efficient processing

Continuous Flow Technology versus Batch Reactions for Formulation Production

Dr. Dirk Kirschneck, Microinnova Engineering GmbH

Agenda

- Background Microinnova
- Lessons learned from Flow Chemistry
- Continuous Formulation Strategy
- Process Development
- Engineering
- Applications & Case Studies

Background Microinnova

Specialists in Process Intensification

process development

engineering & plant

Microinnova combines process knowledge with plant competence

Process intensification step by step

evaluation		verification		development		realization	
step 1	milestone	step 2	milestone	step 3	milestone	step 4	milestone
plant check	potential proof	basic feasibility	basic proof	technical feasibility	parameter optimization	engineering & plants	industrial plant
plant check report		preliminary study lab-scale plant test matrix		device screening critical parameters parameter optimization data for engineering		scale up plant design engineering construction	

turn-key-plant

Customers

- 5 out of Pharma TOP 10
- 3 out of Generic TOP 5
- The largest Chemical Company
- The largest Labchemicals Manufacturer
- The largest Crop Protection Generic Company

Lessons Learned from Flow Chemistry

Learnings for 10 years experience

- Nobody is interested in microreactors or flow chemistry itself – the benefits are of interest
- Universal success do not come from a specific tool
- A knowledge-based approach generates a broader base for significant benefits
- Process understanding is key
- Process Intensification offers a lot of tools
- A useful selection generates benefits

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Continuous Formulation Strategy

Trends in formulations

Level of performance

- higher complexity
- more sophisticated production

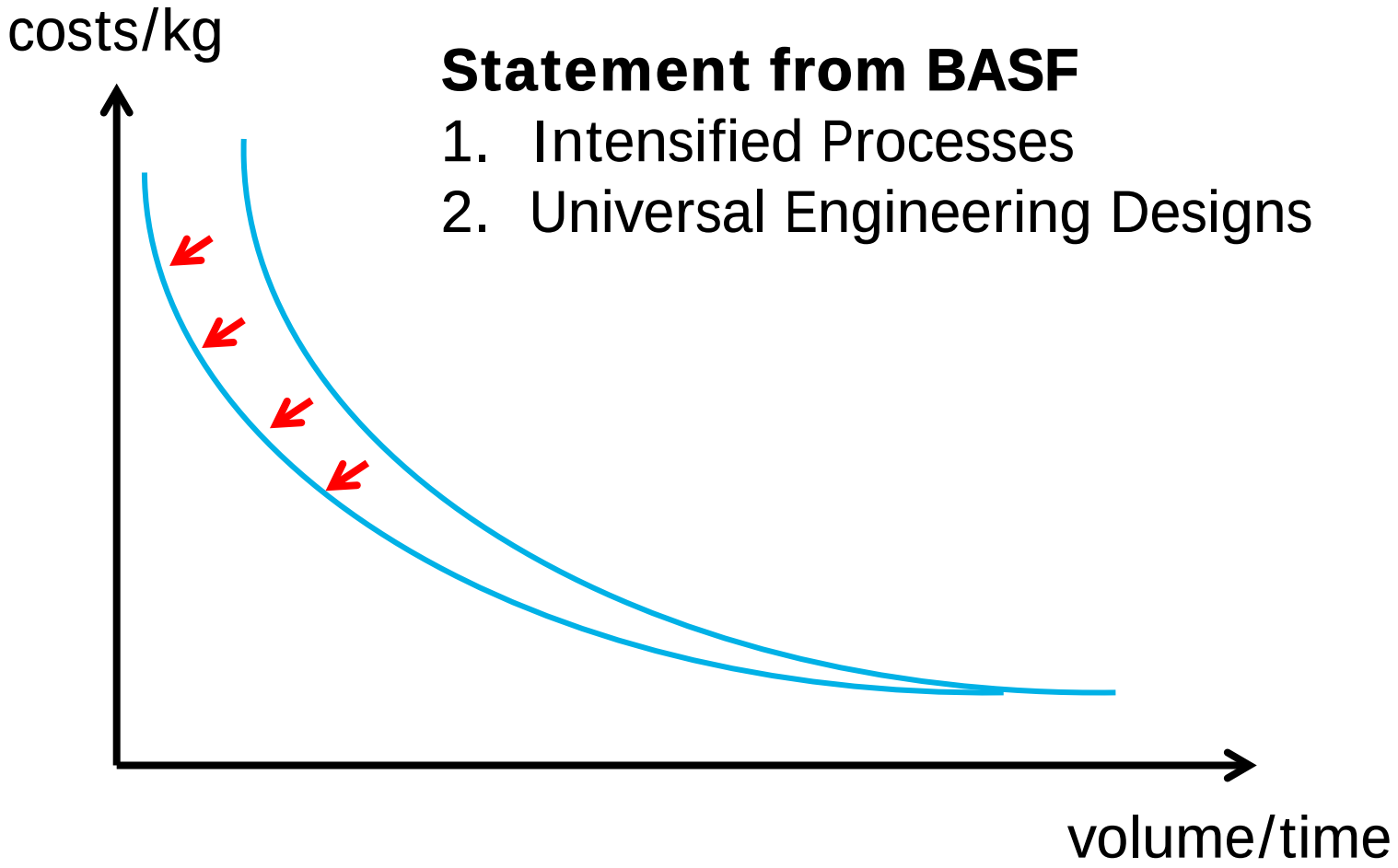
Level of costs

- manufacturing costs
- raw material costs

Level of quality

- tighter specifications
- higher level of control

Reducing the costs per kg (0,7 rule)

