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Dispersions in crystal nucleation and growth rates: Implications of fluctuation in supersaturation



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HIGHLIGHTS

G R A P H I C A L A B S T R A C T

- Stochastic model for supersaturation fluctuations.
- Modeling of dispersions in crystal nucleation and growth rates.
- Predicted morphology distribution for KAP crystal nuclei.
- Experimental validation of predicted growth rate dispersions in KAP crystals.

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ABSTRACT

Crystallization is one of the most commonly used and relatively well explored techniques in industries. Yet there are beleaguering issues towards fundamental understanding of this process. One of the curious observations is the appearance of unavoidable dispersions in nucleation and growth rates of crystalline materials grown under homogenous bulk conditions. These dispersions can contribute significantly towards polydispersity in crystalline products. The classical models such as Gibbs critical nucleation theory and Burton–Cabrera–Frank growth models primarily relate nucleation and growth to supersaturation. Therefore, the dispersions in nucleation and growth rates can be related to the local fluctuations in supersaturation. These local fluctuations are driven by the Brownian motion of solute molecules which affects the local concentration and temperature and hence supersaturation. This article presents a stochastic model to describe fluctuations in supersaturation and thereby dispersions in crystalline materials. The stochastic model is derived from the framework of density and temperature fluctuations. The resulting dispersions in size and shape of nuclei are obtained by multi-dimensional maximization of Gibbs free energy in morphology domain of potassium acid phthalate. The model predictions are validated with the experimental measurements of growth rate dispersions in potassium acid phthalate crystals. The proposed framework provides the first *ab initio* predictions for the observed dispersions in crystallization processes.

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1. Introduction

The advanced techniques to predict (Singh and Ramkrishna, 2013; Singh et al., 2013) and measure (Singh et al., 2012) crystal morphologies and face-specific growth rates have contributed significantly to the understanding of crystallization. The underlying processes of crystallization such as nucleation and growth are known to affect sizes and morphologies of crystals. The

solution crystallization is primarily driven by the supersaturation which is often quantified as the solute concentration relative to its saturation limit. The existing theories of crystal nucleation and growth provide a deterministic relationship of the size and morphology of crystals with the supersaturation (Myerson, 2002). Therefore it is quite natural to expect that under fixed crystallization conditions, including supersaturation, crystals will nucleate of mono-dispersed sizes and morphologies that will grow identically, which are often contrary to the experimental observations. Such evolution of a population of crystals is usually described by hyperbolic population balance equations with Dirac

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delta type forcing function or boundary condition. Clearly, the solutions of such population balance equations at fixed operating conditions should follow a uniform distribution. Randolph and White (1977) showed that the spreading of size distribution is due to random fluctuations in growth rates. The synthesis of nanoparticles in micellar solutions is a good example of batch crystallization where breakage and aggregation are negligible, and the only processes governing their sizes and morphologies are nucleation and growth (Taleb et al., 1997). Non-uniform size and morphology distributions in crystalline materials growing under fixed conditions are commonly observed and so far they have been dealt with empirically in the literature (Randolph and Larson, 1971). This article presents an *ab initio* approach to explain such dispersions in nucleation and growth rates occurring in crystallization, based on the fundamentals of Brownian dynamics.

Growth rate dispersion is defined as the variations in growth rates under fixed thermodynamic and hydrodynamic conditions, including supersaturation. Crystalline materials can show wide range of dispersion in growth rates based on the environmental conditions. Experimental values of growth rate dispersion for different crystalline materials can be found in review articles (Garside, 1985; Ulrich, 1989). The growth of crystals or their faces is due to transfer of solute molecules from bulk to the kink sites on the crystal faces. The growth rates are therefore dependent on the mechanism of kink site formation and the supersaturation of solute molecules, both of which can be stochastic. The densities of kink sites and their evolution are functions of temperature and supersaturation. In general, the growth rates functions (Winn and Doherty, 2000) can be expressed as

$$\dot{H}_i = g(\phi_i^{kink}, T) f(S) \tag{1}$$

where \dot{H}_i is a growth rate of *i*th face, ϕ_i^{kink} the free energy of kink, *T* is the temperature and S is supersaturation defined as ratio of solute concentration to the saturation concentration. Eq. (1) indicates that the growth rates are functions of thermodynamic properties that determine ϕ_i^{kink} and the dynamic conditions such as temperature and supersaturation. The dynamic conditions are the manifestation of Brownian motion of molecules which on a smaller length scale tend to fluctuate. That means, even if the bulk temperature and supersaturation of the crystallizer are fixed they are bound to fluctuate locally due to Brownian motion. Such fluctuations tend to dissipate with increase in length scale. The growth rates are the realization of the progression of kink sites whose length scales are small enough to observe significantly larger fluctuations. The calculations of growth rate dispersion are predicated on the assumption that Eq. (1) may be applied on a time scale in which temperature and supersaturation fluctuate.

Nucleation is another local phenomenon that is primarily driven by supersaturation. The Gibbs critical nucleation theory relates the equilibrium size and shape of crystal nuclei with supersaturation and temperature (Myerson, 2002). Furthermore, the rate of nucleation derived from the Arrhenius law also shows the direct dependence on supersaturation and temperature. In this case, the Brownian motion induced fluctuations in supersaturation and temperature will yield distributions in size and shape of nuclei and the nucleation rates. Calculations of growth rate dispersion, nuclei size and shape distributions and nucleation rate distribution resulting from local fluctuations are shown for potassium acid phthalate crystals.

This article is organized as follows. In Section 2, we present a broad outline of the theory which features its salient implements deferring mathematical details of their development to suitably organized Appendices. Section 3 predicts the nuclei morphology distribution from the distribution of supersaturation using Gibbs critical nucleation theory. Section 4 uses the experimentally measured face-specific growth rate functions of Potassium Acid

Phthalate to predict the growth rate dispersion. Section 5 implements the identified growth rate dispersion and nucleation kernels to population balance equations. Section 6 gives the summary of work with the scope for future extension.

2. Theory

As articulated earlier, our goal is to develop a theory by which experimentally observed dispersion in nucleation and growth rates can be predicted. The theory is built on attributing this observed dispersion to the fluctuations in number density of solute molecules and temperature due to Brownian motion. We start from the usual premise that the supersaturation drives nucleation and growth in crystallization. Supersaturation, defined as the concentration of solute relative to the saturation concentration, can be expressed in many ways. One of the ways to describe supersaturation *S* is

$$S = \frac{c}{c_{sat}[T]} \tag{2}$$

where c is the molar concentration and c_{sat} is the saturation concentration which is a function of temperature T. Predicting the effects of other environmental factors such as co-solvents, additives, pressure, electromagnetic field and sonication on fluctuations in saturation concentration requires more sophisticated theory which is outside the scope of this article. The temperature-dependent saturation concentration is the most common scenario in solutionbased crystallization and thus relating supersaturation to number density of solute molecules and temperature.

The total number n of solute molecules in an infinitesimal volume v tends to fluctuate about the bulk concentration due to Brownian motion. The fluctuations in the number density c of solute govern the fluctuations in mean-square-speed of molecules and hence temperature in the infinitesimal volume. Therefore, the fluctuations in the supersaturation in a small volume v can be written as

$$S(t) = \frac{n(t)}{vc_{sat}[T(t)]}$$
(3)

The magnitude of fluctuations is inversely proportional to the control volume v. Identification of characteristic length scales of nucleation and growth are therefore important for accurate predictions of dispersion. For example, the critical length scale of nucleation can be obtained from Gibbs critical nucleation theory and that of growth is governed by the underlying mechanisms such as spiral growth, 2D nucleation and surface roughening. The critical length scales will set the control volume to predict fluctuations in number n(t) and temperature T(t) whose theories will be discussed in Sections 2.1 and 2.2, respectively.

