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A Combined Random Search and Fuzzy Sets Algorithm for Optimisation of Fed-Batch Biotechnological Processes

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Abstract. Choosing a good initial point matters as much as the optimisation method itself when tuning a biotechnological process, yet the two most common approaches to getting there each carry a cost: fuzzy-set methods give a direct, transparent solution but scale poorly once the decision space grows large, while random-search methods scale well but do not on their own guarantee a well-chosen starting point. This paper develops a combined algorithm that pairs a random-search-with-back-step (RSBS) method for locating a good initial point with a fuzzy-sets-theory (FST) optimisation stage, so that the random search narrows the search region before the fuzzy method is asked to discretise it — directly addressing the scale limitation that otherwise limits fuzzy optimisation. The combined algorithm is applied to the initial-condition and feeding-rate optimal control problem for the fed-batch biotransformation of whey by a strain of Kluyveromyces marxianus var. lactis MC5 in a laboratory stirred-tank bioreactor, raising the optimisation criterion by more than 27% and the final cell concentration by more than 17% relative to the unoptimised process.

Keywords: *fuzzy sets theory; random search with back step; combined algorithm; fed-batch bioprocess; initial condition; optimal control*

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1. Introduction

One of the basic problems in bioprocess development is optimising the initial experimental conditions. A bioprocess outcome is shaped by a large number of parameters, which makes finding a good optimisation method a general concern: a high parameter count narrows the choice of usable methods and is itself a sign of how complex the underlying system is. The methods usually applied for this purpose — simplex search, evolutionary optimisation, and response surface methodology, among others [1–5] — are often not good enough once too many parameters are involved, and can fail to find the optimum.

Fuzzy sets theory (FST) has broad application in modelling, optimisation, and optimal control [6–9], and this work uses an FST-based method [10]. The method's main advantage is that its solution is obtained directly, avoiding the usual weaknesses of numerical solution methods. Its main disadvantage is that it represents variables in discrete form, which makes it progressively less successful as problem scale grows. Methods of random search (MRS), by contrast, do not require calculating gradients, are simple to program, and support adaptive algorithms and algorithms for finding a global extremum. MRS become more effective as the number of control variables grows past about four, because the study space is always divided into two regions — felicitous and infelicitous — and the probability of landing in one or the other does not depend on the number of variables [11].

The choice of a starting point is not a peripheral implementation detail: a recent systematic review of metaheuristic initialisation strategies across the optimisation literature concludes that initialisation is a first-order design decision, on a par with the search operator itself, and identifies it as an under-served area relative to the attention paid to search-operator design [23]. A companion survey covering more than five hundred metaheuristic variants documents how heavily the field still relies on some form of randomised sampling to seed a search, even as operator design has grown far more elaborate [24]. The RSBS-plus-FST combination used in this paper can be read as a domain-specific instance of exactly this general principle: rather than treating initial-point selection and discretisation as independent choices, it uses a random-search stage to do cheaply, over a wide region, what the fuzzy-set stage would otherwise have to do expensively, over a narrow one.

Beyond fuzzy-set and random-search methods specifically, the wider toolkit available for fed-batch optimisation and control has continued to develop. Butkus et al. propose a fuzzy-logic-based adaptive controller for the specific growth rate in fed-batch bioprocesses, keeping the transparency of a rule-based fuzzy approach while adding online adaptivity that a static membership-function formulation does not have [25]. Model predictive control has also been benchmarked directly against alternative fed-batch optimisation strategies and continues to

perform competitively across a range of process types [26], and nonlinear model-predictive schemes built on dynamic flux-balance models extend this line of work to metabolically detailed fed-batch descriptions [27].

In a parallel development, data-driven and machine-learning methods are increasingly used either to replace or to complement mechanistic bioprocess models: recent work applies transfer learning to predictive bioprocess modelling under small-data conditions [28], and a broader review maps the opportunities and current limitations of artificial-intelligence methods across bioprocess modelling, monitoring, and optimisation more generally [29]. Model-driven optimisation and scale-up of fermentation processes remains an active area in its own right [30], and, closest to the present application, a 2026 study models batch ethanol fermentation across seventeen Kluyveromyces marxianus strains using clustering methods together with an evolutionary parameter-identification algorithm, employing a multi-start strategy specifically to reduce the sensitivity of the fit to the initial parameter guess [31] — independent, recent confirmation, from outside this author's own line of work, that initial-point sensitivity remains a live concern for exactly this organism and process class.

