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NBI-RPRGM FOR MULTI-OBJECTIVE OPTIMIZATION DESIGN OF BIO-PROCESSES

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Abstract. In this work we consider multi-objective optimization problems arising from the domain of the design of nonlinear bioprocesses. The goals are to maximize the product profit and to minimize simultaneously the Fixed Capital Investment, by imposing additional constraints in order to ensure cell viability. As a result, the Pareto-optimal set is obtained for Random Perturbation of Reduced Gradient Method (RPRGM) by solving a set of nonlinear programming subproblems of multi objective optimization using the recent Normal Boundary Intersection (NBI), the objective and constraints functions are assumed to be differentiable.

Résumé. Dans ce travail nous considérons des problèmes d'optimisation multi-objectifs qui apparaissent dans le domaine de conception de bioprocess. L'objectif est de maximiser le profit du produit et de minimiser l'investissement du capital fixe simultanément, en imposant des contraintes supplémentaires pour assurer la viabilité cellulaire. En conséquence, l'ensemble Pareto-optimal est obtenu par perturbation aléatoire de la méthode du gradient réduit en résolvant un ensemble de programmes non linéaires, sous-problèmes multi-objectifs obtenus par l'utilisation de la méthode *NBI*; les fonctions objectifs et celles des contraintes sont supposées différentiables.

Introduction

A multi-objective problem consists of a vector-valued objective function to be minimized, and of some equality or inequality constraints, i.e.,

$$\begin{cases} \min & F(x) = (f_1(x), ..., f_\ell(x))^T \\ \text{s. t.} & g_j(x) = 0 \qquad , j = 1, ..., m', \\ & g_j(x) \geq 0 \qquad , j = m'+1, ..., m, \\ & x_l \leq x \leq x_u \end{cases} \tag{1}$$

where $x \in \mathbb{R}^n$ is the vector of decision variables, $f_1, ..., f_\ell$ are objective functions, $g_1, .., g_{m'}$ and $g_{m'+1}, .., g_m$ are possible sets of equality and/or inequality constraints, respectively, which represent process model, and $x_l \in (\mathbb{R} \cup \{-\infty\})^n, x_u \in (\mathbb{R} \cup \{\infty\})^n$ are the lower and upper bounds for the decision variables. This set of constraints defines the feasible space, while the set of all possible values of the objective function constitutes the objective space.

Multi-objective optimization theory shows that in general it is not possible to obtain a single solution which is simultaneously optimal for all the objective function (of course, if there exists such a point, it provides a

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solution to the problem), but instead there will exist multiple optimal solutions, i.e., improving one objective usually means degrading others. Thus, the real purpose of multi-objective optimization is to find the set of solutions which represent the relatively best alternatives (see for instance [7] and [8]). This set is known as Pareto optimal and it can be readily used to choose suitable compromises for the optimal design, and so the concept of optimality has to be replaced by the concept of Pareto optimality [5], there is no unique solution to this problem.

There exist many examples in engineering design [6], location science [4], and management science [10] involving the optimization of multiple objectives, but few applications regarding biochemical systems are found in the literature [11], [15] and [20]. This situation is not surprising, very specially due to the frequent non-convexity of these problems, a consequence of their non-linear and highly constrained nature, which can result in challenging problems even for the single objective case [1] and [12].

Many algorithms have been suggested for generating the Pareto optimal set, for example:

- Weighted sum method,
- Goal attainment method,
- Normal Boundary Intersection (NBI),
- Multi-objective Indirect Optimization Method (see for instance [20]),
- Multi-Objective Evolutionary Algorithm (see for instance [18] and [19]).

In this work, we propose the Normal Boundary Intersection (NBI) method [6], which has the advantage of producting an even spread of points on the Pareto front. NBI works by transforming the non-linear multi-objective optimization problem into a set of nonlinear programming subproblems which are solved by means of Random Perturbation of Reduced Gradient method (RPRGM) [9], our main objective was to compare several solution of NBI-SQP and NBI-RPRGM, highlighting the advantages and drawbacks of each one, by solving one case study: the multi-objective optimization of ethanol production by Saccharomyces cerevisiae.

