

14.13 SEMICONTINUOUS FED-BATCH AND CYCLIC-FED BATCH OPERATION

14.13.1 Concepts Demonstrated

Use of cyclic fed-batch operation in a semi-batch bioreactor to maximize fermentation products when the bioreaction is inhibited by the substrate.

14.13.2 Numerical Methods Utilized

Solution of simultaneous ordinary differential equations with induced variable cycling that often leads to stiff differential equations.

14.13.3 Problem Statement

Substrate inhibition can be minimized by control of the substrate addition to a batch bioreactor as is shown in Figure 14–20. The first step involves the initiation or startup of the reactor from an initial inoculum with substrate feed rate of F_I over time interval from $t = 0$ to t_I . The processing is then followed by controlled addition of the substrate at a rate of F_P over time interval from t_I to t_P during which the reactor volume increases from V_I to V_H . The substrate addition is then stopped and the batch bioreactor is harvested with a discharge flow rate of F_H over time interval from t_P to t_H during which the volume decreases from V_H to V_I . In fed-batch operation, the initiation, processing, and harvesting modes are utilized in a single sequence. Cyclic operation involves the repetitive cycle of processing and harvesting modes where n is the cycle number.

Each operational mode of the bioreactor involved unsteady-state balances material balances on the well-mixed culture volume within the reactor. The appropriate differential equations can be derived by consideration of the general balance on this volume over a time interval Δt . This is accomplished below for a balance on the cells in the initiation mode

Input + Generation = Output + Accumulation

$$F_I X_0 \Delta t + \mu_{\text{net}} V X \Delta t = F X \Delta t + N_X|_{t+\Delta t} - N_X|_t \quad (14-85)$$

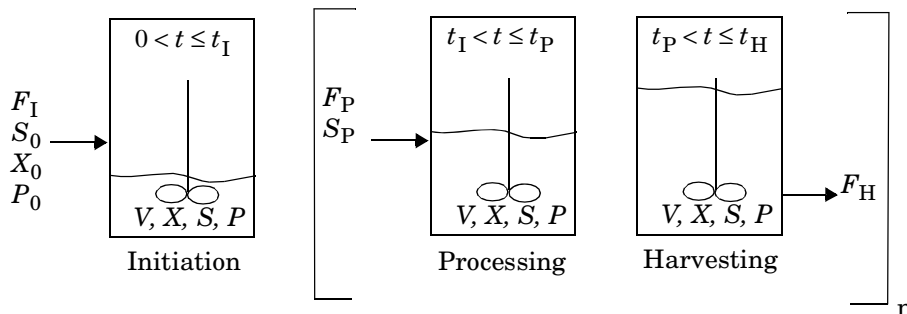


Figure 14–20 Bioreactor in Fed Batch Mode ($n = 1$) and Cycling Mode ($n > 1$)

where F_I is nutrient solution feed flow rate in L/h, X_0 is the cell feed concentration in g/L, X is the cell concentration in the bioreactor and in the outlet stream in g/L, and V is the volume of the culture in L. Since the culture volume is usually changing with time, it is most convenient to use N_X as the total quantity of cells in Equation (14-85). Rearrangement of this equation and taking the limit as $\Delta t \rightarrow 0$ results in the differential equation

$$\frac{dN_X}{dt} = F_I X_0 + \mu_{\text{net}} X V \quad (14-86)$$

and the cell concentration can be calculated from the explicit algebraic equation

$$X = \frac{N_X}{V} \quad (14-87)$$

Note that the above algebraic equation is necessary for calculation of the cell concentration as the current bioreactor volume V is available from a overall material balance.

