

Pharmaceutical Protein Production (III)

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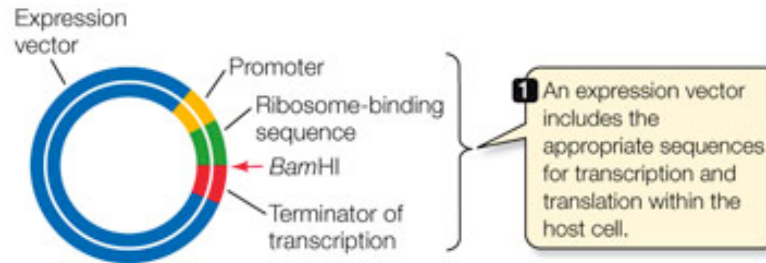
Objectives of this lecture

By the end of this lecture you will be able to:

1. Identify different types of bioreactors
2. Compare between different bioreactors types
3. Compare between different production processes

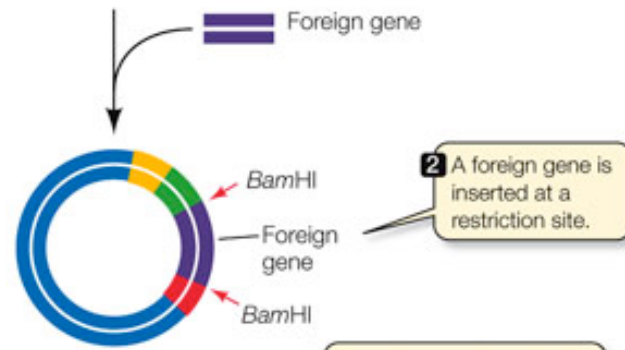
Requirements for recombinant protein production

Vector



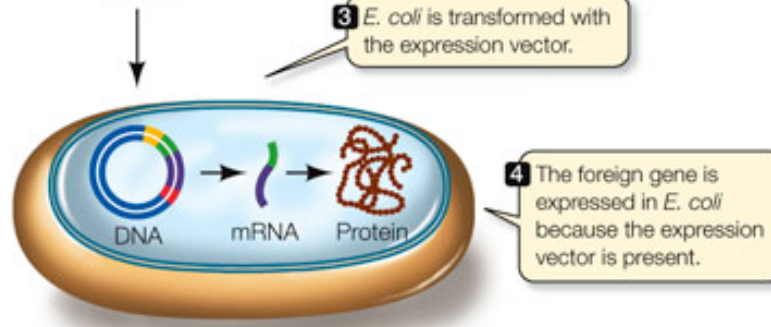
Plasmid

Gene



Insulin

Host



E. coli

Choice of production vehicle

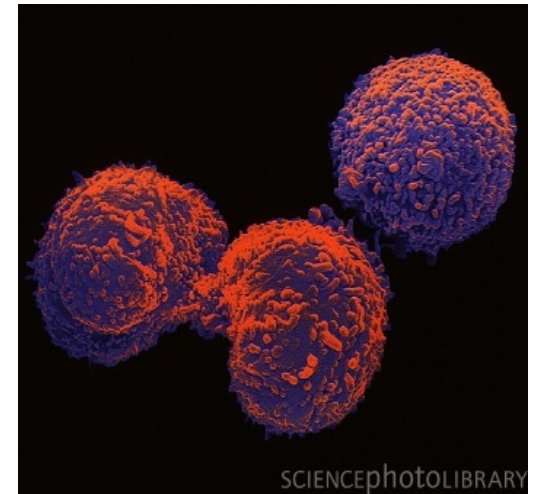
- In principle, any protein can be produced using any genetically engineered organism



