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PRODUCTION OF PURE ENANTIOMERS AT HIGH YIELDS BY INTEGRATING CHROMATOGRAPHY, ISOMERIZATION AND MEMBRANE FILTRATION

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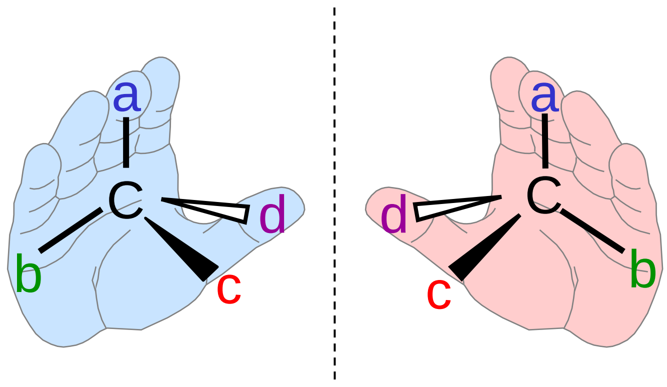
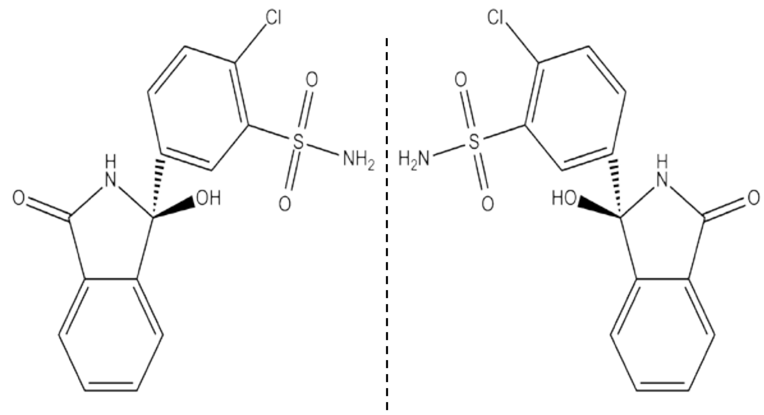
PIN-NL & NL-GUTS 9 April 2014

Motivation and objectives

Enantiomers

- Stereoisomers ("mirror images")

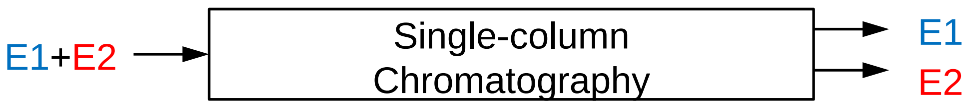




- Basically identical physico-chemical properties
- Often produced as racemate (50/50 mixture)
- Usually only one enantiomer has the desired physiological effect
- Separation? → Chromatography

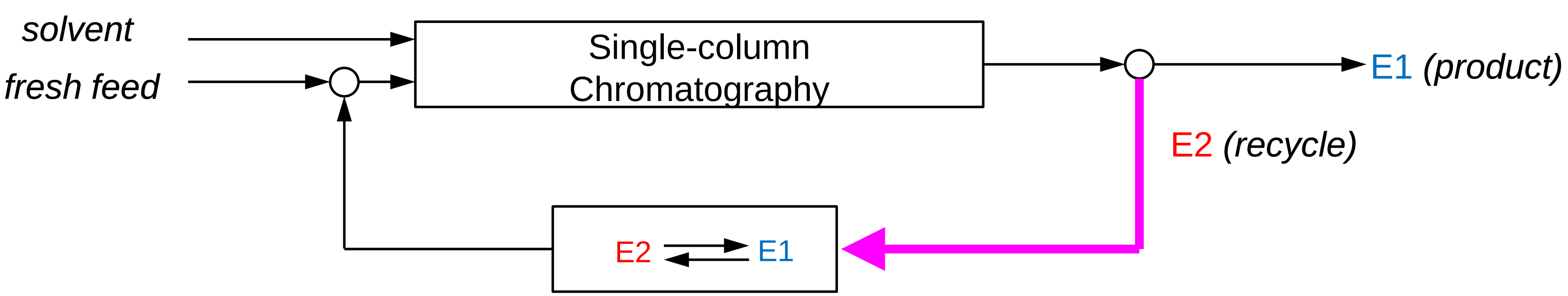
Separation of enantiomers

- Yield limited to 50% only (conventional approach)



E1: Enantiomer 1 (product)
E2: Enantiomer 2

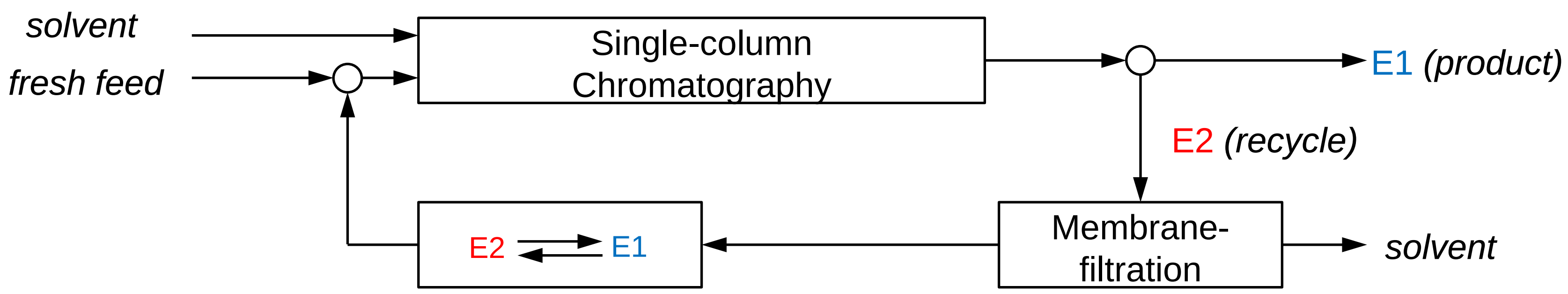
- Reaction required to convert E2 into E1+E2 → isomerization
- Increase yield to 100% by recycling E2



<u>Recycle always diluted!</u>

[1] Bechtold *et al.*, *J Biotechnology* 124 (2006) 146-162

- Inhibit dilution by solvent removal (here: nanofiltration)



