Qualitative frameworks for early stage process design

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Abstract

This papers considers ways of enhancing the contribution of chemical engineers in the early stages of process development. The use of qualitative models has been established as a mechanism to deliver many of the useful conclusions of a mathematical modelling approach, but much earlier in design. A suite of models will be presented that cover the range of behaviours that are relevant to process outcome (reactions and transformations, phase behaviour and spatial distribution of conditions. This extends the range of capabilities of the tools into multiphase reactions and separations (coupled or uncoupled with reaction).

These models have been widely applied by a group of companies in the pharmaceutical and specialty chemicals sectors through a collaborative organisation called BRITEST Limited. The application and benefits of the tools is illustrated with examples from the experience of the BRITEST partners in process development and design.

Introduction

In the early stages of process development, and in particular for complex processes such as those found in pharmaceuticals and specialty chemicals, detailed mathematical modelling is not generally feasible. In those industries, most of the high value process design decisions are taken early in development, and usually by chemists rather than engineers. The involvement of engineers is usually later in design, when a batch recipe is ready to be scaled up, and the engineer can contribute through calculations and experimental work to support the design of mixing and agitation, heat and mass transfer and so forth. These activities support both the translation of the batch recipe to larger scale and the development of suitable scheduling.

The interaction between chemists and chemical engineers in the development activity is limited in a number of ways.

- The activity is more linear than interactive in that the creative degrees of freedom lie more in the domain of the chemist than the engineer.
- The presumption of batch processing makes the task of development fitting the process to the capabilities of the stirred tank; the role of the engineer is one of rating known equipment and feeding back to the chemists any relevant process constraints.
- The lack of a common language makes meaningful dialogue problematic. In particular, engineers are uncomfortable with, and have not had the tools to manipulate, the essentially qualitative

understanding that the chemist has of the complexities of the chemistry. Equally, the effort required by the chemist to provide the quantitation that characterises the engineering approach is often seen as excessive and unnecessary.
- Timescales and budgets for process development are limited, with a strong emphasis on rapid transfer to manufacture and the use of standard (existing) processing equipment.
- Many of the problems in the low tonnage sectors are so complex that they defy analysis using detailed mathematical modelling.

To address these problems, a suite of tools have been developed by BRITEST Limited [1] to promote knowledge capture, sharing and exploitation within interdisciplinary development teams. The philosophy has two elements:

- to capture knowledge in a form that recognises the underlying physical science; all too often do development teams treat the chemistry as a "black box" and implicitly make the assumption that incomplete quantitative knowledge prevents them from carrying out detailed analysis,
- to keep the representations as simple as possible

Science basis of the tools

Almost all individual processing steps can be decomposed into three sets of variables that represent the following behaviours:

- the rate and equilibrium processes that occur (both desired and undesired),
- the phases co-present in the process, and
- the properties that lead to gradients of composition and temperature.

The traditional chemical engineering approach to dealing with problems that are complex combinations of these is mathematical modelling. One might, for example, attempt to model a two-phase liquid batch reaction by combining a set of kinetic models [for the reaction and mass transfer rate processes] with a thermodynamic solubility model [to represent the phase behaviour] and a CFD model to represent the mixing behaviour [and thus concentration and temperature gradients]. To produce accurate predictions from a mathematical model of such a problem is almost certainly beyond current capabilities. Even if we assume that mathematical models of the underlying phenomena were available, the difficulty of preparing and validating a model would be prohibitive given the time and resource constraints applicable.

Of course, the use of correlations and simplified models can bring computational solutions within reach, but this is done at the expense of "lumping" the detail of phenomena together and can hide the critical detail. For example, a complex kinetic scheme might be summarised as a power-law expression representing conversion or yield as a function of time rather than

representing the rates of the individual desired and undesired reactions. Such an approach is unwise until sufficient knowledge has been captured to ensure that information critical to correct scale-up is not masked.

Curiously, though mathematical models are sometime applied in the analysis of low tonnage, their results are not always used quantitatively. Indeed, as with much of modelling, the outcome is insight that supports the identification of an appropriate strategy. It is often possible to develop the same insights on the basis of information of much lower depth. Consider, for example, the consecutive-competitive reaction scheme

$$\begin{aligned} A + B &\rightarrow C \\ C + B &\rightarrow D \end{aligned} \qquad (1)$$

where the desired product is the mono-addition product C. One might obtain the kinetic expressions for the two reaction steps and apply mathematical modelling to generate optimal operating strategies. However, it is evident on the basis of the law of mass action that

- the reaction yield has the potential to be sensitive to mixing (as imperfect mixing will lead to concentration excesses of B that would allow disproportionate formation of D);
- in a batch reactor, the favoured operating strategy will be the semi-batch addition of B to A, so as to minimise concentration excesses of B.

