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# Optimal Biocompatible Solvent Design by Mixed-integer Hybrid Differential Evolution

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***Abstract:*** *In this study, a flexible optimization approach is introduced to design an optimal biocompatible solvent for an extractive fermentation process with cell-recycling. The optimal process/solvent design problem is formulated as a mixed-integer nonlinear programming model in which performance requirements of the compounds are reflected in the objectives and the constraints. A flexible or fuzzy optimization approach is applied to soften the rigid requirement for maximization of the production rate, extraction efficiency and to consider the solvent utilization rate as the softened inequality constraint to the process/solvent design problem. Such a trade-off problem is then converted to the goal attainment problem, which is described as the constrained mixed-integer nonlinear programming (MINLP) problem. Mixed-integer hybrid differential evolution with multiplier updating method is introduced to solve the constrained MINLP problem. The adaptive penalty updating scheme is more efficient to achieve a global design.*

***Keywords:*** *Biocompatible solvent, Flexible optimization approach, Extractive fermentation.*

## Introduction

Bio-ethanol is a bulk chemical and must carry out continuous fermentation to achieve economic and beneficial production. Continuous fermentation can increase production rate; however, it is unable to be carried out on high cell density culture, resulting in low ethanol concentration and a significant loss of residual substrate. To increase the efficiency of the bio-ethanol fermentation process, various cell culture methods have been investigated [7, 13, 20, 21]. Cell-recycling bioreactor coupled with membrane filtering modules has gained considerable interest in recent years in order to achieve higher bio-ethanol concentration. However, such a high ethanol concentration may poison viable microorganisms and abrogate the fermentation process. Extractive fermentation is an alternative technique used to reduce the end product inhibition by removing the fermentation product *in situ* [3, 9, 14, 15, 23]. However, the toxicity of the organic solvent used to remove the end product is always a problem. Few reports have been taken advantage of computer-aided molecular design (CAMD) to design a biocompatible solvent for extractive fermentation process [24, 32]. CAMD problems are, in general, formulated as mixed-integer nonlinear programming (MINLP) problems. Recently, CAMD is a popular technique applying to find a suitable molecular structure for refrigerants [2, 4-5, 12], polymer and polymer blends [17, 30], solvent for gas absorption [18, 22], and solvents for liquid-liquid extraction [10, 18, 22, 26] and so on.

The challenge of MINLP problems stems from the fact that they are highly nonlinear and non-differentiable due to the combinatorial nature of the associated integer-valued variables.

Conventional well-known major approaches to MINLP include the cutting plane method, the branch-and-bound method, the decomposition method, and their variants. These methods have been successfully applied to many practical problems. However, they require a good starting point and gradient information to yield a global solution. Evolutionary algorithms (EAs) are important optimization techniques that emerged in the last decade. The search processes of EAs are based on the ideas and principles of natural evolution. Since they do not require a starting point and gradient information, EAs are particularly suitable for solving difficult optimization problems, such as highly nonlinear, non-differentiable, and multi-modal optimization problems. Hybrid differential evolution (HDE) [1] is a quite simple population based stochastic function method and has extended from the one of the best EAs, differential evolution as introduced by Storn and Price [29]. HDE has been successfully applied to solve biochemical process optimization problems [1, 31]. Unfortunately, HDE is not applicable to optimization problems of MINLP. Lin et al. [16] extended HDE to include a mixed coding strategy and a rounding operation for solving MINLP problems. This extended form of HDE is referred as mixed-integer hybrid differential evolution (MIHDE) and can achieve a global minimum in many test cases. In this paper, MIHDE will be applied to determine an optimal biocompatible solvent for an ethanol extractive fermentation with cell recycling process.

The optimal biocompatible solvent design problem is coupled with complex nonlinear constraints. Such constrained optimization problems are very intractable because the feasible region is greatly suppressed by the constraint functions. In the last few years, several constraint-handling techniques have been proposed by researchers in the evolutionary algorithm community. Michalewicz and Schoenauer [19] surveyed and compared these constraint-handling techniques. Among these techniques, penalty function methods are among the most popular techniques for handling constraints. However, these techniques are quite sensitive to the initial penalty parameters. Small initial penalty parameters, for example, might lead to an infeasible solution. On the other hand, very large initial penalty parameters might cause the penalty functions to be ill conditioned close to the boundary of the feasible region. In this paper, to overcome such drawbacks, we introduce MIHDE with a multiplier updating method using adaptive penalty parameters, to deal with the optimal biocompatible solvent design problem with physical constraints.

## Process formulation

### *Constraints for process*

Fig. 1 shows a schematic drawing of an extractive fermentor with cell recycling for continuous production of ethanol. The fresh substrate is continuously added into fermentor, and a fresh solvent is also added into the fermentor to extract ethanol in order to prevent product inhibition. In this work, ethanol extraction is carried out in a liquid-liquid equilibrium state at the operation temperature $T$ = 308.15 K and pressure $p$ = 1 *atm*. The outlet streams from extractive and raffinate phases are assumed to be in phase equilibrium. In the cell separator, the bioactivity and residence time are negligible and the membrane filtration is assumed to be perfect, thus each filtrate is cell-free.

