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IMPULSE

Integrated Multiscale Process Units with Locally Structured Elements

Integrated Project (IP)

Thematic Priority 3: Nanotechnologies and nano-sciences, knowledge-based multifunctional materials and new production processes and devices (NMP)

The
BIG BOOK
Of

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Contents

1 Introduction

IMPULSE is an acronym applied to a European Framework 6 research project and stands for Integrated Multiscale Process Units with Locally Structured Elements. Implicit within this title is the view that local structure can be beneficial but that not all process units will be equally structured. Member organisations are listed in Annex 1 below.

1.1 Manufacturing Sectors Addressed

The manufacturing sectors studied within IMPULSE have been the pharmaceutical, specialty chemicals and consumer goods sectors. These sectors are characterised by low volume (10's of kilograms per year through to low 1000's of tonnes) and high added value products. While some products are manufactured using continuous processing, most products are manufactured in batch processes in relatively standard equipment and typically process development activity seeks to fit processes into this typical equipment configuration rather than meet the needs of the process/product. A key business driver for these sectors is frequently time-to-market, driven in the pharmaceutical sector by the desire to maximise the value derived from patent protection through to the short product life and by rapidly changing market needs in the consumer goods sector. It is, in part, this business driver that causes these industries to focus their process development activities and manufacturing equipment in this way.

To achieve the benefits in process efficiency available to some processes through the application of microscale facility, it was necessary to develop a methodology which facilitates adoption of new processing options without adversely impacting on time-to-market.

While the methodology developed is particularly directed at these sectors, it is anticipated that the methodology may also be of value in other sectors of the chemical industry.

1.2 Document Purpose & Target Audience

The IMPULSE project has generated several hundred pages or reports, each of which is presented as a standalone document at the level of development in place at its time of generation. These reports represent isolated parts of the methodology, many containing references to preceding deliverables. No single document provides "ready to use" guidelines.

This document seeks to provide a coherent and easily accessible description of the entire methodology to facilitate immediate deployment by experienced process technologists. It is not and cannot be a full design procedure and the process technologist must rely on his previously gained learning and experience. This will be particularly the case for macro- and meso- scale equipment, as much of the more detailed equipment work within the IMPULSE project has been deliberately biased towards micro- scale equipment to address the relative lack of dependable information available to most process technologists for equipment at that scale.

While this document is addressed to the process technologist, it is essential that the process technologist understand that the approach advocated requires the involvement of a whole business team, bringing together a broad range of technical and commercial expertise. All decisions must be taken in a business context by an appropriate team involving inputs from a range of disciplines and taking a balanced view of the requirements of stakeholders. While the methodology addresses mainly the technical decisions within an investment and it is expected that in these aspects the process technologist will have a key role in the decision process. For ease of reading, only the process technologist will be mentioned in most of this document, but at all times the process technologist must recognise that the **involvement of the business team is essential** to achieving an effective business output.

Because of the multiscale approach advocated by IMPULSE, the same considerations and decisions are required regardless of scale – i.e. the methodology itself is scale independent. In many instances, the overall methodology described will set out "what" needs to be decided by the process technologist and business team, but the process technologist and business team should use their experience to determine the appropriate specific method to reach that decision. Only where a new specific method has been developed as a result of IMPULSE activity will sufficient detail to follow it be set out in this document. Where existing methods have been evaluated for suitability as part of the IMPULSE activity, outline information will be provided on the evaluated methods together with references to each method. Whether a specific method has been developed as part of IMPULSE or is recommended by IMPULSE, the process technologist and business team should still consider whether it is the most appropriate method for their particular situation.

1.3 IMPULSE Vision

The vision of IMPULSE is "to match process systems to the needs of the process, commerce and society – precision processing" in order to:

- enable new business models and enhanced sustainability through more efficient, inherently safer processing, distributed manufacture etc.
- achieve step changes in manufacturing capability by exploiting micro- and meso-structured components, control and instrumentation techniques
- deliver [potentially more extreme] conditions very precisely to open opportunities for the delivery of new, previously inaccessible high value products
- develop and transfer new “multiscale” approaches to process development and design to enable technologists to deliver the benefits

IMPULSE aims at effective, targeted integration of innovative process equipment such as microreactors, compact heat exchangers, thin-film devices and other micro and/or meso-structured components, to attain radical performance enhancement for whole process systems in chemical and pharmaceutical production, thereby contributing to significant improvement in supply-chain sustainability for the chemical industry.

Whereas complete miniaturization or intensification of entire process systems is unrealistic and economically prohibitive, the multiscale design approach of IMPULSE provides intensification locally only in those parts of a process and on the time and length scale where it is truly needed and can produce the greatest benefit.

The IMPULSE approach represents a true paradigm shift in chemical process engineering: Rather than adapting the chemical synthesis routes and process operating parameters to be compatible with equipment limitations, IMPULSE adapts the equipment, structure and process architectures themselves in order to create locally the most desirable conditions for a given physico-chemical transformation.

1.4 What Is Meant by Structure?

Clearly, all objects have structure, whether planned or not. In chemical processing, a simple example would be the use of random packing or structured packing in distillation.

Strictly, it would not be true to say that the random packing is unstructured, as any particular installation will have a structure which could, in principle, be measured and mapped. However, even for installations that are intended to be the same, each installation using random packing will be different from the others at the detailed level of analysis – such a system can be considered to be unstructured. This is despite the fact that normal distribution of the random structure means that the performance of a specified depth (the height equivalent to a theoretical plate) will be broadly similar between installations. In the case of the use of structured packing, installations intended to be the same will be identical within the manufacturing tolerances. It is this use of a defined, designed structure which means that the height equivalent to a theoretical plate in structured packing is significantly smaller than in random packing.

In that sense, a structured object is one which has designed dimensions to deliver a closely defined process need. The scale of structure required depends on the process need. Scale of structure will be used when referring to a physical dimension whereas structure will always refer to the process need.

1.5 Why Employ Structure?

The benefit of local structure can be seen by considering that most value added operations in the chemical process industries occur at a molecular level - whether this be an intramolecular reaction, the bringing together of two molecules for an intermolecular reaction or the movement of a molecules relative to each other to achieve a lower energy state either to achieve the separation of dissimilar molecules or the arrangement of molecules (similar or dissimilar) into a defined structure. Such molecular interactions are influenced solely by the conditions local to the molecule(s) involved and not by any equipment dimension. However, local conditions are determined by mass and energy movement within equipment through convection and/or diffusion. Optimal process performance will be achieved where all molecules experience the same history of local conditions and uniformity of local conditions is most readily achieved at small scale or high structure. As a purely technical concept, reduction in scale or increase in structure is usually technically beneficial, although the business benefit of reducing scale/increasing structure may be negligible or negative (see Figure 5-3 below[1])

1.6 What is Multiscale?

A multiscale facility will employ equipment with different scales of structure – i.e. the characteristic dimension of different equipment will be different. While a facility may include equipment with different scales of structure, all of the equipment may be structured in the sense that it offers the designed dimensions required to meet the process need.

1.7 Why Multiscale?

The research work undertaken within the IMPULSE project is directed at the process technologist operating in a commercial environment. Commercial decisions and hence adoption of “solutions” by industry lie not in the technical superiority of one technology over another but instead rely on the commercial benefits afforded by such technologies in a business context. Decisions on scale require a balance between the benefits of increased structure and the problems which may be associated with it. In the general case, it is unlikely that all process operations within a single supply chain will achieve an acceptable balance between the benefits of increased structure and the associated problems at the same scale of structure. As a result, most processes will inevitably be multiscale to some extent.

Although Process Intensification (PI) has been the subject of much research activity over several decades, the uptake of such technology has been disappointingly slow. Contributory factors include:-

- A tendency to focus on technical benefit rather than business benefit
- A lack of a clear methodology to define when increased structure is beneficial
- A lack of a methodology to incorporate different levels of structure into a single process

It is acknowledged that at those examples of uptake which do exist have addressed these factors to some extent, but they have been addressed by local teams working on individual processes rather than with the ambition of developing a generic methodology.

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[1] In this context, conduction is considered as diffusion of energy.

2 Definitions

An **Investment:** is the commitment of time, resource or money to implement a change in product, process, equipment and/or facility to satisfy business drivers.

A Retrofit: is a change in product, process or equipment to satisfy a change in business driver in fixed facility.

Batch Processing in this document refers to both true batch and fed batch processes. Most so-called “batch” processes in industry would more normally be described in academia as “fed batch” or “semi batch” where one process material is added to another. This is necessary in most so called batch processes to maintain process control and avoid runaway rather than the option of the excessive dilution that would be required to minimise the adiabatic temperature rise of a true batch system. In the true batch case, materials are charged when required by the process with no control of rate and no material is removed until the end of the process. The common industry practice of using batch processing to refer to both is used throughout. Where statements are particular to true batch or fed/semi batch[2], this will be clearly stated.

Environment, Health and Safety employ the definitions below

- *Environment:* “Any effect that a process can have outside the boundary of a site or plant (e.g. VOC emissions, water waste, noise pollution etc)”. Recommended metrics include mass intensity, reaction mass efficiency. Examples for consideration include costs of: waste disposal, compliance with environmental regulations (e.g. Seveso-directive, air emissions) rehabilitation of polluted water or soils, as well as investment related to additional treatment or abatement equipment, should also be taken into account.
- *Health: “*Any effect that the chemicals used in a process can have on the health of the workers (i.e., occupational health) involved in running a process”. Here the main focus is on the comparison of adverse material properties which may have impact on the operators at normal operation. Additional areas include protection measures required for deviation from normal operation and current regulations on protection of workers.
  Any impact on the neighbourhood is not discussed here. It is assumed that the relevant masses are mainly related with storage and make up of product, solvents, running the process itself and waste handling.
- *Safety – routine process operation: “*Any effect that the routine running of a process can have on the health of the workers involved in running the process excluding effects from the chemicals themselves”. E.g.: what are the costs associated with routine process operation? Although there may be smaller inventory and reduced reaction time the reaction conditions may exceed remarkable known process conditions regarding concentration, specific heat release, temperature and pressure. In addition small scale variations in temperature or flow can have a significant impact on the performance of the unit. Control of the reaction conditions provokes new and more intelligent regulators as usually applied in traditional production processes. The emerging costs have to be assessed for decision making.
- *Safety – abnormal operation:* “Any effect that a process can have both inside and outside a manufacturing plant that results from a deviation from planned operating parameters.” A detailed risk assessment is usually not available at the early stage of decision making so some ranking in expected costs on additional protection measures must be evaluated at this point. The impact / severity of any incidents or accidents should also be taken into account here.

Intrinsic Scale Requirement: is defined as the geometry of the flow fields which precisely delivers the process needs

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[2] Note that semi-batch can also mean a process where part of the process in continuous, and part of the process is batch (e.g. feeding materials into a static mixer and plug flow pipe reactor for short residence time before charging to a batch stirred tank reactor to complete the reaction and then undergo work-up).

Scale of Structure: within a device is defined based on a physical dimension. IMPULSE proposed the definitions below:

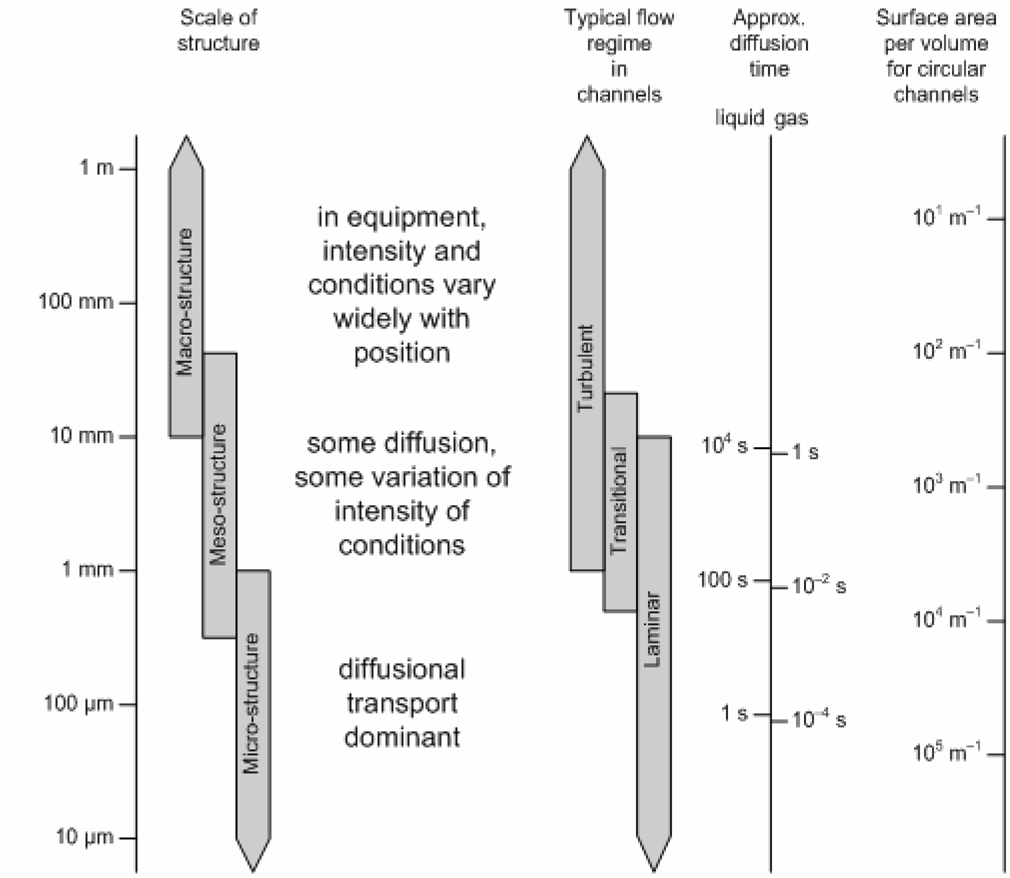

Figure 2-1 Scale of Structure

An Appropriately Structured Device: is then one where the geometry of the device and / or the flow fields in it are designed closely[3] to meet specific processing needs. Under this definition a microreactor whose heat transfer capability and mixing performance resulted in near-maximum reaction selectivity would be seen as structures, while a stirred tank for the same reaction where there was significant yield loss due to local exotherms and poor mixing would be seen as unstructured. However, for a simple process where a stirred tank could deliver close to ideal conditions, the tank could be viewed as structured. In other words, structuring has to be considered **relative to the process needs.** Further information can be found in the ISO/DIN standard definitions: Micro process engineering - Terminology (ISO/DIS 10991:2008) which gives terms and definitions for micro process engineering applied in chemistry, pharmacy, biotechnology and food technology.[a]

Multiscale: highlights the expectation that the intrinsic scale requirement of individual process elements within the overall process system may differ considerably. A facility designed to satisfy the aspiration proposed within IMPULSE **"*To match process systems closely to the needs of the process, commerce and society –"precision processing"*** will almost inevitably contain equipment with different scales of structure

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[3] In this context we need to note that the match may not be precise; "**closely"** simply has to be close enough to deliver performance that meets the objectives. There are several reasons why we do not aim for a precise match.

- The change in performance with scale will likely be one-sided – for example reaction yield may improve with reduced mixing time until the mixing time becomes low enough that further reductions have no impact. Here, it is simply enough that the mixing time is low enough.
- The benefits from a precise match may be insufficient to warrant the cost of delivering it.
- Operability and durability concerns (e.g. in a corrosive system) might make the use of a device undesirable and favour a compromise of the geometry to ensure robustness.
- The precise matching of length scales for different operations across a whole process might be feasible, but the exchanges between length scales along the process chain might be impracticable. Compromises might be required to produce a viable whole process or plant layout.

Scale Out: is a method of increasing throughput by installing a number of identical parallel items of equipment. Subject to an effective distribution system, each item performs identically. Scale out is particularly attractive because has the capability to deliver conditions identical to those investigated in the laboratory despite increase in throughput. Parallel microdevices is one example, although increasing throughput by a factor from a shell and tube heat exchanger (possibly single tube) to a larger shell and tube exchanger where the number of tubes increases by the same factor is also an example – i.e. the “scale out” concept is not unique to microscale. Scale out can be internal or external:-

> **Internal Scale Out:** refers to scale out within a device. This would involve, for example, an increase in the number of plates in a microdevice or an increase in the number of tubes in a shell and tube heat exchanger.
>
> **External Scale Out**: refers to increasing the number of devices, where the devices are identical and each device operates as a parallel stream with the same design intent.

Scale Up: is a method of increasing throughput by installing a larger device which may or may not be of the same type as previously investigated. As physical phenomena change at different rates from each other with change in characteristic dimension and pure chemical phenomena do not change at all, it is not possible to deliver an identical process environment as the scale increases. If undertaken incorrectly, scale up has the potential to deliver a significantly different process outcome from that experienced at smaller scale. However, provided that the process has been appropriately characterised and the scale up factor does not require the use of a physical dimension incapable of meeting the process needs, equivalent performance will be achieved. Note that some processes may benefit from a combination of “scale up” & “scale out”.

3 Investment Context

An opportunity to deploy multiscale technology might arise for many reasons, and even within a single business unit the underlying business case may vary greatly from opportunity to opportunity. In order to understand the role of technology in a process industry investment we can consider 4 areas. In each area we look for the advantage that multiscale processing would bring.

The product	Is the technology required to access a product that could not be made with other technologies? Could the use of structured processing enable the precise delivery of conditions that generate the required product in a way that other processing technologies could not?
Plant items	Could the use of one or more structured device(s) bring substantial benefits in processing performance – materials efficiency, energy efficiency SHE performance, etc.?
Whole process and plant design	Does the use of multiscale bring advantages in time to market, responsiveness, flexibility, reconfigurability, or overall energy and materials efficiency or SHE performance as a result of distinctive capabilities in delivering the whole process outcome?
Facility design	Does the use of multiscale bring advantages in the facility such as cheaper infrastructure, ability to use distributed manufacture, etc?

The division above recognises that in the process industries there are multiple interlinked life cycles associated with an investment – the product lifecycle, the process life cycle, the plant life cycle and the facility life cycle. For a given investment opportunity, the overall business case may draw on a number of related aspects, as illustrated below:

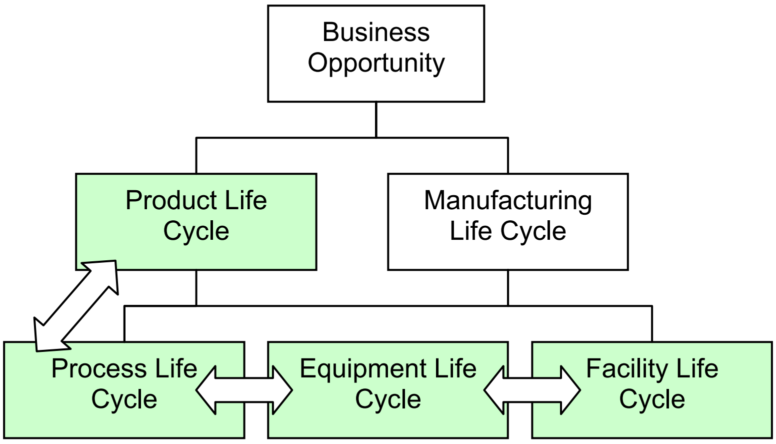

Figure 3-1 Sources of benefit from a process industry investment

Note that for a given business sector or opportunity, one or more of these life cycles may be essentially the same. For example, in petrochemicals the plant, process and product life cycles may essentially be the same – with a company using the same process to make the same product in the same type of plant for the entire duration of the investment. Equally, circumstances can be envisaged where any of the life cycles is partly or wholly independent from the others.

Where a generic process is used to produce a range of products – for example differently perfumed personal care products. Here, we might have a situation with a new product life cycle starting where the facility, plant and process life cycles are at a mature stage.

Where a conversion of batch to continuous manufacture is made, where the product may be progressing to greater maturity, and the process undergoes limited change, but the main changes are in plant and facility.

Each life cycle would typically go through a number of stages, depending on the business sector.

For a given investment it is important to be clear where it fits in each of the 4 life cycles identified in Table 3-1. Such clarity is essential to be able to scope the potential benefits of particular technology choices. For example, the investment case for retrofitting an existing plant (at low capital cost) to produce a new product is very different to that for the manufacture of an existing material more efficiently than other process options.

Table 3-1 Examples of life cycle stages in process industries

Life cycle	**Example of typical stages**
Product	Product Concept Technical Testing Consumer Testing Manufacture and sale Process modification (cost reduction / efficiency improvement) Reformulation Withdrawal
Process (whole process)	(Chemical) Route Identification and Selection Product development process (laboratory) Manufacturing process concept Process development laboratory process Pilot process Manufacturing process Modified manufacturing process (retrofitting) Closure
Plant	Plant conceptual design Plant flowsheet / basic design Plant detailed design Approval from official authorities Plant construction Plant operation Plant modification Plant decommissioning Plant reuse/redeployment or Plant demolition
Facility	Facility concept Facility design Facility construction for first set of intended manufactures Facility modification for changes to manufactures (introduction of new manufacturing processes, uprating, modification of utilities etc) Overhaul Closure and demolition

For the case where all life cycles are relevant, it is typical for three or four business level decision points to be required, though the number in any given case will depend on the situation, company policy and procedures. These are illustrated in Figure 3-1 below.

Each decision point highlights a business level to decision to commit further resources to the business opportunity.

The first indicated decision point refers to a the decision to pursue a Business Opportunity – this may be based on identification of a market need, identification of a product capability which has the potential to meet a market need, identification of underutilised plant or facility which could be employed to deliver business benefit. Having taken the decision to pursue the Business Opportunity, initial activity relates to investigation of product(s) together with process concepts which may be able to satisfy market needs and a better understanding of those market needs.

At some point, the understanding of product, process concept and market will be reviewed to support the second indicated decision point. This will result in a decision to terminate investigation of the Business Opportunity or to commit further resources necessary to a more complete process assessment together with initial plant concepts. In some sectors, the investigation of plant and process may be concurrent as the product properties may be due to the processing techniques adopted.

Still later, the understanding of product, whole process, plant concept and market will be reviewed to support the third indicated decision point. This will result in a decision to terminate investigation of the Business Opportunity or to commit to design of a plant (and possibly facility) to manufacture the product(s) to deliver the Business Opportunity.

The fourth decision point then relates to the decision to invest in the plant for manufacture of the product. Again it is imperative that the understanding of product, whole process, and market be reviewed as part of this decision.

In principle, there is one further decision point relating to the withdrawal of product and/or process. However, for the purposes of this document, this is neglected as implementation of the IMPULSE methodology will incorporate consideration of the impact of product and/or process withdrawal on the plant and facility life cycle.

It is imperative that all past inputs on market, product and process are reviewed at each decision point, as the external environment may have changed through the period in which the Business Opportunity is being pursued and these changes may impact on the value of the proposal.

These major decision points are suggested as typically these are the points at which there is likely to be a significant change in the level of commitment and at which additional specialist functions are likely to be introduced to the opportunity. As such, these decisions will generally be taken at the business level. Depending on which life cycles are relevant, some of these major decision points may be unnecessary.

Many readers will identify several other key decision points through the life of any project each of which is key to effective project management leading to the delivery of the business opportunity. While the critical importance of these key decision points is acknowledged, such decisions are generally taken solely within the active group and only referred to a business level where there is a major deviation from the position understood at the previous business level decision.

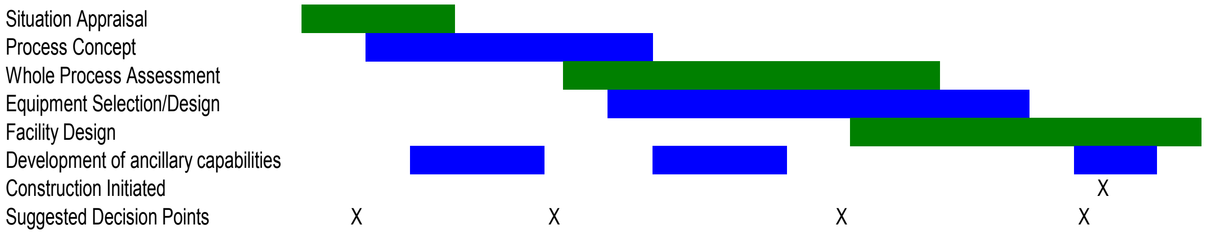

Figure 3-2 Overall Development Plan from Identification of Business Opportunity

4 IMPULSE Methodology

4.1 Project Definition

The first step in any methodology is to define the desired outcome, the stakeholders and the constraints. It must be expected that some of these will change through the life of any project, because, as the project progresses, the external environment will also be changing. For example, where a new product is being developed to meet a particular market need which is not satisfied by currently available products, the value of the product will change significantly if a competitor launches a new product to satisfy that market need or societal changes reduce or increase the market need. As such, it is essential that the assumptions underpinning the assessment of the project requirements be recorded.

Definitions are required both for the project as a whole and for each of the stages in the project and should consist of:

- The System product/output objectives – what is to be achieved? By when? By who? Using what resources?
- Definition of the stakeholder life cycle requirements (stakeholders' success criteria) – this requires the designers to decide who the stakeholders are and by talking to them find out what it is that they need, what they would like and what they do not want.
- Definition of the system boundary – what is and what is not included in the system product.
- Definition of the system interactions (inputs and outputs) and constraints.
- Definition of the system technical requirements – how the concept is to be delivered.
- Assessment of risks – identifying relevant risks and the means to eliminate or mitigate them.
- Identification of the success criteria

Note that all of these elements and particularly the constraints must be continually open to challenge. Frequently, when constraints are set, there is an implicit assumption of the expected return and it is preferable that this assumption is recorded explicitly alongside the constraint. Had the assumed return been different, it is likely that the constraint would have been set differently. For example, if through the course of the project an option is identified which requires resources at a level beyond the constraints but which has much higher value, it will be necessary to test whether that constraint should be relaxed to achieve the higher return. Similarly, if there are no options available which are capable of delivering the previously assumed return, it may be necessary to tighten constraints.

Setting the project objectives requires that stakeholders be identified and these objectives then need to be agreed with key stakeholders.

4.2 Stakeholders

Throughout the lifecycle of the development, design, construction, operation and decommissioning a plant there are a limited number of relevant stakeholders who are directly involved in the system:

- The enterprise (shareholders, creditors, senior management, insurance companies)
- The chemical product customer(s)
- The raw material suppliers
- The process development team (chemists and chemical engineers)
- The plant design engineers
- The plant constructors
- The plant operators
- The plant maintenance teams
- The community
- The regulatory authorities

Given that not all of the stakeholder requirements can be met, it is necessary to specify which ones are to be given priority and hence included in the design. Where possible, it is useful to analyse why the stakeholders have the requirements that they have. This puts them in context and allows the system designer to determine the value that the stakeholder places on the requirement. Mitchell *et al*[b] proposed that stakeholders possessed up to three attributes in their relationship with a system: possession of power, legitimacy and urgency. Figure 4-1 below shows these relationships pictorially.

The goals of the stakeholders that have all three types of relationship with the system must be accommodated within the system. Those with two out of the three relationships carry less weight, but designers will normally try to match their requirements if it is possible. Finally, the remaining stakeholders are considered, but their goals are only given the lowest priority.

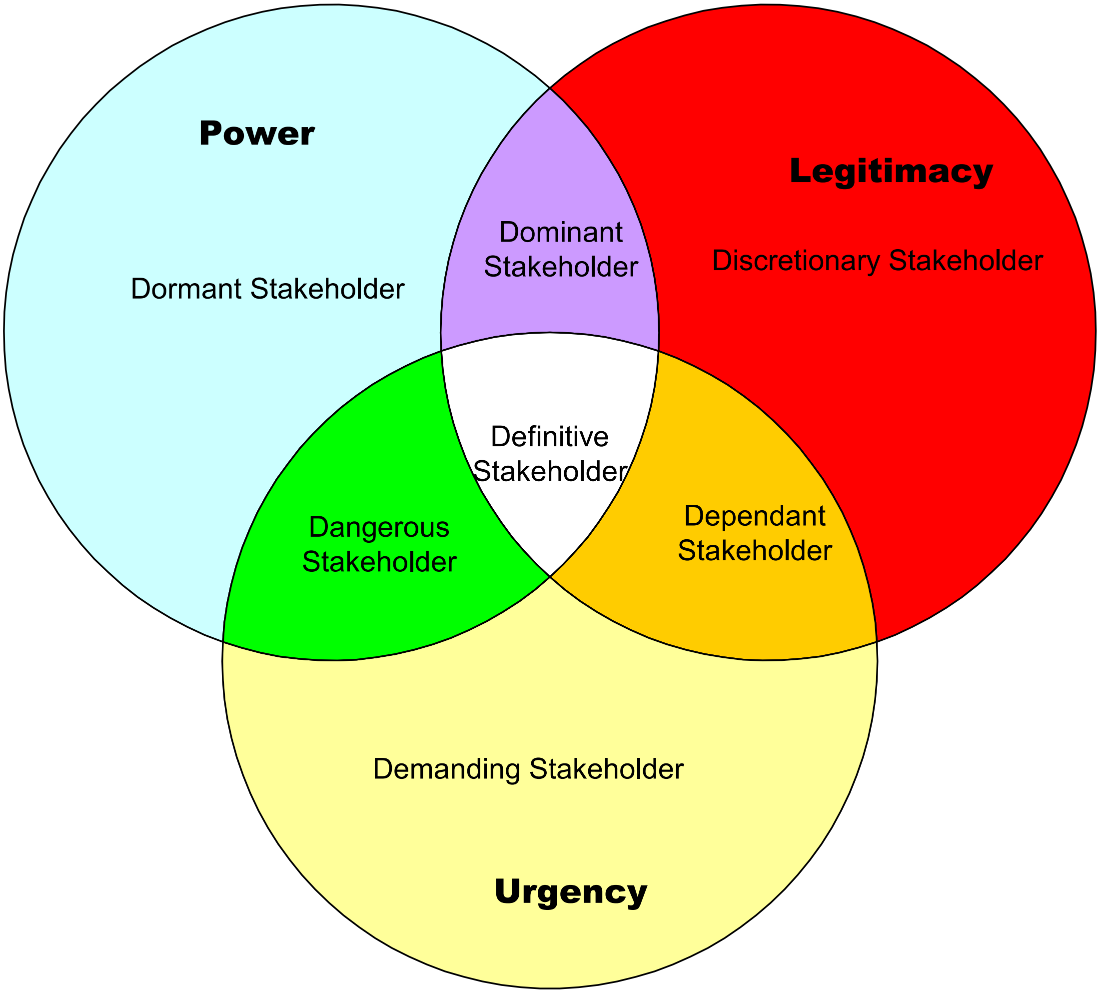

Figure 4-1 Stakeholder Status

The relative importance of some stakeholders may change dramatically during a project – in the early stages groups such as the plant constructors and maintenance teams have limited interest and influence, but as the process becomes more fixed their importance increases. For some stakeholders, the requirements barely change throughout the project – in the case of the enterprise, the typical requirements are: small cash flow, short time to next step, minimal resource requirements and minimal business risk. In this case, the requirements change only when there is a product to sell – in this case the enterprise desires high profit, low customer support, low plant support (maintenance costs), low risk raw material supply chain, and maximal sales per customer. For some products the enterprise may also wish for large numbers of customers or a high security product supply chain. Similarly, the requirements of the community change little throughout the project (and are often in conflict with the desires of the enterprise). In this case, the requirements are for high development resources, locally sourced materials, large training requirements, and long timescales. However, the community supports the business in the areas of risk minimisation - the community wants the projects to succeed as much as the enterprise does.

4.3 The Methodology Cycle

Issues and opportunities arise at each stage of the lifecycle of a plant or product. In this methodology, the lifecycle elements have been defined as:

- Situation Appraisal
- Process / product concept
- Conceptual process design
- Conceptual plant design
- Plant design
- Plant construction, commissioning and validation
- Plant operation & maintenance including supply chain management
- Plant demolition and/or reconfiguration for other purposes

The results from each element have the potential to impact on others, so it is important that the design programme contains "decision points" where some or all of the following are considered:

- A choice of option(s) to investigate further is made;
- Work necessary to do that is identified;
- The business case for the investment is reviewed against the latest knowledge;
- Plans are developed or reviewed fixing/confirming timescales and budgets;
- Decisions related to the timely implementation of the project are made (e.g. ordering of long delivery plant, commencement of civil engineering works and building).

The potential outcomes at each decision point are to:

- continue along previously identified path or minor modification of it;
- iterate within active element(s) of work;
- iterate back to an earlier element of work;
- terminate the opportunity.

As the design activity progresses options are generated and assessed, with only the best options being carried forward, as shown in Figure 4-2 below. There is some natural order[c] to the consideration of options and therefore the decisions. Broadly, with some variations possible depending on the situation, the order is

- Product
- Process chemistry
- Batch/continuous decision
- Core processing technology (often reactor) type
- Ancillary processing options (separations and purification)
- Process conditions optimisation
- Plant layout and infrastructure.

However, at every decision stage it would be desirable to have some consideration of the future issues to be resolved (for example selection of chemistry with a prior view of a suitable reactor type – or at least that feasible reactor types exist). Even when a decision has been made to follow a particular line, further work may indicate infeasibility and a need to abandon the investment or return to an earlier stage and evaluate a new option.

While the aim is always to minimise rework and unnecessary investigation, it is inevitable that options will be pursued that prove infeasible. Only with complete *a priori* knowledge would this be avoidable. In the absence of complete *a priori* knowledge, it may be appropriate to progress a small number of options (typically 2-5) in parallel throughout the design process noting that the degree of differentiation between these options will reduce as the process proceeds - e.g. after the situation appraisal, 2-5 product options (each of which should have at least one viable chemical route) may be progressed until there is sufficient information for a clear decision whereas immediately prior to the decision on the plant to be constructed there may be 2-5 options on equipment vendor for each particular item of equipment to be installed.

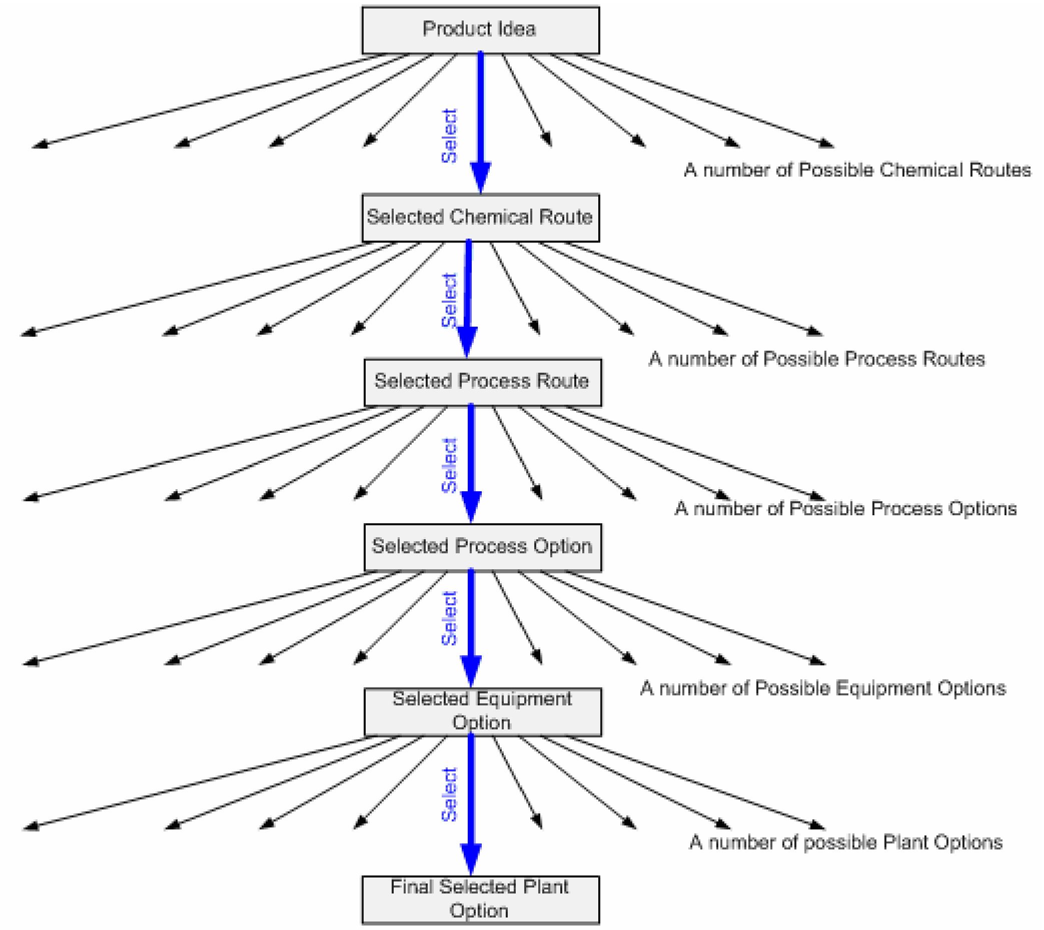

Figure 4-2 Generation of process options within a typical investment project

It is typical for three or four major decision points to be required, though the number in any given case will depend on the situation, company policy and procedures. These major decision points will require review of the status of the project in terms of all of the interacting lifecycles (product, process, plant, facility) and involve as many of the key stakeholders as necessary. Those working within particular elements of the project will see additional decision points (albeit at a lower level) necessary to progress their activity. For example, a design and construction organisation[d] may consider phases such as:

Phase 1: feasibility study to identify business opportunity;
Phase 2: conceptual plant design to select and quantify best option;
Phase 3: Preliminary engineering to finalise and quantify the plan;
Phase 4: complete detailed design and procurement of material / equipment;
Phase 5: Construction of facility;
Phase 6: Start up of facility;
Phase 7: Evaluate completed project and Close-out project.

with decision points between each phase. Note that within the IMPULSE methodology cycle, the process in Phase 1 above would already be complete. Nevertheless, within the design and construction organisation or any other group engaging with the project for the first time, this first activity of reviewing and understanding the status of the business opportunity is an essential component in aiding the new group to participate effectively in future activities. It is also a beneficial review for existing participants who may be required to reassess their own understanding as a result of questions asked by those newly engaged with the project.

