Korean J. Chem. Eng., **28**(3), 886-889 (2011)
DOI: 10.1007/s11814-010-0448-4

RAPID COMMUNICATION

Analytical studies of Jacobson's necessary condition for fed-batch singular control optimization

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(*Received 2 September 2010 • accepted 7 October 2010*)

Abstract−Jacobson's necessary condition for optimality guarantees non-negativity of singular second variation, independently of generalized Legendre-Clebsch condition. Fed-batch is a typical singular bioprocess system. However, no reports exist of using Jacobson's necessary condition in fed-batch optimization problem. This paper suggests its applicability to fed-batch optimization problem by showing its analytical studies for two typical examples: cell mass and metabolite maximization problem.

Key words: Jacobson's Necessary Condition, Fed-batch, Singular Control, Optimization

INTRODUCTION

Many biomaterials like cell mass or metabolites have been produced through the fed-batch fermentation, which is generally known to be more effective than the batch process due to its ability to control the feed rate during the process time. Hence, it is a major issue how to control the feed rate in order to maximize a performance index such as cell mass or metabolite at the final process time. Pontryagin's maximum principle gives rise to several linear necessary conditions for optimality of a performance index for a system through the first variation of the performance index by a calculus variation [1]. Another necessary condition can arise through the second variation of the performance index. The generalized Legendre-Clebsch condition [2] is well known to be that for a singular control problem, which is common in fed-batch fermentation.

Having established the generalized Legendre-Clebsch condition, an effort to generalize the known sufficient conditions for the nonsingular case was continued. However, in the process, a new necessary condition known as Jacobson's condition, guaranteeing nonnegativity of the singular second variation, different from the generalized Legendre-Clebsch condition, was derived by Jacobson. Much less, Jacobson said both the generalized Legendre-Clebsch condition and Jacobson's condition are generally not sufficient for optimality [3].

However, nearly almost all of the research about the control problem of fed-batch fermentation has not ascertained whether the processes satisfy Jacobson's necessary condition for optimality, much less even the generalized Legendre-Clebsch condition. It may be partially because Jacobson's necessary condition contains a system of differential equations compared with the algebraic equation form of the generalized Legendre-Clebsch condition, and thus it needs some cumbersome effort after all of the states over an entire process time are to be known. It's actually difficult to predict the agreement of Jacobson's necessary condition, not knowing state variables over all process time. This paper deals with this case, i.e., how can we make sure the accordance to Jacobson's necessary condition without the knowledge of state over an entire process time.

METHODS

Jacobson's necessary condition without terminal constraints

Let us first introduce Jacobson's necessary condition without terminal constraints [4]. Consider a control problem described by the differential equations

$$\dot{x} = f_1(x,t) + f_u(x,t)u,\ \ x(t_0) = x_0,\ \ |u(t)| \le 1,\ \ t \in [t_0, t_f] \tag{1}$$

The performance index to be minimized is

$$V = \int_{t_0}^{t_f} L(x,t)dt + F(x(t_f), t_f) \tag{2}$$

For a singular arc, the fact that the second variation of the performance index must be nonnegative gives the following conditions called Jacobson's necessary condition.

$$f_u^T(\bar{x},t)[H_{xu}(\bar{x},\bar{u},\bar{V}_x,t) + \bar{V}_{xx}f_u(\bar{x},t)] \ge 0 \tag{3}$$

where

$$\begin{aligned} -\dot{\bar{V}}_x &= H_x(\bar{x},\bar{u},\bar{V}_x,t) \\ -\dot{\bar{V}}_{xx} &= H_{xx}(\bar{x},\bar{u},\bar{V}_x,t) + f_x^T(\bar{x},\bar{u},t)\bar{V}_{xx} + \bar{V}_{xx}f_x(\bar{x},\bar{u},t) \\ \bar{V}_x(t_f) &= F_x(\bar{x}(t_f),t_f) \\ \bar{V}_{xx}(t_f) &= F_{xx}(\bar{x}(t_f),t_f) \end{aligned} \tag{4}$$

