CODOBIO

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EvonUp2Date

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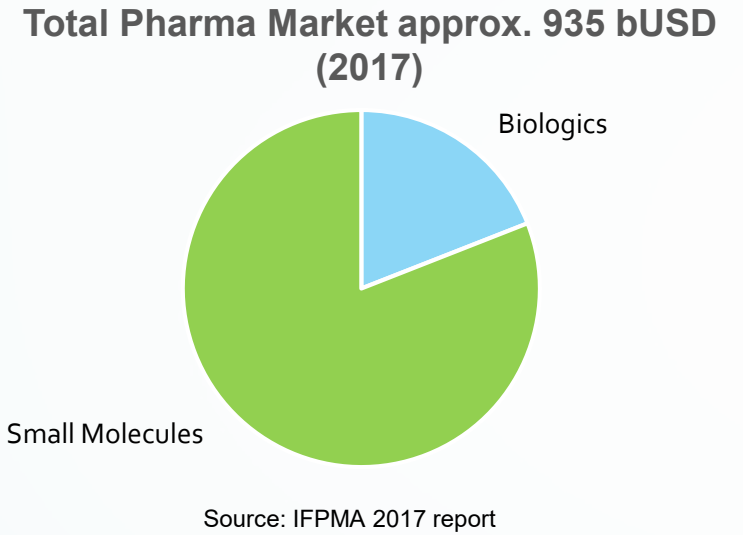
CODOBIO

COntinuous **DO**wnstream Processing of **BIO**logics

Evonik Healthcare

(Bio)Pharma Market Trends



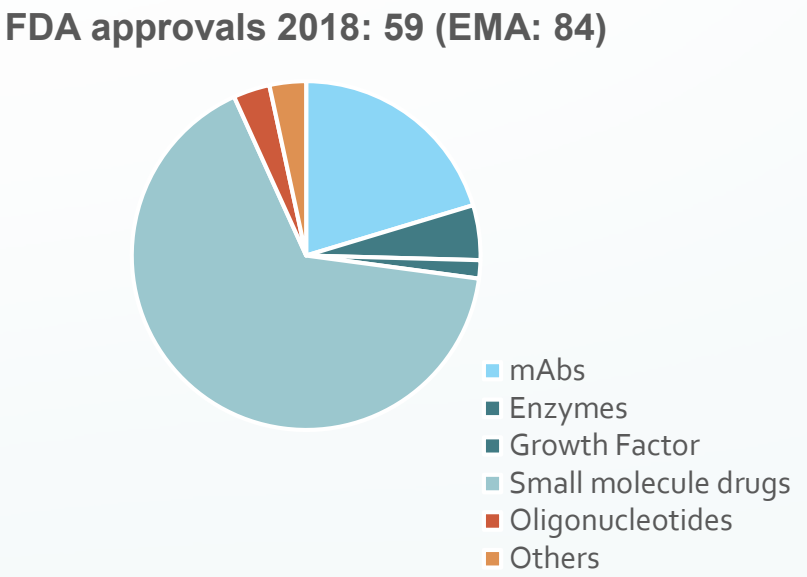
Source: IFPMA 2017 report

Outlook market size:

- Growth to 1170 bUSD expected by 2021
- For Biologics: 237 bUSD (2018)
  → 339 bUSD by 2024 (25 – 30 % market share)

Outlook product approvals:

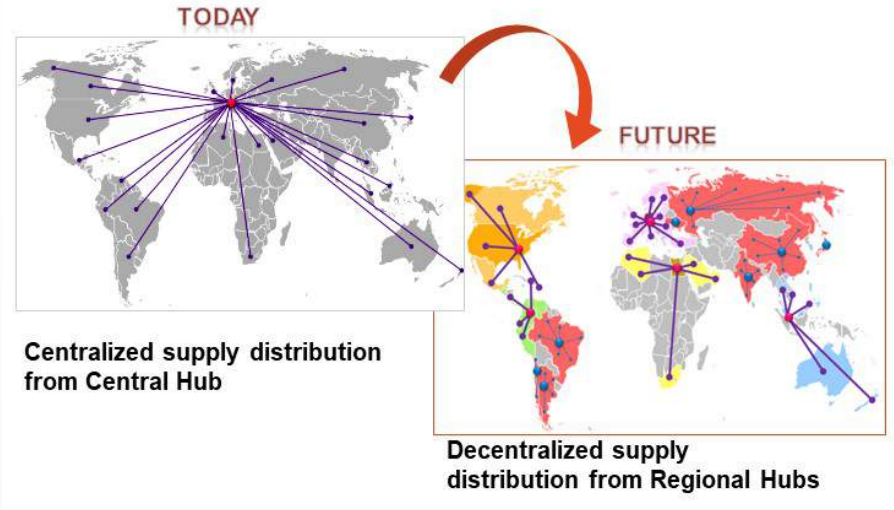
- FDA committed to speed generics and biosimilars approvals, follows EMA
- New formats (Cell and Gene (ATMPs), Oligo-nucleotides) expected to grow



