SECTION III: PHENOMENOLOGY AND BIOPROCESS RUNNING:

LESSON 14. – Scaling-up and Scaling-down

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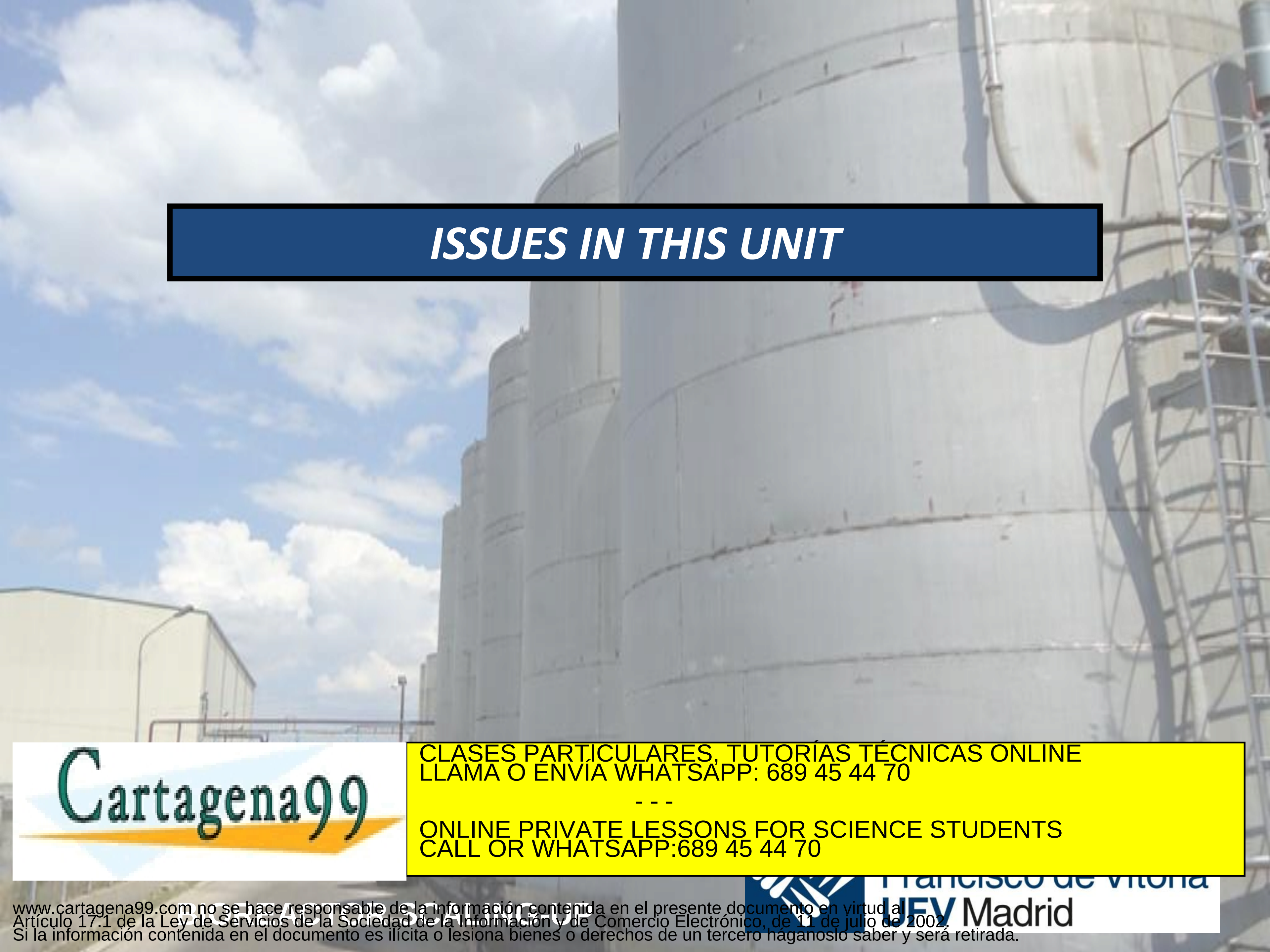


ISSUES IN THIS UNIT

AIMS FOR TODAY'S LESSON

BIORREACTOR SCALING-UP

Definition

Starting point

Scaling-up or numbering-up?

Scaling Criterion

SCALING-UP and SCALING-DOWN

REFERENCES:

- Atkinson, B. (2002), Reactores Bioquímicos, Reverté (Barcelona).
- Doran, P.M. (2010), Bioprocess Engineering Principles, Academic Press (Londres).
- Shuler, M.L. y Kargi, F. (2002), Bioprocess Engineering, Prentice Hall, Upper Saddle River, NJ, EE.UU.

1.- BIOREACTOR SCALING-UP

2.- SCALING-UP AND SCALING-DOWN

1.- BIOREACTOR SCALING-UP

Bioreactor scaling-up

SCALING-UP:

"Operation and staringt-up of a **commercially-sized unit** whose design and operating procedures are based, in part, on experimentation and demonstration on a **smaller scale** of operation"

"Study of **problems associated with the transfer of experimental data** from laboratory and pilot-plant equipment to large scale industrial equipment."

➔ It is the process consisting in achieving a fermentation unit operating

Bioreactor scaling-up

STARTING POINT:

Calculations and experiments carried out on a small scale.

AIM:

Designing one or more large-scale production units.

METHODOLOGY:

Progressive conversions from the starting scale to the **desired production**.

Bioreactor scaling-up

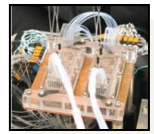
DIFFICULTIES:

- Scaling-up change **cannot be done directly.**
- It **doesn´t consist in increasing the number of small-scale units.**
- **Inaccuracy** in the model.
- Process is affected by changes within **response times**.
- **Some surface phenomena** are not considered.
- Change within the **hydrodynamic regime**.
- **Interactions between phenomena** of mass, energy and momentum transport along the scaling up.

Bioreactor scaling-up

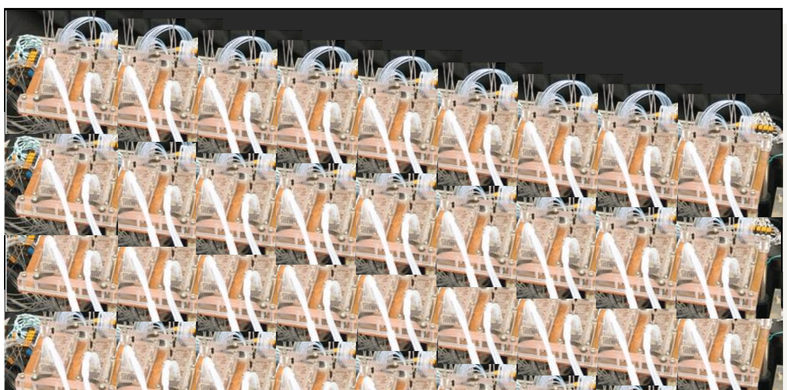
DIFFICULTIES:

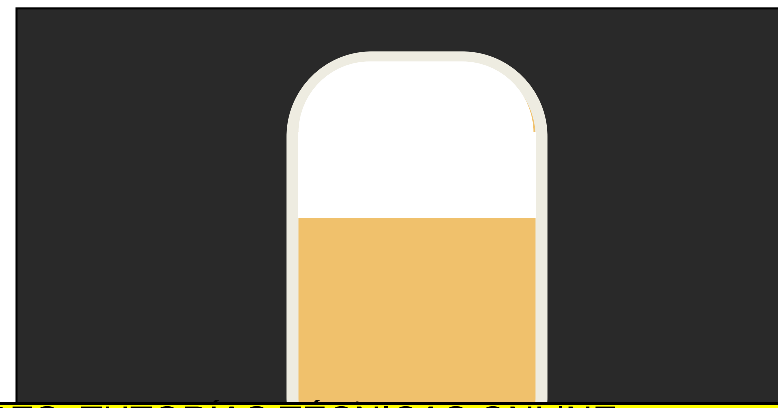
- A protocol developed in a miniature bioreactor should be used for the production of antibiotics.



