1.1 – Batch Reactor

Cell growth

$$r_x = \mu\, x$$

r_x – volumetric growth rate (gX/l.h)
μ – specific cell growth rate (h^{-1})

$$\mu = \frac{\mu_{max}\, S}{K_S + S}$$

μ_{max} – maximum specific cell growth rate (h^{-1})

Substrate consumption

$$r_s = \frac{1}{Y_{x/s}} \mu x$$

r_S – volumetric rate of substrate consumption (gS/l.h)

$$V_s = \frac{r_s}{x}$$

$$V_s = \frac{1}{Y_{x/s}} \mu$$

V_S – specific rate of substrate consumption (gS/gX.h)

$$r_s = \frac{v_{max}\, S}{K_m + S}$$

V_{max} – maximum specific rate of substrate consumption (gS/gX.h)

1.1 – Batch Reactor

Cell growth

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r_x – volumetric growth rate (gX/l.h)
μ – specific cell growth rate (h^{-1})

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Substrate consumption

$$r_s = \frac{1}{Y_{x/s}} \mu x$$

$$r_s = \frac{1}{Y'_{x/s}} \mu x + m x$$

$$V_s = \frac{r_s}{x}$$

$$V_s = \frac{1}{Y_{x/s}} \mu$$

$$V_s = \frac{1}{Y'_{x/s}} \mu + m$$

$$r_s = \frac{v_{\max}\, S}{K_m + S}$$

m – maintenance coefficient (gS/gX.h)

1.1 – Batch Reactor

Product formation

I – <u>Product associated with growth</u>

$$r_p = \frac{dP}{dt} = Y_{p/x}\,\mu\,x$$

$$V_p = \frac{1}{x}\frac{dP}{dt} = Y_{p/x}\,\mu$$

r_p – volumetric product production rate (gP/l.h)

V_p - specific product production rate (gP/gX.h)

Product formation

I – <u>Product associated with growth</u>

$$r_p = \frac{dP}{dt} = Y_{p/x}\,\mu\,x \qquad\qquad V_p = \frac{1}{x}\frac{dP}{dt} = Y_{p/x}\,\mu$$

II – <u>Product partially associated with growth</u>

$$r_p = \frac{dP}{dt} = \alpha\,\mu\,x + \beta\,x \qquad\qquad V_p = \frac{1}{x}\frac{dP}{dt} = \alpha\,\mu + \beta$$

$\alpha = Y'_{p/x}$ – true yield coefficient of product production (gP/gX)

β = specific product formation rate due to maintenance (gP/gX.h) $m_{p} = \beta$

Product formation

I – Product associated with growth

$$r_p = \frac{dP}{dt} = Y_{p/x}\,\mu\,x$$

$$V_p = \frac{1}{x}\frac{dP}{dt} = Y_{p/x}\,\mu$$

II – Product partially associated with growth

$$r_p = \frac{dP}{dt} = \alpha\,\mu\,x + \beta\,x$$

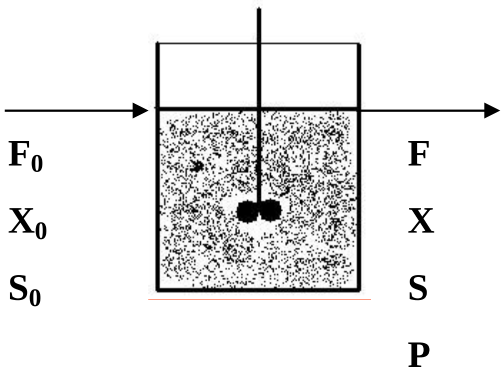
$$V_p = \frac{1}{x}\frac{dP}{dt} = \alpha\,\mu + \beta$$

