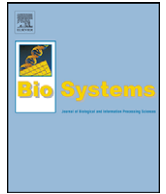




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On the spherical prototype of a complex dissipative late-stage formation seen in terms of least action Vojta–Natanson principle

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ABSTRACT

The spherical prototype of a crystalline and/or disorderly formation may help in understanding the final stages of many complex biomolecular arrangements. These stages are important for both naturally organized simple biosystems, such as protein (or, other amphiphilic) aggregates *in vivo*, as well as certain their artificial counterparts, mimicking either *in vitro* or *in silico* their structure–property principal relationship. For our particular one-seed based realization of a protein crystal/aggregate late-stage nucleus grown from nearby fluctuating environment, it turns out that the (osmotic-type) pressure could be, due to local inhomogeneities, and their dynamics shown up in the double layer tightly surrounding the growing object, still an appreciably detectable quantity. This is due to the fact that a special-type generalized thermodynamic (Vojta–Natanson) momentum, subjected to the nucleus' surface, is manifested interchangeably, whereas the total energy of the solution in the double layer could not be such within the stationary regime explored. It is plausible since the double layer width, related to the object's surface, contributes ultimately, while based on the so-defined momentum's changes, to the pressure within this narrow flickering zone, while leaving the total energy fairly unchanged. From the hydrodynamic point of view, the system behaves quite trivially, since the circumventing flow should rather be of laminar, thus not-with-matter supplying, character.

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1. Introduction

In this work, we are going to convince the reader that an interface-controlled sphere growth in a fluctuating environment (Siódmiak et al., 2007), which may be seen as a crude though still reliable prototype of growing a (complex) crystal, or (bio)molecular aggregate, in late-stage stochastic conditions, may be ruled ultimately by corresponding least action principle(s), pointing fairly to conservative and minimum-dissipation dynamics of the formation at its close-to-equilibrium state.

Thus, in this particular study we wish to stress very much a dynamic aspect of the, in general, complex formation, over its purely thermodynamic counterpart that has been developed elsewhere (Gadomski, 2007). We see a quite appealing need for performing the study of such a type since the dynamic aspects are, as being often hardly accessible experimentally, postponed or left for future studies as quite difficult to perform, except that a computer-simulation oriented stream of research (Bratko and Blanch, 2001)

from time to time attempts on uncovering some interesting aspects of the complex phenomena—realize that crystalline protein aggregations are very often accomplished in practice by trial-and-error “method”, or quite equivalently, by tedious scanning over multi-parametric windows of data (Haas and Drenth, 1998).

Notice that such aggregations also appear unavoidably as by-products of spurious physiological, thus genetic-environmental conditions—they are described as failures to otherwise non-problematic functioning of our organisms (Gspöner and Vendruscolo, 2006)—as an example appearances of neurodegenerative diseases (Parkinson; Alzheimer; Creutzfeldt-Jacob; etc.), often associated with fibril formations, should be invoked (Krebs et al., 2005). In the light of the above, a study based on certain physical, least action concerning principia and (thermodynamic) rules, might be of appreciable help, and this stands for a basic motivation, and novelty, of the present work.

Throughout this study, we will use, for transparency and simplicity reasons, a spherical approximation to otherwise non-spherical problem—the formation of complex biomolecular aggregates such as fibrils and/or non-Kossel crystals (Krebs et al., 2005; Chernov, 1997). The rest of the paper is devoted to explore this approximation in terms of least action, or equivalently, least

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dissipation language (Gambár and Márkus, 2003; Sabater, 2006), whenever appropriate.

2. A Sphere Nested in a Narrow Double-layered Stochastic Envelope

Let $c(\vec{r})$ be a near-distance external concentration field of the Brownian particles viz protein molecules in an aqueous solution, in a narrow domain $\partial\Omega$, circumventing the nucleus made up of proteins too. Let $C(\vec{r})$ be a density of the growing nucleus; \vec{r} is the position vector (field) of the particles' ensemble. At time t the nucleus has the volume $V(t)$ which increases to $V(t_1)$ at time $t_1 > t$ due to incorporation of the proteins from its nearest surroundings ("envelope") $\partial\Omega$. The amount of mass in the nucleus at time t equals

$$m(t) = \iiint_{V(t)} C(\vec{r}) dV \quad (1)$$

and at t_1 (Gadomski et al., 1993) reads

$$m(t_1) = \iiint_{V(t)} C(\vec{r}) dV + \iiint_{V(t_1)-V(t)} c(\vec{r}) dV. \quad (2)$$

The rate of change of mass at time t_1 can be approximated reliably by the net mass flux passing through the nucleus' surface $\sum(t_1)$

$$\frac{m(t_1) - m(t)}{t_1 - t} \approx \iint_{\sum(t_1)} \mathbf{j} \cdot d\mathbf{S} \quad (3)$$

where $\mathbf{j} = \mathbf{j}[c(\vec{r})]$ is the flux of particles whose dependence on $c(\vec{r})$ follows from the physics of the problem (Gadomski et al., 1993; Gadomski, 2007), and $d\mathbf{S}$ is an inward normal to the surface $\sum(t_1)$.