Bacteria

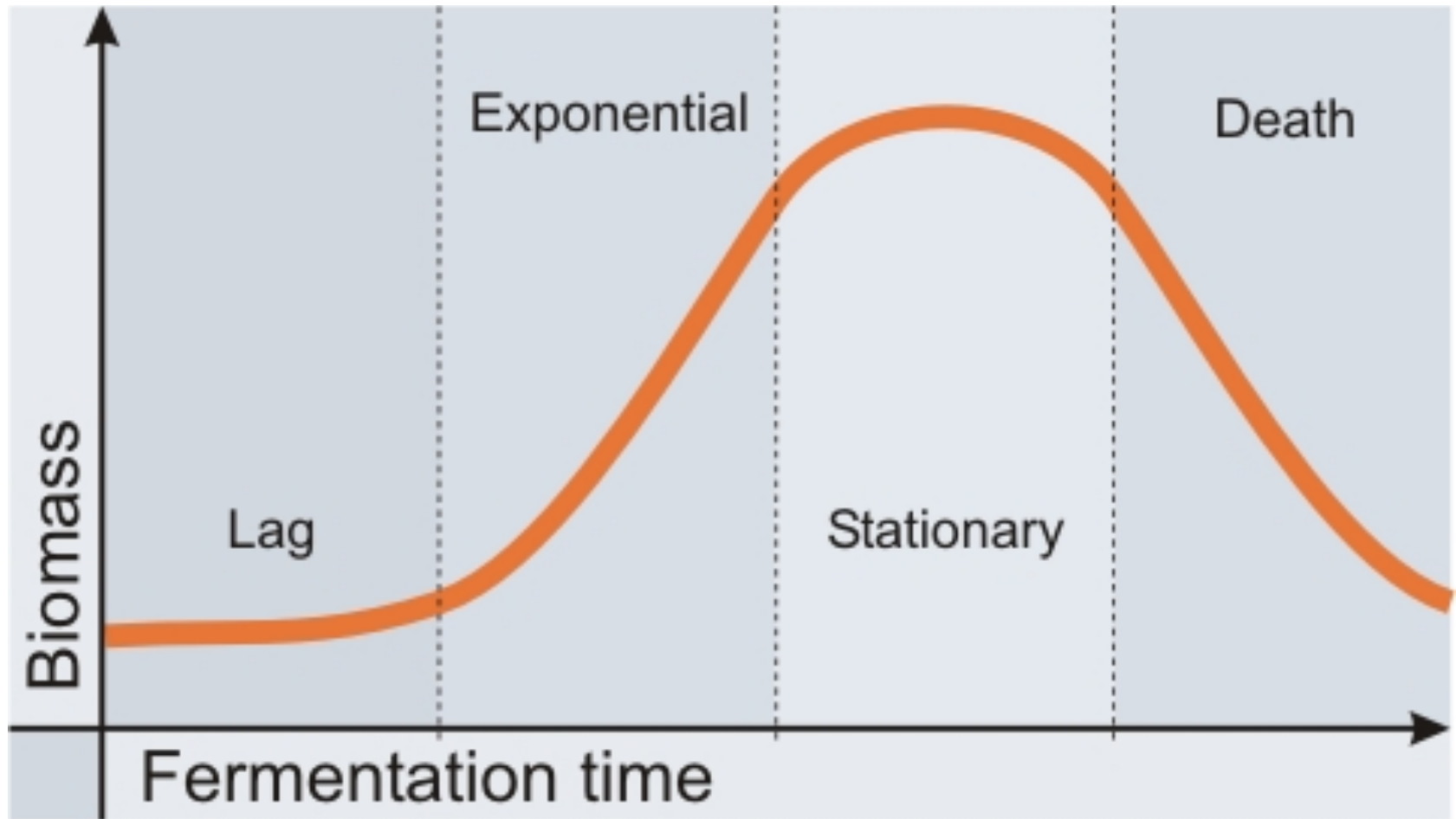


Yeast



Mammalian

Microorganisms Growth Curve

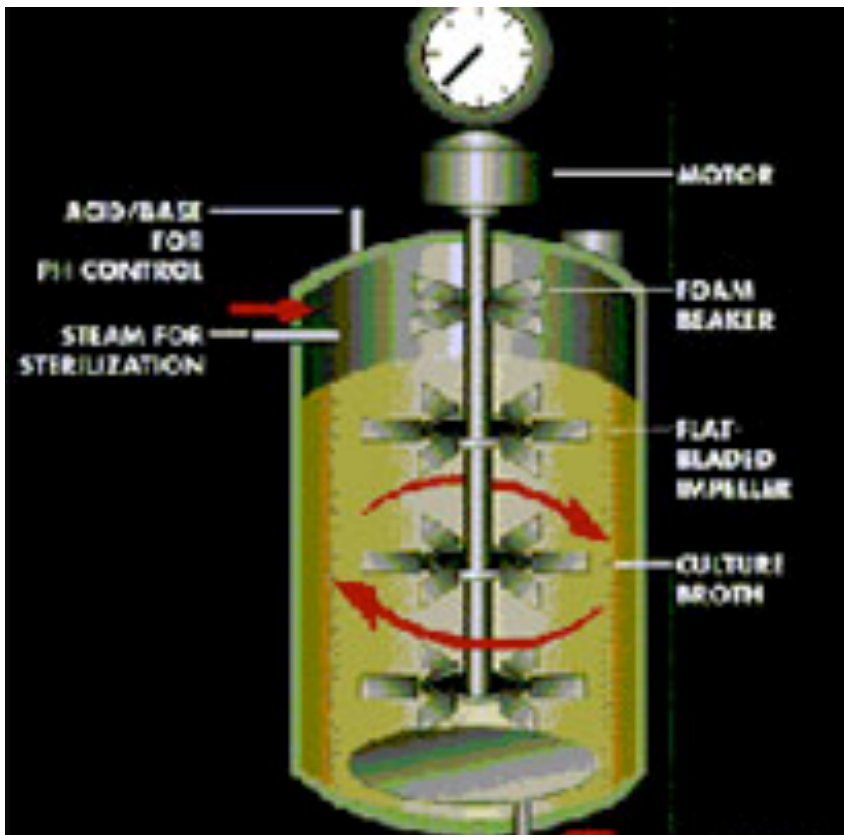


Fermentors and Bioreactors

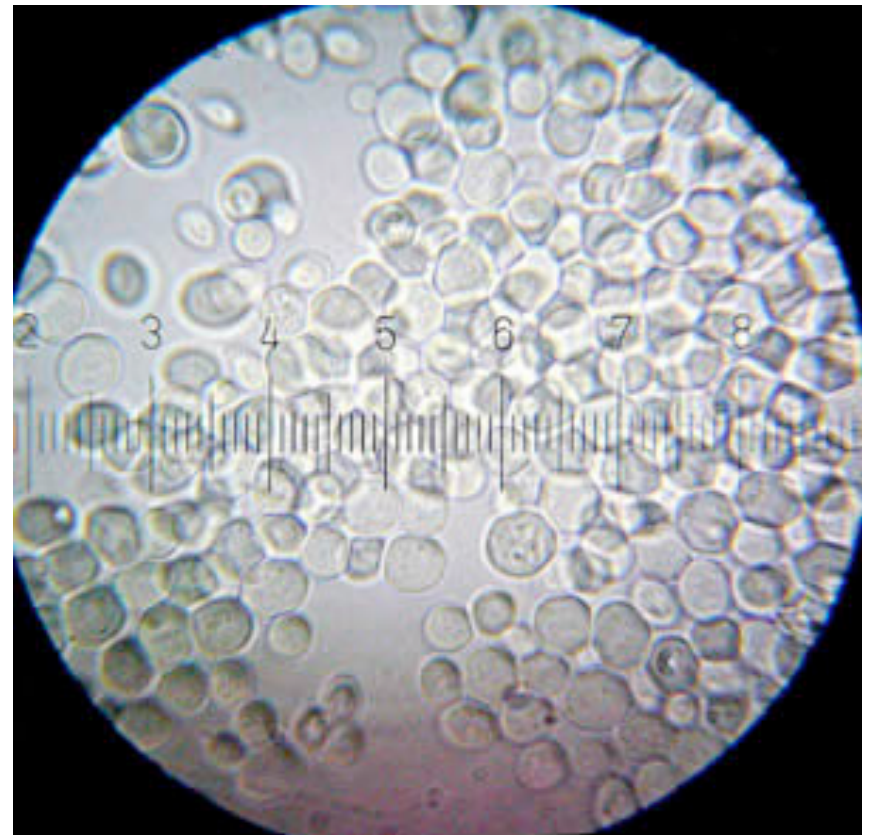
- Larger scale, sustained growth requires bioreactors & fermentors
- Fermentors have been used for centuries – primarily for brewing alcohol and making vinegar
- Modern technology and chemical engineering principles continue to improve fermentor design