The material balances for biomass, substrate and ethanol around the extractive fermentation process at the steady-state are expressed as following:

$$\left(\mu - bD_R\right)X = 0 \tag{1}$$

$$(D_0S_0 - D_RS_R - D_ES_E) - \left(\frac{q_p}{Y_{p/s}}\right)X = 0 \tag{2}$$

$$(D_0P_0 - D_RP_R - D_EP_E) + q_pX = 0, \quad (3)$$

where $D_E$ and $D_R$ are dilution rate based on effluent solvent flow and effluent aqueous flow, $S_0$ is the influent substrate concentration in the fermentor. The dilution rate for the feed stream is given by

$$D_0 = \frac{1}{a} D_R, \quad (4)$$

where *a* is the flow rate ratio.

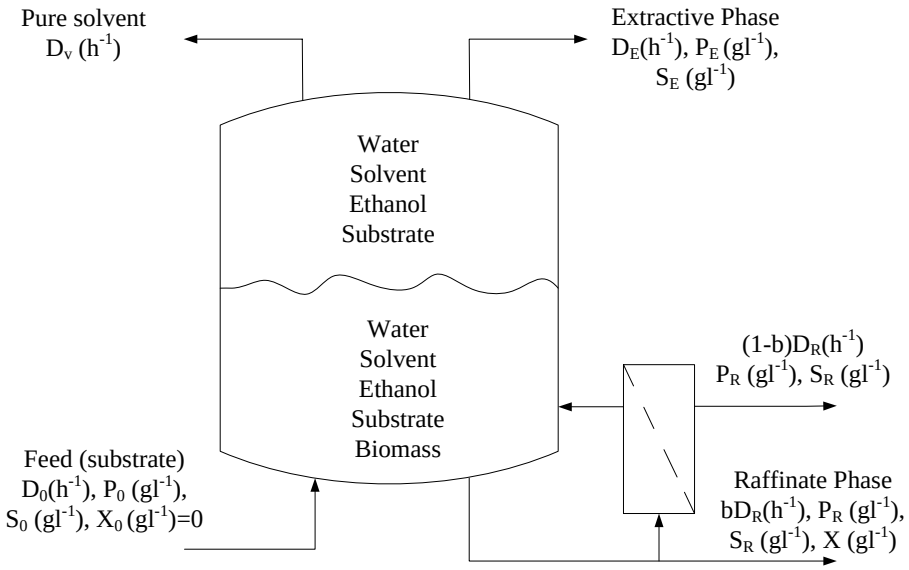


Fig. 1 Extractive fermentation with cell-recycling process

The specific cell growth rate $\mu$ and specific ethanol formation $q_p$ considered in this work were accessed from Wang and Sheu [31], which is to use *Saccharomyces diastaticus* LORRE 316 to produce ethanol. Both specific rate models are expressed as:

$$\mu = \frac{\mu_{\max} S_R}{K_s + S_R + (S_R)^2 / K_{sI}} \frac{K_p}{K_p + P_R + (P_R)^2 / K_{pI}} \quad (5)$$

$$q_p = \frac{\nu_m S_i^R}{K'_s + S_R + (S_R)^2 / K'_{sI}} \frac{K'_p}{K'_p + P_R + (P_R)^2 / K'_{pI}}, \quad (6)$$

where $S_R$ and $P_R$ are the substrate and ethanol concentrations in the raffinate phase. The values of the kinetic parameters in (5) and (6) are listed in Wang and Sheu [31].

The solvent utilization rate is obtained from the material balance equation for solvent at steady-state as expressed in the form:

$$\pi_v = D_v \rho_v = (k_e \frac{x_v^E}{x_e^E} D_E + \frac{x_v^R}{x_e^R} D_R) \frac{P_R}{MW_e} MW_v, \quad (7)$$

where $D_v$, is the dilution rates based on influent solvent flow rate, and $\rho_v$ quantifies the density of the solvent. $x_v^E$ and $x_e^E$ are the mole fractions of solvent and ethanol in the extractive phase, $x_v^R$ and $x_e^R$ are the mole fractions of solvent and ethanol in the raffinate phase, $MW_v$ and $MW_e$ are the molecular weights for solvent and ethanol, and $k_e$ is the

ethanol distribution coefficient.

The process streams from the extractive and raffinate phases are assumed to be phase equilibrium so that the distribution coefficients $k_e$ for ethanol, solvent and water are defined as following:

$$k_e = \frac{\gamma_e^R}{\gamma_e^E}\frac{MW_w}{MW_v}, \tag{8}$$

where $\gamma_e^E$ and $\gamma_e^R$ are the activity coefficients, which are calculated by the universal functional activity coefficient (UNIFAC) method [8], of ethanol in the extractive and raffinate phases. The solvent selectivity $\eta$ and solvent loss $\zeta$ in raffinate phase are two additional constraints that are calculated as follows [8]:

$$\eta = \frac{\gamma_w^E}{\gamma_e^E}\frac{MW_e}{MW_w}, \tag{9}$$

where $\gamma_w^E$ and $\gamma_v^R$ are the activity coefficients of the solvent and water.