1. Pareto optimality

The problem is to find a Pareto optimum of

$$F : \mathbb{R}^n \longrightarrow \mathbb{R}^\ell,$$

i.e. a point $z \in \mathbb{R}^n$ such that there does not exists a point $y \in \mathbb{R}^n$ with $F(y) \leq F(z)$ and $F(y) \neq F(z)$. Here, the inequality sign $\leq$ between vectors is to be understood in a componentwise sense. Likewise, in what follows, a strict inequality $F(y) < F(z)$ is to be understood componentwise, too. Then, the concept of Pareto optimality is introduced as follows:

A feasible solution x^* is said to be a Pareto optimal (non-inferior or efficient) solution if and only if there is no x such that $f_i(x) \leq f_i(x^*)$, for all $i = 1, .., \ell$, with at least one strict inequality. The vector $F(x^*)$ is said to be non-dominated.

The definition above means that it is not possible to improve one objective without degrading one or more of the others. In the absence of any further information about the problem, all Pareto optimal solutions are equally important. Multi-objective optimization implies a decision-making process concerning a great number of optimal solutions. An ideal multi-objective optimization method should be able to find a set of solutions as diverse as possible so that the complete optimal trade-off among the objective is captured. Main difficulties arise from the fact that the Pareto set may present concave parts and/or discontinuities. This situation is rather frequent since most designs of processes are highly non-linear.

Many solving techniques have been proposed in the last decades. The majority of them requires solving repeatedly a set of single-objective NLPs which are formed by assigning preferences to each objective.

To define this concept more precisely, consider a feasible region, S, in the parameter space $x \in \mathbb{R}^n$ that satisfies all the constraints of problem 1, i.e.,

$$S = \{x \in \mathbb{R} : g_j(x) = 0 \quad , j = 1, .., m', \;\; g_j(x) \geq 0 \quad , j = m' + 1, .., m, \; and \; x_l \leq x \leq x_u\}. \tag{2}$$

This allows us to define the corresponding feasible region for the objective function space $\mathcal{F}$, i.e.,

$$\mathcal{F} = \{F(x) : x \in S\}, \tag{3}$$

the performance vector, $F(x)$, maps the parameter space into the objective function space as is represented for a two-dimensional case in Figure 1.

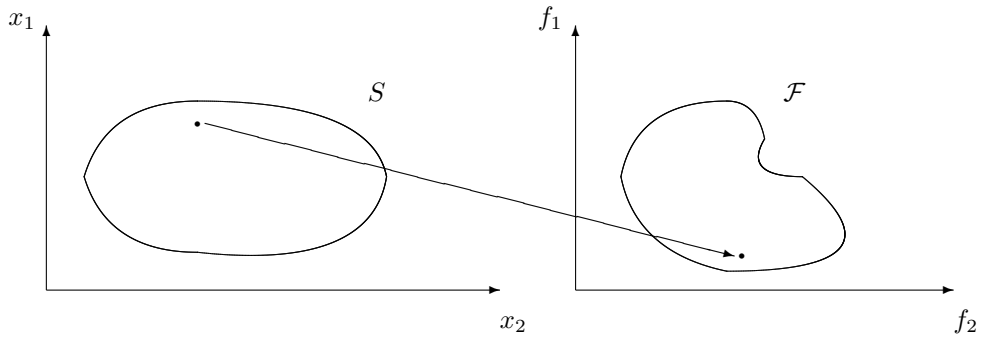

FIGURE 1. Mapping from Parameter Space into Objective Function Space

In the two-dimensional representation of Figure 2, the set of Pareto optimal solutions lies on the curve between C and D. Points A and B represent specific Pareto optimal points. A and B are clearly locally Pareto

