Alternate Control Structures for Chemostat

Anil S. Menawat and Jayaram Balachander
Dept. of Chemical Engineering, Tulane University, New Orleans, LA 70118

An alternate control structure over conventional control scheme for bioreactors can lead to a more robust control action. Usually, the inlet stream flow rate is used as the control variable. Here, the inlet stream concentration is considered as the alternate control variable. The two control schemes are compared for their robustness in meeting the control objective. Two types of chemostats, continuous bioreactors, are considered: a turbidostat where cell concentration is the feedback signal in the form of turbidity, and a nutristat where substrate concentration is the feedback signal. The control objective is to maintain a constant steady-state value of the biomass concentration.

Using the flow rate of the inlet stream to control a continuous bioreactor about a desired steady state has some limitations. For example, when the cell concentration in a turbidostat (cell concentration kept constant) is above the desired value, the controller increases the flow rate to dilute the system. Consequently, the substrate concentration in the reactor rises because the inlet stream contains the growth-limiting substrate that increases the specific growth rate of the cell, thereby slowing down the decrease in cell concentration. On the other hand, when the concentration of the cell is less than the desired value, the control action is to decrease the dilution rate, thus decreasing the concentration of the substrate in the reactor. This decreases the growth rate of the cell, thereby slowing the increase in cell concentration. This is the classical inverse response problem. Using the flow rate as the control variable, therefore, results in a sluggish and nonrobust response. This would be true of all the reactors where the rate of reaction is modeled as a monotonically increasing function with respect to the limiting reactant. Using the inlet stream substrate concentration as the control variable overcomes this problem and results in a more robust operation.

Use of an alternate manipulated variable to control reactors has not been a very popular approach. Though alternate manipulated variables have been used to control chemical reactors, the approach is novel for biochemical systems. Alternate control structures have been studied in detail for distillation column control (Häggblom and Waller, 1988a,b; Waller et al., 1988a,b). Waller and his coworkers used different combinations of control variables and compared the effectiveness of different control schemes. Agarwal and Lim (1984) proposed a novel control scheme for a turbidostat. They proposed two inlet streams instead of one, one containing the limiting substrate in high concentration and the other lacking the substrate. The flow rate of the diluent stream is used as the control variable with the concentrated stream of constant flow. The approach in this study differs from the Agarwal-Lim approach in that here the concentration is used as the control variable directly. That is, the flow rate entering the bioreactor is constant. In Agarwal-Lim approach, both the flow rate and the concentration vary.

Robustness can be interpreted in many ways. Consequently, the performance index for robustness may vary. In recent years, several robustness issues have been discussed for chemical processes (see *Proceedings of 1986 American Control Conference*, session WA1). The stability and the performance deterioration of multivariable closed-loop systems that result from parameter and structural model uncertainties can be analyzed conveniently with the structured singular values (Morari, 1987, 1988). Another useful tool is the relative gain array technique for process interaction (Bristol, 1966). Other techniques also exist in the literature (for a recent reveiw, see Morari, 1988).

By conventional definition, a robust controller meets the control objective in the changing operating conditions or the plant-model mismatch. Interpretation used for this work is a variation of the above: that is, the closed-loop performance should meet the control objective in minimum effort. It is more restrictive than the conventional definition, since it requires minimum effort in addition to meeting the requirement. For now, we shall concentrate only on the minimum effort part. Plant-model mismatch part will be addressed in a forthcoming study.

Discussion

The basis of comparison between the two manipulatable variables are the rise time and the offset with simple proportional controllers. A proper design of a controller starts with the selection of an appropriate control variable. Skogestad (cited in Morari, 1988) has shown that with apt control structure in a distillation column, most of the robustness problems

Correspondence concerning this note should be addressed to A. S. Menawat.