The mole fraction for ethanol, solvent and water in the extractive fermentation process can be calculated by the UNIFAC method [27]. Moreover, the extractive and raffinate phases are in phase equilibrium so that each component needs to hold the following relation:

$$\gamma_j^E x_j^E = \gamma_j^R x_j^R; j = e \text{ (ethanol), } v \text{ (solvent), and } w \text{ (water)}, \tag{10}$$

where $\gamma_j^E$ and $\gamma_j^R$ are the activity coefficients of component $j$ in the extractive and raffinate phases. $x_j^E$ and $x_j^R$ are the mole fraction of component $j$ in the extractive and raffinate phases.

### *Constraints for solvent*

Some requirements need to be specified for the solvent design problem in order to obtain a solvent which satisfies physical, chemical, and biological requirements [33]. In this study, we are interested in finding an optimal solvent as the following types: hydrocarbon, ester, ketone, alcohol, or ether. Accordingly, we should choose the group basis set as G = [$CH_3$, $CH_2$, CH, OH, $CH_3COO$, $CH_2COO$, $CH_3CO$, $CH_2CO$, $CH_3O$, $CH_2O$, CHO]. The molecular groups are then screened by evaluating the feasibility of their molecular structure and primary solvent properties. To ensure that the molecule is structurally feasible, the acyclic octet rule modeled by Odele and Macchietto [22] is employed:

$$\sum_{i=1}^{P_{\max}} (2 - v_j) u_{ji} = 2, \quad j = 1, ..., M, \tag{11}$$

where $P_{\max}$ is the maximum number of positions in a molecule, $v_j$ is the valence of groups $j$, $M$ is the number of available groups in the basis, and the binary variable $u_{ji}$ is defined as:

$$u_{ji} = \begin{cases} 1, \text{ if the structural group } j \text{ appear in i-th position of a molecule} \\ 0, \text{ otherwise} \end{cases} \tag{12}$$

While the structure of a molecule is determined, the biocompatibility -log$L_{C50}$ (mol/L), boiling point ($T_b$, K), melting point ($T_f$, K), and Gibbs free energy ($\Delta G$, KJ/mol) can be evaluated by the group contribution method. Moreover, the evaluated values need to restrict within some boundaries in order to yield a suitable solvent. Such inequality constraints are expressed as follows:

$$-\log L_{C50} = \sum_j \sum_i u_{ji}\delta_j \le B_{L_{C50}} \quad (13)$$

$$T_b^L \le T_b = 198 + \sum_j \sum_i u_{ji} T_{bj} \le T_b^U \quad (14)$$

$$T_f = 122.5 + \sum_j \sum_i u_{ji} T_{fj} \le T_f^U \quad (15)$$

$$\Delta G = 583.57 - \sum_j \sum_i u_{ji} \Delta G_j > 0, \quad (16)$$

where $T_{bj}$, $T_{fj}$, and $\Delta G_j$ are the boiling point, melting point and Gibbs free energy for the contributions of group $j$, respectively, and can be calculated from the literature [11]. Estimating biocompatibility quantitatively could be very difficult, because there is not much experimental data available regarding the toxicity contribution for each group to microbes, so the criterion used for fathead minnow is applied to cope with biocompatibility for microbes [33]. It is supposed that the behaviors of microbes are as same as ones of fathead minnow so the toxicity contribution for each group $\delta_l$ to fathead minnow is as same as one to microbes [6]. Using the group contribution approach, the toxicity of a selected solvent is summed up its contributed value. Here, $L_{C50}$ is the lethal concentration causing 50% mortality in microbes. The boundary values for the biocompatibility ($B_{LC50}$), boiling point ([$T_b^L$, $T_b^U$]), and melting point ($T_f^U$) are assigned by the designer. The lower bound of the melting point ($T_f^U$) is necessary to make sure that solvent is in liquid state at operating conditions. In addition, the upper bound ($T_b^L$) should have 30 K to 50 K difference to the lower bound in order to avoid azeotrope formation and to ensure high relative volatility [26].

## *Optimal design problem*

The aim of the optimal process/solvent design problem is to select a biocompatible solvent and to determine operation conditions for the ethanol fermentation process so that the ethanol production rate is maximized and the extraction efficiency and conversion are greater than the desired values. The objective function for the production rate is therefore expressed as

$$\max_{\mathbf{y},\mathbf{z},\mathbf{u}} PD = D_E P_E + D_R P_R \quad (17)$$

Here the process variables, **y**, consist of the biomass, glucose and ethanol concentration in Eqs. (1)-(3). The operation variables, **z**, consist of the feed solvent dilution rate, $D_v$, the bleed ratio, $b$, and the flow rate ratio, $\beta$. The binary variables, **u**, are used to select a solvent molecular structures as defined in Eq. (11).

