Product-driven process engineering : the eternal triangle molecules, product, process

TU/e technische universiteit eindhoven

Inaugural lecture
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the eternal triangle molecules, product, process

/ department of chemical engineering and chemistry

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Given on 9th January 2004
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Introduction

Mijnheer de Rector Magnificus, dames en heren
This inaugural address will be held in English in order to maximize the number of friends, colleagues and former colleagues, students, and my wife, to fully understand it.

Ladies and gentlemen
Tom Lehrer, an American, was born in 1928, studied piano from his 8th year on and mathematics at Harvard somewhat later. He liked to treat his comrades at campus events with outrageous songs and parodies and became so successful that he spent many years entertaining audiences all over the world. Until 1960, weary from 7 years on the tour, when he retired from the stage to return to teaching mathematics at Harvard and later at the M.I.T. One of the rather humorous songs of Tom Lehrer [1], about a Russian mathematician Nicolai Iwanovitch Lobachevsky who fell victim to plagiarism, mentions the 'eternal triangle, in which Ingrid Bergman played the role of the hypotenuse...' Jean-Claude Charpentier [2] made me think of this song in his paper on the future of chemical engineering and this explains the title of my oration. I leave it for later to determine who plays the role of the hypotenuse in the eternal triangle we discuss today, but you can let your own imagination work already, of course...

In my presentation today I will first dwell on the changes in industry and society that have changed the chemical and process industry over the last 15 years, then I will give an overview of the changes in relative importance of basic process building blocks and illustrate this with an example of an anti-cancer drug. The need to refocus chemical engineering follows naturally from this analysis. Finally I will present some of my views on chemical engineering curricula at universities and indicate some lines of product-driven chemical engineering research.

With process industries we mean the industries manufacturing petroleum products, pharmaceutical products, agro-products and foods, textiles, iron and steel, building materials, glass products, detergents, personal care products, electronics etc.

Trends in industry and society

2.1. The changing architecture of industry

Industries have merged, acquired new businesses and sold parts of their subsidiaries to concentrate on Core Business, defined by strategic analyses. The results of this continuous adaptation are tremendously significant.

Nowadays commodity chemicals, like ethylene, propylene and vinyl chloride, are made by a dwindling number of large ultra-efficient companies, which employ relatively few people. They have to do so in order to remain profitable. Their main strategic objective is 'value preservation'. The products are made in large highly integrated chemical plant, dedicated to making a single product at a rate of many thousands tons/yr. The producer with the lowest manufacturing cost usually makes the most money.

Specialty chemical products and fast moving consumer goods (think of pharmaceutical ingredients, functional ingredients, foods, personal care products, household cleaning and laundry products, crop protection chemicals, coatings, lubricants and so on) have grown tremendously in importance. Companies manufacturing these products have 'value growth' as the main strategic objective. Specialty chemical products like pharmaceutical ingredients and functional ingredients are often made in quantities less than 10 tons/yr. The company that first markets a product tends to get 60% of total sales.

Consumer goods companies like Unilever and Nestlé have carried out strings of acquisitions to strengthen their brand positions (and limiting the total number of brands in particular at Unilever) and to fully concentrate on fast moving consumer goods instead of operating a mix of fast moving consumer goods with specialty chemicals such as flavor houses, catalysts or oleo chemicals.

2.2. Product innovation and process innovation

Innovation times have shown a steady acceleration over the last 30 years. I should note here that we are excluding here new pharmaceutical ingredients that have to go through an elaborate clearance procedure including extensive clinical trials. We can distinguish between

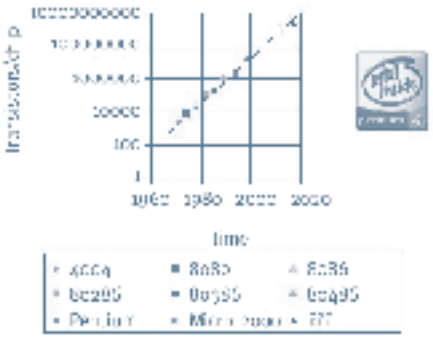
product innovations and process innovations. The classical thinking of Abernathy and Utterback [3] is that process development becomes increasingly important as industries mature. Their reasoning behind this is that in the early phase of an industry's life when product concepts are still being formed, the rate of product innovation will exceed the rate of process innovation. This period lasts until a 'dominant design' has emerged and opportunities for radical product innovation will decrease. Once a dominant design has emerged, due to competition the shift will be towards process innovations to reduce cost price.
This product life cycle model has some flaws. It assumes that process development is mainly driven by cost reductions, while in many cases the ability to rapidly develop and scale up manufacturing processes play a critical role in enabling rapid product innovation, shortening time to market and smooth production ramp-up after product launch [4]. In the pharmaceutical industry where the functionality of a particular molecule has to be tested in extensive clinical trials it is very important that the molecule used in the clinical trials is produced in a process that will be used also at large scale, so the scalability of the process must be assessed as soon as possible in the innovation cycle.
The half-time of a product innovation (or time-to-market) in the early seventies was about 10 years, currently, for products not requiring clinical trials, 2 years is already considered on the long side. This acceleration of innovation time is the result of competitive pressures in the market place. As a rough rule of thumb it is said that the first company to enter the market with a new product can get up to 60% of market share, so there is a high premium on being 'first'. We see a first glimpse of the relations in the eternal triangle Molecules, Product and Process....

