

Magnetic Levitation Technology for Stirred Bioreactors: Integration and Evaluation

Cedric Schirmer

20.06.2024

Levitronix® Bioprocessing Conference

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Zurich University of Applied Sciences

- Located in Switzerland
- Largest multidisciplinary UAS in Switzerland



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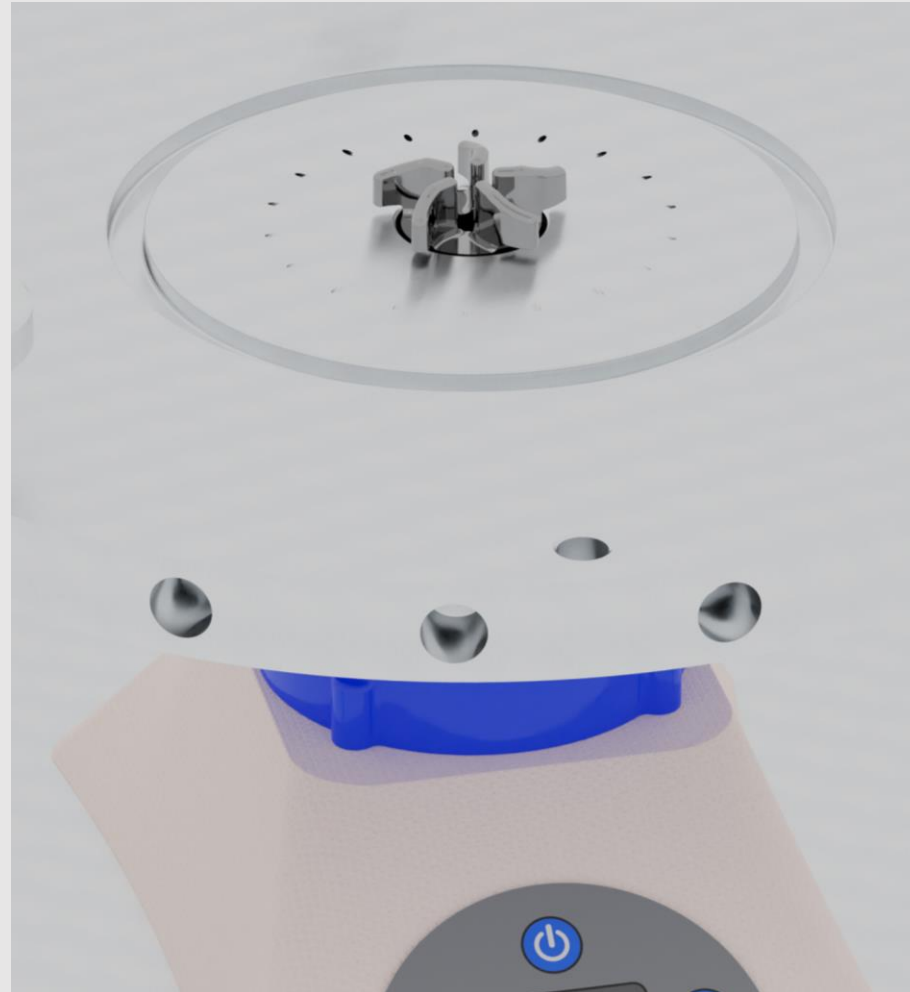
Center for Biochemical Engineering and Cell Cultivation Techniques

- Part of the Institute of Chemistry and Biotechnology
- Headed by Profs. Dieter and Regine Eibl
- Development of production processes based on microbial, plant, insect and mammalian cells (including stem cells)
- CFD modelling and verification

