CBE 40445

11/9/20

(LAST CLASS)

- A LITTLE MORE "BIO"
- SEMI BATCH
  - WHY DO?
- BATCH W/ REFILL
  CLEAN OUT
  - HOW LONG DO YOU LET REACTION RUN
- MULTIPHASE FLOW IN PACKED BED REACTORS

SOME BASIC ENGINEERING CONSIDERATIONS

OXYGEN UPTAKE — "OFTEN LIMITING FACTOR"

IT IS POSSIBLE THAT O_2 ABOVE A CERTAIN CONCENTRATION IS TOXIC

OPTIMUM ~ 5 - 80 % OF SATURATION/AIR

BUBBLES → CAN BURST / COALLESCE AND ACAUSE CELL DAMAGE

⇒ CAN RISE TO SURFACE AND CARRY CELLS WITH THEM.

Table 2.6 Range of cell specific oxygen uptake rates q_{O_2} of different cell lines under non-limiting conditions (adapted from (Henzler and Kauling 1993; Zeng and Bi 2006))

Cell line	q_{O_2} [10^{-10} mmol cell^{-1} h^{-1}]
FS-4	0.5
HeLa	5
Skin fibroblasts	0.6
BHK 21	1–2
MRC-5	1.5
Human hybridom	0.2
Mouse hybridom	1–5
Melanoma	0.7–1
CHO	2–8

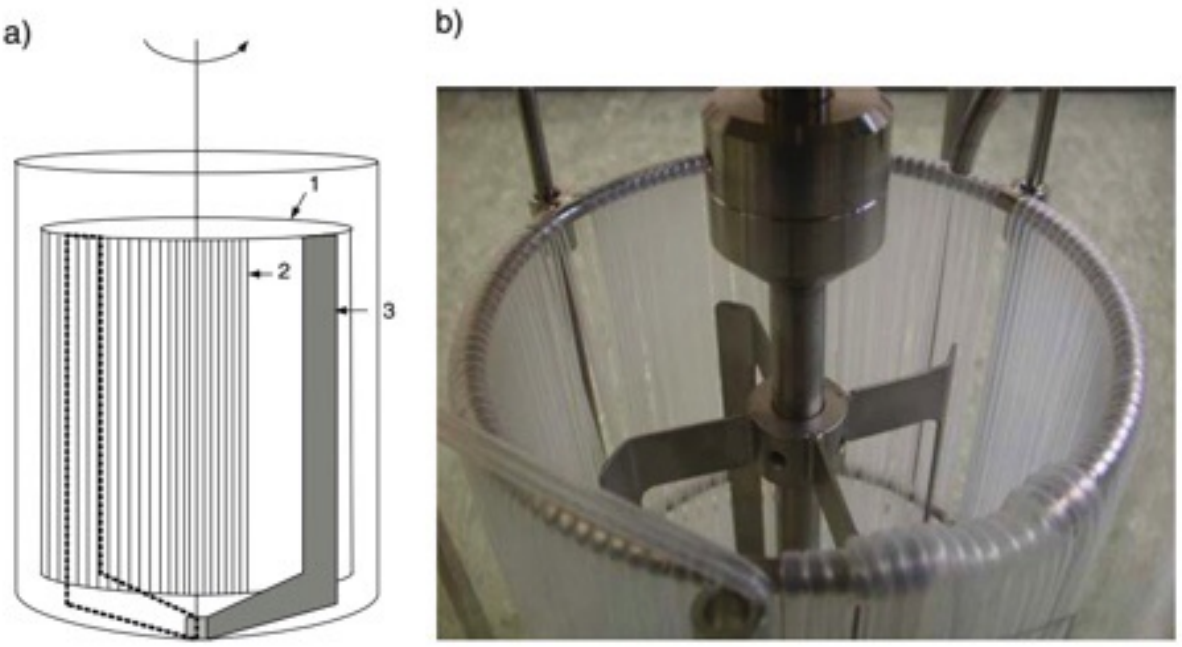


Fig. 4.24 (**a**) Schematic of a standard membrane aeration system (1) membrane basket (2) silicone tubing (3) anchor stirrer (**b**) photograph of membrane basket and anchor stirrer (with courtesy from Bayer Technology Services GmbH, Germany)

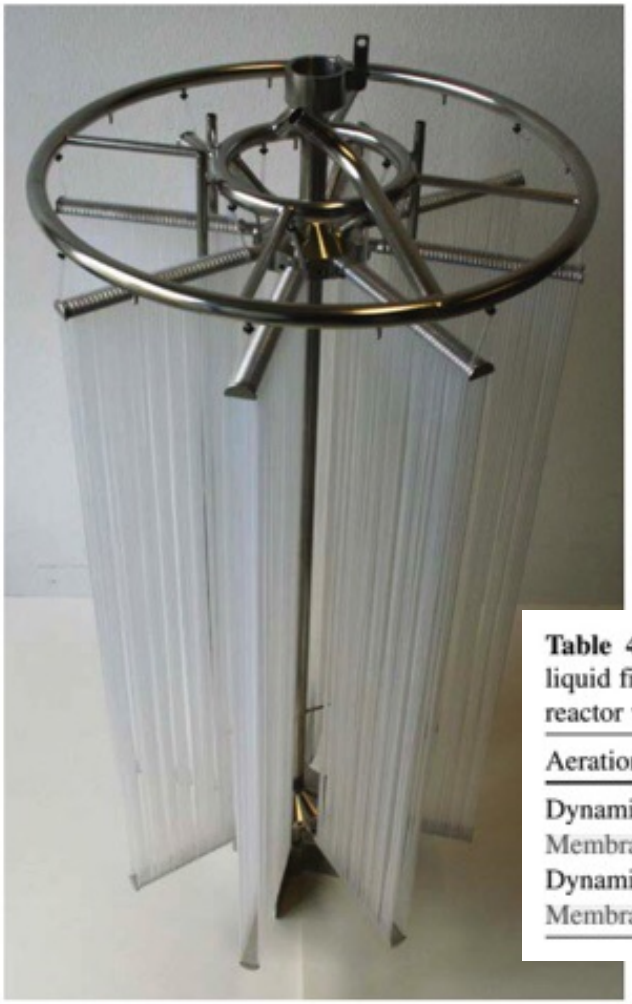


Fig. 4.25 Photograph of the dynamic membrane aeration system (DMA) for a 200 L cell culture reactor (with courtesy from Bayer Technology Services GmbH, Germany)