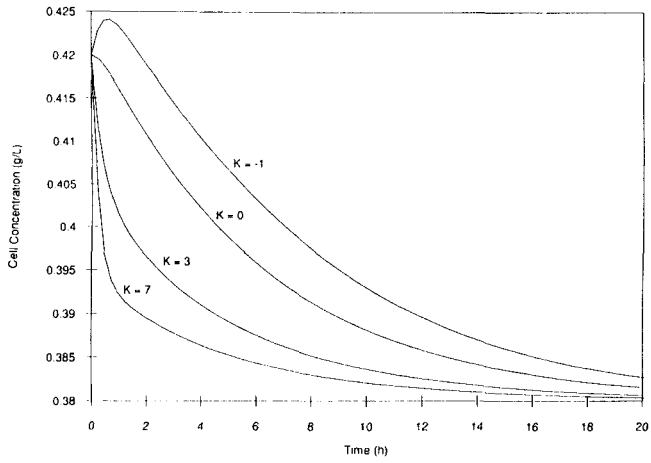

Figure 1a. Cell concentration profile for turbidostat under flow rate control.

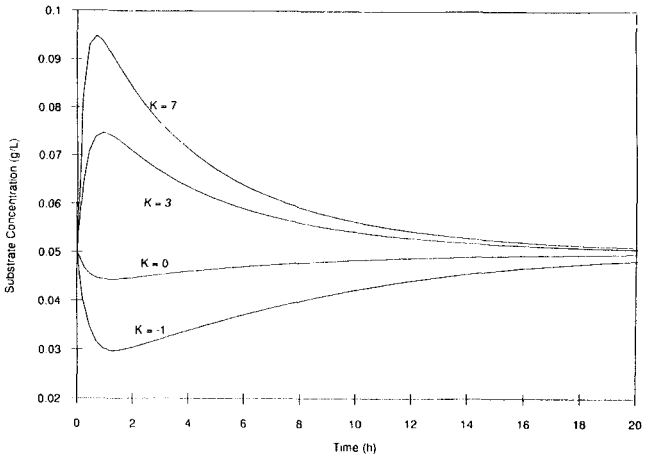

Figure 1b. Substrate concentration profile for turbidostat under flow rate control.

are removed. A similar point is presented here for control of continuous bioreactors. By employing an alternate control variable, more robust control is achieved while the controller synthesis becomes trivial.

A bioreactor is described by the following kinetic and modeling equations:

$$\frac{dx}{dt} = \mu(s)x - Dx \tag{1}$$

$$\frac{ds}{dt} = \sigma(s) + D(s_f - s) \tag{2}$$

where x and s are the state variables representing the cell mass and the substrate concentrations, respectively, D is the dilution rate, and s_f is the substrate concentration in the feed stream. Usually, the dilution rate is the control variable, and since the volume is constant, control may be achieved with the flow rate manipulation. s_f is the control variable in the alternate control structure. The kinetics of the cell mass production is defined in terms of the specific growth rate, μ(s), and the specific substrate consumption rate, $\sigma(s)$. As an example, we shall describe these by the Monod Kinetics.

$$\mu(s) = \frac{\mu_m s}{K_m + s}$$
$$\sigma(s) = -\frac{\mu(s)}{Y} \tag{3}$$

The constant μ_m is the maximum specific growth rate, K_m is the Monod coefficient, and Y is the yield coefficient. The yield coefficient may be a function of the substrate also, but for convenience it has been assumed constant.

For the conventional control scheme with the dilution rate as the manipulation and for the alternate scheme with the feed concentration as the manipulation, the corresponding control laws are:

$$D = D_0 + K\epsilon \tag{4}$$

$$s_f = s_{f_0} - K\epsilon \tag{5}$$

These are simple proportional controllers and are adequate to study comparative robustness. The sign in front of the gain is selected appropriately to assure positive gain values. The error, ϵ, is defined as $(x - x_d)$ for the turbidostat where the cell concentration is the feedback signal and as $(s - s_d)$ for the nutristat with the substrate concentration as the feedback signal.