Numbering up

Scaling up





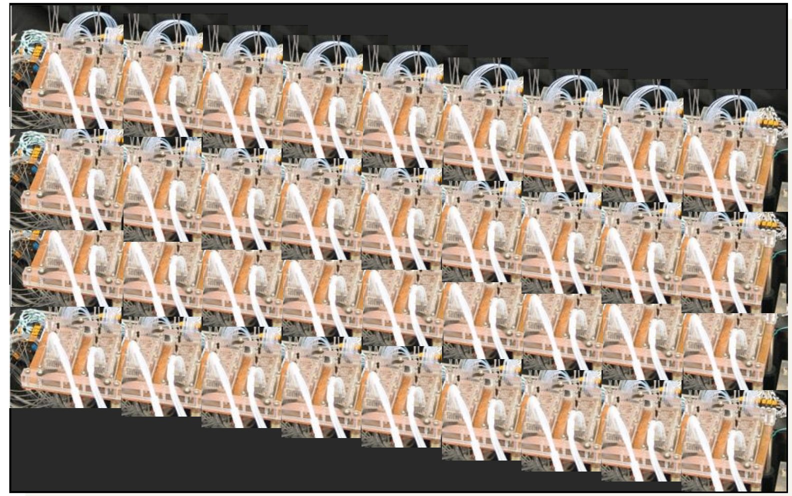
Numbering-up

- Parallel connection of the miniature bioreactors

- **Nature's principle**
  Unicellular→ Multicellular
  Leaves ➔ Tree ➔ Forest

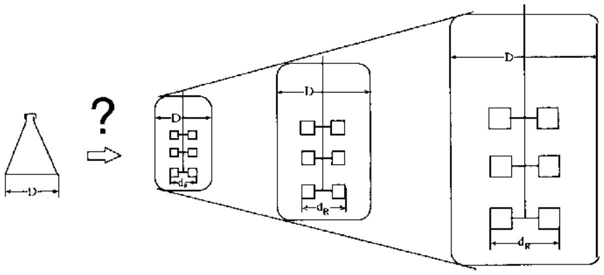
- **Advantages**
  No risks and compromises through scaling-up
  „Process Intensification":
  good energy and material exchange
  (short diffusion distance)

- **Disadvantages**
  Individual process guidance and control for every single miniature reactor necessary



Scaling-up

- Scaling-up in practice
  - e.g. 100 ml shake flask → 3 L lab reactor, 100 L pilot plant → 3000 L production plant
- Bioprocesses are dependent on the scale
  - e.g. mixing time increases sharply with an increase in volume
- Aim of scaling-up
  - Similarity of geometrical and physical influence variables
- Which similarity criteria are relevant?
  - Mass transport (O_2, CO_2)



Geometric similarity:
Prerequisite for scale up

Quelle: Storhas, Bioverfahrensentwicklung, S. 189 ff, S 232 ff

Bioreactor scaling-up

HIGH COMPLEXITY:

EXAMPLE:

Broadly speaking, **height/diameter ratio** between **2:1** and **3:1**.

By **increasing the scale** and keeping this relationship constant, the **surface/volume ratio decreases rapidly.**

➔ The heat transfer with the exterior changes.

➔ The aeration and gas withdrawal requirements increase drastically.

Parameters are affected non-linearly by an increase in size while maintaining the aspect ratio.

Bioreactor scaling-up

HIGH COMPLEXITY:

ANALOGY:

A carpenter receives a client who wants to build a cubic box for a circus show. This client shows a wooden sample box presenting 25 cm each side.

He would like to build a 4 times bigger cube for a show.

Calculate dimensions, surface and volume for the structure to be built. If more than one solution is possible, do the calculations for everyone.

Bioreactor scaling-up

"**A Four times bigger cube**" can be understood in many different ways, so that the solution for the problem could consist in:

- Increasing the **cube side four times**.
- Increasing **total volume four times**.
- Increasinge **total area four times**. ➔ However, interest in this situation is only explained if the expenses of material used need to be controled.

Bioreactor scaling-up

Anyway, equations putting into relationship side, surface and volume of the cubic structure are the following ones:

$$S = 6L^2 \qquad [1]$$

$$V = L^3 \qquad [2]$$

Where,

L, in the side of the cubic structure,

S, is the total surface area of the structure and

Bioreactor scaling-up

Initial situation

$L_0 = 25\ cm = 0,25\ m$

$S_0 = 6 \bullet (0,25)^2 = 0,375\ m^2$

$V_0 = (0,25)^3 = 0,016\ m^3$

Increasing the cube side four times

$L_1 = 4 \cdot 25\ cm = 100\ cm = \mathbf{1\ m}$ — $L_1/L_0 = 4$

$S_1 = 6 \cdot 1^2 = \mathbf{6\ m^2}$ — $S_1/S_0 = 16 = 4^2$

$V_1 = 1^3 = \mathbf{1\ m^3}$ — $V_1/V_0 = 64 = 4^3$

Bioreactor scaling-up

Initial situation

L_0 = 25 cm = 0,25 m

$S_0 = 6 \bullet (0,25)^2 = 0,375\ m^2$

$V_0 = (0,25)^3 = 0,016\ m^3$

Increasing total volume four times

$V_2 = 4 \cdot V_0 = 4 \cdot 0,016 = 0,0625\ m^3 \rightarrow L_2 = \sqrt[3]{V_0 \cdot 4} = \sqrt[3]{4} \cdot L_0 = 0.397m$

L_2 = **0,397 m**

$S_2 = 6 \cdot (0,397)^2 =$ **$0,945\ m^2$**

$V_2 =$ **$0,0625\ m^3$**

$L_2/L_0 = 1,587 = 4^{1/3}$

$S_2/S_0 = 2,520 = 4^{2/3}$

$V_2/V_0 = 4$

Bioreactor scaling-up

Initial situation

L_0 = 25 cm = 0,25 m

$S_0 = 6 \bullet (0,25)^2 = 0,375\ m^2$

$V_0 = (0,25)^3 = 0,016\ m^3$

Increasinge total area four times

$S_3 = 4 \cdot S_0 = 4 \cdot 0,375 = 1,5\ m^2 \rightarrow L_3 = \sqrt{\frac{S_0 \cdot 4}{6}} = \sqrt{\frac{6 \cdot L_0^2 \cdot 4}{6}} = 2 \cdot L_0 = 0,5m$

