Data requirements for reactor selection

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What is my best option for manufacturing scale?

- Microreactor
- Mesoscale tubular reactor
- Tubular reactor
- OBR (oscillatory baffled flow reactor)
- Spinning disk
- 1 $\rightarrow$ n CSTRs
- Recycle flow reactor
- Bubble column

- Batch or semi-batch

Why PI

Most fine chemicals processes can be carried out in batch mode

Operating in batch mode often results in serious compromises to performance

PI devices can be very efficient but in a narrow ‘operating window’

So -

- Realistic choice of PI equipment requires that we define the operating characteristics of equipment

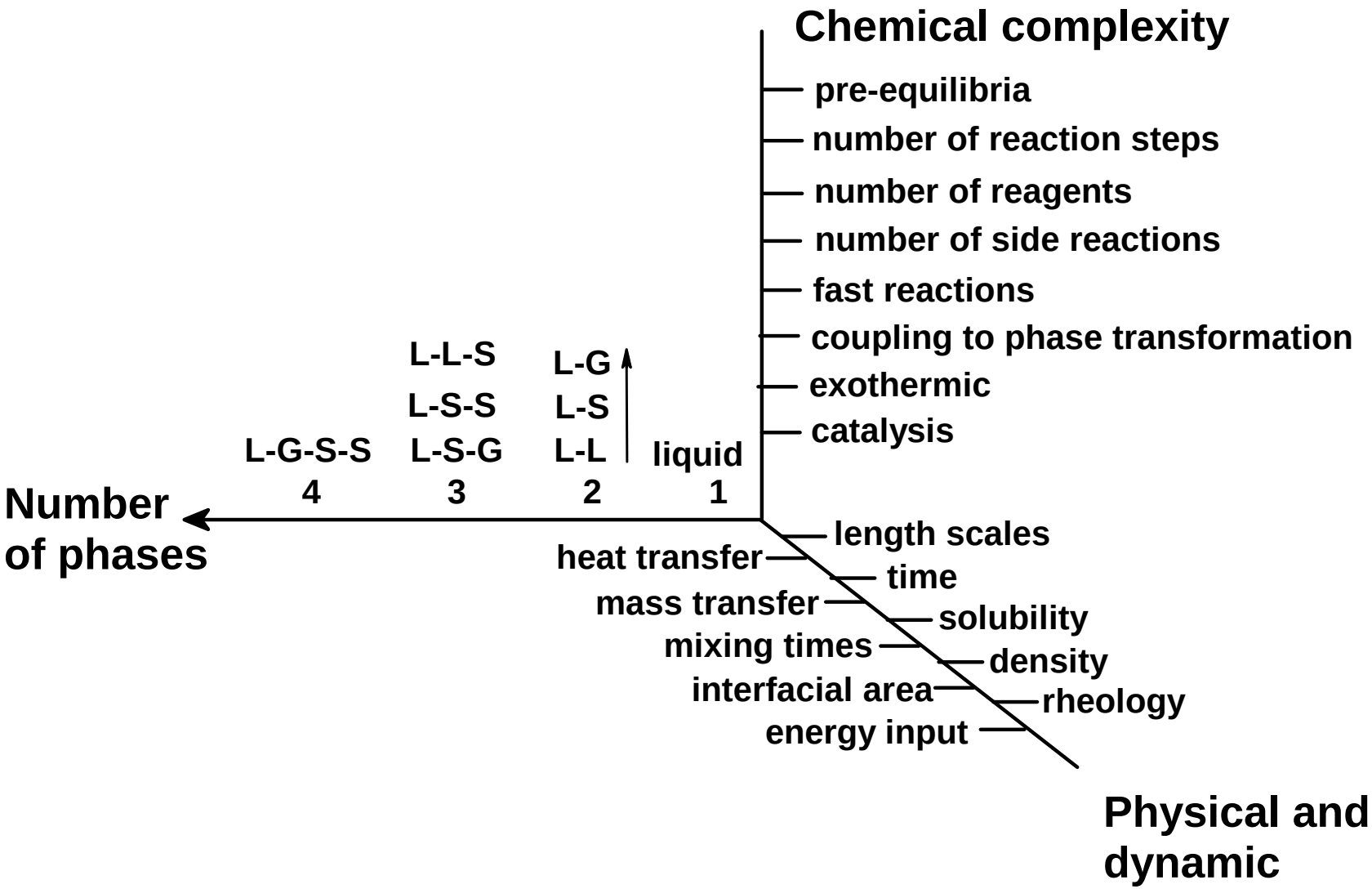
- To choose equipment need to understand
  - process requirements
  - equipment characteristics

What do we need to know about the process?