Two continuous bioreactors—a turbidostat and a nutristat—are simulated for the dilution rate as well as the feed concentration as the control variable. The results for the turbidostat are shown in Figures 1-4. Desired steady-state value, the set point, for the cell concentration is taken as 0.38 g/L. A disturbance of 0.04 g/L is assumed at time zero. As seen in Figure 1 with no controller ($K = 0$), the steady state is stable and the system returns to within 1% of it in little short of 15 hours. The corresponding substrate concentration declines at first to slow down the growth and eventually rises again to the steady-state value of 0.05 g/L. A proportional controller with positive gain reduces the "time to reach 1% deviation," but at the expense of an inverse response in the substrate concentration. The natural response of the system to return to the steady state is by slowing the growth rate, but the flow rate controller accomplishes this by diluting the system. This provides a much faster response initially. With the increased substrate concentration, the natural response of the system takes over with increased growth rate and competes with the controller action resulting in a slower approach to the steady state. A large control action is thus required to rectify the situation imposing a greater demand of substrate. The situation worsens with increasing performance requirements.

A controller that enhances the natural response of the system should be more robust in meeting the control objective. One may argue that by switching the sign of the controller gain, the controller would reduce the substrate concentration instead of increasing it, resulting in better control. This, however, is not true. As the flow rate decreases, the rate of cells leaving the system also decreases, consequently building the cell concentration in the fermenter (cf. Figure 1). This is opposite of the control objective. The performance thus deteriorates further.

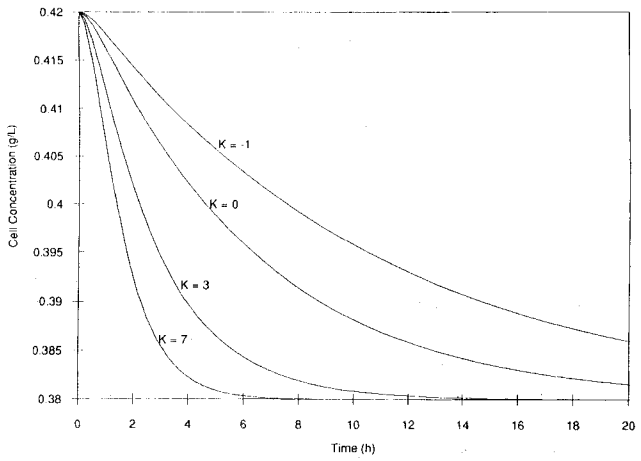

Figure 2a. Cell concentration profile for turbidostat under feed concentration control.

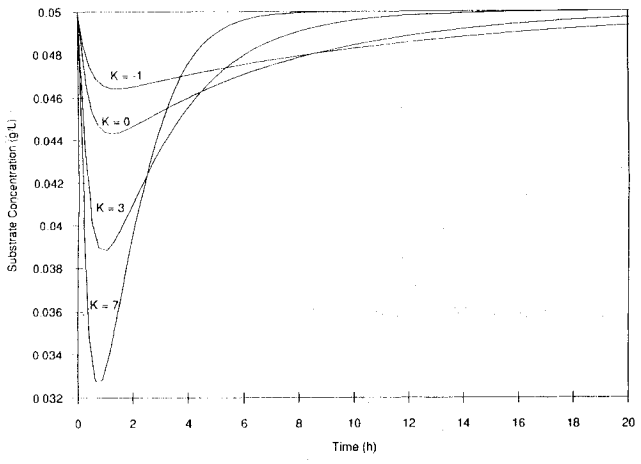

Figure 2b. Substrate concentration profile for turbidostat under feed concentration control.

