

RESEARCH ARTICLE

A complete analytical solution to the integro-differential model describing the nucleation and evolution of ellipsoidal particles

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In this paper, a complete analytical solution to the integro-differential model describing the nucleation and growth of ellipsoidal crystals in a supersaturated solution is obtained. The asymptotic solution of the model equations is constructed using the saddle-point method to evaluate the Laplace-type integral. Numerical simulations carried out for physical parameters of real solutions show that the first four terms of the asymptotic series give a convergent solution. The developed theory was compared with the experimental data on desupersaturation kinetics in proteins. It is shown that the theory and experiments are in good agreement.

KEYWORDS:

integro-differential equations, saddle-point method, phase transformations, supersaturated solutions, applied mathematical modeling

1 | INTRODUCTION

The processes of phase transformations from a metastable liquid state of matter to a solid state underlie many technological processes and natural phenomena.^{1–11} Therefore, the establishment of laws governing such processes is an important practical task that allows one to control the microstructure and properties of solid materials by changing the physical and operational parameters of the phase transformation process. When a substance crystallizes from a highly supersaturated or supercooled liquid, there is a bulk phase transformation associated with nucleation and subsequent growth of solid particles. As this takes place at the intermediate stage of the phase transformation, the nucleating particles are far enough away from each other and can therefore be considered as non-interacting.

Mathematical models of such processes consist of integrodifferential kinetic and balance equations and corresponding boundary and initial conditions. In addition, the boundaries of growing crystals move with time. This means that, in general, the mathematical model of the phase transformation process is also a problem with a moving boundary.^{12–14} This means that there are no general methods for solving such problems, and each individual model requires the development of special approximate approaches to its solution. In the last decade, significant progress has been made in the mathematical description of bulk nucleation and growth of spherical crystals. For example, a solution of such a problem for the first-order kinetic equation was constructed in a series of papers.^{15–19} A generalization of the theory to fluctuations in crystal growth rates leading to the kinetic equation of the second order was made in works.^{19–23} A theory taking into account the runoff of product crystals in the kinetic equation and the presence of external sources in the balance equations was developed in references.^{24–27} However, as is shown in experimental works,^{28–33} the shape of nucleating and growing crystals is not always spherical. To account for the non-sphericity of particles, a natural step in the development of the theory is to use an approximation about their ellipsoidal shape. This paper develops a theory of bulk nucleation and growth of a polydisperse ensemble of ellipsoidal particles in supersaturated solutions.

2 | GROWTH RATES OF ELLIPSOIDAL PARTICLES

Let us begin our analysis of the problem by considering the law of growth rate of an individual ellipsoidal particle in a super-saturated solution. For the sake of certainty and simplicity of reasoning everywhere in the article, we will assume that growing particles keep the shape of their ellipsoidal surface, which is also an isoconcentration surface. In addition, when considering the intermediate stage of phase transformation, we will neglect the interaction between neighboring ellipsoidal crystals (such an interaction should be taken into account only at the final stage of the process). Let us describe the growth of each particle (crystal) in a special curvilinear coordinate system of a prolate ellipsoid of revolution (figure 1). It is important that the ellipsoidal surface is defined by a constant value of the variable σ in this coordinate system.

The Cartesian x, y, z and ellipsoidal σ, τ, φ coordinates are related as follows³⁴

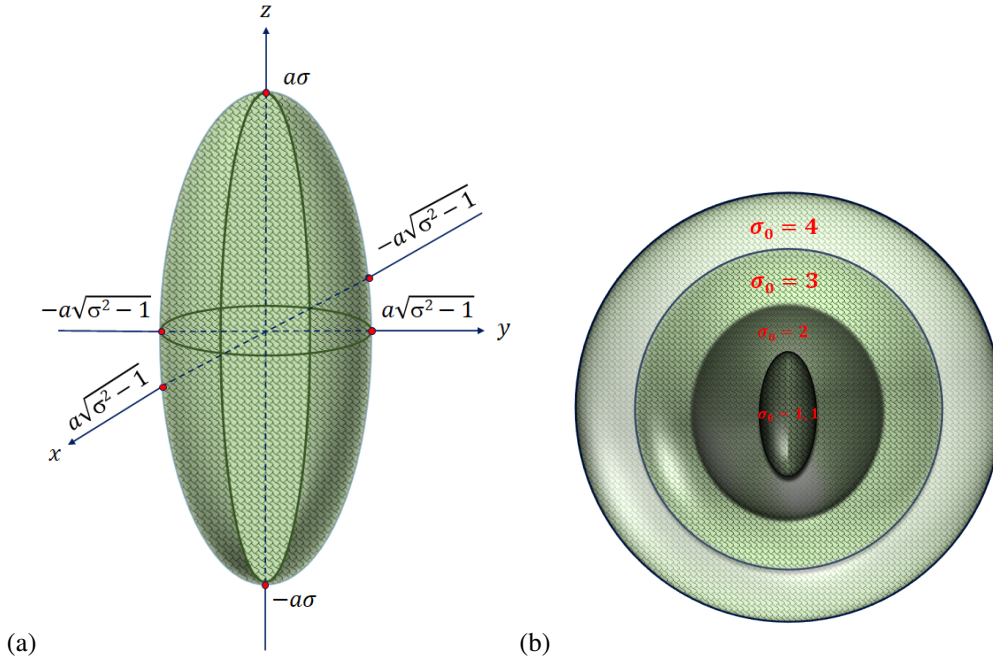


FIGURE 1 An ellipsoidal particle illustrated in the prolate ellipsoid of revolution reference frame (a). Various surfaces $\sigma = \sigma_0$ of evolving ellipsoidal crystals (b).

$$\begin{aligned} x^2 &= a^2 (\sigma^2 - 1) (1 - \tau^2) \cos^2 \varphi, \\ y^2 &= a^2 (\sigma^2 - 1) (1 - \tau^2) \sin^2 \varphi, \\ z &= a\sigma\tau. \end{aligned} \quad (1)$$

Here a describes the size of ellipsoidal crystals, $\sigma \geq 1$, $-1 \leq \tau \leq 1$, and $0 \leq \varphi \leq 2\pi$.