Depends on the process

- The more complex the process,
  the more information is needed

Process Complexity



Phase characteristics
– fine chemicals manufacture

Of 47 processes surveyed:[ref]

~40% had at least one solid phase present during reaction

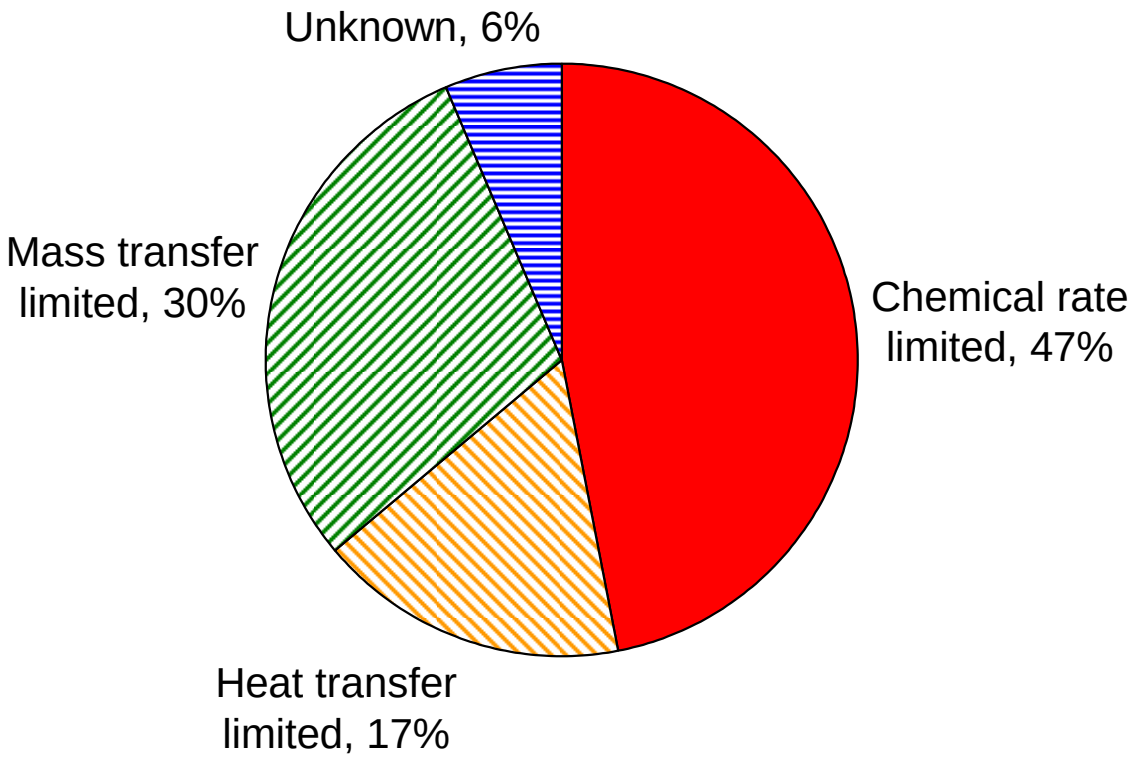
~25% had two or more liquid phases present during reaction

~20% involved a gas phase as reactant, product or purge

~ 60% involved feeding a reactant that was insoluble in the reaction mass

Ref: JH Atherton JM Double, B Gourlay, paper presented at World Congress of Chemical Engineering, Glasgow 2005.

Residence time
Mass transfer
Heat transfer
requirements



Of the chemical rate limited processes, about 40% had residence times less than 1 hour; 15% less than one minute

From: JH Atherton JM Double, B Gourlay, paper presented at World Congress of Chemical Engineering, Glasgow 2005.