Fermentor vs. Fermenter

Fermentor



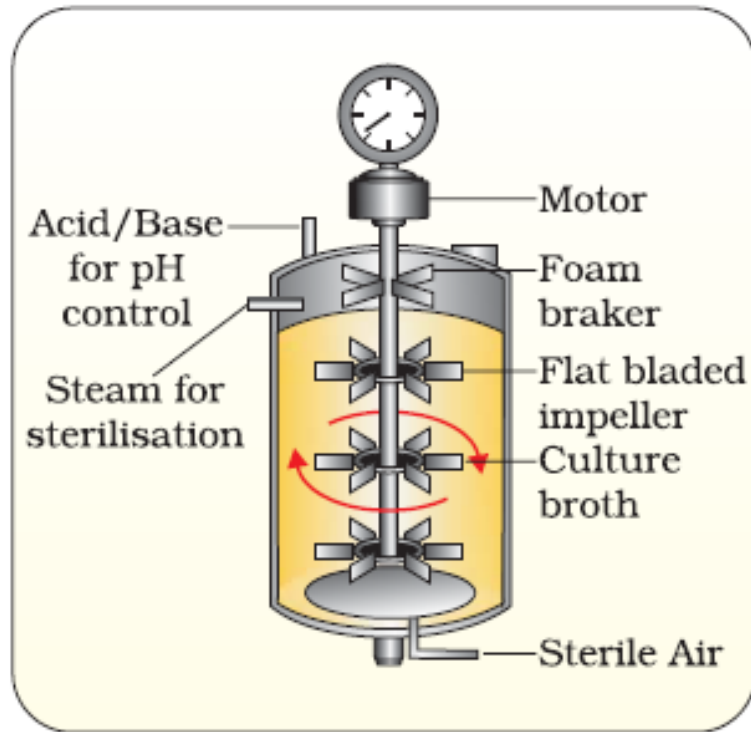
Fermenter



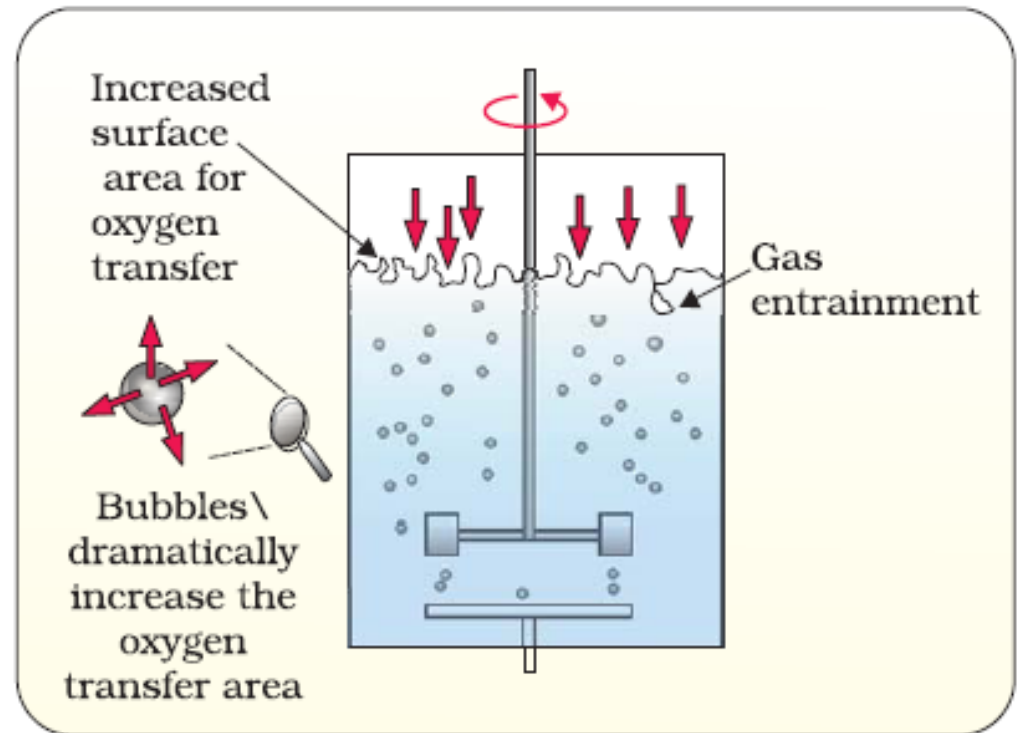
Bioreactors

- **Stirred tank reactors** (mechanical agitation for aeration)
- **Bubble column reactors** (bubbling air into media for aeration)
- **Airlift reactors** (air and media circulate together)
- **Microcarrier (fixed bed) reactor** (cell immobilization on macroporous bed)
- **Membrane bioreactor**: (combination of membrane filtration process with a suspended growth bioreactor)