III – Non-Growth Associated Product

$$r_P = Ax$$

2 – Continuous Reactor

2.1 – Mass balance to the cell concentration



$$\frac{dx}{dt} = \underbrace{\frac{F_0}{V}x_0}_{\text{Cells entering the reactor}} - \underbrace{\frac{F}{V}x}_{\text{Cells exiting the reactor}} + \underbrace{\mu x}_{\text{Cell growth}} - \underbrace{k_d x}_{\text{Cell death}}$$

For $x_0 = 0$ and $\mu \gg k_d$:

$$\frac{dx}{dt} = -\frac{F}{V}x + \mu x$$

$$\frac{F}{V} = D$$

D - dilution rate (h^{-1})

$$\frac{dx}{dt} = \mu x - Dx$$

In steady state:

$$\frac{dx}{dt} = 0$$

$$\boxed{\mu = D}$$

In steady state, without cell death and sterile feeding

2.2 – Mass balance to the substrate

$$\frac{dS}{dt} = \frac{F\,S_0}{V} - \frac{F\,S}{V} - \frac{1}{Y_{x/s}}\mu x - mx$$

Substrate entering the reactor

Substrate exiting the reactor

Substrate used for cell growth

Substrate used for maintenance

$\frac{F}{V} = D$

$$\frac{dS}{dt} = D\,S_0 - D\,S - \frac{1}{Y_{x/s}}\mu x - mx$$

if m is negligible (m « µ):

$$\frac{dS}{dt} = D\,(S_0 - S) - \frac{1}{Y_{x/s}}\mu x$$

In steady state $\frac{dS}{dt} = 0$ $\quad Y_{x/s}\,(S_0 - S) = x$

2.3 – Relationship between substrate concentration and cell concentration with dilution rate

$$\mu = \frac{\mu_{max}\, S}{K_s + S}$$

In a continuous reactor under steady state

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

$$Y_{x/s}\,(S_0 - S) = x \qquad x = Y_{x/s}\left(S_0 - \frac{K_s\, D}{\mu_{max} - D}\right)$$

critical washout rate D_c
(when x=0 and $D \sim \mu_{max}$)

$$D_c = \frac{\mu_{max}\, S_0}{K_s + S_0}$$

2.4 – Cell Productivity

productivity DX

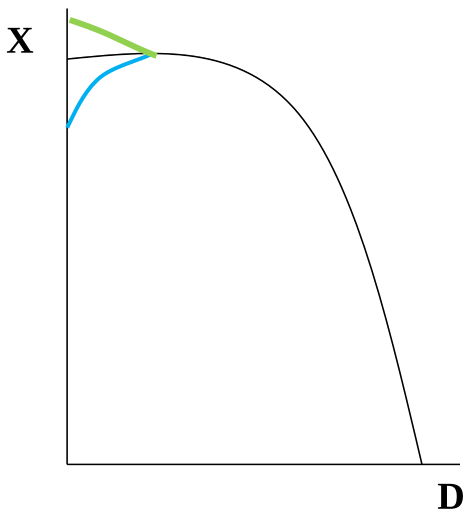
Maximum productivity
$$D_{max} = \mu_{max}\left[1 - \left(\frac{K_s}{K_s + S_0}\right)^{1/2}\right]$$

2.5 – Effect of the maintenance coefficient

Negligible cell maintance
$$x = Y_{x/s}\left(S_0 - \frac{K_s D}{\mu_{max} - D}\right)$$

Considering cell maintenance
$$x = \frac{D(S_0 - S)}{\frac{1}{Y'_{x/s}} D + m}$$

production of intracellular reserves



2.6 – Product production

$$\frac{dP}{dt} = -DP + Y_{p/x}\mu X$$

2.6.1- Product associated to growth

At steady-state

$$DP = Y_{p/x}\mu X$$ (Volumetric productivity (gP/l.h))

$$V_p = Y_{p/x}\,\mu$$ (Specific productivity (gP/gX.h))

2.6.2- Product partially associated to growth

Mass balance to the substrate:

