Journal of Computational and Applied Mathematics 236 (2012) 2268–2276

Contents lists available at SciVerse ScienceDirect

Journal of Computational and Applied Mathematics

journal homepage: www.elsevier.com/locate/cam

Sensitivity analysis and identification of kinetic parameters in batch fermentation of glycerol

Juan Wang [a,c,d,*], Jianxiong Ye [b], Hongchao Yin [c], Enmin Feng [d], Lei Wang [d]

[a] School of Sciences, China University of Petroleum, Qingdao, Shandong 266555, PR China
[b] School of Mathematics and Computer Science, Fujian Normal University, Fuzhou, Fujian 350007, PR China
[c] School of Energy and Engineering, Dalian University of Technology, Dalian, Liaoning 116024, PR China
[d] School of Mathematical Sciences, Dalian University of Technology, Dalian, Liaoning 116024, PR China

ARTICLE INFO

Article history:
Received 11 November 2010
Received in revised form 18 October 2011

Keywords:
Batch culture
Nonlinear dynamical system
Global sensitivity analysis
Parameter identification
Gradient-based algorithm

ABSTRACT

A nonlinear dynamical system was established in our preceding work to describe the batch and continuous bioconversions of glycerol to 1,3-propanediol by *Klebsiella pneumoniae*. The purpose of this article is to analyze the sensitivity of kinetic parameters of the dynamical system and identify their values from experiment. A global sensitivity analysis approach is constructed by combining the local technique with the Monte Carlo method. With only those parameters of higher sensitivity as design variables, we propose a parameter identification model and solve it by a gradient-based simulated annealing algorithm. Numerical results show that our methods are feasible and efficient.

1. Introduction

The bioconversion of glycerol by *Klebsiella pneumoniae* (*K. pneumoniae*) to 1,3-propanediol (1,3-PD) is of interest to industry because of the increasing glycerol surplus on the market and the potential uses of 1,3-PD [1]. Since the 1980s, several mathematical models have been established to describe this bioconversion process [2–5].

In our preceding work [6], a novel mathematical model was proposed to describe the batch and continuous fermentations of glycerol, in which the enzyme-catalytic kinetics on the reductive pathway, the transport mechanisms of glycerol and 1,3-PD across cell membrane, together with the inhibition of 3-hydroxypropionaldehyde (3-HPA) to glycerol dehydratase (GDHt) and 1,3-PD oxydoreductase (PDOR) are all taken into consideration. More influence factors in the fermentation process gives rise to more kinetic parameters, which usually are set to their expected values or fitted to experimental data. However, it is difficult to identify or optimize the kinetic parameters for such an over parameterized model. In consideration of the fact that not all parameters have a significant influence on the behavior of the model, sensitivity analysis technique is needed to identify whether parameters are "significant".

Sensitivity analysis deals with the influence that small changes in nominal values of model parameters exerts on model results [7]. An important classification of the existing methods refers to the way that the parameters are treated. In local sensitivity analysis (or called "one-factor-at-a-time" analysis), only one parameter at-a-time is varied to a given percentage of its expected values while keeping all other model parameters fixed to their expected value [8]. This approach means that the analysis concentrates on estimating the local impact of a parameter on the model output. Opposed to this, global techniques analyze the whole parameter space at once.

* Corresponding author at: School of Sciences, China University of Petroleum, Qingdao, Shandong 266555, PR China. Tel.: +86 41184708351x8025; fax: +86 41184708354.
E-mail addresses: whujuan@163.com (J. Wang), hcyin@dlut.edu.cn (H. Yin).

0377-0427/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cam.2011.11.015

A local analysis method can be integrated to a global one by various methods [9,10], one of which is the sampling-based approach. The Monte Carlo method is one of global sampling methods, which scans in a random or systematic way the entire range of possible parameter values and possible parameter sets [10]. Therefore, combining with Monte Carlo methods, local sensitivity analysis gets integrated to a global sensitivity analysis approach, which is both effective and widely used [11,12].

Up to date, there are a large number of researches developed for parameter identification of kinetic models in glycerol fermentation [13–15]. However, work concerning parameter sensitivity analysis is scarce.

In the present work, a nonlinear dynamical system presented in our preceding work is investigated. To assess the influences of the kinetic parameters on the behavior of the nonlinear dynamical system, we develop a global sensitivity analysis method by combining an existing local technique with Monte Carlo sampling of the parameter space. For the purpose of determining those parameters of higher sensitivity, a parameter identification model is proposed, in which the continuous state inequality constraints are dealt with via the constraint transformation and local smoothing technique, and solved by a gradient-based simulated annealing algorithm, where the gradients of the constraint functions are calculated. Finally, the proposed methods are carried out on the basis of four groups of real experiments in batch culture.

This paper is organized as follows. In Section 2, we briefly introduce the nonlinear dynamical system of glycerol batch fermentation. Section 3 explores a novel global sensitivity analysis technique. A parameter identification model is presented in Section 4. In Section 5, a gradient-based algorithm is developed. Section 6 shows numerical results. Conclusions are presented at the end of the paper.

2. Nonlinear hybrid dynamical system

Let $\mathbf{x} = (x_1, x_2, \ldots, x_8)^T$, the components of which represent the concentrations of biomass (g/L), extracellular glycerol (mmol/L), extracellular 1,3-PD (mmol/L), acetate (mmol/L), ethanol (mmol/L), intracellular glycerol (mmol/L), 3-HPA (mmol/L), intracellular 1,3-PD (mmol/L) in the reactor, respectively. In our preceding work [6], we concluded that there exists a facilitated mechanism for 1,3-PD across cell membranes. Therefore, we assume that both glycerol and 1,3-PD pass the cell membrane by passive diffusion coupled with facilitated transport in this paper. For any positive integer n, we use the notation I_n to represent the set $\{1, 2, \ldots, n\}$. The nonlinear dynamical system of glycerol batch fermentation under this assumption can be described by

$$\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x}, \mathbf{u}), \tag{1}$$

where $\mathbf{u}$ denotes the kinetic parameter vector to be identified. The right hand side of (1) is of the form $\mathbf{F}(\mathbf{x}, \mathbf{u}) = (f_1(\mathbf{x}, \mathbf{u}), \ldots, f_8(\mathbf{x}, \mathbf{u}))^T$ with the components defined as