2.3. From 'Make' to 'Service' to 'Care'

However, the structure of industry has also undergone changes of a different nature. Before the early 1970s industry mainly consisted of companies focussing making specific products which where then sold through retailers, dealers, etc. In the 1980s on top of this so called 'Make' segment a 'Service' segment appeared and grew strongly. This service segment specializes in providing a service to the consumer based on products that it procures from the 'Make' segment and combines them into total customer service packages. The result of the leverage of buying power is that the 'Make' segment has to reduce cost price in

order to stay profitable. In the early 1990s a third segment, the so-called 'Care' segment appears. This segment provides a total 'Care' package to individual consumers, combining several services it procures from the Service industry. More recently the difference between Products, Services and Care has become more and more blurred to the point that the distinction gradually becomes less useful. Companies try to build Service and Care into the Products they sell and try to build Products into every Service or Care package they provide [5]. What remains important that companies try to move out of the classical 'Best Product' strategic position, as described by Porter [6], to either a 'Total Customer Service' position or even a 'Lock-in' position [7,8]. Microchips and Internet provides many innovative opportunities here.

figure 1



Moore's Law, probably valid until 2017

2.4. Computational power and microelectronics

The advances in microelectronics are fabulous, see Fig.1. In the coming decade, an increase in computational speed by combined developments in hardware and software is estimated to be at least a 1,000 fold. IBM's planned new supercomputer Blue Gene represents the first major revolution in computer architecture since the 1980s. A radical cellular SMASH (simple, many and self-healing) concept makes it not only more compact but 500 times faster than the most powerful computers used today. Blue Gene will be self-healing, that is able to isolate and remedy a fault in any of its 1 million processors. These will deliver peta-flop scale performance.

This means that the speed of handling and analyzing information,

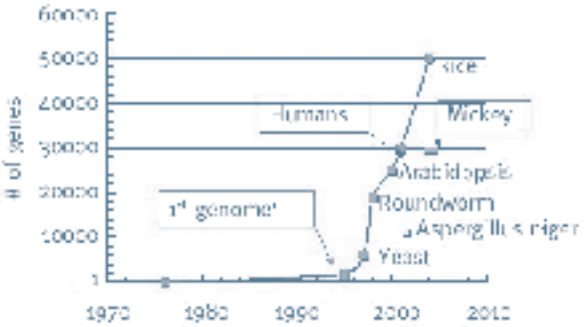
linking vast information sources, modeling of molecular structures, modeling the molecular interactions of micro structure formation, modeling of fluid flows, transport phenomena in process equipment, process systems control, manufacturing operations, etc. will increase tremendously in the coming decades. This will result in stronger and stronger bonds between the three corners of our eternal triangle....
In 2001 more than 400 m people worldwide surfed the Web's 4 billion pages and spent half a trillion $ on goods and services in the process of doing so. The mobile phone and its links to the Internet lead to a very interesting phenomenon that can be described in the mathematics of networks [9]. In the classical 'one-to-many' network of broadcasting the Value (V) of a network is proportional to the size of the audience, say N (Sarnoff's Law). In a 'many-to-many' network like the classical telephone system, the Value is different. With N people connected, the number of possible connections is N^2-N since you cannot make a phone-call to yourself (Metcalfe's Law). Now the Internet adds something extra. Internet users can form groups in a very easy way (discussion groups, auction groups, protest groups, chat rooms, temporary groups of football supporters or -hooligans, etc. etc.). If you have N people, they can form a total of (2^N-N-1) different groups and the Value of this system is proportional to this number (Reed's Law). The extraordinary power of the web to form spontaneous groups will constitute a lot of the value, including the nuisance value, of the web. Connection of mobile phones to the GPS (global positioning system) will even add additional opportunities of targeted communication.
The implications of all these developments for the consumer products industry, where information on dynamics of consumers behavior, marketing and advertising patterns, control of sourcing chains are essential ingredients for a successful business, are staggering. These later Information Technology developments will have a tremendous influence on market research, consumer science and extension of information about product functionality, nutrition and health to individual consumers. Highly interactive communication patterns between a business and its end consumers may emerge with which our current situation simply does not compare at all. For instance in the food industry, personalized diets can be constructed and monitored so that weekly or monthly the adherence to an individual optimal diet can be controlled via suggested menus from a palmtop computer or handy used during shopping or tale-shopping.

They will also have a tremendous impact on our manufacturing systems e.g. more and more 'distributed' manufacturing and therefore on the logistics of supply of our goods to retailers or industrial customers or the homes of individual consumers.

figure 2

Genomics: a fast developing science area.

[1] Graig Venter influenza bacterium



2.5. Life sciences

Life Sciences develop fast, see Fig.2. Since the unraveling of the first total genome of the influenza bacterium by Craig Venter, around 1995, a number of genomes of very important microorganisms, yeasts, molds, animals and plants have been unraveled (e.g. Yeast, Aspargillus, Arabidopsis, Rice, Man and Mice). Knowledge of these genomes is the first step in linking their structure to the myriads of proteins they can specify ('proteomes'). Proteomes in turn determine which metabolic pathways an organism can mobilize (in healthy life and illness), the so-called 'metabolome'. In the future the results of genomics, proteomics and metabolomics will help in designing new molecules for use in effective drugs, fine chemicals, functional foods, improved agricultural crops... The first harbingers are already there.

The impact of these developments on the chemical, pharmaceutical and food industry will be great. On the one hand, raw materials (vegetables, wheat, corn, oil seeds) can be developed that are much more tailor-made to specific product uses through advanced plant breeding techniques and thus only require minimum processing. On the other hand, biochemical conversion processes in our manufacturing operations can become much more selective, mild or otherwise more effective than current

operations, e.g. by using vastly improved enzymes, microorganisms as biocatalysts or bio-mimetic synthesis and process routes.
The extremely complex and exquisitely subtle regulation mechanisms of living cells, be it a micro-organism, a cell in a plant tissue, or the human body will be unraveled in the coming decades. This knowledge can then be used to design molecules for chemical/pharmaceutical products with more precise functionalities and foods with greater nutritional functionality ('functional foods'), improved quality, flavor and keepability. These molecules and the products in which they feature will be manufactured in precise processes with less waste and lower energy consumption designed by chemical engineers.