The extraction efficiency (*EE*) is defined as the ratio of the ethanol recovered in the solvent phase to ethanol production. We therefore have

$$EE = \frac{D_E P_E}{D_E P_E + D_R P_R} \quad (18)$$

The extractive efficiency of one indicates that ethanol is completely extracted from the fermentor. In contrast, the value of zero means that the selected solvent is unable to extract ethanol from broth. As a result, this specification is served as an index to inspect whether the selected solvent is efficient to the fermentation process. The glucose conversion (*Conv*) is another criterion for bioreactor performance analysis. Here we consider that the conversion should be greater than a desired value, 80%, as:

$$Conv = 1 - \frac{D_R S_R}{D_0 S_0} - \frac{D_E S_E}{D_0 S_0} \geq 0.8 \quad (19)$$

*Trade-off design*

The optimal process/solvent design problem is to determine a biocompatible solvent and operation conditions for the extractive fermentation process such that the ethanol production rate and extraction efficiency are maximized and are achieved their preference goals, simultaneously. Moreover, the solvent utilization rate requires less than the desired value. In this situation, the designer would have to carry out an interactive procedure toward obtaining a trade-off result for the optimal process/solvent design problem. In real application, the preference goal and desired value of a design problem are usually an interval instead of the absolute restriction, so that the problem can be formulated as a flexible design problem or fuzzy optimization problem.

In the flexible design problem, the designer usually assigns an interval goal, rather than a rigid value. Here, we consider the interval goals for the production rate $[PD^L, PD^U]$ and for extraction efficiency $[EE^L, EE^U]$, respectively. The flexible goal problem is therefore expressed as

$$\widetilde{\max} J_1 = PD \in [PD^L, PD^U] = [J_1^L, J_1^U] \quad (20)$$

$$\widetilde{\max} J_2 = EE \in [EE^L, EE^U] = [J_2^L, J_2^U] \quad (21)$$

The symbol "$\widetilde{\max}$" denotes the flexible or fuzzy maximization. This means that the design is completely acceptable with the production rate and extraction efficiency obtained as long as the objective functions $J_1$ and $J_2$ are greater than the assigned upper bounds $J_1^U$ and $J_2^U$. Conversely, the design is completely unacceptable if the production rate and extraction efficiency are less than the assigned lower bounds $J_1^L$ and $J_2^L$. While the production rate and extraction efficiency are within $[J_1^L, J_1^U]$ and $[J_2^L, J_2^U]$, the design has some degree of satisfaction.

The solvent utilization rate requires less than the flexible or fuzzy inequality constraint as

$$J_3 = D_v \rho_v \precsim [M_s^L, M_s^U] = [J_3^L, J_3^U], \quad (22)$$

where the symbol "$\precsim$" denotes a fuzzy version of the ordinary inequality "$\leq$". The flexible inequality constraint means that the design is completely acceptable for the solvent utilization rate if the constraint $J_3$ is less than the assigned lower bound $J_3^L$. Conversely, the design is completely unacceptable if the solvent utilization rate is greater than the assigned upper bound $J_3^U$. While the solvent utilization rate is within $[J_3^L, J_3^U]$, the design has some degree of satisfaction.

The interval goals for the objective functions in (20) and (21), and the fuzzy inequality constraint (22) can be quantified by eliciting membership functions from the designer to convert the fuzzy optimal design problem into a flexible or fuzzy goal attainment problem. The membership function for both objectives is defined as:

$$\eta_i(J_i)=\begin{cases}1 & J_i \geq J_i^U \\ d_i & J_i^L \leq J_i \leq J_i^U, i=1,2, \\ 0 & J_i \leq J_i^L\end{cases} \tag{23}$$

where $\eta_i \in [0,1]$ represents the grade of the membership function and $d_i$ is a strictly monotonically increasing function with respect to $J_i$. For concise illustration for fuzzy optimization problems, the membership functions for both objectives are supposed to be identical as shown in Fig. 2.

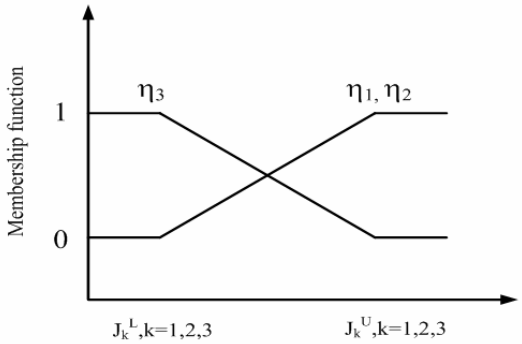


Fig. 2 Linear functions for each objective and the inequality constraint

Following a similar procedure, the membership function for the inequality constraint (22) is expressed as:

$$\eta_3(J_3)=\begin{cases}1 & J_3 \leq J_3^L \\ d_3 & J_3^L \leq J_3 \leq J_3^U, \\ 0 & J_3 \geq J_3^U\end{cases} \tag{24}$$

where $\eta_3 \in [0,1]$ represents the grade of the membership function and $d_3$ is a strictly monotonically decreasing function with respect to $J_3$. The membership function is shown in Fig. 2. If both objective functions and the inequality constraint are less than their lower bounds, the intersection for the membership functions is zero as observed from Fig. 2. Conversely, if both objective functions and the inequality constraint are greater than the upper bounds, the intersection for the membership functions is still zero. The objective of fuzzy optimization is therefore to find a maximum intersection for all membership functions between the desired boundaries.

