

# Разработка биотехнологических процессов.

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# OC Продукты, получаемые с помощью клеток

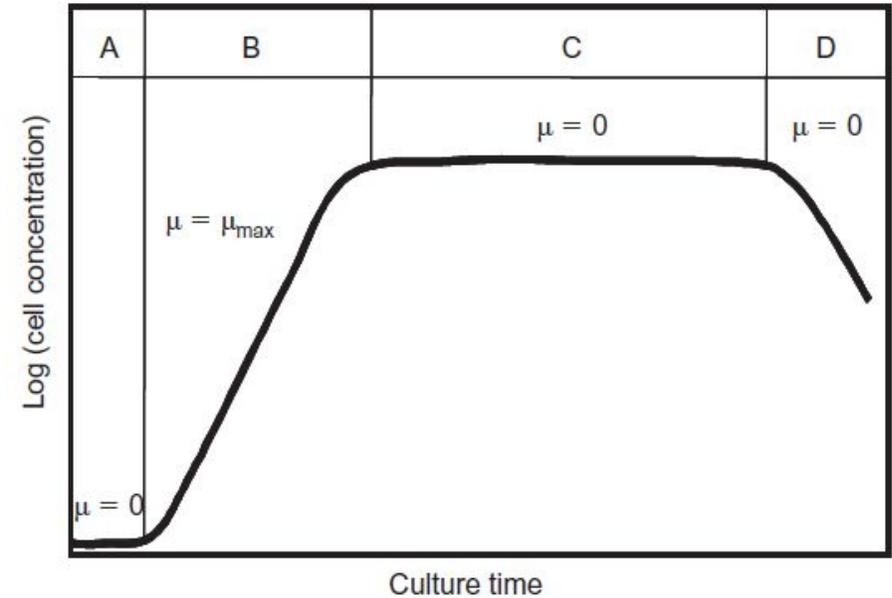
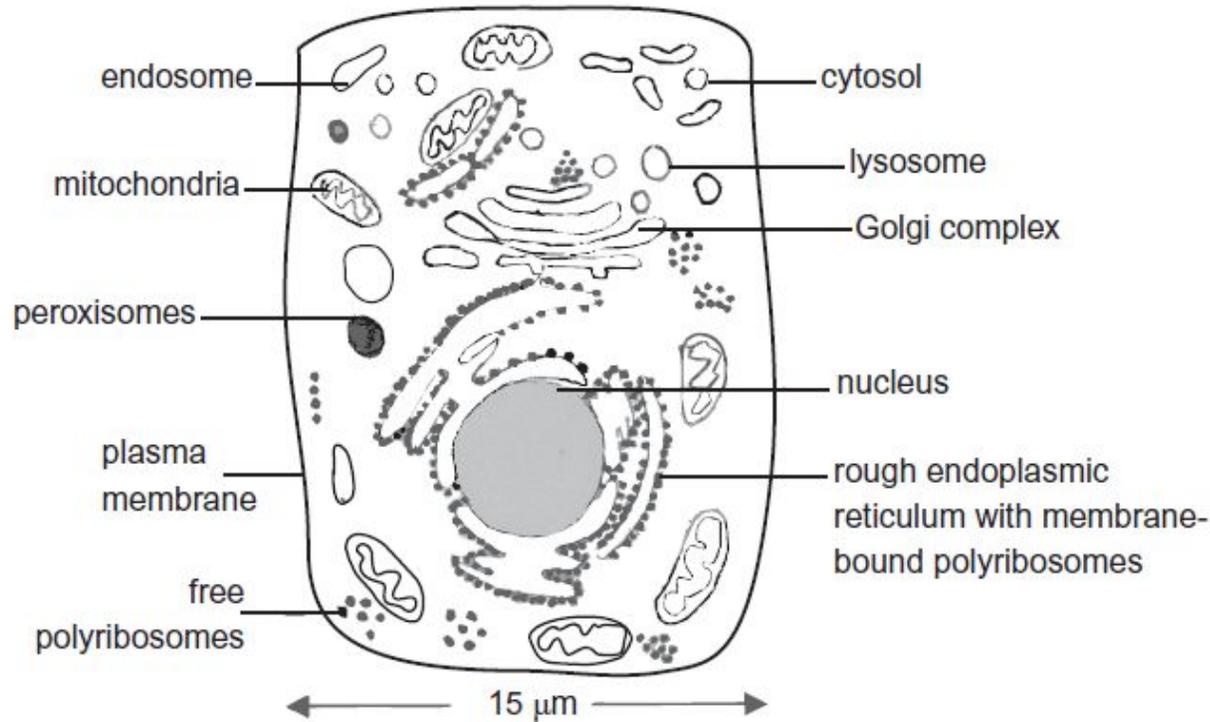
Product	Protein	Use	Cell	Approval year
Avonex <sup>®</sup>	β-Interferon	Multiple sclerosis	CHO	1996
BeneFix <sup>®</sup>	Factor IX	Hemophilia B	CHO	1997
Epogen <sup>®</sup>	Erythropoietin	Anemia	CHO	1989
Gonal-f <sup>®</sup>	Follicle-stimulating hormone	Female infertility	CHO	1995
Herceptin <sup>®</sup> / trastuzumab	mAb	Breast cancer	CHO	1998
Kogenate <sup>®</sup>	Factor VIII	Hemophilia A	BHK	1993
Simulect <sup>®</sup> / basiliximab	mAb	Acute transplanted kidney rejection	Murine myeloma	1998
Campath <sup>®</sup> / alemtuzumab	Humanized mAb	Leukemia	CHO	2001
Xolair <sup>®</sup> / omalizumab	Humanized mAb	Asthma	CHO	2003
Avastin <sup>®</sup> / bevacizumab	Humanized mAb	Colon or rectum carcinoma	CHO	2004

