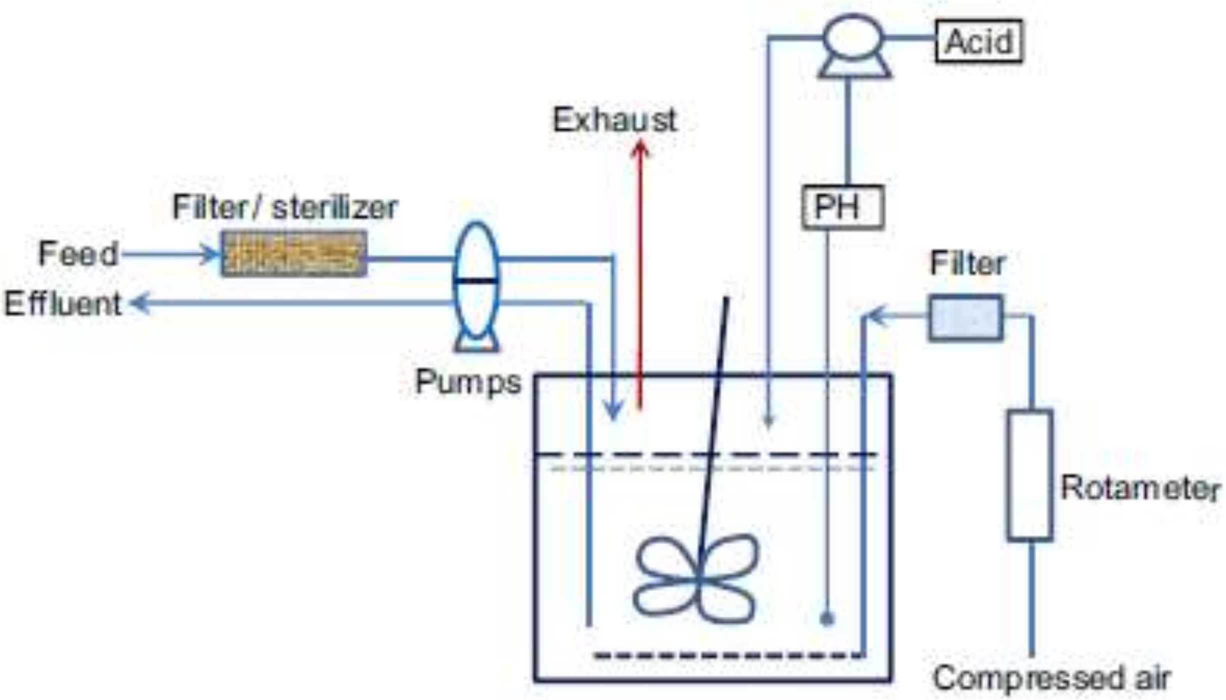
NAČINI VODENJA BIOPROCESOV II

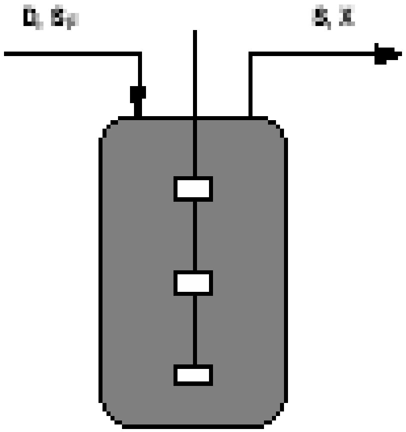
Kontinuirni proces
Kontinuirni proces z reciklom

