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<Ontology terms>

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Technology in synthesis

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<Standfirst> Synthetic organic chemistry is increasingly automated, data-rich and intelligent. At the Automated Synthesis Forum, industry and academia showcased their recent progress towards this augmented future.

<Authors> David M. Heard and Alastair J. J. Lennox*

The field of synthetic organic chemistry continuously evolves as new technologies are integrated into the lab. For example, the rise in popularity of liquid chromatography–mass spectrometry, automated flash chromatography, digital lab notebooks, online databases and retrosynthesis platforms. These innovations have improved efficiency and productivity, thus facilitating the rate of development and frequency of new discoveries. While, these technologies are commonplace in industrial labs, they are only gradually becoming so in academic labs. However, other enabling technologies, such as synthetic electro- and photochemistry, are building momentum in academic labs before transferring over to industry. The ‘industry-heavy’ Automated Synthesis Forum (ASF) — an annual UK event since 1996, held for the first time in Glasgow in 2019 —provides an opportunity for academia and industry to exchange ideas and discuss the next generation of enabling technologies in development.

The meeting was initiated with a view inside the mind — and lab — of Lee Cronin from the University of Glasgow, who presented the work of his group towards their futuristic concept of modular, low-cost synthesis machines called ‘Chemputers'.[1] Initially conceived for the robust, reproducible replication of batch chemistry, the group now intends to help separate the chemist from the fumehood. The Chemputer project aims to combine the encoding of synthetic protocols from the literature for use in synthesis machines, with multiple data feeds from reactors for real-time analysis, and automated in-line purification. Although it does take much of the manual work out of synthesis, this approach still requires a chemist to plan the overall synthetic route, as well as the individual reactions required. However, a team from Merck holds the potential to aid that process with their Synthia™ (formally Chematica) retrosynthesis software programme. Sarah Trice presented this powerful tool at the ASF, and explained how it draws on chemical literature and 70,000+ hand-coded reactivity rules to suggest stereo- and regioselective syntheses.[2] Marcus Koppitz from Bayer discussed their team's efforts towards automated parallel purification By combining these three tools — Chemputer, Synthia, and automated purification, with the fact that commercially available automated synthesis platforms, such as Synple Chem and Chemspeed, are beginning to appear, and suddenly Cronin's vision does not appear too far away.

There is no doubt that the future of organic synthesis will increasingly rely on enabling technologies, and excellence in areas including flow chemistry, electrochemistry and photochemistry were on full display at the ASF. The ability of electrochemistry to access different reactivity or achieve previously challenging reactions was presented by us and also by Kevin Lam.[2,3] Jesus Alcazar from Janssen Pharmaceutica highlighted the advantages of using photochemical flow technology in organozinc reactions (Negishi, Reformatsky and Blaise reactions) that are traditionally difficult to achieve, but work easily when switching to a photochemical strategy.[5] Antimo Gioiello from the University of Perugia demonstrated how flow chemistry could be used to efficiently create libraries of compounds without any manual intervention from a chemist, for medicinal chemistry applications.[6] This approach complemented the impressive 'PicoSAR' efforts from the AstraZeneca iLab team — Javier Mazuela, Pernilla Korsgren, and Victoria Helan described their progress towards using automation to accelerate drug discovery, and showcased a technology that doses nanolitre quantities of compound libraries into assays using acoustic liquid dispensing.

As automation in the field of synthetic chemistry is steadily increasing, the ASF community recognised that these developments need to be supported with high-quality data and robust protocols. Steve Christie and co-workers are working on innovative low-cost solutions that allow existing analytical instrumentation to be used for reaction monitoring. He also described bespoke flow reactors with embedded fibre optics that allow real-time reaction analysis by a number of techniques.[7] The importance of data collection was also raised both by both Cronin and Robbie Warringham from Deepmatter, who are developing innovative products, such as 'Device X', which aims to improve reproducibility by recording how different parameters change during the course of a reaction. The Centre for Rapid Online Analysis of Reactions (ROAR) at Imperial College London facilitates another route to running data-rich experiments by providing the hardware and software needed to study a reaction in detail. Their capabilities include high-throughput robotic reactor platforms, advanced analytics and measuring online, in-situ data-rich kinetics with a number of different techniques, which all help to bridge the gap between the instrumentation available to industry and academia.

In some ways, the difference in approaches for data-collection tools highlighted a certain irony present at ASF 2019. Several academics pitched their low-cost, easily constructed equipment aimed at lowering the financial barriers to adopt techniques, such as automation and flow chemistry. Meanwhile, outside the auditorium, companies such as Vapourtec, Uniqsis, Chemspeed and Syrris demonstrated their vastly capable, yet costly, commercial platforms for the same techniques.[8] The combination of these efforts to render such technologies accessible to both time-rich/money-poor and time-poor/money-rich users confirms their importance to science, and demonstrates that both academia and industry are moving in similar directions.