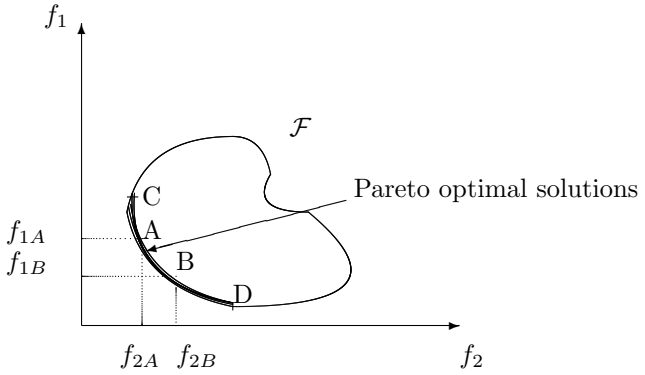

FIGURE 2. Set of locally Pareto optimal

optimal points because an improvement in one objective, f_1, requires a degradation in the other objective, f_2, i.e.,

$$f_{1B} < f_{1A}, f_{2B} > f_{2A}.$$

Since any point in S that is not a Pareto optimal point represents a point in which improvement can be attained in all the objectives, it is clear that such a point is of no value. Multi-objective optimization is, therefore, concerned with the generation and selection of locally Pareto optimal points.

2. The Normal Boundary Intersection (NBI) Method

This recent strategy can be considered as the state of the art regarding deterministic methods. NBI has a number of advantages over other existing methods, including an ensured even spread of points in the Pareto

set [6]. The normal-boundary intersection method uses a geometrically intuitive parameterization to produce an even spread of points on the Pareto surface, giving an accurate picture of the whole surface. Given any point generated by NBI, it is usually possible to find a set of weights such that this point minimizes a weighted sum of objectives, as described above. Similarly, it is usually possible to define a goal programming problem for which the NBI point is a solution. NBI can also handle problems where the Pareto surface is discontinuous or non-smooth, unlike homotopy techniques. Unfortunately, a point generated by NBI may not be a Pareto point if the boundary of the attained set in the objective space containing the Pareto points is nonconvex or 'folded' (which happens rarely in problems arising from actual applications). NBI requires the individual minimizers of the individual functions at the outset, which can also be viewed as a drawback.
The formulation (1), however, must be interpreted as an alternative way. Instead of one objective function, we have ℓ objective functions which we want to reduce subject to the constraints. Since some of the objective functions may conflict with others, one has to find an appropriate compromise depending on priorities of the user. The ideal situation is to compute a vector x^* with

$$(f_1(x^*), ..., f_\ell(x^*)) = (f_1^*, ..., f_\ell^*)$$

where each $f_i^*, \quad i = 1, ..., \ell$, is the individual minimum value of the corresponding scalar problem

$$\begin{cases} \min \quad f_i(x) \\ \text{s. t.} \quad g_j(x) = 0 \qquad , j = 1, ..., m', \\ \qquad\qquad g_j(x) \geq 0 \qquad , j = m' + 1, ..., m, \\ \qquad\qquad x_l \leq x \leq x_u \end{cases} \tag{4}$$

for $i = 1, ..., \ell$. But one has to expect that when reducing one objective function, another one will increase, so that ideal objective function vector

$$(f_1^*, ..., f_\ell^*)$$

will be approximated at most.

It essentially works by solving sequentially a set of single NLPs (NBI subproblems), which are defined as:

$$\begin{cases} \max\limits_{x,t} \quad t \\ \text{s. t.} \quad \Phi w + t\hat{n} = F(x) - f^*, \\ \qquad g_j(x) = 0 \qquad , j = 1, ..., m', \\ \qquad g_j(x) \geq 0 \qquad , j = m' + 1, ..., m, \\ \qquad x_l \leq x \leq x_u \end{cases} \tag{5}$$

Φ be the $\ell \times \ell$ pay-off matrix in which i^{th} column is $F(x_i^*) - f^*$, where f^* is the vector containing the individual minima of objectives (i.e., the utopia point or shadow minimum) and x_i^* is the minimizer of objective function f_i (i.e., minimizers of problem (4)). w is a vector of weights such that $\sum\limits_{i=1}^{\ell} w_i = 1, w_i \geq 0$, and $\hat{n}$ is the quasi-normal direction which has negative components, i.e. it points towards the origin.

