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EDITORIAL

# Meet the flow chemist

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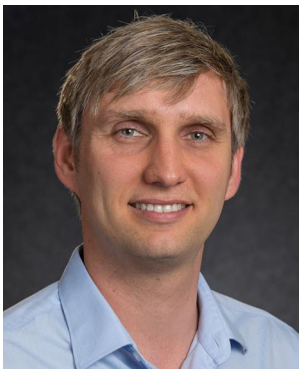
## Meet the flow chemist – Dr. Christian Hornung



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| **Name** | Christian H Hornung |
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1) When did you start with flow chemistry? Describe the first paper or the first experiments.

My first contact with continuous flow microreactors was during my undergraduate student project at the University of Erlangen, supervised by Franziska Scheffler and Wilhelm Schwieger in 2001. The project was concerned with the hydrothermal synthesis of catalytic ZSM-5 zeolite coatings on micro-structured aluminium plates used for gas phase catalysis. At Cambridge I then changed to working with polymer capillary reactors to synthesize heterocycles and other small molecules, before I moved on to making polymers in tubular flow reactors at CSIRO a few years later. In recent years, I have returned to the world of heterogeneous catalysis, working on 3D printed structured catalysts that contain catalytic coatings and are used in continuous flow hydrogenations.

2) What are the main benefits of flow that convinced you to use and implement this technology in your research?

The beauty of the continuous flow processing technology is that the benefits manifest themselves in many different ways, and across a very wide spectrum of chemistry applications. These can include the safe operation of a highly exothermic reaction not manageable at the same process intensity in batch, the scalability of a photochemical reaction that only ever progresses at practical rates on very small scale in batch, the much improved product reproducibility in a manufacturing process, or the capability to link several continuous flow processing steps without the need to isolate and handle toxic, unstable, odorous or otherwise hazardous intermediates. The arguments for a continuous flow process can be manifold; different users in industry or academia will have different priorities, and in some cases it is more than one reason that makes the case for flow over batch.

3) What do you think the future holds for flow chemistry?

Currently there are four main trends that R&D effort within the flow chemistry community focus on: alternative forms of activation, distributed manufacturing, additive manufacturing and artificial intelligence (AI). New tools to facilitate chemical activation using light, electricity or plasma will mature further towards implementation on manufacturing scale. These new methodologies all share one fundamental commonality, namely process intensity-related symbiotic effects between

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the activation method and the continuous flow approach, resulting in superior reaction performance over a corresponding batch process. Distributed or decentralized manufacturing is an idea based on miniaturized plants containing highly process-intensive and compact continuous flow operations, that are often 'containerized' or built as modular and mobile platforms. Both large chemical companies as well as start-ups have adopted this idea and are now producing a new generation of mobile mini-plants for a wide variety of applications, ranging from synthetic fuels to API manufacture, thereby challenging the classical centralized production model based on economy of scale. The combination of additive manufacturing methods such as 3D printing of metals, polymers and ceramics with computer-based design optimization algorithms has an enormous potential to address geometries not feasible with classical subtractive manufacturing methods and hence revolutionize reactor design on lab and production scale. Lastly the introduction of AI will greatly accelerate process development and increase manufacturing efficiency. For instance, the use of machine learning (ML) in closed-loop reaction optimization algorithms can greatly improve design of experiment (DoE) methods and speed up flow chemistry reaction discovery and optimization.

4) Do you have any relevant tips for newcomers in the field?

Before you start your first flow experiment using a brand new piston pump (e.g. HPLC pump) my advice would be to: a) take very good care when preparing your stock solutions that you avoid solid matter (crystals, precipitates etc.) at all costs, b) check twice for solid matter before turning on your pump(!), c) learn how to take your pump apart, clean and put back together again, especially the check valves, or d) if you would rather take the easy way out and avoid using the spanners in your toolbox, swap to syringe pumps, peristaltic pumps or other low-maintenance (valve-less) pumps instead – however you will miss out on a character building exercise.