With such knowledge it is feasible to design appropriate experimentation to identify the details of an operating strategy, without the need for detailed kinetic analysis.

This approach is used throughout – capture and representation of the underlying problem structure rather than early oversimplification or quantification. Qualitative or semi-quantitative representations are used to capture the relevant behaviours in intuitively accessible ways.

The models

The models are broadly organised according to the entities listed above – rate processes, phase behaviour and spatial distribution. Of course, a representation is likely to draw on combinations of representations if multiple behaviours occur in combination. Some of the models and their application are described elsewhere [2,3,4,5]. Walsh [6] describes how the models have been used within GSK to support capture and exploitation of knowledge in both process development and manufacture of pharmaceuticals.

Rate processes

Two representations are used for rate processes – the Transformation Map and the Driving Force Table. The Transformation Map simply captures all transformations and rate processes that occur and represents their topology and the reversibility or irreversibility of transformations. Where reactions are involved it is important to ensure that the full stoichiometric reactions are given, rather than abbreviated forms (as is common, for example, in the pharmaceutical industry).

An example is shown in Figure 1.

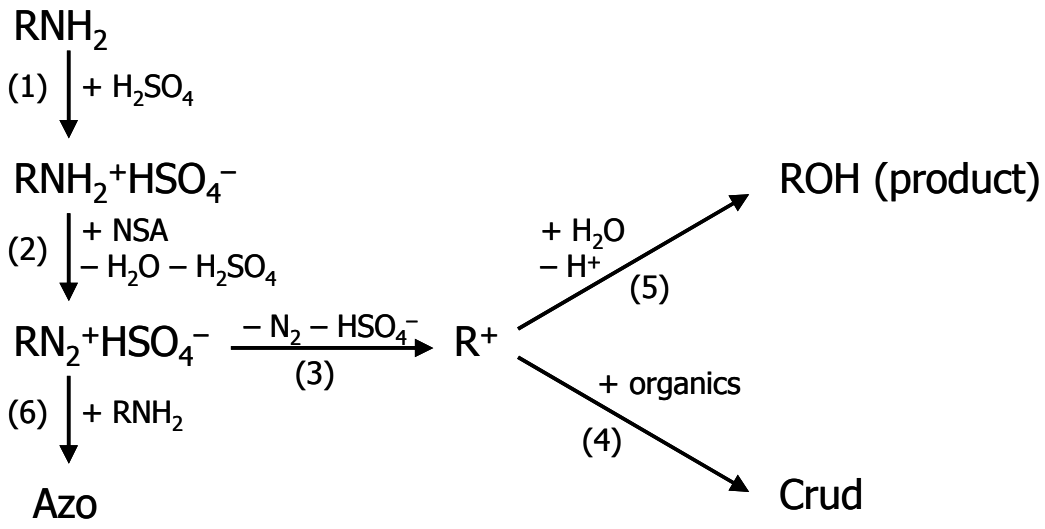

Figure 1 Transformation Map for amine conversion to alcohol

It is also useful to capture information about those factors that influence the rates of the individual processes – clearly manipulating the outcome of a processing step relies on the manipulation of conditions, operating strategy and equipment to maximise he ratio of desired to undesired processes. The rate processes can also involve mass transfer steps. A typical driving force table is illustrated in Figure 2.

Driving force	Reaction 1	Reaction 2	Reaction 3	Reaction 4	Reaction 5	Reaction 6
H_2SO_4	+	.	.	.	.	.
RNH_2	+	.	.	.	.	+
$RNH_3^+HSO_4^-$	-	+	.	.	.	.
NSA	.	+	.	.	.	.
RN_2^+ HSO_4^-	.	.	+	.	.	.
H_2O	.	.	.	.	+	.
R^+	.	.	.	+	+	+
N_2	.	.	.		.	.
ROH	.	.	.	.	.	.
Organic species	.	.	.	+	.	.
Azo	.	.	.	..	.	.
Temperature	+	+	++	+	+	+
pH	.	?	?	?	?	++
Heat of reaction	Moderate exotherm	Moderate exotherm	Strong exotherm For these reactions taken together			Exotherm ?
Reaction time	Very fast (order of ms?)	Few Minutes	Minutes (?)	Fast – possibly instantaneous	Fast – possibly instantaneous	Fast?