Positioned against this literature, the combined RSBS-FST algorithm keeps two properties that the alternatives above do not offer jointly: the fuzzy stage yields its solution directly, without the iterative gradient or population-based search that model-predictive and machine-learning approaches require, while the random-search stage removes the discretisation-scale penalty that a fuzzy-only formulation would otherwise pay. The trade-off is that, unlike the data-driven methods above, it does not learn from additional fermentation runs once deployed; extending the combined algorithm with the kind of small-data transfer-learning components discussed above [28] is a natural direction for future work.

In a series of earlier publications [12, 13], FST has been used to optimise the design and regime parameters of stirred-tank bioreactors, and for the optimal control of biotechnological processes (BTP) [14–17]. In other work [18, 19] a combined algorithm (CA) has been used to optimise the design and operating parameters of a stirred bioreactor; for example, [18] applies a CA to optimise gas-liquid transition in stirred-tank bioreactors. Combining both algorithms makes it possible to overcome the scale disadvantage of the FST-based method. The aim of this work is to summarise the scheme of a combined algorithm for optimising biotechnological processes. In this paper, the CA is applied to optimise the initial conditions and the optimal control of the feeding rate of a fed-batch biotechnological process of lactose oxidation by a strain of Kluyveromyces marxianus var. lactis MC5 in a laboratory stirred-tank bioreactor.

2. Method

2.1 Random Search with Back Step Algorithm

The random search with back step (RSBS) algorithm is well known from the literature [11]. Its rate of convergence — which also holds for other algorithms — depends on the choice of a beginning point. To raise the convergence rate, a preliminary choice of a random set is used, following this scheme. A beginning point in the admissible space is generated by an accidental (random) method:

$$u_{0,i} = u_{min,i} + \xi_i(u_{max,i} - u_{min,i}),\ i = 1, ..., M \quad (1)$$

where umin and umax are the possible limits for the vector control variable, m is the number of control variables, ξi are uniformly distributed random numbers with ξi = URAND(IY), URAND(IY) is a random-number generator on [0÷1], IY is an integer constant, and M is the number of generated points. The point with the best result with respect to some criterion Qa(u) is chosen as the beginning point, after which the RSBS algorithm is applied.

2.2 Fuzzy Algorithm (FA)

FST makes it possible to develop a flexible model [6–10] that reflects, in more detail, all possible values of the criterion and control variables the developed model can take. The developed model itself is treated as the most acceptable; some deviations from it are treated as admissible, but with a lower degree of acceptability. The membership function is presented as a fuzzy set of the following type (Figure 1a):

$$\beta_i(t,u) = 1 / (1 + \varepsilon_i^2) \quad (2)$$

where u is the vector of control variables, t denotes time partitions, εi is the deviation from the basic model, and i = 1, ..., Q, with Q the number of equations in the main model. This flexible model of the process reflects the combined influence of the kinetic variables' acceptable values more fully than a single deterministic model would.

A fuzzy criterion of the type "Qa(u) should be as high as possible" is formulated with the following membership function (Figure 1b):

$$\beta 0(t,u) = \begin{cases} 0 & ;\ Qa(u) < Qa_L \\ [Qa(u) - Qa_L] / [Qa_U - Qa_L] & ;\ Qa_L \le Qa(u) \le Qa_U \end{cases} \quad (3)$$

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$$\{\ 1 \qquad ;\ \ Qa(u) > Qa_U$$

where Qa_L and Qa_U are the low and upper values of the criterion. The membership functions of the model and the criterion are shown in Figure 1.

