An exact analytical solution to the non-stationary coagulation equation describing the endosomal network dynamics

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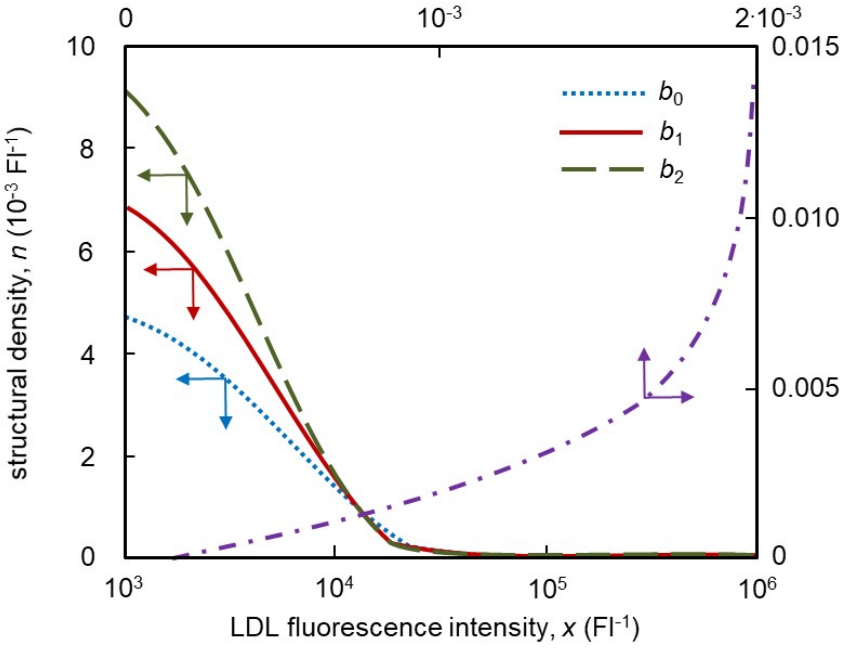
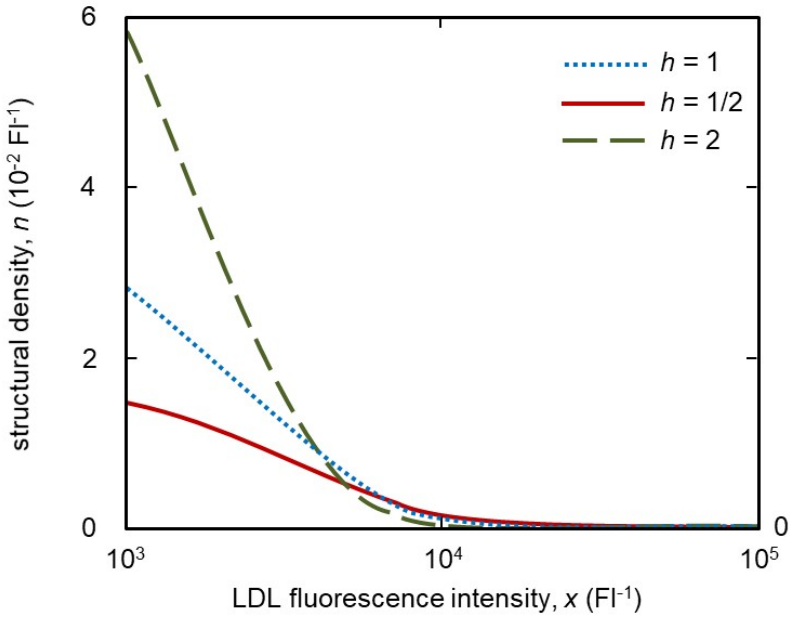
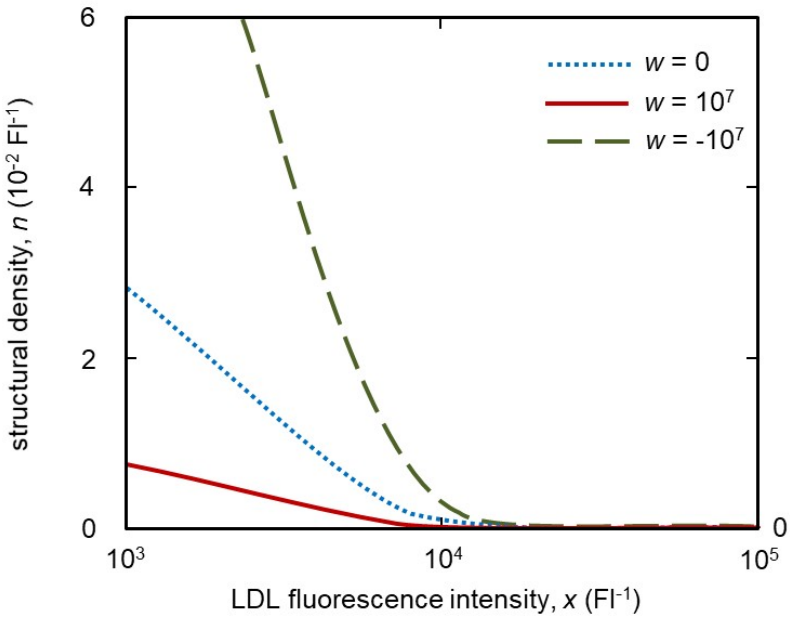
Abstract

