optimization under uncertainty

A universal strategy to solve the task (5) is still to be suggested for all optimization tasks under uncertainty. All strategies aim at finding an optimal solution which is maximum invariant to the incomplete information. Some of the widely applied strategies for optimization under quantitative parametric uncertainties are the following:

Strategies based on the sensitivity. The basic strategy is simultaneously to maximize the basic objective function (5) $Q(\mathbf{x}, \mathbf{d}, \mathbf{p})$ and to minimize the normalized sensitivity function $S_N(\mathbf{x}, \mathbf{d}, \mathbf{p})$

$$\max_{\mathbf{x}\in X,\mathbf{d}\in D} [Q(\mathbf{x},\mathbf{d},\mathbf{p}) - S_N(\mathbf{x},\mathbf{d},\mathbf{p})] \tag{8}$$

where:

$$S_N(\mathbf{x},\mathbf{d},\mathbf{p}) = \sum_{i=1}^{m} \lambda_{pi} \left| \frac{\partial Q(\mathbf{x},\mathbf{d},\mathbf{p})}{\partial p_i} \frac{p_{Ni}}{Q(\mathbf{x},\mathbf{d},\mathbf{p})} \right|, \tag{9}$$

p_{Ni} are the nominal values of p_i and λ_{pi} are the accepted weight coefficients for p_i. Methods for estimation of λ_{pi} can be found in [80].

Another approach is to add the sensitivity to the optimization task as an inequality constraint:

$$\max_{\mathbf{x}\in X,\, \mathbf{d}\in D} Q(\mathbf{x},\mathbf{d},\mathbf{p}) \tag{10}$$

$$\text{s.t. } \left|S_N(\mathbf{x},\mathbf{d},\mathbf{p})\right| \le S_{0i},\ i = 1,2,\ldots,m \tag{11}$$

The main difficulty in the strategy (10), (11) is to define the value of S_{0i}.

Optimization task under uncertainty can be also expressed as a double criteria optimization problem [78, 80] and to be solved using the methods of reference solutions trough minimization of function of losses

$$\min_{\mathbf{x}\in X,\mathbf{d}\in X} \Phi_{loss}(\mathbf{x},\mathbf{d},\mathbf{p}) = \min_{\mathbf{x}\in X,\mathbf{d}\in X} \left\{ \left(\frac{Q_{\max} - Q(\mathbf{x},\mathbf{d},\mathbf{p})}{Q_{\max} - Q_{\min}} \right)^2 + \left(\frac{S_{\min} - S_N(\mathbf{x},\mathbf{d},\mathbf{p})}{S_{\max} - S_{\min}} \right)^2 \right\} \tag{12}$$

or maximization of the function of usefulness

$$\max_{\mathbf{x}\in X,\mathbf{d}\in X} \Phi_{use}(\mathbf{x},\mathbf{d},\mathbf{p}) = \max_{\mathbf{x}\in X,\mathbf{d}\in X} \left\{ \left(\frac{Q(\mathbf{x},\mathbf{d},\mathbf{p}) - Q_{\min}}{Q_{\max} - Q_{\min}} \right)^2 + \left(\frac{S_{\max} - S_N(\mathbf{x},\mathbf{d},\mathbf{p})}{S_{\max} - S_{\min}} \right)^2 \right\} \tag{13}$$

where

$$Q_{\max} = \max_{\mathbf{x}\in X,\mathbf{d}\in X} Q(\mathbf{x},\mathbf{d},\mathbf{p}_N); \tag{14}$$

$$Q_{\min} = \min_{\mathbf{x}\in X,\mathbf{d}\in X} Q(\mathbf{x},\mathbf{d},\mathbf{p}_N); \tag{15}$$

$$S_{max} = \max_{\mathbf{x}\in X, \mathbf{d}\in X} S_N(\mathbf{x},\mathbf{d},\mathbf{p}_N); \quad (16)$$

$$S_{min} = \min_{\mathbf{x}\in X, \mathbf{d}\in X} S_N(\mathbf{x},\mathbf{d},\mathbf{p}_N). \quad (17)$$

The strategies using the *sensitivity function* are suggested for the following cases:

- Small deviations of uncertain parameters;
- Possible linearization of the objective functions in the region of uncertainty;
- The boundaries of the uncertain parameters are known;
- Small number of uncertain parameters.