Stirred Tank



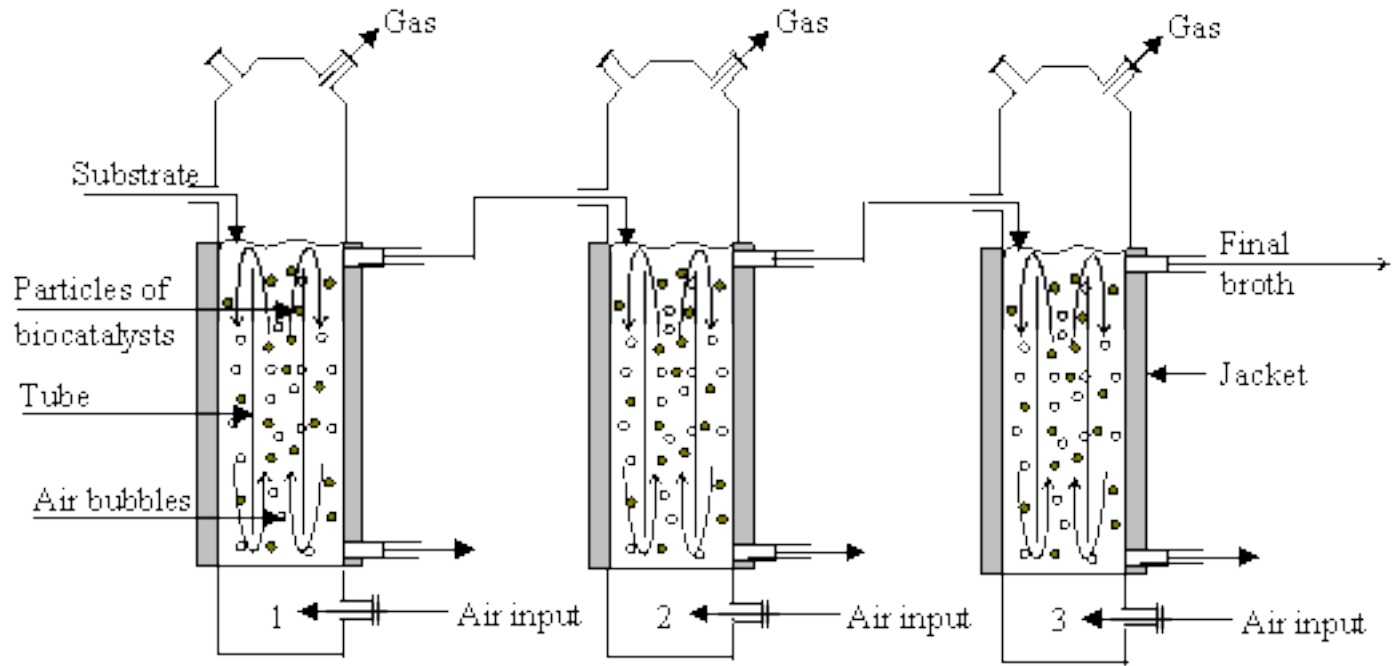
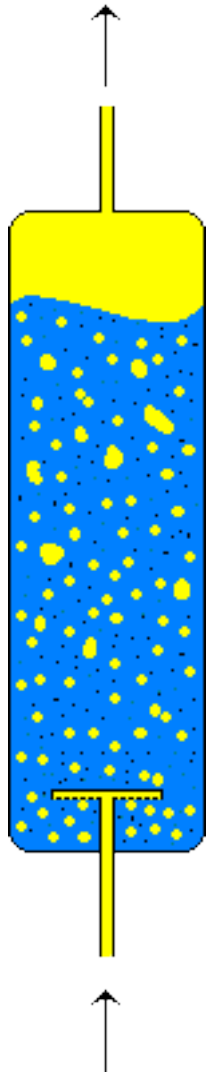
(a)



