

However, if nucleation events are heterogeneous and are related to external fluid interfaces, such as vessel walls or fluid–air interface with a defined surface area, it may be appropriate to express nucleation rate as number of crystals generated per unit surface area per unit time. Furthermore, if nucleation events are related to some other localized environment, such as a region of high shear (*e.g.*, due to pump or agitator), inlet stream mixing point or external field impact (*e.g.*, by ultrasonic transducer), it may be appropriate to express nucleation rate simply as number of crystals generated per unit time within the given local volume.

Dependencies of the nucleation rate on solution composition and temperature within the metastable zone vary widely from system to system. There are currently no reliable tools able to quantitatively (and often even qualitatively) predict how nucleation rates depend on solution composition and temperature, and even the fundamental mechanisms (homogeneous or heterogeneous; single step or multistep) are strongly debated in scientific literature.^{6,8,9} Until there is major progress in predictive computational tools in this area, information about nucleation and growth rates needs to be obtained experimentally.

Experimental measurements of crystal nucleation rates are challenging because nuclei are small so that they have to grow into a detectable range, and nucleation and growth are inextricably linked. In order to measure the nucleation rate, it is possible to count the increase in the number of detectable particles assuming that the change of number of particles is only due to nucleation,^{3,11,12} or it is possible to determine induction times from which primary nucleation kinetics can be estimated using various assumptions (isothermal/polythermal, constant/variable nucleation rate, single/multiple nuclei, growth time to detection, *etc.*).^{13,14}

Fouling and encrustation can be related to (heterogeneous) nucleation and agglomeration of crystals in regions with high local supersaturations such as cooling surfaces, mixing points and contact lines of boiling liquid, air and crystallizer wall. Fouling needs to be monitored¹⁵ and mitigated when operating continuous crystallization processes as it can compromise the steady state operation as well as product quality attributes.

Primary nucleation in stagnant fluid in absence of external fields is typically addressed in textbooks: but what about effects such as mixing, shear, pressure and electromagnetic fields? Effects of pressure waves (ultrasound), high power lasers and fluid shear on nucleation have been observed: can we understand and use them to develop better crystallization processes?

1.2.1.1 *Mixing-induced Supersaturation*

The effect of local concentration gradient can be important when supersaturation is mixing-induced, *e.g.*, in antisolvent or reactive crystallization, where two fluid streams need to be mixed to obtain required solution composition. If the mixing process is much slower than the nucleation