Again we see how developments in life sciences will influence the relations in our eternal triangle...

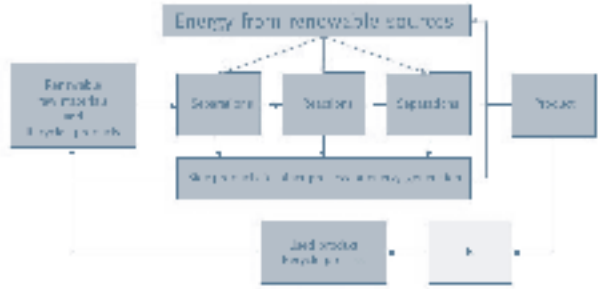
A major related issue is however, how the social, moral and ethical issues as perceived by the consumer towards biotechnology, can suitably be answered by scientists and regulatory bodies. However there is little doubt that advances in bioscience will enable the chemical and food industry to raise the quality and convenience of products in a nature-friendly and save manner.

2.6. Environment and safety

Sustainability [10] is an ideal that appeals to many people: polls tell us that 80% of all people in the world, including the USA, express the opinion that protection of the environment is a 'crucial target'.
The issues concerning sustainability of our environment are huge: greenhouse gases, the size of the ozone hole, decaying biodiversity, logging of virgin forests, population growth, and poverty (1.2 billion people live on less than 1 $/day).
Process technology will play a crucial role in several ways. For instance in reality checks of the production of suitable energy carriers from renewable resources and the proposition of big changes in processes applied in technology for bulk chemicals and fine chemicals. An example of what an ideal process system looks like is given in figure 3, borrowed from Wim van Swaaij [11]. In this scheme all raw materials are renewable (e.g. from agriculture) or recycled disassembled consumer products. Only a limited supply of raw materials is necessary. There are no emissions and waste products have become side products with

an own cycle of use. Energy essentially comes from sustainable energy carriers ('flow-sources').

figure 3



An ideal sustainable process (van Swaaij 2000)

Product safety and production processes that minimize safety hazards have continued attention of the process industry. Legislation in these areas is on the move and will influence future product and process development even stronger than is currently the case.

The eternal triangle Molecules, Product and Process plays again an important role...

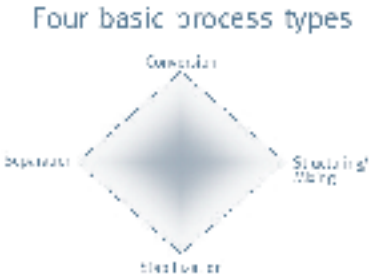
The 4 basic processes

Ladies and Gentlemen

Let us first have a quick look into the morphology of process engineering, see figure 4. We can recognize four major classes of processes. These four categories form two pairs that are each other's opposite.

figure 4

A morphology of process engineering



- Separation processes. The most important category of processes in the process industry is the class of disassembly- or separation processes where a raw material is split into valuable intermediate products that are often used as raw materials for end-product manufacturing processes. Separation processes comprise distillation (e.g. oil refineries), extraction processes (e.g. fractionation of vegetable oils and fats, milk fractionation), but also a host of mechanical separations where mixtures or slurries of particulates are separated into fractions (e.g. treatment of ground ores, flour milling). These processes are very typical to the chemical process industry (large tonnage, bulk products, often continuous processing).
- Structuring processes are the opposite of separation processes. Man-made structured products use assembly-, structuring- or texturizing processes for example crystallization- and emulsion-processes (e.g. margarines, mayonnaises, ice creams, paints, detergents), foaming (e.g. isolation materials, shaving cream, whipped creams), granulation, agglomeration, extrusion processes, dough making, baking, etc. The end product often is a complicated microstructure of dispersed phases

held together by binding forces and a continuous phase. The product microstructure leads to desired product functionality in use.

- Transformation processes. The most important process step in all the branches of the chemical industry is the conversion of reactants into a product. (Bio) converted foods use often highly complex conversion processes where either chemical or biochemical conversions are applied to raw materials yielding ingredients, flavors, fermented products, roasted products (black tea, coffee) and the like.
- Stabilization processes are the opposite of transformation processes. These processes, that combat spoilage, are rather typical for the food industry and pharmaceutical products. Naturally structured foods often use preservation or stabilization processes where the main aim is to eliminate microbial, enzymatic or chemical spoilage of the raw materials that usually are food tissues (fish, meat, vegetables)

An actual total manufacturing process is usually built up of combinations of these basic 4 processes. For instance in the petroleum refining and the bulk chemicals industry the separation processes and conversion processes are dominant. Raw materials are first purified to a certain extent by separation processes (S) and then brought together in a reactor system where transformation processes take place (T) and the reaction product is again purified by separation processes (S). The process flow sheet structure (S-T-S) is almost like the structure of a piece of music from the Classical period, in da-capo form or like a minuet or like a rondo if recycle streams are involved. In the sixties and seventies, in several inaugural lectures at all three Technical Universities in this country, definitions of 'process engineering' and 'process science' were coined. It is remarkable to note that Rietema [12], Thoenes [13], Zuiderweg [14] all emphasize that process engineering/science has to do with manufacturing systems where crude raw materials are converted into bulk products.