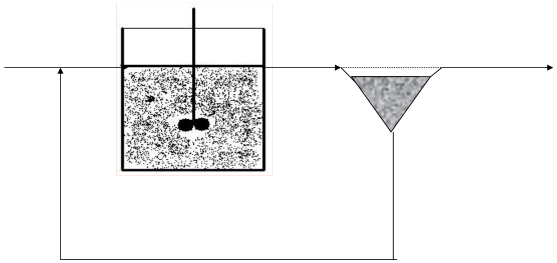
$$\frac{dS}{dt} = DS_0 - DS - \frac{1}{Y'_{x/s}}\mu X - \frac{1}{Y'_{p/s}} r_p - mX$$

r_p – volumetric rate of product formation (gP/l.h)

$$DP = \left(Y'_{p/x}\,\mu + m_p\right) X$$

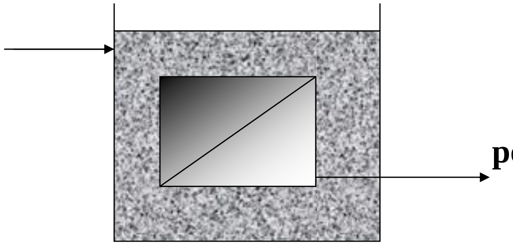
2.7 – Cell recirculation reactors

<u>With a decanter</u>

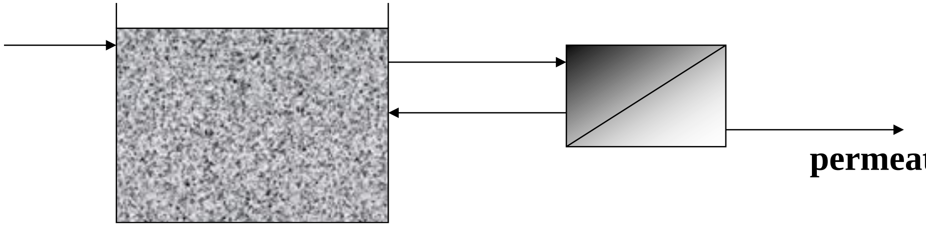


<u>Membrane bioreactors</u>

Submerged

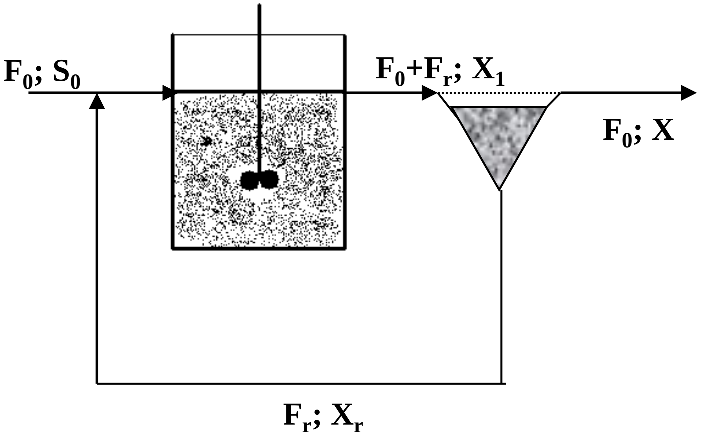


With cell recirculation



2.7 – Cell recirculation reactors

Balance to the biomass:



$$\frac{dX}{dt} = \frac{F_r}{V} X_r - \frac{F_0 + F_r}{V} X_1 + \mu X_1$$

Biomass entering the reactor

Biomass exiting the reactor

Cell growth

At steady-state $0 = F_r\ X_r - (F_0 + F_r)\ X_1 + \mu\, X_1 V$

Balance to the substrate:

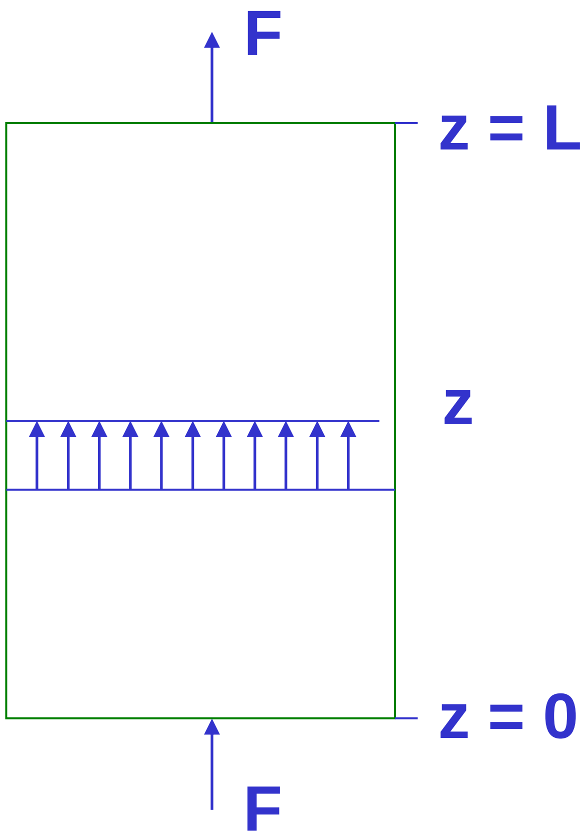
$$\frac{dS}{dt} = D(S_0 - S) - \frac{\mu X_1}{Y_{x/s}} = 0$$

3 – Plug Flow Reactor

3.1 – Definition

Geometry: cylindrical column

Operation: Continuous



Recovery of the product at the top

z – position on a vertical axis (m)

L - column height (m)

F - fluid flow rate in ascending flow (m^3/h)

A - cross section area (m^2)

d - diameter of the cylindrical column (m)

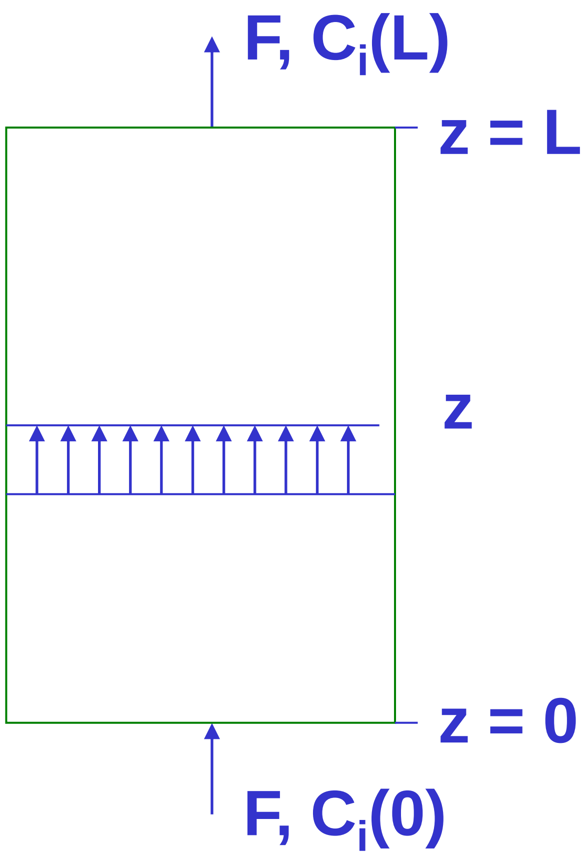
V = AL - column volume (m^3)

Inoculation and introduction of nutrients into the base

3.1 – Definition

Geometry: cylindrical column

Operation: Continuous



Ci(0) - concentration of a generic i component at the base of the column (kg/m^3)

Ci(L) - concentration of a generic i component at the top of the column (Kg/m^3)

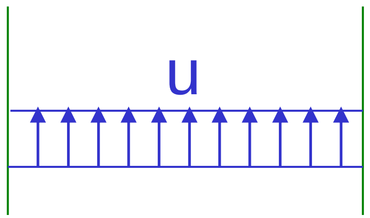
Ci(z) - concentration of a generic i component in a z position of the column (Kg/m^3)

u - axial velocity of the fluid inside the column (m/s)

$$\boxed{u = \frac{F}{A}}$$

3 – Plug Flow Reactor

3.1 – Definition



Velocity profile in plug flow **= CONSTANT**

Therefore:
all fluid elements move at the same velocity u.