Table 4.4 Mass transfer coefficient for oxygen (membrane and liquid film) in dependence of power input per liquid volume (100 L reactor volume) adapted from (Frahm et al. 2007)

Aeration system	P/V (W m^{-3})	k (m h^{-1})
Dynamic membrane aeration	10	0.075
Membrane stator	10	0.055
Dynamic membrane aeration	100	0.09
Membrane stator	100	0.07

$$dc/dt = k_L a(c^* - c_L) - \text{OUR X} \quad (4.18)$$

with:

k_La: mass transfer coefficient, which is the product of k_L, the overall mass transfer coefficient from the gas to the liquid phase (two film model), and a, the gas–liquid interfacial area per unit of the reactor liquid volume (s^{-1})

c_L: concentration of oxygen in solution (kg m^{-3})

c^*: equilibrium solubility of oxygen – oxygen saturation (kg m^{-3})

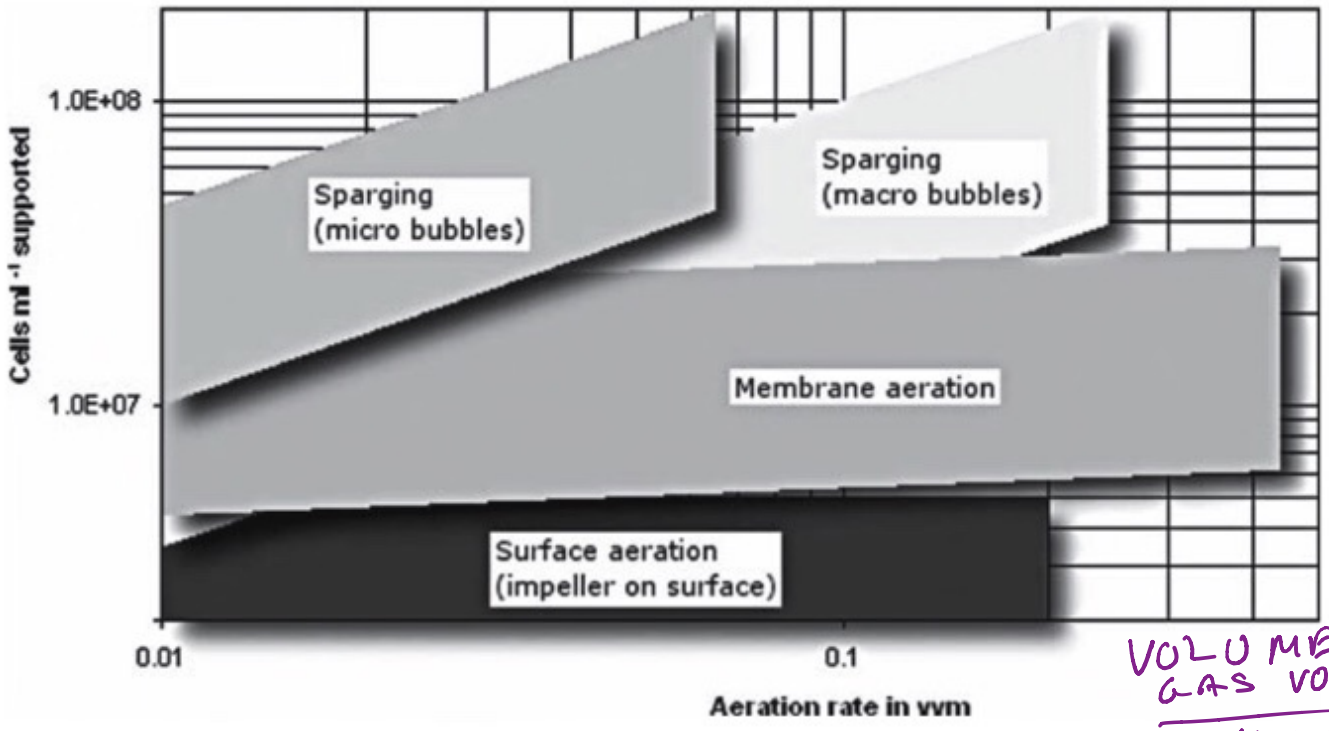
X: cell density (cells L^{-1})

OUR: oxygen uptake rate (kg O_2 10^{-6} cells s^{-1})

t: time (s)

The oxygen transfer rate (OTR) is given by:

$$\text{OTR} = k_L a(c^* - c_L) \quad (4.19)$$



VOLUME OF GAS VOLUME / MINUTE

Fig. 4.26 Limitations in cell density based on oxygen delivery in different aeration systems (adapted from Ozturk (1996) with kind permission of Springer Science and Business Media)

Table 5.7 Volume specific productivity for monoclonal antibodies of hybridom cells grown continuously in fixed bed or fluidized bed bioreactors and in batch suspension culture

Reference	Culture system	Carrier	Antibody productivity (mg L^{-1} d^{-1})	Antibody productivity related to productivity in batch suspension culture
Fassnacht (2001)	Batch suspension		5	1
	Fixed bed	SIRAN, 3–5 mm	450[a]	90
Celonic (2007)	Batch suspension		8	1
	Fluidized bed	SIRAN, 0.7 mm	435[b]	54
Lundgren and Blüml (1998)	Batch suspension		2.5	1
	Fluidized bed	Cytoline 1	40[b]	16
	Fluidized bed	Cytoline 2	110[b]	44

[a]Productivity related to the fixed bed volume
[b]Productivity related to the carrier volume

