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Integrated Process Development: The Key to Future Production of Chemicals

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Abstract. Commercially successful chemical manufacturing needs to take into account stringent environmental and safety constraints already in the early stages of process development. All these necessary criteria have to be considered simultaneously. Information must be exchanged between all stages of development. Development has to be made in parallel. Economic, environmental, and safety criteria have to be considered broadly with respect to time and space. Some research examples of the 'Safety and Enviromental Protection in Chemistry Group' of ETH are briefly sketched.

Introduction

General Remarks to the EH&S Situation of the Chemical Industry

The enormous growth of chemical production particularly after the Second World War created increasing risks concerning environment, health, and safety (EH&S). The energy crisis in the early seventies did not only create a general awareness of limited resources, but also initiated a drastic change of thinking about environmental problems created by human activities. Pollution of ground, rivers, and lakes, and later global atmospheric problems like ozone depletion, made it necessary to increasingly consider environmental problems in the design and operation of chemical plants. The safety awareness of chemical industry has been growing since its existence, but was particularly pushed after severe incidents (Bhopal, Seveso, Schweizerhalle). The drastic changes were most strikingly expressed in the statement of an experienced industrial chemist who started his carrier in the late 50s in the dye-manufacturing industry. He said: 'At the beginning we just enjoyed having a new beautiful dye. Later we were also asked about the costs for production, and even more recently, we had to consider increasingly stricter limits concerning EH&S aspects'. This increasing influence of external constraints is depicted in *Fig. 1*, where it is shown how these constraints have to be considered in process design to optimise production in an acceptable and commercially successful way. The inherent interests of the chemical industry, the increasing public pressure, and the increasingly stringent restrictions by legal authorities forced the chemical industry to solve these problems quickly. Initially, the activities were focused on the treatment of effluent streams and on controlling hazards. These so-called end-of-pipe technologies create enormous costs (*e.g.* [1]). Additionally, safety and environmental requirements often conflict with each other [2].

The more reactive EH&S approach was triggered by a fast growing legislation in this field. Recently, the reactive strategy to solve environmental problems changed towards proactive avoidance and reduction of pollution either by complete process changes or by optimisation of existing processes. Similarly, there is a corresponding trend towards the development of inherently safer processes [3][4]. This is also the only way to allow a possible ecological and safety improvement together with an economic improvement [1][5–10]. To approach these goals proactively, new management tools have to be implemented (product stewardship, responsible care, EMAS [11]). Additionally, there is a severe problem with public perception. Despite huge investments in the EH&S area, the public perception of chemistry is even worse now, at least in Europe [12]. The public aversion can only be improved by an information and discussion procedure between the chemical industry and the relevant stakeholders, a trust-building activity needing patience.

In the following, we will focuse more on the technical aspects of possible proactive process design methodology which considers EH&S aspects.

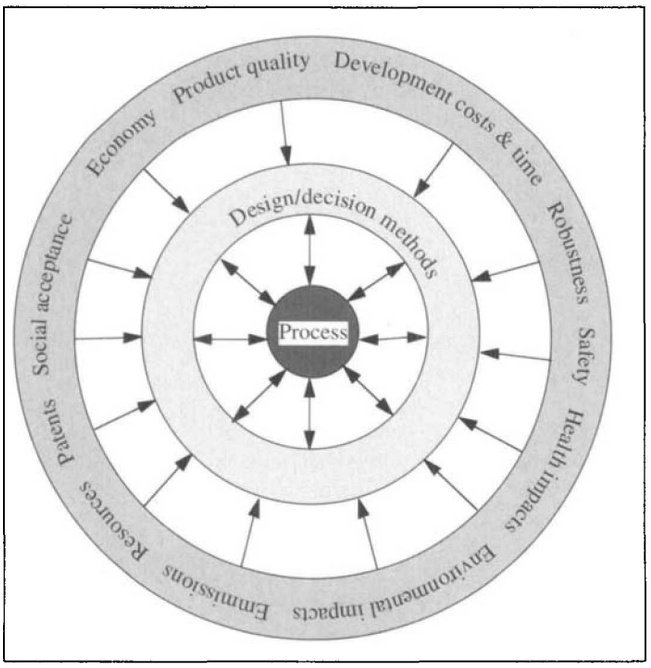

Fig. 1. *Interaction of design criteria and design and decision methods in process development*

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Early Design and Uncertainty

It has been shown in the machine-manufacturing industry that design activities and decisions in early development phases predominantly determine later costs. During the development phase, 70% of the total costs were fixed, whereas the costs for the development activities themselves contributed only 5% to the total expenses [13]. Similar characteristics were also observed by *Züst* [14]. Like costs, also other later process characteristics, such as the environmental burdens, are mainly determined in early phases (*Fig. 2*). The major problem is that in this phase the uncertainties are highest. It seems, therefore, of utmost importance that in this phase all useful information is included in design and assessment. As this has to be done under time pressure, a simple and flexible methodology is required to accomplish this problem. This methodology should be consistent throughout the development process and should promote communication between the various people and groups involved in designing a process. The necessity for such tools has been identified and is leading to new methods [4][15][16].