L_2 = **0,5 m**
$S_2 = 6 \cdot (0,5)^2 = \mathbf{1,5\ m^2}$
$V_2 = (0,5)^3 = \mathbf{0,125\ m^3}$

$L_2/L_0 = 2 = 4^{1/2}$
$S_2/S_0 = 4$
$V_2/V_0 = 8 = 4^{3/2}$

Bioreactor scaling-up

TO SUM UP:

	Relationship Side / Initial Side	Relationship Surface / Initial Surface	Relationship Volume / Initial Volume
Increasing side	4	4^2	4^3
Increasing surface	$4^{1/2}$	4	$4^{3/2}$
Increasing volume	$4^{1/3}$	$4^{2/3}$	4

Bioreactor scaling-up

HIGH COMPLEXITY:

ANALOGY:

Dimensions, total surface and volume do not keep a linear relation between each other, but potential instead, because of the geometry

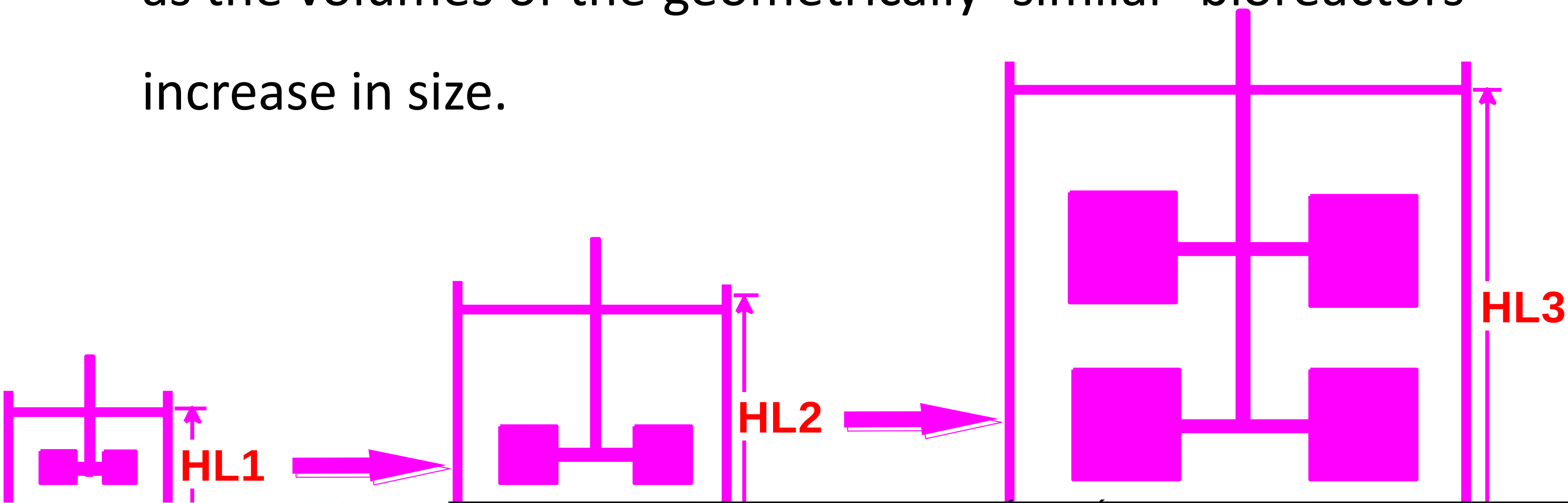
➔ Increasing each characteristics of the cube, does not affect the other ones in the same way.

It is necessary to **clearly define the scale change criterion** to

Scale-up Criterion

IDEAL SCALING-UP CRITERION:

- That **parameter** which has the **same numerical value** as the volumes of the geometrically similar bioreactors increase in size.

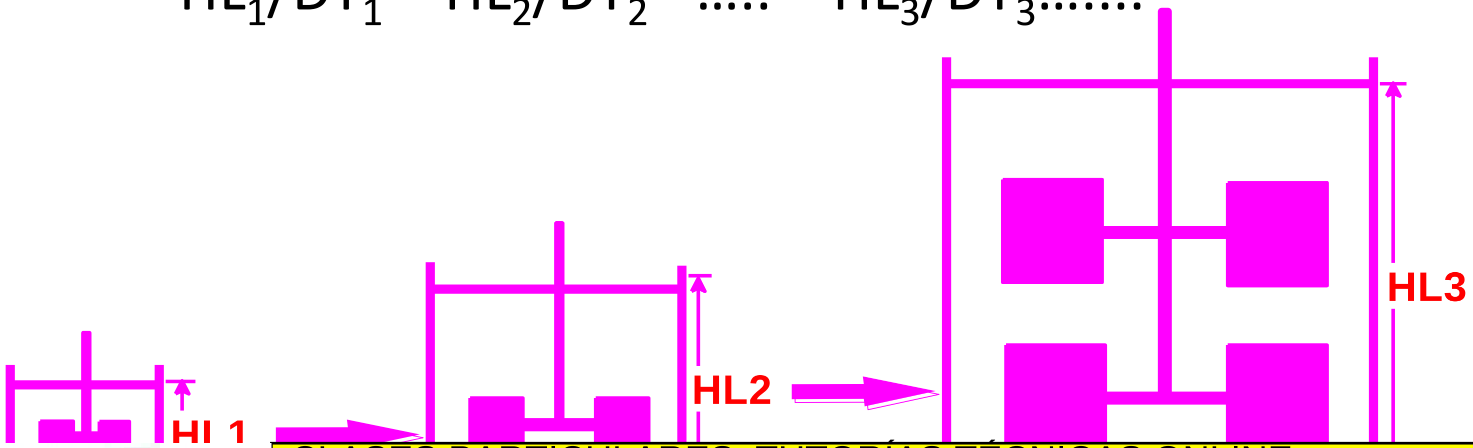


Scale-up Criterion

IDEAL SCALING-UP CRITERION:

- First scale-up criterion is maintaining **Geometrical Similarity**:

$$HL_1/DT_1 = HL_2/DT_2 =\ldots\ldots = HL_3/DT_3\ldots\ldots$$



Scale-up Criterion

EXAMPLE:

For a given

- Medium Composition
- Temperature
- pH

We want to maximize the cell yield factor $Y_{X/S}$.

We start with a 10 L Laboratory scale bioreactor unit and we perform optimization experiments at different volumetric rates of oxygen supply, OTR.