# Часто используемые клеточные линии

Cell line	Source	Applications
COS	Monkey	Transient expression Production of recombinant viruses
HEK-293	Human	Transient and stable expression Production of recombinant viruses
BHK-21	Hamster	Transient and stable expression Vaccine production
CHO.K1, CHO dhfr- Hybridomas, NS0, SP2/0	Hamster Mouse	Transient and stable expression Stable expression Monoclonal antibodies production
MDCK	Dog	Stable expression Vaccines production
Per.C6™	Human	Stable expression Production of recombinant viruses and vaccines
Vero Sf9, Sf21	Monkey Insect	Vaccine production Production of recombinant proteins and baculoviruses
Tn-368, High-Five® BTI-TN-5B1-4	Insect	Recombinant protein production



# Строение и рост клеток

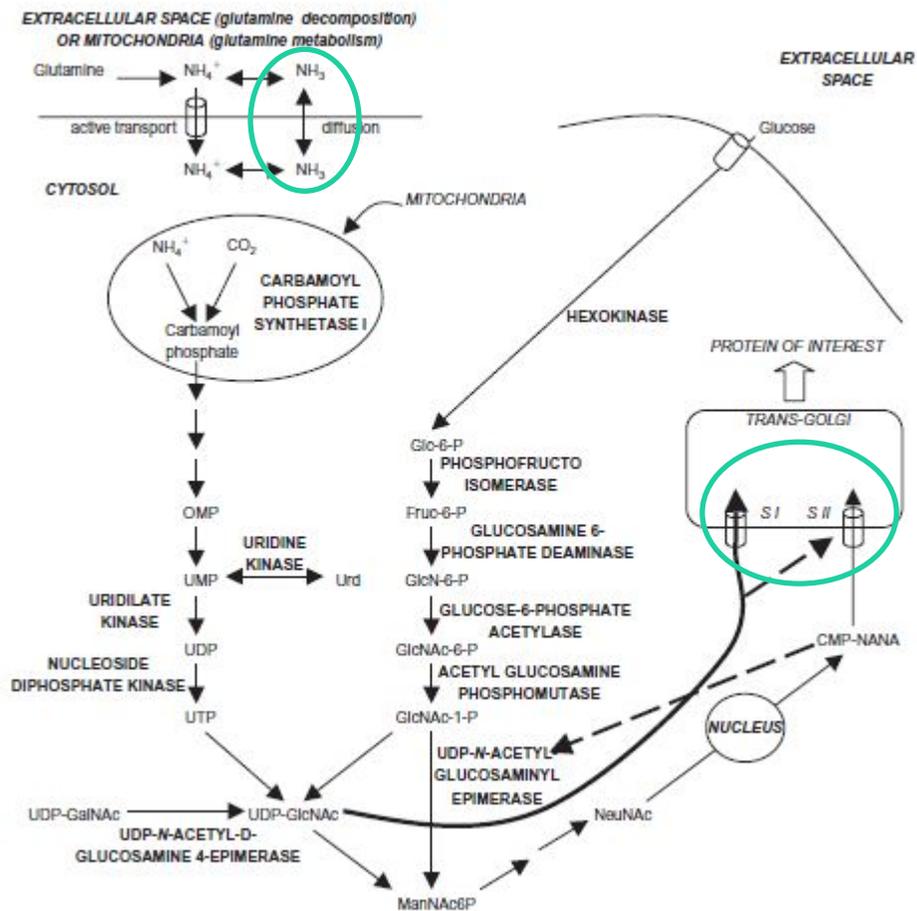
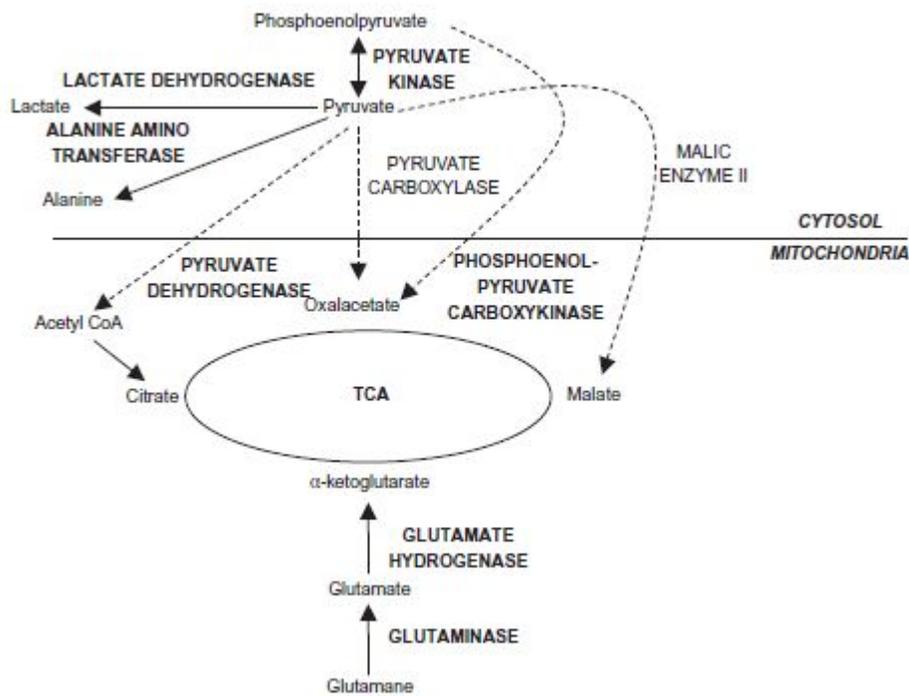


