Análise de modos elementares

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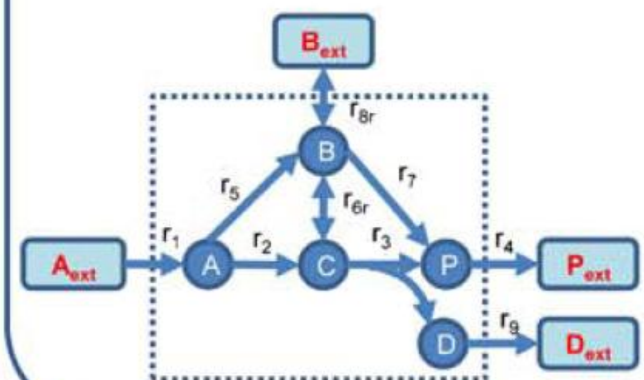
analysis of cellular metabolism

Problem statement

Network



Stoichiometric reactions

r_1: $A_{ext} \rightarrow A$ r_4: $P \rightarrow P_{ext}$ r_7: $B \rightarrow 2P$

r_2: $A \rightarrow C$ r_5: $A \rightarrow B$ r_{8r}: $B \leftrightarrow B_{ext}$

r_3: $C \rightarrow P + D$ r_{6r}: $B \leftrightarrow C$ r_9: $D \rightarrow D_{ext}$

Stoichiometric matrix

$\underline{\underline{S}} =$

	r_1	r_2	r_3	r_4	r_5	r_{6r}	r_7	r_{8r}	r_9
A	1	-1	0	0	-1	0	0	0	0
B	0	0	0	0	1	-1	-1	-1	0
C	0	1	-1	0	0	1	0	0	0
D	0	0	1	0	0	0	0	0	-1
P	0	0	1	-1	0	0	2	0	0

$\underline{r} = [r_1\ r_2\ r_3\ r_4\ r_5\ r_{6r}\ r_7\ r_{8r}\ r_9]^T$

Equations to solve **A**

$\underline{\underline{S}} \cdot \underline{r} = \underline{0}$

Thermodynamic constraints:

$r_{1\text{-}5,7,9} \geq 0$

$$\frac{d}{dt}\underline{C} = \underline{\underline{S}} \times \underline{r} - \mu \times \underline{C},$$

μ.C (negligible)

dC/dt = 0 (steady state)

S.r = 0 (Eq 2)

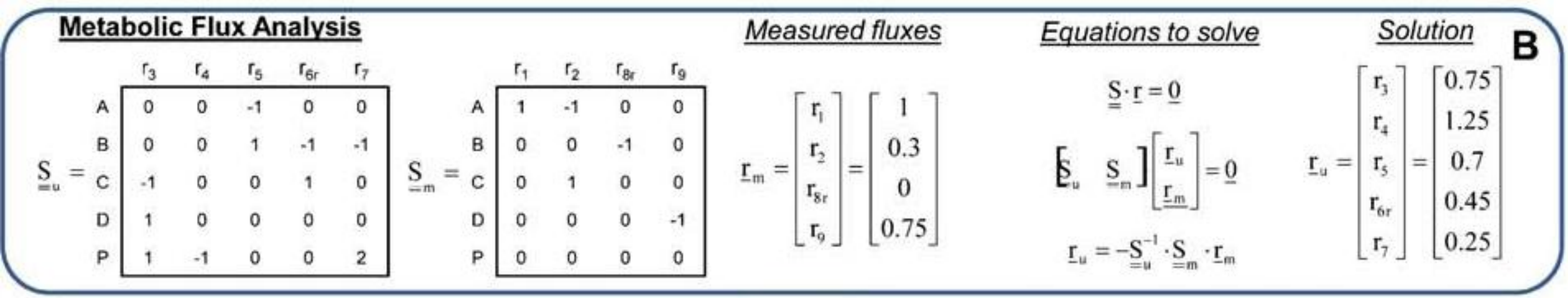
ri $\geq$ 0 (Eq 3)

Tools for analysis of cellular metabolism can be grouped into three categories, all of them developed from the same mathematical model:

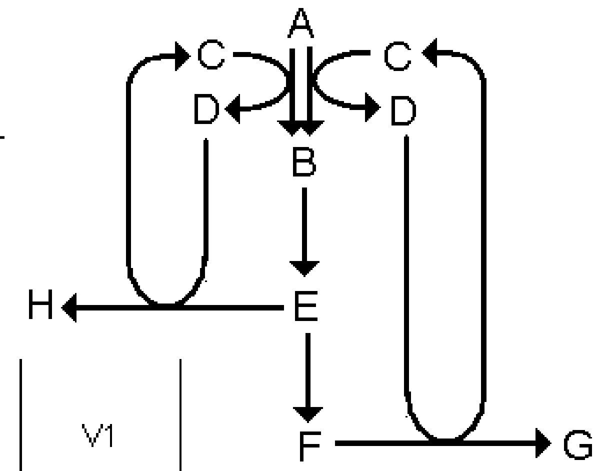
(1) Metabolic flux analysis,

(2) Flux balance analysis and

(3) Metabolic pathway analysis (Elementary mode analysis).



