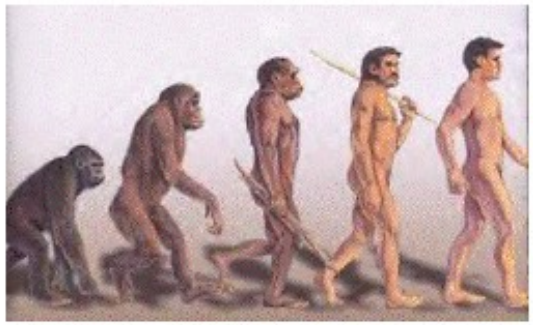
CORNING

Advanced Flow Reactors

Teaming up Chemistry and Chemical Engineering for "Greener" Processes and Improved Economics

Dr. Sergio Pissavini
Business Director

Evolution (Revolution) in Chemical Processing



Glass Fluidic Modules

Corning® Advanced-Flow™ Glass Reactor

Alchemy

Today's Industrial Manufacturing

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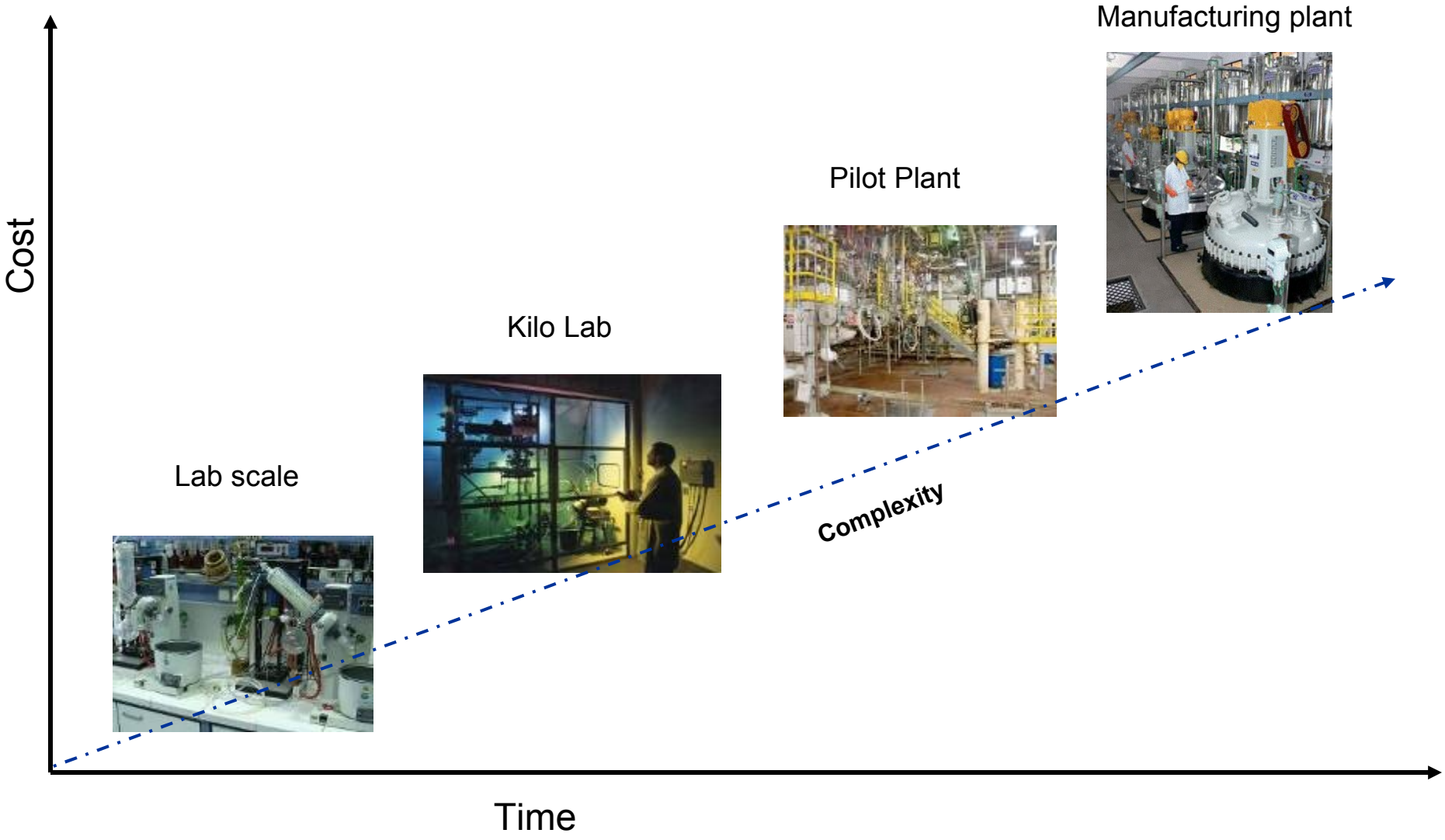
Batch process scale up



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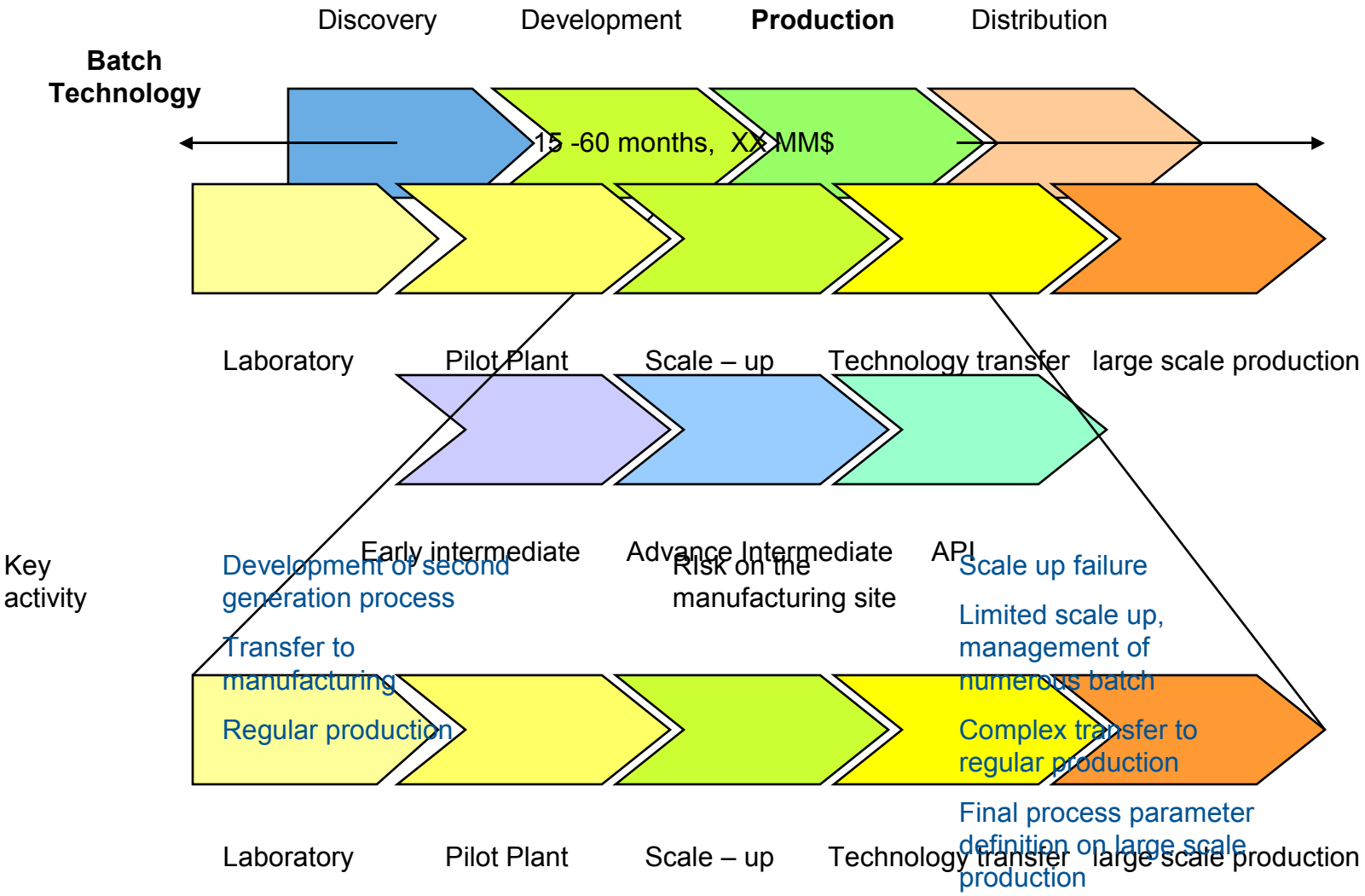
Process develoment benefits

Example: Fine Chemicals and Pharma API production



from: Fine Chemicals

Peter Pollak, Wiley2007

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Fine and Pharma Industries

Simple and fast PAR, Pilot

Advanced Flow Reactor Technology

Production Banks

8 -15 months, X MM$

Laboratory | Pilot Plant | Scale–up | Technology transfer | large scale production

One tool engineered to fit all needs

Key activities →

- Development of second generation process
- Transfer to manufacturing
- Regular production

Risks at the manufacturing site →

- Scale up failure, **no scale up**
- Limited scale up, management of numerous batch **no limitation**
- Complex transfer to regular production **no issues**
- Final process parameter definition for large scale production **simple**

