Meet the flow chemist

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This time, we want to introduce the Flow Chemists Dr. Maria José Nieves-Remacha and Prof. Dr. Thomas Wirth.

Meet The Flow Chemist – Dr. Maria José Nieves-Remacha

Name	Maria José Nieves-Remacha
Date of Birth	1985
Position	Senior Research Scientist at Eli Lilly and Company (Alcobendas, Spain)
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Education	Ph.D., M.S.CEP. (2008–2014) in Chemical Engineering at Massachusetts Institute of Technology B.S., M.S. (2003–2008) in Chemical Engineering at Universidad Complutense de Madrid
Awards	2010 1st Place National Award in Chemical Engineering 2003/2008 by Ministry of Education (Spain) 2008–2010 Fellowship Award for Graduate Studies at Massachusetts Institute of Technology by Fundacion Cajamadrid 2008 Best Academic Performance in Chemical Engineering by Universidad Complutense de Madrid 2003–2007 Academic Excellence Award by Community of Madrid (Spain)

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

I started working with flow chemistry in 2009 as a Ph.D. student under the supervision of Klavs F. Jensen at the Massachusetts Institute of Technology (MIT), where I had the opportunity to work on projects at the MIT-Novartis Center for Continuous Manufacturing. My first flow experiments, which led to my first two published papers, focused on the study of the hydrodynamics of biphasic flow in a heart-shaped flow reactor. This was a very exciting study where we used flow visualization techniques to determine hydrodynamic parameters

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and observed the bubble and droplet size distributions along the flow reactor. It was very interesting to see how strategically placed obstacles in the flow path created pressure changes that caused dispersed phase breakup and recombination, enhancing mass transfer rates that are so relevant in multiphase systems.

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

As it has been already demonstrated by many examples in the literature, flow technology has several benefits over batch processes. I particularly found very interesting that applying high pressures and temperatures in flow for specific reactions leads to better conversions and selectivity for the desired product as compared to batch processes, where head spaces may pose a safety concern, mass transfer rates may be lower, and heat management may not be sufficient at larger batch scales. In addition, continuous flow is an excellent alternative to run electrochemical and photochemical reactions, due to the maximized potential and more uniform light irradiation than can be achieved as compared to batch reactors. And finally, I am particularly interested in the development of autonomous continuous-flow platforms that integrate monitoring techniques and algorithms to perform process self-optimization in flow.

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

I believe that flow chemistry is a technology which implementation will expand and continue at both research institutions and companies across the world. There are today a great number of different flow technologies available out there with many possibilities, including photochemistry and electrochemistry applications. Perhaps the trend is to continue with the development of flexible and modular automated platforms both from the software and the hardware perspectives, and to include artificial intelligence to guide the experimentation or provide recommendations on the synthetic steps and conditions, thus, increasing system autonomy and minimizing human intervention. Miniaturization of process analytical equipment, development of faster analysis methods, and improvement of detection levels,

would contribute to achieve more compact flow systems and accelerate process development times.

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

A newcomer to flow chemistry may be intimidated by the laboratory equipment needed to perform a flow experiment. However, one can start using just the basic equipment: a pump and a flow reactor, which can be as simple as a piece of tubing. Once one gets familiar with it, progressively increase the complexity of the setup. There are some engineering concepts one will need to get familiar with, such as “residence time” or “steady-state”.

If one wants to go beyond, I would recommend exploring 3D printing techniques to design custom flow reactors and pieces, or even programming basic scripts for equipment automation using open-source alternatives (i.e. python), microcontrollers and microcomputers. This will provide you with freedom to develop creatively custom-made solutions.