Figure 2 Driving force table for the reaction scheme of Figure 1 [2]

Phase behaviour

Phase behaviour may be captured in diagrammatic form or tabular form. The best form will depend on the type of information that is relevant. In the simple case of assessing the available phase combinations as a function of temperature, a suitable format might be as in Figure 3.

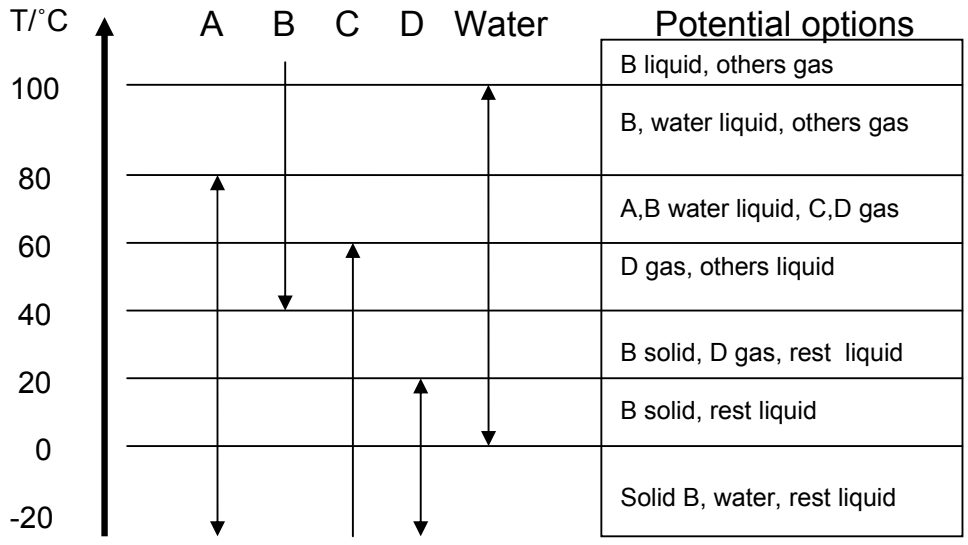

Figure 3 Potential phase combinations for processes involving compounds A to D and water. For each material the arrow represents the liquid range.Often, the relevant data to support assessment of phase behaviour is simple – melting and boiling points and some solubility data.

Spatial distribution

The obvious and simplest to represent the spatial distribution of materials, flow etc is to draw a picture. While there is clearly no originality *per se* in pictorial representations of complex phenomena and processes, it is perhaps surprising that this is rarely done by development scientists dealing with complex, often multiphase systems with multiple coupled phenomena. The use of a picture to capture mechanistic data and as a communication tool is immensely powerful.

Pictures may be relevant at the micro- meso- or macroscales, depending on the nature of the problem.

Examples

The tools have been used to support a range of technical and techno-commercial activities in the pharmaceutical and fine chemicals sectors and at several different stages in the development activity.

Selective decomposition

In this example the desired transformation was a selective catalytic decomposition of one of two isomers of a pharmaceutical intermediate. The process involved a solution of the two isomers A and B, and a supported solid catalyst. The desired reaction was

$$A \rightarrow P + D \qquad (2)$$

where P is the desired product, and D a small molecule. The main impurity Q was a result of isomer B undergoing a similar decomposition.

$$B \rightarrow Q + D \qquad (3)$$

The development team consisted of a mixture or chemical engineers, chemists and catalyst chemists. Significant work had already been carried out before the BRITEST tools were applied, and there was a problem achieving good selectivities at high conversions of A. Indeed, quite a lot of kinetic work had been carried out which had characterised the reaction kinetics for reaction (2), as well as selectivities to P. It had been established that the catalyst was deactivated during the reaction, and effort was being devoted to optimising the catalyst loading. Also, anomalous selectivity behaviour had been identified, with the instantaneous selectivity to P declining with conversion (Figure 4). However, the team could not account for the problem or see a way forward.

