Chapter 9: Operating Bioreactors

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Presentation Outline:

- Choosing Cultivation Methods
- Modifying Batch and Continuous Reactors
- Immobilized Cell Systems
Choosing the Cultivation Method

The Choice of Bioreactor Affects Many Aspects of Bioprocessing.
1. Product concentration and purity
2. Degree of substrate conversion
3. Yields of cells and products
4. Capital cost in a process (>50% total capital expenses)

Further Considerations in Choosing a Bioreactor.
1. Biocatalyst. (immobilized or suspended)
2. Separations and purification processes

Batch or Continuous Culture?

These choices represent extremes in bioreactor choices

**Productivity** \( \rightarrow \) for cell mass or growth-associated products

**Batch Culture:** assume \( k_d = 0 \) and \( q_p = 0 \)

\[
\begin{align*}
\xi &= \text{rate of cell mass production in 1 batch cycle} \\
\xi &= \frac{X_m \cdot X}{t_v} = \frac{Y_{X/e} X_s}{t_v} \\
\text{Exponential growth} & \quad \text{Lag time} \\
t_v &= \text{batch cycle time} = \frac{1}{\mu_{\text{max}}} \ln \frac{X_m}{X_o} + t_f \\
&\rightarrow \text{Harvest & Preparation}
\end{align*}
\]
Batch or Continuous Culture? (cont.)

Continuous Culture: assume $k_d = 0$ and $q_p = 0$

- $r_c = \text{rate of cell mass production in continuous culture}$
- $r_c = D_{opt} X_{opt}$

Set $\frac{dX}{dD} = 0 \Rightarrow D_{opt} = \mu_{max} \left(1 \cdot \sqrt{\frac{K_s}{K_s + S_0}} \right)$

$X_{opt} = Y_{X/S}^M \left(S_o \cdot \frac{K_s D_{opt}}{\mu_{max} \cdot D_{opt}} \right) = Y_{X/S}^M \left(S_o + K_s \cdot \sqrt{(K_s(S_o + K_s))} \right)$

$D_{opt} X_{opt} = Y_{X/S}^M \mu_{max} \left(1 \cdot \sqrt{\frac{K_s}{K_s + S_0}} \right) (S_o + K_s \cdot \sqrt{(K_s(S_o + K_s))})$

$= \frac{Y_{X/S}^M \mu_{max} S_o}{S_o}$ when $K_s << S_o$

Comparing Rates in Batch and Continuous Culture

\[
\frac{r_c}{r_b} = \frac{Y_{X/S}^M \mu_{max} S_o}{Y_{X/S}^M S_o \left( \frac{1}{\mu_{max}} \ln \frac{X_m}{X_0} + t_1 \right)} = \ln \frac{X_m}{X_0} + t_1 \mu_{max}
\]

A commercial fermentation with

$\frac{X_m}{X_0} = 20$, $t_1 = 5 \text{ hr}$, and $\mu_{max} = 1.0 \text{ hr}^{-1}$

\[
\frac{r_c}{r_b} = 8 \Rightarrow \text{Continuous culture method is ~ 10 times more productive for primary products (biomass & growth associated products)}
\]
Batch or Continuous Culture? (cont.)

Why is it that most commercial bioprocess are Batch??

1. Secondary Product Productivity → is > in batch culture
   (SPs require very low concentrations of S, S ≪ S_{opt})

2. Genetic Instability → makes continuous culture less productive
   (revertants are formed and can out-compete highly selected and
   productive strains in continuous culture.)

3. Operability and Reliability
   (sterility and equipment reliability > for batch culture)

4. Market Economics
   (Batch is flexible → can product many products per year)

Batch or Continuous Culture? (cont.)

Most Bioprocesses are Based on Batch Culture
(In terms of number, mostly for secondary, high value products)

High Volume Bioprocesses are Based on Continuous Culture
(mostly for large volume, lower value, growth associated products --
ethanol production, waste treatment, single-cell protein production)
Modified Bioreactors: Chemostat with Recycle

To keep the cell concentration higher than the normal steady-state level, cells in the effluent can be recycled back to the reactor.

