Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

PROJECT ON ICE NUCLEATION IN SEGMENTED FLOW

Topic:	**Development of a segmented flow platform for the study of the ice nucleation kinetics in aqueous solutions**
Type:	Semester Project or Master Thesis
Starting date:	Anytime, preferably from February 2021
Advisor:	Prof. Dr. Marco Mazzotti, ML G27, mazzotti@ipe.mavt.ethz.ch
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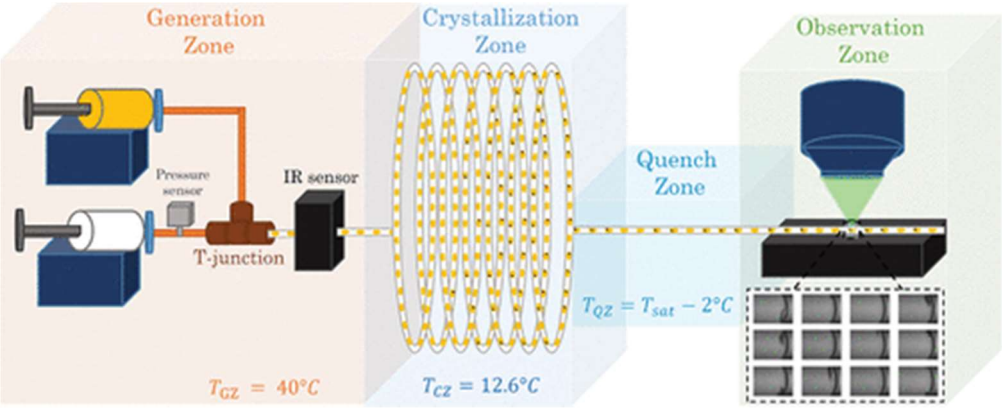
A mechanistic understanding of the freezing kinetics of water and aqueous solutions is of importance in a wide variety of settings in both academia and industry. The freezing process is controlled not only by thermodynamics, but also depends on the kinetics of ice nucleation. Small volumes of highly purified water need to be cooled down to temperatures close to -40°C to initiate homogeneous nucleation. In practice, nucleation temperatures are hard to predict, since nucleation occurs heterogeneously due to impurities or at container walls at temperatures anywhere between -40°C and the equilibrium freezing temperature. Since nucleation is an activated process, the nucleation time and temperature of samples will vary even in case they experience the same freezing conditions. Understanding this inherent stochasticity is essential for the development and optimization of processes that involve freezing. Such processes play a key role in the pharmaceutical industry to extend the shelf life of biopharmaceuticals.



A microfluidic segmented flow platform was developed in our lab [1] to study the nucleation time distribution of adipic acid. A segmented flow is generated in this platform consisting of a large number of independent droplets that act as batch crystallizers. Microfluidic platforms are well suited for nucleation studies due to their capabilities to generate large experimental data sets in short time, i.e. each droplet represents a nucleation experiment.

This project aims on upgrading this platform so it is capable of studying ice nucleation. To do so, a number of design challenges have to be addressed. This includes the design of a cooling system to reach sufficiently low temperatures in the setup using equipment currently available in the lab and the handling of solid, frozen droplets in flow without clogging. There exists some literature on ice nucleation studies in microfluidic setups. However, those setups

are either based on chips [3] or the actual freezing process does not occur in flow, i.e. is static [2], thus severely limiting the applicability of these platforms: Chip-based platforms limit the investigation of nucleation processes to very small volumes, while static platforms experience reduced throughput.

The primary goal of the project is to use the upgraded platform to study the nucleation time distribution and its dependence on temperature for various aqueous solutions. An improved understanding of the nucleation behavior of such solutions will be beneficial in guiding freezing and freeze-drying process development, which is an essential step to extend the shelf life of biopharmaceutical products such as vaccines. While we do not have the capability to handle active pharmaceutical ingredients in the lab, it is planned to use aqueous solutions of compounds that are commonly used as additives for this purpose, such as sucrose and mannitol.

Scope of the Project:

The scope of this project is to upgrade an existing segmented flow platform and to conduct ice nucleation studies in it. Consequently, the first part of the project will cover the design and development of this novel platform. Experiments will be carried out afterwards and their outcome will be analyzed and, in case of fast progress, compared to nucleation studies in a parallelized crystallizer and a freeze-dryer.

Proposed Outline of the Main Project

- Short literature review on the research topic and existing works in this field
- Familiarization with the setup in the lab
- Design of the necessary upgrades for the current platform
- Integration of these upgrades together with a technician
- Updating the control software of the platform accordingly (in LabView)
- Conducting experiments with aqueous solutions in the upgraded platform
- Analyzing the outcome of said experiments and comparison with other methods to study ice nucleation.

Requirements

- Solid background in engineering subjects
- Creative, highly motivated and independent attitude
- Experience in working in a lab/basic programming skills desirable (e.g. Matlab, LabView)

Deliverables

The experiments shall be documented in a digital lab journal (eLABFTW).

Short, schematic reports of what has been done during the week, including methods, results, and discussion and what is planned for the following week should be submitted by email to the supervisors every Friday. The work carried out during the thesis and the results obtained will be presented in two oral presentations, one about halfway through the project and one at the end.

References

[1] Elena Cândida dos Santos, Giovanni Maria Maggioni, and Marco Mazzotti: Statistical Analysis and Nucleation Parameter Estimation from Nucleation Experiments in Flowing Microdroplets. *Cryst. Growth Des.2019, 19, 6159−6174*
https://doi.org/10.1021/acs.cgd.9b00562

[2] Dyhia Atig, Abdelhafid Touil, Manuel Ildefonso, Laurent Marlin, Patrick Bouriat, Daniel Broseta: A droplet-based millifluidic method for studying ice and gas hydrate nucleation. *Chemical Engineering Science 192 (2018) 1189–1197*
https://doi.org/10.1016/j.ces.2018.08.003

[3] Claudiu A. Stan, Gregory F. Schneider, Sergey S. Shevkoplyas, Michinao Hashimoto, Mihai Ibanescu, Benjamin J. Wiley and George M. Whitesides: A microfluidic apparatus for the study of ice nucleation in supercooled water drops. *Lab Chip, 2009, 9, 2293–2305*
https://doi.org/10.1039/B906198C