Before any activity starts there is an initial decision to explore the opportunity, which will be based on the attractiveness of the opportunity, availability of resource and appropriateness of the opportunity for the organisation. This can be regarded as “Decision Stage Zero”. After that decision, it is important that all of the lifecycles proceed in parallel. It will not be necessary for all lifecycles to proceed at the same pace, but it is important that each lifecycle proceed at a sufficient speed to meet the requirements of the next major decision. In some cases, little progress may be necessary in some lifecycles (e.g. capacity expansion for an existing product – where much of the product lifecycle information may be already known and be routinely collected). Also, note that it is inappropriate to expend considerable resource to accelerate one aspect ahead of the others (e.g. fully developing a process when it has not been confirmed that there is a market for the product), if the potential impact of another aspect may render the accelerated work redundant.

At all times, it is expected that there will be some uncertainty in data, whether this be product cost, market demand or technical data. It is assumed that throughout each lifecycle three values for each item of data will be maintained – "best case", "realistic case" & "worst case". The range between best and worst cases would be expected to narrow through the course of the project and the realistic case will lie between these two (possibly at one of them). Note that new information may mean in some cases that the amended range has no overlap with the previous one e.g. new "best case" may be poorer than previous "worst case". Note also that on rare occasions, the current status may have performance poorer than the "worst case" – e.g. where very few experiments have been done in-house, but there is clear literature precedent for better performance.

The tables illustrate suggested progress through each of the lifecycle elements. Processes which support this progress are also listed with links to other parts of this document. There is no guidance on acceptable ranges between "worst case" and "best case", as this must be decided on a case by case base. Each organisation employing the methodology will have a different attitude to risk. Further, the acceptability of risk depends on the balance between implementation cost and reward – so for example a low reward, high implementation cost opportunity may tolerate a lower risk and expect lower ranges between "worst case" and "best case" than a high reward, low implementation cost opportunity. For guidance, Figure 4-3 below suggests data requirements as the opportunity progresses through the phases. Note also the hierarchy of process and technology options and that it may sometimes be sufficient to believe that a technology option to satisfy the needs of a process option may exist rather than deploy resource to define technology options for all process options. Activity on technology options to meet process options which are ultimately rejected may be abortive. However, in some cases it may be possible to reduce time to market by working on technology options suited to groups of process options and in others (e.g. where a product is a structured fluid) the process option and technology option may be inextricably linked. In such cases, investigation of technology options cannot be deferred.

Similarly, while it is suggested that initial assessments be based mainly on comparison of optimistic "best case" outcomes, particular business circumstances will dictate the most appropriate approach. Finally, where not all lifecycles are active, it would be expected that the other lifecycles will have information close to that required for operation and ultimately demolition.

Also, note that the attached spreadsheet provides an outline checklist through the life of the venture, including features which may aid in the decision between batch and continuous and on the scale of structure to be employed. It is anticipated that organisations using this spreadsheet will seek to extend it based on their internal experience.

DB_1h_METHODOLOGY_REV2.XLS

Selection criteria for any decisions fall into five broad categories – Cost, SHE (Safety, Health, Environment), Operability, Technology Issues, and Sourcing. Depending on the business environment in which the company operates and the lifecycles which are active, the detailed selection criteria and the weighting applied to them will vary.

Table 4-1 Product Lifecycle and Overall Business Venture Decisions

Information Topic	Situation Appraisal	Conceptual process design		Plant design		Plant operation & maintenance including supply chain management		
	Output	Input	Output	Input	Output	Input	Output	
	Process/product Concept		Conceptual plant design		Plant construction, commissioning and validation		Plant demolition and/or reconfiguration for other purpose[4]	
	Input	Output	Input	Output	Input	Output	Input	Output
Product Identity	Identified Market Opportunity	Small number of product options	Single product option with outline specification	Single product option with extended specification	Fully specified product		Product specification responding to customer feedback	
Product cost[5]	Materials cost with simplistic operating cost based on judgement of process complexity	Targets for process performance set	Revised materials cost with operating cost based on process options indentified at each step					
Product price[6]	Judgement	Possibly some market intelligence	Update & review for each decision					
Total market volume	Judgement	Possibly some market intelligence	Update & review for each decision					
Expected market share	Judgement	Possibly some market intelligence	Update & review for each decision					
Price-volume relationship	Judgement	Possibly some market intelligence	Update & review for each decision					
Time to market requirements	Judgement	Possibly some market intelligence	Update & review for each decision					
Market location	Judgement	Possibly some market intelligence	Update & review for each decision					
Basis of overall venture decisions	Based on "best case" – some adjustment by "realistic case"?		Based on realistic case tempered by best & worst cases?		Based on realistic case tempered by worst case[7]?			
Decision Processes	Standard tools can be used for prioritising options. These include Pareto Analysis, paired comparisons, Grid Analysis, Decision trees, the PMI method, Force field analysis, Six Thinking Hats, Cost-Benefit Analysis, Kepner Tregoe Decision Analysis and Ishikawa diagrams. The process technologist should select the methodology most appropriate to the problem, their organisation and the quality of the information available. Note that the appropriate decision tool may change as the project progresses.							
	Consider opportunities for innovation (see A4.1 below) Select preferred product options using selected decision tool		Select preferred technology options using selected decision tool and Technology Option Identification database (see section 6 below)		Ongoing review of project taking into account market conditions.		Consider opportunities for re-use, recycle and demolition.	
		Select preferred process options using selected decision tool		Select preferred plant option including detailed equipment design using selected decision tools		Ongoing review of product performance in market place ultimately leading to requirement for expansion or product withdrawal.		

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[4] Reviews continue into the plant demolition and/or reconfiguration period as it is the deterioration in the business case that will ultimately result in the decision for plant closure for either demolition or re-use

[5] i.e. cost to organisation to manufacture

[6] i.e. what the customer is prepared to pay

[7] At this stage, the single biggest resource commitment for a new venture is likely. It would normally be expected that the realistic case meets all of the key stakeholder targets – some organisations may also expect this of the worst case, whereas others may simply seek to assure themselves that the worst case does not have an unacceptable value.

Table 4-2 Process Lifecycle Progress

Information Topic	Situation Appraisal	Conceptual process design		Plant design		Plant operation & maintenance including supply chain management		
	Output	Input	Output	Input	Output	Input	Output	
	Process/product Concept		Conceptual plant design		Plant construction, commissioning and validation		Plant demolition and/or reconfiguration for other purpose	
	Input	Output	Input	Output	Input	Output	Input	Output
Chemical route[8]		At least one viable route per product option remaining	Single chemical route identified					
Separation technology options		At least one viable separation option for each chemical route	Small number of separation options still under investigation for each separation					
Process route[9]			Small number of process options	Single process option				
Batch or Continuous				Whole process batch or continuous decided for each step				
Scale of structure		Initial view of preferred scale of structure for each reaction		Proposed scale of structure to be delivered defined for Whole Process				
Main impurities		Known, relationship between conditions and quantity to be confirmed		Operating space confirmed - causes and control of impurities understood				
Analytical methods		Analytical methods available for product and main impurities	Quantitative analytical methods available		Validated analytical methods available			
Operating conditions		Order of magnitude conditions for each option		Narrowed range	Known control window			
Raw materials availability, specification and cost		Initial view available		Small number or potential suppliers	Raw materials for start-up fixed		Ongoing review of raw materials	
Corrosion/ erosion risks			Preliminary investigation of process corrosivity	Selection of materials of construction				
Safety, Health & Environment status	See Table 4-5 below							
Decision Process	Tools available for option comparison are as shown in Table 4-1 above							
	See section 5.10 below – note that the accuracy required will increase for later decisions. Also, record key assumptions & challenges to review at next step. See also section A4.2 below		See section 5 below Splitting & combining of tasks identified See also section A4.4 below & section A4.5 below					
		See section 5.4 below also Table 4-5 below a4 Also, record key assumptions & challenges to review at next step		Targeted experimentation to provide data for plant design and modelling and/or investigate maloperation scenarios				

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[8] i.e. chemical transformations involved in manufacture

[9] Includes the ancillary operations such as separations

Table 4-3 Plant Lifecycle Progress

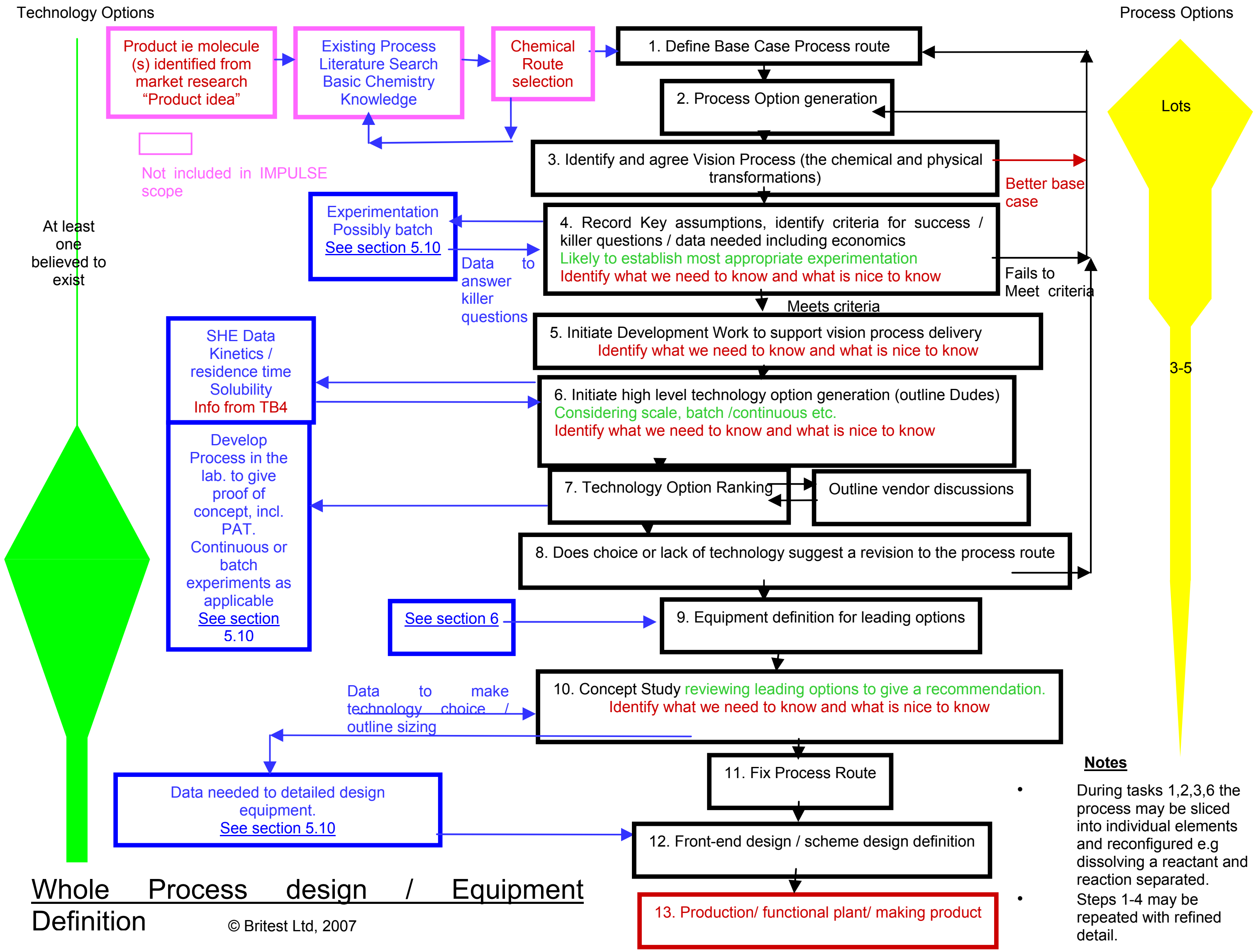
Information Topic	Situation Appraisal	Conceptual process design		Plant design		Plant operation & maintenance including supply chain management		
	Output	Input	Output	Input	Output	Input	Output	
	Process/product Concept		Conceptual plant design		Plant construction, commissioning and validation		Plant demolition and/or reconfiguration for other purpose	
	Input	Output	Input	Output	Input	Output	Input	Output
Batch or continuous			Purely technical batch or continuous decided for each step	Whole process batch or continuous decided for each step				
Scale of structure		Initial view of preferred scale of structure for each reaction	Refinement of options on scale of structure – splitting, combining tasks studied	Whole process scale of structure defined				
Reactor			At least one viable equipment option per process option remaining	Preferred equipment type identified	Specific equipment type and size defined for each duty			
Separation equipment			At least one viable equipment option per process option remaining	Preferred equipment types identified	Specific equipment type and size defined for each duty			
Location	Initial indication of locations under considerations			Final decision on location				
Layout				Outline of equipment requirement and space requirement	Space requirement, relative location and access decided			
Control philosophy			Ideal control parameters defined	Revised control strategy	Control strategy tested by appropriate modelling			
Maintenance philosophy				Initial view on parallel streams – in service and/or on-line spares				
Decision Processes	Tools available for option comparison are as shown in Table 4-1 above							
			See section 6 below for identification of equipment options. Also see section 5.5 below for consideration of fault conditions and section 5.6 below for control considerations along with section 5.9 below for modelling considerations					
		See section 6 below for identification of technology options		Detailed design and vendor discussions for equipment selection. Also see section 5.5 below for consideration of fault conditions and section 5.6 below for control considerations along with section 5.9 below for modelling considerations				

Table 4-4 Facility Lifecycle Progress

Information Topic	Situation Appraisal	Conceptual process design		Plant design		Plant operation & maintenance including supply chain management		
	Output	Input	Output	Input	Output	Input	Output	
	Process/product Concept		Conceptual plant design		Plant construction, commissioning and validation		Plant demolition and/or reconfiguration for other purpose	
	Input	Output	Input	Output	Input	Output	Input	Output
Plant size			Review space availability in existing facilities close to market location		Confirm plant can fit at existing facility			
Utility requirements			Review utility availability in existing facilities close to market location		Expand utilities if required			

Table 4-5 Safety, Health and Environmental Assessment Progress

	Situation Appraisal	Conceptual process design		Plant design		Plant operation & maintenance including supply chain management		Input
	Output	Input	Output	Input	Output	Input	Output	
	Process/product Concept		Conceptual plant design		Plant construction, commissioning and validation		Plant demolition and/or reconfiguration for other purpose	
	Input	Output	Input	Output	Input	Output	Input	Output
Legislative requirements	Overview for locations under consideration							
Organisational targets	Assumed to be clear throughout							
Raw materials information	Start gathering data	Review data and risks of loss of containment throughout. Note that use of a particularly nasty material may be justified if inventory is low enough and benefit is high enough						
Product information	Start gathering data	Review data and risks of loss of containment throughout.						
Safety profile	Start gathering data	Review data and risks of loss of containment throughout.						
Health profile	Start gathering data	Review data and risks of loss of containment throughout.						
Environmental profile	Start gathering data	Review data and risks of loss of containment throughout.						
Sustainability	Start gathering data	Review data and risks of loss of containment throughout.						
Decision process			Revaluate output from previous step at increased process detail – see also A4.3 below.					
		Apply simple high level tools to process options at initially at normal process conditions (see section 5.7.1 below) Review abnormal conditions at high level before passing process options to next stage (see section 5.7.2 below)		Utilise extended HAZOP guidewords alongside normal approaches (see section 5.7.2.1 below) and A4.5 below		Consider application of detailed level tools – see section 5.7 below)		



Notes

- During tasks 1,2,3,6 the process may be sliced into individual elements and reconfigured e.g dissolving a reactant and reaction separated.
- Steps 1-4 may be repeated with refined detail.

Figure 4-3 Guidance on data requirements and option handling

5 Whole Process Design in Multiscale Facility

5.1 What is Whole Process Design?

Whole process design (WPD) is an approach which takes into account all elements of the manufacturing process and seeks to optimise an objective function incorporating all desired business outputs within defined constraints by specifying all of the available process control parameters. This approach has been in place in much of the commodity chemical sector for many years. In some cases, whole process models are built into plant control systems, so that the operation of plant can be immediately adjusted in response to factors such as changes in market conditions or changes in feedstock quality. Such optimisation is critical to these high volume, low margin products.

In the high-value-added sectors it has not been easy to take a whole process view because of the inherent complexity of processes, limited data availability and the lack of suitable modelling tools. Further, time to market is often an important business driver and full process models and optimisation is infeasible in the time available. Historically, the focus has tended to be on delivering the core chemistry within standard manufacturing solutions. IMPULSE WPD recognises the complexity of the sectors and sets out a methodology which guides the user through the design process taking into account the interactions and development of chemistry, business and SHE, equipment specification and selections, measurement, calculations and appropriate modelling and employs the knowledge and experience of the user to address the overall complexity.

In applying the methodology, it must be remembered that good process and plant design is necessarily an iterative process. At all times, it is necessary to maintain some forward view of the planned final outcome in order to determine what information needs to be collected and processed. Early in the life cycle of the product, process or plant, a small number of planned final outcomes may progress in parallel, whilst generating the information which will allow a decision between the options. As the information is collected, some part of the information will inevitably demonstrate that past judgements/assumptions were flawed to some degree. When such information arises, it is necessary to decide whether the cumulative deviation from past judgements/assumptions is sufficient to require a review of the planned final outcome. Such a review may result from a single significant deviation or a series of several minor deviations where the earlier deviations were insufficient to trigger a review. Note also that the information may not be technical and could relate changes in legislation, changes in company strategy or changes in business environment (such as market volume, acceptable sales price or acceptable product quality).

The potential outcomes of a review include:-

- proceeding with the previously planned outcome
- adopting a new planned final outcome moving forward from the current position
- adopting a new planned final outcome starting from an earlier decision point which has been changed as a result of the new information
- terminating the project

The decision inputs will include information and judgements/assumptions with an expectation that the balance should move towards information over time. The decision output should seek to deliver the option which best meets the overall business requirement, where the business requirements include economics, safety, health, environment, sustainability and time. Frequently, each of these factors will have some critical threshold which must be achieved (e.g. the economic assessment of an option must show it will add value, the assessment of safety, health and environment factors must show that legislative compliance will be achieved) and any option which cannot better all critical thresholds must be rejected even if it is superior in all other areas – this means that it is particularly necessary to test that all thresholds are truly critical. Terminating a project where no option can better all critical thresholds is an essential component of good whole process design and should be regarded as a success rather than a failure.

Because of the iterative nature of good process and plant design, the sections below should not be considered to be in any particular order and, in general, the process technologist should apply the contents in the order most appropriate to the particular business circumstances. However, it is recommended that the process technologist commences the first iteration by generating at least one representation of the planned final outcome as described in section 5.3 below.

5.2 Determining Appropriate Structure for Individual Step

A general property of chemical engineering processes resides in the fact that their global performance is the result of a combination of physical and chemical phenomena (chemical reactions, mixing, heat or mass transfer, etc.). Where phenomena are coupled consecutively, the performance is determined by the slowest step and any change to the process environment which does not address the factors which determine the rate of that slowest step will have little effect on overall process performance.

Where there are undesired processes competing with the desired process (typically, by-product reactions competing with the desired reaction sequence), the speed of still other phenomena can influence the overall process outcome. For example, where reaction selectivity is strongly dependent on temperature, ensuring the characteristic time for heat transfer is significantly shorter than the characteristic time for the reactions (desired and undesired) will improve process control and deliver better process performance. For the case of an undesired consecutive reaction where the product can react again with a starting material, it is important to ensure that the characteristic time for mixing is significantly shorter than the characteristic time of the undesired consecutive reaction. Provided this is the case, selectivity will be controlled at a level close to that which would be predicted from the intrinsic kinetics (see section 5.10.2 below). Ensuring the characteristic time for mixing is shorter than the characteristic time of the desired reaction will increase the apparent speed of the reaction and intensify the process, but will have little further effect on selectivity.

Table 5-1 presents a some of the more commonly used characteristic times, covering homogeneous and heterogeneous reactions, as well as transfer phenomena, gravity and surface tension effects. These times and their expressions are presented here in ascending order of their power dependence on the characteristic geometrical dimension. Homogeneous reactions exhibit no dependence on the characteristic dimension whereas transfer phenomena are strongly influenced by the presence of walls and obstacles. A small characteristic time represents a fast phenomenon.

Characteristic time	Expression	Dependence on R
Nth-order homogeneous reaction	$t_{\text{hom}} = \frac{C_0}{r_0} = \frac{1}{k.C_0^{n-1}}$	0
Apparent first-order heterogeneous reaction	$t_{het,1} = \frac{R}{2k_s}$	1
General heterogeneous reaction	$t_{het} = \frac{C}{r}$	Varying
Diffusive mass transfer	$t_{diff} = \frac{R^2}{D_m}$	2
Convective mass transfer at constant Sherwood number[10]	$t_{mass} = \frac{R^2}{Sh.D_m}$	2
Heat conduction	$t_{cond} = \frac{\rho.Cp.R^2}{\lambda}$	2
Convective heat transfer at constant Nusselt number[11]	$t_{heat} = \frac{\rho.Cp}{\lambda}\frac{R^2}{Nu}$	2

Table 5-1 Characteristic times and their dependence on the characteristic dimension R

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[10] The Sherwood number is correlated to Reynolds number for transitional and turbulent flow/. This introduces a further dependence on R – i.e. the dependence on R increases when moving from laminar, through transitional and into turbulent

[11] As above, but for the Nusselt number

As far as transfer phenomena are concerned, a general expression of their characteristic times can be proposed by considering the transfer analogies. A general expression can be written as:

$$t_{transfer} = \frac{R^2}{D_{phen}.N_{\dim}}$$

Eqn 5-1

where R denotes the characteristic dimension, D_{phen} the diffusivity of the transferred property through the considered medium and N_{dim} a dimensionless number required when convection effects are taken into account. The dimensionless number N_{dim} does not appear when the transfer is purely diffusive or conductive. However, it is correlated to Reynolds number under transitional and turbulent flow and this will increase the dependence of the characteristic time of transfer processes on R. Note that the characteristic time of transfer processes decreases with decrease in characteristic dimension, or increase in structure and has no dependence on concentration.

Chemical reactions can also be considered using a general expression of their characteristic times. The construction principle is similar and consists in relating the concentration of a reactant of interest C_0 at initial conditions to the rate of its consumption r_0 at the same initial conditions (index 0 refers to initial conditions):

$$t_{reaction} = \frac{C_0}{r_0}$$

Eqn 5-2

This general expression can be used for homogeneous reactions as well as heterogeneous reactions. It can be simplified for particular cases, as shown in Table 5-1. However, particular attention must be paid to heterogeneous reactions, whose observed kinetics may vary as a function of the operating conditions or reaction conversion. Heterogeneous reactions are possibly best viewed as coupled reaction and mass transfer and it is this feature which results in the dependence on the characteristic dimension in heterogeneous reactions. Note that the intrinsic kinetics (see section 5.10.2 below) will have a shorter characteristic time than the extrinsic kinetics as the rate is not slowed by the transfer phenomena. In general, the characteristic time for intrinsic kinetics may depend on concentration (will except for first order intrinsic kinetics), but has no dependence on R. It is the absence of any dependence on R which means that reduction in the characteristic dimension or increase in structure results in an increase in observed rate until the intrinsic kinetics are attained, but that no further increase will occur once that point has been reached. A further observation is that the characteristics of a chemical reaction change with concentration and, as a result, the required level of structure will usually change as a reaction proceeds. This may mean that it is advantageous to split a reaction task (see section 5.4 below).

In practise, during the technology option identification step, the characteristic time for the desired reaction will be compared with measured characteristic times for the technology options or simple models will be used to match rates.

5.3 Process Representation

The process representation provides a focus for generating, discussing and comparing options. Each process option should be clearly represented in a visual format, so all members of the development team can understand its features. This can be done by to generating a Process Definition Diagram (PDD[12]) or a detailed task diagram to represent each process option. Either a PDD or a detailed task diagram shows:

1. the processing operations or tasks that need to be carried out (reaction, solvent extraction, distillation, crystallisation, filtration etc), and
2. the sequence of process tasks, and the transfers of materials that must occur between the various tasks.

To minimise the total number of options, it may be sensible to make decisions on small sections of the block diagram, but always remembering that decisions on options must be taken based on the business performance of the whole process. For example, even the simple case of an exothermic reaction at a temperature above the temperature of the feed streams between two components each supplied as a solution in a common solvent generates two of feasible alternatives before considering combining or splitting of tasks.

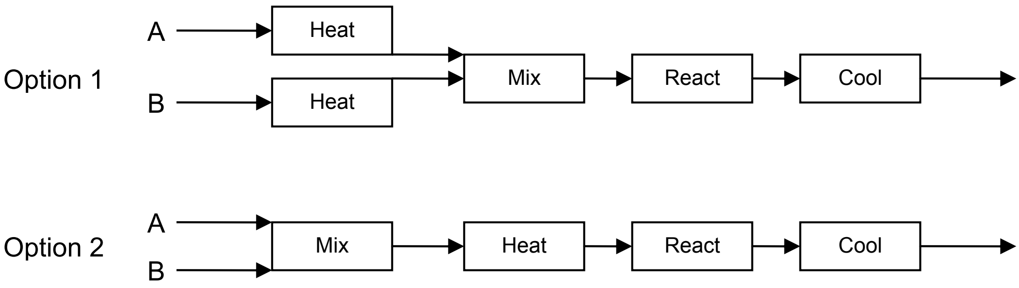

Figure 5-1 Process Options for Simple Reaction

If selectivity is a strong function of temperature with high temperature being favoured, option 1 may be preferable as the reactants are never together at low temperature. However, if A and/or B are unstable at the reaction temperature, option 2 may be preferable as A and B are only at reaction temperature when the other component is present. If both of these problems exist, then selection must be undertaken on a Whole Process basis. It is not sufficient to determine which of options 1 & 2 deliver the higher process yield within the section under consideration. Instead, it is necessary to assess the business impact of the impurity produced as a result of the undesired reaction. The option which delivers the lower yield within the section under consideration may be preferable if the impurity generated in the other option is more difficult to separate from the product or has a much less desirable safety, health or environmental impact.

This simple example is still further complicated when the appropriate multiscale implementation is considered – see section 5.4 below.

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[12] Britest Ltd Intellectual Property

5.4 Determining Appropriate Multiscale Implementation

Many proponents of microscale technology advocate the use of microdevices to replace traditional batch[13] facilities. However, as has previously been mentioned, the aim of the IMPULSE methodology is "to match process systems to the needs of the process, commerce and society – precision processing”. It has also been stated that commercial decisions and hence adoption of “solutions” by industry lie not in the technical superiority of one technology over another but instead rely on the commercial benefits afforded by such technologies in a business context. This requires the process technologist to attribute the benefits of any process change carefully. It is likely that much of the laboratory work will use a combination of batch equipment and microdevices. The use of larger scale equipment is not likely to be feasible in a standard laboratory environment, because the quantity of process materials which would be required for laboratory investigations would be excessive in any normal laboratory environment both in terms of throughput requirements and, in some cases, availability of material.

As a result, the process technologist must consider the choice of equipment in the laboratory carefully (see section 5.10 below). More importantly, the process technologist must recognise that the appropriate choice in the production environment is independent of the choice in the laboratory. Indeed, for successful implementation of multiscale processing, separating the choice of laboratory and production equipment is essential. Taking into account the different prioritisation of decision criteria and stakeholder requirements in production and in the laboratory, this difference in equipment choice should not be a surprise. Failure to recognise this separation can be a barrier to adoption of effective solutions – continuous process options investigated in micro-devices may be rejected for production if the problems associated with the micro-devices were greater than the benefit, whereas recognition of the separation of laboratory and production decisions allows consideration and adoption of multiscale solutions, incorporating micro-, meso- and macro- devices to enable the process to best satisfy the business requirements through achieving the benefits whilst avoiding the problems.

A simplified representation of the choices available to the process technologist in the production environment is represented in Figure 5-2 below. The red arrow illustrates the approach advocated by many proponents of microdevices and “batch-to-continuous”. The process technologist should seek to separately understand the business advantage of crossing both the batch to continuous boundary and the low structure to high structure boundary.

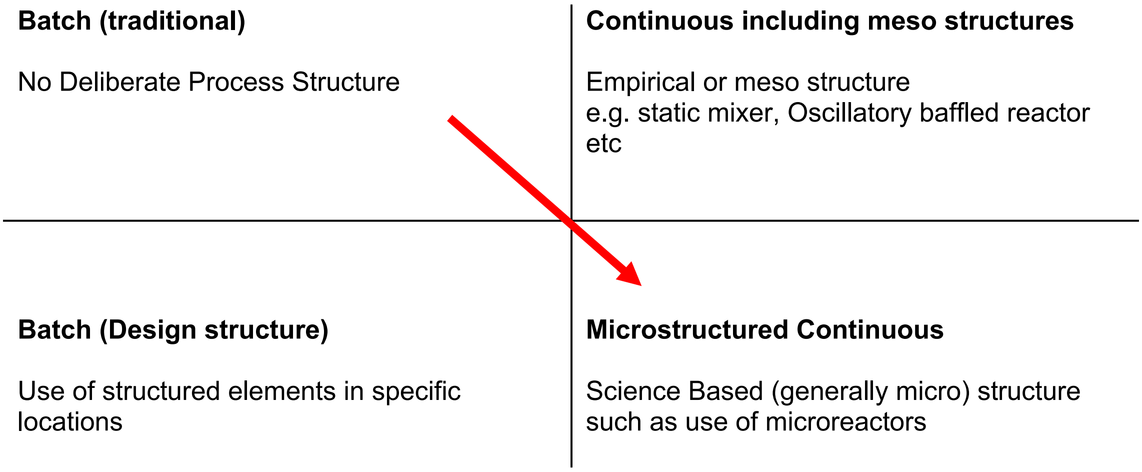

Figure 5-2 Available Operating Strategies

In some cases, a process may be best suited to batch processing, but may be highly sensitive to mixing or heat transfer at the point of introduction of a process material. Such systems may be best operated by providing local structure whilst maintaining an overall batch process – a Buss Loop batch reactor is an example of such a system.

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[13] Note (as indicated section 2 above) that the use of the term “batch processing” encompasses fed batch.

The decision between low structure and microstructure is a continuum rather than the binary decision indicated in Figure 5-2 above and is better illustrated in Figure 5-3 below.

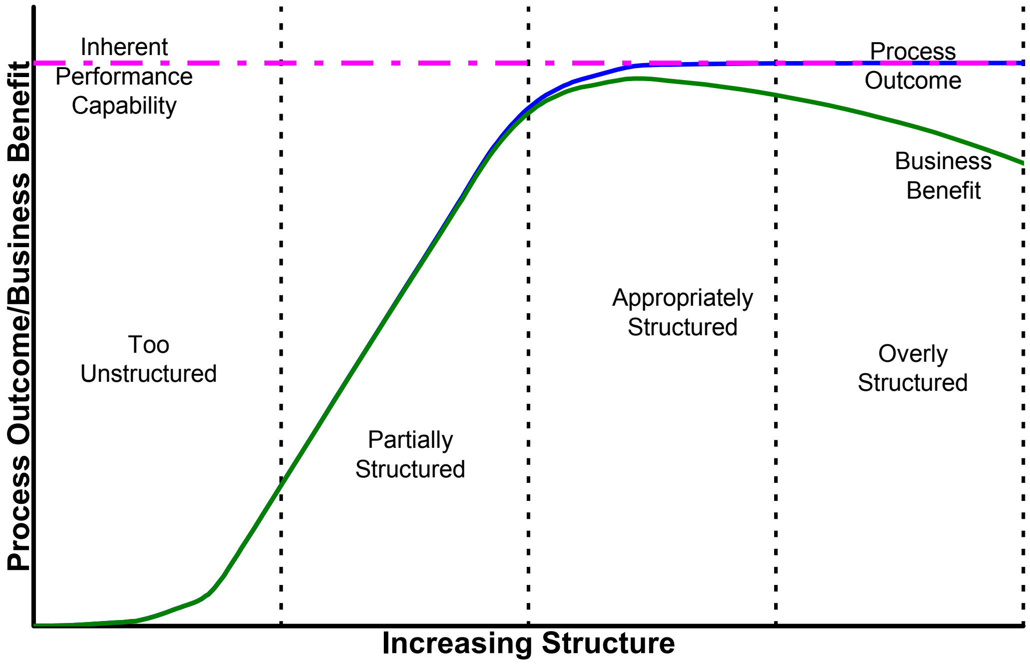

Figure 5-3 Appropriateness of Structure

As stated in the introduction (see section 1.5 above), a purely technical assessment suggests that increase in structure is never detrimental. Increase in structure delivers an asymptotic approach to the inherent process capability. However, in a practical engineering and business environment, increase in structure may result in operating difficulties and/or additional cost. Effectively, the graph represents a traditional cost-benefit analysis where the blue line indicates the theoretical process performance and the green line represents the business benefit. Note that although in the Figure 5-3 above the maximum in business benefit lies close to the inherent performance capability, this may not always be the case and achieving the maximum business benefit may require acceptance of a process outcome significantly below the theoretically achievable inherent performance capability. As "appropriately structured" is defined in IMPULSE in relation to business benefit, this region will always include the maximum point in the business benefit curve. For an individual process step, the boundaries of the "appropriately structured" region would be based on some defined loss of business performance from the maximum. However, the final decision on appropriate structure will always be based on the needs of the overall process. Note that where additional structure would be beneficial, but the issues associated with delivering that structure are excessive, it may sometimes be appropriate to change the structure required by the process rather than changing the delivered structure. For example, if a second order reaction requires a particularly high level of structure, but the production of solids by the reaction presents a serious risk of frequent blockage, dilution of the process would have the dual effect of extending the characteristic time (so that the required level of structure based solely on a technical assessment increased) and reducing the risk of blockage as the increased solvent availability would be capable of maintaining more material in solution.

5.4.1 Effects of Structure and Batch to Continuous on Generic Process

The process assessed will be considered as a fed batch reaction. For simplicity, a generic fed batch reaction is considered:

$$A + B \rightarrow C + D$$

Where	A	is the fed material
	B	is the material initially charged to the reactor
	C	is the product
	D	is a by-product

This reaction is then considered as a series of separate cases where each case has only one undesired pathway so that the transition from batch to continuous and the effect of increase in structure can be examined separately. It should be noted that the transition from batch to continuous introduces an increase in structure – i.e. the characteristic dimension is reduced.

5.4.1.1 Desired Process Decision Factors

As a base case, the situation where this reaction is the only reaction which can occur is considered. The achievable outcome in terms of yield and quality is independent of structure, as there is no route through which material may be lost. Increased structure may increase volume productivity where the rate of mixing or heat removal is the controlling feature in the equipment. In such cases, volume productivity will increase as structure is increased with an asymptotic approach to the inherent chemical rate as structure is increased. The increased volume productivity is a clear technical advantage. Further value may lie in inventory reduction (particularly where the materials handled are toxic or unstable) or simply in a saving in equipment cost. The former has been a driver to adopt a structured design in many cases e.g. Diazomethane production[e].

Note that justifying the adoption of structure solely on a saving in equipment cost may be difficult as the actual saving may be less than the accuracy of the business case financial model.

5.4.1.2 Effects of Undesired Processes on Decision Factors

5.4.1.2.1 <u>Reaction where product C can react with the fed material A</u>

$$A + B \rightarrow C + D$$
$$A + C \rightarrow \text{Waste By-product}$$

This type of situation is exemplified by Jacobsen et al[f], who show that the monoacylation of symmetrical diamines is poorer than a pure kinetic model would predict. This difference in performance is explained by the fact that mixing is not instantaneous and the actual performance is dominated by mixing effects. The paper demonstrates this by showing improved performance in a more dilute system – effectively slowing the chemical reaction while maintaining the mixing rate. The alternative (or complimentary) improvement option is to improve the mixing rate.

In the case where the desired product has an onward reaction with the fed material, a reactor style which offers superior mixing performance delivers superior results where the reactions are faster than the mixing process. Superior mixing performance to that achievable in a fed batch reactor can readily be achieved in any continuous plug flow reactor and performance will continue to improve as the device becomes micro-structured. However, there will also be a desire to minimise the concentration of the fed material A and fed batch with the introduction of A into a structured mixer offering rapid mixing (possibly a device in an external loop) may be preferred. If continuous processing is particularly desired, mixed flow continuous (with multiple feed addition points) would be preferred. Mixed flow is widely used in petrochemical industry and is equally feasible with small structured components).

5.4.1.2.2

Reaction where product C can react with the initial charge material B

$$A + B \rightarrow C + D$$
$$B + C \rightarrow \text{Waste By-product}$$

In this case, it is first necessary to consider why B is the initial charge material, because clearly the rate of onward reaction can be minimised by reducing the concentration of B.

Such a situations may arise where A is unstable at the reaction conditions or A has a faster onward reaction with C than B or for more mundane reasons such as volume considerations or the physical form of B not lending itself to a controlled addition or B being a reaction product of a previous reaction. In such cases, it may be preferable to use A as the fed material.

If there is a particular reason why B must be the initial charge material, then the onward reaction of product C with B is unavoidable in the fed batch case. However, any continuous plug flow device will deliver superior performance simply by minimising the exposure time of the product C to B, so there is likely to be value in the decision to choose continuous over batch. The scale of structure has no effect on this particular feature and the appropriate structure will be determined based on other aspects of the process.

5.4.1.2.3 Instability/onward reaction of product C not involving A or B

$$A + B \rightarrow C + D$$
$$C \rightarrow \text{Waste By-product}$$

The extended reaction time in a fed batch reaction results in a greater loss of product to instability. Again, any continuous plug flow device will deliver superior performance simply by minimising the exposure time of the product C to the reaction conditions. The scale of structure has no effect on this particular feature and the appropriate structure will be determined based on other aspects of the process.

5.4.1.2.4 Instability of B

$$A + B \rightarrow C + D$$
$$B \rightarrow \text{Waste By-product}$$

As discussed in section 5.4.1.2.2 above, the first question to be asked is whether B should instead be the fed material. Minimising the time at reaction conditions for B will reduce the loss of B and again, this will be achieved by any continuous plug flow reactor. The scale of structure has no effect on this particular feature and the appropriate structure will be determined based on other aspects of the process.

