Microfluidics and photonics for the study of crystalline nucleation: probing beyond conventional spatiotemporal barriers

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Nucleation is an activated process driven by thermodynamic fluctuations within a metastable phase, which lead to the formation of the initial seeds of a more stable crystalline phase. Pre-critical nuclei, resulting from low-amplitude fluctuations, are typically reabsorbed into the metastable environment, whereas post-critical nuclei, formed through higher-energy fluctuations, are capable of growing into macroscopic crystals. Critical nuclei emerge at the boundary between growth and dissolution, and their structural and compositional characteristics ultimately govern both the nucleation pathway and the final crystal structure. However, due to their inherently stochastic and transient nature, these early-stage events are challenging to characterize experimentally and remain poorly understood, especially under realistic, dynamic conditions.

In this talk, it will be shown how microfluidic technologies and volumetric confinement strategies can be used to overcome these limitations, by enabling precise control of local supersaturation, enhanced temporal resolution, and access to extended metastable regimes through confinement effects. Several illustrative case studies will be presented, demonstrating how this approach permits the isolation of individual nucleation events and the investigation of both nucleation kinetics and in situ structural evolution. The role of transient metastable intermediates will be discussed in model systems including calcium carbonate [1], rare-earth oxalate precipitation [2], and protein crystallization [3], where such species are often overlooked yet crucial for pathway selection.

Additionally, **ultra-fast mixing microfluidic platforms provide a complementary approach**, enabling the direct observation of rapid transition kinetics when integrated in situ and in operando with photonic and synchrotron-based characterization techniques. The development of an ultra-fast mixing microreactor coupled to small-angle X-ray scattering (SAXS), UV–visible spectroscopy, and X-ray absorption spectroscopy (XAS) will be presented in the context of noble metal nanoparticle synthesis. This integrated methodology has enabled time- and space-resolved studies of gold [4] and silver [5] nucleation and growth, granting access to the earliest stages of crystallization with unprecedented temporal precision, and yielding kinetic and structural parameters that remain inaccessible via conventional batch approaches.

Beyond offering technical advantages, these synergistic approaches invite a reconsideration of how nucleation is studied experimentally. By shifting from bulk-averaged measurements to controlled, event-resolved observations, traditional assumptions (such as those embedded in classical nucleation theories) can be challenged and reinterpreted. Their application to both inorganic and biomolecular systems highlights their potential to disentangle the complex landscape of nucleation phenomena, refine kinetic models, and support a rational design of crystallization protocols.

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