2.1. Density fluctuations

The framework of density fluctuations due to Brownian motion of solute molecules in an infinitesimal volume is developed from the dynamic exchange of molecules between the system and surrounding. Such exchange of molecules in a system of infinitesimal volume v inside a very large volume V containing N solute molecules yields an equilibrium distribution. Appendix A shows that the equilibrium distribution of the number n of solute molecules, uniformly spreads under Brownian motion, follows Poisson distribution.

$$P_n(n) = \frac{\overline{n}^n e^{-n}}{n!} \tag{4}$$

whose mean and variance are equal to the average number of molecules \overline{n} in the volume v. (Chandrasekhar, 1943) This

equilibrium distribution is valid for the homogeneous system below the critical point for phase separation. Moreover, it is independent of the type of molecules and the governing force field. However, the dynamics of number density is dependent on the underlying Langevin equation. The rate of change in number of molecules in a small volume v can be determined from the transition probability Z(m, t|n, 0) that *m* molecules will be found after time *t* in a volume v with initially *n* molecules in it. Smoluchowski (1916) defined the transition probability assuming that (i) molecules move independently without influencing each other and (ii) all positions inside the volume have equal *a priori* probability. Transition probability for *m* molecules can be obtained from the exit probability of single molecule as follows.

The position of a non-interacting molecule in space at any time is given by diffusion equation, whose solution is a Gaussian distribution with variance 2Dt. We define the *probability aftereffect* P_t as the probability that a molecule somewhere inside v will have emerged from it during time t. Since the position of molecule anywhere inside v is equally likely, the probability after-effect can be obtained by integrating the associated probability density (Gaussian distribution) with respect to the initial and final positions of molecule inside volume v. The expression for probability after-effect is derived in Appendix B and is given as

$$P_t(t) = 1 - \operatorname{erf}[K(t)] + \frac{2K(t)}{\sqrt{\pi}} \exp[-K(t)^2]$$

where, $K(t) = \left(\frac{3v}{4\pi(Dt)^{3/2}}\right)^{1/3}$ (5)

where K(t) is a dimensionless number representing the ratio of the radius of a sphere of volume v to the mean distance traveled by a molecule in time t. The probability of finding a molecule inside the control volume increases with the dimensionless number K. For a fixed control volume, the probability after-effect is only a function of time whose behavior becomes more sluggish with increase in the volume. In deriving expression (5) we only considered the effects of Brownian forces; however other effects such as those due to inter-molecular forces can also be accounted for as discussed in Appendix B.

Example 1. Fig. 1 shows the probability after-effect for a Potassium Acid Phthalate (KAP) molecule whose diffusivity in water at



Fig. 1. Variations in the probability after-effect of KAP molecules in Water at 300 K with increasing local volume.

300 K is $D = 6.35 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$. As discussed above, it can be seen that the probability after-effect increases slowly with time for a larger control volume. This is because a molecule takes longer to cross larger volumes. Therefore, the number of molecules in a larger control volume does not change much with time and hence the solution properties tend to remain invariant.

The transition probability Z(m, t|n, 0) of adding k = m - n molecules in a volume v in time t can be determined by considering the exchange of molecules with the surrounding. There could be multiple ways for a system to observe a net change in the number of molecules, all of which must be accounted for in determining the transition probability. The derivation of transition probabilities is discussed in Appendix C, which involves identification of (i) probability $A_n(i, t)$ of *i* molecules leaving the system containing *n* molecules and (ii) probability E(i, t) of *i* molecules entering into the system. If the probability of a molecule leaving the system is given by the probability after-effect then the probability $A_n(i, t)$ that *i* out of *n* molecules will be leaving the system in time tshould follow a Binomial distribution. At equilibrium, the probability of entrance must be equal to the probability of emergence of molecules. Therefore the probability E(i,t) of *i* molecules entering into the system in time *t* is equal to the expected value of the emergence probability $A_n(i, t)$ and is given by a Poisson distribution with mean and standard deviation of $\overline{n}P_t$.

One of the ways of adding *k* molecules is when *i* molecules are leaving and i+k molecules are entering into the system. The probability of adding *k* molecules in this way is given by $A_n(i, t) E(i+k, t)$, which will yield the required transition probability Z(n+k, t|n, 0) when summed over all possible *i's*. Similarly, the transition probability Z(n-k, t|n, 0) of *k* molecules leaving the system during time *t* can be obtained.

The probability $P_n(n,t)$ of finding *n* molecules in a volume v at given time *t* is described by a Master equation,

$$\frac{\partial P_n(n,t)}{\partial t} = \sum_{k=0}^{\infty} [\lambda(k,n-k)P_n(n-k,t) - \lambda(k,n)P_n(n,t)]$$
(6)

where the transition rates $\lambda(k, n)$ is the probability of adding k molecules in unit time to the system containing n molecules and therefore it can be considered as the time derivative of the respective transition probabilities Z(n+k, t|n, 0). Expression for transition rates are also derived in Appendix C.

The solution of the Master equation (6) can be obtained by either taking a finite range of k or considering k and n as continuous variables. If we consider k and n as continuous variables then the Kramers–Moyal expansion (Gardiner, 1985) of Eq. (6) about infinitesimal k would give the Fokker–Planck equation for the probability density $f_n(n, t)$, as follows:

$$\frac{\partial f_n(n,t)}{\partial t} = -\frac{\partial}{\partial n} [\alpha_1(n,t)f_n(n,t)] + \frac{1}{2} \frac{\partial^2}{\partial n^2} [\alpha_2(n,t)f_n(n,t)]$$
(7)

where α_1 and α_2 are first and second moments of the transition rates,

$$\alpha_1(n,t) = \int_{-\infty}^{\infty} k\lambda(k,n) \, dk$$

$$\alpha_2(n,t) = \int_{-\infty}^{\infty} k^2 \lambda(k,n) \, dk$$
(8)

The Ito equation (a stochastic differential equation) associated with the Fokker–Planck equation would give the fluctuations in the number n of molecules in a volume v, which can be written as

$$dn(t) = \alpha_1(n,t) dt + \sqrt{\alpha_2(n,t)} dW(t)$$
(9)

here W(t) is a Wiener process whose time derivative is a white noise. Alternatively, the solution of Eq. (7) can be obtained through solving Eq. (9) sufficient number of times.

Example 2. Consider an infinitesimal volume $v = 22.89 \text{ nm}^3$ in 2.176 M aqueous solution of KAP containing on an average $\overline{n} = 30$ molecules of KAP. Fig. 2 shows the local fluctuations in the number density or concentration of KAP molecules at temperature T = 300K. A set of trajectories at any time t gives a probability density $f_n(n, t)$ of number of molecules in volume v. These trajectories obtained as solutions of Eq. (9) attain a steady-state distribution (shown in Fig. 3) in a very short time interval. As discussed earlier, this steady-state distribution is always a Poisson distribution for any type of molecule.

2.2. Temperature fluctuations

The local temperature in aqueous solution also undergoes fluctuations due to Brownian motion. The temperature of solution can be obtained by equating its thermal energy with the mean



Fig. 2. Dynamics of number of KAP molecules in the small volume $v = 22.89 \text{ mm}^3$ of 22.89 M aqueous solution. The multiple trajectories of the number also describe the temporal evolution of number distribution.