Early design and decision tools are now needed more than ever because of the present reorganisation going on in the chemical industry. The attempt to increase the shareholder value is taken into account by focusing on core competence, by creating large enough units for high risk developments, by shortening development times, and by outsourcing, *i.e.*, by incorporating resources on a global scale. These developments seem to counteract attempts for integrated production, which usually requires a careful balance of material and energy flows within a factory [1][9]. Integrated production is promoted in factories with a wide range of activities, sometimes even reaching from petrochemical processes up to fine chemicals manufacturing (*e.g. Lonza*).

This emerging new organisation with the much higher specialisation and with global distribution of chemicals production may cause a move away from responsible care, if there is not a clear management commitment to consider EH&S problems in all activities of the companies. There must also be an increased awareness of prevention of problems in all stages of development. This preventive thinking and action must become an integral part of everybody's work in the chemical industry. If environmental protection and safety are primarily the job of specialists, necessary action will always be too late, inadequate, and hardly acceptable to design specialists who will experience these actions as restrictions hindering their work. Specialists are needed, but their work should not primarily be experienced as restrictions but as a value-adding activity. Many of these characteristics are incorporated in modern health, safety, and environment policies (*e.g. Novartis*).

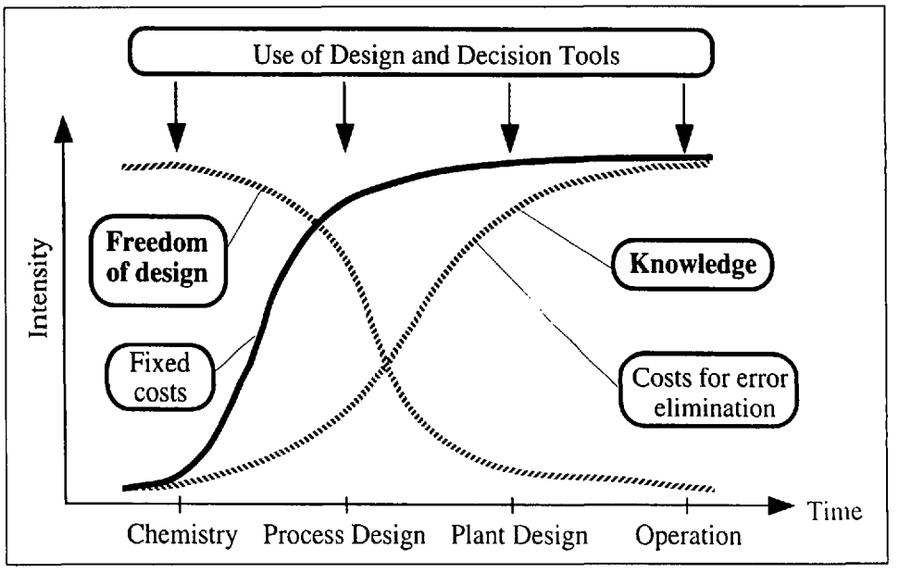

Fig. 2. *Degrees of freedom for design, depth of knowledge, and fixed costs as function of development step.* Arrows indicate assessment and decision taken.

The inherent high uncertainty in early phases may be studied with probabilistic methods as far as the probabilistic uncertainty is concerned. Such studies are gaining increasing popularity and various mathematical presentations of uncertainty have also been compared (*e.g.* [17–19]). The more serious problem is, however, that in the early design phase we can never know with certainty whether we have considered all important data and interactions. Later when complete mass and energy flows are calculated, we can at least prove the consistency of the chosen calculations.

Characteristics of Integrated Process Development (IPD)

Classically, development always relied on a set of specialist teams, each optimising with respect to a small set of criteria, *e.g.*, chemical synthesis route with respect to product quality and yield, process design with respect to selecting, designing and connecting suitable unit operations and process control structure, plant design with respect to equipment and process control. The result is a sequential process with only scarce information transfer between these steps. This can be simplified as shown in *Fig. 3, A*.

The approach to solution of design problems uses teamwork and broad networking, a necessary characteristic of integrated development. This is presented as a control problem in *Fig. 3, B*. A whole network of people with all their expertise is required to create new design alternatives, to sense problems and chances associated with these options, to assess the potential economic, ecological, and safety impacts, and to select alternatives to be further developed. Measured information has to be converted so that it can be communicated to all other people involved in development, as well as to marketing, to management, and to external partners. The same is true for design modifications suggested and for decisions drawn. These are presented as control actions in *Fig. 3, B*.

We can define integrated development (IPD) as a process where:

- in every development step, information of all other steps is considered, design is rather done in parallel than sequentially (time dimension of IPD);
- design alternatives are simultaneously assessed iteratively with increasing depth for multiple criteria – economic, safety, and environmental protection (depth dimension of IPD);
- impacts on local and global environment are simultaneously considered (space dimension of IPD);
- people with various expertises work in a broadly networked multi-disciplinary teamwork (human resource dimension of IPD).

