CRYSTAL NUCLEATION FROM SOLUTION: DESIGN AND MODELLING OF DETECTION TIME EXPERIMENTS

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Crystal nucleation is the process responsible for the appearance of a thermodynamically stable phase from a metastable parent solution. Given its activated nature, nucleation is affected by stochasticity which, despite originating at the molecular level, affects heavily also the macroscopic behaviour of the system.
Being far too small to be observed directly, nuclei are detected by indirect methods, which correlate the formation of the new phase with a measurable change in a property of the system, hence a model linking nuclei formation and crystals detection is always needed.

We have previously presented a model describing nucleation in macroscopic systems as a stochastic Poisson process. The model, despite its general character, can describe industrially relevant processes, e.g. batch cooling at different operating conditions.
The different scales influenced by the stochastic nature of nucleation demand appropriate theoretical and experimental investigations, particularly for applying the model to industrial scale-up, optimisation, and control. Using statistical tools, we have looked into the issue of estimating stochastic processes by collecting a representative, but limited number of data, produced from a homogeneous set. Moreover, using our model, we analysed the sensitivity of crystallising systems on initial and boundary conditions, with particular emphasis on the effect of supersaturation, temperature and detection conditions. Finally, in light of the stochastic nature of nucleation, we also applied statistical meta-analysis to assess the agreement between the fitting and its parameters and experiments, to gain further insight into the quality of the model.

Experimentally, we have first investigated the conditions to perform homogeneous and reproducible measurements, necessary to understand the fundamental physical features and ultimately to estimate reliable kinetic parameters. A second aspect we have explored concerned the size of the crystallising systems. Since in macroscopic reactors various phenomena occur simultaneously (nucleation, growth, breakage, agglomeration) we chose to work with two main system sizes, 1-3 mL reactors (mesoscale) and 1-60 nL reactors (microscale, i.e. microscopic droplets), where at least some of such phenomena could be decoupled.

In the mesoscale crystallisers, one can perform experiments where temperature and transmissivity could be measured online, hence monitoring the appearance and disappearance of crystals. Additionally, the influence of fluid-dynamics, typically turbulent in these reactors, was investigated.
In the microfluidic chips, on the other hand, a very high through-put (thousands of replicas of the same reactor) can be potentially achieved and, thanks to their very small size, high supersaturations, outside of usual experimental reach, could be explored. Additionally, within the microscopic droplets the fluid motion is generally diffusive or laminar convective, hence hindering breakage and agglomeration. One could thus observe systems where nucleation and growth of single crystals (or of few crystals) occur unperturbed. Nevertheless, some main challenges, which we have been addressing, must be tackled before performing reliable crystallisation experiments: the characterisation and the reproducibility of shape and size of the droplets and their stability (i.e. the loss of mass due to evaporation and perspiration through the chip).

In conclusion, we demonstrate that, even if the data are reproducible and reliable, robust probability estimations can be obtained only with a sufficiently large number of experiments, which require careful design to avoid sensitivity regions and data processing to reject the non-homogeneous data.
The different sizes investigated have permitted to gain a better insight into the fundamental phenomena occurring in a crystallising system between the first formation of nuclei until crystal detection, which is of utmost importance for understanding the design of the experiments at an industrially relevant scale.
Moreover, appropriate mathematical tools allowed to assess the reliability of the fitting obtained from independent measurements of the same system at different conditions.