Fig. 3. Steady-state distribution of the number of KAP molecules.

kinetic energy of molecules.

$$3\kappa T = \frac{1}{2}m\overline{v^2} \tag{10}$$

where κ is the Boltzmann constant, *T* is absolute temperature, *m* is the mass of solute molecule and *v* is the speed of molecules. The speed of molecules in arbitrary potential field for constant number, volume and energy (NVE) system follows Maxwell–Boltzmann distribution. For a constant number, volume and temperature (NVT) system, the Langevin equation for the solute molecules will govern their speed, such that

$$d\mathbf{v}_1 = -\frac{\beta}{m} \mathbf{v}_1 \, dt - \frac{1}{m} \nabla_{\mathbf{r}} \boldsymbol{\Phi}(\mathbf{r}_1, \mathbf{r}_2, ..., \mathbf{r}_N) \, dt + \frac{\beta \sqrt{D}}{m} \, d\mathbf{W}(t) \tag{11}$$

where Φ is the total potential acting on one molecule, \mathbf{v}_1 is the velocity of molecule of mass *m* located at \mathbf{r}_1 , β is the friction factor and *D* is the molecular diffusivity. As the molecules are uniformly distributed, integrating Eq. (11) with respect to \mathbf{r}_1 , \mathbf{r}_2 , ..., \mathbf{r}_N would give the equation for velocity of molecules

$$d\mathbf{v} = -\frac{\beta}{m}\mathbf{v} \, dt + \frac{1}{m}\overline{\mathbf{F}} \, dt + \frac{\beta\sqrt{D}}{m} \, d\mathbf{W}(t) \tag{12}$$

under a mean force field,

$$\overline{\mathbf{F}} = -\frac{1}{V^N} \int_{\mathbf{r}_1} \int_{\mathbf{r}_2} \dots \int_{\mathbf{r}_N} \nabla \Phi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) \, d\mathbf{r}_1 \, d\mathbf{r}_2 \dots d\mathbf{r}_N \tag{13}$$

Since the molecule is arbitrary chosen, there is no subscript to the velocity in Eq. (12). The Fokker–Planck equation describing the probability density for molecular velocity can be written as

$$\frac{\partial}{\partial t} f_{\mathbf{v}}(\mathbf{v},t) - \frac{\beta}{m} \nabla_{\mathbf{v}} \cdot [\mathbf{v} f_{\mathbf{v}}(\mathbf{v},t)] + \frac{1}{m} \overline{\mathbf{F}} \cdot \nabla_{\mathbf{v}} f_{\mathbf{v}}(\mathbf{v},t) - \frac{\beta^2 D}{2m^2} \nabla_{\mathbf{v}}^2 f_{\mathbf{v}}(\mathbf{v},t) = 0$$
(14)

The solution to this can be obtained by Fourier transform and the Method of Characteristics:

$$f_{\mathbf{v}}(\mathbf{v},t) = \left(\frac{2}{1 - e^{-\beta t/m}}\right)^{3/2} \\ \times \exp\left(-\frac{m}{D\beta} \frac{\left[\mathbf{v} - (1/\beta)\overline{\mathbf{F}}(1 - e^{-\beta t/m})\right] \cdot \left[\mathbf{v} - (1/\beta)\overline{\mathbf{F}}(1 - e^{-\beta t/m})\right]}{1 - e^{-2\beta t/m}}\right)$$
(15)

The distribution of speed in the NVT system can be obtained from Eq. (15) as

$$f_{\nu}(\nu,t) = C_{\nu} 4\pi \nu^2 \left(\frac{2}{1 - e^{-2\beta t/m}}\right)^{3/2} \exp\left(-\frac{m}{D\beta} \frac{\left[\nu - (1/\beta)\overline{F}(1 - e^{-\beta t/m})\right]^2}{1 - e^{-2\beta t/m}}\right)$$
(16)

where C_v is the normalization factor. The mean square speed of the *N* molecules will govern the bulk temperature, whereas the local temperature in an infinitesimal volume v is controlled by the number of molecules n(t) in it. The mean square speed $\overline{v^2}$ of n(t)molecules is then a random process. If we know the cumulative probability $F_v(v, t)$ of the speed of molecules at steady-state then total of n(t) random numbers, denoted as ξ_i in the range [0, 1], would determine the speed of *i*th molecule, satisfying the equation

$$F_{\nu}(\nu_i, t) = \xi_i, \quad i \in [1, 2, ..., n(t)]$$
 (17)

Temperature fluctuations can now be determined from Eq. (10),

$$T(t) = \frac{m}{6k} \left[\frac{v_1^2 + v_2^2 + \dots + v_{n(t)}^2}{n(t)} \right]$$
(18)

Alternatively, the speed of molecules v_i can also be determined by numerically solving Eq. (11), which can take a much longer time than solving Eq. (17). The Ito equation describing temperature

fluctuations can be derived as

$$dT(t) = \frac{1}{n(t)} \left[\frac{m}{3k} \sum_{i=1}^{n(t)} [v_i(t) \, dv_i] - T(t) \, dn \right]$$
(19)

where the Langevin equation for the speed $v_i = |\mathbf{v}_i|$ can be obtained from Eq. (12). The Ito equation for temperature is thus a linear combination of the Ito equations for number and speed of molecules, which can be lumped as

$$dT(t) = \gamma_1(T, n, v, t) dt + \sqrt{\gamma_2(T, n, v, t)} dW(t)$$
(20)

Example 3. The local temperature (in Eq. (18)) is governed by the instantaneous number of molecules and their speed. Fig. 4 shows the fluctuations in the local temperature inside small volume $v = 22.89 \text{ nm}^3$ of KAP solution. The steady-state distribution of temperature is shown in Fig. 5.



Fig. 4. Fluctuations in the local temperature of KAP solution.



Fig. 5. Steady-state distribution of temperature of KAP solution.

2.3. Supersaturation fluctuations

The local supersaturation in some volume v can be described by Eq. (3), whose derivative would give Ito equation for supersaturation as a function of Ito equations for number and temperature.

Using Eqs. (3), (9) and (20) and neglecting the terms of order higher than dt, we can write

$$dS(t) = \left[\frac{\alpha_1}{vc_{sat}(t)} - S(t)\frac{c'_{sat}(t)}{c_{sat}(t)}\gamma_1 - S(t)\left(\frac{c'_{sat}(t)}{2c_{sat}(t)} - \left(\frac{c'_{sat}(t)}{c_{sat}(t)}\right)^2\right)\gamma_2\right]dt + \left[\frac{\sqrt{\alpha_2}}{vc_{sat}(t)} - S(t)\frac{c'_{sat}(t)}{c_{sat}(t)}\sqrt{\gamma_2}\right]dW(t)$$
(21)



Fig. 6. Local fluctuations in supersaturation of KAP solution.







Fig. 8. Distributions of local concentration and saturation concentration of KAP.

Taking the expected value of drift and diffusion terms would yield Ito's equation for supersaturation

$$dS(t) = \eta_1(S, t) dt + \sqrt{\eta_2(S, t)} dW(t)$$
(22)

Derivation of Eq. (21) using Ito's formula and identification of drift and diffusion terms of supersaturation are discussed in Appendix D. Fluctuations in supersaturation can be computed either directly by solving Eq. (22) or indirectly using the solutions of Eqs. (9) and (20). The corresponding Fokker–Planck equation for the probability density $f_S(S, t)$ can be written as

$$\frac{\partial f_S(S,t)}{\partial t} + \frac{\partial}{\partial S} \eta_1 f_S(S,t) = \frac{1}{2} \frac{\partial^2}{\partial S^2} \eta_2 f_S(S,t)$$
(23)

Clearly the bulk supersaturation $S(\overline{c}, c_{sat}(\overline{T}))$, referred to in the literature as the ratio of the bulk concentration and saturation concentration, is different than the actual mean supersaturation $\overline{S(c, c_{sat})}$ of the bulk solution.

$$\overline{S(c, c_{sat})} \neq S(\overline{c}, c_{sat}(\overline{T}))$$
(24)

Example 4. The calculation of the local supersaturation requires the solubility of KAP. Classically, the solubility is related to



Fig. 9. Variations in the distributions of supersaturation with increasing bulk temperature and bulk supersaturation. The abscissa and ordinate in each plot are supersaturation and percentage probability.