A	B	E	F	C	D	G	H	
-1	1	0	0	-1	1	0	0	V1
0	-1	1	0	0	0	0	0	V2
0	0	-1	1	0	0	0	0	V3
0	0	0	-1	1	-1	1	0	V4
0	0	-1	0	1	-1	0	1	V5



$$F = J - K$$

Flux Balance Analysis

C

Obj: max r_4

s.t.: $\underline{\underline{S}} \cdot \underline{r} = \underline{0}$

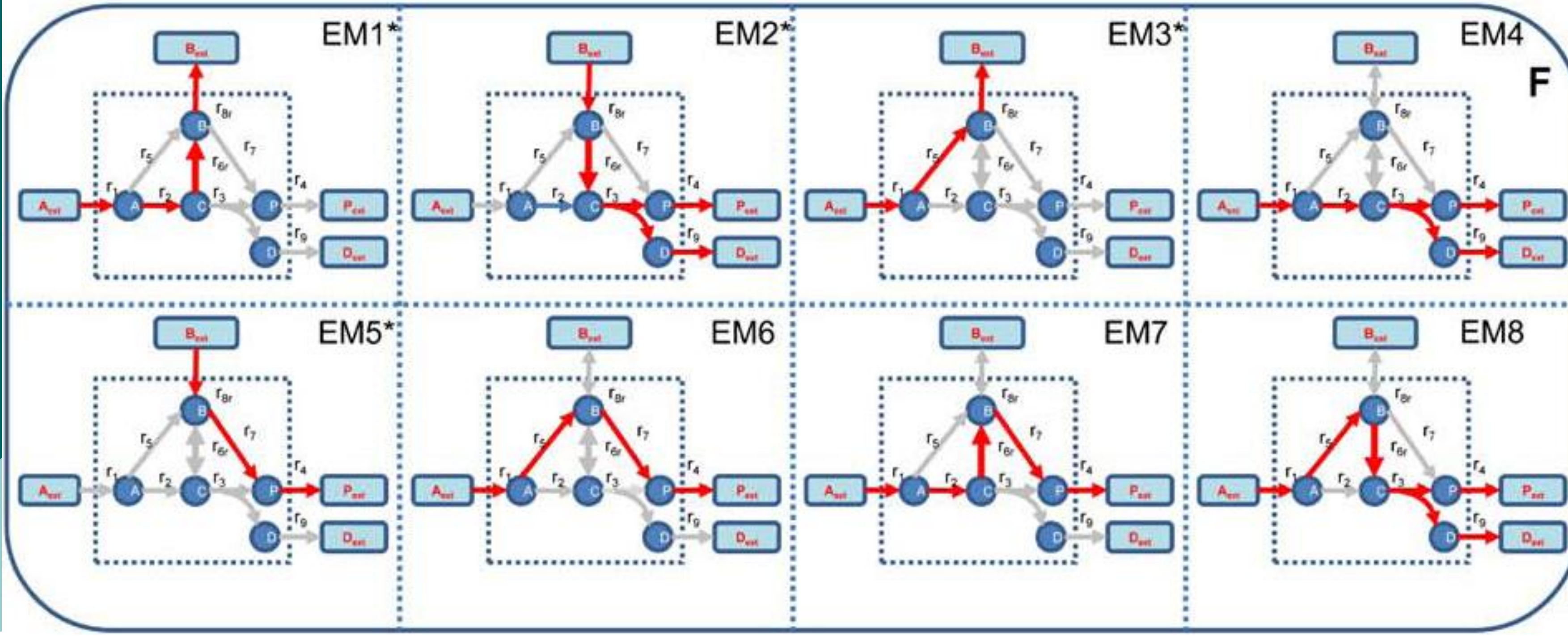
$r_1 = 1$

$r_{8r} = 0$

$r_{2\text{-}5,7,9} \geq 0$

$$\underline{r} = \begin{bmatrix} r_1 \\ r_2 \\ r_3 \\ r_4 \\ r_5 \\ r_{6r} \\ r_7 \\ r_{8r} \\ r_9 \end{bmatrix} = \begin{bmatrix} 1 \\ 0.35 \\ 0 \\ 2 \\ 0.65 \\ -0.35 \\ 1 \\ 0 \\ 0 \end{bmatrix}$$

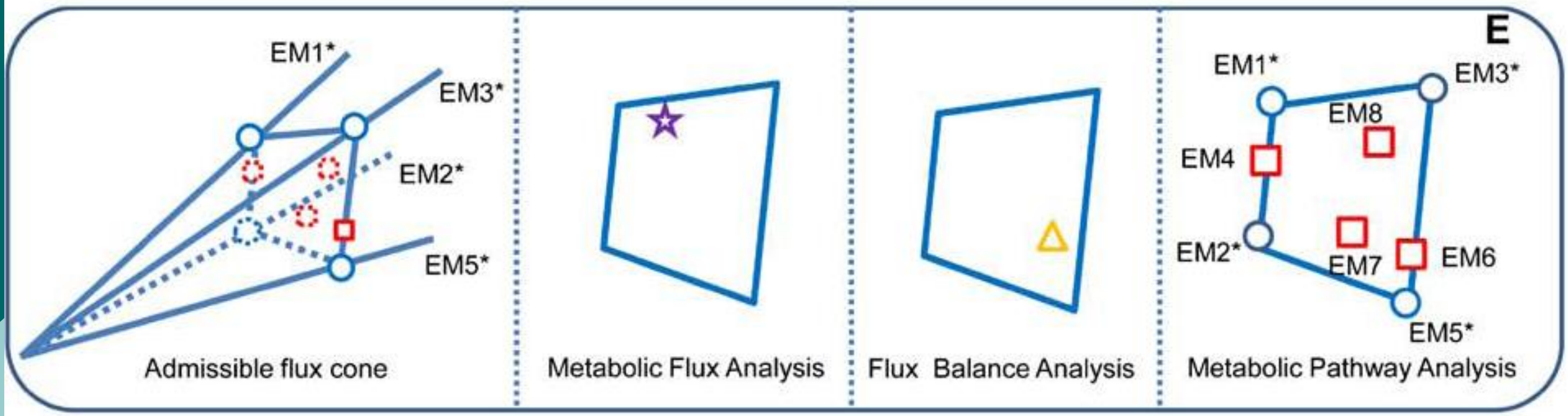
Metabolic pathway analysis (Elementary (flux) analysis)



S.r = 0 (Eq 2)   ri $\geq$ 0 (Eq 3)