Thijssen however [15] emphasized that 'process science' involves the discovery of rules by which processes can be synthesized and realized. According to Thijssen, the building of product technologies can be seen metaphorically as a symphony orchestra giving a performance: process engineering is the conductor, key parts are played by material science, process experience (in Unilever we would say ‘best proven practice’), transport phenomena, reaction engineering and mechanical

engineering. The whole objective of the total performance is to delight the listener. This sounds more like a transition from the Classical music style to the Romantic style. I am convinced that the differing view of Thijssen must have been caused by his industrial experience in a food industry with its focus on making end-consumer products.

Table 1

Relative importance of basic processes for different product types

Industry	Transformation	Stabilization	Structuring	Separation
Bulk chemicals	++++	(+)	+	++++
Specialty Products	++	+	++++	+++
Foods	++	++++	++++	+++

In Table I we show that the importance of the two other basic process types (Structuring processes and Stabilization processes) are much higher in the fine chemicals, the pharmaceutical and the fast moving consumer good industries like the food industry. As we said earlier these industries have grown in importance as employers of chemical engineers. But also in the telecommunications industry, the construction industry and automotive industry needs for better and novel products with a microstructure is important, see Table 2.

Table 2

Some products with microstructure

Industry	Examples
Telecom and electronics	• Integrated circuits • Photovoltaic devices • Magnetic tapes, optical fibres • New ceramics for batteries
Construction	• High density concretes • Improved cements • Lightweight composite polymer materials
Automotive	• Lightweight, high strength corrosion resistant parts
Fast moving consumer goods	• Ice cream, spreads • Washing powders, -tablets, -liquids • Skin creams, soap bars and gels
Pharma	• New drug formulations • Delivery systems • Separation methods • Artificial tissue

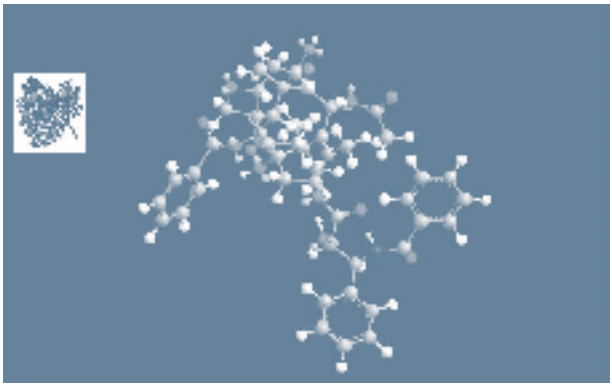
An example: paclitaxel

Ladies and Gentlemen

Let me give you an example of the eternal triangle, an example that involves a molecule with the name paclitaxel... This molecule made it to Molecule of the Month in last year's celebration of the 100th anniversary of the Koninklijke Nederlandse Chemische Vereniging (another Royal Dutch organization in this country). You know, paclitaxel is in fact a nickname, the real formal name in the birth certificate of the molecule is, forgive me for this: 5, 20 epoxy-1, 2 , 4, 7, 10, 13-hydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2R, 3S)-N-benzoyl-3-phenylisoserine. Figure 5 gives the passport photograph of this molecule thanks to my daughter Marion [16]. But why is this molecule important to us?

figure 5

The paclitaxel molecule



Let us look briefly in its family tree, almost literally by the way. This molecule occurs naturally in varieties of the Taxus tree (or 'yew' in English). Two important varieties are the Pacific yew (Taxus brevifolia) on the West coast of America and the European yew (Taxus baccata) that grows from Ireland to Iran and in every garden center in the Netherlands. The Dutch name is 'venijnboom' and its fruits are red berries with the rather disgusting name of 'snottebellen'. The yew tree

grows slowly, and gets very, very old: for instance the Tisbury Yew in Wiltshire in England is said to be 4000 year old. The wood is very hard and our ancestors used it to make bows, spears and drinking cups. Extracts of the tree were used for assassination, suicide, and arrow poison. The trees were symbols of both longevity and death and are found often in sacred places of our ancestors. They got their first hour of glory when Robin Hood used a bow of yew-wood to win the Maid Marion, and then decided to marry her under the branches of a yew tree.

Somewhat later, in the sixties, the National Cancer Institute (NCI) in the United States initiated a program of biological screening of extracts taken from a wide variety of natural sources. Also the pacific yew was sampled and found to exhibit marked anti-tumor activity. It took until 1971 to isolate the responsible molecule in the extract and to determine its molecular structure: it was paclitaxel. It took another 10 years for scientists at the Albert Einstein Medical College to find how it actually worked and the interest in the molecule as a novel anti-cancer drug was awakened because of its unique mode of action. Its mechanism is to stabilize the microtubules formed in the process of splitting the doubled chromosomes in their two strands during cell division. In this way the chromosomes can not divide and thus cell division is stopped in the mitosis phase or M-phase of the cell cycle [17].

Then a big problem arose: the lack of availability of paclitaxel to do clinical trials. The process of isolation of paclitaxel from the pacific yew was very inefficient: its extraction had only a yield of 0.04%. It would take killing four 100-year old trees to provide enough paclitaxel to treat just one patient [18]. Moreover 55% of the trees stand on protected areas for natural habitats of of rare species of fauna, e.g. the spotted owl in North America. Luckily a close European cousin of paclitaxel was found in the leaves of Taxus baccata. This cousin, with the nickname baccatin III, could be transformed into semi-synthetic paclitaxel. Because Taxus baccata did not die of you harvest some leaves and needed clipping anyway, a renewable raw material was found and the supply of paclitaxel for experiments was secured.