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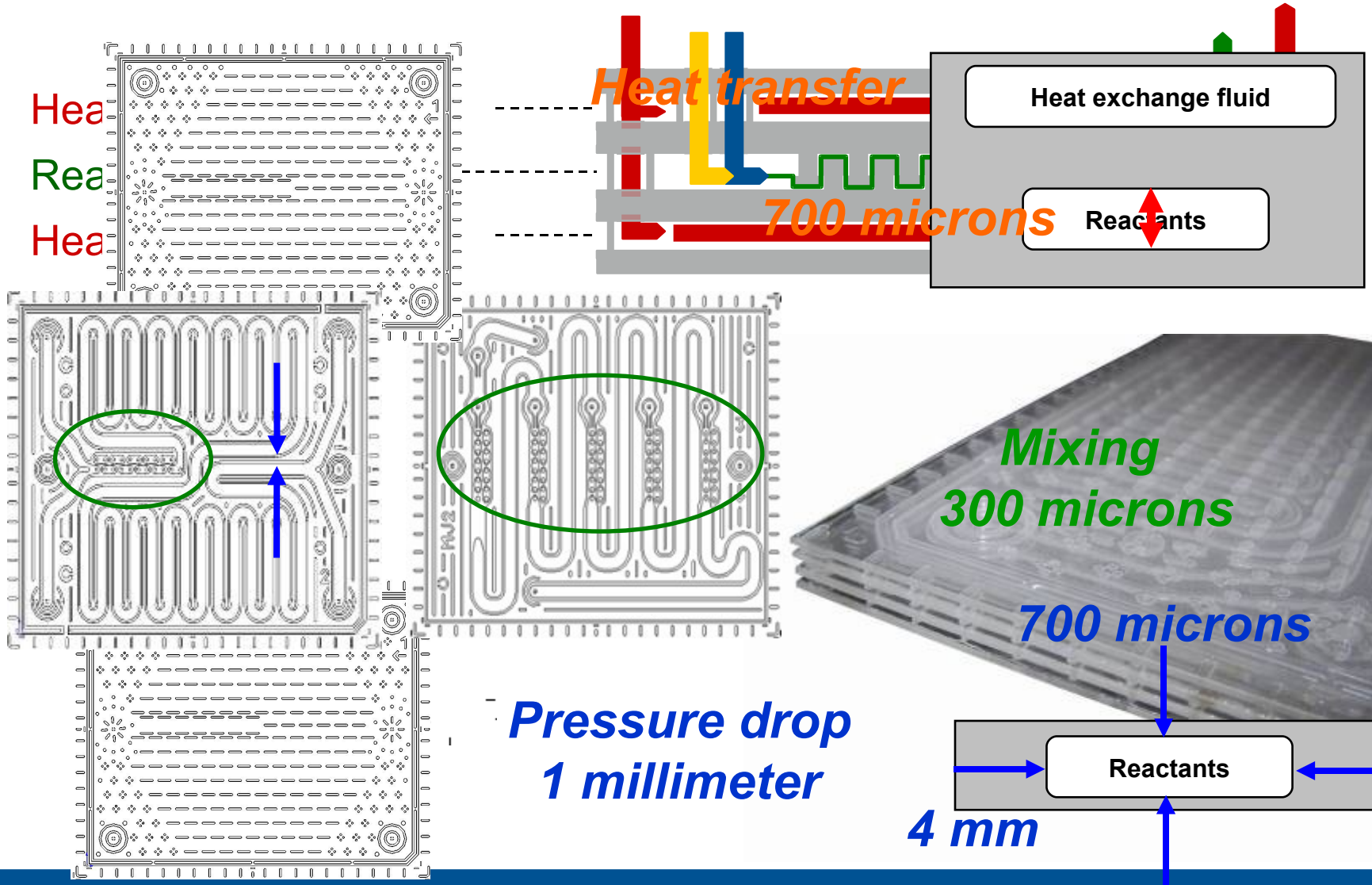
Fluidic modules: concept and library



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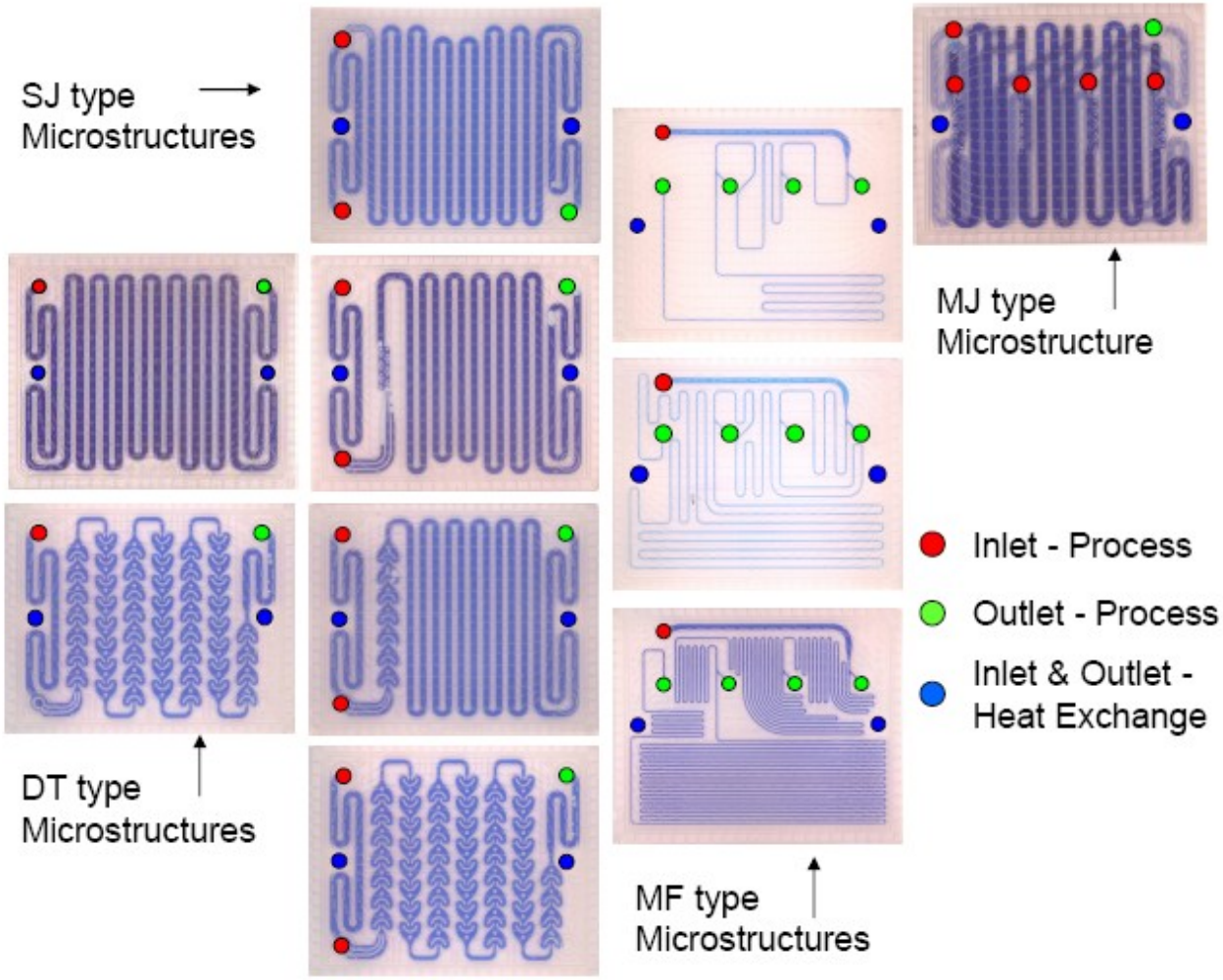
Fluidic modules: concept and library



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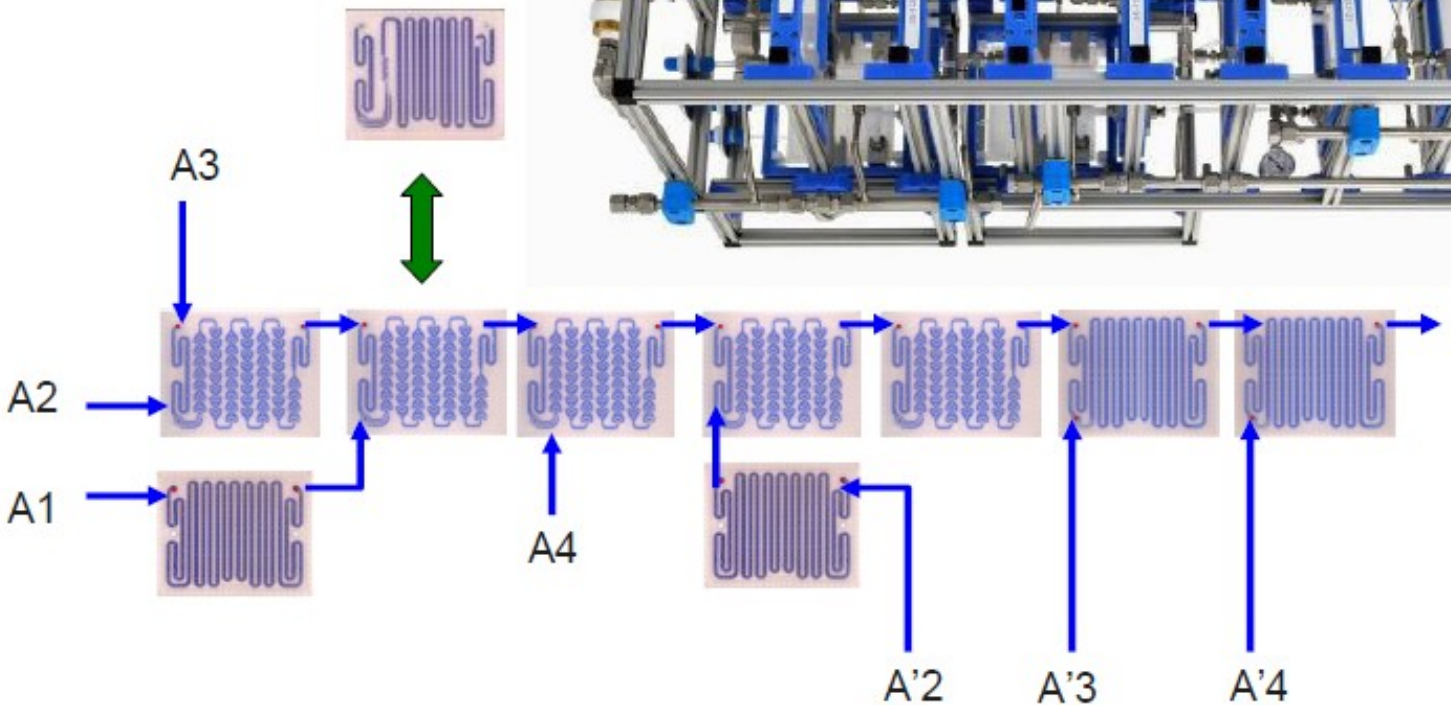
AFR evaluation tool: *flexible with capability all the way to pilot scale*