Φw defines a point on the so-called Convex Hull of Individual Minima (CHIM). Then the set of points in $\mathbb{R}^n$ that are convex combinations of $f_i^* - f^*$, i.e, $\{\Phi w\}$, is referred to as the CHIM.
Now let us illustrate algebraically how any such boundary point can be found by solving an optimization problem. Given barycentric coordinates w, Φw represents a point in the CHIM. Let $\hat{n}$ denote the unit normal to the CHIM simplex pointing towards the origin; then $\Phi w + t\hat{n}, t \in R$ represents the set of points on the normal. The intersection between the normal to the CHIM from the point and the boundary of the objective space $\mathcal{F}$ closest to the origin is expected to be Pareto-optimal. This is done for various w, so that an equally distributed set of them produces an equally distributed set of non-dominated points, which is an useful feature for the decision-making process. If the Pareto set is convex and the individual minima of the objective are the

global ones, the solution to this problem is Pareto optimal. As a drawback, NBI solves the set of NLPs by means of the RPRGM (Random Perturbation of Reduced Gradient Method).
The subproblem (5) shall be referred as the NBI subproblem and written as NBI_w, since w is the characterizing parameter of the subproblem. The solution of these subproblems will be referred to as NBI points. The idea is to solve NBI_w for various w and find several points on the boundary of $\mathcal{F}$, effectively constructing a pointwise approximation of the efficient frontier.
As indicated earlier, all NBI points are not Pareto optimal points. In bio-objective problems, for every Pareto optimal point, there exists a corresponding NBI subproblem of which it is the solution.

3. The Random Perturbation of Reduced Gradient Method (RPRGM)

We assume that $f_1, ..., f_\ell$ and $g_1, ..., g_m$ are twice continuously differentiable functions.

3.1. Generalized Reduced Gradient Method

We consider the following problem:

$$\begin{cases} \text{Minimize } f(x) \\ \text{Subject to } h_i(x) = 0, i = 1, .., m \\ \qquad\qquad 0 \leq x, \end{cases} \tag{6}$$

where f and $h_i, i = 1, ..., m$ are twice continuously differentiable functions.
Let a feasible solution $x^k \geq 0$ with $h_i(x^k) = 0$ for all i be given. By assumption the Jacobian matrix of the constraints $h(x) = (h_1(x), ..., h_m(x))^t$ at each $x \geq 0$ has full row rank and, for simplicity, at the point x^k will be denoted by

$$A = Jh(x^k).$$

The generalized reduced gradient method begins with a basis B and a feasible solution $x^k = (x_B^k, x_N^k)$ such that where $x_B^k > 0$. Now let us assume that the basis is nondegenerate, i.e. only the non negativity constraints $x_N \geq 0$ might be active at the current iterate x^k. Let the search direction be a vector $d^t = (d_B^t, d_N^t)$ in the null space of the matrix A defined as $d_B = -B^{-1}Nd_N$ and $d_N \geq 0$. If we define so, then the feasibility of $x^k + \eta d$ is guaranteed as long as $x_B^k + \eta d_B \geq 0$, i.e. as long as

$$\eta \leq \eta_{max} = \min_{i \in B, d_i < 0} \{\frac{-x_i^k}{d_i}\}.$$

We still need to define $d_N \geq 0$ such that it is a descent direction of f_N projected on to the coordinate hyperplane active at the current point x_N^k. So we have

$$d_j = \begin{cases} 0 \quad \text{if } x_j^k = 0 \text{ and } \dfrac{\partial f_N(x_N^k)}{\partial x_j} \geq 0, \\ -\dfrac{\partial f_N(x_N^k)}{\partial x_j} \quad \text{otherwise,} \end{cases} \qquad j \in N.$$

where $f_N(x_N) = f(x) = f(B^{-1}b - B^{-1}Nx_N, x_N)$.
To complete the description of the algorithm we make a line search to obtain the new point.

$$x^{k+1} = Q(x^k) = \arg \min_{0 \leq \eta \leq \eta_{max}} f(x^k + \eta d_k). \tag{7}$$

If all the coordinates x_B^{k+1} stay strictly positive we keep the basis, otherwise a pivot is made to eliminate the zero variable from the basis and replace it by a positive but currently non basic coordinate.