Kontinuirni bioproces



Načini vodenja procesov

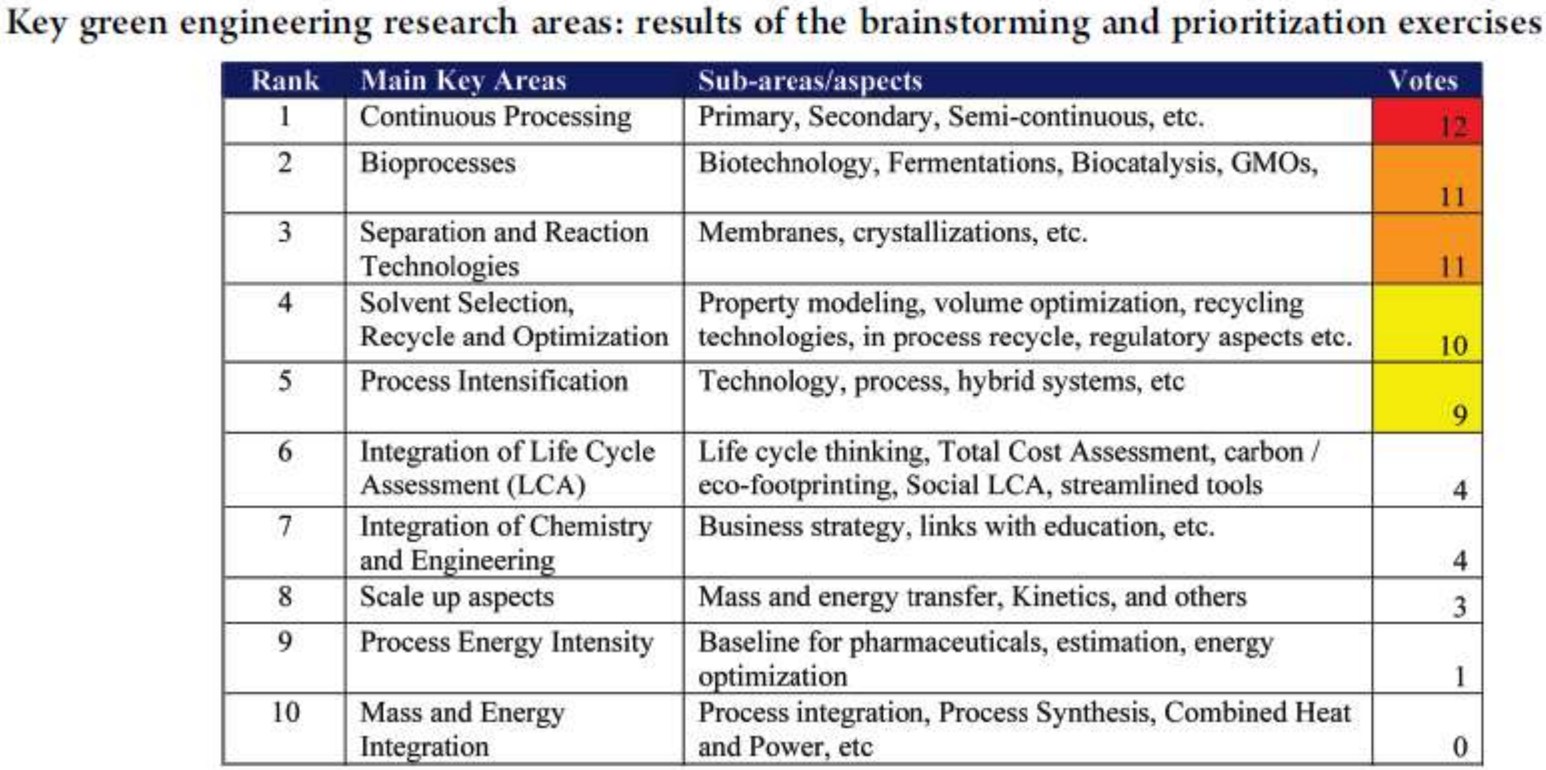
- **Kontinuirni bioproces**
  - vtok in iztok
  - če sta oba pretoka enaka, imamo konstantno prostornino
  - omogočeni stacionarni pogoji: kemostat
  - dolgotrajno delovanje
  - zelo visoke produktivnosti
  - možnost okužb, mutacij



Uporaba kontinuirnih procesov

- **Industrija**
  - Biološke čistilne naprave
  - Proizvodnja „single-cell“ proteinov
  - Kontinuirna proizvodnja piva
  - Kontinuirna proizvodnja amino kislin
  - Kontinuirna proizvodnja organskih kislin
  - Kontinuirna proizvodnja etanola

Ključne prioritete za trajnostno proizvodnjo



Key green engineering research areas: results of the brainstorming and prioritization exercises