SENSITIVITY TO SHEAR

THE CELL MEMBRANE IS COMPOSED OF PHOSPHOLIPIDS THAT BUILD A DOUBLE LAYER

THIS CAN BE DISRUPTED BY SHEAR STRESS PRESENT IN FLUID FLOW

ALSO! SOME CELLS DIFFERENTIATE BASED ON MAGNITUDE OF SHEAR

EQ

$$\tau_{CRIT}\,\lambda_2^2 = 2\lambda_2\,\sigma_2$$

$$\tau_{CRIT} = \frac{2\sigma_2}{\lambda_2}$$

$\sigma_2 \sim 2\times10^{-3}\ N/m$

$\lambda_2 = 50\ \mu m$

$\tau_{CRIT} \sim 600\ N/m^2$

RECALL $\Delta P = \frac{2\sigma}{R}$, $\sigma = 72\ \frac{N}{m}$

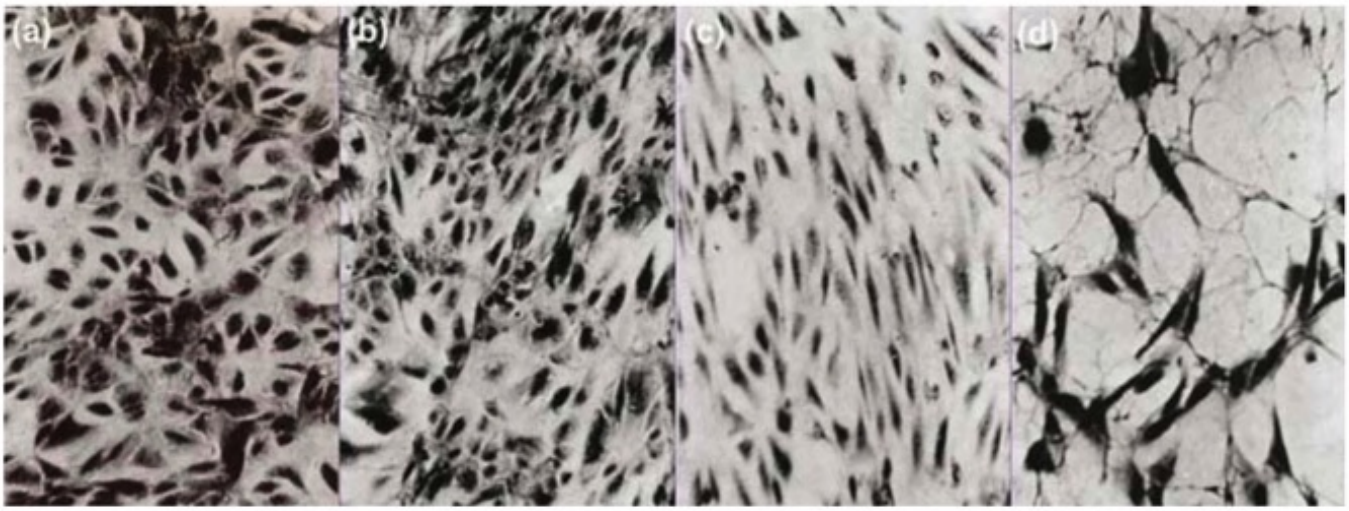


Fig. 4.3 Effect of shear stress on adherent growing primary epithelial cells in a flow chamber after (**a**) 1 week of culture without shear stress (controls), (**b**) 4 h with a shear stress of 1.3 Nm^{-2} (**c**) 24 h with a shear stress of 1.3 Nm^{-2}, (**d**) 24 h with a shear stress of 5.4 Nm^{-2} (adapted from Stathopoulos and Hellums 1985, with kind permission of John Wiley & Sons)

Fig. 4.27 5–10 mm foam layer at the medium surface (cell line: CHO-easyC – CHO-K1 derived line, Cell Culture Technologies GmbH, Zürich, Switzerland; CHO-master HP-1 medium; aerated with a ceramic micro sparger Fig. 4.18

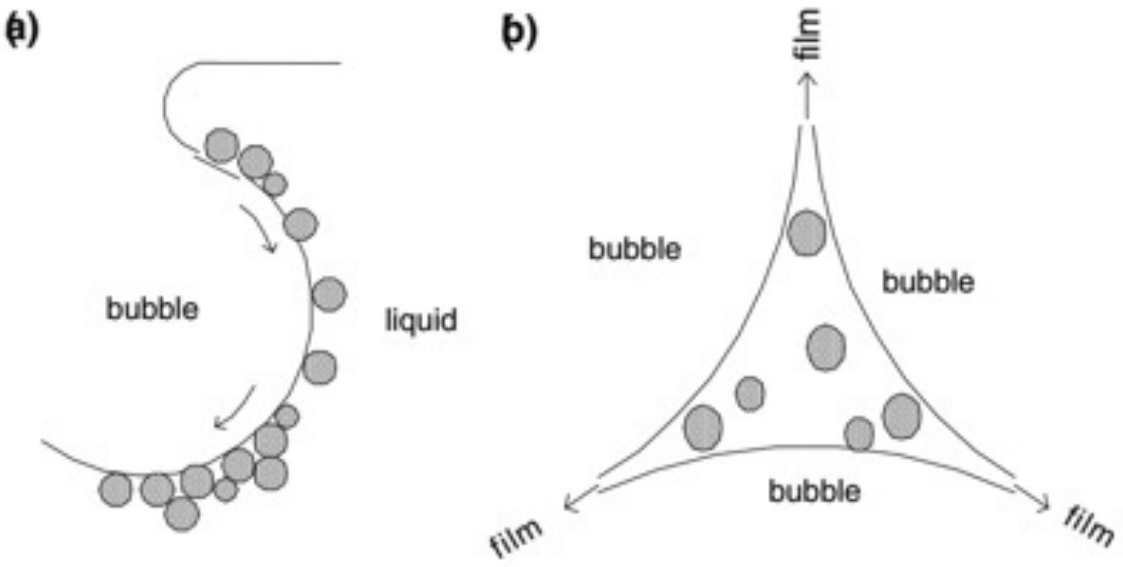


Fig. 4.7 Cell damage in a foam layer (adapted from Papoutsakis 1991, with kind permission of Elsevier). (a) cells near the bubble interface, large shear stress due to bubble break up, (b) cells are sheared in the thinning films either between bubbles or around bubbles

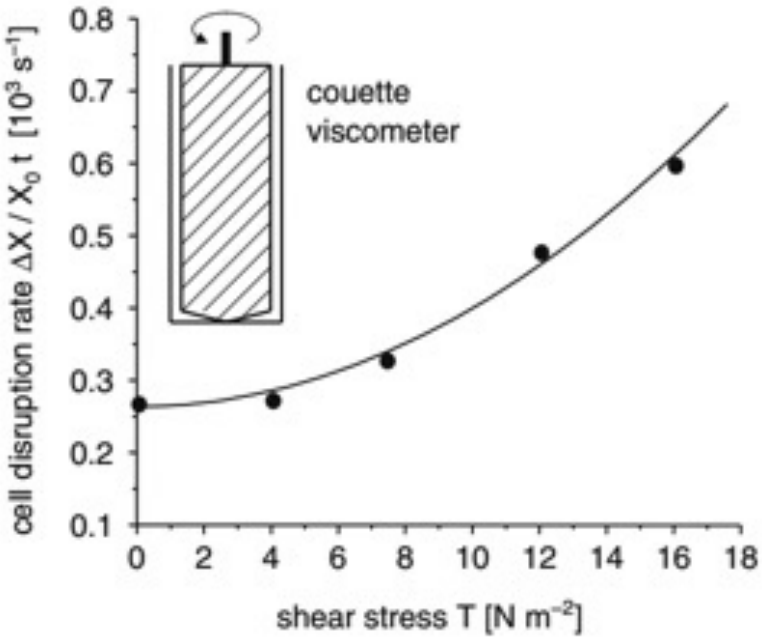


Fig. 4.5 Influence of shear stress on the cell disruption rate of hybriodm cells in a couette viscosimeter (adapted from Kramer 1988)