 Table 1

 Variations in mean and variance of supersaturation with bulk temperature and bulk supersaturation.

\overline{T} (K)	S _b			
	1.1	1.2	1.3	1.4
300	$\overline{S} = 1.3198$	$\overline{S} = 1.4432$	$\overline{S} = 1.5615$	$\overline{S} = 1.6827$
	V(S) = 0.7813	V(S) = 0.9322	V(S) = 1.0946	V(S) = 1.2714
310	$\overline{S} = 1.4762$ V(S) = 1.1891	$\overline{S} = 1.6083$ V(S) = 1.4151	$\overline{S} = 1.7517$ V(S) = 1.6783	$\overline{S} = 1.8861$ $V(S) = 1.9349$
320	$\overline{S} = 1.6019$	$\overline{S} = 1.7549$	$\overline{S} = 1.8968$	$\overline{S} = 2.0478$
	V(S) = 1.6810	V(S) = 2.0255	V(S) = 2.3631	V(S) = 2.7371
330	$\overline{S} = 1.7147$	$\overline{S} = 1.8523$	$\overline{S} = 2.0155$	$\overline{S} = 2.1725$
	V(S) = 2.2313	V(S) = 2.6411	V(S) = 3.0951	V(S) = 3.6048

temperature as

$$\ln c_{sat}(t) = -\frac{\Delta H_{diss}}{RT} + \frac{\Delta S_{diss}}{R}$$
(25)

where *R* is the gas constant, ΔH_{diss} is the dissolution enthalpy and ΔS_{diss} is the dissolution entropy. The dissolution enthalpy and entropy for the aqueous solution of KAP are $\Delta H_{diss} = 18524 J/\text{mol}$ and $\Delta S_{diss} = 57.154 J/\text{mol}$ K (Akhtar and Podder, 2011). The local fluctuations in supersaturation of 2.176 M KAP solution at 300 K are shown in Fig. 6. The steady state distribution of supersaturation in Fig. 7 shows sharp peak at smaller values and a hump followed by a tail at larger values. This typical shape of the supersaturation distribution is due to the governing distributions of *c* and $c_{sat}(T)$, which are shown in Fig. 8.

As c_{sat} depends exponentially on T^{-1} , its distribution is also of exponential form and contributes significantly to the first peak of the supersaturation distribution. Likewise, the hump in the supersaturation distribution is due to the relative position of the distribution of c. Therefore, the variance (or spread) of the supersaturation distribution is not only due to the variances in the distributions of *c* and $c_{sat}(t)$ but also their relative positions. Increasing the bulk concentration at fixed temperature moves the distribution of c further away from the mean of $c_{sat}(t)$ which increases the mean and the variance of the supersaturation. However, increasing the bulk temperature decreases the relative distance between the means of *c* and $c_{sat}(t)$ which results in longer tail portion of the supersaturation distribution. The variation in supersaturation distribution with bulk temperature \overline{T} and bulk supersaturation $S_b = S(\overline{c}, c_{sat}(\overline{T}))$ is shown in Fig. 9. Each column in Fig. 9 represents the variations in supersaturation distributions with increasing bulk temperature at fixed bulk supersaturation. Table 1 shows, according to Eq. (24), that the mean supersaturation in each column are significantly different than the corresponding bulk supersaturation. The mean supersaturation can be as high as 55% more than the bulk supersaturation.

3. Nuclei morphology distribution of potassium acid phthalate crystals

Growing crystals are convex polyhedra bounded by finite number of low-energy faces. The morphology of a crystal with \hat{n} number of low energy faces can be represented by a polyhedron, such that

where **N** is a matrix formed by stacking, in a single column, the unit normals of crystal faces as row vectors, **r** represents position vectors in \Re^3 and $\tilde{\mathbf{h}}$ is a vector of perpendicular distances of faces from the center of the crystal. Therefore, $\tilde{\mathbf{h}}$ is in the non-negative orthant of \hat{n} -dimensional real space $\Re^{\hat{n}}_{+0}$.

The symmetry of crystals allows the classification of faces based on kinetic and geometric similarity. A crystal with \hat{m} groups of kinetically and geometrically similar faces can be represented by \hat{m} distinct perpendicular distances forming a vector $\mathbf{h} \in \Re_{+0}^{\hat{m}}$ such that at any time $\tilde{\mathbf{h}}$ can be reconstructed from \mathbf{h} . Therefore, the dynamics of crystal morphology can be uniquely determined from \mathbf{h} (*h*-vector) (Singh and Ramkrishna, 2013; Singh et al., 2013).

The low-energy faces, the F-faces, can be identified from Hartman–Perdok theory. The F-faces will be considered in the construction of the shape of crystal nucleus as all other faces of higher surface energies will most likely not appear or disappear quickly. The equilibrium shape of a crystal of a fixed volume can be calculated by minimizing its surface energy. Cleary, the minimization problem would yield lesser value to the areas of faces with larger surface energies. Therefore it is reasonable to consider only F-faces in the computation of the equilibrium shapes of nuclei.

The Gibbs free energy change ΔG per molecule during the formation of a faceted nucleus can be written as

$$\Delta G(\mathbf{h}) = \sum_{i=1}^{\hat{n}} A_i(\mathbf{h}) \sigma_i - V_c(\mathbf{h}) \frac{\kappa T \ln(S)}{V_m}$$
(27)

where A_i is the area of the *i*th face, σ_i is the specific surface energy, V_c is the crystal volume and V_m is the molecular volume. The surface energy of an F-face can be approximated by the attachment energy of a crystal face. The surface energy of a crystal in vacuum is given as

$$\sigma_i \simeq \frac{n_L E_{att,i} d_i}{2 \mathsf{v}_L} \quad i = 1, 2, \dots, \hat{n} \tag{28}$$

where n_L is the number of molecules in a unit cell of volume v, d_i is the interplanar spacing of *i*th lattice plane and $E_{att,i}$ is the attachment energy per molecule of *i*th lattice plane.

The maximization of the free energy in the morphology domains (fundamental property of crystals defined in Singh et al. (2013)) would require its gradient to be zero. This implies

$$\nabla_{\mathbf{h}}[\Delta G(\mathbf{h})] = \sum_{i=1}^{\hat{n}} \sigma_i \nabla_{\mathbf{h}} A_i(\mathbf{h}) - \frac{\kappa T \ln(S)}{V_m} \nabla_{\mathbf{h}} V_c(\mathbf{h}) = 0$$
(29)

The solution to the above set of non-linear equations would give the *h*-vector of a critical nucleus for specific bulk supersaturation and temperature. As nucleation is a local phenomenon it is susceptible to the fluctuations in the local supersaturation. The set of non-linear equations in (29), represented as $\mathbf{J}(\mathbf{h}, S, t) = \mathbf{0}$, can be used to relate the fluctuations in \mathbf{h} with the fluctuations in *S*.

$$\frac{d}{dt}\mathbf{J}(\mathbf{h}, S, T) = \nabla \mathbf{J}\frac{d\mathbf{h}}{dt} + \frac{\partial \mathbf{J}}{\partial S}\frac{dS}{dt} + \frac{\partial \mathbf{J}}{\partial T}\frac{dT}{dt} = \mathbf{0}$$
(30)

which after rearranging gives,

(26)

$$\frac{d\mathbf{h}}{dt} = -\nabla \mathbf{J}^{-1} \left[\frac{\partial \mathbf{J}}{\partial S} \frac{dS}{dt} + \frac{\partial \mathbf{J}}{\partial T} \frac{dT}{dt} \right]$$
(31)