Challenges

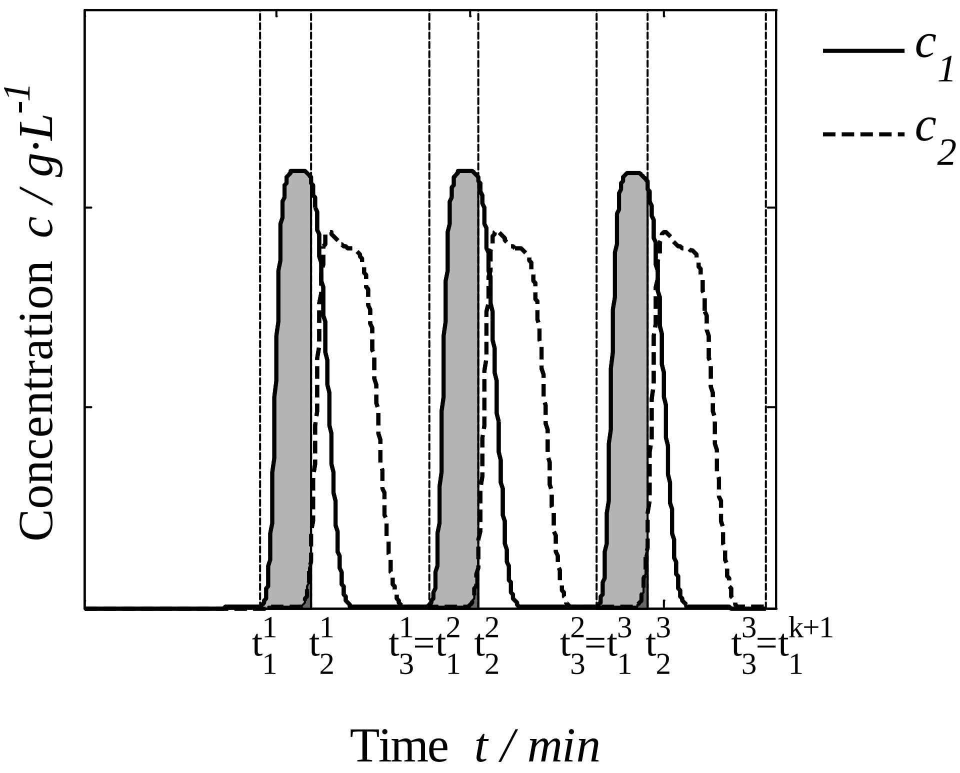
- Design specifications
- Required parameters and models
- Analysis and process behaviour
- Fully continuous implementation
- Experimental validation

Theoretical investigations I

Shortcut process design[2]

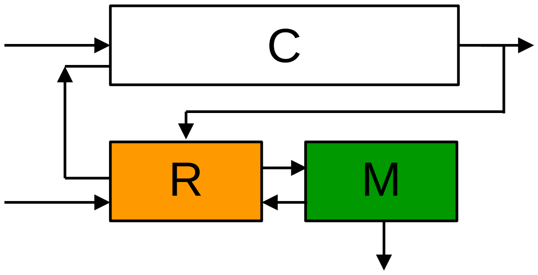
- Reproduce a given chromatogram (simulated or experimental) in each cycle

- Main design parameters:
  - ➢ Feed flow rate Q_{feed}
  - ➢ Permeate flow rate Q_{perm}
  - ➢ Chrom. flow rate Q_{chrom}
  - ➢ Injection width Δt_{inj}
  - ➢ Fractionation times t_1 , t_2, t_3

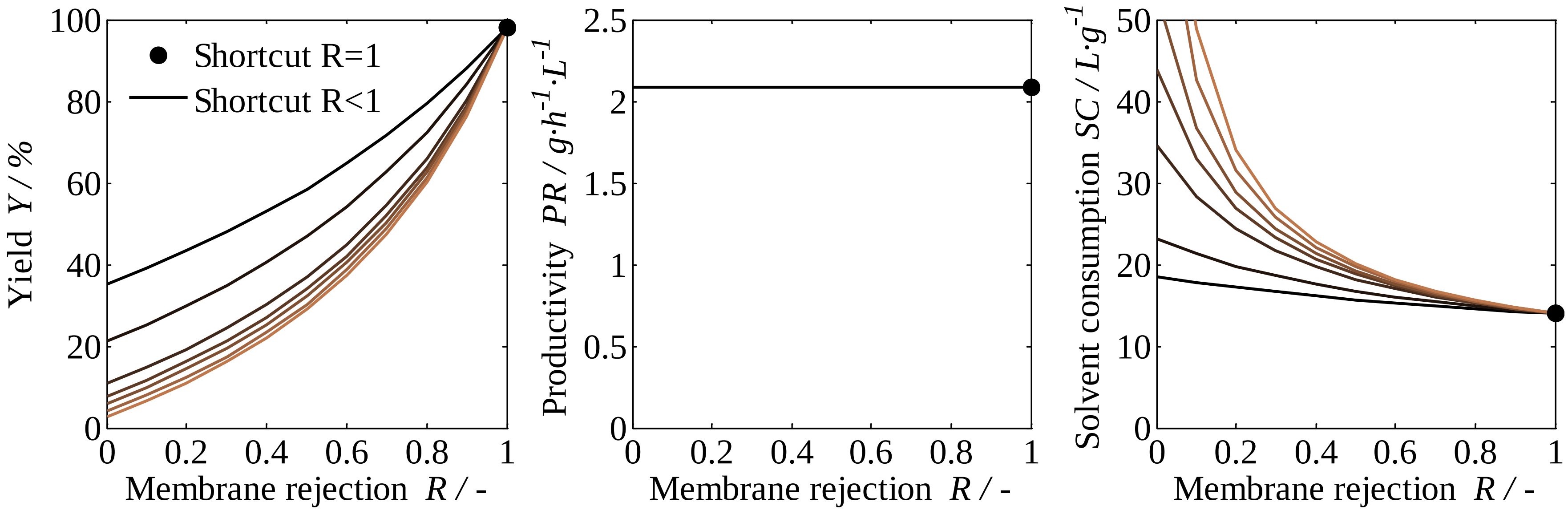


[2] Nimmig, Kaspereit, *Chem Eng Process* 67 (2013) 89– 98

Shortcut process design[2]



- Simple explicit equations
- Easy performance prediction



$$Y = \frac{m_{E1,prod}}{Q_{feed}\left(c_{E1,feed} + c_{E2,feed}\right)}$$

$$SC = \frac{Q_{chrom}\left(\Delta t_{cyc} - \Delta t_{inj}\right) + Q_{feed}\Delta t_{cyc}}{m_{E1,prod}}$$

Detailed process design

C ➢ Chromatography : Equilibrium dispersive model

$$\varepsilon_b \frac{\partial c_i}{\partial t} + (1-\varepsilon_b)\frac{\partial q_i}{\partial t} + u\frac{\partial c_i}{\partial z} = D_{ax,i}\frac{\partial^2 c_i}{\partial z^2}$$

R ➢ Reaction: First order kinetics, CSTR

$$c_i(t)\frac{dV}{dt} + V(t)\frac{dc_i}{dt} = \sum\left(Q_{k,IN}(t)c_{i,IN}(t) - Q_{k,OUT}(t)c_{i,OUT}(t)\right) + r_i$$

