A journey from the **Vapourtec lab**

Vapourtec managing director and founder **Duncan Guthrie** charts the rise and rise of flow chemistry

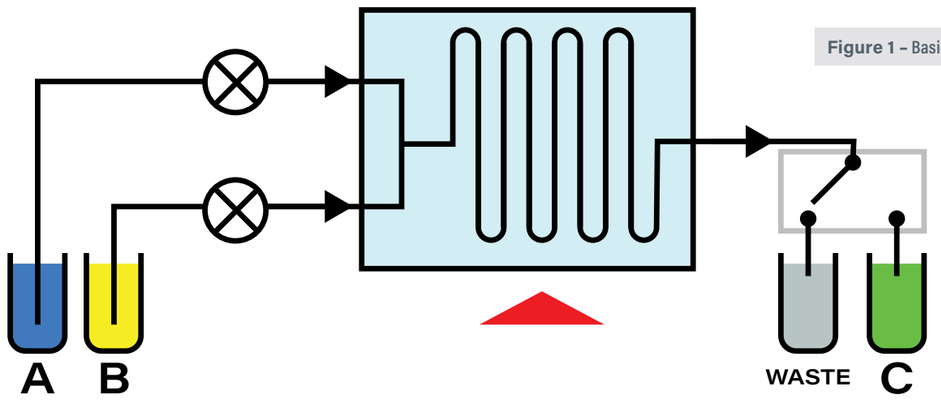


Figure 1 – Basic flow chemistry

Vapourtec's growth since its foundation in 2003 has mirrored that of flow chemistry. Initially, scientists translated 'simple' A+B → >C reactions to flow and photoredox-catalysed library synthesis.[1,2] New solutions were needed, however, to transfer batch processes to flow. By the end of the 2000s, it was clear that continuous flow would soon encompass all aspects of modern chemistry.

No two applications were the same and no two systems should be the same. Otherwise, flow chemistry systems would have become too prescriptive in terms of which chemistries are possible. For that reason, our focus was on developing the most flexible and versatile flow chemistry systems, enabling telescoped reactions, photochemistry or even peptide synthesis, by just changing reactors.

Key components

When looking at a basic flow chemistry diagram, three key components define the type of reagents that can be used and the type of chemical reactions that can be carried out:

1. **Pumps to deliver reagents at a precise flow rate**
2. **Reactors where reactions occur**
3. **A back pressure regulator (BPR) to control the pressure within the reactor**

Reagents come in all physical states (solid, liquid or gas) and each must be handled differently. Gases are usually metered with mass flow controllers or peristaltic pumps; solids are constrained in packed-bed reactors; liquids are pumped. Not all liquids are the same and not all pumps can handle them. Some reactions might require the use of fuming nitric acid; others might need a basic reagent, such as n-butyl lithium.

As time went on, users increasingly wanted to run their chemistry in extreme conditions. Soon, the need to pump corrosive chemicals, operate at extreme temperatures or use gases at (even) higher pressures led us to develop new systems to make these extreme chemistries possible.

Vapourtec focused on the development of new pumping capabilities. Thanks to these, more reactions were successfully translated to flow, some of them proving to be easier and delivering better yields in several key areas:

- **Gas/liquid reactions:** Working with gas under pressure is relatively simple in flow compared to batch. To deliver gas, we integrated mass flow controllers and developed tube-in-tube reactors, allowing reactions like carbonylation and catalytic hydrogenations to run at high pressures[3,4]

- **Corrosive reagents:** Reagents such as TFA, fuming nitric acid and organometallics are hazardous but useful. Nitration chemistry is a good example of what is achievable in flow. Highly exothermic reactions can be precisely controlled, allowing the use of neat fuming nitric acid and pushing reaction kinetics to their limit[5,6]

- **High pressure reactions:** When running high (200-250°C) temperature reactions with volatile reagents, high system pressures are required to maintain everything in the liquid phase. For this, we need pumps able to pump organic reagents at 200 bar

- **Pumping slurries:** Solids can be problematic to handle in flow. Traditional pumps only work with solutions. Free-flowing solids almost invariably risk agglomeration and blockage in any part of the system. We developed a peristaltic pump to handle solids at pressure, operating as either a pump or a BPR, without blocking. Thanks to such features, flow chemistry rapidly expanded as a tool for reaction optimisation. As reactions can be programmed in series, different parameters (stoichiometric ratio, residence time and temperature) could be easily evaluated. Planning experiments with statistical tools, such as Design of Experiments, made flow chemistry an even more powerful tool as an optimisation platform or generator of kinetic models.[7,8]

Automation & analysis

The next logical step was to further automate flow chemistry. The option to handle several different reagents in a flow set-up would allow scientists to expand their research to automated library synthesis. We hit this milestone in 2009 and could then use as many reagents as we wanted, even with just two pumps, which made it possible to rapidly explore a vast array of compounds.