The Ito equation for the *h*-vector can be obtained using Eqs. (20) and (22), as follows:

$$d\mathbf{h} = -\nabla \mathbf{J}^{-1} [\mathbf{J}_{S} \eta_{1} + \mathbf{J}_{T} \gamma_{1}] dt - \nabla \mathbf{J}^{-1} [\mathbf{J}_{S} \sqrt{\eta_{2}} + \mathbf{J}_{T} \sqrt{\gamma_{2}}] dW(t)$$
(32)

where \mathbf{J}_S and \mathbf{J}_T are the partial derivatives of \mathbf{J} with respect to S and T, respectively. Taking expectation of drift and diffusion terms with respect to S, T, nandv would yield fluctuations in \mathbf{h} , such that

$$d\mathbf{h} = \boldsymbol{\omega}_1(\mathbf{h}, t) \, dt + \sqrt{\boldsymbol{\omega}_2(\mathbf{h}, t)} \, d\mathbf{W}(t) \tag{33}$$

 $Nr \le \tilde{h}$

The associated Fokker–Planck equation would give the morphology distribution of crystal nuclei.

$$\frac{\partial f_{\mathbf{h}}(\mathbf{h},t)}{\partial t} + \nabla \cdot \boldsymbol{\omega}_{1} f_{\mathbf{h}}(\mathbf{h},t) = \frac{1}{2} \nabla \nabla : \sqrt{\boldsymbol{\omega}_{2}} \sqrt{\boldsymbol{\omega}_{2}^{\mathrm{T}}} f_{\mathbf{h}}(\mathbf{h},t)$$
(34)

The rate of nucleation is often expressed using the Arrhenius equation

$$\dot{B}(\mathbf{h}) = K_1 \exp\left[-\frac{\Delta G(\mathbf{h}(S))}{\kappa T}\right]$$
(35)

where K_1 is the pre-exponential factor. Eq. (35) can be used to obtain fluctuations in nucleation rate due to supersaturation as

$$d\dot{B} = \zeta_1(\dot{B}, \mathbf{h}, t) dt + \sqrt{\zeta_2(\dot{B}, \mathbf{h}, t)} dW(t)$$
(36)

and the Fokker–Planck equation for the probability density governed by Eqs. (33) and (36) can be used to obtain the nucleation kernel $\Psi(\mathbf{h}, t)$ that will provide initial conditions to the population balance equations.

$$\Psi(\mathbf{h},t) = \int_0^\infty \dot{B}f_{\dot{B},\mathbf{h}}(\dot{B},\mathbf{h},t) \, d\dot{B}$$
(37)

Example 5. Potassium hydrogen phthalate (KAP) crystals are the molecular ionic solids that are used as buffering agents, standards



Fig. 10. Equilibrium morphology of KAP crystal nuclei with {111} faces.



Fig. 11. Size distribution of bi-pyramidal shaped nuclei of KAP crystals.



Fig. 12. Distribution of nucleation rates of KAP crystals at bulk supersaturation and temperature of 3.8513 and 300 K, respectively.

for Total Organic Carbon testing, monochromators and analyzers in X-Ray diffractometers and many other applications. KAP crystallizes in the orthorhombic system with three families of relatively low-energy faces such as {010}, {110} and {111} that are more likely to appear during growth. These three families of faces {010}, {110} and {111} are quantified by their characteristic perpendicular distances h_1, h_2 and h_3 , respectively. The surface energies of $\{010\}, \{110\}$ and $\{111\}$ faces are $0.0760 I/m^2, 0.7934 I/m^2$ and 1.1986 I/m^2 , respectively (Hottenhuis et al., 1988). The multidimensional maximization of Gibbs free energy yields crystals of bi-pyramidal shape (see Fig. 10) formed by {111} faces. The KAP nucleating at bulk supersaturation $S_b = 3.8513$ and bulk temperature \overline{T} = 300 K would be bi-pyramidal shape with size distribution shown in Fig. 11. The mean size of the nuclei is $\overline{h}_3 = 121.75$ nm, which is relatively larger as the contribution of solvent in reducing the surface energies are not considered. The tail region in Fig. 11 will vanish if we consider the metastable zone width in which nucleation does not occur. The corresponding distribution of nucleation rates is given in Fig. 12.

4. Growth rate dispersion in potassium acid phthalate crystals

The growth rate dispersion in crystals are observed as a result of two stochastic processes, firstly the random patterning of kink sites on crystal faces and secondly the fluctuations in supersaturation and temperature. The growth rates of {010}, {110} and {111} faces of KAP in the presence of 0.03 mol% ethylene glycol are experimentally measured by Kuznetsov et al. (1998) and given as

$H_1(\mu m/s) = 0.9078S - 0.9136$	
$\dot{H}_2(\mu m/s) = 1.1920S - 1.1850$	
$\dot{H}_3(\mu m/s) = 2.0620S - 2.0400$	(38)

where \dot{H}_1 , \dot{H}_2 and \dot{H}_3 are the growth rates of {010}, {110} and {111} faces of KAP at $\overline{T} = 300$ K. The growth rate dispersion due to the fluctuations in the supersaturation can be calculated using Eqs. (22) and (38). The nucleation and growth are phenomena of two different length scales viz. nanometers and micrometers, respectively. As the fluctuations due to Brownian motion decreases



Fig. 13. Comparison between experimental measurements and model predictions of standard deviations in growth rates of KAP. The circle, square and diamond markers corresponds to {010}, {110} and {111} faces. The color of markers from light gray to black corresponds to the supersaturation values of 1.01, 1.02, 1.03, 1.04 and 1.05.

monotonically with the volume, the growth rates experience lesser dispersions as compared to nucleation. Fig. 13 shows the comparison between model predictions and experimental measurements (Kuznetsov et al., 1998) of dispersions in the face-specific growth rates at different values of bulk supersaturations. Experimental data (Kuznetsov et al., 1998) shows increase in standard deviation of growth rates at low supersaturation and decrease at higher supersaturation. The model captures this behavior and shows qualitative agreement with the experimental values. However, the model overpredicts some values for {010} faces and under predicts for {110}, which may be due to the competing effects of other stochastic processes such as formation of kink networks and attachment of molecules to kink sites. Nonetheless, the framework of supersaturation fluctuations appears to explain the trend in the observed dispersion in growth rates.

5. Application to population balances

Growth rate dispersion is commonly observed in industrial crystallizers and traditionally modeled with a population balance equation involving an effective diffusive flux. Population balance equation for faceted crystals with dispersion and nucleation terms can be written as

$$\frac{\partial n_{\mathbf{h}}(\mathbf{h},t)}{\partial t} + \nabla \cdot \dot{\mathbf{H}} n_{\mathbf{h}} - \nabla \nabla : \sqrt{D_{\dot{\mathbf{H}}}} \sqrt{D_{\dot{\mathbf{H}}}^{T}} n_{\mathbf{h}} = \Psi(\mathbf{h},t)$$
(39)

where $n_{\rm H}$ is a number density in **h** space, $D_{\rm H}$ is a diagonal matrix of effective diffusion coefficients corresponding to random fluctuations in growth rates and $\Psi(\mathbf{h}, t)$ represents change in number density due to nucleation. The effective diffusion coefficient can be estimated from the Ito equation for the growth rates. Assuming the growth rates are dependent on supersaturation, their Ito equation can be obtained using Eq. (22)

$$d\dot{H}_{i} = \left(\dot{H}_{i}\eta_{1} + \frac{1}{2}\dot{H}_{i}\eta_{2}\right)dt + \dot{H}_{i}\sqrt{\eta_{2}} \,dW(t)$$
(40)

where \dot{H}'_i and \dot{H}''_i are first and second order derivatives of growth rates with respect to supersaturation, respectively. The diffusion

coefficients can be obtained (Ramkrishna, 2000) as

$$D_{\dot{H}_i} = \frac{(\dot{H}_i)^2 \eta_2}{2} \tag{41}$$

The nucleation kernel (37) predicts the size, shape and nucleation rate distribution of crystal nuclei due to supersaturation fluctuations in cooling crystallizers. Here we have derived two important phenomenological quantities such as growth rate dispersion (41) and nucleation kernel (37) from the theory of supersaturation fluctuations, which can be used in predicting crystal size and shape distributions in cooling crystallizers.