Use of the substrate concentration control structure overcomes the above inadequacies. It enhances the natural response of the fermenter and outperforms the flow rate control structure. This is an indirect controller contrary to the previous one. The initial response is slower with noticeable stalling because of the indirect control action. Once that is the past, the rate of response increases as it approaches the steady state as if there is an intrinsic derivative action controller embedded in the system. As expected, the performance increases with increasing controller gain. Yet, the controller gain required to achieve the "time to reach 1% deviation" is much smaller with alternate control structure when compared with the flow rate controller (cf. Figure 3). With the restriction that the flow rate and the substrate concentration into the fermenter must be greater than or equal to zero, there is a natural asymptote for both curves of Figure 3. The limiting value for the flow rate controller is no feed with the fermenter operating in a batch mode. At this point, the fermentation is under kinetic (natural) control, rather than the external forcing (the hydrodynamic dilution). The approach to the limiting value thus depends on the maximum specific growth rate. On the other hand, with the substrate concentration control the limiting value is at no

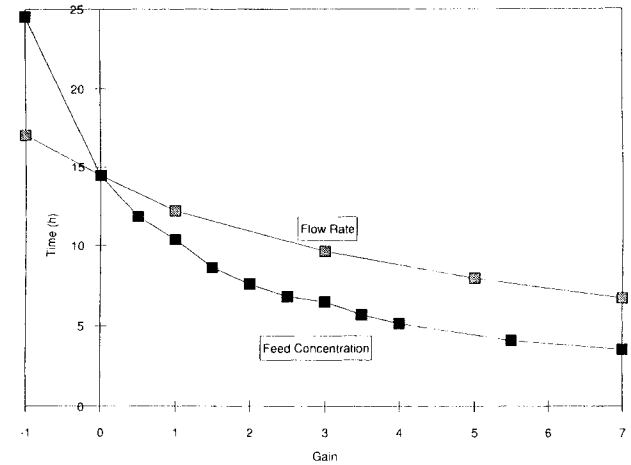

Figure 3. Time to reach 1% deviation in turbidostat.

substrate entering the system but a continuous removal of the cell mass, since the system still maintains the same dilution rate. The reduction in the cell mass is now under natural as well as external control working in the same direction. The objective is met much faster. The approach to the asymptotic value of zero for the "time to reach 1% deviation" is sharper as seen in Figure 3. The results can also be interpreted as substrate concentration having greater sensitivity to the process, which is a robustness issue.

Is it fair to compare the magnitude of the controller gains for two different controllers that do not have the same output variables? The answer of course is no. But it is entirely proper to compare the product of the two control variables as they always appear likewise in the substrate modeling equation (cf. Eq. 2). The product $(s_f \cdot D)$ is the flux of the substrate into the bioreactor and is presented in Figure 4. When one is employed as the control variable, the other is held constant and is considered a parameter for the controller design. The product may be viewed as the controller output, yielding a common basis for comparison. As evident from Figure 4, there is a small deviation from the nominal value required to maintain the steady state for the feed concentration control scheme in con-

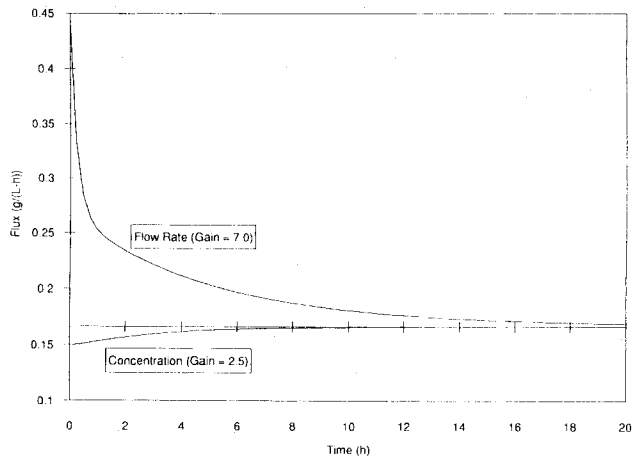

Figure 4. Control effort for same "time to reach 1% deviation."

Flux $[g/(L-h)]$ = dilution rate $(1/h)$ × feed concentration (g/L)

trast to the flow rate control scheme to obtain the same "time to reach 1% deviation." The integrals of the two curves represent the amount of substrate used to achieve the control task. The concentration control not only provides for a faster response but also minimizes the effort and the resources required. This satisfies the speed and the minimum effort criteria of robustness of the feed concentration over the flow rate as a control variable.