5.4.1.2.5

Instability of fed material A

$$A + B \rightarrow C + D \qquad \text{Rate} = k_d . c_A^m . c_B^n$$

$$A \rightarrow \text{Waste By-product} \quad \text{Rate} = k_d . c_A^p$$

This is a common reason for choosing the fed material. In this case the consequence depends on the process detail. There are three possibilities which are discussed separately as there are different conclusions. These possibilities relate to the reaction order of the instability reaction compared to the desired reaction.

- Where the reaction order in A of the desired reaction and the instability reaction are identical (i.e. m=p), there is no opportunity of changing selectivity through selection of batch or continuous. Dividing one rate expression by the other demonstrates that the ratio of consumption of A is independent of the concentration of A. If B is not also involved in the instability reaction, increased structure may deliver benefit, as enhanced mixing will maximise the availability of B.
- Where the desired reaction is of higher order in A than the instability reaction (i.e. m>p), it is beneficial to increase the concentration of A. This will be achieved in any continuous plug flow reactor. The scale of structure has no effect on this particular feature and the appropriate structure will be determined based on other aspects of the process.
- Where the instability reaction is of higher order in A than the desired reaction (i.e. m<p), it is beneficial to minimise the concentration of A. This may mean that batch is best. If a continuous reaction is required to fit with the upstream and/or downstream process then a loop reactor or continuous stirred tank reactor could be employed. Note that these operate at the end of reaction conditions for A & B, which means that the rate is reduced relative to the fed batch reactor and the volume productivity is lower. The alternative of operating at a high stoichiometric ratio of B (so that the reaction is pseudo zero order in B) can avoid this issue, but results in an additional separation of B from C and a requirement to recycle B. The mixed flow system with sequential additions of A will reduce the loss in productivity, but increase the loss of A over the batch reactor or continuous stirred tank reactor.

5.4.1.2.6 Equilibrium Reaction

Continuous operation offers the possibility of improving the control through counter-current operation. Co-current plug flow is no better than batch and may be inferior for those continuous reactor types which are less capable of delivering the removal of product and/or by-product to drive the reaction to completion than the batch reactor. In either case full conversion may require the removal of product and/or by-product. Batch reaction can achieve this end point if the product and/or by-product can be selectively removed. However, where separation is feasible ultimate reaction performance could be achieved through adoption of techniques such as reactive distillation or the continuous counter current reactor (patented by Davy Process Technology)[9].

5.4.2 Splitting and Combining Operations

5.4.2.1 Splitting Tasks

As is discussed in section 5.2 above, the characteristic time of a reaction and/or its rate is a function of concentration. As a result, the scale of structure required to achieve the inherent process performance changes through the course of the reaction. The appropriate structure is the one that delivers the best business outcome. Where a process requires a particular scale of structure at a particular time and a different level of structure at some other time, it may be appropriate to split a task such that the higher level of structure is provided only when it is required and where any potential problems are negligible compared to the benefits of increased structure and a lower level of structure is provided when maintaining the high level of structure would offer little benefit over the lower level of structure and the potential problems of the high level of structure would be greater than its benefits.

For example, if a second order reaction with a stoichiometric ratio of the two reactants has a characteristic time of t_0 and a reaction rate of r_0, then after 90% conversion it has a characteristic time of $t_{0.9}$ (=10. t_0) and a reaction rate of $r_{0.9}$ (=r_0/100) and it may be appropriate to consider the use of 2 or more devices with different scales of structure but which have the appropriate structure for the specific duty. For example, the second order reaction discussed might have 3 devices in series, one with original design input concentration (0% conversion), a second device with a design input concentration corresponding to 68% conversion (initial rate in second device is 10% of the first) and a third device with a design input concentration corresponding to 90% conversion (initial rate in third device is 10% of the second device and 1% of the first). The actual splitting of a task will depend on the particular process and not some arbitrary split as displayed in this example.

Thus, the key criterion for splitting a task is that the required duty varies considerably through the course of the task

5.4.2.2 Combining Tasks

For operations to be combined in a single item of equipment, the following criteria should assessed:

1. the materials present in all of the tasks to be combined should be compatible with each other, i.e. all possible pairs of compounds should be considered, and no pair of compounds present should undergo an undesired side reaction to an unacceptable extent,
2. the required processing conditions should be similar, and
3. the duties required of the equipment should be similar.

Criterion 1 is obviously important to prevent undesired side reactions.
Criterion 2 is important because the compromises in conditions needed to combine two tasks that need dissimilar conditions will tend to lead to a single item of equipment that is more expensive in capital and/or operating cost than two separate, optimised equipment items[h,i].
Criterion 3 is the opposite of the criterion for splitting a single task into separate items: if duties are dissimilar in the two tasks, then there is little point in attempting to combine them because the resulting compromises will lead to a higher overall cost.
Tasks can beneficially be combined where the balanced assessment of these criteria show that the benefit of combining the task exceeds any detrimental effect.

It is particularly important to consider combining steps, even if the devices remain separate, as operations may commence earlier or finish later than the process representation suggests. For example, in Figure 5-4 below, the reaction will actually start in the mixer whether this is desired or not. The process materials do not know the arbitrarily designated design function of any device and will undergo whatever processes are compatible with the process conditions. It there are particular requirements of a mixer which mean that it cannot be combined with the reactor then it is important that both the residence time in the mixer and the separation between mixer and reactor is minimised. Figure 5-4 below displays an incomplete selection of alternatives which could apply to option 1 from Figure 5-1 above. Option 2 would have a separate collection of alternatives.

5.4.2.3 Examples of Splitting/Combining Based on Previous Process Representation

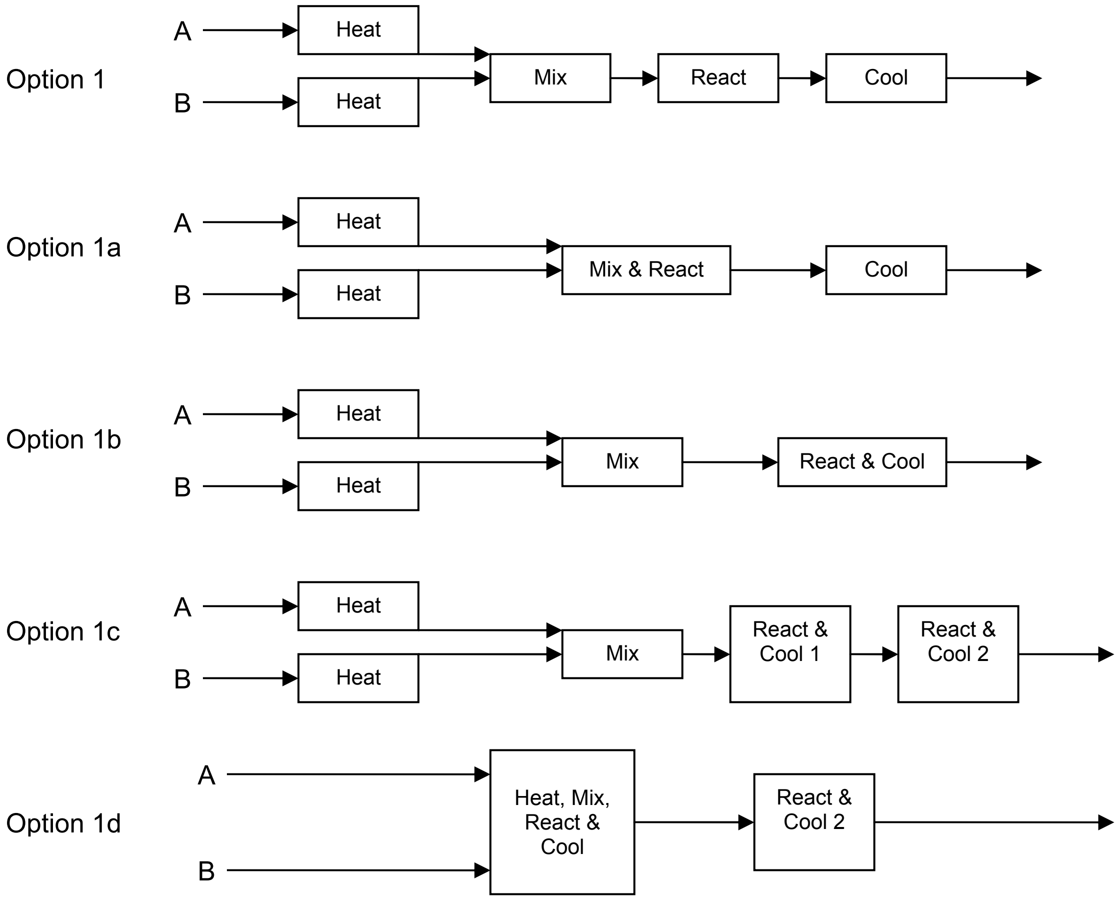

Figure 5-4 **Extended Options for Simple Reaction**

Option 1a shows the combination of mixing and reaction, with the reaction being allowed to experience its adiabatic temperature rise before cooling (as is also the case in option 1). Option 1b combines the reaction and cooling to control the reaction temperature profile (this combination is likely to be frequently employed), while option 1c shows a system which takes advantage of the change in characteristic time and rate to deliver two devices in series each of which is likely to have a different scale of structure but where each device has structure appropriate to its duty. Option 1d is also potentially interesting and may be more credible in microdevices where the high heat transfer capability means that low temperature differences can be employed. In such cases, a service fluid at, say 50ºC, could readily be used to deliver a reactor exit temperature of ~50ºC but also act as a source of heat for incoming reactants. Note that the options displayed are not intended to represent a complete set.

5.4.3 Specification of Duty

Fed batch processes are commonly considered isothermal despite the fact that high exotherms coupled with high rates can result in local thermal effects. Similarly, while many papers on microreactors assume isothermal performance, few have undertaken characterisation to validate that assumption and, as indicated in the modelled system shown in Figure 5-12 below, the true performance can be very different.

Whilst it may be tempting for the process technologist to specify isothermal operation, such performance is truly feasible only where dilution is high and/or heat of reaction is low. Specification of duty must be based on justifiable process need and that justification must be based on business benefit. Thus, the process technologist should not seek simply to specify a duty, but should investigate the business consequences of a series of duty specifications.

For example, if a maximum temperature rise of 1ºC is specified for a highly exothermic process, this may deliver a higher yield with fewer impurities than if a maximum temperature rise of 5ºC were specified, but it will also require a higher level of structure (additional cost and increased risk of blockage, increased susceptibility to corrosion, etc.) and/or increased dilution (increased solvent cost and/or recycle cost and increased environmental impact whether from solvent disposal or energy for a recycle process).

5.4.4 Multiscale Implementation

Section 5.5.3.3 below illustrates some of the connection options between devices of different scale. The illustrated cases particularly focus on systems with a degree of external scale out and where adjacent operations may have a different scale out factor. The consideration of multiscale implementation is likely to be particularly relevant to such cases, but will also apply to single streams where the different dynamics of adjacent devices will have the potential to affect downstream and possibly upstream processing.

Much of the discussion so far has focussed on the separate decisions of batch or continuous and of scale of structure with consideration of adjacent operations limited to whether they can be combined because they have similar structure or consideration of operations with changing requirements and whether they should be split. At the end of these considerations, the process technologist will have a process representation which has an initial decision on batch or continuous and on scale of structure for each option on the process representation. Note that this representation will be different from the initial one and will incorporate the re-ordering, combining and splitting that the other considerations have introduced. At this stage, the process technologist should assess the potential complications of connecting the adjacent elements.

For example, if there were 10 steps in the process representation and every second stage (2, 4, 6, 8 & 10) would be better in batch processing while the remaining stages would be better operated continuously, the potential complications of several batch to continuous transformations would need to be reviewed. Taking into account these complications, the overall whole process business outcome may be better by compromising the decisions on some stages to reduce the number of batch to continuous transformations. An alternative preferred configuration (with the same number of process steps in each category) could have stages 1-5 better in batch processing and 6-10 better in continuous processing. Such a single transformation between batch processing and continuous processing may be much less problematic.

Similar considerations may apply to structure where a step where the appropriate structure is meso-structure located between two micro-structured steps may benefit from a reduction in scale (increase in structure) to avoid potential issues with change of scale. In some cases, it may be appropriate to change both scales of structure towards a common position.

Note that it is never appropriate to simply seek to move adjacent operations towards a common scale of structure or towards a common adoption of batch or continuous simply to achieve commonality. The appropriate structure and operating strategy for an individual step is exactly that and should only be adjusted where it is found that the disadvantages of maintaining the independently generated appropriate structure for the individual step are greater than the benefits in technical performance. In other words, consideration of multiscale implementation and any adjustment in structure should be viewed as a move from process step appropriate structure to whole process appropriate structure.

5.4.5 Design of Distribution System in Microchannel Devices

IMPULSE has studied distribution in microchannels, developed guidelines for design and assessed the consequences of partial blockages. The conclusions are provided here and a summary of the work done to generate this conclusions are provided in Annex 2 below.

It has been shown that:

- The way N channels are arranged over M scales is of major importance to ensure a uniform flow distribution through the N channels.
- Increasing the number of scales M generally enables to improve the quality of the flow distribution and the global performance of the network

  e.g. if distributing a flow from a single pipe between 400 channels, the flow distribution achieved by distributing the flow into 20 large channels of intermediate scale and then distributing the flow in each large channel into 20 channels will be better than distributing the flow from the single pipe directly into 400 channels.
- Increasing the hydrodynamic resistance ratio between the larger and smaller channels improves flow distribution

  The flows involved are laminar, so the Hagen-Poiseuille law applies and the pressure drop through each individual channel can be expressed as

  $$\Delta P = 32\lambda\mu\frac{L}{D_h}u = RQ$$

  Eqn 5-3

  where ΔP is the pressure drop, λ denotes a geometrical factor, μ is the dynamic viscosity, L is channel length, D_h is the hydraulic diameter, u is the flow velocity R is the hydrodynamic resistance and Q is the flow-rate.

  If R_1 is determined for the microchannels and R_2 is determined for the distributor then maximising the ratio of R_1 to R_2 improves the quality of distribution.
- The consequence of the above feature is that blockage of individual microchannels acts to increase the hydrodynamic resistance of the microchannels still operating and the flow distribution improves.

  However, note that as the blocked microchannels reduce the effective volume, the residence time within the microdevice is reduced and where this is critical to process performance blockage is still a problem. One strategy which may be advantageous in certain circumstances may be to ensure that the residence time in the microdevice is slightly longer than that required for safe and effective operation of downstream equipment so that some degree of blockage can be tolerated.

While most users of this document will not themselves design microchannel distribution systems, it is expected that some validation of this conclusions will be required. Both the design algorithm for microchannel distribution and a summary of the validation using experimental and modelling techniques are provided in Annex 2 below.

5.5 Deviations from Design Intent

See also section 5.7.2 below which deals with abnormal conditions resulting in a safety, health or environmental consequence. This section seeks to highlight some particular features of microscale equipment in multiscale facilities and deals with deviations likely to result in quality problems or a requirement for maintenance.

5.5.1 Normal Deviations - Effect of Maldistribution

Microreactors and microstructured reactors are based on the principle of parallel channels which are all supposed to operate identically. Similar considerations apply to many meso-scaled devices such as parallel tubes in a multi-tube reactor, although the total number of parallel channels may be very much higher in a microdevice. It is usual to assume ideal similarity between the channels and uniform partition between channels. This allows the performance of an industrial microstructured system or any parallel processing system to be extrapolated by numbering-up.

In reality, uniformity of distribution is difficult and this may be particularly the case where successive distribution steps are required to achieve distribution with a significant change in the level of structure. Further, as scale reduces, the potential impact of manufacturing tolerance on uniformity may be greater. In particular, geometrical defects may appear during catalyst coating or be induced by chemical deposit during operation which can partially or totally block specific channels. As a result, channels may not operate identically because of flow maldistribution. This loss of performance is demonstrated below.

Assuming a plug flow system, the efficiency of an operation (heat and mass transfer or reaction conversion) is an increasing function of the residence time of the fluid in the channel. In the case of a reactive system with multiple reactions, the selectivity for the desired products is also a function of the residence time. Consider two parallel channels, A and B, which are intended to be identical. In the case of ideal distribution, optimum selectivity is achieved at point O in Figure 5-5(b) below. Where there is maldistribution[14], the residence time is different in the two channels. Because of the concavity of the operating curve, the mean operating point M has a lower efficiency and a lower selectivity. Generally, any deviation to flow uniformity in the channels induces a performance decrease. However, note that where a high level of structure is required by the process, the loss of performance associated with maldistribution may be much less than the loss in performance through failure to provide sufficient structure.

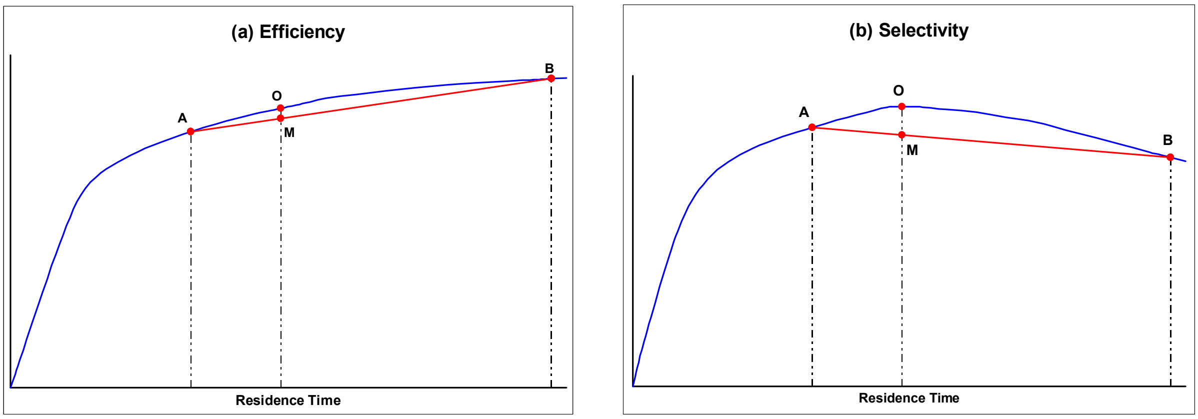

Figure 5-5: Evolution of the efficiency (a) and selectivity (b) as a function of the residence time.

Further, facilities incorporating microscale devices will frequently employ both internal scale out and external scale out. It is necessary to consider the degree of deviation from uniformity in both the internal and external numbering up systems and it may be beneficial to consider the optimum balance of internal and external numbering up by studying the fluid dynamics of the alternative systems. Study of the fluid dynamics such as CFD may be useful in determining both the degree on

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[14] Note that the location of the mean is not equally spaced between points A & B. The location of the mean can be determined using the "lever rule" which brings in conservation of mass. For this diagrammatic representation, 75% of the flow is directed down channel A, with the remaining 25% going down channel B.

non-uniformity during normal operation and the development of non-uniformity as problems develop. IMPULSE has studied distribution in microchannels, developed guidelines for design and assessed the consequences of partial blockages. This information is discussed briefly in section 5.4.5 above presented more fully in Annex 2 below.

5.5.2 Deviations in Business Requirements

Plants and the associated facilities are generally designed for a particular product of a particular quality at a particular throughput to meet the perceived market requirements. Perhaps the most likely deviation from design intent is that the business requirement will change during the lifecycle of the product and/or plant and/or facility. As part of the design process, the process technologist may wish to consider how to facilitate accommodation of changes in business requirement. Note that given the level of uncertainty, companies may not be willing to increase expenditure to accommodate unknown and unpredictable future needs (although it will generally be appropriate to explicitly decide whether or not this is the case). However, early consideration of potential future needs may allow incorporation of flexibility at no additional cost.

For example, perhaps the most likely change in business requirement is a change in market demand requiring a change in plant throughput. Some devices, such as Oscillatory Flow Baffled Reactors are able to maintain performance over a wide range of flowrates. Others such as microreactors have less flexibility, as an increase in flowrate would reduce the residence time in the device and would result in a reaction conversion at the reactor exit of less than design intent whereas a reduction in flowrate would increase micromixing time and could result in reduced selectivity. However, it is highly probable that systems incorporating microreactors will have some level of parallelisation and simply by recognising the potential business requirement for throughput flexibility, the process technologist can incorporate facilities to isolate some streams to deliver reduced throughput if required and employ an equipment layout which facilitates later addition of further parallel streams should an increase in throughput be required.

5.5.3 Deviations due to Fault Conditions

Reliability can be defined as *“The ability of a system or component to perform its required functions under stated conditions for a specified period of time”*[i]. However, it is also necessary to consider the consequence of unreliability or the mode of failure. Broadly, there are three possible modes of failure:-

- An incipient failure which could be detectable with suitable tests, but has no discernable impact on immediate performance. However, it provides a trigger event that would make a future failure inevitable unless it was corrected.
- A recoverable failure where there would be a discernable impact, but intervention by the user or a control system can adjust operation to allow continued function within specification.
- A catastrophic failure where the system fails to deliver the required output at the correct time, in the desired amount and to the design specification. Such failures may lead to a hazardous situation or simply prevent further production without maintenance.

Microscale devices have fast dynamics and can provide an operating environment which satisfies the operating requirements of fast processes. However, these same fast dynamics mean that the system response to a deviation is also rapid and the effects of a deviation will propagate rapidly through a microscale facility. For multiscale facilities, there will be a mixture of microscale systems with fast dynamics through to macroscale systems with slow dynamics. It will be necessary to ensure that the slower macroscale systems are not adversely affected by a fault propagated from connected microscale systems. Similarly, it will be necessary to understand the duration of any fault created in macroscale systems and its effect on the connected microscale systems.

5.5.3.1 Variability in Feed Quality

Feed materials will inevitably vary in quality as all materials will be purchased to a specification and measurement against any specification will include analytical error. In that sense, constant quality feed is not feasible. Usually, the specification of the desired feed component will be high (e.g. greater than 95% strength) and the degree of error or variation in such main feed components will be low. Of greater concern may be the specification of impurity contents (e.g. less than 1%), where the degree of variation may be from none to the specified limit and variations in physical properties. Such variations may have significant impact on the operation of a system particularly where these minor components may, for example, poison a catalyst or result in formation of an impurity which may block channels. Acceptance of this variability is one of the reasons why an excess of one reactant is generally employed. By selecting a sufficient excess of the selected reactant(s) taking into account the variation in quality of feedstocks, it is possible to ensure that the same material is always in excess so that the downstream process always has the duty of dealing with the consequence of that excess rather than sometimes having to deal with the consequences of one material being in excess and sometimes the other as would result from variations in feed quality in a process operating at the stoichiometric ratio of the reactants.

Having adopted this philosophy to determine the excess to be used, in a typical batch process such variations are generally within the capability of the process to adapt through the use of in process testing and pre-determined corrective measures. In the extreme case, a batch subject to an unacceptable deviation can be quarantined for later disposal or corrective action. In continuous processing (whether microscale or not), such deviations will propagate through the system and it will be necessary to identify detection methods and corrective actions. It will be particularly important to note that locally some deviations may appear as incipient failures, causing no apparent problems in the location where they are introduced, and result in a failure several process operations downstream. Variation in feed quality to one step will almost inevitably result in a deviation in output quality and, except for the final step, that output will be the feed to a subsequent step. It is recommended that a chart be created showing the propagation of faults through the total system and the detection opportunities. For each fault detection opportunity, it will also be beneficial to list the possible causes and particularly note those cases where the same apparent consequence has several different root causes each requiring different action.

Such understanding would benefit from modelling where feasible and is a key requirement to develop an appropriate control strategy. In identifying variations in feed quality, it may be appropriate to use HAZOP guide words as a support and to consider temperature, pressure, etc. to be attributes of the feed. Note that for this use, the intention is to identify all potential fault conditions including incipient failures and not just those leading to a potential hazardous event.

5.5.3.2 Equipment Failure

One of the perceived major causes of poor reliability in any microdevices within a multiscale plant is blockages. Blockage is likely to develop over time with channels which become partially blocked experiencing reduced flow resulting in greater deposition and ultimately complete blockage. As a result, it may be more likely for blockage to progress from channel to channel rather than equally in all channels. This is similar to experience of blockage in multitube devices such as shell and tube heat exchangers and tubular reactors. Therefore, there is a need to find methods of detecting “non-fatal” component failures. Further, it may be beneficial to consider cleaning in situ as part of the process (e.g. by periodic flow reversal) although taking into account the rapid dynamics of microdevices, the consequence of introducing this planned fluctuation on neighbouring equipment (upstream, downstream and in parallel) must also be assessed. Particularly for microdevices, CFD may be a useful tool to allow investigation of how blockage of a number of channels would change observable parameters.

Traditional condition monitoring techniques (vibration analysis, pressure drop, temperature drop etc.) are expected to be just as applicable to microdevices, but it is necessary to assess the degree of deviation from design intent which will be necessary to result in a detectable change in condition.

It is also necessary to consider the response to catastrophic failure. In a traditional batch plant, it may be possible to undertake operations normally carried out in the failed equipment in adjacent processing units accepting some reduction in throughput. Even where this is not possible, the maximum loss of product due to the equipment failure will often be limited to the material contained in the failed equipment (as generally batch processes are designed so that the end condition in each item of equipment is stable for extended periods both in terms of safety and quality). In a continuous facility (whether microscale or not), the problem will affect the whole plant unless the failed equipment is installed with parallel streams.

These parallel streams may be in-service, in which case the failed stream should be isolated and either the upstream and downstream plant is run at reduced throughput or each parallel stream is required to operate at increased throughput while maintaining the same overall plant throughput. Clearly, an intermediate position is also available with a partial reduction in overall throughput and a partial increase in the throughput of the parallel streams. Alternatively, the parallel stream may be an installed spare, in which case some switchover mechanism will be required, but plant capacity will be maintained after switchover. Note, however, that there may still be some process disturbance as the installed spare will not be at the normal steady state conditions when the switchover occurs. This is considered further in the discussion of maintenance below (see section 5.5.3.3 below).

Again identification of potential conditions may benefit from use HAZOP guide words as a support and to consider temperature, pressure, etc. to be attributes of the feed. Note again that for this use, the intention is to identify all potential fault conditions including incipient failures and not just those leading to a potential hazardous event. Again, it will be important to determine how the fault might be detected and to record all downstream consequences of the deviation introduced. In some cases, the sensitivity of the process to a particular fault may be greater several operations downstream than in the device in which the fault occurs.

5.5.3.3 Maintenance

The process technologist will need to decide whether to accept that each item failure results in plant shutdown (in which case reliability of the plant will be low as it is the product of the reliability of each item in the plant) or to install parallel streams and, if so, whether these will be in-service or installed spares. Where the process technologist chooses not to install parallel streams, it may be important to estimate the mean time to failure without maintenance and seeking to ensure that this time is significantly greater than the foreseeable maximum operating period.

Where parallel streams are provided, it will be necessary to provide isolation systems and/or switchover systems to isolate the failed item and introduce any installed spares. The process technologist should also decide whether the failed item will be repaired/replaced while the rest of the plant is operating or whether the failed item will be left in place in an unusable condition until the next planned maintenance for the plant. In this latter case, the process technologist should also consider the response to the failure of further parallel items, ultimately leading to plant shutdown if an excessive number of parallel stream fail.

While the item is in a failed condition and unusable, it will be necessary to consider the response of the plant and process to the deviation introduced. As a minimum, the process technologist should consider the effect of the reduced flow in upstream and downstream equipment and/or the increase in flow in the parallel streams. In early design, this may rely on judgement and simple qualitative models, but later in the design process quantitative modelling is recommended where feasible (see section 5.9 below). Further the process technologist should consider the consequences of any additional spacing required to isolate and, where on-line maintenance is planned, access the equipment items. Provision of isolation/switchover valves and spacing allowing maintenance access will result in greater separation of equipment. Particularly, where microscale devices are incorporated, the volume of the additional interconnections and valves may be significant compared to the volume of the microdevice and the consequences of this additional residence time in connecting systems must be understood. Again, in early design, this may rely on judgement and simple qualitative models, but later in the design process quantitative modelling is recommended where feasible (again, see section 5.9 below).

Particularly where the volume of the connecting system is considered detrimental, it may be preferable to provide parallel streams containing several close coupled items of equipment which are isolated as a single system for maintenance rather than isolating individual items.

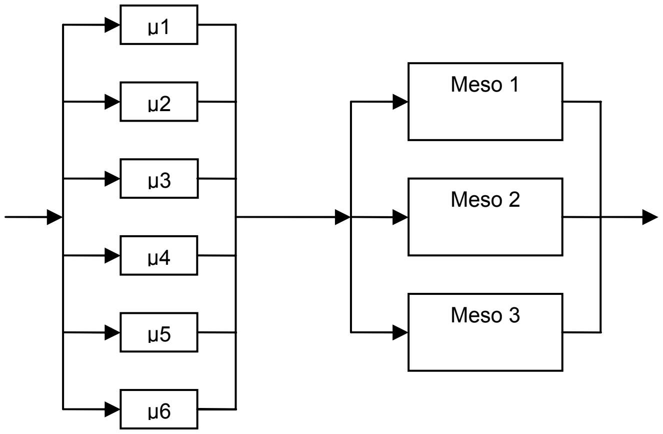

Figure 5-6 Connection Scheme based on Individual Items

For example, in Figure 5-6 above, failure of a single item would require isolation of the individual item and this maximises the spacing and its potential consequences. Failure of a micro device would mean that each of the other microdevices would require to operate at 120% of design throughput to avoid downstream effects or each meso device would need to operate at 83% of design throughput or some corresponding intermediate position (e.g. each microdevice at 110% of design throughput and each meso device at 92% of design throughput). Failure of a meso device would mean that each of the microdevices would be required to operate at 67% of design throughput or each meso device would need to operate at 150% of design throughput or some corresponding intermediate position.

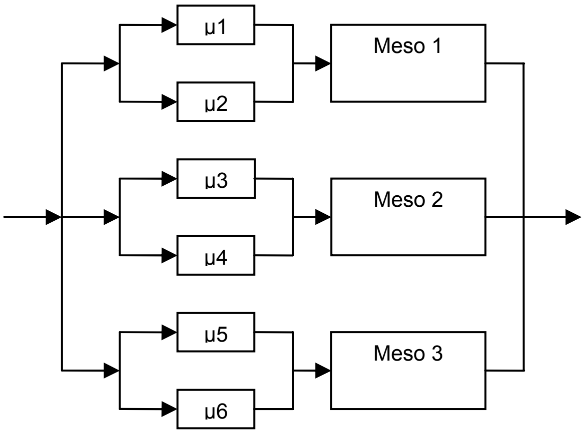

Figure 5-7 Connection Scheme based on Grouped Items

The alternative configuration in Figure 5-7 above potentially allows close connection between the microdevices and the mesodevices. However, it must be accepted that this system operates at 67% of design throughput or the two adjacent streams operate at 150% of design throughput or some corresponding intermediate position if any one item in a stream fails (e.g. µ1, µ2 or Meso 1)

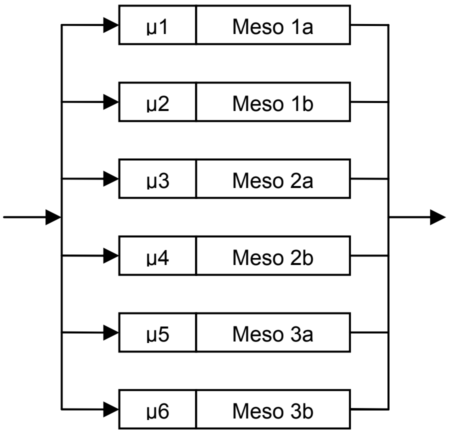

Figure 5-8 **Connection Scheme based on Individual Streams with Close Coupling**

Finally, closest coupling will be available by increasing the number of meso items (though each one is smaller) as shown in Figure 5-8 above. Here, failure of either a micro or meso device will require both to be taken out of service. The parallel units would then be required to operate at 120% of design throughput to avoid impact on upstream and downstream equipment or the upstream and downstream equipment throughput would need to be reduced to 83% of design intent or some intermediate position. Note that all decisions to accept a reduction in throughput will have the same impact on upstream and downstream equipment.

5.5.3.4 Fault Detection Conclusions

The use of the modified HAZOP guidewords for multiscale plants (see section 5.7.2.1 below) seems appropriate for the detection of potential fault conditions and their consequences. The use of a cause and effect diagram to show linkages is recommended particularly as the fast dynamics of the microscale elements will allow quick propagation of faults through the plant and process. Further, several potential causes may exhibit closely related consequences and the consequence of some faults may not be particularly apparent in the location in which they develop (e.g. a deviation which results in an increased impurity formation in one reaction may not be apparent until several steps downstream if the impurity has no effect until it poisons a catalyst in a subsequent reaction). Ideally, such a diagram may benefit from incorporation of some measure of likelihood and consequence whether qualitative or quantitative. To avoid losing the hazardous consequences in a mass of deviations which the control system would be expected to address, it may be appropriate to operate the fault detection process as a separate exercise to the hazard identification (although any hazards identified should be recorded for incorporation into the hazard study process).

5.6 Process Control & Monitoring

Process control and process monitoring are separate, but complimentary activities. Process control is employed to maintain the operation of the process within a defined operating window. Process monitoring seeks to identify potential problems as they develop. For example, if deposition of solids in a channel were to occur and process flow is controlled, the process control system would act to maintain the specified flow by opening a control valve further or increasing pump speed. Monitoring the controlled parameter, in this case flow, would give no indication of the developing deposition problem until the problem developed to a point beyond the ability of the control system to compensate. Process monitoring records and monitors non-controlled parameters with the aim of detecting faults as they are developing, so that plant personnel can plan and carry out appropriate corrective actions. In the case of the deposition example described, process monitoring might monitor the position of a control valve or speed of the pump or the pressure drop between two points.

5.6.1 Process Control

At an overview level, process control of a multiscale plant is no different to any other plant. Under normal operation, process control of any continuous facility can be considered simpler than process control of a batch plant as the design intent of the control system for a continuous plant is to maintain steady state whereas the design intent of a control system for a batch plant is to maintain the same profile of control parameters through a period of unsteady state operation further complicated by a greater likelihood of operator intervention at different points from one batch to the next. However, in a real system, process control of a batch plant deals with a reasonably simple system with little coupling to upstream and downstream equipment such that each batch control system is centred on a single vessel which is controlled as a separate entity. Deviations do not propagate through the system. In the continuous plant, each deviation propagates through the plant with each successive control system seeking to adapt to the deviation and modifying the input deviation to create a new deviation for each downstream system.

The key requirement for a continuous control system is therefore to select a control strategy that delivers a stable response to process deviation. This requirement is no different whether the plant is mesoscale, microscale or multiscale. The new challenge of the microscale and multiscale plant is the faster dynamics of the process and equipment together with a greater sensitivity to deviation. In order to meet the needs of these faster dynamics, fast response instruments will be required. These must be low volume and capable of being located in close proximity to the controlled device so that there is minimal time delay between any change in conditions in equipment and its detection. Further, the sensitivity of microscale processes to conditions (as displayed in Figure 5-12 below) will result in a requirement for low signal noise to avoid the instability which could occur by the response of the control system to noise.

In the latter stages of design, this dynamic nature of the microscale elements within a microscale or multiscale system will require investigation of the response of the control system to deviation through an unsteady state simulation of the process and plant in a model incorporating both the process performance and the control dynamics. Such a model will allow investigation of alternative control strategies.

5.6.1.1 Control for External Scale Out

See for example, in Figure 5-6 above. The process technologist will have the option of providing independent control systems for each device or a single control system for each group of devices. The appropriate selection may depend on the control parameter and the sensitivity of the process to the control parameter. For example, the process technologist may choose to install a control system which controls the total flow to the microdevices and rely on the distribution and collection system to evenly distribute the flow. If the performance of the distribution system is considered unlikely to be adequate, the process technologist may choose to control the total flow and also control the individual flows to all but one of the microdevices. Such approaches may be valid where there is no possibility of blockage. However, if the likelihood of blockage is high and residence time in each device is important, these approaches could lead to uneven distribution as blockage is likely to occur at different rates in each device. Finally, the process technologist could choose to individually control the flow to all microdevices (total flow is not controlled and is simply the sum of the individual flows). Note that in the case of flow, whichever of these systems is specified then determines the total flow to all downstream equipment and the choice of flow control strategies for downstream equipment is then limited to relying on the distribution system or controlling the flow to all but one of the parallel streams. Similar options apply to all other control parameters.

The most appropriate system will depend on the detail of the process and its potential deviations and no clear preference for one of these systems can be expressed here. Clearly, the greater the number of individual streams that are independently controlled, the greater the complexity and cost of the control system. However, the potential adverse impact on business performance of not providing this higher level of control must be assessed and the decision must be based on a cost-benefit balance and not on the avoidance of cost. Also note that each of the connection schemes shown will have different control strategies available at different cost and with different effectiveness. These differences must be assessed as part of the decision on connection strategy.

5.6.1.2 Instruments

Siemens report that they have developed mass flow and density measurement using micro-Coriolis devices based on Micro-Electro-Mechanical Systems (MEMS) technology. Pressure sensors have also been developed and flow measurement using paired pressure sensors was reported by Siemens at CHISA 2008. Access to these devices for use other than research within IMPULSE is by negotiation with Siemens. As it is expected that the technology and products on offer will continue to progress so that any details listed here would quickly become obsolete and discussion with Siemens will be required to gain access and to assess suitability for a particular duty, no further details are included in this guide.

Drawbacks of MEMS technology include the reliance on silicon, specifically the issue of chemical attack/corrosion. Some work has been completed which suggests that this can be addressed through the use of SiC coatings. Again, it is expected that the technology and products on offer will continue to progress so that any details listed here would quickly become obsolete and the process technologist should investigate the commercial options available to them for their specific duty. Note that it will be necessary to consider the measurement dynamics of the whole of the instrument installation. Even a small instrument with a fast response will deliver a slow response if located in a relatively stagnant position.

It is known that there are other providers of MEMS technology (although not whether any of these providers are offering systems for chemical production) and the process technologist may wish to investigate other vendors in parallel with discussions with Siemens.

