The science of chemical discovery: probing the unknown with new technologies

'We have seen the first iteration of integrating the technologies for high-speed chemistry.'

The 20th century has seen several noteworthy technologies emerge, evolve and, ultimately, change the way we live and think. The silicon microchip is the most striking example, with the distantly related information technology and internet explosion taking the headlines at the turn of the century. It is not yet obvious whether the latter part of the 20th century has seen the beginnings of an exponential change in the science of chemical discovery by synthesis. But what are these new technologies, and has anything really improved?

Technology

R.B. Woodward demonstrated that it would be possible to synthesize almost any complex molecule. Other researchers have since substantiated this with target-driven organic synthesis accompanied by the continued invention of new reagents, reactions and other synthetic 'tools'. The science of chemical discovery probes into the unknown, and has the potential to be profitable by gaining access to larger repertoires of molecules available for functional screening.

The term 'high-speed' chemistry, now essentially synonymous with 'combinatorial' chemistry, reflects technologies that improve the speed and efficiency of synthetic organic chemistry. The technology is not a single device, but rather an array of approaches and methodologies that have originated and co-evolved over a ten-year period. Solid-phase organic synthesis (SPOS), inspired by the pioneering work of Merrifield, led to a small number of early achievements in the 1970s; a more serious exploration of many chemistries began in the 1990s. SPOS has demonstrated the feasibility of generating large (>10,000 compounds) libraries by split-and-mix synthesis and smaller (<10,000 compounds) libraries by what is synthesis by parallel processing. The reality of SPOS is that the actual development of the chemistry is challenging and slow, and only a relatively small subset of known chemical reactions can be relied on without considerable effort. In response to the limitations of SPOS, other concepts have been invented, which include polymer-supported reagents and catalysts, and soluble polymers. Such technologies have taken the chemistry back into the solution phase, albeit at higher speed, by virtue of the rapid parallel synthesis that is possible.

Implementing and interfacing the technology

The capacity to synthesize more molecules rapidly and efficiently has brought with it a burden of requirements for other technological advances. This ranges from improvements in the analysis of organic compounds (e.g. solid-phase ^{1}H-NMR spectroscopy and LC–MS) to robotics and automation technology for the manipulation of large numbers of reagents and products. Furthermore, the input of reagents and the output of defined compounds (individual or mixtures) has demanded some system of chemical informatics and databases. The hardware for chemical reactions can vary from conventional glassware to microchip-like fluidics. The implementation of high-speed chemistry has clearly been much further developed than simply changing the way a reaction is carried out. However, it has been a struggle to interface all the technologies, and scientists who can bring together these elements are scarce. In particular, there has been considerable competition between various manufacturers to establish a robotic parallel-synthesis platform for organic synthesis. There is no clear winner at present, but what is more of a concern is that parallel processing of bench chemists sometimes appears to be a preferred route to library synthesis.

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Has anything changed?

A quick walk around almost any industrial laboratory will confirm that advances in the past decade have made an impact on the synthetic chemistry techniques used in the chemical discovery process. In the face of the scepticism and reluctance of some chemists, high-speed organic synthesis and the associated technologies have been integrated to some degree and appear to be here to stay. An alternative perspective is that of the academic discovery chemist with more limited resources. Even with moderate resources, it is now feasible to explore molecular problems by implementing new technologies. This capability should open the doors to more curiosity-driven discovery processes, which might take us closer to understanding the relationship between structure and function: the holy grail of the molecular sciences.

Show me the drugs

The ultimate barometer for success gives a disappointing reading. The drug industry is short of claims that a noticeable impact on the drug pipeline has been made. However, specific processes, such as lead optimization, have benefited. The speculation and claims made by enthusiasts in the early 1990s set a high expectation of what could be achieved and how soon. However, the necessary elements for successful integration of high-speed technology were not taken into consideration at that time.

Following a decade of creativity and evaluation, we have seen the first iteration of integrating technologies for high-speed chemistry. Although the accompanying change in culture is limited to only the more enterprising of chemists, as judged by speed and efficiency of molecular synthesis, success can be justifiably claimed. The molecular design or discovery challenge does not have the predictability of the seemingly flawless logic of parallel processes in a microchip. The input of even more intellect into the design of compound libraries, based on substantiated science and an avoidance of dogma, will enhance the prospect of future successes. For the technology to help deliver substantially more molecules that are functional, a longer term view is required.

Shankar Balasubramanian

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