Having elicited the membership function for the objective functions and constraint, the fuzzy optimization problem is thus expressed as a maximizing decision problem in the form:

$$\max_{\mathbf{y},\mathbf{z},\mathbf{u}\in\Omega} \eta_D, \tag{25}$$

where $\eta_D$ denotes as an aggregation function. Several aggregation functions were introduced in the textbook by Sakawa [28]. Observe that the aggregation function can be interpreted as representing an overall degree of satisfaction with the goals. The aggregation function in this study is therefore expressed as the fuzzy goal attainment problem in the form:

$$\min_{\mathbf{y},\mathbf{z},\mathbf{u}\in\Omega} \eta_D = \min_{\mathbf{y},\mathbf{z},\mathbf{u}\in\Omega} \left\{ \max_{k=1,3} \left\{ (\bar{\eta}_k - \eta_k) \right\} + \sigma \sum_{k=1}^{3} (\bar{\eta}_k - \eta_k) \right\} \tag{26}$$

The first term of the aggregation function is applied to determine the optimal trade-off solution that is nearest to the ideal preference goals $\overline{\eta}_k$, which is 100% satisfaction. The second term is employed to avoid inspection of a unique test for optimality, in which the constant $\sigma$ is a sufficiently small positive value of $10^{-3}$~$10^{-5}$ [28].

## Mixed-integer hybrid differential evolution

*Algorithm*

The fuzzy goal attainment problem belongs to a constrained MINLP problem. In this work, we applied MIHDE [16] to solve the MINLP problem in order to obtain a global solution. This method extends from the real-value version of hybrid differential evolution (HDE) introduced by Chiou and Wang [1]. The basic operations for MIHDE are similar to the conventional evolutionary algorithms. However, MIHDE includes two additional operations, acceleration and migration, as shown in Table 1. The MIHDE structure is a parallel direct search algorithm which utilizes multiple vectors of the decision variables in the MINLP problem as a population for each generation. The mutation of MIHDE adopted from evolution algorithm (EA) [29] is the essential ingredient, compared with other evolutionary algorithms. Such a mutation uses the difference between two randomly chosen individuals as a search direction. A mutant individual is then yielded from a parent individual and the perturbed mutation. The crossover operation in EA and MIHDE is employed to increase the local population diversity, which is similar to the conventional evolutionary algorithms.

Table 1. The basic operations for evolutionary algorithms and MIHDE

| Evolutionary Algorithm | Mixed-Integer Hybrid Differential Evolution |
|---|---|
| 1. Representation and initialization | 1. Mixed-coding representation and initialization |
| 2. Mutation | 2. Mutation with rounding operation |
| 3. Crossover operation | 3. Crossover operation |
| 4. Selection and evaluation | 4. Restriction operation |
| 5. Repeat steps 2 to 4 | 5. Selection and evaluation |
| | 6. Acceleration operation if necessary |
| | 7. Migration operation performed naturally or enforced if necessary |
| | 8. Repeat steps 2 to 6 |

When using an evolutionary algorithm to optimize a function, an acceptable trade-off between convergence and population diversity must generally be determined. Convergence implies a quick consensus even though it may be to a local optimum. On the other hand, population diversity guarantees a high probability of obtaining the global optimum. When the population diversity is small, the candidate individuals are closely clustered. Therefore, the mutation and crossover operations can no longer generate the next better individual because a premature solution is obtained. An accelerated operation and a migration are embedded in the MIHDE algorithm, and these two operations serve as trade-off operations. The accelerated operation is used to speed up convergence. According to our experience, by using EA to solve optimization problems, the best fitness does not descend continuously from generation to generation. It usually descends toward a better fitness after several generations. Under this situation, the acceleration operation can be used to speed up convergence. When the best fitness in the present generation is no longer improved by mutation and crossover operations a local search method is then applied to push the best individual toward obtaining a better solution.

The rate of convergence can be improved by acceleration. However, faster descent usually results in finding a local minimum. In addition, performing this operation frequently can make the individual candidates gradually cluster around the best individual so that the population diversity decreases. Furthermore, the closely clustered individuals cannot reproduce better individuals by mutation and crossover operations. As a result, a migration operation is used to escape this local cluster. The new candidate individuals are regenerated on the basis of the best individual in the current generation. Correspondingly, the diversity of the candidates can be restored by using such a regeneration procedure. Migration in MIHDE is performed only if a measure of the population diversity fails to satisfy the desired tolerance. Lin et al. [16] proposed a measure called the degree of population diversity to check whether migration function should be carried out.

