Science ABC related to the large scale industry production of chemicals

TRENDS IN BIOPRODUCTION AND BIOREACTOR DESIGN IN RELATION TO PRODUCTION OF SPECIALTY CHEMICALS

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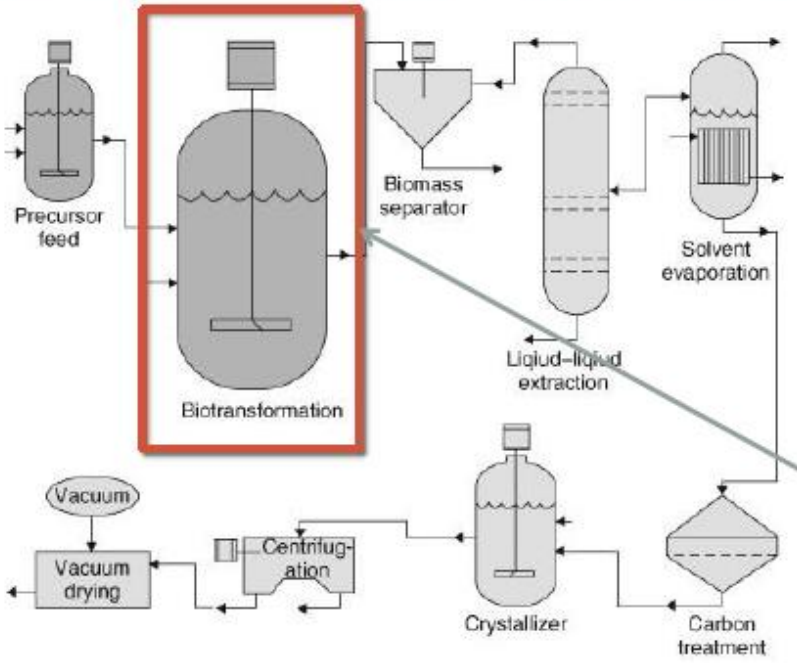
Example of producing bio-based chemicals

Technologies / unit operations

UPSTREAM	DOWNSTREAM	REACTION / FORMU-LATION
Mixing raw materials	Cell separation (filtration, centrifugation, sedimentation)	Reaction (enzymatic, catalytic)
Sterilization	Purification (crystallization, filtration, chromatography, IX, etc.)	Mixing
Fermentation	Concentration (filtration, spray-drying, etc.)	Concentration (filtration, spray-drying, etc.)

Process lay-out example

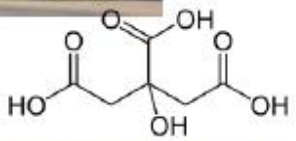
(biocatalysis of ferulic acid to vanillin by *Streptomyces sp.*, Givaudan)



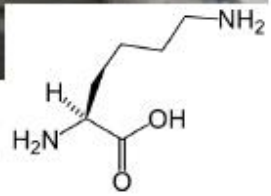
Typical fermentation factories

Biopharmaceuticals

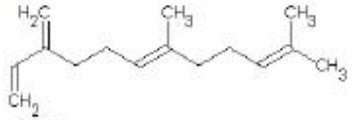
Citric acid (C6)



Lysine (C6)



Farnesene (C10)

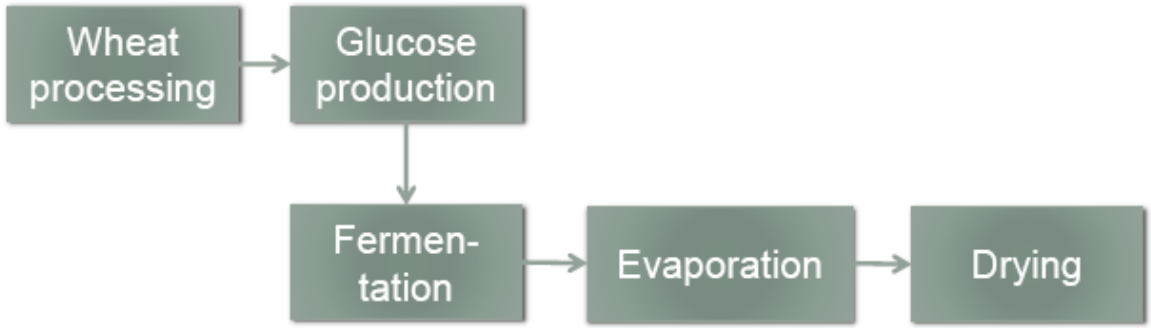


Requirements to run a fermentation process

- Raw materials
- Gene technology
- Fermentation equipment (up to large scale)
- DSP equipment
- Process and fermentation knowledge
- Sterility engineering
- Operational excellence
- ……

Starch
Sugar
Cellulose
Carbohydrates
Glycerol
……..

