Case Study

Materials Science and Engineering group, CSIRO, Australia

About CSIRO

The Commonwealth Scientific and Industrial Research Organisation (CSIRO http://www.csiro.au/) is Australia's national science agency and one of the largest and most diverse research agencies in the world, with ~ 6000 staff in 56 sites across Australia and overseas.

Their Clayton site (in the state of Victoria, located adjacent to Monash University) employs more than 800 people.

More than half of CSIRO Materials Science and Engineering (CMSE) and the majority of their materials research group are based on this site.

Getting into Flow Chemistry

CMSE have a history of developing synthesis routes up to pilot scale. But as their statute prevents them from actually manufacturing, the aim is always to deliver a working process.

A few years back it had become apparent that other organisations were getting into continuous flow chemistry, and the CMSE Division (http://www.csiro.au/org/CMSE.html), always keen to add new capabilities, wanted to understand more about it (especially after seeing the work going on in the Ley Group in Cambridge).
Flow appealed because it promised processes that could be

- efficient
- sustainable
- easy to scale-up.

To get up to speed rapidly, the group took the approach of both recruiting chemists with existing experience of flow, and also sending staff on secondment to Steve Ley's laboratory in Cambridge for 2 years.

Now, in less than 3 years, the flow group within CMSE has become well established and numbers 8-10 staff.
There is a variety of equipment, including

- 5 Vapourtec R Series
- 1 Uniqsis Flow Syn
- 2 Thales Nano H cubes
- 1 Biotage Initiator microwave system (with adapters for flow experiments)
- several "homemade" systems comprising syringe pumps and chip microreactors

The lab has the capability for handling corrosive fluids, organometallics, highly exothermic reactions, multistep reactions, liquid/gas reactions (using tube in tube membrane reactors) and scale-up to kilogram quantities. They also have lab and pilot scale photochemistry.

And, as mentioned later, there is the capability for continuous polymer synthesis.
For CMSE, building expertise in flow allows them to differentiate themselves from other academic groups, as well as to extend the research offering they can make to industry.

The Work

The bulk of the work is currently funded by the Australian government but an increasing proportion of the work for industrial customers is privately funded. Ownership of the IP generated varies in each case.

Clients are mostly from within Australia but are occasionally from overseas (or from Australian subsidiaries of global corporations).

Application areas in flow are varied, and the track record is impressive given how recently the flow project started.

- multistep synthesis of bioactive compounds (histrionicotoxin alkaloids, isoxazolidines)
- API process development
- synthesis of ionic liquids
- synthesis of photochromic dyes
- synthesis of platform chemicals and biofuels from renewable resources.
- polymer synthesis using Reversible Addition–Fragmentation chain Transfer (RAFT) and conventional polymerisation technologies

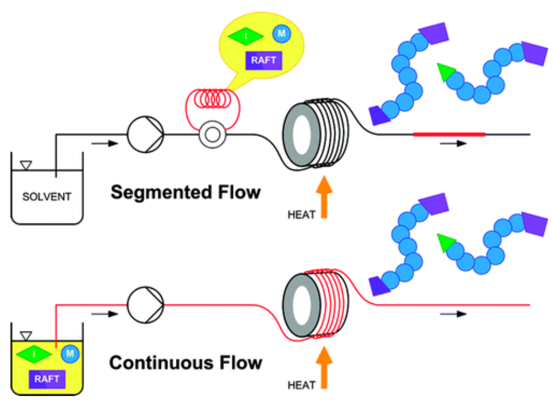
http://www.csiro.au/science/flow-chemistry-innovative-tool.html

RAFT

RAFT (Reversible Addition Fragmentation chain Transfer), a type of controlled radical polymerization, was invented by CSIRO in 1998 but developed in partnership with DuPont over a long term collaboration. Conventional polymerisation is fast but gives a wide distribution of polymer chain lengths. (known as a high polydispersity index).
RAFT is more versatile than other living polymerization techniques, such as atom transfer radical polymerization (ATRP) or nitroxide-mediated polymerization (NMP), it not only leads to polymers with a low polydispersity index and a predetermined molecular weight, but it permits the creation of complex architectures, such as linear block copolymers, comblike, star, brush polymers and dendrimers.
Monomers capable of polymerizing by RAFT include styrenes, acrylates, acrylamides, and many vinyl monomers.

CSIRO is the owner of the RAFT patents and is actively commercialising the technology. There are 12 licences in force and CSIRO is pursuing interest in a number of fields including human health, agriculture, animal health and personal care.
RAFT is the dominant polymerization technique for the creation of polymer-protein or polymer-drug conjugates, permitting (for example) the combination of a polymer exhibiting high solubility with a drug molecule with poor solubility..

Though RAFT can be carried out in batch, it also lends itself to continuous flow processing, as this processing method offers an easy and reproducible scale-up route of the oxygen sensitive RAFT process. The possibility to effectively exclude oxygen using continuous flow reactors in combination with inline degassing methods offers advantages over batch processing at scales beyond the laboratory environment.



Challenges associated with the high viscosity of the polymer product solution can be controlled using pressuriseable continuous flow reactor systems.

http://www.csiro.au/products/RAFT.html

CMSE and Vapourtec

John Tsanaktsidis, (Research Program Leader) first met Vapourtec on a visit to the UK. At the time, he says, what was promised by Vapourtec in terms of willingness to interact and solve problems was very attractive.
"And Vapourtec have been good to their word", he says. "Advice is always forthcoming, service has always been timely, and Vapourtec have always been willing to help with proposals for future projects that we both know may come to nothing (such is the nature of research).
"All in all, Vapourtec gets a big tick on the service front. And they have good quality instruments."

Future of Flow

Tsanaktsidis says that while flow at CSIRO is still "on an upward trend", there are always doubts to overcome.
"Chemists are creatures of habit, and some reject new technologies almost on principle. Others point to previous technologies (Combichem, Microwave) that 'overpromised', and say that flow is no different. The only way to address this is with plenty of clear successes."

It has been necessary to get buy-in both internally (within CSIRO) and externally (from clients). Part of the approach involves bringing in as many different types of project, to show how wide the application of flow can be.
That said, Tsanaktsidis is "happy with the way flow has been taken up".
"In fact in some respects it has been easier than expected".

Tsanaktsidis sees a bright future for flow, where one day every lab will have a flow system as part of the standard set of chemist's tools.
And a necessary part of that dream is the eventual inclusion of flow in the undergraduate chemistry curriculum. Monash University, through its Centre for Green Chemistry (http://www.chem.monash.edu.au/green-chem/) ,is one of leaders in this respect.

But it doesn't stop in Victoria.
"There are 30+ universities in Australia teaching undergraduate chemistry" points out Tsanaktsidis.