- A – лаг-фаза (адаптация)
- B – лог-фаза (экспоненциальный рост)
- C – стат-фаза
- D – фаза гибели

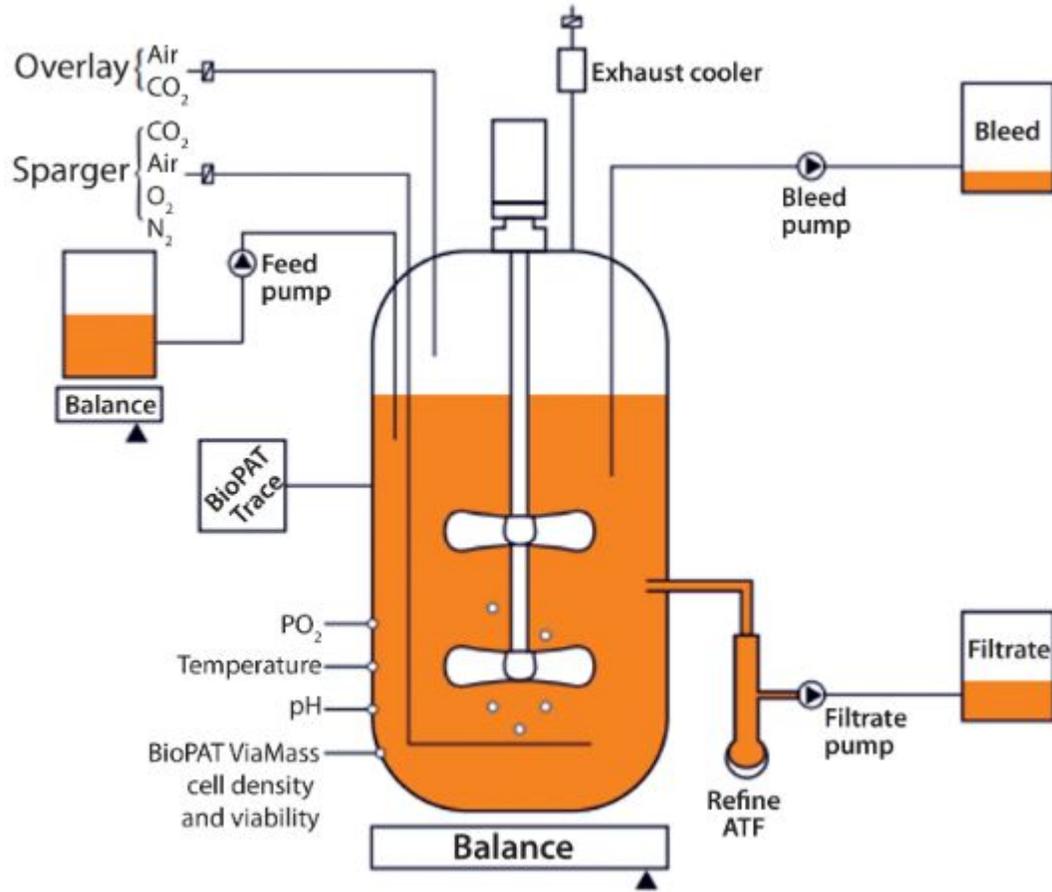




# Метаболизм глутамина

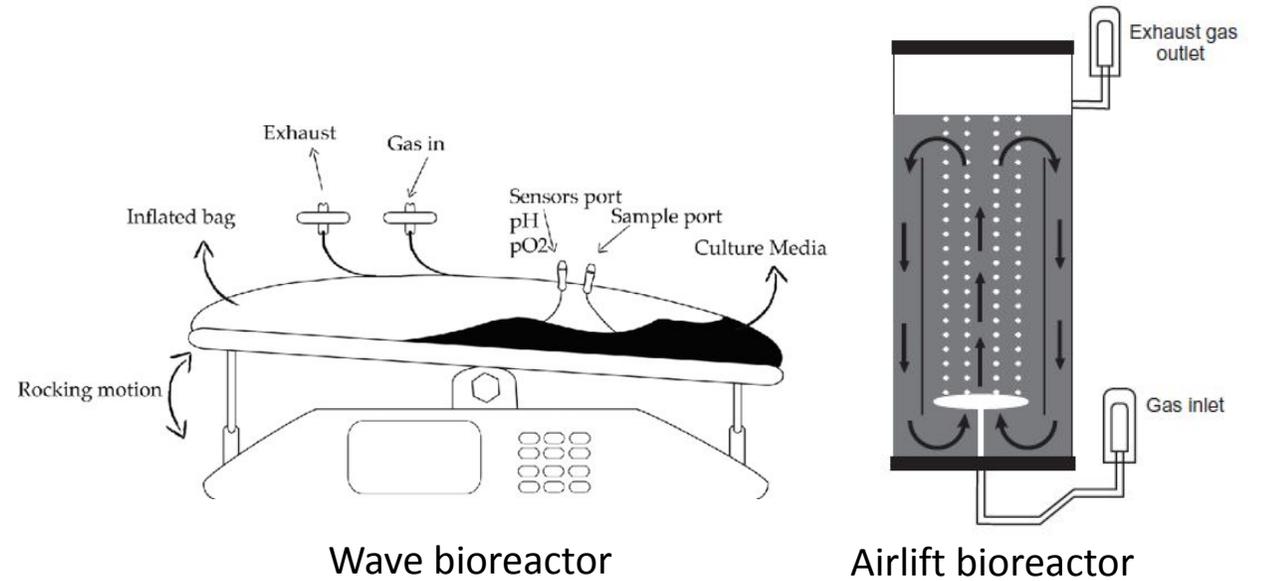
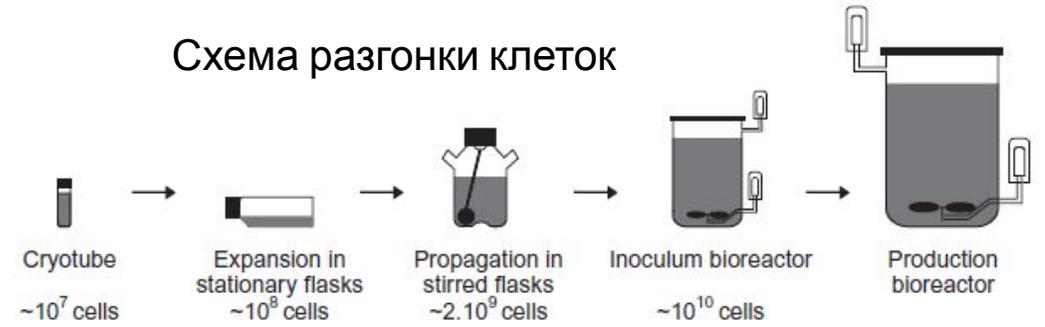