Similar material balances can be made on the other reacting components resulting in the following sets of differential and algebraic equations

$$\frac{dN_S}{dt} = F_I S_0 - \frac{\mu_{\text{net}} X V}{Y_{X/S}} \quad (14-88)$$

$$S = \frac{N_S}{V} \quad (14-89)$$

$$\frac{dN_P}{dt} = \frac{\mu_{\text{net}} X V}{Y_{X/P}} \quad (14-90)$$

$$P = \frac{N_P}{V} \quad (14-91)$$

Note that this equation development makes the resulting equation set very general for whatever operation changes the bioreactor culture volume. However, an overall material balance is needed to obtain the differential equation for the culture volume. For example, the initiation mode yields

$$\frac{dV}{dt} = F_I \quad (14-92)$$

The production rate can be obtained for the cycling mode from

$$\frac{dPR}{dt} = \frac{F_H P}{t_{\text{cycle}}} \quad (14-93)$$

where t_{cycle} is the total time for the processing and harvesting cycle.

The differential equations are summarized in Table 14-9. Note that it will take several repetitions of the cycle to achieve a reproducible pattern of concentration profiles when the bioreactor is utilized in the cyclic fed-batch mode. Continuous integration of the differential equations given in Table 14-9 allows simulation of this cyclic reactor operation.

Table 14–9 Differential Equations for Fed Batch and Cyclic Fed Batch Bioreactors

Differential Equations	Initiation	Processing	Harvesting
$\frac{dN_X}{dt} =$	$F_I X_0 + \mu_{\text{net}} X V$	$\mu_{\text{net}} X V$	$- F_H X + \mu_{\text{net}} X V$
$\frac{dN_S}{dt} =$	$F_I S_0 - \frac{\mu_{\text{net}} X V}{Y_{X/S}}$	$F_P S_P - \frac{\mu_{\text{net}} X V}{Y_{X/S}}$	$- F_H S - \frac{\mu_{\text{net}} X V}{Y_{X/S}}$
$\frac{dN_P}{dt} =$	$\frac{\mu_{\text{net}} X V}{Y_{X/P}}$	$\frac{\mu_{\text{net}} X V}{Y_{X/P}}$	$- F_H P + \frac{\mu_{\text{net}} X V}{Y_{X/P}}$
$\frac{dV}{dt} =$	F_I	F_P	$- F_H$

Consider the fed-batch operation of a laboratory pilot plant antibiotic fermentation bioreactor where the glucose is added to the fermentation culture in order to minimize the glucose substrate inhibition. The bioreaction kinetics are: $\mu_m = 0.3 \text{ h}^{-1}$, $K_S = 1 \text{ g glucose/L}$, $K_I = 100 \text{ (g glucose/L)}^2$, $Y_{X/S} = 0.4 \text{ g cells/g glucose}$, and $Y_{X/P} = 0.15 \text{ g product/g glucose}$. The cell death rate and endogenous metabolism can be neglected. Thus

$$\mu_{\text{net}} = \mu_g = \frac{\mu_m S}{K_S + S + S^2/K_I}$$

The initiation mode is started at $t = 0 \text{ hr}$ with a volume of 0.8 L containing 30 g cells/L and negligible glucose. The glucose concentrations are fixed at $S_0 = S_P = 200 \text{ g glucose/L}$. Initial operation is such that $F_I = 0.2 \text{ L/hr}$ until $t = 1.0 \text{ hr}$. Then $F_P = 0.5 \text{ L/hr}$ until $t = 6 \text{ hr}$ and $F_H = 2.5 \text{ L/hr}$ until the culture volume is reduced to $V = 1.0 \text{ L}$ at $t = 7 \text{ hr}$.

- Create a single graph of the concentrations (S , X , and P) within the bioreactor as a function of time for the fed-batch operation to time $t_H = 7 \text{ hr}$. This represents the initiation and the first cycle of processing and harvesting.
- Repeat part (a) for the case where the initiation is followed by three complete cycles of processing and harvesting. Graph the concentrations (S , X , and P) as a function of time.
- Carry out the processing and harvesting cycles of part (b) into the cyclic fed-batch operation where the process repeats itself from cycle to cycle. Calculate the production of P in g/hr under continuous cycling. (Assume the third cycle, $n = 3$, represents the cyclic operation.)
- Optimize the substrate feed concentration to the fed-batch process in part (c) that will maximize the production rate of P . All processing conditions and times remain the same. Calculate the average production rate of P in g/hr under continuous cycling. (Assume the third cycle represents the cyclic operation.)