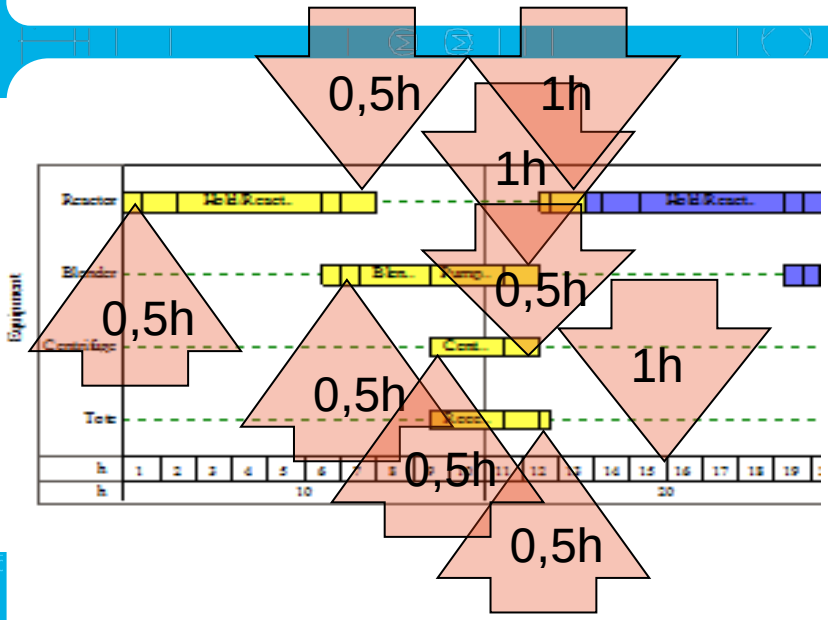


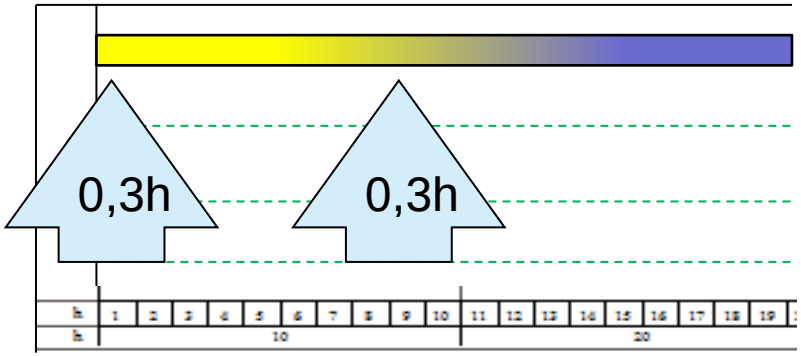
Statement from BASF

1. Intensified Processes
2. Universal Engineering Designs

T. Stammer (BASF) et al, Presentation, CHISA 2014, Prague

More labor efficiency

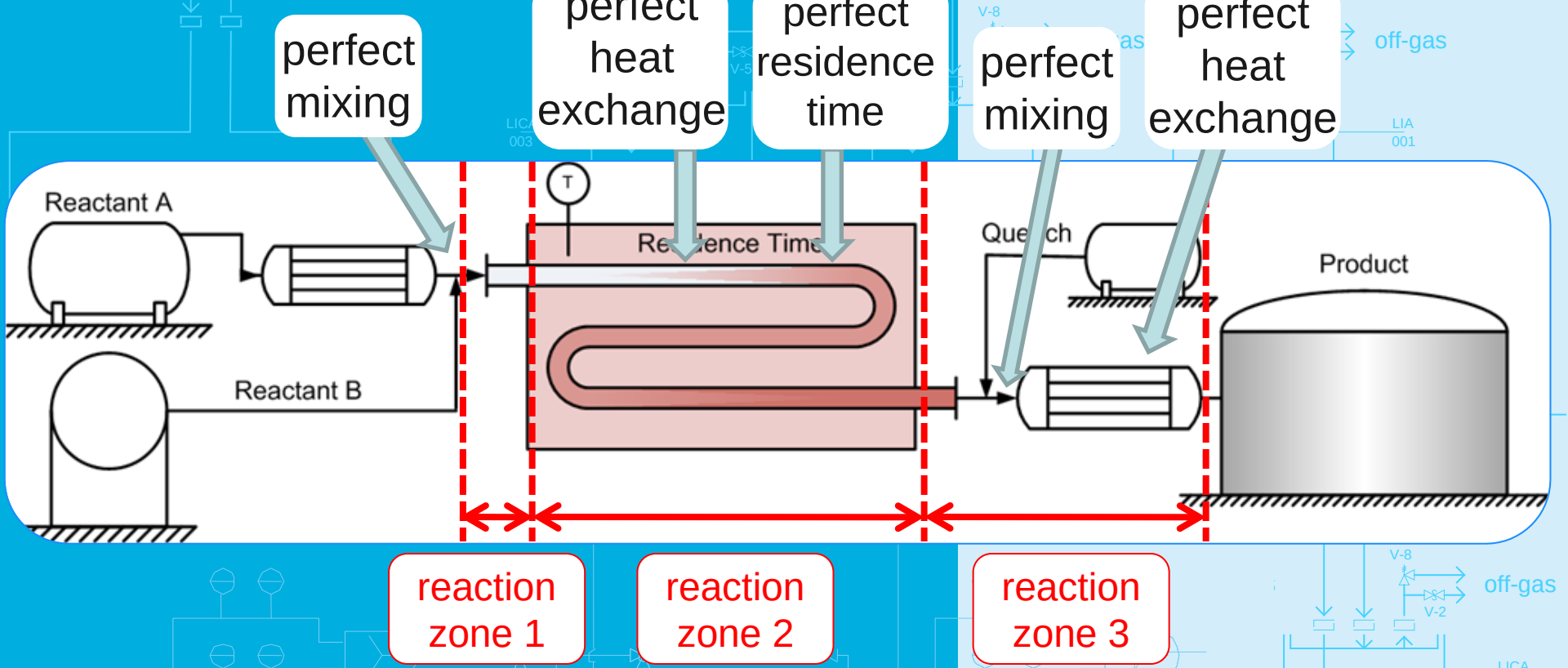




Batch: 6 h/Shift

Flow: 0,6 h/Shift

Towards perfect processing



- narrow residence time distribution
- no backmixing
- no hot spots
- ideal stoichiometry
- no high concentration spots
- no dead zones

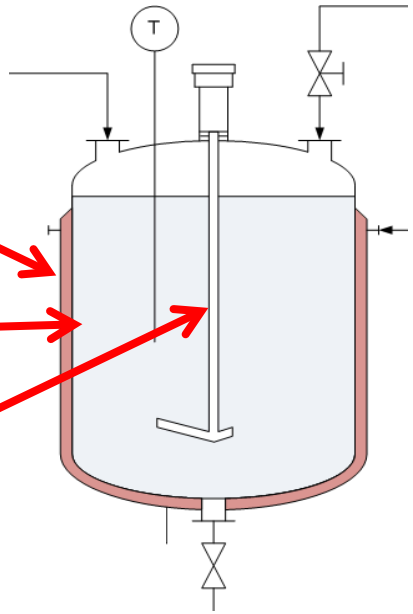
Heating up a viscous mixture in batch

Manufacturing Records of Pharma TOP 20

Wall Temp. 130°C

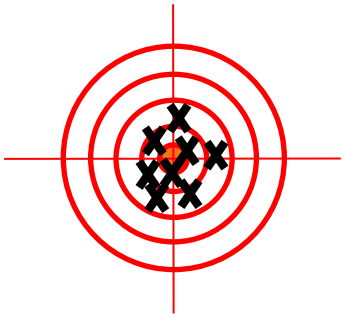
Temp. near wall 120°C

Center Temp. 70°C

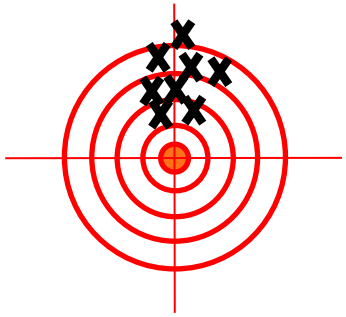


Is the technology capable to do the job?