Assessment Criteria

Design methods in all development phases require assessment criteria and methods to characterise the performance of various process alternatives for comparison and to identify critical process

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steps. A variety of methods are available for quick economic and safety assessment [20][21]. The ecological assessment is still very difficult. The most interesting, but not well enough developed method for this purpose, is life-cycle analysis (LCA). Various groups have realised early that the application of LCA in design of either products or processes needs special screening and streamlined methods [22–26]. Particularly in the early design stages, where most influence on the final process design is possible, most of the data necessary are not available for a detailed LCA. Energy consumption would generally be an interesting indicator for the environmental performance of a chemical process. Its use for LCA screening in the development of fine-chemical processes does not seem to be presently realistic because there is almost no data available in early design phases. Even from existing batch processes, there is only very limited information available on the actual energy consumption.

The Steps of Early Process Development

Various steps are now separately discussed keeping in mind that these are embedded in an IPD procedure, as depicted in *Fig. 3, B*. Process development for the manufacturing of a specified chemical product starts with the definition of a new project, usually for the manufacturing of a new product or less frequently for retrofitting an existing process. For each of these cases, we need adequate design and decision tools, indicated by arrows in *Fig. 2*. In the case of a new process, the available data are usually very limited. After starting a new project, the chemical synthesis route is defined first.

The Role of Chemistry

The chemical synthesis route predetermines many things, and mistakes can only partly be compensated later by engineering process improvement. The importance of chemical synthesis for pollution prevention was most clearly addressed by *Sheldon* [27][28]. Organic synthesis methods are quite mature, and much of the design work in industry is combining various synthesis steps to an optimal synthesis route. Less and less experimentation is required, which was expressed by *Sheldon* [27] in the following way 'Organic synthesis has become a primarily intellectual exercise, much like playing chess'. Numerous attempts are made to make the broad knowledge of chemical synthesis generally available to chemists. An interesting example is Crossfire, the computer version of *Beilstein*. This programme is extremely useful but is restricted to historical, published information. Innovation is entirely left up to the chemist. More and more sophisticated retro-synthetic tools are emerging which help to speed up the organic chemists' work in this field [29]. Presently, these tools do not yet seem sufficiently mature to assist daily synthetic work effectively and efficiently.

For the synthesis of modern complex chemicals for biological applications (food, pharma, and agro), reactions have to be very selective with various respects (chemo-, diastereo-, enantio-, regio-, stereoselectivity). As a consequence, synthesis routes are often complex with multiple steps. For pharmaceutical products, the synthesis route is usually fixed very early because of registration procedures carried out with governmental authorities, *e.g.*, the FDA. The choice of a synthesis route is also most important for the environmental performance of a later technical process [30][31]. Coupled products are inherently bound to a particular synthesis route. Required substrates, usually also solvents and other utility materials, are already defined at this point. Here, basic steps of separation are defined as well. At this point, main goals are yield and product quality.

Integrated into the development of synthesis routes is catalysis, a discipline contributing to more economic and more ecological processes at the source, avoiding