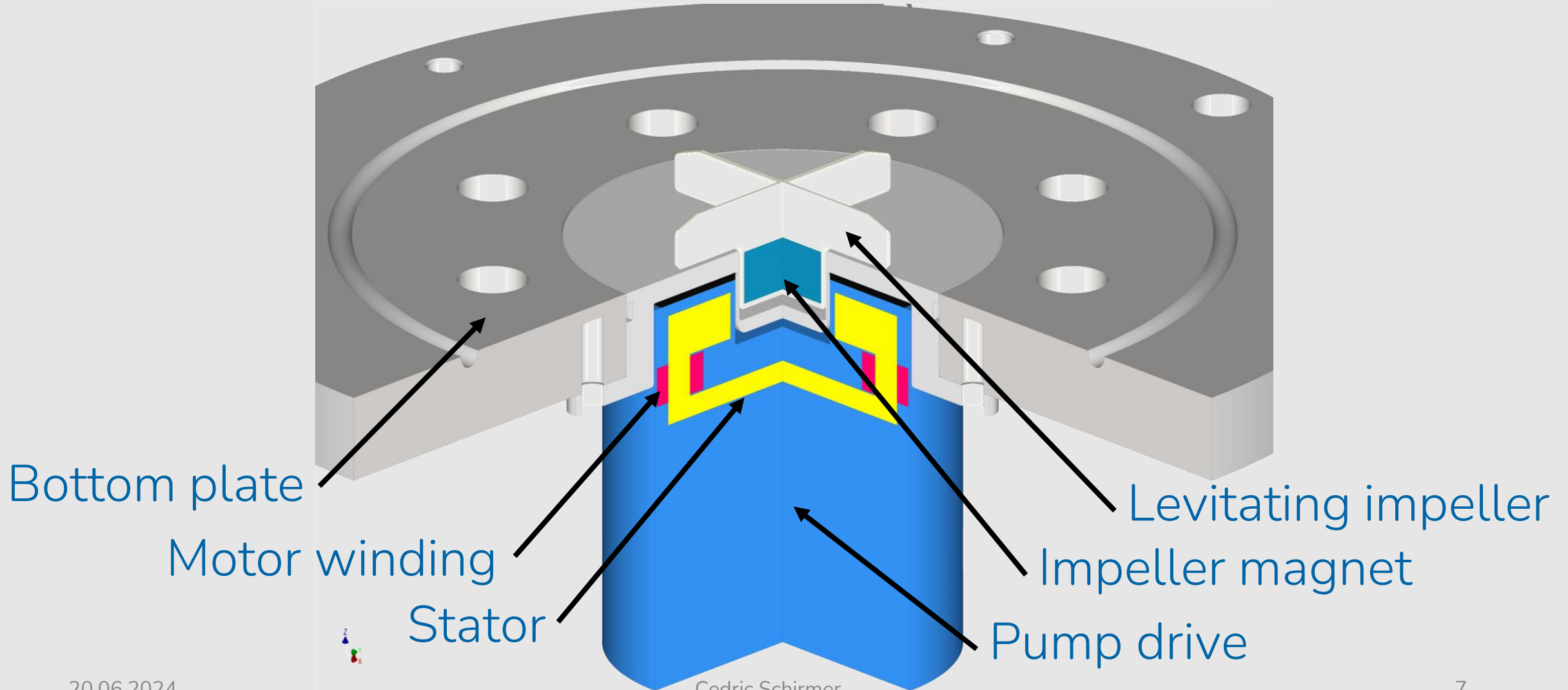
Bioreactor system



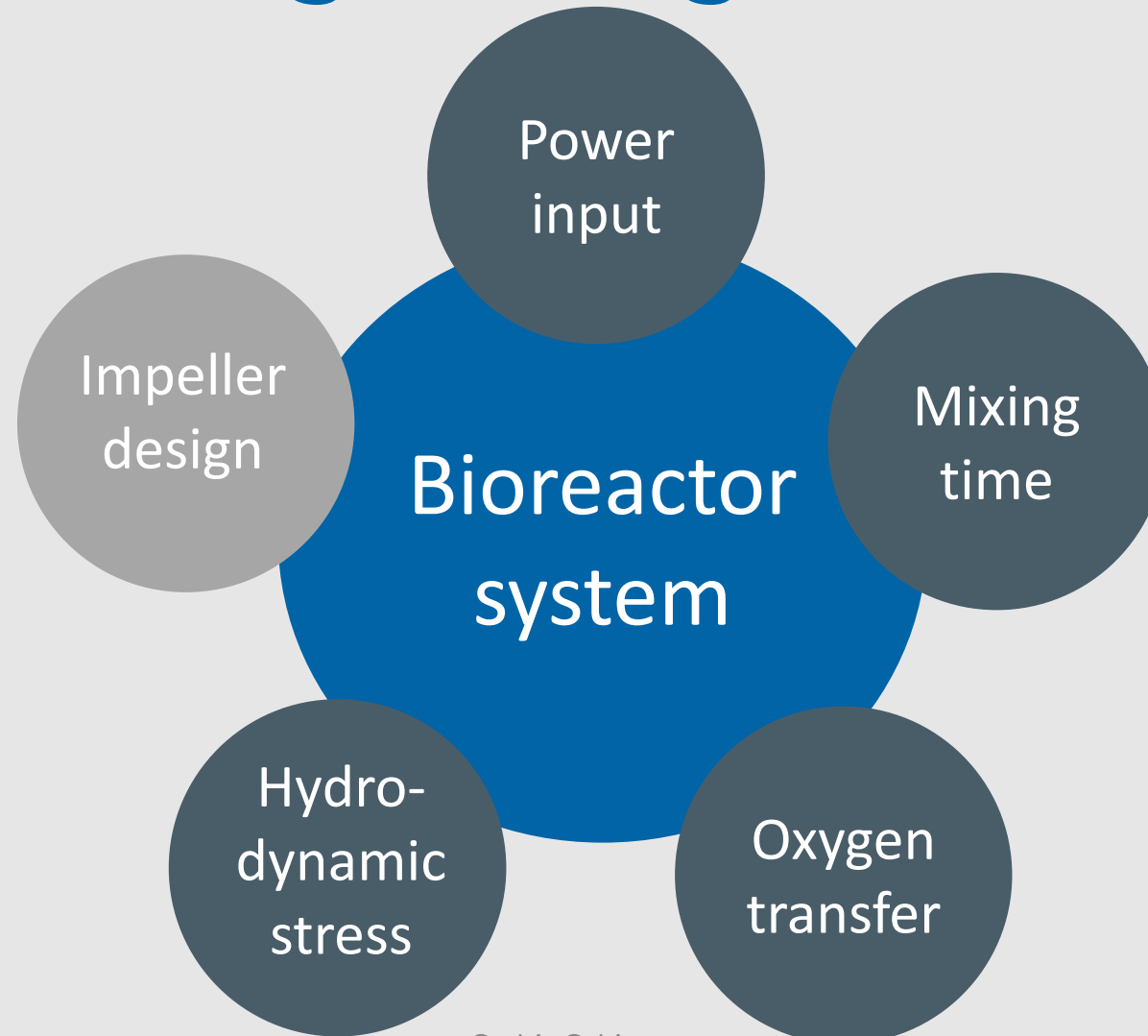
Bioreactor system



Bioreactor system



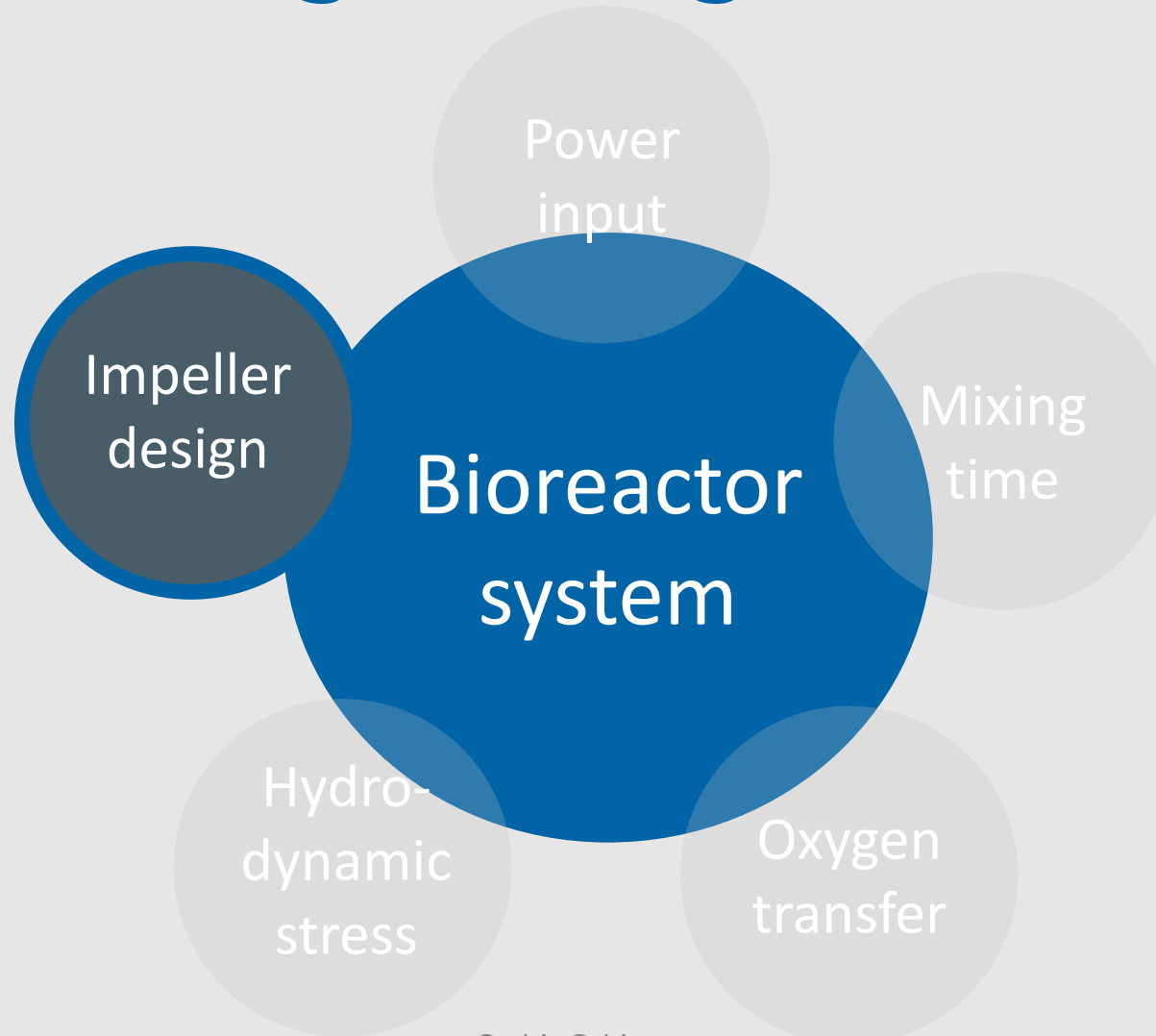
Biochemical engineering characterisation



Key Characteristics

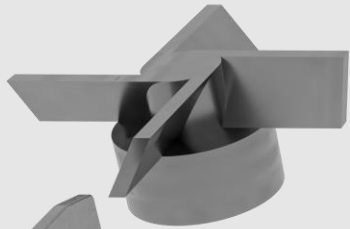
	Microorganisms	Mammalian cell culture
Shear sensitivity	Low	High
Power input	High ($> 5 \text{ kWm}^{-3}$)	Low ($50 \text{ — } 200 \text{ Wm}^{-3}$)
Oxygen demand	High ($k_L a \geq 500 \text{ h}^{-1}$)	Low ($k_L a < 80 \text{ h}^{-1}$)
Mixing time	Short ($t_m < 10 \text{ s}$)	Moderate ($t_m \leq 120 \text{ s}$)
Cooling capacities	High (H/D ratio of 3:1)	Low (H/D ratio of 2:1)
Flow pattern	Radial pumping impeller	Axial pumping impeller

Biochemical engineering characterisation



Impeller designs

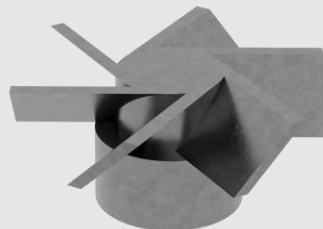
60° 40x8 mm



45° 40x8 mm



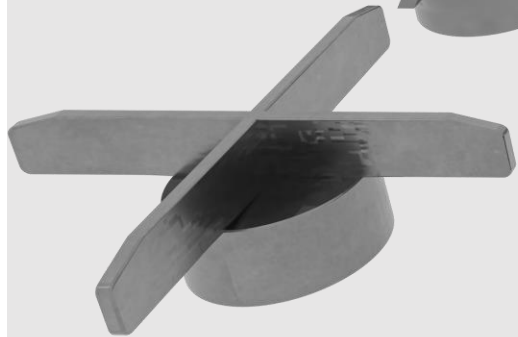
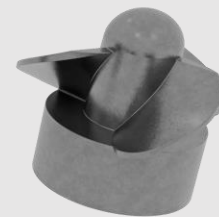
45° 40x8 mm



