



Massachusetts
Institute of
Technology



Continuous, efficient multistage extraction

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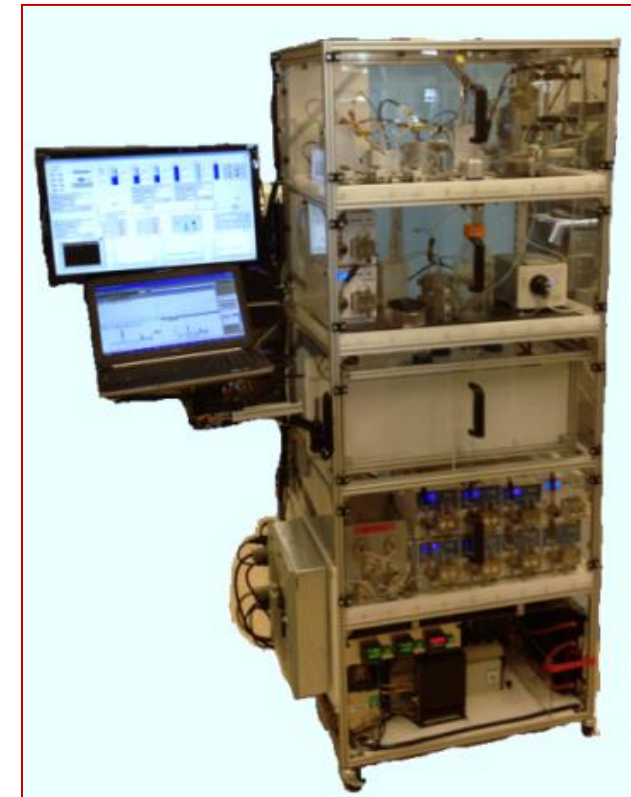
Zaiput Flow Technologies

Department of Chemical Engineering, MIT

Munich– 01 February 2017



Pharmacy on Demand - POD



MIT-Novartis consortium:



The problem - Zaiput's solution

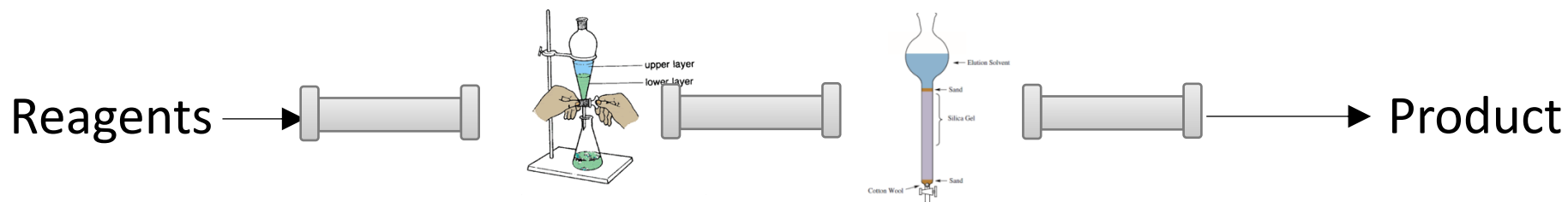


Continuous Flow Synthesis of drugs, the future of complex chemical synthesis.
(larger parameter space, more robust/repeatable processes, cost reduction)