Rank	Main Key Areas	Sub-areas/aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous, etc.	🟥 12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs,	🟧 11
3	Separation and Reaction Technologies	Membranes, crystallizations, etc.	🟧 11
4	Solvent Selection, Recycle and Optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.	🟨 10
5	Process Intensification	Technology, process, hybrid systems, etc	🟨 9
6	Integration of Life Cycle Assessment (LCA)	Life cycle thinking, Total Cost Assessment, carbon / eco-footprinting, Social LCA, streamlined tools	4
7	Integration of Chemistry and Engineering	Business strategy, links with education, etc.	4
8	Scale up aspects	Mass and energy transfer, Kinetics, and others	3
9	Process Energy Intensity	Baseline for pharmaceuticals, estimation, energy optimization	1
10	Mass and Energy Integration	Process integration, Process Synthesis, Combined Heat and Power, etc	0

Vir:

Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers

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Uporaba kontinuirnih procesov

- **Raziskave**
  - Fiziološke in biokemijske študije za nadzor hitrosti rasti

  Vpliv dejavnikov okolja/ procesnih parametrov na rast in tvorbo produkta

      Indukcija, represija, hitrost rasti, vpliv temperature, pH itd.

  - Mikrobna ekologija

    Izbor populacij, ki rastejo počasi
    Interakcije žrtev-plenilec
    Kompetitivnost (npr. plasmidi +/-)

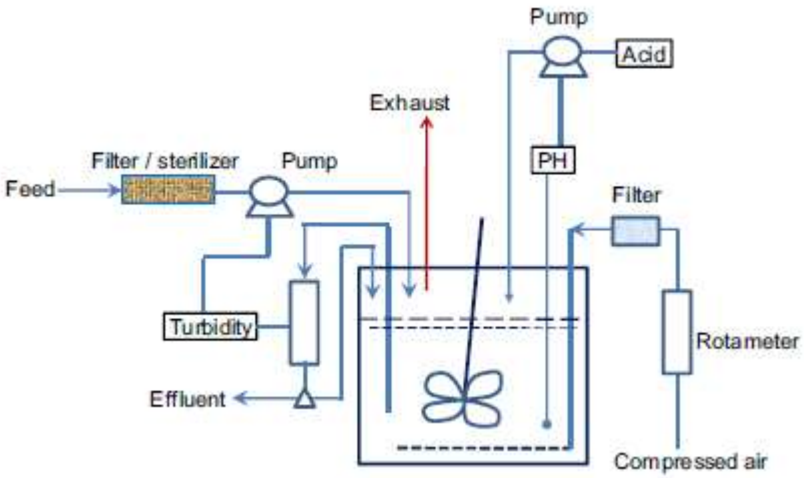
  - Kinetične študije

    Izračun rastnih konstant, podatki o fermentacijah

Tipi kontinuirnih obratovanj

Glede na metodo nadzora:

- Kemostat - reguliran na osnovi nadzora koncentracije limitnega hranila
- Turbidostat - reguliran na osnovi nadzora biomase z uporabo optične gostote (fotoelektrična celica)



- Biostat - reguliran na osnovi sistema za nadzor biomase, ki ne temelji na optični gostoti (npr. proizvodnja CO_2)

Snovne bilance – kontinuirni proces

- za biomaso (X):

$$\frac{dX}{dt} = \mu X - \frac{FX}{V} = \mu X - DX$$

- za substrat (S):

$$\frac{dS}{dt} = \frac{F S_V}{V} + r_S - \frac{F S}{V} = D(S_V - S) + r_S$$

- za produkt (P):

$$\frac{dP}{dt} = r_P - \frac{FP}{V} = r_P - DP$$

Kemostat

- Stacionarno stanje
- Biomasa:

$$0 = \mu X - D X$$

$$\mu = D$$

- Substrat:

$$0 = D(S_v - S) + r_S$$

$$X = Y_{X/S}(S_V - S)$$

$$S = \frac{\mu K_s}{\mu_{max} - \mu}$$

$$S = \frac{D K_s}{\mu_{max} - D}$$

Kemostat – tvorba produkta

$$D(P_F - P) + Y_{P/X} \cdot \mu \cdot X = 0$$

Če je $P_F = 0$

$$P = \frac{Y_{P/X} \mu X}{D}$$

Uporaba kemostata: določanje porabe substrata za vzdrževanje m_S

$$V_R \cdot \frac{dS}{dt} = F \cdot S_F - F \cdot S - V_R \cdot \mu_g \cdot X \cdot \frac{1}{Y^M_{x/S}} - V_R \cdot q_P \cdot X \cdot \frac{1}{Y_{P/S}}$$