Source: FDA Homepage, C&EN Jan 2019,,
invivo.pharmaintelligence.informa.com
EMA homepage

(Bio)Pharma Market Trends - Geography

- **China as a biomanufacturing hub**
  - Chinese Drug Administration reform (CFDA → State Administration for Health Security)
  - Regulatory and legal changes (member of ICH, collaboration, acceptance of clinical data)
  - Joint ventures with foreign companies
- **World-wide:**
  - Shortage in trained and experienced staff / managers
  - Gap in cell and gene therapy manufacturing capacity
  - High level of investment in capacity, also in high cost countries
- **Manufacturing location:**
  - Centralized vs. de-centralized
  - Autologous cell therapy manufacturing close to the patient (e.g. CAR-T)



Bio(Pharma) Market Trends

- **Main technology trends**
  - **Flexible manufacturing** (single use) vs. Stainless steel
  - Batch processing vs. **Continuous processing**
  - **Precision medicine**, orphan indications (higher productivity, less demand)
  - New protein formats (bi-specific antibodies, Ab-fragments, other proteins)
  - Next generation therapies

Status of continuous manufacturing in biotechnology

Biopharmaceutical purification – Gesundheitsindustrie BW

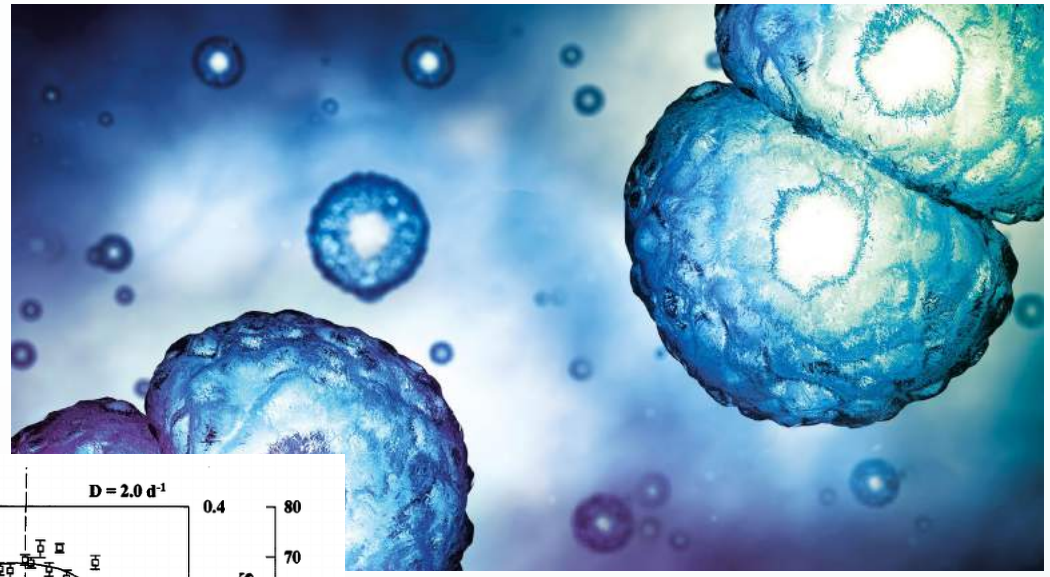
Oil refinery Saudi Arabia – Gulf News

Mainly batch based production
Manual labour, limited control systems

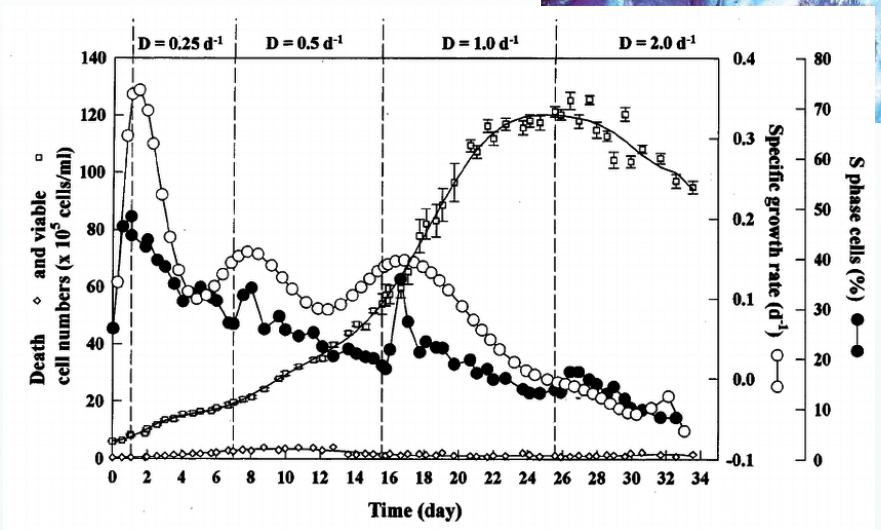
Fully continuous production
Fully automated process wide control systems