6. Conclusions

Dispersions in nucleation and growth are often observed during crystallization and so far they have been dealt with empirically in the literature. This article presents a development of this phenomenon by ascribing it to the local fluctuations in supersaturation. The local fluctuations in supersaturation are driven by the Brownian motion of molecules affecting local number density and temperature. As the primary driving force for the process of adding solute molecules through nucleation and growth is the local supersaturation, their rates tend to fluctuate and yields dispersions under uniform bulk conditions. The fluctuations in nucleation and growth rates are strong functions of local volume which must be chosen appropriately based on the characteristic lengths scales of underlying processes.

The framework presented here consists of a sequential determination of number, temperature and supersaturation fluctuations. Computationally, one can solve Eqs. (9) and (20) to obtain local number n(t) and temperature T(t) profiles and use them to calculate S(t) from Eq. (3). The fluctuations in local number density (or concentration) are driven by the probability after-effect which becomes sluggish with increase in local volume and cause dampening of the fluctuations. The stationary distribution of local number density attains a Poisson distribution and is independent of inter-molecular potentials. The local temperature is a function of mean-square speed of the molecules in the local volume which is governed by the instantaneous local number density. The exponential dependence of saturation concentration with the inverse of temperature, given by Van't Hoff equation, yields the stationary exponential distribution of saturation concentration. The resulting fluctuations in supersaturation follow bimodal distribution where each mode is the signature from the governing distributions of local concentration and saturation concentration. The non-linearity of supersaturation function can create a significant difference between bulk and mean supersaturation. The analysis shows that the mean supersaturation can be as high as 55% more than the bulk supersaturation at fixed conditions. The variance in the supersaturation depends on the variances of the governing distributions and the relative distances between the means of c and c_{sat} . Hence, the variance in supersaturation increases with increase in bulk temperature and bulk concentration. Clearly, the dispersion in crystalline materials can be minimized by operating crystallizers at lower temperatures.

Nucleation and growth of a crystal population in the presence of fluctuating supersaturation would require a parabolic population balance equation as it would contain diffusion terms for growth. This is in contrast to the more usually occurring hyperbolic first order partial differential equation when crystal growth is viewed as deterministic. The identification of such population balance equations requires diffusivity and nucleation kernel to be determined from the supersaturation fluctuations. The nuclei morphology distribution of KAP crystals was determined by multidimensional maximization of Gibbs free energy. The equilibrium morphologies takes bi-pyramidal shape whose sizes qualitatively follow steep exponential distribution. The nucleation kernel derived from Arrhenius law and nuclei morphology distribution can provide the necessary boundary condition for the population balance equation. As direct observation of nuclei morphology distribution is beyond the scope of experimental techniques, the possible way to verify nucleation kernels is through inverse problem as discussed by Mahoney et al. (2002).

The diffusion terms in population balance equations can be determined from the diffusivity in growth rates, for example see Chapter 2 of Ramkrishna (Ramkrishna, 2000). The growth rate dispersion for {010}, {110} and {111} faces of KAP were estimated using the similar framework of supersaturation fluctuations at the length scale of a few micrometers. The model predictions of growth rate dispersion in Fig. 13 show qualitative agreement with experimental measurements. The deviations in model predictions from experimental measurements are maybe due to other competing stochastic effects involved in crystal growth.

The methodology presented here gives a fresh perspective on the dispersion in crystallization processes based on the local fluctuations in supersaturation. However, there could be other stochastic effects such as process of self-assembly of molecules to form nuclei, formation of kink sites on crystal surfaces and attachment of solute molecules to those kink sites that can contribute to the overall dispersion. Comparison of the estimates based on supersaturation fluctuation with available data (Fig. 13), does however show them to be reasonable, providing a direction for minimizing dispersion such as by suitable choice of temperature.

Nomenclature

Δ.	area of ith face of the crystal [m ²]		
Λ _i	area of ith face of the crystal [III]		
$A_n(l, l)$	probability that i molecules will be leaving during time t		
	from the volume v containing <i>n</i> molecules		
	[dimensionless]		
<i>B</i> (h)	nucleation rate [s ⁻¹]		
С	solute concentration [mol m ⁻³]		
C	average solute concentration in volume v [mol m^{-3}]		
Csat	solubility or saturation concentration [mol m^{-3}]		
C_{v}	normalization factor for f_v [m ⁻² s ²]		
d _i	interplanar spacing of the <i>i</i> th lattice plane [m]		
D	diffusion coefficient [m ² s ⁻¹]		
D _{ii}	diagonal matrix of diffusion coefficients D_{μ} of growth		
	rates $[m^2 s^{-1}]$		
E(i, t)	probability that <i>i</i> molecules entered into the volume v		
	during time t [dimensionless]		
E _{att.i}	attachment energy per molecule of the <i>i</i> th slice []		
$f_n(n,t)$	probability density of number <i>n</i> of molecules		
	[dimensionless]		
$f_{\nu}(v,t)$	probability density of speed of molecules $[m^{-1} s]$		
$f_{\nu}(v,t)$	probability density of velocity of molecules $[m^{-3} s^3]$		
$f_{\mathbf{h}}(\mathbf{h},t)$	probability density of h $[m^{-\hat{m}}]$		
$f_{\dot{B}}(\dot{B}, \mathbf{h}, t)$ probability density of \dot{B} and $\mathbf{h} [m^{-\hat{m}} s]$			
$F_{v}(v,t)$	cumulative probability of the speed of molecules		
	[dimensionless]		
F	mean force [J m ⁻¹]		
F	mean force vector [] m ⁻¹]		
ĥ	<i>n̂</i> dimensional vector of perpendicular distances of crys-		
	tal faces from the center [m]		
h	\hat{m} dimensional vector of perpendicular distances of		
	crystal faces from the center [m]		
H _i	growth rate of <i>i</i> th face $[m s^{-1}]$		

J gradient of the free energy change for the formation of crystal nucleus [J m⁻¹]