$Y^M_{x/S}$ ...maksimalni izkoristek X/S

Če ni tvorbe produkta + stacionarno stanje:

$$D \cdot (S_F - S) = \mu_g \cdot X \cdot \frac{1}{Y^M_{x/S}} \qquad D = \mu_g - k_d = \mu$$

$$D \cdot (S_F - S) - (D + k_d) \cdot X \cdot \frac{1}{Y^M_{X/S}} = 0 \quad /:X$$

$$D\left(\frac{S_F - S}{X}\right) - \frac{D}{Y^M_{X/S}} - \frac{k_d}{Y^M_{X/S}} = 0 \qquad /:D$$

$$\frac{1}{Y^{AP}_{X/S}} = \frac{1}{Y^M_{X/S}} + \frac{k_d}{Y^M_{X/S} \cdot D} = \frac{1}{Y^M_{X/S}} + \frac{m_S}{D}$$

$$m_S = \frac{k_d}{Y^M_{X/S}}$$

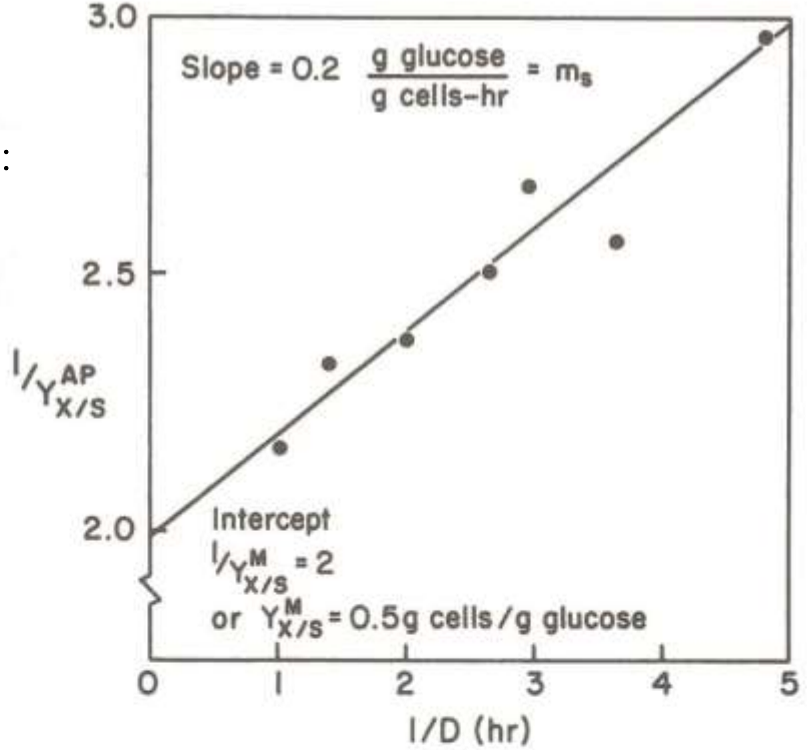
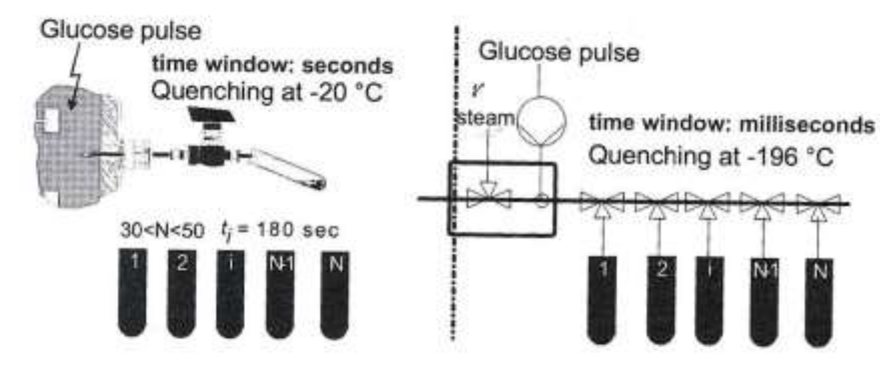


Figure 6.19. Graphical approach to estimating $Y^M_{X/S}$ and m_s for chemostat data for *E. coli* growing on glucose as the limiting nutrient.