Scale-up Criterion

EXAMPLE:

Where:

$$OTR = K_{La} (C_L^* - C_L)$$

$$= (\text{moles } O_2)/(L)(hr)$$

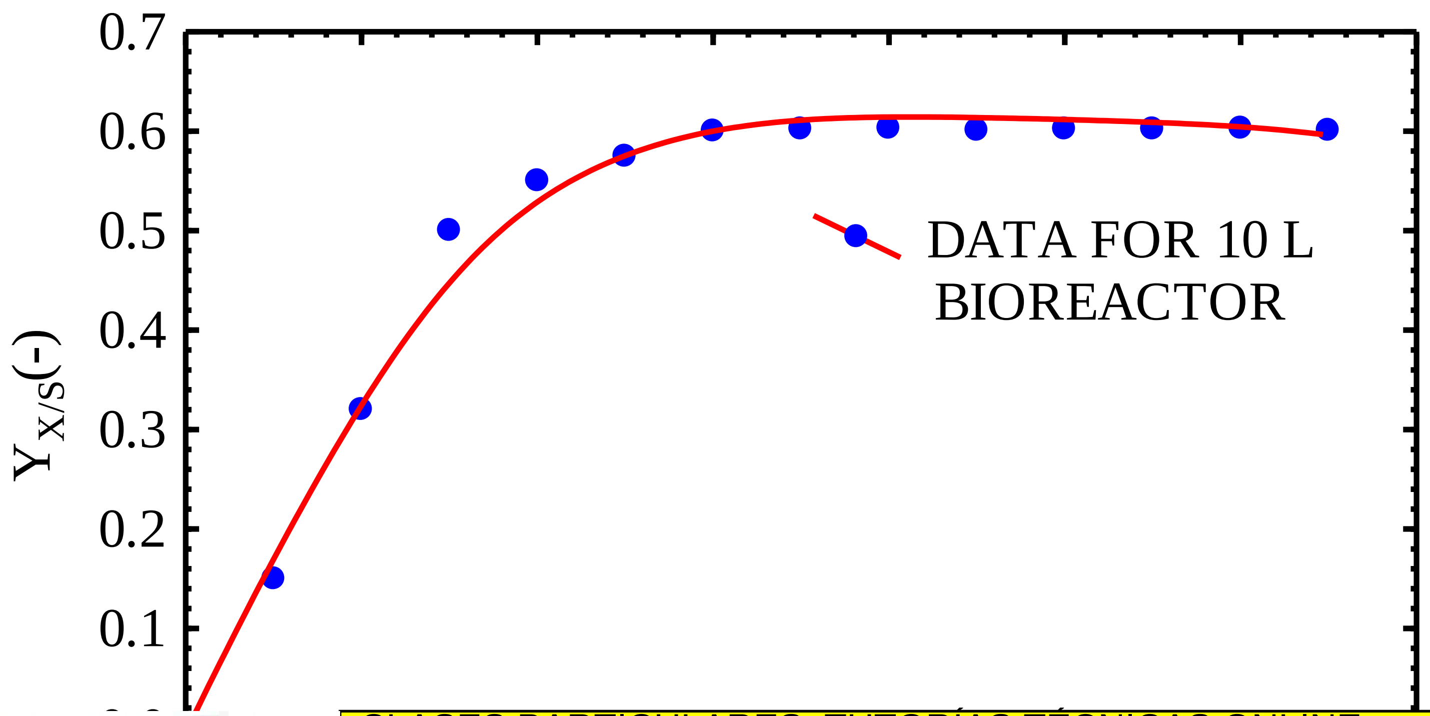
$$Y_{X/S} = \text{Cell to substrate yield}$$

$$= (\text{g CDW yeast cells})/(\text{g glucose used})$$

Using the 10 L laboratory scale bioreactor we carry out experiments and we get the following hypothetical results shown in the following Figure.

Scale-up Criterion

EXAMPLE:



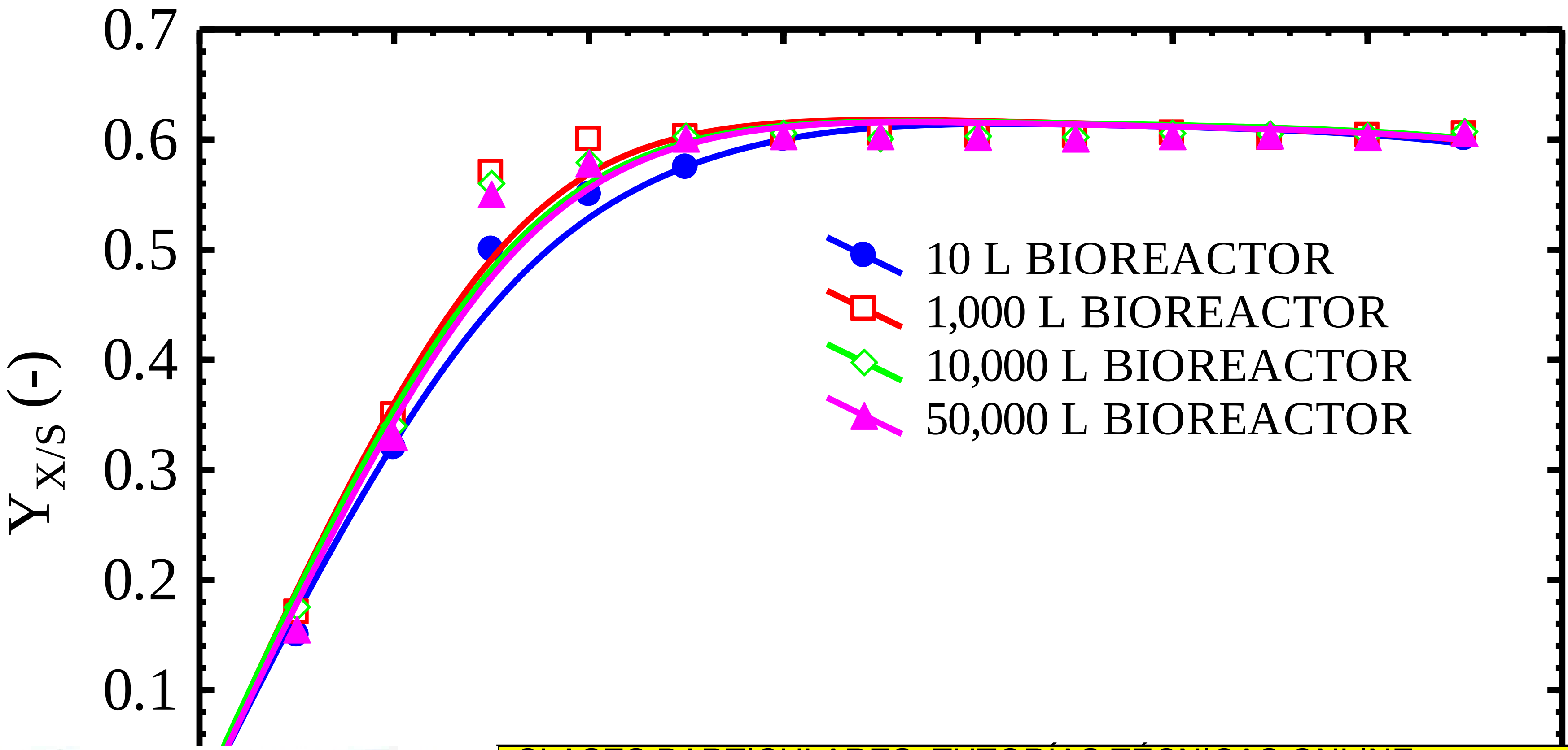
Scale-up Criterion

EXAMPLE:

When we scale-up to 50,000 L bioreactor system, are we going to get the same YX/S vs. OTR relationship?