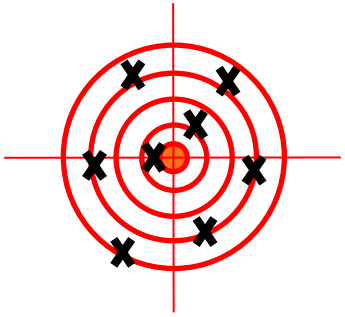
hit target small spread



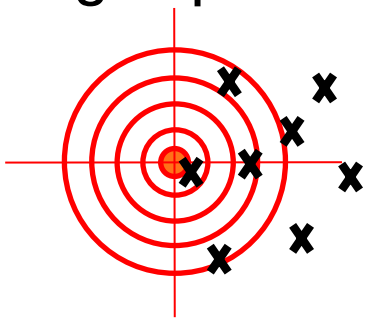
miss target small spread



hit target large spread



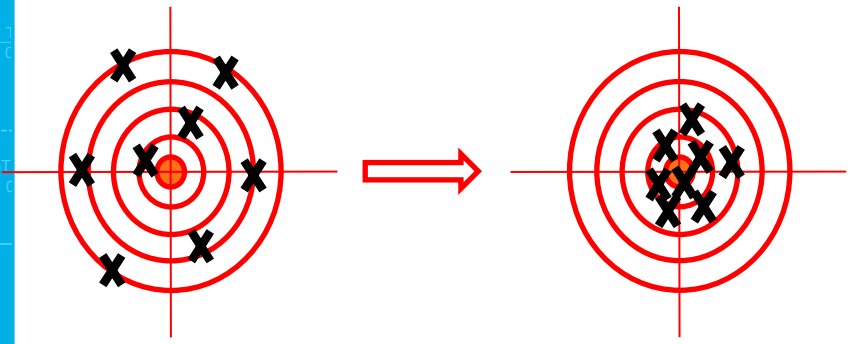
miss target large spread

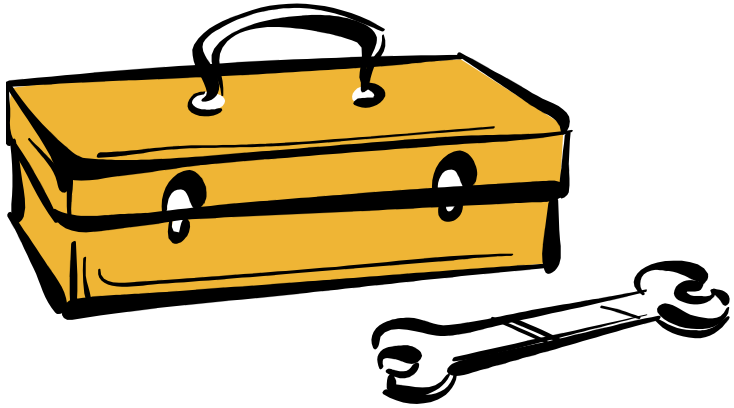


Improvement Potential for Flow

Better Control

New Strategies





How to design a flow process?