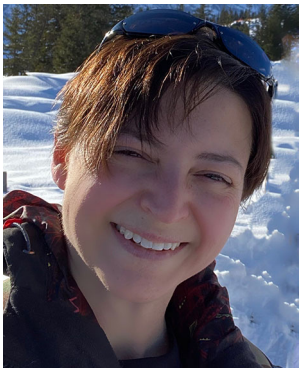
**My three most relevant papers related to flow chemistry are:**

1) Hornung, C.H.; Mackley, M.R.; Baxendale, I.R.; Ley, S.V. (2007) 'A Microcapillary Flow Disc Reactor for Organic Synthesis' Org. Process Res. Dev. Vol. 11, issue 3, pp. 399–405. (This is the first description of a multi-capillary microreactor system made from polymer extrudates, and its use in general organic synthesis. This work describes early research on simple 'home-made' flow reactor systems fabricated from cheap materials such as LLDPE ribbons containing multiple microchannels, and the potential for internal numbering-up.)
2) Kuroki, A.; Martinez-Botella, I.; Hornung, C.H.; Martin, L.; Williams, E.G.L.; Locock, K.E.S.; Hartlieb, M.; Perrier, S. (2017) 'Looped flow RAFT polymerization for multiblock copolymer synthesis' Polymer Chemistry Vol. 8, issue 21, pp. 3249–3254.

(The first demonstration of a semi-continuous closed loop approach to synthesize well-defined multiblock copolymers using controlled radical polymerization; a sequential process that allows for an automated process, combining long reaction times of batch processing with the superior process control of flow.)
3) Avril, A.; Hornung, C. H.; Urban, A.; Fraser, D.; Horne, M.; Veder, J.-P.; Tsanaktsidis, J.; Rodopoulos, T.; Henry C.; Gunasegaram, D. R. (2017) 'Continuous flow hydrogenations using novel catalytic static mixers inside a tubular reactor' Reaction Chemistry & Engineering. Vol. 2, pp180–188.

(This work describes 3D printed catalytic static mixers (CSMs) for the first time; a technology invented by CSIRO and used as a structured catalyst platform for continuous flow hydrogenations and other heterogeneous catalysis flow reactions.)

# Meet the flow chemist – Prof. Dr. Francesca Paradisi



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| **Name** | Francesca Paradisi |
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| **Homepage** | www.paradisiresearch.com |
| **Education** | 2002 PhD in Chemistry, University of Bologna (Italy) with Prof. Sandri<br>1998 BSc in Chemistry, University of Bologna (Italy) with Prof. Cainelli |
| **Position** | 2002–2005 Post Doc with Prof. Engel, University College Dublin |
| **Awards** | 2018 Wellcome Prime Fellowship – University of Nottingham, UK<br>2016 Senior Fellow of the Higher Education Academy, UK<br>2015 Visiting Scholar Fellowship U.C. Davis, California |

1) When did you start with flow chemistry? Describe the first paper or the first experiments.

We almost accidentally decided to try and integrate flow chemistry in our research in 2015. A colleague in a different filed of chemistry gave a seminar explaining how they were immobilizing catalysts to perform their reactions in flow. We had been immobilizing our enzymes for several years at that point but never explored flow as an option and the penny dropped. We started playing with very rudimentary pumps and tubings, virtually nothing was published at that time on cell-free flow biocatalysis (whole cells flow biocatalysis had several examples already), and we set up a first single step biotransformation using a transaminase and a very standard set of substrates. Initially our yields were not that impressive but already better than what had been achieved before. Steadily we improved our reaction set up and calibrated residence time and ratio of reagents and we published our first paper on the topic in 2017 (M. Planchestainer et al. *Green Chemistry* 2017, 19, 372–375).

2) What are the main benefits of flow that convinced you to use and implement this technology in your research?