Advantages of Cell Recycle
1. Increase productivity for biomass production
2. Increase stability by dampening perturbations of input stream properties

Chemostat with Recycle: Schematic Diagram
Figure 9.1

α = recycle ratio
C = cell concentration ratio
X₁ = cell concentration in reactor effluent
X₂ = cell concentration in effluent from separator

“Bioprocess Engineering: Basic Concepts”
Shuler and Kargi, Prentice Hall, 2002
Chemostat with Recycle: Biomass Balance

\[ \dot{X} + \alpha F C X_x - (1 + \alpha) F X_x + V_R \mu X_x = V_R \frac{dX_x}{dt} \]

at steady-state \( \frac{dX_x}{dt} = 0 \) and sterile feed \( X_o = 0 \)

\[ \alpha F C X_x - (1 + \alpha) F X_x + V_R \mu X_x = 0 \]

and solving for \( \mu \)

\[ \mu = [1 + \alpha(1 - C)]D \]

Since \( C > 1 \) and \( \alpha(1 - C) < 0 \), then \( \mu < D \)

A chemostat can be operated at dilution rates higher than the specific growth rate when cell recycle is used.

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Chemostat with Recycle: Biomass Balance

\[ \mu = [1 + \alpha(1 - C)]D \]

Monod Equation, \( \mu = \frac{\mu_{max} S}{K_s + S} \)

Substitute Monod Eqn. into above, solve for \( S \)

\[ S = \frac{K_s D (1 + \alpha(1 - C))}{\mu_{max} - D (1 + \alpha(1 - C))} \]
Chemostat with Recycle: Substrate Balance

\[ \frac{FS_o + \alpha FS - (1 + \alpha)FS - VR}{FS_o + \alpha FS - (1 + \alpha)FS} \cdot V_R \frac{\mu X_{1}}{Y_{X/S}} = V_R \frac{dS}{dt} \]

at steady state \( \frac{dS}{dt} = 0 \)

\[ FS_o + \alpha FS - (1 + \alpha)FS - VR \cdot \mu X_{1} = 0 \]

and solving for \( X_{1} \)

\[ X_{1} = \frac{D}{\mu} Y_{X/S} (S_o - S); \quad \text{But } \frac{D}{\mu} = \frac{1}{[1 + \alpha(1 - C)]} \]

\[ X_{1} = \frac{Y_{X/S} (S_o - S)}{[1 + \alpha(1 - C)]} = \frac{Y_{X/S}}{[1 + \alpha(1 - C)]} \cdot S_o - \frac{K_S D (1 + \alpha(1 - C))}{\mu_{max}} - \frac{D (1 + \alpha(1 - C))}{\mu_{max}} \]

Chemostat with Recycle: Comparison

Figure 9.2

\( \alpha = 0.5, C = 2.0, \mu_{max} = 1.0 \ \text{hr}^{-1}, K_S = 0.01 \ \text{g/L}, Y_{X/S} = 0.5 \)

\( X_1 = \text{cell concentration in reactor effluent with no recycle} \)

\( X_{1(\text{recycle})} = \text{cell concentration in effluent with recycle} \)
Multiple Chemostat Systems

Applicable to fermentations in which growth and product formation need to be separated into stages:

Growth stage

Product formation stage

“Bioprocess Engineering: Basic Concepts”
Shuler and Kargi, Prentice Hall, 2002

Multiple Chemostat Systems (cont.)

1. Genetically Engineered Cells:

Recombinant DNA

“Bioprocess Engineering: Basic Concepts”
Shuler and Kargi, Prentice Hall, 2002
Features of Genetically Engineered Cells:

→ have inserted recombinant DNA (plasmids) which allow for the production of a desired protein product.

→ GE cells grow more slowly than original non-modified strain (due to the extra metabolic burden of producing product).

→ Genetic Instability causes the GE culture to (slowly) lose ability to produce product. The non-plasmid carrying cells or the cells with mutation in the plasmid (revertants) grow faster.

Genetically Engineered Cells (cont.):

In the first stage, only cell growth occurs and no inducer is added for product formation. The GE cells grow at the maximum rate and are not out-competed in the first chemostat by revertant cells. When cell concentrations are high, an inducer is added in the latter (or last) chemostat to produce product at a very high rate.
Multiple Chemostat Systems (cont.)