Stochastic strategies. If the probability function of distribution $f(\mathbf{p})$ of uncertain parameters p_i is known the following strategy can be used

$$\max_{\substack{\mathbf{x}\in X\\ \mathbf{d}\in D}} \left\{ \iiint_{\mathbf{p}\in P} Q(\mathbf{x}, \mathbf{d}, \mathbf{p}) f(\mathbf{p}) d\mathbf{p} \right\} \quad (18)$$

or to minimize the risk of the solution

$$\min_{\substack{\mathbf{x}\in X\\ \mathbf{d}\in D}} \left\{ \iiint_{\mathbf{p}\in \Gamma} \left[\max_{\substack{\mathbf{x}\in X\\ \mathbf{d}\in D}} Q(\mathbf{x},\mathbf{d},\mathbf{p}) - Q(\mathbf{x},\mathbf{d},\mathbf{p}) \right] f(\mathbf{p}) d\mathbf{p} \right\} \quad (19)$$

For the tasks of optimal design and optimal operation the following strategy is proposed in [24]:

$$\max_{\mathbf{d}\in D} \underset{\mathbf{p}\in X}{E} \left\{ \max_{\mathbf{x}\in X_x} Q(\mathbf{x},\mathbf{d},\mathbf{p}) \right\} \quad (20)$$

For the same optimization task subject to constraints in [59, 78] the following strategy is proposed:

$$\max_{\mathbf{d}\in D} \max_{\mathbf{x}\in X} \underset{\mathbf{p}\in P}{E} \{Q(\mathbf{x},\mathbf{d},\mathbf{p})\} \quad (21)$$

$$\underset{\mathbf{p}\in P}{E} \{h_j(\mathbf{x},\mathbf{d},\mathbf{p})\} = 0, \quad \forall j = 1,2,...,m_1 \quad (22)$$

$$\underset{\mathbf{p}\in P}{E} \{g_j(\mathbf{x},\mathbf{d},\mathbf{p})\} \geq 0, \quad \forall j = 1,2,...,m_2 \quad (23)$$

where $\underset{\mathbf{p}\in P}{E}\{...\}$ is a mathematical expected value of $\{...\}$ in the region of uncertainty $\mathbf{p}\in P$.

The comparative analysis of the strategies (20) and (21) in [59] solving some practical problems is showing that the strategy (21) is giving almost the same optimal solutions as (20) but the time for solution is much shorter.

The amount of calculations of stochastic methods is very large. The stochastic methods are suggested for the following cases:

- The function of distribution of uncertain parameters is known;
- The deviations of the uncertain parameters are large;
- The objective function is non linear in respect to the uncertain parameters.

***Strategies using the game theory* (min-max *strategies*)**. The basic game strategies used for optimization under uncertainty are the following

$$\min_{\mathbf{p}\in P} \left[\max_{\mathbf{x}\in X, \mathbf{d}\in D} Q(\mathbf{x},\mathbf{d},\mathbf{p}) \right] \quad (24)$$

The following strategy is proposed in [59, 78]

$$\max_{\mathbf{x}\in X,\,\mathbf{d}\in D}\left\{\min_{\mathbf{p}\in P}\left[\frac{\max\limits_{\mathbf{x}\in X,\,\mathbf{d}\in D} Q(\mathbf{x},\mathbf{d},\mathbf{p}) - Q(\mathbf{x},\mathbf{d},\mathbf{p})}{\max\limits_{\mathbf{x}\in X,\,\mathbf{d}\in D} Q(\mathbf{x},\mathbf{d},\mathbf{p})}\right]\right\} \tag{25}$$

The *game theory strategies* are better for discrete number of solutions and suggested if:

- The boundaries of the uncertain parameters are known;
- The objective function is linear in respect to the uncertain parameters.

Strategies for optimization under uncertainty with discreet number of variants

The number of possible variants for selecting the optimal one is a finite number V_j, $j = 1, 2, \ldots, M$ in many practical optimization tasks. Let us assume existence of a finite number of combinations θ_j, $j = 1, 2, \ldots, K$ of possible uncertainties. For example it is necessary to invest in one of three possible biotechnologies in the presence of two uncertainties: p_1 – the energy price and p_2 – the price of raw materials in order to maximize the annual profit $Q(V, p) \to \max\limits_{V}$. Let us assume that the combinations of the possible uncertainties of p_1 and p_2 is also finite number θ_j, $j = 1, 2, 3, 4$ created by the four boundaries of the uncertain parameters $p_{i\min}$ and $p_{i\max}$. The following strategies are used in such cases:

Stochastic strategy. The probabilities S_j of the combinations θ_j, $j = 1, 2, \ldots, K$ are given. The optimal variant is selected by

$$\max_{V_i}\sum_{j=1}^{K} S_j Q(V_i,\theta_j) \tag{26}$$

"Pessimistic" game strategy. The optimal variant is

$$\min_{V_i}\max_{\theta_j}\{Q(V_i,\theta_j)\} \tag{27}$$

"Optimistic" game strategy. The optimal variant is:

$$\max_{V_i}\max_{\theta_j}\{Q(V_i,\theta_j)\} \tag{28}$$

The strategy of "regret". The values of the objective function for each variant of the possible uncertainties θ_j are transformed to a "matrix of regret" r_{ij}. The optimal variant is searched by

$$\min_{V_i}\max_{\theta_j}\{r_{i,j}\} = \min_{V_i}\max_{\theta_j}\left\{\frac{\max\limits_{V_i,\theta_j}[Q(V_i,\theta_j)] - Q(V_i,\theta_j)}{\max\limits_{V_i,\theta_j}[Q(V_i,\theta_j)] - \min\limits_{V_i,\theta_j}[Q(V_i,\theta_j)]}\right\} \tag{29}$$

Neutral strategy (bracketing strategy, average max-min strategy). The optimal variant is

$$\max_{V_i}\{\overline{Q}_i\} = \max_{V_i}\left\{\left[\max_{\theta_j} Q(V_i,\theta_j) + \min_{\theta_j} Q(V_i,\theta_j)\right]/2\right\} \tag{30}$$

Bracketing strategy with weight coefficients. Weight coefficients α_V, $0 \le \alpha_{V_i} \le 1.0$, $\sum_{i=1}^{n}\alpha_{V_i} = 1.0$ for the variants are given and used. The optimal decision is

$$\max_{V_i} \overline{Q}_i^{(\alpha)} = \max_{V_i} \left\{ \alpha_{V_i} \max_{\theta_j} \left[Q(V_i, \theta_j) \right] + (1 - \alpha_{V_i}) \min_{\theta_j} \left[Q(V_i, \theta_j) \right] \right\} \tag{31}$$

The steel non solved optimization problems under uncertainty are relative to qualitative, structural and dynamic uncertainties.

Multicriteria optimization of biotechnological processes and systems

Multicriteria optimization task is formulated when the requirements for several criteria $y_j(x),\ j = 1, 2, ..., m$ (useful product yield, biological activity, toxicity, stability, solubility, economic criteria) have to be fulfilled simultaneously. The set of several objective criteria (32) is called *vector criterion*:

$$\mathbf{y}(\mathbf{x}) = [y_1(\mathbf{x}), y_2(\mathbf{x}), ..., y_m(\mathbf{x})] \tag{32}$$

The optimization task with a vector criterion requires to find a set of control variables $\mathbf{x}^*$, called *optimal decision,* under which the objective parameters $y_j(\mathbf{x}^*),\ j = 1,2,...m$ will meet the complex requirements. This task is a basic task for quality control of production of bio-products. The multicriteria optimization task is incorrect, because there is not a sole solution of the task. The number of solutions is infinite. The multicriteria optimization task can be converted to the classical task if one criterion is chosen and all the others are imposed as constraints.

During recent years lots of strategies have been proposed in order to find the so called Pareto – optimal solutions, which are compromised solutions satisfying to certain extent the imposed requirements of all objective criteria [14, 15, 79, 80, 86, 90]. The concept of Pareto-optimality, proposed by Vilfredo Pareto [58, 80] is mostly used in multicriteria optimization tasks. The *Pareto-optimal solution* (*Pareto-optimal control*) has the property that each deviation from it for the purpose of improving one or more criteria leads to a deterioration of at least one or more of the remaining criteria. The *Pareto-optimal solutions* are also called *effective*, *non dominative*, *non improved*, *compromise* or *acceptable*.

The basic strategies of solving vector criteria optimization problems are the following:

- Strategies of reference points;
- Strategies of goal programming;
- Scalarisation of the vector criteria;
- Methods of weight priorities;
- Finding a set of Pareto-optimal solutions.