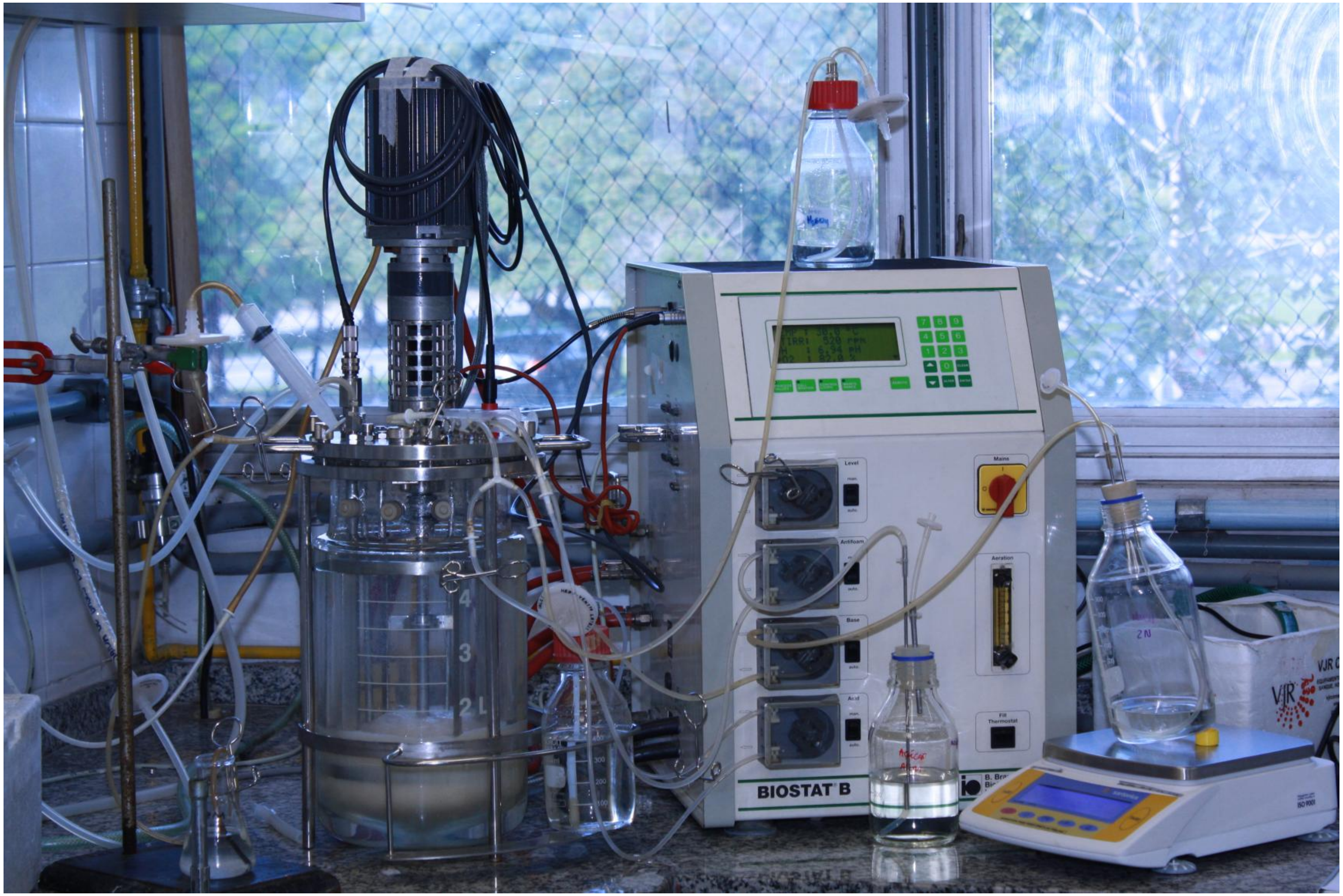
Elementary mode analysis calculates all solutions in the admissible flux space by solving Eq 2 in conjunction with the thermodynamic constraint (3) and additional non-decomposability and systematic independence constraints. Each solution (re)presents an elementary (flux) mode.

Interpretação Geométrica



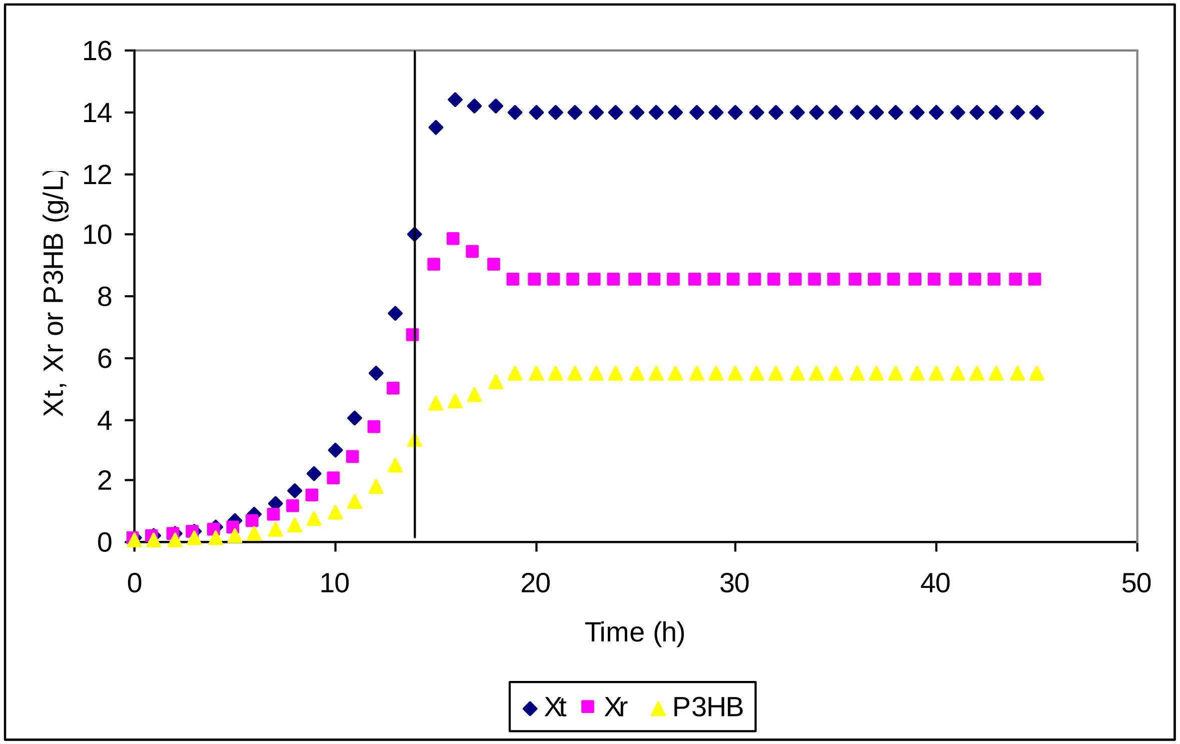
- ✓ O cone de fluxos admissíveis representa todas as possíveis vias que podem existir.
- ✓ Alguns modos elementares ficam na face ou na base do cone.
- ✓ AFM identifica somente uma via que se localiza em qualquer local do cone. ABF representa somente uma via em qualquer local do cone e satisfaz a função objetivo definida.
- ✓ AVM identifica todas as vias geneticamente independentes, com vias extremas em azul e modos elementares em vermelho.