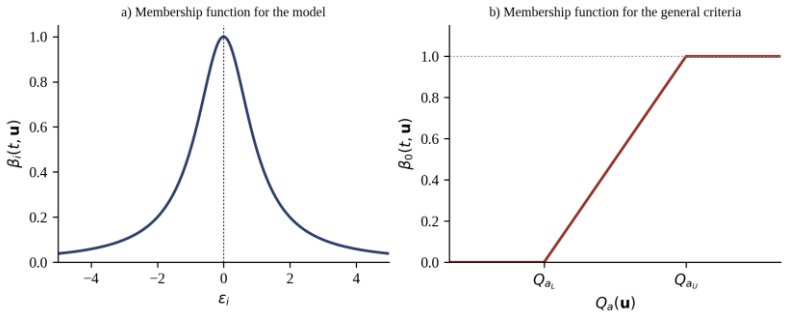


Figure 1. Membership functions of the model and criterion.

The following optimisation problem, in the class of fuzzy mathematical programming problems, can then be formulated:

$$J(u) \cong m\tilde{a}x\ [Q_a(u)] \qquad (4)$$

where m̃ax denotes possibility maximum, and ≅ means "comes into view approximately in the following relation." To determine problem (3), an approach generalising the Bellman–Zadeh method is used [10]. The fuzzy set of the solution is presented with a membership function βD(t,u), the conjunction of the membership functions of the fuzzy set of the criterion β0(t,u) and of the model βi(t,u):

$$\beta D(t,u) = (1-\gamma) \prod_{i=0}^{Q} [\beta i(t,u)]^{\theta i} + \gamma \{ 1 - \prod_{i=0}^{Q} [1 - \beta i(t,u)]^{\theta i} \} \qquad (5)$$

where γ is a parameter characterising the compensation degree, and θi are parameters that give weights to βi(t,u), for i = 0, 1, ..., Q. The solution is obtained using the common defuzzification method BADD [20]:

$$u_0 = \Sigma_{i=1}^{q} [\beta_D(t,u)\theta_i\, u_i] / \Sigma_{j=1}^{p} [\beta_D(t,u)\theta_j] \qquad (6)$$

where i = 1, ..., q, q is the number of discrete values of the vector $\boldsymbol{u}$, and $p = q^m$, with m the number of control variables. An effective combined algorithm for process optimisation is synthesised using these fuzzy sets.

2.3. A Combined Algorithm for Optimisation of Fed-Batch Biotechnological Processes

The model of the biotransformation process of whey by a fed-batch culture of Kluyveromyces lactis MC5 captures the dependences between the concentrations of the basic process variables — cell concentration, substrate concentration, and dissolved oxygen concentration in the liquid phase [14–17, 19]:

$$dX/dt = \mu(S,C)\cdot X - (F/V)\cdot X \quad (7)$$

$$dS/dt = (F/V)(Sin - S) - (1/Y1)\cdot\mu(S,C)\cdot X \quad (8)$$

$$dC/dt = kla(C^* - C) - (1/Y2)\cdot\mu(S,C)\cdot X - (F/V)\cdot C \quad (9)$$

$$dV/dt = F \quad (10)$$

where the specific growth rate follows Monod kinetics in substrate combined with Andrews (Haldane-type) inhibition kinetics in dissolved oxygen:

$$\mu(S,C) = \mu_m \cdot [S / (k_S + S)] \cdot [C / (k_C + C + C^2/k_i)] \quad (11)$$

Here μ(S,C) is the specific growth rate of the cells (h^{-1}); μm is the maximal growth rate (h^{-1}); X is the cell concentration (g/L); S is the substrate concentration (g/L); C is the oxygen concentration (g/L); C* is the mean (saturation) oxygen concentration (g/L); V is the volume (L); kS, kC, ki, Y1, Y2 are coefficients; Sin is the feed substrate concentration (g/L); kla is the volumetric mass-transfer coefficient (h^{-1}); εG is the gas hold-up; and F is the feeding rate (L/h).

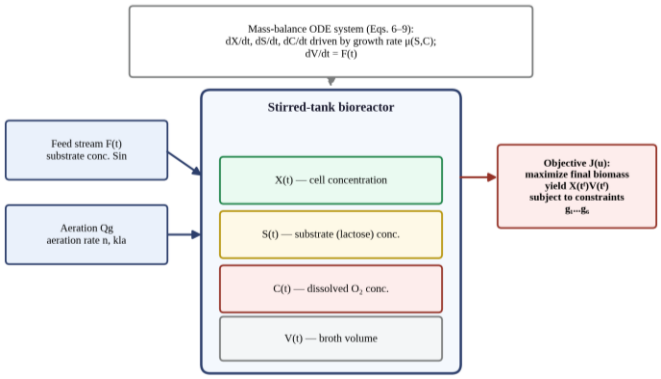


Figure 3. Schematic of the fed-batch bioreactor process and its state variables.