### *Handling constraints*

In real world applications, MINLP problems are, in general, coupled with complex nonlinear constraints. In this paper, we will consider a general mixed-integer nonlinear programming problem with constraints as follows:

$$\min_{\boldsymbol{\chi},\mathbf{u}} f(\boldsymbol{\chi},\mathbf{u}) \tag{27}$$

subject to

$$h_j(\boldsymbol{\chi},\mathbf{u}) = 0,\ \ j = 1,\ldots,m_e \tag{28}$$

$$g_j(\boldsymbol{\chi},\mathbf{u}) \le 0,\ \ j = 1,\ldots,m_i, \tag{29}$$

where $\boldsymbol{\chi}$ represents an $n_C$-dimensional vector of continuous variables, which consists of the process variables **y** and operation variables **z**, **u** is an $n_I$-dimensional vector of discrete or integer variables, and $h_j(\boldsymbol{\chi},\mathbf{u})$ are equality constraints as described the process constraints, and $g_j(\boldsymbol{\chi},\mathbf{u})$ are inequality constraints as described the solvent constraints. We will use a compact notation, $\varsigma = (\boldsymbol{\chi},\mathbf{u})$, in the following discussion.

Penalty function methods are some of the most popular techniques for handling constraints [19]. Such techniques convert the primal constrained problem into an unconstrained problem by penalizing those solutions which are infeasible. A square penalty function is given as

$$L_p(\varsigma) = f(\varsigma) + \sum_{k=1}^{m_e} \alpha_k h_k^2(\varsigma) + \sum_{k=1}^{m_i} \beta_k \langle g_k(\varsigma) \rangle_+^2, \tag{30}$$

where $\alpha_k$ and $\beta_k$ are the positive penalty parameters and the bracket operation in Eq. (30) is defined as $\langle g_k \rangle_+ = \max\{g_k, 0\}$. The penalty term associated with equality and inequality constraints is added to the objective function. As a result, the penalty term reflects violation of the constraints and assigns the high cost of the penalty function to a candidate individual that is far from the feasible region. When we use MIHDE or EA to solve the penalty problem, any candidate individuals that violate the constraints will inherit poorer fitness and find it difficult to survive.

The penalty function methods are easy to implement. However, the main limitation of the penalty function is the degree to which each constraint is penalized. Powell [25] has noted that the classical optimization methods that employ penalty functions have certain weaknesses that become most serious when the penalty parameters are large. More seriously, large penalty parameters make the penalty function ill conditioned such that it is difficult to achieve a good

solution. On the other hand, if the penalty parameters are too small, the constraint violation will not impose a high cost on the penalty function. Thus, the optimal solution based on the penalty function may not be feasible. Therefore, choosing appropriate penalty parameters is not a trivial.

Lagrange methods have traditionally been used to solve real-valued constrained optimization problems. These methods can significantly improve the drawbacks of penalty methods. Lin et al. [16] have introduced MIHDE with a multiplier updating method to solve MINLP problems. The augmented Lagrange function for MINLP is defined as

$$L_a(\varsigma, \mathbf{v}, \mathbf{\upsilon}) = f(\varsigma) + \sum_{k=1}^{m_e} \alpha_k \left\{ \left[ h_k(\varsigma) + v_k \right]^2 - v_k^2 \right\} + \sum_{k=1}^{m_i} \beta_k \left\{ \left\langle g_k(\varsigma) + \upsilon_k \right\rangle_+^2 - \upsilon_k^2 \right\}, \quad (31)$$

where $\alpha_k$ and $\beta_k$ are positive penalty parameters, and the corresponding Lagrange multipliers $\mathbf{v} = (v_1, \ldots, v_{m_e})$ and $\mathbf{\upsilon} = (\upsilon_1, \ldots, \upsilon_{m_i}) \geq 0$ are defined as $\lambda_k = 2\alpha_k v_k$ and $\mu_k = 2\beta_k \upsilon_k$.

The penalty parameters in Eq. (31) are, in general, fixed for the computation. However, when we use smaller penalty parameters for the augmented Lagrange function, an infeasible solution may still be obtained. To overcome this drawback, Lin et al. [16] introduced the global convergence method of Powell [25] into MIHDE along with a multiplier updating method to enforce global convergence for constrained MINLP problems.

## Results and discussion

The proposed algorithm is applied to solve the optimal process/solvent design problem. All computations were performed on a Pentium IV computer using Microsoft Windows XP. We use Compaq Visual Fortran to implement the MIHDE algorithm. The user has to provide four setting factors for the MIHDE. The setting factors used for all runs are listed as follows. The crossover factor is set to 0.5. Two tolerances used in the migration operation are set to 0.05. The population size of 5 is used in the computation. In HDE, the mutation factor is taken as a random number in [0, 1]. Three initial penalty parameter values, 0.1, 10, and $10^3$, are respectively assigned for the penalty function (30) and the augmented Lagrange function (31) to investigate the performance of the evolutionary computation for solving the constrained optimization problem.

To solve the flexible or fuzzy goal attainment problem (26), we use the linear membership function to judge the fuzzy preference for the objective functions and constraint. We assign the interval goals for ethanol production rate to be between 20 g/hL and 80 g/hL, extraction efficiency to be between 80% and 90% and that for the solvent utilization rate to be between 1000 g/hL and 4500 g/hL. The lower and upper bounds for the interval goals and constraint are provided for the membership functions in Eqs. (23) and (24) to evaluate the degree of satisfaction with respect to the objective functions and constraint. Fig. 2 shows the relationship for each membership function. The membership function value of one indicates that the corresponding objective or constraint is completely acceptable. In contrast, the value of zero is completely unacceptable. The fuzzy goal attainment approach is to find a maximum intersection of the three membership functions.