- It depends on **what scale-up criteria** we use.
- If the volumetric rate of oxygen transfer OTR were a true scale-up criterion, then the relationship between $Y_{X/S}$ vs. OTR for the 10 L bioreactor **should be exactly the same** for any bioreactor size.
- if experiments were done with bioreactors of 10 L, 1,000 L, 10,000 L,

Scale-up Criterion

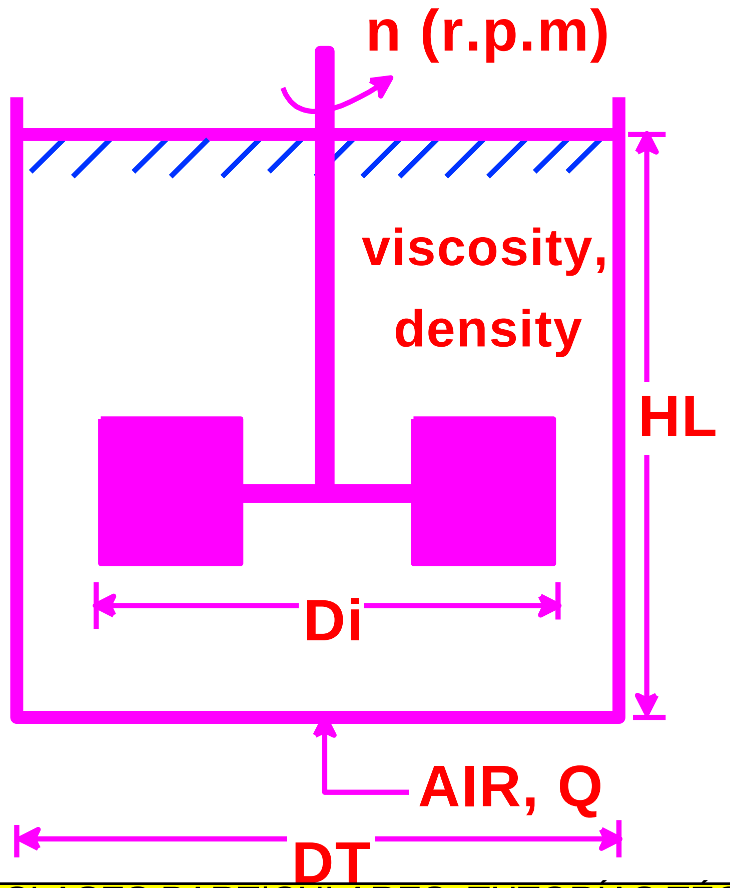


$$R = K_L a (C_L^* - C_L)$$

Scale-up Criterion

- In reality scale-up of laboratory and pilot-plant data to commercial size industrial bioreactors is **very difficult and complicated**.
- **No actual data or correlation** exist for scale-up.
- **Different people use different scale-up criteria** to design commercial size bioreactor systems.
- In industry there are a lot of **trade secrets** on scale-up of bioreactors, and **very few published** results exist in the literature.

Scale-up Criterion



Scale-up Criterion

- Scale-up criteria in general are a function of independent variables **N, Di, DT, HL, Qg, μ, ρ.**

- Once a criteria is selected, then you make sure that the **numerical value of this scale-up criterion is the same** for the small and large size bioreactor.

Scale-up Criterion

In general, the choice of scale-up criterion depends on two considerations:

a) Nature of fermentation and culture morphology

- Aerobic / Anaerobic.
- Bacteria / Fungi / Mammalian Cells / Plant Cells.
- Exothermic character.
- Thermophilic organisms.
- Viscosity of culture.
- Newtonian fluid / Non-Newtonian fluid.

Scale-up Criterion

In general, the choice of scale-up criterion depends on two considerations:

b) What is being looked for to be maximized:

- Yield of product or biomass
- Concentration of cells
- Concentration of the product
- Activity of the product.
- Productivity per unit volume of the bioreactor.

Scale-up Criterion

- Different scale-up criteria have been used **depending on the type of fermentation** and the **objective of optimization**.

- The **first assumption is geometric similarity** between bioreactor vessels of different sizes.

- However, in **some scale-up cases geometric similarity is not preserved**. This makes scale-up much **more complex**.

Scale-up Criterion

- K_{La}
- Power Per Unit Liquid Volume
- Tip Velocity of the Impeller
- Aeration Number
- Impeller Reynolds Number.

Scale-up Criterion (1) Volumetric Mass Transfer Coefficient

$$(KLa)_1 = (KLa)_2$$

Where:

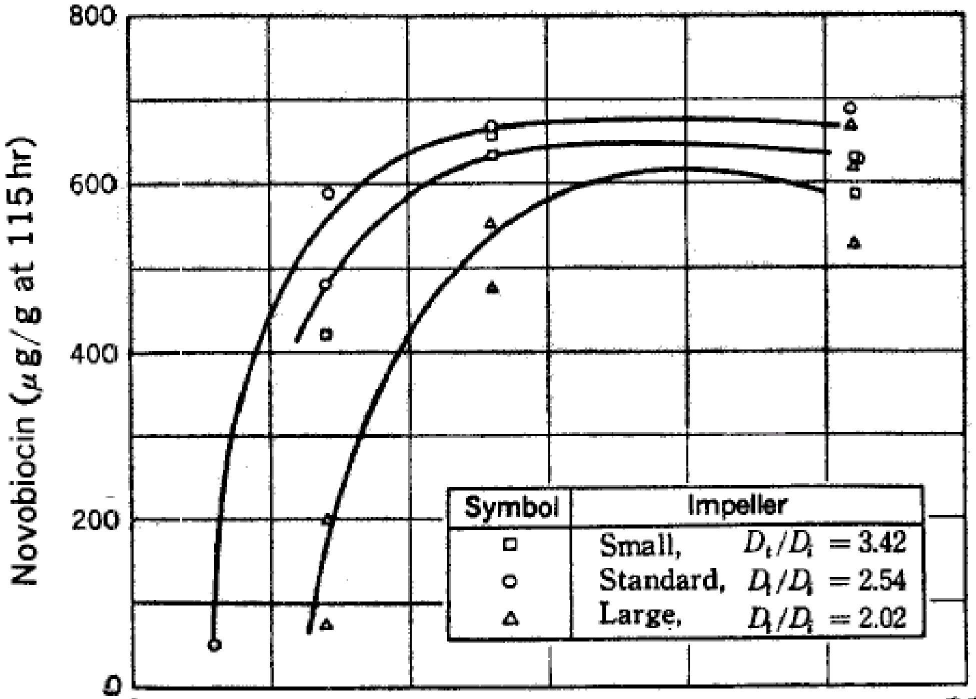
1 = small scale bioreactor

2 = large scale bioreactor

This criterion is usually applied to **aerobic systems** where **oxygen concentration is most important** and affects metabolism of the microbial cell.