Steady state



Steady state

Continuous culture



Steady state

Continuous culture

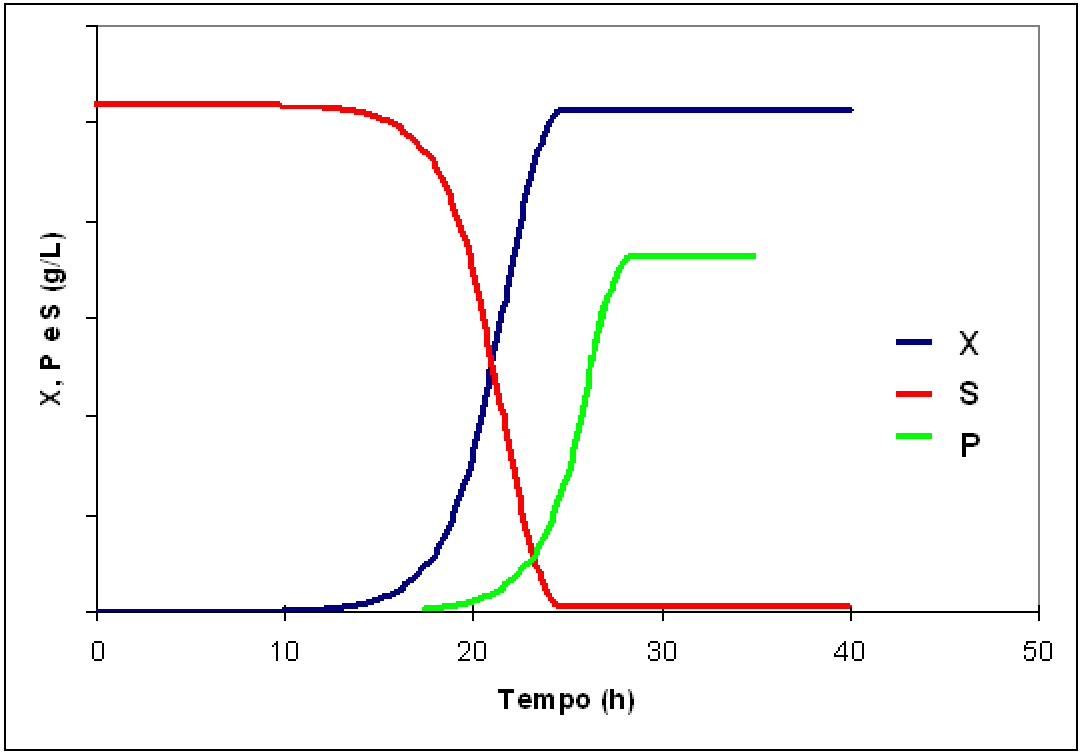
$$\frac{dX}{dt}\frac{1}{X} = \mu = \text{constante}$$

$$\frac{dP}{dt}\frac{1}{X} = q_P = \text{constante}$$

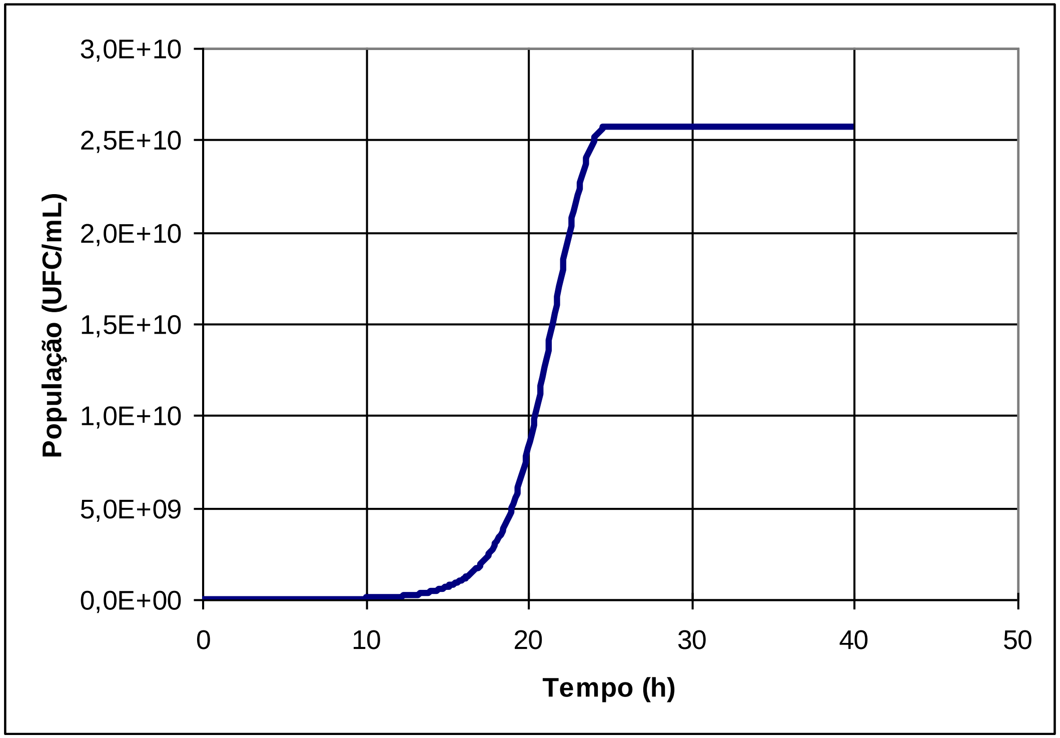
$$\frac{dS}{dt}\frac{1}{X} = q_S = \text{constante}$$

Y são constantes?