Difficulties in biotechnology

- Production through living systems
  - High complexity
  - Limited process understanding
  - Limited monitoring
  - Limited control



Mammalian cells – BPI magazine



Groth rate and process conditions – „Use of cell cycle analysis to characterise growth and interferin-y production in perfusion culture of CHO cells" Leelavatcharamas et al, 1999

Restrictions in biotechnology

- High regulatory demands
  - Patent safety
  - Process control and repeatability
  - Product quality and composition

Quality Guidelines

Q1A - Q1F	Stability
Q2	Analytical Validation
Q3A - Q3D	Impurities
Q4 - Q4B	Pharmacopoeias
Q5A - Q5E	Quality of Biotechnological Products
Q6A- Q6B	Specifications
Q7	Good Manufacturing Practice
Q8	Pharmaceutical Development
Q9	Quality Risk Management
Q10	Pharmaceutical Quality System
Q11	Development and Manufacture of Drug Substances.
Q12	Lifecycle management

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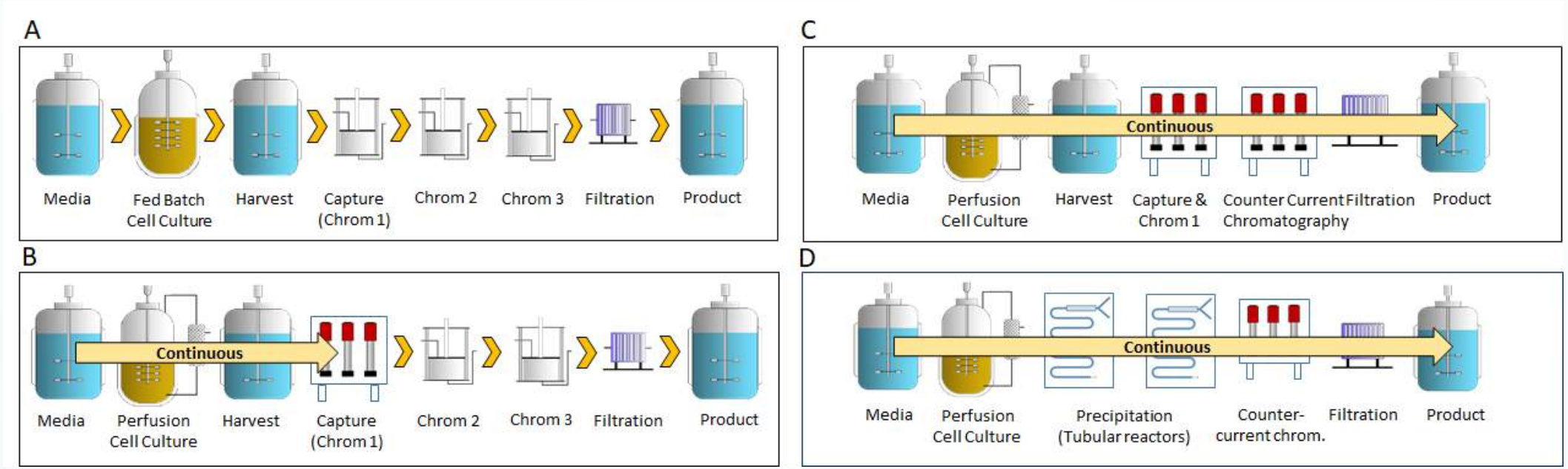
FDA Quality Guidelines

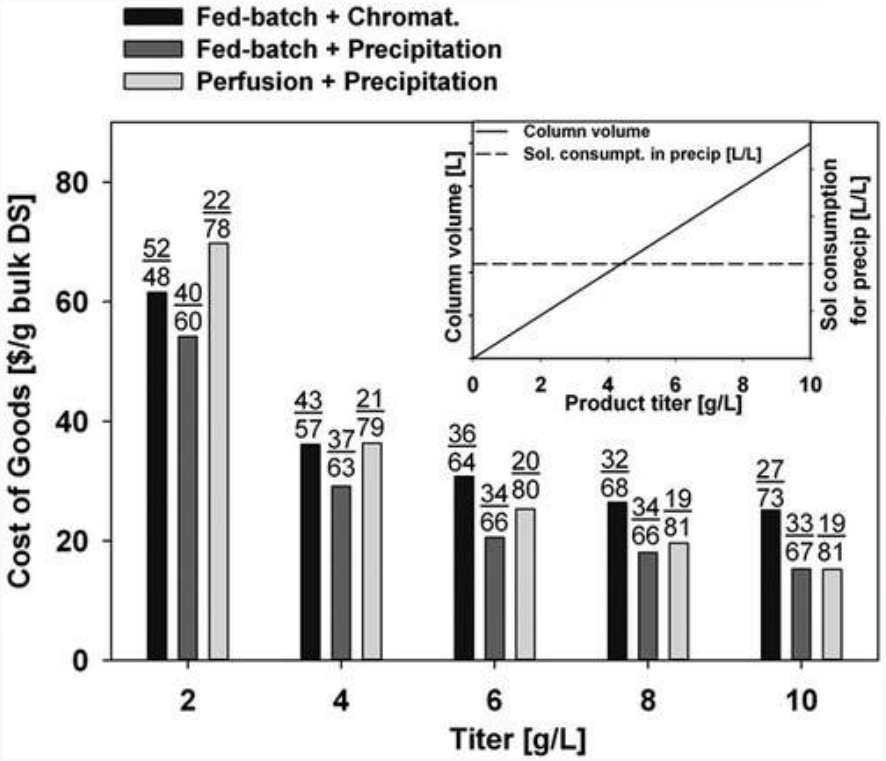
Why continuous processing for biologics?