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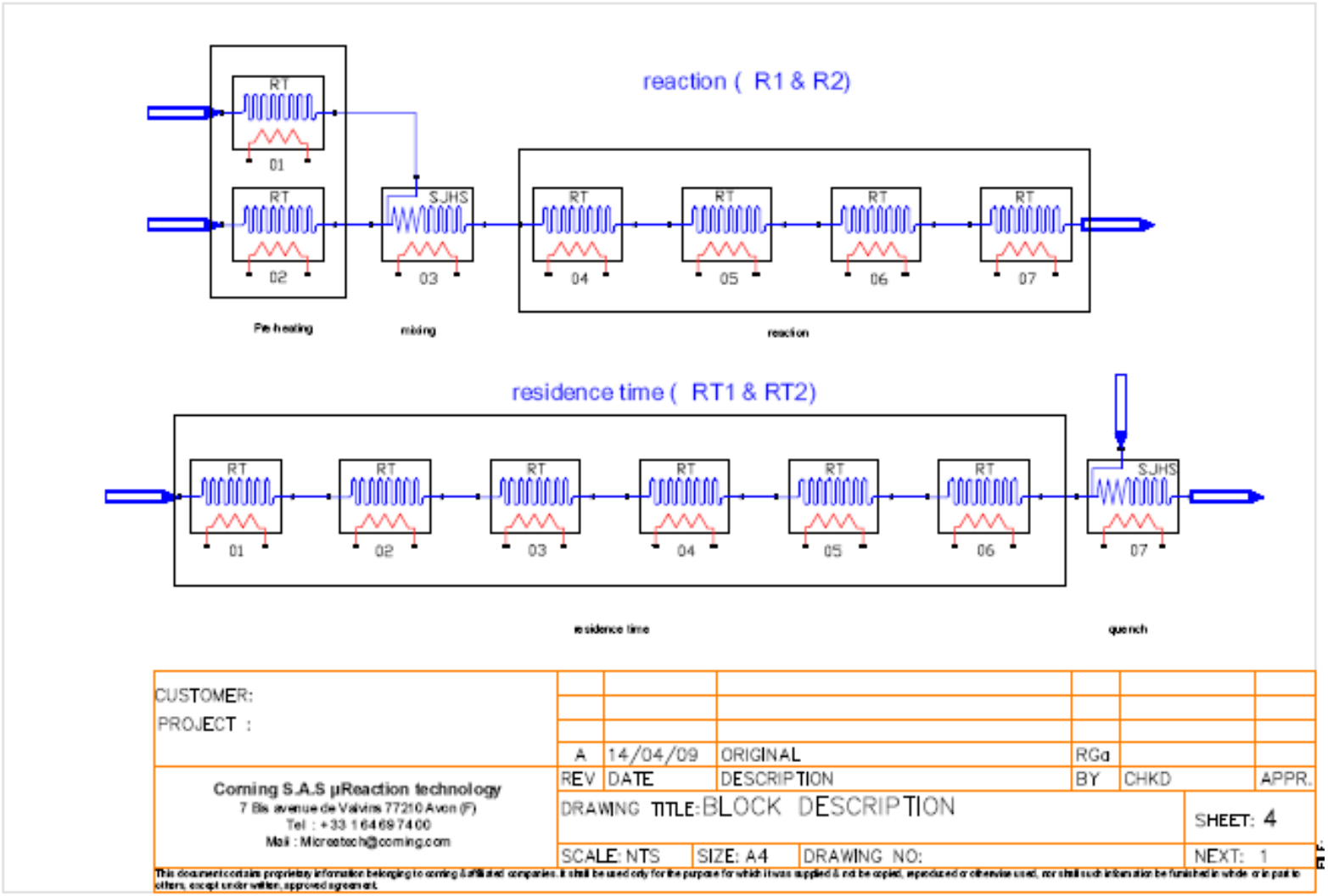
MPP Pilot Plant - Block description



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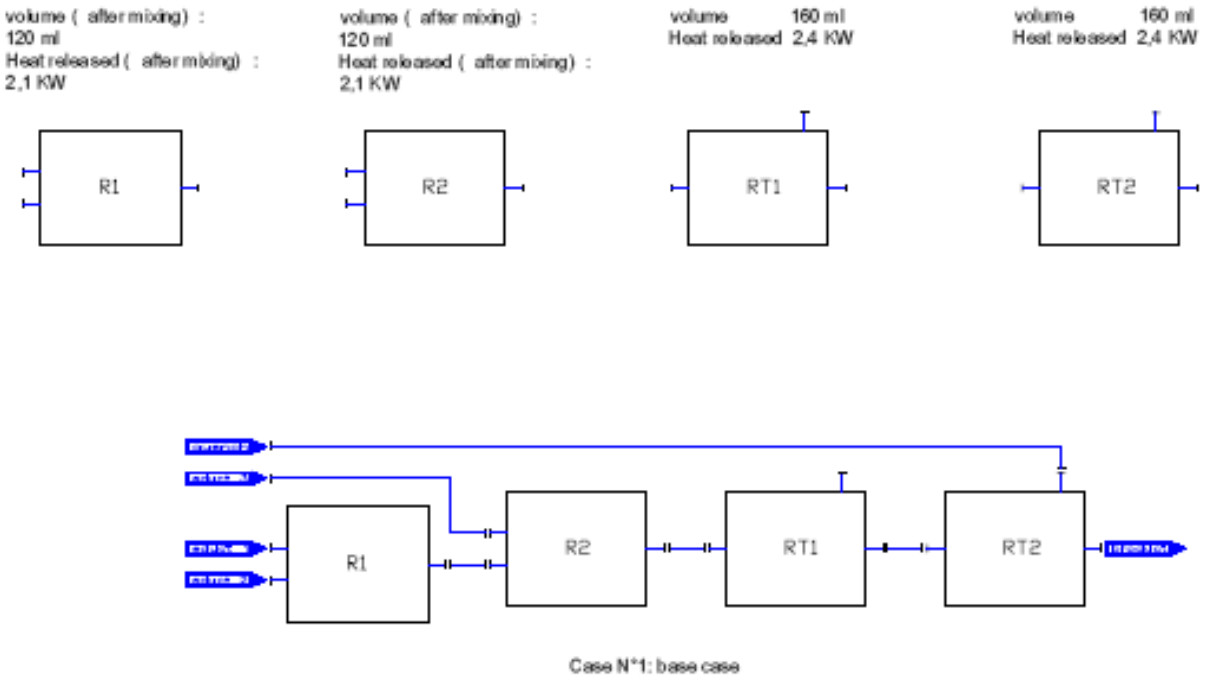
MPP Pilot Plant - Block diagram 1



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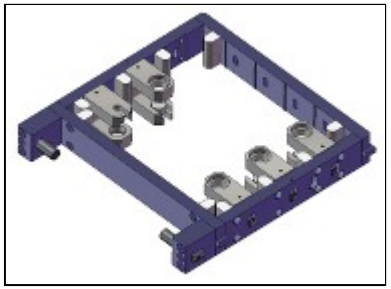
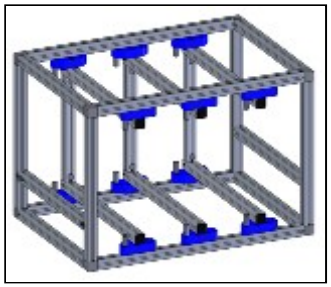
Engineered reactor components



Interfaces



Frames

Standard Fittings

Connectors

Tubing

Sensing

O-ring seals

Fluidic Modules

Labelling

Add-on (insulation…)

Instrumentation (Pressure relief valve…)