Motivated by important applications in materials science and biology, we consider a non-stationary coagulation equation with in-flux and out-flux of particles (cargo). An exact analytical solution to this integrodifferential equation is found in a parametric form. This solution behaves as a decaying exponent with respect to the particle volume (fluorescence intensity in the case of coagulation of endosomes). We demonstrate that our exact solution substantially depends on coagulation kernels (fusion and fission rates) as well as the in-flux and out-flux processes of cargo.







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RESEARCH ARTICLE

An exact analytical solution to the non-stationary coagulation equation describing the endosomal network dynamics

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Motivated by important applications in materials science and biology, we consider a non-stationary coagulation equation with in-flux and out-flux of particles (cargo). An exact analytical solution to this integrodifferential equation is found in a parametric form. This solution behaves as a decaying exponent with respect to the particle volume (fluorescence intensity in the case of coagulation of endosomes). We demonstrate that our exact solution substantially depends on coagulation kernels (fusion and fission rates) as well as the in-flux and out-flux processes of cargo.

KEYWORDS:
coagulation, endosomes, integrodifferential equations, phase transformations, applied mathematical modeling

1 | INTRODUCTION

The phenomenon of particles sticking together as a result of loss of aggregative stability is called coagulation. Coagulation is the process of reducing the degree of dispersion and the number of particles in the dispersed system by cohesion of primary particles. Coagulation usually results in precipitation (sedimentation) of the dispersed phase, or at least a change in the properties of the primary dispersed system. The coagulation theory for the first time was developed by Marian Smoluchowski[1,2] on the basis of the following idea: particles in the dispersed phase move independently of each other in Brownian motion, until the distance between the centres of two particles approaching each other is equal to the so-called radius of influence. This value is approximately equal to the sum of the radii of particles, which corresponds to their direct contact. At this distance the interaction forces between the particles immediately appear, which creates the possibility of their aggregation. Coagulation results in the interaction of only two particles, as the collision probability of a larger number of particles is very low. Thus, single particles collide, forming twins, singles with twins, twins with each other, triplets with singles, etc. This representation of the coagulation process allows us to formally reduce it to the theory of bimolecular chemical reactions.

