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Kinetic–thermodynamic effects accompanying model protein-like aggregation: The wave-like limit and beyond it

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Abstract

A fairly idealized, mainly spheroid-type (dis)ordered aggregation of proteins is considered. The consideration is basically given in terms of the nonequilibrium thermodynamics at a mesoscopic level, quite commonly abbreviated by *MNET* (mesoscopic nonequilibrium thermodynamics). The mesoscopic level of description offered is supplemented by some involvement of certain important microscale dynamic sub-effects, mostly the ones characteristic of growth-layer dynamics (towards non-Kossel crystal formation) and/or fibril formation within the growing object (towards spherulitic growth). It is argued that the kinetic part of the overall kinetic–thermodynamic description proposed is due to the memory effects originating from a deeper penetration of the time scale also involved in *MNET*. The thermodynamic part, in turn, is closely related with the Boltzmann-type free energy available for the protein-like aggregation, constituting the Kramers' barrier, that appears to be primarily dependent upon the curvature impact on the growing object, although one is able to diversify the description, depending whether the (un)constrained aggregation is assumed to occur on one nucleation seed or appears to take place on many of them. In both cases, the Smoluchowski-type equation, revealing the aggregation dynamics in a phase space, governs the overall spheroid-type formation, exemplified throughout the paper's body mainly by some lysozyme (poly)crystalline aggregates. The natural wave-like limit characteristic of ballistic growth is pointed out. A behavior of the system outside the limit is also discussed, and the morphological phase diagram of the nucleation-growth phase transformation is addressed in a sketchy way.

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1. Introduction

The main goal of the present paper is to make use of a mesoscopic nonequilibrium thermodynamic (*MNET*) description [1] of the soft-matter aggregations, exemplified throughout the paper's body mostly by some lysozyme (poly)crystalline forms mentioned below. The notion of the soft matter involved here specifically means that we are going to talk about model protein-type aggregations in which the interaction energies between the protein molecules, being typically of nanometer size, and/or their clusters (growing even up to a

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sub-millimeter size scale), are weak [2], being typically of order of a few thermal-energy units [3–8], $k_B T$, where T —the temperature, and k_B —the Boltzmann’s constant.

As one may know, such aggregations addressed above can yield either ordered or disordered microstructures. A landmark example of the ordered microstructure would be a solution grown non-Kossel protein crystal [4,5], whereas a more disordered polycrystalline aggregate termed spherulite may emerge under quite similar physico-chemical circumstances, especially when one goes out of the single-crystal-formation conditions, being eventually left outside the so-called crystallization window shown by the phase diagram [6].

It is accepted that the theory of protein aggregation and interface motion towards external phase may readily point to a mesoscopic character of the process rooted in irreversible thermodynamics [4]. Certain properties of an object’s smooth advancing towards its external phase, sometimes termed the continuous-growth property, indicate the rule that every piece of the surface is able to advance normal to itself, irrespective of whether the surface is diffuse or not, and whether there appear or not, certain anomalies of the surface-tension behavior, characteristic of the (dis)ordered protein aggregate. Trying then to argue whether and when the continuous growth of such a type is possible to occur a criterion of interaction of the matter-aggregating front with its nearby surroundings has to be introduced [6]. Then, it will be recognized in our type of modelling as some viscosity-dependent property characteristic of the interfacial region (depletion zone) of the resulting spheroid formation that, under such circumstances, is allowed to occur on one nucleation center in a bath of Brownian protein-type particles dispersed in the nearby, typically entropic aqueous solution [7,8].

The comprehensive modelling we would like to offer is rooted in nonequilibrium thermodynamics at a mesoscopic level. Its polymers-involved dynamics—no matter whether the aggregation is considered on one chosen nucleation seed or on a certain number of them—is well described by the Smoluchowski-type equation¹ in a phase space, with the Kramers’ barrier thoroughly involved in the presented approach, being generically of hydrodynamic nature [9]. The dispersive systems in which the protein aggregation under study may appear usually consist of protein matter dispersed in the solution. Thus, they are naturally binary mixtures. An important point to realize is about the concentration of the dispersed matter since it establishes, at a given temperature, T , the conditions for a nucleation-growth transition to occur [10]. Typically, the bigger the concentration is the greater the number of the nuclei can be. As a consequence, being however, restrictively applied to the total constant-volume conditions [9], it would frequently happen that a more geometrically constrained aggregation results [4]. Knowing the concentration only is, however, not the sufficient condition to propose a firm prediction of the transition in such binary mixtures. A certain knowledge on how the concentration is going to change in the course of the overall process [11] seems to be a decisive factor [10]. For example, in protein–water systems, presumed that they are not very well mixed, aggregation occurs in both protein-rich as well as in protein poor phases [5,6]. It is interesting to know that even though a protein-rich phase is a minority phase, it can distribute over a major part of the system, and form a gel-like microstructure, mostly thanks to phase separation mediated by viscoelasticity of the solution [11]. A similar situation can be observed in colloidal suspensions [12], and in both protein- as well as colloid-containing solutions such a mechanism is proposed to be responsible for phase ordering. Such a behavior is commonly called viscoelastic phase separation, and has recently been established as an experimentally justified fact [11–13].

Throughout the present study a basic question frequently arises in quite various contexts: When the aggregation becomes ordered (an enthalpy factor prevails) and when it does not (towards some domination of entropy)? This is a legitimate question to appear here, i.e., under a generally entropic context in which the protein aggregate emerges [1,7]. Thus, an attempt has occasionally been made towards answering it from the kinetic–thermodynamic point of view [4], readily pointing to memory effects involved in the spatio-temporal forms of the diffusion coefficients [13] as well as in the Boltzmann-type free-energy contribution [1,7,8].

By performing the present study we are going to show how one can benefit from the *MNET*-based kinetic–thermodynamic modelling of two complex types of the round-shape-yielding formations mentioned the foundations of which [1] have been outlined in Section 2. The formation of first type, Section 3, assumed to occur on one nucleation seed, can be classified roughly as constrained growth for which the driving force of the phase transition generally decreases with increasing the distance from the interface into the

¹This paper has been written on the occasion of 100th anniversary of Marian Smoluchowski’s substantial contribution to statistical physics of colloid-type systems which falls on the year 2006.

solution—therefore the transition becomes extremely efficient when the driving force operates in the actual vicinity of the growing object [7,8]. The formation of second type, in turn, is named unconstrained growth [4] (see, Section 4) since the aggregation goes over really many nuclei. It is, however, assumed to occur in a constant total volume [9,14,15]. (Its direct ‘predecessor’ can be the unconstrained and unseeded growth [4] sometimes named the droplet formation.) In Section 5, the wave-like late temporal behavior, leading to a constant tempo in which the aggregate emerges, has been utilized as a kinetic criterion of the more ordered than disordered protein aggregation of ballistic type [11]. In Section 6, some preliminary discussion on the so-called morphological (dynamic) phase diagram has been offered, pointing to a full kinetic–thermodynamic criterion of appearance of the ordered phase composed of aggregated proteins. The conclusions collected in Section 7 are thought of to give a certain summary of the performed study.