Wish



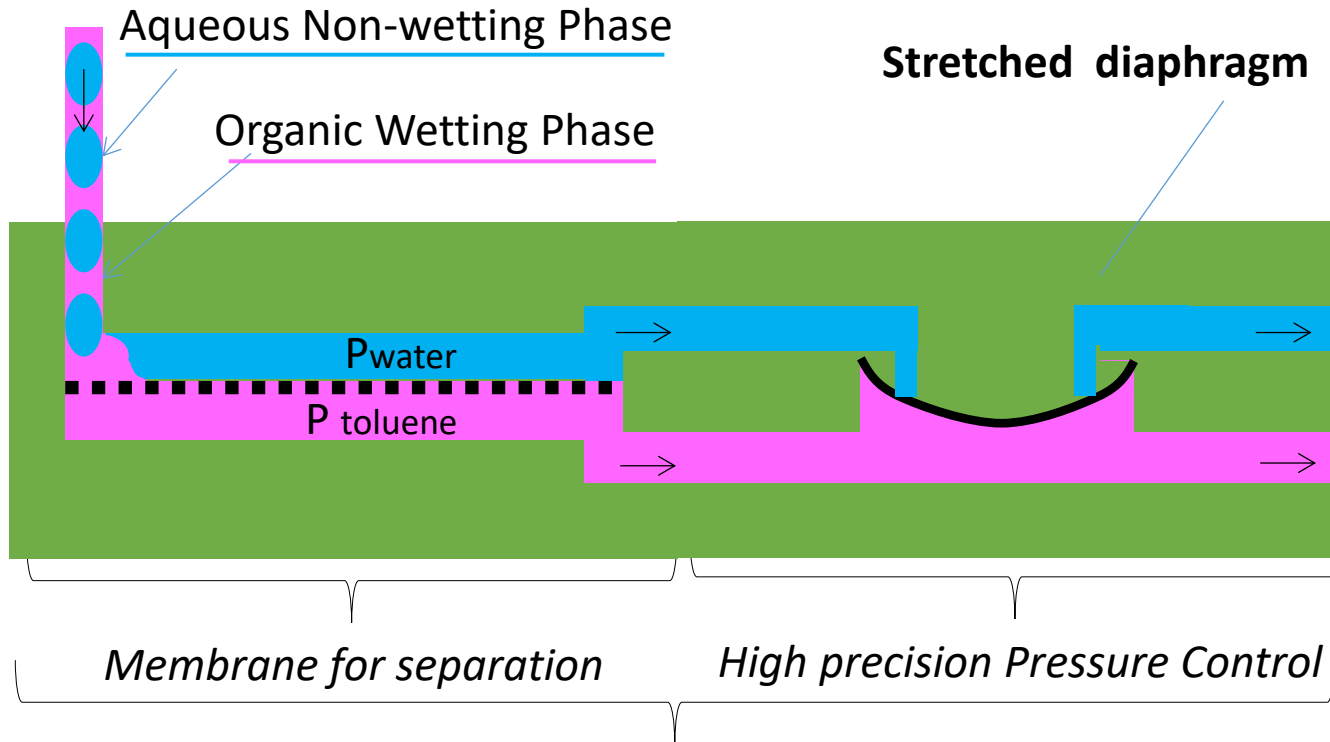
Reality



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

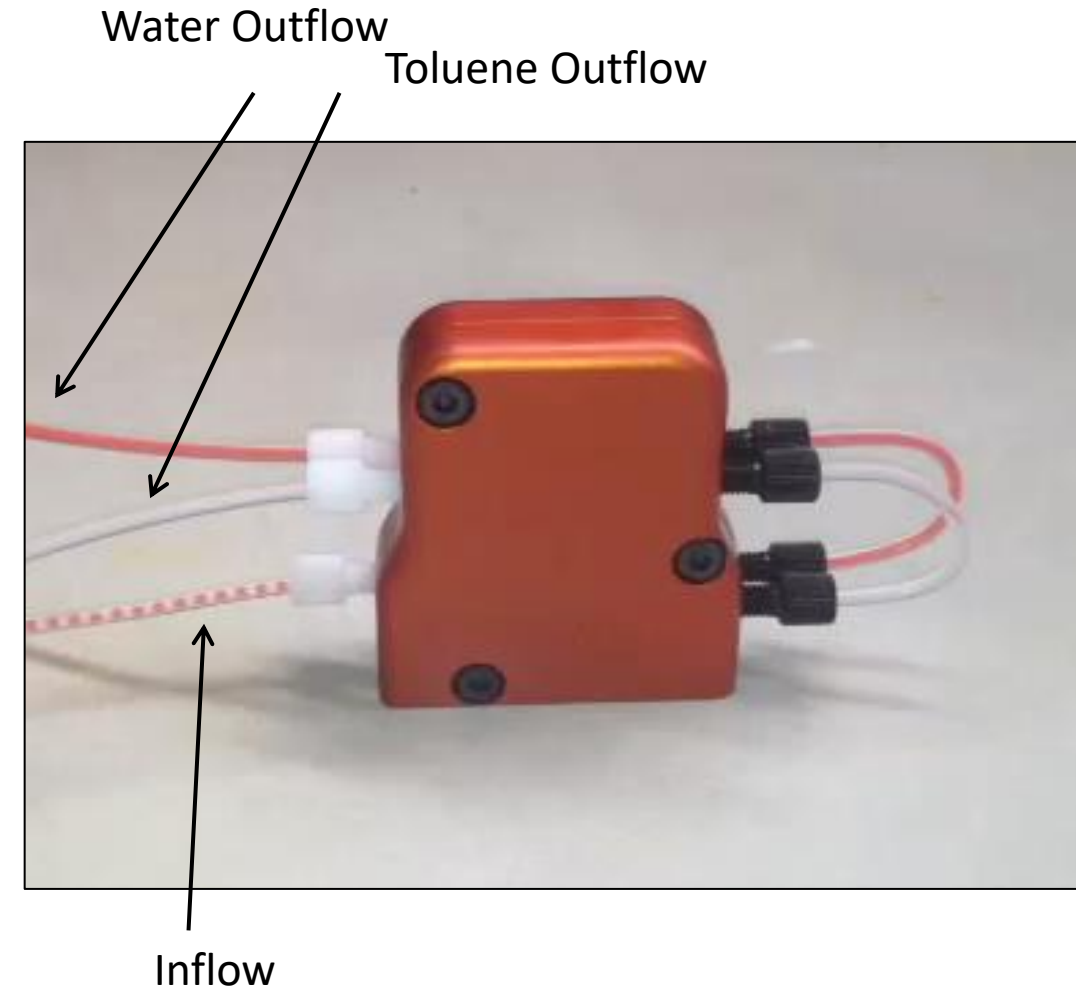


Integrated self tuning liquid-liquid separator

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

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

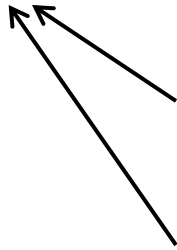
$$P_{water} = P_{diaphragm} + P_{toluene}$$



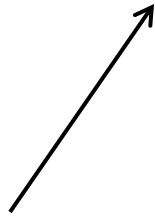
Integrated liquid-liquid separator



Outflow



Inflow



Summary of advantages



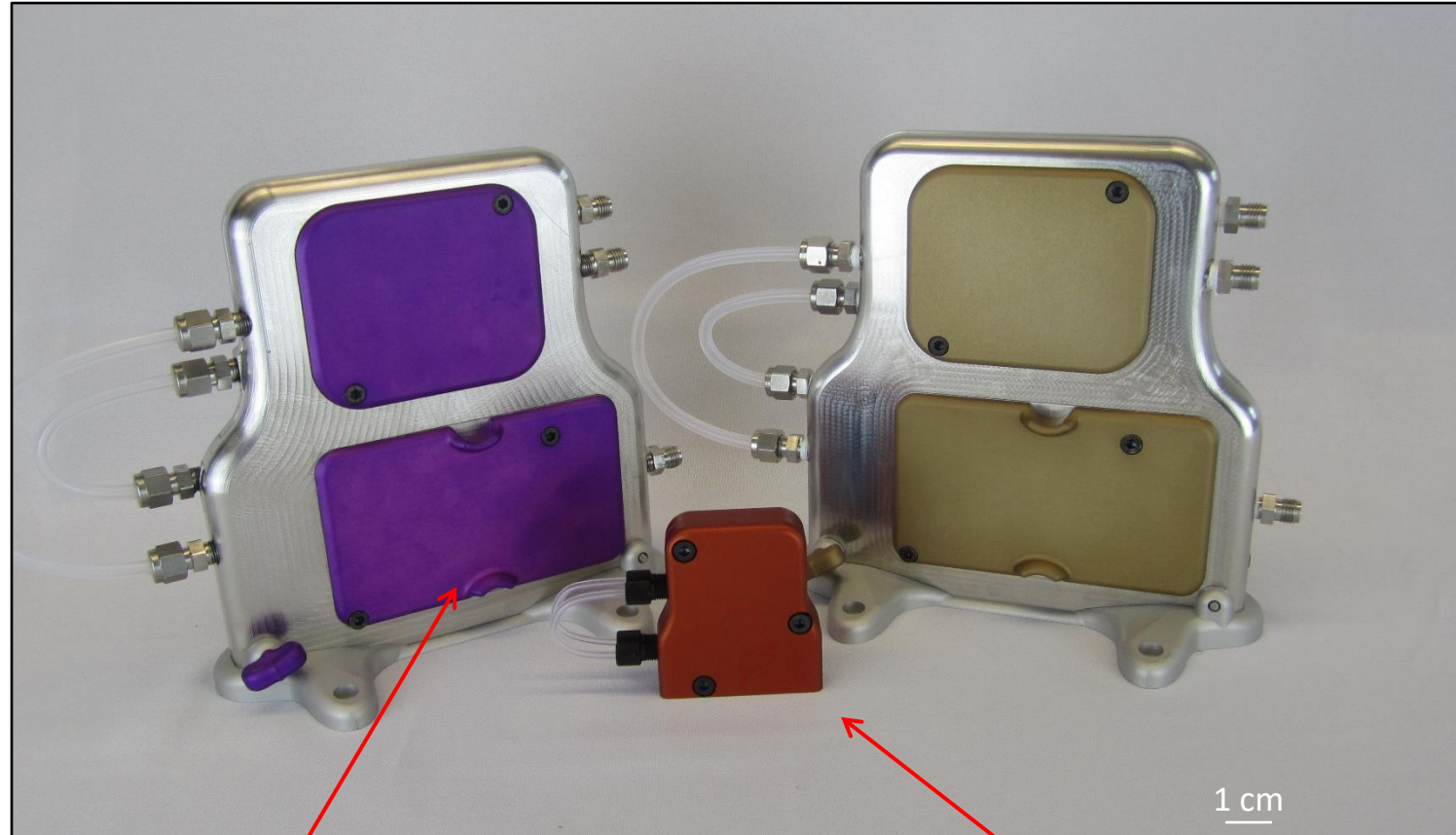
- Easy to use
- Passive device
- Truly continuous
- No dead volume
- Scalable

- ❑ 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



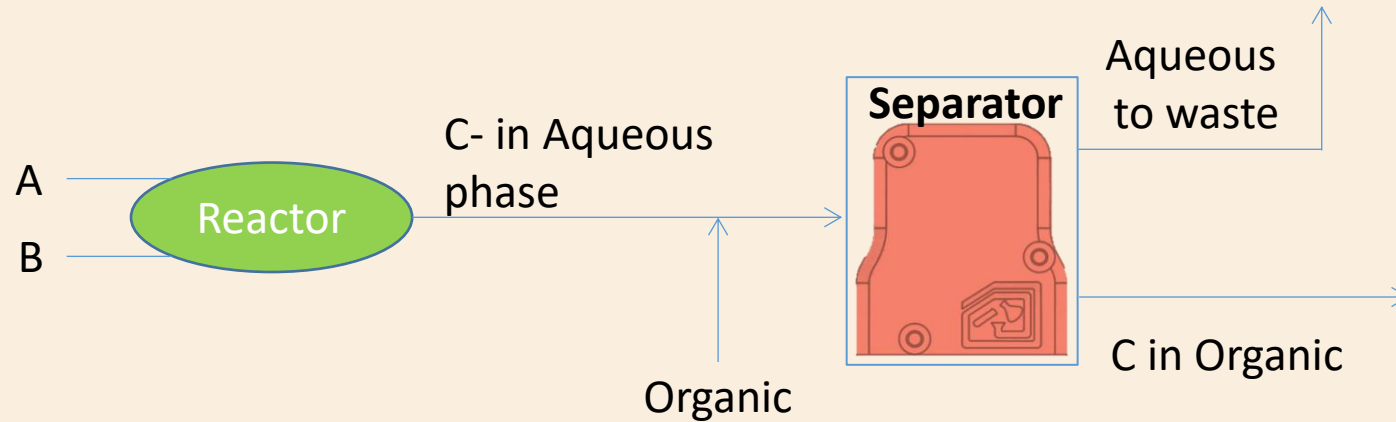
Small production/pilot plant
Max flow rate 200 ml/min