The equation describing the particle coagulation process is a time-dependent integrodifferential equation whose solution is complicated by the presence of a coagulation kernel (collision-frequency function). The form of this kernel is determined by the predominant coagulation mechanism (Brownian coagulation, coagulation of particles falling under gravity, shear coagulation and the like[3,4,5]). Thus, considering proper initial and boundary conditions, we have a strongly nonlinear problem with no common methods for solving it. As a special note, the existence of exponentially damped, self-similar and stationary solutions of some particular cases has been discussed by Herrmann, Laurençot, and Niethammer[6], Crump and Seinfeld[7], Simons[8], the global existence of solutions has been proved for a large class of data by Laurençot[9], self-similar solutions and the behavior of solutions over long times have been investigated by Alyab'eva, Buyevich and Mansurov[10] and Alexandrov[11,12].

The coagulation equation derived by Smoluchowski[1,2] accounts for the basic mechanism of the process: the merging of two closely approaching particles leads to the formation of a new greater particle. However, when considering endosome fusion and fission within living cells, clustering and transport of cargoes within endosomes to the cell nucleus, a more complex coagulation

equation must be considered. Such an equation also includes the appearance of new endosomes when cargo flows, disappearance of early endosomes and their conversion to late endosomes, the processes when endosomes take up additional cargo by fusing with endocytic vesicles, and when they lose cargo by budding off vesicular structures [13]. Such an equation is more complex than the classical Smoluchowski equation and requires the development of new approaches to its solution. One of the possible approaches to obtain an exact analytical solution of such a non-stationary coagulation equation is developed in this paper.

2 | COAGULATION EQUATION AND ITS ANALYTICAL SOLUTION

Let us consider the particle coagulation equation derived by Foret et al [13] in the form of

$$\frac{\partial n}{\partial t} = \frac{1}{2}\int_0^x K(x', x-x')n(x',t)n(x-x',t)dx' - n(x,t)\int_0^\infty K(x,x')n(x',t)dx' + \int_0^\infty K'(x,x')n(x+x',t)dx' - \frac{1}{2}\int_0^x K'(x',x-x')n(x,t)dx' + I(x) - \gamma n(x,t) + \left(v_{out} - v_{in}\right)\frac{\partial n}{\partial x}, \tag{1}$$

where n is the structural density of endosomes per cell, s is the low-density lipoprotein (LDL) fluorescence intensity, t is the process time. Let us especially underline that $n(x)\Delta x$ represents the number of Rab5- positive endosomes per cell for which the LDL fluorescence intensity lies between x and $x + \Delta x$ [13]. This equation describes the endosome network dynamics and characterizes the degradative cargo distributed into a network of early Rab5-positive endosomes that can transform into late Rab7-positive endosomes and lysosomes [13,14,15]. Here the term cargo plays the role of viruses or nanoparticles that are capable to penetrate inside the living cell through its membrane. The first two contributions on the right-hand side (r.h.s.) of equation (1) characterize the fusion process of endosomes with x and x' of cargo amounts. Their fusion going with the rate $K(x, x')$ produces a new endosome containing the LDL amount $x + x'$. These contributions represent the standard particle coagulation terms obtained by Smoluchowski [1,2]. The next two integral contributions describe the fission process of an endosome with the cargo amount $x+x'$, which leads to the appearance of two endosomes with cargo amounts x and x' (here $K'(x, x')$ stands for the rate of this process) [13]. The source term $I(x)$ describes the initiation of new endosomes containing the cargo amount x as a result of cargo flows [13]. The transformation process of early endosomes into the late endosomes is described by the term $-\gamma n(x, t)$. The last contribution in the r.h.s. of equation (1) shows how endosomes take up extra cargo by fusing with endocytic vesicles and lose the cargo by budding off vesicular structures [13,16,17]. Note that v_{in} and v_{out} represent the average cargo amount per unit of time gained and lost by an endosome [13].