M ➢ Nanofiltration: Simplified solution diffusion model

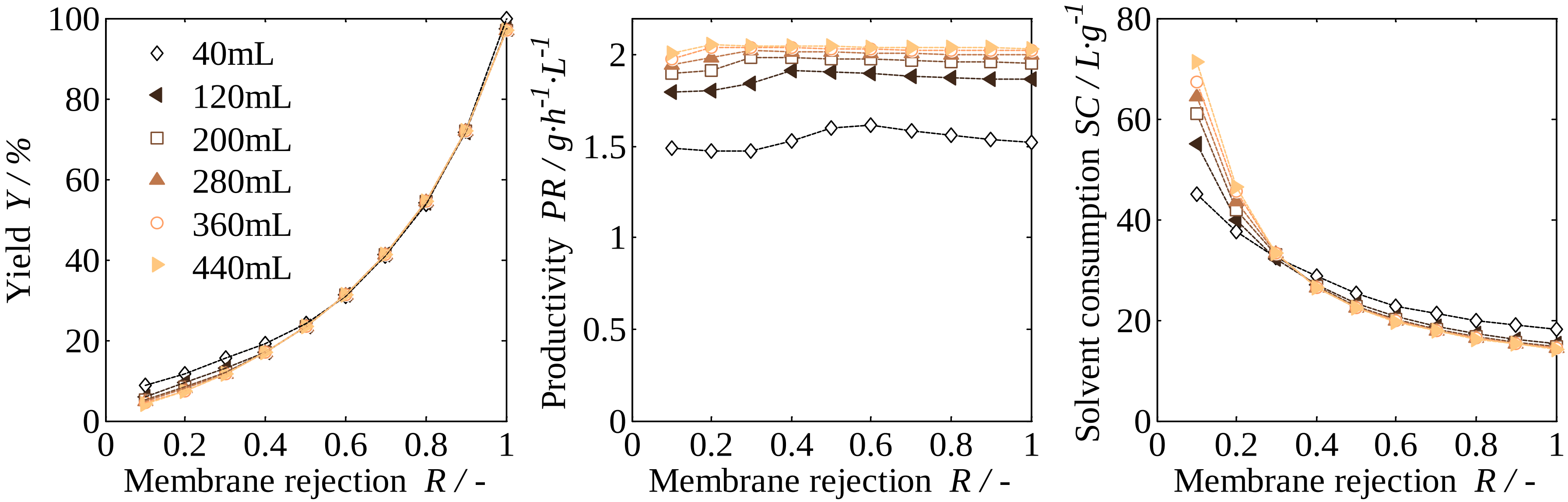
$$Q_{perm} = Q_{Eluent} + Q_{compound}$$

$$Q_{perm} = k_1\, A(\Delta p - \Delta\pi) + k_2 A\, \Delta c_{compound}$$

- Implementation in MatLab

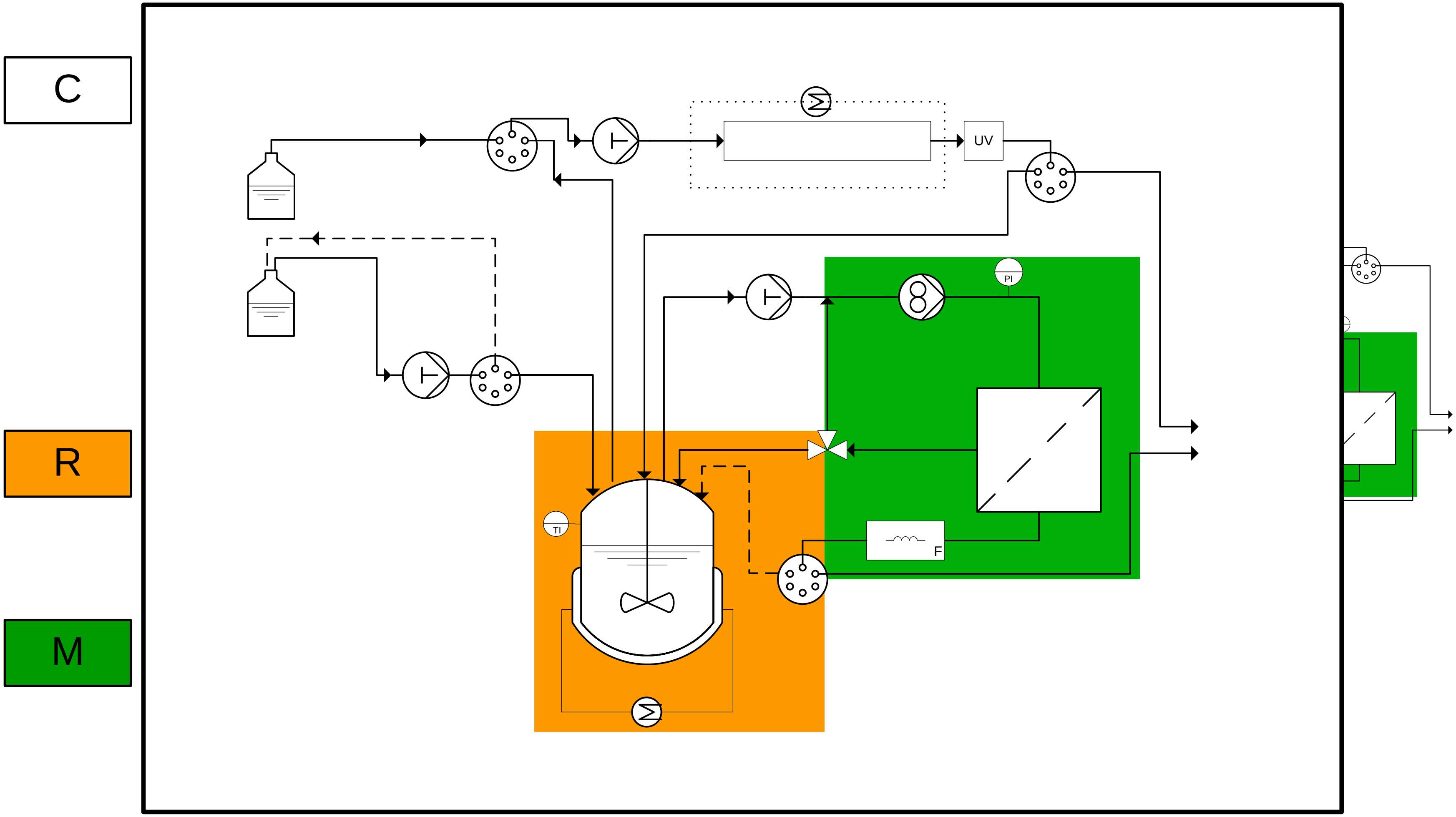
Detailed process design

- Fully continous connection
- Performance prediction:



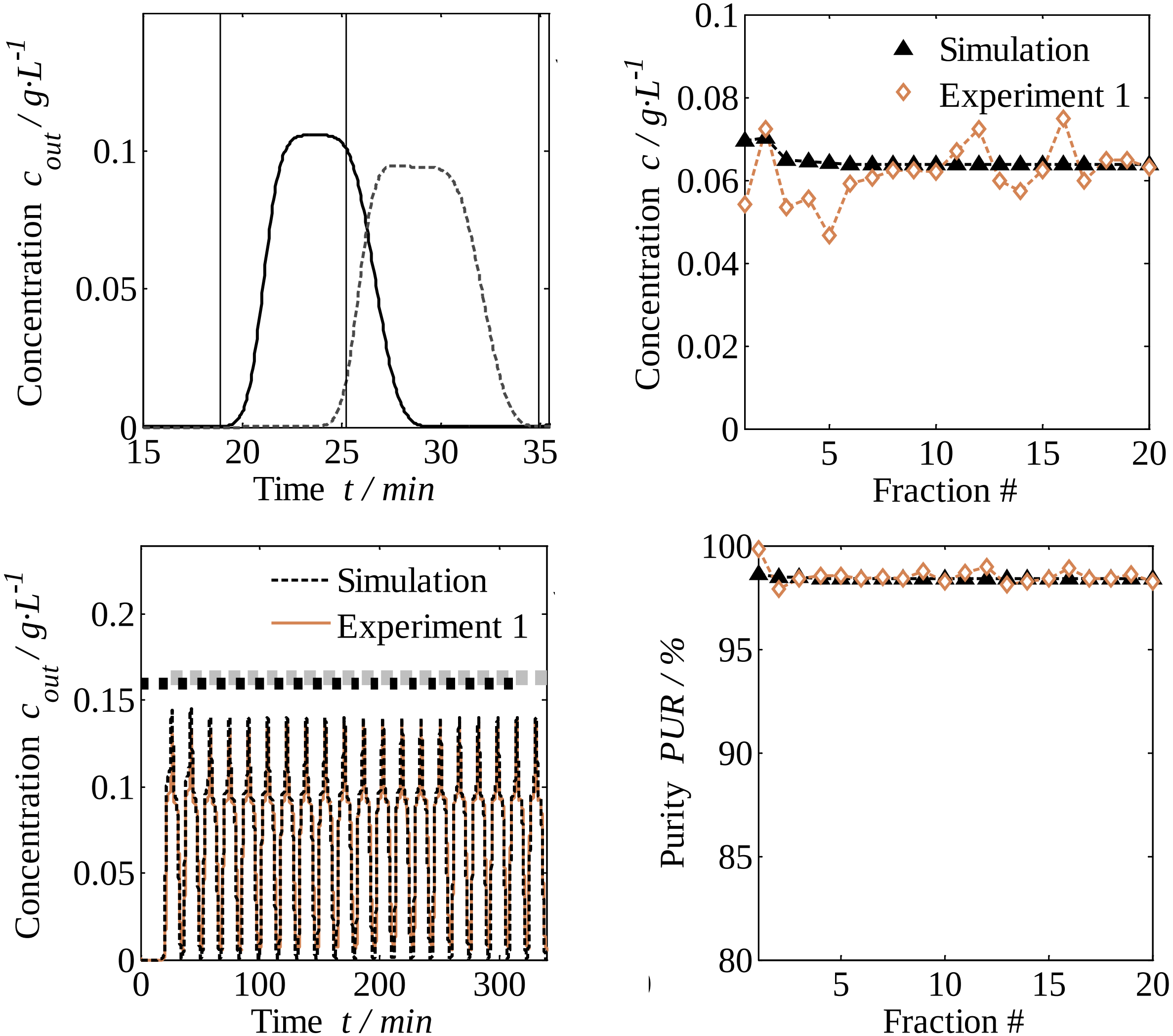
Experimental validation

Experimental setup and conditions



- Sample storage: $\vartheta = -20°C$

Experiment 1 – Design via detailed simulation

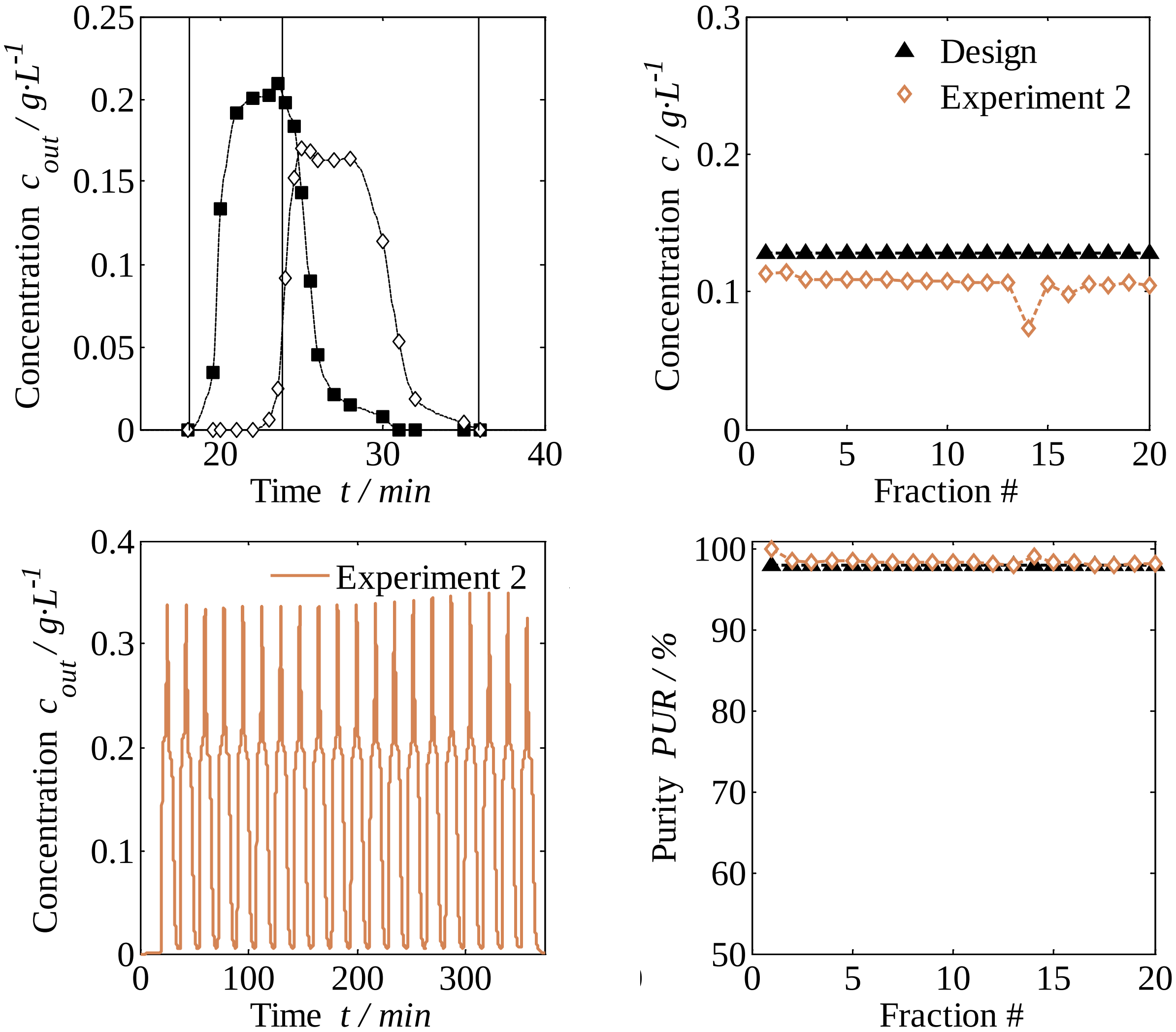


$Y = 76.8\%$

$V_{inj} = 12mL$

$V_R = 100mL$