Lysine production process



World capacity:
1,5 MT/ year

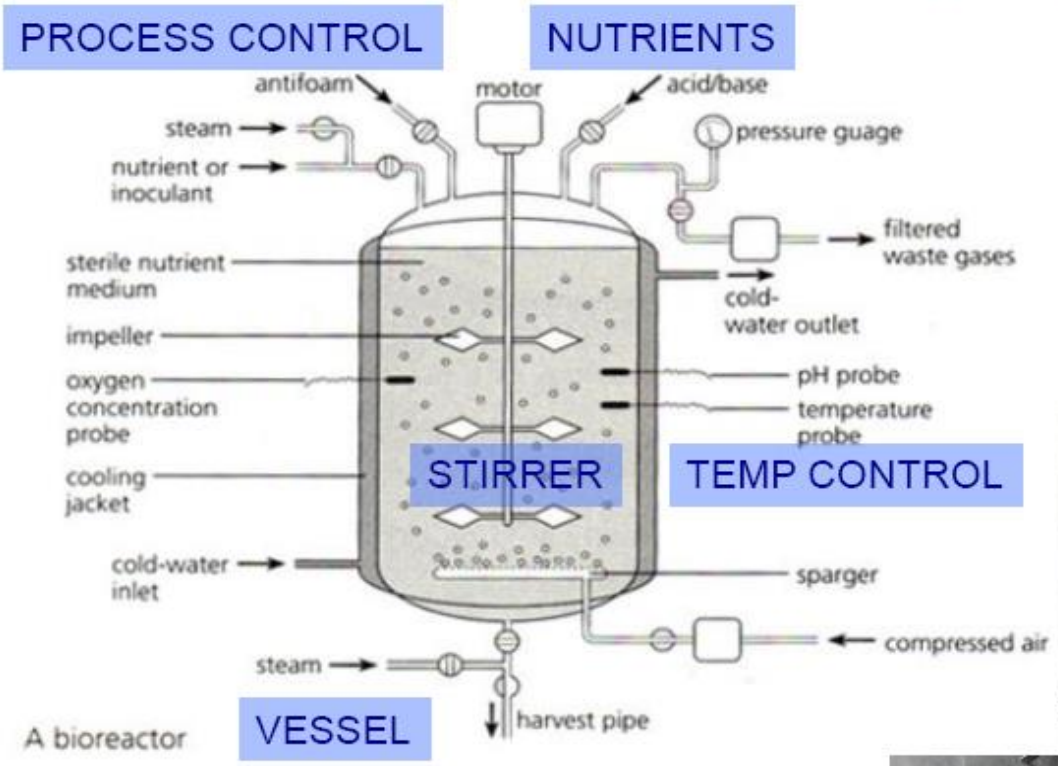
China, US, Brazil, S-Korea

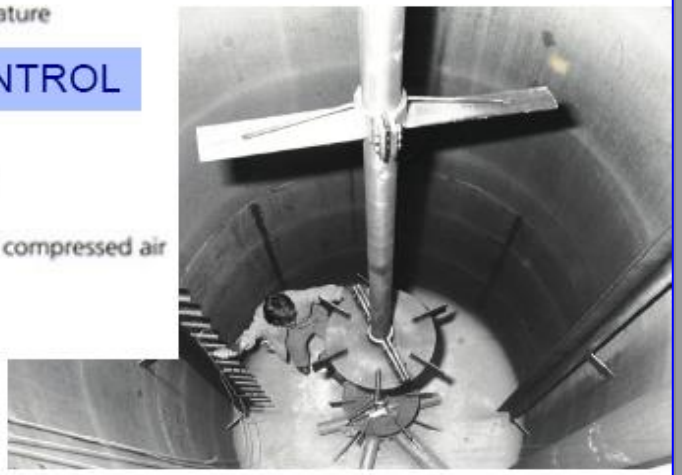
Corn, wheat

COP: ± 1-1,5 €/kg

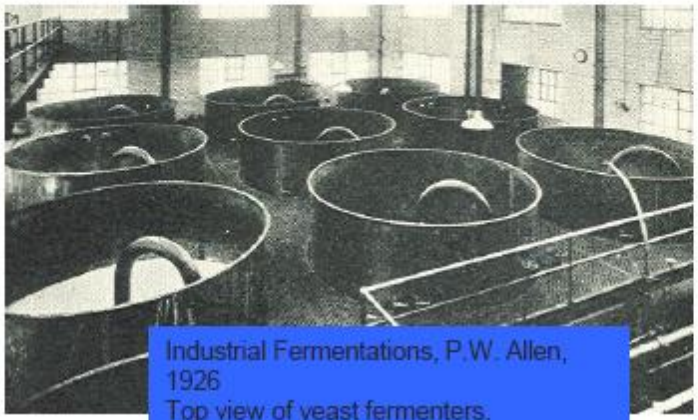
Lysine – factory under construction (Russia)

(Traditional) stirred tank bioreactor (STR)