First, we assign the initial penalty values of 0.1 for MIHDE-MUM-APP to solve the flexible goal attainment problem (26). In the computations, we defined the sum of the constraint

violation (SCV) to inspect the feasibility of the optimal solution. SCV is defined as

$$\mathrm{SCV} = \sum_{k=1}^{m_e} |h_k| + \sum_{k=1}^{m_i} \max\{0, g_k\} \quad (32)$$

The first term in Eq. (32) indicates the sum of the equality constraint violations, and the second indicates the sum of inequality constraint violations. Eq. (32) investigates that an optimal solution with a smaller SCV is a more feasible solution for the problem. The SCV of 2.7e-10 indicates that the optimal solution can be considered as a feasible solution. The optimal results obtained by MIHDE-MUM-APP are shown in Table 2. Case 1a shows that the optimal solvent structure consists of three $–CH_3$ groups, one –CH group, and one $–CH_2COO$ group. Such a structure was referred to as methyl isovalerate, which was identified by the CAS registry numbers as 556-24-1. This structure is identical to the result obtained from Wang and Achenie [33], which was considered to minimize solvent utilization rate to an extractive fermentation process. The optimal production rate, extraction efficiency and the solvent utilization rate are 45.66 g/hL, 82.8% and 3002.9 g/hL, which correspond to the overall satisfactory grade of 42.77%, respectively. The solvent selectivity and biocompatibility were 11.9 wt/wt and 1.97 mol/L, respectively.

Next, we applied MIHDE with multiplier updating method using fixed penalty parameters (refers to MIHDE-MUM-FPP) to solve the problem (26). The optimal results obtained by MIHDE-MUM-FPP are shown in Case 1b of Table 2. The corresponding compound is methyl isovalerate ae well. However, the SCV of 7.4e-4 is greater than that obtained by MIHDE-MUM-APP. It means that the optimal solution is less feasible than that obtained by MIHDE-MUM-APP so that both production rate and extraction efficiency are a little greater than those obtained by MIHDE-MUM-APP. Following the similar procedures, MIHDE with penalty function method is also applied to the penalty function problem (30). The computational results are also shown in Case 1c of Table 2. The solvent obtained is referred to as an ethyl isopropyl ketone, which was identified by CAS registry number as 565-69-5. However, the SCV of 0.24 is high violation to constraints so the solution departs from the feasible domain.

Following the similar procedures, MIHDE-MUM-APP, MIHDE-MUM-FPP and MIHDE-PFM with the initial penalty parameters of 10 and $10^3$ are respectively applied to solved the flexible goal attainment problem (26). For the initial penalty parameters of 10 and $10^3$, MIHDE-MUM-APP can be still obtained feasible solutions as shown in Case 2a and 3a of Table 2, respectively. However, for the smaller penalty parameters, the adaptive penalty updating scheme is able to achieve a global solution as observed from Case 1a and 2a, so the solvent for both cases are identical. If we use the smaller penalty parameters for the fixed computational algorithm, both MIHDE-MUM-FPP and MIHDE-PFM cannot find a feasible solution as observed from Table 2. Conversely, for the larger penalty parameters, i.e. $10^3$, the three methods can achieve a feasible design, as shown in Case 3, but it is a premature solution.

Table 2. Comparison of optimal design results for MIHDE-MUM-APP, MIHDE-MUM-FPP and MIHDE-PFM with using different initial penalty parameter values

| Case | Initial penalty value | Solving method | Solvent | *PD* (g/hL) | *EE* (%) | *Conv* (%) | $\pi_v$ (g/hL) | $\eta$ (wt/wt) | -log$L_{C50}$ (mol/L) | SCV |
|---|---|---|---|---|---|---|---|---|---|---|
| 1a | 0.1 | MIHDE-MUM-APP | methyl isovalerate | 45.66 | 82.8 | 99.1 | 3002.9 | 11.9 | 1.97 | 2.7e-10 |
| 1b | | MIHDE-MUM-FPP | methyl isovalerate | 45.74 | 82.9 | 99.7 | 2998.3 | 11.9 | 1.97 | 7.4e-4 |
| 1c | | MIHDE-PFM | ethyl isopropyl ketone | 52.07 | 86.0 | 99.6 | 2629.0 | 10.8 | 2.38 | 2.4e-1 |
| 2a | 10 | MIHDE-MUM-APP | methyl isovalerate | 45.76 | 82.9 | 99.8 | 2996.9 | 11.9 | 1.97 | 1.1e-6 |
| 2b | | MIHDE-MUM-FPP | ethyl isopropyl ketone | 43.16 | 86.4 | 79.6 | 2843.8 | 11.0 | 2.38 | 4.8e-3 |
| 2c | | MIHDE-PFM | ethyl isopropyl ketone | 46.46 | 85.2 | 78.8 | 2843.8 | 10.9 | 2.38 | 6.4e-2 |
| 3a | 1000 | MIHDE-MUM-APP | ethyl isopropyl ketone | 22.25 | 86.5 | 80.2 | 1487.5 | 11.0 | 2.38 | 5.0e-11 |
| 3b | | MIHDE-MUM-FPP | ethyl isopropyl ketone | 45.21 | 83.2 | 80.4 | 3029.5 | 11.0 | 2.38 | 7.5e-8 |
| 3c | | MIHDE-PFM | ethyl isopropyl ketone | 42.80 | 87.0 | 82.6 | 2843.8 | 11.0 | 2.38 | 7.3e-8 |