2. MNET scheme applied to round-shaped protein-type aggregates

MNET formalism is able to propose an adequate theoretical scheme based on which one can quantitatively consider the behavior of complex systems defined at the mesoscale. The formulation of any MNET-type theory essentially relies upon a certain reduction of the observational time and length scales of a system of interest. Such a reduction usually involves an increase in the number of the degrees of freedom which have not yet equilibrated what automatically influences the total dynamics of the system. Such degrees of freedom, x – s , with x —here the volumes of the growing nuclei, $x \propto r^d$ (r —the actual radius of a single round-shaped object, d —Euclidean dimension, with practical emphasis placed typically on $d = 2, 3$ [14,15]) may represent the stochastic reaction coordinate of the system, very characteristic of MNET, suitably defining the state of the system under nucleation-growth phase change in the x -space, called further the phase space throughout. The characterization of the state of the system basically relies on the knowledge of $P \equiv P(x, t)$, the probability density of finding the system at the state $x \in (x, x + dx)$ at time t . One can then rewrite the Gibbs’ entropy postulate in the form [1]

$$S = S_{eq} - k_B \int P(x, t) \ln \frac{P(x, t)}{P_{eq}(x)} dx, \quad (1)$$

where S_{eq} is the entropy of the system when the degrees of freedom, x , are at equilibrium. If they are not at equilibrium, the contribution to the entropy arises from deviations of the probability density $P(x, t)$ from its equilibrium value $P_{eq}(x)$ given by a standard formula

$$P_{eq}(x) \sim \exp(-\beta \Delta \Phi(x)), \quad (2)$$

where $\Delta \Phi(x)$ is the minimum reversible work required to create that state, $1/\beta = k_B T$, and k_B, T —see above.

Thus, the minimum-work variations for the protein matter-aggregating system are generally expected to be Ref. [1]

$$\Delta \Phi = \Delta E - T \Delta S + p \Delta V - \mu \Delta M + \sigma \Delta A + \dots, \quad (3)$$

where, after invoking a standard notation, extensive quantities refer to the system and intensive ones to the heat bath. The last term of the r.h.s. represents the work performed on the system to modify its surface area, A , whereas σ designates the surface tension.

In order to obtain the dynamics of the mesoscopic degrees of freedom [9] one first gets variations in Eq. (1)

$$\delta S = -k_B \int \delta P(x, t) \ln \frac{P(x, t)}{P_{eq}(x)} dx, \quad (4)$$

focusing only on the nonequilibrated degrees of freedom.

The probability density evolves in the x -space along with the local continuity equation

$$\frac{\partial P(x, t)}{\partial t} + \frac{\partial J(x, t)}{\partial x} = 0, \quad (5)$$

where $J(x, t)$ is an unknown probability density flux [16], also called by others the probability current [17], though a mixed *current vs. flux notation* seems acceptable too [1]. In order to obtain its quantitative characteristics, one proceeds to get the expression of the entropy change dS/dt which results from the

continuity equation (5) and the Gibbs' equation, here given by (4). After a partial integration, one then provides [1]

$$\frac{dS}{dt} = - \int \frac{\partial}{\partial x} J_S dx + \sigma_S, \quad (6)$$

where $J_S = J(x, t) \ln(P(x, t)/P_{eq}(x))$ is the entropy flux, and

$$\sigma_S = -k_B \int J(x, t) \frac{\partial}{\partial x} \left(\ln \frac{P(x, t)}{P_{eq}(x)} \right) dx, \quad (7)$$

is the entropy production which is expressed in terms of fluxes and conjugated thermodynamic forces defined in the x -space.

We will now assume a linear flux-force relation, typically characteristic of near-equilibrium systems [1]

$$J(x, t) = -k_B L(P(x, t)) \frac{\partial}{\partial x} \left(\ln \frac{P(x, t)}{P_{eq}(x)} \right), \quad (8)$$

where $L \equiv L(P(x, t))$ is an Onsager's coefficient, which in general depends on the state variable $P(x, t)$, in particular on the reaction coordinate x [1]. To derive this expression, locality in x -space has to be assured, for which only fluxes and forces with the same values of x contribute to their mutual coupling [9].

The resulting kinetic equation can then be obtained by inserting Eq. (8) to the continuity equation (5)

$$\frac{\partial P(x, t)}{\partial t} = \frac{\partial}{\partial x} \left(D(x, t) P_{eq}(x) \frac{\partial P(x, t)}{\partial x P_{eq}(x)} \right), \quad (9)$$

where we have defined the diffusion coefficient as $D(x, t) \equiv k_B L(P(x, t))/P(x, t)$. This equation, which because of Eq. (2) applied together with Eq. (3) can also be written as

$$\frac{\partial P(x, t)}{\partial t} = \frac{\partial}{\partial x} \left(D(x, t) \frac{\partial P(x, t)}{\partial x} + \beta D(x, t) \frac{\partial \Delta \Phi}{\partial x} P(x, t) \right), \quad (10)$$

is the Smoluchowski-type equation [16], accounting readily for the evolution of the probability density in our x -space. This implies that the spheroid-type formation in question is generously given the Smoluchowski dynamics [1,9], where the dynamics are realized as drifted and time-involving (memory effect) diffusion processes along the reaction coordinate, x , which is here the volume of a single spheroid: A volume in the space of $d = 3$ and an area in $d = 2$, with d as above.

3. Spheroid-type formation on one seed—towards non-Kossel crystals

Mesoscopics literally means a deterministic (kinetic) description of the open thermodynamic system with an account of the fluctuations of the leading stochastic variable, here x or r , involved. The primary advantage of using *MNET* for describing the ordered protein cluster formation is that we mostly deal with a tool being more flexible than the Langevin equation in describing the formation dynamics. Actually, such a tool appears to be the Smoluchowski-type equation [16] for the probability density $P(r, t)$ of forming an object characteristic of a linear size (viz, the radius), r , at time t [1,9,13].