$$f_1(\mathbf{x}, \mathbf{u}) = \mu x_1, \tag{2}$$

$$f_2(\mathbf{x}, \mathbf{u}) = -q_2 x_1, \tag{3}$$

$$f_3(\mathbf{x}, \mathbf{u}) = q_3 x_1, \tag{4}$$

$$f_4(\mathbf{x}, \mathbf{u}) = q_4 x_1, \tag{5}$$

$$f_5(\mathbf{x}, \mathbf{u}) = q_5 x_1, \tag{6}$$

$$f_6(\mathbf{x}, \mathbf{u}) = \frac{1}{k_7}\left(k_8 \frac{x_2}{x_2 + k_9} + k_{10}(x_2 - x_6) N_{R_+}(x_2 - x_6) - q_{20}\right) - \mu x_6, \tag{7}$$

$$f_7(\mathbf{x}, \mathbf{u}) = k_{11} \frac{x_6}{K_m^G\left(1 + \frac{x_7}{k_{12}}\right) + x_6} - k_{13} \frac{x_7}{K_m^P + x_7\left(1 + \frac{x_7}{k_{14}}\right)} - \mu x_7, \tag{8}$$

$$f_8(\mathbf{x}, \mathbf{u}) = k_{13} \frac{x_7}{K_m^P + x_7\left(1 + \frac{x_7}{k_{14}}\right)} - k_{15} \frac{x_8}{x_8 + k_{16}} - k_{17}(x_8 - x_3) N_{R_+}(x_8 - x_3) - \mu x_8. \tag{9}$$

Here, K_m^G and K_m^P are Michaelis–Menten constants. $N_{R_+}(\cdot)$, the indicator function of a real number ξ, is defined as

$$N_{R_+}(\xi) = \begin{cases} 1, & \xi > 0, \\ 0, & \xi \le 0. \end{cases}$$

The specific cell growth rate μ, the specific consumption rate of extracellular glycerol q_2 and the specific formation rate of extracellular 1,3-PD q_3 are expressed in [6]

$$\mu = \mu_m \frac{x_2}{x_2 + K_s}\left(1 - \frac{x_2}{x_2^*}\right)\left(1 - \frac{x_3}{x_3^*}\right)\left(1 - \frac{x_4}{x_4^*}\right)\left(1 - \frac{x_5}{x_5^*}\right), \tag{10}$$

$$q_2 = k_1 \frac{x_2}{x_2 + k_2} + k_3(x_2 - x_6) N_{R_+}(x_2 - x_6), \tag{11}$$

$$q_3 = k_4 \frac{x_8}{x_8 + k_5} + k_6(x_8 - x_3) N_{R_+}(x_8 - x_3), \tag{12}$$

where μ_m is the maximum specific growth rate and K_s is a Monod saturation constant. x_i^*, $i = 2, 3, 4, 5$, are the critical concentrations of glycerol, 1,3-PD, acetate and ethanol for cell growth, respectively.

While the uptake of extracellular glycerol and the formation of acetate together with ethanol are all considered as "black box" models, the specific consumption rate of glycerol q_{20}, the specific formation rate of acetate q_4 and that of ethanol q_5 can be expressed in [5,14]

$$q_{20} = m_2 + \frac{\mu}{Y_2} + \Delta q_2 \frac{x_2}{x_2 + K_2^*}, \tag{13}$$

$$q_4 = m_4 + \mu Y_4, \tag{14}$$

$$q_5 = m_5 + \mu Y_5. \tag{15}$$

Here, $m_i, Y_i, i = 2, 4, 5, \Delta q_2$ and K_2^* are kinetic parameters. The kinetic parameter vector is defined as $\mathbf{u} := (u_1, u_2, \ldots, u_{25})^T := (k_1, k_2, \ldots, k_{17}, m_2, m_4, m_5, Y_2, Y_4, Y_5, \Delta q_2, K_2^*)^T \in \mathbb{R}^{25}$.

The allowable sets of $\mathbf{x}$ and $\mathbf{u}$ are denoted by $W_a := \prod_{i=1}^{8}[0, x_i^*]$ and $D_u := \prod_{j=1}^{25}[u_{j*}, u_j^*] \subset \mathbb{R}^{25}$, respectively, with the values of x_i^*, $i \in I_8$, u_{j*} and u_j^*, $j \in I_{25}$, given in our preceding work [6]. Let $[0, T]$ be the total fermentation time interval and $\mathbf{x}^0$ the initial state; then the nonlinear dynamical system (1) can be rewritten as

$$\dot{\mathbf{x}}(t) = \mathbf{F}(\mathbf{x}(t), \mathbf{u}), \quad \mathbf{u} \in D_u, \ t \in [0, T], \qquad \mathbf{x}(0) = \mathbf{x}^0. \tag{16}$$

According to the actual experiments, we assume the following.

(H1) No medium is pumped inside or outside the reactor in the process of batch fermentation.
(H2) The concentration of reactants are uniform in the reactor, while time delay and nonuniform space distribution are ignored.

Under the assumptions (H1)–(H2), we have proved the following properties for system (16) in our preceding work [6].

Property 1. *The function* $\mathbf{F}(\mathbf{x}, \mathbf{u})$ *defined in (2)–(15) satisfies*

(1) $\mathbf{F}(\mathbf{x}, \mathbf{u})$ *is Lipschitzian in* $\mathbf{x}$ *on* W_a *and continuous in* $\mathbf{u}$ *on* D_u*;*
(2) *for fixed* $\mathbf{u} \in D_u$*, there exist positive constants* a*,* b *such that the linear growth condition holds, i.e.,*

$$\|\mathbf{F}(\mathbf{x}, \mathbf{u})\| \le a\|\mathbf{x}\| + b, \quad \forall \mathbf{x} \in W_a,$$

where $\|\cdot\|$ *is the Euclidean norm;*
(3) *for fixed* $\mathbf{u} \in D_u$*, there exists a unique solution to system (16), denoted by* $\mathbf{x}(\cdot; \mathbf{u})$*. Furthermore,* $\mathbf{x}(\cdot; \mathbf{u})$ *is continuous in* $\mathbf{u}$ *on* D_u*.*

We define the following sets.

$$S(\mathbf{u}) := \{\mathbf{x}(\cdot; \mathbf{u}) \mid \mathbf{x}(\cdot; \mathbf{u}) \text{ is a solution to (16) with } \mathbf{x}^0 \in W_a\}, \tag{17}$$

$$S_w(\mathbf{u}) := \{\mathbf{x}(\cdot; \mathbf{u}) \mid \mathbf{x}(\cdot; \mathbf{u}) \in S(\mathbf{u}) \text{ and } \mathbf{x}(t; \mathbf{u}) \in W_a, \forall t \in [0, T]\}, \tag{18}$$

$$D_{uw} := \{\mathbf{u} \in D_u \mid \mathbf{x}(\cdot; \mathbf{u}) \in S_w(\mathbf{u})\}. \tag{19}$$

Property 2. *If the sets* $S(\mathbf{u})$, $S_w(\mathbf{u})$ *and* D_{uw} *are all nonempty, then* $S(\mathbf{u})$ *and* $S_w(\mathbf{u})$ *are compact in* $C([0, T], \mathbb{R}^8)$ *with* D_{uw} *compact in* $\mathbb{R}^{25}$*.*

3. Parameter sensitivity analysis

In this section, we shall develop a novel global sensitivity analysis method by combining an existing local technique with Monte Carlo sampling of the parameter space. This enables us to determine which set of parameters from the entire set has to be tuned/optimized [16].