Scale-up Criterion (2) Power Per Unit Liquid Volume

$$(P/V_L)_1 = (P/V_L)_2$$



The majority of aerobic fermentor systems have been scaled-up on the KLa basis and very few on the P/V_L basis.

Scale-up Criterion (3) Tip Velocity of the Impeller

$$(N \cdot D)_1 = (N \cdot D)_2$$

This scale-up criterion is used for **shear sensitive fermentations** where a maximum shear rate is allowed to prevent possible irreversible shear damage to the cells growing inside the bioreactor.

In some cases where the **cells have a tendency to form dense flocks**, it is necessary to provide at least the minimum shear rate required to break-up these flocks.

Scale-up Criterion (4) Aeration Number

$$(N_a)_1 = (N_a)_2$$

$$N_a = Q/(n\,D_i^3) = Q/[(n\,D_i)(D_i^2)]$$

In cases where expense on stirring is desive.

Scale-up Criterion (5) Impeller Reynolds Number

$$(Re)_1 = (Re)_2$$

This criterion is used sometimes when the **heat transfer rate** from the fermentation broth to the cooling coils inside the bioreactor vessel is of paramount importance.

This is especially important for **thermophilic microorganisms**.

The **heat transfer coefficient is a function of impeller Reynolds number**

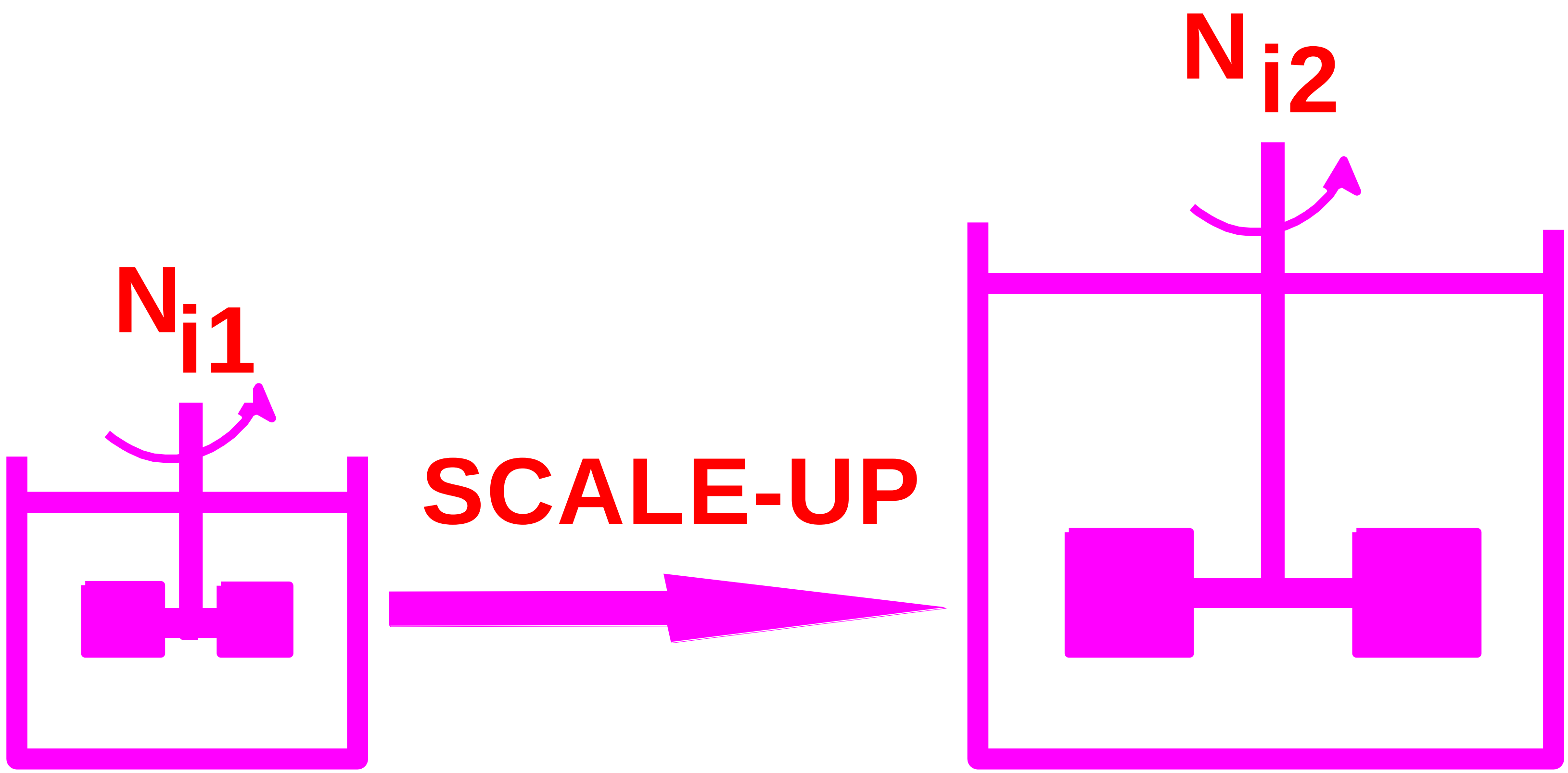
Scale-up Criterion

EXAMPLE:

Oldshue worked out relationships between properties for scale-up from 80 L to 10,000 L bioreactor, which was not aerated but agitated with a six blade turbine impeller.

- Standard geometry vessel was used and geometric similarity was applied.
- Volumetric scale-up ratio = V_2/V_1 = 10,000/80 = 125
- Impeller diameter scale-up ratio = Di_2/Di_1 = 5

Scale-up Criterion



(1) Scale-up Criterion:

$$(P/V_L)_1 = (P/V_L)_2$$

Property	80 L bioreactor	10,000L bioreactor
P (ungassed power)	1.0	125.00
N_i (r.p.m)	1.0	0.34
D_i (imp. diameter)	1.0	5.00
F (pumping rate)	1.0	42.50
F/V_L (liquid circ. rate)	1.0	0.34
N_iD_i (imp. tip speed)	1.0	1.70
N_{Re} (Reynolds No.)	1.0	8.50

Note: $N_{Re} = (N_iD_i^2\rho)/\mu$

(2) Scale-up Criterion: Same Liquid Circulation Rate $(F/V_L)_1 = (F/V_L)_2$

Property	80 L Small scale	10,000L large scale
P (ungassed power)	1.0	3125.0
P/V_L	1.0	25.0
N_i (r.p.m)	1.0	1.0
D_i (imp. diameter)	1.0	5.0
F (pumping rate)	1.0	125.0
N_iD_i (imp. tip speed)	1.0	5.0

(3) Scale-up Criterion:

Same Impeller Tip Velocity $(N_iD_i)_1 = (N_iD_i)_2$

Property	80 L Small scale	10,000L Large scale
P	1.0	25.0
P/V_L	1.0	0.2
N_i	1.0	0.2
D_i	1.0	5.0
F	1.0	25.0
F/V_L	1.0	0.2