Drivers

- Operation Reduction
- Selectivity
- Labor Efficiency

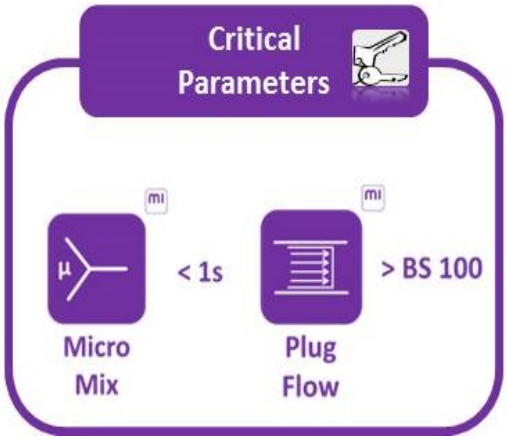
Critical Parameters

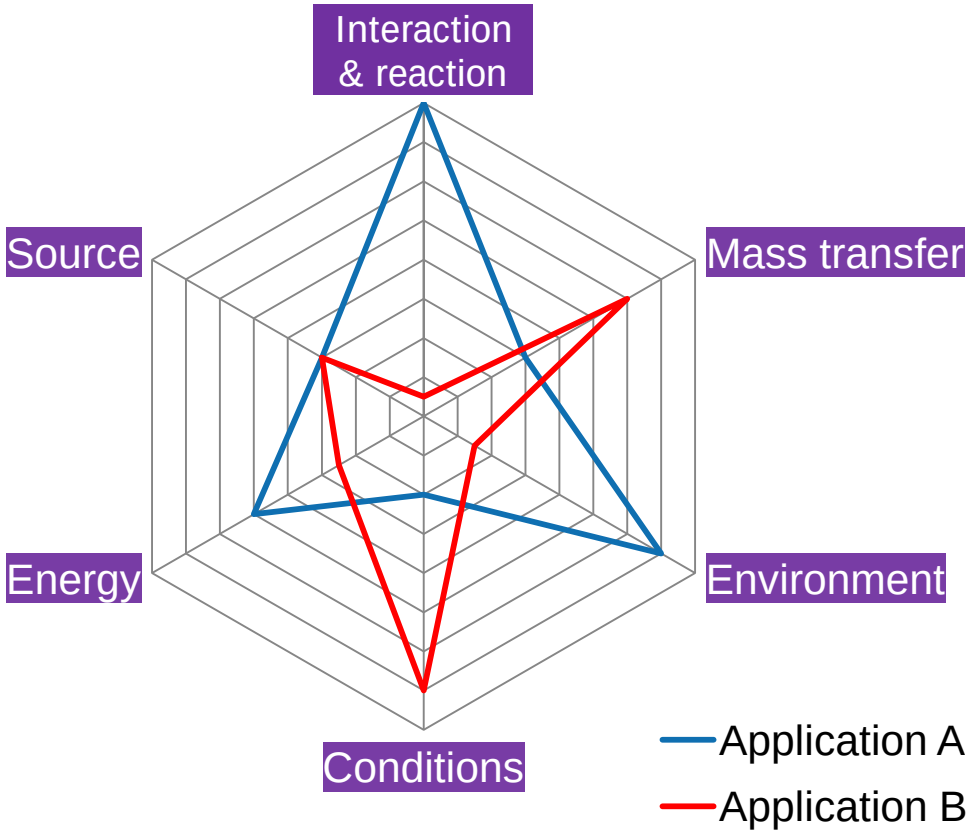
- Micro Mix: < 1s
- Plug Flow: > BS 100

Tools

- Micro Mix
- Plug Flow
- Micro Heat Exchange

Application Profile





Process intensification toolbox

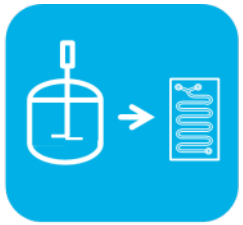
Micro Mix

Micro Heat Exchange

Unstable Reagents

Plug Flow

Cascade



Small Volume

Mass Transfer

Precise Processing

Novel Process Windows

Rotor Stator

Quench

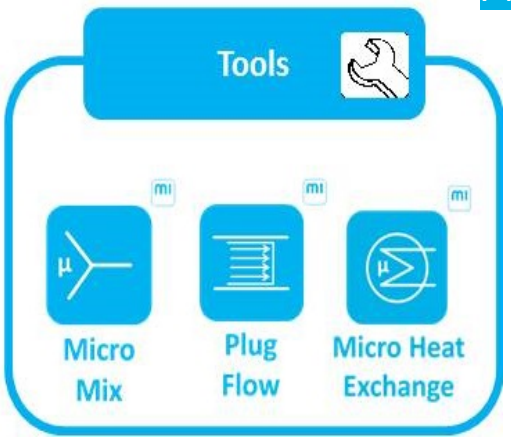
Microwave

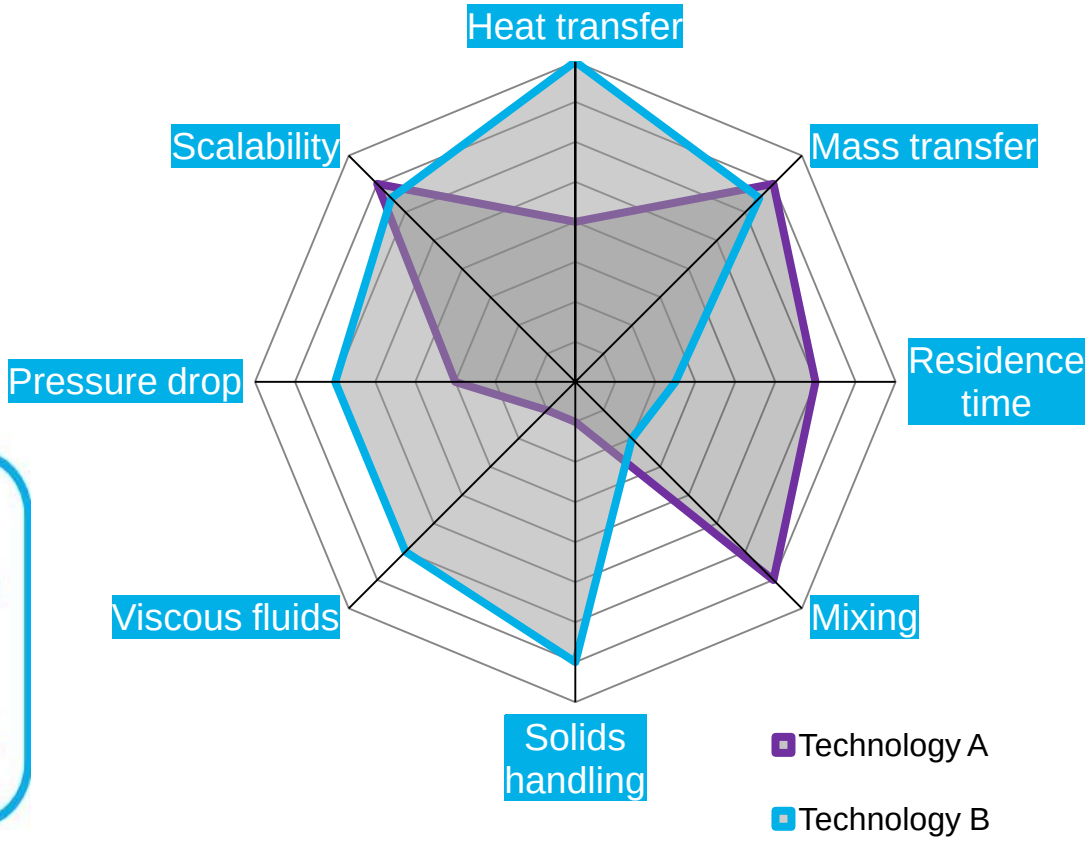
Ultrasound

Membrane

Extrusion

Technology Comparison





Technology Example: **Extrusion**

Continuous generation of one substream of a Healthcare formulation

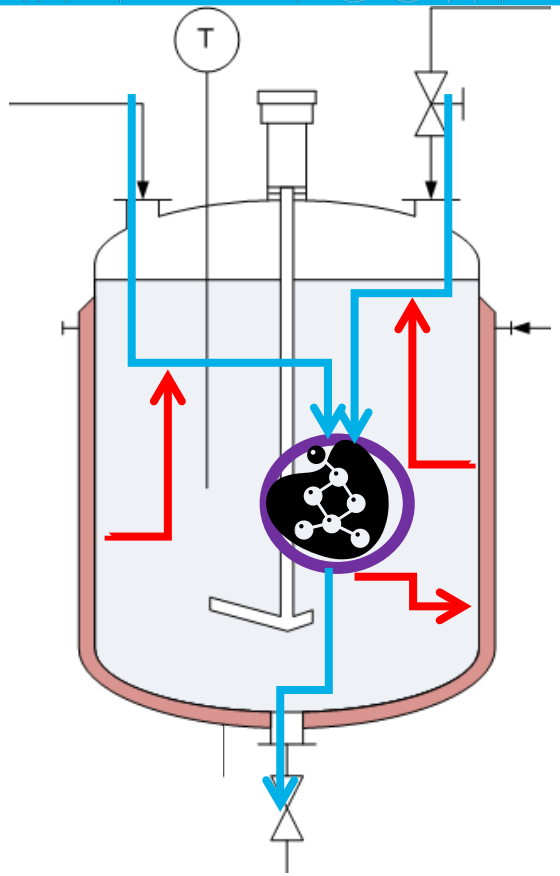
Pharma Top10 Company

Technology-Example: **Rotor-Stator-System**

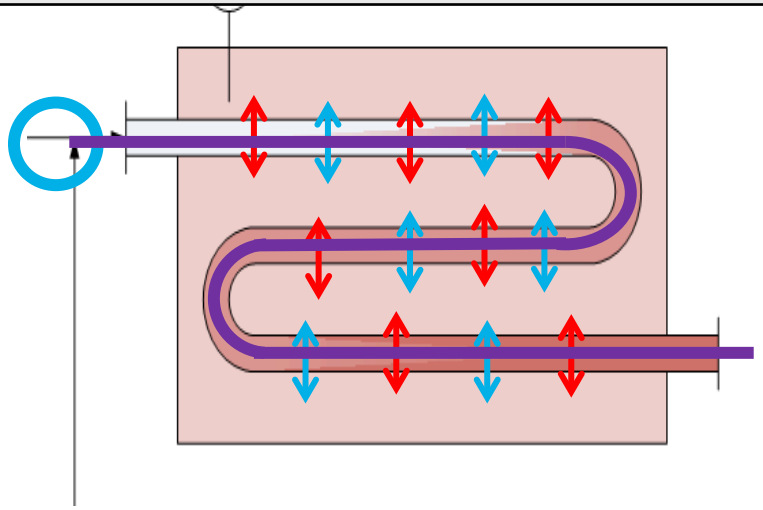
Continuous generation of

- solutions
- emulsions
- suspensions

Value by optimizing mass & heat transfer



Operation	Batch	Flow	Factor
Interaction	5 min	5 min	0
Mass Transfer	50 min 1 m	0,5 min 1 cm	100
Heat Transfer	25 min 0,5 m	0,5 min 1 cm	50