To switch to curvilinear coordinates in the mass transfer equation, as well as the boundary condition, we need the Lamé parameters

$$H_\sigma = a\sqrt{\frac{\sigma^2 - \tau^2}{\sigma^2 - 1}}, \quad H_\tau = a\sqrt{\frac{\sigma^2 - \tau^2}{1 - \tau^2}}, \quad H_\varphi = a\sqrt{(\sigma^2 - 1)(1 - \tau^2)}. \quad (2)$$

For simplicity of analysis, we will use the assumption of quasi-stationarity of the concentration field around the growing ellipsoidal crystal. This approach agrees with the previously developed theory of spherical crystal growth in quasi-stationary fields of temperature and concentration of dissolved impurity.³⁵⁻³⁹ Taking this into account, it is important to note that the particle growth rate is given by the mass balance condition on the crystal surface, and the equation of impurity diffusion in the liquid is written in quasi-stationary approximation $\nabla^2 C = 0$, where C represents the impurity concentration. Taking into account that the

impurity concentration in the curvilinear coordinate system depends only on the distance σ from the surface of the ellipsoidal crystal, let us write down the diffusion equation in the form of

$$\frac{d}{d\sigma} \left((\sigma^2 - 1) \frac{dC}{d\sigma} \right) = 0. \quad (3)$$

It is also important to emphasize that the impurity diffusion inside the solid particle is neglected. Keeping this in mind, we come to the mass balance boundary condition at the solid/liquid interface (at $\sigma = \sigma_0$)

$$(1 - k_0)CV_n = -D\nabla C \cdot \mathbf{n}, \quad (4)$$

where k_0 is the partition coefficient (the constant ratio of concentration in the solid and liquid phases at the crystal surface), D is the diffusion coefficient, \mathbf{n} is the normal vector directed towards the supersaturated solution, and V_n is the normal velocity of crystal growth.

The normal velocity V_n can be represented through the growth rate of solid/liquid interface $\dot{\sigma}_0$ in the form of $V_n = H_\sigma \dot{\sigma}_0$. Combining this expression with the mass balance condition (4) and taking into account expressions (2), we have

$$\dot{\sigma} = -\frac{D}{(1 - k_0)a^2C} \frac{\partial C}{\partial \sigma} = \frac{\beta_*}{a} (C - C_p), \quad \sigma = \sigma_0, \quad (5)$$

where β_* and C_p represent the kinetic coefficient and the concentration at saturation. Let us especially emphasize that the second equality (5) defines the growth rate of solid/liquid interface as a function of driving force $C - C_p$.

To close the problem, the impurity concentration in the liquid phase away from the growing crystal must be assumed to be known

$$C \rightarrow C_l, \quad \sigma \gg 1. \quad (6)$$

Leaving trivial mathematical manipulations aside, let us write down the final solution to the problem (3)-(6) of ellipsoidal particle growth in a supersaturated solution as⁴⁰

$$C(\sigma) = C_l + C_3 \ln \left(\frac{\sigma - 1}{\sigma + 1} \right), \quad \dot{\sigma}_0 = \frac{\beta_*}{a} \left[\Delta C + C_3 \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) \right], \quad (7)$$

where C_3 satisfies the quadratic equation

$$\ln^2 \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) C_3^2 + b_0 C_3 + C_l \Delta C = 0, \\ b_0 = (C_l + \Delta C) \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) + \frac{2D}{a\beta_*(1 - k_0)(\sigma_0^2 - 1)},$$

and $\Delta C = C_l - C_p$ is the supersaturation.

Keeping in mind the expressions for ellipsoidal semiaxes $a\sqrt{\sigma_0^2 - 1}$ and $a\sigma_0$ (see also figure 1), we come to the crystal volume V and its growth rate dV/dt in the form of

$$V = \frac{4}{3}\pi a^3 (\sigma_0^2 - 1) \sigma_0, \quad \frac{dV}{dt} = \frac{4}{3}\pi a^3 (3\sigma_0^2 - 1) \dot{\sigma}_0. \quad (8)$$

An important point is that $\dot{\sigma}_0$ is a function of σ_0 and ΔC , i.e. $\dot{\sigma}_0 = \dot{\sigma}_0(\sigma_0, \Delta C)$. Moreover, as follows from formula (8), $\sigma_0 = \sigma_0(V)$ is given by a cubic equation

$$\sigma_0^3 - \sigma_0 - \frac{3V}{4\pi a^3} = 0. \quad (9)$$

By this is meant that dV/dt from (8) is a function of V and ΔC

$$\frac{dV}{dt} = \frac{4}{3}\pi a^3 [3\sigma_0^2(V) - 1] \dot{\sigma}_0(\sigma_0(V), \Delta C). \quad (10)$$

It is significant that formulas (9) and (10) also describe the evolution of spherical particles in the asymptotic case $\sigma_0 \gg 1$.

To demonstrate the nonlinear dependence (10) for the volume growth rate as a function of the current volume V and supersaturation ΔC , we use the following dimensionless variables

$$V_1 = \frac{3V}{4\pi a^3}, \quad w = \frac{\Delta C}{\Delta C_0}, \quad t_1 = \frac{\beta_* \Delta C_0 t}{a}, \quad (11)$$

where $\Delta C_0 = C_0 - C_p$, and C_0 is the initial value of impurity concentration C_l .

Combining (10) and (11), we arrive at

$$G_R(w, V_1) = \frac{dV_1}{dt_1} = (3\sigma_0^2 - 1) \left[w + \frac{C_3}{\Delta C_0} \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) \right], \quad (12)$$

where $\sigma_0(V_1)$ is given by the cubic equation $\sigma_0^3 - \sigma_0 - V_1 = 0$ following from (9).

