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64 MINI-REACTORS: COMBINATORIAL CHEMISTRY TESTS COMPOUNDS WITH LIGHTNING SPEED

**Amsterdam company Avantium employs combinatorial chemistry to search for new compounds. Hundreds of samples can be processed daily.**

***by Rob van den Berg***

Chemists they may be, the researchers at the Amsterdam company Avantium, but they bear little resemblance to the classic picture that the name invokes. No bubbling flasks of coloured liquids, in fact Erlenmeyers and other glassware no longer form part of the standard equipment. When they want to know how one of their reactions is going, they make use of an electronic link. Here, everything is computer-controlled, from the accurate dosing of starting materials and the adjustment of temperature and pressure, to the analysis of the products. And not just in one, but in sixty-four mini chemical plants simultaneously.

This parallel experimentation - an advanced methodology for conducting large numbers of experiments simultaneously - has become commonplace in the development of new drugs, and in DNA and protein analysis, and to an increasing extent is now being applied in research into new materials such as catalysts or superconductors. Research today must increasingly justify itself in terms of financial pay-out and a discovery needs to come to market as soon as possible.

That's something Avantium director Ian Maxwell knows all about. At the Shell laboratory in Amsterdam he was involved in catalysis research for more than twenty years. He had no doubts though, when the opportunity arose to give up this 'safe' position in exchange for heading a new company. Actually, the start of Avantium went reasonable smoothly, explains Maxwell in his office close to Amsterdam Sloterdijk station. "At Shell we had been doing this kind of research since 1994. However, there came a time when Shell had to choose between investing heavily itself, or working in cooperation with others."

Shell opted for cooperation. The necessary capital was raised from various sources. Besides the three Dutch technological universities, private investors and major companies such as Shell, Akzo Nobel and GlaxoSmithKline also brought in both capital and technology giving Avantium a flying start.

The company now employs some 120 people spread across sites in the Netherlands, US and UK in the area that has become known as combinatorial chemistry. This new trend arose in the early nineties as a rapid and fully automated way of making many thousands of biologically active compounds and testing them for activity. Where previously the introduction of new medicines required long processes of trial and error and gigantic costs, it now became possible to screen the enormous numbers of possibly active substances much more rapidly. Although the technology was originally developed for application in the pharmaceutical industry, its potential for other areas in chemistry, and particularly in materials research, rapidly became evident. Catalysts and high-temperature superconductors, for example, consist essentially of combinations of elements: compounds of - often exotic - metals with others such as oxygen and sulphur. The problem is that there are some sixty candidate metals. The number of three-at-a-time combinations is already astronomically large, while further variation arises from the proportions in which they

are combined, the carrier material upon which they are supported, and the temperature employed to form the catalyst. However, combinatorial techniques offer a methodology for preparing and testing large numbers of such combinations.

MILLIONS OF COMPOUNDS

It was the American company Symyx in California, founded by a chemistry professor at Berkely, that vigorously promoted this new technology. In the year 2000 it claimed to have synthesized, analyzed and tested no less than one million compounds. However, the path to new product introductions remains a difficult one. This is no surprise to Maxwell. "The situation is analogous to the pharmaceutical industry, where the screening of ten thousand molecules may only produce two 'hits'. The introduction of combinatorial techniques giving the ability to screen much larger numbers did not lead automatically to more hits. The enormous choice among candidate compounds means that, increasingly, the key factor is intelligent searching." Maxwell disputes the often heard claim that combinatorial chemistry offers nothing more than the ability unthinkingly to do vast numbers of experiments. "The necessity for proper insight has actually increased".

Another problem is that many seemingly promising compounds fail to fulfill their promise in the later development stages. The reason for this is explained by senior researcher Peter van den Brink: "Large numbers of ingenious combinatorial techniques have been developed, in both companies and universities, for accelerating the exploratory phase of an investigation. These often make use of flat arrays of miniscule samples, mounted on a surface. It is, however, well-nigh impossible to predict how sample hits identified in such a manner will behave in three-dimensional practical situations. Time saved in the exploratory stage is rapidly lost in the upscaling phase."

In addition, the screening techniques employed to recognize the most promising candidates from an entire combinatorial 'library' are also capable of considerable improvement, according to Van den Brink. Compared with the search for, say, a new colour TV phosphor, catalysts present much more formidable problems. Some groups employ a heat-sensitive camera to register the activities of catalyst samples arrayed on a surface and exposed to the same feed stream. The most active will light up as 'hot spots' but such experimentation provides little real insight into such important aspects as to how selective the 'hot' catalyst may be.

For these reasons Avantium has chosen a different approach. It employs, among other catalyst testing tools, 'nanoflow' units, with reactors capable of handling gas and liquid streams a thousand million times smaller than those of industrial practice. In these reactors, catalysts (themselves prepared by robotically controlled parallel techniques) are contacted with feed streams and the products periodically monitored. The company uses advanced computer modelling to analyze the data generated and simulate how the reaction would proceed on the large scale.

And all this simultaneously in 64 reactors. Van den Brink: "The 'nanoflows' have been developed during the past ten years at the Shell laboratory. Shell transferred the know-how to Avantium in return for a share of the company." The computer is also essential for selecting, with the help of statistical software, from the large numbers of possible candidates. For this purpose a massive database has been set up for the storage of data on different catalysts. Thanks to the acquisition of a specialized American company, Avantium has assured itself of a firm basis in this important area of high throughput software development. The company anticipates

that there will be an attractive market for the equipment and software that the company has now developed.

MORE EFFICIENT PROCESS ROUTES

At present, this equipment is processing some hundred samples daily for a broad range of clients. These include pharmaceutical companies, for whom Avantium can help find a more efficient production route for a particular drug. Maxwell: "A producer is obliged, even before the beginning of clinical trials, to register the process to be employed for commercial-scale production of a drug. Owing to its limited catalytic expertise the number of catalysts employed in the industry is small. We are able to find a more suitable catalyst within a short time period."

Some twenty patents have already been applied for or are in preparation. University groups have contributed substantially. The technological universities in particular are, according to Maxwell, strongly industry-oriented. "We talk the same language. The success of their research is likewise measured in part on the basis of their patent applications. Furthermore, through our association we have access to large numbers of promising researchers." In a joint development with researchers at Delft University of Technology a titanium catalyst has recently been developed for a particular reaction; with the help of techniques developed by Avantium it proved possible strongly to suppress the formation of by-products.

The costs of entry into this relatively new market are still very high and substantial investment is required before experimentation can commence. It looks as if Avantium is on the right track and a sizable turnover is anticipated in 2001. Nevertheless, the costs of the operation and of maintaining and improving the technology remain high and Avantium is planning this summer to approach new and existing investors for additional financing.