Massachusetts Institute of Technology

ZAIPUT FLOW TECHNOLOGIES

Continuous, efficient multistage extraction

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Zaiput Flow Technologies

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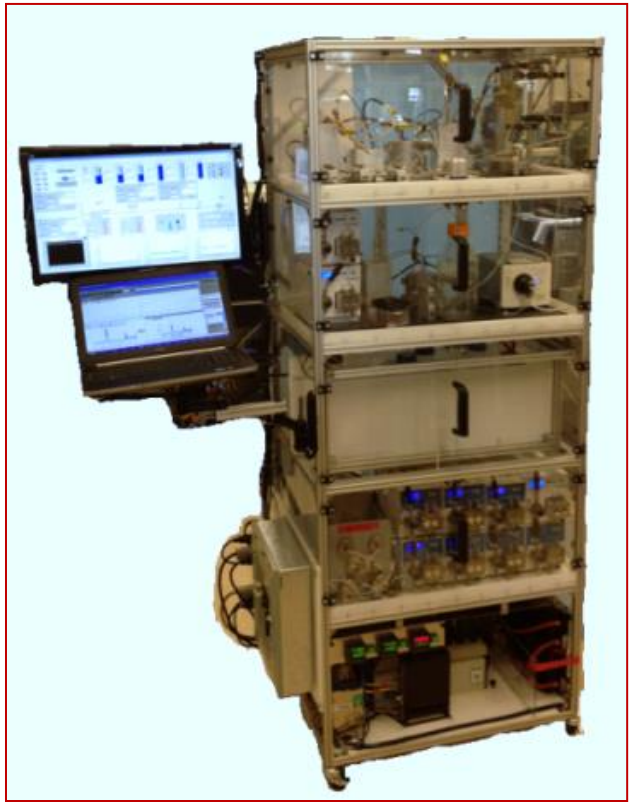
Munich– 01 February 2017

Back ground - MIT's efforts in continuous manufacturing

Pharmacy on Demand - POD

DARPA



MIT-Novartis consortium:

Massachusetts Institute of Technology

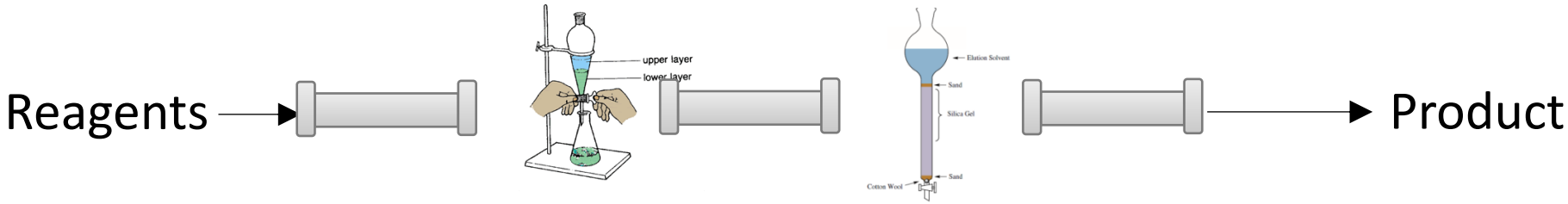
NOVARTIS

The problem - Zaiput's solution

Continuous Flow Synthesis of drugs, the future of complex chemical synthesis.
(larger parameter space, more robust/repeatable processes, cost reduction)