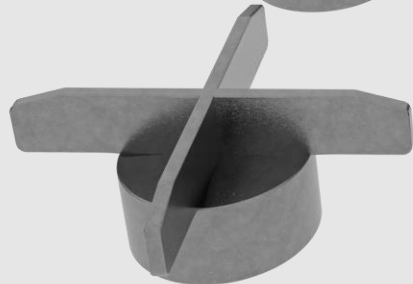
80° 30x8 mm



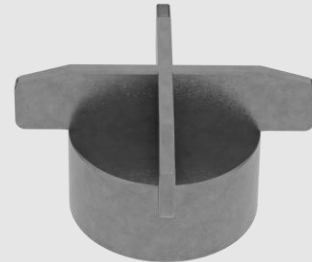
50° 30x8 mm



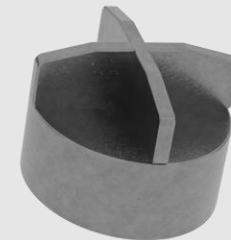
50x7 mm



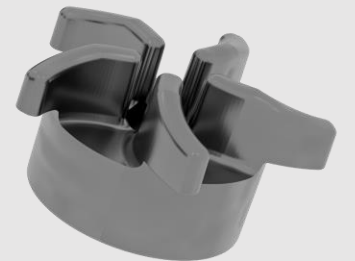
40x7 mm



30x7 mm

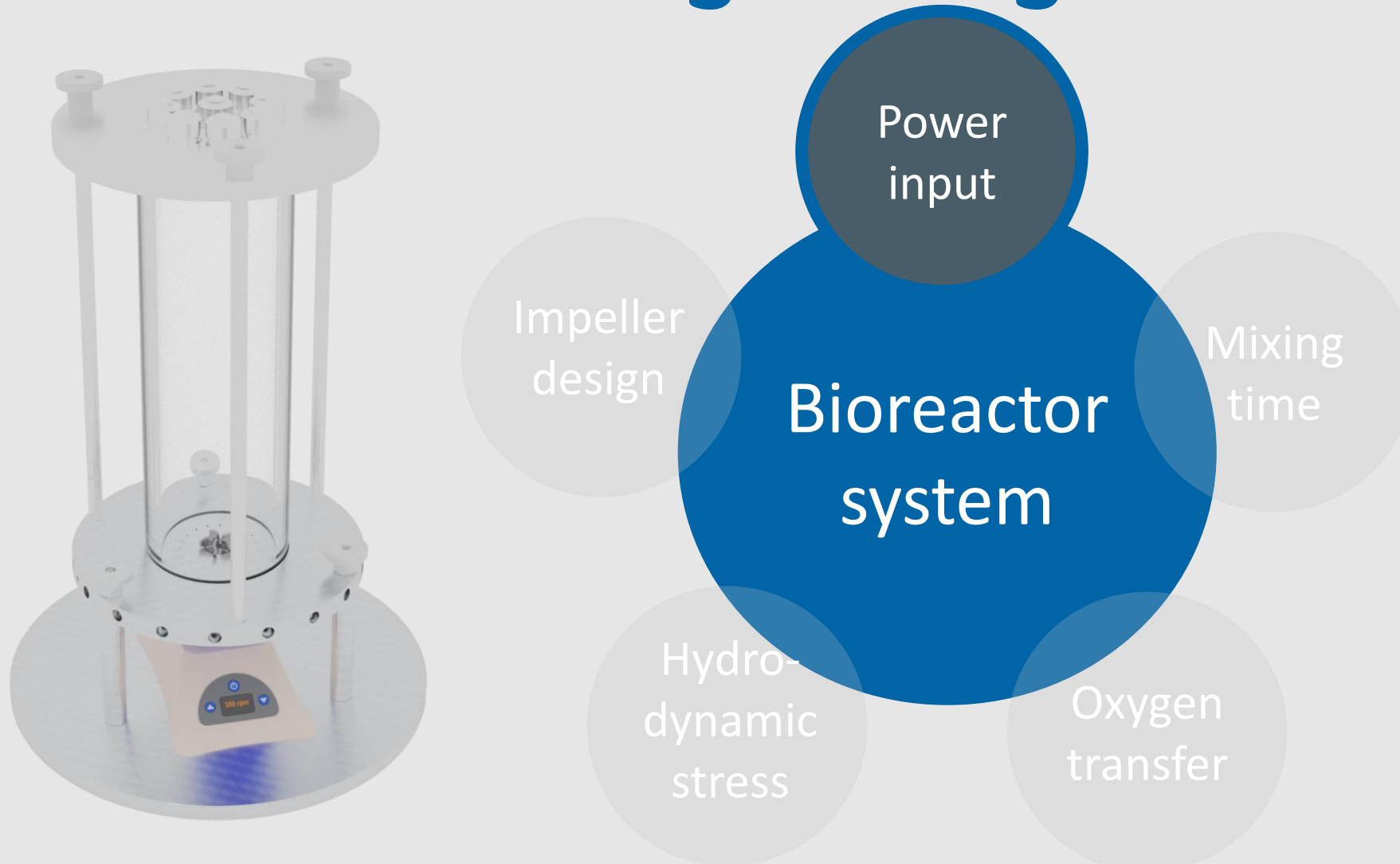


20x7 mm

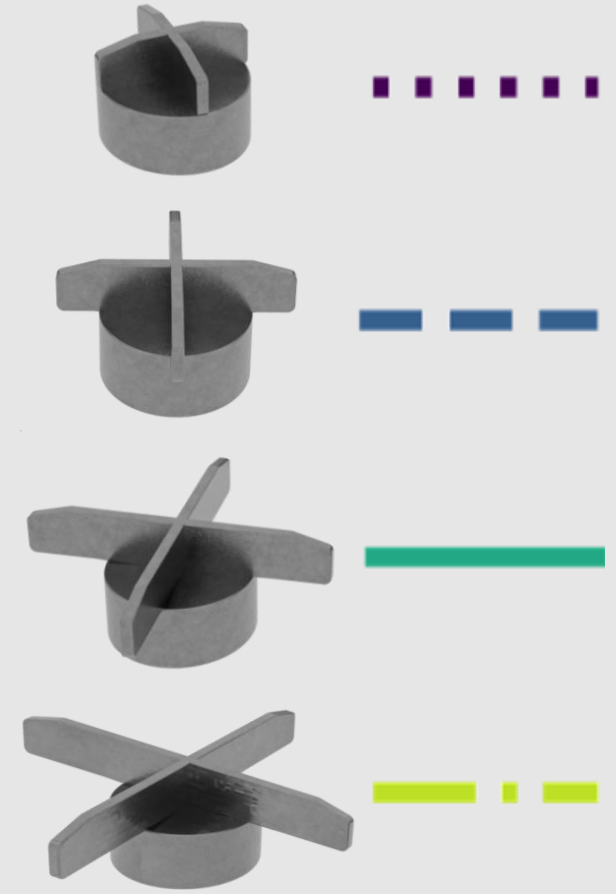
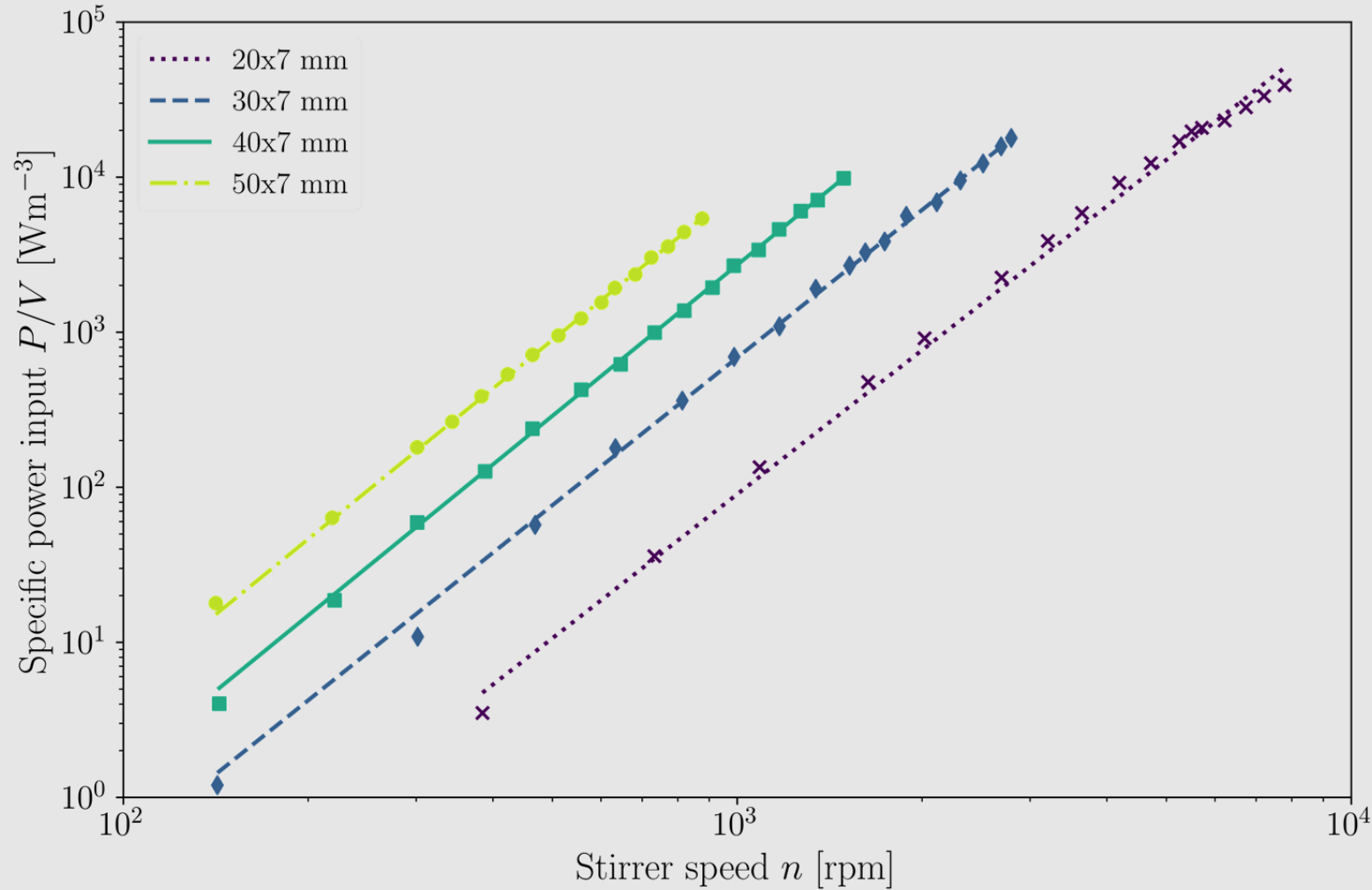


50x7 mm

Biochemical engineering characterisation



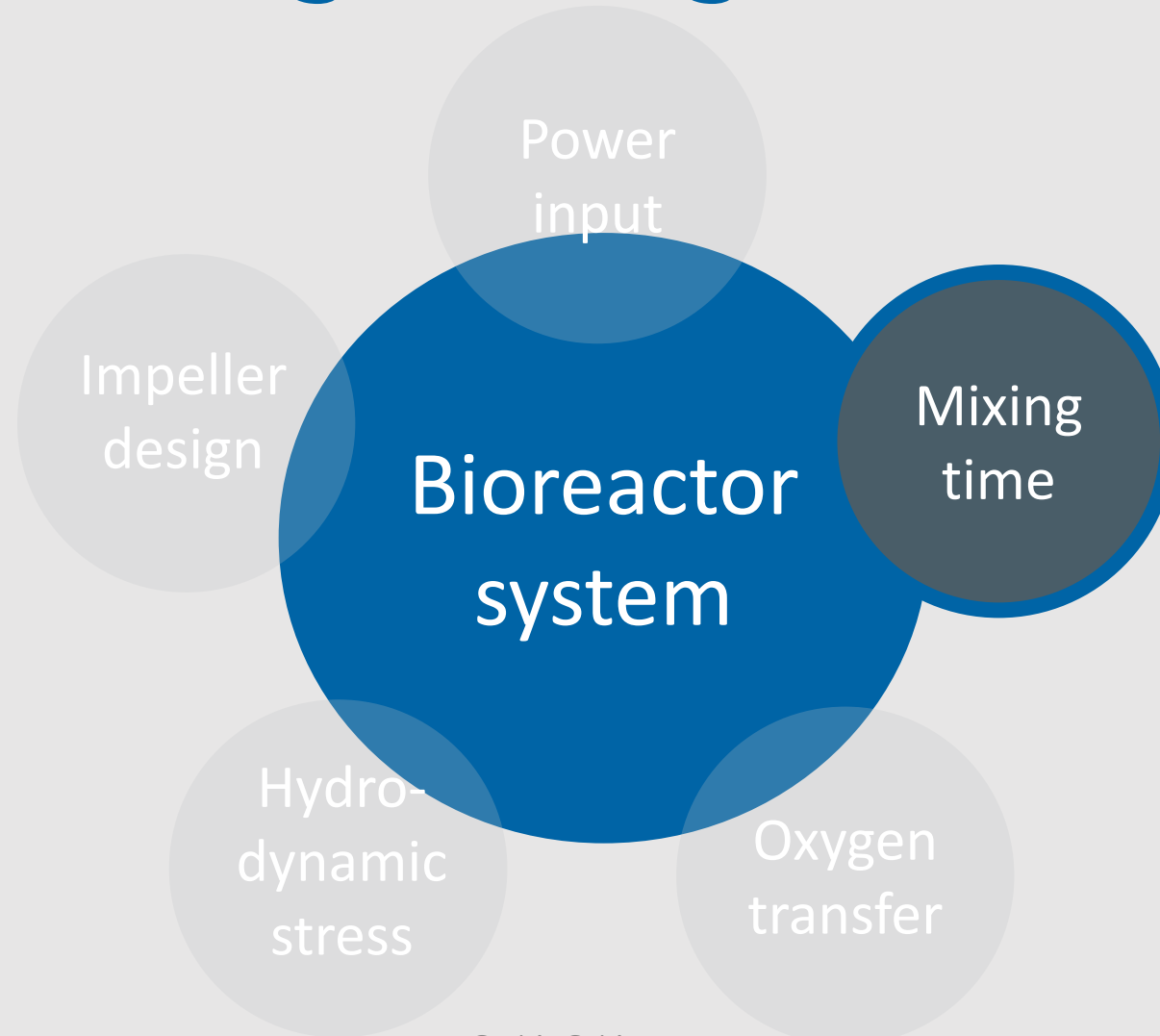
Power input



Power input

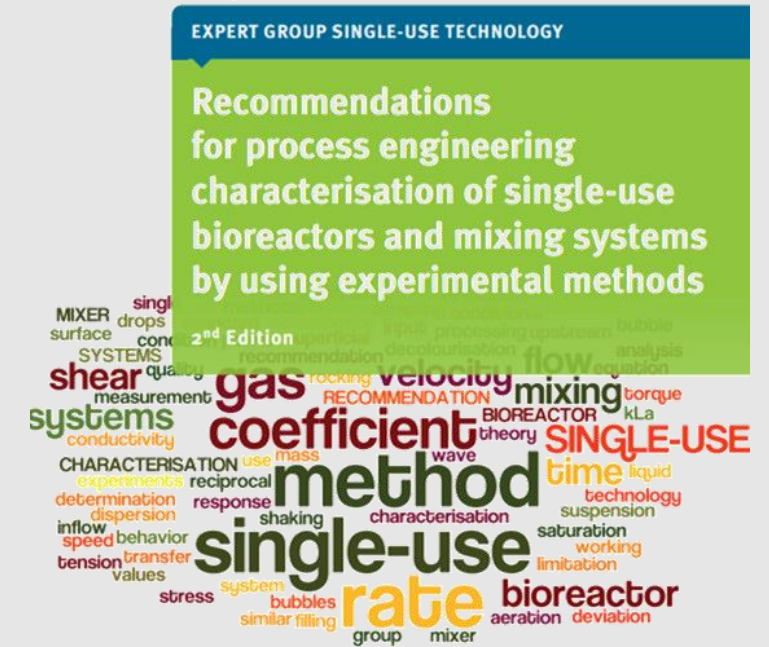
- Powerful Drive BPS-i30
 - 1 rpm to 9000 rpm
 - 1 Wm^{-3} to 50 kWm^{-3}
 - Suitable for universal use:
 - Microorganisms: $> 5 \text{ kWm}^{-3}$
 - Mammalian cells: 50 — 200 Wm^{-3}
 - hMSCs: $< 5 \text{ Wm}^{-3}$