Process Development

Processes range of executed projects

Projects

- Soluble Concentrates
- Oil-based Suspensions (liquid)
- Oil-based Pastes (viscous)
- Microencapsulation
- Emulsion Polymerisation

Customer segments

Customer Care	Health Care	Medical Care	Pharma	Agro

Lab facilities at Microinnova

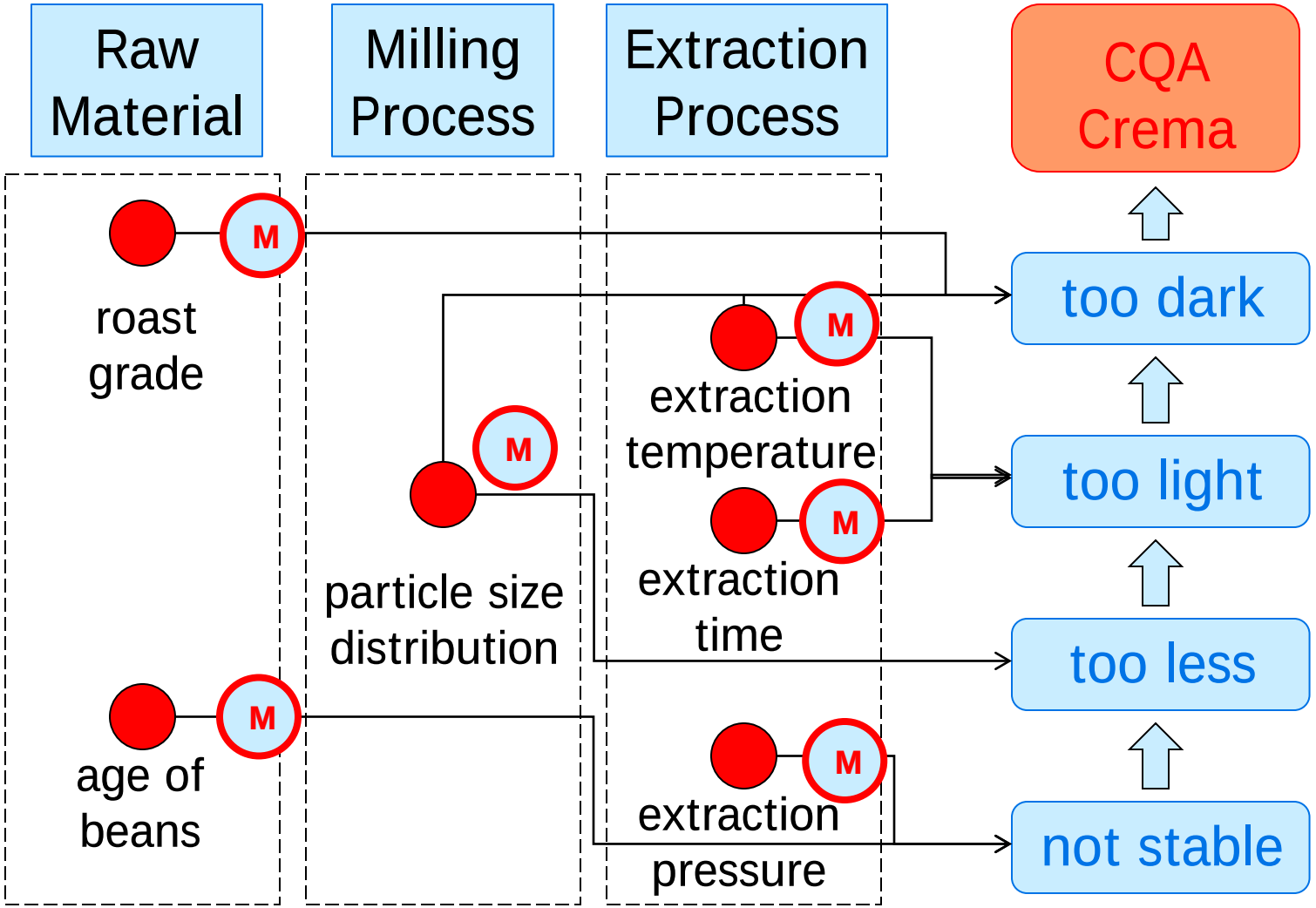
- 4 flow plants for projects
- 25 Structured static devices
  - SS, Hastelloy, Tantal, Glass
  - Fluitec, Corning, IMM, LTF, KIT
- Dynamic Principles (e.g. Rotor-Stator), Ultrasonic Units and more
- Analytics (2 GCs, FT-IR, PSD, 3 HPLCs, UV-Vis, Visk., Titr., pH, Conductivity…)
- Basic pilotplant facilities (< 30 kg/h)
- Workshop (miniplant constr.)
- Storage of several tons flammables

Continuous formulation projects

Data of example project done at Microinnova
(not the technical limits!)

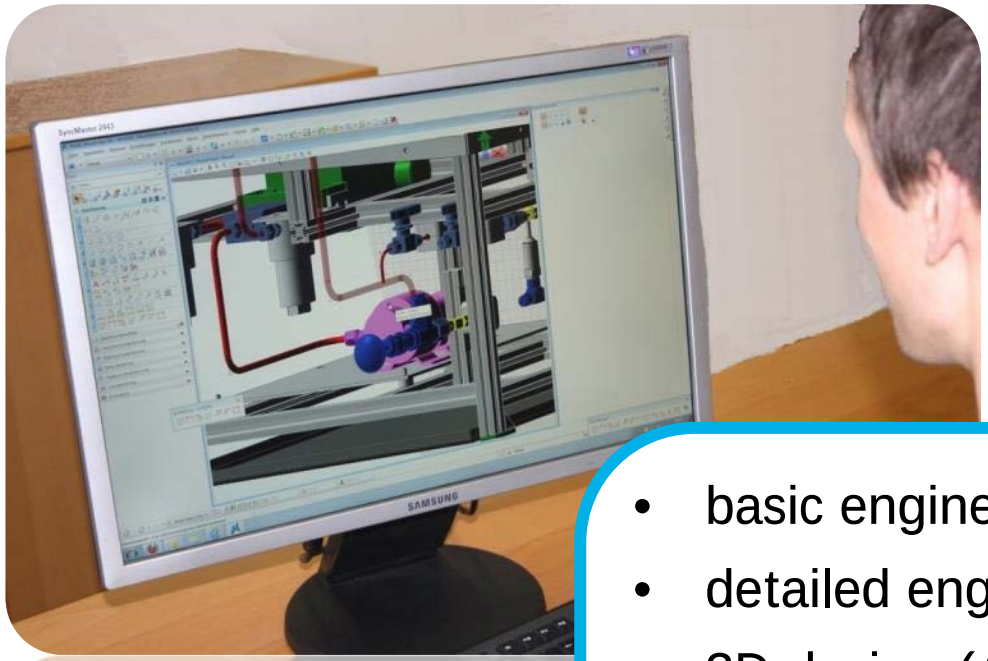
- Viscosity range:
  1000 cP – 20000 cP (60000 cP)
- Solid content up to 37 %