Process development
Max flow rate 12ml/min

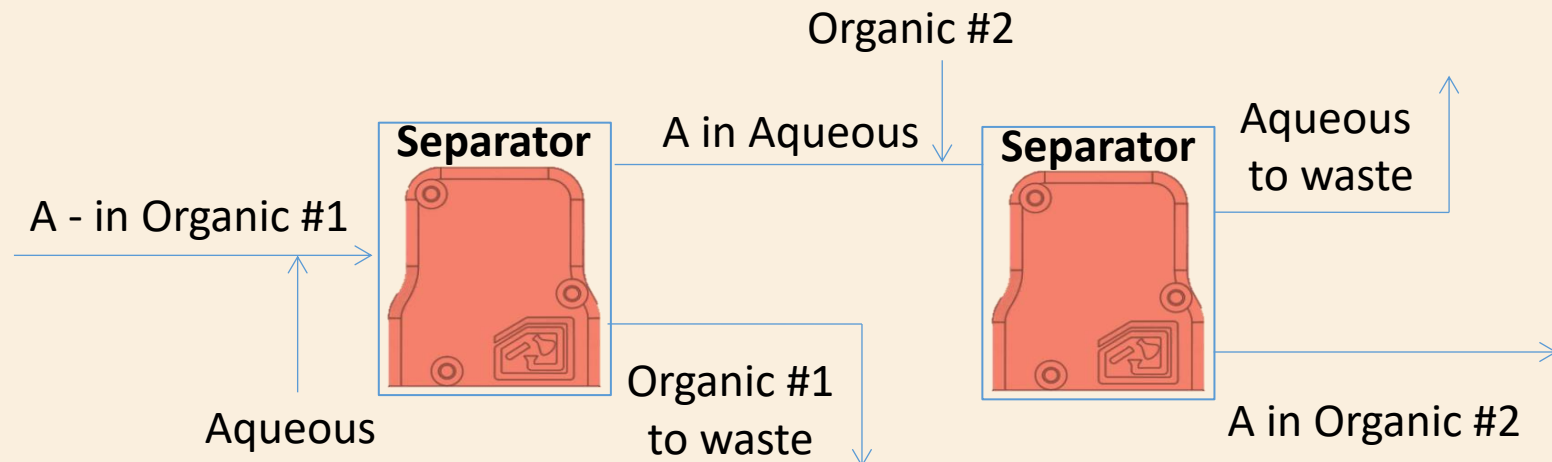
Examples of applications



Reaction followed by an extraction



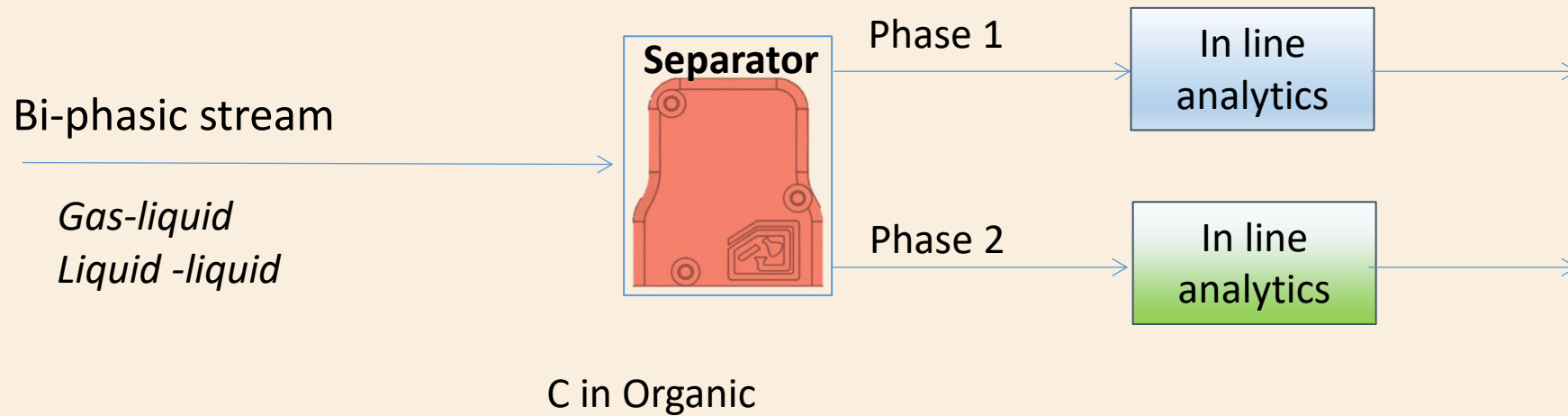
Solvent Swap



Examples of applications



Analytical / process monitoring

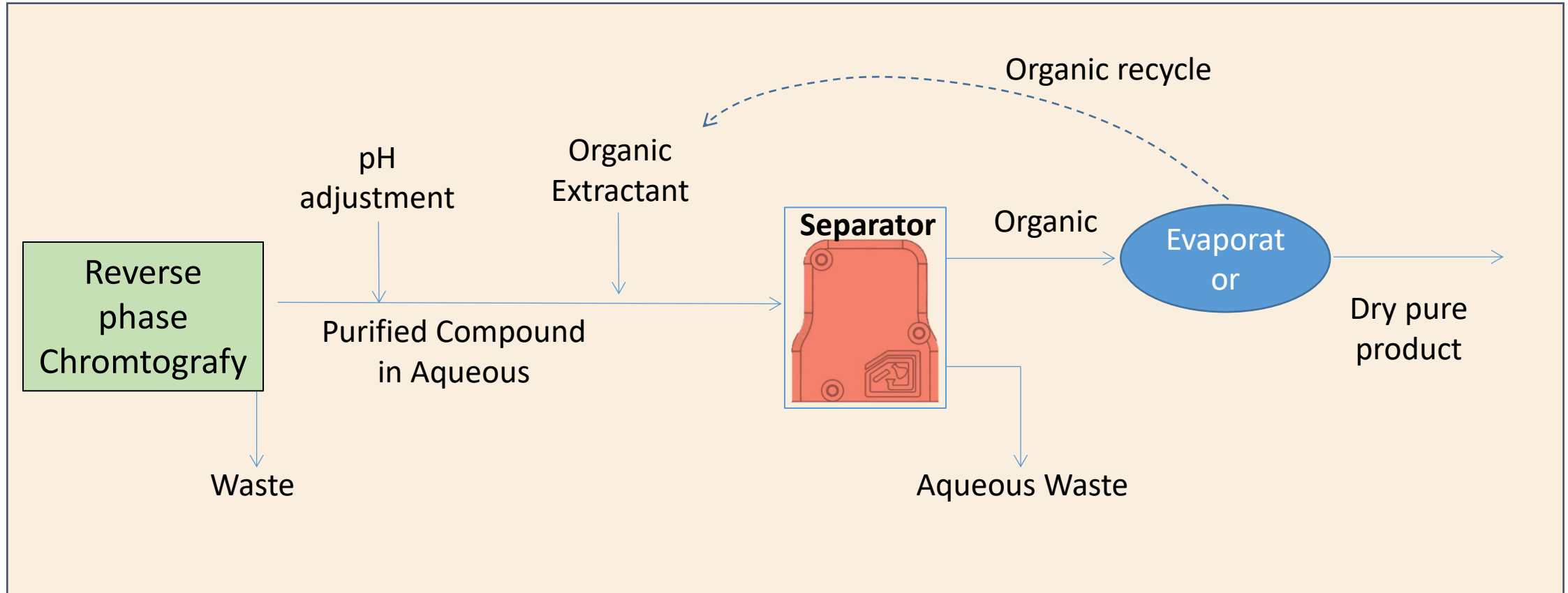


Typically used with small scale device
Example of Analytics (IR, UV-Vis, Raman, etc...)

Examples of applications

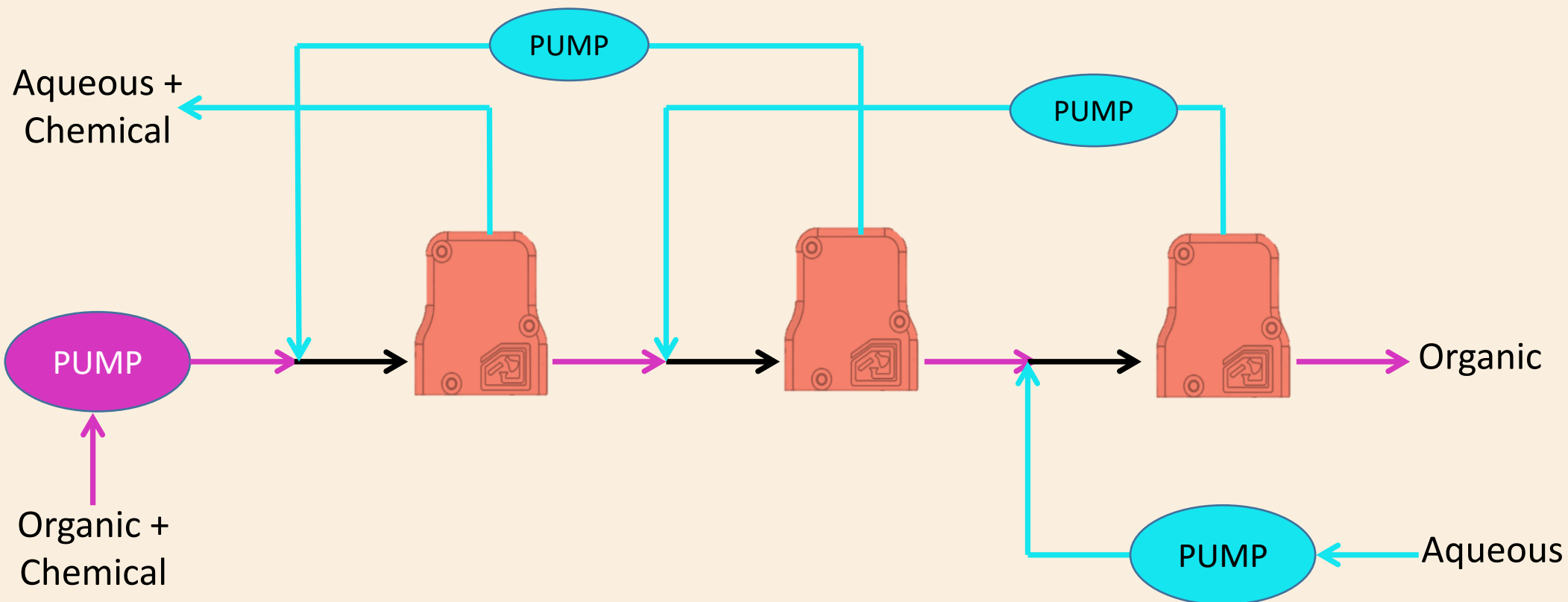


Continuous product isolation after Chromatographic purification





Counter current extraction



Current literature on Zaiput shows:



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

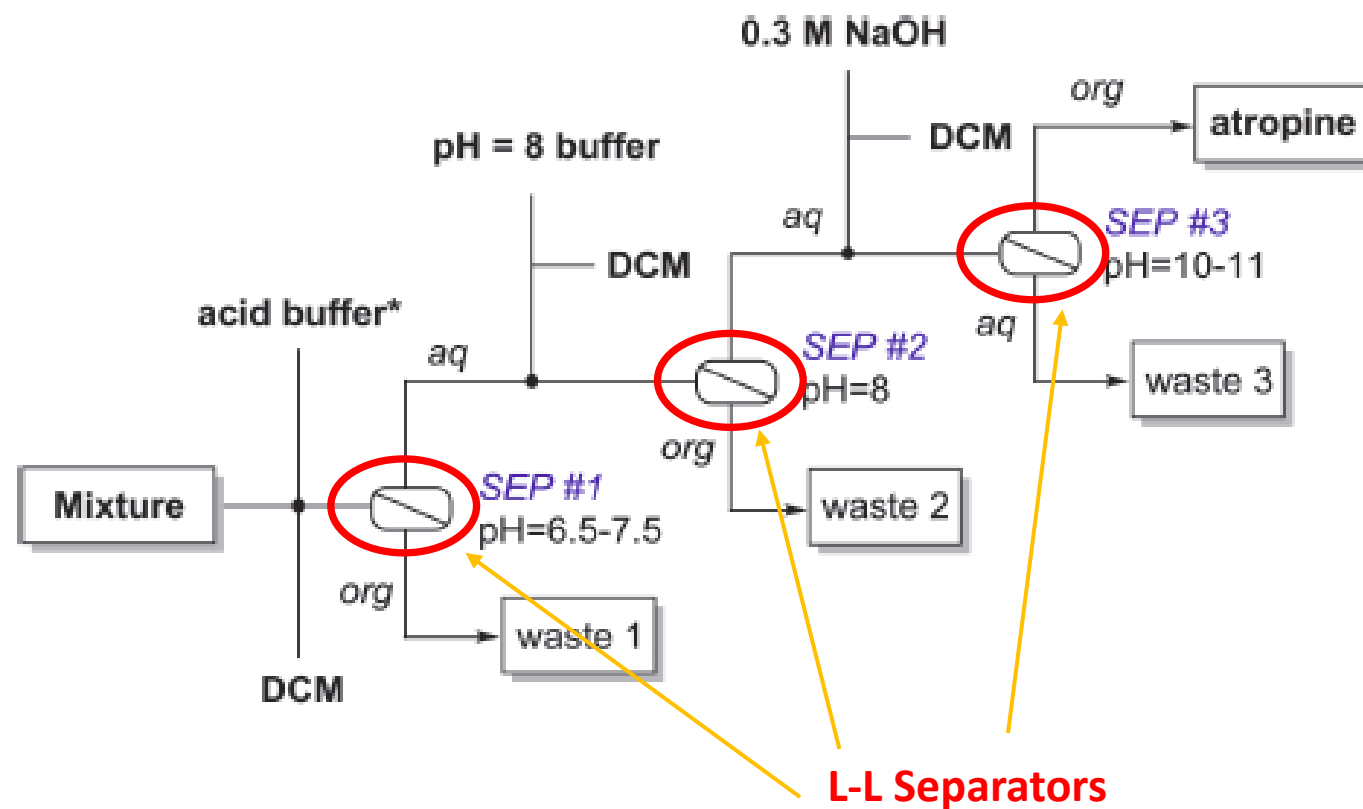
Types of uses divided by chemistry need:

- 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



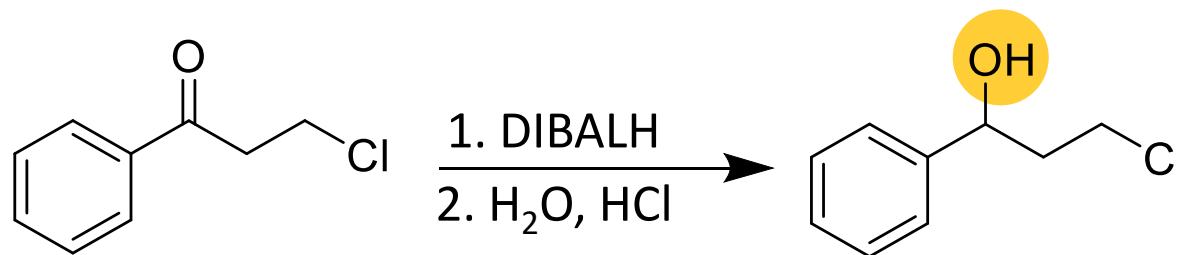
Continuous-flow purification of atropine, 3 sequential extractions with in line pH adjustments (Acid – base extraction)



Example of use - Fluoxetine

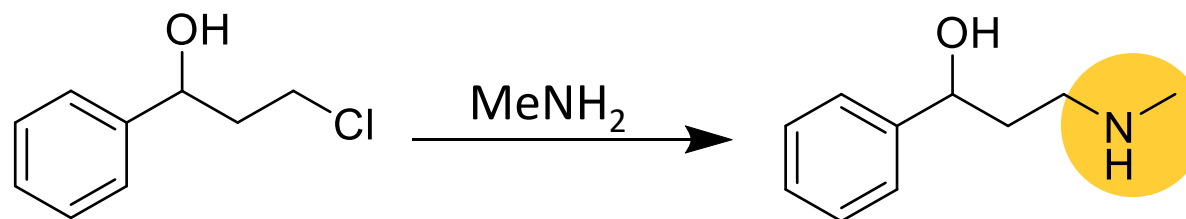


1
(ketone reduction)



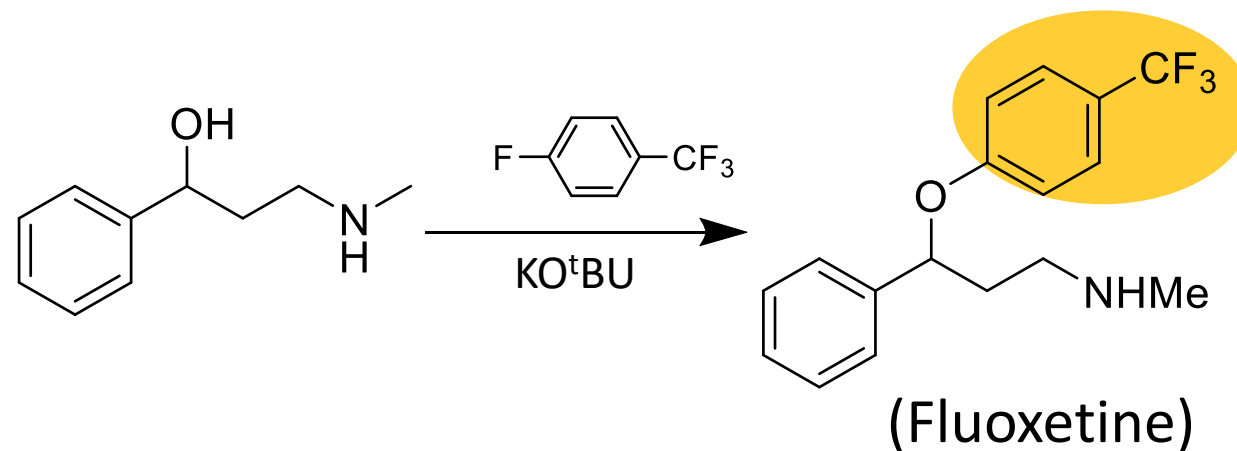
Incompatible with **2**
Al salt

2
(amination)