The kinetic effect (the natural response) is notable as was seen with the flow rate control. It was responsible for the inverse response in the substrate concentration. In other words, the response of the bioreactor depends on the substrate concentration. The control scheme that can directly manipulate the substrate concentration in the bioreactor should, therefore, be more effective. Any alteration in s_f directly affects the substrate concentration only, whereas a change in D affects both of the states, the cell and the substrate concentrations. By employing the feed concentration control, the regulation is achieved by manipulating the kinetics of the system in cooperation with the natural response, whereas with the flow rate control it is adversarial.

A similar trend is observed with a nutristat where the substrate concentration is the feedback signal. The concentration control scheme provides more robust operation over the flow rate scheme. These results are in agreement with Agarwal and Lim (1984) and with Edwards et al. (1972). The gain for the flow rate control is still larger than the feed concentration scheme. The nutristat, however, required larger gains than the turbidostat. This is expected because the control objective is to maintain the biomass constant, which is the feedback signal employed in the turbidostat. For nutristat with the substrate concentration signal being fedback, the controller is of inferential type. The error in cell concentration must manifest as an error in the substrate concentration due to the natural response before the controller may act upon it. In other words, there is a built-in state estimator where the deviation in the cell mass is realized in terms of the substrate concentration. From which the control action is derived to meet the control objective on the cell mass. The substrate kinetics are the dynamics of the observer which increases the response time. A larger gain controller is thus necessary to achieve the same "time to reach 1% deviation" performance.

The robustness of control is a sensitivity issue. For linear systems, it is typically measured with the singular values of the gain matrix. However, there is no direct extrapolation for nonlinear systems. Analysis by linearization around a nominal trajectory is acceptable only if the operation is restricted to the neighborhood of the reference. System property of reachability provides more insight, because this study is not concerned primarily with evaluating a controller design for robustness, but comparing the robustness of the two different control variables. Consider the system described by Eqs. 1 and 2. The pair (x, s) defines R^2; however, the physical constraint of the cells being produced from the substrate forces the system to satisfy the stoichiometry which is a very small portion of R^2. In short, the pair (x, s) must lie on a differentiable manifold M, assuming stoichiometric relationship is a smooth function. Further, the conservation of mass assures the system to be analytic $(x+s>0)$. For such a system which is of dimension two, the following theorem provides the strongest form of reachability (Casti, 1985).

Theorem: Consider a system Σ

$$\dot{x} = f(x) + g(x)u, \quad x(0) = x_0 \epsilon M$$

where M is a connected real-analytic two-dimensional manifold. Let f and g be real-analytic vector fields on M, that are linearly independent at some point $x \epsilon M$, and let u be a real scalar input. Further, suppose that every nontrivial integral curve of g has a point p where f and g are linearly-dependent, with $g(x) \neq 0$ and that the Lie bracket $[f,g]$ and g are linearly-independent at p. The system Σ is globally controllable from any x_0 such that the dimension of the Lie algebra dim $\{f,g\}_{LA} = 2$ at x_0. ■

The Lie algebra for the conventional scheme is spanned by the columns of the following controllability matrix:

$$\mathfrak{C} = \begin{pmatrix} (s_f - s) & -\sigma' x(s_f - s) \\ -x & -\mu' x(s_f - s) \end{pmatrix} \tag{6}$$