2-Stage Chemostat System Analysis

Stage 1 - cell growth conditions, \( k_d=0, q_p=0 \), steady-state

\[
\mu_1 = \frac{\mu_{max} S_1}{K_s + S_1} = D_1 \quad \text{from biomass balance}
\]

rearranging,

\[
S_1 = \frac{K_s D_1}{\mu_{max} - D_1}
\]

where \( D_1 = \frac{F}{V_i} \)

\[
X_1 = Y_{X/S}^M (S_0 - S_1)
\]

from substrate balance

Stage 2 - product formation conditions, \( k_d=0, F^{P}=0 \), steady-state

\[
FX_1 - FX_2 + V_2 \mu_2 X_2 = V_2 \frac{dX_2}{dt} = 0 \quad \text{biomass balance}
\]

\[
\mu_2 = \frac{\mu_{max} S_2}{K_s + S_2} = D_2 \left(1 - \frac{X_1}{X_2} \right)
\]

where \( D_2 = \frac{F}{V_2} \)

\[
FS_1 - FS_2 - V_2 \frac{\mu X_1}{Y_{X/S}^M} - V_2 q_p X_2 = V_2 \frac{dS_2}{dt} = 0 \quad \text{substrate balance}
\]

\[
FP_1 - FP_2 + V_2 q_p X_2 = V_2 \frac{dP_2}{dt} = 0 \quad \text{product balance}
\]
Multiple Chemostat Systems (cont.)

2-Stage Chemostat System Analysis

Stage 2 - product formation conditions, $k_d = 0$, $F' = 0$, steady-state

\[
\mu_2 = \frac{\mu_{\text{max}} S_2}{K_S + S_2} = D_2 \left(1 - \frac{X_1}{X_2}\right) \quad \text{biomass balance}
\]

\[
S_2 = S_1 - \left(\frac{\mu_2 X_2}{D_2 Y_{X/S}} + \frac{q_b X_2}{D_2 Y_{P/S}}\right) \quad \text{substrate balance}
\]

2 equations, 2 unknowns ($S_2, X_2$)

\[
FP_1 - FP_2 + V_q X_2 = V_2 \frac{dP_2}{dt} = 0 \quad \text{product balance}
\]

use $X_2$ in product balance to solve for $P_2$

Fed-Batch Operation

Useful in Antibiotic Fermentation

→ reactor is fed continuously (or intermittently)
  reactor is emptied periodically

→ purpose is to maintain low substrate concentration, $S$

→ useful in overcoming substrate inhibition or catabolic repression, so that product formation increases.
Fed-Batch Operation (cont.)

Before \( t = 0 \), almost all of the substrate, \( S_0 \), in the initial volume, \( V_0 \), is converted to biomass, \( X_m \), with little product formation (\( X = X_m = Y_{X/S} S_0 \)) and \( P \approx 0 \).

At \( t = 0 \), feed is started at a low flow rate such that substrate is utilized as fast as it enters the reactor. Therefore, \( S \) remains very low in the reactor and \( X \) continues to maintain at \( Y_{X/S} S_0 \) over time. The volume increases with time in the reactor and product formation continues.

Fed-Batch Operation (cont.)

Behavior of \( X, S, P, V, \) and \( \mu \) over time

"Bioprocess Engineering: Basic Concepts"
Shuler and Kargi,
Prentice Hall, 2002
Fed-Batch Operation (cont.)

Analysis of Fed-Batch Operation

Volume: \( \frac{dV}{dt} = F \implies V = V_o + Ft \)

Biomass: \( F X_o^* + V \mu X = \frac{d(XV)}{dt} = \frac{V}{dt} \frac{dX}{dt} + X \frac{dV}{dt} \)

\( V \mu X = X \frac{dV}{dt} \implies \mu = \frac{1}{V} \frac{dV}{dt} = \frac{F}{V} = D \)

\( \mu = \frac{F}{V} = \frac{F}{V_o + Ft} = \frac{D_o}{1+D_o t} \)

Fed-Batch Operation (cont.)

Analysis of Fed-Batch Operation (cont.)

Total Biomass: \( X_t \) (g cells) vs time

\( \frac{dX_t}{dt} = 0 \) or \( \frac{d}{dt} \left( \frac{X_t}{V} \right) = V \left( \frac{dX_t}{dt} \right) - X_t \left( \frac{dV}{dt} \right) = 0 \)

rearranging \( \frac{dX_t}{dt} = \frac{X_t \frac{dV}{dt}}{V} = \frac{X_m F}{V} = Y_{X/S} F \)

integrating \( X_t = X_o + Y_{X/S} S_o Ft = (V_o + Ft) X_m \)
Fed-Batch Operation (cont.)