As mentioned in the literature [17], a definition of sensitivity analysis should involve models, model input and model output. In this work, the input and the output of system (16) are, respectively, the parameter vector $\mathbf{u}$ and the state vector $\mathbf{x}$.

Generally, the sensitivity index is basically the ratio of the change in output to the change in input while all other parameters remain constant [18]. Then, we give a definition of the sensitivity index as follows.

Definition 1. The sensitivity index of the state vector $\mathbf{x}$ with respect to the ith component of $\mathbf{u}$ with a perturbation ru_i is defined as

$$R_i^r(\mathbf{u}) := \frac{\int_0^T \frac{\|\mathbf{x}(t; (u_1, \ldots, u_i + ru_i, \ldots, u_{25})^T) - \mathbf{x}(t; \mathbf{u})\|}{\|\mathbf{x}(t; \mathbf{u})\|} dt}{|r|}, \quad i \in I_{25}, \tag{20}$$

where ru_i is the perturbation in u_i with $|r| \le 1$.

For the reason that a local method only evaluates sensitivity at one sample point in the parameter space and this sample may be defined by default values or a crude manual model calibration, we use Monte Carlo techniques to perform random sampling from the feasible parameter space D_{uw} and assess the average sensitivity of all the sample points.

Let M_1 be the size of the Monte Carlo experiments. Denote the perturbation vector $\mathbf{r} := (r_1, r_2, \ldots, r_{M_2})^T$, i.e., there are M_2 different perturbations at each component of a fixed sample point. Let π be a partition of $[0, T]$ given by

$$\pi := \{0 = t_0 < t_1 < \cdots < t_{M_3-1} < t_{M_3} = T, M_3 \in \mathbb{N}\},$$

with $t_i := iT/M_3$, $i \in I_{M_3}$. Then, the sensitivity analysis method is presented as follows.

Algorithm 1.

Step 1.1 Set positive integers M_1, M_2, M_3 and perturbation vector $\mathbf{r}$, and set $m := 1$, $k := 1$.
Step 1.2 If $m < M_1 + 1$, randomly generate a sample point $\mathbf{u}$ from D_{uw}, denote $\mathbf{u}^{(m)} = \mathbf{u}$, goto Step 1.3. Else goto Step 1.5.
Step 1.3 If $k < M_2 + 1$, goto step 1.4; else calculate the sensitivity index

$$\bar{\bar{R}}_i := \frac{1}{M_2}\sum_{k=1}^{M_2} \bar{R}_i^{r_k}, \quad i = 1, \ldots, 25$$

stop.
Step 1.4 Compute

$$R_i^{r_k}(\mathbf{u}^{(m)}) = \frac{\sum_{n=0}^{M_3} \frac{\sqrt{\sum_{j=1}^{8}[x_j(t_n;(u_1^{(m)},\ldots,u_i^{(m)}+r_k u_i^{(m)},\ldots,u_{25}^{(m)})^T)-x_j(t_n;\mathbf{u}^{(m)})]^2}}{\sqrt{\sum_{j=1}^{8}[x_j(t_n;\mathbf{u}^{(m)})]^2}} \cdot \frac{T}{M_3}}{|r_k|},$$

$i = 1, \ldots, 25$. Set $m := m + 1$, goto Step 1.2.
Step 1.5 Compute

$$\bar{R}_i^{r_k} := \frac{1}{M_1}\sum_{m=1}^{M_1} R_i^{r_k}(\mathbf{u}^{(m)}), \quad i = 1, \ldots, 25,$$

set $k := k + 1$, goto Step 1.3.

Then, $\bar{\bar{R}}_i$ is the sensitivity index of the state vector $\mathbf{x}$ with respect to the parameter $u_i, i \in I_{25}$. Additionally, denote $\bar{\bar{R}} := (\bar{\bar{R}}_1, \bar{\bar{R}}_2, \ldots, \bar{\bar{R}}_{25})^T$ as the sensitivity index of the state vector $\mathbf{x}$ with respect to the parameter vector $\mathbf{u}$.

4. Parameter identification model

For convenience, the components of $\mathbf{u}$ are rearranged in order of decreasing sensitivity index, and the allowable set D_u is also reordered. Assume that there are q parameters of higher sensitivity. Denote the new parameter vector by $\mathbf{v} \in \mathbb{R}^{25}$ and the allowable set $D_v := \prod_{i=1}^{25}[v_{i*}, v_i^*]$ with $v_{i*} = v_i^* = v_i$, $i = q + 1, \ldots, 25$, i.e., the last $25 - q$ components of $\mathbf{v}$ are kept constant. Then, system (16) can be rewritten as the following equivalent formulation.

$$\dot{\mathbf{x}}(t) = \mathbf{F}(\mathbf{x}, \mathbf{v}), \quad t \in [0, T], \ \mathbf{v} \in D_v, \qquad \mathbf{x}(0) = \mathbf{x}^0. \tag{21}$$

Obviously, system (21) has similar properties to system (16). According to (17)–(19), we can define the set D_{vw} as follows.

$$D_{vw} := \left\{\mathbf{v} \in D_v | \mathbf{x}(\cdot; \mathbf{v}) \text{ is a solution to (21) with } \mathbf{x}^0 \in W_a \text{ and } \mathbf{x}(t; \mathbf{v}) \in W_a, \forall t \in [0, T]\right\}.$$

Suppose that there are N groups of experiments in batch culture, and that we have measured the substance concentrations at $L(n)$, $n \in I_N$, different instants during the whole fermentation process of the nth experiment. Let $\mathbf{y}^{n,l} := (y_1^{n,l}, y_2^{n,l}, y_3^{n,l})^T \in \mathbb{R}^3$ be extracellular experimental results of biomass, glycerol and 1,3-PD at the observation time $t_{n,l}$, $l \in I_{L(n)}$, $n \in I_N$, and $x_i(t_{n,l}; \mathbf{v})$, $i = 1, 2, 3$, the corresponding computational results from system (21). The parameter identification problem can be formulated as

$$\text{PIP}: \ \min J(\mathbf{v}) := \frac{1}{N}\sum_{n=1}^{N}\sum_{l=1}^{L(n)} \frac{\sum_{i=1}^{3}|x_i(t_{n,l}; \mathbf{v}) - y_i^{n,l}|}{\sum_{i=1}^{3}|y_i^{n,l}|} \tag{22}$$

$$\text{s.t. } \mathbf{v} \in D_{vw}.$$

According to the actual fermentation process, we assume the following.