In the above, $(\bar{x},\bar{u},\bar{V}_x,\bar{V}_{xx})$ means optimal properties over a singular arc. Looking into the condition about $\bar{V}_x$, we can notice it is just adjoint variables. The condition is independent of the generalized Legendre-Clebsch condition. The necessary condition (Eq. (3)) is dependent on ordinary differential Eq. (4). Hence, given state values over a singular arc, we can obtain $\bar{V}_x$ and $\bar{V}_{xx}$ by integrating Eq. (4). And then, substituting the calculated values into Eq. (3) tells us whether the proposed singular arc is optimal of not. Secondly, Eqs. (3) and (4) can be combined into the original problem. This allows

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us to find optimal trajectory satisfying the necessary condition. However, what would happen if we could have adjoint variables constituting only state variables? In this case, we can use Eq. (3) directly. On the other hand, with constrained terminal states, the conditions are more complex (not shown). In this case, we cannot use the necessary condition with terminal condition constrained even if we could know adjoint variables formed with only state variables. With this idea, we will apply Jacobson's necessary condition into fed-batch fermentation to maximize cell mass and maximize metabolites.

Fed-batch fermentation model for maximizing cell mass

First, we will deal with the case that the specific properties μ and σ are a function of only substrate concentration. Here, the performance index is $\underset{F(t)}{\mathrm{Min}} - x_1(t_f)$. And, the dynamic behaviors are expressed by

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix}=\begin{bmatrix}\mu x_1\\ -\sigma x_1\\ 0\end{bmatrix}+\begin{bmatrix}0\\ s_F\\ 1\end{bmatrix}u,\quad x_3-V_{max}\le 0,\quad 0\le u\le u_{max} \tag{5}$$

$x_1=xV$, $x_2=sV$, $x_3=V$

where x, s, and V mean cell mass, substrate concentration and volume, respectively. We have an inequality constraint about volume. If we could reformulate the original fed-batch fermentation problem with an inequality constraint into that without constraints, Eq. (3) could be used directly with adjoint variables consisting of only state variables. This can be possible by introducing a new variable.

The inequality condition can be rewritten as follows.

$$x_3-V_{max}+\frac{1}{2}\alpha^2(t)=0 \tag{6}$$

Differentiating Eq. (6) with respect to time and rewriting with Eq. (5) gives

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{\alpha}\end{bmatrix}=\begin{bmatrix}\mu x_1\\ -\sigma x_1\\ 0\\ 0\end{bmatrix}+\begin{bmatrix}0\\ -s_F\alpha\\ -\alpha\\ 1\end{bmatrix}\alpha_1\qquad \underline{X}(t_0)=\begin{bmatrix}x_{10}\\ x_{20}\\ x_{30}\\ \pm\sqrt{V_{max}-x_{30}}\end{bmatrix} \tag{7}$$

As shown above, a new control variable α_1 appears. Now, we apply the classical Pontryagin minimum principle into Eq. (7). The Hamiltonian is

$$H=(\lambda_1\mu-\lambda_2\sigma)x_1+(-S_F\alpha\lambda_2-\alpha\lambda_3+\lambda_4)\alpha_1 \tag{8}$$

The corresponding necessary conditions are

$$\begin{bmatrix}\dot{\lambda}_1\\ \dot{\lambda}_2\\ \dot{\lambda}_3\\ \dot{\lambda}_4\end{bmatrix}=-\begin{bmatrix}\lambda_1\mu-\lambda_2\sigma\\ (\lambda_1\mu'-\lambda_2\sigma')\left(\frac{x_1}{x_2}\right)\\ (\lambda_1\mu'-\lambda_2\sigma')\left(-\frac{x_1x_2}{x_3^2}\right)\\ -(\lambda_2S_F+\lambda_3)\alpha_1\end{bmatrix} \tag{9}$$

$$\phi=-S_F\alpha\lambda_2-\alpha\lambda_3+\lambda_4=0$$

$$\dot{\phi}=\alpha(\lambda_1\mu'-\lambda_2\sigma')\left(\frac{x_1}{x_3}\right)(S_F-S)=0 \tag{10}$$

$$\ddot{\phi}=\alpha\left(\frac{x_1}{x_3}\right)(S_F-S)\begin{bmatrix}-(\lambda_1\mu-\lambda_2\sigma)\mu'\\ +(\lambda_1\mu''-\lambda_2\sigma'')\frac{\{-\sigma x_1+(S_F-S)(-\alpha\alpha_1)\}}{x_3}\end{bmatrix}=0$$