Wish

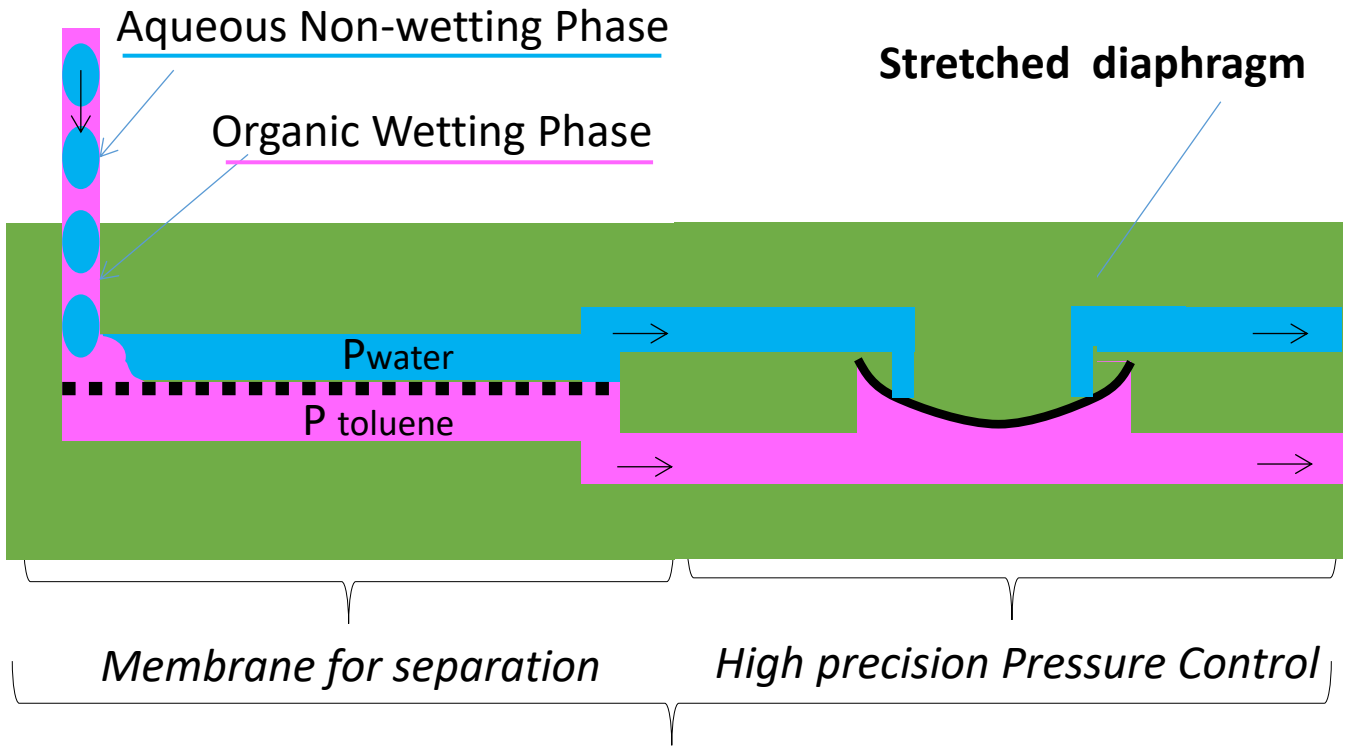
Reality

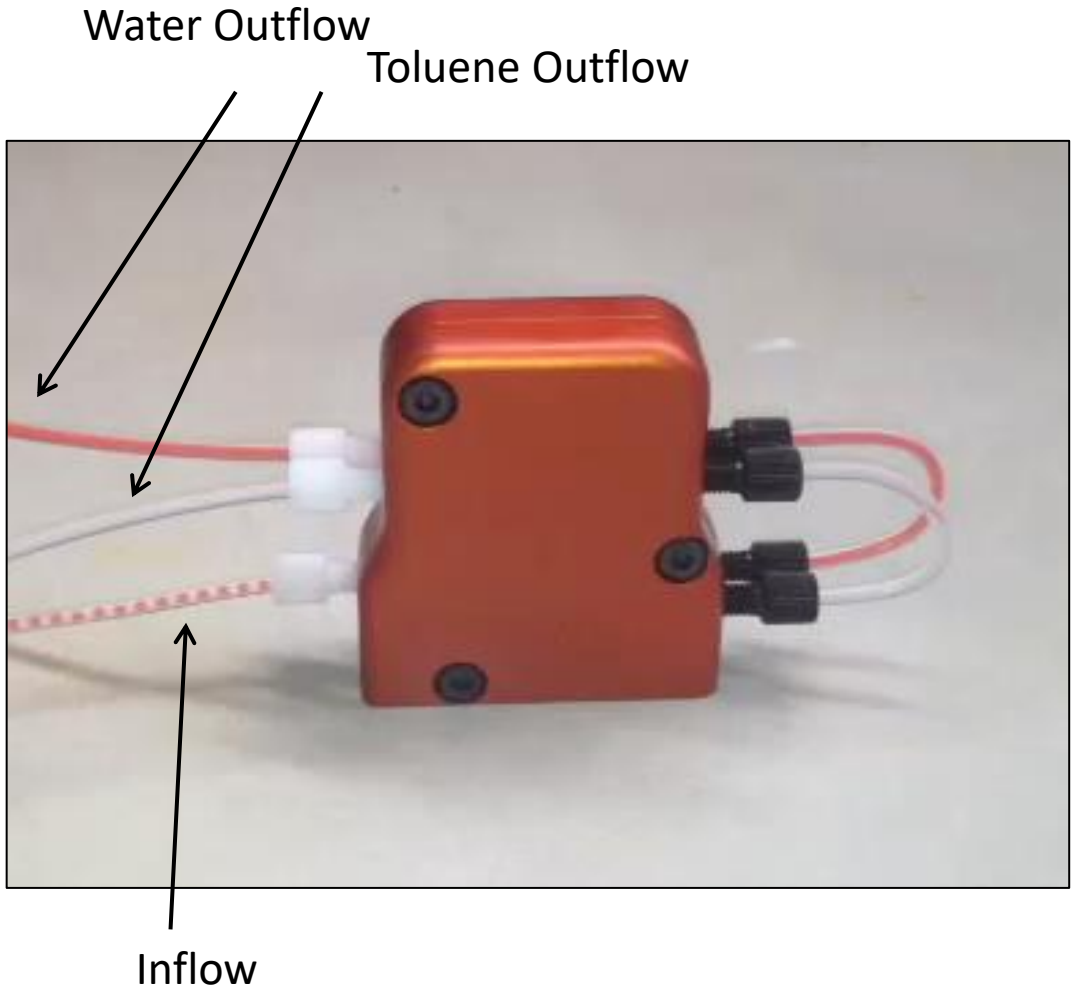


Currently, reaction steps are not linked, chemical work-up needed

Zaiput provides the link
thus enabling real continuous flow process

Inline extraction enabled by continuous separation



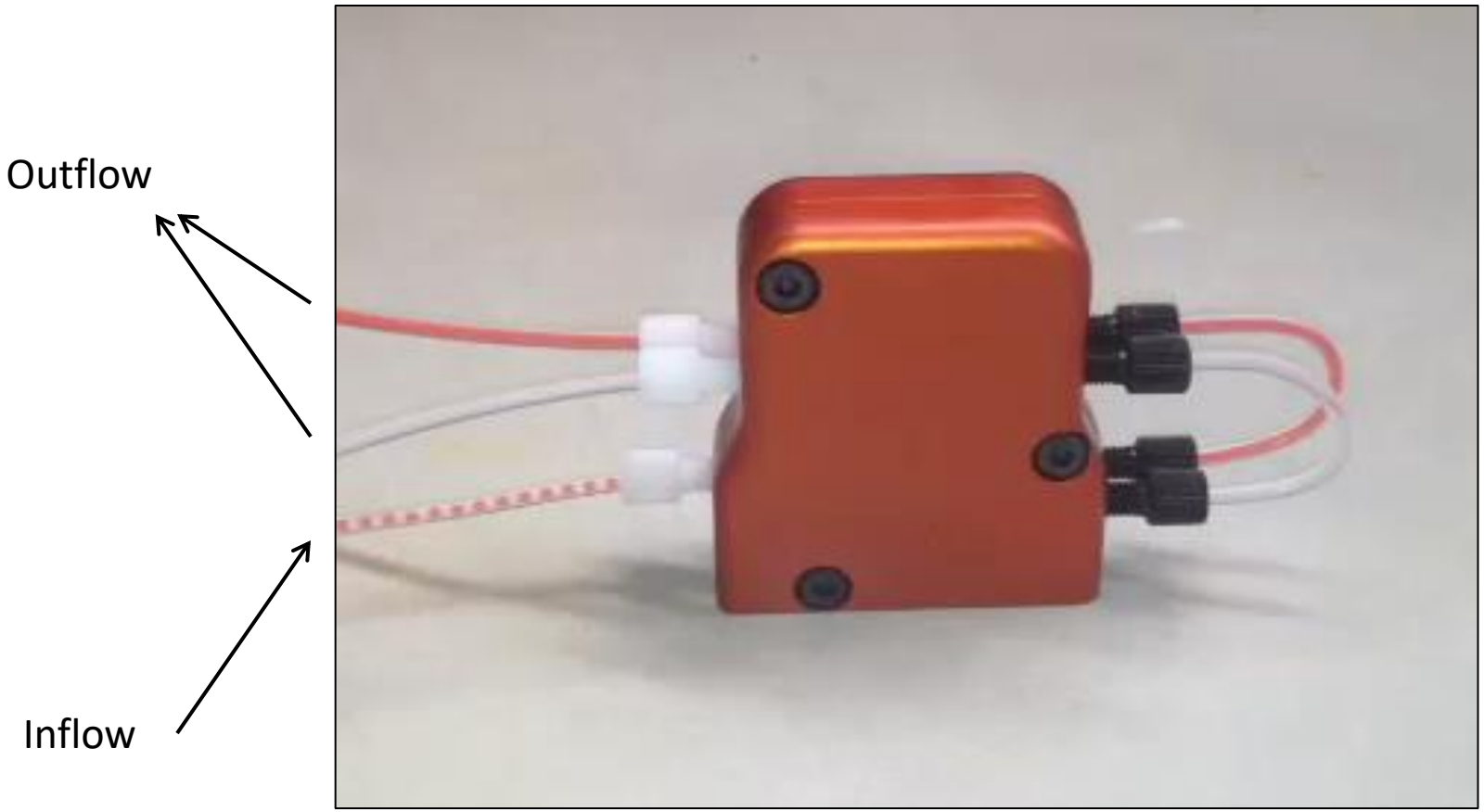


$$P_{cap} > (P_{water} - P_{toluene}) > P_{per}$$

$$P_{cap} > P_{diaphragm} > P_{per}$$

$$P_{water} = P_{diaphragm} + P_{toluene}$$

Integrated liquid-liquid separator



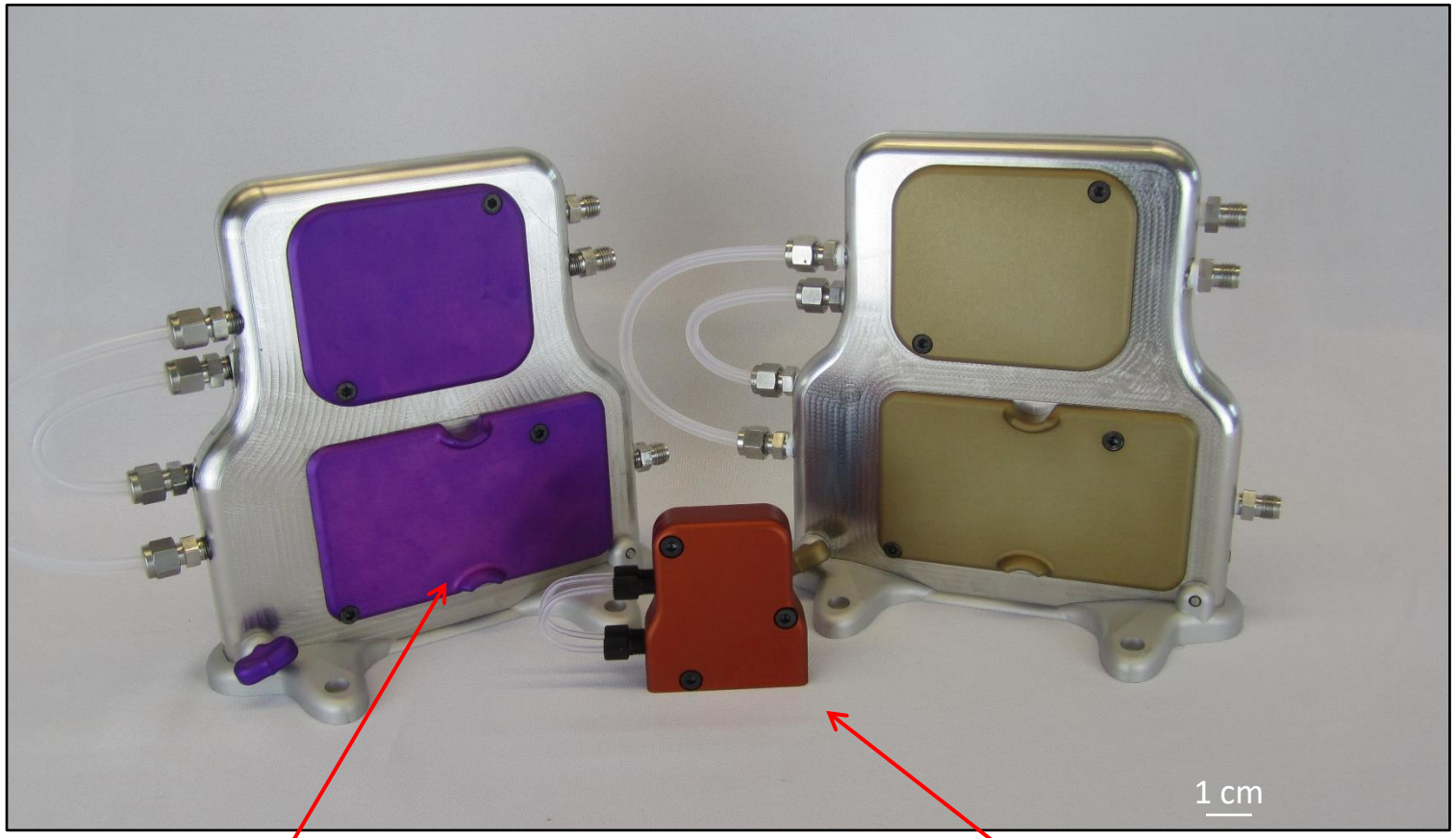
Summary of advantages

- Easy to use
- Passive device
- Truly continuous
- No dead volume
- Scalable

- ❑ NO need of manual adjustments, *plug* & *play* operation)
- ❑ Excellent chemical compatibility (wetted parts ETFE, PFA and PTFE)
- ❑ Operation under pressure (300 psi/20 bar max) and in line
- ❑ Low separation pressure differential (suitable for the majority of aqueous/organic pairs)
- ❑ **GAS/LIQUID separation**
- ❑ **Separation of Emulsions**
- ❑ **Inherently safe**