Experiment 2 – Design via shortcut method



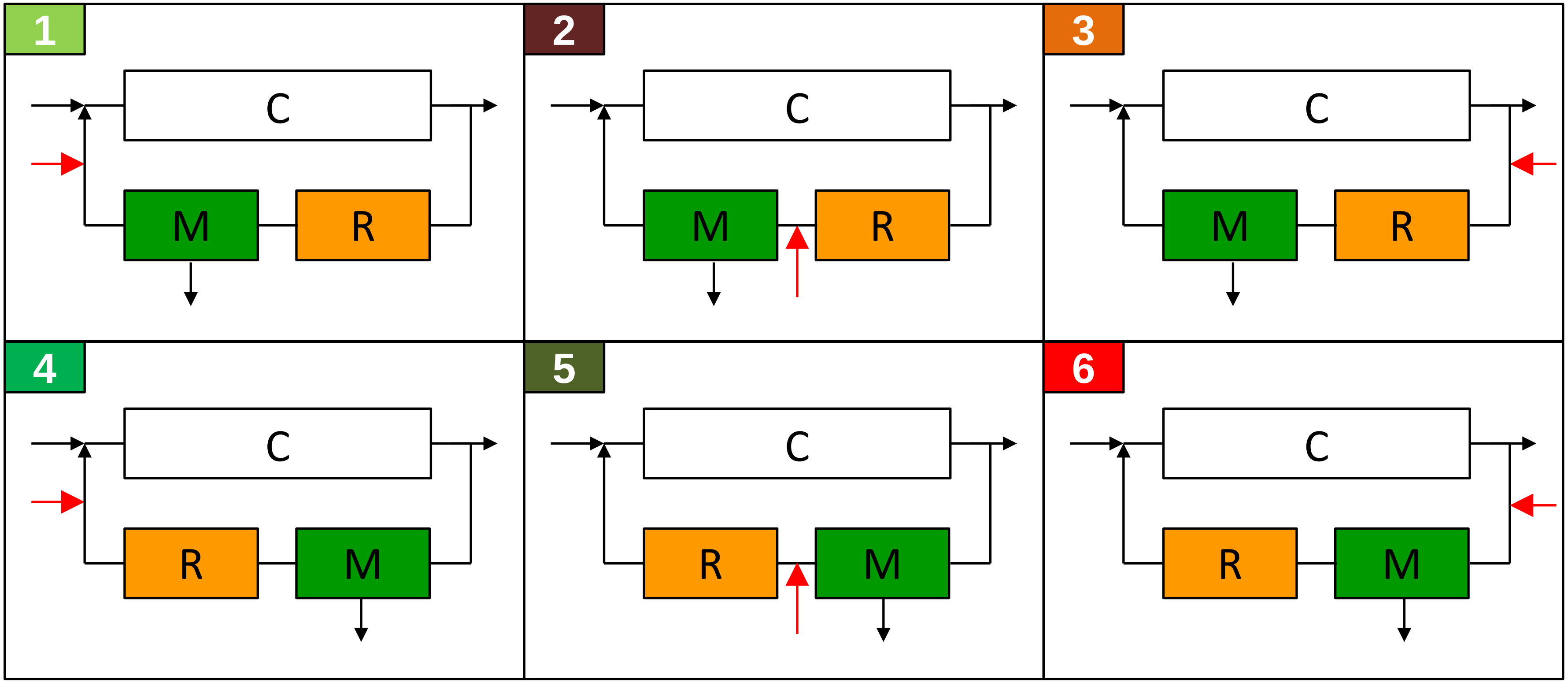
$Y = 69.0\%$

$V_{inj} = 12mL$
$V_R = 100mL$

Theoretical investigations II

Unit Arrangements

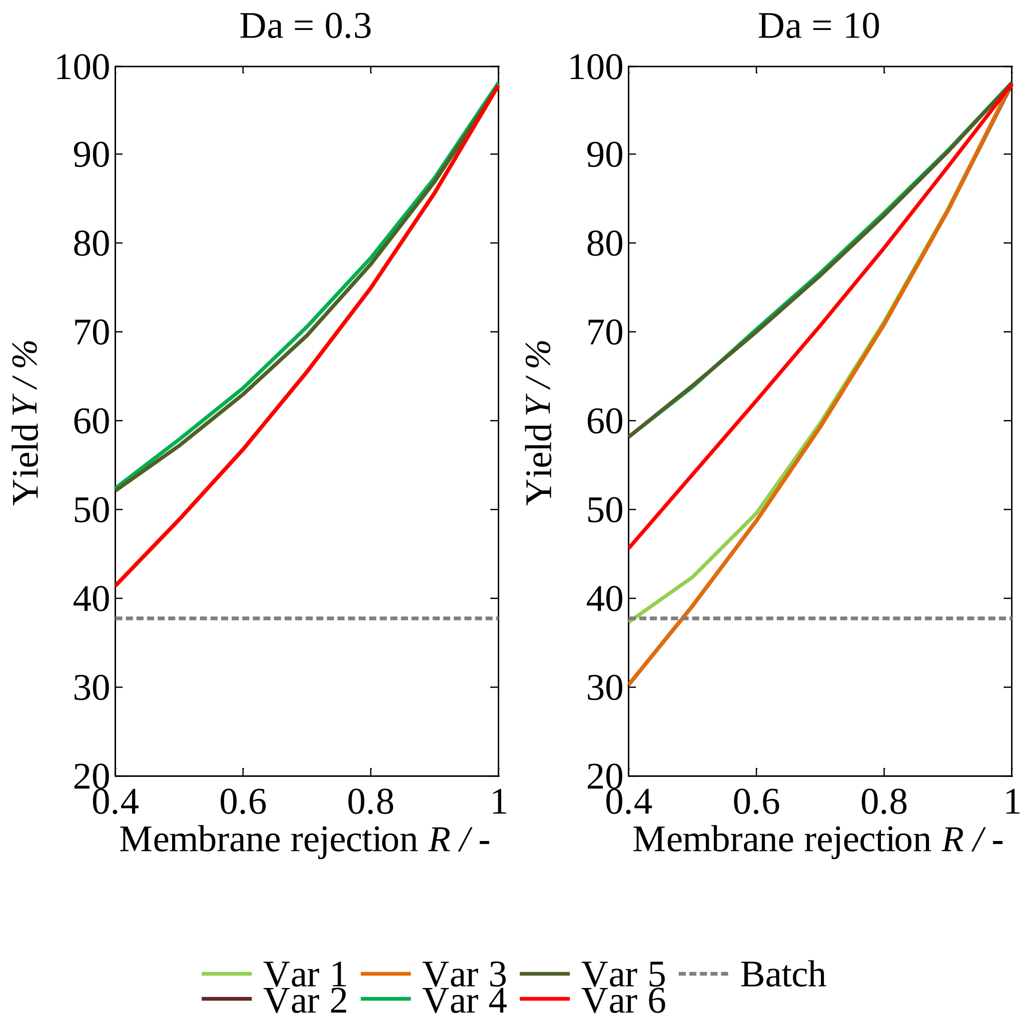
Different setups - different performance?