As concerns the deterministic part, in order to formulate the on-one-nucleus-based growing conditions, we begin with a mass-conservation law in a standard form of the integro-differential equation, where the integration goes over the volume of a nucleus, V_n , closed by its surface area, S_n , over which also the second matter flux involving integral is taken. The differentiation goes over time and is applied to the volume integral expressing a net mass change of the system. Finally, both the volume as well as the surface integrals are equated to each other [7]. The nucleus, assumed for simplicity in our model as being homogeneous, i.e., of constant density C , is supplied by an external concentration field, $c(\vec{r}, t)$ with the Brownian-type protein particles, and also with their clusters, dispersed in the solution. All sources of chemical reaction, virtually contributing to changing C and/or $c(\vec{r}, t)$ are postponed, this way giving ultimately rise to state [7,8]

$$\frac{\partial}{\partial t} c(\vec{r}, t) + \text{div}[\vec{J}(\vec{r}, t)] = 0, \quad (11)$$

where \vec{r} stands for the position of a protein within the growth layer [5,6], and \vec{J} denotes the matter flux, i.e., actually arriving at a local version of the qualitatively described above mass conservation law, i.e., Eq. (11). Now, referring to some experimental facts [6,7], let us confine ourselves to propose a ballistic case in which for a model protein-type system, e.g. because of virtual emergence of (protein) clusters [18,19], the matter flux is of truly mass-convective nature [7]

$$\vec{J}(\vec{r}, t) = c(\vec{r}, t)\vec{v}(\vec{r}, t), \tag{12}$$

where $\vec{v}(\vec{r}, t)$ is the velocity vector field, preferentially acting in the interfacial region the bounds of which can be limited by the Stern-type double layer enclosing the growing object [7,8].

This clearly influences the form of the deterministic kinetic equation that results from applying, here without any substantial loss of generality, Eq. (11) with Eq. (12) together, to a spherical object of radius $r = R$, still with $C = const.$, assuming that $c(\vec{r}, t)$ because of spherical symmetry practically going as $c(\vec{r}, t) \rightarrow c_e(R)$, i.e., it is readily specified at the object’s surface [7,8], or practically, well within the double layer. The equilibrium concentration $0 < c_e(R) \ll C$ can then be taken as the one given by Gibbs–Thomson (GT) condition $c_e(R) = c_0[1 + \Gamma_D K_1(R)]$ (Γ_D —capillary constant; $K_1(R) = 2/R$ —twice the mean curvature) but exclusively for low-dimensional viz nonmacromolecular crystals emerging from a supersaturated solution. The above yields the kinetic equation as follows:

$$\frac{d}{dt}R = \sigma_R^e \times v_F, \tag{13}$$

where the dimensionless supersaturation $\sigma_R^e = c_e(R)/(C - c_e(R))$, and v_F can be considered as a parameter, here a Frenkel-type constant velocity of the macroion near the spheroid surface. This is, however, by no means the case of high-dimensional or protein (more generally, colloid-type [10,12,18]) crystal growth—for them a modification of the GT boundary condition is required [7]. This and the stochastics of $v(\vec{r}, t)$, i.e., formally considered in a scalar form, will further be discussed.

3.1. Protein aggregation-sensitive modification of the boundary condition

A suitable modification of the GT equilibrium boundary condition for the protein crystal formation results in either some expanded GT condition of equilibrium type (originating from more refined consideration about the molecular nature of the surface tension) or gives rise to typically mild nonequilibrium effects at the boundary, especially the ones coming from the nucleation-oriented elastic interactions [7] between the boundary proteins and its nearby surroundings of electrolytic type, or when some defects, e.g. vacancies, are created within the object’s surface [6].

The modification of the boundary condition can be proposed as follows [7,8]:

$$c_{ne}(R) = c_0 \left[1 + \Gamma_D K_1(R) + \Gamma_T^2 K_2(R) + \sum_{i=1}^3 \alpha_i y^{(i)}(R) \right], \tag{14}$$

where Γ_T Tolman length, $K_2(R) = 1/R^2$ Gaussian curvature, α_i the elastic coefficients, and $y^{(i)}(R) = (R^i - R_0^i)/R_0^i$ [7] (R_0 is the initially taken object’s radius), with the latter representing three main crystal-surface-nucleation-mechanisms ($i = 1, 2, 3$) [7]. When additionally a term of $-\beta_{kin} \times dR/dt$ is added to the r.h.s. of the above Eq. (14), where β_{kin} stands for a phenomenological coefficient, and dR/dt (the speed of the interface) is assumed to address readily the ‘truly nonequilibrium character’ of the boundary condition [8], violating somehow the continuous-type growing mode invoked above. But it is only expected to occur for one-nucleus formed spherulites [7], e.g. those of lysozyme type. Because of rewriting Eq. (14) in such a ‘mildly nonequilibrium’ form (see the role of $y^{(i)}(R)$ therein) [7], one is now able to write down a more general kinetic equation for describing the spheroid formation, namely [7]

$$\frac{d}{dt}R = \sigma_R^{ne} \times v_F, \tag{15}$$

where now

$$\sigma_R^{ne} = \frac{c_{ne}(R)}{C - c_{ne}(R)} \quad (16)$$

under a requirement that all mechanisms prescribed at the boundary, and contributed to Eq. (14), do not need to operate at the same time together. On the contrary, they have to do their jobs whenever physically appropriate [4–6,10].

To be more specific, let us offer some example based on lysozyme crystal growth. In a computer simulation, the lysozyme molecules, typically of 3 nm of linear size, are represented by spheres and the bonds between them by line segments. Molecule attachment and detachment (and, removal) kinetics are taken into account, and the driving force of such an isothermal crystallization is given very similarly as in our Eq. (26) stated below, referred to as $\Delta\mu\beta$ in Ref. [2], and belonging roughly to an interval of (1, 10), depending on whether a more rough or rather smooth surface of the crystal is actually of interest; it then points to a surface-nucleation mechanism to be assumed on a growing crystal phase [2]. By means of our modelling, even by using its deterministic part only, we are able to reproduce some typical signatures of the lysozyme crystal growth such as estimation of its expected speed. It can be demonstrated in the long times' limit in a most convenient way. Namely, when looking carefully at Eqs. (14)–(16), and neglecting for the moment the explicit elastic mechanism incorporated in Eq. (14), i.e., $\alpha_i = 0$ (specifically for $i = 2$), which can be more pronounced in certain nonlate stages of the growing process [7], we may readily take into account the curvature peculiarities [2] by means of the two first r.h.s. terms of Eq. (14) that exactly match the desired case [8]. But for large times' limit $\sigma_R^{ne} \rightarrow \sigma_0^e$, which is independent of R since $\sigma_0^e = c_0/(C - c_0)$, representing the dimensionless supersaturation parameter mentioned above. The Frenkel-type velocity of the lysozyme macroion, v_F , is typically of order $v_F \sim 10^{-2} - 10^{-1}$ (cm/s) [6], whereas σ_0^e can be taken [7,8] as $\sigma_0^e \sim 10^{-4} - 10^{-3}$ (soft crystals, full of water, and possibly, other ionic species, facilitating the nucleation stage [2,5]), thus correctly estimating [4,6] the speed of the lysozyme crystal formation to be of ca. $10^{-6} - 10^{-4}$ (cm/s) on average, cf. Eq. (15).