Foret et al. [13] have considered the case of constant fusion and fission rates, i.e. $K = \text{const}$ and $K' = \text{const}$. Note that such an approach is frequently used when studying various particle coagulation processes [3,4,10,18,19]. Keeping this in mind and introducing the dimensionless parameters

$$\tau = Kt, \quad \kappa = \frac{\gamma}{K}, \quad h = \frac{K'}{K}, \quad w = \frac{v_{out} - v_{in}}{K}, \tag{2}$$

we rewrite equation (1) as

$$\frac{\partial n}{\partial \tau} = \frac{1}{2}\int_0^x n(x',t)n(x-x',t)dx' - n(x,t)\int_0^\infty n(x',t)dx' + h\int_0^\infty n(x+x',t)dx' - \frac{hx}{2}n(x,t) + \frac{I(x)}{K} - \kappa n(x,t) + w\frac{\partial n}{\partial x}. \tag{3}$$

Let us now consider the case when the source term $I(x)$ is switched off. This process can take place from a certain point in time, when this contribution becomes small enough to be neglected. Following the theory developed by Schumann [18], we will look for a solution to equation (3) in the form

$$n(x, \tau) = a(\tau)\exp\left[-b(\tau)x\right], \tag{4}$$

where $a(\tau)$ and $b(\tau)$ will be found below.

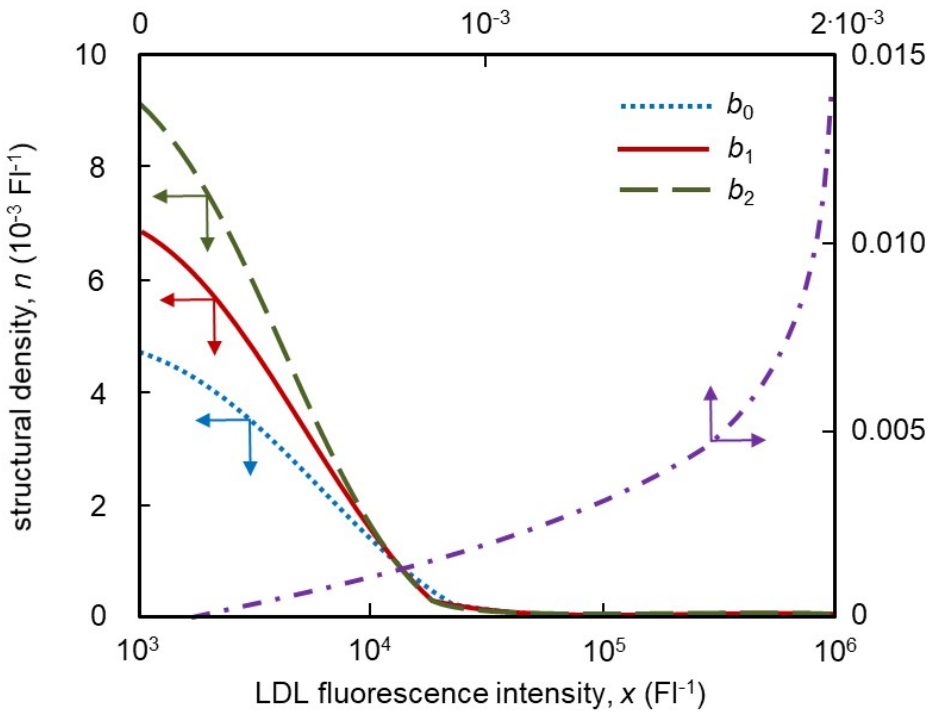

FIGURE 1 The structural density $n(x, b)$ (scale of values on the left) accordingly to expression (10) and time $\tau(b)$ (scale of values on the right) accordingly to expression (9). System parameters are $h = 1$, $\kappa = 9.375$, $w = 0$. The blue dotted distribution is taken from Foret et al.[13] and represents the initial condition at $b_0 = b(0) = 1.386 \cdot 10^{-4}$ and $a(0) = 5.383 \cdot 10^{-3}$ ($\tau = 0$). The red solid and green dashed distributions are plotted at $b = b_1 = 1.7 \cdot 10^{-4}$ ($\tau = 6.315 \cdot 10^{-5}$) and $b = b_2 = 2 \cdot 10^{-4}$ ($\tau = 1.237 \cdot 10^{-4}$), respectively.