Let us also especially note that

$$\frac{C_3}{\Delta C_0} = \frac{-b_0/\Delta C_0 \pm \sqrt{D_1/\Delta C_0^2}}{2 \ln^2 \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right)}, \quad \frac{b_0}{\Delta C_0} = \left(2w + \frac{C_p}{\Delta C_0} \right) \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) + \frac{1}{\beta_{**}(\sigma_0^2 - 1)},$$

$$\frac{D_1}{\Delta C_0^2} = \left(\frac{b_0}{\Delta C_0} \right)^2 - 4 \ln^2 \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) w, \quad \beta_{**} = \frac{a\beta_*(1 - k_0)\Delta C_0}{2D}.$$

As is easily seen from figure 2, the dimensionless volume growth rate G_R of an ellipsoidal particle increases with increasing the current volume V_1 and liquid supersaturation w . Note that this behavior of particle growth rate in a supersaturated solution is similar to the bulk crystallization in a supercooled melt.⁴¹

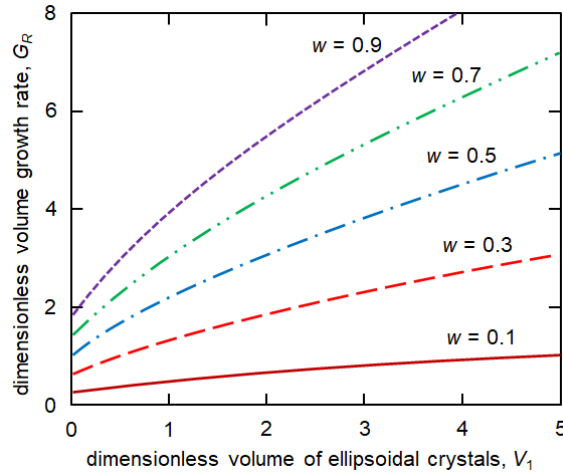


FIGURE 2 The dimensionless rate G_R as a function of crystal volume V_1 at fixed values of dimensionless supersaturation w . The system parameters are estimated as follows^{39,42} $C_p/\Delta C_0 = 2$, $\beta_{**} = 0.01$.

3 | GOVERNING EQUATIONS

In this section, we consider the nonlinear dynamics of growth of a polydisperse ensemble of crystals in a supersaturated solution neglecting fluctuations in their growth rates, i.e. neglecting the diffusion term in the kinetic equation. We will consider the initial metastable state of the system defined by supersaturation ΔC_0 at time $t = 0$. We will also assume that only those nucleated particles are capable of further evolution whose volume exceeds a fixed critical value V_* . In other words, this means that if a particle of smaller volume than the critical one appears in the metastable solution, such a particle dissolves. Whereas when a particle volume exceeds the critical one (or equal to the critical volume), such a particle evolves. Thus, the supersaturated

solution turns out to be filled with particles of different volumes at different moments of the crystallization process. In addition, we assume that the density of such polydisperse crystals in the metastable solution is small and any interaction between the particles can be neglected. Note that as the particles grow, they absorb the impurity dissolved in the liquid, thereby lowering its supersaturation (metastability degree) $\Delta C = C_l - C_p$.

The particle-volume distribution function $f(V, t)$ in the metastable liquid satisfies the Fokker-Planck type kinetic equation, which in the absence of particle fluctuations, their withdrawal from the solution and the inflow of additional mass has the form

$$\frac{\partial f}{\partial t} + \frac{\partial}{\partial V} \left(\frac{dV}{dt} f \right) = 0, \quad V > V_*, \quad t > 0, \quad (13)$$

where t and V are the time and volume variables.

As this takes place, the transient behavior of supersaturation ΔC satisfies the mass balance law, which reads as^{43,44}

$$\Delta C(t) = \Delta C_0 - K \int_{V_*}^{\infty} V f(V, t) dV, \quad t > 0, \quad (14)$$

where $K = C_p$ denotes the concentration at saturation.

The governing integro-differential equations (13) and (14) should be supplemented with the following initial and boundary conditions

$$f(V, 0) = 0, \quad \Delta C(0) = \Delta C_0, \quad t = 0, \quad (15)$$

$$\frac{dV}{dt} f = I(\Delta C), \quad V = V_*, \quad (16)$$

where $I = I(\Delta C)$ stands for the nucleation frequency or rate. Considering two frequently met nucleation kinetics (the Weber-Volmer-Frenkel-Zel'dovich or WVFZ and Meirs kinetics), we arrive at^{15,20,44,45}

$$I(\Delta C) = \begin{cases} I_* \exp[-p \ln^{-2}(C_l/C_p)], & \text{WVFZ} \\ I_* (\Delta C)^p, & \text{Meirs} \end{cases},$$

where I_* and p are assumed to be constants. It seems important to note that condition (16) defines the flux of crystals crossing the energy barrier of nucleation.

Thus, the model under study for the nucleation and growth of ellipsoidal (as well as spherical) particles in a supersaturated solution consists of a closed system of equations, initial and boundary conditions (13)-(16). Note that the crystal growth rate dV/dt , which is a function of V and ΔC , is described by formula (10).