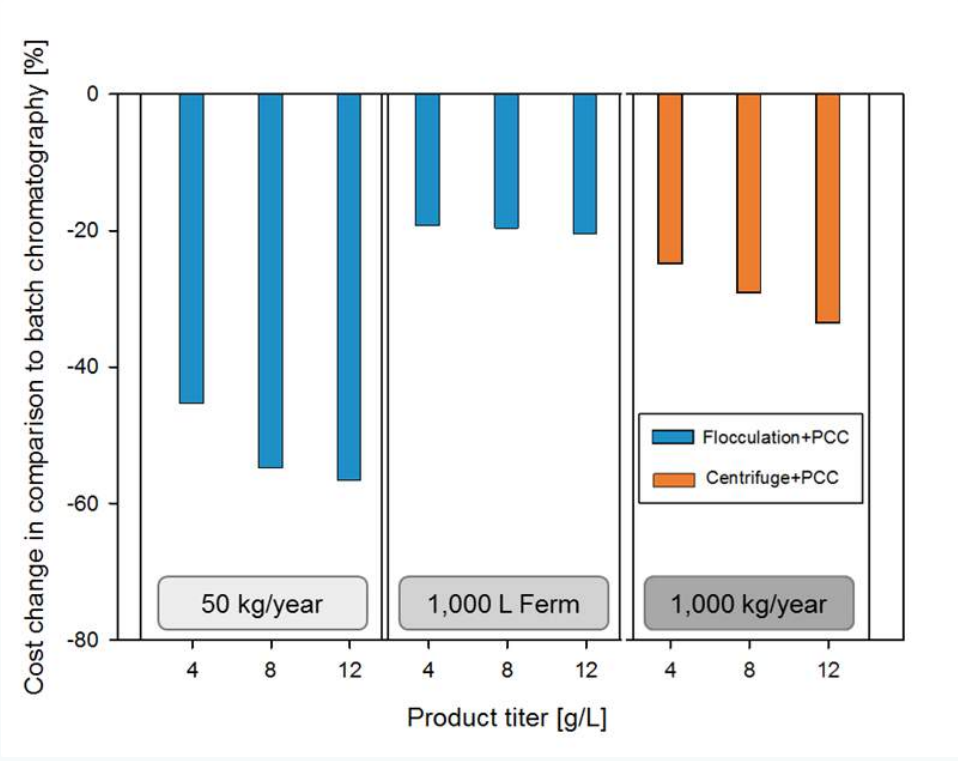
One seamless unit operation from upstream to downstream

Why continuous processing for biologics?

- Cost reduction and better quality



„Economics of recombinant antibody production processes at various scales: Industry-standard compared to continuous precipitation"– Hammerschmidt et al - 2014



CoG reduction for the switch from batch to continuous operation – ACS 2019 – Cataldo et al

Who am I to talk about continuous processing?

- Horizon 2020 NextBioPharmDSP
  Continuous purification of monoclonal antibodies (cancer therapy)

- Tackled the implementation of a pilot scale continuous operated mAb purification

- Missing Topics
  - Automation and Control
  - Experienced personell

Why a training network and research?

- **We need qualified personnel**
- We need applied science for realizing the benefit of continuous operation
- We need to overcome the reluctance of management to change

Batch chromatography

Reports of continuous periodic chromatography since 2010, concepts discussed earlier

Academia

Instruments available since 2012
Dedicated instruments available since a few years