3.2. Protein-involving velocity field close to the spheroid surface

In the deterministic part of the *MNET*-oriented description one may anticipate a certain involvement of the Frenkel-type velocity of the macroions incorporated in the resulting equation, see v_F in Eq. (15). In order to embark on a more realistic description of the process, one is motivated to offer a correlational proposal for $v(\vec{r}, t)$. Although it can split into its spatial (\vec{r}) and temporal (t) parts, in the very vicinity of the crystal, i.e., mostly in the diffusive part of its Stern-type double layer, see Ref. [8] and references therein, the spatial correlations can likely be postponed since they are hard to detect in such a narrow region, especially when a ballistic-type motion of the proteins is expected to occur because of electrostatic interactions between the charged proteins and some oppositely charged spots of the growing object. The temporal correlations in $v(\vec{r}, t)$, however, cannot be ruled out easily. They appear because the viscosity in the diffusive part of the Stern double layer would tend to decrease with time while the crystal is growing. Since the crystal becomes larger the double layer expands as well, and because the external-concentration conditions are often assumed unchanged (or, slowly varying with time), a protein-influenced viscosity change near the crystal surface results in some viscosity decrease in time. This can be attributed to the depletion-zone effect, arising around the object, and being characteristic of colloid-type growing systems such as ours. It is due to some diffusivity, $D(t)$, increase in time which comes from the time correlations in $v(\vec{r}, t)$ to be inferred from the Green–Kubo formula, i.e., when the fluctuation–dissipation theorem can be effectively applied [1]. Although the Green–Kubo formula can basically be applied only to systems near equilibrium, by constructing such a model we may offer some extension of the (temporal) distance from equilibrium because of expanding the time zone by effectively engaging the time correlations, cf. Eqs. (17) and (18) below. For both non-Kossel crystals as well as for the spherulites studied below, because of the memory effects we always propose to merely augment (appropriately rescale) the time scale by introducing a power law such as $t \rightarrow (t/\tau_{char})^\kappa$, where some exponent κ obeys $\kappa \geq 1$, and τ_{char} is proportional to the correlation time τ_{cor} ; moreover, both τ_{char} and κ may depend at least upon T and d , see also some examples, coming from Avrami-type phase-change kinetics, given below. Thus, after some natural postponement of the spatial correlations in the narrow interfacial region, the correlational

proposal should involve temporal correlations, and may be a stationary Gaussian but correlated, though with a zero deterministic velocity part

$$\langle v(t) \rangle = 0, \quad K(|t - s|) = \langle v(t)v(s) \rangle, \quad t \neq s, \quad (17)$$

where the time correlations $K(q)$, with the characteristic time, τ_{cor} , see below, given by means of a temporal average $\langle \rangle$, are related to $D(t)$ by

$$D(t) = \int_0^t K(q) dq, \quad q > 0. \quad (18)$$

Eq. (17) implies that the temporal average of the velocity field is always zero but there exists, as an appropriate measure of the growth speed $\langle v^2(t) \rangle^{1/2}$ which is certainly a nonzero quantity, and which under the below stated power-law proposal for the correlations, taken within a small-parameter limit (the exponent γ , stated below, being of negligible value) properly yields the constant tempo of the process, see the rationale given below. One may also invoke here a well-known analogy with classical Brownian motion for which the variance is a nonzero quantity, but the first moment (its mean) always disappears. This is to say that the growing process readily goes by protein velocity fluctuations, or presumably by fluctuations [10] of velocities of the protein clusters that can emerge during the crystal formation too [2,4,6]. Therefore, it is found [7,8] that for a given characteristic time τ_{cor} the most suitable correlational proposal to be offered for objects grown from protein solution can be the one of power-law type [7,8,18]

$$D(t) \propto \left(\frac{t}{\tau_{cor}} \right)^{1-\gamma}, \quad t \gg t_0, \quad (19)$$

where $\gamma \in (0, 1)$ is a fractional exponent, and t_0 is taken as an initial instant. It can be foreseen [8] that, if $\gamma \rightarrow 0$ is obeyed, the protein-spheroid formation points to an overall ballistic, hydrodynamically stable growing asymptotic mode, since $D(t) \propto t$ eventually suits the constant-tempo growing mode, fairly characteristic of both non-Kossel as well as spherulitic formations [14,15,20]. It unquestionably contributes to the total hydrodynamic stability of the formation, especially in a readily mature growing stage, since for $t \gg t_0$ the late-time solutions of the stochastic

$$\frac{d}{dt} R = \sigma_R^{ne} \times v(t), \quad (20)$$

cf. relation (17), and the discussion below it, $R \equiv R(t)$, are given by $R \sim t$, pointing to on-average-constant speed of the formation $dR/dt \rightarrow const.$, which is true because σ_R^{ne} typically suppresses to a constant value when $t \gg t_0$ and $v(t)$ can ultimately be replaced by a characteristic macroion's velocity v_F as far as the deterministic character of the approach is concerned. (There is a delicate matter to prove, or to properly argument, whether $\langle v^2(t) \rangle^{1/2}$, taken from the correlations K , would obey $\langle v^2(t) \rangle^{1/2} \rightarrow v_F$ when $t \gg t_0$ holds, and the limiting case of $\gamma \rightarrow 0$ applies. From it a possibility of finding a connection between a small parameter γ and v_F can then be argued.) It is another signature of the ballistic character of the process, herein at the “macroscopic” (thus, higher than its either meso- or microscopic counterparts) level. It should be pointed out that it is also a well-established experimental fact [4,6]. At a purely mesoscopic level of the model protein–matter organization one may rather opt for the relation given by Eq. (12) as some signature of a ballistic character of the process, whereas its microscopic counterpart corresponds to Eq. (19) with $\gamma \rightarrow 0$.

The most interesting situation that can happen here is, however, that Eq. (20) is fully equivalent to a Smoluchowski-type equation [16] in R -space which can be solved with suitable boundary conditions characteristic of a two-state dynamic process with a surmountable Kramers-type energetic barrier, $\Delta\Phi$ [21], fully derivable from the offered *MNET* proposal [1]. This barrier, denoted further by $\Delta\Phi$, can be determined exactly, and both its height and shape can be generally controlled by temporal fluctuations [10] of the radius of the spheroid given by the diffusion function involved in the Smoluchowski-type dynamics, $D(R, t) = D[R(t)]$, defined as

$$D[R(t)] = \frac{\int_0^\infty R^2 P(R, t) dR}{2t}, \quad (21)$$

whereby the above relation is the Einstein-type relation in the one-dimensional phase space of stochastic variable R in which the overall spheroid-type formation takes place. Thus, following the above-mentioned way, one is capable of controlling the Kramers' barrier by means of the fluctuations [9,21].

3.3. Smoluchowski dynamics in R -space

It is interesting to point out that the global mass conservation law, now represented by its simplified stochastic form, Eq. (20), describing the evolution of the round-shaped protein object of radius $r = R$ grown in the entropic milieu (e.g., lysozyme non-Kossel crystals in an aqueous solution [7]), eventually yields the Smoluchowski-type equation for the probability density $P(R, t)$

$$\frac{\partial}{\partial t} P(R, t) = \frac{\partial}{\partial R} \left(D[R(t)] \frac{\partial P(R, t)}{\partial R} + \beta D[R(t)] \frac{\partial \Delta \Phi(R)}{\partial R} P(R, t) \right), \quad (22)$$

where $\Delta \Phi(R) \equiv \Delta \Phi[R(t)]$ becomes the free energy of the formation, unambiguously constituting the Kramers' barrier and $\beta = 1/k_B T$ applies again. Eq. (22) is completely equivalent to Eq. (20) (mass conservation law) with Eqs. (17) and (18), and suits very well our general *MNET*-oriented framework introduced above.