5.6.2 Process Monitoring

As has already been stated, process control will seek to maintain process conditions within a previously defined operating window. However, the actions of the control system may mask developing problems (see section 5.5.2 above). Such incipient problems may result from a deviation from design intent in an item of equipment which the control system is capable of mitigating (e.g. a temperature control system may compensate for fouling of a heat transfer surface by adjusting the flow and/or temperature of the service fluid; or a flow control system may compensate for a developing blockage by opening a control valve further or increasing a pump speed) or from a fault in the measurement system (e.g. build up of a deposit on a temperature sensor increasing its response time or partial blockage of the flow path within a flow measurement device). Such incipient failures have the potential to develop if undetected into catastrophic failures beyond the capability of the plant or its control system to respond. Monitoring systems of this kind are not uncommon on large continuous processes and the combination of more complex processes with smaller channel sizes in microscale elements mean that there may be a still greater requirement for process monitoring in a multiscale plant for the manufacture of pharmaceuticals, specialty chemicals or consumer goods. Such monitoring should not record the values of control parameters but should instead monitor the action of the control system (e.g. valve position, heat transfer fluid flow, heat transfer temperature, etc.) and such additional parameters as the process technologist believes may aid detection of incipient failures from a study of the potential effects of process and equipment deviations. The "normal" state of these parameters at steady state should be recorded as a design expectation and early in the life of the plant. If the early values of these parameters are significantly different from the design expectation, then the possibility of a design error or having installed one or more items of failed equipment should be investigated. Thereafter, the values of these parameters should be compared with the early steady state values and any deviations should be investigated. In the longer term, it may be possible to develop an expert system which will support the linkage of deviation to cause, but it is expected that early in the life of a plant there will be a requirement for expert review.

5.7 Safety, Health & Environment Considerations

This section cannot and should not seek to replace engagement with the safety, health and environment professionals who will be available within any competent organisation manufacturing chemicals regardless of scale. Many of the methodologies for the final assessment of safety, health and environmental performance can only be deployed effectively through facilitation by one or more of these professionals. As part of the IMPULSE project, available methodologies were reviewed and the proposed methodologies were:-

- CML 2001 for life-cycle impact assessment for environmental assessment
- Inherent Safety Index based on the ITI method for safety assessment in the earlier phase of the project followed by the Safety Index of the ARAMIS method for later phases
- INSET HHI for initial health assessments (believed to be available from this website, although access terms are not known) with adjustments based on EDIP-screening[k] and the BASF Eco-efficiency method followed by SHOW Score for the later phases

It would be hoped that the safety, health and environment professionals will have some familiarity with these methods, although it is acknowledged that they may have different preferences and that it may be more effective to use the method with which they have most familiarity.

When selecting between process, plant, facility and location alternatives, the ideal solution would be to select the option which has the lowest environmental impact and is safest and has the lowest health impact and is most sustainable and offers the best financial performance. Inevitably, it will be rare for a single alternative to be best against all of these criteria and it will be necessary to establish some method of weighting between the criteria. Given that all feasible alternatives will be compliant with all relevant legislation and be financially viable, it is unlikely that there will be a legislatively imposed weighting system. It would be inappropriate for IMPULSE or any other external body to impose some pre-defined weighting system, but it would be equally inappropriate for every project team to select their own. It is suggested that the weighting system between the listed criteria should be determined at a corporate level.

While the more formal assessment of safety, health and environmental criteria will necessarily involve the relevant professionals and the use of methods acceptable to the company, it is nevertheless helpful to consider some simplified approaches directly usable by the process technologist with the project team. Further, at the time of preparing this document, microscale and multiscale facilities are somewhat unfamiliar and it is therefore also considered helpful to provide some specific comments relating to such facilities to supplement the lower level of experience with such facilities. At this simplified level, the required outcomes in terms of safety, health, and environment performance are independent of scale. Processes in plants within production facilities must be operate without harm to the public (whether as consumers of the finished goods or as residents local to the production facility or the waste disposal location), without harm to the personnel of the company producing the goods and without harm to the environment. Avoidance of harm can be considered to be achieved when exposure to chemical species does not exceed the relevant exposure standard whether this be an environmental quality standard or an occupational exposure standard.

As a result, broadly the same approaches can be applied to macroscale and microscale facilities although, as shown below, the emphasis on certain aspects may be different. Multiscale facilities require a mixture of these approaches. As always, safety, health and environmental considerations must be considered under two scenarios, the normal and the abnormal. These are discussed further below. Guidance on issues for consideration when deciding between batch and continuous and between micro-, meso- and macro- structure is provided in Annex A4.3 below.

It is anticipated that there will be three broad levels of decision:-

1. High level – **Which product or process**?
   Initial setting of business objectives, financial and timeline targets with business metrics set for the product.
   Stakeholders: Board, senior managers and project team
2. Medium level – **Which location and equipment option**?
   Initial screening of process options to determine whether some options can be quickly discounted. This is likely to be carried out within the project team based on go/no go options where, for example, the equipment cannot deliver the required process conditions.
   Typical stakeholder to be considered: Project team + technical experts.
3. Detailed level – **Which equipment**?
   Comparison of typically two or three options with in-depth assessment and comparison for the final financial cases.
   Typical stakeholders to be considered: board of directors; branch or division manager; R&D/design/engineering teams.

Level of Decision	Decision Type	Health	Safety	Environment
High level - Which product or process	Go, No-Go Regulatory step-change	Toxicology of materials and intermediates. Are any stoppers (e.g. fatal - category 1 ; CMR-substances: category 1 A)?	Is there step change in risk, e.g. hazard categories, reaction energy?	Can process achieve regulatory compliance? High level comparison of processes (e.g. mass intensity)
Medium level - Which location and general equipment type	High level process comparisons. Regulatory step- change	Comparative toxicity of processes? Containment available at sites?	Comparison of process risks -high level HAZOP type approach (e.g. pressure, temperature, concentration).	Different site waste disposal options? More detailed review of processes (e.g. mass intensity)
Detailed level - Which specific equipment	Equipment and process differences identified in detail	Containment requirements, charging/discharging of materials, manual handling etc.	Compare "cost" of incidents. Primary and secondary containment needs. Risk assessment for different equipment and process options	Comparison of environment efficiency of process. Costing of waste disposal, effluent treatment emission reduction.

It is likely that the high level decisions will be based mainly on the anticipated normal operating conditions, as the level of definition will be insufficient to allow comparison of the abnormal conditions. At the medium level, some more detailed consideration of the more obviously serious abnormal conditions would be expected to be combined with the normal conditions as part of the assessment. At the detailed level, still deeper consideration of the abnormal conditions will be required alongside further assessment of the better understood normal conditions, possibly including at least some use of the more detailed methods recommended above. Note that although for simplicity this is presented as a three step review, anticipated performance should be reviewed on an ongoing basis and further reviews should be initiated if the options under investigation deviate significantly from assumptions included in earlier decisions.

5.7.1 Normal Operating Conditions

5.7.1.1 Containment Aspects for Safety & Health

With regard to safety and health, it is reasonable to assume that each system under consideration has been designed to achieve the same safety and health standards under normal circumstances and, as a result, any differential in process conditions and/or scale between options will have been addressed through the course of the design – e.g. a process which requires more operator intervention may require higher expenditure on equipment to control operator exposure.

At a particular scale, the simplest comparison of safety and health cost can be based on the magnitude of the difference between the normal operating conditions and ambient conditions together with an assessment of the likely corrosion and erosion. Simplistically, a process operating at high pressure and temperature will be more expensive to contain than one at near ambient conditions. Similarly, a highly corrosive process mixture will be more expensive to contain than a relatively inert process mixture due to the requirement for more exotic and hence more expensive materials of construction. Finally, processes with more benign chemicals will be favoured over processes with toxic (to people and/or the environment) chemicals. Such simple guides are already familiar to the experienced process technologist.

However, the application of these simple guides within a multiscale facility or between alternatives at different scales requires the process technologist to use a higher level of judgement. As scale reduces, the thickness of a particular material required to contain a defined pressure also reduces. To a first approximation, required thickness is proportional to the diameter of the containment device. As a result, provision of a 100barg capability in internal 1m diameter reactor is likely to be more expensive than a 10barg capability in a reactor of the same diameter, but a 100barg capability in a 10mm diameter reactor is likely to be less expensive than the 10barg capability in a 1m diameter reactor. Note, however, that the choice of design pressure may depend on the desire for containment under abnormal conditions (see section 5.7.2 below) rather than the intended operating conditions.

Similarly, as scale reduces and particularly for internal surfaces within microstructured devices, the reduced thickness means that the equipment is more susceptible to corrosion – a corrosion rate of 0.1mm/yr may be acceptable in a large device with a 10mm wall thickness, but will be unacceptable in a microdevice which may have surface thicknesses less than 0.1mm. As a result, as scale reduces, the acceptability of corrosion reduces and there will be a greater need for more exotic and more expensive materials of construction. However, while the need to use the more exotic and more expensive materials is greater, the cost may be lower as the quantity of material used in the manufacture of a microscale device is lower. The potential requirement for more exotic materials in smaller devices should be noted when using the Equipment Database. If an identified option is microscale, it will be necessary to consider whether a more exotic material of construction than previously assumed will be required. If an identified option is macroscale and the material of construction had been specified on the expectation of microscale, it may be possible to use a lower cost material than previously assumed.

Many advocates of microscale devices claim reduced inventory as an advantage. This neglects the fact that for a given production capacity, the requirements for storage of raw materials and products is unchanged. It is the case that if the technology employed improves process performance and reduces waste that there will be less (or no) storage associated with waste and/or recycling. Similarly, if the use of alternative technology eliminates or reduces the requirement for a process solvent, storage associated with the solvent is avoided. The use of microscale equipment may allow elimination or reduction of solvent for reactions between two liquid reactants as the enhanced heat transfer capability reduces the requirement for a heat sink. However, the use of microscale equipment may alternatively result in an increase in solvent requirement where a reactant, intermediate or product could be solid under the process conditions and it is considered necessary to avoid the presence of solids in the equipment. As a result, it is not possible to arrive at a generalised conclusion on the effect of scale on total site inventory and systems should be compared on the basis of total site inventory. Thus, the risks and consequences of loss of containment associated with material storage are likely to be independent of technology choice.

However, the greatest risk of loss of containment may lie in the production plant. In this situation, the reduced inventory of the microscale facility is advantageous but this must be considered alongside any increased risk which may be associated with the microscale equipment if it employs more extreme process conditions.

A particular case where a microscale facility may have a clear advantage is where it generates and consumes a toxic intermediate so that there is only a small inventory in the process (and hence on site). This will almost always be preferable to a process which stores the toxic intermediate. Indeed, this may even be preferable to a macroscale process with a much larger inventory of a less toxic chemical. Further, most early examples of processes being converted from batch to continuous in the low volume sectors have been implemented with this advantage in mind.

While these issues can be presented here, ultimately the feasible approaches are a function of the particular process and the reliability of the process information. Such information is only available to the project team considering the options and the decision relies on the application of their experience and judgement.

5.7.1.2 Critical Diameter for Safe Operation

Generally, if a process is fully under control, it operates within a narrow temperature range determined by the process designer. Clearly, the process designer is at liberty to choose to operate the process adiabatically or following a selected temperature profile. Indeed, as discussed in section 5.4.3 above, unnecessarily seeking a close approach to isothermal operation can lead to increased cost with no business benefit. However, for many reactions adiabatic operation can attain temperatures at which thermal decomposition occurs or selectivity may be reduced.

For early assessments of process safety, it is reasonable to assess the equipment requirements of a design which maintains a pre-determined maximum temperature. Operation under these conditions is achieved when the rate of accumulation of heat in the reactor is compensated by the heat losses – i.e. the system has heat removal capability greater than or equal to the heat generation capability.

To assess the critical diameter, the simplest approach assumes that a constant temperature profile exists across each channel of a microreactor (Semenov model). However, the assumption of a constant temperature profile in microreactors fails, as the heat flux is mainly controlled by the molecular thermal conductivity of the reaction medium inside the channels and only partly by turbulent mixing of the reaction mixture. Frank Kamenetskii used the thermal conductivity to define steady state conditions without auto-acceleration of the reaction mixture. The temperature profile across a channel is not constant but has the shape of a parabola given by the thermal diffusivity.

In this assessment, the potential complex channel structure of MS-equipment is simplified by a tubular reactor with an equivalent diameter d_r, although it is known that deviating geometrical forms lead to different parameters which has to be accounted for when applying the equations to different geometric forms of the channels. Similarly, other parameters which influence the heat transfer are not fully considered (including the effect of convective heat transfer which becomes significant as diameter increases).

For conductive heat transfer, the Frank-Kamenetskii model gives:-

$$\frac{dT_{medium}}{dt} \approx \frac{-\lambda}{d_r^{\,2}} \bullet \frac{4f}{(c_p * \rho)} \left(T_{medium} - T_{wall}\right)$$

Eqn 5-4

Specifying $\vartheta = T_{medium} - T_{wall}$ then

$$\left(\frac{d\vartheta}{dt}\right)_{cooling} \approx \frac{-\lambda}{d_r^{\,2}} \bullet \frac{4f}{(c_p * \rho)} \vartheta$$

Eqn 5-5

For heat release by chemical reaction inside tubular reactor with diameter d_r (Frank-Kamenetskii model):

$$\left(\frac{d\vartheta}{dt}\right)_{reaction} \approx k_0 \bullet \exp\left(\frac{-E_A}{RT_{wall}}\right) \bullet \exp\left(\frac{E_A \vartheta}{RT_{wall}^{\,2}}\right) \bullet (1-\chi)^m \bullet \Delta T_{adiabatic}$$

Eqn 5-6

with T_{medium} = Fluid temperature at centre of channel
T_{wall} = Wall temperature
θ = $T_{medium} - T_{wall}$
t = time
λ = thermal conductivity
d_r = hydraulic diameter
f = geometry factor (3.66 for circular channel)
c_P = specific heat capacity
ρ = density
k_0 = frequency factor
E_A = activation energy in Arrhenius equation
χ = chemical conversion ratio
m = reaction order
$\Delta T_{adiabatic}$ = potential adiabatic temperature rise

Note that Eqn 5-6 is only correct for small temperature gaps between medium and wall, which is the case for the demanded boundary limits for safe processing. The usual assumptions for the Frank-Kamenetskii model apply.

Inherently safe processing is obtained when the actual flow diameter of the microreactor is smaller than a critical tube diameter $d_{critical}$. If the chemical conversion with time is not considered, a simple relationship between $d_{critical}$ and T_{wall} can be derived from Eqn 5-5 and Eqn 5-6 with the assumption of steady state between heat release and cooling capacity:

$$d^2{}_{critical} \approx \frac{\vartheta}{\Delta T_{adiabatic}} \bullet \frac{1}{k_0 \bullet \exp\left(\frac{-E_A}{RT_{wall}}\right) \bullet \exp\left(\frac{E_A \vartheta}{RT_{wall}^{\,2}}\right)} \bullet \frac{4f\lambda}{\rho c_p}$$

Eqn 5-7

with $\vartheta \approx 10K \quad depending\ on\ T_{wall}\ and\ E_A$

This equation, Eqn 5-7, applies equally to liquid and gaseous reaction systems. In the case of catalysed gaseous reactions the kinetic is determined by the activity of the catalyst and the physical absorption processes on the surface. A meaningful generic rate constant cannot be given.

For homogeneous liquid phase reactions, the dependence of the critical diameter, $d_{critical}$, on the both the operating temperature and the temperature difference between the maximum operating temperature and the wall temperature for a band of activation energies is presented Figure 5-9 and Figure 5-10 respectively.

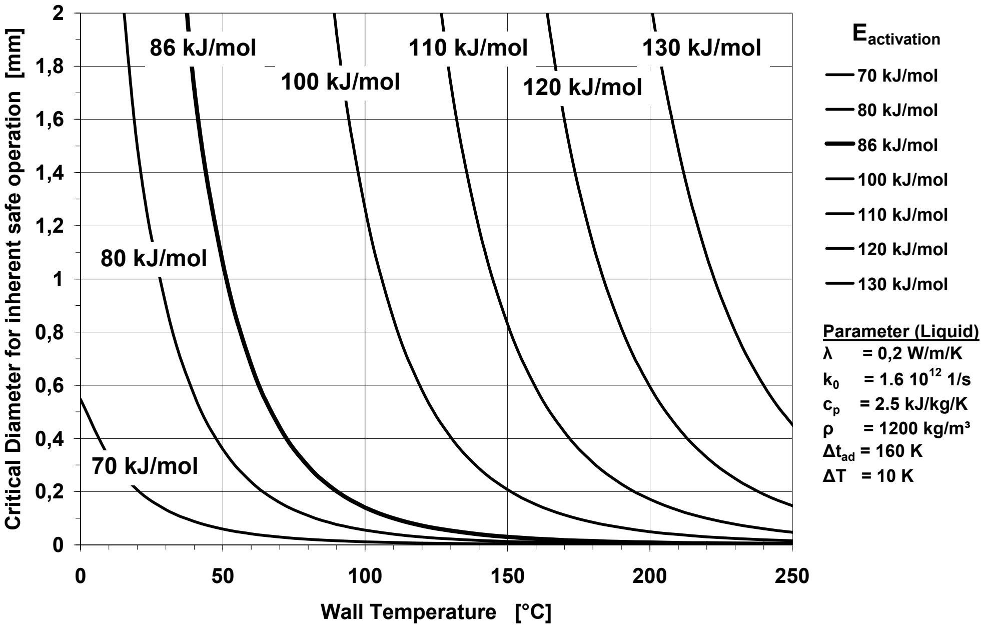

Figure 5-9 Dependence of critical diameter on wall temperature for a range of activation energies

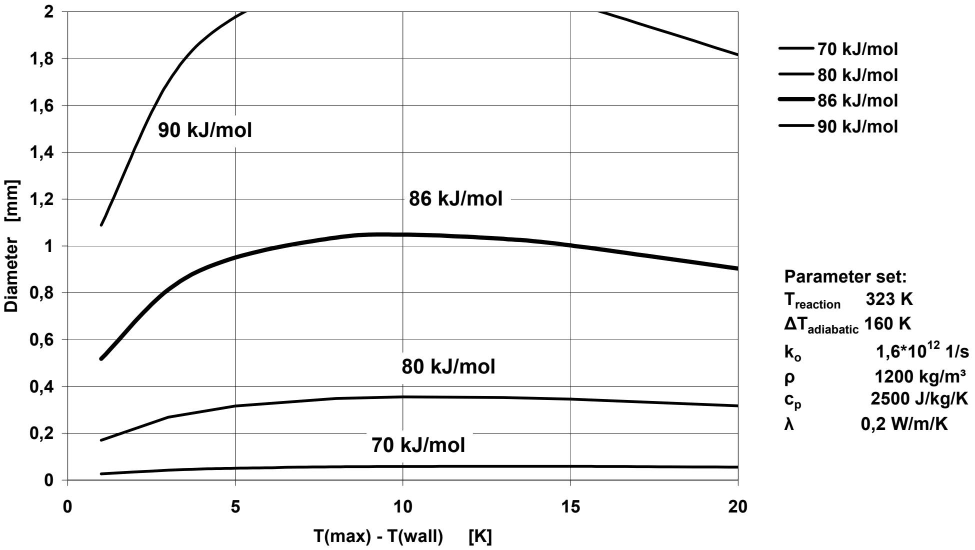

Figure 5-10 Dependence of critical diameter on temperature difference for a range of activation energies

Clearly, there are several other parameters in the equation for the calculation of the critical diameter and these graphs are indicative only of the effect of temperature as a design variable and activation energy as a process parameter. The other parameters used in this example are taken from published data for the alkylation of methylimidazole by diethylsulphate (Böwing[l], Renken[m]).

One further feature which is worth highlighting is that if the critical diameter is found to be lower than would be acceptable due to other process requirements, it should be noted that the critical diameter is inversely proportional to the square root of the adiabatic temperature rise. Thus, if there is a minimum acceptable channel size due to some other process requirement, it will be possible to increase the critical diameter by reducing the adiabatic temperature rise – e.g. by diluting the reaction mixture with (additional) solvent.

5.7.1.3 Environmental Comparisons

There are many environmental comparison metrics available, all of which are reasonably simple but have some deficiencies which will require the process technologist to consult within their organisation and apply judgement. Of the many available, IMPULSE recommends the use of those listed below, each of which considers specific features of waste generation.

- Mass intensity & Mass Productivity[n]
  Mass intensity is a simple environmental metric which takes account of mass of reagents used, solvent usage and yields. This metric deliberately *excludes water* used in the process as it is assumed that water will have a low environmental impact. This is an attempt to avoid discriminating against processes with a larger quantity of low environmental burden waste over processes with a higher environmental burden. Mass productivity is then the reciprocal of mass intensity expressed as a percentage. High mass productivity is preferred. This is an overall metric.
  Mass Intensity = (Total mass used in process or process step excluding water) / (Mass of product)
  Mass productivity = (1/ mass Intensity) x 100
- Reaction Mass Efficiency[o]
  This is a specific metric for comparison of reactions and has been proposed by GSK. It incorporates atom economy (a metric normally at 100% yield and stoichiometric reactant ratios) and also includes yield and the stoichiometry of reactants. It excludes solvents and catalysts. It is intended to compare reactions schemes and is superior to atom economy as it takes into account stoichiometry and yield. High reaction mass efficiency is preferred.
  Reaction Mass Efficiency = (Mass of product) / Total mass of reactants used
- Solvent Efficiency
  Solvent efficiency is a measure of the amount of solvent used as a percentage of the total waste produced. This means that a low % solvent efficiency is preferred as most of the waste produced is not from the solvents used in the process. This is metric is related to the reaction concentrations and any recycle processes.
  Solvent Efficiency = (Mass of solvent excluding water used / Total Mass of waste excluding water produced) x 100

While these metrics have reasonable strength in comparing broadly similar processes or for use to prioritise improvement opportunities within a process, they may lack the sophistication to discriminate between process options generating waste streams of significantly different environmental burden as may arise through the application of the IMPULSE methodology. For example, a low inventory microscale facility may allow adoption of a process with a toxic intermediate which results in a small quantity of toxic waste and the alternative process may be use a different chemical route with no toxic waste but a much larger quantity. Is the greater mass productivity of the option with toxic waste better or worse than the lower mass productivity of the option with no toxic waste? Such a decision requires the process technologist to apply judgement after consultation with the broader organisation. Further, the decision on which is better may depend on site location, as one site may have a facility for rendering the toxic waste harmless while another can more readily handle the large quantity of non-toxic waste. As a result, these metrics are recommended for use in conjunction with the judgement of the process technologist and consultation with the broader organisation.

It also must be noted that care must be taken when comparing processes and assigning environmental metrics as, during early phases of decision making, some processes may be ill-defined and not well developed. This can result in the deselection of the most developed process (to avoid known problems while the problems of the less developed options remain unknown) or the automatic selection of the most developed process (as it has the best demonstrated performance) and either practice should be avoided. For the very first pass, it may be appropriate to assess the processes on an equal footing, such as the assumption of 100% yield, 1:1 stoichiometry and 100% solvent recycle. However, it should be noted that this will fail to differentiate between microscale and macroscale even where microscale has a significant advantage. As a result, it may be appropriate to adopt a similar strategy to that proposed for cost comparisons (see section 4.3 above) and maintain for each option the optimistic performance (the best it could do), the pessimistic performance (the worst it could do), the realistic performance (the most likely outcome) and the current performance. As options proceed, this range should narrow. Initial comparisons should possibly place greatest weight on the optimistic performance, while later comparisons will place greater weight on the realistic performance although at some points it may prove necessary to reject options where the pessimistic performance does not satisfy some minimum criterion. Each of these performance assessments should be recorded with full documentation of the assumptions and data underlying the assessment.

It should be noted that whilst some advocates of microreactors claim that the high reaction rates employed in microreactors allows the use of stoichiometric ratios, this is unlikely to be the case in a real manufacturing facility. While the speed of reaction may allow the use of stoichiometric ratios, part of the reason for an excess of one reagent is to compensate for errors in flow measurement and analysis which mean that actual flows of reactants will differ from the design intent. Attempting to operate at stoichiometric ratio means that sometimes there will be an excess of one reactant[15] and sometimes the other and this places an uncertain duty on any downstream separation equipment (see also section 5.5.3.1 above). Use of an appropriate excess guarantees that one particular reactant is always in excess and the duty of the downstream separation process is always the removal of that excess reactant although the quantity to be removed will vary within a range determined by the potential fluctuations in the ratio. Indeed, depending on the particular needs of a reaction, it may be necessary to employ a higher stoichiometric ratio in scaled out systems to compensate for the additional potential deviation from design intent of non-uniform distribution (see section 5.5.1 above).

In later assessment it will be appropriate to consider the cost of disposal and abatement of waste. As has previously been mentioned, such costs may differ by location and it is important to ensure that the boundary of the costings is known and consciously stated.

Is the boundary a) just the process b) process + abatement costs, c) process + abatement + solvent or reagent recovery costs d) costs to plant boundary, e) costs to site boundary, f) full life-cycle cost analysis etc. Early decision making points may be based on just the process, progressing to more detailed levels as the project proceeds. For these later costings, for products to be manufactured in a centralised facility, it may be necessary to include location as part of each option and the “best” process choice may differ between one location and another due to differences in waste handling capability. For products to be manufactured in distributed facilities, assuming that a single manufacturing process will be deployed in all locations but that each facility may use its most suitable local waste handling capability, a more complex balance of waste treatment costs will be required.

Where possible, it is recommended that waste costs to the site boundary are considered, as this presents a wide enough boundary to encompass nearly all differences between processes and most companies have readily accessible data for the waste disposal costs at the site boundary. It is important not to forget solvent abatement costs and those from decontamination of waste streams (e.g. cyanide removal by treatment with bleach and NaOH, treatment to avoid self-heating etc.).

5.7.1.4 ATEX & Pressure Equipment Directive for Microdevices

At the time when the IMPULSE project was underway, few examples of microdevices existed in a production environment. It is hoped that as time passes, microdevices in a production environment will be more common and these comments on ATEX and the Pressure Equipment Directive (PED) will be unnecessary. However, lack of knowledge of the impact of these areas of legislation on implementation of microdevices is a potential impediment to adoption of the technology and some initial consideration has been undertaken. Note that this consideration has addressed requirements within the EU and it will need to be reviewed more extensively for other locations.

ATEX regulation place a requirement on the plant operator to assess the extent and frequency of flammable atmospheres, record that assessment process and the designate zones delineating the different levels of risk (zones). Equipment used must then be suitable for use within the zone. The introduction of microdevices is not expected to have any impact on compliance with ATEX.

The situation with the PED has some slight potential to impact on project timelines, but effective early consideration of the issues has the potential to avoid any impact. The first question is whether microdevices will be standardised or custom devices. In the former case, it would be expected that

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[15] Or impurities produced due to that reactant being in excess

the manufacturer will have already achieved the PED requirements for their standard microdevice. A custom device will require consideration on a case by case basis.

A preliminary view of the requirements can be determined by considering the equipment characterisation as defined in the PED using Figure 5-11 below where PS is the system design pressure in barg and V is the volume in litres. Note that the system design pressure may need to be specified so that the equipment will contain an abnormal event either within the device or in neighbouring devices and may therefore be significantly higher than the operating pressure. Some items of equipment will fall within the zone marked “Article 3, paragraph 3” and will fall outside the scope of the PED. For such devices, the requirement is that the device be designed and manufactured using sound engineering practice. For custom devices falling outside this region, interaction between the operator, the equipment vendor and an appropriate independent authority will be required. To avoid adverse impact on the timeline, it is recommended that this interaction be initiated in consultation with the relevant professionals within the process technologist’s organisation as soon as the possible requirement is identified. FZK have successfully achieved the necessary approvals on at least one industrial device with no reported difficulties.

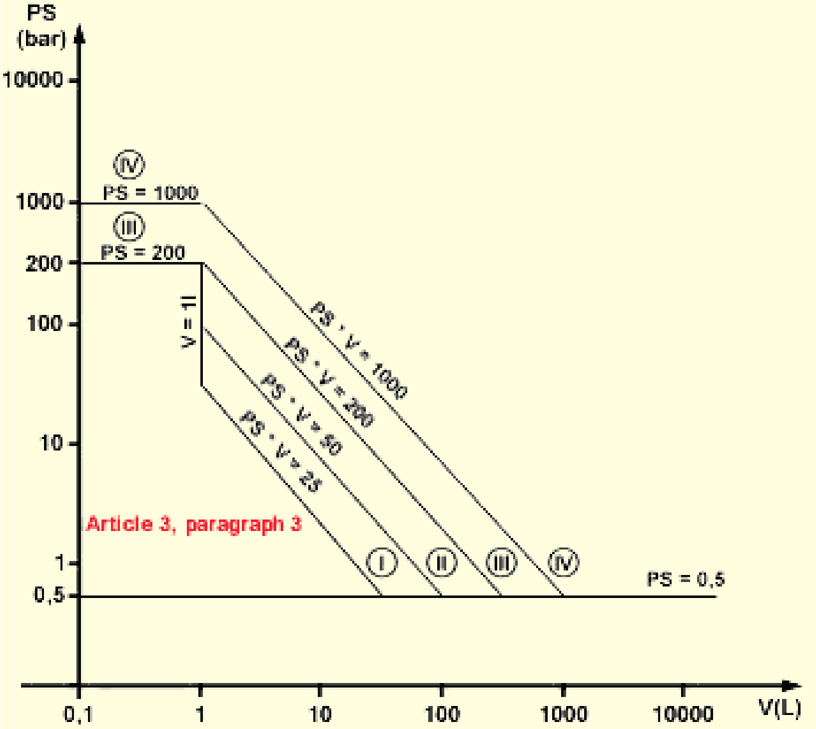

Figure 5-11 PED Categorisation

5.7.2 Abnormal Operating Conditions

See also section 5.5 above.

It is presumed that process technologists are familiar with the assessment of hazards and techniques for their investigation in macroscale and mesoscale equipment. The major advantages of the HAZOP method is the systematic way in which the study is carried out with well defined and codified guiding words for the deviations, especially for less familiar systems. In this way, no major deviations should be overlooked. However, HAZOP studies are generally carried out at a fairly advanced stage when the piping and instrument diagram (PID) becomes available. A technique is required which can be employed and is useful even when comparing options and where the level of definition of each option is low (e.g. a simple process representation of the type described in section 5.3 above). The most promising method for multiscale systems is a synergy between the HAZOP and Preliminary Hazard Assessment (PHA) methods because the three weak points of the HAZOP method sited above can be addressed by the principles of the PHA method. This objective is then to obtain a HAZOP-LIKE method that favours the following benefits:

- it is applicable to thermodynamic systems and fluid flows,
- the basic concept of the HAZOP method is widely used in industry,
- it is well structured and the systematic approach is translated into a list of fixed guiding words for defining the deviations to be studied,
- it gives the opportunity to prioritise the efforts to improve the safety of the installation,
- it can be carried out at the early stages of design in order to evaluate the potential trouble spots as early as possible in order to integrate the necessary safety measures. This method can also be used at later stages of the design process to verify that the hazards are kept at an acceptable level.

Such a technique is considered applicable to microscale equipment, but the particular characteristics of microscale equipment will require some adjustments, partly to compensate for teams having less familiarity with microscale devices. Annex 3 below highlights some particular additional considerations for some existing HAZOP keywords and suggests some extensions to the use of HAZOP keywords as will be discussed further in section 5.7.2.1 below.

Much has been written about the advantages of microscale devices, indeed turning these potential advantages into business benefit is the primary purpose of developing the IMPULSE methodology. However, much of what has been written about microscale devices has been written by those advocating their use and the advantages are frequently not balanced by the disadvantages. Claimed advantages which have associated but frequently unstated disadvantages include:-

- Low inventory so that in the event of catastrophic failure the quantity of material released is reduced, but, while this is a clear advantage in comparison to a batch facility, the release from a continuous facility is a function of the process flow and the time to detect the catastrophic failure and stop the flow.
- High heat removal allowing operation closer to runaway conditions where this has a business benefit and preventing runaway, but this also means that the process operation is much more sensitive to coolant temperature and flow and there is greater potential to overcool and allow incomplete reaction products to pass to downstream equipment which cannot safely contain the unintended inventory of reactants.

As with all aspects of multiscale design, it is necessary to focus neither on the advantages nor on the disadvantages. The requirement is to deliver the balance of advantages and disadvantages which best satisfy the business requirement.

5.7.2.1 Background to the Amended HAZOP Keywords

Characterisation of the heat transfer performance of microdevices shows an excellent heat removal capability. Heat removal capabilities in the range 5000-15000kW.m^{-3}.K^{-1} can be delivered. These heat removal capabilities allow operation at conditions which could not be delivered in a device with larger dimensions. However, this same capability also creates some additional sensitivity. The graph below shows the output of a simplified model for the performance of a microdevice under normal and abnormal circumstances. For simplicity, an isothermal coolant has been assumed and plug flow with no axial temperature, concentration or velocity gradient has been assumed on the reaction side. The system modelled assumes a design intent of 95% completion at the end of the reaction with a 50ºC coolant temperature. The reaction is assumed to have:-

- reaction feeds instantaneously mixed on entry to the reactor at 50ºC
- an activation energy of 120kJ.mol^{-1}
- a second order rate constant of 10^{-4} l.mol^{-1}.s^{-1} at 50ºC
- a heat of reaction of -90kJmol^{-1} which is constant in the temperature range of interest
- a starting concentration of 3mol.l^{-1} for the limiting reactant and a 5% excess of the other
- 800kg.m^{-3} density and a specific heat of 2.5kJ.kg^{-1}.K^{-1}
- Giving an adiabatic temperature rise of 135ºC for complete reaction

Two cases are displayed, one with the coolant at the design intent of 50ºC, the other with the abnormal condition of coolant at 49ºC.

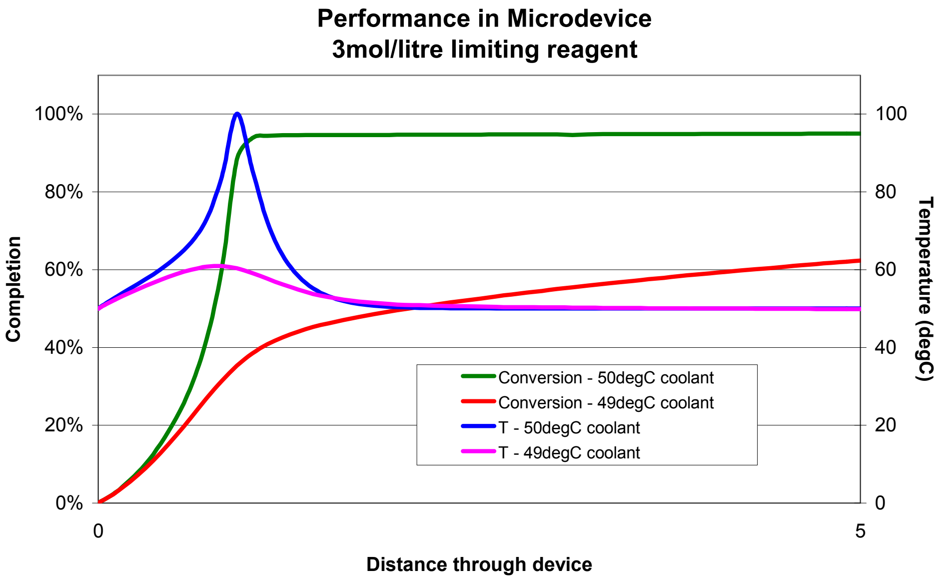

Figure 5-12 Sensitivity of Microdevices – Temperature Effects

As can be seen from the displayed profiles, a 1ºC difference in coolant temperature can reduce the achieved conversion from the design intent of 95% to 63%. As a result, the initial rate of reaction in the downstream device will be ~30 times higher than its design intent. While the microreactor is not directly adversely affected by this minor deviation, the downstream effects have the potential to be serious including the potential for a runaway reaction in downstream equipment. The particular sensitivity in Figure 5-12 above arises because a 50ºC coolant temperature is above the critical temperature at which a runaway reaction occurs and even the high heat transfer capability of a microdevice is incapable of controlling the runaway until the reaction is nearing completion. The minor reduction in coolant temperature brings the reaction under control. Similarly, a reduction in concentration can both bring the reaction under control and reduce sensitivity to temperature and Figure 5-13 below shows the same reaction with an initial concentration of 2.75mol.l^{-1} of the limiting reactant. Note also the difference in residence time between the two cases with the “design intent” case in Figure 5-12 requiring a residence time of only 5 seconds, whereas the less concentrated case requires a residence time of 68seconds. With 49ºC coolant, the design intent conversion of 95% is achieved after 70 seconds from a starting concentration of 3mol.l^{-1} and 78seconds from a starting concentration of 2.75mol.l^{-1}.

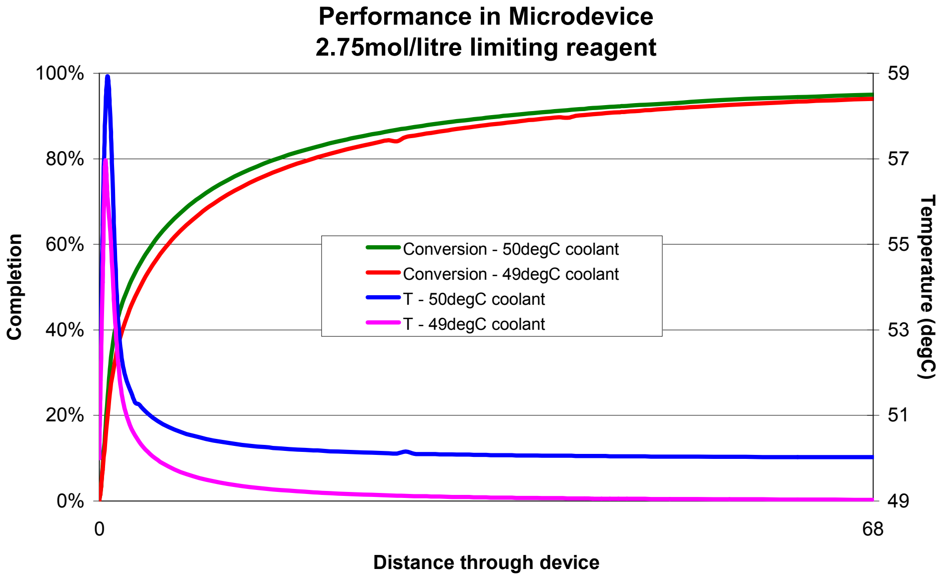

Figure 5-13 Sensitivity of Microdevices – Lower Concentration

This highlights the need to carefully characterise both the reaction and the device and the importance of modelling. The original “design intent” case would not be apparent in experimentation as the exit temperature remains close to the coolant temperature and will only be understood through proper characterisation. In addition to the potential to cause problems in downstream devices, it should be noted that the operation of the microdevice at design intent is far from isothermal. This highlights the need to consider temperature effects when fitting kinetics even in a microdevice (see section 5.10.2.2 below). Further, the output of the model invalidates its own assumptions of no axial gradients within a channel. Given the extent of the deviation from isothermal behaviour, an axial temperature gradient must be expected in addition to the axial velocity profile which is known to be present in laminar flow.