Integrated liquid-liquid separator

2 sizes already available. **Forthcoming 3 liter/min version**

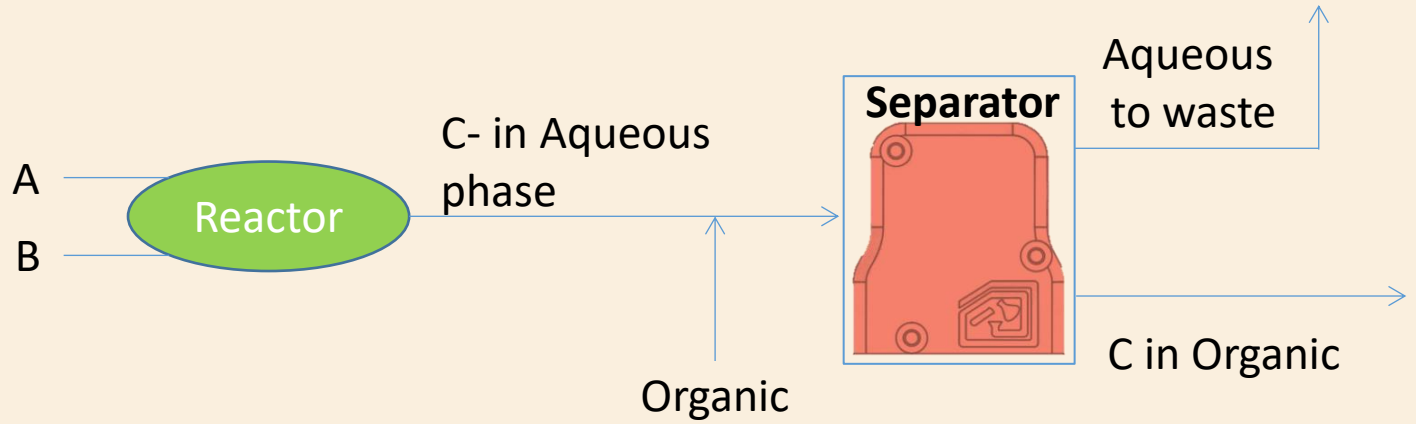


Small production/pilot plant
Max flow rate 200 ml/min

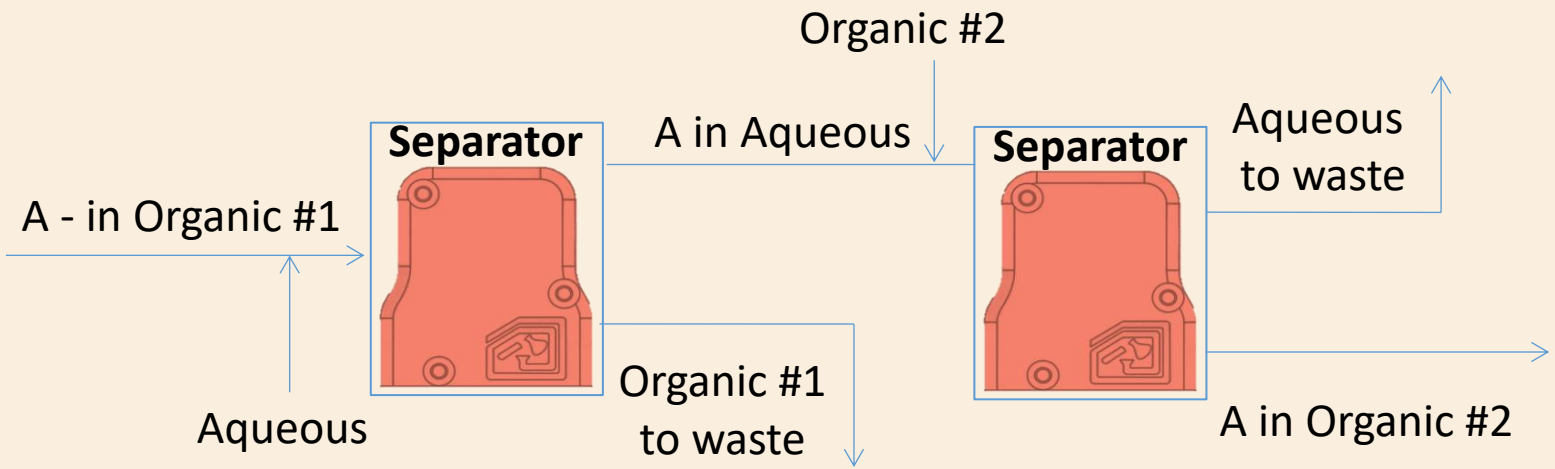
Process development
Max flow rate 12ml/min

Examples of applications

Reaction followed by an extraction

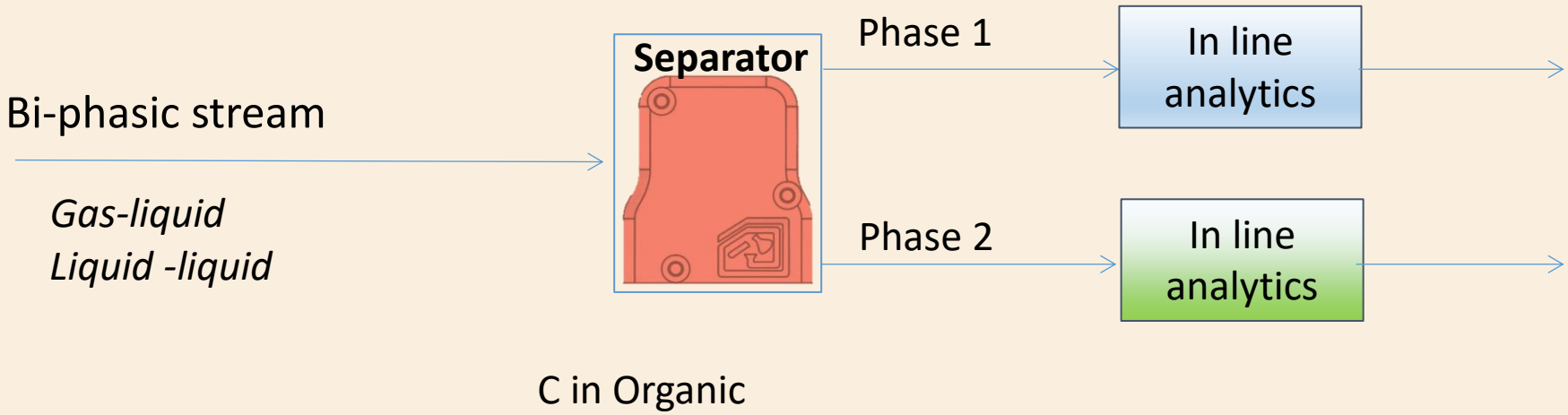


Solvent Swap



Examples of applications

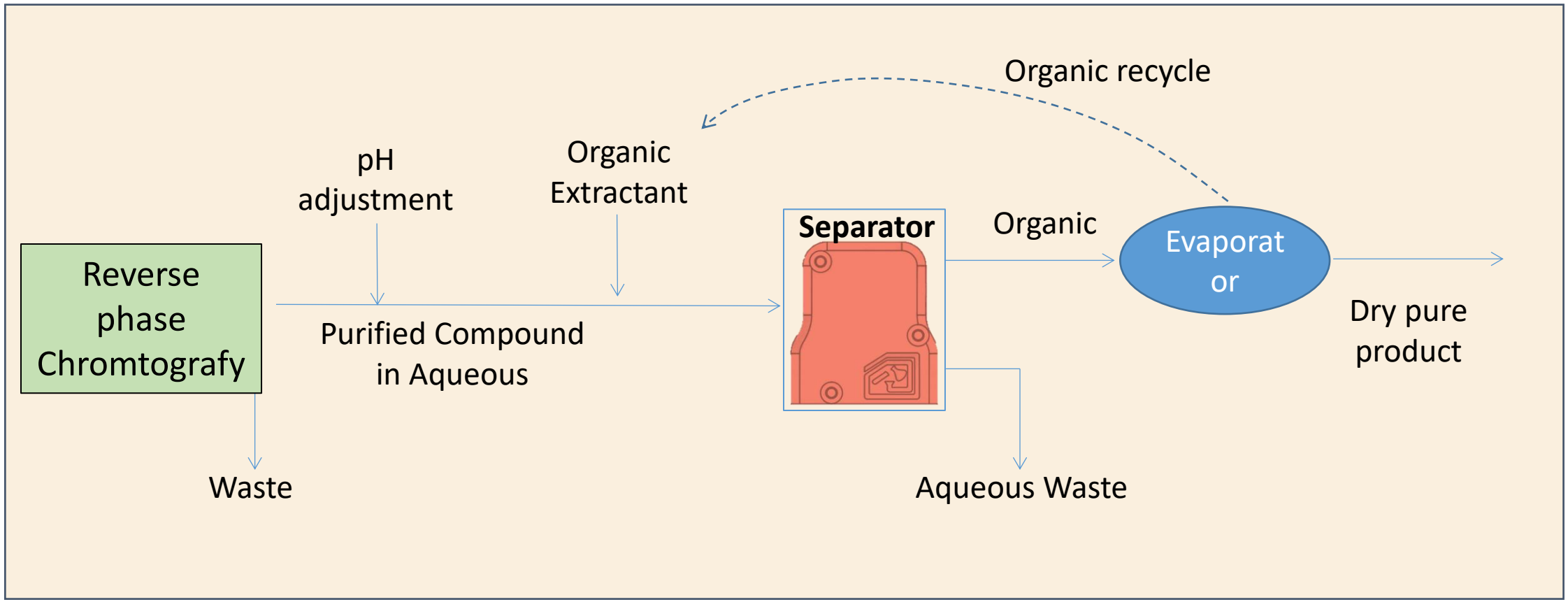
Analytical / process monitoring



Typically used with small scale device
Example of Analytics (IR, UV-Vis, Raman, etc…)