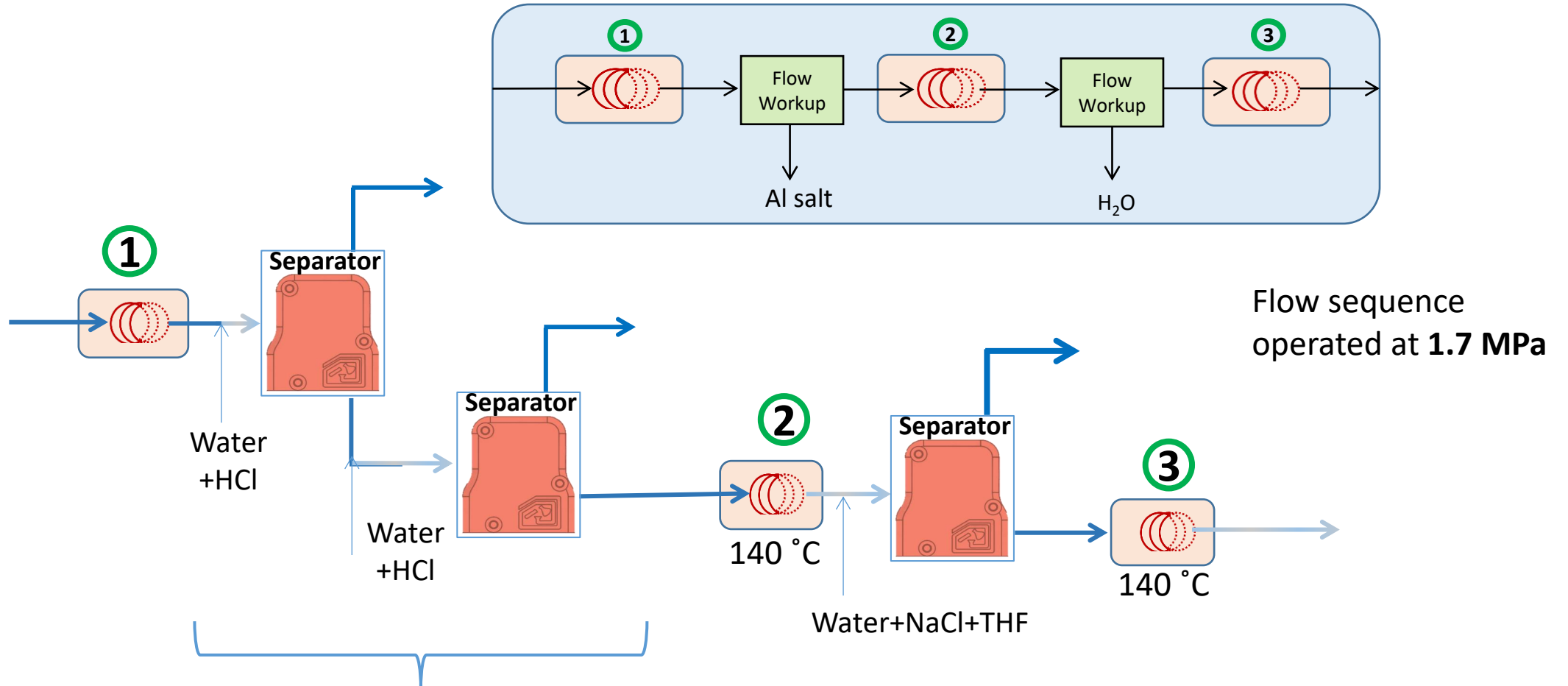


Water hinders **3**

3
(aromatic substitution)



Fluoxetine - Complete process



**Multistage Extraction
Possible because of device
modularity**

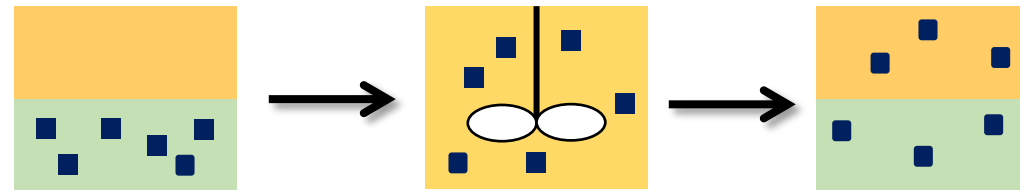
When do you use multi-stage extraction ?



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

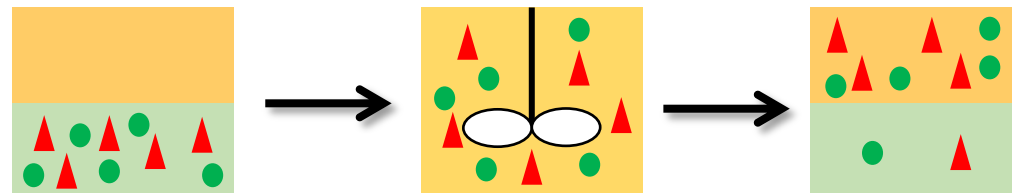
K_i	% extraction with 1 stage
1	50%
5	83%
10	91%
100	99%

- 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)

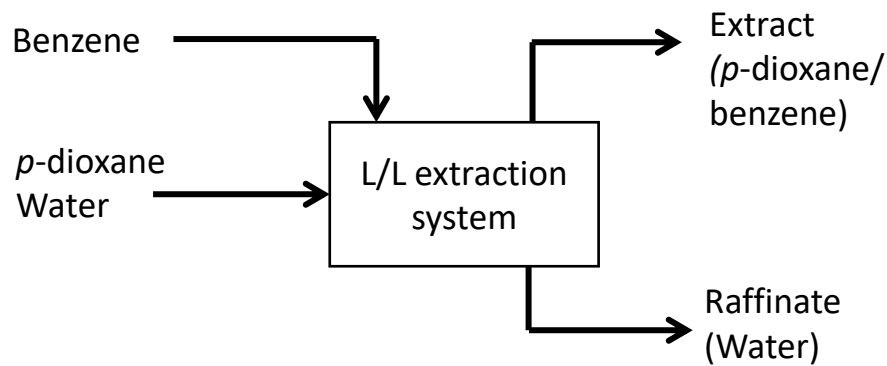
$$SF_{A/B} = \frac{K_A}{K_B}$$



Countercurrent cascading is the most efficient

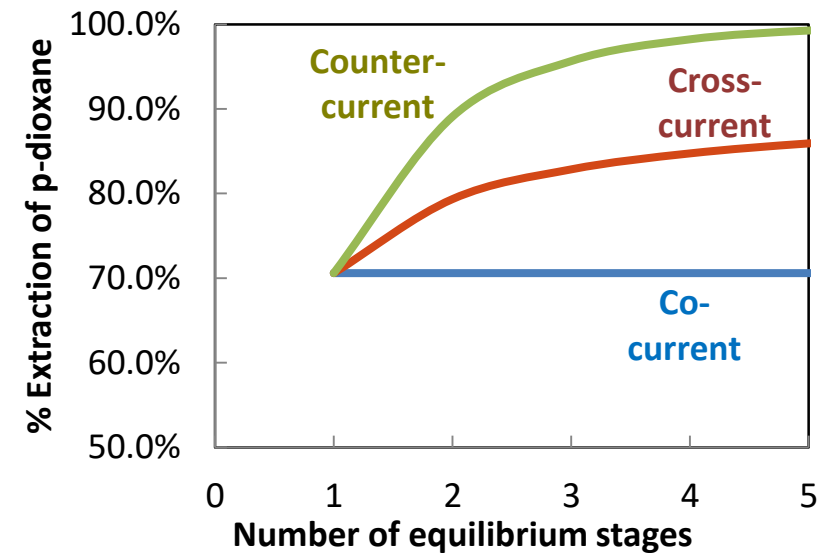


	Single stage	Co-current	Cross-current	Counter-current
% left in raffinate (K_i is partition coefficient)	$\frac{1}{1 + K_i}$	$\frac{1}{1 + K_i}$	$\frac{1}{(1 + K_i/N)^N}$	$\frac{1}{\sum_{n=0}^N K_i^n}$