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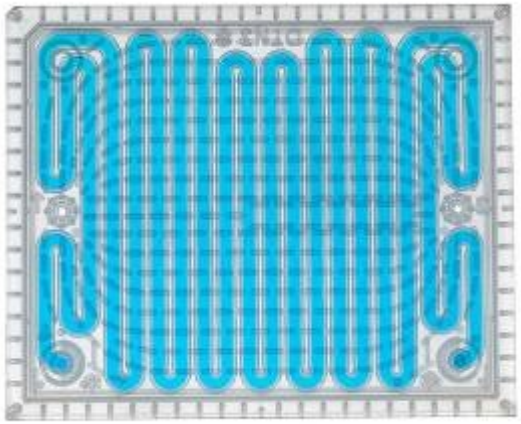
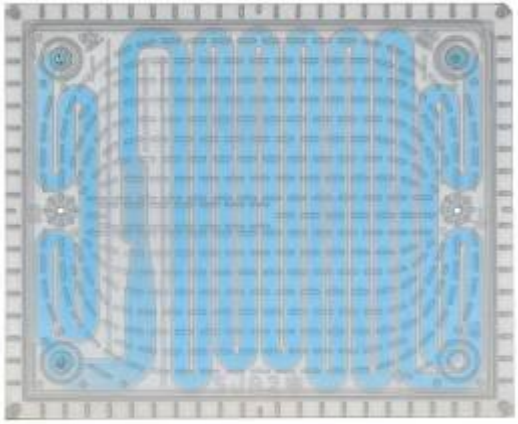
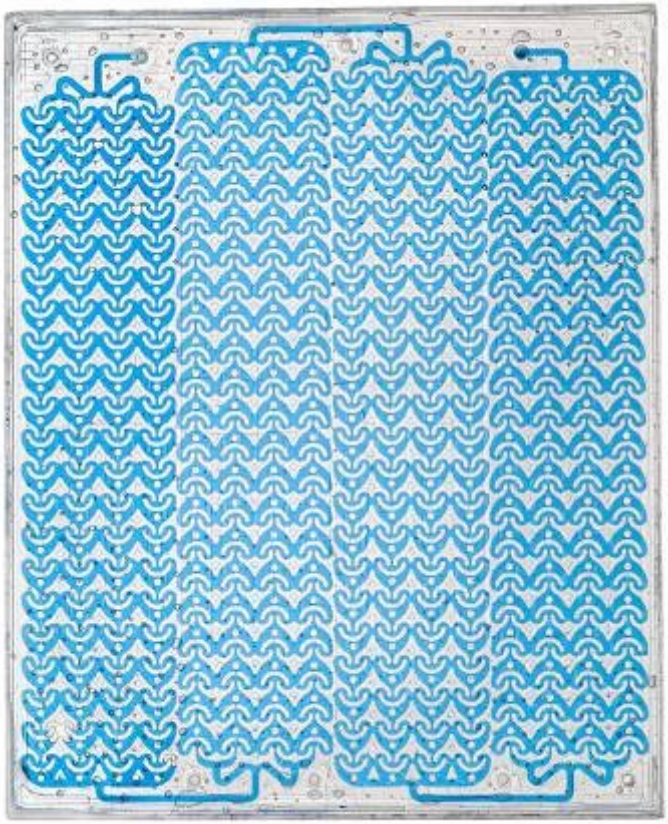
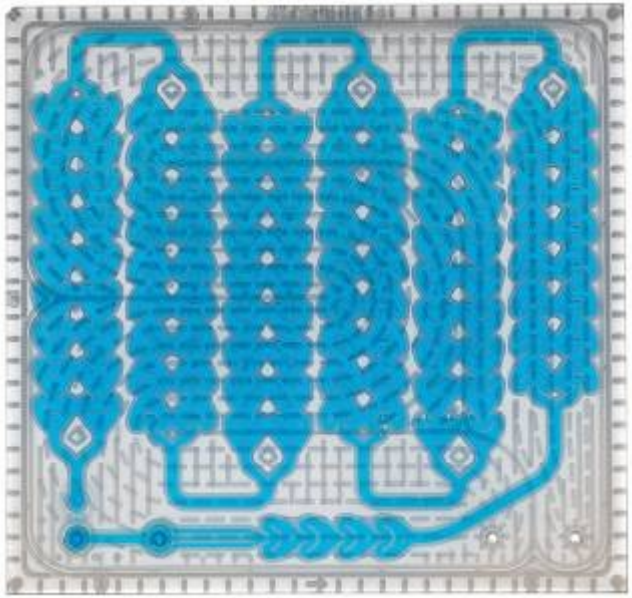
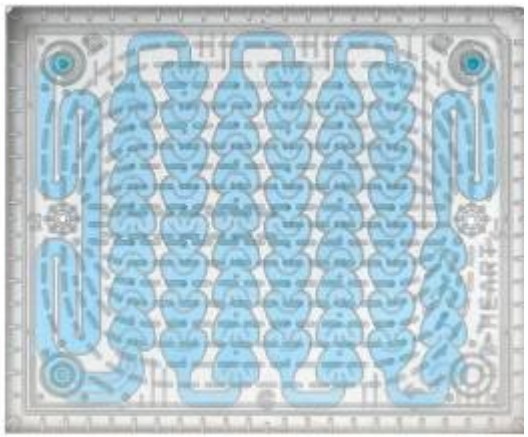
Glass Fluidic Modules are the building blocks











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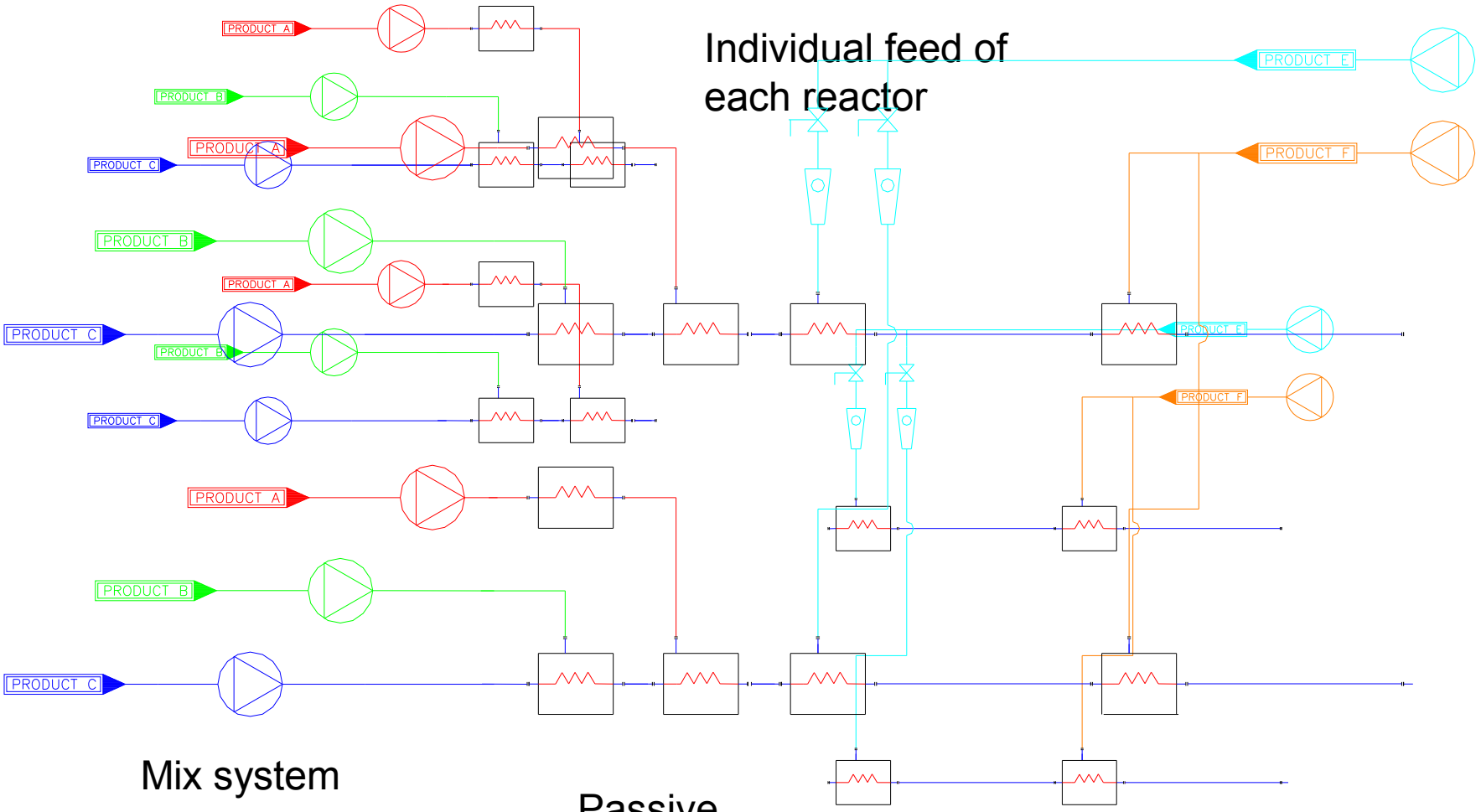
Numbering up: system distribution



Individual feed of each reactor

Mix system

Passive distribution

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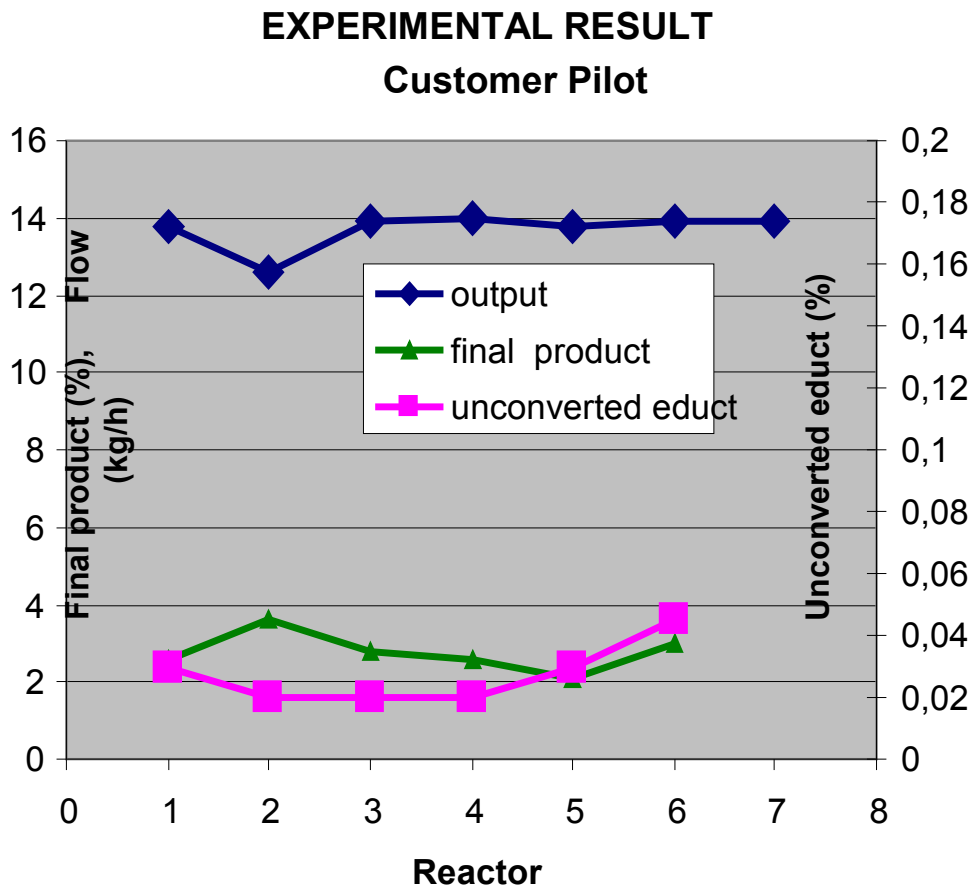
Numbering up: system distribution