Batch

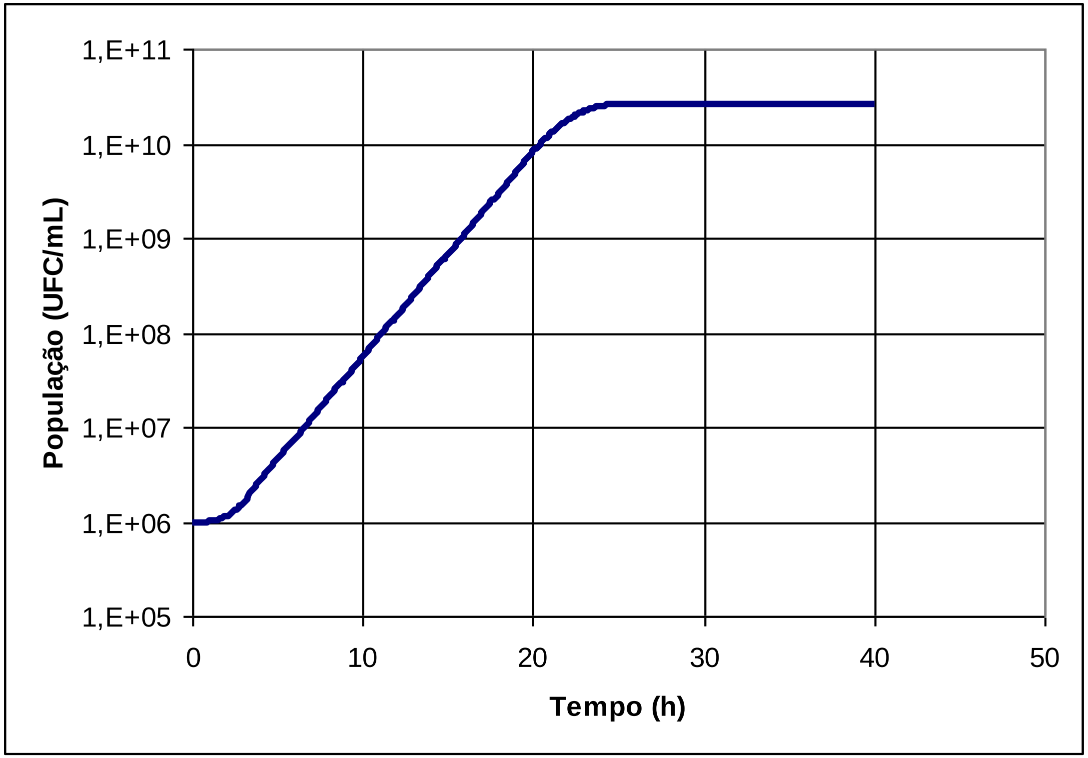


Fases de crescimento



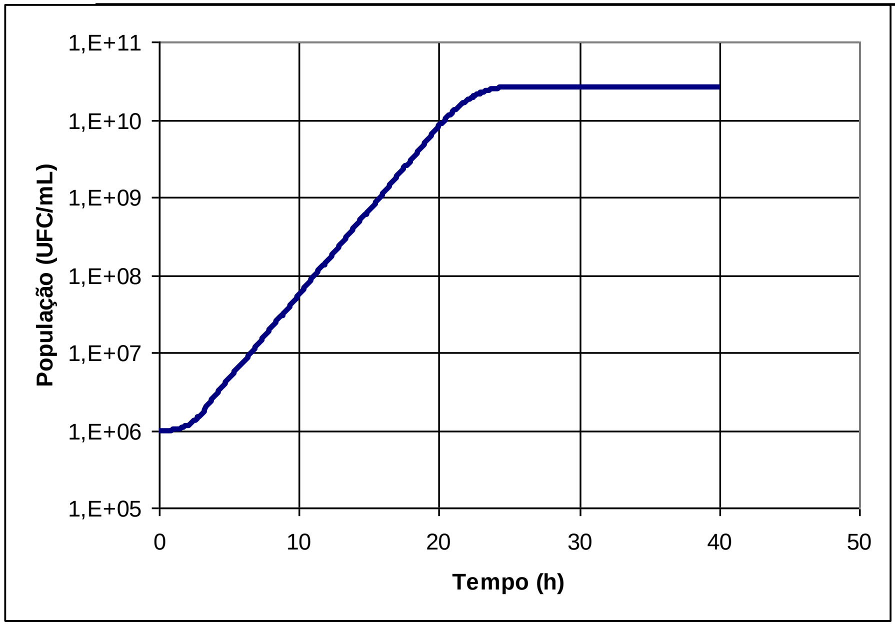
Lag
Exponencial
Estacionária

Fases de crescimento

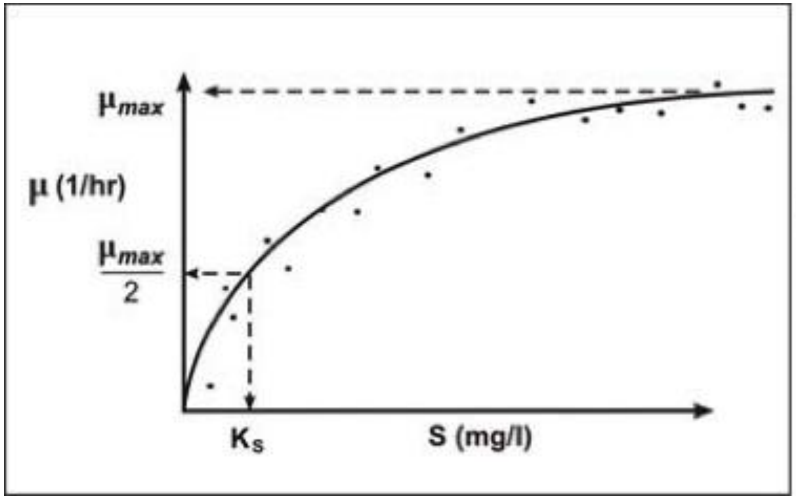


Lag
Exponencial
Estacionária

Fases de crescimento



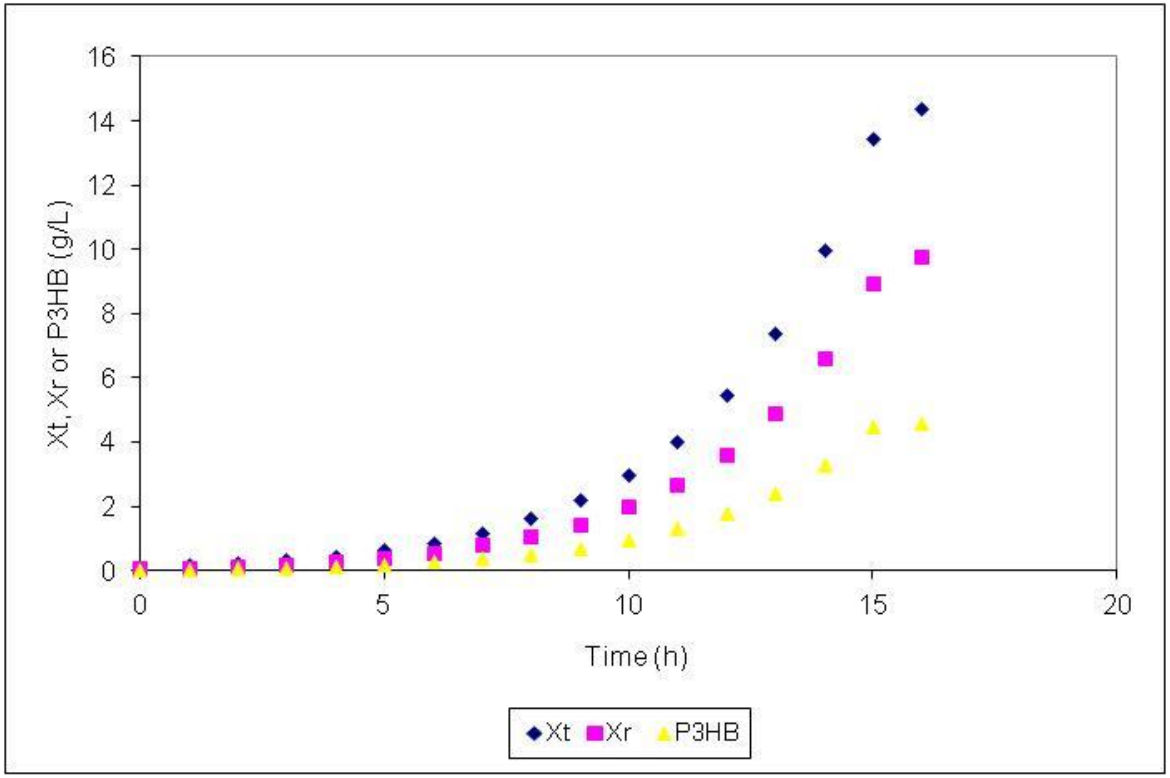
Lag
Aceleração
Exponencial
Desaceleração
Estacionária