Uporaba kemostata: študij metabolnih fluksov



pulzni vnos glukoze

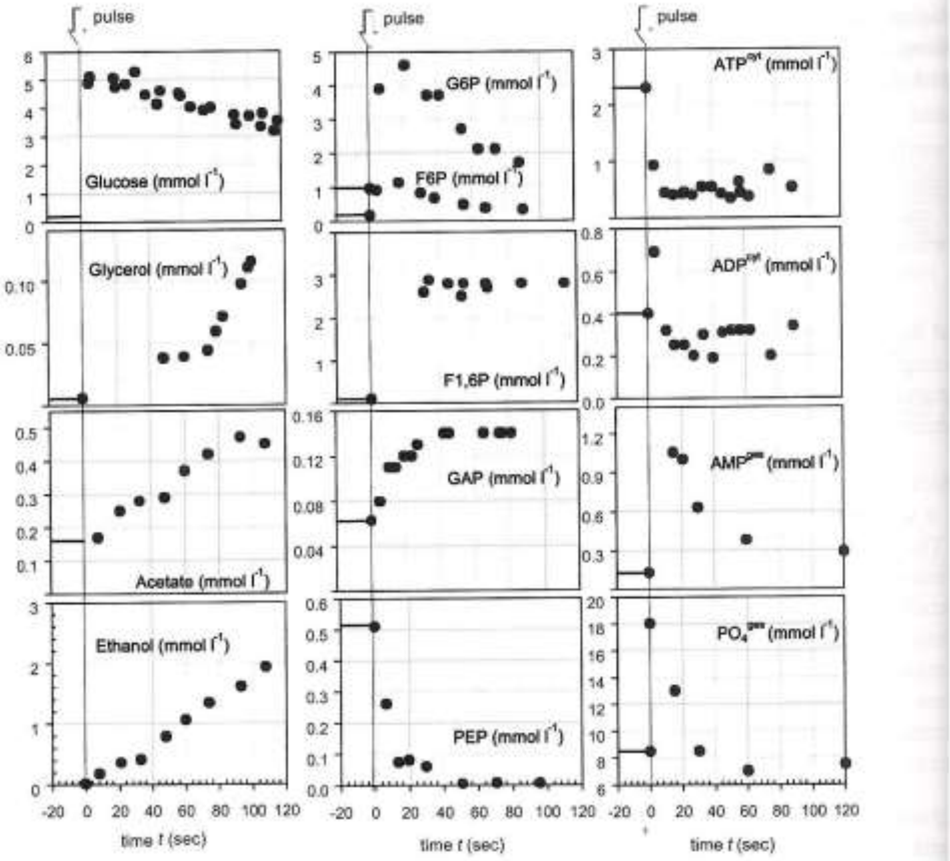
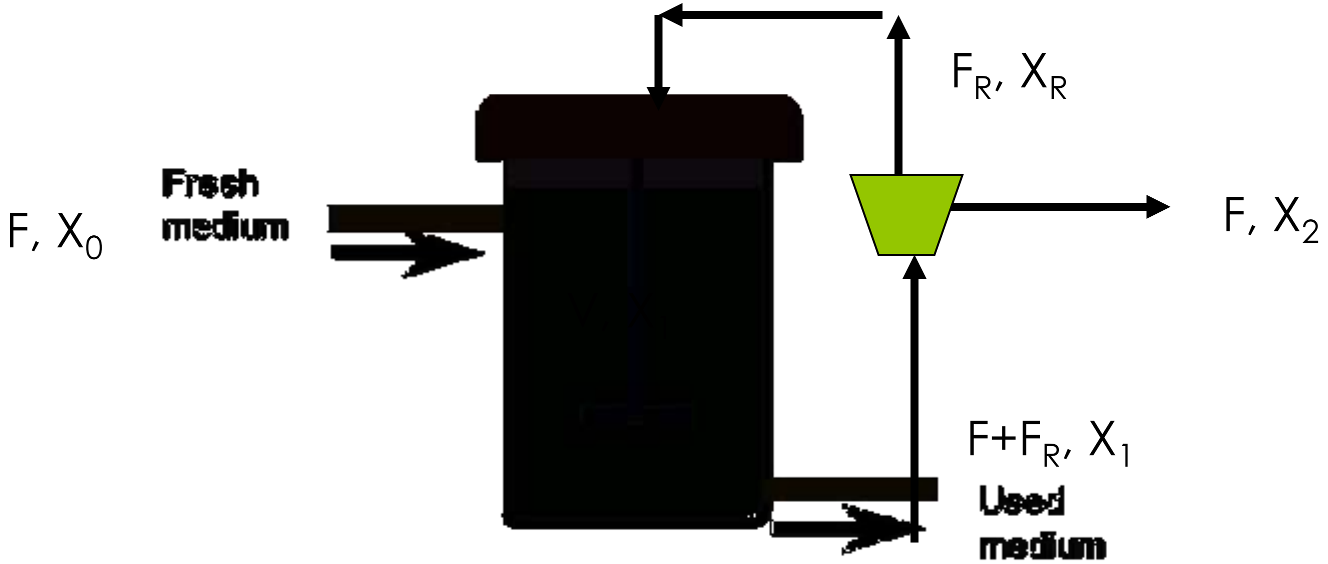