(4) Scale-up Criterion: Same Impeller Reynolds Number $(N_{Re})_1 = (N_{Re})_2$

Property	80 L Small scale	10,000L Large scale
P	1.0	0.2
P/V_L	1.0	0.0016
N_i	1.0	0.04
D_i	1.0	5.0
F/V_L	1.0	0.2

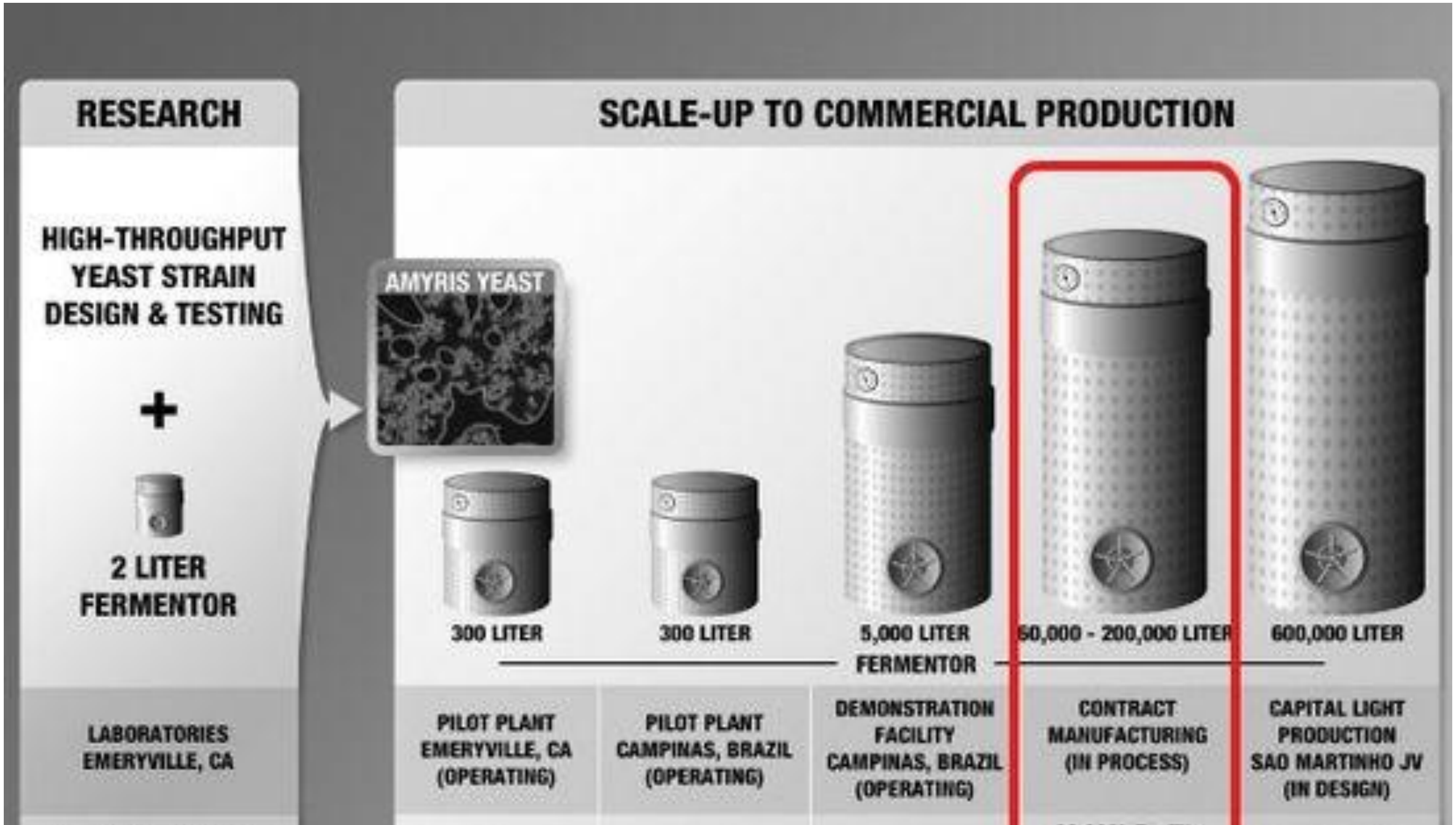
Bioreactor scaling-up

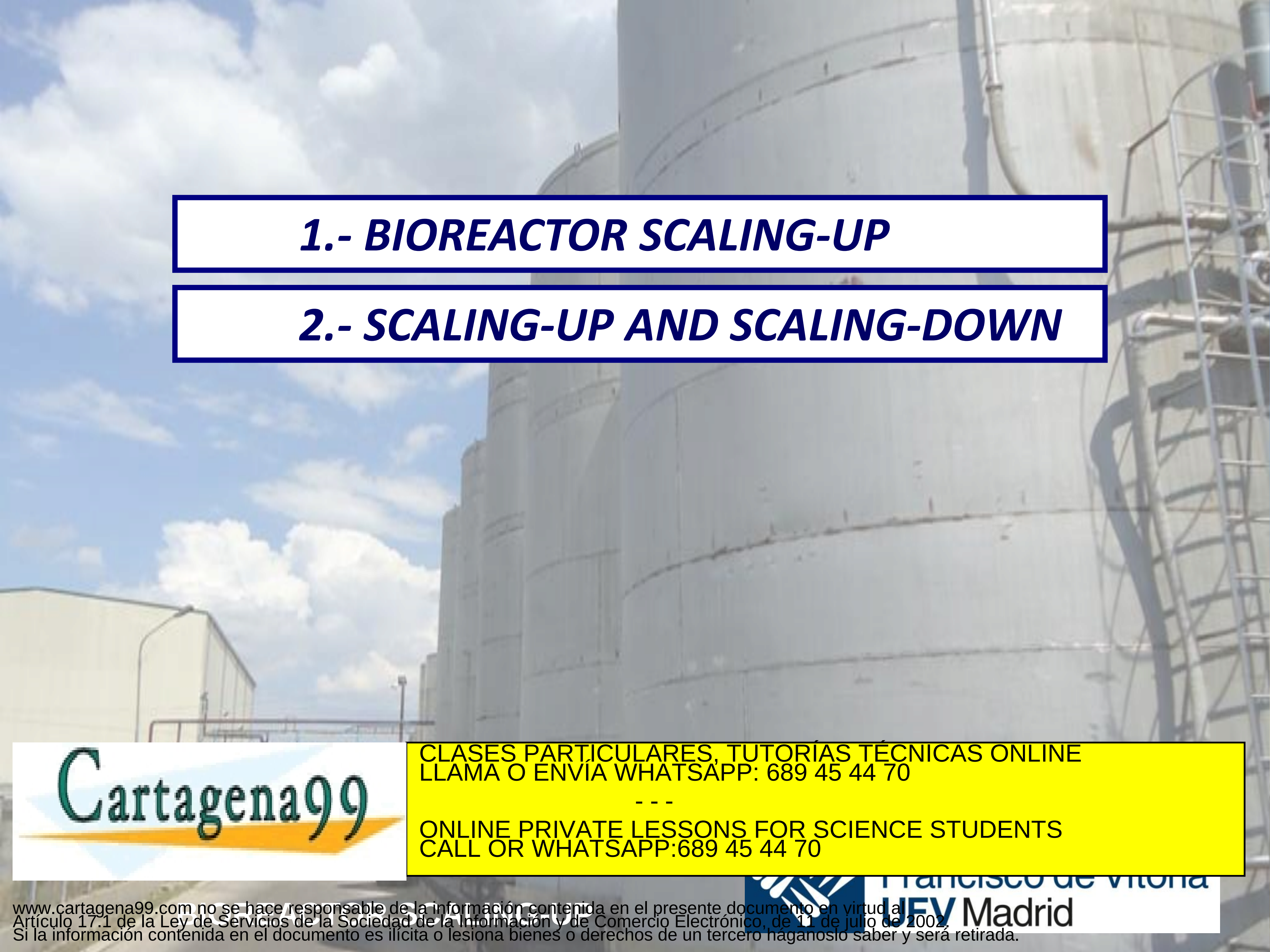
Parameter	Definition	Scale-Up Factor	Why is this Important?
Mixing Time	Amount of time it takes the bioreactor to create a homogeneous environment	$N_2=N_1(D_1/D_2)^{1/4}$ N_2 agitation speed in scale-up N_1 agitation speed in scale-down D_1 impeller diameter of scale -down D_2 impeller diameter of scale-up	•Want to ensure that the materials are well-mixed in a timely manner
Power Input per Volume (P/V)	Amount of power transferred to a volume of cell culture through the agitator shaft and impellers	$P/V \approx N^3/D^2$ P- power supplied V- Volume of Bioreactor N- Agitation Speed D- Impeller Diameter	•Mammalian cells cannot handle a lot of power introduced into the culture media as it can cause small eddies that will shear the fragile cell membranes
Tip Speed	Related to the shear rate	$N_2=N_1(D_1/D_2)$ N_2 agitation speed in scale-up N_1 agitation speed in scale-	•High shear rates can cause the cell membrane to tear and the cells to die.