# Types of bioreactors



Bioreactor with perfusion system

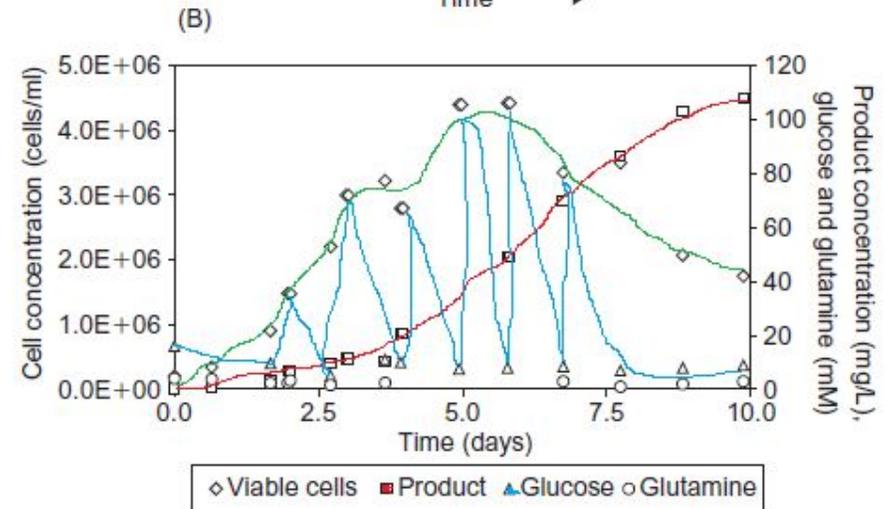
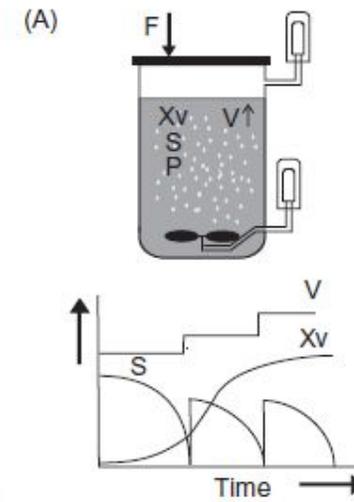
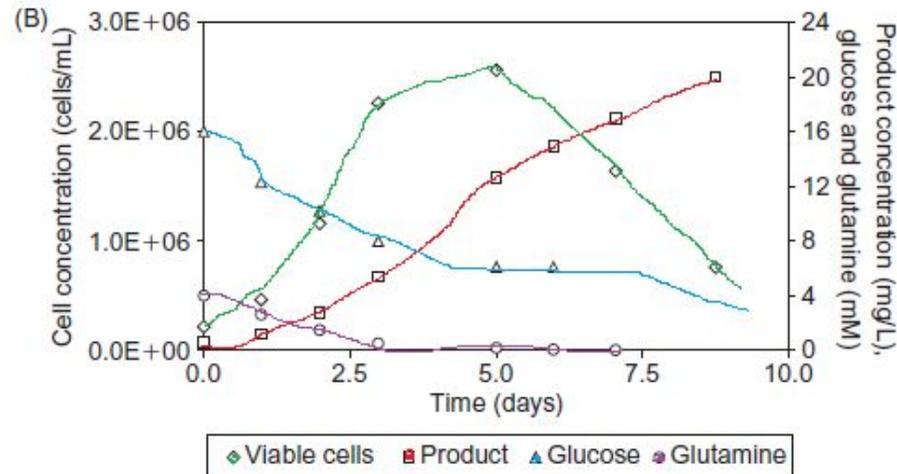
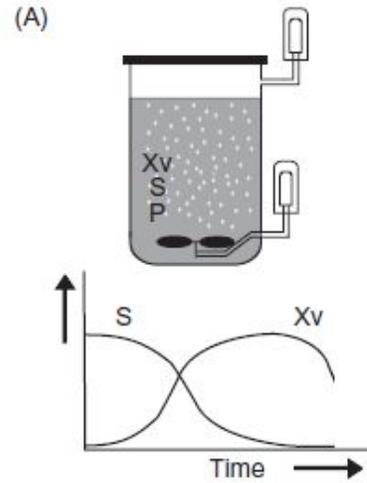
## Cell expansion scheme