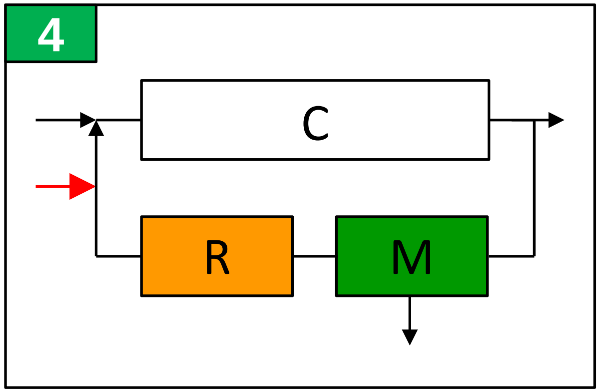
R: Reactor C: Column

M: Membrane → : Fresh Feed

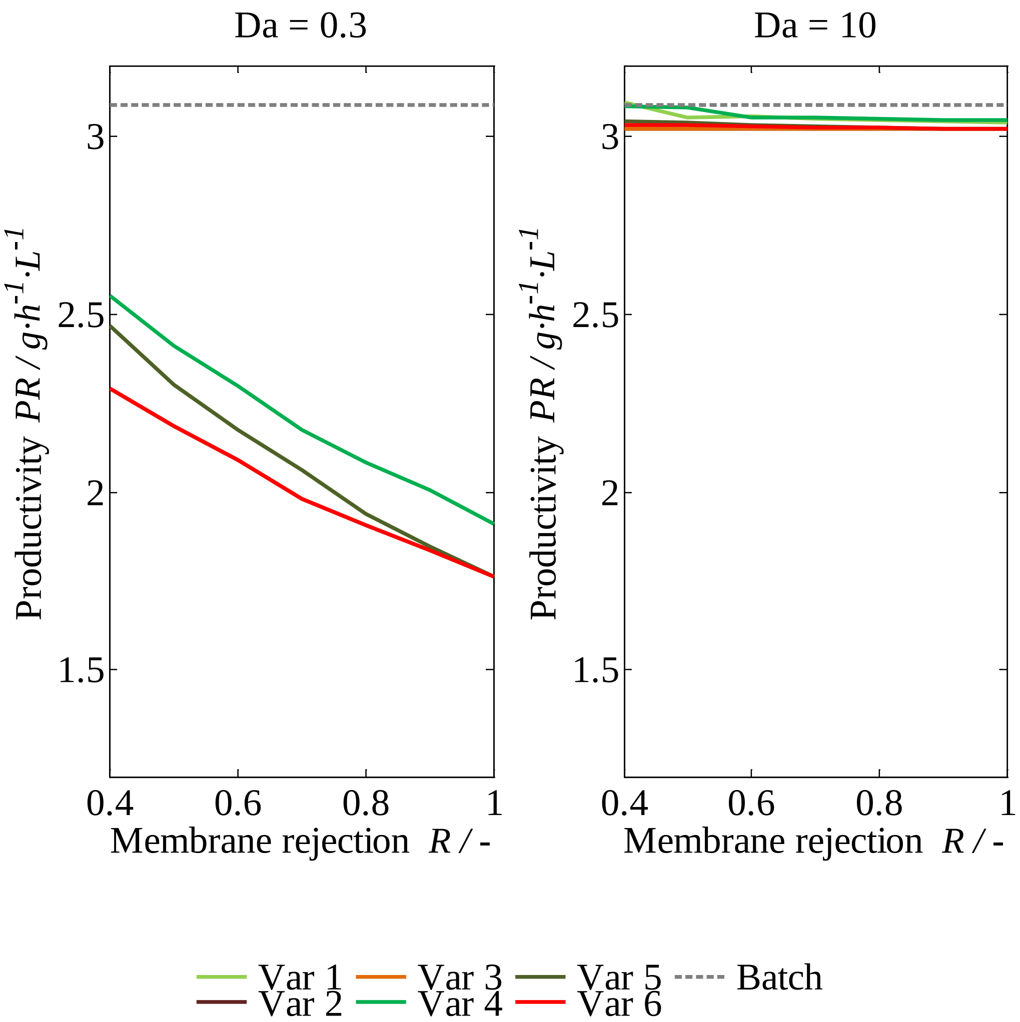
Perfomance prediction - Yield



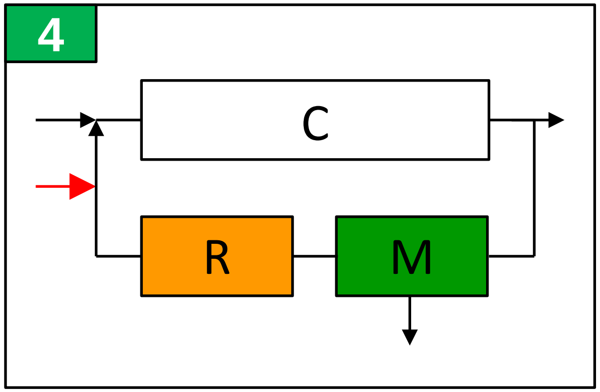
Best choice:



Perfomance prediction - Productivity



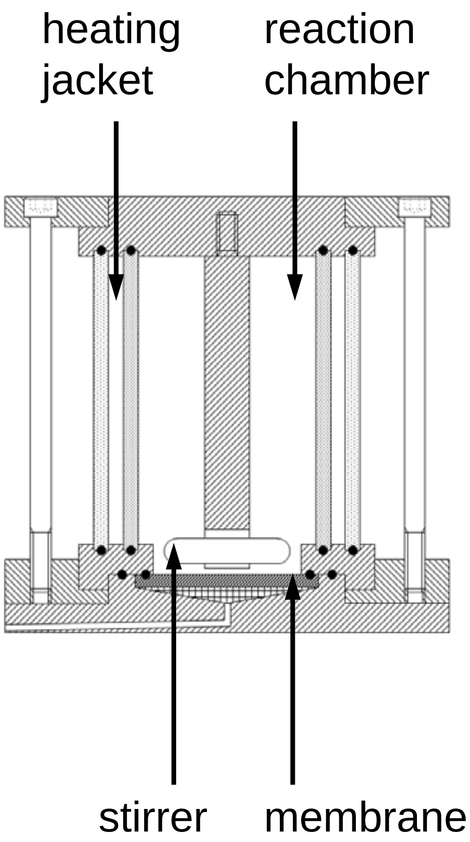
Best choice:

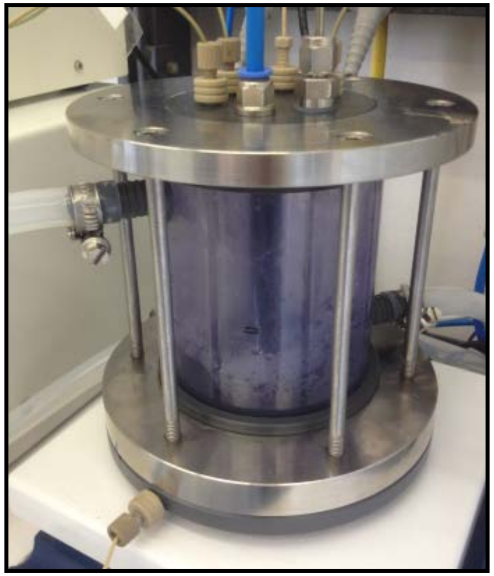


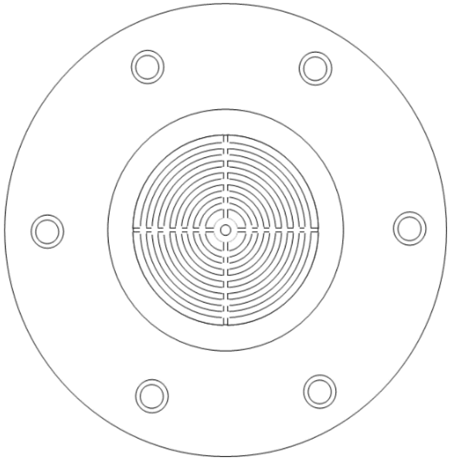
Further extensions of concept?