Supplier

Instruments in the toolbox of process development
No large scale production yet

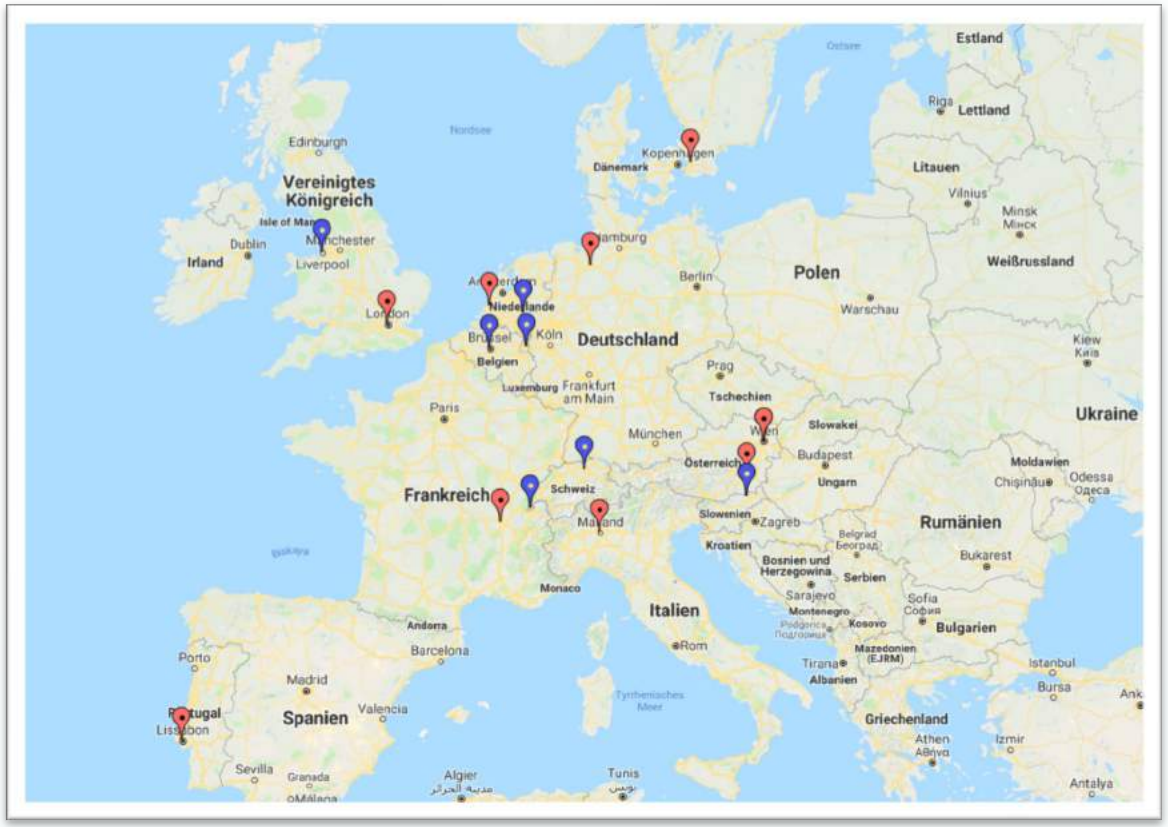
Manufacturing

Periodic counter current chromatography

Who are we, who is CODOBIO ?

15 PhD students at 9 research institutions and companies in 8 different countries around Europe

ACIB GmbH (coordinator)	Academia	AT
Technische Universiteit Delft	Academia	NL
NovaSep Process	Industry	F
Jacobs University Bremen GmbH	Academia	DE
Lunds Universitet	Academia	SE
Evon GmbH	Industry	AT
Instituto Superior Tecnico	Academia	PT
Politecnico di Milano	Academia	IT
University College London	Academia	GB



What do we do in CODOBIO ?

COntinuous **DO**wnstream Processing of **BIO**logics

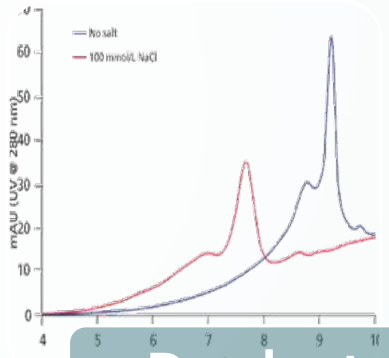
- **Process control and Modelling** of Continuous Downstream Processes
- **Miniaturization,** Scale Up and Scale Down of Continuous Downstream Processing
- **Process Design & Development** of Integrated Continuous Downstream Processes