In 1991 Bristol-Myers Squibb Company was selected by the NCI to be its commercial partner in developing Taxol ® (paclitaxel) injection and signed an agreement with the NCI. Bristol-Myers Squibb rapidly

contributed to a dramatic increase in the flow of Taxol ® supplies and a worldwide expansion of the clinical trials program

Still important problems surrounded paclitaxel. The molecule is highly hydrophobic with water solubility less than 0.5 mg/L. It is an off-white crystalline powder that melts at 216 C. To administer such a powder in an infusion is not easy. The current Product form of paclitaxel, with brand name Taxol ®, is a viscous solution of paclitaxel with an adjuvant consisting of Cremophor ® EL (polyoxyethylated castor oil) and dehydrated alcohol. This paclitaxel solution is intended for dilution with a suitable parental solution prior to intravenous infusion, its registered brand name: Taxol ® .

Paclitaxel, under the registered brand name Taxol ®, received clearance from the US Food and Drugs Administration (FDA) for ovarian and breast cancer in the 90's. In 1995 the semi-synthetic form of paclitaxel, manufactured from the renewable source of Taxus baccata, received clearance for marketing from the FDA.

The Taxol ® Product form, from a consumer/patient point of view, is far from ideal. It has been shown that the adjuvant Cremophor ® EL causes very serious side effects. Some of the side effects are nephrotoxicity, anaphylactoid hypersensitivity, hyperlipidemia and peripheral neuropathy To minimize the risks of these side effects the patients have to be prepared for a Taxol treatment with other drugs that suppress the threats caused by these side effects [19]. So the development of alternative carriers to administer paclitaxel continues. Starting with the consumer/patient it would be ideal to deliver paclitaxel at the right time to the desired location with a concentration high enough over a sufficiently long period.

One direction of product-driven process engineering in our example is to deliver the drug in very small particles ('nanoparticles') of biodegradable polymers, which have a size small enough to allow intracapillary or transcapillary passage and appropriate surface coating to escape from macrophage uptake. The size of such particles would be say less than 300 nm.(or $300*10^{-9}$ meter). Such nanoparticles could provide controlled, targeted delivery of encapsulated paclitaxel, or other drugs, with high efficiency and minimum side effects [20, 21, 22]. There are many ways to produce microstructured particles to deliver paclitaxel [18]:

- nanoparticles of biodegradable polymers using various mechanisms from physical chemistry to make them (e.g. high speed emulsification/homogenisation, the use of salting out, emulsification/diffusion mechanisms)
- nanoparticles from supercritical fluid spraying of polymer solutions
- nanoparticles by in-situ polymerization techniques, using micelles
- liposomes for delivery of paclitaxel have been studied extensively and may become available commercially [23, 24]
- liposomes-in-microspheres ('LIM's) is a novel concept where the drug is first loaded into liposomes. Then the liposomes encapsulated into polymeric microspheres

figure 6a and 6b

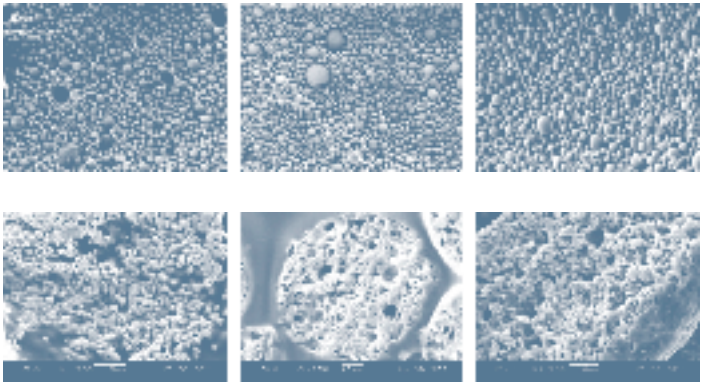


Figure 6a shows some SEM images of particles containing paclitaxel in a biodegradable polymer, Poly(lactide-co-glycolide), using different emulsifiers. They were made by a high speed emulsification technique by Si-Shen Feng from the Faculty of Engineering of the University of Singapore and Su Chen from the University of California (SanDiego). The size of the particles is about 200-300 nm. Figure 6b shows liposomes and liposomes in microspheres from the same authors.

I hope this example has shown you that the microstructure of a product has significant influence on the in-use properties of a product, in this case a product to deliver one of the most important anti-cancer drugs known, with annual sales world wide of US$ 1.5 billion.

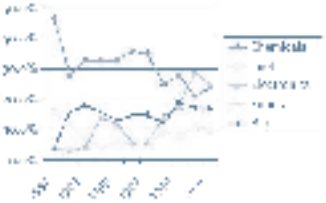
The example also shows that a shift in emphasis in chemical engineering research and teaching with more emphasis on structuring processes and stabilization processes is required. In particular structuring processes are important to provide the desired in-use functional properties of many products.
In the chemical industry there are technologies for structured products e.g. paints and coatings, rubber, plastic composites, agglomerated powders, extruded products, foams, controlled release pharmaceutical delivery systems. It is an area where, according to Villermaux, traditional chemical engineering research and teaching relatively speaking have not spent much attention [25]. Also in the food industry structuring processes are of great importance. The end-product has a complicated multiphase microstructure held together by binding forces between the various phases. This microstructure leads to desired product texture. The mouth-feel and flavor release kinetics related to this texture and to its destruction during mastication is the key to final product quality and appreciation by the consumer.

Refocusing chemical engineering

The points I have tried to make so far are:

- Changes in society and industry have shifted the potential work fields of chemical engineering: life sciences, green chemistry and ecology, smart materials, pharmaceutical products and drug delivery systems, the food industry
- Less and less chemical engineers go to work in the conventional chemical and petrochemical industries. Quoting Prausnitz [26]: "...only 20% of the recent graduates of Berkeley do this. Most recent graduates find employment in industries that did not exist 20-10 years ago or did not, until recently, discover the usefulness and relevance of chemical engineers in their operations..." Figures for the whole of the USA over the period 1991 to 2002 were given by Cussler and Wei [27].