Advocates of microdevices outside of IMPULSE frequently advocate a simple scale out concept, where it is suggested that the fact that one microdevice operates effectively in the laboratory means that increased throughput can be achieved simply by increasing the number of devices. The example illustrated above shows that the dynamics of microdevices are such that minor deviations in input parameters can result in major deviations in output and the time available to react to a process deviation is much shorter than in larger equipment with slower dynamics.

For process technologists less familiar with microscale devices, such small deviations may be given little consideration. In a batch reactor, the reaction above would be operated at a much lower rate by reducing the overall concentration and titrating one reactant into the mixture so that the reaction rate was within the capability of the heat removal system and the quantity of accumulated unreacted material in the reactor could not cause a loss of containment (under normal operation). Typically, the coolant temperature may be 20ºC or more below the reaction temperature and a short term 1ºC fluctuation in coolant temperature will have little effect. Indeed, the cooling capability might be reduced by 5% if the coolant temperature increased by 1ºC, but a control system could easily cope with this. In the microdevice, the deviation is potentially more severe and there is less time to act. As a result, an extension to the HAZOP methodology is proposed with additional guidance to be applied to microscale devices. Further, it is suggested that the traditional HAZOP record table is amended to include an additional column to record how a deviation will be detected.

For example, if corrosion/erosion is occurring in a microdevice, can it be detected before failure of the equipment? In larger scale equipment, the time to loss of integrity due to corrosion/erosion will be measured in months or years and periodic physical inspection is a reasonable protective measure. How would this be achieved for a microdevice which is both more difficult to inspect and has a shorter time to failure due to thinner walls? Similar examples could be presented for many other deviations.

This extended HAZOP guidance is provided in Annex 3 below. Note that this is additional to any other HAZOP guidewords normally applied.

5.7.2.2 Capability of Microdevices to Quench Explosions

Flame and explosion arrestors employ narrow channels and it could be postulated that the narrow channels of microdevices can suppress an explosion initiated in the adjacent equipment. Within IMPULSE, currently available literature has been reviewed and it has been concluded that (based on the work of Lewis[p] and the work within the SAFEKINEX-project[q]) microdevices can be considered as inherently safe regarding initiation of a propagating explosion inside of the equipment. The energy density per volume is too low in general to initiate sustainable combustion.

However, review of literature relating to explosions initiated in connected devices (Brandes[r], Liebner[s], Pfeifer[t], Wu[u] and data in the Chemsafe® databank[v]) indicates that inherently safe microdesigned equipment regarding suppression of explosions is unlikely to be achieved for applications at pressures above atmospheric and allowing for pressure piling in connected equipment, microdevices should not be considered capable of suppressing explosions. Where a risk of explosion exists, appropriate additional measures should be incorporated in the design to reduce the risk and/or consequence to an acceptable level.

5.8 Distributed Production

In some cases, a move to multiscale processes may be more suited to distributed production than traditional processing, particularly where a process is suited to continuous processing in micro- and meso- devices. Typically, the benefit of distributed production is proximity to market, which facilitates reduced stock holding of the final product and greater responsiveness to market demand. There will be a corresponding increase in the quantity of stock of the feed materials for the distributed facilities. However, the final product is the highest added-value material and the value of the stock holding and hence the working capital is minimised. However, the capital cost of multiple smaller facilities is likely to be greater than the capital cost of a single facility even where it is feasible to use a common design for each facility.

A further benefit is that each of the distributed facilities is smaller than a central facility and the consequence of any accident should be correspondingly reduced. Note that when comparing the consequence, the comparison should be between the distributed multiscale facilities and a central multiscale facility. The comparison between traditional and multiscale is a separate decision.

It should be noted that there are also other disadvantages of distributed production. The quantity of raw materials requiring transport will generally exceed the quantity of product requiring transport (except where a locally available raw material is a major component of the product), so the total cost and environmental impact of transport will often increase compared to a central facility. Further, where the raw materials are hazardous, the number of transport vehicles and hence the likelihood of a transport accident increases – albeit with potentially reduced consequence due to reduced inventory.

Globally, distributed production facilities require a greater number of trained personnel with each location requiring a similar number of staff directly involved in operation to that required for a single central facility. Further, if each distributed production facility is wholly independent, there are likely to be fewer personnel providing the support functions for the production facility. As a result, each of the support staff will be responsible for a broader range of functions and locally available expertise will be lower than would be available in a single central facility. This latter potential issue may be addressed by choosing to group several distributed production facilities for different products to a level which justifies a critical mass of key support personnel.

Similarly, provision of effluent treatment for individual distributed facilities (or transport of waste back to a central facility) will incur additional cost. Options for provision of site utilities may be more limited, more expensive and less environmentally sound. Again, these potential issues may be partially addressed by choosing to group several distributed production facilities for different products

With regard to accidents, the probability of an incident associated with each distributed facility will be no lower than that of the central facility (and may be higher if it is not possible to provide similarly qualified personnel in the distributed facilities). As a result, the probability of an incident somewhere in the company associated with a product being manufactured in distributed facilities is higher than it would be in a single central facility by a factor of at least the number of distributed facilities. However, it is reasonable to assume that any incident which does occur will be less severe.

Ultimately, the working capital, market responsiveness and probable reduction in incident severity must be balanced against the potential increases in capital cost, environmental impact and likelihood of an incident. Both the benefits and the potential problems have a strong dependence on the nature of the product, its production process and the company strategy. As a result, decisions on distributed manufacture must be considered on a case-by-case basis by the business team, although it may first be necessary to develop company strategy at a still higher level.

5.9 Modelling in Multiscale

Simulation is the act of representing some aspects of the *real world* by numbers or symbols which may be manipulated to facilitate their study. With respect to multiscale processing, the *real world* is a chemical process described by a process flowsheet. During the IMPULSE project, the Aspen software suite has been used as a foundation for modelling though it has been necessary to add user-specified modules from programs such as Fluent (CFD) and Matlab or user-written modules in FORTRAN.

As is discussed in section 5.5 above, process deviations propagate through a continuous plant. Whilst the pharmaceutical, fine chemicals and consumer goods sectors have used mainly batch processing, there has been scope to implement a considered response to process deviation by manual intervention (even where that intervention may be to abandon a batch). Many multiscale processes will include continuous processing and this requires a prior understanding of the consequence of process deviations together with an understanding of the appropriate strategies to implement in response to deviation. Such evaluations may be undertaken based on the judgement of the process technologist, but a better approach would be the application of process simulation.

The fundamental approach is set out in the flowsheet below:-

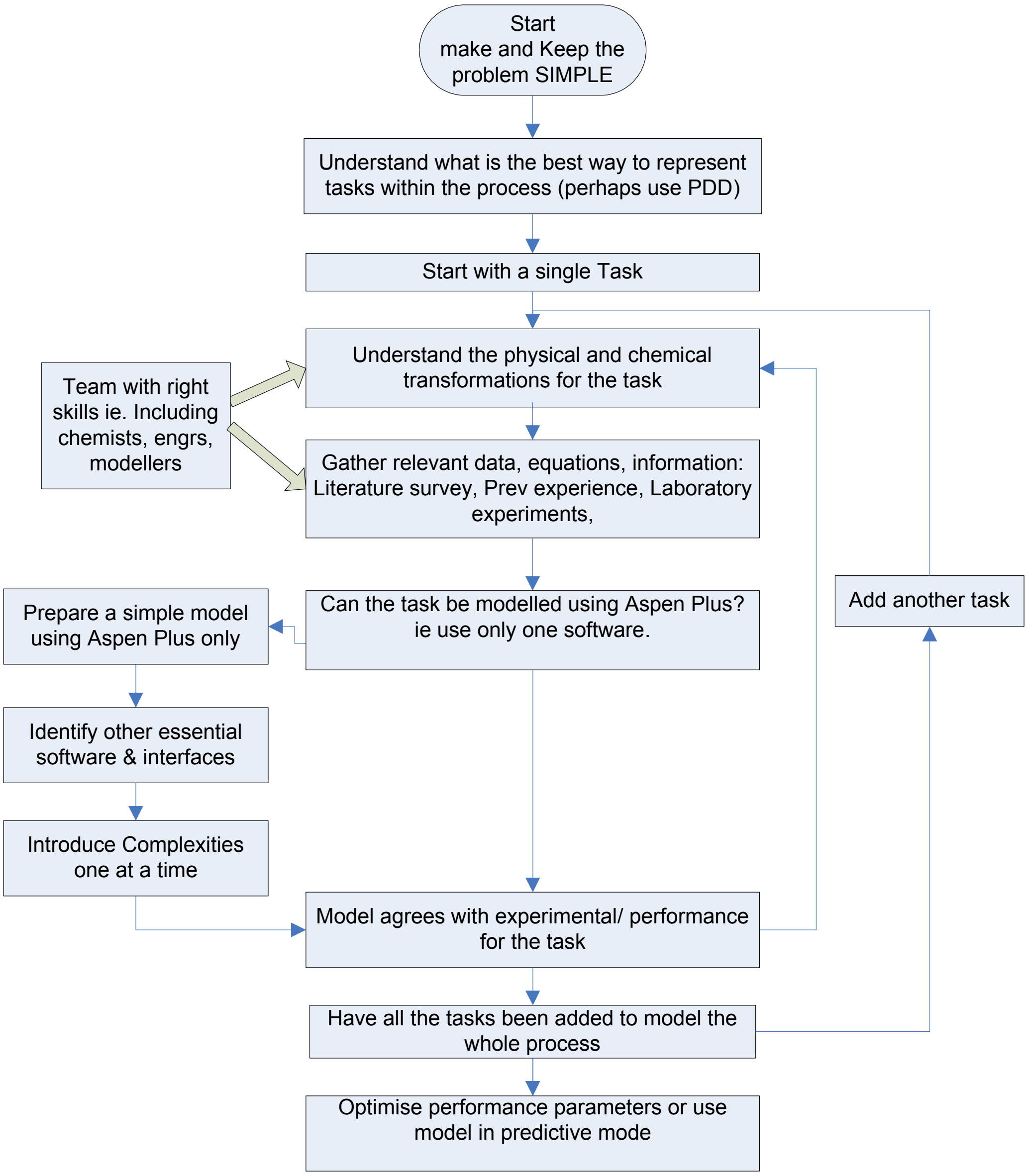

Figure 5-14 Generic methodology of whole process modelling

Particular issues associated with modelling in the pharmaceutical, fine chemicals and consumer goods sectors include the fact that many mixture components (other than solvents and the simplest raw materials) are not available in commercially available component databases. If process simulation is to become a common approach, it is necessary for process technologists to store information on compounds which are not in the commercially available database in a form and in a location which is at least accessible within their own company. Where such information is measured and made available for use within the commercially available application, it is essential that the datasets are mutually consistent (e.g. if NRTL parameters to describe a vapour-liquid equilibrium are fitted using one set of vapour pressure correlations but will be used with a different set of vapour pressure correlations within the simulation, an immediate systematic error is introduced[16]). Selection of standard correlations to be used should take place before any experimental measurements so that any fitting of experimental measurements undertaken will be built on those standard calculations.

Similarly, some process operations will not be available in commercial simulators and user modules will need to be generated using Aspen Custom modeller or some other tool which can be readily interfaced with the simulation package. Note that as indicated in Fig above, each module should be

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[16] This can be particularly problematic is using published fits for binary equilibrium systems. A ternary vapour-liquid equilibrium will generally be simulated using data fitted to the three binary pairs, A-B, A-C & B-C. If different vapour pressure correlations are used for A and/or B and/or C in the published fits, then the fitted parameters should not be used. In such circumstances, it is preferable to refit experimental data using a single vapour pressure correlation for each species.

tested as a separate entity before combining it with adjacent modules. If modules are not available in the commercial software, it is highly preferable that the process technologist ensure that the modules are stored in a location which is at least accessible within their own company. This will require the modules to be written so that physical properties are acquired from the main simulator package and not built into the module. Microdevices are typically not included within commercial software systems and will require the generation of user-specific modules. However, two modules have been made available within IMPULSE which allow simple simulation of scale out to multiple devices. These are "ESCALADR" (which multiplies the output of a single device by N to scale out to N parallel devices) and "REDUC-X" (which divides a stream by N so that it can be modelled as N parallel devices in a scale out scenario). Note that it may be worth modelling microdevices as two parallel blocks of N_1 and N_2 devices (where N_1 and N_2 add to N, but may not be equal to each other) to simplify the investigation of maldistribution. Also note that once these modules are used to simulate the scale out to multiple parallel devices, it may be possible to use an existing commercial module to model the individual device.

Finally and particularly in the case of microscale equipment, it should be noted that the volume and residence time of connecting pipe work may be significant in comparison to the microdevice. Consideration should always be given to modelling the residence time in the pipe work.

Since there can be many ways to solve a set of equations representing a mathematical model, it is necessary to have a simulation strategy which ensures that the simulation problem is solved efficiently and that the simulation results are reliable. Reliability also depends on the model correctness. Use of inappropriate models or model parameters may result in erroneous simulation results. Results verification is the most important step of process simulation. Where feasible, it should initially be applied to individual modules, building up gradually by adding tasks to the final model. The following main attributes of solution must be verified at least:

- The results should be in reasonable agreement with known experimental results
- The trends of solution(s) must match the observed result trends and must be physically acceptable
- When some discrepancy arises, a new cycle of model development with modified problem specification (including the new model assumptions) should be started

Early implementation of process simulation may be problematic because of the absence of property information on key compounds and the lack of key process modules. Provided that the property information on compounds and developed process modules are readily accessible, process simulation will become progressively simpler. Ultimately, process simulation should be the preferred approach although early examples may need to proceed based on the judgement of the process technologist and selected experimental investigation of deviations from design intent. Nevertheless, examining the propagation of process deviations through a continuous multiscale facility, it should be clear that process simulation has the potential to offer much greater value than continued reliance on judgement and selected experimental investigation. If adoption of multiscale processing is a serious goal, development of a simulation strategy based on availability of property information for compounds not in the commercial software and availability of modules to model novel equipment.

5.10 Obtaining Data in Support of Decisions and/or Modelling

5.10.1 General Data Requirements

All data is subject to some uncertainty and will have an associated accuracy. As part of the collection or measurement of data, it is essential that there is some assessment of the accuracy of the data. Further, the overall performance of the business opportunity should be assessed across the range of possible values of the data gathered and the sensitivity to potential error in the data assessed. This applies equally to technical data and business environment data. The success or failure of a business opportunity is at least as dependent on the business environment as it is on technical data. For all data, it can be important to ask:-

1. How do I intend to use the information?[17]
2. How accurate does the information need to be?
3. Can I obtain the information sought from a reliable source with the required level of accuracy?
4. If I need to collect the data, can I collect any additional data for little additional cost at the same time for later use?

During the design process, data is required on the market, the legislative situation, the facility location and services, the plant, the equipment, the process and the product. Existing sources of information are assumed to be used for the market, the legislative situation and the facility location and services. Equipment data will be generated through a combination of the design process and interaction with vendors. Some equipment data may be available in the Equipment Database and, particularly later in the design process, it may be necessary to characterise the performance of some items of equipment for the actual process under consideration.

Plant, process and product data will be generated through the design process. Process and product data requirements include physical properties for single compounds, equilibrium data and rate data. Physical properties for single compounds and equilibrium data are scale independent and existing techniques can and should be used for their collection. As is discussed in section 5.2 above, mass and heat transfer rates have scale dependence and homogeneous chemical reaction rates do not. However, observed chemical reaction rates are frequently determined by the interaction between the chemical reaction and transfer phenomena. As such, care is required in the collection and use of chemical reaction rate data. This will be discussed further below.

Mass and heat transfer data is strongly scale and equipment dependent and, during the early part of the design, it will frequently be appropriate to obtain characterisation data from the vendor or from the Equipment Database. Such characterisations will generally have been undertaken using simple operating conditions and low hazard materials and it will be necessary to apply judgement to decide how the data should be adjusted for particular process conditions and mixture of real materials. In the latter part of the design process, it may be appropriate to characterise the process in equipment which is a close representation of the planned final equipment. This may be obtained by employing practices supplied by the vendor or by employing a modification of the equipment characterisation instructions (see also section 6.1 below).

5.10.2 Chemical Reaction Rate Data

5.10.2.1 Understanding the Reaction System

Progress of a chemical reaction can be monitored by analysing the reaction mixture through the course of the reaction. The data obtained will represent the observed reaction rate at the

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[17] This may be particularly important in the earlier stages of the design process. Unless there is an immediate need to use the information to confirm or negate a key hypothesis, it may be more effective to undertake some other activity with a higher potential to impact the business performance. For example, if a particular reaction is considered to be very fast, highly exothermic and have selectivity sensitive to temperature, it will be clear at the conceptual design stage that a microreactor is the appropriate technology choice. Knowing how fast and how exothermic only becomes important later in the design process, so effort should not be directed at measuring the kinetics and thermodynamics. However, if the reaction needs to be undertaken to provide material to measure information important in a downstream process step and there is an opportunity to make the measurements with little additional effort, the opportunity should be taken.

experimental conditions employed. However, the observed rate results from a combination of all of the chemical and physical phenomena occurring in the experimental environment.

A kinetic determination study must clearly distinguish between chemical rate effects, chemical equilibrium effects and physically induced phenomena, including heat and mass transfer. To assist in assessing the interactions between the chemical effects and the physically induced phenomena, a diagrammatic representation should be drawn showing as much as is known of the phenomena involved. Britest's Rich Picture[18] offers one method of representation.

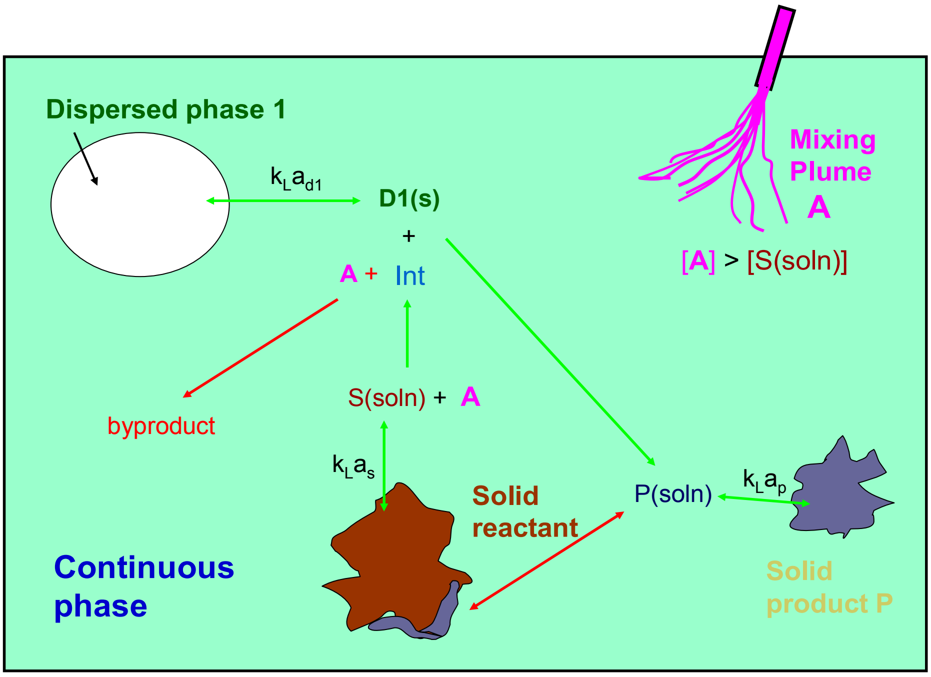

Figure 5-15 Process Representation

Having developed the representation, it can be used in combination with the process technologist's judgement and the project requirements to determine what level of kinetic study is appropriate. Three levels are potentially accessible: the extrinsic, the apparent and the intrinsic kinetics.

- ***Extrinsic kinetics*** can be used for simple approaches and ignore mass/heat transfer induced limitations. The reaction rate data is fitted to an empirical model which integrates all of the phenomena involved into a single rate expression. Some further adjustment may be possible to include effects related to gross mixing times and diffusion through the laminar films. The integration of all of the phenomena into a single expression mean that it is extremely sensitive to the reaction environment in which it was measured and the particular balance of phenomena delivered by the equipment in which the data was measured. This approach can be useful for a fast, yet fully empirical, modelling applied to existing processes in particular equipment. However, extrapolation of this type of model to a different reactor type or different reaction conditions is likely to be extremely unreliable.
- ***Apparent kinetics*** can be employed for some heterogeneous systems and internal transport limitations are included in the model. Measuring kinetics on a full-sized pellet is an example of this approach. This is a pragmatic driven strategy and may be appropriate for investigations around a limited operation window centred on realistic operation conditions for catalyst layers staying within a limited and constant range. Some independence of reactor type may be achieved (provided the catalyst layers throughout the reactor all stay within that fitted range), but extrapolation to different forms or sizes of the same catalyst is extremely unreliable.
- ***Intrinsic kinetics*** are obtained when all the effects of mass/heat transports have been stripped out and when the obtained model represents only the "true" happening chemistry. This is the most useful form of kinetic as it can be implemented in any reactor model, independently of any device induced effect. However, it can be difficult to access and may

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[18] Britest Ltd Intellectual Property

be impossible in some tricky cases. In such cases, *justified* simplifications such as *lumping* may be appropriate.

The representation of the chemical and transfer phenomena can be used to define experimental conditions where any effects of chemical equilibria or transfer phenomena can be eliminated or controlled. Further the representation can be used to consider how to test that the limitations of the non-reaction phenomena have been overcome. For example, if mixing and/or mass transfer has the potential to influence the apparent reaction performance, it may be appropriate to measure the reaction performance under two significantly different mixing regimes. If both cases show the same reaction performance, it is likely the mixing and/or mass transfer rates delivered are not limiting the observed reaction rate. If the reaction performance is different in the two cases, then one or both of the experimental regimes are limited by mixing and/or mass transfer and the observed performance is not the intrinsic performance. In such cases, further study with improved mixing and/or mass transfer would be required to obtain intrinsic kinetic data.

5.10.2.2 Experimental Design for Kinetic Measurement

Early in IMPULSE, the use of microstructured elements as laboratory tools for kinetic studies was reviewed. Despite the claims that microstructured elements could be used for this purpose, none of the published papers reviewed sought to measure kinetics as the primary purpose of the reported work. Further, where kinetic analysis was undertaken, isothermal operation with no transfer limitations is generally assumed with little or no characterisation of the device. Such an assumption may appear valid as exit temperature will frequently be close to the coolant temperature, although as can be seen from the simple model in Figure 5-12 above, the reality may be somewhat different.

Nevertheless, structured microreactors possibly offer the closest approach to a system which overcomes the limitations of transfer phenomena and may be an appropriate tool for measurement of intrinsic kinetics in some cases. As can be seen from the example, a close approach to isothermal operation should only be assumed after careful consideration. Initial work under high dilution conditions to give a first indication of the kinetics may be appropriate and can be combined with data on the heat of reaction to generate a simple model such as that in Figure 5-12 above. Such a model can then be used to determine the extent to which characterisation of the microreactor in terms of Residence Time Distribution, heat and mass transfer performance is required to allow creation of a reactor model for fitting the intrinsic kinetics. Solely measuring the kinetics under dilute conditions is not appropriate as the kinetic expression should be demonstrably capable of modelling the reaction over the range of concentrations which will be experienced in the production system.

Rather than using solely microreactors for kinetic measurements, the process representation (Figure 5-15 above), pre-existing process knowledge (e.g. empirical assessment of reaction time), expectation of full-scale reactor type and characterisation of available equipment types should be evaluated to select the appropriate experimental set-up. While microreactors may be less susceptible to local temperature and concentration variations, they are not free from such effects and may be unsuited to systems containing solids. Also, microreactors and some other reactor types may allow measurement only of entrance and exit composition and obtaining measurements at more than one level of reaction completion requires the use of systems with different residence times. Unless in-line sampling or measurement is feasible or reactor length is readily changeable, the different residence times will require the use of different flowrates and this means that each point may represent a different heat and mass transfer intensity.

A key challenge will be the provision of an effective analysis technique, providing accurate, timely analysis of a sufficient number of process components including the minor components. Particularly for fast reactions, this may require an in-line analytical technique or include a requirement for a rapid quench to stop the reaction at the sampled time. For all reactors, residence time between the end of the intended active reaction zone (the reactor itself) and the sample location must be clearly understood and considered in the generation of data. Particularly in the case of a microreactor, the residence time between the reactor and the sample/analysis system can easily be of a similar order of magnitude to the reactor and further reaction may be occurring in that space.

A further requirement of the experimental design is that consideration must be given to the materials used. The use of pure materials may simplify the data interpretation. However, it is also necessary to use materials of a composition likely to be typical of the material to be used in the ultimate production process as impurities in materials may catalyse or poison reactions or participate in undesired reactions. Further, and particularly in the case of microstructured devices, it is necessary to consider whether the device is resilient to the reaction conditions as for highly structured devices even minor corrosion or erosion could modify the internal structure and have an important effect. Also, again particularly in microstructured devices with their high surface area to volume ratio, the ability of the device material to catalyse the desired or undesired reaction should be tested. Even if the material has no capability of catalysing the desired reaction, it may be capable of catalysing degradation of the product. If undetected, such activity can hinder the interpretation of the kinetics. Blank tests with starting materials, product and mixtures lacking one required component for the desired reaction are required to detect such undesired reactions, so that these effects can be incorporated into the analysis of the kinetics for the desired reaction.

Tests should be undertaken under a range of experimental conditions likely to cover the operating range of interest. Data from some subset of the experimental results should be reserved for validation and not used in the fitting of the kinetics. The data reserved for validation should be as different as possible from the data employed in fitting and should be compared to the performance predicted by the fitted kinetics. If the fit is poor, the fitted kinetics are not a good representation of the reaction and further consideration will be required.

5.10.2.3 Kinetic software

A wide variety of software has been used in IMPULSE member companies to fit kinetics. These include solvers (such as Scientist, Parametra, Madonna, ….), specific solvers for reaction engineering (such as ReactOP, Kineticus, ….), dedicated kinetics suites (such as Presto-Kinetics, Chemical Workbench & Chemkin), technical languages (such as Matlab, Femlab, Scilab,….), process simulators (such as Aspen Custom Modeler & gProms) and specific suites for particular reactor types (such as CR & Dynochem).

Given the different core purposes, it is not practical to compare and rate the available software. Indeed, most simple systems, used sensibly by a trained process technologist, will be capable of reach a good modelling result on the basis of available real experimental results. The key determining feature is the quality of the input data and no software can create more precision than is available from the input data. The challenge is to be aware of the inner limits of each suite in order to select the one the most suitable for the specific task. In many cases for kinetic studies, a best practice approach would favour the use of very simple reactor which will be ideally represented by simple models avoiding a need for complex software. In general, it is suggested that:-

- Specific suites for particular reactor types are restricted to cases where the experimental and production reactor are pre-determined and there is no intention to use the generated kinetics for some other reactor type.
- Process simulators are generally not the best tools for an early kinetic study, as this is not their primary purpose. They are appropriate tools for techno-economic evaluation of the process and plant design, but this strength should not compel their use for kinetics studies where they are less capable.
- Kinetic devoted suites will be helpful for various problems, in part depending on their historical purpose and development. For example, Chemkin is strong for homogeneous gas phase reactions having initially been developed for combustion simulations, whereas Chemical Workbench is based upon databases and model based calculations with estimation of kinetic parameters for a wider range of reactions (however, its effectiveness may depend on the quality and suitability of the database used).
- Technical languages are not always user friendly, although graphical user interface (GUI) systems such as Femlab can be added to enhance this. They are not necessarily immediately able to cope with every possible problem. While extensive programming skills are required to build one's own toolboxes, there is the advantage that such toolboxes can be stored and shared for re-use. Some commercial toolboxes are also available.
- Standard solvers and specific solvers for reaction engineering are the probably most convenient, despite the requirement to self-define the reaction system on the basis of mass/heat/momentum balances and thermodynamic calculations or correlations. This self-definition can be perceived by some users as a weakness over kinetic suites, but may in fact be a strength as the user must carefully consider and understand the reaction system

rather than the "black box" numerical fit which can arise from inappropriate use of a kinetic suite.

No particular recommendation of a software application is made.

Where a software suite offers more than one algorithm for fitting data, it is recommended that some subset of the available algorithms is used. For less stable algorithms, it may be appropriate to specify initial values from a more stable algorithm. However, in all cases for at least one algorithm, it is important that significantly different initial values are employed. It is important to use different initial values and different algorithms, if available, as the software will seek to minimise some objective function used to measure the quality of fit. Use of different initial values and different algorithms reduces the risk that the generated output is from a local minimum in the objective function. If the output varies with changes in the initial values or algorithm, further consideration of the fitting strategy will be required.

Further, it should be noted that the input data contains measurement error and it is good practice to apply random noise to the input data. The adjusted data with the added random noise should be separately fitted. It may be appropriate to generate more than one artificial dataset with random noise. If the output varies significantly between fits with and without the random noise, then the fit is excessively sensitive to the input data quality. This may mean either that the structure of the model is wrong (i.e. the pathways represented in the model do not represent the true pathways) or that the accuracy of the available input data is insufficient. In the former case, it will be necessary to re-evaluate the model, whilst in the latter it will be necessary to obtain measurements of better quality. Some fitting software will have an internal capability to add noise, although if necessary this can be reasonably easily achieved using Excel. For example, the Excel expression *NORMINV(RAND(),0,**value**/3)* can be used where ***value*** is the maximum error.

5.10.2.4 Conclusion

The final model should be given with the confidence range associated to the parameter estimation retained. If it is a simplified model, it would be recommended that the lumping protocol be described as well putting the stress on the simplification applied and their justification. Where extra mathematical forms are required to cope with the calculation of the various terms of the rate they would have to be communicated simultaneously.

For example, in a gas-liquid-solid system, the chemical reaction rate may contain the concentration of the dissolved gas. If in the fitting of the data, the concentration of the dissolved gas was not measured directly but was calculated from the partial pressure of gas using a Henry's law coefficient, the quality of fit is depends on the use of the Henry's law coefficient. For a kinetic expression where the reaction order in dissolved gas is 1, the use of a Henry's law constant which is different by x% from that used in the fitting of the kinetic expression will immediately introduce a systematic error of x% in the rate of reaction calculated in the model.

While validation of the kinetic data is a key part of the generation of the data, it is also important that the first and any later process model be validated against any pilot data which later becomes available.

6 Technology Option Identification

6.1 Equipment Characterisation

Equipment characterisation is covered more fully in the “Equipment Characterisation Instructions” document. It is hoped that manufacturers will characterise their equipment following these protocols and the data will be incorporated in the Equipment Database. It may appear that the process technologist requires little further knowledge of Equipment Characterisation and simply needs to use the Equipment Database, but this is not the case.

The process technologist needs to understand equipment characterisation for the following reasons:-

1. The characteristics available in the database are undertaken using simple, low hazard materials and the physical properties of process materials will be different. The reported characteristics depend on the features of the equipment and the properties of the materials and actual characteristics with the process fluid will differ from those reported.
2. The characteristics in the database are presented as a range for Technology Option Identification and are not suitable for the more detailed process evaluations that will be required in the later stages of the design. The process technologist will need to obtain more representative values from the equipment vendor or characterise the equipment for the specific duty.
3. For modelling applications, it may be necessary to characterise the process. This can be achieved in the same manner as characterisation of the equipment.

To characterise equipment or process, it is recommended that the process technologist refer to the “Equipment Characterisation Instructions” document. This section gives a high level explanation of the characterisation to give the process technologist the background to apply judgement to the specification of required equipment characteristics when searching the Equipment Database.

The proposed standard working fluids for characterisation tests and calculations are:

- gas: nitrogen
- liquid: water
- second liquid: heptane[19]

Except for heat transfer tests, characterisation temperatures should normally be expected to be at a temperature of 20-25ºC. Clearly, neither the temperature nor the fluids are likely to be typical for real processes and they have been chosen to simplify characterisation. As a result, it is necessary to adjust measured characteristics based on real process conditions. Whilst initially it was intended to include a built-in adjustment protocol between the real fluids and the test fluids, this proved impractical because in some cases the operating principles of devices are different (e.g. in microdevices diffusion can be the major mixing process, whereas in a stirred tank the forced convection induced by the mixer is the major mixing process) and, even in similar devices, the adjustment is different depending on whether flow is laminar, transitional or turbulent.

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[19] Note that some vendors may choose to use an alternative water immiscible liquid with a higher flashpoint where they cannot handle low flashpoint liquids in their testing laboratories

6.2 Why Use These Characterisation Parameters?

To simplify the selection process, the characteristics selected are characteristics which are mainly related to process rate. Volume and residence time ranges are retained, as these can be specified based on an understanding of the reaction rate and desired end-point. Devices with the capability to deliver the required residence time can be identified. In combination with the desired throughput, the residence time can be used to determine the required reactor volume and this can be compared with the available size range. If the required volume falls below the available size range, the reactor type may be infeasible although it may be worth discussing with the vendor whether smaller sizes may be feasible. If the required volume falls within the size range, a single device may be feasible, whilst if the required volume is larger than the available size range, the external scale out factor can be assessed (multiple parallel devices).

From that same understanding of reaction rate, the characteristic time for the reaction can be estimated based on Eqn 5-2 above. Ideally, to truly deliver the intrinsic rate, both the bulk mixing time and the micromixing time should be less than this characteristic time. However, if the characteristic time of the desired reaction is of the same order of magnitude as either the bulk mixing time or the micromixing time, it may be more important to compare the characteristic time of the undesired reactions with the mixing time closest in magnitude to the desired reaction. Provided that the characteristic time of the fastest undesired reaction is reasonably longer than the relevant mixing time, selectivity should not be particularly poorly affected.

While the IMPULSE approach seeks to match equipment time and length scales to process requirements, calculation of the characteristic heat and mass transfer times is not the most practical approach to deliver this intention. Equipment characterisation is more capable of measuring heat and mass transfer rate and it is sufficient to compare the required rate to achieve the intrinsic reaction rate with the achievable rate. In most circumstances, it will be sufficient to ensure that the achievable rate exceeds the intrinsic rate – although note that in some circumstances, it may be preferable to deliver less than the intrinsic rate rather than more (e.g. some asymmetric hydrogenation reactions where at high hydrogen availability the non-catalysed parallel reaction may be faster than the catalysed asymmetric route[20]).

From understanding of the rate, heat of reaction and acceptable process temperatures together with available/acceptable service temperatures, heat transfer performance can specified in terms of UA. This product of heat transfer coefficient and area is preferred over the separate values, as this eliminates potential issues with different calculation methods for area and because it can be directly characterised. If the heat transfer coefficient and area were to be separated, the process designer would immediately recombine them when assessing a device.

Finally, mass transfer rates can be specified in terms of k_La, so that the mass transfer rate has the capability of being faster than the intrinsic reaction rate. Note that in some cases, it may be decided that a mass transfer controlled system is acceptable and lower values of k_La would be specified.

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[20] Note: This is not a general rule. Some asymmetric hydrogenations deliver maximum selectivity at low hydrogen availability, some at high hydrogen availability and for some selectivity is relatively independent of hydrogen availability.

6.3 Use of the Technology Option Identification Database

The purpose of Technology Option Identification is to present the process technologist with a reduced list of potentially feasible technology options. It is not intended to be used to select a specific equipment type or even technology option. This approach is taken because the information in the database will inevitably lag behind the development of actual capability. More importantly, the final selection of equipment will be based on the balance of a range of factors appropriate to the business requirements and the process need. Such factors can include equipment cost, equipment delivery time, equipment reliability and the differential in value between equipment types. It will not always be appropriate to select the technical option which best meets the process need, as the difference in performance between the best technical option and some alternatives may be of less value than any higher lifecycle cost between the best technical option and some alternative. As always, the selection criterion advocated by the IMPULSE methodology is the adoption of the solution which best satisfies the business needs and not the adoption of the best technical option. Such factors cannot be incorporated into the search tool with adequate reliability at this time and these decisions are left to the process technologist.

While a Whole Process Design methodology progresses process design and plant design at the same time, it is rarely appropriate to progress both to the same level of detail in the earlier stages of process design. This situation arises because the plant design requires a reasonable level of process detail. In the early investigations of the process design, several alternatives may be under investigation. While collection of process data relevant to all/most of the alternatives may be of value, it is unlikely that collection of process data relevant to a single alternative will be of value.

Early in the process design, it may be appropriate to apply a simple exclusion tool to investigate whether at least one technology option is available. Alternatives where no technology options are available would either be rejected as infeasible or, if the alternative has the potential to be of much higher value than the others, it may be decided to collect further process detail to investigate technology options at a greater level of detail and test whether the alternative is truly infeasible. Such initial searches can reasonably be restricted to the ability to handle the combination of phases present[21], the process technologist’s judgement of required residence time and operating temperature and pressure.