We rapidly discovered that our knowhow in enzyme immobilization on different types of supports, exploiting different chemistries, gave us a very solid base to enhance the durability of the biocatalyst under continuous flow. In my mind this became a "cell-free but cell-like" environment where the enzyme is put in contact with the substrate in a highly efficient manner, much better than in batch. Also, we could achieve exceptionally high local catalyst concentration in our packed bed reactor which sped up the reaction rate dramatically even for very unfavorable substrates. Literally a new world of opportunities opened up. Through flow technology we could perform multi-step reactions which were in fact not possible in batch due to cross reactivity between product and unreacted starting material; now we could mimic more complex artificial pathways selecting the best enzymes for the job and avoid any metabolic side reaction with are a common downside of whole cell biotransformations.

3) What do you think the future holds for flow chemistry?

I imagine a future where highly modular systems will enable the integration of biocatalysis, conventional organic chemistry, photocatalysis, and who knows…likely new approaches we do not have yet, to assemble complex synthetic routes in a very sustainable manner. I think machine learning will be key in speeding up this process of integration. I also think that major steps will be done towards minimizing downstream waste, through recovery and recycling of solvents and unreacted materials we will drastically reduce the environmental impact of multi-step synthesis. While automation will increase, I believe the meticulous ground work which will open up new possibilities, as well as the precious intuitions of brilliant upcoming scientists will never be replaceable.

4) Do you have any relevant tips for newcomers in the field?

I would say that flow chemistry is a tool, something certainly worth trying because it can offer incredible opportunities beyond what can be achieved in batch. However, it is essential to remember that like any other tools, a flow set up does not fit all needs, it may simply be that for whatever reason your reaction is in fact much better in batch than in flow. To give you some examples, in my specific field, the enzyme you need to use, may not immobilize well, or your

support is not that inert and itself may cross react with your reagents/products. So my best tip is to keep in mind the end goal, and while you are trying to solve practical problems to transfer your reaction in flow, it is not a failure to stick to batch if that works best for now. I would also advise to be adventurous and combine old and new technologies, try different types of reactors and catalysts, think of the key elements that your reaction requires and see if in a flow set up they can be reinvented. The world of flow-technology is your oyster!

**My three most relevant papers related to flow chemistry are:**

1) M. Planchestainer, M.L. Contente, J. Cassidy, F. Molinari, L. Tamborini, **F. Paradisi** "Continuous flow biocatalysis: production and in-line purification of amines by immobilised transaminase from *Halomonas elongata*" *Green Chemistry* **2017**, 19, 372–375 (This paper was our first paper in the field and we demonstrated how the enzyme was capable of achieving a level of productivity which was an order of magnitude above batch. We also showed the incredible working stability that the biocatalysts had once immobilized and subjected to continuous reactions).

2) M. L. Contente, **F. Paradisi** "*Self-sustained closed-loop multienzyme-mediated conversion of amines into alcohols in continuous reactions*" *Nature Catalysis* **2018**, 1, 452–459 (In this paper we assembled the first multi-step multi-enzyme cascade, showing the incredible range of substrates we could use by swapping reactors in a plug-and-play mode. We also showed how we could recover cofactors and reuse waste waters in a closed-loop system, increasing 20-fold the overall productivity with exceptional reduction on waste produced).

3) M. Contente, S. Farris, L. Tamborini, F. Molinari, **F. Paradisi** "*Flow-based enzymatic synthesis of melatonin and other high value tryptamine derivatives: a five-minute intensified process" Green Chemistry* **2019,** 21, 3263–3266 (In this paper we have stepped up our game and moved away from analytical scales. Here we show how a 2 mL reactor containing just about 2 mg of biocatalyst could deliver more then 30 g per day of pure melatonin without any loss of activity. And this was not an extrapolated value, it was real productivity. We want to show that it is really possible to implement biocatalysis in flow on a large scale).