(H3) Given $\mathbf{x}^0 \in W_a$, system (21) is controllable and observable.
(H4) D_{vw} is nonempty in $\mathbb{R}^{25}$.

Similar to our preceding work [6], we can prove the following theorem.

Theorem 1. *Suppose that assumptions* (H1)–(H4) *are satisfied, then, there exists an optimal solution* $\mathbf{v}^*$ *to* PIP, *i.e.,* $\exists \mathbf{v}^* \in D_{vw}$ *such that*

$$J(\mathbf{v}^*) \le J(\mathbf{v}), \quad \forall \mathbf{v} \in D_{vw}.$$

5. A gradient-based algorithm

PIP is essentially an optimization problem subject to continuous state constraints. In this section, the constraint transform and local smoothing technique [19,20] shall be applied to PIP, and a gradient-based simulated annealing algorithm shall be developed to solve the transformed identification problem.

In PIP, it is difficult to directly judge whether the constraint condition $\mathbf{v}^* \in D_{vw}$ holds or not. In fact, the essential difficulty lies in the judgment of the condition $\mathbf{x}(t;\mathbf{v}) \in W_a, \forall t \in [0,T]$.

Let

$$\begin{aligned} &g_k(\mathbf{x}(t;\mathbf{v})) := x_k(t;\mathbf{v}) - x_k^*, \\ &g_{8+k}(\mathbf{x}(t;\mathbf{v})) := x_*^k - x_k(t;\mathbf{v}), \end{aligned} \quad k \in I_8,\ \forall t \in [0,T].$$

Then, the condition $\mathbf{x}(t;\mathbf{v}) \in W_a, \forall t \in [0,T]$, is equivalently transcribed into $G(\mathbf{v}) = 0$, with $G(\mathbf{v}) := \sum_{k=1}^{16} \int_0^T \max\{0, g_k(\mathbf{x}(t;\mathbf{v}))\}dt$. However, $G(\mathbf{v})$ is non-smooth in $\mathbf{v}$. Consequently, standard optimization routines would have difficulties in dealing with this type of equality constraints. The following smoothing technique is to replace $\max\{0, g_k(\mathbf{x}(t;\mathbf{v}))\}$ by

$$\hat{g}_{k,\epsilon}(\mathbf{x}(t;\mathbf{v})) := \begin{cases} 0, & \text{if } g_k(\mathbf{x}(t;\mathbf{v})) < -\epsilon, \\ \dfrac{(g_k(\mathbf{x}(t;\mathbf{v})) + \epsilon)^2}{4\epsilon}, & \text{if } -\epsilon \le g_k(\mathbf{x}(t;\mathbf{v})) \le \epsilon, \\ g_k(\mathbf{x}(t;\mathbf{v})), & \text{if } g_k(\mathbf{x}(t;\mathbf{v})) > \epsilon, \end{cases} \tag{23}$$

where $\epsilon > 0$ is an adjustable parameter controlling the accuracy of the approximation. Note that

$$\hat{G}_\epsilon(\mathbf{v}) := \sum_{k=1}^{16} \int_0^T \hat{g}_{k,\epsilon}(\mathbf{x}(t;\mathbf{v}))dt \tag{24}$$

is a smooth function in $\mathbf{v}$. The equality constraint $G(\mathbf{v}) = 0$ can now be approximated by

$$\hat{G}_\epsilon(\mathbf{v}) = 0. \tag{25}$$

In fact, (25) is slackened to the following inequality constraint in the actual computation

$$\tilde{G}_{\epsilon,\gamma}(\mathbf{v}) := \hat{G}_\epsilon(\mathbf{v}) - \gamma \le 0, \tag{26}$$

where $\gamma > 0$ is an adjustable parameter controlling the feasibility of constraint (26).

Next, we shall give the gradient formula for the constraint functionals with respect to the control parameters.

Theorem 2. *For each* $\epsilon > 0$, $\gamma > 0$, *the derivatives of the constraint functionals* $\tilde{G}_{\epsilon,\gamma}(\mathbf{v})$ *with respect to the parameters are*

$$\frac{\partial \tilde{G}_\epsilon(\mathbf{v})}{\partial v_i} = \int_0^T \frac{\partial H(\mathbf{x}(t;\mathbf{v}), \mathbf{v}, \lambda(t))}{\partial v_i} dt, \quad i = 1, 2, \ldots, 25, \tag{27}$$

where

$$H(\mathbf{x}(t;\mathbf{v}), \mathbf{v}, \lambda(t)) = \sum_{k=1}^{16} \int_0^T \hat{g}_{k,\epsilon}(\mathbf{x}(t;\mathbf{v}))dt + \lambda^T(t)\mathbf{F}(\mathbf{x}(t;\mathbf{v}), \mathbf{v}), \tag{28}$$

and

$$\lambda(t) = (\lambda_1(t), \lambda_2(t), \ldots, \lambda_8(t))^T, \tag{29}$$

is the solution of the costate system

$$\dot{\lambda}(t) = -\frac{\partial H(\mathbf{x}(t;\mathbf{v}), \mathbf{v}, \lambda(t))}{\partial \mathbf{x}}^T, \tag{30}$$

with the boundary conditions

$$\lambda(0) = \lambda(T) = (0, 0, 0, 0, 0, 0, 0, 0)^T. \tag{31}$$

Proof. Since

$$\frac{\partial \tilde{G}_{\epsilon,\gamma}(\mathbf{v})}{\partial \mathbf{v}} \equiv \frac{\partial \tilde{G}_{\epsilon}(\mathbf{v})}{\partial \mathbf{v}},$$