Biochemical engineering characterisation

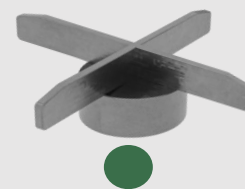
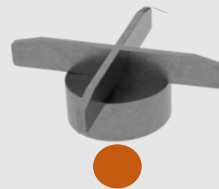
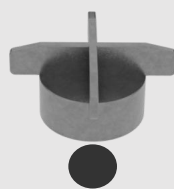
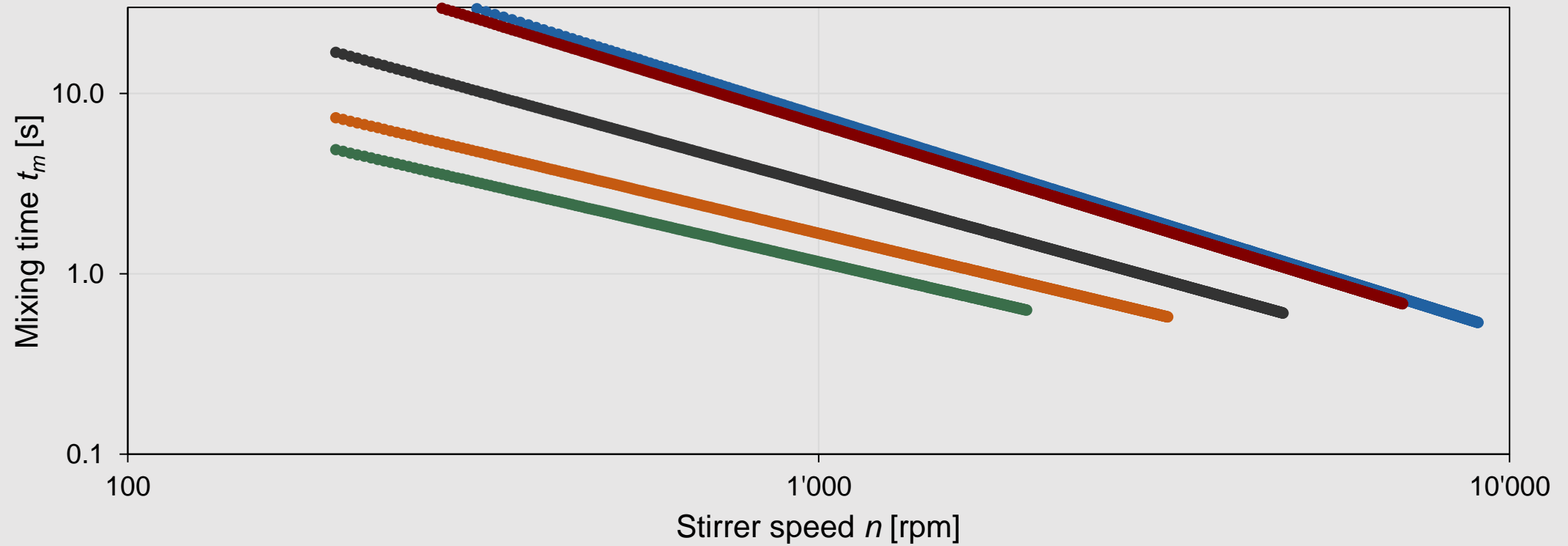


Mixing time

- According to DECHEMA guideline [1]
 - Decolorisation method
- Design of Experiment approach
 - Central Composite Design CCF
 - 19 x 3 experiments per impeller



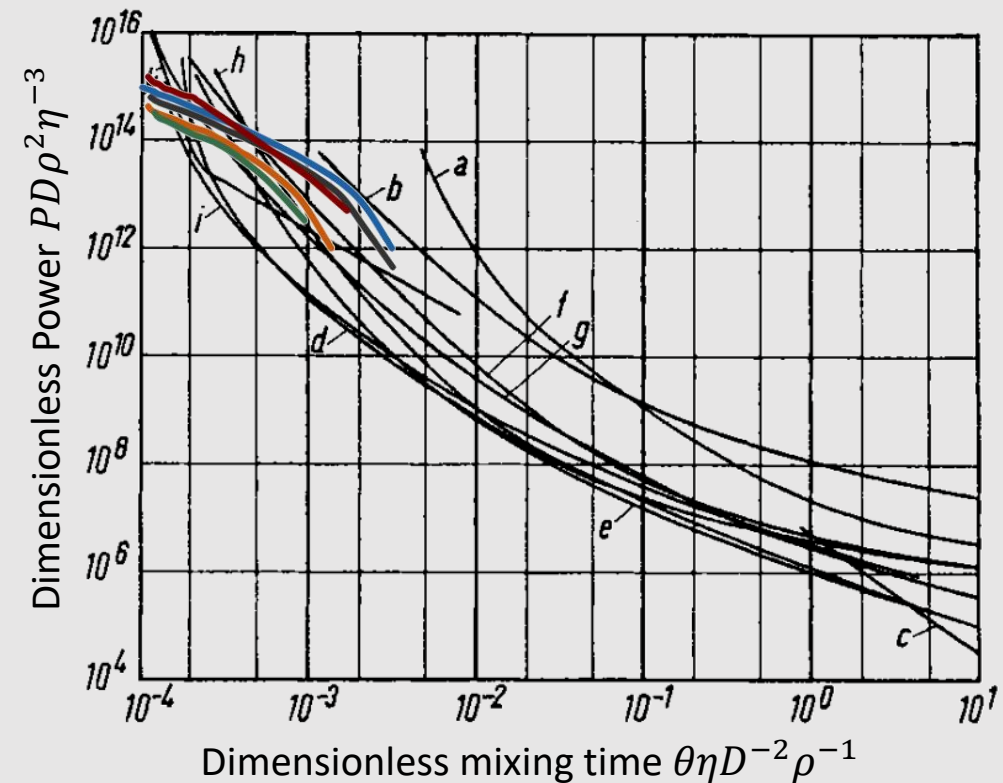
Mixing time



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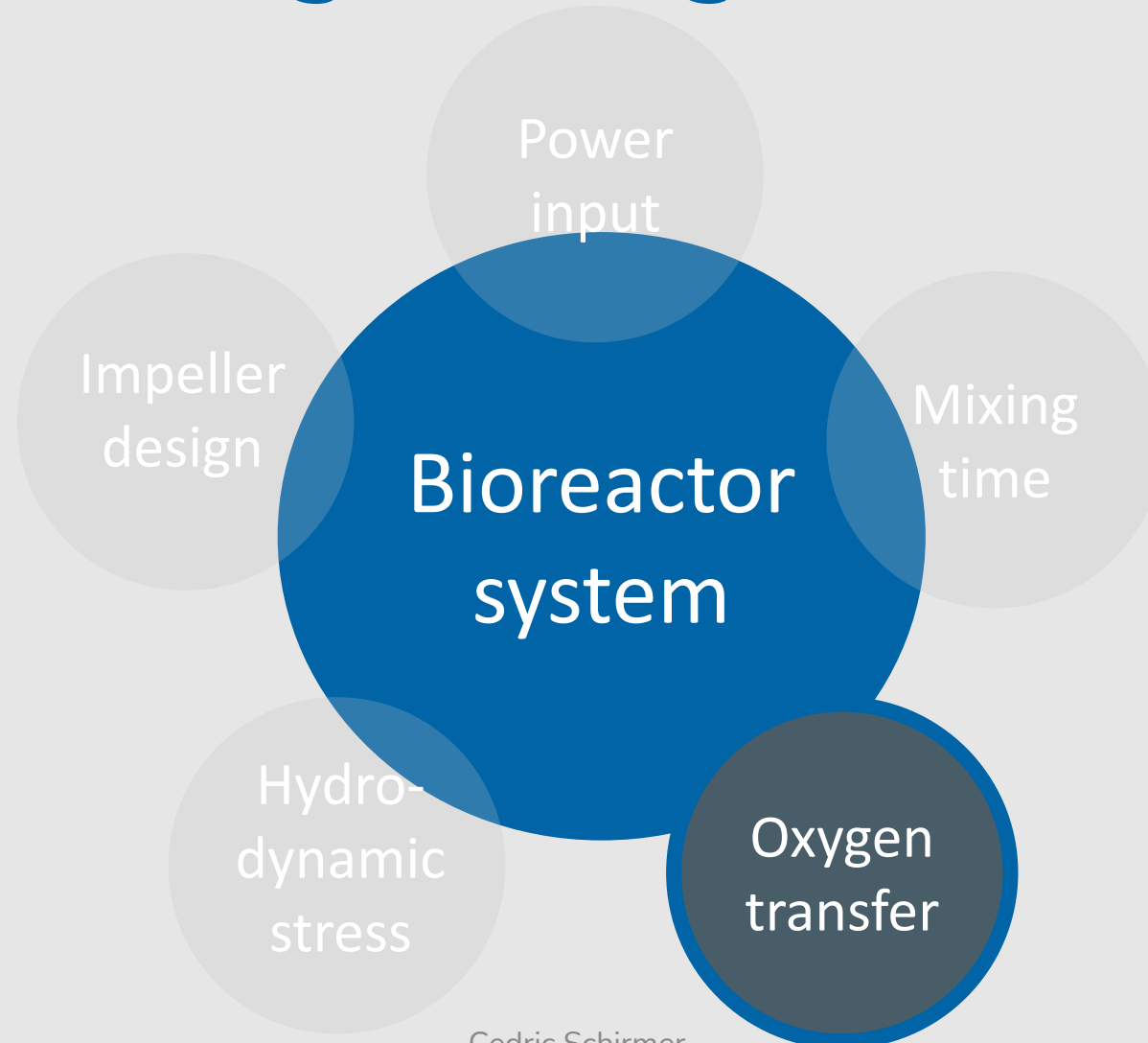
Power input and mixing time

- Mixing work increases slightly with decreasing impeller diameter
- Mixing work is comparable to other impellers [2]