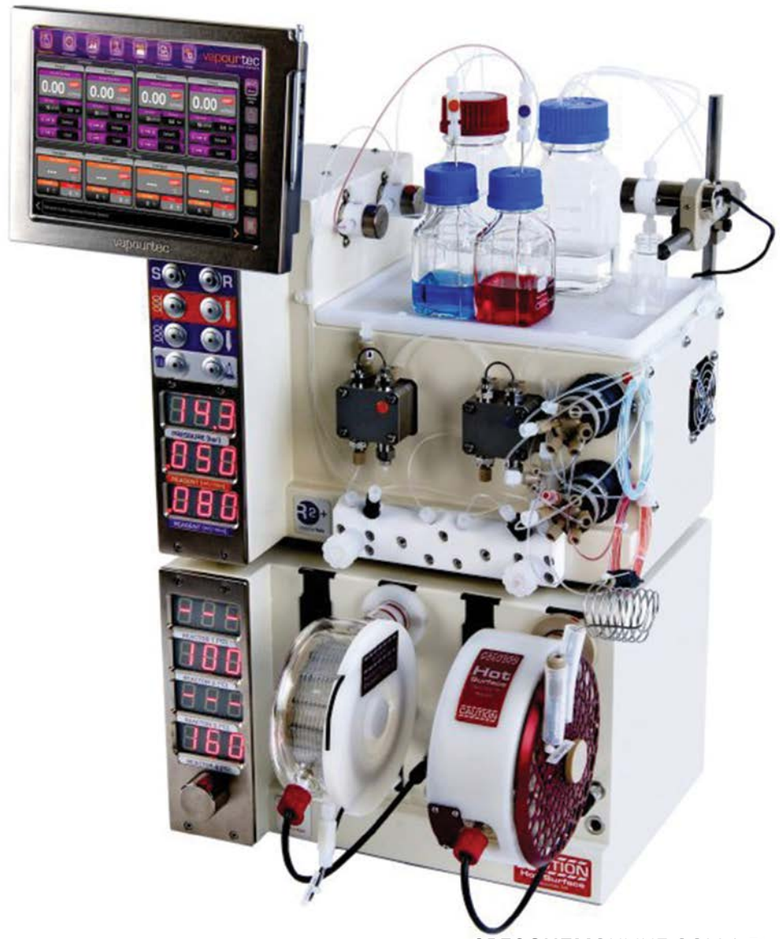
After this, analysing all the products became the limiting step. Integrating inline analysis, such as UV/Vis, IR, Raman spectroscopy or HPLC, can provide an insight into the reaction kinetics by either following product consumption or reagent formation.[9] This live data can also be used to determine which reactions were successful without further off-line analysis.

All the while, scientists were exploiting the technological advantages of continuous flow, especially in photochemistry. Batch photochemistry has some key limitations: uneven irradiation fields and difficulties in controlling the reaction's temperature make these reactions very difficult to replicate.

Scientists developed photoreactors in their labs by simply wrapping a polymer tube around a UV source.[10] These handmade reactors enabled photochemistry to reach a key milestone with the development of an efficient photochemical route for anti-malaria drugs.[11]

Vapourtec launched its photochemical reactor, the UV-150 in 2015. This can control both temperature and UV irradiation from exchangeable sources, from energetic UV (220 nm) to visible light (up to 700 nm). It enabled flow chemists to explore photoredox catalysis, singlet oxygen formation and even photobromination with one reactor.[12-14]

Launched in 2006, the R-Series was Vapourtec's first flow chemistry platform



The UV-150 is Vapourtec's photochemical reactor

The VFBR can carry out SPS in flow

Solid-phase synthesis

One of the rapidly expanding areas of continuous flow has been solid-phase synthesis, where a solid media substrate is used to build molecules step by step. Peptides, oligonucleotides and oligosaccharides have all been synthesised in continuous flow, yielding a more efficient synthesis thanks to the interaction between the solid media and the reagents.[15-18]

Peptide synthesis in flow has been explored in the past but has been limited to the use of packed bed reactors. However, these have a fixed volume, do not allow the molecule to grow and can lead to impurities due to the channelling of reagents and/or increased pressure.

To address these challenges, Vapourtec launched its Variable Bed Flow Reactor (VBFR) in 2020. This monitors and controls the packing density of the solid media by changing its internal volume. Thus, there is no channelling of reagents or any pressure build-up throughout the synthesis.

AI in flow

Implementing machine learning into flow chemistry has been the latest big development. Combining an automated flow chemistry platform and self-learning algorithms can potentially reshape the way we understand chemistry. In a nutshell, a self-optimised algorithm plans reactions, modifying the parameters until it reaches its objective.

The user then gives a range of reaction parameters for modification - typically residence time, temperature, UV intensity, concentration or even type of solvent – and a set of goals. These cover a broad spectrum; the optimisation can be focused, for example, to achieve, lowest cost, highest yield, a more efficient usage of reagents or fastest reaction.

Once the goals and parameters have been set and there is a suitable analytical technique to analyse the products, it will start iterating between reaction conditions to meet the goal. By relying on inline analytical techniques, the self-optimised algorithm will evaluate the success of each run and plan the next reaction ahead.[19] ●

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