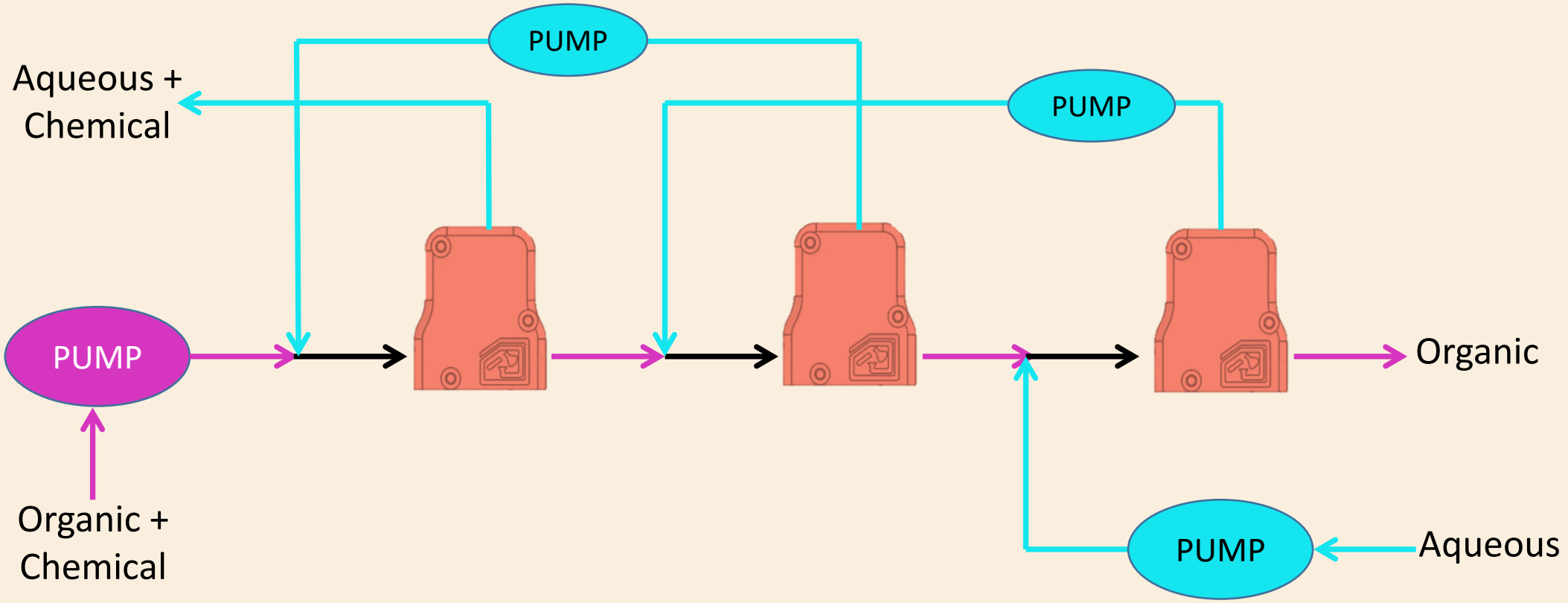
Examples of applications

Continuous product isolation after Chromatographic purification



Example of applications

Counter current extraction



Adamo et al., *Ind. Eng. Chem. Res.*, July 2013

Current literature on Zaiput shows:

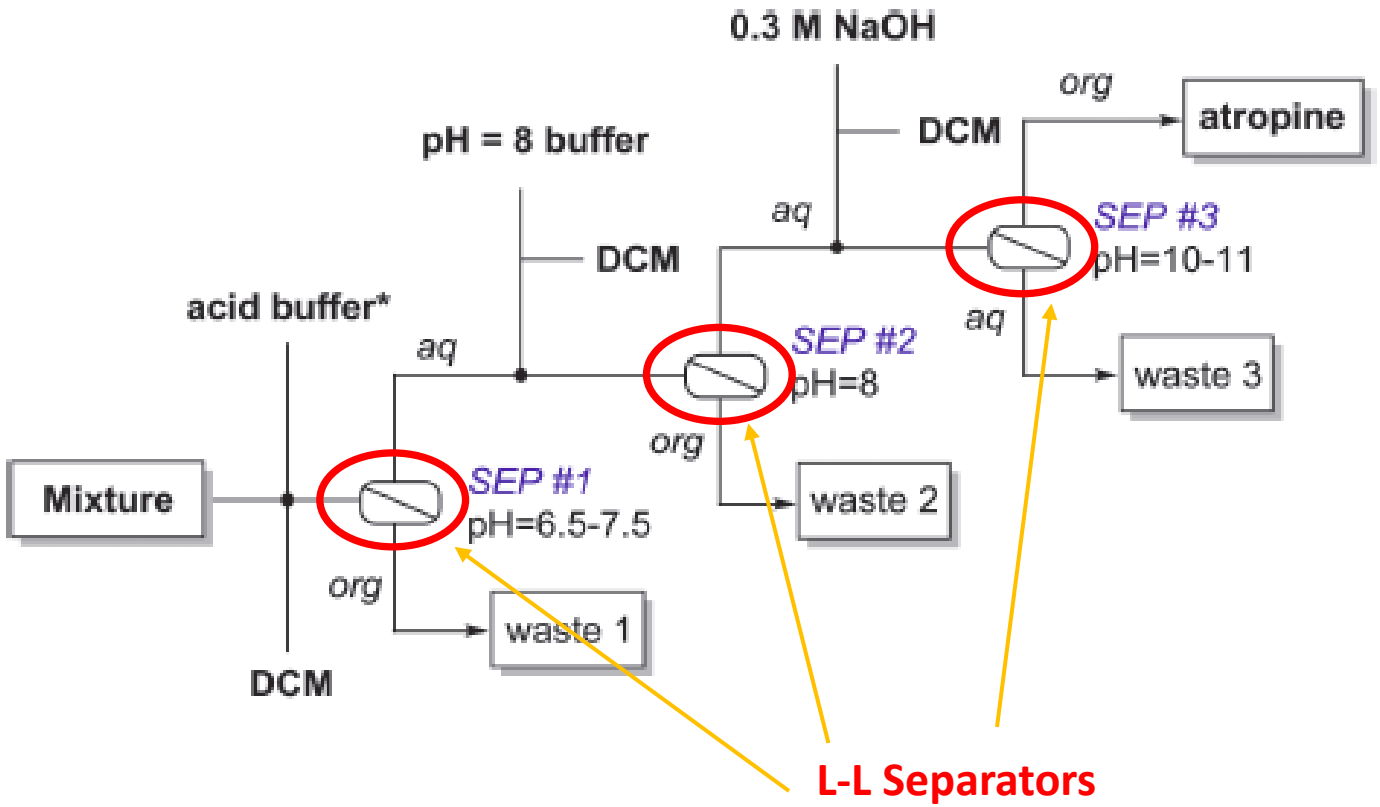
Customers have written a variety of papers, types of uses are:

Types of uses divided by chemistry need:

- Liquid-liquid extraction and simple in line work up
- Biphasic reaction and quenching
- Solvent Switch
- Homogeneous catalyst recovery
- Separation of hazardous material after in-situ production

Examples of applications

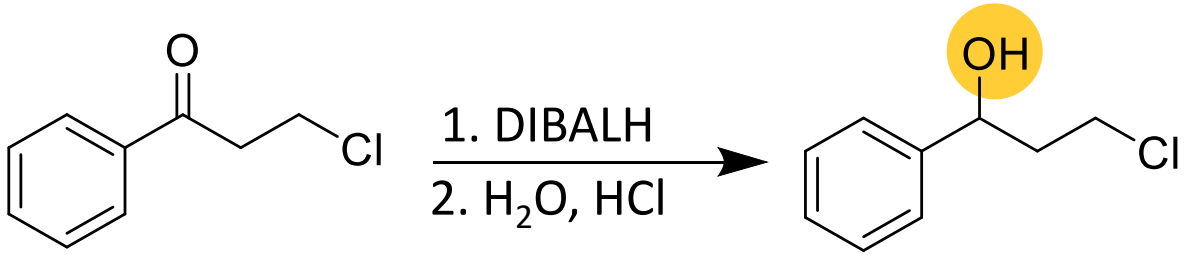
Continuous-flow purification of atropine,
3 sequential extractions with in line pH adjustments (Acid – base extraction)



C. Dai et al. - *J. Flow Chem*. 2015

Example of use - Fluoxetine

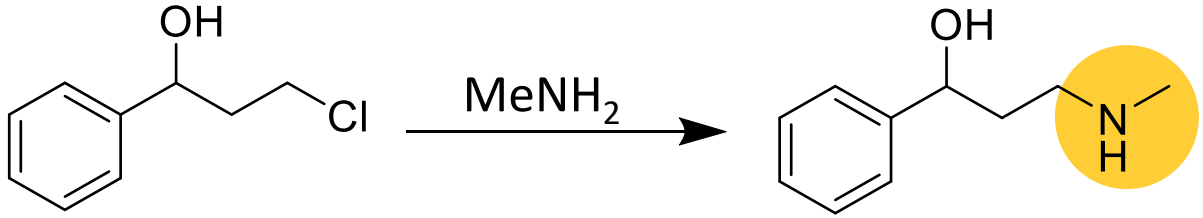
1 (ketone reduction)