For the Lie algebra to be two dimensional, the determinant of the above matrix must not vanish for any $x_0 \epsilon M$. However, that is not the case. Recall that the real analytic manifold for the present problem is the subset of the two-dimensional Hausdorff space where stoichiometry must be satisfied. Because of the stoichiometry constraint, the process must follow $\mu(s)(s_f - s) + \sigma(s)x = 0$ at steady state. If the yield coefficient is constant (i.e., $\mu = y\sigma$), both the columns of $\mathfrak{C}$ become linearly-dependent with a one-dimensional Lie algebra, instead of the full rank of two. The process at steady state is only one-dimensional. The system of Eqs. 1 and 2 is therefore not fully reachable with the conventional scheme of control with the dilution rate. Only one state is controllable, restricting the ability to drive the system anywhere on the state space. If the yield coefficient is not a constant, we may adopt a model with maintenance coefficient with the effective yield given by:

$$y_{\text{eff}} = \frac{\mu y}{\mu + ymx} \tag{7}$$

where y is the yield constant and m is the maintenance constant. The order of magnitude analysis shows that the specific growth rate (μ) is at least twofolds greater than the product $(y \cdot m \cdot x)$ even at very high cell concentrations, and normally it is threefolds greater. The two columns of the controllability matrix are very close to being linearly-dependent with one-dimensional Lie algebra. The two singular values of the controllability matrix would be far apart. Physically, it means that as the system approaches closer to the steady state, the ability to effectively control is diminished. This was observed in Figure 1 with very rapid response initially that deteriorated as the cell concentration approached closer to the steady state.

Similarly, the Lie algebra for the modified scheme is spanned by the columns of the following controllability matrix:

$$\mathfrak{C} = \begin{pmatrix} D & -\sigma' xD + D^2 \\ 0 & -\mu' xD \end{pmatrix} \tag{8}$$

The columns of the above matrix are linearly-independent over the entire real analytic manifold M. The Lie algebra thus gen-

erated by the modified control scheme is full-dimensional throughout. The continuous bioreactors operating with feed concentration as the control variable are fully reachable from every point on the manifold M. There is no loss of controllability at all.

Notation

$\mathfrak{C}$ = controllability matrix
D = dilution rate
K = proportional controller gain
K_m = monod constant
M = real analytic manifold
m = maintenance constant
R = real Euclidean space
s = substrate concentration
s_d = desired substrate concentration
s_f = feed concentration
x = cell concentration
x_d = desired cell concentration
Y = yield coefficient
y = yield constant
y_{eff} = effective yield

Greek letters

ϵ = error
μ = specific growth rate
μ_m = maximum specific growth rate
σ = specific substrate uptake rate

Literature Cited

Agarwal, P., and H. C. Lim, *Advances in Biochemical Engineering/ Biotechnology,* **30**, 62 (1984).

Bristol, E. H., "On a New Measure of Interactions for Multivariable Process Control," *IEEE Trans. Auto. Cont.*, **AC-11**, 133 (1966).

Casti, J. L., *Nonlinear System Theory,* Academic Press, New York (1985).

Edwards, V. H., R. C. Ko, and S. A. Balogh, "Dynamics and Control of Continuous Microbial Propagators to Subject Substrate Inhibition," *Biotech. Bioeng.*, **15**, 939 (1972).

Häggblom, K. E., and K. V. Waller, Report 88-7, Dept. of Chemical Engineering, Process Control Laboratory, Åbo Akademi, Finland (1988a).

Häggblom, K. E., and K. V. Waller, "Transformations and Consistency Relations of Distillation Control Structures," *AIChE J.*, **30**(10), 1634 (1988b).

Morari, M., "Robust Process Control," *Chem. Eng Res. Des.*, **65**, 463 (1987).

Morari, M., "Advances in Process Control Theory," *Chem. Eng. Prog.*, **84**(10), 60 (1988).

Waller, K. V., D. H. Finnerman, P. M. Sandelin, K. E. Häggblom, and S. E. Gustaffson, "An Experimental Comparison of Four Control Structure for Two-Point Control of Distillation," *Ind. Eng. Chem. Res.*, **27**, 624 (1988a).

Waller, K. V., D. H. Finnerman, P. M. Sandelin, and K. E. Häggblom, "Disturbance Sensitivity of Distillation Control Structures," *AIChE J.*, **34**, 853 (1988b).

Manuscript received June 4, 1990, and revision received Jan 3, 1991.