Overview of data requirements

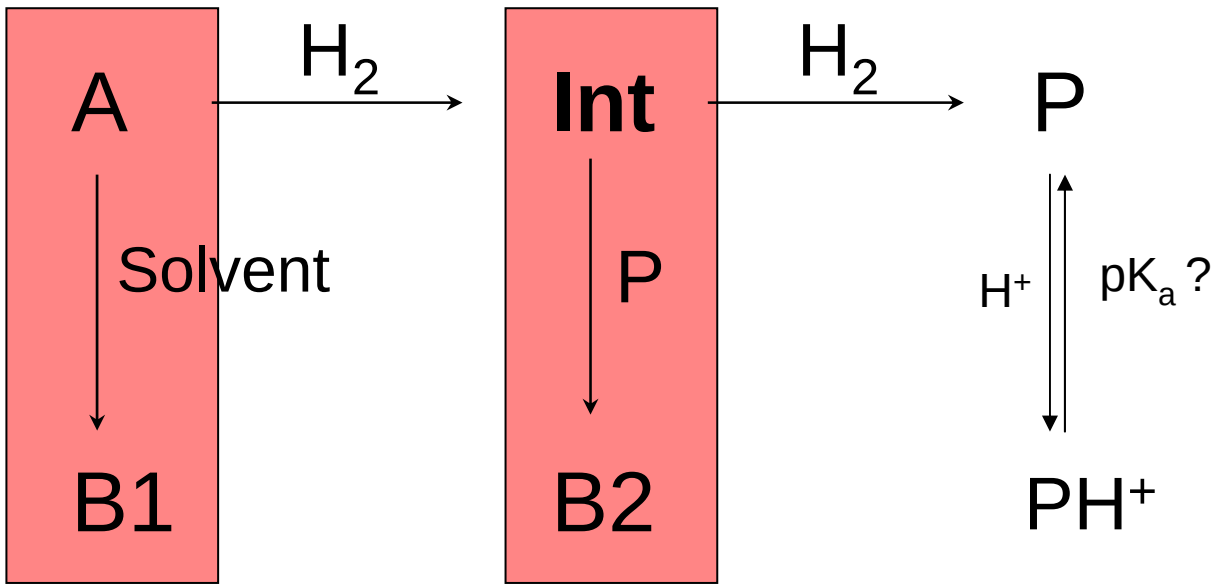
- Phase characteristics
- Kinetics
  - chemical
  - coupled physical processes
- Physical properties
- Thermochemistry

Phase characteristics - question

- What are the phase characteristics of your reactants, starting materials and products