⇨ plug flow $$Re = \frac{\rho\, u\, d}{\mu} > 2000$$ (Nº Reynolds)

ρ – Specific mass of fluid (Kg/m^3)

u – axial velocity of the fluid (m/s)

d – column diameter (m)

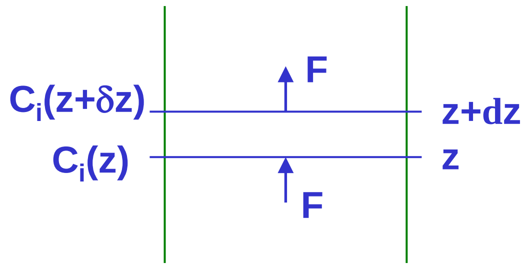
μ – Viscosity of the fluid (Pa.s)

PFR: TOTAL SEGREGATION
CSTR: PERFECT MIX

3 – Plug Flow Reactor

3.2 – Material balances

Material balance to the infinitesimal section of the column with height dz a generic ‘i’ component



Mass of ‘i’ that enters z per unit of time + **Mass of ‘i’ produced by reaction in Adz volume per unit of time** = **Mass of “i” leaving z+dz per unit of time**

$$FC_i(z) \quad + \quad r_i(z)Adz \quad = \quad FC_i(z+dz)$$

It's only true if dz is infinitely small

$$\boxed{r_i = u\frac{dC_i}{dz}}$$

Eq. of material to component ‘i’ em PFR

Note: r_i – volumetric rate of i production

3.3 – Kinetics

Example: product formation associated with growth (Type I)

Reaction: S $\longrightarrow$ X + P

Kinetics:

$$\mu = \frac{\mu_{max} S}{k_m + S}$$

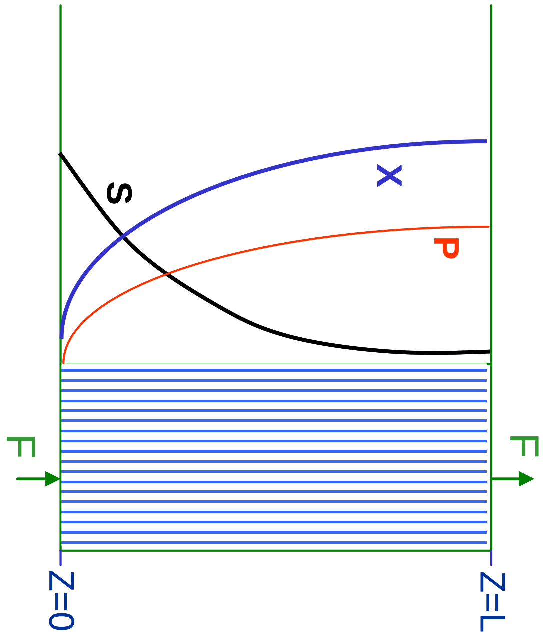
(assuming Monod kinetics)

Material balances:

$$u\frac{dX}{dz} = \mu X - k_d X - k_e X$$

$$u\frac{dS}{dz} = -\frac{\mu X}{y'_{XS}} - m_S X$$

$$u\frac{dP}{dz} = \frac{\mu X}{y'_{XP}}$$



Typical Concentration Profile for Type I Product

Analytical integration just for the case de μ≃μmax (high excess of S)