It can also be rewritten in a ballistic-type manner [16] as

$$\frac{\partial P(R, t)}{\partial t} + \frac{\partial [v_{sph}(R, t) P(R, t)]}{\partial R} = 0, \quad (23)$$

where $v_{sph}(R, T) = -D[R(t)] \ln[P(R, t) \sigma_R^{ne}]$ stands for the matter flux velocity [16] characteristic of spheroid formation. It then enables, after using Eq. (2) (Boltzmann distribution, characteristic of the equilibrium state [1]) as well as (26) stated below, and finally after applying Eq. (19) in the limit of $\gamma \rightarrow 0$, to determine the asymptotic value (for $t \gg t_0$) of $v_{sph}(R, t)$, namely $\overline{v_{sph}(t)}$ to be a linear function of the time t , i.e.,

$$\overline{v_{sph}(t)} \simeq 2t \ln[\sigma_0^e], \quad (24)$$

where for σ_0^e —see above, and compare with Eq. (13). This is another signature of the frequently invoked ballistic-type (say, kinematic) growing mode but taken at a purely mesoscopic level of the description offered [13]. It is right now interesting to note, that as in Ref. [2], if $\ln[\sigma_0^e]$ can be accepted as an asymptotic (practical) measure of the driving force for the lysozyme crystal formation to occur, then by means of formula (24) given above, we are able, for a given time t , to reproduce the tendency of the increasing speed $\overline{v_{sph}}$ of the crystal formation with increasing values of the driving force, cf. Fig. 5 of Ref. [2].

Proceeding further in the same vein, we may also speak of an ensemble-average $\{R(t)\} = \int_0^\infty R P(R, t) dR$ which can be stated unambiguously. This is also the case of $\{R^2(t)\} = \int_0^\infty R^2 P(R, t) dR$ which is the mean-squared displacement of the $\Delta \Phi$ -drifted superdiffusive process in the R -space [16]. Thus, the reduced variance, $\varepsilon(t)$, given by

$$\varepsilon(t) = \frac{\{R^2(t)\}}{\{R(t)\}^2} - 1, \quad (25)$$

as a measure of the fluctuations in the R -space, can be determined too. Moreover, one is able to derive $\Delta \Phi(R)$ in a Boltzmann-like form as Ref. [7]

$$\Delta \Phi(R) = \frac{1}{\beta} \ln[\sigma_R^{ne}], \quad (26)$$

with σ_R^{ne} determinable from Eq. (16), also pointing to the Boltzmann-type (nonnormalized) probability, W_B , defining the number of possible microstates in the system such as the (growing) protein spheroid immersed in its dispersive environment. Note that in Ref. [2] a driving force for the lysozyme crystal formation, based upon a late-stage estimate of the $\beta \Delta \Phi(R)$ from Eq. (26) has been presented in a form proportional to $\ln[\sigma_0^e] \equiv \ln[c_0/\Delta c]$, where $\Delta c = C - c_0$, and it can be referred to as the equilibrium lysozyme solubility in the crystalline material [2]. Based on it, this is now to say that the formation is also controlled by the surface, and its thermodynamics, since $W_B = \sigma_R^{ne}$ clearly holds, and also because the equilibrium protein (here, lysozyme) surface concentration fully participates in determination of the driving force [2,8]. $D[R(t)]$ can also be

determined from the *MNET*-type proposal already formulated above, and reads ultimately

$$D[R(t)] = D(t) \times [\sigma_R^{ne}]^2, \quad (27)$$

where $D(t)$ is generally stated by Eq. (18) (a general time-correlational proposal) or by Eq. (19) with the limit of $\gamma \rightarrow 0$, i.e., when the specific ballistic-type proposal indicating the fully hydrodynamic stable mode of the overall process,² taking place within the Stern-type double layer, is addressed. Note that compared Eq. (27) with the Einstein-type definition of $D[R(t)] := \{R^2(t)\}/2t$ (Eq. (21)), one has to have $\Delta\Phi(R) < 0$ while changing it with R (thereby indicating a natural thermodynamic course of the process), i.e., a superdiffusion in our R -space; the case of $\Delta\Phi(R)$ of constant value will particularly correspond to the standard (Einstein) diffusion. When $\Delta\Phi(R) > 0$ with increasing R , appears to hold because of anomalous elasticity-involved boundary effects [7,27], one anticipates thermodynamic–kinetic anomalies either at the crystal surface, or within the interface [6], apparently in a certain accord with the action of the protein–velocity correlational field already mentioned above.

3.4. Towards a morphological phase diagram for non-Kossel type protein crystals

From Eqs. (26) and (27), it is seen that the involvement of the Kramers' barrier given by $\Delta\Phi(R)$ appears to yield $\Delta\Phi(R)$ as a complicated function of the main parameters of the process, such as the ones involved in Eqs. (14)–(16), and the time t . Since we have mostly built our time dynamics upon the interfacial-region concept [6] underlined above, we may let the reader know which is the basic rationale accompanying the construction of the morphological phase diagram of the formation. In order to propose the basic formula of the diagram we may adopt a typical surface-physics involving reasoning and look for $D[R(t)]/D(t)$ as a function of $\beta\Delta\Phi$. Based upon Eqs. (26) and (27) one arrives at

$$\frac{D[R(t)]}{D(t)} = e^{2\beta\Delta\Phi}, \quad (28)$$

what automatically gives the barrier as follows:

$$\Delta\Phi \equiv \Delta\Phi[R(t)] = \frac{1}{2\beta} \times \ln \left[\frac{D[R(t)]}{D(t)} \right]. \quad (29)$$

This implies that $\Delta\Phi$ is unambiguously determined by the global Smoluchowski-type mesoscopic dynamics in the phase space as well as by the local temporal microscopic dynamics assigned to the protein velocity field in the narrow interfacial region [7]. The morphological phase diagram, and its analysis, can then rely upon systematic exploration of Eq. (26) in close interconnection with Eq. (28) (or, Eq. (29) in total), which means, by having object's boundary characteristics σ_R^{ne} from Eq. (16) readily involved.