Now substituting (4) into (3) and equating the terms with the same powers of x, we obtain

$$\frac{da}{d\tau} = a(\tau)\left[\frac{h - a(\tau)}{b(\tau)} - \kappa - wb(\tau)\right], \qquad a(\tau) = h - 2\frac{db}{d\tau}. \tag{5}$$

Combining these equations and introducing the new function $g(b) = db/d\tau$, we come to

$$\frac{dg}{db} = \left(1 - \frac{h}{2g}\right)\left[\frac{2g}{b} - \kappa - wb\right], \qquad a(b) = h - 2g(b). \tag{6}$$

Expression (4) implies that

$$n(x, 0) = a(0)\exp\left[-b(0)x\right]. \tag{7}$$

Since the initial structural density $n(x, 0)$ should be known from experiments, parameters of this distribution, $a(0)$ and $b(0)$, should be known as well. It means that the initial value of the function $g = g_0$ at $\tau = 0$ is also known and given by

$$g_0 = \frac{h - a(0)}{2}. \tag{8}$$

Now we conclude that the first line of (6) together with the initial condition (8) represent the one-point Cauchy problem for the determination of $g(b)$. As this takes place, $a(b)$ is defined by the second line of expression (6) and $\tau(b)$ is given by

$$\tau(b) = \int_{b(0)}^{b} \frac{db_1}{g(b_1)}. \tag{9}$$

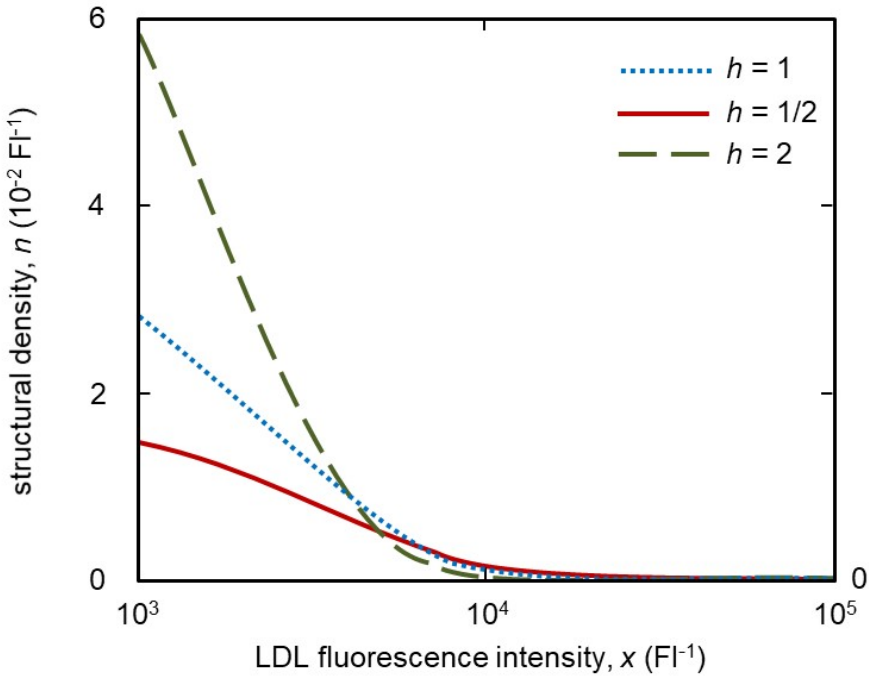

FIGURE 2 The structural density $n(x, b)$ accordingly to expression (10) for different h at the same time $\tau = 5 \cdot 10^{-4}$. System parameters correspond to Figure 1 . The red solid, blue dotted and green dashed distributions are illustrated at $b = 2.6075 \cdot 10^{-4}$, $b = 3.835 \cdot 10^{-4}$ and $b = 6.269 \cdot 10^{-4}$, respectively.