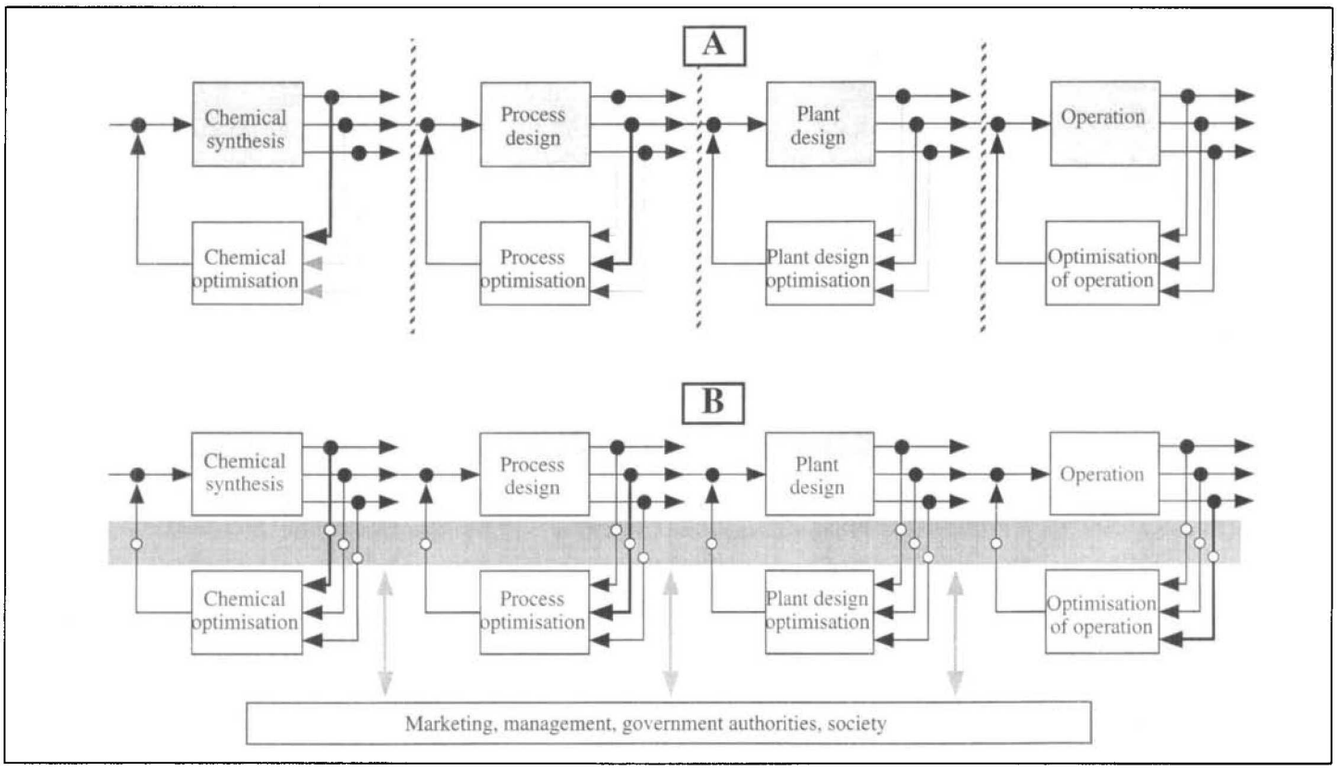

Fig. 3. *Information flow in the design process. A*) Classical sequential process with few interaction between development steps and groups; *B*) integrated process with information feedback from all stages to all other stages. The dashed bar indicates a kind of information bus accessible for everybody involved in the design activity. Thickness of lines indicate intensity of interaction (measurement, control).

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side reactions and promoting high degrees of conversion. A whole recent issue of CHIMIA (3/96) was dedicated to 'Catalysis in Switzerland'.

Process Design

After determining the chemistry to be used, detailed reaction conditions and the basic layout of a future process are defined. This includes the process scheme with reaction and separation steps. Sometimes it will be even necessary, or advisable, to change synthesis parameters (*e.g.* route, catalyst, solvent, and other auxiliary materials). Such changes are usually not possible or are, at least, very costly for products with strict registration procedures (*e.g.* pharmaceuticals). In this step, pilot experiments may be necessary.

Tools for the development of chemical processes based on a limited set of identified synthetic routes have been recently receiving more attention. A group at MIT created the so-called Batch Design Kit which supports development and design of batch processes for the manufacturing of fine chemicals and pharmaceuticals [32–34] and is now available from *Gensym*. This tool is not intended to replace experts, but to support their work by quickly providing help in the design process, including assessment using various criteria. A similar programme, Batchplus, became recently available from *Aspentech*. This programme will allow the complete interaction with the well-known extensive data banks, physical property estimation, and distillation design tools of AspenPlus. Another interesting approach is taken by *Intelligen* who is selling SuperProDesign, a flowsheeting-like batch programming system. There are numerous very interesting activities in the area of linear and nonlinear programming and generally in the incorporation of expert knowledge into design as has been reviewed recently by *Han* and *Stephanopoulos* [35]. It is, however, hard to imagine that design may be completely automatic. A critical point is the easy man-computer programme interaction, which allows each development expert to interact quickly and intuitively himself.

Via *Scaleup to Production*

In a next step, scaleup has to be made, reaction and separation processes have to be assigned to distinct devices, and all the detailed engineering work must be completed. Energy and waste minimisation are also possible and necessary during batch scheduling (*e.g.* [36]). After implementation, production starts and usually there is a learning phase during which the process is further optimised. In these later stages, the number of degrees of freedom is usually much lower and consequently improvements are typically more limited.

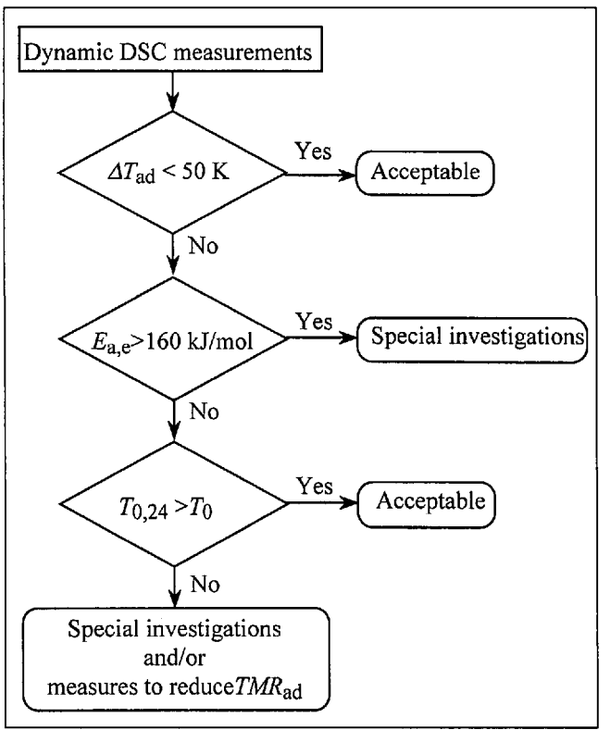

Fig. 4. *Screening procedure for the early thermal safety characterisation of a chemical process* (adapted from [42])

Process Development and Time Pressure

In the development procedure, time is usually a critical factor. Prolonged development time reduces available time for production under patent protection and increases time to market. An ideal development procedure would, therefore, involve extended and fast computer simulation and data generation. As indicated above, there are, however, only few simulation tools available which are generally suitable for batch process development, some are in development. Besides a clear lack of design tools, there are also limitations in optimised experimental laboratory techniques and in the availability of suitable design criteria to be applied throughout the development procedure. This is particularly true for environmental characteristics. Therefore, we initiated research activities in these fields.