As the process design progresses, the number or process alternatives under consideration will fall and the focus of attention will move towards decisions on plant alternatives. At this stage in the process investigations, it would be expected that sufficient process information will be available to allow database searches on the equipment characteristics. As has already been discussed in section 6.1 above , it will be necessary to adjust the required characteristics based on physical properties and process conditions to the values which would be required for the test fluids at 20-25ºC. Where there is some perceived equipment preference, scaling rules appropriate to that type of equipment should be used. As a general rule, for short characteristic reaction times (less than ~10 seconds), it may be appropriate to scale assuming laminar flow in highly structured devices. For longer characteristic reaction times, assumption of turbulent flow in meso- or macro- scale equipment may be more appropriate. As each item of equipment is specified with an operating range and a “fuzzy” extension has been included. The advantage of applying a fuzzy limit is that it avoids exclusion of equipment that may have the potential to fulfil the process needs.

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[21] Note: It is necessary to consider the phases present at the start of the process step, during the process step and at the end of the process step. The presence of a transient phase during the course of a reaction could have a significant impact on the suitability of equipment

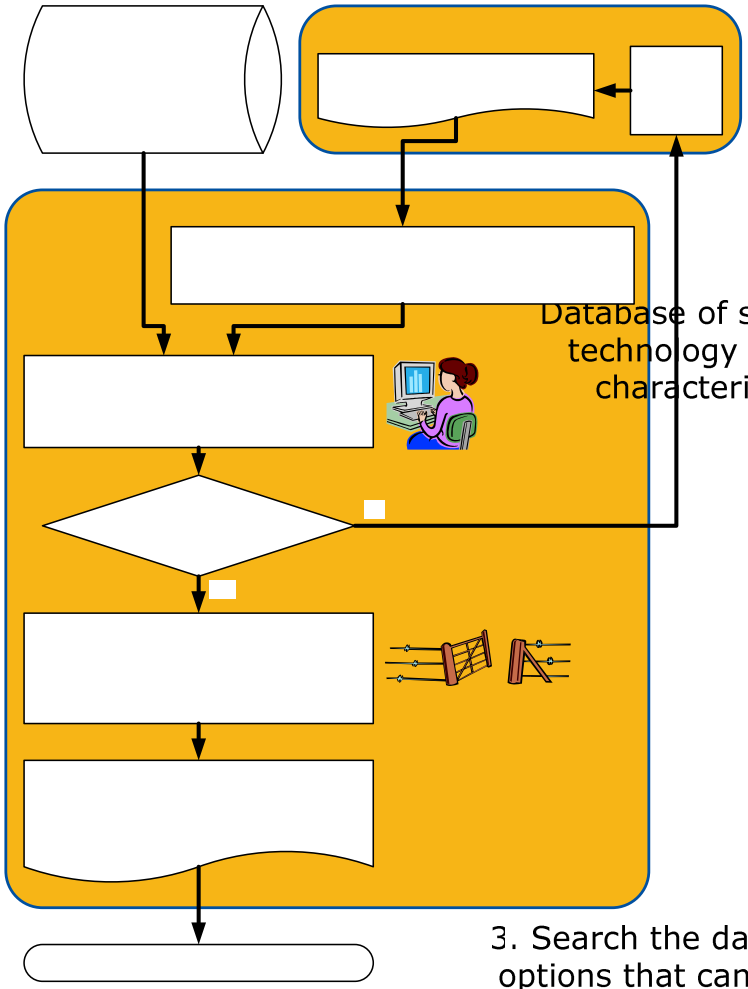


Figure 6-1 **Flow diagram summarising the Technology Option Identification Methodology (TOIM)**

Particularly note that the database search uses “AND” logic when prioritising technology options (i.e. technology options prioritised at least “might meet” all specified criteria included in the search). It is therefore important that only essential criteria are specified in initial searches to avoid exclusion of options which lack the ability to satisfy “nice to have” criteria. If the prioritised technology option list generated based on the essential criteria, it may be appropriate to reduce the list by incorporating additional “nice to have” criteria in order of importance until the list is reduced to manageable size.

Where a process alternative is rejected as infeasible, the number of available technology options is shorter than desired or a particular technology option (which is not displayed as feasible) is preferred due to a desire to re-use an existing plant or item of equipment, it is important to consider whether the process concept can be modified to retain most of the potential value but eliminate the infeasibility. The modification of the process concept could be as simple as a change in concentration (e.g. lower concentration could dissolve solids which might otherwise be problematic or could reduce a reaction rate to within the capability of equipment). Alternatively, it may be appropriate to split the task, so that the particular challenges of the early part of the original task can be satisfied using one technology option and the particular challenges of the later part of the original task can be satisfied in the second (e.g. a fast second order highly exothermic reaction which generates a solid late in the reaction may be suited to a microreactor to deliver the high heat transfer required in the early part of the reaction followed by a shell & tube heat exchanger for the latter part where solids are generated).

A flow diagram for Technology Option Identification is shown in Figure 6-1 above. Note that
The database output will be presented as a colour coded list using a traffic light system.

- **green** indicates that the technology option ***will meet*** the criterion

- **yellow** indicates that the technology option ***might meet*** the criterion
- **red** indicates that the technology option ***does not meet*** the criterion

The output a technology option ***might meet*** the criterion is based on the use of "fuzzy" limits on the equipment characteristics and means that the process need falls outside the range specified in the database but within the extended range after application of fuzzy limits. The prioritisation applied to the technology option list is that technology options which will meet all criteria are prioritised over options which only might meet some criteria. Options which only might meet some criteria are prioritised so that those which have a lower number of "might meet" criteria are more highly rated. However, the process technologist should note that there is no weighting of the criteria. If one selection criterion is of particular importance, options with several "yellow" lights, but a "green" light on that particular criterion may be preferred over options with a lesser number of "yellow" lights which include a "yellow" light on the particular criterion.

LINK to Database User Guide

7 Some Specific Examples

The Introduction to this document highlights that the IMPULSE Vision is "to match process systems to the needs of the process, commerce and society". The Whole Process Design approach advocated by IMPULSE and set out in this document seeks to aid the user in selecting the most appropriate technology incorporating appropriate structure to meet the business need. Inherent within this approach is the avoidance of dogmatic application of any particular option whether this be:-

- distributed or centralised production
- batch or continuous operation
- the absence of designed structure or a designed structure whether this be microstructure, mesostructure or macrostructure

As a result, the case studies presented below seek to set out the thought process for particular elements of the Whole Process Design approach and arrive at different technology solutions based on the particular business requirements and process needs. Also note that the information provided is greatly simplified and discusses only the major decisions omitting the many more detailed considerations.

7.1 Deciding Mode of Operation - Hydrogenation Example

Within the IMPULSE project, the hydrogenation of a pharmaceutical intermediate was studied. The aspiration was to design a continuous locally structured device to perform the hydrogenation. This system would then be compared with a conventional batch hydrogenation facility.

7.1.1 Motivation for Study

The perceived benefits of the continuous locally structured device were:-

- Reduction in catalyst usage per unit weight of product produced

  The cost contribution of palladium on carbon to many products is not insignificant despite the normal practice of returning spent catalyst to the catalyst vendor for recovery of the metal.

  This also reduces the handling of the catalyst and the health and safety implications of the handling process. Handling of spent catalyst can be particularly problematic as residual hydrogen bound to the catalyst can make the spent catalyst pyrophoric.
- Reduced inventory of hydrogen in the reactor

  It was accepted that the hydrogen storage requirements would remain similar, but it is considered less likely that loss of control leading to loss of containment would occur in a storage system than in a reactor. As a result, there is considered to be some advantage in a smaller inventory in the reactor.
- Enhanced mass transfer of hydrogen through provision of structure together with enhanced heat transfer.

  Either mass or heat transfer limits the achievable rate of hydrogenation in a typical batch facility. A locally structured device was considered capable of delivering more area for heat transfer and of controlling the interfacial area for mass transfer. Also, being smaller, operation at higher pressure can be contemplated.

7.1.2 Study Results

Early experiments to measure the kinetics used a microreactor with catalyst-coated channels and a packed bed of catalyst in a thin ribbon-like channel. It was found that the catalyst deactivated on a timescale of days and attempts to regenerate the deactivated catalyst were unsuccessful.

Use of the microreactor with catalyst-coated channels could only be contemplated if the device were sufficiently low cost that it could be considered disposable. This was considered to be highly unlikely and there would also be a requirement for a continuous switchover capability to maintain operation or regular start-up and shut-down. Based on both the cost implications and the operational difficulties, this option was rejected. Similarly, unpacking spent catalyst and repacking fresh catalyst in microchannels was found to be too difficult to consider as a regular production operation.

However, the use of a meso-scale packed reactor was considered worthy of further investigation. To achieve an acceptable pressure drop, this meso-scale packed bed employs granular catalyst rather than powdered catalyst. The meso-scale packed bed was suitable for regular repacking and was used in the demonstration. This packed bed is installed in a recirculation loop around a batch reactor.

Perceived advantages of this system are:-

- Controlled contact with catalyst – reduced risk of variation between different sites attempting to operate the same process
- It is possible to re-use the same catalyst bed for several batches which reduces the catalyst usage per unit weight of product – although the potential issues in terms of cGMP manufacture of this re-use are still under review
- Possibility to use catalyst cartridges – while these are not currently available commercially, this would be advantageous in the longer term in reducing the health and safety aspects of catalyst handling. Such cartridges will be investigated in collaboration with the catalyst supplier if this solution is adopted.

At the time when this report was produced, the initial demonstration runs had shown poorer performance than the commercial batch process. However, the potential benefits are considered sufficient to justify further work to develop the new process and address the current performance deficiency.

7.1.3 Study Conclusions

The Whole Process Design methodology supports the decision process by ensuring that the potential advantages of the alternative approach are considered and evaluated at least qualitatively. Early recognition that one of the aspirations was to reduce the catalyst usage ensured that the approach being taken was promptly reviewed when catalyst deactivation was detected during kinetic studies.

This review together with the data collected facilitated the identification of a new alternative approach. This was reviewed to determine whether it also had the potential to offer commercial advantages over the current batch manufacture and was ultimately developed and implemented. Some issues remain unresolved and are the subject of ongoing development activity. However, throughout the activity the Whole Process Methodology supports a clear understanding of the challenges to be addressed, the success criteria and the value of success.

In this particular case, batch hydrogenation is clearly the most appropriate business solution, though the decision between the current unstructured batch process and the new batch process with a meso-scale catalyst bed is not yet resolved. However, it should also be noted while this is the preferred solution for this particular hydrogenation, the project team still believe that a locally structured microdevice may be more appropriate for other hydrogenation reactions significantly less susceptible to catalyst deactivation.

Finally, this study demonstrates the fact that the appropriate choice in the production environment is independent of the choice in the laboratory (as stated in section 5.4 above). In this study, the initial data collection employed microreactors and the data generated was used to support the decision to employ a batch reactor with a meso-scale packed bed. The decision to use microreactors to generate the initial data was to satisfy both the need to generate data for the hydrogenation project and the need to generate information on and gain familiarity with the use of microreactors to support the wider IMPULSE project. Had this latter additional requirement to use microreactors not been in place, a different scale may have been used for data collection.

7.2 Splitting and Combining Tasks - Alkylation Example

Within the IMPULSE project alkylation using diethylsulphate to produce Ionic Liquid was studied.

7.2.1 Motivation for Study

In the laboratory environment, ionic liquids have been produced in stirred flasks as small scale batches. As manufacture is scaled up, the ionic liquid produced tends to become progressively more coloured. The chemical species responsible for the colour is not known – this is not uncommon and often levels of contaminant capable of causing colouration are below the detection limits of other analytical techniques. The experience of colouration during scale up is generally attributed to inadequate mixing and/or inadequate control of local temperature. Both mixing and heat transfer deteriorate with increase in scale (see characteristic times, section 5.2 above).

The perceived benefits of the continuous locally structured device were:-

- Reduction in characteristic dimension/time, leading to improved heat & mass transfer

  Processes with short characteristic times for both the desired reaction and any undesired reactions are clear candidates for locally structured operation.
- Reduced inventory of diethylsulphate in the reactor

  It was accepted that the diethylsulphate storage requirements would remain similar, but it is considered less likely that loss of control leading to loss of containment would occur in a storage system than in a reactor. As a result, there is considered to be some advantage in a smaller inventory in the reactor.

7.2.2 Study Results

Initial process representations suggested a choice between:-

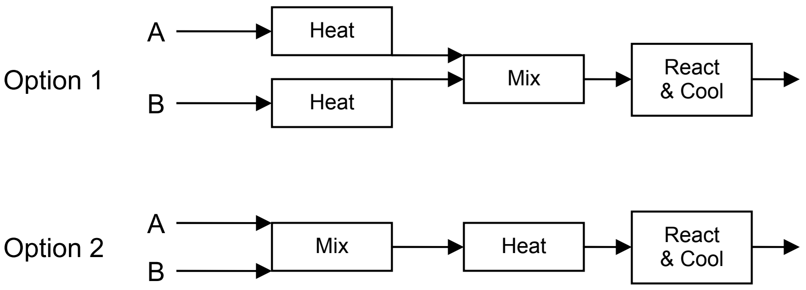


Figure 7-1 Initial Alkylation Options

However, in initial investigations, it was observed that some colourisation occurred even in option 2. This was attributed to the reaction between the reactants together with the resulting exotherm being faster than the mixing and the undesired colour forming reaction being sufficiently fast that it could also occur before mixing was complete. Based on these observations an alternative configuration was proposed:-

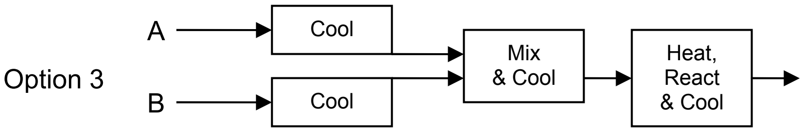


Figure 7-2 Alkylation Option which Avoids Colourisation.

By providing cooling of the reactants, prior to and during the mixing process, the extent of any reaction prior to the completion of mixing is minimised. Due to the low temperature differences which can be employed in a locally structured device, a single heat transfer fluid at a temperature close to the intended reaction temperature could then be used to heat the mixed reactants to the intended temperature and, in the remainder of the device, cool the reactants to avoid the temperature rising to a level at which colourisation might occur.

This revised option proved to be adequate for the laboratory scale production of ionic liquids. However, consideration of the proposed production scale of 100-200kg/day indicated that the size of the microreactor would be excessive. Recognising that the actual rate of reaction reduces as the reaction proceeds, the requirement for structure reduces as the reaction proceeds. The reaction was initially split between a microreactor and a 1/8inch diameter tube, but experiments showed colourisation of the ionic liquid suggesting that the 1/8inch diameter tube had insufficient structure or had been introduced too early. A system incorporating a 1/16inch diameter tube between the microreactor and the 1/8inch diameter tube was then proposed

The connection between the cooled mixer and the microreactor was also considered. As these were of similar structure and close coupling was preferred (to avoid unintended reaction in the connecting pipe) a microreactor construction was developed which provided and initial mixing and cooling section and a reaction section at a second higher temperature (initially heating and then cooling the reaction) – effectively each channel of the mixer outlet is directly connected to an individual reactor channel. Thus the final configuration adopted in the demonstration unit is:-

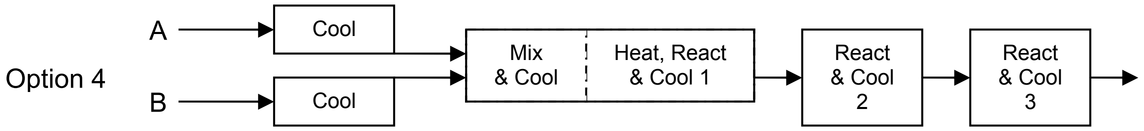


Figure 7-3 **Final Process Representation**

This configuration has been constructed as a demonstration unit and has successfully produced colourless ionic liquid at a throughput equivalent to 100-200kg/day.

7.2.3 Study Conclusions

The generation of process representations provides clarity on the options under investigation which facilitates discussion of the options, prioritisation and selection of options and the design of experiments to test the options. As occurred in this case, it seems unlikely that the process configuration employed in the final manufacture will be one of the initially generated options. This case study demonstrates the use of the process representation together with experimental data and other business information to support the evolution of the process and plant design.

From a pure business perspective, the study has also provided a facility for the manufacture of ionic liquids at a rate and cost which had previously been unattainable.

Finally, this case study demonstrates both that the use of continuous locally structured elements is essential to the commercial scale manufacture of the ionic liquids considered in this study and that a multiscale approach is effective.

7.3 Distributed Production – Integration of Primary and Secondary Pharmaceutical Manufacturing

For those unfamiliar with the pharmaceutical industry, primary manufacturing refers to the manufacture of the chemical entity which is the active drug and generally involves several chemical transformations. Frequently, the final transformation in primary manufacture is the formation of the particular salt of the chemical entity which is present in the final delivery form.

Secondary manufacturing refers to the further processing to formulate the drug into the form which will be provided to the patient or medical practitioners. There are no chemical transformations and the operations in secondary manufacturing are designed to incorporate other materials (sometimes including one or more additional active drugs) and change the physical form. The form of the final product ranges from relatively simple tablets and solutions to controlled release forms where the active drug is enclosed within another material which ensures it is released only at the rate and location in the body.

7.3.1 Motivation for Study

A single manufacturing location serving a global market requires significant stocks in each local market in order to be responsive to fluctuations in demand. In addition to the stock held local to each market, additional material is in transit between locations. Particularly where material is transported by sea, several months of stock may be in transit at any time. The material in local warehouses and in transit can represent a significant level of working capital. If the working capital can be reduced, the capital released can be employed in a manner which generates additional return for the business.

Also, it is assumed that manufacture close to the market will reduce the environmental impact of transport operations.

7.3.2 Progress of Study

The many issues relevant to distributed manufacturing were initially brainstormed for further investigation. The IMPULSE approach encouraged the use of a whole business assessment rather than taking decisions on a small subset of potential decision criteria. As each issue was investigated, further issues were identified and/or previously undetected connections between issues were detected.

In particular, in an economic context it became clear that many of the issues/opportunities were not within the control of the operating company and that government policies on grants and taxes frequently had much greater effect on business performance than choosing to distribute or not to distribute manufacture – i.e. a significant differential in tax on profit in neighbouring countries could mean that any financial gain through stock reduction due to distributing manufacture could be less than the additional tax on profit which would occur through not manufacturing solely in the country with the lower tax regime. Similarly, significant levels of import taxes may drive the adoption of distributed manufacture even where the benefit of reduction in working capital is low.

Also considering the financial implications, for some low volume, high value drugs, it is known that it is financially beneficial to transport the material as hand luggage by courier rather than using conventional freighting methods – as the cost of courier transport is much less than the adverse financial impact of the working capital which would otherwise be incurred.

When considering the manufacturing logistics, only conventional manufacturing options could be reviewed. In this context, it is apparent that there is a significant difference in scale between primary manufacturing and secondary manufacturing in terms of the active drug. Typically primary manufacturing operates with batch sizes of high 10's to 100's of kilograms with occasional examples in low tonnes. However, secondary manufacture batches tend to be of the order of kilograms to low 10's of kilograms. This supports the current position of relatively centralised primary manufacture (typically 2-4 sites worldwide) with a higher number of secondary sites – i.e. there is already a greater level of distributed manufacture in secondary processing than in primary processing. The larger batch sizes of primary manufacture are feasible in readily available batch equipment and operating at this larger scale delivers economies of scale. The smaller batch sizes of secondary manufacture arise both because the active ingredient is often only a minor proportion (by weight/volume) in the final form and because some of the technologies involved (e.g. milling) cannot delivery the required energy intensity at larger scales. Moving away from centralised primary manufacturing must not lose the current economies of scale associated with the larger batch size and this is likely to require a change in technology such as multiscale processing.

Considering the environmental implications, clearly if all products could be produced locally from materials obtained from sustainable local sources then this would result in the lowest environmental impact due to transport. However, the manufacture of drugs uses many complex manufactured chemicals. In reviewing transport arrangements associated with the current distributed secondary manufacture, it is apparent that the level of transport required is no higher and frequently lower than would be required for centralised secondary manufacture. This is because all of the material transported to the secondary manufacturing location is expected to be incorporated into the final product. Thus, with centralised sourcing of all materials supplied to the distributed secondary manufacture, the total weight of material transported to the distributed secondary manufacturing locations is equal to the total weight of material which would be transported from a centralised secondary manufacturing location. However, some ingredients (including, for example, purified water) can be sourced local to the distributed secondary manufacturing site and this has the effect that the total transport requirements and hence the environmental impact due to transport is lower for distributed secondary manufacturing than for centralised secondary manufacturing.

For primary manufacturing, current manufacturing technology requires the use of 10's of kilograms of raw materials per kilogram of product produced. At some point in the supply chain, some key materials are produced in relatively centralised locations. This means that if distributed manufacturing were employed then at some point in the supply chain raw materials would be sent from centralised locations to the distributed locations. As the quantity of raw materials relative to product is high, the overall transport requirements will increase.

Integration of the financial, environmental and logistical issues proved too complex to complete with current manufacturing options. It seems unlikely that current primary manufacturing technology will lend itself to effective distributed primary production, but multiscale processing may enable this to be reconsidered.

7.3.3 Study Conclusions

The problem of determining the appropriate level of distributed manufacture is somewhat more complex than had been initially envisaged, particularly considering the current difference in scale between primary and secondary manufacturing. With traditional primary manufacturing, integration of primary and secondary manufacturing is unlikely to be feasible but this must be reviewed if/as the use of multiscale facilities allows the effective use of distributed primary manufacturing.

7.4 General Learning

The Whole Process Design methodology was developed in parallel with sector projects including those described in the case studies above. In some cases the methodology arises from the approach taken by the team working on a sector project, in others methodology was proposed prior to need and was tested and developed within a sector project and finally some parts of the methodology were developed to address perceived gaps encountered by the sector projects.

The common theme from all of the sector projects was the need to collect, share and process information and it is this need that the Whole Process Methodology seeks to address. Recognising that the product, process, plant and facility have separate linked lifecycles shows that there is a need for information exchange throughout all of the lifecycles. Particularly if a broad range of technology is under consideration, it is necessary to engage product, process and plant designers so that limitations of other lifecycles can be avoided and opportunities can be accessed.

It is this need to exchange information in a meaningful way that the Whole Process Design methodology seeks to support. Additionally, it has been recognised that there is a need for characterisation of available equipment types and sharing of that information. It is undoubtedly the case that further development both of the methodology and the technology option identification database will be required, but the IMPULSE project members believe that they have delivered an important step in allowing commercial operation of multiscale processes using locally structured elements.

Annex 1 IMPULSE Member Organisations

Partner	**Country**
ARTTIC	France
BRITEST Limited	UK
Centre National De La Recherche Scientifique	France
DECHEMA Society For Chemical Engineering And Biotechnology E.V.	Germany
Evonik Degussa GmbH	Germany
Forschungszentrum Karlsruhe	Germany
GlaxoSmithKline	UK
Institute Of Chemical Technology Prague	Czech Republic
Institute Of Chemical Process Fundamentals Of The Czech Academy Of Sciences	Czech Republic
Institut Für Mikrotechnik Mainz	Germany
Institut National De L’environnement Industriel Et Des Risques	France
Institut National Polytechnique De Lorraine	France
Procter And Gamble International Operations	Switzerland
Rheinisch Westfälische Technische Hochschule Aachen	Germany
Siemens Ag A&D Solutions Process Industries	Germany
Solvent Innovation Gmbh	Germany
Nederlandse Organisatie Voor Toegepast-Natuurwetenschappelijk Onderzoek	Netherlands
Universitat Rovira I Virgili	Spain
University Of Manchester	UK
Warsaw University Of Technology	Poland

Annex 2 Design of Distribution Systems

A2.1 A Design Algorithm for Distribution in Microchannels

The objectives of this section consist in developing a general methodology enabling to estimate quickly the flow maldistribution and the pressure-drop through a multi-scale network, without any specific computation. To reach that goal, the user should only need a pocket calculator and design charts.

A2.1.1 Definition of the maldistribution

For the purposes of the design algorithm, maldistribution is defined as Fd [%]:

$$\mathrm{Fd}[\%] = 100\,\frac{\max(q) - \mathrm{mean}(q)}{\max(q)}$$

A2.1.2 Design charts

Two charts are useful to apply the methodology described below. Figure A2-4 presents the evolution of the flow maldistribution Fd [%] as a function of the number of channels n for different values of the resistance ratio r. Figure A2-5 presents the evolution of the normalized global resistance as a function of the number of channels for different values of the resistance ratio r. Sub-charts corresponding to enlarged views of these main charts are available but not included in the present deliverable.

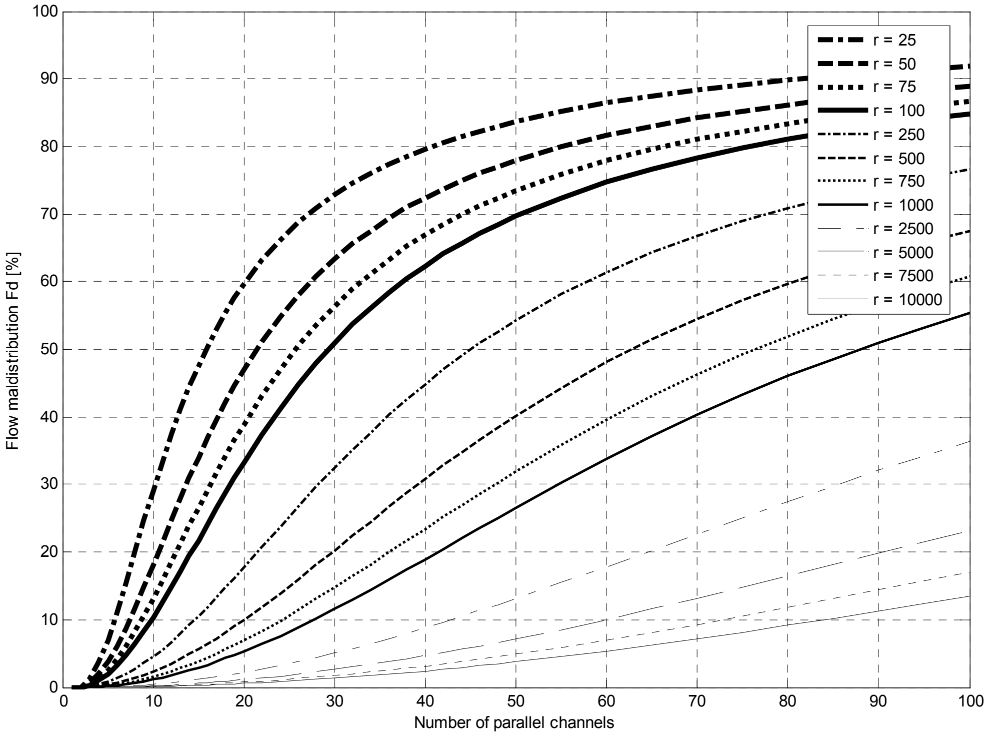


Figure A2-4 **Evolution of the flow maldistribution Fd [%] as a function of the number of channels for different values of the resistance ratio r.**

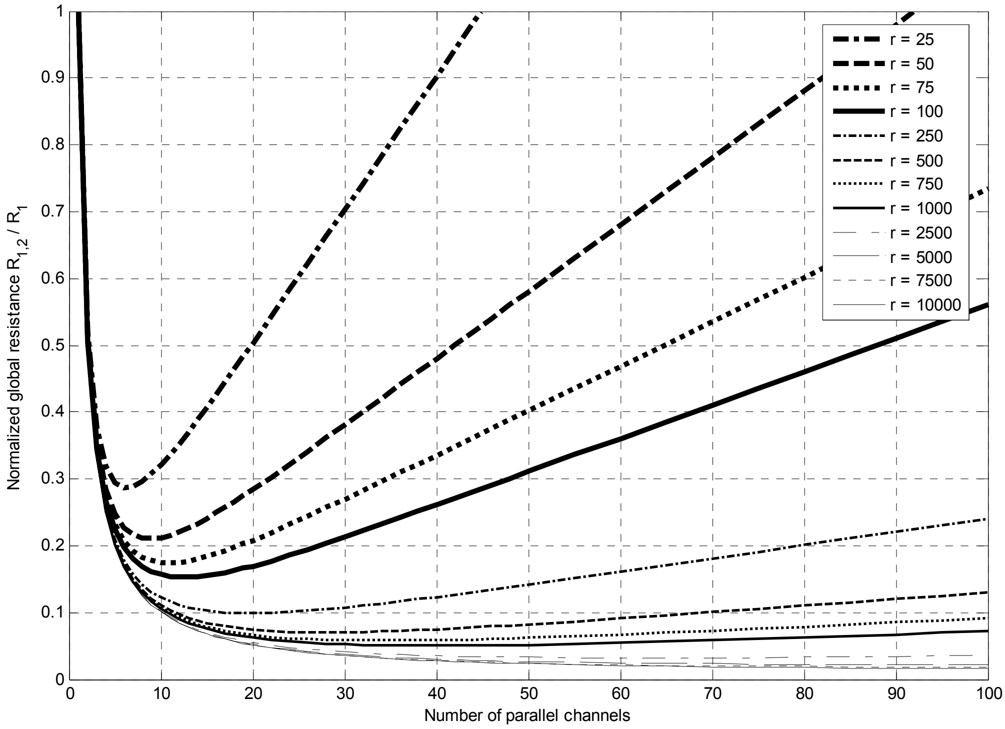


Figure A2-5 **Evolution of the normalized global resistance as a function of the number of channels for different values of the resistance ratio r.**

A2.1.3 Application of the general methodology

To simplify the use of the general methodology, it will be presented here for four-scale systems that are likely to become the most-common topologies of multi-scale reactors, since they correspond to parallel stacks of plates. The general methodology can be applied to any number of scales but the algorithm then becomes difficult to read. Step-by-step application of the four-scale algorithm enables to apply it to a larger number of scales if required. Application to fewer scales is also discussed.

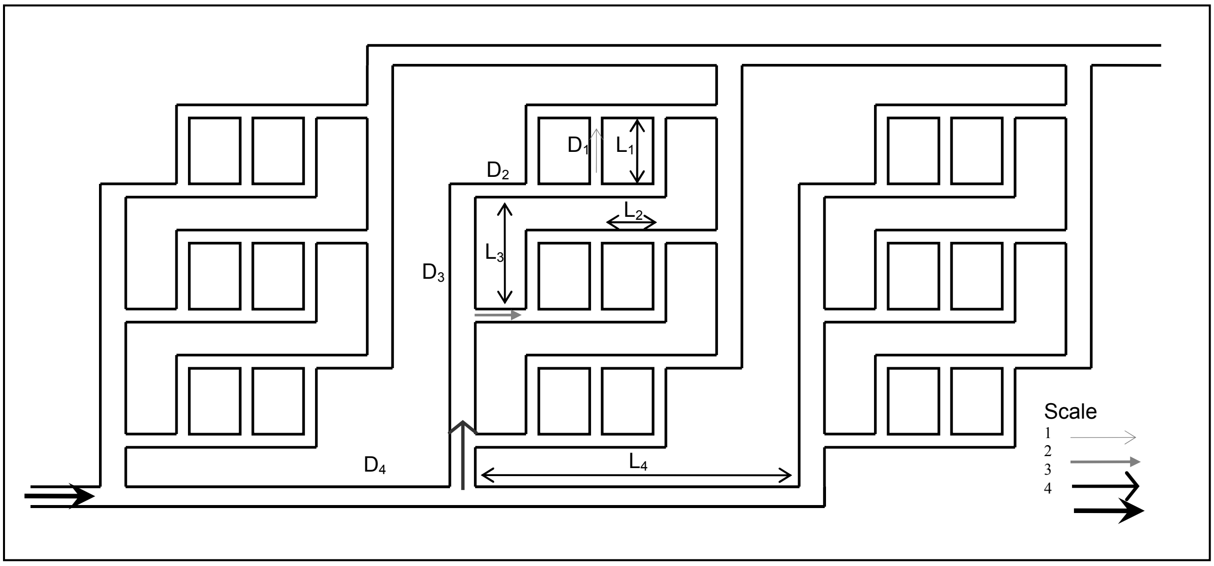


Figure A2-6 **Example of a four-scale structure: [n_1, n_2, n_3] = [3, 3, 3].**

Figure A2-6 presents the topology of four-scale systems. Generally, the elementary channels are assembled in a multi-scale structure of n_1 channels, grooved on an individual plate. Then, n_2 plates are connected in a stack constituting a compact device. Finally, n_3 devices are connected in one macro-scale single equipment.

Due to the complexity of multi-scale structures, many design methodologies could be established depending on the design constraints to be taken into account. Nevertheless, in spite of the necessity of some constraints, they will not be included in the methodology but will be discussed below. As a consequence, the use of the present methodology requires to have previously chosen some parameters:

- N, the total number of channels to be arranged in the multi-scale reactor.
- L_1 and D_1, the length and diameter of the channels of the first scale.
- D_2 and L_2, the diameter and channel-to-channel distance of the distributor and collector of the second scale. A first constraint can relate these dimensions to L_1 and D_1. It is recommended to have $D_2 \geq D_1$. And it is technically necessary to have $L_2 > D_1$. If this latter constraint is not satisfied: adjacent channels overlap.
- D_3 and L_3, the diameter and channel-to-channel distance of the distributor and collector of the third scale. Similar constraints as above relate these dimensions to L_2 and D_2. Additional constraints should be included depending on the technical method used to build the reactor.
- D_4 and L_4, the diameter and channel-to-channel distance of the distributor and collector of the fourth scale. Similar constraints as above relate these dimensions to L_3 and D_3. Additional constraints should be included depending on the technical method used to build the reactor.

Based on these constraints, an algorithm which can be used to design four-scale networks is presented below. This algorithm facilitates calculation of the characteristics of the multi-scale network for a given arrangement $[n_1, n_2, n_3]$ of the N channels over the four scales of the system. The algorithm should be applied for each system under consideration and the most preferred configuration can then be selected.

1. Choose an arrangement $[n_1, n_2, n_3]$ so that $N = n_1.n_2.n_3$. Importantly note that the arrangements $[n_1, n_2, n_3]$ and $[n_2, n_1, n_3]$ or $[n_3, n_2, n_1]$ are different and yield different results.
2. Using the previously fixed values of L_1, D_1, L_2 and D_2, calculate the flow resistance R_1 and R_2 defined as:

$$R_1 = \frac{128.\mu.L_1}{\pi.D_1^{\;4}} \quad \text{and} \quad R_2 = \frac{128.\mu.L_2}{\pi.D_2^{\;4}}$$

3. Read Figure A2-4 and Figure A2-5 using $n = n_1$ and $r = R_1/R_2$ to obtain respectively $(Fd_1)_{chart}$ and $(R_{1.2}/R_1)_{chart}$.
4. Calculate the flow resistance $R_{1.2}$ as:

$$R_{1.2} = \left(\frac{R_{1.2}}{R_1}\right)_{chart}.R_1$$

5. Using the previously fixed values of L_3 and D_3, calculate the flow resistance R_3 defined as:

$$R_3 = \frac{128.\mu.L_3}{\pi.D_3^{\;4}}$$

6. Read Figure A2-4 and Figure A2-5 using $n = n_2$ and $r = R_{1.2}/R_3$ to obtain respectively $(Fd_2)_{chart}$ and $(R_{1.3}/R_{1.2})_{chart}$.
7. Calculate the flow resistance $R_{1.3}$ as:

$$R_{1.3} = \left(\frac{R_{1.3}}{R_{1.2}}\right)_{chart}.R_{1.2}$$

8. Using the previously fixed values of L_4 and D_4, calculate the flow resistance R_4 defined as:

$$R_4 = \frac{128.\mu.L_4}{\pi.D_4^{\;4}}$$

9. Read Figure A2-4 and Figure A2-5 using n = n_3 and r = $R_{1.3}/R_4$ to obtain respectively $(Fd_3)_{chart}$ and $(R_{1.4}/R_{1.3})_{chart}$.
10. Calculate the flow resistance $R_{1.4}$ as:

$$R_{1.4} = \left(\frac{R_{1.4}}{R_{1.3}}\right)_{chart}.R_{1.3}$$

11. Calculate the global characteristics of the network:
    - Global flow maldistribution Fd_{glob}:

$$Fd_{glob} = 1-(1-Fd_1)(1-Fd_2)(1-Fd_3)$$

    - Overall pressure-drop through the network:

$$\Delta P_{tot} = R_{1.4}.Q_{tot}$$

    - Total volume of the system:

$$V_{four-scale} = n_3\left(n_2\left(n_1.\pi\frac{L_1.D_1^2}{4}+2.n_1.\pi.\frac{L_2.D_2^2}{4}+2.\pi.\frac{L_3.D_3^2}{4}\right)+2.\pi\frac{L_4.D_4^2}{4}\right)$$

Depending on the design objectives, additional criteria can be calculated as a function of these characteristics. As previously discussed, these characteristics can then be used to compare systems. Design of two-scale and three-scale networks is achieved by stopping the algorithm at steps 4 or 7 respectively, and adapting the expressions of step 11. Similarly, the algorithm can be extended to more scales.

A2.2 Validation of Flow Distribution

The conclusions of the work undertaken in IMPULSE on design of microchannel arrangements is summarised in section 5.4.5 above. However, it is likely that many process technologists would wish to view some detail which validates this summary. A summary of the work undertaken is presented below.

A2.2.1 Modelling of Flow Distribution

The hydrodynamic modelling was performed using an isothermal and laminar flow model, which relates linearly the pressure drop to the flow rate through each part of the device. This approach was preferred over the use of Computational Fluid Dynamics as it is more flexible, easier and requires less computational time.