An important point is that (4) can be rewritten in a parametric form as

$$n(x, b) = a(b) \exp(-bx), \tag{10}$$

where $a(b) = h - 2g(b)$ accordingly to the second line of (6).

Thus, expressions (4), (6), (8)–(10) determine the exact analytical solution to the non-stationary coagulation equation found in a parametric form (with a decision variable b). Note that the solution obtained represents a decaying exponential solution with increasing the variable x. As this takes place, an exponential form of this solution evolves with time due to time-dependent behaviour of the functions $a(\tau)$ and $b(\tau)$. A particular case $K' \ll K$ when the fission rate is much smaller that the fusion rate is considered in the Appendix A. In this case, the solution has a simpler parametric form.

Our exact analytical solutions plotted accordingly expressions (9) and (10) are illustrated in Figure 1 . The initial structural density $n(x, 0)$ (parameters $a(0)$ and $b(0)$ in accordance with expression (7)) were found from real experimental data obtained by Foret et al.[13]. This initial structural density, $n(x, 0)$, is shown by the blue dotted line corresponding to the initial value of the parameter $b_0 = b(0)$. The dynamics of structural density are demonstrated by the red solid and green dashed lines corresponding to greater values of b and dimensionless times τ. As is easily seen the structural density substantially increases with increasing b and τ for $10^3 \lesssim x \lesssim 10^4$. As this takes place, all distributions represent exponentially decreasing functions of the LDL fluorescence intensity x. Such behaviour follows from expression (4) in the form of which we were looking for a solution to the original integrodifferential equation.

Parameter h represents the ratio of the fission and fusion rates of endosomes. If the fission rate prevails $h > 1$, the structural density grows for $10^3 \lesssim x \lesssim 10^4$ (see Figure 2). In the opposite case, $h < 1$ ($K > K'$), the structural density decreases at a fixed moment in time.

If endosomes take up additional cargo by fusing with endocytic vesicles more intensively than they lose cargo by budding off vesicular structures, $w < 0$ ($v_{in} > v_{out}$), the structural density is greater than in the opposite case, $w > 0$, or in the case when these processes are of the same order, $w \approx 0$ (Figure 3).

Let us especially underline that the peculiarities analyzed in Figures 2 and 3 on the basis of exact analytical solutions can be used for a more precise description of endosome coagulation and cargo clustering when describing intracellular transport of nanoparticles or viruses.