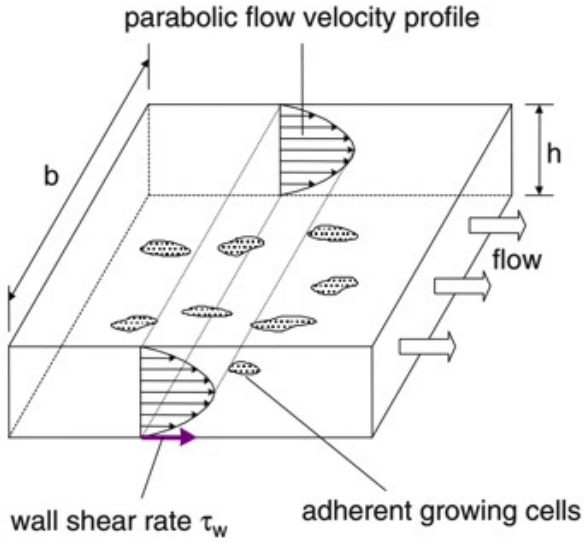


Fig. 4.2 Determination of wall shear rate in a flow chamber for investigation of shear effects on adherent cells

SHEAR STRESS ON THE WALL OF A CHANNEL

$$\tau_{WALL} = \mu \frac{\partial u}{\partial y}$$

$$u(y) = \frac{6\left(-\frac{dP}{dx}\right)}{bh^3}\left(hy - y^2\right)$$

$$\tau_w = \frac{6\mu\left|-\frac{dP}{dx}\right|}{bh^2}$$

2.5 Kinetic Modelling of Cell Growth and Metabolism

2.5.1 Introduction to Kinetic Modelling for Mammalian Cells

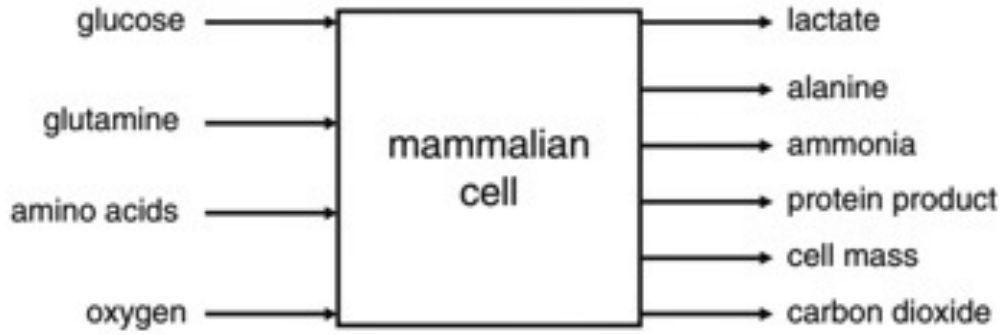


Fig. 2.9 Simplified diagram of material flows of growth and metabolism of mammalian cell cultures

2.5.2.1 Cell Specific Growth and Death Rate

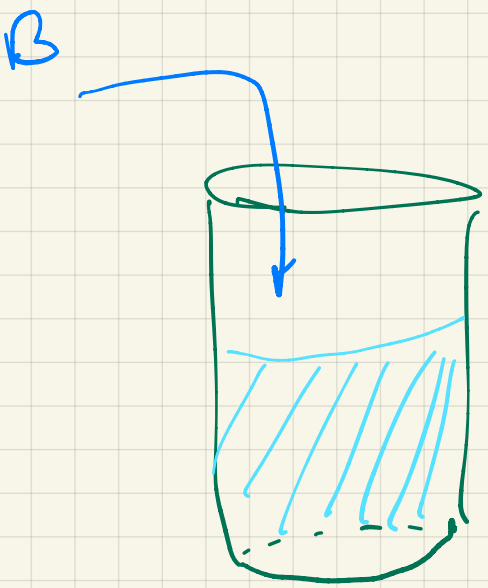
Formal equations for cell specific growth rate, defined as the number of new cells produced per unit of living cells present in the culture medium per unit time, can be derived from a Monod-type equation

$$\mu = \frac{\mu_{\max} c_s}{k_s + c_s}, \tag{2.1}$$

where μ_{max} is the maximum specific growth rate, c_S is the concentration of the controlling substrate such as glucose, and k_S is the concentration of the controlling substrate where the specific rate is half of the maximum rate (Adams et al. 2007) .

WE HAVEN'T TALKED ABOUT SEMI-BATCH ...

WHY WOULD YOU DO IT?



$A + B \rightarrow M$

M IS DESIRED

N IS NOT!!

SLOWLY ADD B, KEEP CONCENTRATION LOW

$$A + B \xrightarrow{k_1} M + B \xrightarrow{k_2} N$$

$k_1 > k_2$ BUT NOT BY MANY ORDERS OF MAGNITUDE

REACTION + A ARE AT HIGHER T, OR DIFFERENT pH FROM B THUS

$B + B \rightarrow S$

ALSO UNDESIRED

MAKING GRAVY

CORNSTARCH/WATER WILL MAKE LUMPS IF YOU ADD IT TOO FAST!!