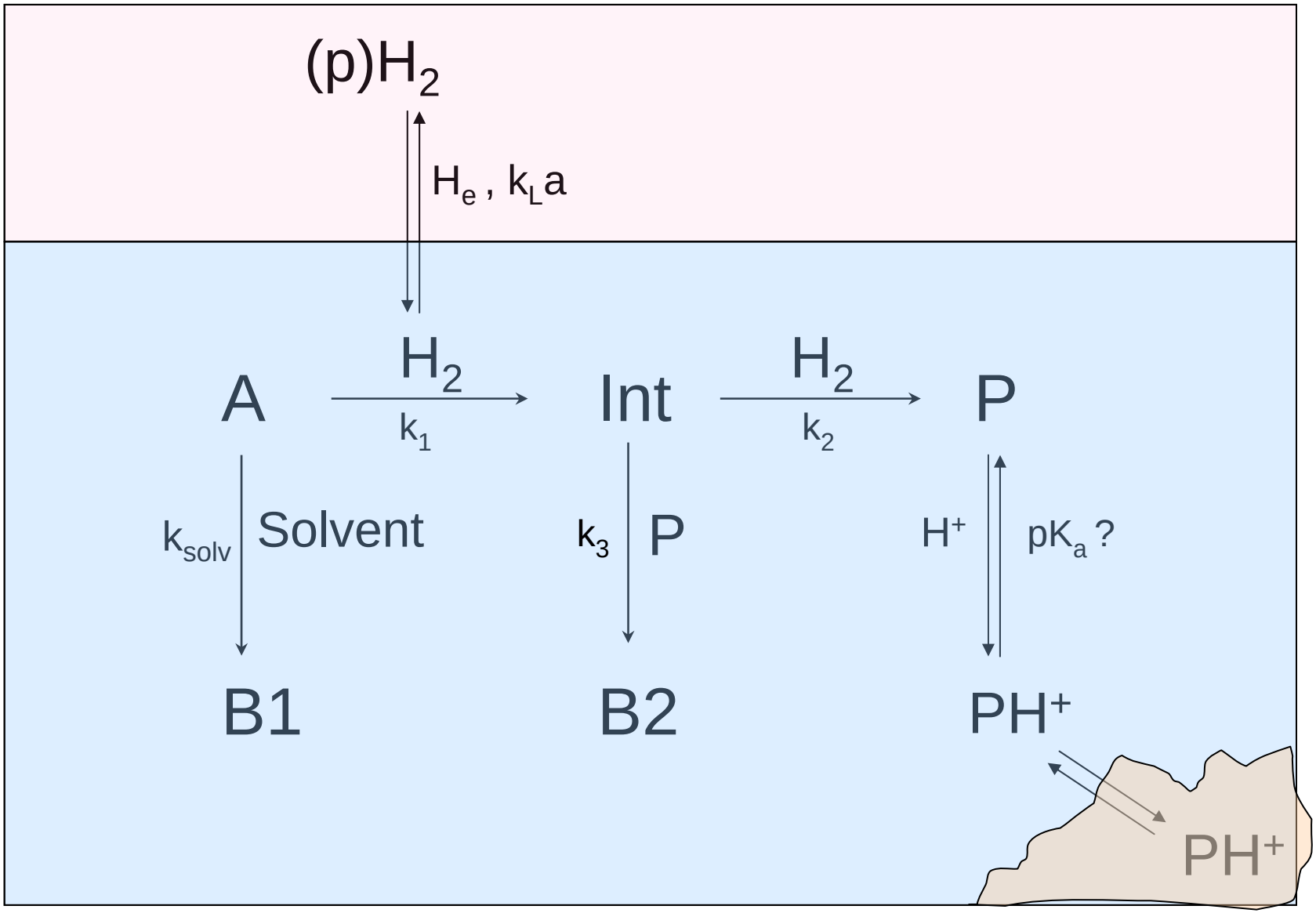
Chemical reaction scheme

A picture of the relevant chemistry with (if relevant) ionic equilibria and competing processes is needed to select the appropriate reactor configuration



Use to identify ‘branch points’ in the reaction scheme

Reaction picture



Some chemistry questions

- How fast are the main and side reactions
  - What is the required residence time in the absence of heat and mass transfer limitations
- What are the important side reactions?
- Are any protonation equilibria involved that influence the rate or selectivity?
- What is the heat of reaction

  (highly exothermic reactions are often sensitive to the mixing method)
- Is the selectivity sensitive to how fast the reactants are mixed?
- Are there any enforced reagent stoichometries
  - the hydrogenation example

Physical properties

- What are the rheological properties of the reaction mass?
  - pipe pressure drop is viscosity dependent
  - shear thinning fluids can be a big problem in pipes
- What are the heat transfer requirements?
- What are the mass transfer requirements?

Multiphase reactions

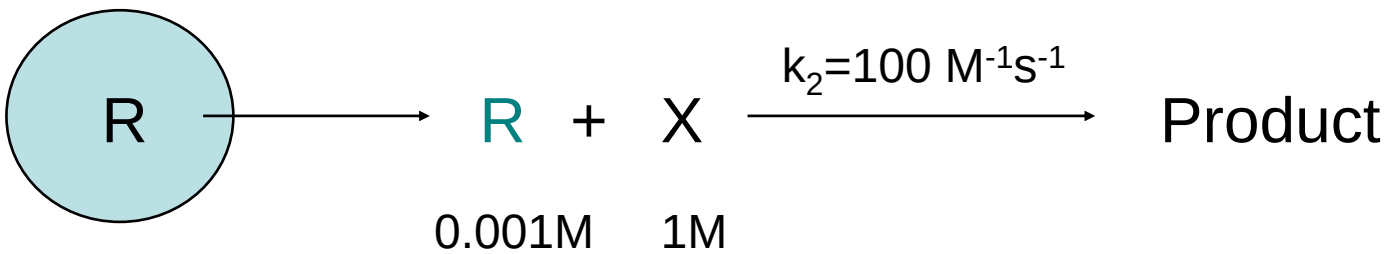
- The overall rate will be a function of both the chemical reaction rate and the mass transfer rate.
- The nature of the overall rate function depends on how the two processes are coupled.
- At the extremes:
  - fast reactions with low solubility reactants have rates proportional to interfacial area (in-film reactions)
  - slow reactions with good co-solubility of reactants have rates proportional to the volume of the phase in which reaction occurs
- to select a reactor it is necessary to understand these aspects of the process

Problems with poorly soluble reactants

- Reactions where the chemistry is intrinsically fast can be overall very slow if one or more components has low solubility, e.g.