only the derivation of the gradient of the function $\tilde{G}_{\epsilon}(\mathbf{v})$ with respect to $\mathbf{v}$ is given below. Let $\mathbf{v} \in D_{vw}$ be an arbitrary but fixed vector and δ_i, $i \in I_{25}$, an arbitrary real number. Define

$$\mathbf{v}^{i,\sigma} := (v_1, \ldots, v_i + \sigma\delta_i, \ldots, v_{25})^T,$$

where $\sigma > 0$ is an arbitrary small real number such that $v_{*i} < v_i + \sigma\delta_i < v_i^*$, $i \in I_{25}$. Thus, $\tilde{G}_{\epsilon}(\mathbf{v}^{i,\sigma})$ can be expressed as

$$\tilde{G}_{\epsilon}(\mathbf{v}^{i,\sigma}) := \sum_{k=1}^{16} \int_0^T \hat{g}_{k,\epsilon}(\mathbf{x}(t; \mathbf{v}^{i,\sigma}))dt + \int_0^T \lambda^T(t)[\mathbf{F}(\mathbf{x}(t; \mathbf{v}^{i,\sigma}), \mathbf{v}^{i,\sigma}) - \dot{\mathbf{x}}(t; \mathbf{v}^{i,\sigma})]dt,$$

where λ is yet arbitrary. Thus, it follows that

$$\begin{aligned}\triangle\tilde{G}_{\epsilon}(\mathbf{v}^i) &:= \left.\frac{d\tilde{G}_{\epsilon}(\mathbf{v}^{i,\sigma})}{d\sigma}\right|_{\sigma=0} = \frac{\partial \tilde{G}_{\epsilon}(\mathbf{v})}{\partial v_i}\delta_i \\ &= \int_0^T \left\{ \frac{\partial H(\mathbf{x}(t; \mathbf{v}), \mathbf{v}, \lambda(t))}{\partial \mathbf{x}} \triangle\mathbf{x}(t; \mathbf{v}) + \frac{\partial H(\mathbf{x}(t; \mathbf{v}), \mathbf{v}, \lambda(t))}{\partial v_i}\delta_i - \lambda(t)\triangle\dot{\mathbf{x}}(t; \mathbf{v}) \right\} dt,\end{aligned} \tag{32}$$

where $H(\mathbf{x}(t; \mathbf{v}), \mathbf{v}, \lambda(t))$ is defined as in (28). Integrating (32) by parts and combining (28)–(31), we have

$$\frac{\partial \tilde{G}_{\epsilon}(\mathbf{v})}{\partial v_i}\delta_i = \int_0^T \frac{\partial H(\mathbf{x}(t; \mathbf{v}), \mathbf{v}, \lambda(t))}{\partial v_i}\delta_i dt. \tag{33}$$

Since δ_i is arbitrary, conclusion (28) of the theorem follows. The proof is completed. □

Let $D_{\epsilon,\gamma} := \{\mathbf{v} \mid \mathbf{x}(\cdot; \mathbf{v}) \in S(\mathbf{v}) \text{ and } \tilde{G}_{\epsilon,\gamma}(\mathbf{v}) \le 0\}$. Then, PIP can be approximated by the following problem.

$$\begin{aligned}\text{PIP}_{\epsilon,\gamma}: \ &\min J(\mathbf{v}) := \frac{1}{N}\sum_{n=1}^{N}\sum_{l=1}^{L(n)} \frac{\sum_{i=1}^{3} |x_i(t_{n,l}; \mathbf{v}) - y_i^{n,l}|}{\sum_{i=1}^{3} |y_i^{n,l}|} \\ &\text{s.t. } \mathbf{v} \in D_{\epsilon,\gamma}.\end{aligned} \tag{34}$$

Similar to the work [19,20], we can prove the following theorem.

Theorem 3. *Let* $\mathbf{v}^*_{\epsilon,\gamma}$ *be the optimal solution of the approximate problem* $\text{PIP}_{\epsilon,\gamma}$. *Suppose that there exists an optimal solution,* $\mathbf{v}^*$, *of the original problem* PIP. *Then*

$$\lim_{(\epsilon,\gamma)\longrightarrow(0,0)} J(\mathbf{v}^*_{\epsilon,\gamma}) = J(\mathbf{v}^*).$$

Next, we shall develop a gradient-based simulated annealing algorithm to solve the approximate problem $\text{PIP}_{\epsilon,\gamma}$.

Suppose Q_1 and Q_2 are the total number of steps of the outer- and inner-iteration in our annealing algorithm, respectively. Q_3 is the number of sample points which are randomly generated from the set D_{vw}. According to the approach proposed in [21], the initial temperature T_0 can be estimated as $T_0 := \varsigma\theta$ with θ the standard deviation of the cost function of Q_3 sample points and ς a coefficient. Additionally, the formulas for determining the acceptance probability and temperature lowering way are given by the generalized Boltzmann–Gibbs statistics [22] and the pseudo Cauchy distribution [23], respectively. To limit the new sample points within the set D_{vw}, we introduce the gradients of the constraint functions with respect to the parameters into our algorithm, which is then constructed as follows.

Algorithm 2.

Step 2.1. Set parameters $Q_1, Q_2, Q_3, \varsigma, \beta, \eta, \epsilon, \gamma$. Generate the initial sample point $\mathbf{v}^0$ from D_{vw}. Set $\mathbf{v}^{\text{opt}} = \mathbf{v}^{\text{next}} = \mathbf{v}^{\text{current}} := \mathbf{v}^0, J(\mathbf{v}^{\text{opt}}) = J(\mathbf{v}^{\text{next}}) = J(\mathbf{v}^{\text{current}}) := J(\mathbf{v}^0)$, $k := 0$ and $m := 0$.

Table 1
Sensitivity index $\bar{\bar{R}}$ of the parameter vector $\mathbf{u} \in \mathbb{R}^{25}$ of system (16) under four groups of experiments.