Bioreactor scaling-up

Parameter	Definition	Scale-Up Factor	Why is this Important?
Vessel Volumes per Minute (VVM)	means the volume of gas flow (usually measured in slpm, standard liters per minute) per bioreactor volume per minute.	Volume of Gas Flow/time	•necessary to ensure that enough oxygen will be supplied to the cells
Superficial Gas Velocity (V_s)	volume of gas per cross-sectional area of the vessel.	$V_s = Q_{gas}/A_v$ V_s- superficial gas velocity Q_{gas}- gas volumetric flow rate A_v- inside cross-sectional area of vessel	•increasing V_s causes an increase in foam generation

Bioreactor scaling-up





1.- BIOREACTOR SCALING-UP

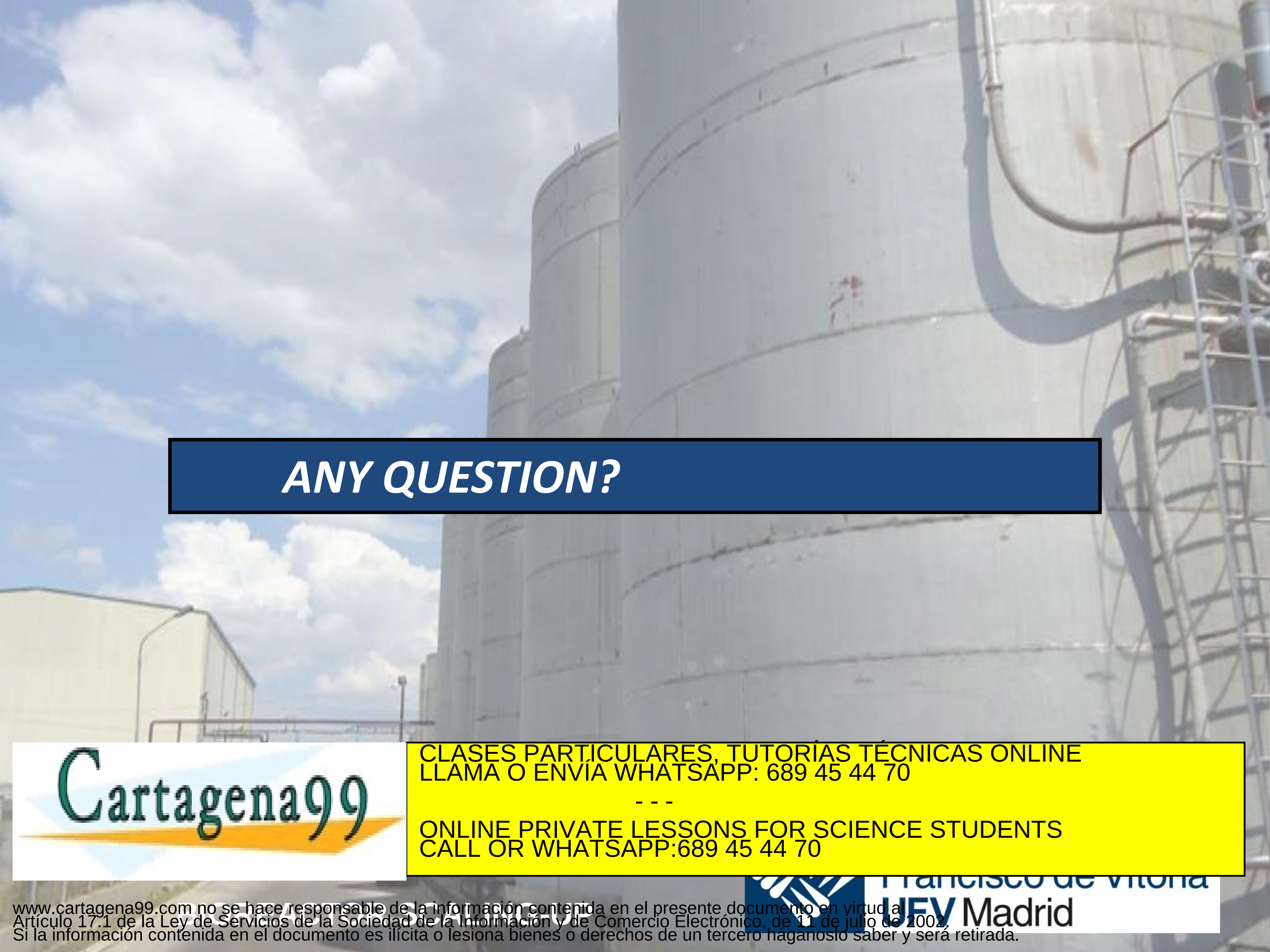
2.- SCALING-UP AND SCALING-DOWN

2.- SCALING-UP AND SCALING-DOWN

SCALING-DOWN

"Building a smaller experimental system that replicates the conditions existing on a current bigger one."

- **Imitate or reproduce** installations on a smaller scale.
- Parameters can be evaluated **more quickly**, and at lower cost.
- The **calculations** used when scaling-down **are the same** when scaling-up.



ANY QUESTION?

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LESSON 14. – Scaling-up and Scaling-down

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