A2.2.1.1 Model Structure

The model structure is exemplifies by the two scale structure and equations shown below. Figure A2-7 shows a typical configuration with *n* microchannels in parallel between a distribution channel, that distributes the fluid from the reactor inlet, and a symmetrical collection manifold, that collects the fluid. The first scale of this design is constituted by the *n* parallel microchannels of hydraulic diameter D_1 and length L_1, whereas the second scale includes the symmetrical distribution and collection cylindrical channels of hydraulic diameter D_2. The length L_2 corresponds to the distributor portion length between two successive elementary channels. To adapt the following analysis to any value of *n*, the notations q_i, Q_i and Q_i' respectively denote the volumetric flow rates through the microchannel *i*, distributor part *i* between two successive elementary channels and the related collector portion *i*

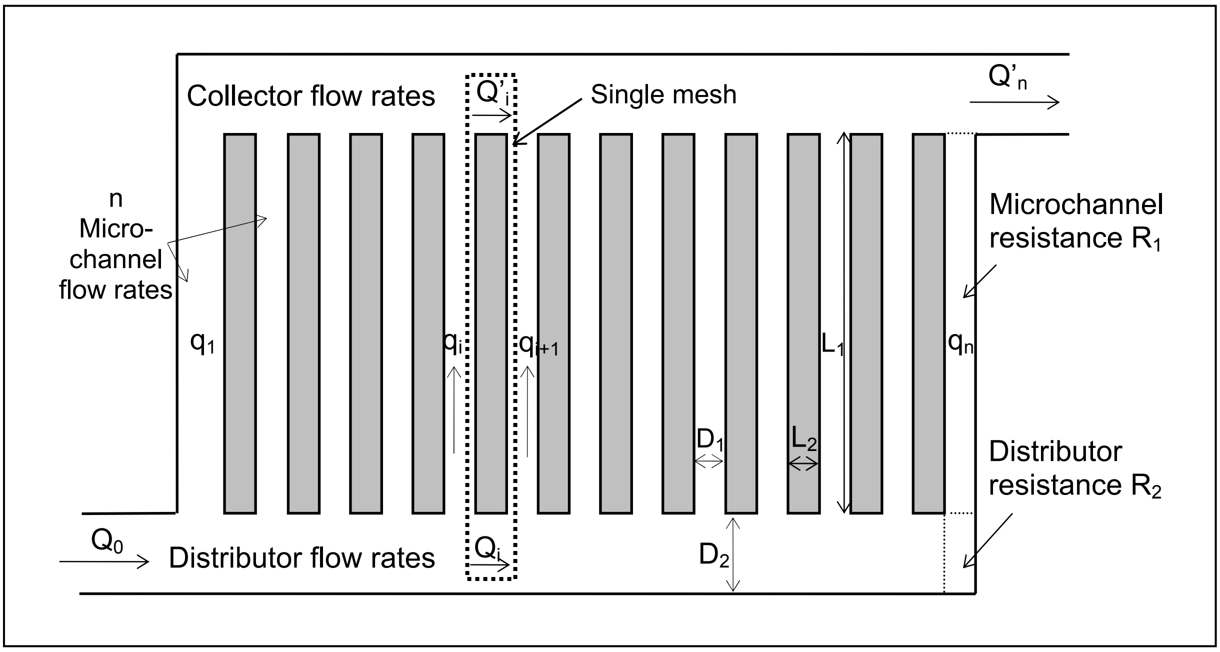


Figure A2-7 Two-scale structure showing form of model

For this structure, mass conservation balances can be written as:

$$Q_{k-1} = Q_k + q_k \qquad k = 1, n-1$$

$$Q_{n-1} = q_n$$

The flow rate in the distributor is related to the flow rate in the collector by:

$$Q_0 = Q_k + Q_k' \qquad k = 1, n-1$$

Equations in junctions between the collector and the microchannels are not necessary and this enables a reduction in the number of unknown variables. Figure A2-8 shows a single channel and the relevant flows. The Hagen-Poiseuille law applies and the pressure drop through each individual channel can be expressed as:

$$\Delta P = 32\lambda\mu\frac{L}{D_h}u = RQ$$

With R_1 representing the resistance in the microchannel and R_2 representing the resistance in the distributor and collector.

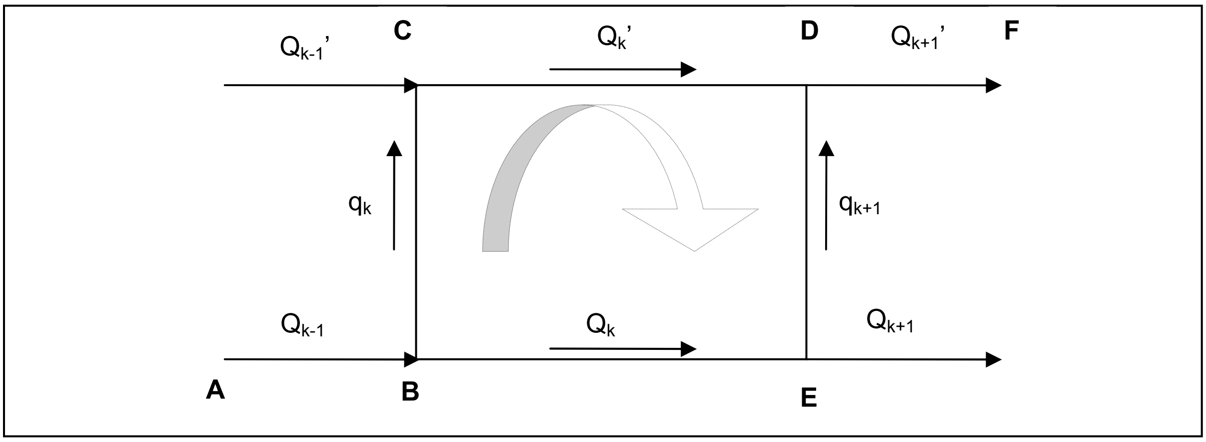


Figure A2-8 Diagram representing Single Channel

This allows the creation of a pressure balance equation

$$R_1.q_k + R_2.Q'_k = R_1.q_{k+1} + R_2.Q_k \quad \text{k = 1, n-1.}$$

And substituting from the mass conservation balances gives the general set of equations:

$$(R_1 + R_2).Q_0 - 2(R_1 + R_2).Q_1 + R_1.Q_2 = 0$$

$$R_1.Q_0 + R_1.Q_{k-1} - 2(R_1 + R_2).Q_k + R_1.Q_{k+1} = 0 \quad \text{k = 2, n-2}$$

$$R_1.Q_0 + R_1.Q_{n-2} - 2(R_1 + R_2).Q_{n-1} = 0$$

Defining the resistance ration, $r_{1.2}$ as $r_{1.2} = \frac{R_1}{R_2}$

The calculation matrix can be presented as:

$$\begin{bmatrix} -2(r_{1.2}+1) & r_{1.2} & 0 & \cdots & 0 \\ r_{1.2} & -2(r_{1.2}+1) & \ddots & \ddots & \vdots \\ 0 & \ddots & -2(r_{1.2}+1) & \ddots & 0 \\ \vdots & \ddots & \ddots & -2(r_{1.2}+1) & r_{1.2} \\ 0 & \cdots & 0 & r_{1.2} & -2(r_{1.2}+1) \end{bmatrix} . \begin{bmatrix} Q_1^* \\ Q_2^* \\ \vdots \\ \vdots \\ Q_{n-1}^* \end{bmatrix} = \begin{bmatrix} -(r_{1.2}+1) \\ -1 \\ \vdots \\ \vdots \\ -1 \end{bmatrix}$$

This matrix makes it possible to calculate the normalized flow rates in the manifold and the flow rates q_k circulating in the microchannels of the first scale can also be computed.

This approach was then extended to multiscale networks with the above equations applying between adjacent scales.

A2.2.1.2 Hydrodynamic Criteria

Several definitions of maldistribution are feasible. Initial work used mainly the definition $Md[\%] = 100\,\dfrac{max(q) - min(q)}{max(q)}$ although the design algorithm uses the definition:

$$\mathrm{Fd}[\%] = 100\,\frac{\max(\mathrm{q}) - \mathrm{mean}(\mathrm{q})}{\max(\mathrm{q})}$$

where q denotes the vector-grouped flow rates through the *n* microchannels. Fd is most readily usable in the design algorithm whereas Md represents the extreme flow differences and a better indicator if flow non-uniformities are likely to create a local hot spot and consecutive thermal runaway of the reactor.

This is not a problem as the two definitions can be related with the relationship shown in

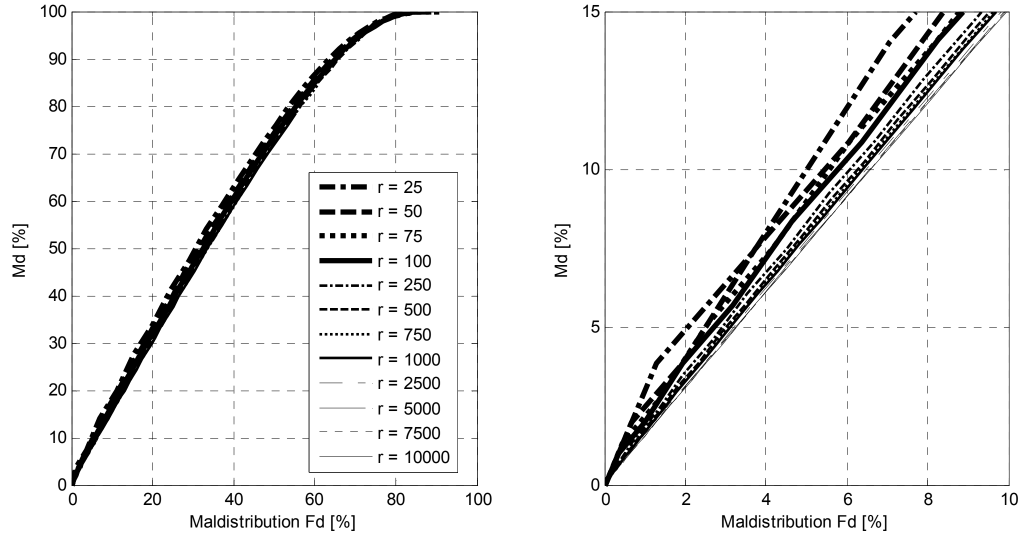


Figure A2-9 Relationship between Md & Fd for assessing maldistribution

A definition based on standard deviation is most relevant to chemical reaction where deviations throughout the entire network are important and can be calculated from

$$Sd = 100\,\frac{\sqrt{\dfrac{1}{n-1}\sum_{i=1}^{n}(q_i - \widehat{q})^2}}{\widehat{q}}$$

where $\widehat{q}$ denotes the average value of the vector q.

A2.2.1.3 Selected Calculation Results

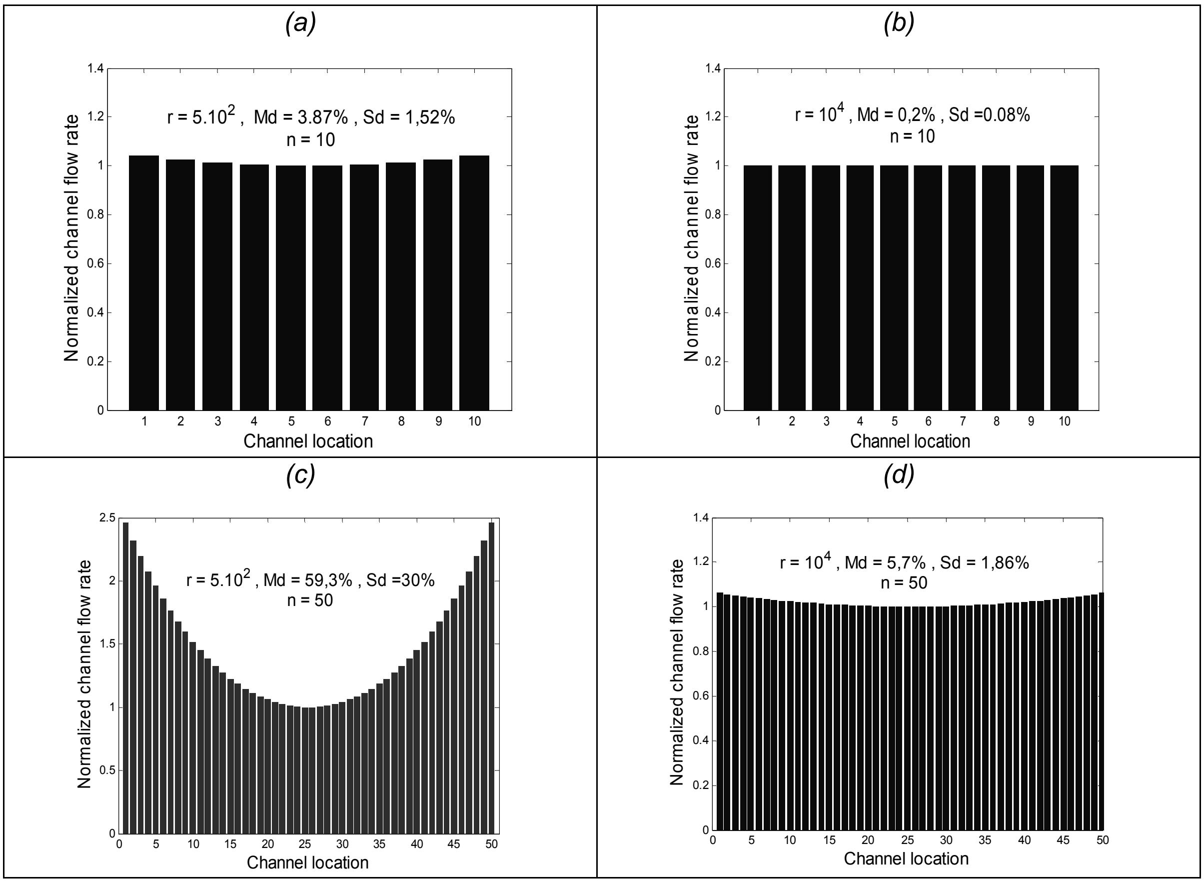


Figure A2-10 Normalised Flow distributions showing effect of channel number, n, and relative resistance, r

These calculation results show that increasing the number of channels at constant relative resistance tends to increase the maldistribution and that increasing the relative resistance tends to decrease maldistribution.

A series of results are presented in Figure A2-11

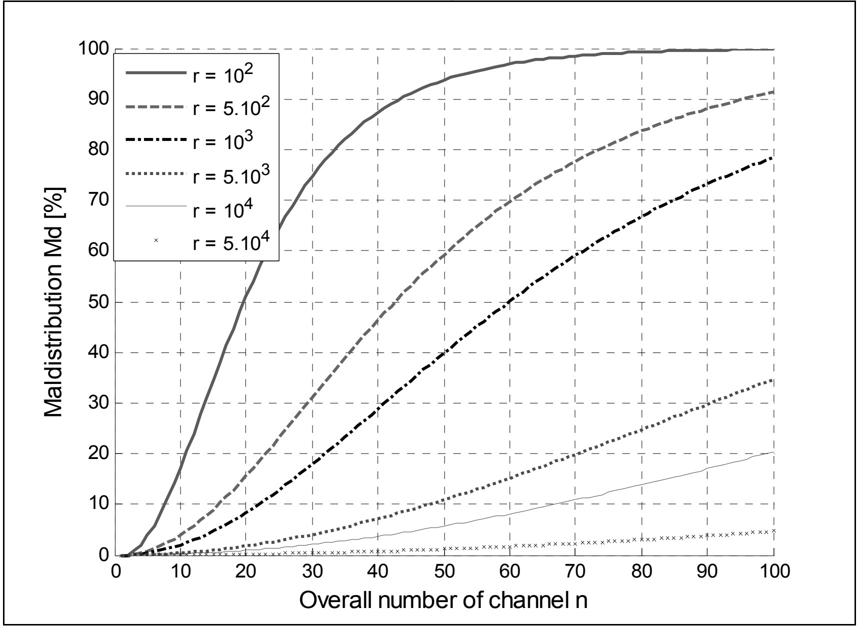


Figure A2-11 Effect of channel number, n, and resistance, r, on maldistribution.

Results in multiscale networks were also generated, but are not summarised here as there are significantly more degrees of freedom and a generalised summary is not feasible. However, the key relevance of flow distribution is the effect which it can have on process performance. Section A2.2.1.4 below shows how the design of the distribution system can impact on temperature and concentration profiles with clear potential effects on process performance.

A2.2.1.4 Importance of Distribution

Flow distribution in itself may be of little importance. If we are simply passing a single chemically stable fluid through a number of parallel channels, the only observable effect if all of the flow passes through a single channel or is equally distributed through all channels is a variation in pressure drop. In manufacturing processes, the purpose of any item of equipment which adds value is to change some property of the material passing through it whether that property be composition, temperature, physical state or any combination of properties. Not achieving a uniform change in the property or properties is potentially detrimental to the process and reduces added value.

A particular strength of the computationally simpler approach adopted to model the hydrodynamics of the distribution systems is the ability to add further equations describing heat transfer and/or reaction.

A2.2.1.4.1 Temperature Distribution

An illustrative example is presented below. The flow of water at 10ºC (283K) to a range of different two-scale exchanger is modelled with a fixed wall of 350 K. The Nusselt number is assumed to be constant and equal to 3.66. The channel length is $L_1 = 30.D_1$ and the distributor length between two successive channels is $L_2 = 10.D_1$. n_1 denotes the overall number of channel at the first scale. The exchanger configurations are presented in Table A2-1below and the system is modelled at a flow of 1ml/s.

Table A2-1 Exchanger Configurations

Configurations	***Md [%]***	η_t ***[%]***	h_t ***[W/m^{2}K]***	NTU_t	T'_n ***[K]***	A_t ***[m^2]***
a: $n_1 = 10$, $D_2 = 1D_1$	93,98	0,53	2005	0,76	318,64	1,60.10^{-3}
b: $n_1 = 50$, $D_2 = 1D_1$	99,99	0,89	1150	2,18	342,41	7,80.10^{-3}
c: $n_1 = 10$, $D_2 = 5D_1$	1,06	0,58	890	0,88	322,09	4,10.10^{-3}
d: $n_1 = 50$, $D_2 = 5D_1$	25,23	0,99	882	4,34	349,13	2,04.10^{-2}

The exchangers modelled have different areas and cannot be directly compared in terms of their thermal performance. Nevertheless it is possible to see the extent to which the design of the distribution system has the capability to influence the range of temperature experienced in the device. The performance of the different configurations is displayed in
Clearly, if the device was intended as a reactor with a reaction temperature of ~350K, the extent of reaction could vary considerably between channels, with configuration (a) showing the greatest variability in temperature.

Further, while device (d) shows the most consistent temperature profile in the collector and at the channel exits, it is worth noting that even in this case, there is a difference in temperature history for the flows in each channel due to the temperature profile experienced in the distributor.

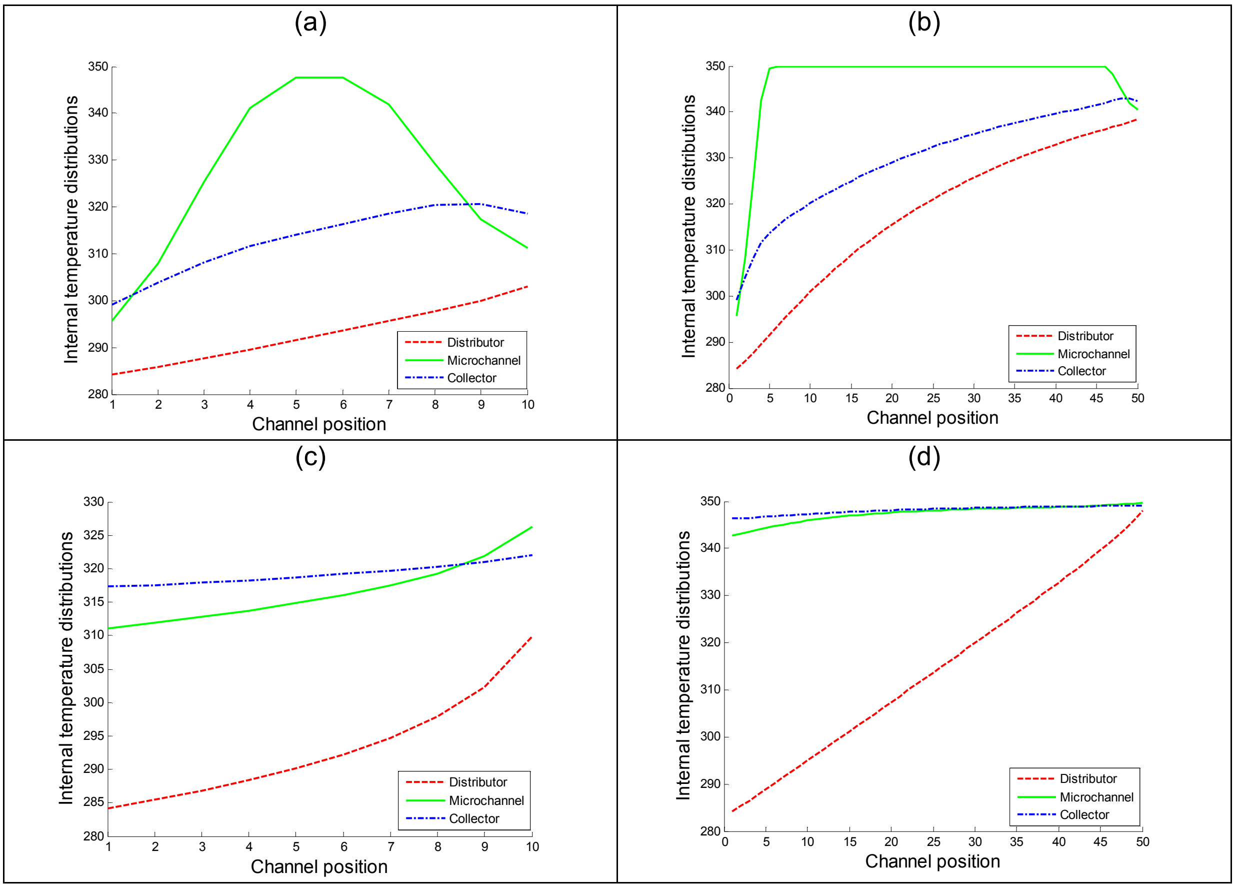


Figure A2-12 Internal temperature distributions for the different device configurations

A2.2.1.4.2 Reaction Performance

The studied reaction is an apparent first-order reaction taking place in the gas phase, which only takes place in the microchannels whose surface is assumed to be coated with a catalyst. A, B and C respectively denote the reactant, the desired intermediate product and the by-product, and C_{ji} is the molar concentration of the different species (j=A, B, C) at the outlet of channel *i*. In each channel, gaseous plug flow is assumed and properties of nitrogen are considered. The expression of the reaction yield towards the desired product B not only takes into account the kinetic rates of the reactions but also the mass-transfer rate from the bulk gas to the catalytic wall:

$$\frac{C_B}{C_{A0}} = \frac{K_1}{K_2 - K_1}(e^{-K_1\tau} - e^{-K_2\tau})$$

with $K_1 = \frac{k_1 k_d}{k_1 + k_d}$, $K_2 = \frac{k_2 k_d}{k_2 + k_d}$ and $K = \frac{K_2}{K_1}$

where k_d, k_1 and k_2 respectively denote the mass-transfer coefficient (k_d = Sh.D/D$_1$), the rate constant of first reaction A→B and the rate constant of second reaction B→C. Sh denotes the Sherwood number assumed to be constant and independent of the Reynolds number (Sh = 4) and D (assumed to be 10^{-5} m^2/s) is the diffusion coefficient of the different species in the fluid.

The optimum space time τ_{opt} enabling to reach the maximum yield of the desired species B in these consecutive catalytic reactions was calculated as follows:

$$\tau_{opt} = \frac{1}{K_2 - K_1} ln\left(\frac{K_2}{K_1}\right)$$

Assuming completely uniform flow distribution, this optimum space time was then used to calculate the optimum microchannel length to deliver this maximum yield. Different systems were then studied to determine the effect of flow distribution on the global yield. For each network configuration, the following parameters are calculated:

- the flow maldistribution *Md* and the standard deviation *Sd* (see A2.1.1 above)

- the yield deviation *dv* with respect to the optimal value estimated as:

$$dv = 100 \frac{C_B^{opt} - \hat{C}_B}{C_B^{opt}}$$

where $\hat{C}_B$ is the mean concentration expressed as:

$$\frac{\hat{C}_B}{C_{A0}} = \frac{\sum_{i=1}^{i=N} \left(q_i \cdot \frac{C_{Bi}}{C_{A0}} \right)}{\sum_{i=1}^{i=N} q_i}$$

(34)

- the overall pressure drop ΔP* normalized by the pressure drop through a single channel calculated assuming a uniform flow distribution.
- the normalized pressure drop defined as a ratio of the overall pressure drop of the entire network to the channel pressure drop that would be obtained in the case of a uniform flow distribution:

$$\Delta P^* = \frac{N.\Delta P}{R_1 .Q_1}$$

It has been shown in A2.2.1.3 above that the flow distribution within these two-scale configurations is symmetric with a minimum flow rate in the centre channels. As a result the space-time distributions are symmetric with a maximum space time through the centre channels. For a 225 microchannel system, the space-time distribution for different values of the resistance ratio *r* is presented below.

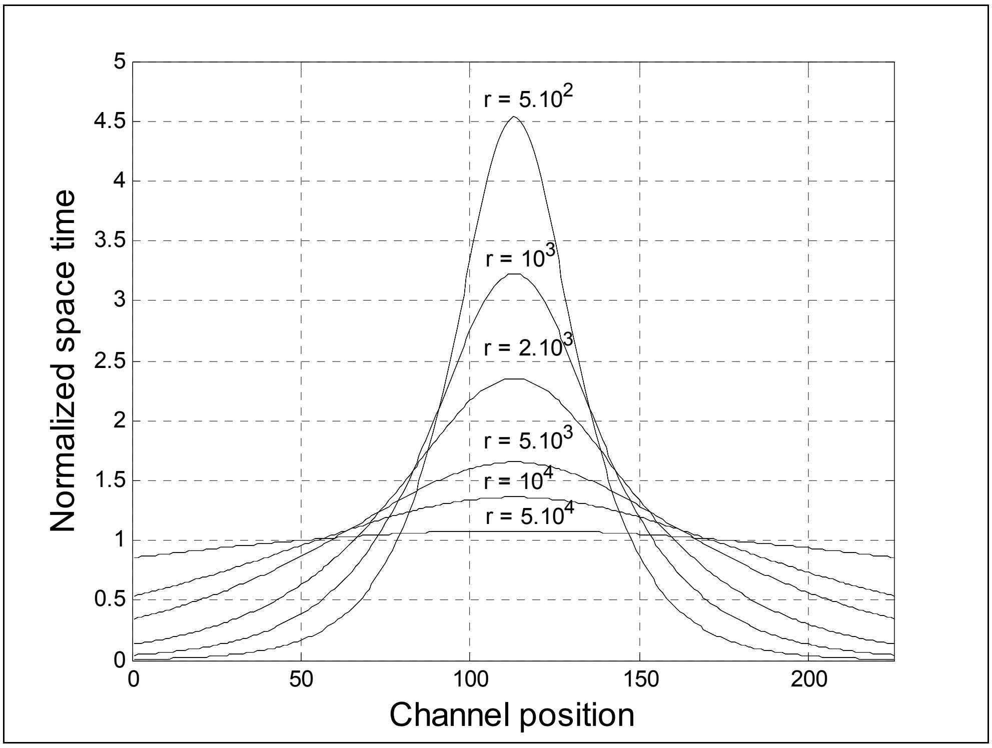


Figure A2-13 Space-time distribution through the 225 microchannels (normalized by the mean space time in case of a uniform flow distribution) for various ratios r

Figure A2-14 below then shows the effect of flow maldistribution on yield with $k_2=0.01k_1$ and the microchannel length specified to give the optimum space time yield for completely uniform distribution. This study shows a surprisingly high tolerance to flow maldistribution – although this could be increased if combined with the thermal effects in A2.2.1.4.1 above.

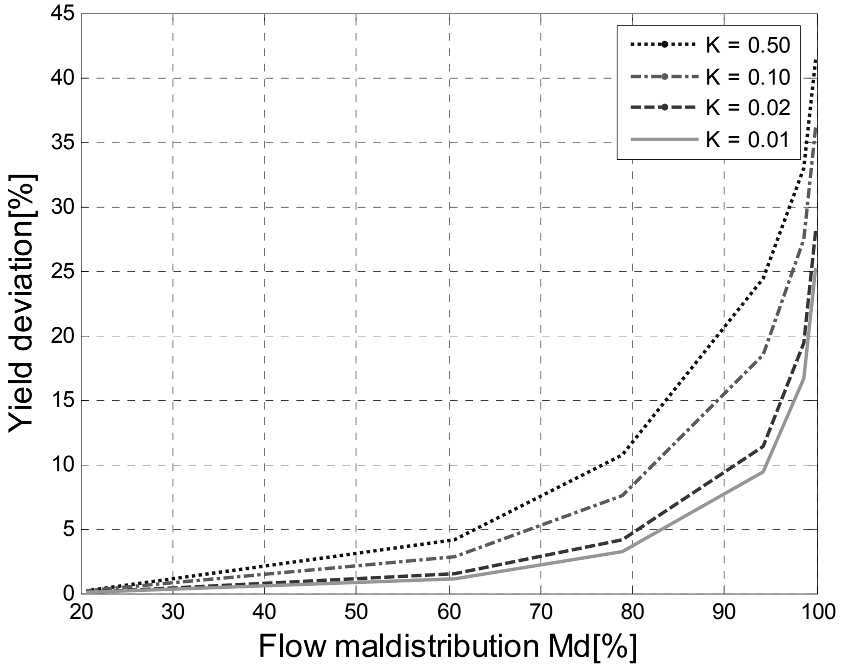


Figure A2-14 Effect of flow maldistribution on yield

Finally, multiscale networks were studied in 225 channel multiscale networks:-

Table A2-2 Impact of channel arrangement in three-scale design on the network performances (K = 0.5).

Channels [n_1-n_2]	*Md [%]*	*dv [%]*	ΔP^*	*Sd [%]*
[45-5]	53,2	2,1	9,4	21,4
[25-9]	55,3	2,5	9,0	23,6
[75-3]	75,8	9,0	15,0	46,7
[15-15]	76,2	9,8	11,7	48,8
[9-25]	90,7	20,9	16,9	78,8
[5-45]	97,6	30,3	27,6	112,1
[3-75]	99,4	36,8	43,4	140,4

Table A2-3 Impact of channel arrangement in four-scale design on the network performances (K = 0.5).

Channels [n_1-n_2-n_3]	*Md [%]*	*dv [%]*	ΔP^*	*Sd [%]*
[5-3-15]	9,1	0,03	1,6	2,6
[3-5-15]	10,0	0,04	1,6	2,8
[5-5-9]	11,0	0,06	1,7	3,5
[3-3-25]	11,4	0,06	1,5	3,6
[15-3-5]	12,8	0,05	2,4	3,3
[9-5-5]	15,1	0,13	2,2	5,3
[15-5-3]	21,5	0,25	3,1	7,2
[25-3-3]	23,1	0,25	3,6	7,3
[5-9-5]	26,4	0,56	2,5	10,9
[3-15-5]	40,9	1,55	3,2	18,4
[5-15-3]	54,0	3,38	4,6	27,5
[3-25-3]	70,8	7,68	6,6	42,7

together with investigation of the impact of blocked channels where it was assumed that four microchannels were completely blocked in a two-scale structure with n_1 = 50 and r = 10^3. Results suggest that the global shape of the flow distribution remains unchanged and the yield distribution is always symmetric to the centre. A small decrease in the flow maldistribution is recorded while an increase in the yield deviation and the pressure drop are observed.

Table A2-4 Impact of clogging of four microchannels on the two-scale network characteristics (K = 0.5, n_1 = 50, r = 10^3)

Number of blocked channels	*dv [%]*	*Md [%]*	*ΔP^**	*Sd [%]*
0	1,38	39,8	0.33	12,4
4	1,43	37,3	0.34	23,6

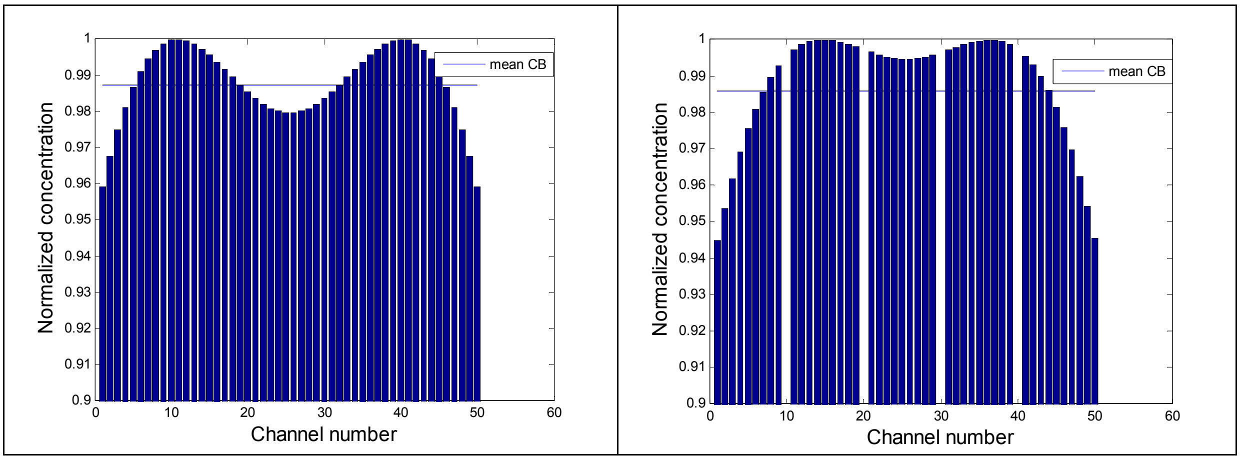


Table A2-5 Concentration distribution in microchannel outlets of a two-scale structure without blocked microchannels (left) and with presence of four blocked microchannels (right). The line corresponds to the average value of the desired product concentration (K = 0.5).

It is noted that clogging problem in multi-scale network can affect the network characteristics differently depending on the rate of clogging, the number and the location of the blocked channels. Defining cr as the ratio of the resistance of a partially blocked channel to an unblocked channel (so cr=1 represents an unblocked channel), Table A2-6 assesses the effect of partial clogging in two different networks. A well designed four-scale configuration [5-3-15] with good network performance is compared to a less well designed three-scale configuration [5-45] presenting the same total number of microchannels. It was found that the impact of channel clogging on the reaction yield is more visible in the case of the better designed network.

Table A2-6 Impact of clogging of 45 microchannels on the three- and four-scale network characteristics

Configurations	*Four-scale [5-3-15]*			*Three-scale [5-45]*		
cr	**1**	**10**	**100**	**1**	**10**	**100**
dv [%]	0,03	4,2	2,4	30,3	32,9	32,3
Md [%]	9,1	7,6	7,5	96,3	96,2	96,3
ΔP^*	1,6	1,8	1,8	27,6	28,1	28,1
Sd [%]	2,6	44,1	49,6	112,1	121	124,2

A2.2.2 Experimental Validation

A2.2.2.1 Experimental set-up

To enable the flow visualization inside microstructured devices, channels have been grooved in plates made of Altuglas, whose transparency depends on the plate thickness. All the tested microstructured plates have channels with rectangular cross section.

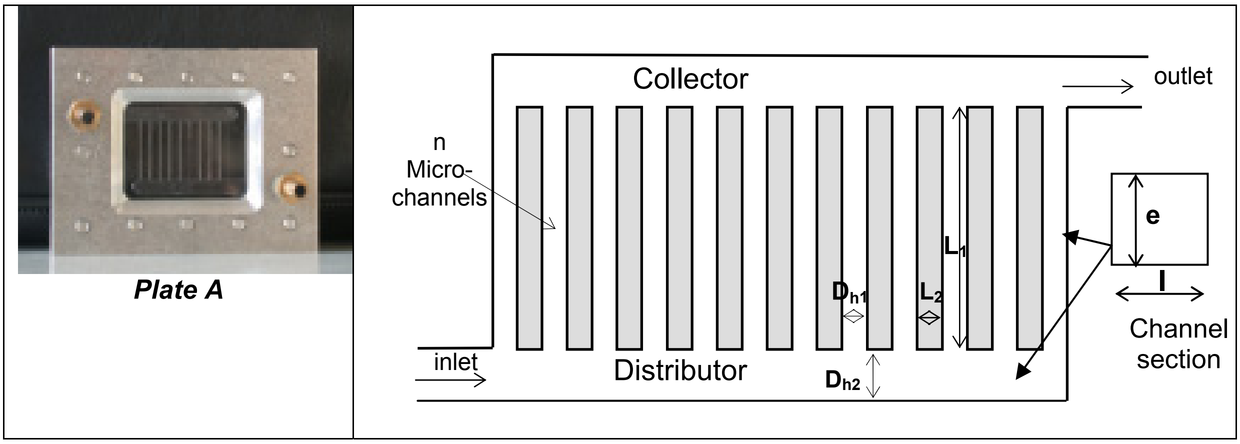


Plate A

Figure A2-15 Example of the fabricated plate (left) and internal device configuration for the 3 devices analyzed (right).

The different dimensions related to configurations A, B and C are presented in Table 3.1. Each device is examined solely using the same experimental set-up.

Table A2-7 Geometrical dimensions of the three plates

Configuration	n	l [mm]	e [mm]	L_1 [mm]	L_2 [mm]	D_{h1}	D_{h2}	r
Plate A	10	5	0.5	20	3	0.5	0.91	66666
Plate B	5	0.5	0.5	50	20	0.5	0.5	2,5
Plate C	5	5	0.5	30	10	0.5	0.91	30000

An experimental method was developed to measure the flow distribution in two-scale microstructured plates. The residence time distribution measurements were performed by monitoring nigrosine flow as a tracer using a high-speed camera equipped with a zoom lens (260 x 260 pixels, VNR, Sys MAT Industries). A monochrome light was located under the plate to illuminate the flow channels. The liquid was delivered to the microreactor by a syringe pump (Kd Scientific, Model 200). Images were acquired in black and white mode, separated by a known temporal interval and recorded using an acquisition system.

The grey signal corresponding to the dye dilution in water is influenced by the environmental perturbations and the lighting effects. To minimise these effects, the camera and the plate are located inside a dark room as showed in Figure A2-16. The dye evolution in time is correlated to the dye concentration and temporal variation of dye concentration is controlled at two points of each parallel channel.