‘Acylation’ of a poorly soluble amine in an aqueous system

Batch process – cycle time 5 hours



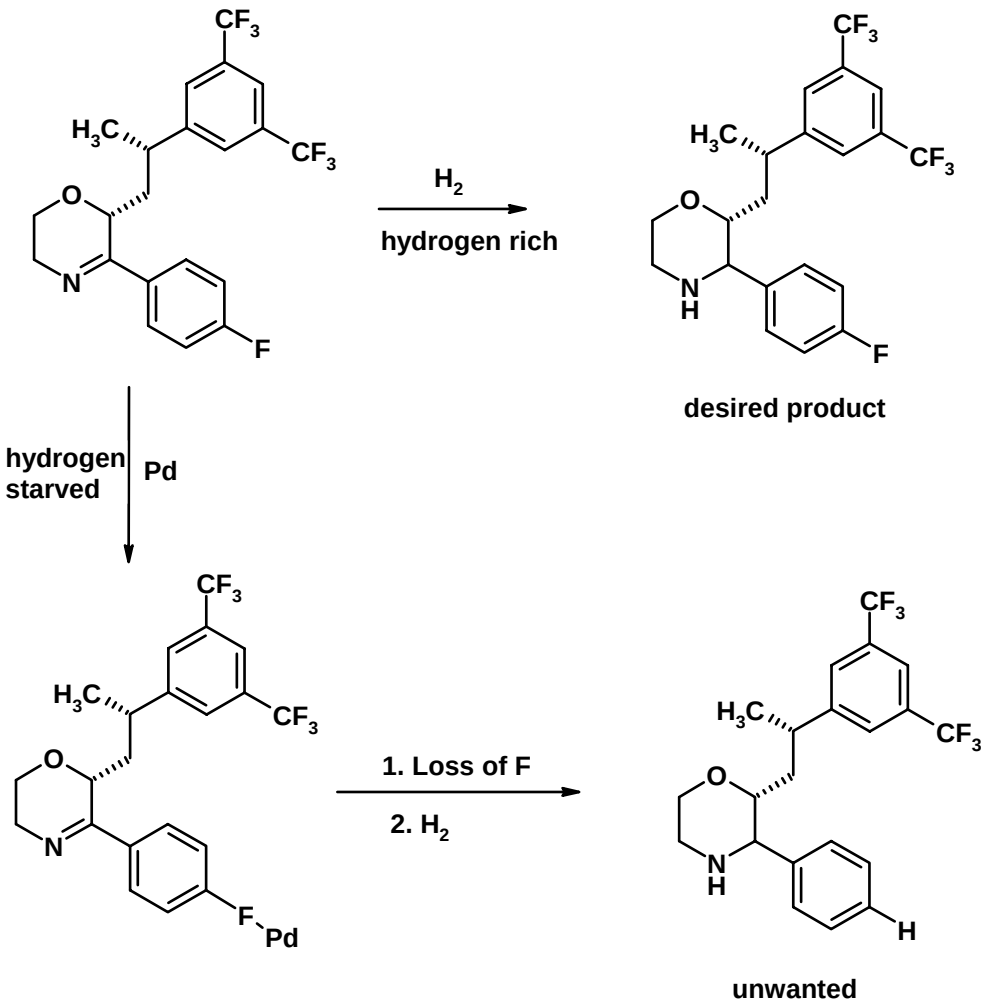
Laboratory continuous process, high shear mixer as reactor – residence time required was 2 minutes

Mass transfer

- mass transfer requirements need to be defined – now becoming recognised as ‘best practice’ in pharma development

- can impact on selectivity as well as rate

Influence of mass transfer on impurity formation



The process was improved by:

- reducing the catalyst loading
- increasing the hydrogen pressure
- improving the agitation

Merck Research, NJ, OPRD **2006**, 10, 109 -117 (10 authors)

Overview of data requirements

- Phase characteristics
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to permit logical selection of appropriate PI device

Some challenges

Methodology

- selection protocol involving identification of
  - **process requirements**
  - equipment capability

Development of techniques for controlled feed of solids to continuous reactors.

and finally -

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- Offers expertise in chemical process ‘systems analysis’ and in chemical and physicochemical data acquisition
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