Incompatible with **2**

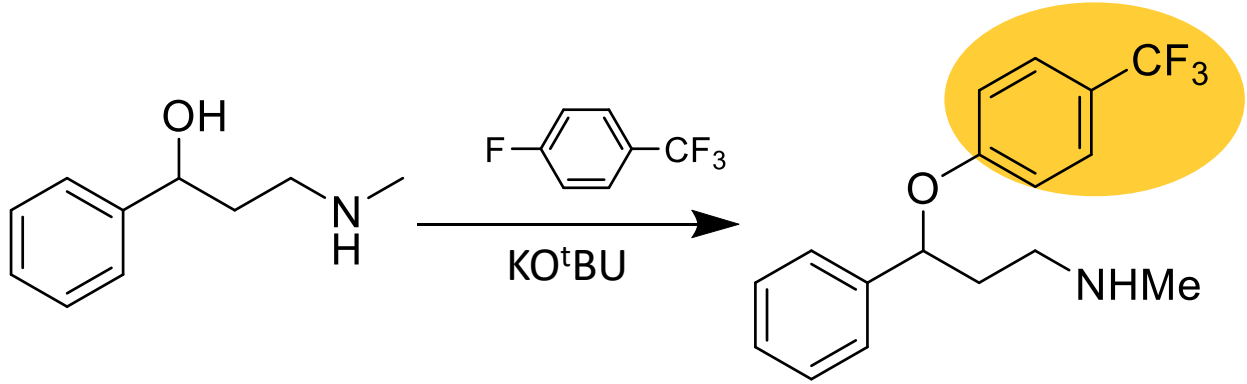
Al salt

2 (amination)



Water hinders **3**

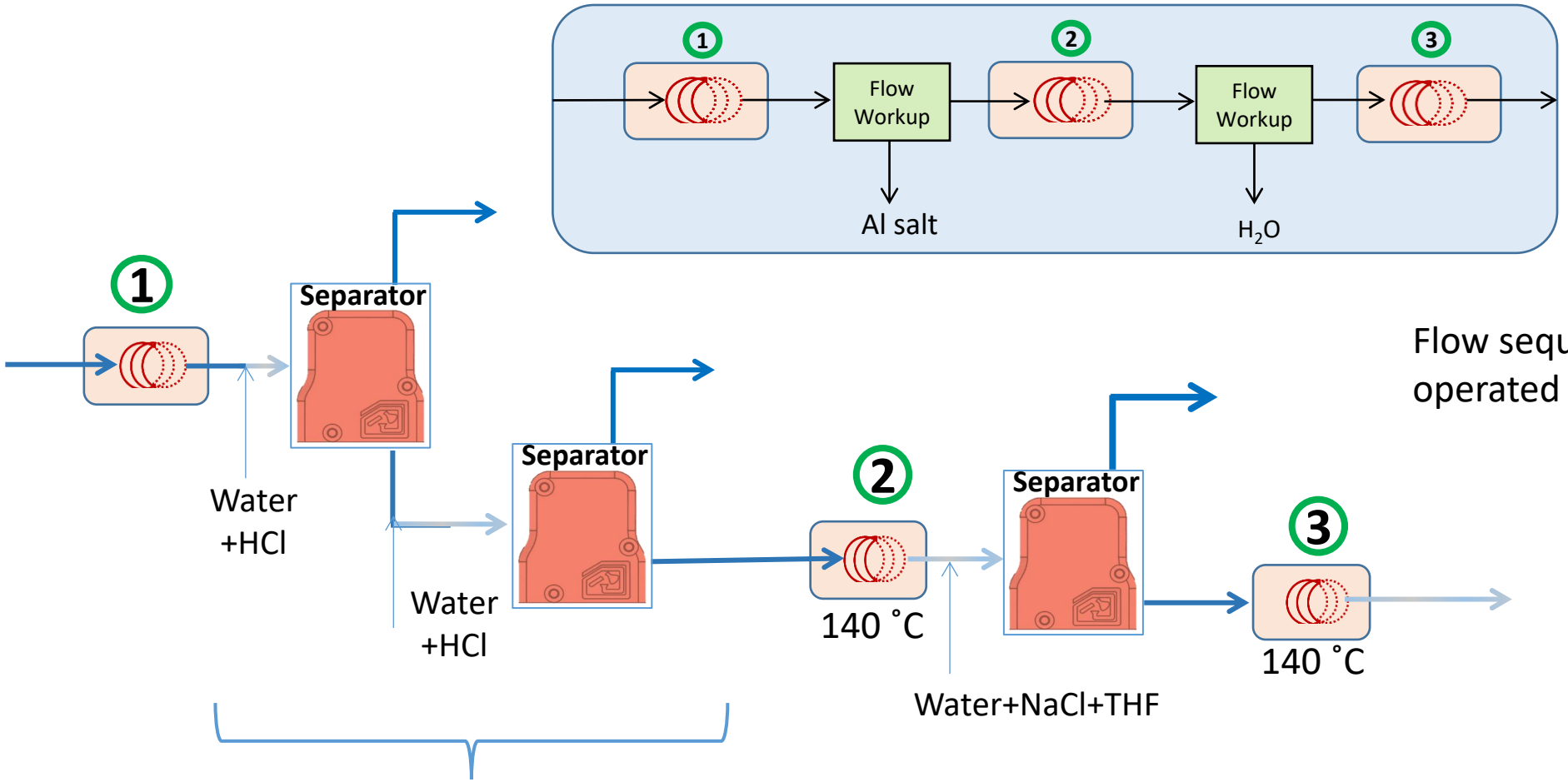
3 (aromatic substitution)



(Fluoxetine)

Adamo et al. *Science* **2016**

Fluoxetine - Complete process



Flow sequence operated at **1.7 MPa**

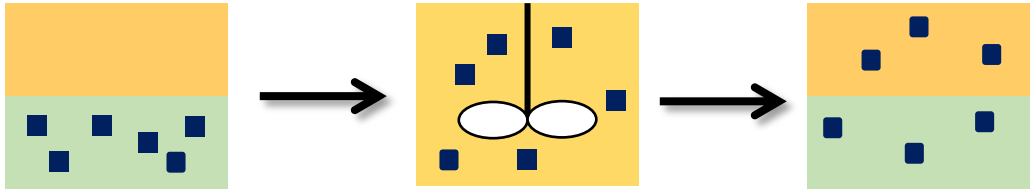
Multistage Extraction Possible because of device modularity

When do you use multi-stage extraction ?

Partition coefficient: $K_i = \frac{C_{i,organic}}{C_{i,aqueous}}$

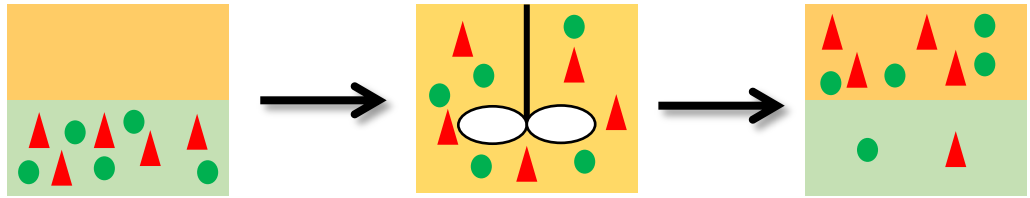
K_i	% extraction with 1 stage
1	50%
5	83%
10	91%
100	99%

1) Low or medium partition coefficient (K_i < 10 for most ternary systems)

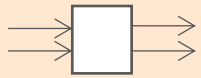
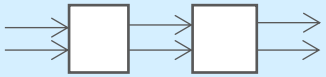
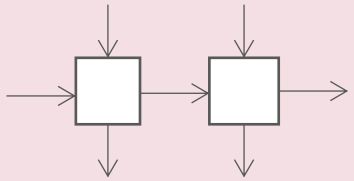
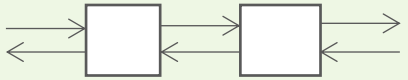


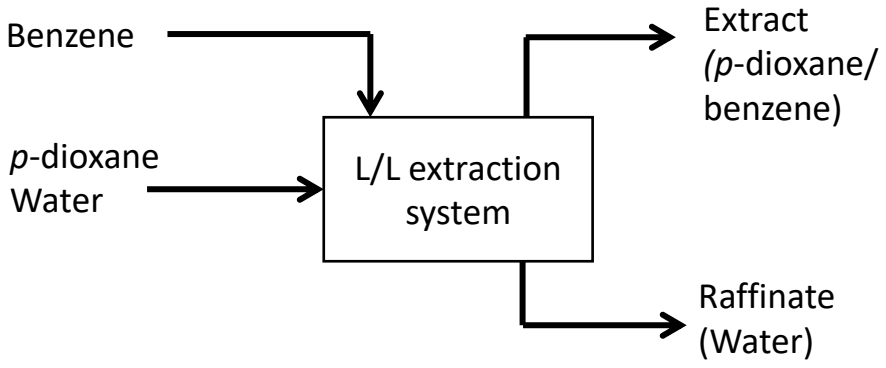
2) The system with molecules with similar partitions (i.e. Separation Factor $SF_{A/B}$ is close to 1)

$SF_{A/B} = \frac{K_A}{K_B}$



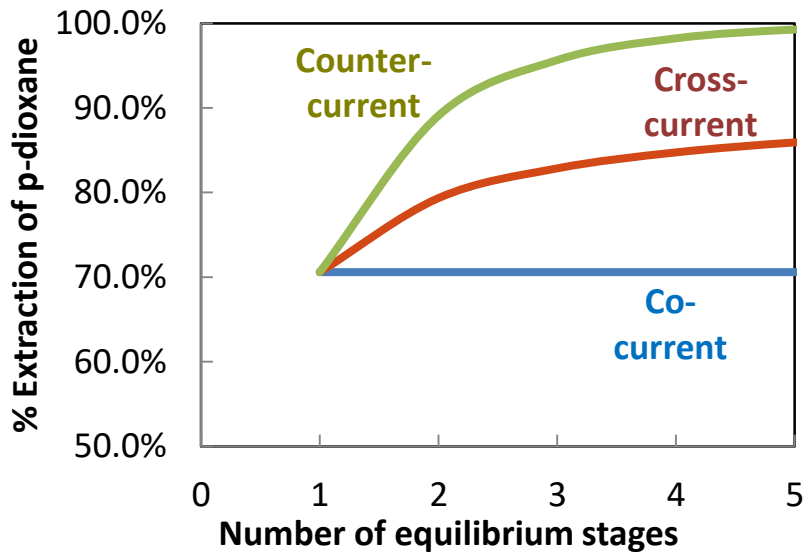
Countercurrent cascading is the most efficient