$$\mu = \mu_{max}\left(\frac{S}{S+K_S}\right) \quad (5)$$

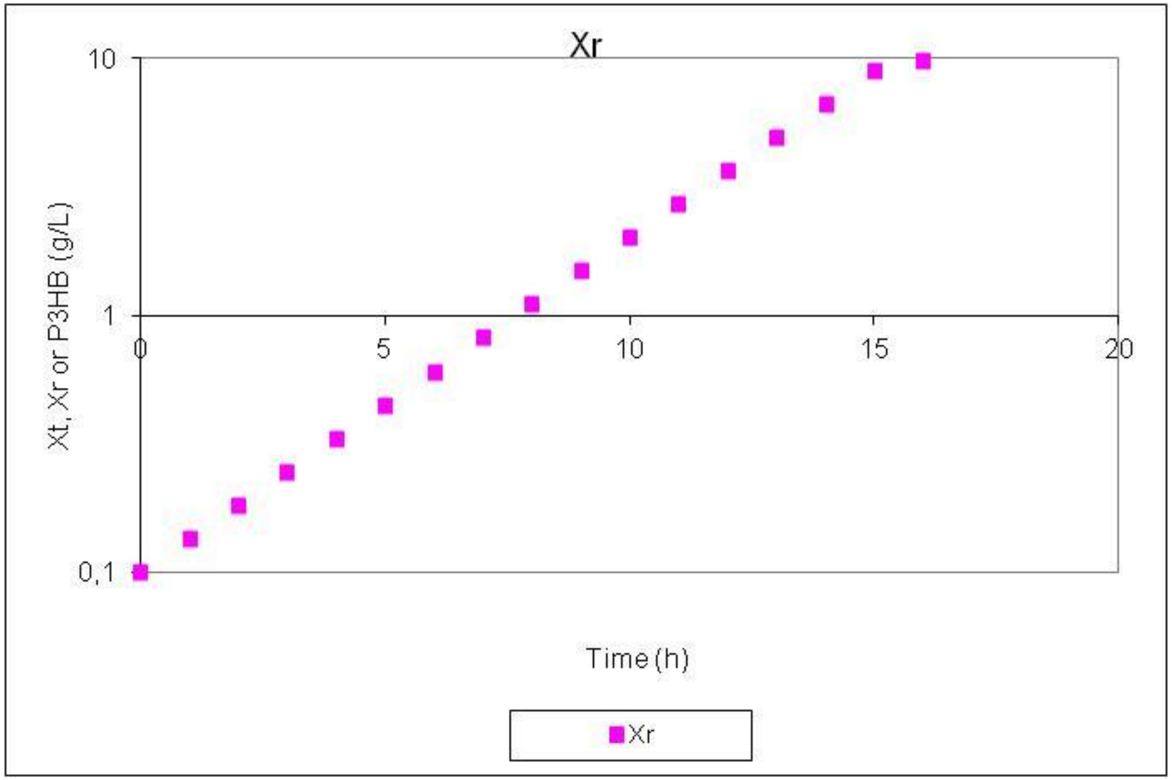
(Pseudo or Quase)Steady state

Batch – Exponential Growth phase



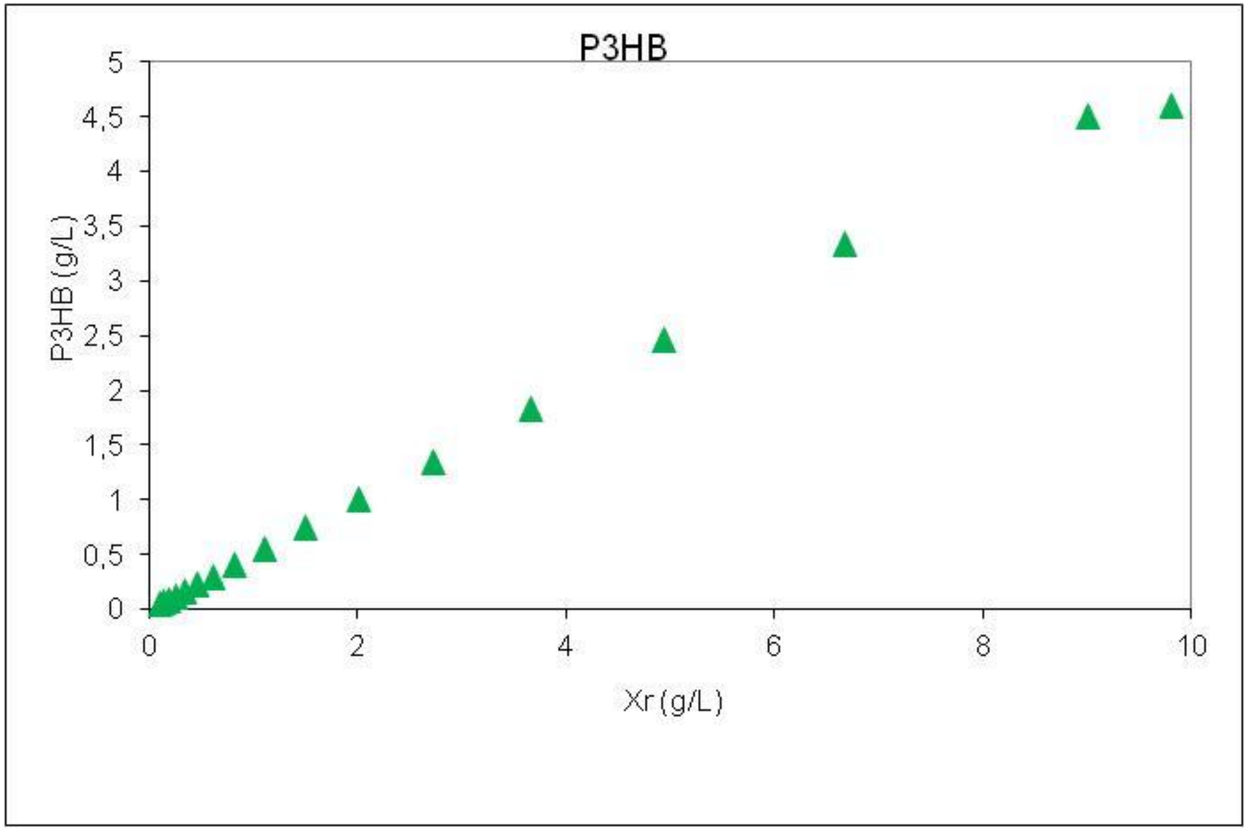
(Pseudo or Quase)Steady state

Batch – Exponential Growth phase



(Pseudo or Quase)Steady state