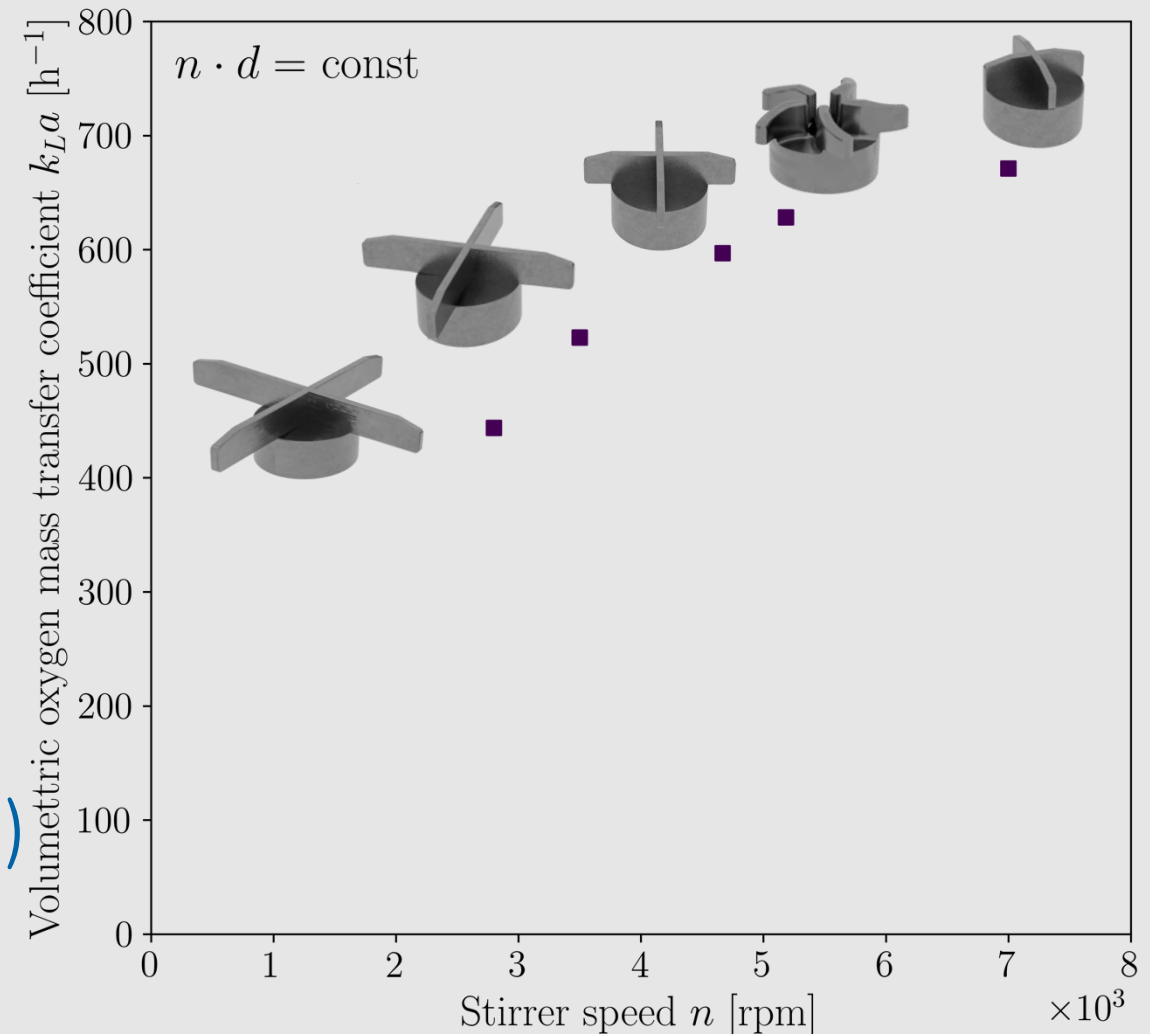
Zlokarnik, 1967, Eignung von Rührern zum Homogenisieren von Flüssigkeitsgemischen, 10.1002/cite.330390909

Biochemical engineering characterisation

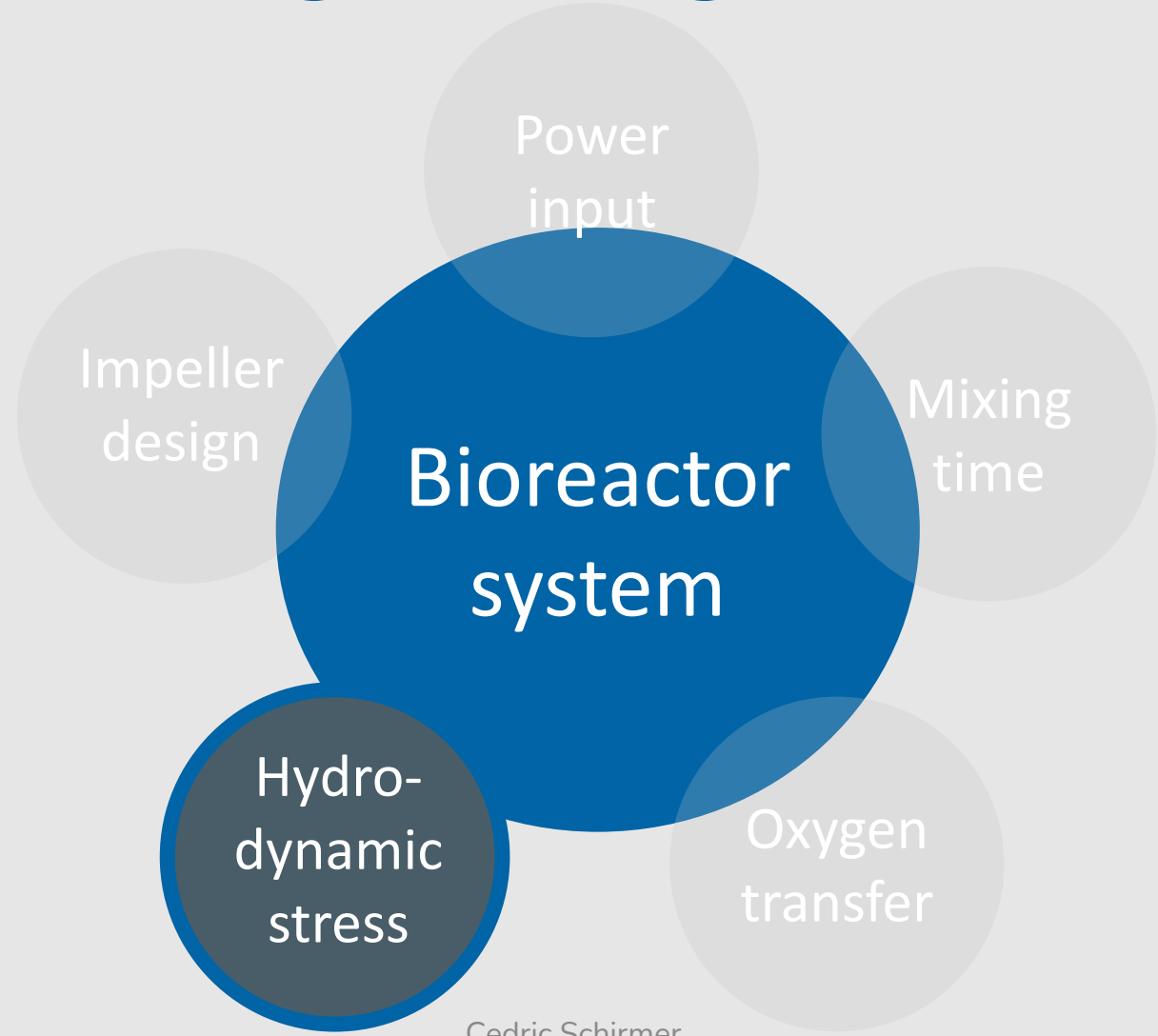


Oxygen transfer

- According to DECHEMA guideline
 - Degassing method
- DoE approach
- $k_L a$ values up to 700 h^{-1}
- Smaller impeller achieves higher $k_L a$ (constant tip speed)