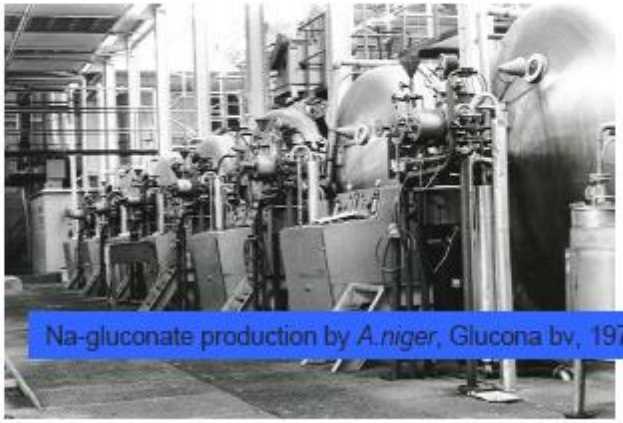




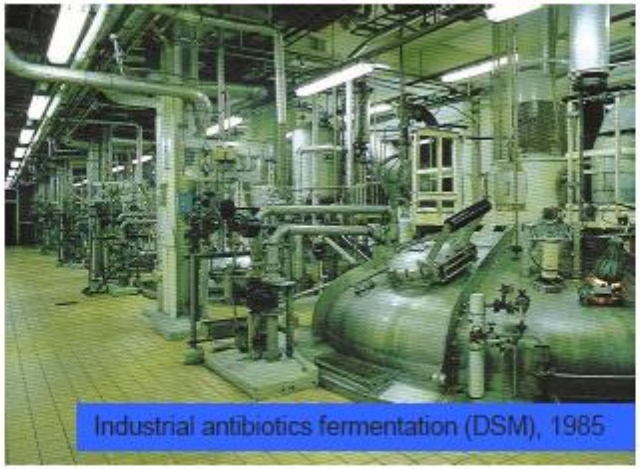
Microbial: not only STR



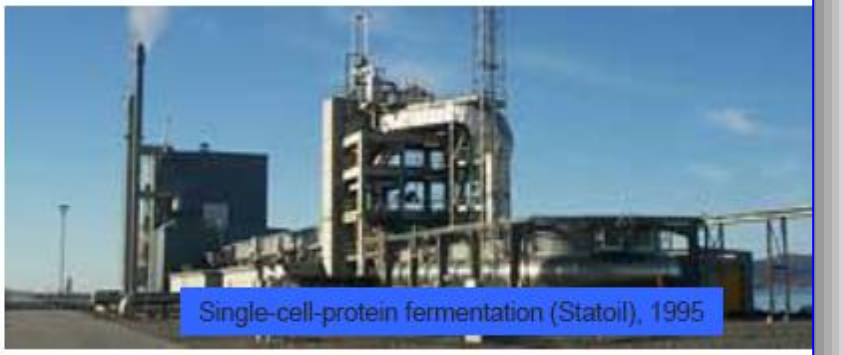
Industrial Fermentations, P.W. Allen, 1926
Top view of yeast fermenters.



Na-gluconate production by *A.niger*, Glucona bv, 1979.