It is noteworthy that much of the science presented was achieved by relying on strong, diverse skillsets — whether through interdisciplinary collaborations or by involving synthetic chemists that are also, for example, able to write code or use Computer Aided Design (CAD). The increasing demand for technological fluency and the changing nature of the skillset required by synthetic chemists prominently featured at the forum. Steve Christie spoke about the recent integration of these skills into the undergraduate practical teaching course at Loughborough University. At postgraduate level, the Dial-a-Molecule Summer School has had success in disseminating awareness and hands-on training in enabling technologies. Of equal importance is the work by academics seeking to facilitate moves across traditional boundaries for those wishing to make use of new technologies. Examples of this is Cronin's Chemify technology that translates synthetic protocols from natural language into code, as well as a tool developed by Christie that allows chemists to design custom 3D-printed flow reactors without the need to be fluent in CAD. Nikil Kapur, from the University of Leeds, presented the freely available resources (https://freactor.com/) on flow and continuous stirred tank reactors (including the commercialised fReactor), which were equally well received.

Overall, the ASF highlighted the ever-growing importance of technology in synthesis, the creative ways in which researchers make the most of the technology currently available, and the technical challenges the field will seek to address over the next 20 years. Through both the high-quality research presented and the atmosphere of collaboration, the attendees demonstrated that this field is thriving and well-placed to solve the problems posed by contemporary synthetic chemistry.

<Affiliation> David M. Heard and Alastair J. J. Lennox are in the University of Bristol, School of Chemistry, Cantock's close, Bristol, BS8 1TS.

<email address> a.lennox@bristol.ac.uk

www.lennoxlab.com

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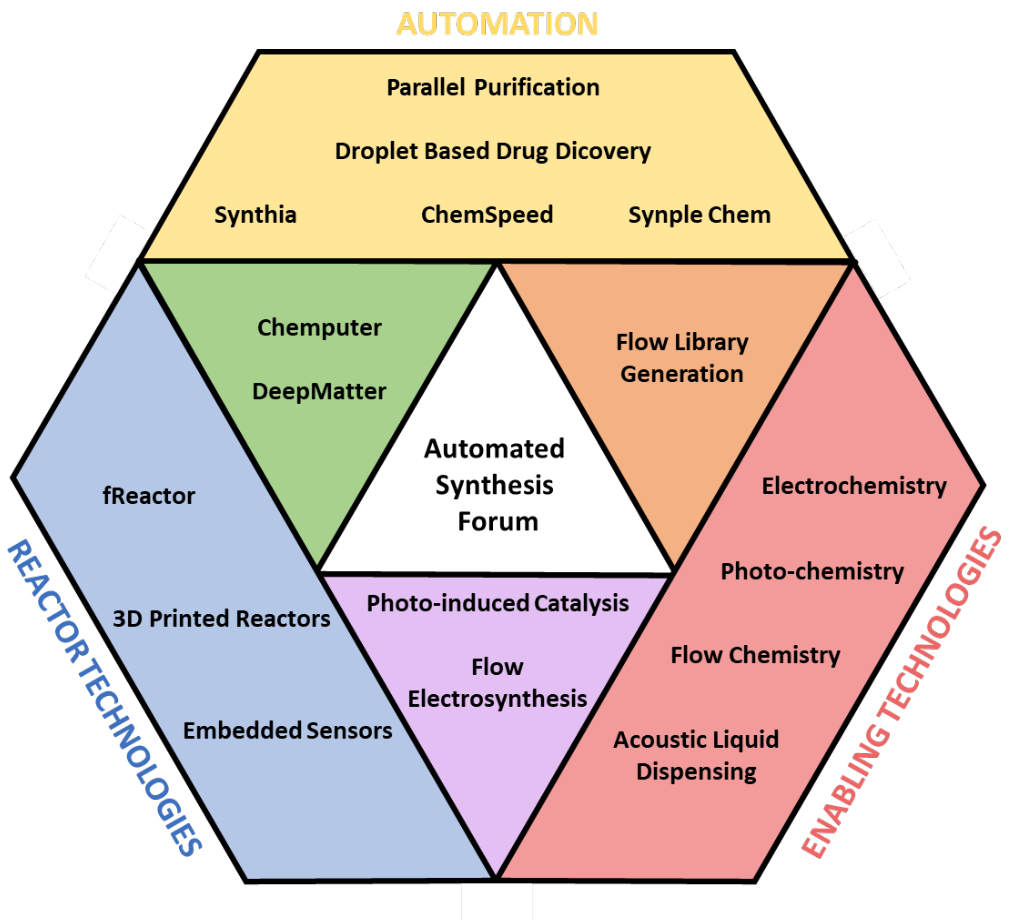

<Figure caption> The Automated Synthesis Forum showcases the latest developments automation, reactor technologies and enabling technologies.

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