To have the experimentally motivated chance [4,20,22] to approach the ballistic mode completely, and in a versatile, matter-organization-level involving way, we have to introduce now the long-time (super)diffusive scaling formula, namely

$$D[R(t)] \sim t^\chi, \quad (30)$$

where $\chi \geq 0$ holds for $t \gg t_0$. $\chi = 0$ corresponds to the standard diffusion, and can serve as a reference case, wherein $\Delta\Phi$ does not change with R , or particularly tends to a constant, thus indicating that the detailed balance is not violated in the R -space. Otherwise, because of $\Delta\Phi$ changing with R , a matter drift measured by means of $\partial\Delta\Phi/\partial R$ occurs, the detailed balance is ultimately violated, causing the aggregation to be not at equilibrium. From the ballistic-type-aggregation point of view, the most relevant “linear” case appears when $\chi = 1$, i.e., when $\{R^2(t)\} \sim t^2$, because now both global and local modes agree very well, and the reduced variance, $\varepsilon(t)$, given by Eq. (25) reduces for $t \gg t_0$ to a constant but again only if Eq. (19) with $\gamma \rightarrow 0$ holds. Under such conditions the global (R -space involved, or v_{sph} -driven) and local (interfacial viz $v(t)$ -controlled) dynamic modes operate in a full mutual agreement, thoroughly contributing to the overall hydrodynamics-stability mode (the so-called wave-like limit [20]) over all relevant dynamic scales mentioned above. It is again

²Also consequently termed the wave-like limit [20] throughout the paper's body.

worth noting that the situation described above seems plausible if a temporal proposal of power-law (superdiffusive) type is thoroughly introduced.

4. Spheroid-type formation on many seeds—towards spherulitic polycrystals

In this section, we are going to consider the formation of round-shaped complex polycrystalline objects termed spherulites, that may emerge on many nuclei, available in an entropic (aggregating viz viscosity-changing) inhomogeneous environment. Although the description offered here apparently contrasts with the one given for the ordered non-Kossel type formation, occurring on one stable nucleus, and presented in the preceding section, the resulting kinetic–thermodynamic *MNET*-involving characteristics appear to be of very similar type. The main working conjecture of our investigation can be now briefly stated as: The spherulites are generally able to follow the Avrami–Kolmogorov (AK) phase-change kinetics at the mesoscale [20,22]. Thus, in the case of the polynuclear formation of interest, our nucleation-growth phase transition is postulated to bear a characteristic time-involving fingerprint of AK type. An additional assumption would be that a formation of fibrils within the growing spheroid-type object can stabilize, and ultimately terminate the spherulitic formation, giving finally rise, as in the case of non-Kossel crystals, to a constant-tempo late-time growing mode as the chief kinetic criterion of the weakly ordered (polycrystalline) formation, being undoubtedly an experimentally justified observation [14]. This criterion, in turn, indicates the wave-like hydrodynamically stable [20,22,23] growing mode³ of the protein aggregate under study.

The perennially alive AK phase-change description continues to remain the most popular method also for obtaining (bio)polymer crystallization kinetics information [20,24]. The conceptual foundation of this description is based on the famous combinatorial (raindrop) problem leading to a Poissonian distribution. For spherulites it can be reformulated by quantitatively determining the probability of a point being run over by exactly Q evolving spherulites, $P_{sph}(Q)$, being in the original combinatorial description termed as the number of the wave-fronts. $P_{sph}(Q)$ takes on the standard Poissonian form

$$P_{sph}(Q) = \frac{e^{-\bar{Q}} \bar{Q}^Q}{F(Q)}, \quad (31)$$

where \bar{Q} stands for the average number of the evolving spherulites passing through a point; $F(Q)$ denotes the factorial of Q . The probability of any point not being run over by a spherulite is given by the value of $P_{sph}(Q = 0)$, eventually resulting in

$$P_{sph}(Q = 0) = e^{-\bar{Q}}, \quad (32)$$

since $F(Q = 0) = 1$.

As a consequence of the above, $P_{sph}(Q = 0)$ also represents the points which are still amorphous, i.e., not been passed over by the spherulites, and thus, it is equal to amorphous fraction, θ , which in turn results in having $1 - \theta$ as its crystalline counterpart. Comparing then $1 - \theta$ with $P_{sph}(Q = 0)$ automatically yields

$$\theta = 1 - e^{-\bar{Q}}, \quad (33)$$

which provides the formula for the crystallized fraction.

The problem finally reduces to determine \bar{Q} as a function of geometric assumptions on the nuclei forms as well as the time t after which the children spherulitic phase is born from the parent phase of amorphous type. It then leads to the time-dependent solution to Eq. (33)

$$\theta \equiv \theta(t) = 1 - e^{-\varepsilon t^\nu}, \quad (34)$$

where $\bar{Q} = \varepsilon t^\nu$ is assumed to hold, which involves two parameters: ε and ν . ε is recognized to be dependent on the shape of the growing crystalline germs as well as on the amount and type of nucleation. ν depends upon the nucleation type and growth geometry but not upon the amount of nucleation [24].

³For example, see a discussion about $R(t) \sim t$ late-time asymptotics in under-constant-tempo phase-separating binary fluid mixtures [23], pointing to some hydrodynamically stable mode.

5. Wave-like behavior and beyond it: toward polycrystalline and/or amorphous phase formation

One of the most solid observations on the spherulitic formation, as often as possible reported in the literature, is that the formation very often occurs (asymptotically) in a constant-tempo kinetic–thermodynamic regime [4–8,14,15,18]. This is due to the fact that the droplets-involving amorphization kinetics, usually pronounced in a vigorous manner, is successfully balanced in a dynamic way during the phase change by a counter-effect which appears to be the fibrillization, which always precedes the spherulitic formation [20]. Here, we have in mind the recent experimentally supported assertions that indicate the spherulitic protein formations in soft tissues as a certain possible cause of the neurodegenerative diseases [20] such as the prion-like [25]. One may also have in mind a lysozyme spherulitic growth from aqueous solution in which some viscoelastic effects due to liquid–liquid phase separation can be observed [11,26]. It is demonstrated that the formation goes over a polynuclear path and that its tempo may arrive at the constant (wave-like) limit. The formation is kept isothermal at $T = 22^\circ\text{C}$ with 4% wt lysozyme and 5% wt NaCl as initiators, showing up needles viz fibrils (i.e., rod-like objects) growing radially from an amorphous core [26], an effect to be incorporated and elucidated by means of the below proposed mechanism.

The effect is fully manifested in the late-time zone, and because the fibrillization leads ultimately to a surface-clustering sub-effect caused by the pieces (rods) of the crystalline skeleton, it somehow acts in its final stage as the surface-tension action in case of close-to-equilibrium systems, i.e., as if the system was (for the moment) in quasi-equilibrium with its outer phase (thermostat). Yet, the system departs from this local quasi-equilibrium if there is still an ample place for the pieces to enter the as-yet unoccupied space within the growing object. If there is actually no ample place left, the overall evolution terminates, showing up a characteristic cessation-to-growth stage, frequently reported by experimenters [26].