- stability
- robustness
- versatility



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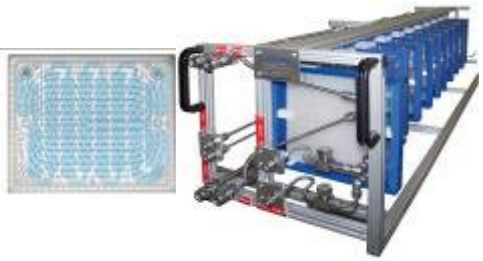
Scaling the technology to industrial production in 2 ways:

Scale-out = increase the total fluidic channel path length/fluidic module

Scale-up = increase the number of fluidic modules



Gen I

Process Development and Pilot Production Capable

Gen II

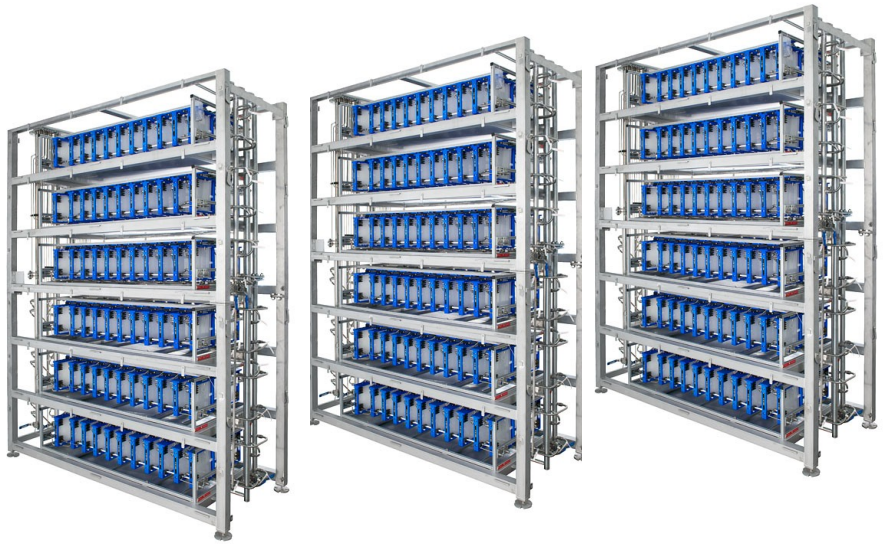
scale-out

Stacking scale-out

Gen III

scale-out

Scale-up: simple numbering up to full production



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AFR: wide range of throughput for production of Fine, Pharma and Specialty chemicals

T -60°C - 230°C
P up to 18 bar

g/min	15	160	400	660	1600	3200
kg/h	1	10	25	40	100	200
Tons / 5600h	5	56	140	220	560	1120
Tons / 8000h	7	80	200	320	800	1600

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Broad range of applications

- Reactions which have already benefited from Corning Advanced-Flow Reactor
  - Alkylation
  - Amidation
  - Bromination
  - Condensation
  - Metal Organic
  - Hydrogenation
  - Oxidation
  - Nitration

- In mono or multi phase environments
  - Miscible liquid feeds
  - Non miscible feeds – emulsions
  - Liquid and gas feeds
  - Suspensions

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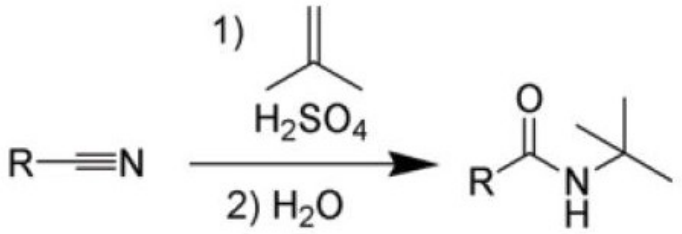
Safer processing: Diasteroselective Ritter reaction

- Active Pharmaceutical Ingredient, ophthalmic drug



- Process
  - Highly exothermic reaction
  - Possible reaction run-away and decomposition of product: operating conditions (temperature, pressure, flow rate) have to be carefully managed.
  - Critical handling of reactants (corrosive behavior and instability of H_2SO_4).
  - Possible undesirable formation of sulfate salts before the quench and of sodium salts during the quench.

Presented by PCAS at the Scientific Update conference, 2008

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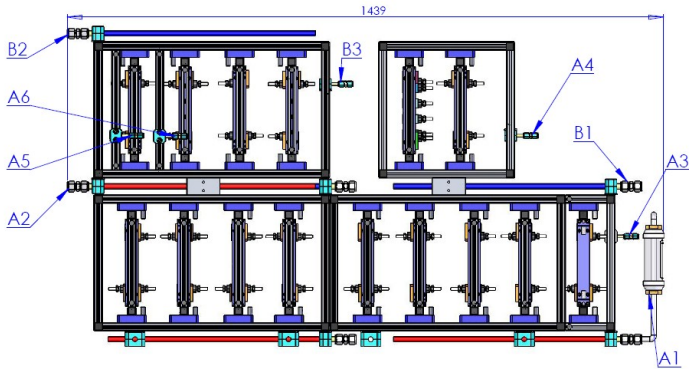
Safer processing
Diasteroselective Ritter reaction



- Efficient mixing and heat transfer performance
- Minimal reactant inventories
- No local over-concentration of H_2SO_4 and CH_3CN
- Increased production capacity and productivity
- Operating conditions easily managed
- Conversion reproducibility
- Constant quality
- Safer operation

- 1 multi-injection module (CH_3CN + H_2SO_4)
- 1 residence time module (AcOEt)
- 1 single-injection module (NaOH)

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Cost breakdown for 300 T/years

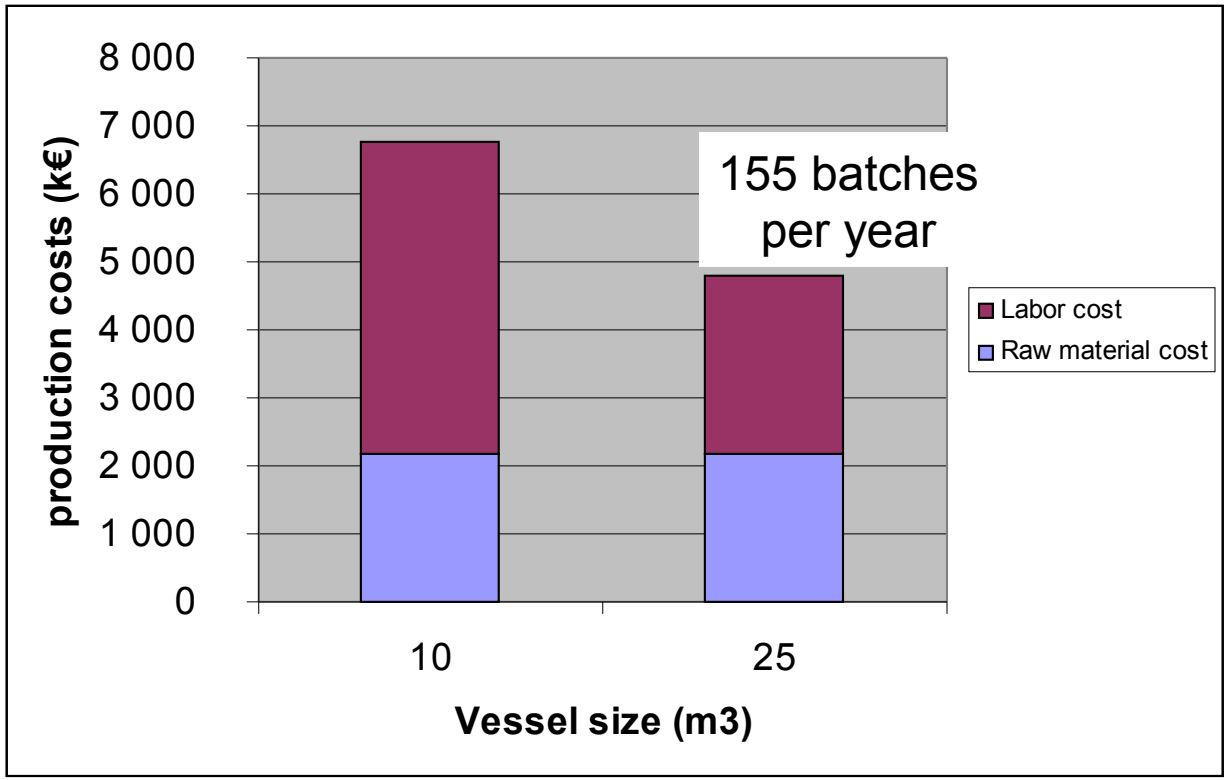
Data for 10 m³ vessel

Raw material per batch

Substrate: 1100 kg
Acetonitrile: 1469 kg
Acetic acid: 5797 kg
Sulfuric acid: 1820 kg

Labor cost per batch

Vessel charging: 4 h
Heat-up time: 2 h
Addition of Sulfuric acid: 8h
Addition of water: 8 h
Neutralization: 12 h
Cooling time: 4 h
Filtration time: 12 h
Reactor clean down/drying: 16 h
Total labor: 66 h at 200€/hour