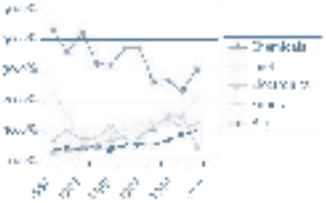
figure 7



Where BSc chemical engineering graduates go in the USA (Cussler and Wei 2003)

In figure 7 we see the percentage of BSc graduates finding a job in the chemical industry decreasing from about 45% in 1991 to 26% in 2002. Figure 8 shows that for PhD graduates the drop over the same period is from 46% to 24%.

figure 8



Where PhD chemical engineering graduates go in the USA (Cussler and Wei 2003)

- Chemical engineers will be more and more involved in designing end-consumer products and suitable processes to manufacture them
- The process types with which chemical engineers are familiar (high throughput, continuous operating process plant) have a less dominant place in the wider field of job opportunities. In particular structuring processes for end-consumer products is a point in case [28].

On the 9th June 1994 Ramesh Mashelkar from India delivered the 9th P.V. Danckwerts memorial lecture in London. Mashelkar emphasized the blurring of the boundaries between the various branches of the natural sciences and the richness of application of chemical engineering approaches in areas totally outside the classical arena of manufacture of bulk chemicals.

At the 5th World Congress of Chemical Engineering, in the summer of 1996 in San Diego, the late Professor Jacques Villermaux from France gave a brilliant plenary address with the title: New Horizons in Chemical Engineering [25]. Villermaux suggested that understanding of organization at levels of increasing complexity with many scales of length and time might perhaps be the third paradigm of Chemical Engineering.

On the 6th and the 7th November 1996 my then Unilever colleague Professor Mike Edwards organized a meeting in our Port Sunlight Laboratory in the UK. We met there as a group of 34 academics and industrialists. He had called this meeting, which was cosponsored with Elsevier's Chemical Engineering Science journal, 'Putting Structure into Chemical Engineering'. The results of this meeting were summarized by John Villadsen [28] from Denmark. Form his report I quote: "...The main purpose of this conference was to send a message, loud and clear to the chemical engineering faculties that somehow the direction of the education must be changed to put the product rather than the process into focus..."

On the 24th November 1998 it was Klaus Wintermantel from BASF, Germany who delivered the Danckwerts Memorial lecture in London [29]. He emphasized the importance of product engineering and remarked that:"...The background knowledge that these chemical engineers need to have differs considerably in some ways from that of

'classically' educated process engineers. They need to fully understand processes at the molecular level (e.g. surface physics and –chemistry) to be able to design production processes that ensure those products can consistently meet customers' quality requirements..."

Cussler et al. [27,30,31] from the USA have recently and repeatedly discussed the needs to refocus chemical engineering. So there are voices emphasizing a necessary change. In the Netherlands we have of course Hans Wesselingh [32], who has been the driving force behind several initiatives in this area.

In Product-driven process engineering, the thinking about a process should start with the customer or the consumer, which of the two depends on the structure of the supply chain. The consumer wishes and consumer-perceived product properties have to be translated into physical and chemical product properties, in the USA this is called customer-driven engineering [33]. In this way the main physical attributes of a product are determined, including an idea about the desired microstructure. Next a functional analysis is done to determine the minimum necessary transformations needed to create the product. Then a morphological analysis, as pioneered by Judson King [34] at Berkeley generates alternatives for each of the functions. Morphological analysis can probably be helped tremendously by applying methods like TRIZ to generate alternatives. Finally, a conceptual process design exercise, similar to the approach pioneered by Douglas [35] in Massachusetts, is done to generate possible process routes to achieve the desired product properties. This sequence of events is in my vision the core of product-driven process engineering. This approach avoids what I call the 'unit operations trap', because it does not fix the mindset to only consider traditional reactor design and separation process steps to build a process. In Unilever Research, Michel Vander Stappen initiated work in this area in a cooperation with Professor Grievink from Delft and the group of Professors Mike Doherty and Mike Malone at the University of Massachusetts [36].

The first step, translating consumer wishes and consumer-perceived product properties into physical and chemical product properties, is not easy in particular for non-pharmaceutical products. A method called Quality Function Deployment (QFD) is often used. QFD, or building

the 'house of quality' [37] was pioneered by Mitsubishi in their Kobe shipyards and extended by Toyota. Today Kodak, 3M, Philips, Unilever and many other companies use it in their new product development activities. QFD is a team effort that starts with establishing WHAT the consumer/customer wants. This is done by interviews and so-called focus groups and the result is a list of statements expressing wishes. The next step is to rank these so-called 'WHAT's' by giving them a weight. After this the physical and chemical attributes that could deliver the desired consumer attributes are established: the so-called 'HOW's'. This involves intensive discussions about choice of raw materials (i.e. which molecules do we want), physical mechanisms, desired product structure etc... In the QFD method a number of additional steps are carried that I will not discuss here for brevity. The bottom line is that we can use QFD to 'translate' consumer benefits of a product into required or desired physical and chemical product properties that, together, deliver the consumer benefits in an optimum way. At the same time however, we have moved from the Molecules corner of our eternal triangle to the Product corner...

The second step, functional analysis of transformations needed to create the product, can be compared to making a recipe. Examples of transformations are: 'make a droplet with diameter of 1 μm', encapsulate component X in particles smaller than 50 nm', 'dissolve solid X in solvent Y', 'cool', 'react A with B' etc. These transformations are not necessarily unit operations! The total set of transformations changes raw materials into the desired product with the desired microstructure. For each of the transformations we can generate a number of alternative ways to achieve them. A method to do this is morphological analysis. The result is a number of very rough sketches of process alternatives. We are moving from the Product corner of our eternal triangle to the Process corner...