5.1. Amorphization: de-activating the asymmetric rods-involving growing mode

Let us assume that the phase change takes place in a system of constant total volume, $V_{sph} = \text{const.}$ [14,15,24]. The growth rate of the spherulitic formation can be unambiguously determined by the *MNET* formalism outlined above, with the volume x playing its pivotal role. Proceeding as indicated previously, Section 2, one provides the matter flux [8]

$$J(x, t) = -\frac{L(x)}{TP} \left[\beta^{-1} \frac{\partial P(x, t)}{\partial x} + P(x, t) \frac{\partial \Delta\Phi}{\partial x} \right]. \quad (35)$$

Interpreting $\Delta\Phi \equiv \Delta\Phi(x)$ as an entropic (Gibbs) potential suitable for the spherulitic formation, with

$$\Delta\Phi(x) = C_G \ln(x), \quad (36)$$

asymptotically ($C_G < 0$ —a T and d dependent pre-factor [27]; note that, contrary to the non-Kossel crystal-formation case described above, $\Delta\Phi(x)$ from Eq. (36) practically never achieves a constant-value limit), and assuming naturally that the volume-dependent Onsager's coefficient $L(x)$ follows a power law of the type⁴ x^δ , where $\delta = (d - 1)/d$, with d the Euclidean dimension of the system, one eventually provides the expression of the Smoluchowski-type [16] matter flux

$$J(x, t) = -D(x, t) \frac{\partial P(x, t)}{\partial x} - \beta D(x, t) \frac{\partial \Phi}{\partial x} P(x, t), \quad (37)$$

where $D(x, t)$ is a spherulitic memory-effect involving diffusion coefficient, obeying asymptotically [14,15]

$$D(x, t) = D_0 x^\delta t^\mu, \quad (38)$$

with a reference constant $D_0 > 0$. Note that $\Delta\Phi(x)$ again constitutes the Kramers' barrier, characteristic of the two-state amorphization-spherulitization picture that we would like to offer, being of the Boltzmann-type logarithmic form—exactly as in the case of model non-Kossel crystals, see above.

⁴Thus, $x^\delta \equiv x^{(d-1)/d}$ represents the d -dimensional surface of the spherulite, which scales for $d = 3$ as R^2 and for $d = 2$ as R^1 since, as mentioned before, $x \propto R^d$ applies.

In Eq. (38) one sees that $D(x, t)$ is again proposed (see, Section 3) to be factorized into two parts: a x -dependent part, with the geometrical exponent δ being involved (it pinpoints to the spherulite-surface prevailing behavior, e.g. the one in which surface tension may thoroughly be involved), as well as some time-dependent part, in which the spherulite-formation exponent μ depends upon the Kolmogorov-type amorphization measure $d + 1$ [27] and upon the rod-like spherulitic-skeleton involving behavior, represented by the exponent v_r , usually obeying $v_r \approx \frac{1}{2}$ [14,15]. The dependence upon the time in Eq. (38), and also in its non-Kossel counterpart above, Eq. (27), are manifestations of memory effects, accompanying both types of the protein–object formation under study.

The dependence upon time (t) comes from the fact that the time-dependent part of $D(x, t)$ from Eq. (38) originates from a small ε approximation (the approximation applied to AK-parameter from Eq. (34)), which typically holds for highly viscous systems as ours, and which, because of the linear expansion of the exponent in Eq. (34) [14], ultimately arrives at an algebraic asymptotic behavior of $\theta(t)$ like

$$\theta(t) \sim t^v, \quad (39)$$

wherein $v \simeq v_r \approx \frac{1}{2}$ typically applies [14,15]. This power-law type t^{v_r} contribution is assumed to enter then the diffusion function $D(x, t)$ leading ultimately to a certain time-rescaling of the observables arising from the entire Smoluchowski-equation-based context [16]. Such an overall time-rescaling, involving the exponent μ below, is needed to shift the process from close-to-equilibrium to far-from-equilibrium, which is typically the case of spherulites [24].

Thus, the exponent μ can be defined, similarly as in previous studies [14,15,27], i.e., by means of a simple competition-type formula, as follows:

$$\mu \equiv \mu(d, v_r) = v(d) - v_r, \quad (40)$$

where $v(d) = d + 1$ (a d -dependent part) and v_r generally obeys $v_r \in [\frac{1}{2}; 1]$ with a strong preference towards $v_r \approx \frac{1}{2}$, i.e., when the nucleation of rods is athermal but its rate manifests diffusively viz kinetically.

For the amorphization kinetic–thermodynamic formalism that does not lead at all to the typical spherulitic formation since it over-estimates its average tempo dR/dt , with R becoming now the average spherulite radius⁵ which has to asymptotically conform to constancy of dR/dt , one has to conjecture the rods-involving contribution [28] to be rejected, i.e., $v_r = 0$. Thus, there is no above-mentioned competition involved, and finally,

$$\mu(d, v_r = 0) = v(d) = d + 1, \quad (41)$$

what leads to a strongly superdiffusive (hydrodynamic) overall behavior in x -space, ultimately resulting in a nonconstant behavior of dR/dt , leaving it as an increasing function of time, i.e., arriving at a hydrodynamically unstable mode [23]. This way, the asymmetric rods-involving crystalline mode is switched off, and we finally end up with a fluctuating randomly close-packed system ($v(d) = d + 1$ is primarily a measure of random close-packing, very characteristic of generically amorphous systems) containing the randomly placed and oriented non-crystalline drops [27,28].

5.2. Polycrystallization: activating the asymmetric spherulite-yielding growing mode

When one is able to conjecture, see Refs. [20,28], and the rationale presented therein, that the rods-involving contribution is ultimately not being rejected, as is the case of the spherulite, i.e., when $v_r \neq 0$ applies, one activates the competition (asymmetry) mode, and finally arrives at

$$\mu(d, v_r \neq 0) = v(d) - v_r \approx d + \frac{1}{2}, \quad (42)$$

which yields $\mu(d, v_r \neq 0)$ to be a fractional competition-type exponent; $d = 2, 3$ applies again—these are the most typical cases, the former being the so-called cylindrolite [15] whereas the latter is the ‘real’ three-dimensional spherulite [14]. If it is involved for both spherulitic formations on either athermal or thermal

⁵It can be evaluated after calculating the two first central moments of $P(x, t)$, $\langle P(x, t)^i \rangle$, $i = 0, 1$, where $\langle P(x, t)^1 \rangle = V_{sph} = const.$, $\langle P(x, t)^0 \rangle$ —easily determinable from the overall Smoluchowski- or Fokker–Planck type formalism [1,9,27], and $\langle P(x, t)^0 \rangle R^d \propto V_{sph} = const.$ finally applies.