3.2. **Stochastic Perturbation**

The main difficulty remains the lack of convexity; if f is not convex, the Kuhn-Tucker points may not correspond to global minima. In the sequel, we shall improve this point by using an appropriate random perturbation.
The sequence of real numbers $\{x^k\}_{k\geq 0}$ is replaced by a sequence of random variables $\{X_k\}_{k\geq 0}$ involving a random perturbation $\mathcal{P}_k$ of the deterministic iteration (7). A simple strategy consists in

$$X_0 = x^0 \; ; \; \forall k \geq 0, \; X_{k+1} = Q_k(X_k) + \mathcal{P}_k \tag{8}$$

Equation (8) is a perturbation of the descent direction d_k, which is replaced by a new direction $D_k = d_k + \mathcal{P}_k/\eta_k$ and the iterations (7) become $X_{k+1} = X_k + \eta_k D_k$. The random perturbation $\mathcal{P}_k$ can be generated as follows: Let us introduce a sequence of n-dimensional random vectors $\{Z_k\}_{k\geq 0} \in S$ where S is the set of constraints in the global optimization problem (6). We consider also $\{\zeta_k\}_{k\geq 0}$, a suitable decreasing sequence of strictly positive real numbers converging to 0 and such that $\zeta_0 \leq 1$.
The procedure generates a sequence $U_k = f(X_k)$. By construction this sequence is decreasing and lower bounded by $U^\star$.

$$\forall k \geq 0 : U^* \leq U_{k+1} \leq U_k \tag{9}$$

Thus, there exists $U \geq U^\star$ such that $U_k \to U \; for \; k \to +\infty$.
The convergence to a global minimum is ensured by the following results (see, for instance, [13], [14]):

Lemma 3.1. *Let* $\{U_n\}_{n\geq 0}$ *be a* decreasing *sequence,* lower bounded by U^*. *Then, there exists* U *such that*

$$U_n \longrightarrow U \quad \text{for} \quad n \to +\infty \; .$$

Assume that, in addition, for any $\theta \in]U^*, U^* + \nu]$, *there is a sequence of strictly positive real numbers* $\{c_n(\theta)\}_{n\geq 0}$ *such that*

$$\forall \; n \geq 0 \; : \; P(U_{n+1} < \theta \mid U_n \geq \theta) \geq c_n(\theta) > 0 \; ; \; \sum_{n=0}^{+\infty} c_n(\theta) = +\infty. \tag{10}$$

where $P(\; . \mid . \;)$ *is the conditional probability. Then* $U = U^*$ *almost surely.*

The lemma 3.1 is applied to the sequence $\{U_n\}_{n\geq 0}$ as follows:

Theorem 3.2. *Let*

$$\zeta_k = \sqrt{\frac{c}{\log(k+d)}} \tag{11}$$

If $x^0 \in S$ *then* $U = U^\star$ *almost surely.*

Proof: (11) satisfies the condition (10).

4. **Multi-objective optimal design of a biochemical reactor**

This design problem is considered in [3] and [2]. The process consists of a well-stirred, aerobic fermentor in which Saccharmoyces cerevisiae grows in a medium of sugar cane molasses, and a centrifuge for recovery of cell mass. The fermentor outlet stream contains biomass and substrate in concentrations X and S, respectively. After centrifugation, a fraction α of the dilute substrate is recycled to the fermentor.
The constrained multi-objective optimization problem is formulated, assuming steady state operation, to maximize the product profit (P) and minimize simultaneously the Fixed Capital Investment (FCI) by adjusting seven independent variables: $h, X, S, \alpha, F_c, F, f_v$.