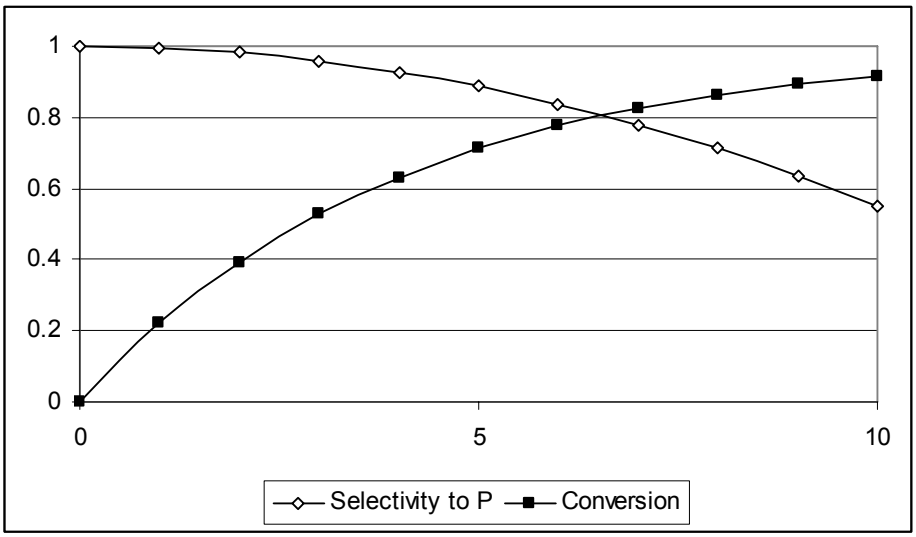

Figure 4 Schematic representation of conversion of A and selectivity

The tools were used to build a qualitative model of the system, and through development of the transformation map it was immediately evident that equations (2) and (3) were inadequate to explain the experimental observations. Reaction (3) could only occur catalytically, yet its rate relative to the desired reaction was increasing with time. It was evident that another rate process was necessary to account for the observations, and that this rate process had to involve the catalyst. The fact that almost none of reaction (3) occurred initially meant that there had to be at least two forms of the catalyst, and the scheme of equation (4) was proposed. There, Cat2 is a partially deactivated catalyst that promotes both reactions (2) and (3)

$$Cat \rightarrow Cat2 \rightarrow Inactive$$

Given this hypothesis, the catalyst chemists were able to give a likely mechanism. Material D was, based on existing and available knowledge, likely to be a catalyst poison, and indeed that deactivation by D was likely to be stepwise rather than "on/off"; however the catalyst chemists had not considered that to be important and other team members had not asked.

The qualitative model was now able to explain the observations, and the development team was able to refocus its efforts on the real problems. While in retrospect, the situation was quite simple, it had been missed by the team. Individuals within the team were addressing issues using their own skill set, and using technically advanced methods, but oblivious of the relevant knowledge of other team members. By sharing a simple qualitative model of the system they were able to understand. This is a good example of the problems of lumped modelling – the kinetic model assumed that there was selectivity, but little thought had been invested in why that selectivity might arise. By returning to the underlying (qualitative) structure of the problem, a useful and testable insight could be obtained.

Catalytic elimination scale-up problems

A second problem involved scale-up of a catalytic multiphase reaction. Here, the substrate S had a functional group removed by a solid catalyst. The removed group K was volatile, and would later be removed from the reaction as a gas – the reaction was run under reflux. Laboratory results were excellent, with high yields of the desired product R.

At scale-up an unexpected impurity Z was identified in significant quantities. Chemically, it was evident that Z was the result of reaction of R with K over the catalyst. The development team could not explain the observation – and indeed were unable to replicate the formation of the impurity in the laboratory plant. A programme of work was under way to identify the possible causes – with the difficulty of accurate temperature control at large scale being a prime suspect. There was also evidence that quite a lot of the Z was formed early in the reaction – during the heat-up phase – though slow heating in the laboratory again failed to replicate the observation. At this point, a study was carried out using the qualitative modelling tools.

The transformation map in Figure 5 illustrates the relevant rate processes and equilibria.