Batch – Exponential Growth phase



(Pseudo or Quase)Steady state

Batch – Exponential Growth phase

$$\frac{dX}{dt}\frac{1}{X} = \mu = \text{constante}$$

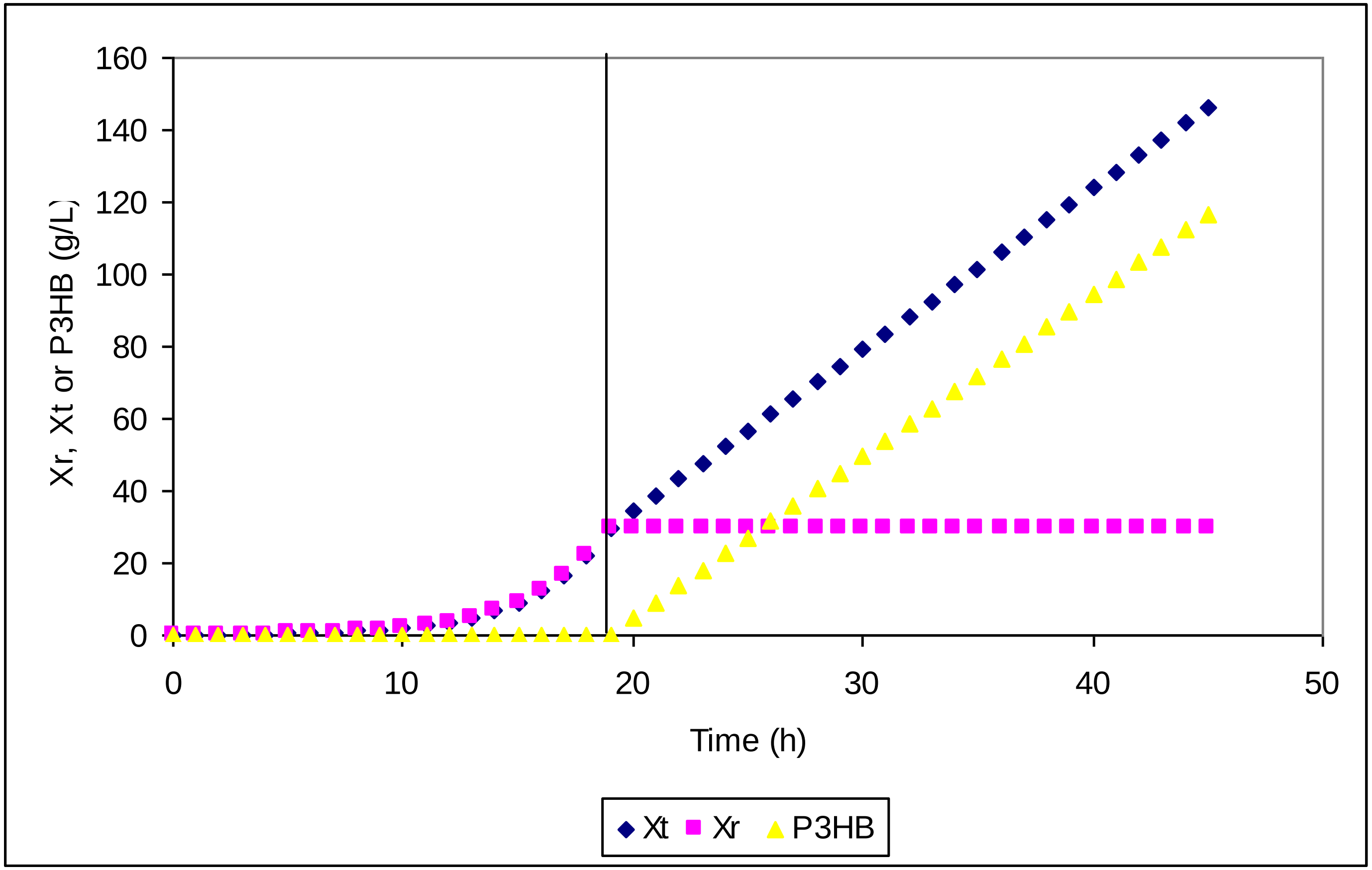
$$\frac{dP}{dt}\frac{1}{X} = q_P = \text{constante}$$

$$\frac{dS}{dt}\frac{1}{X} = q_S = \text{constante}$$

Y são constantes?