Figure 4. Changes in the concentration of extracellular products and substrates (lef side), intracellular metabolites (middle) and intracellular co-metabolites (right hand sid a glucose pulse at t=0 sec.

Kemostat z reciklom celic



F – pretok napajalne raztopine

V – volumen reaktorja

X_1 – koncentracija biomase v reaktorju

X_2 - koncentracija biomase v iztoku

X_R - koncentracija biomase v reciklu

F_R – pretok recikla

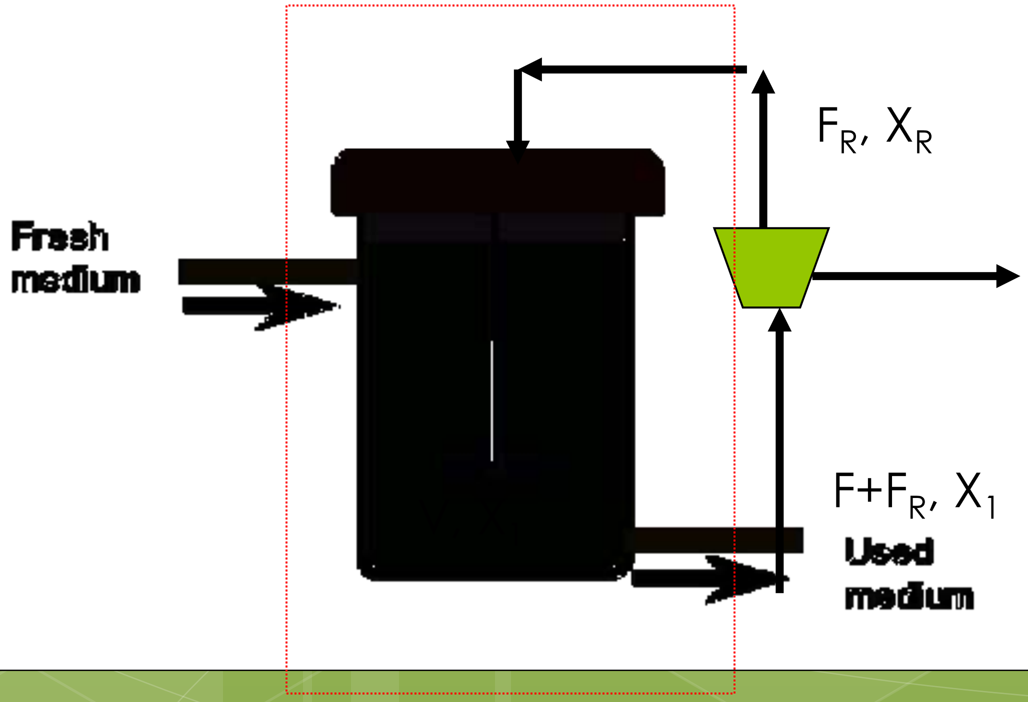
Kemostat z reciklom celic

Snovna bilanca za biomaso v stacionarnem stanju (V=konst.):