Biochemical engineering characterisation



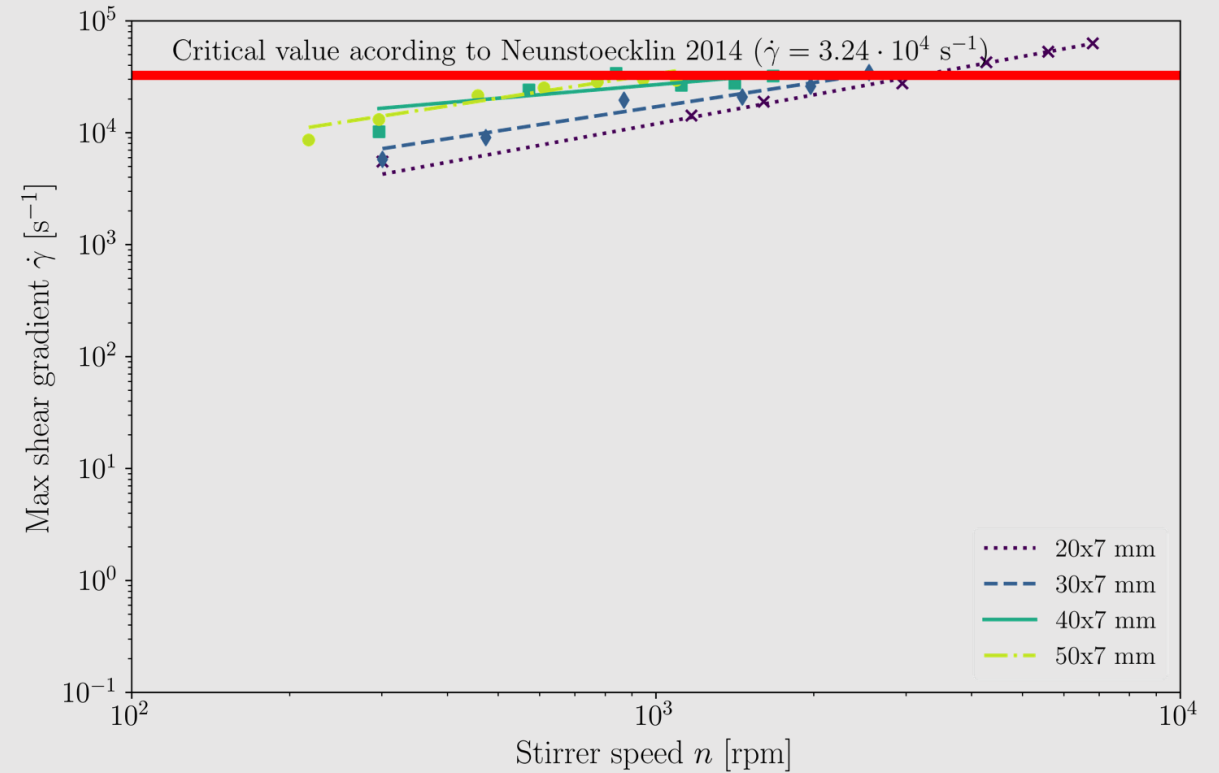
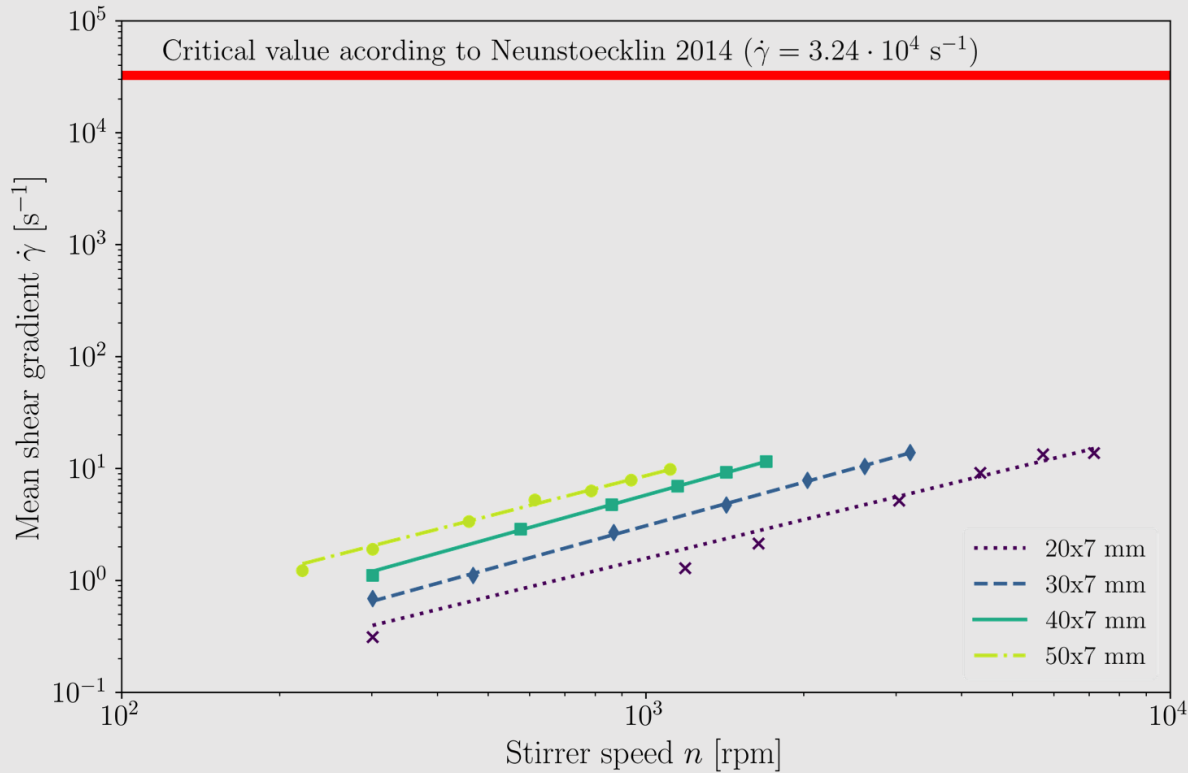
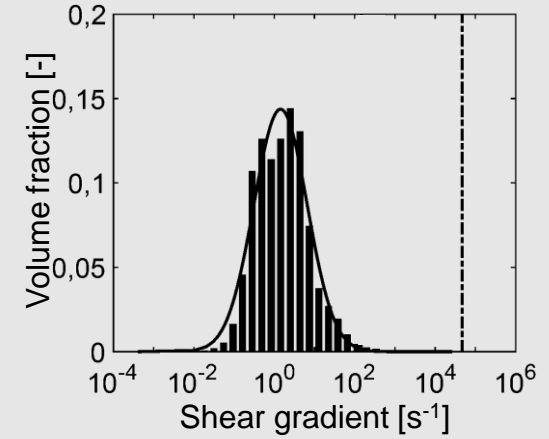
CFD and Hydrodynamic stress

- CFD based evaluation
 - Power input
 - Hydrodynamic stress
 - Mixing time
 - “Cup rinsing”

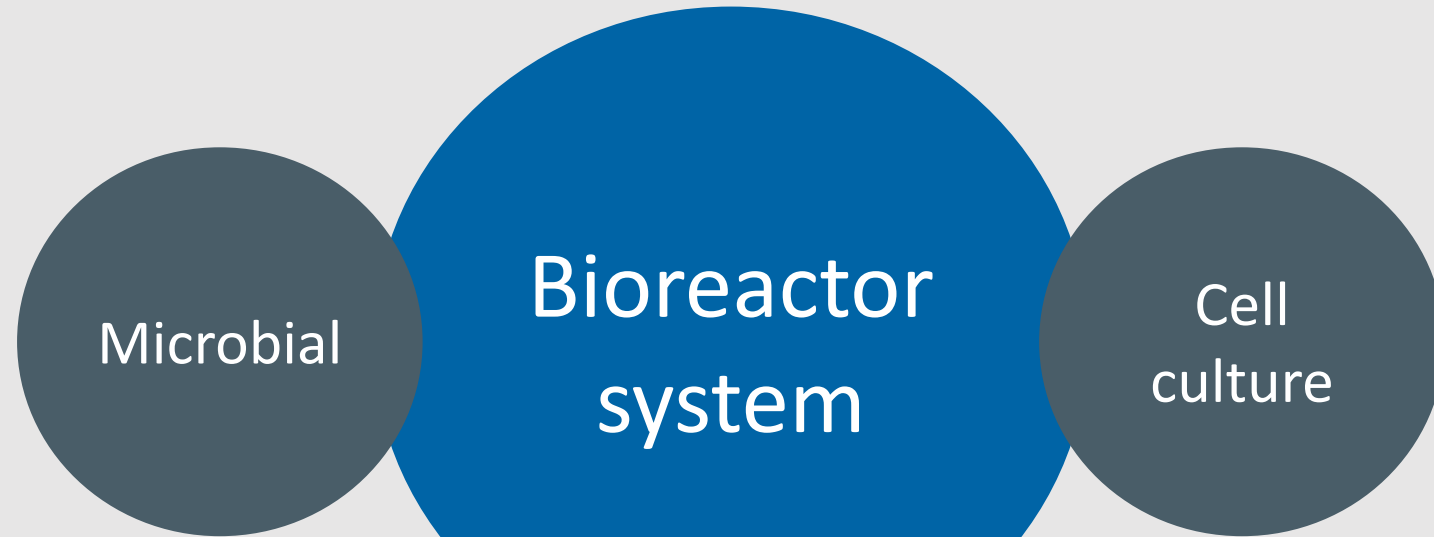
- Software: Ansys Fluent



Hydrodynamic stress



Biological evaluation

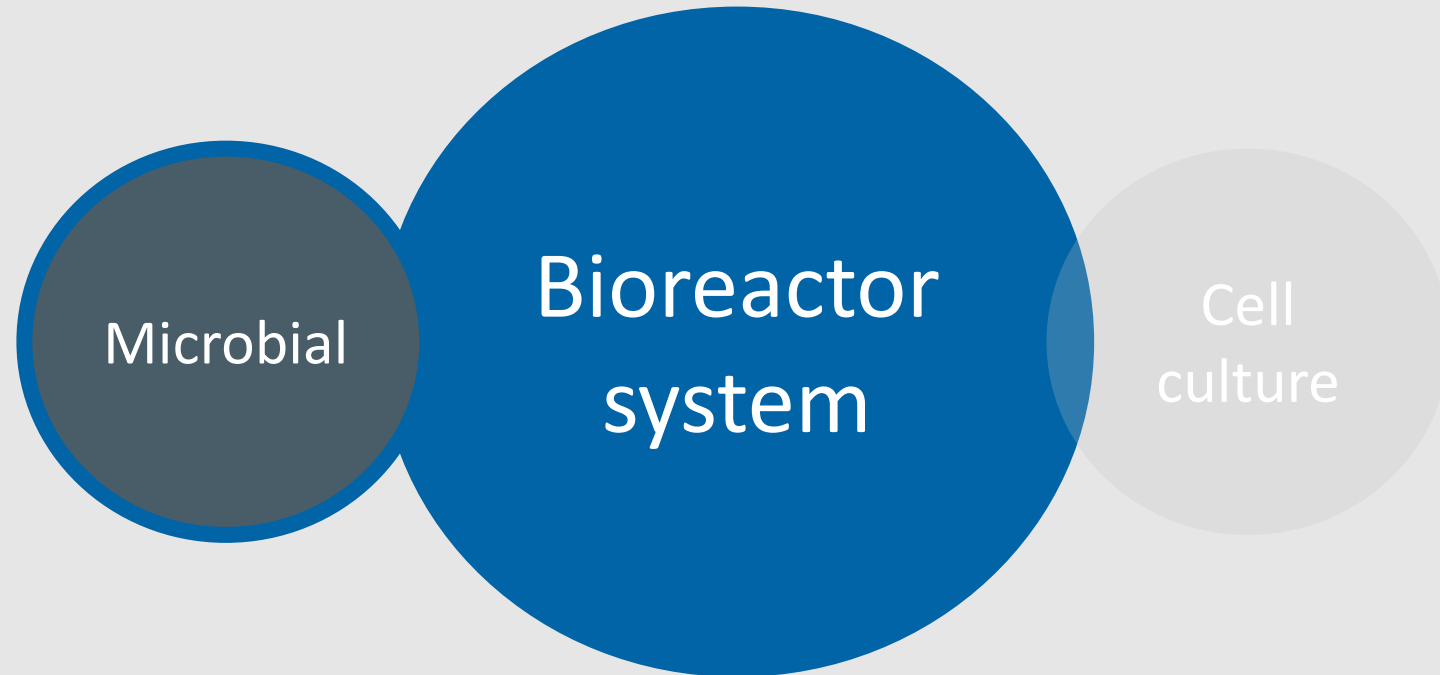


Biological evaluation

- Microbial
 - *Escherichia coli* W3110
- Cell culture
 - ExpiCHO-S 6H8



Biological evaluation



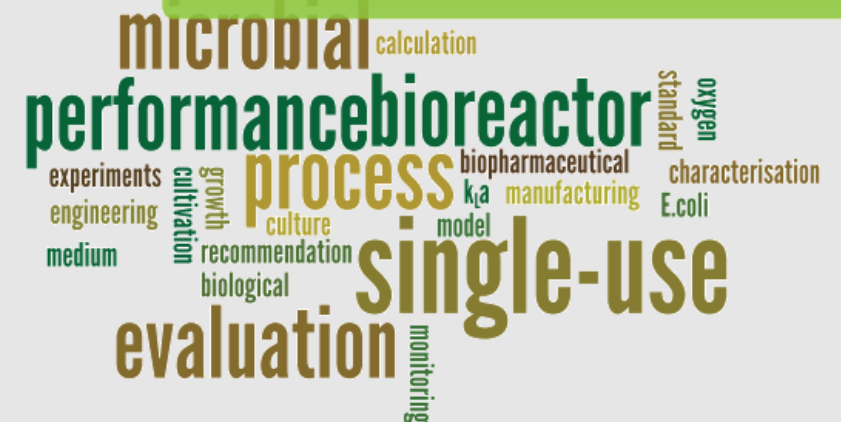
E. coli cultivations

- *E. coli* batch and fed-batch
- DECHEMA model process
- Cultivation parameters
 - 7730 rpm
 - 42 kWm⁻³
 - 37 °C
 - pH 6.8
 - DO 40 %