Analysis of Fed-Batch Operation (cont.)

Product Formation: total product, \( P_t = PV \)

For many secondary products, the specific rate of product formation is a constant = \( q_p \)

\[
\frac{dP_t}{dt} = q_p \, X_t = q_p \left( V_o + Ft \right) X_m
\]

integrating, \( P_t = P_0 + q_p \, X_m \left( \frac{V_o}{V} + \frac{Ft}{2} \right) t \)

or \( P = P_0 \, \frac{V_o}{V} + q_p \, X_m \left( \frac{V_o}{V} + \frac{Ft}{2} \right) t \)

or \( P = \frac{P_0 \, V_o}{(V_o + Ft)} + q_p \, X_m \left( \frac{V_o}{(V_o + Ft)} + \frac{Ft}{2(V_o + Ft)} \right) t \)

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Immobilized Cell Systems; 9.4

Restriction of cell mobility within a confined space

Potential Advantages:

1. Provides high cell concentrations per unit of reactor volume.
2. Eliminates the need for costly cell recovery and recycle.
3. May allow very high volumetric productivities.
4. May provide higher product yields, genetic stability, and shear damage protection.
5. May provide favorable microenvironments such as cell-cell contact, nutrient-product gradients, and pH gradients resulting in higher yields.
### Potential Disadvantages/Problems:

1. If cells are growing (as opposed to being in stationary phase) and/or evolve gas (CO$_2$), physical disruption of immobilization matrix could result.

2. Products must be excreted from the cell to be recovered easily.

3. Mass transfer limitations may occur as in immobilized enzyme systems.

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### Methods of Immobilization

**Active Immobilization:**

1. Entrapment in a Porous Matrix:

   - **Polymeric Beads:**
     - **Polymers:**
       - agar, alginate
       - $\kappa$-carrageenan
       - polyacrylamide
       - gelatin, collagen
     - **Inert/solid core**
     - **Porous polymer matrix**
     - **Cells**
Methods of Immobilization (cont.)

Encapsulation:
- hollow spherical particle
- liquid core with cells
- "less severe mass transfer limitations"

Membrane:
- nylon, collodion,
- polystyrene,
- polylysine-alginate hydrogel
- Cellulose acetate-ethyl acetate

Encapsulation:
- "less severe mass transfer limitations"

Hollow Fiber Membrane Reactor:
- liquid in shell side
- shell
- tube
- cells
- semi-permeable membrane
- products
- nutrients
Methods of Immobilization (cont.)

2. Cell Binding to Inert Supports:

**Micro-porous Supports:**

```
| micropores |
| d_p > 4 d_c |
| • cells in micropores |
```

“mass transfer limitations occur”

- porous glass, porous silica, alumina
- ceramics, gelatin, activated carbon
- Wood chips, poly propylene ion-exchange resins
  (DEAE-Sephadex, CMC-), Sepharose

Methods of Immobilization (cont.)

**Binding Forces:**

- **Electrostatic Attraction**
- **Hydrogen Bonding**

Diagram showing interactions:

- Cell
- Support
- Ion exchange
- Electrostatic attraction
- Hydrogen bonding

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Methods of Immobilization (cont.)

Binding Forces:

**Covalent Bonding: (review enzyme covalent bonding)**

- Support materials: CMC-carbodiimide
- Support functional groups
  - OH, -NH₂, -COOH

Binding to proteins on cell surface

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Methods of Immobilization (cont.)

**Overview of Active Cell Immobilization Methods:**

<table>
<thead>
<tr>
<th>Support</th>
<th>Adsorption</th>
<th>Capacity</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porous silica</td>
<td>low</td>
<td>weak</td>
<td></td>
</tr>
<tr>
<td>Wood chips</td>
<td>high</td>
<td>weak</td>
<td></td>
</tr>
<tr>
<td>Ion-exchange resins</td>
<td>high</td>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>CMC</td>
<td>high</td>
<td>high</td>
<td></td>
</tr>
</tbody>
</table>

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Methods of Immobilization (cont.)