$$F X_0 + F_R X_R - (F + F_R) X_1 + V\mu X_1 = \frac{dX_1}{dt} V$$

$\alpha = F_R / F$

$C = X_R / X_1$



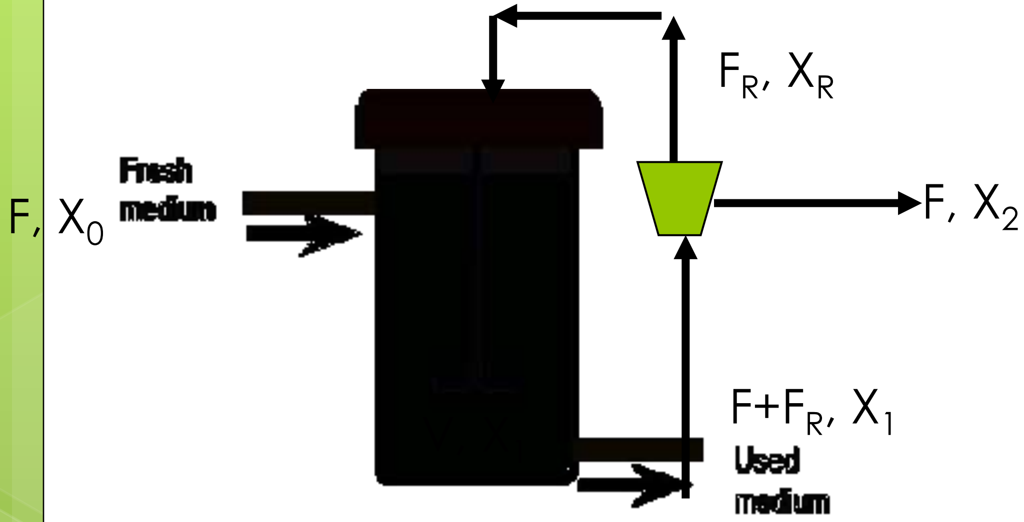
F, X_0

F_R, X_R

F, X_2

$F+F_R, X_1$

Kemostat z reciklom celic



Izpeljava

- $F + F_R = (1 + \alpha)F$
- $F_R \cdot X_R$ člen

$F_R = F \cdot \alpha$

$X_R = C \cdot X_1$

$F_R \cdot X_R = \alpha \cdot C \cdot F \cdot X_1$

$$F X_0 + F_R X_R - (F + F_R) X_1 + V\mu X_1 = \frac{dX_1}{dt} V$$

$$F X_0 + \alpha C F X_1 - (1 + \alpha) F X_1 + V\mu X_1 = \frac{dX_1}{dt} V$$

Kemostat z reciklom celic

- Predpostavke
  - Stacionarno stanje: $\frac{dX_1}{dt} = 0$
  - Sterilni vtok: $X_0 = 0$

$$(\alpha C - 1 - \alpha)F + V\mu = 0$$

Če je D = F/V, velja za recikel:

$$\mu = D(1 + \alpha(1 - C))$$

če je $C > 1$ (konc. celic), potem je $\alpha(1 - C) < 0$ in je $\mu < D$

Kemostat z reciklom lahko deluje pri $D > \mu_{max}$

Bilanca za substrat- Recikel

$$FS_0 + \alpha FS - V\frac{\mu X_1}{Y_{X/S}} - (1+\alpha)FS = V\frac{dS}{dt}$$

- V stacionarnem stanju in menjavi D za μ:

$$X_1 = \frac{D}{\mu}Y_{X/S}(S_0 - S) = \frac{Y_{X/S}(S_0 - S)}{(1+\alpha-\alpha C)}$$

Bilanca za substrat- Recikel

- Upoštevamo kinetiko Monoda

$$S = \frac{K_S D(1+\alpha-\alpha C)}{\mu_{\max} - D(1+\alpha-\alpha C)}$$

$$X_1 = \frac{Y_{X/S}}{(1+\alpha-\alpha C)}\left[S_0 - \frac{K_S D(1+\alpha-\alpha C)}{\mu_{\max} - D(1+\alpha-\alpha C)}\right]$$