The model (13)-(16) corresponds to the case of a phase transformation in supercooled single-component melts.^{15,20,44,45} When considering such systems, the concentration of the dissolved impurity must be replaced by the supercooled liquid temperature. In addition, it is also necessary to change the law (10) of particle growth to the law of growth in supercooled melts due to the fact that the law of single crystal growth in supersaturated solutions and in supercooled melts is described by different mathematical models with moving boundaries. The difference between such models consists of the different form of mass and heat balance conditions at the phase transition interfaces of evolving particles.^{15,35,38,46-48}

4 | ANALYTICAL SOLUTIONS

It is convenient to find the solution of the problem in dimensionless form, using the following formulas

$$\begin{aligned} \tau = \frac{t}{t_0}, \quad s = \frac{V}{V_0}, \quad w(\tau) = \frac{\Delta C(t)}{\Delta C_0}, \quad F(s, \tau) = V_0^2 f(V, t), \quad V_0 = \left(\frac{\beta_* \Delta C_0}{I_0} \right)^{3/4}, \\ I_0 = I(\Delta C_0), \quad t_0 = (\beta_*^3 \Delta C_0^3 I_0)^{-1/4}, \quad \frac{V_0}{t_0} = \frac{(\beta_* \Delta C_0)^{3/2}}{I_0^{1/2}}, \quad s_* = \frac{V_*}{V_0}, \quad \xi = \frac{K}{\Delta C_0}. \end{aligned} \quad (17)$$

Here τ and s are the dimensionless time and volume variables, w is the dimensionless supersaturation, and F is the dimensionless particle-volume distribution function.

The integro differential model (10), (13)-(16) can be written out using expressions (17) as

$$\frac{\partial F}{\partial \tau} + \frac{\partial}{\partial s} \left(\frac{ds}{d\tau} F \right) = 0, \quad s > s_*, \quad \tau > 0, \quad (18)$$

$$w = 1 - \xi \int_{s_*}^{\infty} s F ds, \quad \tau > 0, \quad (19)$$

$$\frac{ds}{d\tau} = \Psi(s)w, \quad \Psi(s) = \frac{4\pi a^2}{3V_0^{2/3}}(3\sigma_0^2 - 1) \left[1 - \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) \beta_{**}(\sigma_0^2 - 1) \right], \quad (20)$$

$$F = 0, \quad w = 1, \quad \tau = 0, \quad (21)$$

$$F = \frac{\exp[p g(w)]}{\Psi(s_*)w}, \quad s = s_*. \quad (22)$$

It is important to note that the following approximations were used in deriving the growth rate (20)

$$\left(\frac{b_0}{\Delta C_0} \right)^2 \gg 4 \ln^2 \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right) w, \quad \frac{1}{\beta_{**}(\sigma_0^2 - 1)} \gg \left(2w + \frac{C_p}{\Delta C_0} \right) \ln \left(\frac{\sigma_0 - 1}{\sigma_0 + 1} \right).$$

These approximations follow from the estimates of the characteristic parameters for protein and insulin crystals^{39,42} and our computations illustrated in figure 2 .

Also note that $\sigma_0 = \sigma_0(s)$ entering in formulas (20) is defined as

$$\sigma_0^3(s) - \sigma_0(s) - bs = 0, \quad b = \frac{3V_0}{4\pi a^3}, \quad a^3 = mV_*, \quad (23)$$

where m is constant.

It is significant to highlight that the function $g(w)$ entering in (22) depends on the rate of particle nucleation. Paying our attention to the aforementioned expressions for $I(\Delta C)$, we have^{15,35,44}

$$g(w) = \ln^{-2} \left(1 + \frac{1}{w_p} \right) - \ln^{-2} \left(1 + \frac{w}{w_p} \right), \quad (\text{WVFZ}); \quad g(w) = \ln w \quad (\text{Meirs}), \quad (24)$$

where $w_p = C_p/\Delta C_0$.

It is significant to emphasize that formulas (18)-(24) also characterize the growth of a polydisperse ensemble of spherical particles at large values of σ_0 . Indeed, paying our attention to this crystallization scenario, we get ($\sigma_0 \gg 1$)

$$\sigma_0(s) = (bs)^{1/3}, \quad \Psi(s) = Gs^{2/3}, \quad G = 4\pi \left(\frac{3}{4\pi} \right)^{2/3}. \quad (25)$$

Note that the following theory developed for ellipsoidal particles can be compared with the case of spherical particles based on the formula (25).

Taking expressions (21) and (22) into account let us write out the solution to the Fokker-Planck equation (18) in the form of

$$F(s, \tau) = \frac{\exp[p g(w(x-y))]}{w(x-y)\Psi(s)} \eta(x(\tau) - y(s)), \quad (26)$$

where

$$x(\tau) = \int_0^\tau w(\tau_1) d\tau_1, \quad y(s) = \int_{s_*}^s \frac{ds_1}{\Psi(s_1)}. \quad (27)$$

Here x and y represent the modified time and volume variables, and $\eta(\cdot)$ is the Heaviside function.

Now we reformulate the mass balance condition (19) by means of substitution $x(v) = x(\tau) - y(s)$.^{15,18} Taking $ds/\Psi(s) = -wdv$ into account, we get

$$w(\tau) = 1 - \xi \int_0^\tau s(\tau, v) \exp[p g(w(v))] dv, \quad \tau > 0, \quad (28)$$

where $s(\tau, \nu)$ is described by expression (20). Moreover, let us highlight that $s = s_*$ if $\nu = \tau$ and $s = s_m$ if $\nu = 0$ (s_m represents the maximal volume of ellipsoidal crystals that nucleated at the initial moment). Combining formulas (20) and (27), we obtain

$$\int_{s_*}^{s(\tau, \nu)} \frac{ds_1}{\Psi(s_1)} = \int_{\nu}^{\tau} w(\tau_1) d\tau_1 = x(\tau) - x(\nu). \quad (29)$$

Let us note that the right-hand side of equation (28) depends on w . It means that the mass balance (28) is the integral equation for the determination of metastability degree w . Let us use below the saddle-point technique^{18,49} to find an asymptotic solution to this equation in series.

To do this, we note that $dg/d\nu < 0$ for both nucleation kinetics under consideration (see formulas (24)). Indeed, w decreases when time increases and $dg/d\nu = 2w_p^{-1} \ln^{-3}(1 + w/w_p) dw/d\nu$ (WVZ) and $dg/d\nu = w^{-1} dw/d\nu$ (Meirs). Keeping this in mind we conclude that $g(\nu)$ attains its maximum at $\nu = 0$.