Passive Immobilization:

- wastewater treatment
- mold fermentations
- fouling of processing equipment

Support

Liquid phase

Biofilm (biopolymer + polysaccharides)

Analysis of Biofilm Mass Transfer

Figures 9.1, 9.12

Substrate/product diffusion in biofilms

O₂ diffusion in biofilms

"Bioprocess Engineering: Basic Concepts"
Shuler and Kargi,
Prentice Hall, 2002
Analysis of Biofilm Mass Transfer (cont.)

Differential Substrate Balance:

Material volume in biofilm, \( \Delta V = \Delta x \Delta y \Delta z \)

Rate of diffusion out through the area \( \Delta x \Delta z \)

\[-D_x \left. \frac{dS}{dy} \right|_{y+y} \Delta x \Delta z \]

Rate of diffusion in through the area \( \Delta x \Delta z \)

\[-D_x \left. \frac{dS}{dy} \right|_{y} \Delta x \Delta z \]

Rate of substrate consumption in the volume \( \Delta V = \Delta x \Delta y \Delta z \)

\( \frac{1}{Y_{X/S}} \frac{\mu_{\text{mm}} S}{K_S + S} X \Delta x \Delta y \Delta z \)

Rate of substrate consumption in the volume \( \Delta V = \Delta x \Delta y \Delta z \)

\( \frac{1}{Y_{P/S}} \frac{q_S S}{K_S + S} X \Delta x \Delta y \Delta z \)

Differential Substrate Balance at Steady-State:

Rate of diffusion \( \Delta x \Delta z \) - Rate of diffusion \( \Delta x \Delta z \) - Rate of substrate consumption in the volume \( \Delta V = \Delta x \Delta y \Delta z \)

\[-D_x \left. \frac{dS}{dy} \right|_{y+y} \Delta x \Delta z \] - \[-D_x \left. \frac{dS}{dy} \right|_{y} \Delta x \Delta z \] - \( \frac{1}{Y_{X/S}} \frac{\mu_{\text{mm}} S}{K_S + S} X \Delta x \Delta y \Delta z = 0 \)

Divide through by \( \Delta x \Delta y \Delta z \) and switch order of first 2 terms

\[ \frac{1}{Y_{X/S}} \frac{\mu_{\text{mm}} S}{K_S + S} X = 0 \]
Analysis of Biofilm Mass Transfer (cont.)

Differential Substrate Balance at Steady-State:

\[ D_s \frac{d^2 S}{dy^2} = \frac{1}{Y_{X/S}} \frac{\mu_{\text{max}} S}{K_s + S} X \quad \text{eqn 9.49} \]

Boundary Conditions
\[ S = S_a \quad \text{at} \ y = 0 \quad \text{(at the biofilm / liquid interface)} \]
\[ \frac{dS}{dy} = 0, \quad \text{at} \ y = L \quad \text{(at the biofilm / support interface)} \]

Analysis of Biofilm Mass Transfer (cont.)

Dimensionless Substrate Balance at Steady-State:

\[ \frac{d^2 \bar{S}}{d\bar{y}^2} = \frac{\phi \bar{S}}{1 + \beta \bar{S}} \quad \text{eqn 9.51} \]

where
\[ \bar{S} = \frac{S}{S_a}, \quad \bar{y} = \frac{y}{L}, \quad \beta = \frac{S}{S_a}, \quad \phi = L \sqrt{\frac{\mu_{\text{max}} X}{Y_{X/S} D_s K_s}} \]

"Thiele Modulus"

Boundary Conditions
\[ \bar{S} = 1, \quad \text{at} \ \bar{y} = 0 \quad \text{(at the biofilm / liquid interface)} \]
\[ \frac{d\bar{S}}{d\bar{y}} = 0, \quad \text{at} \ \bar{y} = 1 \quad \text{(at the biofilm / support interface)} \]
Analysis of Biofilm Mass Transfer (cont.)