$$
\left\{
\begin{array}{l}
\left\{
\begin{array}{l}
\max\limits_{h,X,S,\alpha,F_c,F,f_v} f_1 = P(\$10^7/yr) = 504.10^{-4}(c_1XF_0 - c_2F - c_3F_c - c_4XF_0/3600) \\
\min\limits_{h,X,S,\alpha,F_c,F,f_v} f_2 = FCI(\$10^7) = 1.18.10^{-7}(F_{bm,v}B_vV^{0.724} + F_{bm,c}B_c(XF_0)^{0.444})
\end{array}
\right. \\
\textbf{Subject to} \\
\left\{
\begin{array}{ll}
\frac{F+F_c-(1-\alpha)\mathbf{f_v h}^{0.5}}{\pi \mathbf{R^2}} = 0 & (i) \\
\frac{-X(F+F_c+\alpha f_v h^{0.5})}{\pi R^2 h} + kXS.e^{\frac{-S}{\mathbf{K}}} = 0 & (ii) \\
\frac{F(S_F-S)+F_c(S_c-S)}{\pi R^2 h} - \frac{kXS.e^{\frac{-S}{\mathbf{K}}}}{a+bS} = 0 & (iii)
\end{array}
\right. \\
\left\{
\begin{array}{l}
0.05S_{in} - S + y_1 = 0 \\
Q_{min} - XF_0 + y_2 = 0 \\
-h + 1.8R + y_3 = 0, \quad h - 3.6R + y_4 = 0 \\
F_c + y_5 = 4, \quad F + y_6 = 7 \\
S + y_7 = 0.5, \quad X + y_8 = 50 \\
f_v + y_9 = 5, \quad \alpha + y_{10} = 1 \\
h, F_c, F, S, X, f_v, \alpha \text{ and } y_i \geq 0, \quad i = 1, .., 10,
\end{array}
\right.
\end{array}
\right. \tag{12}
$$

where

$$F_0 = f_v h^{0.5},$$

F and $S_F = 0.3$ are the flow rate and substrate concentration of the feed (F_c and $S_c = 1$) of the concentrated feed; $h, R = 2.1$ and

$$V = \pi R^2 h$$

are the height of liquid holdup, radius and volume of the fermentor, f_v is the valve constant; $k = 1$, $\mathbf{K} = 0.12$, $a = 5.4$ and $b = 180$ are constants in the kinetic model; $c_1 = 5, c_2 = 10.8, c_3 = 150$ and $c_4 = 0.04$ are cost coefficients, and B ($B_v = 1836.5$, $B_c = 54325$) and F ($F_{bm,v} = 4.5$, $F_{bm,c} = 3.4$) are base cost and bare module factors for the fermentor and centrifuge. The equality constraints (i)-(iii) in (12) are the mass balances, and the inequality constraints consist of several design specifications, with S_{in} the effective inlet feed concentration,

$$S_{in} = \frac{S_F F + S_c F_c + S\alpha f_v h^{0.5}}{f_v h^{0.5}}$$

and Q_{min} the minimum capacity of production for the system, which is fixed arbitrarily at 6.
The $y_1, .., y_{10}$ are slack variables in order to as equality constraints. The NBI_w subproblems of multi objective problem (12) can be transformed into an equivalent set of subproblems in the form of problem (6), this idea applied too in the problem (5) by adding slack variables in inequality constraints.

w^t	$(0.00, 1.00)$	$(0.05, 0.95)$	$(0.10, 0.90)$	$(0.15, 0.85)$	$(0.20, 0.80)$	$(0.25, 0.75)$	$(0.30, 0.70)$
h	3.8592	3.7942	4.8942	5.6418	5.5715	6.9934	7.2492
F_c	0.8819	0.0382	0.0789	0.0868	0.1255	0.0618	0.1455
F	2.0100	1.1913	0.6618	1.4576	1.4414	1.2719	0.5922
S	0.0686	0.1108	0.2004	0.1037	0.1550	0.2643	0.3504
X	3.9562	3.4101	3.7248	3.5248	4.5625	5.1602	9.0992
f_v	1.0645	1.2177	1.1483	1.4650	1.3921	1.0863	0.7156
α	0.0000	0.4700	0.7024	0.5505	0.5154	0.5295	0.6120
P	0.3239	1.1014	1.4281	1.6410	2.0448	2.5759	2.9460
FCI	0.0738	0.0723	0.0798	0.0892	0.0952	0.0989	0.1026

TABLE 1. Results of NBI_w giving by RPRGM for $w_1 : 0.00 \rightarrow 0.30$

w^t	$(0.35, 0.65)$	$(0.40, 0.60)$	$(0.45, 0.55)$	$(0.50, 0.50)$	$(0.55, 0.45)$	$(0.60, 0.40)$	$(0.65, 0.35)$
h	7.3994	7.3924	7.4772	7.4859	7.4821	7.5166	7.4882
F_c	0.2410	0.3438	0.4718	0.6378	0.7746	1.0204	1.1018
F	0.4244	0.4053	0.4662	0.4244	0.5075	0.3682	0.5387
S	0.3640	0.3556	0.3499	0.3444	0.3467	0.3341	0.3491
X	11.5696	13.6435	15.5258	17.9135	20.9703	23.3204	27.6966
f_v	0.6750	0.6902	0.7241	0.7497	0.7391	0.7877	0.7260
α	0.6260	0.6088	0.5241	0.4750	0.3595	0.3564	0.1718
P	3.2997	3.6325	3.9259	4.2061	4.5514	4.7768	5.2425
FCI	0.1125	0.1198	0.1278	0.1361	0.1431	0.1524	0.1573