$$A + B \rightarrow M$$

$$\frac{d}{dt} V C_A = -k C_A C_B V$$

$$\frac{d}{dt} V C_B = q C_{B0} - k C_A C_B V$$

$$V = V_0 + q t$$

$$\frac{d}{dt}\left(C_A (V_0 + q t)\right) = -k C_A C_B (V_0 + q t)$$

$$\frac{d}{dt}\left(C_B (V_0 + q t)\right) = q C_{B0} - k C_A C_B (V_0 + q t)$$

```
Plot[{ca[t] /. ansbatch[[1]], cb[t] /. ansbatch[[1]], cm[t] /. ansbatch[[1]], cn[t] /. ansbatch[[1]]},
 {t, 0, 100}, AxesLabel → {"time (s)", "moles A and B in reactor"}, PlotLegends → "Expressions",
 PlotStyle → {Red, Green, Blue, Purple}, PlotRange → {0, 1}]
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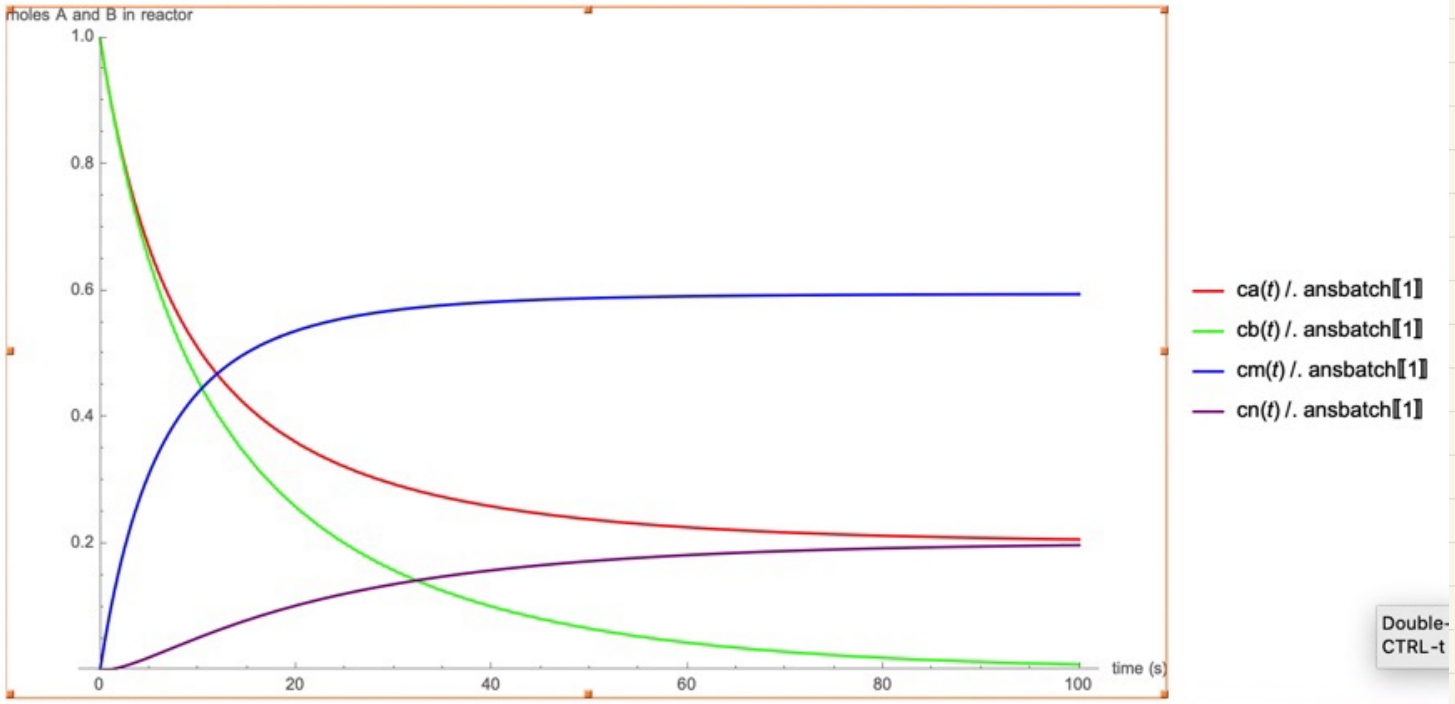

Double-
CTRL-t