From $\dot{\phi}=0$ of Eq. (10),

$$S_F\lambda_2+\lambda_3=\frac{\lambda_4}{\alpha}$$

$$\lambda_1\mu'-\lambda_2\sigma'=0,\ \alpha\neq 0 \tag{11}$$

Substituting Eq. (11) into (9), the differential equations of adjoint variables are

$$\begin{bmatrix}\dot{\lambda}_1\\ \dot{\lambda}_2\\ \dot{\lambda}_3\\ \dot{\lambda}_4\end{bmatrix}=\begin{bmatrix}-(\lambda_1\mu-\lambda_2\sigma)\\ 0\\ 0\\ \lambda_4\frac{\alpha_1}{\alpha}\end{bmatrix} \tag{12}$$

Integrating $\dot{\lambda}_4=\lambda_4(\alpha_1/\alpha)$ from (12) gives

$$\lambda_4=\lambda_{4,0}\frac{\alpha}{\alpha_0} \tag{13}$$

where $\lambda_{4,0}$ and α_0 are both values of λ_4 and α at an initial time t_0. If λ_4 from (13) is substituted into the first Equation of (11) and constant value of λ_3 is used,

$$\lambda_2=\lambda_2^*=\left(\frac{\lambda_{4,0}}{\alpha_0}-\lambda_3^*\right)\Big/S_F \tag{14}$$

Substituting (14) into the second Equation of (11) results in

$$\lambda_1=\frac{\sigma'}{\mu'}\left(\frac{\lambda_{4,0}}{\alpha_0}-\lambda_3^*\right)\Big/S_F \tag{15}$$

Applying the Generalized Legendre-Clebsch condition for a singular control gives

$$(-1)\frac{\partial}{\partial\alpha_1}\frac{d^2}{dt^2}H_{\alpha_1}=\alpha^2(x_1/x_3^2)(S_F-S)^2(\lambda_1\mu''-\lambda_2\sigma'')\ge 0 \tag{16}$$

If $\alpha=0$ and finally $x_3=V_{max}$, the generalized Legendre-Clebsch condition is trivially satisfied. However, if $\alpha\neq 0$, $\lambda_1\mu''-\lambda_2\sigma''$ must be positive or identically zero.

$\overline{V}_x$ is same adjoint variable. Hence, Eq. (3) is equal to

$$f_u^T(\bar{x},t)[H_{xu}(\bar{x},\bar{u},\overline{V}_x,t)+\lambda_x f_u(\bar{x},t)]\ge 0 \tag{17}$$

Now, we can have f_u, H_{xu}, and λ_x in forms of state variables only. The vector or matrix forms of these three properties are

$$f_u=[0\ \ -S_F\alpha\ \ -\alpha\ \ 1]^T$$
$$H_{xu}=[0\ \ 0\ \ 0\ \ -S\lambda_2^*-\lambda_3^*]^T \tag{18}$$
$$\lambda_x=\begin{bmatrix}0 & \frac{\sigma''\mu'-\sigma'\mu''}{(\mu')^2}\frac{\lambda_2^*}{x_3} & -\frac{\sigma''\mu'-\sigma'\mu''}{(\mu')^2}\frac{x_2\lambda_2^*}{x_3^2} & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & \frac{\lambda_{4,0}}{\alpha_0}\end{bmatrix}$$

Substituting Eq. (18) into (17) gives rise to

$$-(S_F\lambda_2^*+\lambda_3^*)+\frac{\lambda_{4,0}}{\alpha_0}\geq 0 \tag{19}$$

However, if we substitute Eq. (11) into Eq. (13),

$$-(S_F\lambda_2^*+\lambda_3^*)+\frac{\lambda_{4,0}}{\alpha_0}=0 \tag{20}$$

Conclusively, Jacobson's necessary condition (19) is trivially satisfied in this cell mass production model. This is a simple but very important result to be checked out whether a proposed control containing singular arcs is real optimal or not, although Jacobson's necessary condition with the generalized Legendre-Clebsch condition would not be sufficient for the optimality of a control. Let us go to the typical model of maximizing a metabolite in fed-batch fermentation.

Fed-batch fermentation model for maximizing a metabolite

A simple and typical model for maximizing a metabolite in a fed-batch fermentation is as below.