Noting now that $dw/d\nu$ at $\nu = 0$ is nonzero and considering the case of large Gibbs numbers $p \gg 1$, we get^{18,49}

$$w(\omega) = 1 - \frac{\xi}{p} \sum_{k=0}^{\infty} a_k(\omega) p^{-k}, \quad \omega = s(\tau, 0), \quad (30)$$

$$a_k(\omega) = \frac{(-1)^{k+1}}{k!} \Gamma(k+1) \left(h(\nu) \frac{d}{d\nu} \right)^k (s(\tau, \nu) h(\nu))_{\nu=0}, \quad h(\nu) = \frac{1}{g'(\nu)},$$

where $\omega = s_m = s(\tau, 0)$ defines the maximal volume of particles, $\Gamma(\cdot)$ is the gamma function. Also, we note that the ν -derivatives of the function $s(\tau, \nu)$ at $\nu = 0$ are the definite functions of ω . In addition, we have the integral equation for ω

$$\int_{s_*}^{\omega} \frac{ds_1}{\Psi(s_1)} = x(\tau) = \int_0^{\tau} w(\tau_1) d\tau_1. \quad (31)$$

The modified time variable τ can be expressed in terms of ω too. Taking (20) and (29) into account one can get

$$\tau(\omega) = \int_0^{\omega} \frac{d\omega_1}{\Psi(\omega_1) w(\omega_1)}. \quad (32)$$

It is significant to emphasize that the analytical solutions (26), (30)-(32) are constructed in a parametric form (with parameter ω). From a practical point of view, to illustrate the solution found, we need to enter the i -th approximation of the solution as follows

$$w(\omega) = w_i(\omega) = 1 - \frac{\xi}{p} \sum_{k=0}^i a_k(\omega) p^{-k}, \quad \tau(\omega) = \tau_i(\omega) = \int_0^{\omega} \frac{d\omega_1}{\Psi(\omega_1) w_i(\omega_1)}. \quad (33)$$

Note that if $i = 0$, we have the main contributions w_0 and τ_0 to the infinite series (33), if $i = 1$, the first corrections are added to the main solution, and so on. The obtained solution will converge if adding the next contribution does not change the solution in its absence.

Expressions (30) lead us to the following coefficients a_k to explicitly define first four contributions to the asymptotic solution

$$\begin{aligned} a_0(\omega) &= -\frac{\omega}{g'(0)}, \quad a_1(\omega) = \frac{\Gamma(2)}{g'(0)} \left[\frac{1}{g'(0)} \left(\frac{\partial s}{\partial \nu} \right)_{\nu=0} - \frac{\omega g''(0)}{g'^2(0)} \right], \\ a_2(\omega) &= -\frac{\Gamma(3)}{2g'^2(0)} \left\{ \frac{1}{g'(0)} \left(\frac{\partial^2 s}{\partial \nu^2} \right)_{\nu=0} - 2 \frac{g''(0)}{g'^2(0)} \left(\frac{\partial s}{\partial \nu} \right)_{\nu=0} + \omega \left[\frac{2g''^2(0)}{g'^3(0)} - \frac{g'''(0)}{g'^2(0)} \right] \right\}, \\ a_3(\omega) &= \frac{\Gamma(4)}{6g'^3(0)} \left\{ \frac{1}{g'(0)} \left(\frac{\partial^3 s}{\partial \nu^3} \right)_{\nu=0} - 3 \frac{g''(0)}{g'^2(0)} \left(\frac{\partial^2 s}{\partial \nu^2} \right)_{\nu=0} \right. \\ &\quad \left. + 3 \left[\frac{2g''^2(0)}{g'^3(0)} - \frac{g'''(0)}{g'^2(0)} \right] \left(\frac{\partial s}{\partial \nu} \right)_{\nu=0} + \omega \left[\frac{6g''(0)g'''(0)}{g'^3(0)} - \frac{6g''^3(0)}{g'^4(0)} - \frac{g^{(4)}(0)}{g'^2(0)} \right] \right\}. \end{aligned} \quad (34)$$

The derivatives at $\nu = 0$ entering in (34) can be found from formulas (24) for the WVFZ and Meirs kinetics as

$$\begin{aligned}
 g'(0) &= \kappa_1 \left(\frac{dw}{d\nu} \right)_{\nu=0}, \quad g''(0) = -\kappa_2 \left(\frac{dw}{d\nu} \right)_{\nu=0}^2 + \kappa_1 \left(\frac{d^2w}{d\nu^2} \right)_{\nu=0}, \\
 g'''(0) &= \kappa_3 \left(\frac{dw}{d\nu} \right)_{\nu=0}^3 - 3\kappa_2 \left(\frac{dw}{d\nu} \right)_{\nu=0} \left(\frac{d^2w}{d\nu^2} \right)_{\nu=0} + \kappa_1 \left(\frac{d^3w}{d\nu^3} \right)_{\nu=0}, \\
 g^{(4)}(0) &= -6\kappa_4 \left(\frac{dw}{d\nu} \right)_{\nu=0}^4 + 6\kappa_3 \left(\frac{dw}{d\nu} \right)_{\nu=0}^2 \left(\frac{d^2w}{d\nu^2} \right)_{\nu=0} - 3\kappa_2 \left(\frac{d^2w}{d\nu^2} \right)_{\nu=0}^2 \\
 &\quad - 4\kappa_2 \left(\frac{dw}{d\nu} \right)_{\nu=0} \left(\frac{d^3w}{d\nu^3} \right)_{\nu=0} + \kappa_1 \left(\frac{d^4w}{d\nu^4} \right)_{\nu=0}, \quad (35) \\
 \kappa_1 &= \begin{cases} \frac{2 \ln^{-3} \zeta}{1 + w_p}, & \text{WVFZ} \\ 1, & \text{Meirs} \end{cases}, \quad \kappa_2 = \begin{cases} \frac{6 \ln^{-4} \zeta + 2 \ln^{-3} \zeta}{(1 + w_p)^2}, & \text{WVFZ} \\ 1, & \text{Meirs} \end{cases}, \\
 \kappa_3 &= \begin{cases} \frac{24 \ln^{-5} \zeta + 18 \ln^{-4} \zeta + 4 \ln^{-3} \zeta}{(1 + w_p)^3}, & \text{WVFZ} \\ 2, & \text{Meirs} \end{cases}, \quad \kappa_4 = \begin{cases} \frac{20 \ln^{-6} \zeta + 24 \ln^{-5} \zeta + 11 \ln^{-4} \zeta + 2 \ln^{-3} \zeta}{(1 + w_p)^4}, & \text{WVFZ} \\ 1, & \text{Meirs} \end{cases},
 \end{aligned}$$