Process integration: Membrane reactor

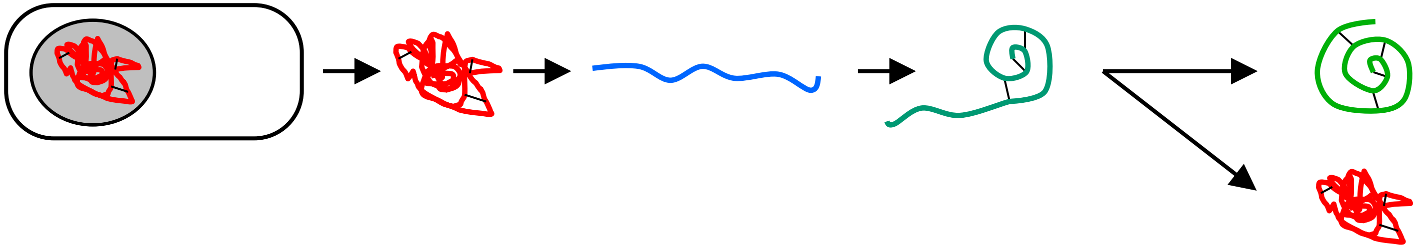
- Stirred and tempered membrane reactor developed:
- Simple connection to HPLC
- Online monitoring:
    - Pressure
    - Permate flow
    - pH
    - Temperature
- Dimensions:
    - $V = 10 \text{ up to } 250\ mL$
    - $A_M = 26.4\ cm^2$

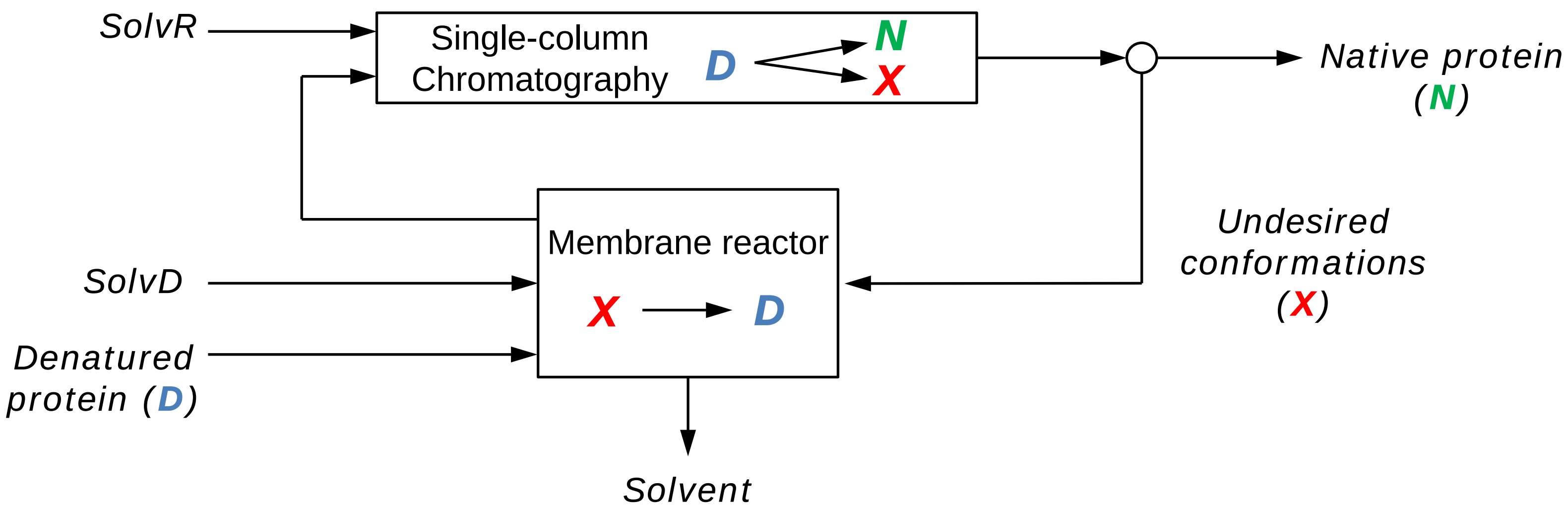






On-column protein refolding





Summary

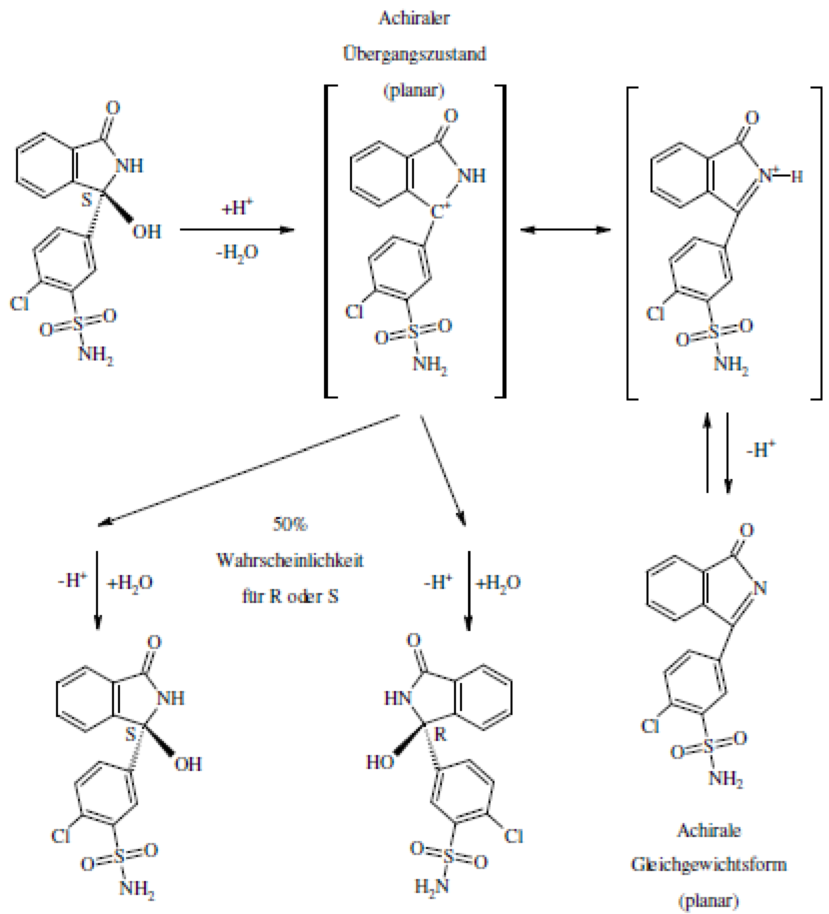
- Proposed concept capable of significantly improving yield and performance
- Shortcut methods developed for basic design, full model for detailed design
- Performance limited mainly by membrane rejection
- Process setup influences performance
- First successful realization of such process in directly coupled operation

Outlook

- Potential application to industrial relevant compunds?

Thank you for your attention!