The initial conditions and coefficients in the model are: X(0) = X0 = 0.2 g/L; S(0) = S0 = Sin = 44 g/L; C(0) = C0 = 6.0×10^{-3} g/L; C* = C0; μm = 0.89 h^{-1}; kS = 1.62; kC = 3.37×10^{-3} g/L; ki = 0.47 g/L; Y1 = 2.238; Y2 = 3.24×10^{-3}.

The coefficient kla and the gas hold-up εG are determined by [12–14, 19]:

$$k_l a = 52(P/V)^{0.38}\cdot W_G^{0.23}, \quad \varepsilon_G = 0.53(Q_G/nd^3)^{-0.014}$$

where P is the power input (W), with $P = 60.9\rho n^3 d^5 Re^{-0.4}$ (W); V is the volume (m^3); ρ is the liquid density (kg/m^3); n is the agitation speed (s^{-1}); d is the impeller diameter (m); Re is the Reynolds number; WG is the gas velocity, $WG = 4QG/\pi D^2$ (m/s); QG is the air flow rate (m^3/s); and D is the bioreactor diameter (m).

2.4 Control Variable Constraints

The initial dissolved-oxygen concentration in the fermentation medium across the six fermentation runs performed varies within C0 ∈ [6.0–7.0]$\times10^{-3}$ g/L. Accessible literature data provide no reference value for the initial cell-mass concentration, so it is bounded within X0 ∈ [0.1–0.3] g/L. In the literature [21, 22], the maximum initial lactose concentration reaches at most 50 g/L, so the initial lactose concentration is bounded within S0 ∈ [] g/L, and the input lactose concentration is bounded within Sin ∈ [] g/L. The decision variables are bounded in the solution space as:

$$0 \le F(t) \le F\max, \quad \text{Fmax} = 50.0\times10^{-3}\ \text{L/h} \quad (13)$$

Since the feed rate F(t), as a function of time, is to be chosen in this optimal control problem, the problem is an infinite-dimensional one. To solve it efficiently, the feed flow rate is first represented as a finite set of control parameters F(j) over the time interval tj−1 < t < tj:

$$F(t) = F(j), \ j = 1, \ldots, N \quad (14)$$

where N is the number of time partitions.

3.2 Formulation of the Optimisation Problem

The optimisation problem is to determine the optimal initial conditions of the kinetic variables — X0, S0, C0, Sin — and the feeding profile F(t), such that the following criterion is maximised:

$$\max_{\mathbf{u}} J = [X(t_f)V(t_f) - X0\ V0] / t_f \quad (15)$$
$$- \Sigma_{k=1}^{5} r_k \int_0^{t'} g_k(t)dt - r_6\, g_6(t_f)$$

The penalty parameters rk are positive constants, ri = 10^2 for i = 1, ..., 6; tf is the final fermentation time, tf = 12 h. The decision vector u consists of the initial conditions X0, S0, C0, and Sin — u = $[X0, S0, C0, Sin]^T$ — and the feeding rate is accepted as a control variable u.

4. Results and Discussions

All programs were written in COMPAQ Visual FORTRAN 90. All computations were performed on a dual-core AMD Athlon computer running Microsoft Windows 11. The currency of the cited literature and the vintage of the computing environment answer two different questions, and the two should not be conflated. The 2023–2026 citations added above position the random-search-plus-fuzzy-sets strategy relative to the current optimisation and bioprocess-modelling literature; they establish that initial-point sensitivity remains an active concern for this exact problem class today [25], and that the toolchains now used to study it are typically Python or MATLAB [25], [31].