$K_i = 2.4$
S/F ratio = 1

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

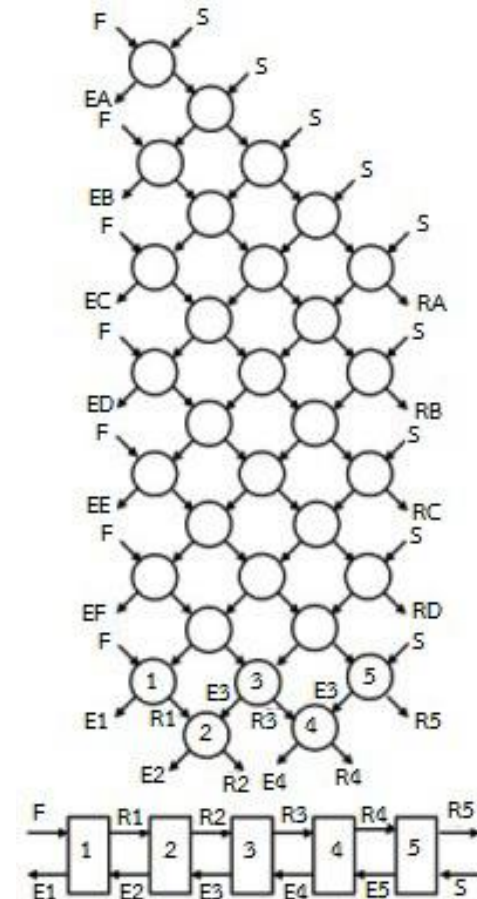


[1] J.D. Seader et al, Separation Process Principles, 2nd edition, 2006

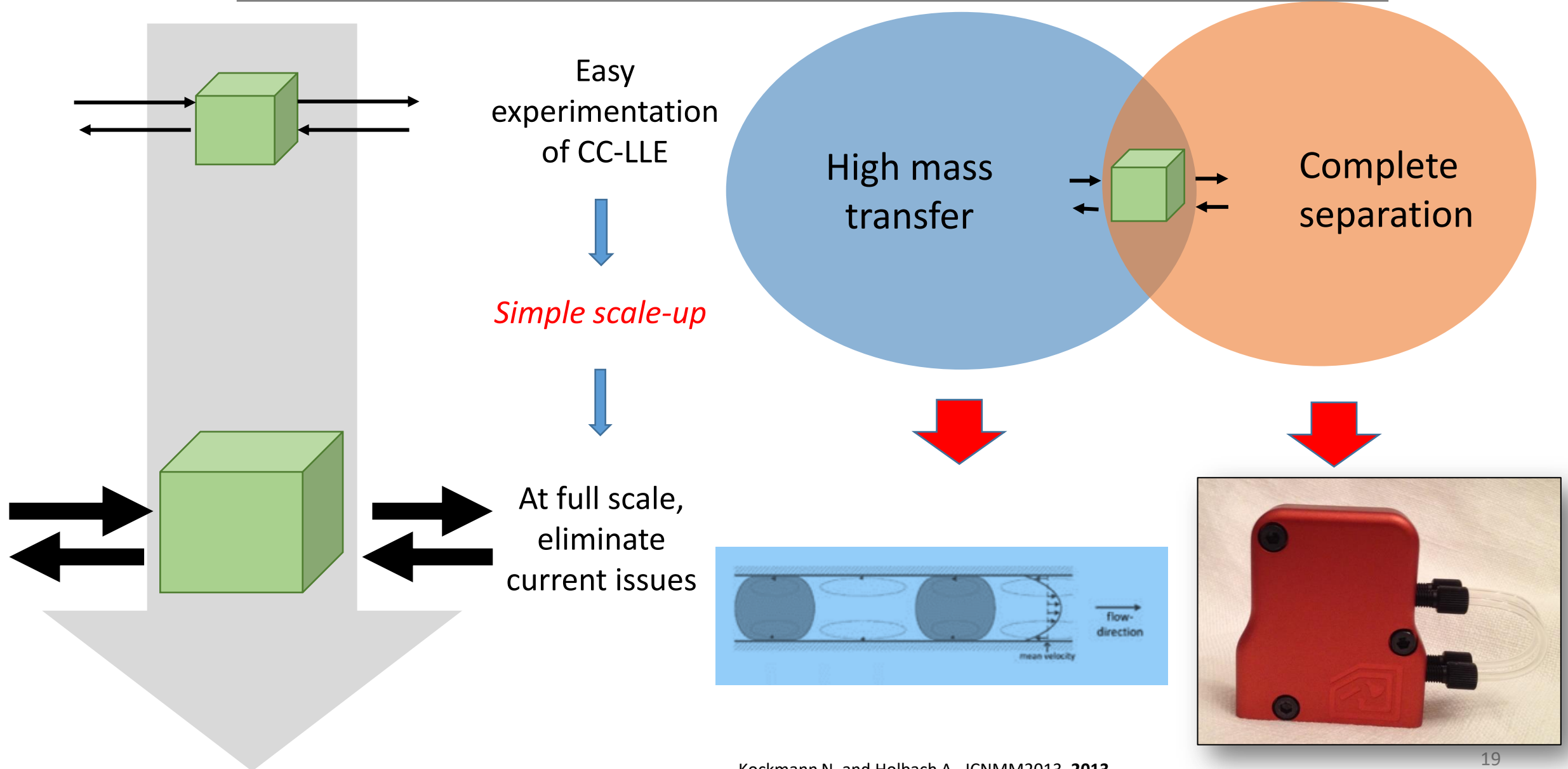
[2] R.J. Berdt et al., *J. Am. Chem. Soc.*, 1944, 66, 282-284



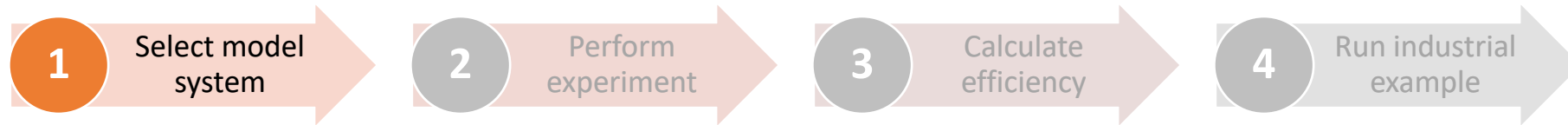
- K values are now interdependent, and varied over range of concentrations
- Equilibrium data generally obtained by thermodynamic models (e.g. UNIQUAC, NRTL)
 - **Inaccurate** due to lack of equilibrium data
 - **Unavailable** physical property data especially for **unidentified** molecular species
-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