Wave bioreactor

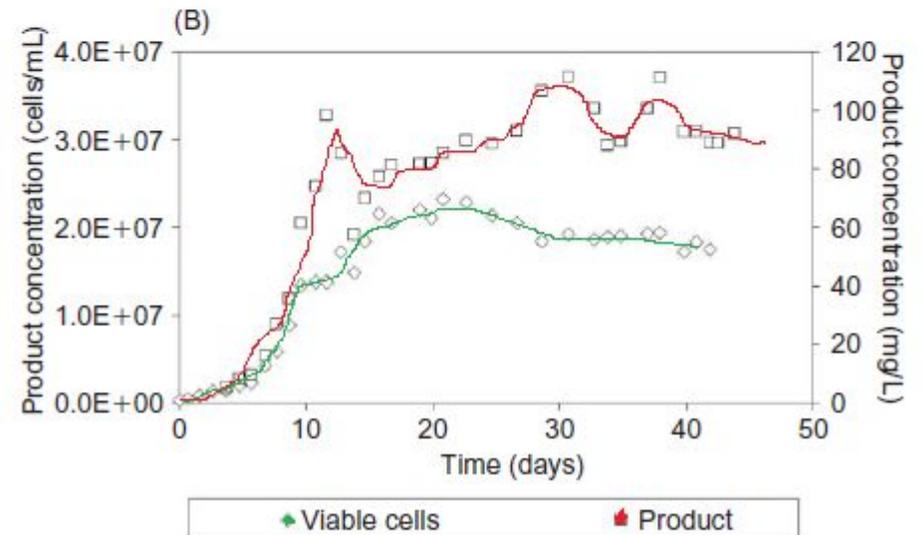
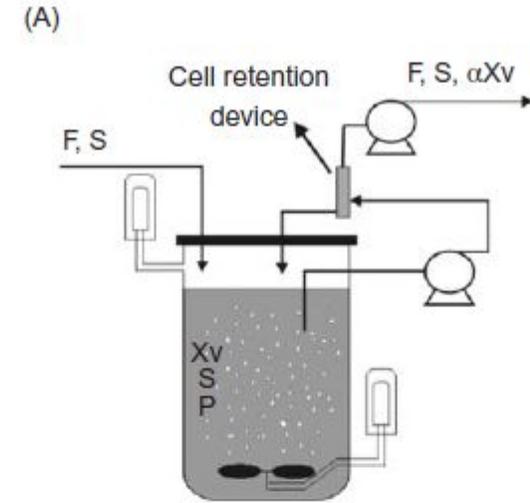
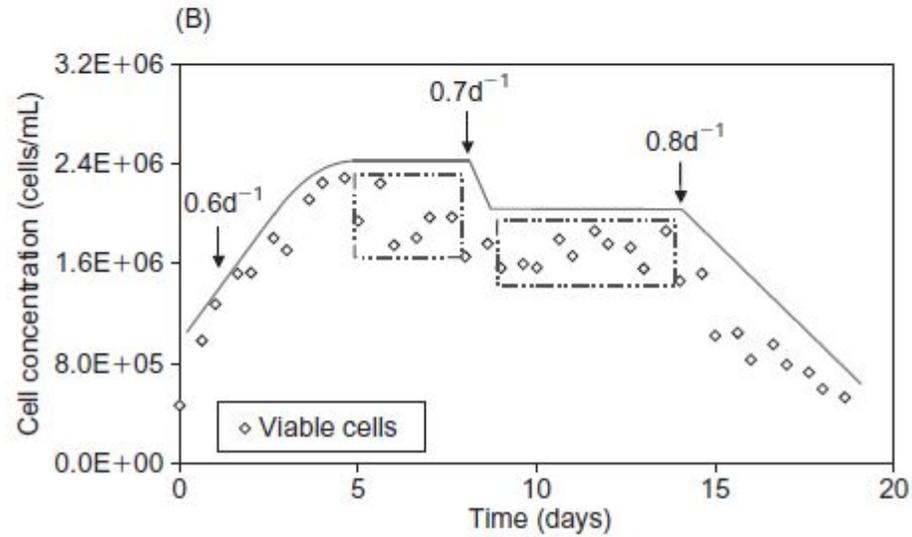
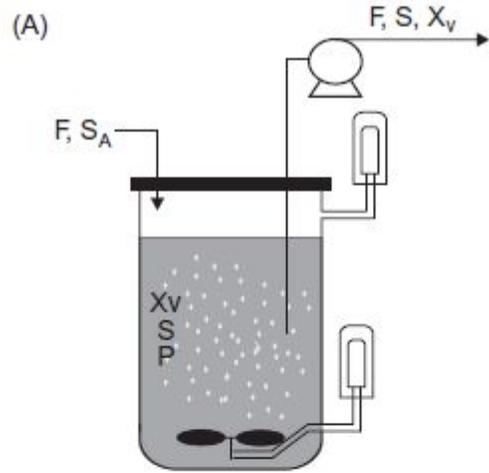
Airlift bioreactor