where $\zeta = 1 + w_p^{-1}$. Here the derivatives of $w(\nu)$ at $\nu = 0$ can be found from the integral equation (28). Keeping in mind that $s(\tau, \tau) = s_*$, we obtain

$$\begin{aligned}
 \left(\frac{dw}{d\nu} \right)_{\nu=0} &= -\xi s_*, \quad \left(\frac{d^2w}{d\nu^2} \right)_{\nu=0} = \xi^2 s_*^2 p \left(\frac{dg}{dw} \right)_{w=1} - \xi \Psi(s_*), \quad \left(\frac{d^3w}{d\nu^3} \right)_{\nu=0} = 2\xi^2 s_* \Psi(s_*) \\
 &\quad - \xi \Psi(s_*) \Psi'(s_*) - 2\xi^3 s_*^3 p^2 \left(\frac{dg}{dw} \right)_{w=1}^2 - \xi^3 s_*^3 p \left(\frac{d^2g}{dw^2} \right)_{w=1} + 2\xi^2 s_* p \Psi(s_*) \left(\frac{dg}{dw} \right)_{w=1}, \\
 \left(\frac{d^4w}{d\nu^4} \right)_{\nu=0} &= \xi^4 s_*^4 p \left(\frac{d^3g}{dw^3} \right)_{w=1} + 6\xi^4 s_*^4 p^3 \left(\frac{dg}{dw} \right)_{w=1}^3 + 7\xi^4 s_*^4 p^2 \left(\frac{dg}{dw} \right)_{w=1} \left(\frac{d^2g}{dw^2} \right)_{w=1} \\
 &\quad - 7\xi^3 s_*^3 p^2 \Psi(s_*) \left(\frac{dg}{dw} \right)_{w=1}^2 - 4\xi^3 s_*^2 p \Psi(s_*) \left(\frac{d^2g}{dw^2} \right)_{w=1} - 8\xi^3 s_*^2 p \Psi(s_*) \left(\frac{dg}{dw} \right)_{w=1} \\
 &\quad + 2\xi^2 s_* p \Psi(s_*) \Psi'(s_*) \left(\frac{dg}{dw} \right)_{w=1} + 3\xi^2 \Psi^2(s_*) + \xi^2 p \Psi^2(s_*) \left(\frac{dg}{dw} \right)_{w=1} \\
 &\quad + 5\xi^2 s_* \Psi(s_*) \Psi'(s_*) - \xi \Psi^2(s_*) \Psi''(s_*) - \xi \Psi(s_*) \Psi'^2(s_*).
 \end{aligned}$$

Here the derivatives of $g(w)$ at $w = 1$ can be calculated from formulas (24) as

$$\left(\frac{dg}{dw} \right)_{w=1} = \begin{cases} 2w_p^{-1} \ln^{-3} \zeta, & \text{WVFZ} \\ 1, & \text{Meirs} \end{cases}, \quad \left(\frac{d^2g}{dw^2} \right)_{w=1} = \begin{cases} -6w_p^{-2} \ln^{-4} \zeta, & \text{WVFZ} \\ -1, & \text{Meirs} \end{cases}, \quad \left(\frac{d^3g}{dw^3} \right)_{w=1} = \begin{cases} 24w_p^{-3} \ln^{-5} \zeta, & \text{WVFZ} \\ 2, & \text{Meirs} \end{cases}.$$

Also note that the derivatives of $s(\tau, \nu)$ at $\nu = 0$ in formulas (34) are defined in the form of

$$\begin{aligned}
 \left(\frac{\partial s}{\partial \nu} \right)_{\nu=0} &= -\Psi(\omega), \quad \left(\frac{\partial^2 s}{\partial \nu^2} \right)_{\nu=0} = \Psi(\omega) (\xi s_* + \Psi'(\omega)), \\
 \left(\frac{\partial^3 s}{\partial \nu^3} \right)_{\nu=0} &= \Psi(\omega) \left[\xi \Psi(s_*) - \xi^2 s_*^2 p \left(\frac{dg}{dw} \right)_{w=1} - 3\xi s_* \Psi'(\omega) - \Psi(\omega) \Psi''(\omega) - \Psi'^2(\omega) \right]. \quad (36)
 \end{aligned}$$

Now all coefficients entering in dimensionless supersaturation (33) are found. An important point is that the fundamental solution $w_0(\omega)$ is the same for spherical and ellipsoidal particles. The remaining summands are found using formulas (34)-(36). Let us write down the four main summands in (33) as

$$\begin{aligned}
 w_0(\omega) &= 1 - \frac{\omega}{\kappa_1 s_* p}, \quad w_1(\omega) = w_0(\omega) - \frac{\xi a_1(\omega)}{p^2}, \\
 w_2(\omega) &= w_1(\omega) - \frac{\xi a_2(\omega)}{p^3}, \quad w_3(\omega) = w_2(\omega) - \frac{\xi a_3(\omega)}{p^4}. \quad (37)
 \end{aligned}$$

Let us especially emphasize that the constructed solutions are valid for large values of the dimensionless Gibbs number p . Therefore, the convergence of the asymptotic solution (37) increases with increasing p .