Toolbox for countercurrent LL extraction



Performance studies



Ethyl acetate-acetic acid-water

$$K_{ow} \sim 0.84$$

$$\sigma < 6 \text{ dyne/cm}$$

titration

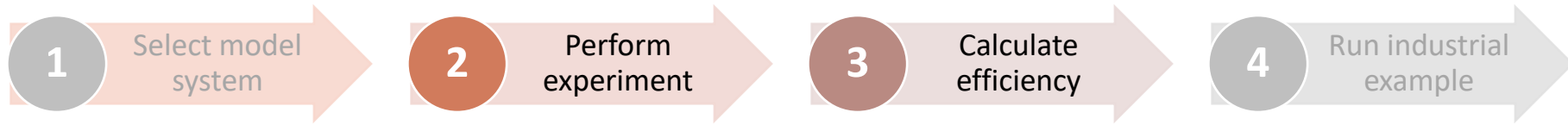
Toluene-acetone-water

$$K_{ow} \sim 2.90$$

$$\sigma = 22 \text{ dyne/cm}$$

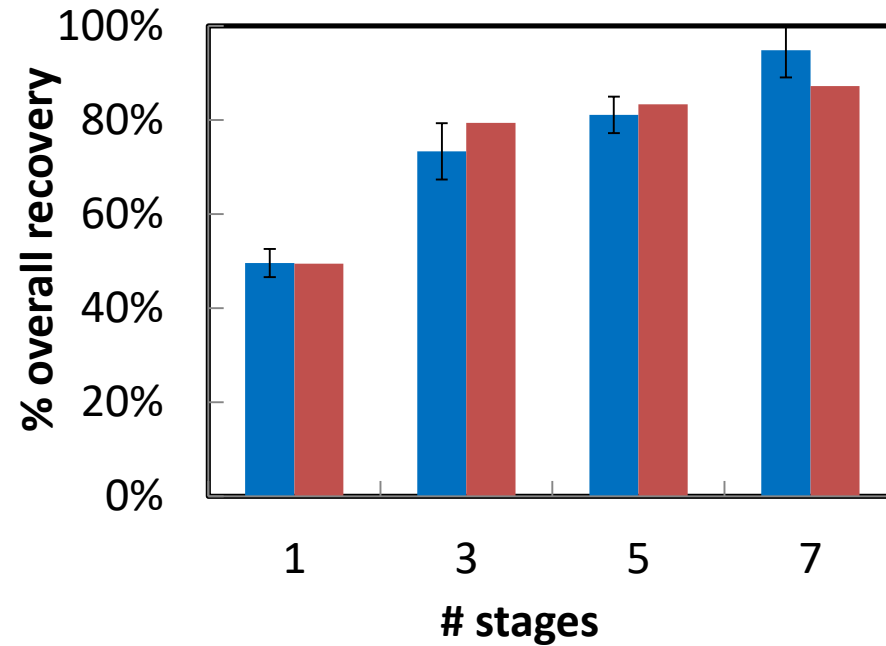
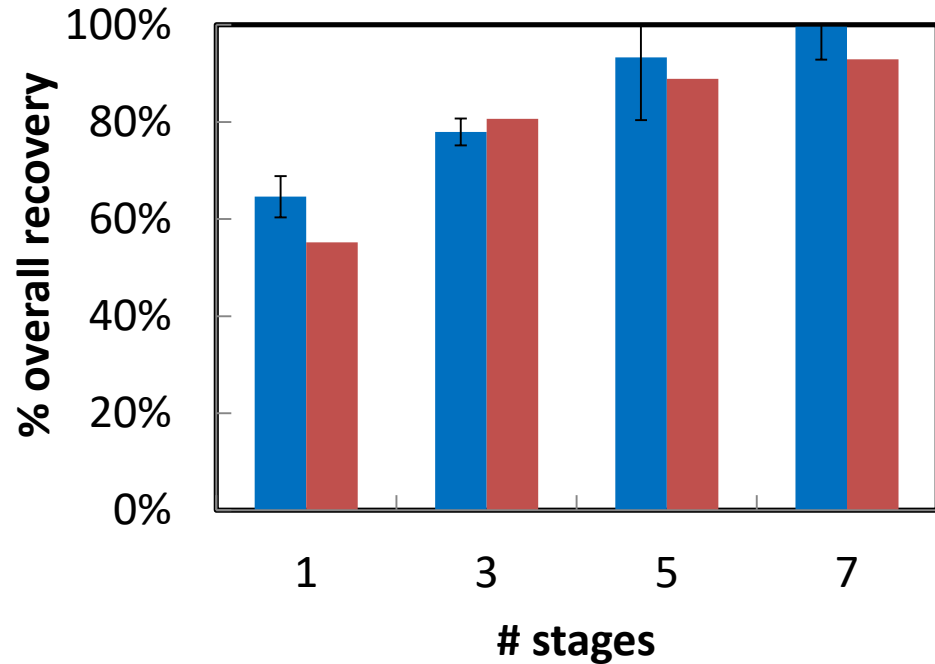
GC

The problem - Zaiput's solution



Ethyl acetate-acetic acid-water

Toluene-acetone-water

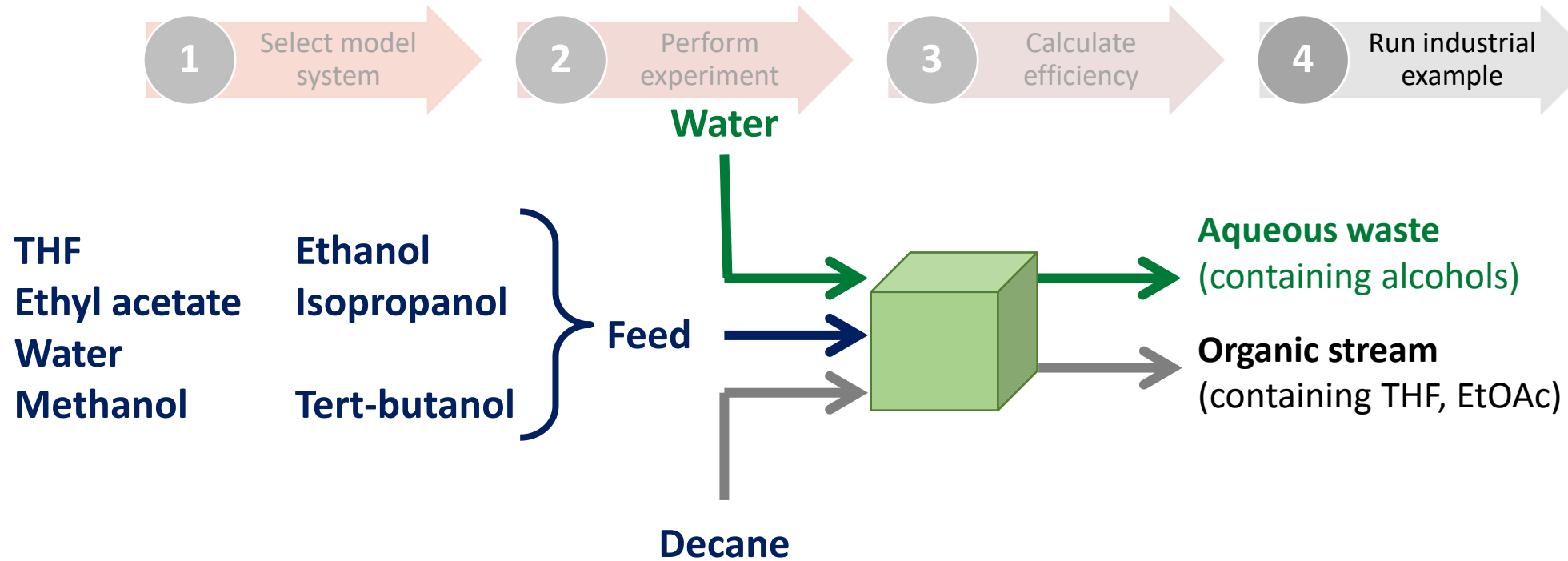


■ Experimental
■ ASPEN simulation with 100% efficiency

Case study : THF and Ethyl Acetate recovery



- Challenging system with very low interfacial tension, $\sigma = 4$ dyne/cm

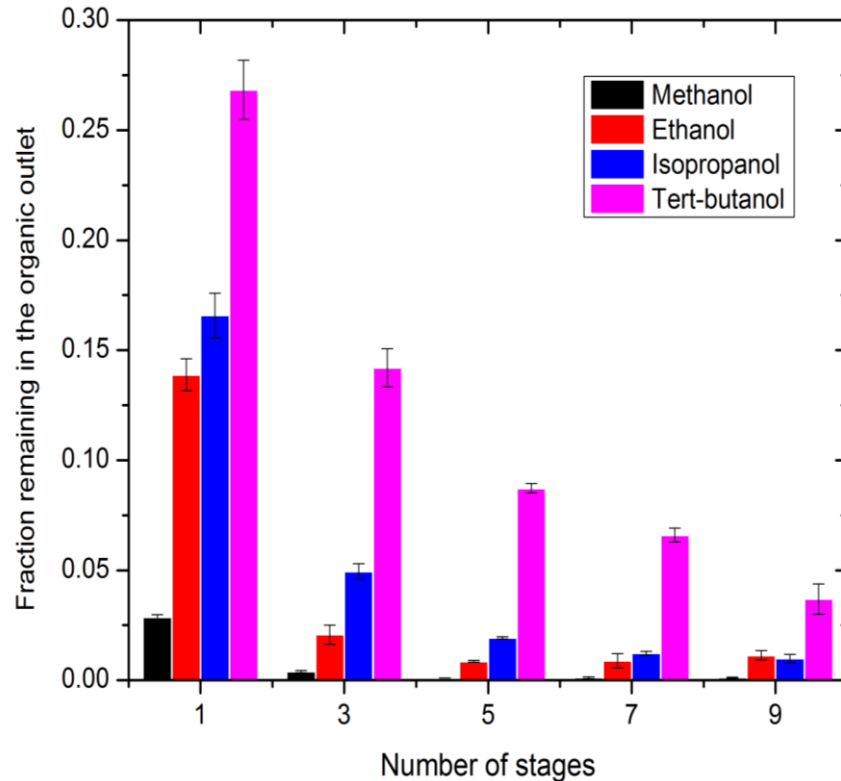


- Very low interfacial tension (Low P_{cap})
- Thermodynamic models are not good enough to simulate multicomponent L-L system
- Variation in flow rates between stage is unknown prior to experimental runs