Industrial antibiotics fermentation (DSM), 1985



Single-cell-protein fermentation (Statoil), 1995

Evolution of bioreactor and its trends / developments

Cell culture bioreactors

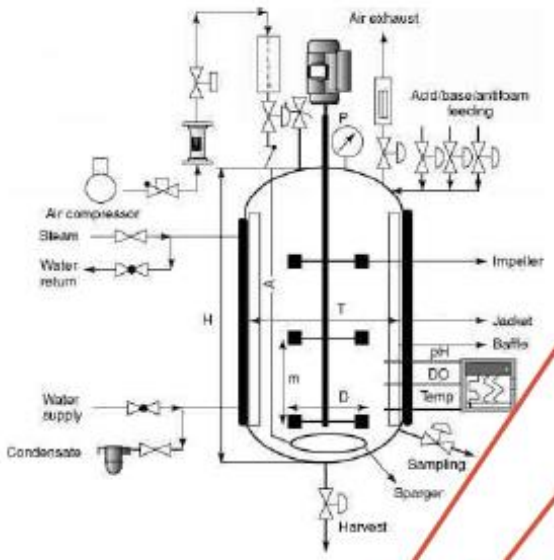
Roller bottles
1980

Vaccine production (verocells), Sanofi-Pasteur, 1985

Steel stirred bioreactors, 1995

Single-use bioreactor, 2013

Stirred bioreactor – most commonly used



Special stirrer design:
Rushton
Curved blade
(inter)-MIG
A316

Improved mixing

Less energy

Higher mass transfer

Low shear

Combinations

Bioreactor development over the last century

Steel (HDPE) → Stainless st[illegible] → Single-use




1920 1970 2000 2010 2015

Special stirrer designs
Rushton
(inter)-MIG
A316

SAFETY
- Pre-sterilized
- No contamination

COSTS
- No cleaning
- Simple infrastructure
- Lower maintenance

Bioreactor trends

- Large-scale bioreactors
  - special stirrer designs / combinations
- Single-use
  - No cleaning (validation)
  - Less infrastructure
  - Sterility guarantee
- Continuous processing => smaller bioreactors
  - Perfusion – high cell density / volumetric productivity
  - Micro-carriers – new (dissolving) materials
- Instrumentation
  - Better level of process control
  - More in-line / difficult for single-use
  - Model based process control

Dedicated facilties

Smaller reactors

Biopharmaceuticals

- All based on gene technologies
- Produced in multi-purpose installations
- Dedicated purification processes

AND:

- Introduction of single-use equipment makes installations more versatile

- Installations can be used for production of:
  - Toxins
  - Viruses
  - Modified bacteria / viruses
  - Etc.

Single-use bioreactors

SAFETY

- Pre-sterilized
- No contamination

COSTS

- No cleaning
- Simple infrastructure
- Lower maintenance

REQUIREMENTS

- Equipment
- Bags
- Components
- Clean room(s)
- Experience

Type of single-use bioreactors

Stirred systems 0.1 L- 2000 L	Wave mixed systems 0.1 L- 500 L	Orbitally shaken systems 1mL – 2500 L	Pneumatically driven systems 1.5 L–500 L (2500 L*)


Hyclone S.U.B.


BIOSTAT CultiBag STR


GE Wave


BioStat CultiBag


OrbShake


CURRENT Bioreactor

CELL-tainer


Xcellerex XDR


PadReactor


PBS Biotech


Protalix Bioreactor


CellMaker

Biotoxin production: requirements

- (Single-use) bioreactor
- Simple laboratory
- Micro-organism + process
- Simple filtration or purification (crystallization)

Product	Production strain	Process
Dysport®	Hall	Fermentation Dialysis Chromatography
Azzalure®	Hall	Fermentation Dialysis Chromatography
Botox®	Allergan "hyper"	Fermentation Precipitation "Crystallisation"
Vistabel® & Vistabex®	Allergan "hyper"	Fermentation Precipitation "Crystallisation"
Xeomin®	Hall	[Unpublished]
Bocouture®	Hall	[Unpublished]

Biotoxins:

LD50 = 0,0004 – 0,002 µg/kg

or: at 75 kg => 0,03 – 0,2 µg

very little amounts needed of biotoxins

Conclusions in relation to (bio)chemical weapons

LARGE SCALE PROCESSES

- Fermentation processes are very dedicated
- Raw material position required
- Capital and energy intensive productions
- Bio-building blocks to be used for further chemical modifications

SMALL SCALE PROCESSES

- Introduction of single-use technologies: less infrastructure required
- Limited number of technology suppliers (US/Europe)
- Installations too small for production of chemical weapons
- Avaibalilty of genetic modification techniques
- Production of bio-toxins / viruses / bacteria becomes more easy

Top-aera's of fermentation industry/capacity