None of this bears on whether the numerical results reported below are correct, because RSBS and FST are not the kind of computation whose outcome depends on hardware or library generation. Both algorithms operate entirely in IEEE 754 double-precision floating-point arithmetic, which COMPAQ Visual FORTRAN 90, contemporary Python, and contemporary MATLAB all implement identically at the level of the individual arithmetic operation; the FST stage evaluates the closed-form membership and defuzzification expressions in Equations (1)–(5) on a fixed discretisation grid, with no dependence on parallel-reduction order, GPU kernels, or other sources of cross-platform non-determinism; and the RSBS stage's random-number generator is seeded by the integer constant IY, so its output sequence is reproducible given the same generator and seed, independently of the operating system. This stands in contrast to computation classes — stochastic-gradient training of large models is the standard example — where hardware and library version genuinely can shift results; RSBS-FST optimisation of a low-dimensional fed-batch control problem is not in that class.

A further, purely empirical safeguard applies here: the reported improvements (+27% in the optimisation criterion, +17% in final cell concentration) are before/after comparisons in which the unoptimised and optimised runs share the same model, the same solver, and the same toolchain. Any systematic bias that the legacy compiler or operating system might in principle introduce would apply to both runs alike and would therefore cancel, to first order, in the relative comparison that constitutes the paper's central quantitative claim. Notwithstanding this justification, we recognise that independent, contemporary-toolchain reproduction is the stronger standard, and we did not want to assert platform-independence without also committing to it in practice: a Python re-implementation of the combined algorithm, released as supplementary code alongside a revised version of this manuscript, is planned so that the reported results can be checked bit-for-bit against a modern reference implementation rather than only argued for on theoretical grounds.

The optimal values of the kinetic variables obtained after combined-algorithm optimisation are: X0 = 0.28 g/L; S0 = 49.7 g/L; C0 = 6.3×10^{-3} g/L; F0 = 15.0×10^{-3} L/h; Sin = 67.0 g/L. Table 1 summarises these values alongside the process's starting (pre-optimisation) conditions.

Table 1. Initial Conditions and Criterion Before and After Combined-Algorithm Optimisation of the Whey Fermentation Process

Variable	Before optimisation	After CA optimisation
Initial cell concentration, X0 (g/L)	0.20	0.28
Initial substrate concentration, S0 (g/L)	44.0	49.7
Initial oxygen concentration, C0 ($\times10^{-3}$ g/L)	6.0	6.3
Feed substrate concentration, Sin (g/L)	44.0	67.0
Feeding rate, F0 ($\times10^{-3}$ L/h)	—	15.0
Optimisation criterion J	baseline	+27% vs. before
Final cell concentration	baseline	+17% vs. before

Note: percentage changes for the criterion J and the final cell concentration are as reported for the optimised process relative to the unoptimised process over the tf = 12 h fermentation.

The combined algorithm's optimal feeding-rate profile rises from the start of the fermentation, reaches its highest values around the middle of the 12-hour run, and then steps back down toward the end, reflecting the changing balance between substrate demand and the accumulating broth volume as the fermentation progresses.

Applying the combined algorithm raises the optimisation criterion by more than 27% relative to the process before optimisation. The biomass, substrate, and oxygen concentration profiles before and after optimisation likewise change consistently with a more productive fermentation: the substrate concentration after optimisation runs higher than before optimisation — that is, substrate assimilation is comparatively lower — while the dissolved-oxygen concentration after optimisation runs lower than before, indicating that oxygen assimilation by the strain improves after optimisation. Taken together with the higher final biomass concentration, these shifts are consistent with the optimised feeding profile supporting more efficient conversion of the available substrate and oxygen into cell mass.

5. Conclusion

The proposed combined algorithm for optimisation, based on the random-search-with-back-step method and fuzzy sets theory, vastly reduces the time needed to solve the optimisation problem. Applying the combined algorithm eliminates the main disadvantage of the fuzzy optimisation method used on its own, namely by reducing the number of discrete values the control variables require. This lets the algorithm handle problems of larger scale. The combination developed here, for simultaneously optimising the initial conditions and regime parameters, is presented for the first time. This approach raises the effectiveness of the batch fermentation process of lactose oxidation by the strain Kluyveromyces marxianus var. lactis MC5: the cell concentration increases by more than 17% after optimisation. The optimal feed-flow-rate profile obtained, and the results of the theoretical optimisation,

clearly demonstrate the practical applicability of the techniques used, in particular for maximising process productivity. The combined algorithm can be applied to other optimisation problems in the area of bioprocess systems.

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