	Single stage	*Co-current*	*Cross-current*	*Counter-current*
				
% left in raffinate (K_i is partition coefficient)	$\frac{1}{1+K_i}$	$\frac{1}{1+K_i}$	$\frac{1}{(1+K_i/N)^N}$	$\frac{1}{\sum_{n=0}^{N} K_i{}^n}$



K_i=2.4
S/F ratio = 1

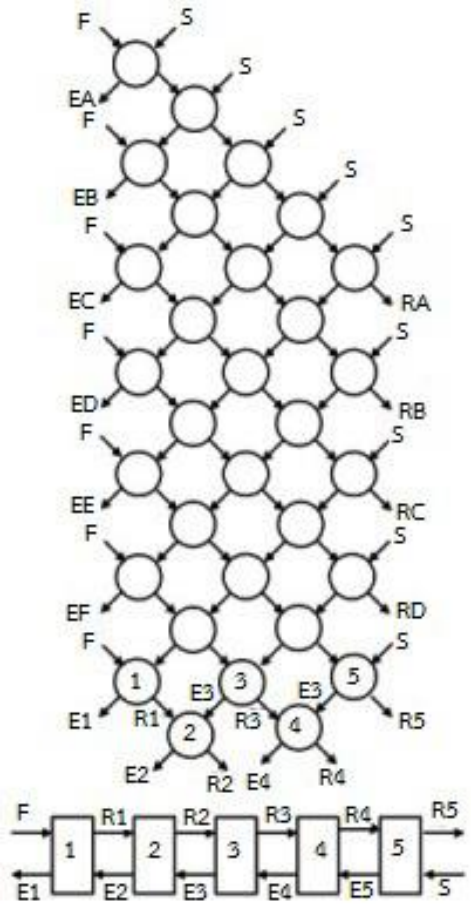
$$(K_i) = \frac{C_{i,organic}}{C_{i,aqueous}}$$



[1] J.D. Seader et al, Separation Process Principles, 2nd edition, **2006**
[2] R.J. Berdt et al., *J. Am. Chem. Soc.*, **1944,** 66, 282-284

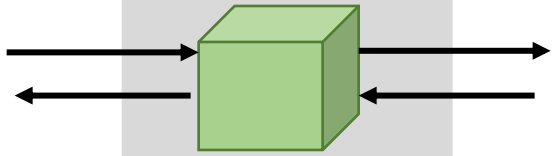
Process development of CC LLE presents challenges

- K values are now interdependent, and varied over range of concentrations
- Equilibrium data generally obtained by thermodynamic models (e.g. UNIQUAC, NRTL)
  - **Inaccurate** due to lack of equilibrium data
  - **Unavailable** physical property data especially for **unidentified** molecular species
- Experimental data is needed
  - Batch simulation of CC-LLE is too tedious



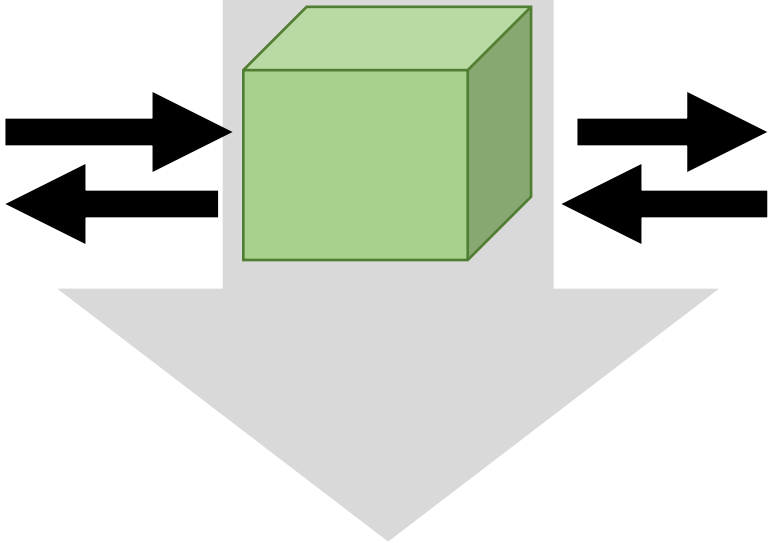
U. Injarean et al., *Energy Procedia*, **2014**, 56, 129-134

Toolbox for countercurrent LL extraction

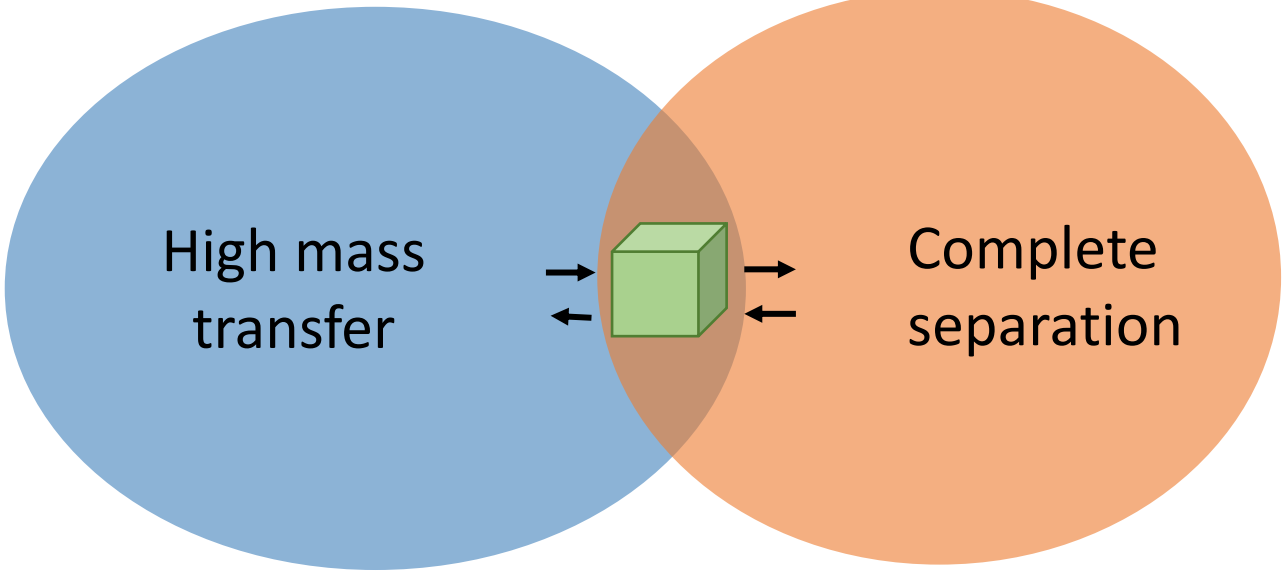


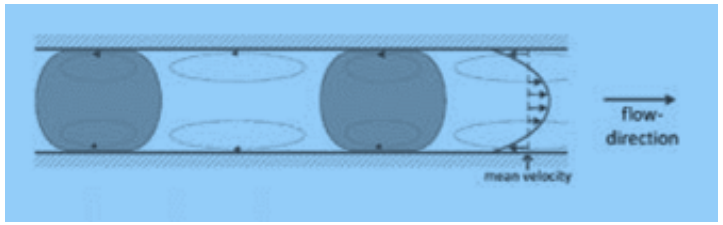
Easy experimentation of CC-LLE

Simple scale-up



At full scale, eliminate current issues





Kockmann N. and Holbach A., ICNMM2013**, 2013**

Performance studies

1. Select model system
2. Perform experiment
3. Calculate efficiency
4. Run industrial example

Interfacial tension

Low ← → High

Ethyl acetate-acetic acid-water

K_{ow} ~ 0.84

σ < 6 dyne/cm

titration

Toluene-acetone-water

K_{ow} ~ 2.90

σ = 22 dyne/cm

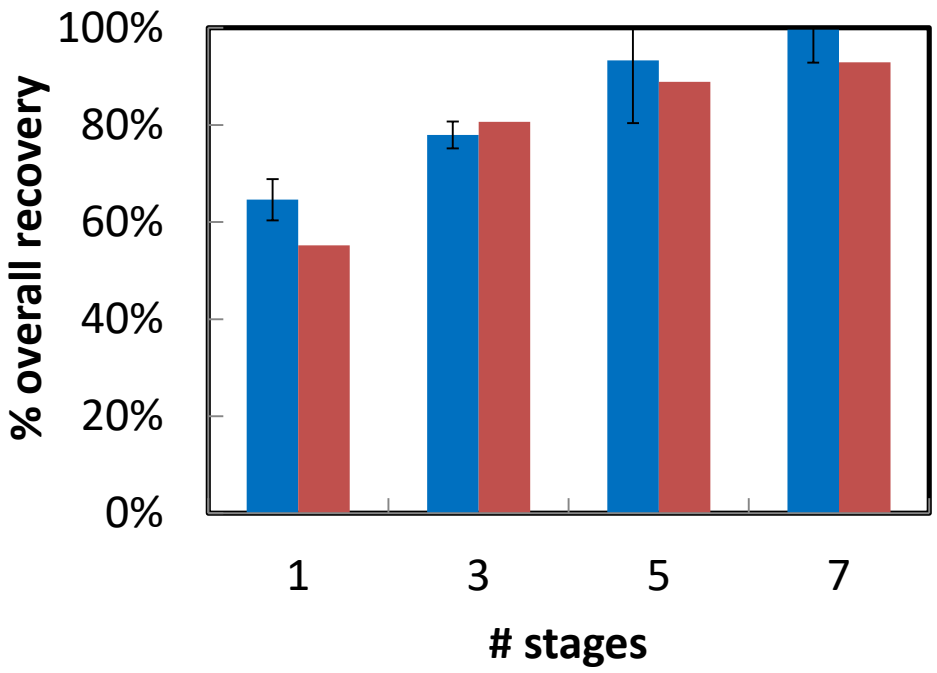
GC

A.W. Islam et al., *Chem.Process Eng*, **2012,** 33 (2), 243-253
"Recovery of acetic acid by means of liquid-liquid extraction." QVF, PDF.