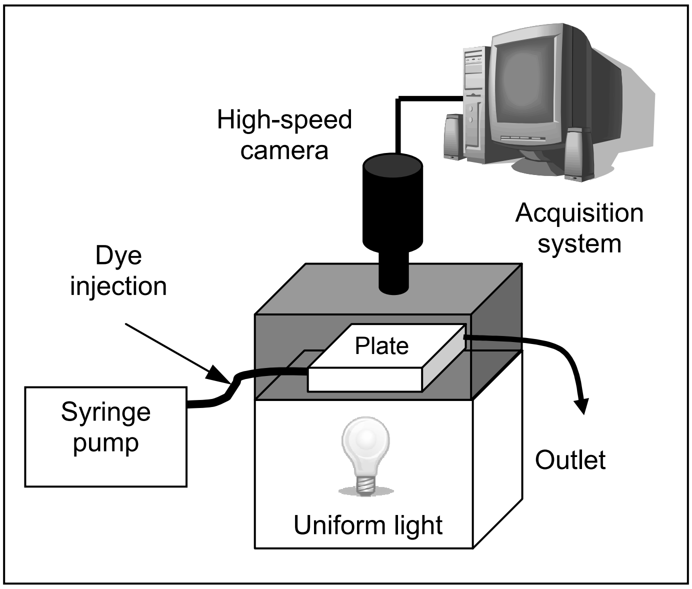


Figure A2-16 Experimental Setup

A2.2.2.2 Flow visualization

Flow visualization is performed using the camera. It has been confirmed that, at low Reynolds number, the flow regime is still laminar despite the different junctions exist in the microchannel plate. No recirculation loops were observed under the flow conditions analyzed, but, as can be seen in Figure A2-17, dead volumes are observed in the distributor/collector extreme zones.

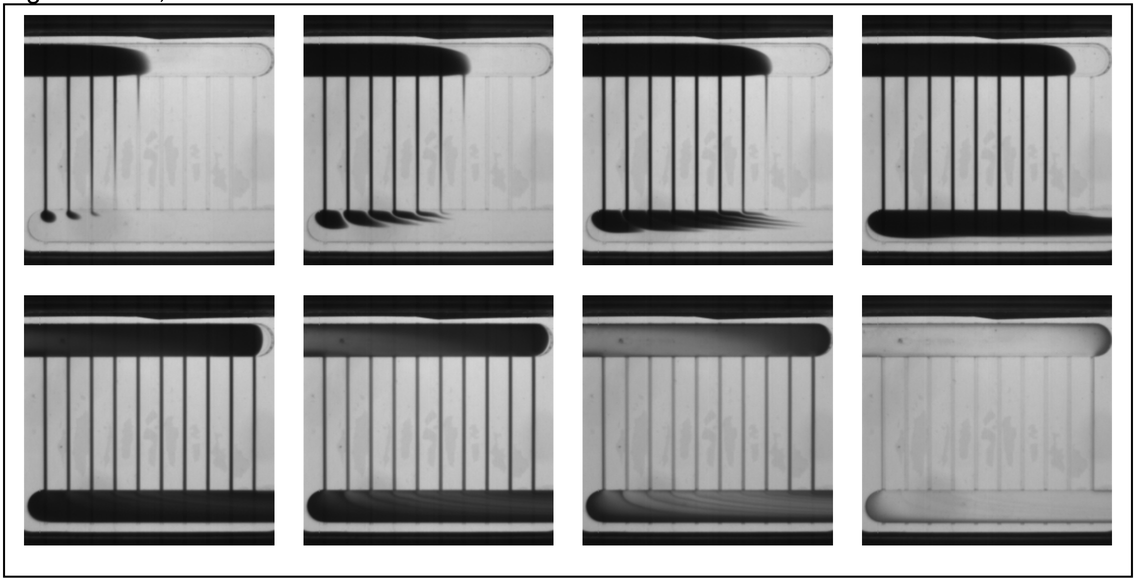


Figure A2-17 Dye flow through the microstructured plate 'A' at fixed flow rate (Re = 2).

A2.2.2.3 Image analysis

The residence time distribution curves provide information concerning the hydrodynamic behaviour of these microstructured plates. The mean residence time corresponding to each channel is estimated as the difference between the inlet mean residence time (estimated from the E(t)-inlet curve) and the outlet mean residence time (estimated from the outlet curve) both expressed as follows:

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)dt} \text{ with } \int_0^\infty E(t)dt = 1$$

$$\overline{\tau} = \int_0^{\infty} tE(t)dt$$

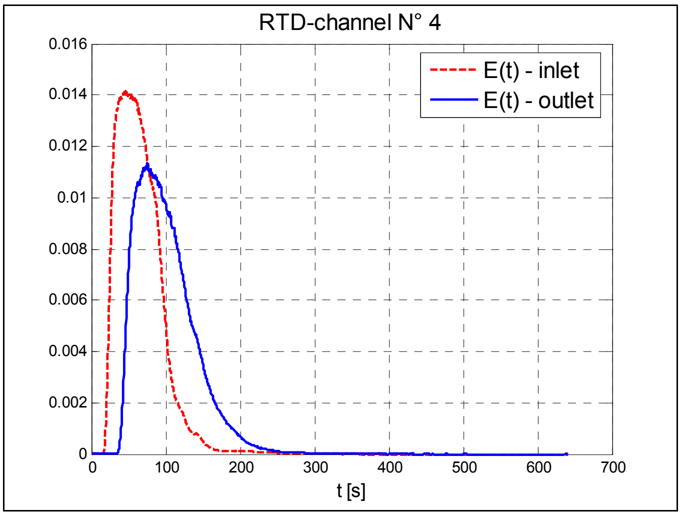


Figure A2-18 **Example of residence time distribution curves recorded at the inlet and the outlet of an individual channel in structure B.**

Figure A2-18 illustrates the residence time distribution curves registered for a single channel (as an example channel n°4) from configuration B. The difference between these two mean residence times facilitates calculation of the corresponding flow rate through the channel.

A2.2.2.4 Results

A2.2.2.4.1 Flow distribution through configuration A

Figure A2-19 presents the flow distribution through the 10-channel plate obtained experimentally and predicted by the flow model.

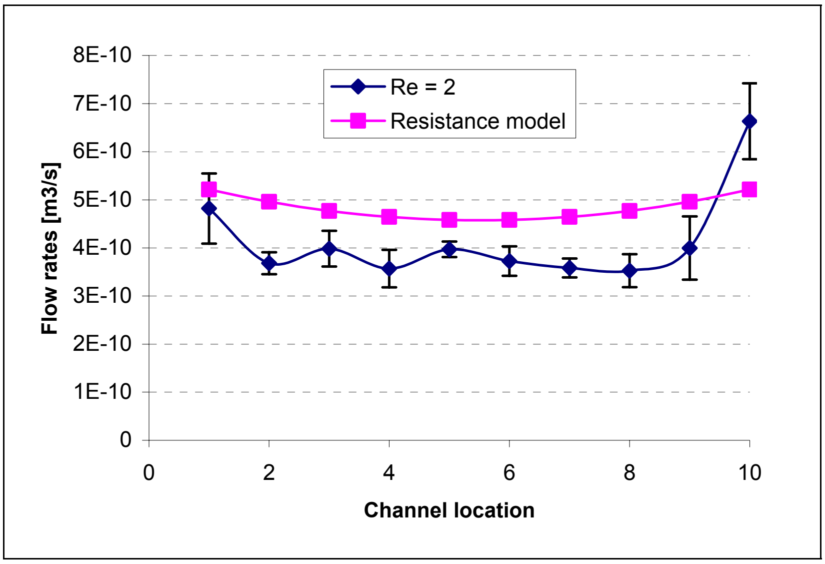
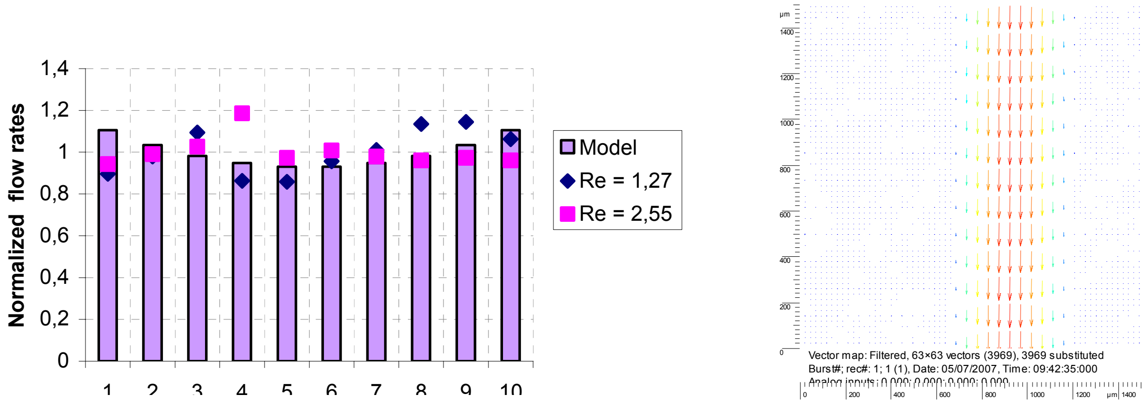


Figure A2-19 **Flow distribution through the 10 channels of the plate with configuration A (see dimensions in table 3.1).**

The plate with 10 channels presents a large resistance ratio. Using the resistive model, a small flow maldistribution can be calculated. The experimental flow rates reveal a relatively small flow maldistribution as predicted by the modelling. However, the quantitative estimation of the total flow rate exhibits a deviation with respect to the model values. This deviation is likely to be caused by a combination of the experimental uncertainties and the dead volumes at the end of the distributor and collector. In particular, these dead volumes result in a large tail appears in some of the RTD curves, causing large signal fluctuations that are difficult to analyse, especially in channel 10.

The flow behaviour has also been observed using a non-intrusive optical technique µPIV (Micro Particle Image Velocimetry). The flow rate distribution is estimated from the velocity field corresponding to each channel in the structure "*A*". Based on the assumption of a laminar flow velocity profile, a value of half of the maximum velocity recorded in each channel has been considered to estimate flow rate value. This technique was feasible only for configuration "*A"*.



Single Channel

Figure A2-20 Flow rates distribution through configuration A determined using PIV system (left) and the measured velocity vectors in an individual channel (right).

Figure A2-20 presents the results by micro-PIV and compares then to the model prediction. On the left, the dots correspond to the flow rates measured in the 10 channels of the reactor for two values of the channel Reynolds number. On the right, the figure displays the flow field measured by microPIV, which was then numerically analyzed to deduce the mean flow rate over the channel. Similar flow fields have been measured in each channel to obtain the flow rates reported in the figure on the left.

Experimental measurements carried out by µPIV also demonstrate that normalized flow distribution is almost uniform and the distribution tendency is very close to the modelled one.

A2.2.2.4.2 Flow distribution through configuration B

Simulation results show that such a structure presents, under laminar and isothermal flow, a large maldistribution caused by the small resistance ratio. This is confirmed by the experimental results (see Figure A2-21). As the model predicts, the flows through the channels in the middle of the network are small compared to those flowing through the first and last channels.

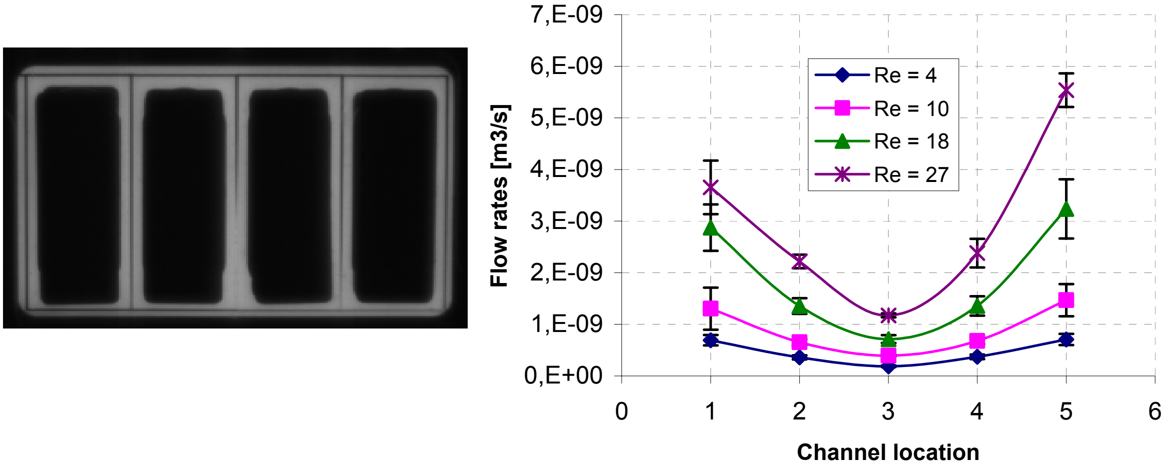


Figure A2-21 Flow distribution through configuration B.

At very low Reynolds numbers, the symmetry of the distribution of flows is also experimentally observed. At higher Reynolds number (Re > 20), a deformation in the symmetry of the distribution appears. The flow rate through the first channel is reduced compared to that through the last channel. This kind of flow distribution had been observed in the model when the effect of the singularities has been taken into account in the model, although for Reynolds numbers closer to 100 and for configurations presenting a very large ratio r.

A2.2.2.4.3 Flow distribution through configuration C

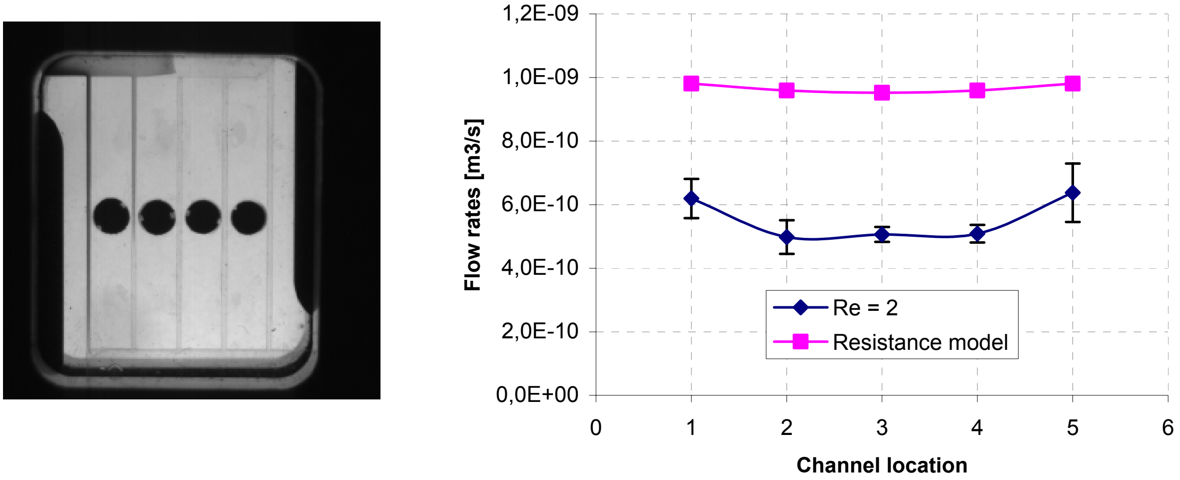


Figure A2-22 Flow distribution (right) through configuration C (left).

The present structure is characterized, on one hand by a low number of parallel channels and on the other hand, by a large resistance ratio. The flow maldistribution calculated numerically is relatively low under these geometrical conditions. Experiments performed for the given plate reveal the presence of the same flow behaviour. The experimentally-determined flow rates are somewhat lower than to those estimated by the model.

A2.2.2.5 Conclusion

A simple experimental method has been developed to the flow behaviour of network configuration composed of parallel channels. Such configurations have already been analyzed using a model based on resistive flow networks. Experimental results (including uncertainties) show that the flow distributions are qualitatively very close to the numerical predictions for the three configurations.

While the deviations between the experimental results and the model are different for each of the three configurations, this can be explained by the facts that:-

- The dye concentration is estimated from the grey intensity recorded in the captured images. However, this represents the concentration on the channel surface and does not take into account channel thickness.
- The experimental uncertainties are different for each plate thickness
- The deviation between the designed channel dimensions and the actual channel dimensions will be different between the three configurations
- Only the model definitely uses the designed channel dimensions

Given these potential sources of deviation, quantitative validation will require further work. However, the qualitative similarity suggests that it is reasonable to conclude that the information obtained from model can be reasonably applied.

Annex 3 Additional HAZOP Guidance for Microscale

These are additional to parameters and guide words normally employed and are intended to provide additional guidance sue to the lower familiarity with microscale devices and their faster dynamics. Italics have been used to suggest where the requirements for microscale require further consideration. As has been discussed in section 5.7.2.1 above, an extended recording table is also recommended to record how the deviation will be detected.

Further, it is recommended that these guidewords be initially applied with an early process representation so that differences between options can be evaluated.

Name of process - Reaction section								
N°	**Deviation/Malfunction**	**Causes**	**Consequences**	**S**	**P**	**Possibility of detection**	**Safety measures**	**Comments**

Table A3-8 Possible Recording Table

Parameters	Guiding words		Specific to MS
Pressure	1	too high	Issue of interface traditional/micro-equipment primarily
	2	fluctuation (in time)	On the time scale below seconds
	3	too low	Avoid evaporation, flashing, two phase flow
Temperature	4	too high	Critical due to reaction conditions close to "runaway" / decomposition
	5	too low	Risk of incomplete reaction / condensation / crystallization
Flow rate	6	too high	
	7	fluctuation / inhomogeneity (in time and space)	On the time scale below seconds and space scale of MS-equipment
	8	too low / no	Partial/full blocking of single channels more probable
	9	Adverse	
Concentration	10	wrong ratio of reactants	Reduced solvents more likely[22]
	11	fluctuation / inhomogeneity (in time and space)	On the time scale below seconds and space scale of MS-equipment
Structural integrity[23]	12	Deterioration	Scale of MS-equipment
Secondary containment	13	loss of	Alternative safety measure for MS-equipment
Medium	14	Other than correct (e.g. solid contaminants, impurities, detachment of catalyst, crystallization of reaction products)	Regard scale of MS-equipment
	15	leakage of cooling media into process stream	intrusion of heating/cooling medium and vice versa
	16	leakage of process stream into cooling media	intrusion of heating/cooling medium and vice versa
Reaction	17	too fast	
	18	too slow	
	19	other reaction products / side reactions	
Cooling capacity	20	loss of or less	
Utilities	21	loss of (e.g. electrical energy, cooling water, instrument air, inerting gas)	
Multi channel area inhomogeneity on process side	22	Unequal temperature between channels	See text
	23	Differences in flow resistance with consequences on individual flow rates	See text

Table A3-9 Extended HAZOP guidewords

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[22] Problems of etc. risk of crystallization, enhanced heat release

[23] Causes: false design; inaccurate manufacturing / maintenance; incorrect operation / cleaning; aging of equipment; enlargement by corrosion / erosion; deposits of solid impurities; higher mechanical resistance etc.

Annex 4 Method Detail Where Not Covered Elsewhere

As stated in section 1.2 above, this target audience for this document is process technologists but a key principle of the methodology is that all decisions should be taken in a business context rather than a technical context. As a result, a key element of the methodology is engagement of the whole project team and adopting the principles below is strongly recommended.

1. All decisions between options should be **taken by a team** and not just one individual. This ensures that more than one discipline's viewpoints and experience are used. It also avoids one person's personal preferences (hobby-horses) having predominance thereby providing a more balanced assessment of the options. Suggested minimum membership of the team is: chemist, chemical engineer, plant representative, HS&E professional and business representative/project manager.
2. **Weighting** will be necessary to balance the competing requirements of the different criteria. This should be determined by the team to reflect the business circumstances and stakeholder requirements. This weighting change as the business environment changes through the product lifecycle and should be reviewed periodically.
3. Wherever possible, the basis of comparison should be **Financial** and should reflect the value, cost or magnitude of the issue being considered, either as absolute or relative numbers. Particularly note that it is important to consider magnitudes in relation to the overall value of the opportunity – thus a difference between €100k & €500k may be significant in a project with an overall value of €5M, but may be insignificant in a project with a value of €500M. Similarly, in many cases, the difference between an option costing €1k & €10k will be insignificant despite being larger in relative terms than the difference between €100k & €500k.
4. A comparable **level of detail** should be used with similar optimism (or pessimism) in the assumptions in each option under consideration. Best case should be compared with best case (or worst with worst), but seldom best case with worst case (key exception is that where an option has a best case which has less value than another options worst case it will generally be reasonable to reject it without further consideration).
5. It must be accepted that not all **values** will be quantifiable and it is reasonable to expect that personal experience, expert judgement or even subjective perceptions will be required to assign some numerical, or proxy values, when comparing some systems. Particular consideration of the sensitivity of the decision to these values is essential and where the decision is particularly dependent on these values consideration should be given to options for better quantification.

A4.1 Identification of Opportunities for Innovation

Input: *Business situation is established; Outline of investment basis "the business concept".*
Output: *Potential benefits of innovation identified; Key targets for process performance from business perspective identified*

In chemical industries, the opportunities for innovation exist to gain competitive edge for three main reasons depending on the stage of the "product lifecycle":

1. For early delivery especially being the first to launch in the market
2. To reduce overall cost (including capital and operating)
3. To offer a better quality product

The table below suggest features which should be considered in comparing the options.

Table A4-10 Some Differentiating Features Between Technology Options

Cost benefits

- Fixed costs
    - Operators[24]
    - Sales, marketing, admin
    - Land/plant footprint[25]
- Variable costs
    - Key raw materials
    - Solvents
    - Waste
    - Packaging
    - Utilities
    - Consumables
    - Maintenance
    - Value of "work in progress"
    - Value of raw materials stored
    - Value of products stored

SHE benefits

- Waste volumes generated
- Emissions
- Improved process efficiency
- REACH
- Regulatory compliance
- Sustainability
- Inventory/toxicology/COMAH benefits[26]
- Primary containment (equipment)
    - Cost of failure
    - Impact of failure
- Secondary containment
    - Plant location and environment
- Operator protection and training
- Interfaces with upstream and downstream processing
- Change in rate process nature as a result of changing equipment types

Operations benefits

- Lead times
- Cycle times
- Equipment flexibility
- Robustness of process/ operating envelope
- Turndown
- Automation
- Process analytics
- Breakpoints (to accommodate variable process dynamics at different stages)
- Linking batch and continuous operations

Technology transfer benefits

- Scale-up/ scale-out
- Development time
- Scale of operation
- Parametric sensitivity[27]
    - Product quality control
    - Safety
- Availability of material[28]
- Opportunities to do something that can't be done with existing infrastructure
- Opportunities to improve process
- Mitigation against something that may not be possible in future

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[24] Note that in comparing two processes only the cost of operators may change

[25] This assumes that the decision on the location is made irrespective of the type of plant

[26] Breakpoints can be defined for inventory to determine whether the impact is local to the plant, site-wide or beyond the site boundary

[27] Needs to be considered in the context of each stage in the whole process

[28] Some continuous process options may not be viable, e.g. where there are only small amounts of high value material available for trial purposes that cannot be lost in unsteady state operations such as start-up and shut-down

A4.2 Sample Selection Table for Opportunities for Innovation

Table A4-11 Ranking of Technology Options

Risk / benefit parameter	**Weight**[29]	**Traditional/base case**		**Meso structured**		**Micro /Hybrid Structured etc.**	
		Score 1,2 or 3	**Score x weight**	**Score 1,2 or 3**	**Score x weight**	**Score 1,2 or 3**	**Score x weight**
Cost benefit							
Fixed cost	*10?*						
Variable cost	*10?*						
Operational benefit							
Lead times	*10?*						
Cycle times	*10?*						
flexibility	*9?*						
etc							
SHE Benefits							
Waste Volumes	*8?*						
Sustainability							
Emissions							
Meeting REACH requirements	*9?*						
Etc.							
Technology transfer Benefits							
Scale-up/ scale-out							
Development time							
Scale of operation							
Process financial performance							
etc							
Total			**X**		**Y**		**Z**

In addition to this table, there should be a set of criteria which each option must meet before being considered. Inability to meet these mandatory criteria means that the option is not viable. Criteria may appear both a mandatory and discretionary (requiring scoring) – e.g. if development time cannot exceed 12 months, options unable to meet this would be excluded. However, it would still be appropriate to score an option with a development time of 2 months more highly than one with a development time of 6 months.

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[29] Example weightings only

Also note that scores should be in a business context. For example, if some other activity is on the critical path and its duration means that a period of 6 months is available for development, then all options with a development time less than 6 months should be scored equally as none of them impact the business case as the project programme will be determined by the same critical path activity.

A4.3 Potential HS&E Differences when Comparing Processes at Different Scales

This comparison table is, by no means, a comprehensive list and is here to stimulate people thinking in the area. It is NOT to be used as a checklist. Consideration of the fundamental (scientific) differences between the processing options allows for a significantly improved, rigorous and systematic approach to decision making.

The critical question that should be asked by the project team filling in the table is: which of the following areas is/are true for the system under consideration, and how do they manifest themselves in the processes under consideration.

Area for Consideration	**Batch, Fed- or Semi-Batch macro structure**	**Batch, Fed- or Semi-Batch with localised structure**	**Continuous processing with Meso-scale structures (e.g. CSTR, static mixer with residence time unit, OPR**	**Continuous processing with Micro-scale structures (e.g. plug flow micro-reactor)**
In-process Inventory.	Large: Impact of an accident very high – safety and environment. Higher level of containment required?		Reduced inventory vs batch lower. Impact of accident likely to be small. Level of containment required?	Smallest inventory. Impact of accident minimised. → consider isolation of adjacent equipment as additive safety measure to minimise product releases Low level for containment required Separation of process steps more complex including new hazard areas
Intermediate storage / buffer volumes			Does continuous processing increase or reduce intermediate storage / buffer volumes?	
Storage Inventory	Does rate of manufacture and batch size mean higher or lower inventories required?		Does rate of manufacture mean higher or lower storage inventories required? Does smaller scale units allow for decentralised manufacture (possible increase in transport of raw materials required as a result)?	
Equipment	Known robustness/lifetime of components?	Impact of manufacturing variability on equipment safety? Known robustness/lifetime of components?	Impact of manufacturing variability on equipment safety? Known robustness/lifetime of components?	Highest manufacturing specification (lowest tolerance). Impact of erosion or corrosion? Exotic MOC required to minimise this? Bespoke manufacture? Known robustness/lifetime of components?

Area for Consideration	**Batch, Fed- or Semi-Batch macro structure**	**Batch, Fed- or Semi-Batch with localised structure**	**Continuous processing with Meso-scale structures (e.g. CSTR, static mixer with residence time unit, OPR**	**Continuous processing with Micro-scale structures (e.g. plug flow micro-reactor)**
Process control	What are requirements – can be low or high. Often longer reaction time, and can be lower temperature. Often needs less equipment, but more manpower.	What are requirements – can be low or high. Needs higher control of charging reactor, dosing time, temperature	May require new type of process control (e.g. feed rates, mixing device control, pressure sensors)? Automated process with fewer operators needed? What is impact of variability? May need less process control (e.g. only pressure sensors and flow rate monitoring) once process validated.	May require new type of process control (e.g. feed rates, mixing device control, pressure sensors)? New small-sized sensors with fast response time required? What is impact of variability? Automated process with fewer operators needed? May need less process control (e.g. only pressure sensors and flow rate monitoring) once process validated.
Reaction yield and purity	Baseline case	Does improved mass and heat transfer improve selectivity and hence yield and purity?	Does improved mass and heat transfer improve selectivity and hence yield and purity?– if so, better environmental metrics Access to reaction/operation conditions out of scope for conventional technology	Does improved mass and heat transfer improve selectivity and hence yield and purity?– if so, better environmental metrics Access to reaction/operation conditions out of scope for conventional technology
Mixing	Can be highly variable in mixing flume – lower selectivity/yields? Gives slowest mass transfer and mass transport if multi-phase	Deep concentration slope around reactant inlet – loss of selectivity?	Improved control Depending on reaction kinetics: reduced side products, may allow increase in reaction temperature and reduced reaction time May allow avoidance of cryogenic reaction conditions and reactions to be run at higher temperatures If run under pressure, can avoid cavitation / evaporation / allow for reactions to be run above boiling points of solvents.	Excellent control Depending on reaction kinetics: reduced side products, may allow increase in reaction temperature, reduced reaction time (a significant preconditions for application) Discard of cryogenic reaction conditions If run under pressure, can avoid cavitation / evaporation / allow for reactions to be run above boiling points of solvents. Best mass transfer for heterogeneous or multiphase reaction conditions. (note possible difficulties with solids)
Solids handling:- **(Care: dependant upon solids characteristics)**	Can deal with slurries better so may use less solvent	Can deal with some slurries / solids – will depend on process and structure.	May need more solvent (or other solvent) to deal with solids - higher environment costs? May need process changes to dissolve solids before charging May cope with some slurries	May need more solvent (or other solvent) to ensure no solids: higher environment costs May need process changes to dissolve solids before charging Likely to block channels if solids present or product crystallizes under reaction conditions– what impact does this have?

Area for Consideration	**Batch, Fed- or Semi-Batch macro structure**	**Batch, Fed- or Semi-Batch with localised structure**	**Continuous processing with Meso-scale structures (e.g. CSTR, static mixer with residence time unit, OPR**	**Continuous processing with Micro-scale structures (e.g. plug flow micro-reactor)**
Heat transfer	Generally poor. Extended reaction time. Higher dilution for heat dispensation (extra solvent)	Does localised structure allow for high localised heat load removal (e.g. for exothermic higher order reactions)	Excellent, does it improve yield, selectivity, allow avoidance of cryogenics or allow reactions to be run hotter with reduced residence times? Can reaction run more concentrated with less solvent or in reduced time?	
Processing conditions	Often run slower (fed batch), cooler and at lower pressure to compensate for poor heat/mass transfer	Local structure allows for better mixing and heat transfer – what impact does this have?	Often run faster, hotter and at higher P. Do new processing conditions allow use of lower excesses or less toxic materials? Safety gap to point of decomposition of reaction mixture can be narrowed (due to higher cooling capacity and less spatial variability of temperature). Batch reactions usually run 100°C below decomposition onset temperature – in more structured equipment, this safety margin can be significantly decreased. Is secondary containment required?	
Pressure	Does increase/decrease in pressure allow for different regulatory rating (function of both pressure and volume)?			
Volatile Emission treatment	”Standard” technology (e.g. scrubbers, condensers etc). Economy of scale but relatively low efficiency. Consider future regulatory requirements.		State of the art: closed system to suppress evaporation of volatile substances Minimizes emissions	State of the art: closed system at process conditions to suppress evaporation of volatile substances Minimizes emissions
Waste	Do options offer different waste burdens – consider, aqueous effluent, organic effluent, VOC's, energy usage Options for solvent recycle? Consider impact of future regulatory requirements.			
Cleaning	Volume of solvents likely to be large. Main vessel easier to visually inspect – what about upper works though?		Volume of solvents likely to be small. Difficult to visually inspect. May require new approach, especially for QA inspections – but has been done	Volume of solvents likely to be smallest. Difficult to visually inspect. May require new approach, especially for QA inspections – but has been done
New chemistry or products achievable			Production on demand possible – increase or reduction of transport/storage Decentralised manufacturing possible Does use of novel technology allow for innovative synthesis / products / continuous processing?	
Flexibility	Very flexible, usually able to provide wide range of processing conditions in 1 vessel – does this improve any HS&E aspects?		Relatively little flexibility – but is flexibility required?	
Scale-up	Scale-up required – higher risk of abnormal occurrence with change is scale and equipment?		Little or no scale-up required – less risk of abnormal occurrences	

A4.4 Sample Selection Table for Equipment Options

Table A4-12 Ranking of various equipment against desired performance requirement

Equipment performance parameter	**Weighting** *(Numbers given as examples only)*	**Traditional/base case**		**Meso structured**		**Micro /Hybrid Structured etc.**	
		Score 1,2 or 3	**Score x weighting**	**Score 1,2 or 3**	**Score x weighting**	**Score 1,2 or 3**	**Score x weighting**
Capital Cost <X	10?						
Operating cost<X	10?						
Heat transfer>X	9?						
Mass transfer>X	8?						
Low Inventory<X							
Able to handle solid							
Low Corrosion<x/y	9?						
Development time<1yr	7?						
Process performance	10						
Etc							
Total			**X**		**Y**		**Z**

Again note the need to consider the scores in a business context. A capital cost of €5k vs. a capital cost of €50k may seem a large difference (an order of magnitude). However, if the project is providing a plant for a multi-million Euro/pound profit opportunity, the difference in performance between the two options may be much more important. For example, a 10% improvement in profit potential for the equipment with a €50k capital cost on a product with €10M p.a. profit potential would recover the additional cost in 2-3 weeks. Weighting and scoring need to take the impact on business performance into account.

A4.5 Sample Comparison of HS&E features for Whole Process Options

Owner:		**Decision level:**		**Date:**			
Business benefit HS&E features	**Weighting**	**Process Option 1**		**Process Option 2**		**Process Option 3**	
		Impact / Cost	**Product of score and weighting**	**Impact / Cost**	**Product of score and weighting**	**Impact / Cost**	**Product of score and weighting**
Environmental							
Environmental metrics [I]							
Abatement and waste disposal [II]							
Regulatory compliance [III]							
Plant location and environment [IV]							
Health							
Process Hazards [V]							
Regulatory compliance [VI]							
Containment requirements [VII]							
Safety – Routine Process Operation							
Process Inventory and processing conditions [VIII]							
Process Control Requirements [IX]							
Primary or Secondary containment plus any additional protection measure [X]							
Safety – Abnormal occurrence							
”Cost” of incident distinguished for areas [XI]							
		Total=		**Total =**		**Total =**	

Interpretation of the table: notes

I. Use appropriate environmental impact assessment method (see section 5.7 above)

II. Disposal costs will vary between processes and sites. Abatement costs MUST be considered.

III. Regulatory Compliance: at high level, looking for step change only, do processes sit within different levels of regulatory framework (e.g. SEVESO, air emissions, compound toxicity etc)?

IV. Extra cost on restrictions in air emissions, e.g. odour, noise, energy consumption, availability of infrastructure as waste treatment, spill control, cooling medium etc.

V. What are the adverse health effects of the materials used in the processes, are there any significant differences; do the processes have an enhanced risk of exposure to plant personnel at normal operation / malfunction.

VI. Do processes differ in containment or materials handling requirements for employee or operator’s health (more/less toxic materials, different processing conditions required?).

VII. What are the differences between the processes under normal operating conditions

VIII. See section 5.7.1.4 above.

IX. Differences in process safety control requirements –, fast responding control instruments (seconds) / continuous analytical devices, change in product quality assurance program, e.g. PAT. Step change vs current practices?

X. Do processes require different levels of primary or secondary containment? What other containment measures may be required (e.g. quench tank, sprinkler systems, forced ventilation). It may be more efficient for meso- or micro-structured reactors to use secondary safety measures for preventing hazards to operator and environment compared to traditional control by instruments etc. due to the reduced masses in the critical stage.

XI. Items that should be considered for putting a value against for abnormal events should include: human costs (e.g. sick leave), lost productivity, equipment repair or replacement, lost business opportunity etc.

A4.6 Sample Selection Table for Whole Process Options

Table A4-13 Evaluation of the techno-economic option

Benefit / Risk parameter	**Weighting** *(Numbers given as examples only)*	**Base case**		**Option 1**		**Option 2**	
		Score 1,2 or 3	**Score x weighting**	**Score 1,2 or 3**	**Score x weighting**	**Score 1,2 or 3**	**Score x weighting**
Cost benefit							
Fixed cost< 2m	10						
Variable cost<250K/yr	10						
Operational benefit							
Lead times<12 mths	10						
Flexibility change over time between products< 1day	9						
etc							
SHE Benefits							
Rating from A4.5 above							
Technology transfer Benefits							
Scale-up/ scale-out	8						
Development time	6						
Scale of operation	**8?**						
etc							
Total			**X**		**Y**		**Z**

At this stage it is also worth identifying where the money is for each of the above options. One of the simplest methodologies adopted here can be by doing a simple financial analysis. To do this a simple mass and heat balance needs to be carried out if possible based on a few simple assumptions.

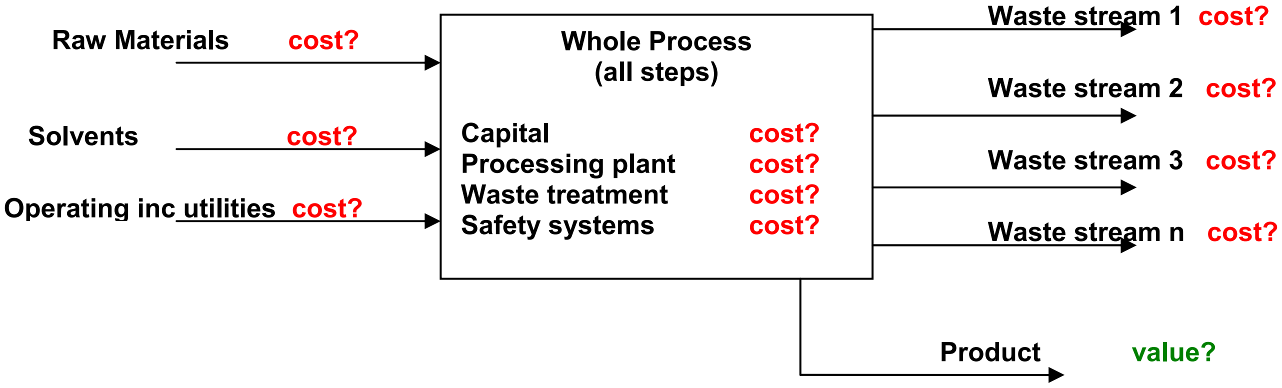

Figure A4-23 Cost & Value Breakdown

This will help identify where the money is and where the resources should be allocated for further investigation.

An alternative comparator between options than that shown in Table A4-13 above is the generation of a full business case for each option and use this alongside a SHE assessment. Where this is possible, it is likely to be the better comparator. The representation shown in Figure A4-23 above is even more important where this approach is adopted, as the business case outputs of Net Present Value, Payback Period and Internal Rate of Return do not display the features contributing to the differentiation between options which would otherwise be possible by comparing the weighted scores in Table A4-13 above.

Annex 5 References

The document is based on all approved WPB deliverables. References below are transferred with the text from those deliverables.

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