Reference point strategies

The most widely used strategies for multicriteria optimization are the so called *reference point approach strategies* [26, 78, 85, 88, 89, 90]. These methods are a part of the wide class of the *scalarizing methods.*

Each objective variable is given a *referenced value* (*referenced point*) y_{jr}, j = 1, 2, …, m. The idea in the different variants of the method is to maximize the exceeding over the referenced value y_{jr}, or/and to minimize the insufficiency to the referenced value y_{jr}.

The reference point approach has a few modifications:

- Function of losses method (optimistic approach);
- Function of usefulness method (pessimistic approach);
- Bracketing approach (combined optimistic and pessimistic approach);
- Statistical-average referenced point method [85];
- Desirability function method [26].

Optimistic strategy (***function of losses method***). This approach is called "*optimistic*" because the best values y_j^*, $j = 1,2,...,m$ are assigned to the referenced values of the objective functions $y_j(x)$ depending on the required value (maximum or minimum) and the losses, i.e. the under-achievement to the optimistic values are minimized. The generalized function of loses $F_a^{opt}(\mathbf{x})$ to be minimized is

$$F_a^{opt}(\mathbf{x}) = \frac{1}{m}\sum_{j=1}^{m}\left(\frac{y_j^* - y_j(\mathbf{x})}{y_{j\max} - y_{j\min}}\right)^2 \to \min_x \tag{33}$$

where $y_{j\max}$ and $y_{j\min}$ are accepted as the maximal and minimal values of each objective parameter $y_j(x)$ used to normalize the function of losses.

Pessimistic strategy (***function of usefulness method***). In this strategy the "*pessimistic*" values (minimal or maximal admissible) y_j^{pes} are assigned to the referenced values of the objective functions $y_j(\mathbf{x})$ and the over-achievement above them, called "*usefulness*" $\eta_j(x)$ is maximized

$$F_a^{pes}(\mathbf{x}) = \frac{1}{m}\sum_{j=1}^{m}(\eta_j(\mathbf{x}))^2 = \frac{1}{m}\sum_{j=1}^{m}\left(\frac{y_j(\mathbf{x}) - y_j^{pes}}{y_{j\max} - y_{j\min}}\right)^2 \to \max_{\mathbf{x}} \tag{34}$$

In the generalized function of usefulness (35) weight coefficients W_j, ($j = 1,2,...,m$) [40, 41, 80] can also be introduced in order to express the priorities of the objective functions $y_j(\mathbf{x})$ in the compromise optimal solution:

$$F_{aw}^{pes}(\mathbf{x}) = \frac{1}{m}\sum_{j=1}^{m}(\eta_j(\mathbf{x}))^2 W_j \to \max_{\mathbf{x}} \tag{35}$$

Besides the generalized arithmetic mean function of usefulness $F_a^{pes}(\mathbf{x})$ (34) geometric mean (multiplicative) generalized function of usefulness $F_a^{pes}(\mathbf{x})$ is also applied in the pessimistic strategy:

$$F_g^{pes}(\mathbf{x}) = \sqrt[m]{(\eta_1(\mathbf{x}))^2.(\eta_2(\mathbf{x}))^2...(\eta_m(\mathbf{x}))^2} \to \max_x \tag{36}$$

The function (36) is used in order to reduce the risk in finding a compromise solution which is in or near to the most undesired value y_j^{pes} of some objective functions [81]. The geometric mean function (36) usually is multimodal and needs a method for searching global maximum.

Bracketing approach for multicriteria optimization. The *bracketing approach* combines the *function of losses method* and the *function of usefulness method*, i.e. the optimistic and the pessimistic approach. The optimal compromise solution is searched by simultaneous *minimizing* the under-achievement to the *best values* (*desired, ideal values*) y_j^* and *maximizing* the over-achievement over the *necessary* (*required*) *values* y_j^{pes}.

$$\max_{\mathbf{x}}\left\{F^{br}(\mathbf{x})\right\}=\max_{\mathbf{x}}\left\{\sum_{j=1}^{m}\left(\frac{y_j(\mathbf{x})-y_j^{pes}}{y_{j\max}-y_{j\min}}\right)^2-\sum_{j=1}^{m}\left(\frac{y_j^*-y_j(\mathbf{x})}{y_{j\max}-y_{j\min}}\right)^2\right\} \tag{37}$$