Research of the Safety and Environmental Technology Group of the Chemical Engineering Department of ETH

In what follows, we want to outline some possible relevant contributions to the integrated development coming from the chemical engineering academic world, in particular from the Safety and Environmental Technology Group at ETH. Chemical engineering is traditionally an interdisciplinary activity using chemical, physical, technical, and economic knowledge and methods. Typically, research is focusing on special topics, treating them in depth. As contribution to IPD, we urgently need broad research projects involving industrial case studies. As indicated earlier, we want to focus our research on the elaboration of EH&S criteria to be used throughout the development procedure, particularly in early phases of development. Secondly, we want to contribute to the development or adaptation of design methods to be practically applicable in the present industrial environment. The-se methods shall be developed and tested in conjunction with industrial case studies.

Criteria for Assessment of Chemical Processes During Development

Economic criteria are well established but are also subject of continuous improvement [20]. Economic evaluation and assessment are of central importance and are closely observed by the management. Safety and occupational health standards provided by legal authorities are on a very high standard, at least in highly developed countries. These criteria are, however, not directly applicable in early development phases. Screening methods are required which will primarily focus on the input characteristics of a future process.

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Safety Screening Methods

Process safety standards are continually improving. It is generally accepted that all accidents must be prevented. The methods are well developed, and a whole series of test methods and design concepts is used in industry [21][37–39]. Some of these methods (*e.g.* [40][41]) are quite complex and expensive and often need a rather large amount of sample. There is a need of quick and cheap screening methods which would allow a fast assessment with a small sample size. In thermal safety, dynamic scanning calorimetry (DSC) is well established (*e.g.* [21]). We are focusing our work on the extraction of maximum information out of as few as necessary DSC measurements. In a recent study [42], we simulated DSC measurements and thermal runaway. From these simulations and from industrial experience, it was possible to suggest a modified screening methodology as summarised in *Figs. 4* and *5*. In *Fig. 4*, the essential part of the screening procedure is schematically shown. From one single DSC measurement, first ΔT_{ad}, the adiabatic temperature rise caused by thermal decomposition, is compared with an empirical threshold value of 50 K. If ΔT_{ad} is less than 50 K, the process is considered to be safe. If $\Delta T_{ad} \geq$ 50 K, further assessment, is needed. From the DSC measurement an apparent activation energy, $E_{a,e}$, is calculated. If this estimate is above 160 kJ mol^{-1}, somewhere up to 80% of total heat production from decomposition, the decomposition is considered to be autocatalytic and needs to be investigated further. If $E_{a,e}$ is less than 160 kJ mol^{-1}, the maximum process temperature which guarantees an adiabatic time to maximum rate, TMR_{ad}, of more than 24 h, $T_{0,24}$, again a value defined by industrial experience, is determined from the onset temperature, T_{onset}, of the DSC measurement (*Fig. 5*). It is compared with the actual maximum process temperature after cooling failure, T_0. If $T_{0,24} > T_0$, the thermal risk of this process is considered acceptable. Otherwise, T_0 has to be reduced or further investigations are necessary, *e.g.* a real adiabatic experiment. This DSC method is very quick and allows the classification of reactions into a majority of acceptable reactions and into a minority of those needing further investigation. Presently, a further refinement of the screening method, especially for autocatalytic reactions, is in progress. A contribution to thermal safety characterisation later in process development using reaction calorimetry is given in this issue of CHIMIA by *Regenass* [43].

Environmental Screening Methods

The environmental impact can be assessed with various methods. The conventional and most simple one compares the effluents with those legally tolerated. This corresponds to an analysis with the fence of the factory as boundary layer. This method corresponds to minimum required legal compliance. It has, however, a limited horizon which can easily lead to undesired surprises caused by changing emission limits or by discovery of problems hidden somewhere else in the supply and emission chains. Life-cycle analysis (LCA) considers all environmental impacts from cradle to grave. It is increasingly gaining popularity, particularly for the characterisation of the environmental impact of products. Some publications are already available in the literature using LCA for comparison of process alternatives (*e.g.* [44] [45]). In industry, LCA is already used for screening large numbers of products [44]. There are further contributions to this field in this issue of CHIMIA [26][47]. As this methodology needs information about all substrate and auxiliary material inputs and all emissions created, it is hardly applicable in very early process development phases. Additionally, the handling of such complex programmes presently needs specialists and quite a lot of man power. This may be improved by future computer versions.