# OC Batch & Fed-batch





# Continuous process

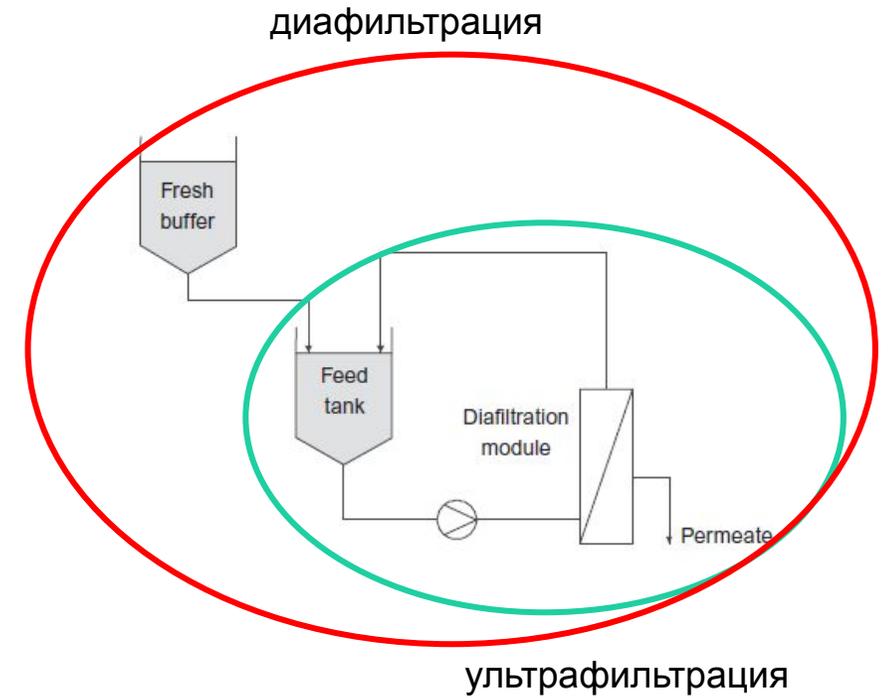
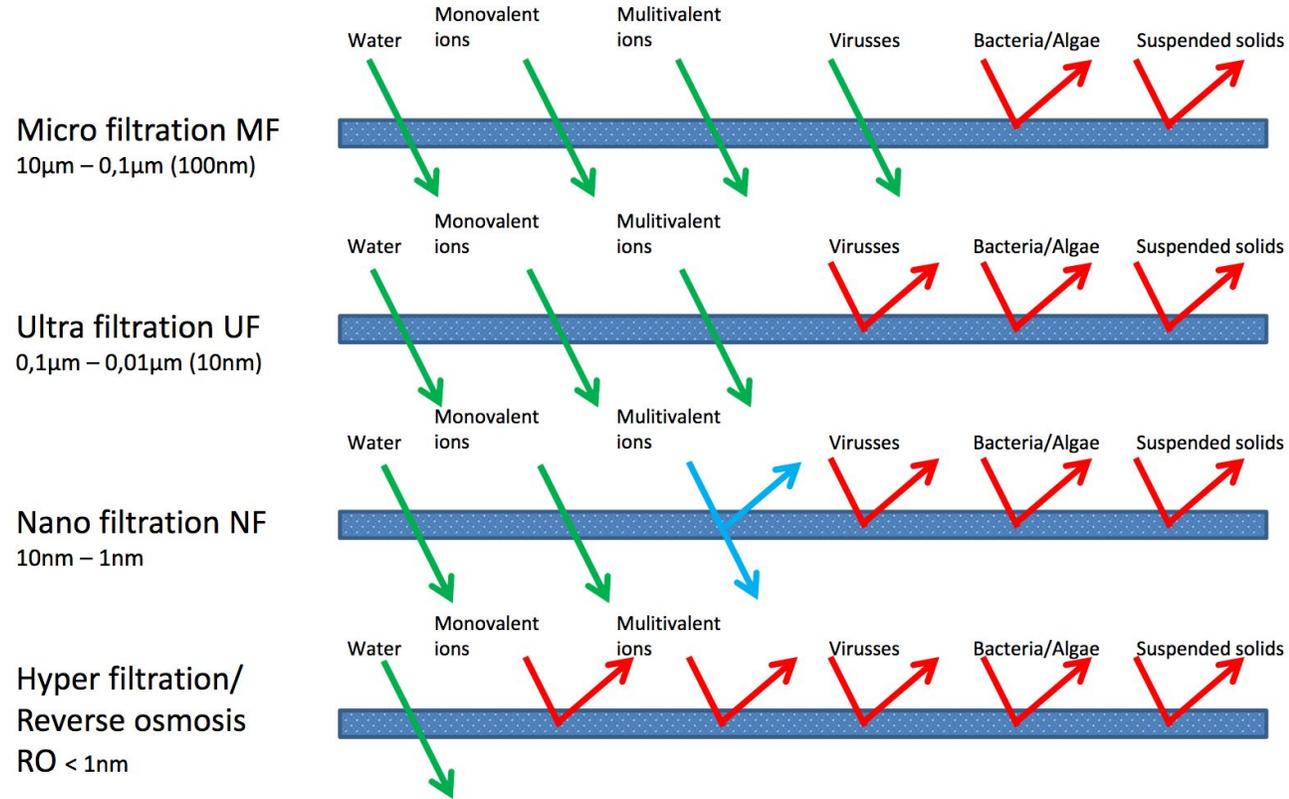