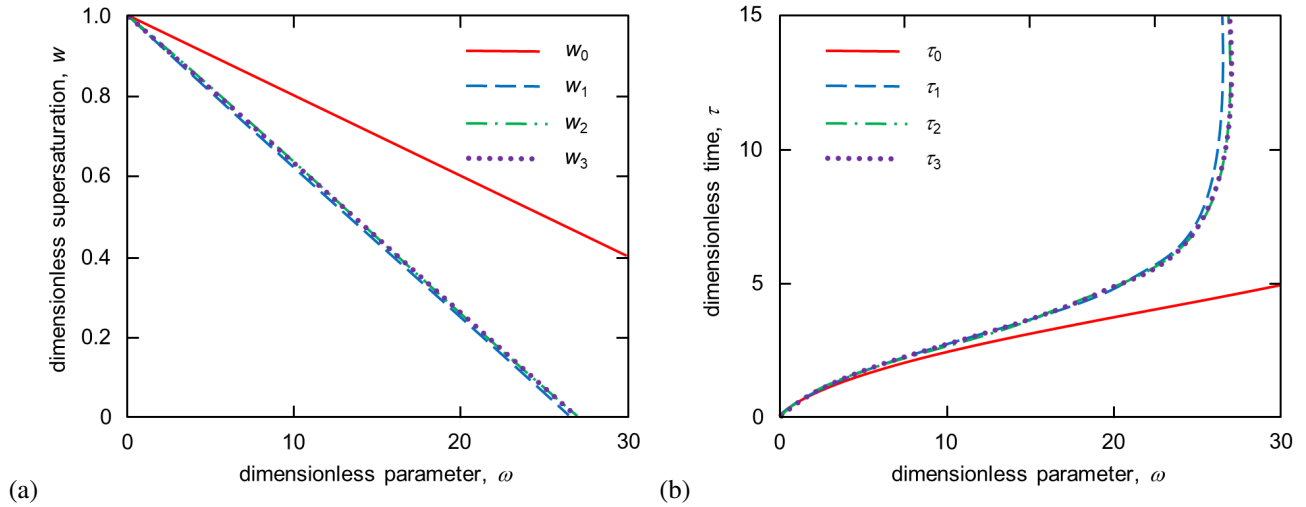


FIGURE 3 Dimensionless supersaturation w (a) and crystallization time τ (b) as functions of dimensionless parameter ω for ellipsoidal crystals in the case of Meirs kinetics. The system parameters are estimated as follows $p = 10$, $s_* = 5$, $m = 10^{-2}$, $\xi = 2$, and $\beta_* = 0.01$.

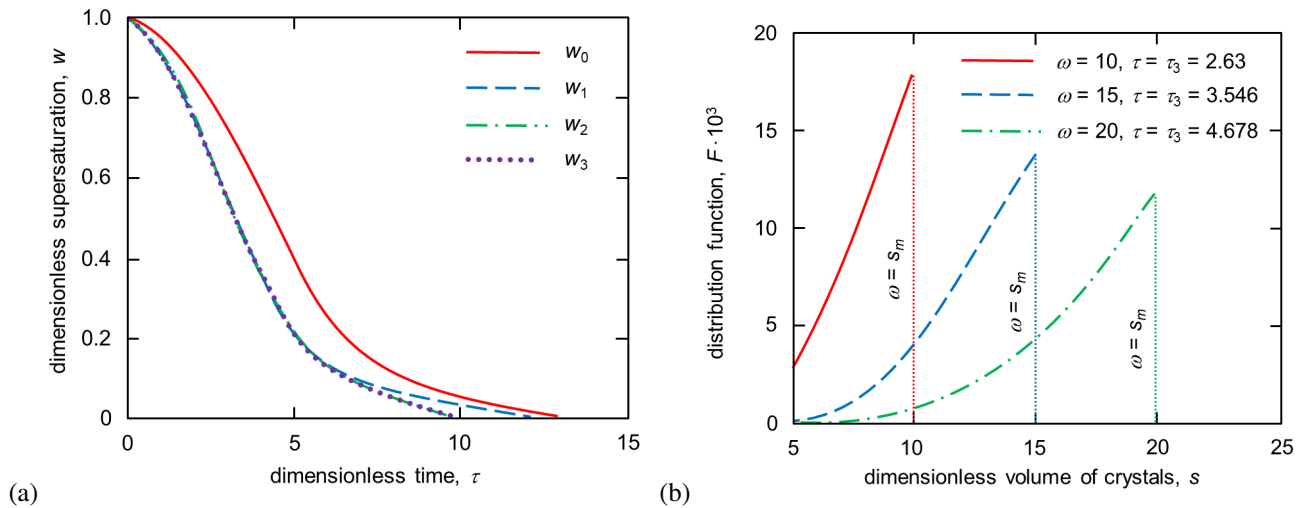


FIGURE 4 Desupersaturation dynamics (a) and particle-volume distribution function (b) for ellipsoidal crystals in the case of Meirs kinetics. The system parameters are the same as in figure 3 .

5 | DISCUSSION AND CONCLUSION

Figure 3 shows four contributions in dimensionless supersaturation accordingly to expressions (37) and corresponding time contributions in a parametric form. As is easily seen the main contributions w_0 and τ_0 substantially differ from other contributions w_i and τ_i ($i = 1, 2, 3$). In other words, taking into account only the main contributions would provide only a qualitative solution, far from reality. Indeed, taking into account the following three contributions to the analytic solution shows its asymptotic convergence, since the fourth approximation (w_3 and τ_3) practically coincides with the third one (w_2 and τ_2).