It has been found also in other fields that during design screening and streamlined methods are needed [25]. *Flower et al.* [48] proposed a graphical mass balancing method to design cleaner processes. We have started from the ideas presented by *Sheldon* [27] and by *Schmidt-Bleek* [23] and have shown how mass flows can be analysed in the begining of the design [49]. Similarly, *Mak et al.* [50] already apply such a methodology during the development of pharmaceutical processes. These seem to be a first good indication of possible environmental problems. We try to extend this methodology by allocating all mass streams to defined origins: coupled products associated with desired reaction, incomplete conversion, bad selectivity, impurities contained in substrates, solvents, catalysts, and other auxiliary materials needed. A mass loss index is assigned to each of these non-idealities

$$MLI_i = \sum_{j=1}^{nS} \frac{m_{i,j}}{m_P} \qquad (1)$$

where m are mass flows and nS is the number of substances involved, j indicates the substance involved, i the type of non-ideality, and P the desired product. Considering all mass flows, a mass index, *MI*, is then defined

$$MI = 1 + \sum_{i=1}^{nN} MLI_i \qquad (2)$$

where nN is the number of non-idealities. *MI* also includes the mass flow to desired product which is represented by *Eqn. 1*. *MI* represents the total mass of input needed per unit mass of product. If allocation is not possible at a certain stage, it can be incorporated later. For a preliminary economic analysis, all mass flows are multiplied with corresponding costs. Here also waste streams are included. Preliminary to this, waste streams have to be allocated to a specific waste treatment method whose

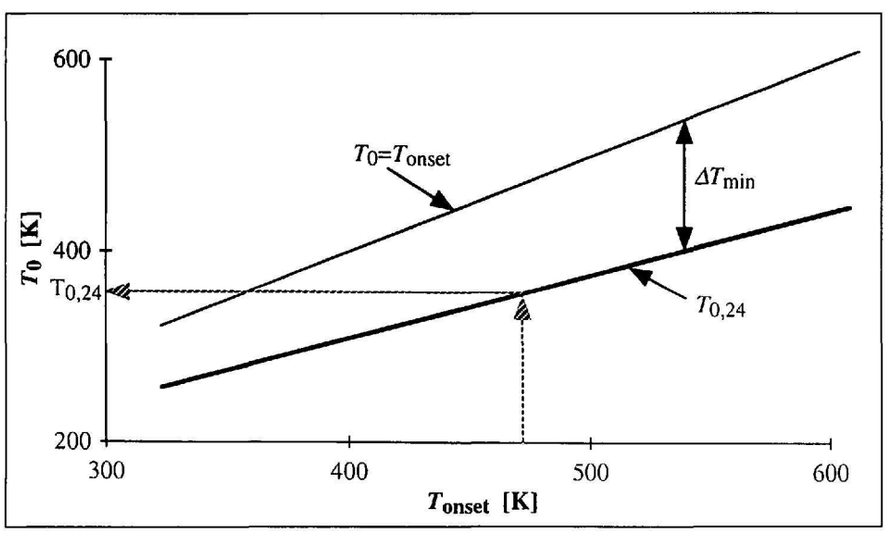

Fig. 5. *Determination of maximum allowable process temperature, T_0, to guarantee a time to maximum rate of more than 24 h, from the onset temperature, measured by DSC* (adapted from [42])

costs are known. A more detailed environmental and safety characterisation is obtained by applying ABC analysis, a semiquantitative classification into nonproblematic, medium problematic, and unacceptable process streams. Here, either the number of unacceptables can be counted and compared for competing process options [50], or to each class a weighing number is assigned and further multiplied by the corresponding process stream. This can then again be plotted for comparison.

An example of such a plot for one single process step of the fine chemical industry is given in *Fig. 6*. It can be observed that in the economic analysis the solvent and auxiliary contributions become less important. In the ABC-input-oriented analysis, the relative importance of solvents for reaction increases because of the utilisation of nonreneweable raw materials of limited known resources. Similarly, product, coupled product formation, and product losses in purification gain importance. The output-ABC analysis increases the importance of coupled product formation and purification losses because of toxicities of product and coupled product. The method is designed such that it can easily be used throughout the whole process design procedure by continually refining initially rough estimates.

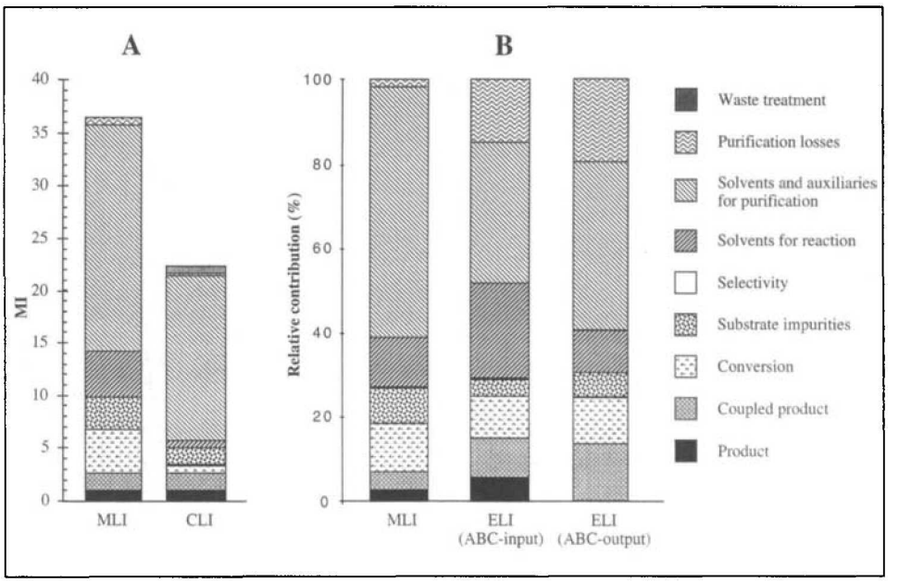

Fig. 6. *Characterisation of a process from the fine chemical industry using the screening procedure developed by* Heinzle et al. [49]. *A*) mass (*Eqns. 1* and 2) and economic indices (costs), *B*) ecological evaluation with mass flows using weighed ABC-input and ABC-output analysis.