# Методы очистки белков

Principle of separation	Technique	Capacity	Yield	Resolution	Cost
Solubility	Liquid-liquid extraction	High	High	Low	Low
	Fractional precipitation	High	High	Low	Low
Size	Microfiltration, ultrafiltration, dialysis	High	Medium	Low	Low
	Molecular exclusion chromatography	Medium-low	High	Medium-low	Medium
Electrical charge	SDS-PAGE	Very low	High	High	Medium
	Electrofocusing	Very low	High	High	Medium
	Ion exchange chromatography	Medium	Medium	Medium	Medium
Specific interaction with ligands	Affinity chromatography	Medium-low	Low	Very high	High
Surface hydrophobicity	Reverse phase chromatography	Medium	Medium	High	High
	Hydrophobic interaction chromatography	Medium	Medium	Medium	Medium

# Фильтрация





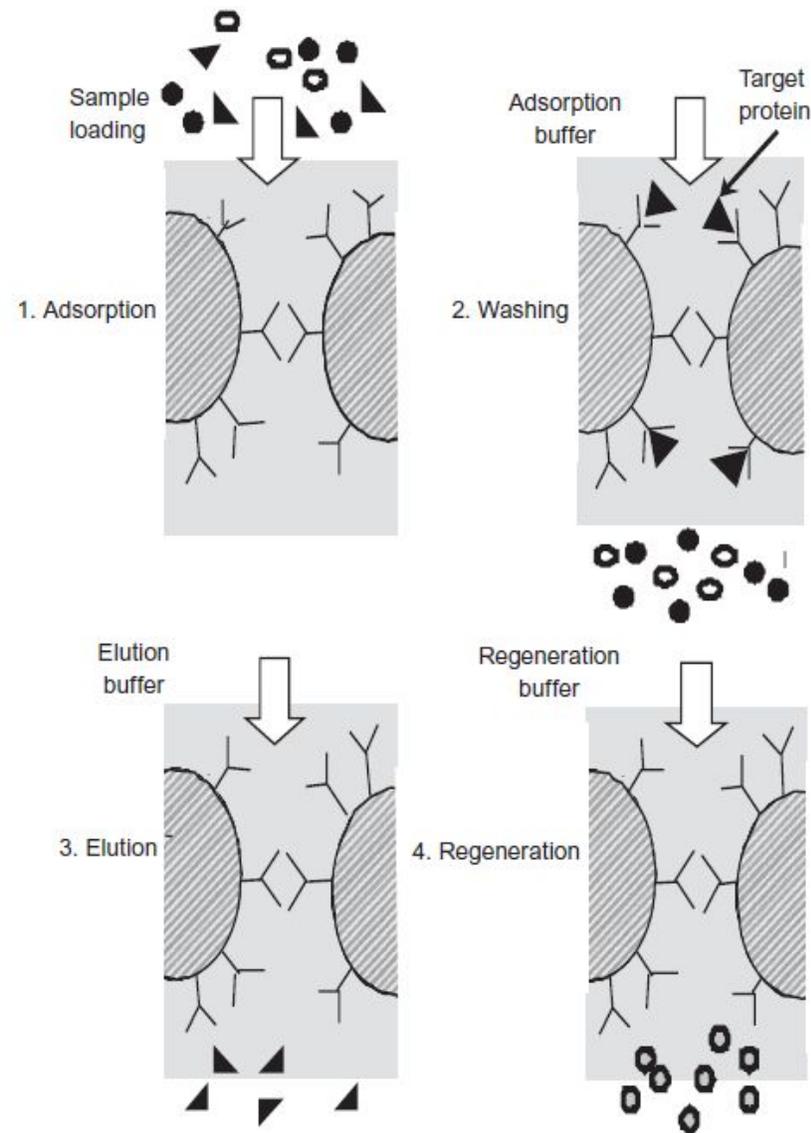
# Хроматография

Аффинная хроматография

Хроматография гидрофобных взаимодействий

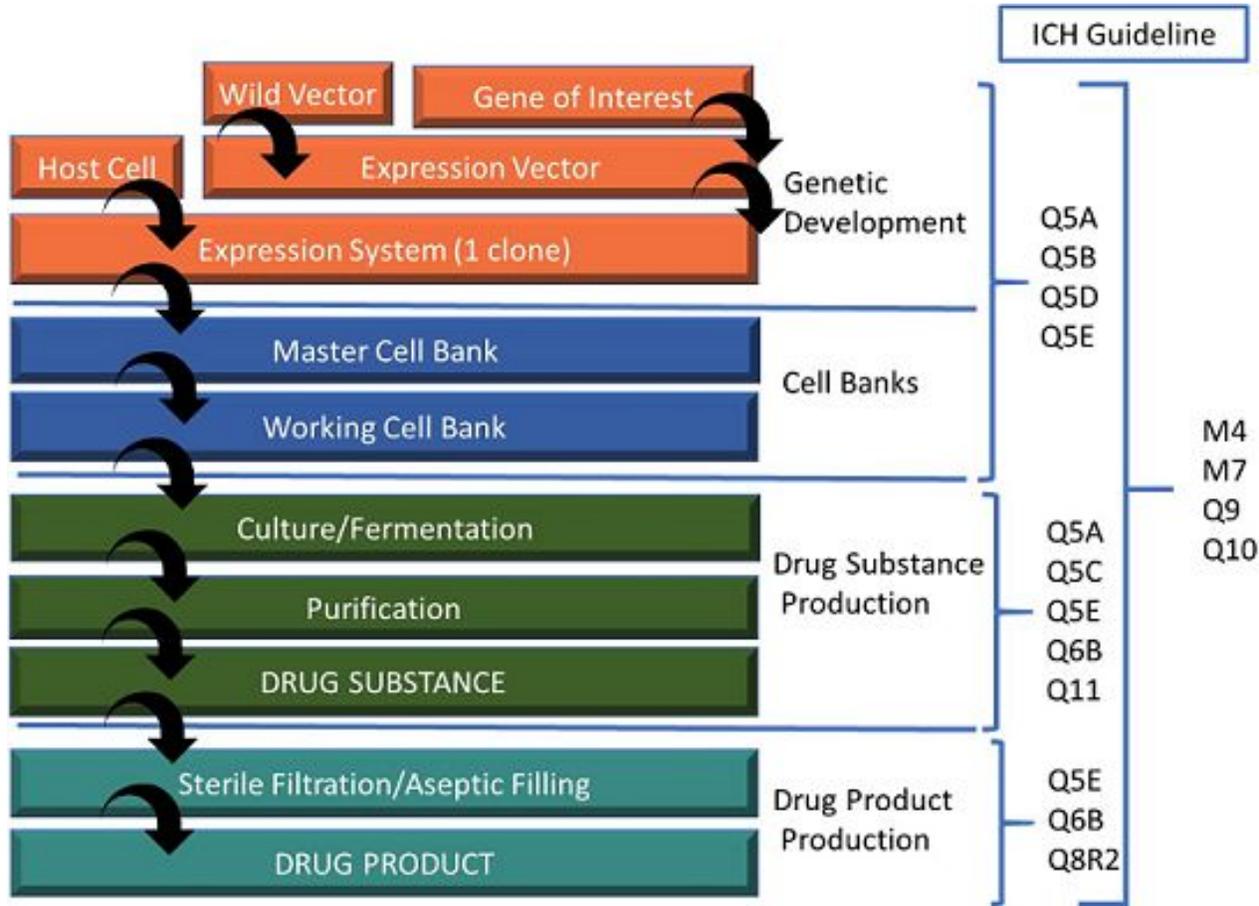
Обратно-фазовая хроматография

Ионообменная хроматография



Formula	Group
<b>Strong anion exchangers</b>	