- ratio of radius of sphere of volume v to the mean squared Κ length traveled by the molecule in time *t* [dimensionless]
- K_1 pre-exponential factor for nucleation rate $[s^{-1}]$
- mass of solute molecule [kg] т
- ŵ number of groups of kinetically and geometrically similar faces [dimensionless]
- number of solute molecules in v [dimensionless] п
- number density of crystals in **h** space $[m^{-\hat{m}}]$ nh
- number of molecules in the unit cell of the lattice nı [dimensionless]
- \overline{n} average number of solute molecules in v [dimensionless]
- number of low-energy faces of crystal [dimensionless] ñ total number of solute molecules in volume V Ν
 - [dimensionless]
- Ν $\hat{n} \times 3$ matrix of normal vectors of crystal faces [dimensionless]
- probability of finding n molecules in v in an infinite pool P_n [dimensionless]
- probability of finding *n* molecules in v in a large pool of $P_{n,N}$ volume V containing N molecules [dimensionless]
- $P_{\mathbf{r}}(\mathbf{r}_2, t | \mathbf{r}_1, 0)$ probability of finding molecule at \mathbf{r}_2 after time t when it was initially at \mathbf{r}_1 [dimensionless]
- probability after-effect [dimensionless] P_t
- position vector of *i*th solute molecule [m] **r**_i
- S supersaturation [dimensionless]
- S average supersaturation in volume v [dimensionless]
- bulk supersaturation, defined as supersaturation at bulk Sb temperature and bulk concentration [dimensionless] t
- time [s] Т temperature [K]
- T average temperature in volume v [K]
- infinitesimal volume [m³] v
- speed of solute molecules $[m s^{-1}]$ v
- v_L volume of the unit cell [m³]
- velocity of *i*th solute molecules [m s⁻¹] Vi
- V total volume containing N solute molecules [m³]
- V_c volume of crystal [m³]
- V_m molecular volume [m³]
- W(t)Wiener process [s^{1/2}]
- vector of independent Wiener processes [s^{1/2}] W(t)
- Z(m, t|n, 0) transition probability that m molecules will be found after time *t* in a volume v with initially *n* molecules in it [dimensionless]
- drift coefficient for number *n* of molecules $[s^{-1}]$ $\alpha_1(n,t)$
- diffusion coefficient for number *n* of molecules $[s^{-1}]$ $\alpha_2(n,t)$
- friction factor $[kg s^{-1}]$ β
- drift coefficient for local temperature T [s^{-1} K] γ_1
- diffusion coefficient for local temperature T [s^{-1} K²] γ_2
- vector of drift coefficients for \mathbf{h} [m s⁻¹] $\boldsymbol{\omega}_1$
- diagonal matrix of diffusion coefficients for $h [m^2 s^{-1}]$ ω_2
- surface free energy per unit area of the *i*th face $[I m^{-2}]$ σ_i
- drift coefficient for local supersaturation $S[s^{-1}]$ η_1
- diffusion coefficient for local temperature $S[s^{-1}]$
- η_2 ζ_1 ζ_2 drift coefficient for nucleation rate $[s^{-2}]$
- diffusion coefficient for nucleation rate [s⁻³]
- Boltzmann constant [] K^{-1}] κ
- $\lambda(k, n)$ transition rates, defined as probability of adding kmolecules per unit time to the volume v containing nmolecules $[s^{-1}]$
- ϕ_{i}^{kink} free energy of kink sites $[J mol^{-1}]$
- Φ potential energy between solute molecules []]
- nucleation kernel $[m^{-\hat{m}} s^{-1}]$ $\Psi(\mathbf{h}, t)$
- ξi normal random number in the range [0, 1] [dimensionless]
- ΔG free energy change per molecule for the formation of a faceted nucleus [J]

dissolution enthalpy $[] mol^{-1}]$ ΔH_{diss} dissolution entropy $[J mol^{-1} K^{-1}]$ ΔS_{diss}

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Appendix A. Distribution of number of molecules in a control volume

Consider a small volume v inside a very large volume V containing N solute molecules. As the solute molecules are uniformly distributed under Brownian motion, the probability of finding a molecule inside v is v/V and outside v is 1 - v/V. Therefore, the probability $P_{n,N}(n)$ that some *n* molecules will be found inside v is a Binomial Distribution such that

$$P_{n,N}(n) = \frac{N!}{n!(N-n)!} \left(\frac{\mathbf{v}}{V}\right)^n \left(1 - \frac{\mathbf{v}}{V}\right)^{N-n}$$
(42)

If the average number of molecules inside v be \overline{n} , then

$$\overline{n} = N(\nu/V) \tag{43}$$

can be used in Eq. (42) to replace v/V with \overline{n}/N , such that

$$P_{n,N}(n) = \frac{N!}{n!(N-n)!} \left(\frac{\overline{n}}{N}\right)^n \left(1 - \frac{\overline{n}}{N}\right)^{N-n}$$
$$= \frac{\overline{n}^n}{n!} \left(1 - \frac{1}{N}\right) \left(1 - \frac{2}{N}\right) \dots \left(1 - \frac{n-1}{N}\right) \left(1 - \frac{\overline{n}}{N}\right)^{N-n}$$
(44)

NT .

As the solution volume V and the number of solute molecules N in it are usually larger than \overline{n} and v, a limiting case would arrive if N and V both tend to infinity in such a way that \overline{n} remains constant.

$$P_n(n) = \lim_{N \to \infty} f_N(n)$$

= $\frac{\overline{n}^n}{n!} \lim_{N \to \infty} \left(1 - \frac{\overline{n}}{N} \right)^{N-n}$ (45)

which leads to a Poisson distribution.

$$P_n(n) = \frac{\overline{n}^n e^{-\overline{n}}}{n!} \tag{46}$$

Therefore the distribution of the number of molecules in a small volume v follows the Poisson distribution with the mean and variance equal to the average number of molecules \overline{n} (Chandrasekhar, 1943). For large values of \overline{n} the distribution of number converges to Gaussian distribution, given as

$$P(n) = \frac{1}{\sqrt{2\pi\overline{n}}} \exp\left[-\frac{(n-\overline{n})^2}{2\overline{n}}\right]$$
(47)

Appendix B. Probability after-effect

Non-interacting molecules

From the diffusion equation we can obtain probability that a molecule will be at \mathbf{r}_2 at time *t* when it was at \mathbf{r}_1 at t = 0 which is given as

$$P_{\mathbf{r}}(\mathbf{r}_{2},t|\mathbf{r}_{1},0) = \frac{1}{(4\pi Dt)^{3/2}} \exp\left[-\frac{|\mathbf{r}_{1}-\mathbf{r}_{2}|^{2}}{4Dt}\right]$$
(48)

where D is the molecular diffusion coefficient. The probability after-effect can be readily obtained by integrating Eq. (48) with respect to \mathbf{r}_1 in v and \mathbf{r}_2 in V - v, as follows:

$$P_{t}(t) = \frac{1}{v} \int_{\mathbf{r}_{1} \in v} \int_{\mathbf{r}_{2} \in V - v} P_{\mathbf{r}}(\mathbf{r}_{2}, t | \mathbf{r}_{1}, 0) \, d\mathbf{r}_{1} \, d\mathbf{r}_{2}$$
$$= \frac{1}{(4\pi D t)^{3/2} v} \int_{\mathbf{r}_{1} \in v} \int_{\mathbf{r}_{2} \in V - v} \exp\left[-\frac{|\mathbf{r}_{1} - \mathbf{r}_{2}|^{2}}{4Dt}\right] \, d\mathbf{r}_{1} \, d\mathbf{r}_{2}$$
(49)

Since the probabilities of finding molecule at \mathbf{r}_2 in v and V - v are mutually exclusive and exhaustive events, we can re-write Eq. (49) as

$$1 - P_t(t) = \frac{1}{(4\pi Dt)^{3/2} v} \int_{\mathbf{r}_1 \in v} \int_{\mathbf{r}_2 \in v} \exp\left[-\frac{|\mathbf{r}_1 - \mathbf{r}_2|^2}{4Dt}\right] d\mathbf{r}_1 \, d\mathbf{r}_2 \tag{50}$$