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{x}_4\end{bmatrix}=\begin{bmatrix}\mu x_1\\ -\sigma x_1\\ \pi x_1-kx_3\\ 0\end{bmatrix}+\begin{bmatrix}0\\ s_F\\ 0\\ 1\end{bmatrix}u,\quad x_4-V_{max}\leq 0,\quad 0\leq u\leq u_{max} \tag{21}$$

$x_1=xV$, $x_2=sV$, $x_3=pV$, $x_4=V$

where x, s, p and V symbolize cell mass concentration, substrate concentration, metabolite concentration, and volume, respectively. We first consider the case of k=0 in Eq. (21). Let us rewrite the inequality equation for volume as below:

$$x_4-V_{max}+\frac{1}{2}\alpha^2(t)=0 \tag{22}$$

Eq. (21) can be reformulated, resulting in a model with a new control variable α_1.

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{x}_4\\ \dot{\alpha}\end{bmatrix}=\begin{bmatrix}\mu x_1\\ -\sigma x_1\\ \pi x_1\\ 0\\ 0\end{bmatrix}+\begin{bmatrix}0\\ -s_F\alpha\\ 0\\ -\alpha\\ 1\end{bmatrix}\alpha_1\qquad \underline{X}(t_0)=\begin{bmatrix}x_{10}\\ x_{20}\\ x_{30}\\ x_{40}\\ \pm\sqrt{V_{max}-x_{40}}\end{bmatrix} \tag{23}$$

The Hamiltonian for Eq. (23) is

$$H=(\lambda_1\mu-\lambda_2\sigma+\lambda_3\pi)x_1+(-S_F\alpha\lambda_2-\alpha\lambda_4+\lambda_5)\alpha_1 \tag{24}$$

The necessary conditions for optimality are

$$\begin{bmatrix}\dot{\lambda}_1\\ \dot{\lambda}_2\\ \dot{\lambda}_3\\ \dot{\lambda}_4\\ \dot{\lambda}_5\end{bmatrix}=-\begin{bmatrix}\lambda_1\mu-\lambda_2\sigma+\lambda_3\pi\\ (\lambda_1\mu'-\lambda_2\sigma'+\lambda_3\pi')\left(\frac{x_1}{x_3}\right)\\ (\lambda_1\mu'-\lambda_2\sigma'+\lambda_3\pi')\left(-\frac{x_1x_2}{x_3^2}\right)\\ 0\\ -(\lambda_2S_F+\lambda_4)\alpha_1\end{bmatrix} \tag{25}$$

$$\begin{aligned}&\phi=-S_F\alpha\lambda_2-\alpha\lambda_4+\lambda_5=0\\ &\dot{\phi}=\alpha(\lambda_1\mu'-\lambda_2\sigma'+\lambda_3\pi')\left(\frac{x_1}{x_3}\right)(S_F-S)=0\\ &\ddot{\phi}=\alpha\left(\frac{x_1}{x_3}\right)(S_F-S)\Big[-(\lambda_1\mu-\lambda_2\sigma+\lambda_3\pi)\mu'\\ &\qquad+(\lambda_1\mu''-\lambda_2\sigma''+\lambda_3\pi'')\frac{\{-\sigma x_1+(S_F-S)(-\alpha\alpha_1)\}}{x_4}\Big]=0\end{aligned} \tag{26}$$

The first and second equation in (26) gives

$$\begin{aligned}&S_F\lambda_2+\lambda_4=\frac{\lambda_5}{\alpha}\\ &\lambda_1\mu'-\lambda_2\sigma'+\lambda_3\pi'=0,\ \alpha\neq 0\end{aligned} \tag{27}$$

Substituting Eq. (27) into (25), the differential equations of adjoint variables are

$$\begin{bmatrix}\dot{\lambda}_1\\ \dot{\lambda}_2\\ \dot{\lambda}_3\\ \dot{\lambda}_4\\ \dot{\lambda}_5\end{bmatrix}=\begin{bmatrix}-(\lambda_1\mu-\lambda_2\sigma+\lambda_3\pi)\\ 0\\ 0\\ 0\\ \lambda_5\frac{\alpha_1}{\alpha}\end{bmatrix} \tag{28}$$