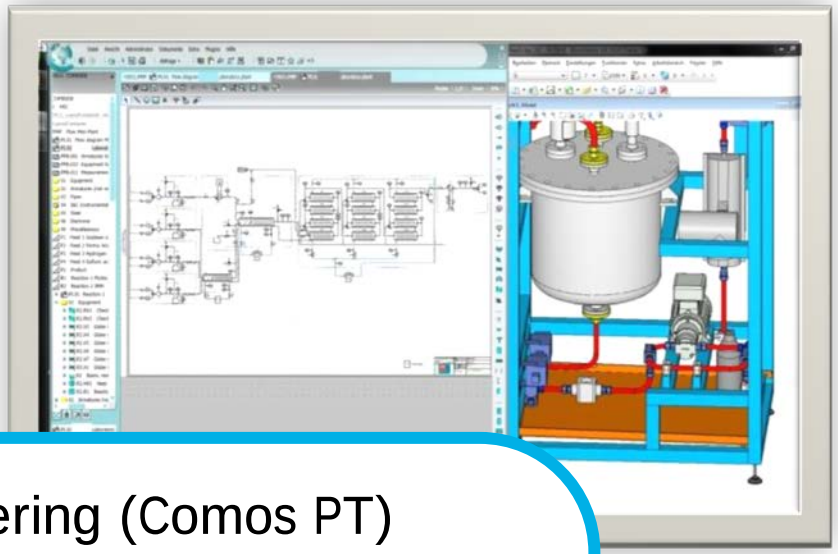
QbD: Critical process parameter map



Engineering

Engineering Competence Microinnova

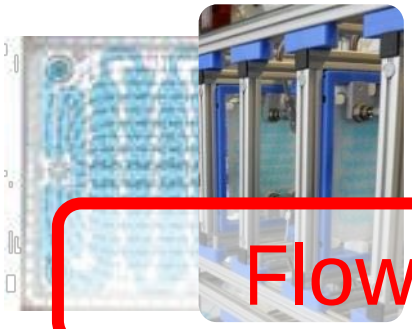
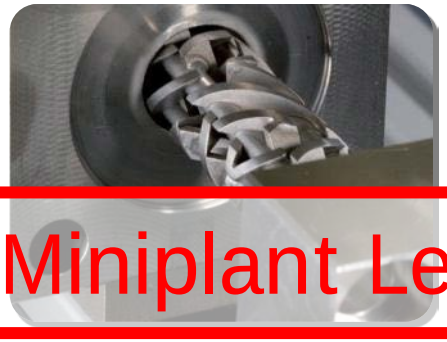




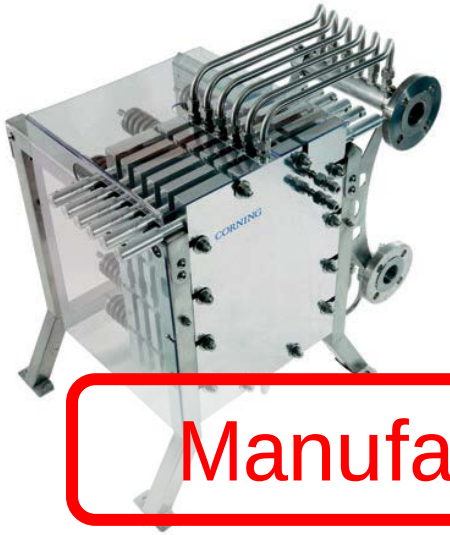
- basic engineering (Comos PT)
- detailed engineering (Comos PT)
- 3D design (AutoCAD)
- automation solutions
- plant construction
- commissioning
- CE, ATEX, UL, UL-Ex, cGMP

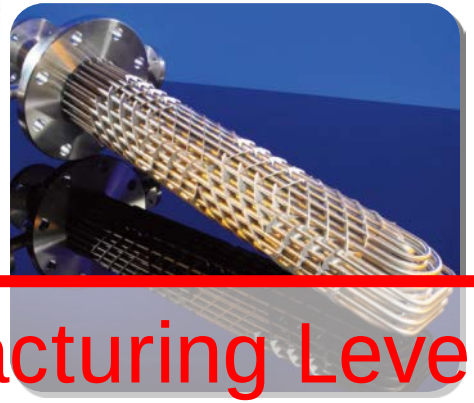
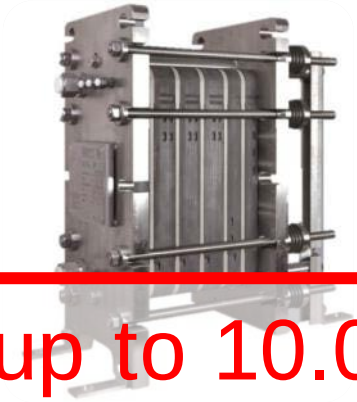
Scale up of flow processes