Automation for continuous manufacturing

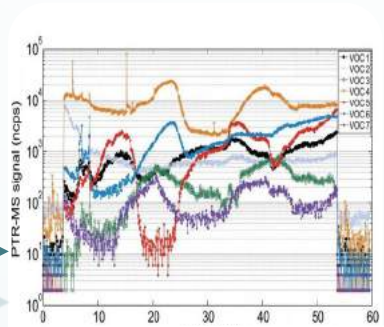
CODOBIO

High variance

Static process

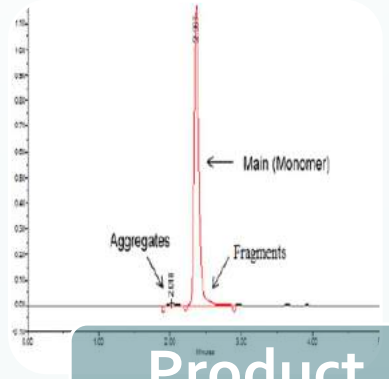


Product variance



Online monitoring

Variable process



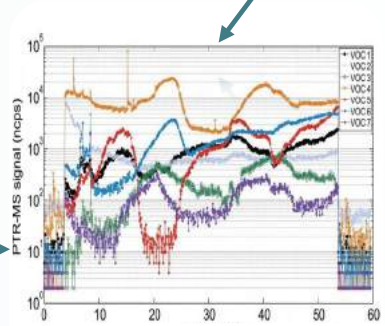
Product stability

Research focus in CoDoBio

Downscaling the process
Microfluidics

High variance

Advanced monitoring for integrated processes



Online monitoring

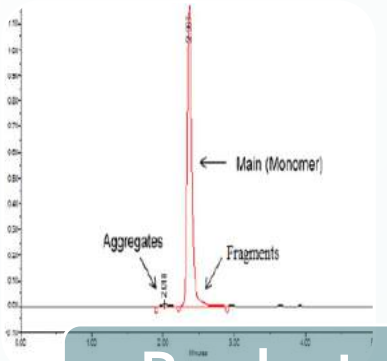
Seamless process integration

Process modeling

Process Control

Variable process

New purification technologies



Product stability

Product collection

Research focus in CoDoBio

Downscaling the process Microfluidics

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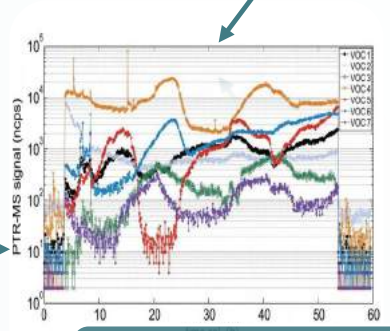
Advanced monitoring for integrated processes



Online monitoring

Seamless process integration

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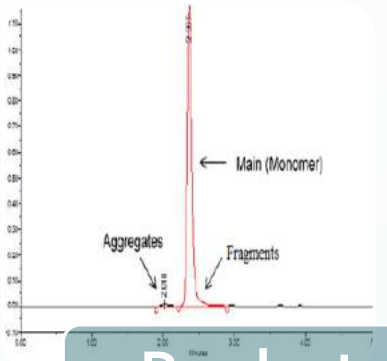
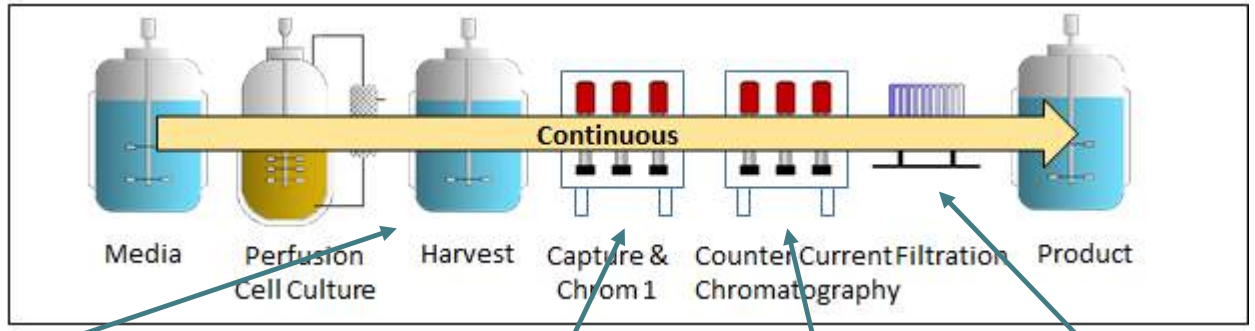
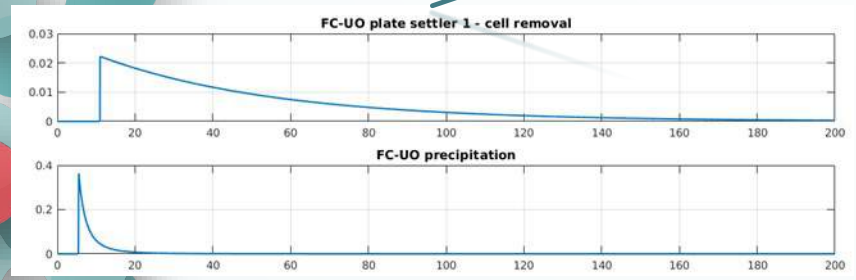