3.4 – Productivity

Volumetric productivity of product

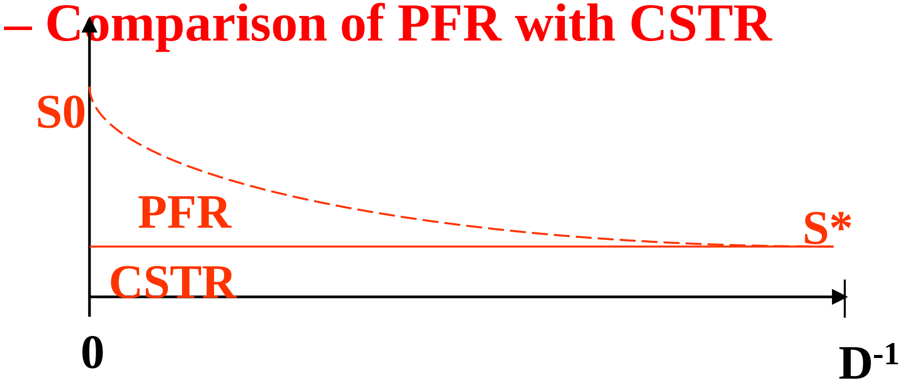
$$\boxed{\mathrm{Prod} = \frac{\mathrm{F\,P(z = L)}}{\mathrm{V}} = DP(z = L)}$$

g product l^{-1} h^{-1}

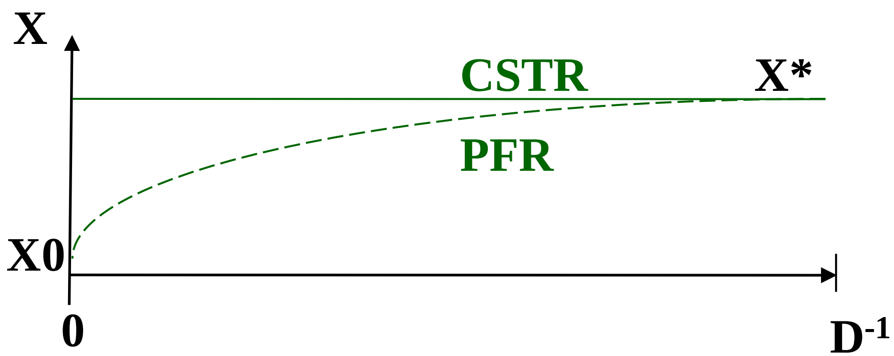
F	Flow rate (l/h)
P(z=L)	conc. of product at the top of the column (at the exit of the reactor) (g/l)
V	reactor volume (1)

3 – Plug Flow Reactor

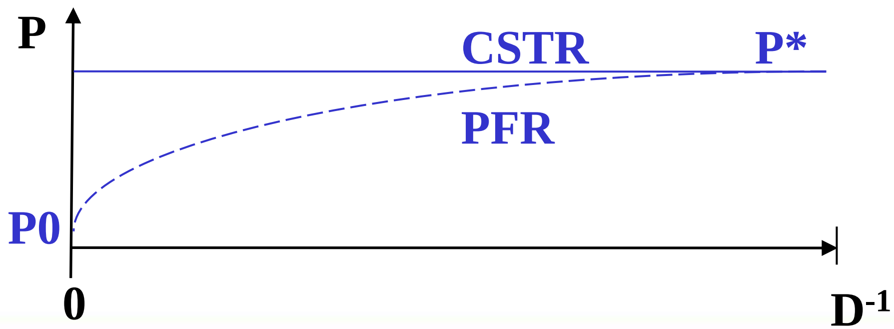
3.5 – Comparison of PFR with CSTR



$S_{PFR} \geq S_{CSTR}$



$X_{PFR} \leq X_{CSTR}$



$P_{PFR} \leq P_{CSTR}$

3.5 – Comparison of PFR with CSTR

Case 1: Negligible growth (X_{PFR}= X_{CSTR}= constant over time)