```
Plot[{ca[t] /. anssbatch[[1]], cb[t] /. anssbatch[[1]], cm[t] /. anssbatch[[1]], cn[t] /. anssbatch[[1]]},
 {t, 0, 100}, AxesLabel → {"time (s)", "moles A and B in reactor"}, PlotLegends → "Expressions",
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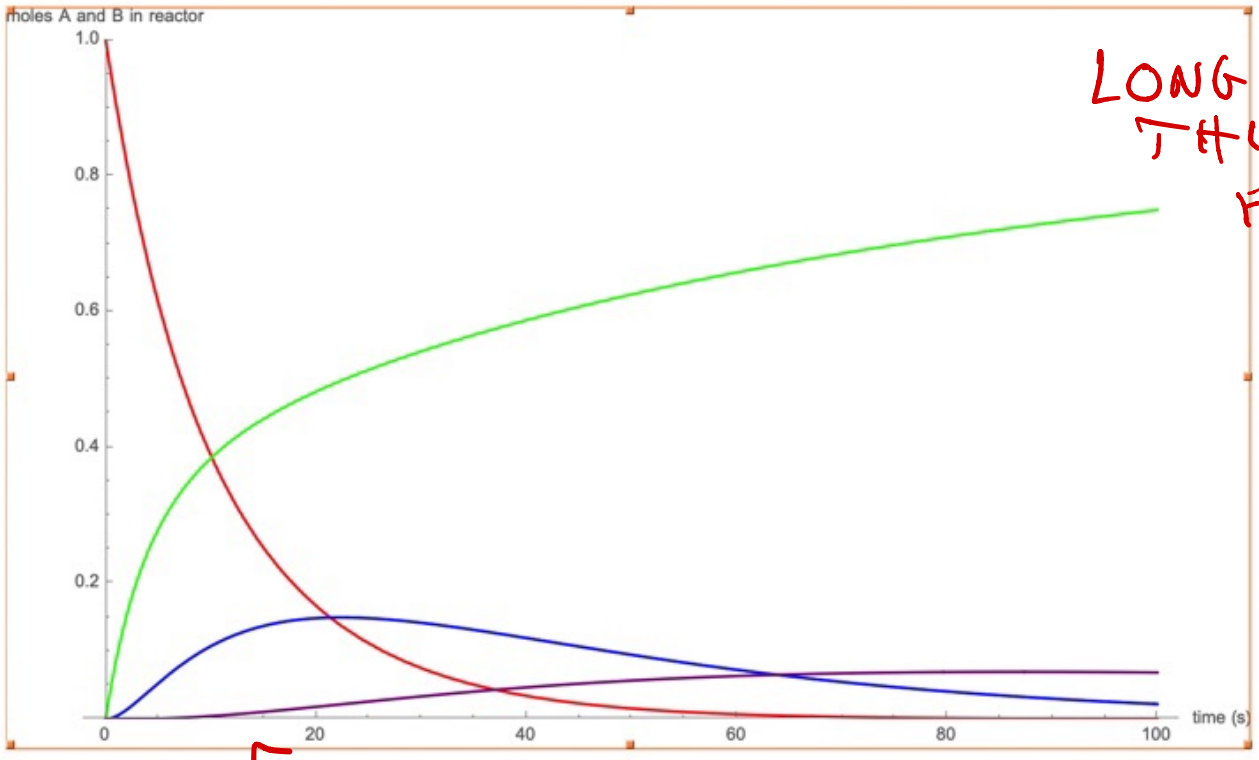
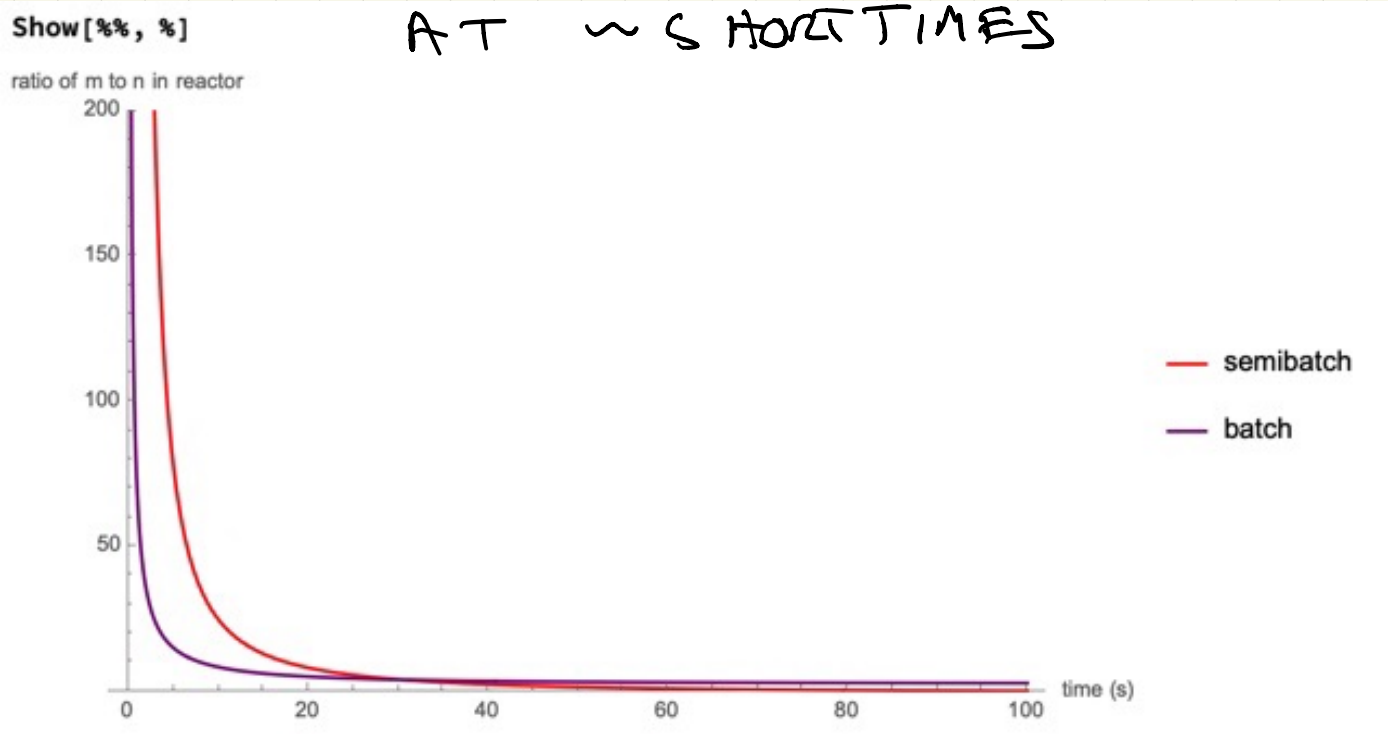


LONG TERM THIS DOESN'T HELP

GOOD FOR SHORT TIMES

CAN GET GOOD SELECTIVITY AT ~5 HOUR TIMES



FOR BATCH PROCESSING

$$\frac{\text{MOLES}}{\text{TIME}} = \frac{\text{MOLES}}{\text{BATCH}} \times \frac{\text{BATCH}}{\text{TIME}}$$

$$\simeq \frac{C_{Af} \times V}{t_B}$$

THEN WE SAID SOMETHING LIKE

$$\exp(-4) \leq .02$$

SO BATCH TIME (FIRST ORDER)

$$t = \frac{4}{k}$$

THIS MAXIMIZES CONVERSION

BUT WHAT IF WE NEED TO INCLUDE DOWNTIME ?

NOW INCLUDE:

DRAIN, CLEANOUT, REFILL = t_f

0 ORDER KINETICS

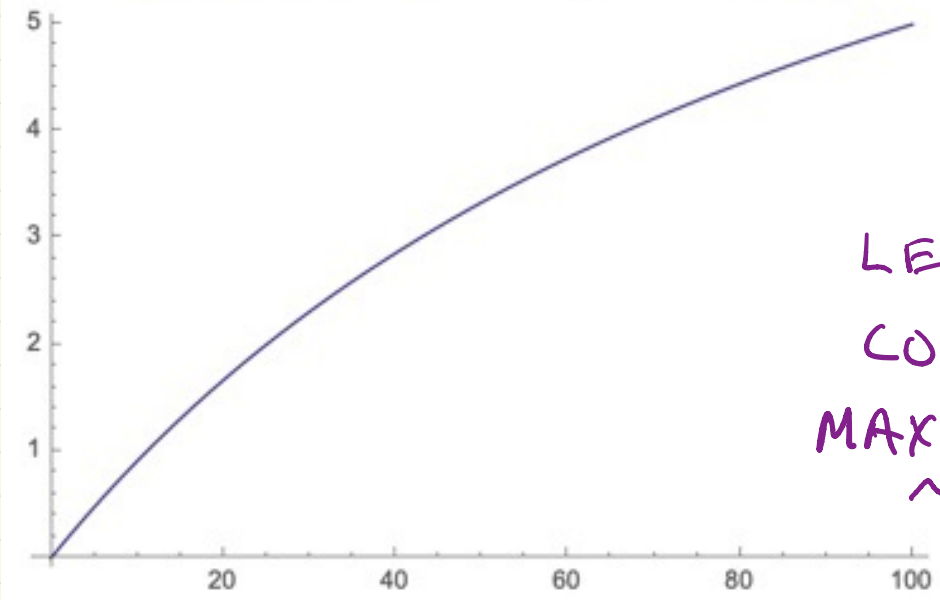
$$\text{RATE} = k^0$$

AMOUNT PRODUCED:

$$k^0 t V$$

$$\text{PRODUCTION} = \frac{k^0 t V}{(t_f + t)}$$

```
Plot[Production0 /. {k → .1, V → 100, tfixed → 100}, {t, 0, 100}]
```



LET GO TO COMPLETION

MAX IS: $kV = 10$

$\sim T > 800$

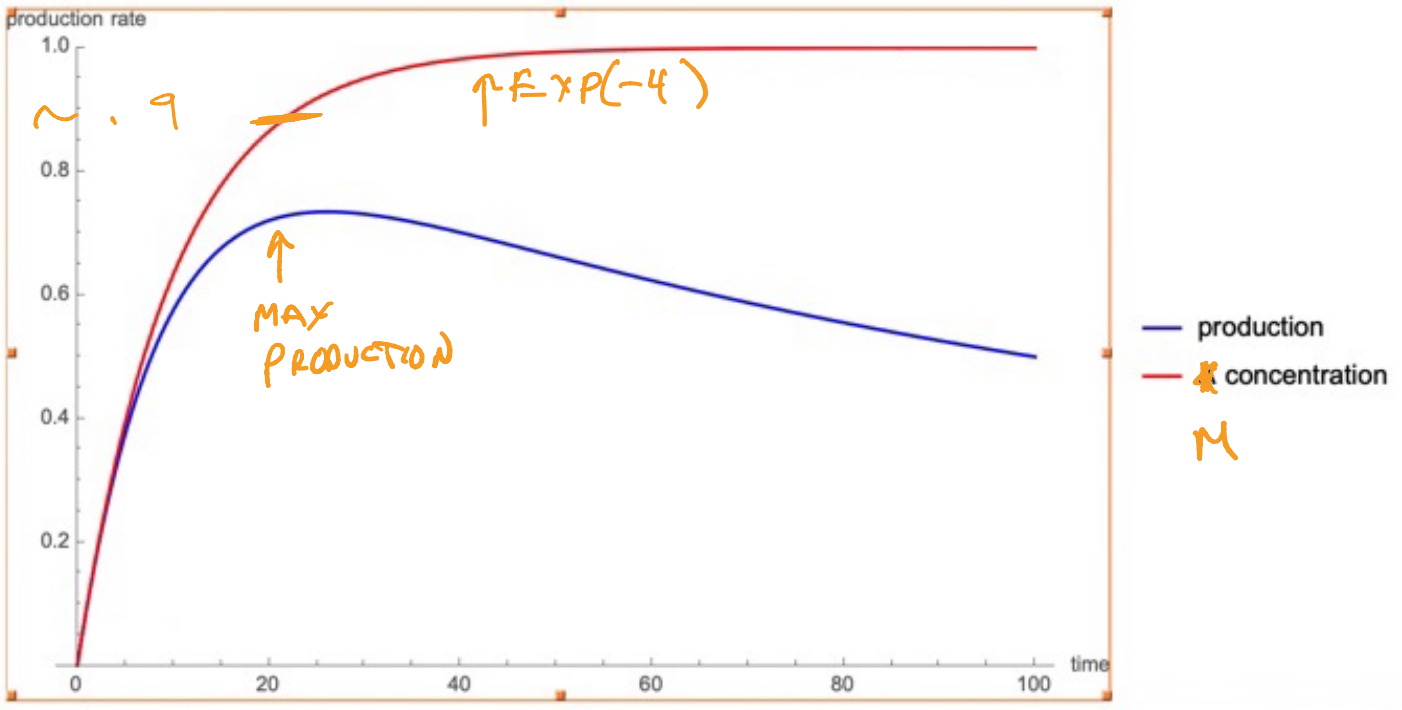
TIME

1ST ORDER KINETICS

$$A \rightarrow M$$

$$\text{PRODUCTION} = \frac{C_{A0}\left(1 - \exp(-kt)\right) V}{(t_f + t)}$$

```
Plot[{(Production1 /. {k → .1, Ca0 → 1, V → 100, tfixed → 100}), 1 - Exp[-.1 t]}, {t, 0, 100},
 PlotRange → {0, 1}, AxesLabel → {"time", "production rate"}, PlotStyle → {Blue, Red},
 PlotLegends → {"production", "A concentration"}]
```



WITH SOME WORK BEYOND TAKING THE DERIVATIVE:

$$t(\text{MAX PRODUCTION}) = \frac{\ln(1+kt_s)}{k}$$

$$\exp(kt) > k(t+t_s)$$

FOR SMALL k

$$t_{MAX} = \sqrt{\frac{2t_s}{k}}$$

GAS - LIQUID FLOW IN A PACKED BED

"TRICKLE FLOW"

"PULSING FLOW"

MASS TRANSFER BEHAVIOR IS DIFFERENT, CAN THIS AFFECT REACTION OUTCOME?

https://studio.youtube.com/video/EnTgCmSzNNA/edit

PERGAMON

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Chemical Engineering Science

www.elsevier.com/locate/ces

Phenylacetylene hydrogenation in a three-phase catalytic packed-bed reactor: experiments and model