nucleation seeds, it always properly yields the constant average tempo dR/dt of the overall formation [14,15,20,22,29], pointing to the stable hydrodynamic mode, i.e., when being stabilized by the counter-effect considered, which is also recognized as a kinetic–thermodynamic fingerprint of the spherulitic growth, revealed by the present study. The model proposed here, taken without time-rescaling coming from the involvement of AK phenomenology presented above, cannot properly account for the constant tempo of the process. This is because it gives $R(t) \sim t^{1/(d+1)}$ in the long times' limit [27], i.e., for $d = 2$ one can recover the so-called Lifshitz–Slyozov phase separation asymptotics, $R(t) \sim t^{1/3}$, which is characteristic of a spherical domain growth. Rescaling time by $t \rightarrow t^{\mu(d, \nu, \neq 0)}$ gives rise to a proper temporal evolution of the spherulite, and its on average constant growing tempo; here, the overall averaging procedure must be applied to a thermodynamic bath composed of both thermal and athermal seeds what has been shown in Refs. [14,15]. This way, another proposal for describing spherulitic formation has been offered, with possible application to an insulin–water spherulitic, and above all, fibrillar system, studied in Ref. [22]. This is because to the radially emerging fibrils the above designed rod-like crystalline properties can be assigned, and the analogy can then be used in a way sketched above, or given in a more detailed way in Refs. [14,15], though another type of argumentation towards diffusion-controlled biopolymer adsorption, and its influence on the overall behavior of the fluctuating system, had been offered in it, cf. Ref. [15].

6. Brief discussion on the overall morphological phase diagram for (dis)ordered aggregation

As in Ref. [26], in both cases studied, see Section 3 (model non-Kossel crystals [4–8]) and Sections 4 and 5 (the spherulitic growth [14,20,29]), we consequently argue that the spheroid-type formation in a complex environment, that we consider, follows a surface- and/or interface-integrated kinetics. This implies that the bulk properties of the overall system are not the ones governing the emergence of the formation, as is often pointed out in many experimental studies on this subject matter [6,5,26], see also Refs. [7,8], and the references therein.

Thus, as is shown in Section 3.4 for model non-Kossel crystals, also in a more general (i.e., spherulite-containing) case, one will be looking for a relationship built upon the overall diffusion function, either $D[R(t)]$ from Section 3.3, Eq. (27), or $D(x, t)$ from the preceding section, as a function of the Kramers' barrier, Eqs. (26) and (36), respectively. *Mutatis mutandis*, we can construct such a diagram by a certain case-sensitive replication of the procedure outlined in Section 3.4, mostly resting upon either Eq. (28), or when looking for the properties of the Kramers' barrier, upon Eq. (29).

Certain bounds of the procedure against misleading usage can be prejudiced. For the non-Kossel crystals, and their formation, the interface-integrated kinetics means the application of $D(t)$ of Eq. (27) and σ_R^{ne} of Eq. (27). Thus, the integration is truly surface- (σ_R^{ne}) as well as interface- ($D(t)$) involving, and appears to be of fully kinetic–thermodynamic nature. For the spherulitic growth, in turn, for which the diffusion function is perhaps constructed in a somewhat phenomenological way, see Eq. (38) and the relations beneath, one might also anticipate the fully stated surface–interface integration kinetics to be seen in relation (38), also assisted by the thermodynamics of the process, Eq. (36) [27]. The “a priori” bounds of the procedure must also refer to the fact that one object (non-Kossel crystal) is presumed to grow on one ripe nucleus, whereas its polycrystalline counterpart is taken as a net product of polynuclear growth, rather. This observation should also be realized in each case studied. It is interesting enough to emphasize the fact that both types of performed growing procedures ultimately lead to qualitatively the same types of characteristics—therefore, the procedure of inventing any morphological phase diagram here bears some quite universal aspects, based thoroughly on *MNET*-type formalism, engaging extensively the Smoluchowski dynamics [16], with the Kramers' barrier being readily involved [21].

As for specific aspects of the proposed modelling, it is interesting to note that the formation of fibrils, which involves the rods-containing mode [24,28], can also be studied within the proposed formalism, see Section 5.2, perhaps supporting, or at least supplementing this way valuably, some numerical studies of a d -dimensional spherulitic growth based on phase field model [29,30]. Moreover, because it is widely recognized as a material failure and undesired side-effect [20,22], one would be able, while based on our type of modelling, to state the thermodynamic and kinetic parametric conditions in which such a formation can be limited or even avoided. Thus, the overall modelling may readily serve to offer some arguments in the discussion on how to

grow—from a kinetic–thermodynamic point of view perfect protein single crystals, and try to avoid the often undesired protein aggregations, such as the ones of polycrystalline and inherently fibrillar nature [5,20,29].

7. Conclusions

In this study, a fairly idealized, spheroid-type aggregation of proteins has been considered in terms of *MNET*, i.e., mesoscopic nonequilibrium thermodynamics [1]. The basically mesoscopic level of the description has been supplemented by taking into account certain really relevant microscale dynamic (accompanying) sub-effects, quite commonly termed as the surface- and/or interface-integrated kinetics [26], revealing this way the complex kinetic–thermodynamic phenomenon [4,6], namely the studied model-protein (dis)ordered aggregation. It turns out that the kinetic part of the overall description is due to the memory effects [13] originating from readily applying the *MNET*, with reaction coordinate and time dependent Onsager's coefficient [9], to such a colloid-type viscoelasticity-involving aggregation [3,12]. The thermodynamic part, in turn, is inevitably related to the Boltzmann-type free-energy barrier available for the aggregation, known as the Kramers' barrier [1,21], that typically appears to be dependent upon the curvature (molecular) impact on the growing object, generically pointing to the inherently molecular nature ascribed to the surface tension [27], and some of its peculiarities [7,8]. One is also able to make the proposed description quite comprehensive, depending whether the (un)constrained aggregation preferentially occurs on one nucleation seed or appears to take place on many of them [4]. In both cases, united somehow under the Smoluchowski-equation based [13,16] flag, one is able to draw the rules of spheroid-type formations in question. The wave-like limit [20], characteristic of a constant overall tempo of the formation, which is also recognized as a ballistic type of growth throughout the whole paper's body, appears also very naturally in both cases studied, and at all levels of model-protein matter organization. How to go beyond this limit, i.e., where and when the process becomes more superdiffusive than in the case of its constant tempo, being presumably in favor from a hydrodynamic viewpoint [11,12,23], due to possibly small dissipation of association energy during the formation [2], has also been shown. The morphological phase diagram of the overall nucleation-growth phase transformation [6,18], in particular by showing the way of how the model solution grown protein spheroid, such as the lysozyme (dis)ordered aggregate [2,26], may have chances to become a single crystal [6], and when some polycrystal [20,24], has also been briefly considered. Last but not least, it should be stated clearly that what comes out from the offered Smoluchowski-type theory is that, as recently revealed by the experimentalists [4–6,20,22], such a type of modelling readily points to complex scenario of the presented formations, often arriving at asymptotically constant speed of the formation, though sometimes the process goes out of this constancy, cf. Refs. [4,6] and references therein. We hope that our discussion of the described model protein formations will help in both understanding and interpreting at least some of their interesting results [5,6,20,22,26].

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