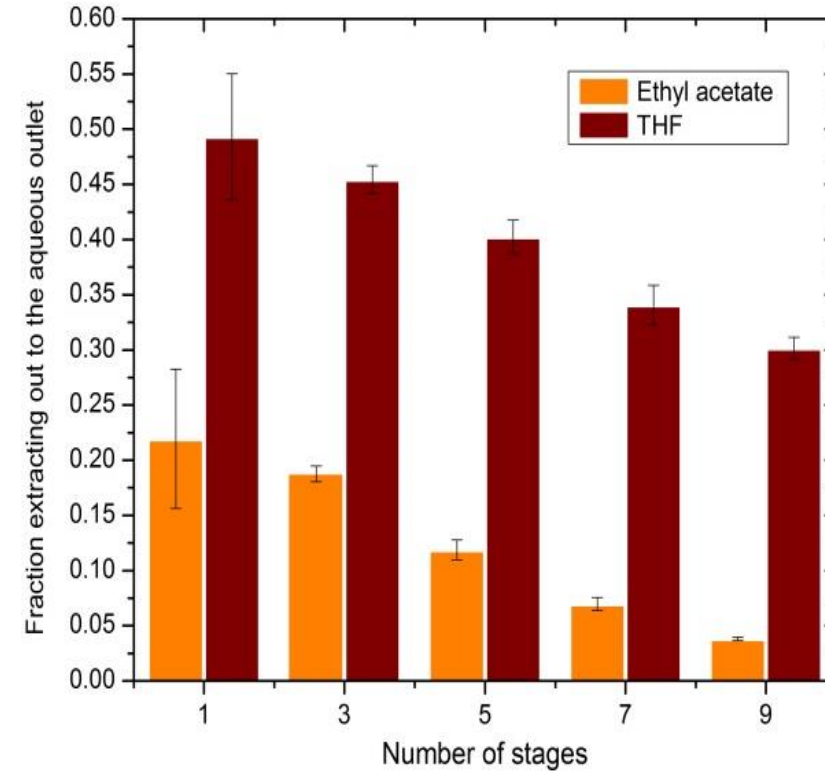
Multistage extraction is needed



Fractions in the Organic



Fractions in the Aqueous



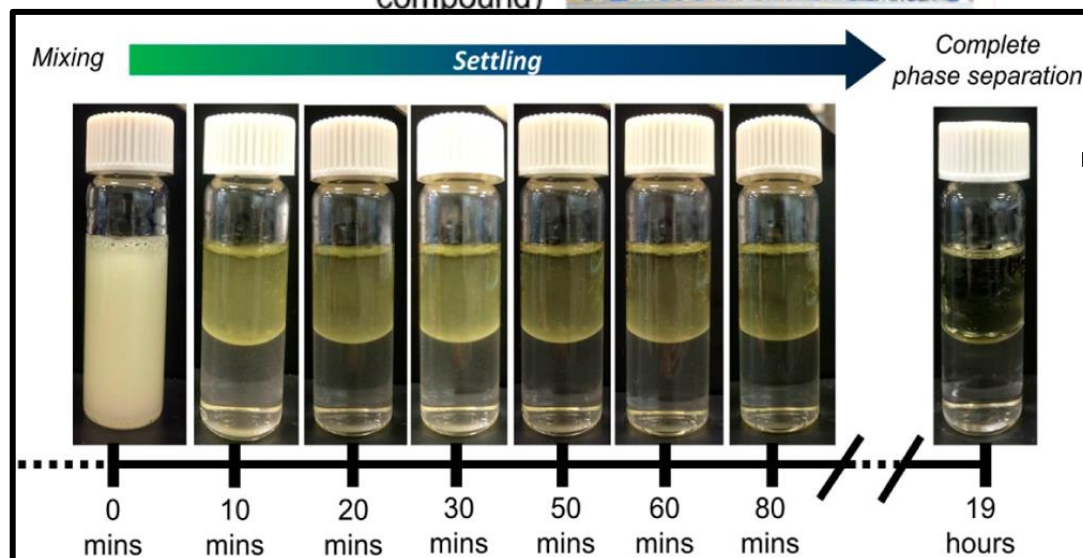
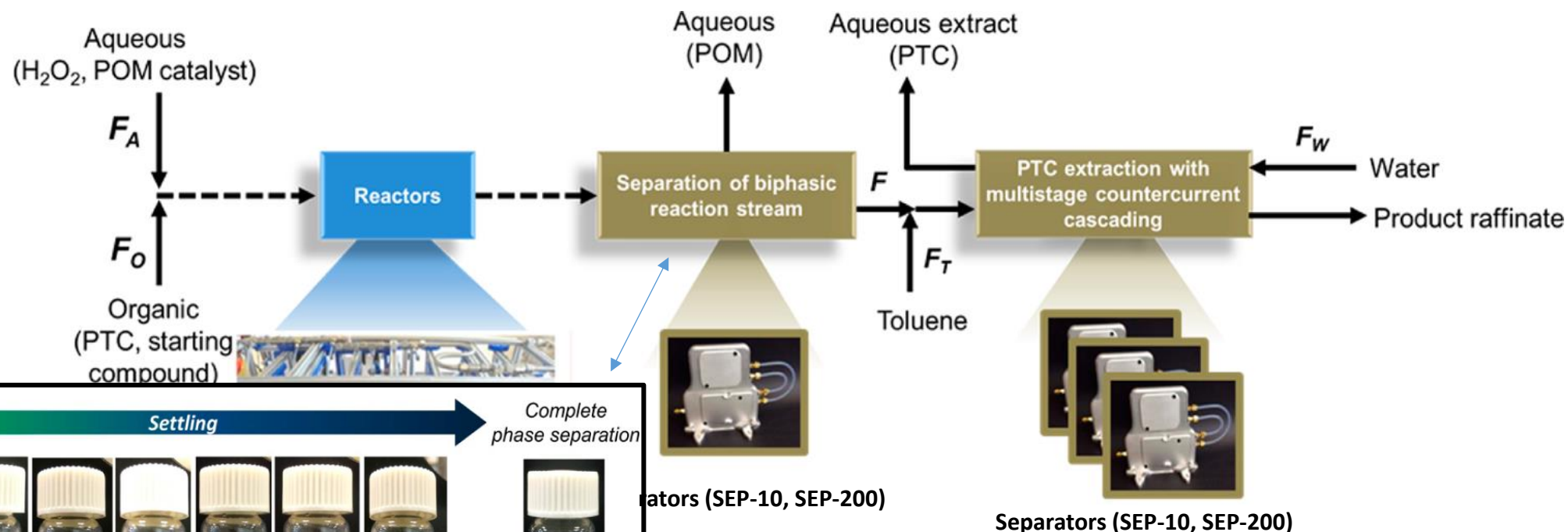
- Maximize removal of alcohols from the desired organic outgoing stream
- Maximize recovery of THF and ethyl acetate into the organic outgoing stream
- Steady state within 10 min

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

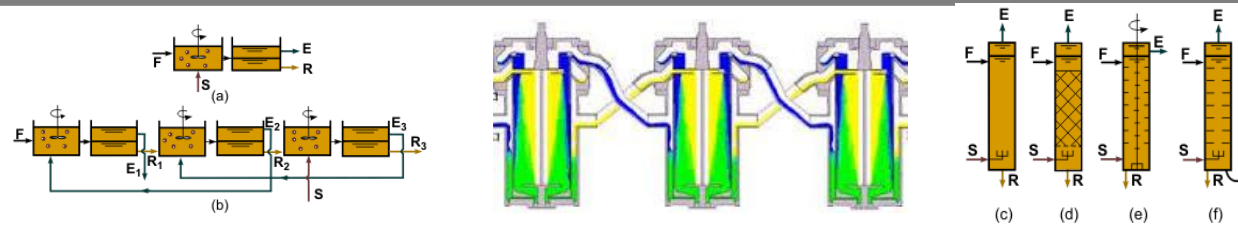
Multistep extraction – Example and scale up



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



Multistage extraction - Comparison



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



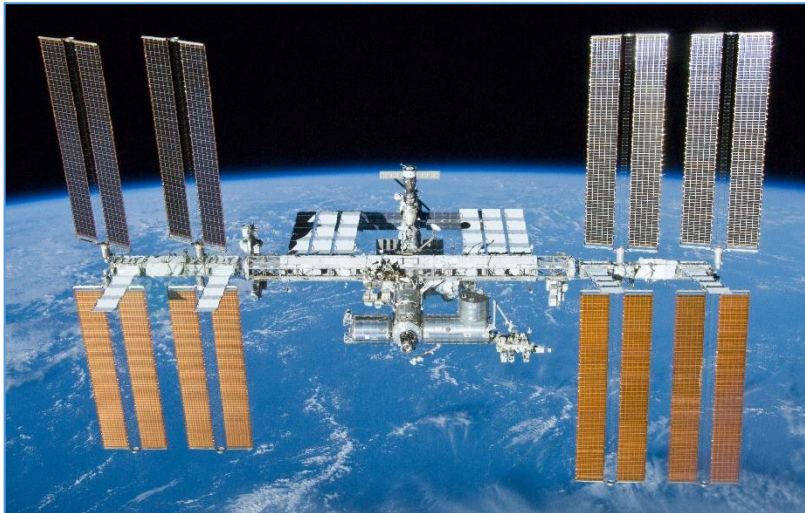
Acknowledgements



- Nopphon Weeranoppanant
- Klavs Jensen



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NOVARTIS

Questions ?