Corning	**Fluitec**	**ESK**	**IMM**
AFR	XR	MR	Star-Lam

Flow Miniplant Level up to 10 l/hour



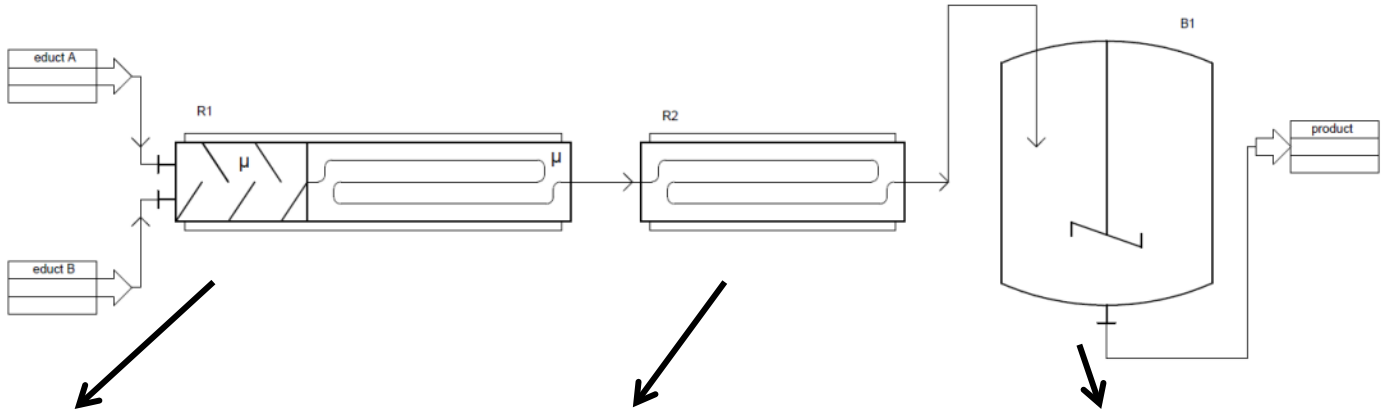




Manufacturing Level up to 10.000 l/hour

Combination of technologies

Most of the projects need a combination of new process intensifying technologies and traditional technologies.

Microinnova can do both!