Zero Order Substrate Consumption Kinetics:

\[
\frac{d^2 \Omega}{d \bar{y}^2} = \phi \frac{\bar{S}}{1 + \beta \bar{S}}, \text{ for } \beta \gg 1, \text{ and } \phi < 1
\]

\[
\frac{d^2 \Omega}{d \bar{y}^2} = \frac{\phi}{\beta} \quad \text{zero-order substrate consumption kinetics}
\]

\[
\frac{d \Omega}{d \bar{y}} = \frac{\phi}{\beta} \quad \Rightarrow \quad \int d \left( \frac{d \Omega}{d \bar{y}} \right) = \int \frac{\phi}{\beta} d \bar{y}
\]

\[
\frac{d \Omega}{d \bar{y}} = \frac{\phi}{\beta} \bar{y} + C_1
\]

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Analysis of Biofilm Mass Transfer (cont.)

Zero Order Substrate Consumption Kinetics:

Boundary condition #2, at \( \bar{y} = 1 \), \( \frac{d \Omega}{d \bar{y}} = 0 \)

\[
0 = \frac{\phi}{\beta}(1) + C_1 \quad \Rightarrow \quad C_1 = -\frac{\phi}{\beta}
\]

\[
\frac{d \Omega}{d \bar{y}} = \frac{\phi}{\beta} \bar{y} - \frac{\phi}{\beta} 
\]

Integrate again, \( \int d \bar{\Omega} = \int \left( \frac{\phi}{\beta} \bar{y} - \frac{\phi}{\beta} \right) d \bar{y} \)

\[
\bar{\Omega} = \frac{\phi}{2\beta} \bar{y}^2 - \frac{\phi}{\beta} \bar{y} + C_2
\]

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Analysis of Biofilm Mass Transfer (cont.)

Zero Order Substrate Consumption Kinetics:

Boundary condition #1, at \( \bar{y} = 0 \), \( \bar{S} = 1 \)

\[
1 = \frac{\dot{\varphi}}{\beta}(0) - \frac{\dot{\varphi}}{\beta}(0) + C_2 \quad \Rightarrow \quad C_2 = 1
\]

\[
\bar{S} = \frac{\dot{\varphi}}{2\beta} \bar{y}^2 - \frac{\dot{\varphi}}{\beta} \bar{y} + 1 \quad \text{or} \quad \bar{S} = \frac{\dot{\varphi}}{\beta} \left( \frac{\bar{y}^2}{2} - \bar{y} \right) + 1
\]

for \( \frac{\dot{\varphi}}{\beta} \ll 1 \)

Biofilm Effectiveness

The effectiveness factor is calculated by dividing the rate of substrate diffusion into the biofilm by the maximum substrate consumption rate.

Solve for the Effectiveness Factor, \( \eta \)

\[
N_x A_2 = -A_2 D_s \frac{dS}{dy} \bigg|_{y=0} = \eta \left( \frac{\mu_{\text{max}} X}{Y_{X,s} (K_s + S)} \right) (A_3 L)
\]

Rate of substrate diffusion into biofilm through an area \( A_3 \) at the surface at \( \bar{y} = \bar{0} \)

Volumetric rate of substrate consumption within the biofilm in a volume \( (A_3 L) \)
Effectiveness Factor

Biofilm is most effective for $\beta \gg 1$.

$\eta$ increases as $\phi$ decreases for any value of $\beta$.

"Bioprocess Engineering: Basic Concepts"  
Shuler and Kargi, Prentice Hall, 2002

Spherical Particle of Immobilized Cells
Figure 9.14

$V_p$ is particle volume  
$A_p$ is particle area

"Bioprocess Engineering: Basic Concepts"  
Shuler and Kargi, Prentice Hall, 2002
Analysis of Mass Transfer in Spherical Particle

Dimensionless Substrate Balance at Steady-State:

\[
\frac{d^2\bar{S}}{dr^2} + \frac{2}{r} \frac{d\bar{S}}{dr} = \frac{\phi}{1 + \beta \bar{S}}
\]

where \( \bar{S} = \frac{S}{S_0}, \quad r = \frac{r}{R}, \quad \beta = \frac{S_0}{K_S}, \)

and \( \phi = R \sqrt{\frac{\mu X}{Y_{X:S} D_K S}} \) "Thiele Modulus"

Boundary Conditions

\( \bar{S} = 1 \) at \( r = R \) (at the particle / liquid interface)
\( \frac{d\bar{S}}{dr} = 0 \), at \( r = 0 \) (at the particle center)

Particle Effectiveness

If all of the particle cells "see" substrate at a concentration \( S_0 \) or high enough to grow maximally, then the particle is said to have an effectiveness of 1.