Substrate costs are not included

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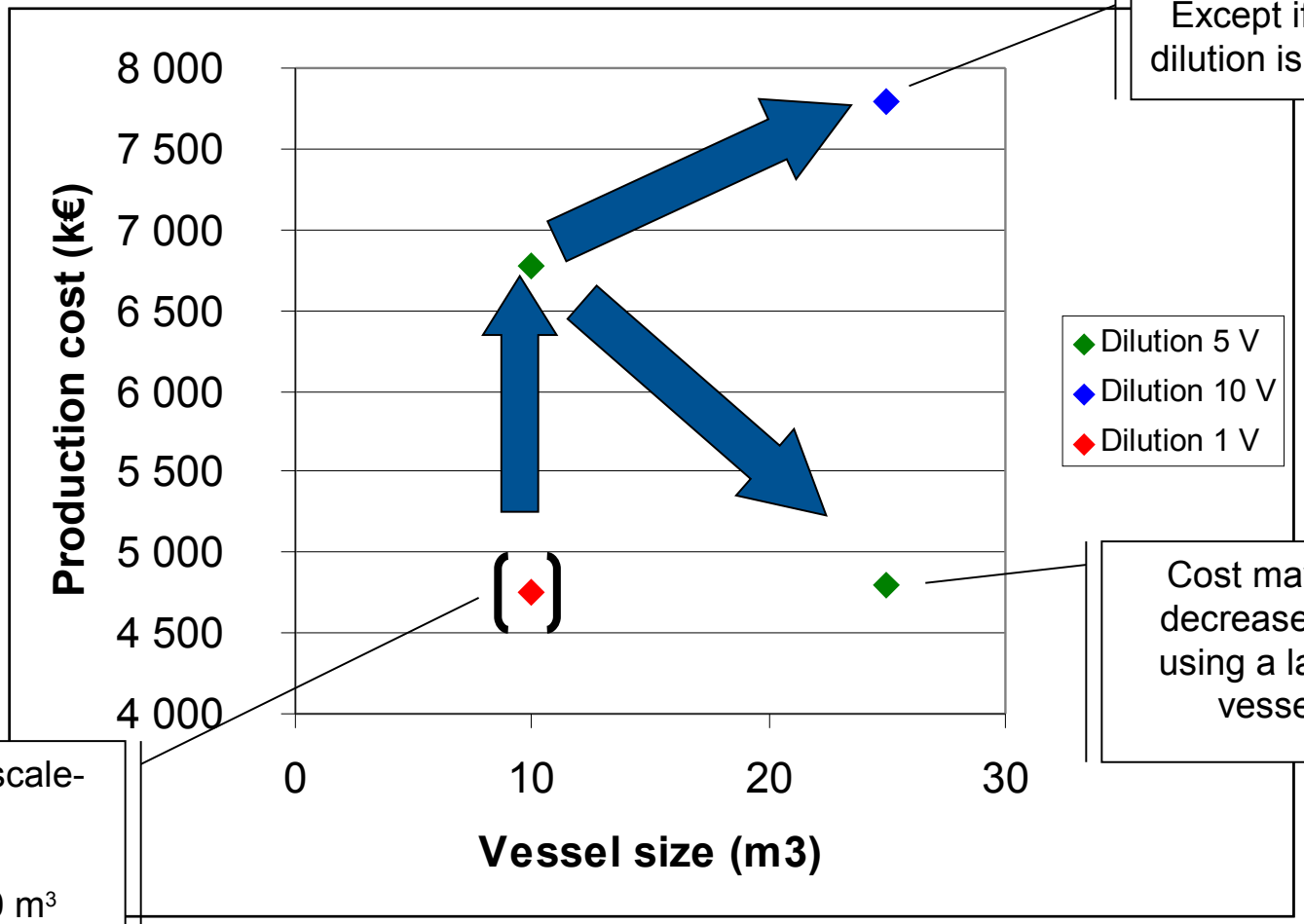
Heat exchange impacts manufacturing cost through vessel size and dilution



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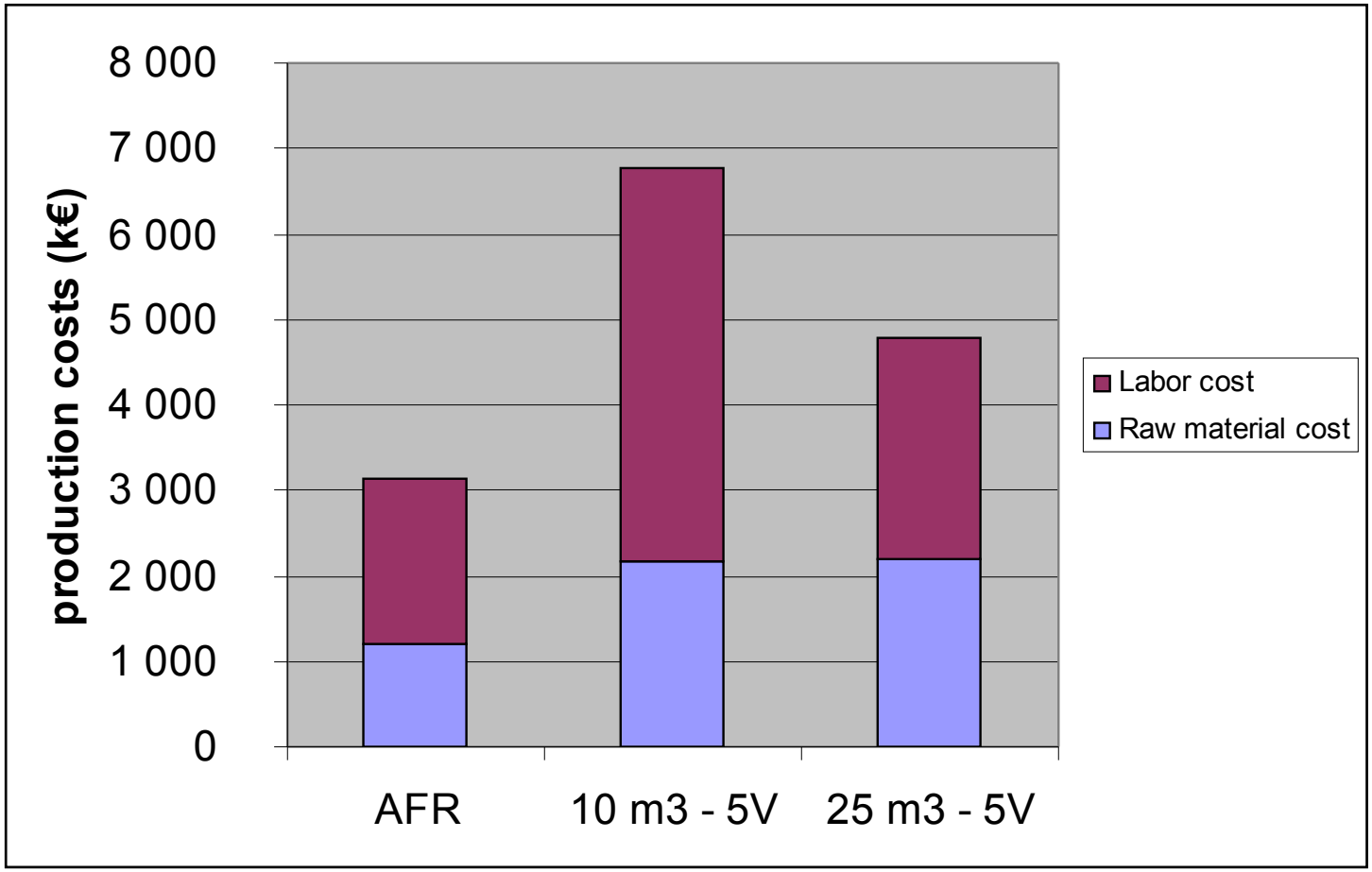
With AFR, the process is run at the lowest dilution



Assumption: AFR labor cost = labor cost for 25 m^3 vessel at same dilution

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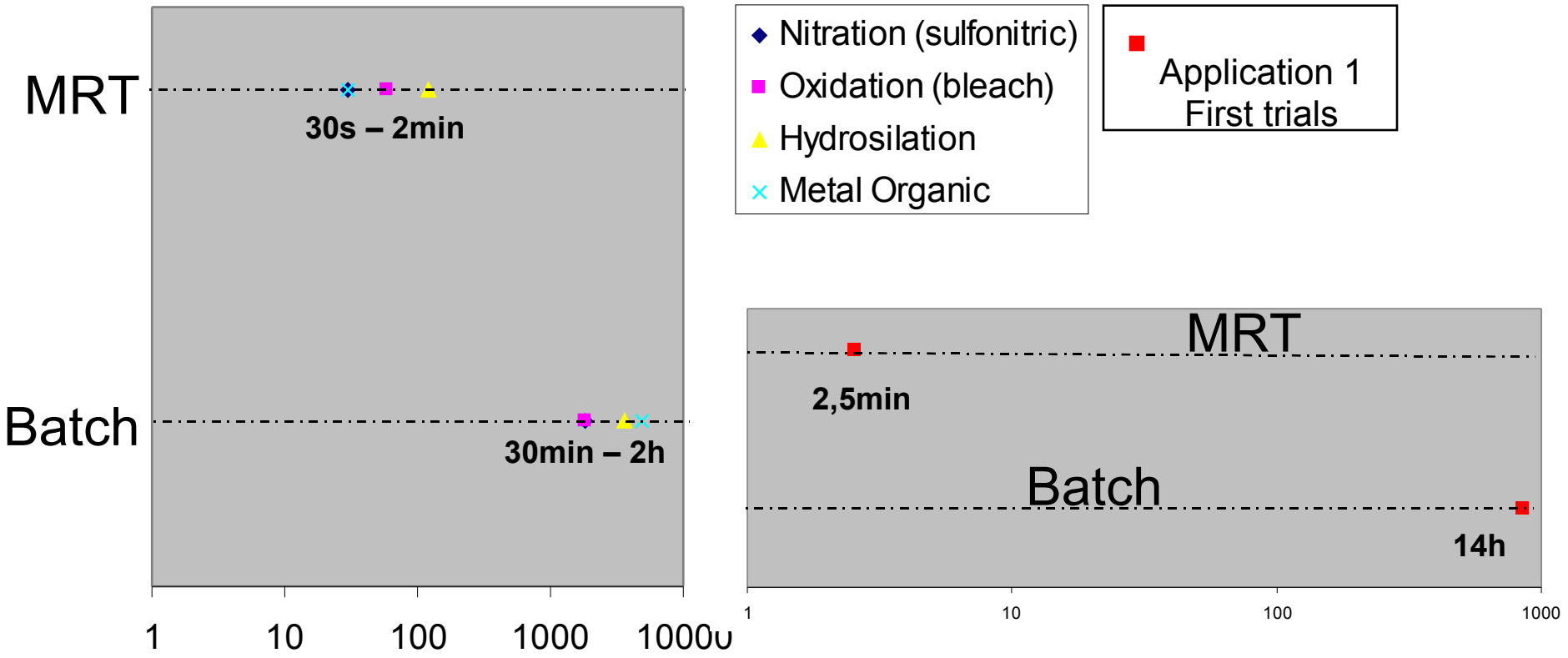
Batch vs MRT – Reaction time