Experiment 1: $T = 7.3$ h, $\mathbf{x}^0 = (0.102$ g/L, 418.2609 mmol/L, 0, 0, 0, 0, 0, $0)^T$, $\bar{\bar{R}} = (5.6632, 0.0595, 6.2537, 18.6033, 4.1909, 9.1109, 6.0481, 0.5023, 0.0035, 6.3448, 30.9978, 0.0206, 0.998, 0.8642, 0.9649, 0.6322, 9.0698, 0.01909, 0.8456, 5.6401, 0.4706, 10.7913, 6.0902, 0.2279, 0.0105)^T$
Experiment 2: $T = 6.6$ h, $\mathbf{x}^0 = (0.2025$ g/L, 441.337 mmol/L, 0, 0, 0, 0, 0, $0)^T$, $\bar{\bar{R}} = (6.2543, 0.0753, 7.0641, 24.2536, 4.5856, 13.8853, 6.8256, 0.5535, 0.0044, 7.1486, 28.714, 0.0206, 0.9833, 0.9018, 1.0219, 0.6455, 13.7616, 0.021, 0.8564, 7.1402, 0.5338, 13.6238, 7.7768, 0.2495, 0.0129)^T$
Experiment 3: $T = 6.8$ h, $\mathbf{x}^0 = (0.173$ g/L, 402.9348 mmol/L, 0, 0, 0, 0, 0, $0)^T$, $\bar{\bar{R}} =$ $(5.9587, 0.0762, 6.2282, 19.3686, 3.9353, 10.5956, 5.9919, 0.5275, 0.0045, 6.3059, 26.2665, 0.0194, 0.9805, 0.7901, 0.9937, 0.5589, 10.5124, 0.0201, 0.9318, 6.2682, 0.5183, 12.3381, 7.005, 0.2372, 0.0131)^T$
Experiment 4: $T = 8$ h, $\mathbf{x}^0 = (0.2245$ g/L, 509.8913 mmol/L, 0, 0, 0, 0, 0, $0)^T$, $\bar{\bar{R}} = (5.9574, 0.0587, 7.9242, 22.2547, 4.131, 12.8212, 7.7116, 0.5248, 0.0035, 8.0184, 28.0036, 0.0172, 0.9604, 0.8191, 0.9965, 0.5748, 12.7096, 0.01989, 0.9023, 7.4127, 0.4895, 13.7292, 7.8102, 0.2384, 0.0103)^T$

Step 2.2. Randomly generate Q_3 sample points from D_{vw}, denoted by $\mathbf{v}^{(i)}$, $i = 1, 2, \ldots, Q_3$. Compute the cost functions $J(\mathbf{v}^{(i)})$, $i = 1, 2, \ldots, Q_3$, and the standard deviation θ of them, and set the initial temperature $T_0 := \varsigma\theta$.

Step 2.3. If $k > Q_1$, output $\mathbf{v}^{\text{opt}}$ and $J(\mathbf{v}^{\text{opt}})$, stop; else goto Step 2.4.

Step 2.4. If $m < Q_2$, goto Step 2.5; else set $k := k+1$, $m := 0$, and reduce temperature by setting $T_k := T_0\beta^k$, goto Step 2.3.

Step 2.5. Generate a random variable ξ from the interval $(0, 1]$.

Step 2.6. Compute $\mu := T_k \text{sgn}(\xi - 0.5)[(1 + \frac{1}{T_k})^{|2\xi-1|} - 1]$, and the next point $\mathbf{v}^{\text{next}} := \mathbf{v}^{\text{current}} + \mu(\mathbf{v}^* - \mathbf{v}_*)$, where $\mathbf{v}^*$ and $\mathbf{v}_*$ are the upper and lower bounds of the parameter sample $\mathbf{v}$, respectively. Compute $\tilde{G}_{\epsilon,\gamma}(\mathbf{v}^{\text{next}})$ by (26), goto Step 2.7.

Step 2.7. If $\tilde{G}_{\epsilon,\gamma}(\mathbf{v}^{\text{next}}) \le 0$, goto Step 2.8; else compute

$$\mathbf{h}(\mathbf{v}^{\text{next}}) := \left.\frac{\partial \tilde{G}_\epsilon(\mathbf{v})}{\partial \mathbf{v}}\right|_{\mathbf{v}=\mathbf{v}^{\text{next}}},$$

and the point

$$\mathbf{v}^{\text{next}} := \mathbf{v}^{\text{next}} - \rho(\mathbf{v}^{\text{next}})\mathbf{h}(\mathbf{v}^{\text{next}}),$$

with $-\mathbf{h}(\mathbf{v}^{\text{next}})$ the search direction and $\rho(\mathbf{v}^{\text{next}})$ the step-size selected by Armijo line search, goto Step 2.8.

Step 2.8. Compute $J(\mathbf{v}^{\text{next}})$ and $\triangle J := J(\mathbf{v}^{\text{next}}) - J(\mathbf{v}^{\text{current}})$. If $\triangle J < 0$, compute $\mathbf{v}^{\text{opt}} := \arg\min\{J(\mathbf{v}^{\text{opt}}), J(\mathbf{v}^{\text{next}})\}$, and let $\mathbf{v}^{\text{current}} := \mathbf{v}^{\text{next}}$, $m := m + 1$, goto Step 2.4. Else compute the acceptance probability $P := [1 - (1-\eta)\frac{\triangle J}{T_k}]^{1/(1-\eta)}$, and let $\mathbf{v}^{\text{bad}} := P\mathbf{v}^{\text{next}} + (1-P)\mathbf{v}^{\text{current}}$. Compute $\tilde{G}_{\epsilon,\gamma}(\mathbf{v}^{\text{bad}})$ by (26), goto Step 2.9.

Step 2.9. If $\tilde{G}_{\epsilon,\gamma}(\mathbf{v}^{\text{bad}}) \le 0$, set $\mathbf{v}^{\text{current}} := \mathbf{v}^{\text{bad}}$, goto Step 2.10; else compute

$$\mathbf{h}(\mathbf{v}^{\text{bad}}) := \left.\frac{\partial \tilde{G}_\epsilon(\mathbf{v})}{\partial \mathbf{v}}\right|_{\mathbf{v}=\mathbf{v}^{\text{bad}}}$$

and

$$\mathbf{v}^{\text{current}} := \mathbf{v}^{\text{bad}} - \rho(\mathbf{v}^{\text{bad}})\mathbf{h}(\mathbf{v}^{\text{bad}}),$$

with $-\mathbf{h}(\mathbf{v}^{\text{bad}})$ the search direction and $\rho(\mathbf{v}^{\text{bad}})$ the step-size selected by Armijo line search, goto Step 2.10.

Step 2.10. Set $m := m + 1$, goto Step 2.4.

6. Numerical example and results

Given $\mathbf{r} = (-0.2, -0.1, 0.1, 0.2)^T$, $M_1 = 500$ and $M_3 = 100$ in Algorithm 1, we obtained the sensitivity index of the parameter vector of system (16) under four groups of experiments as listed in Table 1.