Kinetics	CSTR $V = \frac{F(S_0 - S^*)}{r(S^*)}$ S_{CSTR} P_{CSTR}		PFR $V = \frac{F(S_0 - S^*)}{\bar{r}_S}$ S_{PFR} P_{PFR}
		$<$ $>$	
Order 0 $r_S = k_0$ (indepedent of S)	=		=
Order 'n' $r_S = k\,S^n$	---		+++
Michaelis-Menten $r_S = \frac{r_{S\max} S}{K_m + S}$	---		+++
Inhibition by S (S ↗ r_s ↘)	+++		---
Inhibition by produt (P ↗ rs ↘)	---		+++

Note: the signs "+++" refer to the best reactor and "---" to the worst reactor

3.5 – Comparison of PFR with CSTR

Case 2: significant cell growth (i.e. autocatalytic kinetics)

	CSTR		PFR
	$V = \dfrac{F(S_0 - S^*)}{r\ (S^*)}$		$V = \dfrac{F(S_0 - S^*)}{\bar{r}_S}$
	X_{CSTR}	$>$	X_{PFR}
Autocatalitic $r_s = v_s\ X$	+++		---

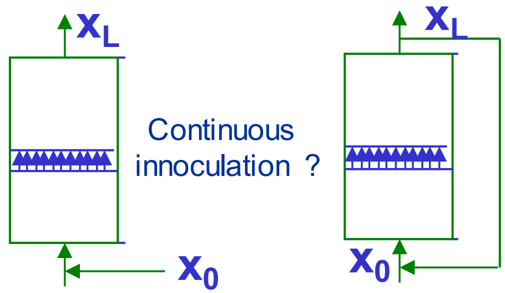
∴ Biocatalysis with cells (bacteria, fungi, animal cell lines) CSTR tends to be more productive

∴ Biocatalysis with enzymes PFR tends to be more productive

3 – Plug Flow Reactor

3.6 – Discussion about PFR

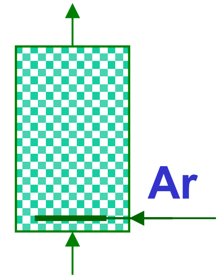
1. How to do Innoculation?



Continuous innoculation ?

Output Recycle to entrance !

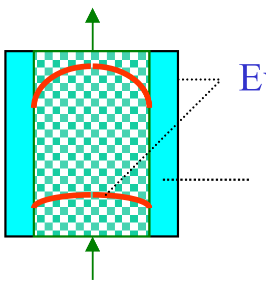
2. How to make areation?



Bubbling at the bottom of the reactor promotes mixing.
PFR tends to CSTR

3. How to control temperature?

heat transport less efficient than in CSTR



Evolution of temperature profile

Cooling jacket

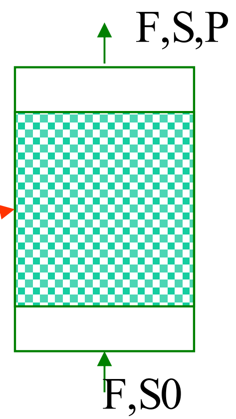
4. How to control pH?

5. How to control the concentration of any component?

PFR with cells in suspension (and remarkable cell growth) is an impractical construct. It can, however, occur in practice in association with other bioreactors (example: plug flow associated with CSTRs)

3.6 – Discussion about PFR

Exception: tubular bioreactor with immobilized cells (or enzymes)



solid support
Cells grow adherent to solid support or 'incarcerated' in a polymer matrix

- Very stable cultures that remain viable for long periods of time (months, years)
- Cells at rest (low maintenance)
- High cell density (much higher than cells in suspension). Cells grow adherent and form biofilms
- After a growth phase, cell density remains constant over time (new cells simply replace the dying cells)
- Higher dilution rates because washout cannot occur

μ negligible
⇒kinetically favorable to the PFR regarding the CSTR