TABLE 2. Results of NBI_w giving by RPRGM for $w_1 : 0.35 \rightarrow 0.65$
The correspondent t_{max} of subproblem (5) is the subproblem NBI_w with $w^t = (0.45, 0.55)$.

w^t	$(0.70, 0.30)$	$(0.75, 0.25)$	$(0.80, 0.20)$	$(0.85, 0.15)$	$(0.90, 0.10)$	$(0.95, 0.05)$	$(1.00, 0.00)$
h	7.4928	7.4599	7.4619	7.0005	7.3607	7.1498	7.5600
F_c	1.3768	1.2184	1.4320	1.6796	1.9755	2.2080	2.3081
F	0.5156	0.5699	0.3945	0.1633	0.0787	0.0000	0.0000
S	0.3425	0.3669	0.3631	0.3498	0.3391	0.3185	0.3212
X	31.1670	35.6377	39.0048	43.3306	43.5723	43.9738	43.6213
f_v	0.7516	0.6446	0.6586	0.6861	0.7470	0.8258	0.8470
α	0.0792	0.0001	0.0000	0.0000	0.0000	0.0072	0.0047
P	5.4740	6.2912	6.6419	7.0346	7.2748	7.7769	8.1520
FCI	0.1664	0.1649	0.1719	0.1781	0.1871	0.1934	0.1979

TABLE 3. Results of NBI_w giving by RPRGM for $w_1 : 0.70 \rightarrow 1.00$

In Ref. [16] the multi-objective problem formulated above was solved by considering a set of 50 randomly generated initial points. Original NBI-SQP starts with the search for the individual optima of each objective function, which are then used to compute the Pareto optimal set.

The stability analysis shows that the only stable solution is point P_3, corresponding to the minimum FCI. The dynamic behavior near equilibrium point of selected designs (Table 4) is analyzed by computing a solution

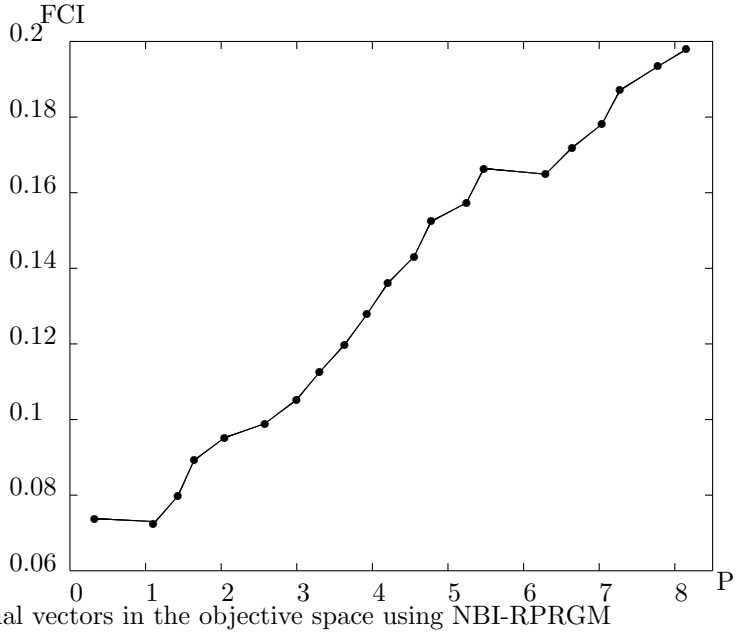

FIGURE 3. Pareto optimal vectors in the objective space using NBI-RPRGM
The example of some globally Pareto optimal points: (P=0.3239, FCI=0.0738), (P=4.7768, FCI=0.1524) and (P=5.4740, FCI=0.1664).