According to Table 1, parameters u_{11}, u_4, u_{22}, u_6, u_{17}, u_{23}, u_{10}, u_3, u_7, u_{20}, u_1 and u_5 are identified as sensitive. On the other hand, u_i, $i = 2, 8, 9, 12$–$16, 18, 19, 21, 24, 25$, are considered insensitive for the reason that their sensitive index are all smaller than 1.

Denote $\mathbf{v} = (v_1, v_2, \ldots, v_{25})^T := (u_{11}, u_4, u_{22}, u_6, u_{17}, u_{23}, u_{10}, u_3, u_7, u_{20}, u_1, u_5, u_{15}, u_{13}, u_{19}, u_{14}, u_{16}, u_8, u_{21}, u_{24}, u_2, u_{18}, u_{12}, u_{25}, u_9)^T$. With the values in Table 2, where every parameter takes the corresponding average value of 500 sample points in Algorithm 1, the problem PIP is solved by solving the problem $\text{PIP}_{\epsilon,\gamma}$ using Algorithm 2. The parameters chosen are as follows: $Q_1 = 1000$, $Q_2 = 500$, $Q_3 = 500$, $\beta = 0.98$, $\eta = -5$, $\epsilon = 0.0001$, $\gamma = 0.0001$. For selecting the best value for ς, we run the algorithm for some different values of ς and finally determine its value by $\varsigma = 12$. Consequently,

Table 2
Fixed values of the insensitive parameters of system (16).

u_2	u_8	u_9	u_{12}	u_{13}	u_{14}	u_{15}	u_{16}	u_{18}	u_{19}	u_{21}	u_{24}	u_{25}
3.8710	46.1633	2.7467	185.242	45.9992	1.3341	6.9401	26.6321	3.1453	−1.0522	0.0066	36.8436	16.2526

Table 3
Approximately optimal values of parameters v_i, $i = 1, 2, \ldots, 12$.

$v_1(u_{11})$	$v_2(u_4)$	$v_3(u_{22})$	$v_4(u_6)$	$v_5(u_{17})$	$v_5(u_{23})$	$v_6(u_{10})$	$v_7(u_3)$	$v_8(u_7)$	$v_9(u_{20})$	$v_{10}(u_1)$	$v_{10}(u_5)$
38.7706	144.066	53.3623	85.2486	71.8511	12.8892	4543.09	101.122	8.2813	2.8003	51.4459	3.7595

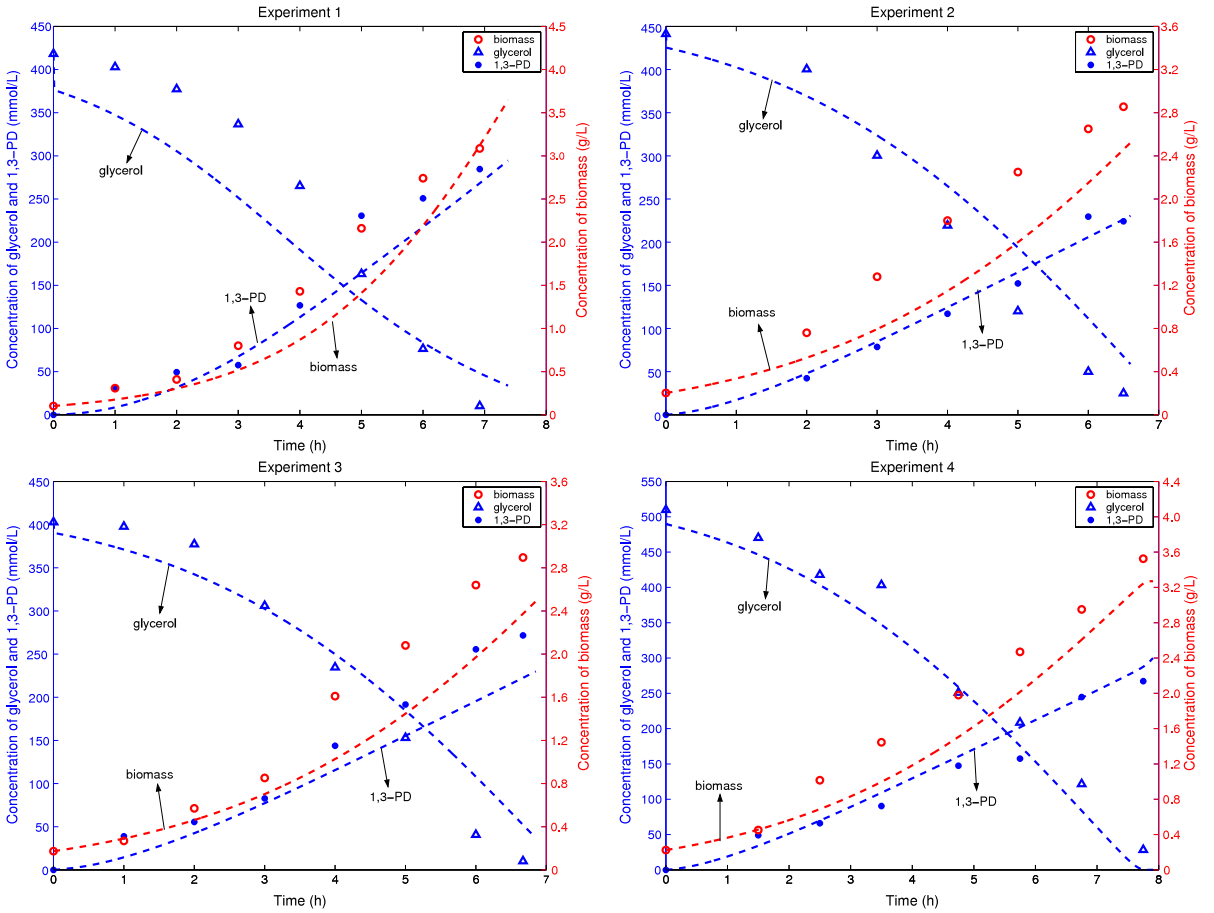

Fig. 1. Comparisons of experimental data and simulating curves of biomass, glycerol and 1,3-PD concentrations in batch culture based on four groups of experimental results. The horizontal axes represent time. The left vertical axes represent the concentrations of glycerol and 1,3-PD, while the right vertical axes apply for biomass.

we obtained the approximately optimal values of those sensitive parameters u_{11}, u_4, u_{22}, u_6, u_{17}, u_{23}, u_{10}, u_3, u_7, u_{20}, u_1 and u_5, i.e., v_i, $i = 1, 2, \ldots, 12$, as listed in Table 3.