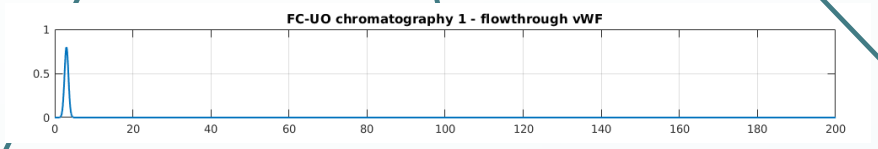
Product stability

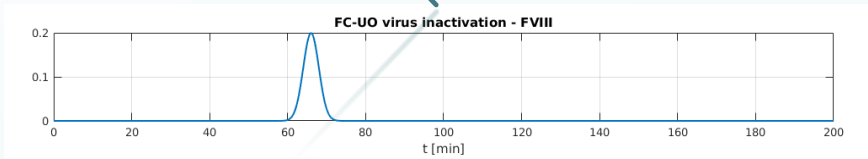
Product collection

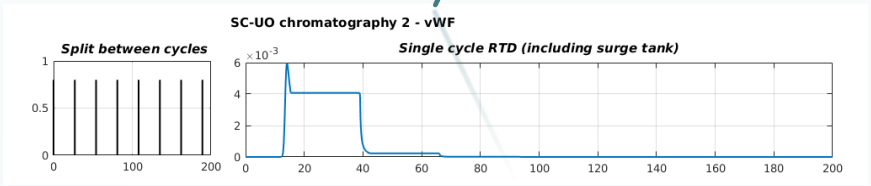
Research focus in CoDoBio – Process models