The rigid boundary values in Eqs. (13)-(15) are assigned as $B_{Lc50}$ = 3.5 mol/L, $[T_b^L, T_b^U]$ = [383 K, 403 K], $T_f^U$ = 288 K

MIHDE-MUM-APP: MIHDE with multiplier updating method using adaptive penalty parameters

MIHDE-MUM-FPP: MIHDE with multiplier updating method using fixed penalty parameters

MIHDE-PFM: MIHDE with penalty function method

## Conclusions

Bio-ethanol is a bulk chemical and needs continuous fermentation to be carried out in order to achieve economic beneficial In this study, we introduced the extractive fermentation processes with cell recycling to achieve a higher cell density in the fermentor and to reduce ethanol inhibition, which can in turn enhance ethanol production rate. The process/solvent design problem was formulated as a fuzzy multiobjective optimization problem. A trade-off method was introduced to convert the multiobjective optimization problem in to the goal attainment problem, which was described as the constrained MINLP problem. Three MIHDE computational algorithms were employed to solve the constrained MINLP problem,

respectively. The adaptive penalty updating scheme was able to achieve a global design if we assigned a smaller penalty parameters. Conversely, for the larger penalty parameters, the three methods could yield a feasible design, but it is a premature design.

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## Nomenclature

| | |
|---|---|
| $a$ | flow rate ratio for the extractive fermentor |
| $b$ | bleed ratio for extractive fermentor |
| $Conv$ | substrate conversion (%) |
| $D_0$, $D_R$ | dilution rate based on influent and effluent aqueous flow rate for extractive fermentor ($h^{-1}$) |
| $D_v$, $D_E$ | dilution rate based on influent and effluent solvent flow rate for extractive fermentor ($h^{-1}$) |
| $EE$ | extraction efficiency (%) |
| $k_e$ | distribution coefficient for ethanol between extract and raffinate phase (wt/wt) |
| $K_s$ | saturation coefficient for cell growth on glucose |
| $K_s^{'}$ | saturation coefficient for ethanol production on glucose |
| $K_{sI}$ | inhibition coefficient for cell growth on glucose |
| $K_{sI}^{'}$ | inhibition coefficient for ethanol production on glucose |
| $K_p$ | saturation coefficient for cell growth on ethanol |
| $K_p^{'}$ | saturation coefficient for ethanol production on ethanol |
| $K_{pI}$ | inhibition coefficient for cell growth on ethanol |
| $K_{pI}^{'}$ | inhibition coefficient for ethanol production on ethanol |
| $L_{C50}$ | the lethal concentration causing 50% mortality in fathead minnow (mol/L) |
| $MW_j$ | molecular weight for $j$ component |
| $P_R, P_E$ | effluent ethanol concentration in raffinate and extractive phase (g/L) |
| $q_p$ | specific production rate for extractive fermentor ($h^{-1}$) |
| $S_0$ | influent substrate concentration (g/L) |
| $S_R$, $S_E$ | effluent substrate concentration in raffinate and extractive phase (g/L) |
| $V_i$ | the volume for the $i^{-th}$ extractive fermentor (L) |
| $x_j^E$ | mole fraction of component $j$ in extractive phase for the extractive fermentor |
| $x_j^R$ | mole fraction of component $j$ in raffinate phase for the extractive fermentor |
| $X_0$, $X$ | influent and effluent cell concentration in raffinate phase (g/L) |

***Greek letters***

| | |
|---|---|
| $\mu$ | specific growth rate for the extractive fermentor ($h^{-1}$) |
| $\mu_{max}$ | maximum specific growth rate ($h^{-1}$) |
| $\delta_l$ | contribution of group $l$ in group contribution-based model for $L_{C50}$ |
| $\eta$ | the overall solvent selectivity (wt/wt) |
| $\gamma_j^E$ | activity coefficient of component $j$ in extractive phase for the extractive fermentor |
| $\gamma_j^R$ | activity coefficient of component $j$ in raffinate phase for the extractive fermentor |

$v_j$ valence of group $j$
$\pi_v$ mass flow rate of fresh solvent (g/hL)
$\rho_v$ density of solvent (g/L)

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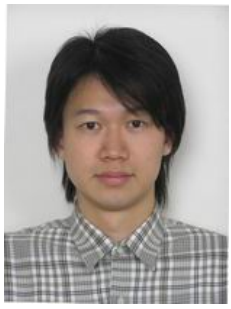

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