What is needed and largely lacking in chemical engineering is the development of a chemical product design methodology with a sound basis in thermodynamics, physical chemistry, polymer physics, biochemistry and transport phenomena. The subject is ideally suited to case studies, but it should not consist only of a series of cases. Some very valuable attempts have been made (e.g. Cussler [30], and Wesselingh [38]) to bring structure in teaching the subject, but much leaves to be done.

Chemical Engineering curricula

Most of the changes in the structure of the business environment of the chemical industry outlined before seem to have so far only spawned limited changes in chemical engineering curricula. Much of the teaching focus in chemical engineering has stayed on the classical Separation processes and Transformation processes essential to oil refining and the bulk petrochemical industries.

An exception in the Netherlands is the effort of Hans Wesselingh at Groningen University and his effort now at the Danish Technical University in Lyngby.

Again, I think that approaches like Quality Function Deployment, TRIZ and morphological analysis of process functions could be very helpful and chemical engineering students should have some training in these methods. The nice thing is that this training requires good insight in the basics of chemical engineering (phase equilibrium, transport phenomena, Prandtl's boundary layer, Lewis' and Whitman's film theory, chemical reactors, Danckwerts' residence time distributions,..) and physical chemistry (interfaces, colloids). In this way the basic skills are reinforced by applying them in a useful context.

In the past year I have had the opportunity to experiment in lectures with two groups of students, one group in their fourth year of study and one group of post-graduate students (so called TWAIO's in Dutch academic vernacular). My experience is very positive and feedback from the students proofs that they see the lectures as a valuable addition to their studies.

At the University of Groningen and the TU's of Delft and Eindhoven initiatives have materialized to give product-driven process engineering a place in the curriculum. In Eindhoven a new 'capacity group' Process Systems Engineering will be set up to which the part-time chair Product-driven process engineering will belong together with the chairs Transport Phenomena and Separation Processes and Process and Product Design.

Challenges for research

Some challenges for product-driven process engineering that, in my vision, are almost inevitable and thus must be faced are:

6.1. Linking scales in structuring processes.
In most Structuring Processes, the product microstructure manifests itself at a scale that is almost 10^7 smaller than the size of the equipment that forms the structure. The challenge is to reduce this gap ('process intensification') and to understand how phenomena at a smaller length scale relate to properties and behavior at a longer length scale.

Areas of particular interest are computing the behavior of biomolecules, ensembles of molecules or larger colloidal particles in our products and processes. Since many products are structured on the mesoscopic scale, linking the atomistic length and time scales and the mesoscopic length and time scales is the issue. A very interesting development in this area is the dissipative particle dynamics (DPD) [39,40,41,42] and further recent developments along similar lines. The long-term challenge is to combine the thermodynamics and physics of local structure-forming processes like network formation, phase separation, agglomeration, nucleation, crystallization, sintering etc. with multiphase CFD.

This linking game is however not easy. If the details of the lower levels are necessary in modeling of the higher levels, computation-power becomes the limiting factor and will stay so for a long time to come. My Unilever colleague Tildesley [43] always spoke of 'the 20 nanosecond barrier' to indicate that atomistic calculations are restricted to intervals shorter than this time scale in a reasonable CPU time of about 1 month[1]. DPD and similar approaches are so fascinating because they simulate much longer real times within reasonable CPU times.

6.2. Functional molecules: third generation functional foods and drugs
One can expect fascinating developments when the progress by the fast moving science of proteomics and metabolomics has found out which genes are responsible, for certain characteristics or physiological

figure 9

disorders in humans. Figure 9 shows how this area is fed by rapid growth in micro-technology and micro-electronics.

Drivers leading to 3d generation functional molecules

The interest of consumers in what they eat (and what medication to take when ill) influences their immediate and longer-term health. This interest will strongly increase by the scientific developments just mentioned. The future could be that at the end of the current decade first novel functional food ingredients ('nutraceuticals') will have been identified with clear-cut health benefits. These ingredients could then be employed in foods personalized to the individual consumer, with her individual risk profile for chronic diseases and health problems. A highly interactive communication pattern between the foods business and its end consumers may then emerge with which our current situation simply does not compare at all. Personalized diets could be constructed and monitored promoting adherence to an individual optimal diet via suggested menus from a palmtop computer while shopping or tele-shopping on the Web. This needs a rather different supply chain structure than the current ones and opens novel business concepts. Chemical engineers will be instrumental in designing the manufacturing and supply-chain systems needed to convert these ideas to reality.

6.3. From service to care: blurring boundaries

The trend to move to total packages of services mentioned earlier will continue. Drivers for this are trends in society like the wish to use free

time in a quality manner rather than to do domestic chores like house cleaning and cooking. Opportunities are offered by E-commerce on the web like on-line supermarkets.

Such scenarios trigger the need to rethink future supply chain structures. The major challenge to a fast moving consumer goods business is to deliver to customers branded products that satisfy consumer's needs; through an optimum supply chain. This means a supply chain with short lead times to new product introductions in response to changes in customer/consumer demands, with lowest stocks and minimum off-spec products and minimum waste/by products. The 'Make' part of the future business will certainly have to do all it can in order to keep a reasonable margin.

Ladies and Gentlemen

Chemical engineers have learned to think in systems and to model them, to compartmentalize problems into sub-problems and make educated guesses of unknown parameter values. This makes them eminently suitable to be the integrating force behind all the teamwork activities necessary to create a new product and to coordinate the movements in the eternal triangle Molecules – Product - Process. At the end of the day, what we want to achieve with movements in this triangle is a new profitable product. In my view the role of the hypotenuse in the eternal triangle is the connection between Product and Process. In Hans Thijssen's metaphor that I quoted earlier: Process engineering plays the role of the conductor of the orchestra. The form of the piece of music will certainly not be a minuet or a rondo. Much of the music will have to be performed without knowing all the details of the musical score: improvisation will be required... Engineers have the intransigence and persistence to provide solutions to problems for which in fact not enough knowledge is yet available. That is the beauty of our profession! The future is difficult to predict, but we can invent it...