micro reactor

plug flow reactor

cascade CSTR

Comparison batch versus conti / flow

advantage batch
- flexibility
- multipurpose

advantage conti/flow
- process performance
- safety
- easy automation

process is adjusted to the plant

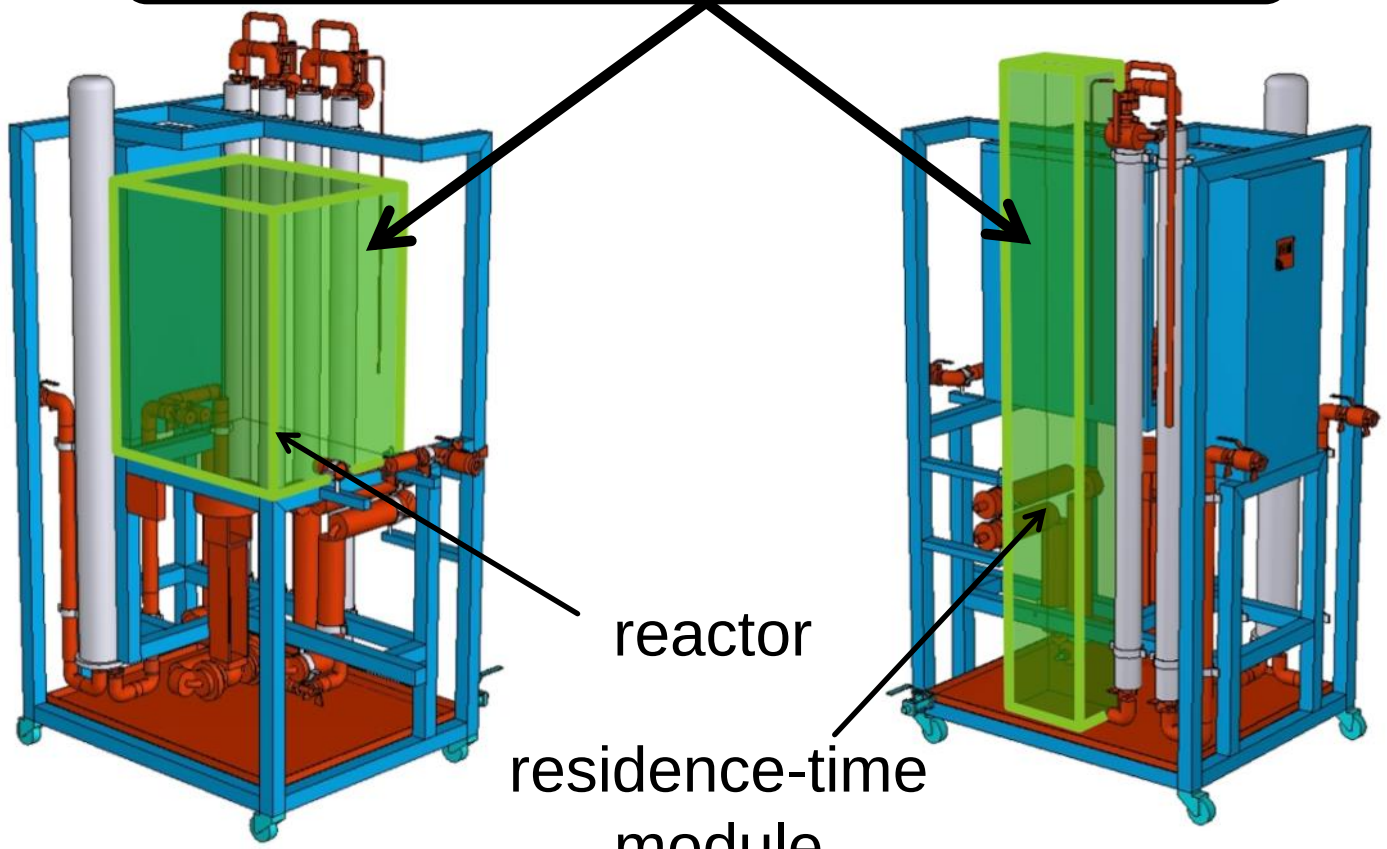
plant is adjusted to the process

concept necessary, which combines batch flexibility with continuous performance

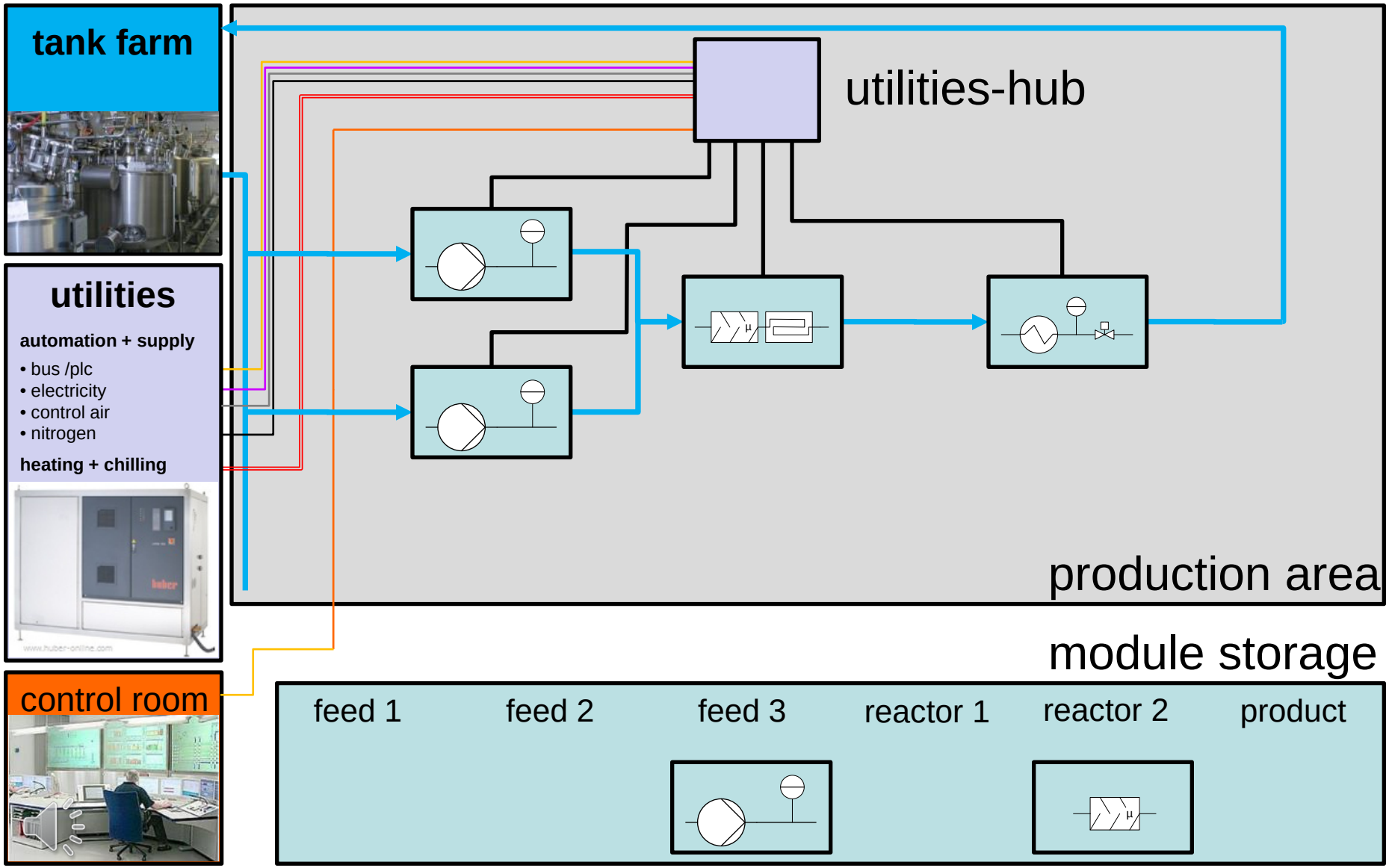
On-module flexibility

on-module adaption by exchanging specific parts

engineered spaces for adaption



Modular plant design



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Applications & Case Studies

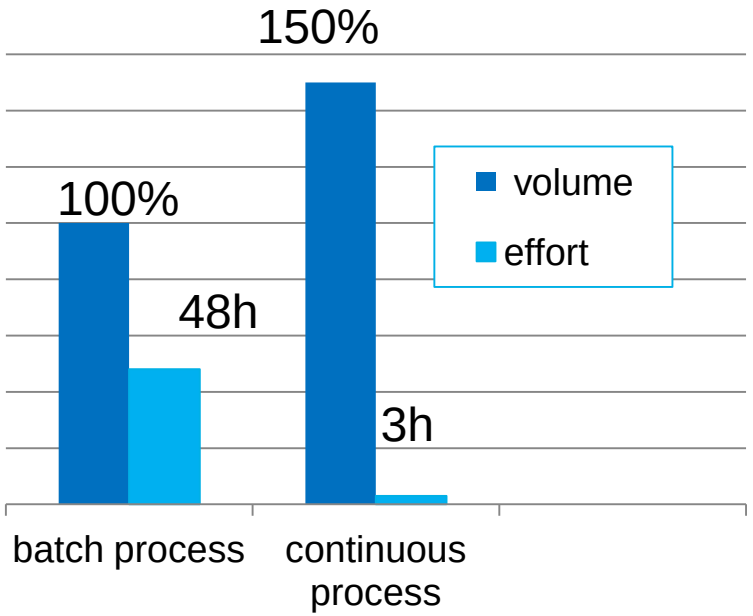
More labor efficiency

Breakthrough in savings program:

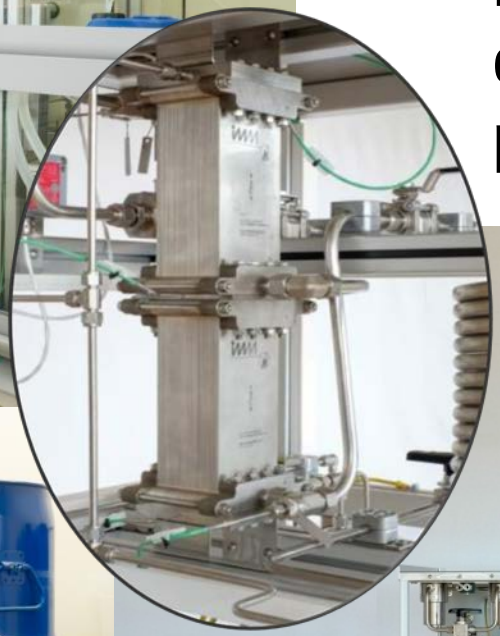
- Reduce production costs
- Increase yield
- Increase production volumes

Results:

- Personal use: - 94%
- Production volume: + 50%
- Yield: doubled
- 2 reactors only instead of 4
- Workflow accelerated
- Errors eliminated



Case study: Flow Miniplant



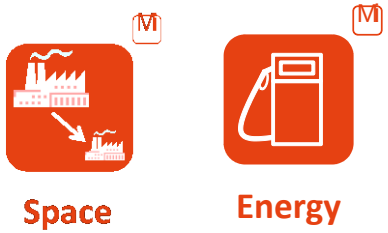
Flow Miniplant

Example of a 20 kg/h development or small scale production system

More capital efficiency

Minimal intervention with maximum effect

- **Save process efforts**
- **Increase capacity**
- **cut-down energy costs**



Results:

- Process simplified
- Production volume doubled
- Costs for cooling and rewarming eliminated
- Investment costs 1/10 of conventional

Summary

Level of performance

- strategies to deal with complexity
- more knowledgebased processing

Level of costs

- influencing manufacturing costs
- no strategy for raw material costs

Level of quality

- a way to tighter specifications
- a way to a higher level of control

Meet some people who make it happen

Dipl.-Ing. Walter Linhart, perfectionist

"We set up modular manufacturing systems that will allow our customers to transfer their competences into productivity in the highest degree.

Dr. Günter Tekautz, puzzle freak

Yield and process stability increases to the same extent as the number of possible synthesis routes can be expanded by flow and other intensification technologies.

The research leading to these results has received funding from the European Community's Seventh Framework Programme [FP7/2007-2013] under grant agreement no. CP-IP 228853-2

Please contact me:

+43-3182-62626-110

dirk.kirschneck@microinnova.com