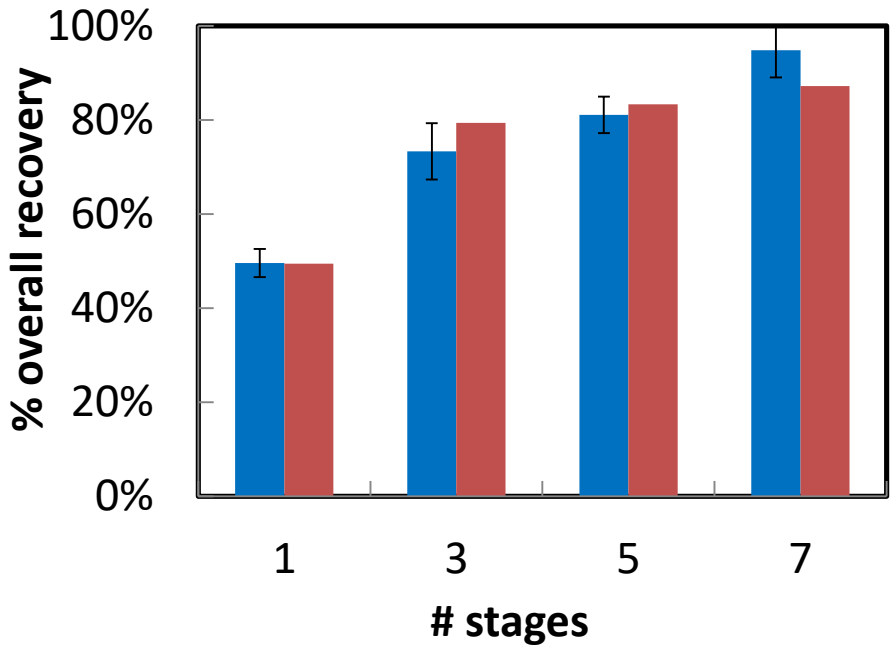
The problem - Zaiput's solution

1. Select model system
2. Perform experiment
3. Calculate efficiency
4. Run industrial example

Ethyl acetate-acetic acid-water



Toluene-acetone-water

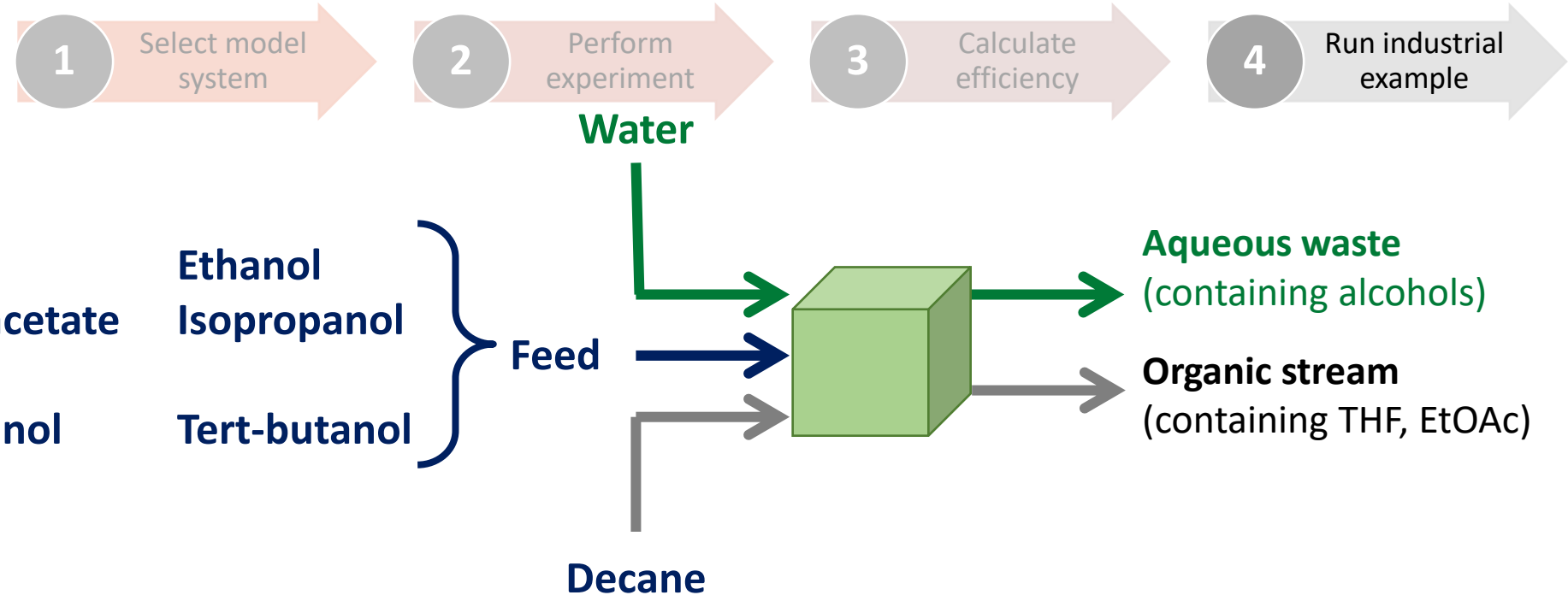


Experimental

ASPEN simulation with 100% efficiency

Case study : THF and Ethyl Acetate recovery

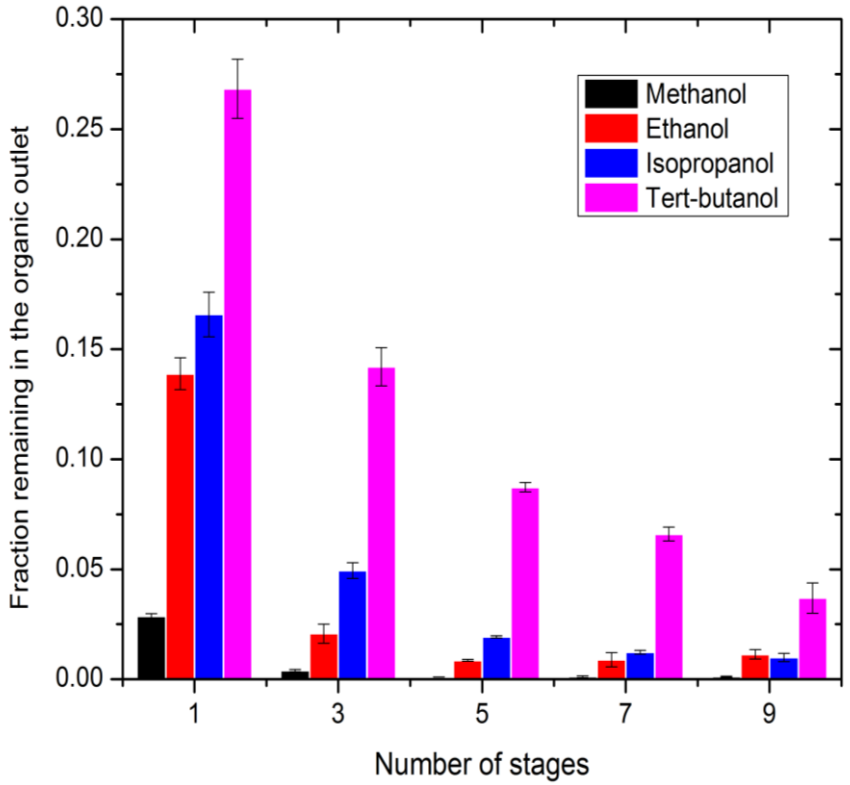
- Challenging system with very low interfacial tension, σ = 4 dyne/cm