[1]Dominic Tildesley: "Molecular dynamics time steps are roughly 2.10^{-15} s to follow the fastest bond vibrational modes of the molecule accurately. Therefore, a simulation of 20 ns takes 20.10^{6} time steps. This is a massive amount of computing time on any workstation (perhaps a month of CPU time). On a modern massively parallel, one might be able to reduce this by an order of magnitude depending on the system size. If you can find funding to get full time access on a massively parallel machine, you could perform a simulation of protein folding. The world record is held by Peter Kollman in the US who simulated a protein for approximately a microsecond. This took an enormous dedicated resource for nine months. The question is what simulations can you perform routinely to give you interesting science and I believe that the 20 ns barrier is a good marker..."

Words of thanks and hope

Ladies and Gentlemen,
At the end of my address I want to say a few words of thanks, for which I will switch to Dutch.

Allereerst gaat mijn dank uit naar het College van Bestuur en het bestuur van de faculteit Scheikundige technologie voor de slagvaardige wijze waarop zij mijn benoeming gerealiseerd hebben. Het Bestuur van het Hoogewerff-Fonds, het fonds dat het initiatief tot het instellen van de leerstoel Productgeleide Procestechnologie nam, dank ik voor het aan mij geschonken vertrouwen deze leerstoel hier aan de Technische Universiteit Eindhoven vorm te geven. Ik wil hier graag memoreren dat deze leerstoel uiteindelijk mogelijk is gemaakt door mevrouw C.M. de Vlieger-Warmoltz uit Rijswijk die besloten had nog tijdens haar eigen leven aan de wens van wijlen haar echtgenoot Ir. Johan H. de Vlieger, gehoor te geven en een substantieel deel van haar aandelenkapitaal te legateren aan het Hoogewerff-Fonds.

Graag wil ik een ogenblik stilstaan bij twee mensen die een grote rol gespeeld hebben in mijn wetenschappelijke ontwikkeling. Professor Henk Leniger in Wageningen en Professor Hans Thijssen in Eindhoven. Henk Leniger was de systematicus, helder formulerend, de man die voedingsmiddelentechnologie in Nederland op de kaart zette. Hans Thijssen de enthousiaste, gedreven stimulator, de lateraal denkende innoverende geest. Er hangt een portret van hem aan de wand van het collegezaaltje van onze groep. Vaak als ik daar bezig ben denk ik: "...wat zou Hans ervan gedacht hebben...".

Toen ik in 1980 door Wiero Beek werd overgehaald naar Unilever Research te komen was ik in feite de opvolger van Wim Herman de Groot als manager van de Process Engineering Division. Met veel plezier ontmoette ik Wim weer hier in Eindhoven, en ik ben tot op zekere hoogte ook nu weer zijn opvolger.

Bart Drinkenburg, Jaap Schouten, Piet Kerkhof en Jos Keurentjes zijn nu mijn directe collega's. Jaap heeft mij in zijn groep gastvrij een eerste thuisbasis verschaft, een goede plek totdat de verdere ontwikkeling van de capaciteitsgroep Process Systems Engineering gestalte heeft gekregen.

Hans Wesselingh, een oud-collega van het Shell Lab in Amsterdam, en emeritus van de Rijks Universiteit Groningen is in Nederland de man die de eeuwige driehoeksrelatie Moleculen-Product-Proces weer centraal stelde in de scheikundige technologie. Zijn enthousiaste drive heeft er mede toe geleid dat productgestuurde procestechnologie of kortweg producttechnologie in Groningen, Delft en Eindhoven gestalte gaan krijgen. Tom Broekhuis van de Rijks Universiteit Groningen, Peter Appel van de TU Delft en ik hebben een Nederlands klankbord gevormd om de productgestuurde procestechnologie verder gestalte te geven.

Mijnheer de Rector, dames en heren, ik heb getracht U een overzicht te geven van het samenspel tussen moleculen, producten en processen: de eeuwige driehoek. Designer moleculen die door hun specifieke vormgeving in principe veelbelovende functionaliteit van producten kunnen genereren. Producten met optimale binnenhuisarchitectuur zodat de designer moleculen optimaal hun werk kunnen doen. Processen die de producten bouwen met efficiënte scheduling, de juiste hulpmaterialen en apparaten en met zo min mogelijke overlast voor de omgeving.

U allen dank ik voor uw aandacht

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Curriculum Vitae

Solke Bruin (1940) graduated from the Wageningen Agricultural University in the Netherlands where he completed his PhD in 1969. After postdocs at TU/e (Prof.dr.ir. H.A.C. Thijssen) and the USDA's Western Regional Research Center in Berkeley (Calif.) in 1970, he joined the Royal Shell Research Laboratories in Amsterdam in the Equipment Engineering Division. In 1974 he was appointed full-time professor in Process Engineering at Wageningen Agricultural University. Research activities included drying of food materials (calculation methods for dehydration with strongly concentration dependent diffusion coefficients), adsorption of chemicals from aqueous solutions to active carbon and modelling storage of agricultural products.

End 1980, he joined Unilever Research Vlaardingen. In Unilever Research he fulfilled various senior positions in research management. In his latest position he was responsible for Exploratory Research in the Foods Processing area in both the Colworth House (UK) and Vlaardingen (NL) Research Laboratories and member of the management committee of Unilever Research Vlaardingen. He retired from Unilever in May 2001.

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