(Pseudo or Quasi)Steady state

Batch or Fed-batch



(Pseudo or Quasi)Steady state

Batch or Fed-batch
(stationary phase)

$$\frac{dX}{dt}\frac{1}{X} = \mu = \text{constante} = 0$$

$$\frac{dP}{dt}\frac{1}{X} = q_P = \text{constante}$$

$$\frac{dS}{dt}\frac{1}{X} = q_S = \text{constante}$$

$$\frac{dX}{dt} = \text{constante} = 0$$

$$\frac{dP}{dt} = \text{constante}$$

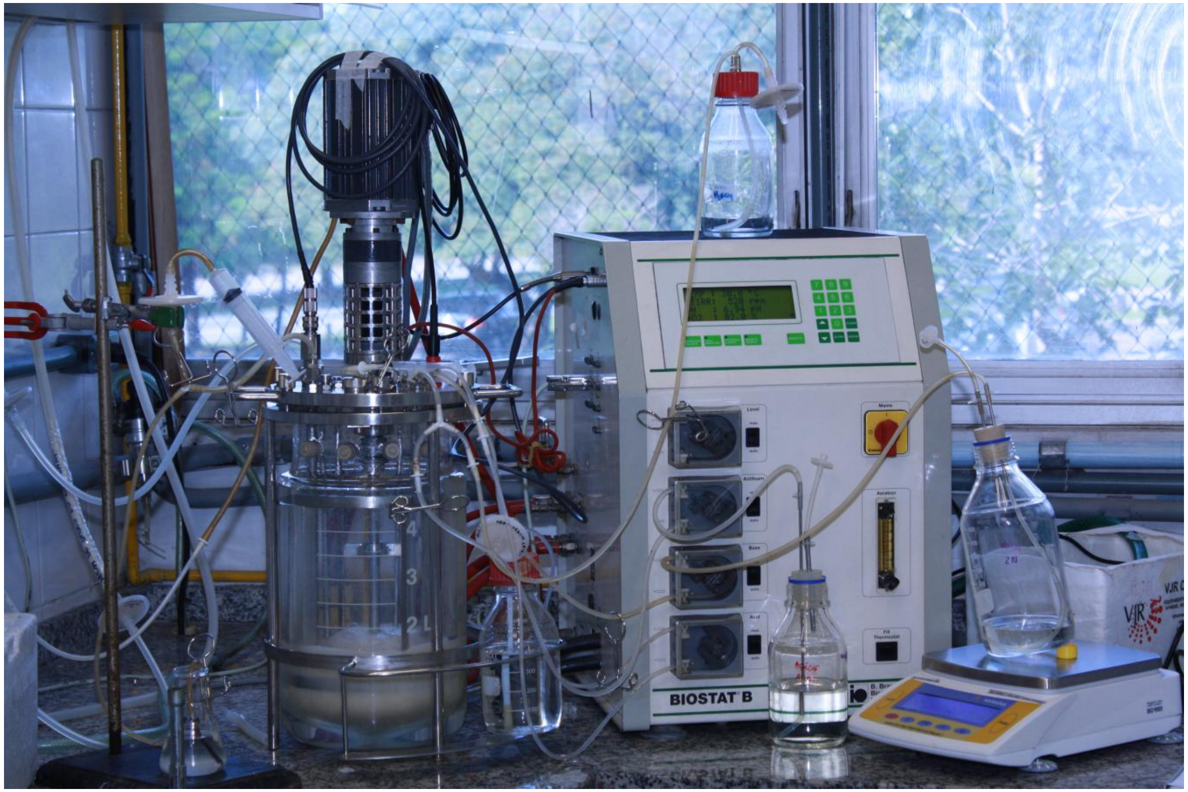
$$\frac{dS}{dt} = \text{constante}$$

Y são constantes?

(Pseudo or Quasi)-Steady state

Fed-batch

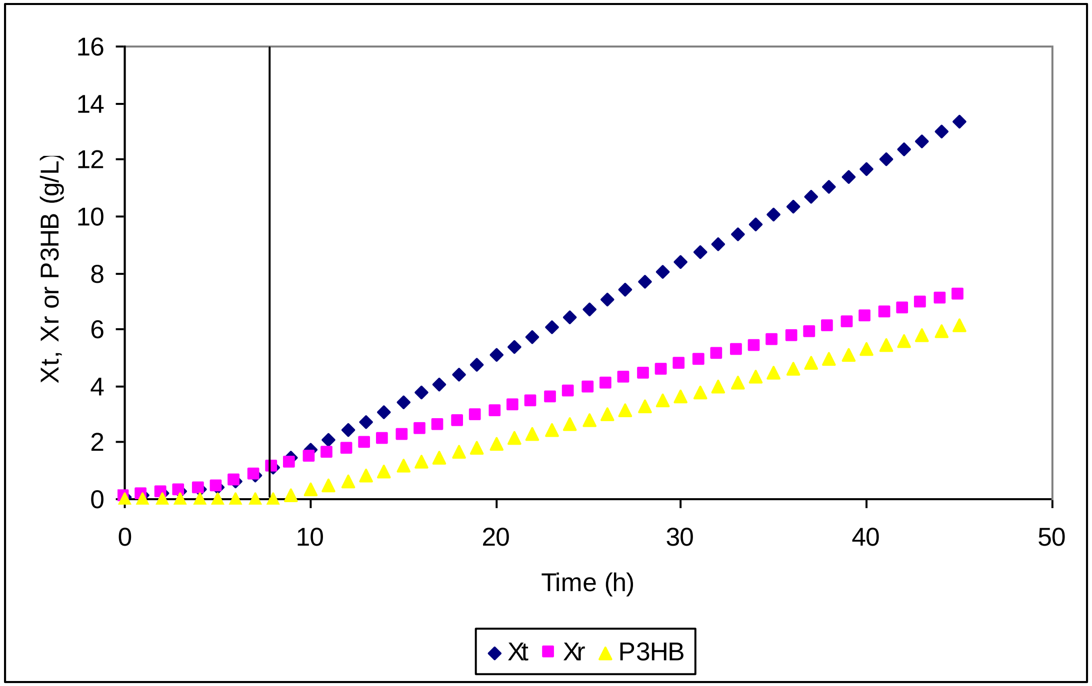
Continuous feeding



(Pseudo or Quasi)-Steady state

Fed-batch

Continuous feeding



(Pseudo or Quasi)-Steady state

Fed-batch

Continuous feeding

$$\frac{dX}{dt}\frac{1}{X} = \mu \text{ (Não constante)}$$

$$\frac{dP}{dt}\frac{1}{X} = q_P \text{ (Não constante)}$$

$$\frac{dS}{dt}\frac{1}{X} = q_S \text{ (Não constante)}$$

$$\frac{dX}{dt} = \text{constante}$$

$$\frac{dP}{dt} = \text{constante}$$

$$\frac{dS}{dt} = \text{constante}$$

Y são constantes?