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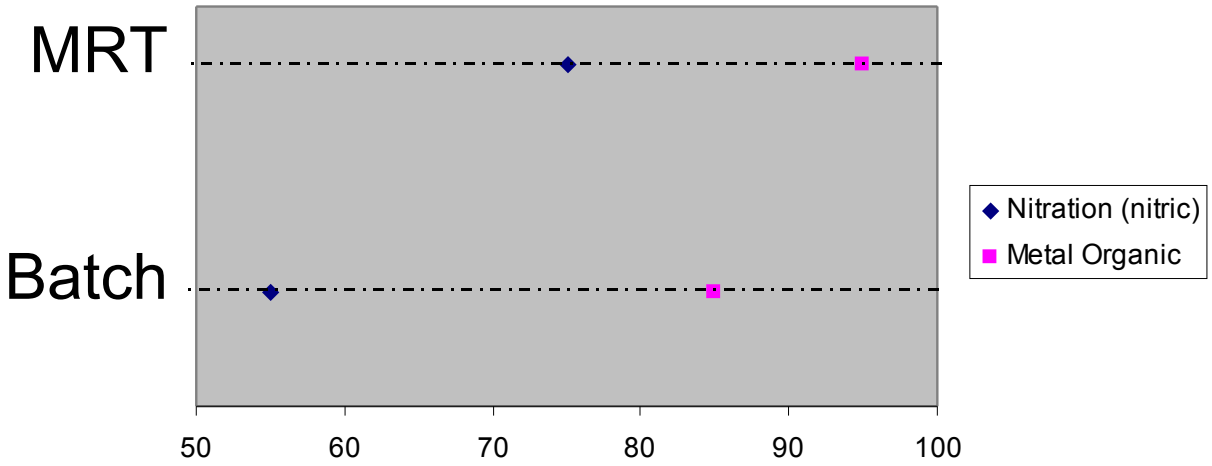
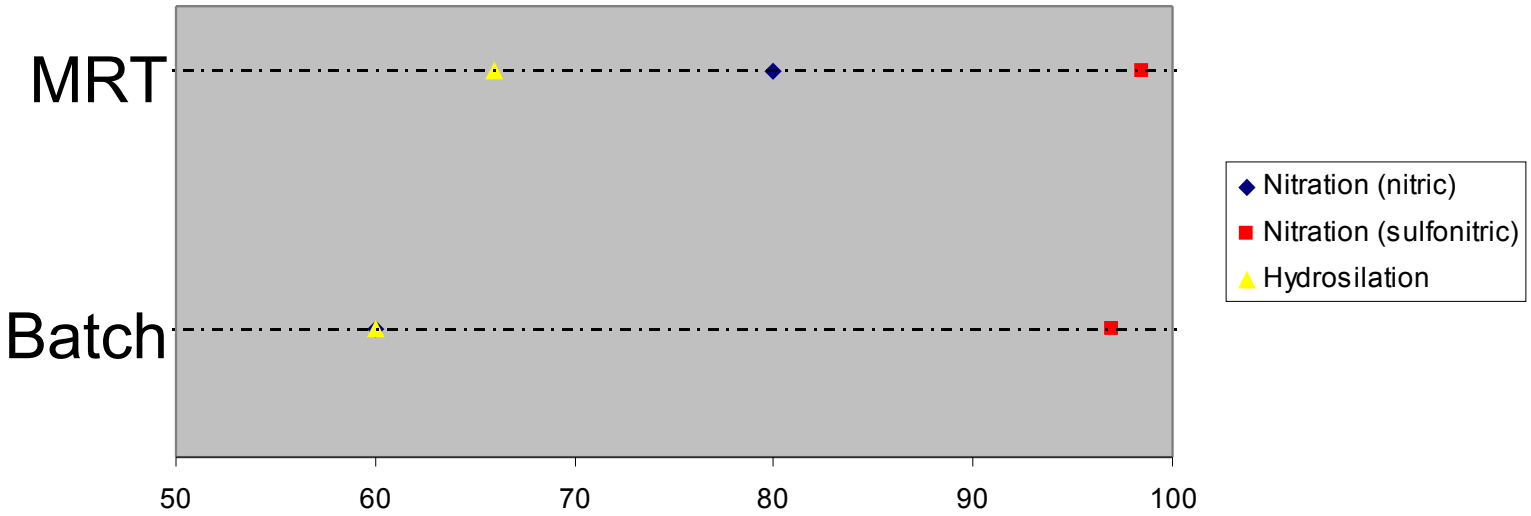
Batch vs MRT – Yield and Purity



Yield (%)



Purity (%)

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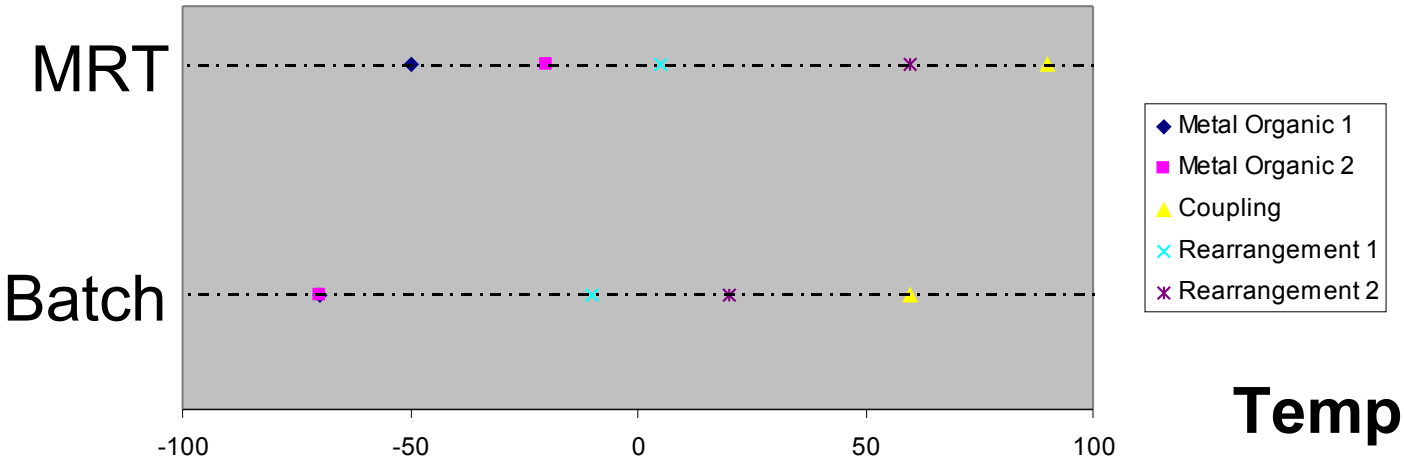
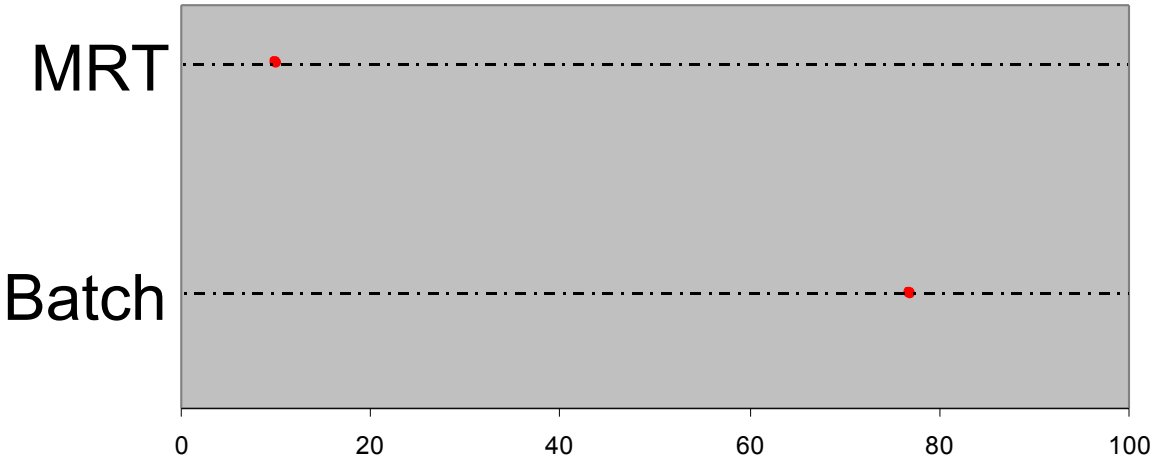
Batch vs MRT – Temperature and Solvent



Temperature (°C)



Solvent ratio (wt %)