My three most relevant papers related to flow chemistry:

1. **OpenFOAM computational fluid dynamic simulations of two-phase flow and mass transfer in an advanced-flow reactor** (MJ Nieves-Remacha, L Yang, KF Jensen, *Ind. Eng. Chem. Res.*, **2015**, *54*, 6649–6659) In this paper we implemented a solver based on an open-source simulation framework to simulate two-phase hydrodynamics in a flow reactor to study the effect of fluid properties and reactor geometry at a detailed level.
2. **Mass transfer characteristics of ozonolysis in microreactors and advanced-flow reactors** (M. J. Nieves-Remacha, K. F. Jensen. *Journal of Flow Chemistry*, **2015**, *5*, 160–165) In this paper we demonstrated the safe scale-up of an ozonolysis reaction from micro to milli-scales in flow using a multichannel micro reactor and Advanced-Flow reactors.
3. **Automated platforms for reaction self-optimization in flow** (C. Mateos, M. J. Nieves-Remacha, J. A. Rincón, *React. Chem. Eng.* **2019**, *4*, 1536–1544) This mini-review highlights the most recent progress in continuous flow self-optimizing platforms integrating monitoring techniques and intelligent algorithms to guide the optimization with minimal human intervention.

Meet The Flow Chemist – Prof. Dr. Thomas Wirth

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

My flow chemistry started with Batool, a joined PhD student between Prof. Barrow in engineering and myself. Prof. Barrow already had constructed small chip devices to produce emulsions for the food industry. Batool then learned quickly to make such devices in the clean room and then brought them to chemistry for experiments. The first experiments were very boring from the organic chemistry perspective as Batool performed only the basic hydrolysis of an ester. But she found that the reaction rate increases of about two orders of magnitude just by flowing the biphasic reaction mixture down a capillary rather than stirring it in a flask. Her results were then published as our first paper in this area: *Enhancement of Reaction Rates by Segmented Fluid Flow in Capillary Scale Reactors*: B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, 348, 1043–1048.

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

One of the main benefits is the safe generation of hazardous compounds or reagents, which can be used directly in flow processes to make valuable target molecules. In collaboration with the French pharmaceutical company Pierre Fabre, the PhD student Simon has developed a continuous and efficient flow synthesis of diazo compounds. He could then employ the methodology to make derivatives for an efficient production of a

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Education	1984–1989 chemistry studies (University of Bonn, Germany) 1989–1992 Ph.D. thesis (Technical University of Berlin, Germany) 1992–1993 post-doctoral studies (Kyoto University, Japan) 1994–1999 Habilitation (University of Basel, Switzerland) since 2000 Chair of Organic Chemistry, Cardiff University, United Kingdom
Awards	2000 Werner Prize from the New Swiss Chemical Society 2012 JSPS fellowship at Kyoto University, Japan 2016 Wolfson Research Merit Award (Royal Society) 2016 Elected fellow of The Learned Society of Wales 2016 Bader award (Royal Society of Chemistry) 2017–2018 Distinguished Visiting Project Professor at Kyoto University, Japan

drug precursor molecule, which he carried out in the company in Southern France. This process now allows a scalable synthesis for the company as before they had to use alternative and longer routes as detailed in the publication: *Towards a large scale approach to Milnacipran analogues using diazo compounds in flow chemistry*: S. T. R. Müller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, 20, 495–502.

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

In 10 years time, flow chemistry will be integrated as a concept in the teaching curriculum and regarded as a useful additional technology. It will be clear that flow chemistry is not the cure for all problems or difficulties in chemical synthesis. It will have its place as alternative technology when hazardous or unstable molecules are needed or when precise reaction conditions even outside the normal range are required. Flow chemistry will be used for better synthesis and to complement other already existing methodologies.

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

Concentrate on new chemistries and let the available technology help with your creativity.

My three most relevant papers related to flow chemistry:

1. **Continuous Flow Electrochemical Generator of Hypervalent Iodine Reagents: Synthetic Applications** (M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folguez-Amador, C. Génot, T. Wirth, *Angew. Chem. Int. Ed.* **2019**, 58, 9811–9815) Herein, we describe the application of flow electrochemistry towards the synthesis of unstable, but highly convenient iodine(III) compounds and their use in synthetic applications.
2. **Towards a large scale approach to Milnacipran analogues using diazo compounds in flow chemistry.** (S. T. R. Müller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, 20, 495–502.)
3. **Enhancement of Reaction Rates by Segmented Fluid Flow in Capillary Scale Reactors.** (B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, 348, 1043–1048.)