

On the Engineering of Chemical Synthesis: Humans and Machines Working in Harmony

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Words and phrases such as Artificial Intelligence, Machine Learning, Neural Networks, Robotics, the Cloud, Big Data and the Internet of Things are typically associated with many modern technological and scientific developments. Until recently, however, they have not been applied systematically to the chemical assembly of society's functional molecules. Indeed, due to the lack of suitable tools, chemical synthesis in the past has tended to rely heavily on robust labour intensive batch processes that were often developed decades ago. This situation is changing rapidly owing to many reasons and, in particular, to the continuing need to discover new reactivity and new reactions, especially more sustainable processes. Smart, self-optimising platforms for continuous compound production along with a vast range of new analytical, monitoring and control devices for improved management of research experimentation and for accelerating the synthesis process are now available.

Indeed, for a number of years we have been advocating a machine assisted approach to synthesis. This makes sense for so many reasons not least of which is how to best maximize the human resource by increasing efficiency and giving people more time to think, plan and make discoveries. As in all the sciences collaboration between the different disciplines leads to synergistic benefits. Nowadays engineering of multi-step chemical synthesis adopts a holistic systems approach to the subject that requires full integration of all the chemistries together with the device engineering and the necessary underpinning informatics. Continuous flow chemistry methodology has added yet another component to our armory. When linked to current batch methods, this generates new capabilities and process windows providing enhanced robustness through better control and data feedback. The coordination of multiple pieces of equipment through cheap microprocessors such as

the Arduino and Raspberry Pi allows a new level of laboratory management, making way for machine to machine learning algorithms and the upcoming artificial intelligence revolution.

The beginnings of augmented and virtual reality techniques are already impacting on how we present our science today. Video capture of information with digital cameras for monitoring or for thermal and high speed imagery, provide a rapid return of kinetic data and adds a further safety element to our experimental audit trails. This leads naturally to the future use of head-up displays and other wearable or handheld devices. Even mundane facilities such as fume-hoods are evolving to be more responsive to energy saving techniques or the use of face-recognition software to map equipment configurations and their dynamics during usage. Mobility and flexibility are also features of any new laboratory design. Repetitive tasks for scale-up, reaction optimization and during original reaction discovery programs, these can all be relegated to machinery and advanced robotics. With this said it is also imperative however, to understand that synthesis is a highly complex task that requires the marshalling of a huge range of experience and skills, both intellectual and practical, acquired over a significant period of time. Serendipity also has a role to play; it is not easy to automate synthesis.

As a serious synthesis chemist trained over many years with a notable record of achievement, I recognize that to replace a bench chemist with a machine is not only unrealistic but impossible. What is realistic is to use this rapidly developing array of equipment and novel concepts to supplement and enable new events to take us way beyond where we are today. To use the word automation is to do a disservice to what will be possible in the future. Our machines will aid in the decision making process and reinforce learning and understanding.

Computational algorithms and predictive methods should be an integral part of any modern synthesis program. Interestingly, how we deliver electrons to a chemical process, whether through the increasingly popular methods of electro- or photo-chemical means, is reliant to some extent on the innovative design of the equipment used. Harnessing enzymes in synthesis also goes beyond the basic bio-transformation to exploit directed evolution methods, immobilization and recyclability of the systems for multistep applications. Compartmentalisation techniques, plug flow reactors and sequential processing are all ideas more akin with how a cell assembles complex functional materials. Clearly there are many lessons to be learnt. For example, microfluidics and integrated machine assisted screening can help expedite the early phase of molecule discovery.

Also advances in flow chemistry, for real-time monitoring has led to further miniaturisation with the generation of new benchtop NMR, IR, UV and mini mass spectrometer devices. In turn this has encouraged synthesis chemists to explore greater levels of multi-step reaction telescoping using interlinked reactors with controlling software packages, such as LabView for example. Inevitably this suggests also that the traditional electronic laboratory notebook (ELN) is in need of a major overhaul to reflect the new ways of working.

While we can argue that we are quite good at designing and making molecules we still have downstream isolation and waste product issues where greater equipment innovation is required. Switching solvents between reaction steps is still a problem and although some bespoke device engineering exists there is considerable scope for improvement. The use of immobilized reagents and selective scavengers for generating clean reaction streams are especially attractive for multi-step synthesis sequences but are yet to be fully exploited. Useful automation for liquid-liquid separation using gravity or membrane technology is with us now and can be used to

help integrate batch and flow methods. Engineering problems while handling slurries and solids is always challenging and often presents its own special needs and equipment design.

In recent times flow based machinery has enabled many areas of chemistry, which traditionally were considered problematic in batch mode, to become manageable under continuous processing conditions. These include exothermic reactions and particularly so when using organometallics that are water and air sensitive. Also new chemoselective processes are achievable under these dynamic, heat/mass transfer regimes. Handling of other notoriously hazardous materials, such as diazo compounds and other reactive intermediates, can be nicely and safely contained within the confines of modern flow equipment. Also, unsurprisingly, systems can be assembled to handle reactive gases either singly or during multiple applications. Toxic gases, for example HCN, CO, H₂, CH₂N₂ *etc.*, can also be made on-demand, delivered to their site of reaction and immediately consumed to afford useful products.

The Green agenda is something that has been a journey for over 20 years as a charter for life as synthesis chemists but in our view it is now in need of some updating. Although it is true that many machine enabled technologies play well to the general principles of green chemistry greater emphasis needs to be placed on leadership and accepting responsibility for our actions. There is also a need to protect the human resource from routine, labour intensive practices and to live in harmony with our machines.