(b)

Figure 11.7 (a) Simple stirred-tank bioreactor; (b) Sparged stirred-tank bioreactor through which sterile air bubbles are sparged

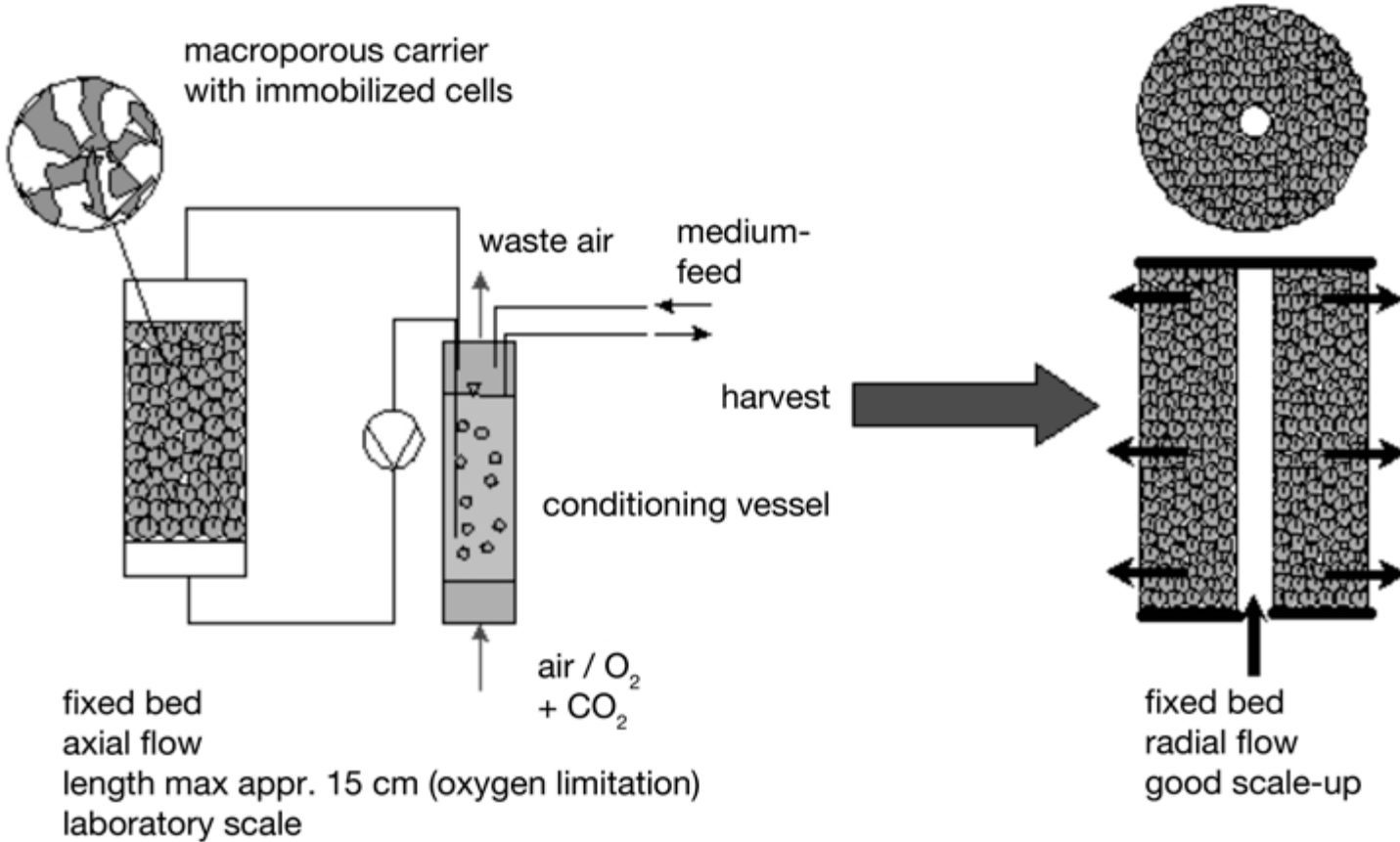
Bubble Column and Airlift



Airlift reactor

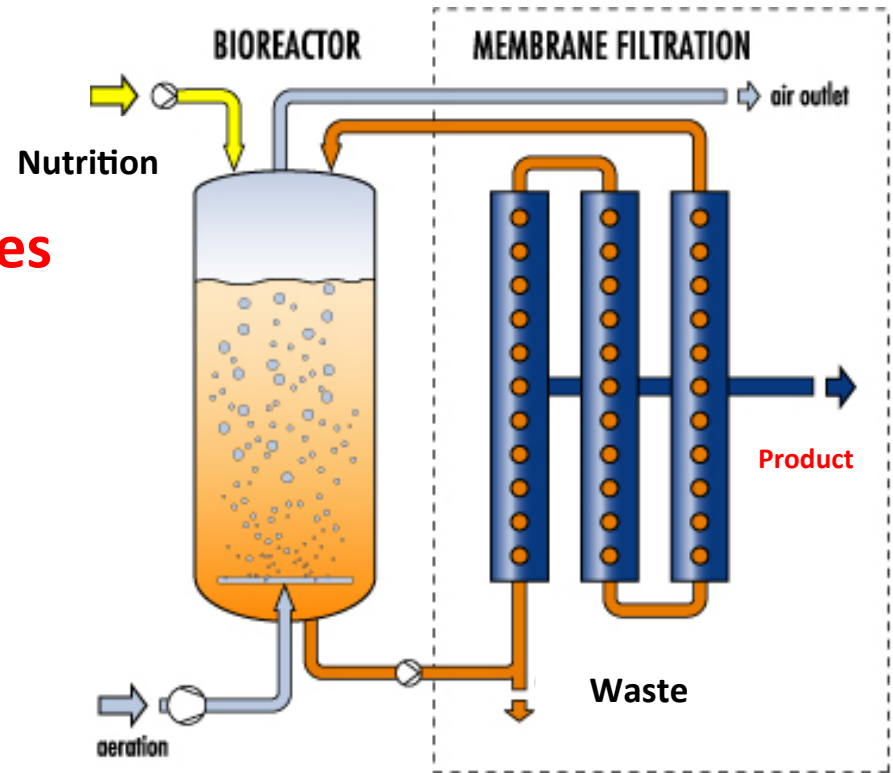
Bubble column reactor

Fixed-bed reactor

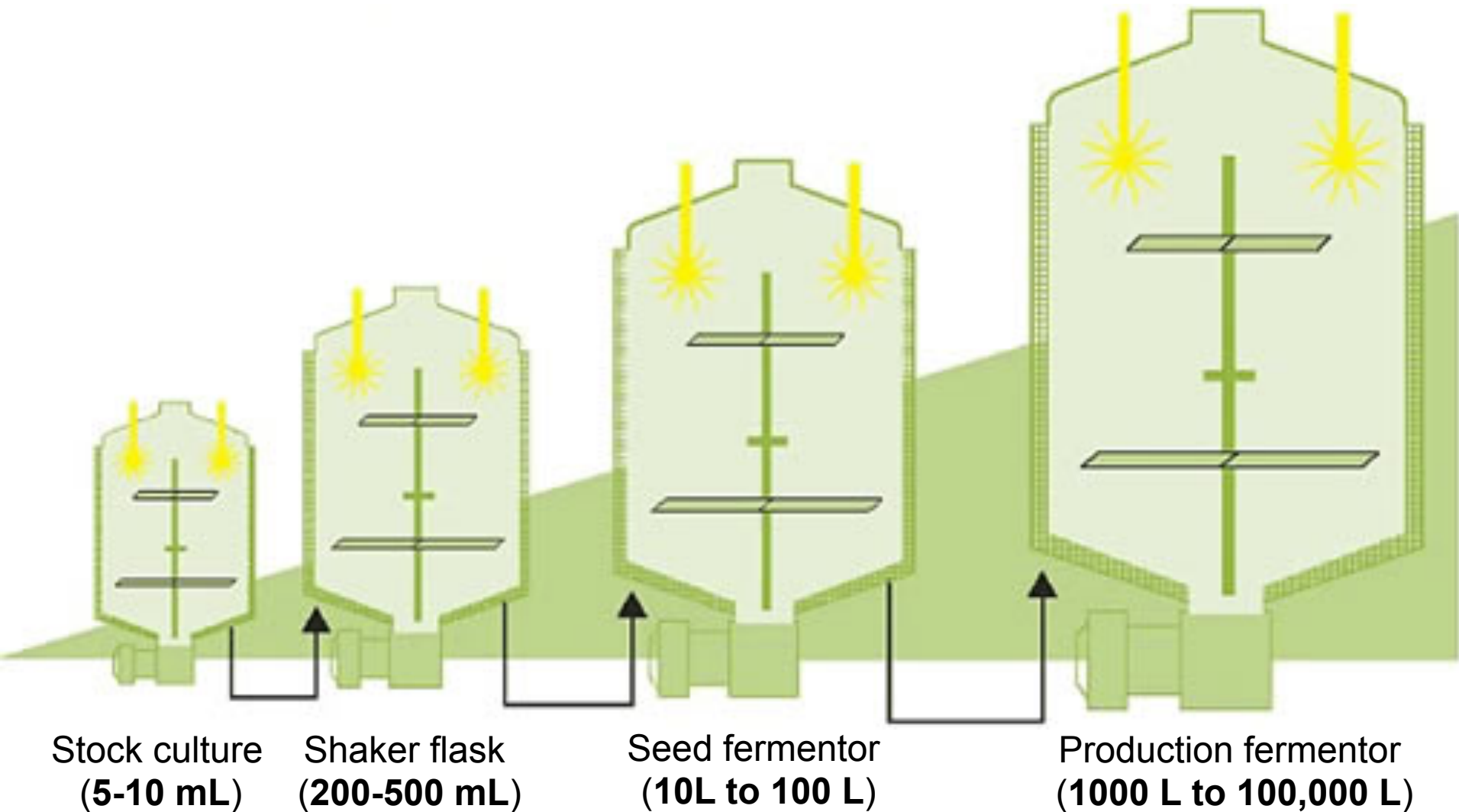


Membrane Bioreactors

- **Combine conventional biological treatment processes with membrane filtration**
- Used widely in municipal and industrial wastewater treatment



Fermentor Scale up



Series of fixed-bed reactor systems in different scales



10 mL
axial-flow



100-mL
axial-flow



1.5 L
radial-flow



5.6 L
radial-flow

Production Process

- **The most common growth processes are:**
 1. Batch
 2. Continuous
 3. Fed Batch
- **The mode of feeding determines the classification of the bioreactor**

Batch Process

- **The bioreactor is only fed once**
- The bioreactor will be allowed to run till completion:
 - In aerobic batch reactors, stopping oxygen supply will turn the system anaerobic and the will be the end of the batch