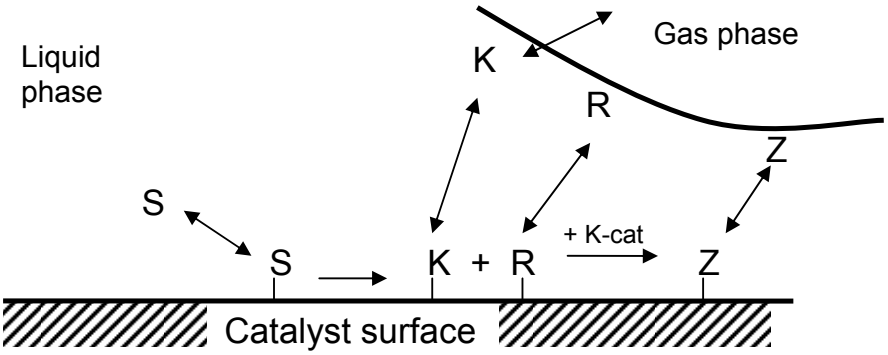

Figure 5 Transformation Map for surface-catalysed reaction

A driving force table was prepared, and using existing knowledge the driving forces of the transformation and mass transfer steps were identified. The rates of the transformation and mass transfer steps were mostly fast, with the likely limiting step being the chemical transformations at the surface. The only credible difference in driving force between the small and large scale was the concentration of K at the surface. The knowledge amassed in the table indicated that temperature was not likely to have much effect.

To investigate the problem further, a pictorial representation of the reactor was developed, identifying the major flow patterns and related movement paths for K. It was clear that there were order of magnitude differences in the timescales for removal of K from the laboratory system (short path length,

rapid recirculation, high gas sweep per unit volume via reflux) and the large scale (slow recirculation time, lower gas sweep per unit volume, higher hydrostatic head increasing partial pressure of K). The concentration of K at the catalyst surface was almost certainly much higher in the large scale reactor.

The new model was able to explain the reasons for the previously inexplicable observations at the plant scale, and to suggest both a range of confirmatory experiments and operating strategies to mitigate the problems. The collection and organisation of existing knowledge allowed the multidisciplinary team to develop a shared understanding that relied on both chemistry and chemical engineering knowledge. In this case the subtle coupling of macroscopic flow and hydrostatic properties of the reactor with the catalytic chemistry gave rise to a problem where standard chemical engineering rules of thumb had failed. The reactor had been scaled up at constant power per unit volume in an attempt to ensure that mixing effects were controlled. However, the failure to recognise that it was macromixing rather than micromixing that was important, together with a failure to identify the importance of hydrostatic head resulted in the unexpected results.

The experimental work at laboratory scale was able to mimic reaction conditions much more closely as the experiments were designed to allow control of the concentration of K in solution. Understanding of the importance of K also allowed the identification of engineering approaches such as redesigning the agitation system and the consideration of an inert sparge. Note that no mathematical modelling was needed to develop these solutions – they flowed naturally from the understanding.

Discussion and Conclusions

The use of simple representations to capture, share and exploit knowledge has been described and illustrated. The method allows capture of detailed knowledge that is insufficient to be part of a detailed mathematical model, but can still be used to understand problems and to identify options. This approach is particularly useful in the low tonnage sectors where time is always short, and the availability of quantitative data suitable for mathematical modelling is limited.

By focussing on the underlying science, and not "lumping" critical phenomena in an attempt to quantify, the models are able to facilitate the identification of new insights. In the two examples, the information and knowledge necessary to understand the situations were available, but the normal dialogue between technologists from different disciplines was insufficient to synthesise a suitable model. The examples illustrate a more general finding – that in an attempt to quantify chemical engineers often fail to obtain a sufficient understanding of the underlying chemistry. These tools help to build understanding and allow critical appraisal.

Acknowledgements

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References

[1] BRITEST Limited (2005) www.britest.co.uk

[2] Sharratt PN, Wall K and Borland JN (2003) "Generating innovative process designs using limited data", J. Chem Tech and Biotech, 78, 156-160

[3] Wall K, Sharratt PN, Sadr-Kazemi N and Borland JN (2000) "Plant-independent Process Representation", Computer Aided Chemical Engineering 8: European Symposium on Computer Aided Process Engineering-10, Pierucci S., (Ed.), Elsevier Science BV., ISBN 0-444-50520-2

[4] Wall K, Sharratt PN, Sadr-Kazemi N and Borland JN (2001) "Plant-independent Process Representation", Org Proc Res & Dev, 5 (4): 434-437 Jul-Aug 2001

[5] Obenndip D.A. and Sharratt P.N. (2005) "Enhancing Fine Chemicals Process Chemistry: A Practical Approach", Trans IChemE, Part A, 83(A8): 1–7

[6] Walsh J (2004) "An integrated Approach to Chemical Engineering & Chemistry Input in Process Design", Proc 2nd Symp Batch to Continuous Processing, ICheme/RSC London, November 2004