	P_1	P_2	P_3	P_4	P_5	P_6	P_7	P_8
h	7.5600	7.5600	3.7800	4.4559	3.7800	3.7800	3.7800	3.7800
F_c	2.4437	0.0000	0.0000	0.8968	0.9109	0.6914	0.4033	0.0000
F	0.0000	4.6083	1.2369	0.0000	3.0895	0.0000	0.0000	2.0965
S	0.3107	0.1301	0.1184	0.3969	0.1966	0.4132	0.4850	0.1343
X	42.2704	4.8962	2.5955	46.3447	10.7192	46.8137	43.1549	4.4733
f_v	0.8888	1.6760	1.1890	0.4248	1.4550	0.3556	0.2295	1.1813
α	0.0000	0.0000	0.4650	0.0000	0.0000	0.0000	0.0961	0.0872
P	7.5562	3.1775	0.8388	3.6936	2.2378	2.9293	1.8032	1.4478
FCI	0.2041	0.1202	0.0684	0.1367	0.1489	0.1222	0.1012	0.0814

TABLE 4. Selected designs from the Pareto front

diagram where the steady-state dimensionless cell mass concentration (C_1) varies as a function of the Damkohler number (Da).

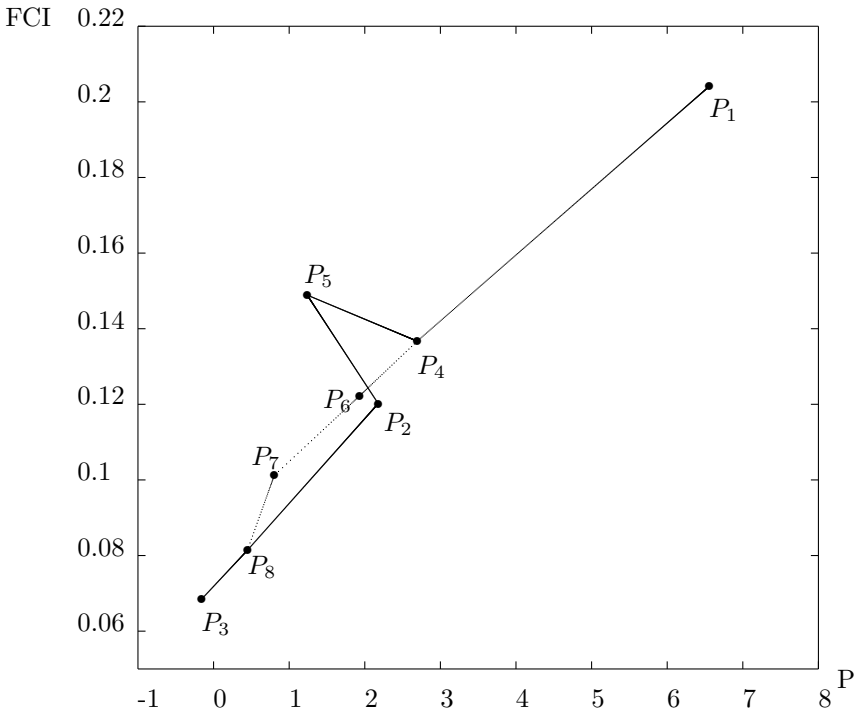

FIGURE 4. Pareto optimal vectors in the objective space using standard NBI-SQP

5. **Conclusions and Future Work**

In this paper the Pareto optimal points of any smooth, constrained multi-objective problem with any number of objective functions find by means of NBI method. Customized RPRGM for solving the NBI subproblem will also be investigated.

Comparing the results of multi-optimization for the optimal design of biochemical reactor between the original NBI-SQP (which uses a local method, SQP) and NBI-RPRGM. The NBI method works reasonably well for a two-objective problem. It is able to produce an accurate approximation of the Pareto curve by generating an even spread of points. Although the algorithm requires repeated solution of the NBI subproblems, they are solved very efficiently. However, for more than two objective functions, some Pareto optimal solutions are overlooked. Moreover, several dominated solutions were obtained.

In a future work, nonsmooth multi-objective problem will be considered using variable metric method via stochastic perturbation [17].

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