Eliminating the parameter $\omega = s(\tau, 0)$, which is equal to the maximal size of crystals s_m , one can obtain the metastability degree as a function of crystallization time illustrated in figure 4 a. Here one can also see that the solution converges asymptotically, and the fourth correction gives an approximation that can be used for practical calculations of the kinetics of supersaturation removal. The crystal-volume distribution function calculated using expression (26) is demonstrated in figure 4 b. This function

is limited by the maximum size s_m of crystals that have grown in the supersaturated solution by certain points in time (vertical dotted lines in figure 4 b). The crystal volume distribution function shifts to the right over time as the crystals grow. Its maximum decreases as the number of large particles in the metastable system is less than the number of small ones.

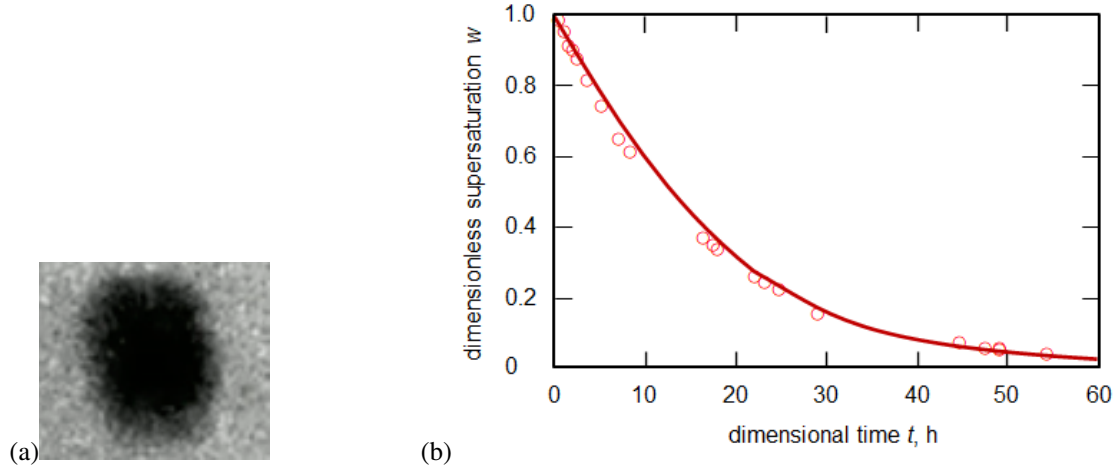


FIGURE 5 A sketch of lysosim crystals⁵⁰ (a). Desupersaturation dynamics for lysozyme crystallization accordingly to the theory (solid curve) and experiment⁵¹ (open circles) (b). The system parameters are estimated as follows $p = 10$, $s_* = 0.1$, $m = 10^{-4}$, $\xi = 2$, $\beta_* = 0.01$, and $t_0 = 0.16$.

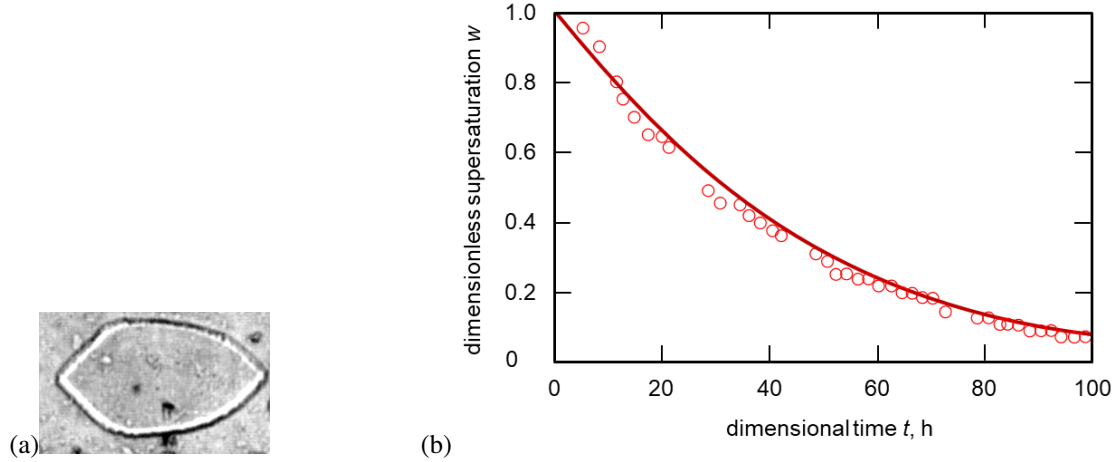


FIGURE 6 A sketch of canavalin crystals⁵² (a). Desupersaturation dynamics for canavalin crystallization accordingly to the theory (solid curve) and experiment⁵³ (open circles) (b). The system parameters are estimated as follows $p = 10$, $s_* = 0.1$, $m = 10^{-4}$, $\xi = 2$, $\beta_* = 0.01$, and $t_0 = 0.385$.

Figures 5 and 6 compare the theory under consideration with experimental data on protein crystallization in the case of Meirs nucleation kinetics. As is easily seen, the real shape of lysozyme and canavalin crystals essentially differs from the spherical one (panels a in figures 5 and 6). Therefore, it is natural to describe such stretched crystals as ellipsoids. For both proteins, panels b show that the metastability degree w decreases with time to small (almost zero) supersaturation.

An important circumstance here is the fact that it is incorrect to use a model of the intermediate phase transformation stage up to zero supersaturation values. This is caused by the fact that at low supersaturation when there are already a sufficient number of crystals in the liquid, they begin to interact with each other through the processes of Ostwald ripening, coagulation, and

agglomeration.^{54–61} Taking these processes into account will lead to a strong change in the mathematical model and, accordingly, its solutions. Generally speaking, consideration of each of these processes occurring at the final stage of phase transformations in a particular metastable system requires a detailed study.

An important direction in the development of the theory of bulk particle nucleation is to consider the joint realization of bulk and directional crystallization, when particle evolution occurs simultaneously with the growth of dendrite-like crystals.^{62–65} The development of such a generalized theory based on integro-differential models of new phase growth will be the subject of future research.

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Author contributions

The authors contributed equally to the present research article.

Conflict of interest

The authors declare no potential conflict of interests.

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