Analysis of Well-Mixed Fed-Batch Cultures using Unstructured Models

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Introduction

Fed-batch cultures are the most complex of the three modes of operating a bioreactor. Fed-batch cultures are dynamic and have volume change. Like a continuous culture, feb-batch cultures have an input feed stream into the reactor. However, unlike chemostats, there is no outflow from the reaction vessel in a fed-batch reactor. Thus, the working volume in the reactor increases over time diluting the contents of the vessel. In this lecture, we'll develop a mathematical description of fed-batch cultures using the general material balances, and then explore how the performance of the fed-batch culture can be optimized.

General model equations for fed-batch cultures. Let's start with the general material balances we derived previously:

$$\frac{dC_j}{dt} = \sum_{s=1}^{\mathcal{S}} v_s D_s C_{j,s} + \left(\sum_{r=1}^{\mathcal{R}} \sigma_{jr}\hat{r}_r\right) + \left(\sum_{k=1}^{\mathcal{T}} \tau_{j,k} q_k\right) X - \frac{C_j}{V}\frac{dV}{dt} \qquad j = 1,2,\dots,\mathcal{M} \quad (1)$$

$$\frac{dX}{dt} = \sum_{s=1}^{\mathcal{S}} v_s D_s X_s + (\mu - k_d)\, X - \frac{X}{V}\frac{dV}{dt} \quad (2)$$

$$\frac{dV}{dt} = \sum_{s=1}^{\mathcal{S}} v_s \frac{\rho_s}{\rho} F_s - \frac{V}{\rho}\frac{d\rho}{dt} \quad (3)$$

where the quantity D_s, called a *dilution rate* (hr^{-1}), is given as:

$$D_s \equiv \frac{F_s}{V} \qquad s = 1,2,\dots,\mathcal{S} \quad (4)$$

The quantity C_j denotes the concentration of the jth extracellular metabolite, V denotes the working volume of the culture and X denotes the cellmass. In a fed-batch culture, there are in-flows, but no out-flow from the culture vessel, thus $D_{s^-} = 0$ where s^- denote the set of outflow streams. Because there is no out-flow, there is a volume change ($dV/dt > 0$), and all the dilution terms in the material balances are non-negative:

$$\frac{dC_j}{dt} = \sum_{s=1}^{\mathcal{S}^+} v_s D_s C_{j,s} + \left(\sum_{r=1}^{\mathcal{R}} \sigma_{jr}\hat{r}_r\right) + \left(\sum_{k=1}^{\mathcal{T}} \tau_{j,k} q_k\right) X - \frac{C_j}{V}\frac{dV}{dt} \qquad j = 1, 2, \ldots, \mathcal{M} \tag{5}$$

$$\frac{dX}{dt} = \sum_{s=1}^{\mathcal{S}^+} v_s D_s X_s + (\mu - k_d) X - -\frac{X}{V}\frac{dV}{dt} \tag{6}$$

$$\frac{dV}{dt} = \sum_{s=1}^{\mathcal{S}^+} v_s \frac{\rho_s}{\rho} F_s - \frac{V}{\rho}\frac{d\rho}{dt} \tag{7}$$

Analysis of a simple fed-batch culture. To better understand the dynamics of a fed-batch culture, let's simplify the general equations by assuming a Monod growth model (1), a single limiting nutrient S, a single sterile input feed stream (s=1) with similar density to the working volume, no density change as a function of time, stable substrate and product, and no maintenance utilization of substrate. With these assumptions the general fed-batch balances reduce to:

$$\frac{dS}{dt} = D_1 S_1 - \frac{1}{Y^*_{X/S}}\mu X - \frac{1}{Y_{P/S}} q_p X - \frac{S}{V}\frac{dV}{dt} \tag{8}$$

$$\frac{dP}{dt} = D_1 P_1 + q_p X - \frac{P}{V}\frac{dV}{dt} \tag{9}$$

$$\frac{dX}{dt} = (\mu - k_d) X - \frac{X}{V}\frac{dV}{dt} \tag{10}$$

$$\frac{dV}{dt} = F_1(t) \tag{11}$$

If we substitute the volume balance into the substrate, product and cellmass balances (and drop the stream index on the dilution rate), we arrive at the simplified system of equations:

$$\frac{dS}{dt} = D(S_1 - S) - \frac{1}{Y^*_{X/S}}\mu X - \frac{1}{Y_{P/S}} q_p X \tag{12}$$

$$\frac{dP}{dt} = D(P_1 - P) + q_p X \tag{13}$$

$$\frac{dX}{dt} = (\mu - k_d) X - DX \tag{14}$$

$$\frac{dV}{dt} = F(t) \tag{15}$$

where μ is given by:

$$\mu = \mu_g^{max}\left(\frac{S}{K_g + S}\right) \tag{16}$$

and we assume the Luedeking and Piret model for product formation (2):

$$q_p = \alpha\,\mu + \beta \tag{17}$$

The cellmass, substrate, product and volume balances are coupled nonlinear differential equations which can be solved numerically using common packages such as MATLAB or JULIA (3).

Growth associated production formation.

Non-growth associated production formation.

Mixed product formation.

How do we measure the performance of a bacterial culure?

References

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