- Very difficult to achieve in real life because there should be no input to or withdrawal from the bioreactor even for sampling

Cells Retention in Batch Bioreactor

- **Cells are not lost throughout the fermentation**
- **They have time to adapt and multiply to its maximum rate in the batch bioreactor**
- **They will completely biotransform the substrate to products provided other nutrient and environmental parameters are sustained**
- **They will enter the stationary phase either due to limiting nutrients or accumulation of toxic products**

Continuous Process

- **The bioreactor is fed continuously**
- The amount of feed introduced into the bioreactor equals the removed volume
- The process is sensitive and subjected to influence from various factors

Cells Retention in Continuous Bioreactor

- Continuous wash of cells
- Cells always need to continually adapt to the input of nutrients
- This is reduced if the cells are immobilized or recycled

Fed Batch Process

- **The addition of nutrients is controlled to allow temporal variations in the supply nutrients**
- **Possible to control the rate of growth of the microorganisms or the concentration of the biomass by controlling the feed parameters**
- The most common process in industry

Cells Retention in Fed Batch Bioreactor

- Cells are exposed to intermittence of new input of nutrients
- But the cells are maintained in healthy state

Feed Dosing of The Bioreactors

- The stability of the composition of the microbial population depends on:
 1. The impact of the changes
 2. The rapidity of the microorganisms to adjust to the changes forced upon the microorganisms
- Concentration, stable composition of the feed and how the feed is introduced will affect the performance of the bioreactor especially with:
 1. Very sensitive and fastidious microorganisms
 2. Very slow growers
 3. Very small bioreactors
 4. Bioreactors operated on very short retention time

Now you are able to:

- ✓ Identify different types of bioreactors
- ✓ Compare between different bioreactors types
- ✓ Compare between different production processes