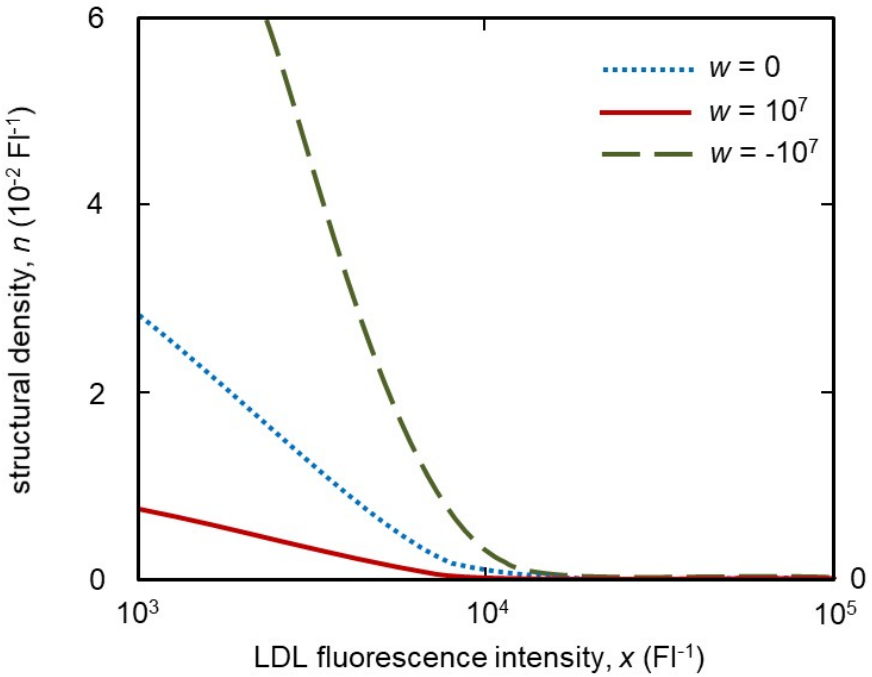

FIGURE 3 The structural density $n(x, b)$ accordingly to expression (10) for different w at the same time $\tau = 5 \cdot 10^{-4}$. System parameters correspond to Figure 1 . The red solid, blue dotted and green dashed distributions are illustrated at $b = 3.86 \cdot 10^{-4}$, $b = 3.835 \cdot 10^{-4}$ and $b = 3.773 \cdot 10^{-4}$, respectively.

3 | CONCLUSION

In summary, an exact analytical solution to the non-stationary integrodifferential coagulation equation is constructed. The solution is represented by a decaying exponent whose amplitude $a(\tau)$ and power coefficient $b(\tau)$ are dependent on time τ. The analytical solution is obtained in a parametric form where b stands for a decision variable. Our solution describes cargo distribution inside endosomes as a result of their fusion and fission mechanisms as well as the in-flux and out-flux processes of cargo [13]. We show that the evolution of structural density $n(x, \tau)$ essentially depends on the fission and fusion rates of endosomes as well as on how endosomes pick up additional cargo by fusing with endocytic vesicles and how they lose cargo by budding off vesicular structures.

The analytical solutions obtained in this paper rely on the assumption of constant fusion and fission rates, K and K'. However, these kernels entering the corresponding integral contributions depend on the mechanism of interaction between particles (see, among others, [3,4,5]). Therefore, the development of the theory for the non-constant K and K' is of considerable interest. Here, for example, one can use the method of averaging K and K' over all possible volumes of particles [18]. In the case of such averaging the aforementioned method for constructing an exact analytical solution takes place as before.

The method developed in this work for finding analytical solutions to the non-stationary integrodifferential coagulation equation can be applied to the final stage of phase transformation in supersaturated solutions and supercooled melts, when simultaneous coexistence of Ostwald ripening, fragmentation, and coagulation of particles or aggregates is possible [11,20,21,22,23,24].

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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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APPENDIX A

In this section, we present an exact analytical solution in the case $h = 0$ (when the fission rate K' is much smaller than the fusion rate K).

If this is really the case, we have from equations (5)

$$\begin{aligned} \frac{1}{2}\frac{da}{db} &= \frac{a}{b} + \kappa + wb, \\ a(\tau) &= -2\frac{db}{d\tau}. \end{aligned} \tag{11}$$

Integrating the first equation (11), we arrive at

$$\begin{aligned} a(\tau) = a(b(\tau)) &= -2\kappa b(\tau) + 2wb^2(\tau)\ln b(\tau) + C_0 b^2(\tau), \\ C_0 &= \frac{a(0)}{b^2(0)} + \frac{2\kappa}{b(0)} - 2w\ln b(0). \end{aligned} \tag{12}$$

Now substituting the first line of (12) into the second line of (11) and integrating the result, we get

$$\tau(b) = 2\int\limits_{b(0)}^{b} \frac{db_1}{2\kappa b_1 - 2wb_1^2\ln b_1 - C_0 b_1^2}. \tag{13}$$

Thus, expressions (12) and (13) determine exact analytical solutions in a parametric form, where b is a desicion variable.

□