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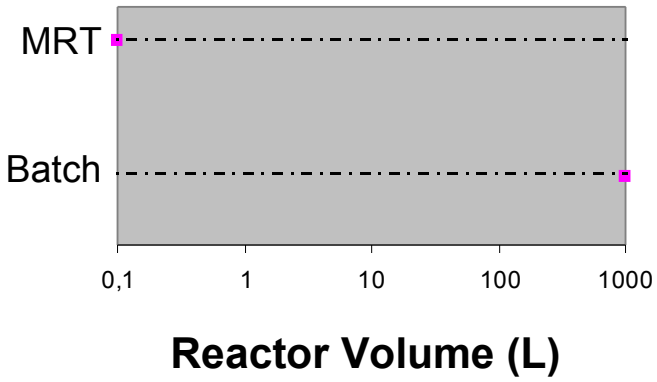
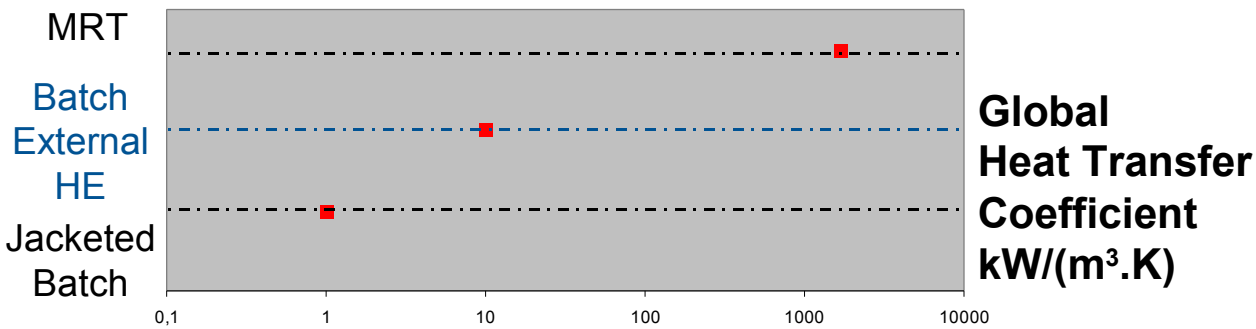
Batch vs MRT – Safety

END-USER CASE	CONVENTIONAL TECHNOLOGIES	CORNING Reactors
Oxydation with bleach	Scale-up issues Hazardous reaction	Safer operation
Coupling in presence of sulfuric acid	Initial reaction mixture at 60°C dumped into a quench solution	Operation always under full control at 90°C
Autocatalytic nitration	Acculumation risks No scale-up possibe	Safer operation
Nitration reaction	Dedicated equipment	Safer operation





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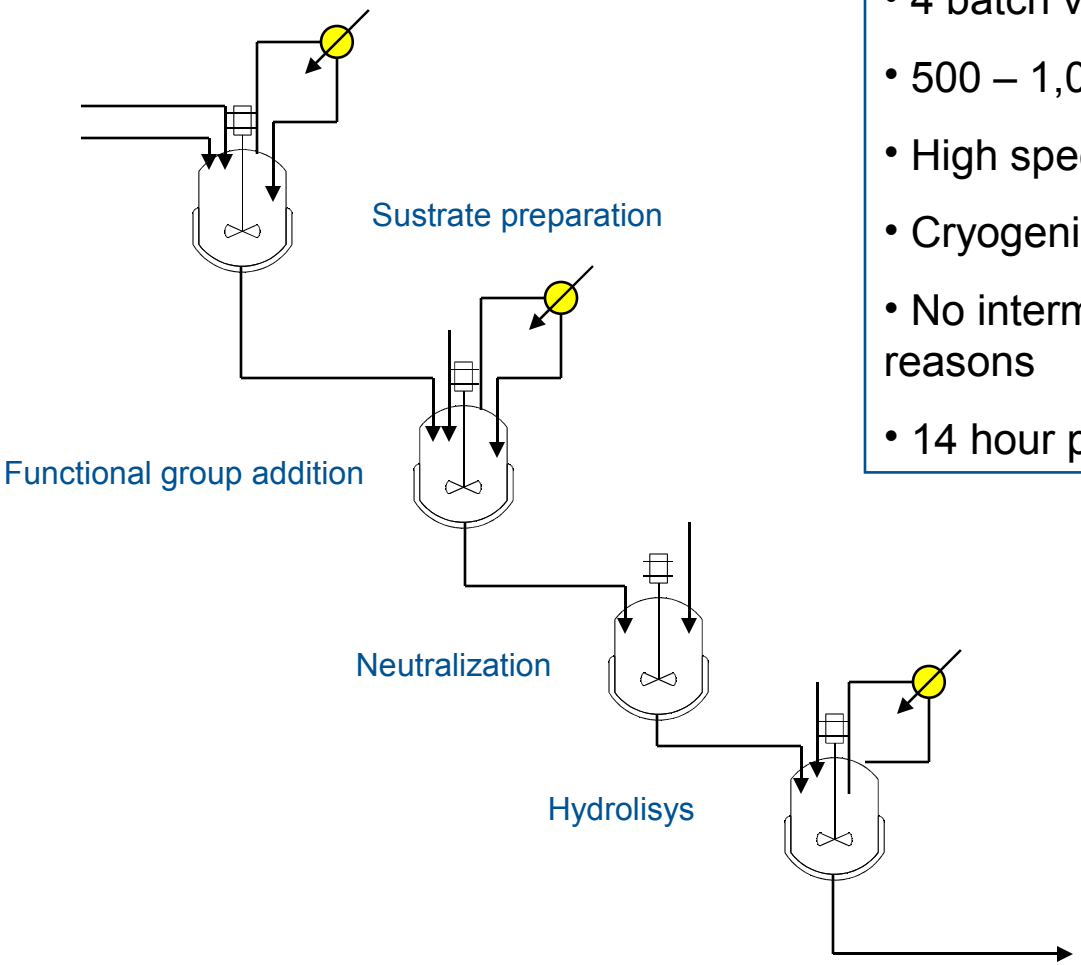
Batch process example with one API step



- 4 batch vessels in cascade with concrete structure
- 500 – 1,000 liter vessel limitation
- High speed agitation and reflux system
- Cryogenic batch vessel at step 2
- No intermediate storage allowable for safety reasons
- 14 hour process

Process Data

- 40 % yield
- 35:1 solvent-substrate ratio
- impurity: 5%

➢ distillation

➢ crystallization

Expensive!

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Same reaction using the Advanced Flow Reactor

- 2 banks AFR (1800mm x 600mm x 2200mm)
- 900 kg total weight
- 6 pumps for step 2, 2 pumps for step 1, 1 pump for steps 3 and 4
- Distribution system, PLC controlled
- No cryogenic system required
- 70 sec residence time

Process Data

- 55 % yield
- 14:1 solvent:substrate ratio
- impurity: 2%

➢Distillation step ***eliminated***

➢ crystallization with 50% lower solvent content

BIG cost savings

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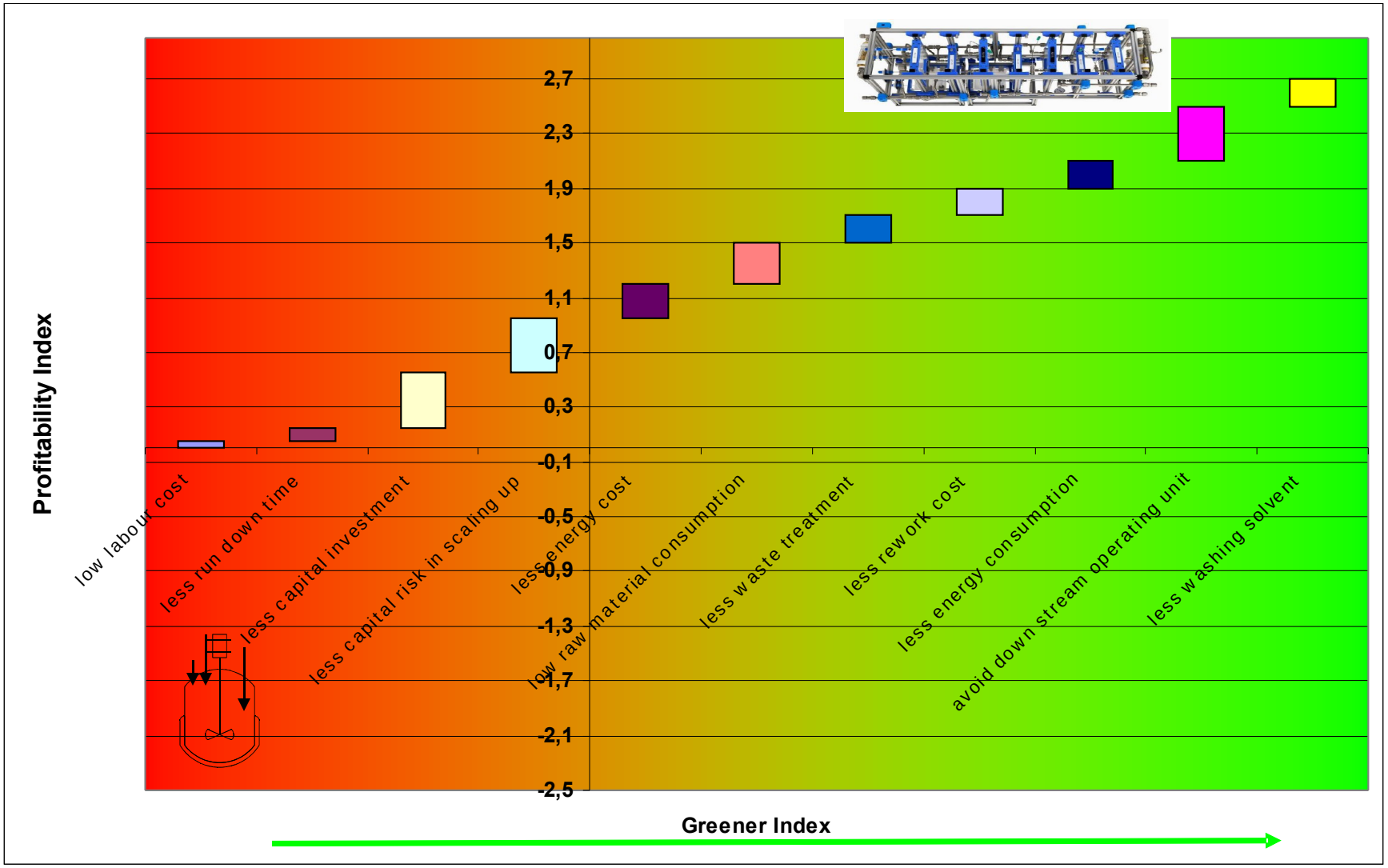
Advanced Flow Reactors: Greener and More Economical



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