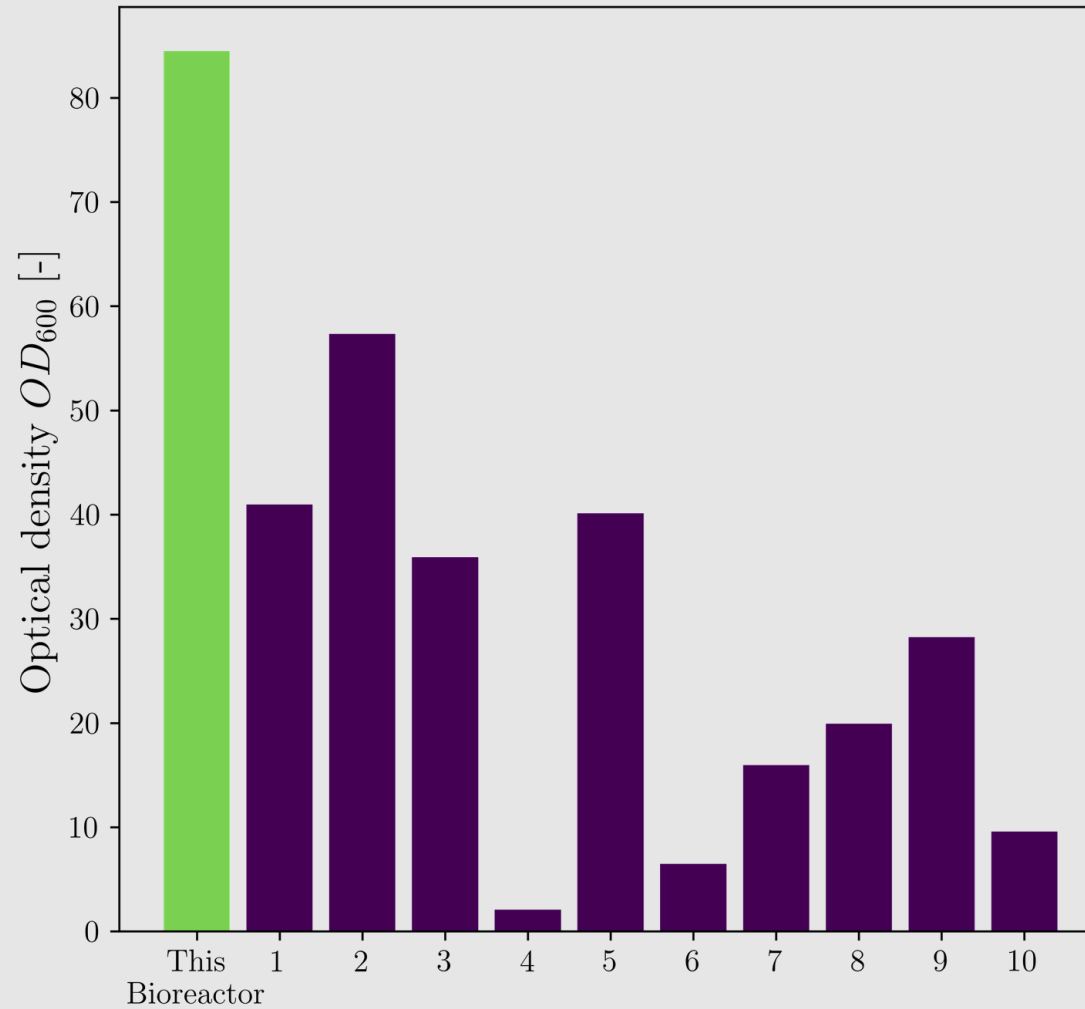


EXPERT GROUP SINGLE-USE TECHNOLOGY

Recommendation for
biological evaluation
of bioreactor performance
for microbial processes

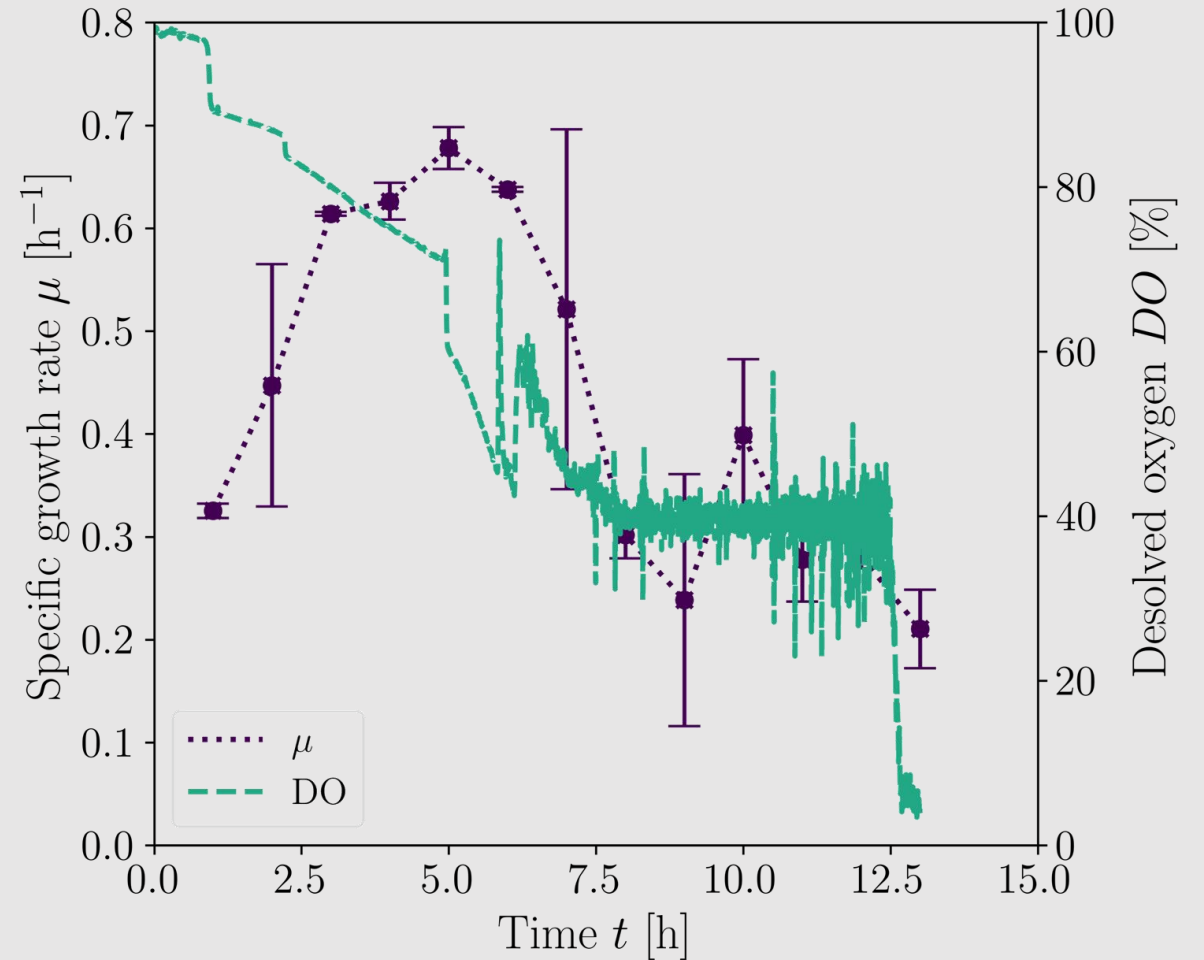
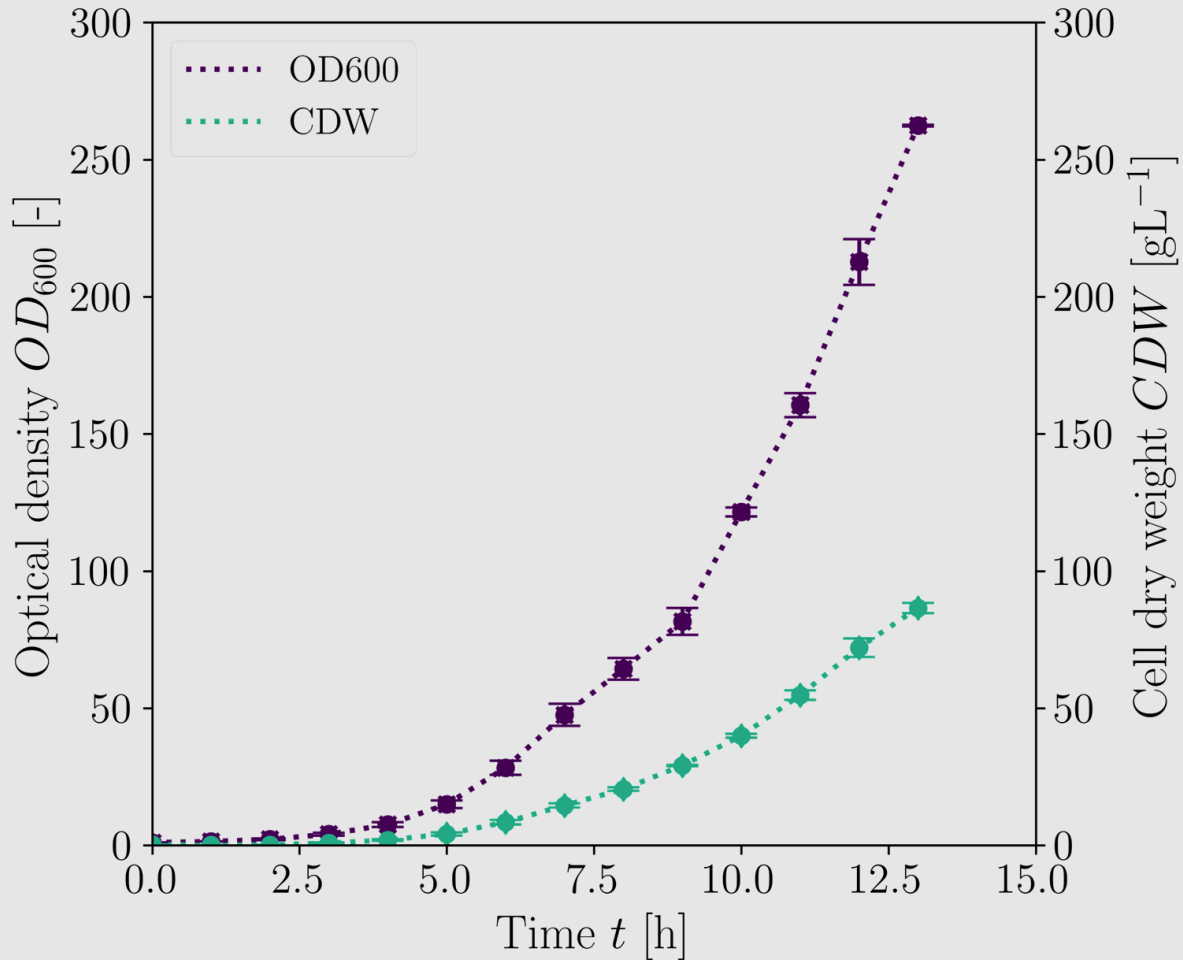