Rate of \( S \) consumption by a single particle

\[
N_S A_p = -A_p D \frac{dS}{dr} \bigg|_{r=R} = \eta \left( \frac{\mu X}{Y_{X:S} (K_S + S_0)} \right) V_p
\]

Rate of substrate diffusion into particle through an area \( A_p \) at the surface at \( r = R \) Volumetric rate of substrate consumption within the particle in a volume \( V_p \)
Equation 9.58 can be solved analytically for limiting cases:

Case 1, for $S_o << K_s$ (very dilute substrate)

$$\eta = \frac{1}{\phi} \left[ \frac{1}{\tanh 3\phi} - \frac{1}{3\phi} \right]$$

$$\phi = \frac{V_p}{A_p} \sqrt{\frac{\mu_{\text{m}} X}{Y_{X/I} D_k K_s}}$$

"Thiele Modulus"

Case 2, for $S_o >> K_s$ (very concentrated substrate)

$$D_4 \left[ \frac{d^2 S}{dr^2} + \frac{2}{r} \frac{dS}{dr} \right] = \frac{\mu_{\text{m}} S}{Y_{X/I} (K_s + S)} X = \frac{\mu_{\text{m}} X}{Y_{X/I}^M}$$

Boundary Conditions

$S = S_o$ at $r = R$ (at the particle / liquid interface)

$\frac{dS}{dr} = 0$, at $r = 0$ (at the particle center)
Equation 9.58 can be solved analytically for limiting cases:

Case 2, for $S_o >> K_S$

Use a variable transformation, $S' = S/r$

$$1 \frac{d^2 S'}{dr^2} = \frac{\mu_{\infty} X}{Y_{\infty, \gamma} D_e}$$

Solution for $S'$ is:

$$S = S_o - \frac{\mu_{\infty} X}{6 Y_{\infty, \gamma} D_e} (R^2 - r^2)$$

At a critical radius ($\eta$), $S = 0$

$$0 = S_o - \frac{\mu_{\infty} X}{6 Y_{\infty, \gamma} D_e} (R^2 - r^2)$$

$$\left( \frac{R_o}{R} \right)^2 = 1 - \frac{6 D_e S_o Y_{\infty, \gamma}}{\mu_{\infty} X R^2}$$
The single particle analysis for $\eta$ can be used in the analysis of bioreactors having immobilized cells:

"Bioprocess Engineering: Basic Concepts"  
Shuler and Kargi, Prentice Hall, 2002

Consider a plug flow reactor filled with immobilized cell particles:

A differential balance on a thin slice of particles within the reactor:

$$\text{Rate of substrate flow into element} - \text{Rate of substrate flow out of element} = \text{Rate of mass transfer into particles within element}$$

$$\left. F S_d \right|_{z=0} - \left. F S_d \right|_{z=\Delta z} = N \Delta z$$
Using the definition of $\eta$:

$$N_p A_p = \eta \left( \frac{\mu_{\text{max}} S X}{V_{\text{Y/p}} (K_s + S_p)} \right) V_p$$

$$\frac{dS_a}{dz} = \eta \left( \frac{\mu_{\text{max}} S X}{V_{\text{Y/p}} (K_s + S_p)} \right) \frac{V_p}{A_p} a A$$

where $a = \text{surface area of particle per unit volume of bed (cm}^2 / \text{cm}^3 \text{ bed)}$

$A = \text{cross-sectional area of the bed (cm}^2)$

At $z = 0$, $S_a = S_{ao}$; integrating assuming $\eta$ is constant

$$K_s \ln \left( \frac{S_a}{S_p} \right) + (S_a - S_o) = \eta \left( \frac{\mu_{\text{max}} V_p X a A}{V_{\text{Y/p}} F A_p K_s} \right) H$$

for low substrate concentration ($S_a << K_s$)

$$\ln \left( \frac{S_a}{S_a} \right) = - \eta \left( \frac{\mu_{\text{max}} V_p X a A}{V_{\text{Y/p}} F A_p K_s} \right) H$$

note $\Xi = \chi \left( \frac{V_p}{A_p} \right) a$ (average cell mass conc. in the bed)