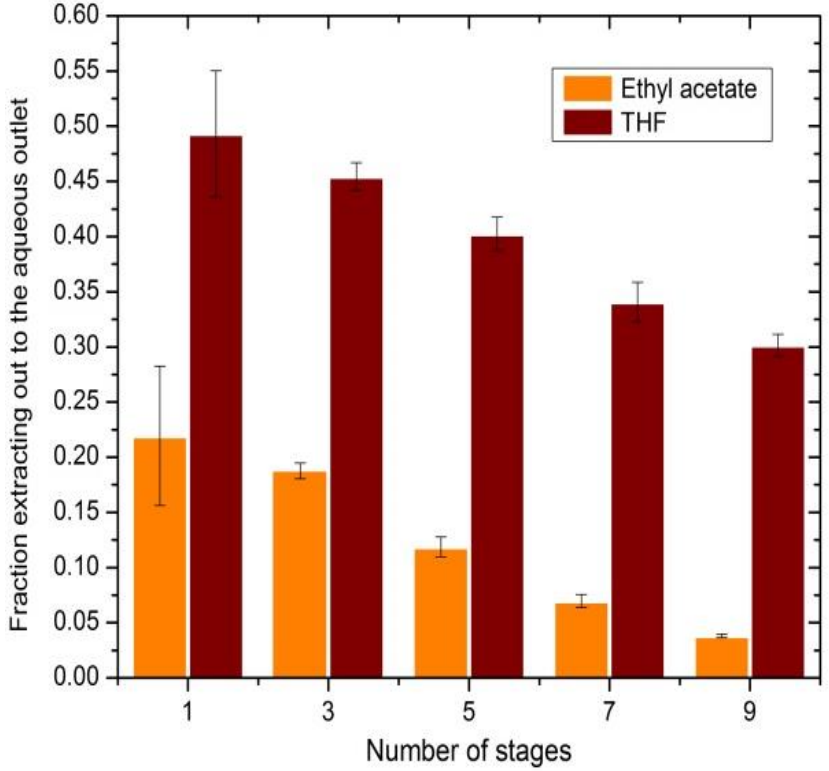
- Very low interfacial tension (Low P_{cap})
- Thermodynamic models are not good enough to simulate multicomponent L-L system
- Variation in flow rates between stage is unknown prior to experimental runs

Multistage extraction is needed

Fractions in the Organic



Fractions in the Aqueous

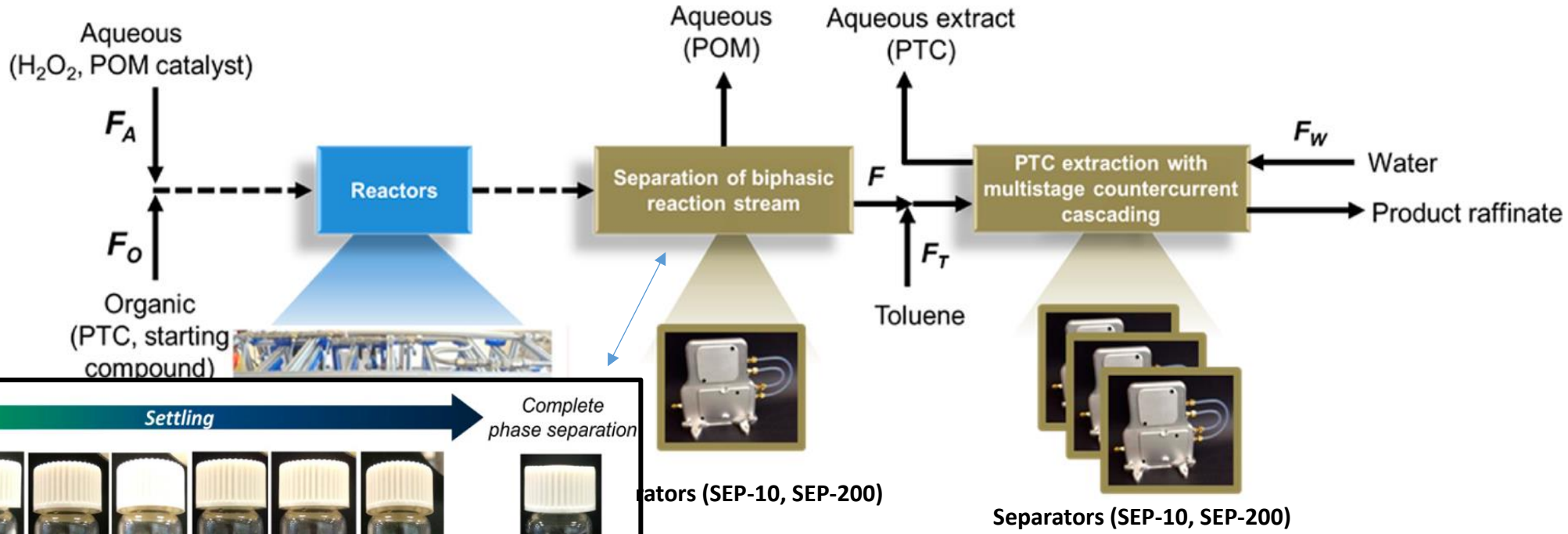


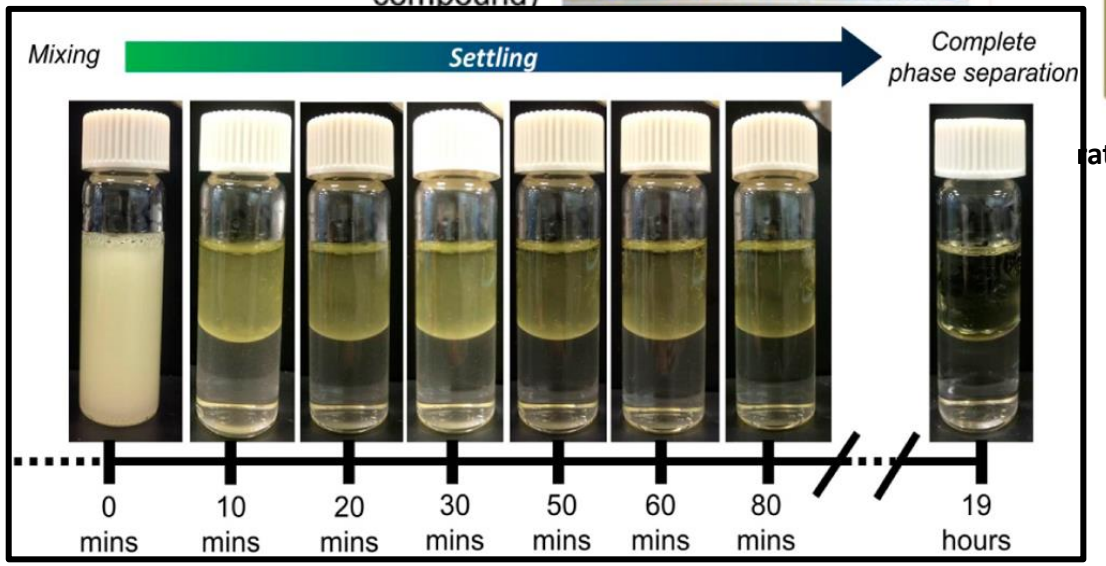
- Maximize removal of alcohols from the desired organic outgoing stream
- Maximize recovery of THF and ethyl acetate into the organic outgoing stream
- Steady state within 10 min

	Feed	Decane	Water
Entering at	Middle stage	N^{th} stage	1^{st} stage
Flow rate (mL/min)	2	3	4

Multistep extraction – Example and scale up

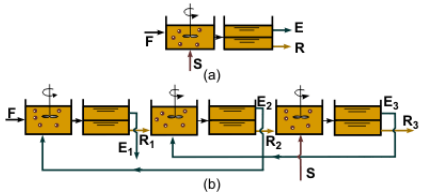
Biphasic Catalytic Hydrogen Peroxide Oxidation of Alcohols in Flow: Scale-up and Extraction - recovery of Phase Transfer Catalyst (PTC)

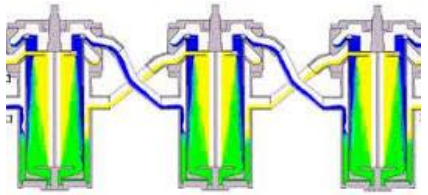


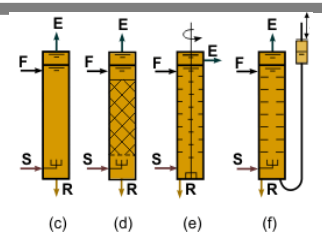


Peer et al. - DOI: 10.1021/acs.oprd.6b00234 Org. Process Res. Dev. August 2016

Multistage extraction - Comparison





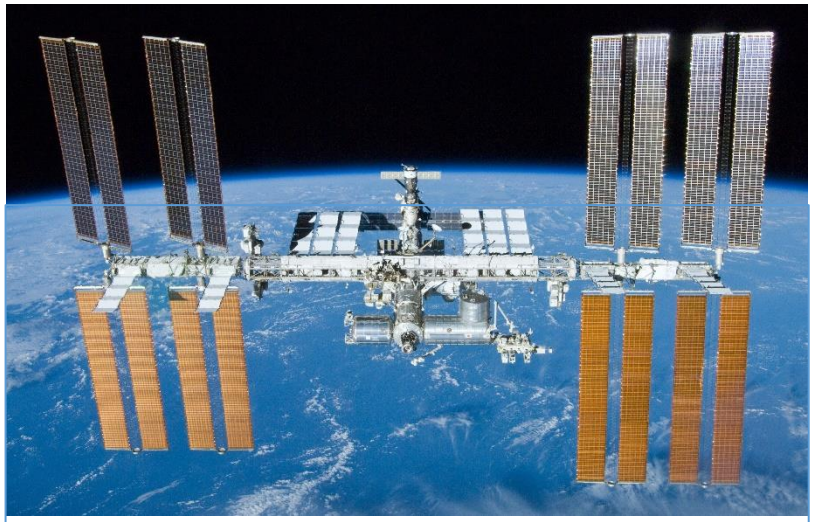


	Mixer-settler	Centrifugal	Column	Zaiput
Flexible capacity				
Simple hydrodynamics				
Easy scale-up				
High extraction efficiency				
Handling of emulsions				
Liquids with similar density				
Dead volume (time to steady state)				
Cost				
Suitability for many stages				?
Presence of solids				

Acknowledgements

- **Nopphon Weeranoppanant**
- Klavs Jensen

Massachusetts Institute of Technology



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Questions ?