E. coli cultivations (batch)



Bioreactor
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E. coli cultivations (fed-batch)



Biological evaluation



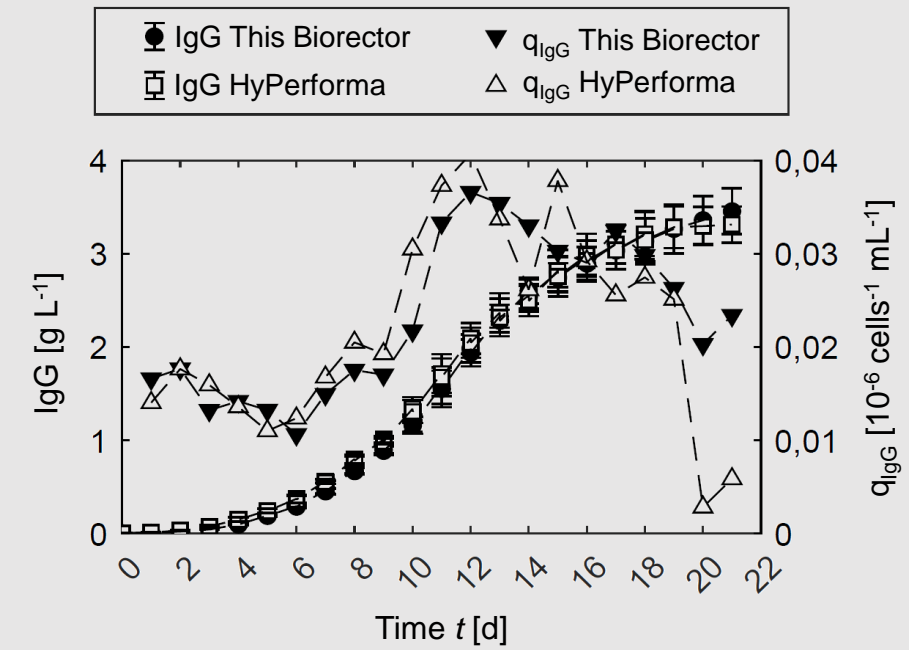
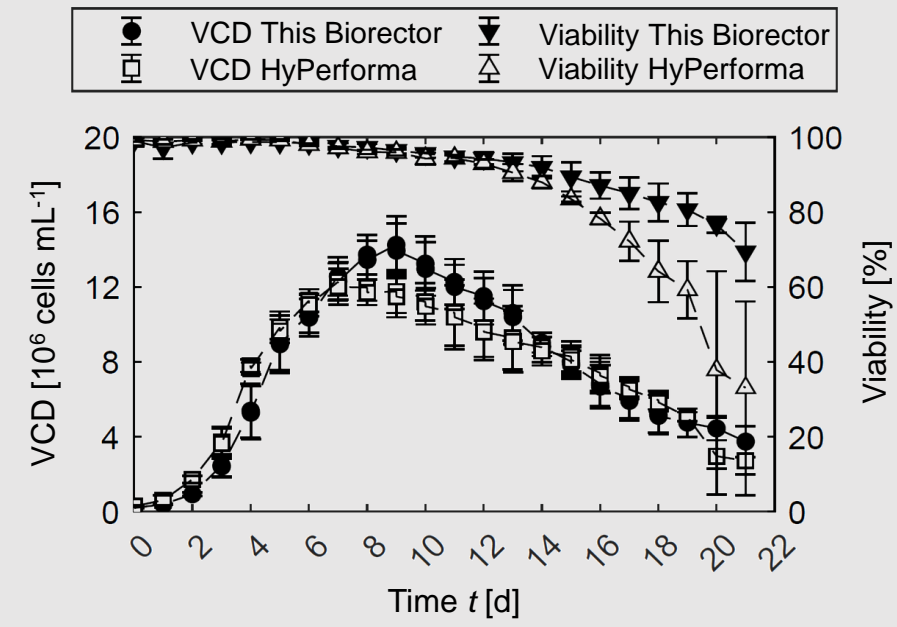
Microbial

Bioreactor
system

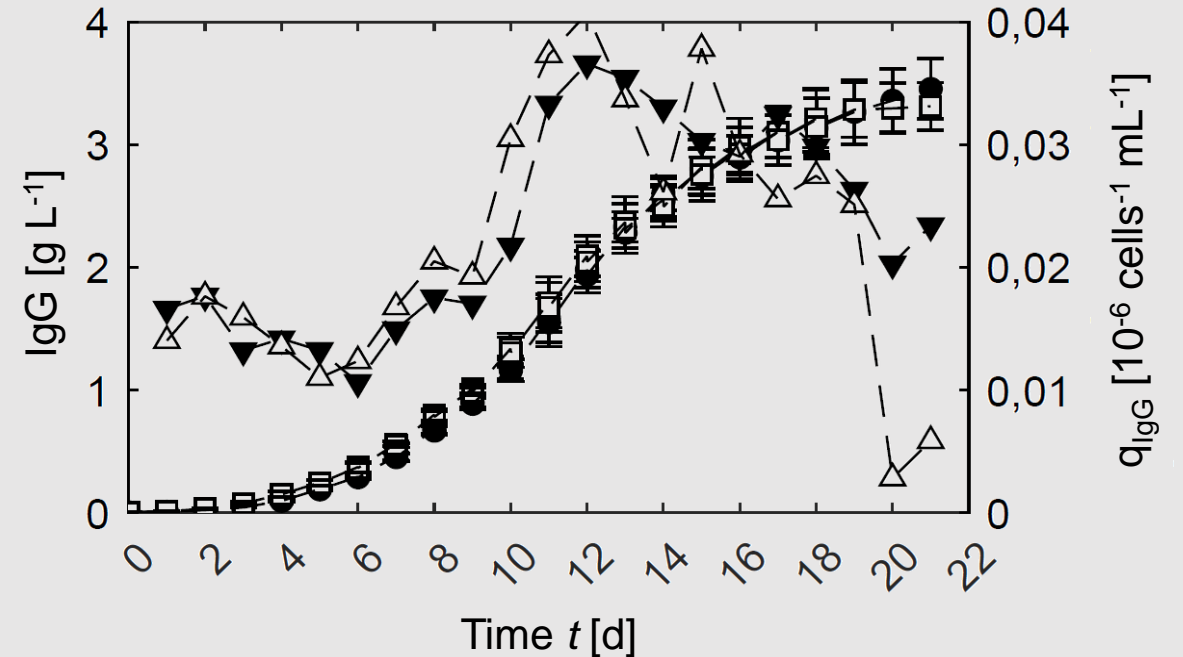
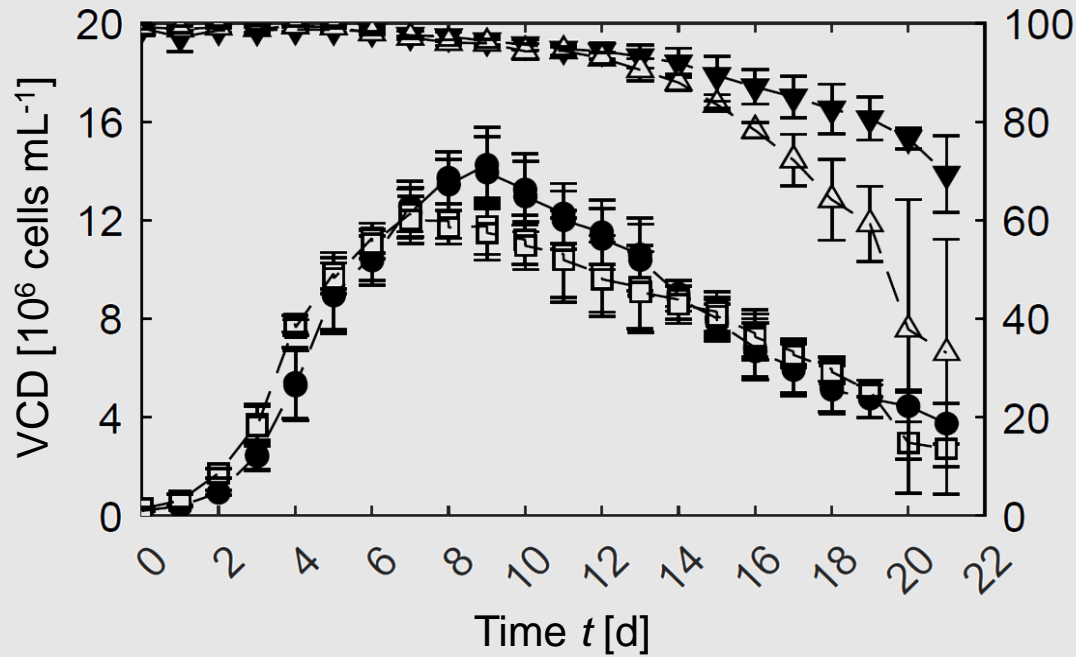
Cell
culture

CHO cell cultivations

- CHO ExpiCHO-S 6H8
- Medium
 - ExpiCHO™ Stable Production Medium and Efficient Feed C+
- Scale-up criteria
 - Mixing time $t_M = 16$ s
- Similar cell densities and IgG concentrations compared to commercially available cell culture bioreactors



CHO cell cultivations



Summary

- Simple design
- More flexibility in the head area of the bioreactor
- Suitable for single-use and reusable bioreactor applications
- Almost maintenance-free
- Risk of contamination is reduced
- Universal use due to the wide power input range

Thanks



Vivian Ott



Stefan Seidel



Dieter Eibl

Attribution

- [1] Bauer et al. 2020, Recommendations for process engineering characterisation of single-use bioreactors and mixing systems by using experimental methods (2nd Edition), Gesellschaft für Chemische Technik und Biotechnologie e.V
- [2] Zlokarnik, 1967, Eignung von Rührern zum Homogenisieren von Flüssigkeitsgemischen, 10.1002/cite.330390909
- [3] Neunstoecklin et al. Determination of the maximum operating range of hydrodynamic stress in mammalian cell culture. Journal of Biotechnology, 194:100–109, 2015. ISSN 18734863. doi: 10.1016/j.jbiotec.2014.12.003. URL <http://dx.doi.org/10.1016/j.jbiotec.2014.12.003>.
- [4] Schirmer et al. 2019, Recommendation for biological evaluation of bioreactor performance for microbial processes, Gesellschaft für Chemische Technik und Biotechnologie e.V
- [5] Schirmer et al. 2018, Development, Engineering and Biological Characterization of Stirred Tank Bioreactors, in Biopharmaceuticals, DOI: 10.5772/intechopen.79444



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