$-\text{CH}_2\text{N}^+(\text{CH}_3)_3$	Trimethylaminomethyl (TAM)
$-\text{C}_2\text{H}_4\text{N}^+(\text{C}_2\text{H}_5)_3$	Triethylaminoethyl (TEAE)
$-\text{CH}_2\text{N}^+(\text{CH}_3)_3$	Quaternary amine (Q)
<b>Weak anion exchangers</b>	
$-\text{C}_2\text{H}_4\text{N}^+\text{H}_3$	Aminoethyl (AE)
$-\text{C}_2\text{H}_4\text{N}^+\text{H}(\text{C}_2\text{H}_5)_2$	Diethylaminoethyl (DEAE)
<b>Strong cation exchangers</b>	
$-\text{SO}_3^-$	Sulfonate (S)
$-\text{CH}_2\text{SO}_3^-$	Sulfomethyl (SM)
$-\text{C}_3\text{H}_6\text{SO}_3^-$	Sulfopropyl (SP)
<b>Weak cation exchangers</b>	
$-\text{COO}^-$	Carboxy (C)
$-\text{CH}_2\text{COO}^-$	Carboxymethyl (CM)

# ICH Guidelines



- Q1:-Stability testing
- Q2:-Analytical validation
- Q3:-Impurities
- Q4:-Pharmacopoeias
- Q5:-Biotechnological products
- Q6:-Test procedures acceptance criteria
- Q7:-Good manufacturing practices
- Q8:-Pharmaceutical development
- Q9:-Quality risk management
- Q10:-Pharmaceutical quality system



Спасибо за внимание!