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LETTERS TO THE EDITOR

On “Feedback Stabilization of Fed-Batch Bioreactors: Non-Monotonic Growth Kinetics”

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The referenced paper (Smets, I. Y.; Bastin, G. P.; Van Impe, J. *Biotechnol. Prog.* **2002**, *18*, 1116−1125) deals with the control of the substrate concentration of fed-batch bioreactions with non-monotonic growth kinetics. First, a straightforward feedback linearization control strategy is introduced that assumes that both biomass and substrate concentrations are available for feedback. However, as the authors assert in section 3.6 of their paper, this assumption is generally not verified because on-line substrate concentration measurements are not available and observers based on biomass concentration are not a valid alternative for stabilization of non-monotonic fed-batch processes. To overcome this drawback, a modified version of this preliminary linearizing control strategy is presented that is much more realistic from a practical viewpoint. Its main advantage is that the implementation only requires the measurement of biomass concentration and the estimation (based on this measure) of the specific growth rate. Then, the authors attempt to demonstrate that the fed-batch process can still be stabilized around any desired set-point all along the non-monotonic kinetics by introducing a discontinuity in the feedback gain. Unfortunately, the stability analysis developed by the authors is not entirely consistent with the proposed control law based only on biomass measurement. So, the claimed demonstration of global stability without feedback of the substrate concentration is not completely valid. In this context, this letter is aimed at clarifying some points of this demonstration and showing that the control law proposed by the authors effectively stabilizes the substrate concentration at any set-point on the non-monotonic kinetics.

Note that replacing the control law (eq 5) in the mass balance equation (eq 2) does not yield the linear dynamics (eq 4). (This can also be verified in Figure 2, which does not display the typical exponential response of linear systems). Similarly, the control law (eq 6) does not lead to the closed-loop dynamics (eq 7). (Actually, to obtain the closed-loop dynamics (eq 7), the set-point C_S^* should be replaced by the actual substrate concentration C_S in the denominator of both terms in the right-hand side of eq 6, but this correction would introduce feedback of C_S and the most attractive feature of this control strategy would be lost). Consequently, the stability analysis developed from (eq 7) in section 3 requires some corrections to effectively demonstrate that the control law (eq 6) as proposed by the authors (i.e., without on-line measurement or estimation of C_S) globally stabilizes the system at any desired set-point C_S^* all along the non-monotonic kinetics. We give here some guidelines for this demonstration and derive some necessary and sufficient conditions.

First of all, it is convenient to reformulate the gain τ_μ in eq 6 as a linear function of biomass: $\tau_\mu = kC_X/Y_{X/S}$. Also, after some trivial algebra, the growth rate error ($\mu - \mu^*$) for a Haldane kinetics can be written in eq 6 as

$$\mu - \mu^* = -\frac{\mu}{C_S}\frac{1}{b}(C_S - C_S^*)(C_S - C_{S,a}^*)$$

where $b = K_I\mu_m/\mu^*$. Then, replacing eq 6 in the mass balance eq 2, the following closed-loop dynamics results

$$\frac{\mathrm{d}(C_S - C_S^*)}{\mathrm{d}t} = -\left(m + \frac{1}{Y_{X/S}}\frac{\mu}{C_S^*}g(C_S)\right)\frac{C_X}{C_{S,in} - C_S^*}(C_S - C_S^*)$$

where the function $g(C_S)$ is given by

$$g(C_S) = C_S + \frac{k}{b}(C_S - C_{S,in})(C_S - C_{S,a}^*)$$

For the sake of simplicity, the stabilizing maintenance coefficient m is hereinafter neglected. Then, to accomplish global stability at any C_S^*, $g(C_S)$ must be strictly positive for all achievable values of C_S, i.e., $\forall C_S \in [0, C_{S,in}]$. After some manipulation, the quadratic polynomial $g(C_S)$ can be written as

$$g(C_S) = ak\left[\frac{C_S^2}{C_{S,in}C_{S,a}^*} - \frac{C_S}{C_{S,in}C_{S,a}^*}\left((C_{S,in} + C_{S,a}^*) - \frac{b}{k}\right) + 1\right]; \quad a > 0$$

Clearly, the necessary and sufficient conditions for global stability are

- $g(0) > 0$.
- $g(C_S)$ has no root in $[0, C_{S,in}]$

To satisfy these stability conditions, the gain k should be selected within the range

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$$0 < k < \bar{k} = \frac{b}{C_{\mathrm{S,in}} + C^*_{\mathrm{S,a}} - 2\sqrt{C_{\mathrm{S,in}} C^*_{\mathrm{S,a}}}}$$

In fact, selecting $k < 0$ violates the stability condition $g(C_{\mathrm{S}}) > 0$ for some values of C_{S} below $C^*_{\mathrm{S,a}}$, whereas selecting $k > \bar{k}$ violates the condition $g(C_{\mathrm{S}}) > 0$ for some values of C_{S} above $C^*_{\mathrm{S,a}}$. (Actually, due to the presence of the maintenance coefficient, stability is achieved with a slightly larger range of k, in particular with $k = 0$, i.e., the "open-loop" control (eq 3) of the above paper also stabilizes the system.)

Remark 1: A performance analysis reveals that growth rate error feedback with $k > 0$ improves the local convergence to a set-point on the left flank of the Haldane kinetics, whereas it deteriorates the local response around a set-point on the right flank. Actually, to speed up the convergence toward this latter set-point, the gain k should be negative, but the response from low initial substrate concentrations might be unstable.

Remark 2. If appropriate discontinuous feedback is introduced, for instance, replacing k by $|k| sign(C^*_{\mathrm{S,a}} - C_{\mathrm{S}})$ in the expression of τ_μ, then the stability condition $g(C_{\mathrm{S}}) > 0$ $\forall C_{\mathrm{S}} \in [0, C_{\mathrm{S,in}}]$ is verified for all k, and hence for all τ_μ. This discontinuity is equivalent to the switching factor introduced by the authors to achieve stability. It has been shown here, however, that including discontinuous feedback is not a necessary condition to guarantee stability. Anyway, it is useful to improve the closed-loop performance, particularly for operation at high substrate concentration levels.

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