Method of a mean statistical desired value. The method [85] is a variant of the bracketing approach. A recommended mean value $\bar{y}_j$ for each objective $y_j(\mathbf{x})$ is given. The normalization of the deviation between $y_j(\mathbf{x})$ and $\bar{y}_j$ is in respect to an accepted standard deviation S_{yj}.

$$F_x^{stat}(\mathbf{x})=\frac{1}{m}\sum_{j=1}^{m}ABS\left[\frac{y_j(\mathbf{x})-\bar{y}_j}{S_{yj}}\right]\rightarrow\min_{\mathbf{x}} \tag{38}$$

Method of desirability function. All objectives $y_j(\mathbf{x})$ are transformed in a function of desirability $d_j(\mathbf{x})$ using the formula [26, 80]

$$d_j(\mathbf{x})=\exp\{-\exp[-(b_{oj}+b_{1j}y_j(\mathbf{x}))]\} \tag{39}$$

The compromised solution is searched by maximization of the *generalized multiplicative function of desirability D*(x)

$$D(\mathbf{x})=\sqrt[m]{d_1(\mathbf{x})d_2(\mathbf{x})...d_m(\mathbf{x})}\rightarrow\max_{\mathbf{x}} \tag{40}$$

The exponential transformation (39) is giving much slow transition to the desired and undesired values for each objective comparing to the linear transformations in functions of losses, usefulness and bracketing transformation. The generalized function of desirability is usually multimodal. Solved problems for multicriteria optimization of biotechnological processes are given in [61].

Noise reduction in biotechnological processes

The experimental data taken from fermentation and other bioprocesses and used for modeling of the processes are significantly influenced by various disturbances. In order to reduce the risk of making wrong conclusions and taking wrong decisions the data are usually filtered. The following digital filters are mostly used for smoothing the data: filters of *Butterworth* [57], *Chebishev* [77] and E*lliptic* filter [25]. The choice of the best filter is still under investigation [1, 71].

Optimal control of biotechnological processes and systems

An effective method for optimal control of biotechnological systems has to be chosen. The method has to assure an adequate optimal control having in mind the strong nonlinearity of biotechnological systems, the process memory problem and large number of control and state variables. An additional problem to appear is related to the uncertainty in process development and necessity of parametric identification in reasonable real time. The methods of maximum principal of Pontryagin [62] and dynamic programming of Bellman [2] are mainly used for optimal control of biotechnological processes and systems.

The maximum principle of Pontryagin seems to be one of the most perspective methods for optimal control for biotechnological processes. The necessity of strongly adequate mathematical model of the process and well defined constraints, relatively precise defined initial and final conditions as well the necessary and sufficient conditions to apply the method make the maximum principle of Pontryagin still one with restricted practical application.

The method of dynamic programming using the formulated by Bellman "optimality principle" [2] has found large application for optimization of multistage in the space and the time biotechnological processes and systems. Dynamic programming is mostly used for finding the optimal control profile for batch or fed – batch processes using discretization of the system functioning time in intervals and finding the optimum control for each time interval. The optimization task is to find the optimal control strategy $\mathbf{u}_{opt}(t)$ of each stage (i = 1, 2, …,N) or of each discreet time interval which will assure maximum (or minimum) of the selected integral criteria for optimality of the process subject to the imposed constraints. The optimal discretization of the time interval is also an optimization task.

To overcome the so called "the curse of dimensionality" in dynamic optimization the researches are still looking for improving the computational process. The following dynamic programming methods with improved computational efficiency have been developed during the recent years:

- Iterative dynamic programming [46, 47, 48, 49, 50, 51];
- Neuro-dynamic programming [3, 30, 31, 32, 35, 37];
- Combined – dynamic programming methods [28, 29, 33, 34, 36].

However these methods need global search on each stage of the numerical procedure and also a comparative study of their efficiency.

Conclusion

A lot of strategies and methods have been proposed for dealing with multimodal optimization tasks, tasks with parametric uncertainties, tasks with several objective functions and tasks for optimal dynamic control of biotechnological systems. Many of these strategies are still not sufficient enough. For further investigations it is expected that combined methods and algorithms would be developed, which would be more effective and reliable to overcome the problems of finding global solutions, maximum robust to the incomplete information, dealing with vector criteria and searching for optimal control with a reduced amount of computations. The choice of the relevant methods has to be based on the comparative analysis of the most perspective methods and algorithms, taking into account the specific features of biological processes with regards to their modeling, optimization and control.

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