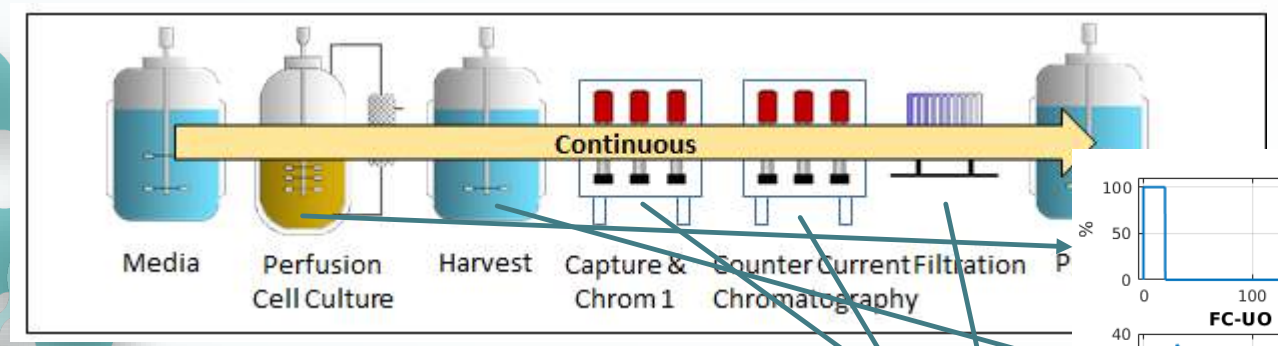


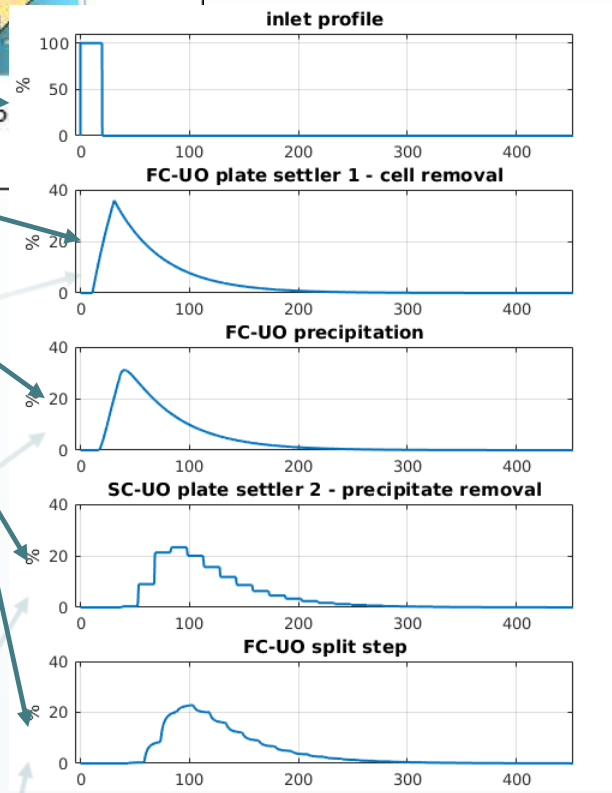


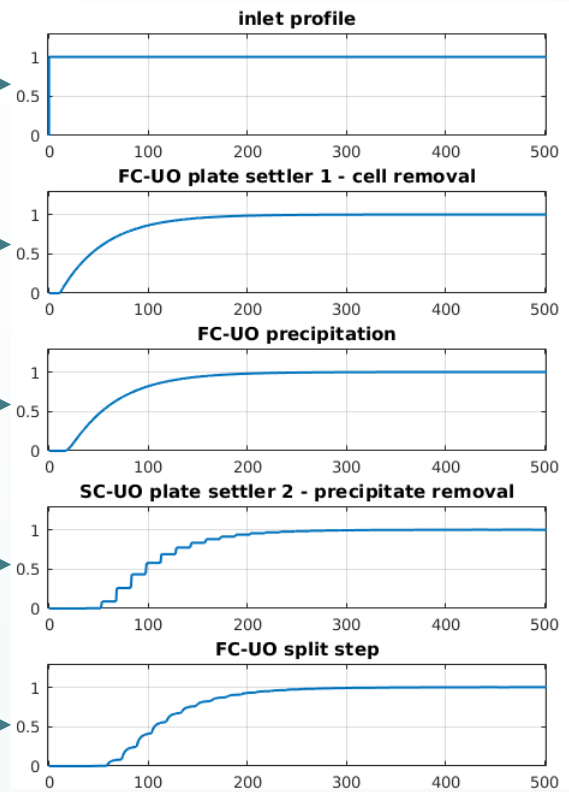




Research focus in CoDoBio – Process models

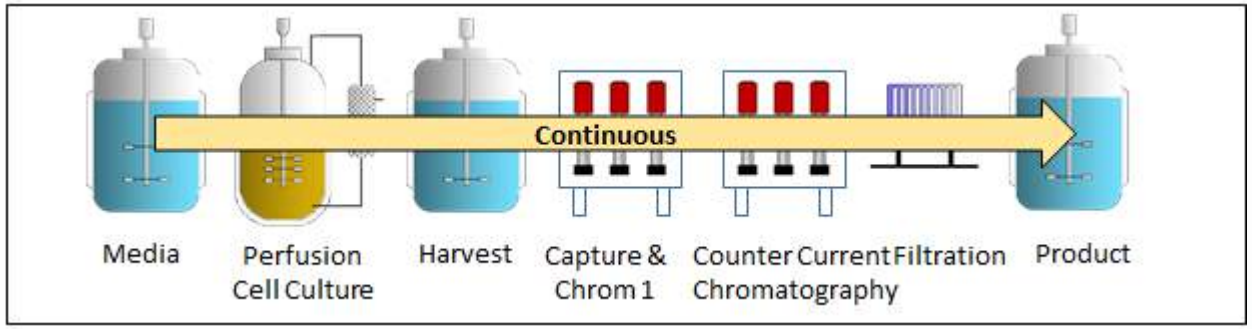






Advanced process models necessary

Research focus in CoDoBio – Up- and Downscale



Microscale

Tecan journal – liquid handling & robotics

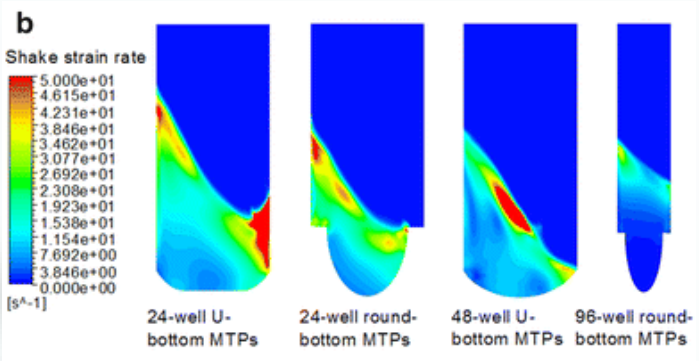
Labscale / Pilotscale

Downstream processing– Gesundheitsindustrie BW

Production scale

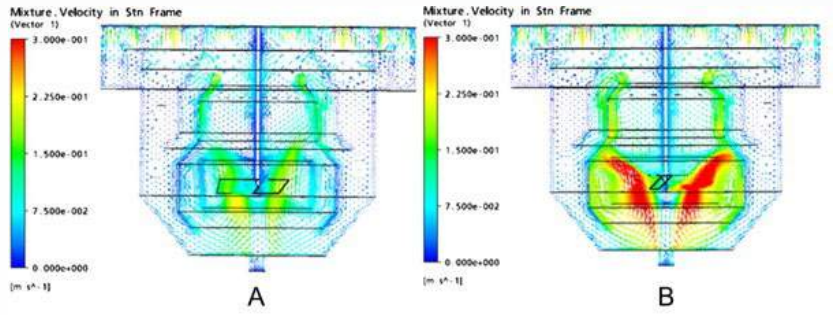
Biopharmaceutical purification – Gesundheitsindustrie BW

Research focus in CoDoBio – Up- and Downscale



CFD optimization of continuous stirred-tank (CSTR) reactor for biohydrogen production – Ding et al. 2010

Upscale Models



High-throughput system for screening of high L-lactic acid-productivity strains in deep-well microtiter plates, Lv et al, 2016

Microscale

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Labscale / Pilotscale

Downstream processing– Gesundheitsindustrie BW

Production scale

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Training focus in CoDoBio

Technical skills

Soft skills

Training focus in CoDoBio

Technical skills

- Basic in Bioprocess Engineering
- Economics and environmental modeling
- Process control and monitoring
- Analytical principles and quality control in biomanufacturing
- Regulatory aspects

Soft skills

- Scientific communication
- Project management
- Entreperneurship
- Data management
- Innovation management

What can you expect from CODOBIO?

Chemical integrated continuous production of Active Pharmaceutical Ingredients at GSK – Zeton News

We want that, but for biologics

- The technology
- The process control
- The personnel

Acknowledgements

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