Chlorthaidone racemization

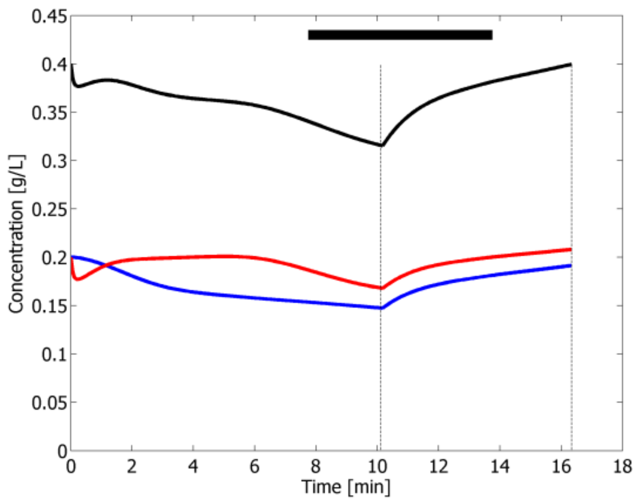


Racemization under acid conditions

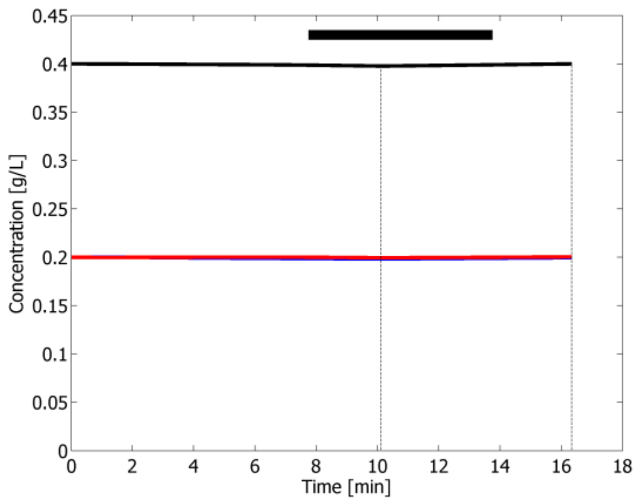
- Nearly insolubile in Water
- Increasing solubility in MeOH/H_2O
- MW =338 g/mol
- Kinetics known as function of pH-value and temperature[3]

[3] J. G. Palacios, B. Kramer, A. Kienle, M. Kaspereit, J Chromatogr A 1218 (2011) 2232-2239

Reactor concentration behavior for different Volumes

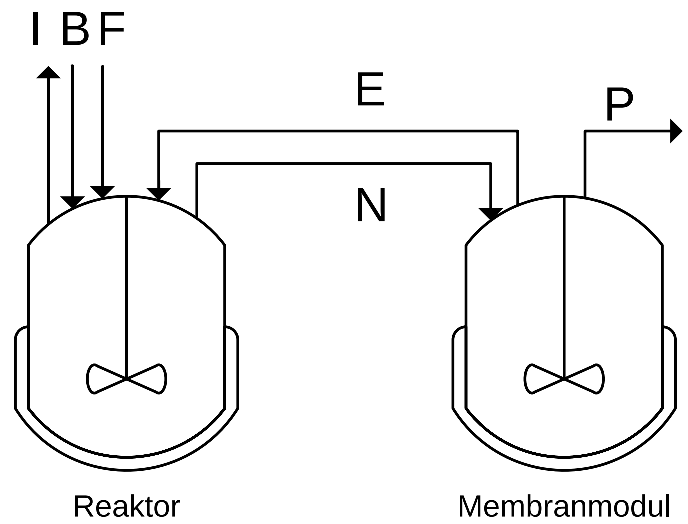


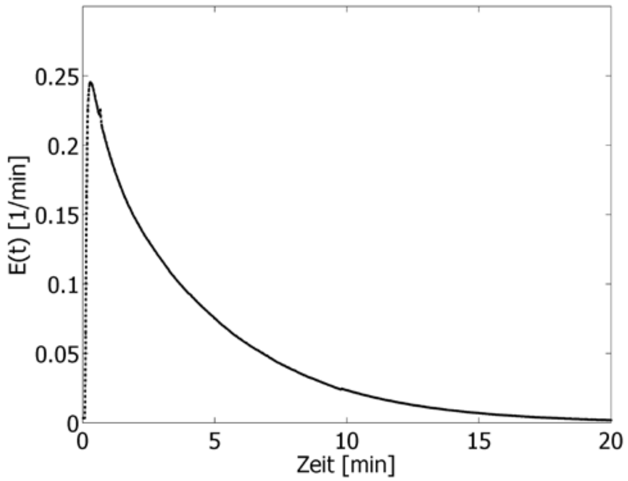
V_R=1mL



V_R=1000mL

• Membran ←→Reactor design

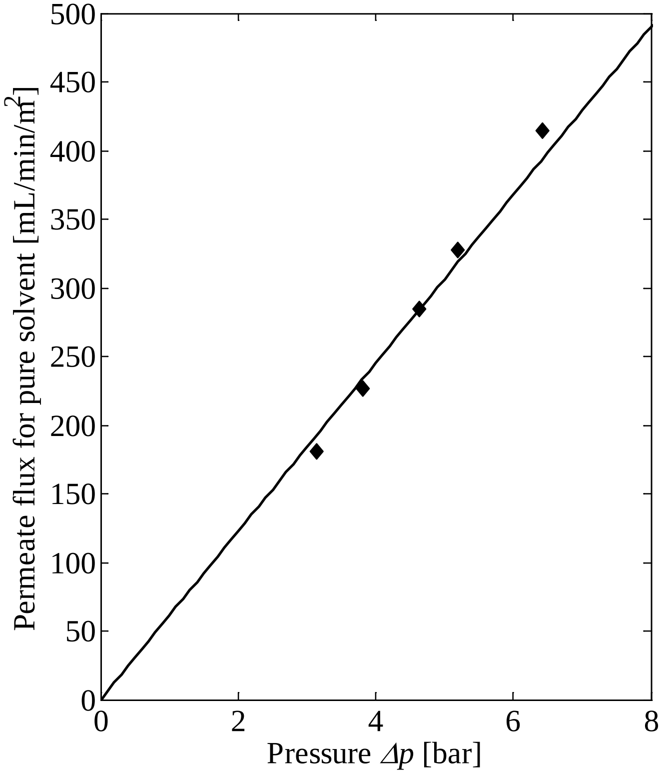




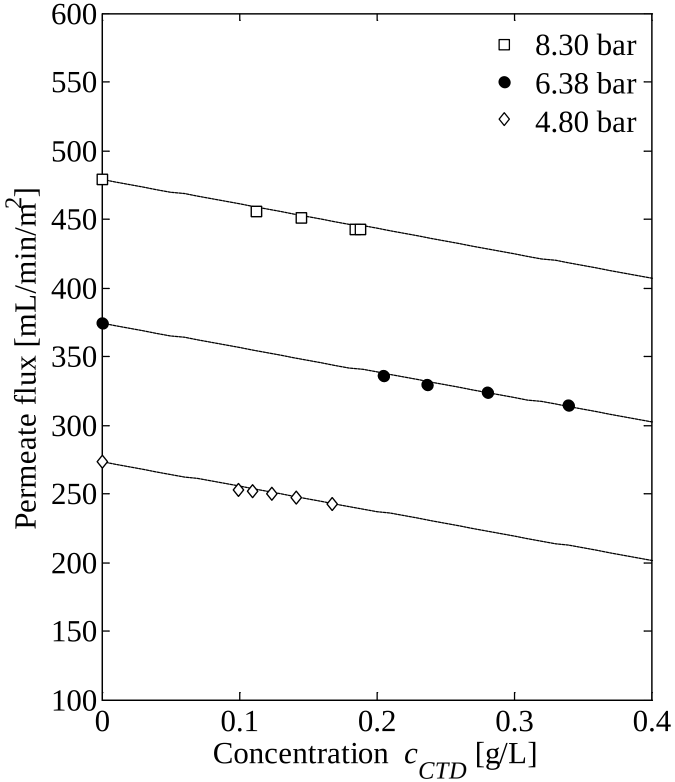
• Membrane unit acts as CSTR (residence time function)

Parameter determination - Nanofiltration

Pure water experiments (k1)



Batch concentration experiments (k2)



$$Q_{perm} = k_1\, A(\Delta p - \Delta\pi) + k_2 A\, \Delta c_{compound}$$

- Parameter determination - Racemization