Using the transformation $\mathbf{x} = \mathbf{r}_1 - \mathbf{r}_2$ and $\mathbf{y} = \mathbf{r}_1 + \mathbf{r}_2$ whose Jacobian has determinant $|J(\mathbf{r}_1, \mathbf{r}_2)| = 1$

$$1 - P_t(t) = \frac{1}{(4\pi Dt)^{3/2} \mathbf{v}} \int_{\mathbf{x}} \int_{\mathbf{y}} \exp\left[-\frac{|\mathbf{x}|^2}{4Dt}\right] \left| J(\mathbf{r}_1, \mathbf{r}_2) \right| \, d\mathbf{x} \, d\mathbf{y}$$

Normalizing and simplifying further would give,

$$P_{t}(t) = 1 - \operatorname{erf}[K(t)] + \frac{2K(t)}{\sqrt{\pi}} \exp[-K(t)^{2}]$$

where, $K(t) = \left(\frac{3v}{4\pi(Dt)^{3/2}}\right)^{1/3}$ (51)

Interacting molecules

The Langevin equation for the velocity of a molecule under potential field is given by Eq. (11). The movement of molecules in viscous medium, which usually is the case with the supersaturated solution, is essentially governed by the diffusion. Under such conditions, the velocity distribution relaxes faster than the position distribution to attain steady-state. At steady-state condition, Eq. (11) on substituting $\mathbf{v}_1 dt = \mathbf{r}_1$ becomes

$$d\mathbf{r}_{1} = -\frac{1}{\beta} \nabla \Phi(\mathbf{r}_{1}, \mathbf{r}_{2}, ..., \mathbf{r}_{N}) dt + \sqrt{D} d\mathbf{W}(t)$$
(52)

since all other particles at $\mathbf{r}_2, \mathbf{r}_3, ..., \mathbf{r}_N$ are uniformly distributed we can approximate the force acting on a particle \mathbf{r}_1 by a mean-field force $F(\mathbf{r}_1)$, such that

$$\mathbf{F}(\mathbf{r}_1) = -\frac{1}{V^{N-1}} \int_{\mathbf{r}_2} \int_{\mathbf{r}_3} \dots \int_{\mathbf{r}_N} \nabla \Phi(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) \, d\mathbf{r}_2 \, d\mathbf{r}_3 \dots d\mathbf{r}_N$$
(53)

Integrating Eq. (52) with respect to $\mathbf{r}_2, \mathbf{r}_3, ..., \mathbf{r}_N$ would give

$$d\mathbf{r}_{1} = \frac{1}{\beta} \mathbf{F}(\mathbf{r}_{1}) dt + \sqrt{D} d\mathbf{W}(t)$$
(54)

The associated Fokker-Planck equation for the Probability Aftereffect under mean potential field is given as

$$\frac{\partial}{\partial t} P_{\mathbf{r}}(\mathbf{r}_1, t) + \frac{1}{\beta} \nabla \cdot \mathbf{F}(\mathbf{r}_1) P_{\mathbf{r}}(\mathbf{r}_1, t) - \frac{D}{2} \nabla^2 P_{\mathbf{r}}(\mathbf{r}_1, t) = 0$$
(55)

Appendix C. Transition probability

The probability $A_n(i, t)$ that *i* molecules will be leaving during time *t* from the volume v containing *n* molecules can be expressed using probability after-effect as

$$A_n(i,t) = \frac{n!}{i!(n-i)!} P_t(t)^i [1 - P_t(t)]^{n-i}$$
(56)

Under equilibrium the a priori probabilities of entrance and emergence of molecules must be equal. The probability E(i, t) that *i* molecules entered into the volume v during time *t* can be written as the expectation of $A_n(i, t)$, such that

$$E(i,t) = \overline{A_n(i,t)} = \sum_{n=1}^{\infty} P_n(n)A_n(i,t)$$
(57)

Substituting Eqs. (4) and (56) above and simplifying would give Poisson distribution of mean and standard deviation $\overline{n}P_t$,

$$E(i,t) = \frac{(\overline{n}P_t)^i e^{-\overline{n}P_t}}{i!}$$
(58)

Now the transition probability Z(n+k,t|n,0) that the *k* molecules will be added into the system during time *t* can be written as

$$Z(n+k,t|n,0) = \sum_{i=0}^{n} A_n(i,t)E(i+k,t)$$
(59)

Similarly, the transition probability of k molecules leaving the system during time t can be written as

$$Z(n-k,t|n,0) = \sum_{i=k}^{n} A_n(i,t)E(i-k,t)$$
(60)

The transition rates are given as the time derivatives of respective transition probabilities such that,

$$\lambda(k, n-k)dt = Z(n, dt|n-k, 0) = \frac{\partial Z(n, t|n-k, 0)}{\partial t}dt$$
$$\lambda(k, n)dt = Z(n+k, dt|n, 0) = \frac{\partial Z(n+k, t|n, 0)}{\partial t}dt$$

which, using Eq. (59), yields

$$\lambda(k,n) = \frac{\partial P_t(t)}{\partial t} \sum_{i=0}^n \left\{ \left[A_n(i,t) E(i+k,t) \right] \left[-\overline{n} - \frac{n-i}{1 - P_t(t)} + \frac{2i+k}{P_t(t)} \right] \right\}$$
(61)

Appendix D. Ito's formula for supersaturation

According to Ito's lemma, a twice differentiable scalar function of a random variable is itself a random variable. Ito's formula relates drift-diffusion processes of a random variable with that of the associated scalar function (Gardiner, 1985). Supersaturation is a scalar function of two random variables n(t) and T(t). According to Ito's formula,

$$dS(t) = \frac{\partial S}{\partial n} dn + \frac{\partial S}{\partial T} dT + \frac{1}{2} \frac{\partial^2 S}{\partial T^2} dT^2$$
(62)

From Eq. (3),

$$dS(t) = \frac{1}{vc_{sat}(T)} dn(t) - S(t) \frac{c_{sat}'(T)}{c_{sat}(T)} dT(t) - \frac{S(t)}{2} \left(\frac{c_{sat}'(T)}{c_{sat}(T)} - 2 \left(\frac{c_{sat}'(T)}{c_{sat}(T)} \right)^2 \right) dT(t)^2$$
(63)

On substituting Eqs. (9) and (20), we get Ito's equation for Supersaturation

$$dS(t) = \left[\frac{\alpha_1}{\mathsf{v}c_{sat}(T)} - S(t)\frac{c_{sat}'(T)}{c_{sat}(T)}\gamma_1 - S(t)\left(\frac{c_{sat}'(T)}{2c_{sat}(T)} - \left(\frac{c_{sat}'(T)}{c_{sat}(T)}\right)^2\right)\gamma_2\right]dt + \left[\frac{\sqrt{\alpha_2}}{\mathsf{v}c_{sat}(T)} - S(t)\frac{c_{sat}'(T)}{c_{sat}(T)}\sqrt{\gamma_2}\right]dW(t)$$
(64)

Therefore the expected value of drift and diffusion terms of supersaturation is given as

$$\eta_{1} = \iiint \left[\frac{\alpha_{1}}{\mathsf{v}c_{sat}(T)} - S(t) \frac{c_{sat}'(T)}{c_{sat}(T)} \gamma_{1} - S(t) \left(\frac{c_{sat}'(T)}{2c_{sat}(T)} - \left(\frac{c_{sat}'(T)}{c_{sat}(T)} \right)^{2} \right) \gamma_{2} \right]$$

$$\times f_{n} dn f_{T} dT f_{v} dv$$

$$\eta_{2} = \iiint \left[\frac{\sqrt{\alpha_{2}}}{\mathsf{v}c_{sat}(T)} - S(t) \frac{c_{sat}'(T)}{c_{sat}(T)} \sqrt{\gamma_{2}} \right]^{2} f_{n} dn f_{T} dT f_{v} dv$$
(65)

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