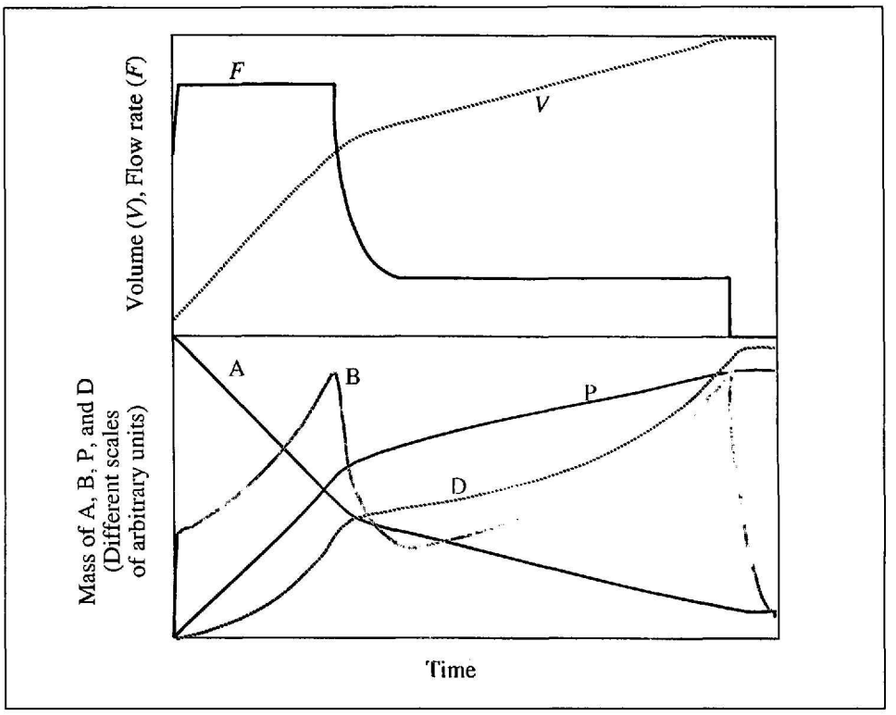

Fig. 7. *Simulated feed profile of an industrial process when controlling the feed rate with constant selectivity and constraint of maximum allowable temperature of reaction given in* Eqn. 3 [56]. *F* = feed rate; *V* = volume; A, P, B, D = concentrations of A, P, B, and D. Scales are in arbitrary units and different for different variables.

Design Methods

Numerous methods are available for designing chemical processes. For improving EH&S characteristics of processes, many of these just need to be applied. This is, however, complicated by the increasingly stringent time pressure. More complicated methods, or those where user-friendly software and data bases are not available, are rejected by the industrial community. An attempt has therefore to be made to first identify those design procedures, where the potential for improvement is highest and where present methods as accepted by industry are insufficient.

Chemical reaction is the heart of any process, and adjunct non-idealities cause complications in downstream processing. An ideal process having no coupled products would not need any separation step. Even if most money is spent for downstream processing, the roots for all problems are in the chemical reaction. Most significant problems are: selection of the best possible reaction [27][28], selection of optimal auxiliaries, *e.g.* solvents or catalysts [51][52], identification of reaction kinetics and supply of material data. For downstream separation processes mainly the lack of materials data is significant.

The Role of Modelling of Kinetics

We started some work in the field of industrial reaction kinetics, where kinetic models are very rare. Possible reaction schemes are first elaborated using all available knowledge of expected side reactions. Kinetic experiments can either be made in small laboratory reactors or in reaction calorimeters [43]. Additionally, data from existing production processes can be used. Modelling should be as simple as possible. Complexity should only be introduced as far as required and as far as is justified from the existing knowledge. Clear balancing methodology and simple, user-friendly programmes make the setup of mathematical models and their simulation very easy, even for less

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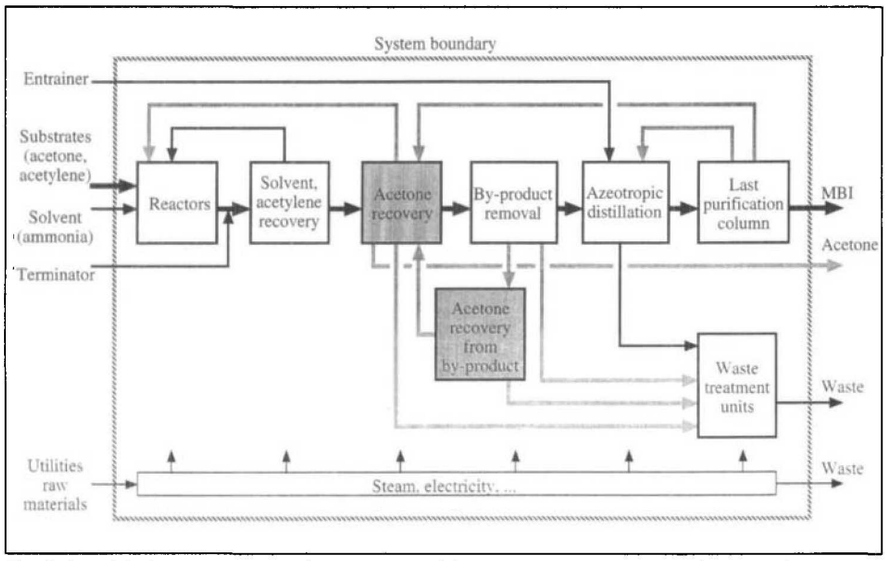