Fig. 1 shows the comparisons between experimental results and simulating curves of biomass, glycerol and 1,3-PD concentrations in batch culture under four groups of real experiments, where the scattergrams denote experimental results and the dashed lines display simulating curves. From Fig. 1, we can find that the nonlinear dynamic system can simulate the glycerol consumption and 1,3-PD formation well, but the simulation of biomass growth is not ideal. The reason may be that the multistage growth of cell in batch culture is not considered in our model.

7. Conclusions

In this paper, aiming to reduce the number of kinetic parameters to be identified and to save the computational cost of parameter identification, we carry out parameter sensitivity analysis of a nonlinear dynamical system by a global technique,

which is constructed based on combining "one-factor-at-a-time" method with Monte Carlo samplings. To determine those parameters with higher sensitivity, a parameter identification model is established and solved by a gradient-based simulated annealing algorithm. Numerical results based on four groups of real experiments show both the feasibility and validity of our algorithm.

The current work deals with the kinetic parameter sensitivity analysis and parameter identification of a nonlinear dynamical system of glycerol batch fermentation. In a future work, we will consider multistage analysis and optimal control of this dynamical system.

Acknowledgments

This work was supported by 863 Program (Grant No. 2007AA02Z208), 973 Program (Grant No. 2007CB714304), the National Natural Science Foundation of China (Grant Nos. 10471014, 10671126 and 10871033) and the Fundamental Research Funds for the Central Universities.

References

[1] K. Menzel, A.P. Zeng, H. Biebl, W.D. Deckwer, Kinetic, dynamic, and pathway studies of glycerol metabolism by klebsiella pneumoniae in anaerobic continuous culture: I. the phenomena and characterization of oscillation and hysteresis, Biotechnol. Bioeng. 52 (1996) 549–560.
[2] A.P. Zeng, A. Rose, H. Biebl, C. Tag, B. Guenzel, W.D. Deckwer, Multiple probuct inhibition and growth modeling of clostridium butyricum and klebsiella pneumoniae in glycerol fermentation, Biotechnol. Bioeng. 44 (1994) 902–911.
[3] A.P. Zeng, W.D. Deckwer, A kinetic model for substrate and energy consumption of microbial growth under substrate-sufficient condition, Biotechnol. Prog. 11 (1995) 71–79.
[4] Z. Xiu, A. Zeng, L. An, Mathematical modelling of kinetics and research on multiplicity of glycerol bioconversion to 1,3-propanediol, J. Dalian Univ. Technol. 40 (2000) 428–433.
[5] Y. Sun, et al., Mathematical modeling of glycerol fermentation by klebsiella pneumoniae: concerning enzyme-catalytic reductive pathway and transport of glycerol and 1,3-propanediol across cell membrane, Biochem. Eng. J. 38 (2008) 22–32.
[6] J. Wang, J. Ye, E. Feng, Z. Xiu, B. Tan, Complex metabolic network of glycerol fermentation by klebsiella pneumoniae and its system identification via biological robustness, Nonlinear Anal. Hybrid Syst. 5 (2011) 102–112.
[7] W.H. Zangemeister, S. Lehman, L. Stark, Sensitivity analysis and optimization for a head movement model, Biol. Cybern. 41 (1981) 33–45.
[8] F. Fenneteau, Jun Li, Fahima Nekka, Assessing drug distribution in tissues expressing *P*-glycoprotein using physiologically based pharmacokinetic modeling: identification of important model parameters through global sensitivity analysis, J. Pharmacokinet. Pharmacodyn. 36 (6) (2009) 495–522.
[9] Morris, Factorial sampling plans for preliminary computational experiments, Technometrics 33 (2) (1991) 161–174.
[10] A. van Griensven, T. Meixner, S. Grunwald, T. Bishop, M. Diluzil, R. Srinivasan, A global sensitivity analysis tool for the parameters of multi-variable catchment models, J. Hydrol. 324 (2006) 10–23.
[11] D.M. Hamby, A review of techniques for parameter sensitivity analysis of environmental models, Environ. Monit. Assess. 32 (1994) 135–154.
[12] J.C. Helton, et al., Survey of sampling-based methods for uncertainty and sensitivity analysis, Reliab. Eng. Syst. Saf. 91 (2006) 1175–1209.
[13] G. Wang, E.M. Feng, Z.L. Xiu, Vector measure for explicit nonlinear impulsive system of glycerol bioconversion in fed-batch cultures and its parameter identification, Appl. Math. Comput. 188 (2007) 1151–1160.
[14] C. Gao, Z. Wang, E. Feng, Z. Xiu, Parameter identification and optimization of process for bio-dissimilation of glycerol to 1,3-propanediol in batch culture, J. Dalian Univ. Technol. 46 (5) (2006) 771–774.
[15] J. Wang, J. Ye, E. Feng, H. Yin, Z. Xiu, Modeling and identification of a nonlinear hybrid dynamical system in batch fermentation of glycerol, Math. Comput. Modelling 54 (2011) 618–624.
[16] S. Koteswara Rao, Rayees Imam, Karthik Ramanathan, S. Pushpavanam, Sensitivity analysis and kinetic parameter estimation in a three way catalytic converter, Ind. Eng. Chem. Res. 48 (2009) 3779–3790.
[17] A. Saltelli, et al., Global Sensitivity Aanlysis. The Primer, John Wiley Sons Ltd., The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, 2008, pp. 1–6.
[18] T.J. Krieger, C. Durston, D.C. Albright, Statistical determination of effective variables in sensitivity analysis, Trans. Am. Nucl. Soc. 28 (1977) 515–516.
[19] K.L. Teo, C.J. Goh, A computational method for combined optimal parameter selection and optimal control problems with general constraints, J. Aust. Math. Soc. Ser. B 30 (1989) 350–364.
[20] L.S. Jennings, K.L. Teo, A computational algorithm for functional inequality constrained optimization problems, Automatica 26 (1990) 371–375.
[21] M.-T. Vakil-Baghmisheh, A. Navarbaf, A modified very fast simulated annealing algorithm, in: IST, 2008, pp. 61–66.
[22] C. Tsallis, Possible generalization of Boltzmann–Gibbs statistics, J. Stat. Phys. 52 (1988) 479–487.
[23] I. Ingher, Very fast simulated re-annealing, Math. Comput. Modelling 12 (1989) 967–973.