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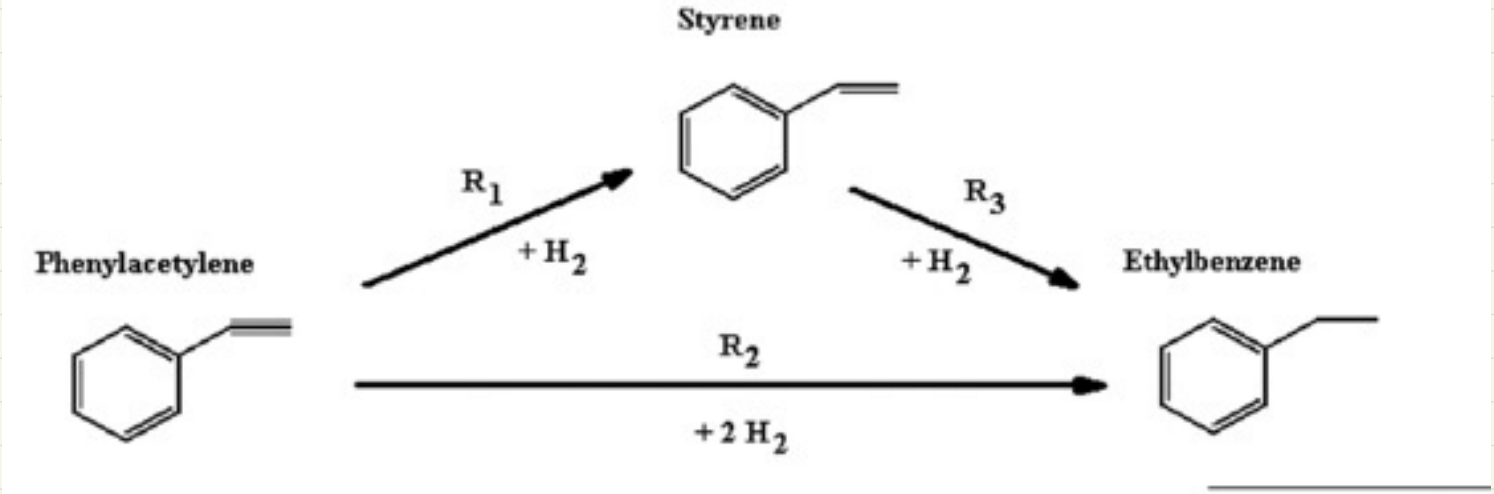
Received 23 September 2002; accepted 30 January 2003

catalyst:



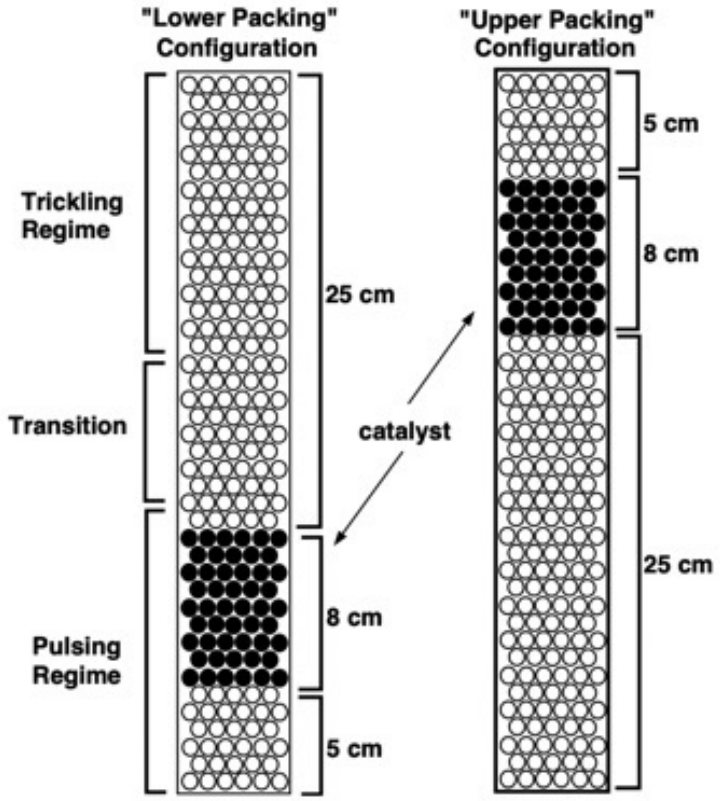


Fig. 1. Schematic diagram of lower- and upper-packing configurations. (●) catalyst, (○) inert packing.

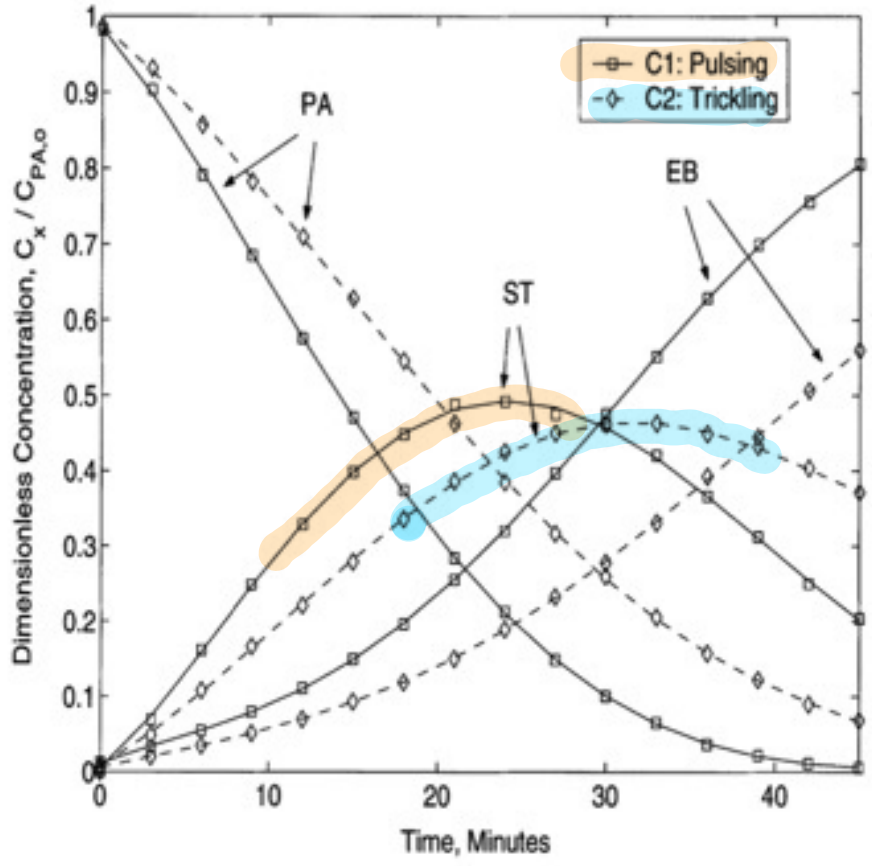


Figure 6. Reactor performance for Series C experiments.