Fig. 8. *Simplified waste-oriented block diagram of the MBI process and its modifications.* Grey blocks and grey arrows indicate simulated process modifications (modified from [59]).

experienced chemists [53]. We have successfully modelled two industrial processes during two diploma studies [54][55]. One of these processes has a reaction of the following type

$$\begin{aligned} &\overset{r_1}{\rightarrow} \\ &A + B \rightarrow P \\ &\overset{r_2}{\rightarrow} \\ &B + B \rightarrow D \end{aligned} \qquad (3)$$

The first reaction is the desired reaction, whereas the second reaction creates enormous problems in the product isolation section. B is fed to the reactor. With the model setup it was possible to study various feed profiles, considering also the heat transfer capacity of the reactor. Constraints were the heat removal capacity of the reactor to keep the temperature below a maximum value. In one simulation study, a constant accumulation of B in the reactor was used to control the feed rate. In another study, the selectivity was kept constant by controlling the feed rate of B. Typical time profiles of feed rate, volume, and concentrations of A, B, P, and D are given in *Fig. 7*. The resulting feed-rate profile is characterised by a maximum allowed feed rate in the first phase and by a lower feed rate towards the end of the reaction, which is rather easy to implement in the industrial process. Higher set points for the selectivity caused the cycle time to increase and therefore productivity to decrease. Selectivity and productivity can be used in a combined objective function to calculate an optimal feed profile. Goals of future research are the introduction of experimental and modelling tools, which will be applicable already in very early development phases with minimal effort.

Batch Design

It is generally thought that the energy consumption would be a realistic indicator for the overall environmental impact of a process. Energy allocation in industrial batch production is, however, very difficult [36]. We have started a project with *Ciba Speciality Chemicals* to allocate energy consumption in a batch plant and to create methods to allow real energy consumption to be estimated in early process development stages. The results of this project could be useful for early environmental screening. Another project with industrial collaboration deals with the early estimation of cost and environmental impact of batch processes and the influence of uncertainty in this procedure.

Retrofit Hierarchical Method

Waste minimisation through process design is increasingly applied [12][57]. In our group, a hierarchical procedure was applied to the optimisation of a real industrial plant to reduce wastes, as well as energy and raw-material consumption [58][59]. In the case studied, the continuous production of 2-methylbut-3-yn-2-ol (MBI), acetylene reacts with acetone. The solvent ammonia and acetylene are recycled to the reactor. Unreacted substrates and by-products are separated from the product stream by distillation. Part of the unreacted acetone can be reused for other purposes after distillation. A substantial part of the unreacted substrates and by-products is delivered to a wastewater treatment plant. These waste streams constitute a substantial problem for the operation of this plant.

First, waste streams were characterised and tracked back to their origin. Following a hierarchical design procedure [60][61], the overall input-output structure was fixed. The entrainer in the present process was critically examined, and options were suggested. Then various recycle schemes were considered for later detailed study. *Fig. 8* shows the process layout, and the optional changes are highlighted.

The existing plant was simulated using AspenPlus. After adjusting the model to all important aspects of the real process scheme, excellent agreement between actual process performance data and simulation was obtained. The various process schemes were simulated and assessed for their economic and ecological performance. The objective functions used included utility, substrate, and catalyst costs, as well as costs for wastewater treatment. Additionally, the environmental burden related to energy supply was accounted for by a carbon dioxide tax, as suggested by the Nordic countries. The process changes included separation of unreacted acetone from the product stream and recycling to the reactor. By-products were converted back to substrates in an additional reactor separation system and recycled. In various simulated process configurations and operational schemes, substantial economic and ecological saving were achieved. This study demonstrates the usefulness of hierarchical approaches, combined with process simulation for plant optimisation.

Similar case studies appear increasingly in [44][62][63]. *Dantus* and *High* [64] set up a superstructure of a complete process, formulated it as MINLP problem, which was then optimised with AspenPlus using economic criteria.

Further work in our group simulates process steps in the vitamin production and aims also at retrofitting. Additionally, it should supply information for validation of early design screening methods.

Concluding Remarks

Integrated process development is an activity which deserves more attention by academia. It seems clear that research is not only possible by extremely narrow and deep research. Broad interdisciplinary work is of high relevance for the economic success of chemical manufacturers, as well

as for successful proactive incorporation of safety and environmental considerations. IPD is also an essential part of teaching and education on all levels and needs integral case studies [65]. It can only be successful, if this type of thinking is included into everybody's activity.

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