Integrating from $\dot{\lambda}_5=\lambda_5(\alpha_1/\alpha)$ (28) gives

$$\lambda_5=\lambda_{5,0}\frac{\alpha}{\alpha_0} \tag{29}$$

where $\lambda_{5,0}$ and α_0 are both values of λ_5 and α at an initial time t_0. If λ_5 from (29) is substituted into the first equation of (27) and a constant value of λ_4 is used,

$$\lambda_2=\lambda_2^*=\left(\frac{\lambda_{5,0}}{\alpha_0}-\lambda_4^*\right)\Big/S_F \tag{30}$$

Substituting (30) into the second equation of (27) results in

$$\lambda_1=(\lambda_2^*\sigma'-\lambda_3^*\pi')/\mu' \tag{31}$$

Applying the generalized Legendre-Clebsch condition for a singular control gives

$$(-1)\frac{\partial}{\partial\alpha_1}\frac{d^2}{dt^2}H_{\alpha_1}=\frac{\alpha^2x_1}{x_3x_4}(S_F-S)^2(\lambda_1\mu''-\lambda_2\sigma''+\lambda_3\pi'')\geq 0 \tag{32}$$

If $\alpha=0$ and finally $x_3=V_{max}$, the generalized Legendre-Clebsch condition is trivially satisfied. However, if $\alpha\neq 0$, $(\lambda_1\mu''-\lambda_2\sigma''+\lambda_3\pi'')$ must be positive or identically zero.

Now, we can have f_u, H_{xu}, and λ_x in forms of state variables only. The vector or matrix forms of these three properties are

$$\begin{aligned}&f_u=[0\ \ -S_F\alpha\ \ 0\ \ -\alpha\ \ 1]^T\\ &H_{xu}=[0\ \ 0\ \ 0\ \ 0\ \ -S\lambda_2^*-\lambda_4^*]^T\\ &\lambda_x=\begin{bmatrix}0&\frac{\partial\lambda_1}{\partial x_2}&0&\frac{\partial\lambda_1}{\partial x_4}&0\\ 0&0&0&0&0\\ 0&0&0&0&0\\ 0&0&0&\frac{\lambda_{4,0}}{\alpha_0}&0\\ 0&0&0&0&\frac{\lambda_{5,0}}{\alpha_0}\end{bmatrix}\end{aligned} \tag{33}$$

Substituting Eq. (33) into (17) gives rise to

$$-(S_F\lambda_2^* + \lambda_4^*) + \frac{\lambda_{5,0}}{\alpha_0} \geq 0 \tag{34}$$

However, if we substitute Eq. (27) into the first equation of Eq. (29),

$$-(S_F\lambda_2^* + \lambda_4^*) + \frac{\lambda_{5,0}}{\alpha_0} = 0 \tag{35}$$

Like the cell mass production problem, this is trivially satisfied. We have also thought of the case that $k \neq 0$. Although not shown in detail, Jacobson's necessary condition is trivially satisfied. In this case, the forms of f_u, H_{xu}, and λ_x properties are the same as Eq. (33) except that $\lambda_1 = (\lambda_2^* \sigma' - \lambda_{3,0} e^{kt} \pi')/\mu'$.

CONCLUSION

Jacobson's necessary condition is an important necessary condition independent of the generalized Legendre-Clebsch condition. However, it is actually not considered in many cases, especially in numerical calculation of a control problem. Through this paper, we can ascertain it is trivially satisfied in the typical model for maximizing cell mass or metabolite by fed-batch fermentation. Although this work does not give any necessary condition to narrow the optimal control area further due to its triviality, it is meaningful to do this kind of analysis in that following.

(1) Our approach shows the way to inspect for a system to satisfy Jacobson's necessary condition through not numerically but analytically.

(2) We dealt with control systems with an inequality constraint, and it is successful to consider a reformulated system by introducing another control variable.

(3) Actually, we did not show a system with terminal constraint, for example, reactor volume is full at the final time. These kinds of problem are more complex to analyze analytically. However, let us think of $|\alpha| \leq \varepsilon$, $\lim_{t \to t_f} \varepsilon = 0$, $\varepsilon(t_f) \neq 0$. Then, the inequality condition can mimic a terminal state-constrained problem. Not absolutely but practically, our inequality approach approximately explains the case.

ACKNOWLEDGEMENT

This work was supported by INHA UNIVERSITY Research Grant (INHA-40875).

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