When exploiting the limit of $t \rightarrow t_1$, one, after making use of Eqs. (1)–(3), finally arrives at an integro-differential equation for a growing nucleus, namely

$$\frac{d}{dt} \iiint_{V(t)} [C(\vec{r}) - c(\vec{r})] dV = \iint_{\sum(t)} \mathbf{j} \cdot d\mathbf{S}. \quad (4)$$

For colloid- and protein-type (dis)orderly aggregations, in particular non-Kossel crystal formations, one proposes $\mathbf{j}[c(\vec{r})] = c(\vec{r})\vec{v}$ (Gadomski, 2007), wherein \vec{v} represents the velocity vector-field of proteins in the narrow domain ("envelope") $\partial\Omega$. Thus, one provides ultimately a colloid-type aggregation overall pace (Gadomski et al., 1993) as follows

$$\frac{d}{dt} \iiint_{V(t)} [C(\vec{r}) - c(\vec{r})] dV = \iint_{\sum(t)} [c(\vec{r})\vec{v}] \cdot d\mathbf{S}. \quad (5)$$

Note that no special assumptions have been made about the shape of the nucleus so far, whether it is spherical or deviates from sphericity. When, however, one is making use of spherical symmetry readily, and for simplicity assumes that always $|\vec{v}| = v_{\text{prot}} = \text{const.}$ applies, one is left with a deterministic evolution equation for unperturbed sphere of radius R , namely (Gadomski and Siódmiak, 2005)

$$\frac{dR}{dt} = v_{\text{prot}} \times \frac{\sigma R + R_c}{R - R_c}; \quad R \equiv R(t) \quad (6)$$

the full solution of which reads (Gadomski et al., 1993)

$$R(t) - R(t=0) - (R_c + 2\Gamma) \ln \left[\frac{R(t) + 2\Gamma}{R(t=0) + 2\Gamma} \right] = \sigma v_{\text{prot}} t \quad (7)$$

where $\sigma = c(R)/[C - c(R)]$ —supersaturation (Siódmiak et al., 2007), v_{prot} —constant protein velocity, both of them detected in the double-layered "envelope" $\partial\Omega$; R_c stands for the critical nucleus' radius, $R_c = 2\Gamma c_0/(C - c_0)$ (Gadomski and Siódmiak, 2005), where

Γ stands for the Gibbs–Thomson type constant,¹ and $c \rightarrow c_0$ when $R \gg R_c$ holds. C , the density of the spherical nucleus, is given a constant value, $C = \text{const.}$ (A full usage of the spherical-symmetry conditions also implies that the vector coordinate \vec{r} is suitably replaced by its radial counterpart R ; as a consequence, now one anticipates a concentration value of $c(R)$ at the surface of the sphere, as a natural limit of $c(\vec{r})$ (Gadomski, 2007).) Let us realize that when $R \gg R_c$ appears to be effective, an asymptotic (late-stage) solution to Eq. (6) conforms to a simple scaling formula of $R(t) \propto t$ (for $t \gg t_0$, with $t_0 \geq 0$ —initial time), with the proportionality constant obeying $0 < c_0 v_{\text{prot}}/(C - c_0) \ll 1$, see below.

3. Late-stage of Nested-sphere Damped Growth According to Vojta-type Variational Principle: Least Action vs. Minimum Entropy-production Paradigm Reconsidered

Let us name the sphere under consideration as a nested sphere since it is from now on assumed to be truly nested in a very delicate envelope made up of the circumventing Stern type double layer (thus, the proteins would become macroions; Siódmiak et al., 2007) in which the concentration in the external (upper) zone of the layer is always considered as twice so big when compared with the same quantity measured at the internal (lower) layer's zone, cf. (Gadomski, 2007) and refs. therein. The supremum of both quasi-equilibrium concentrations mentioned is $2c_0$ at $R \gg R_c$; this value is, however, always assumed to be small compared to C . Thus, the condition of $C \gg 2c_0$ constitutes the so-called depletion-zone condition, very characteristic of colloid-type aggregations. Therefore, our conception of uniformly supplied-with-matter envelope unites under a common flag the double layer (toward protein crystal growth and aggregation) and depletion-zone (toward colloid (dis)orderly aggregation). It also assures an existence of radially oriented local "structural" gradient $(2c_0 - c_0)/\Delta r = c_0/\Delta r$, where Δr denotes the double layer width. This structural gradient cannot be constant under transient stages of the growth, even if they approached some close-to-equilibrium condition(s). It should, however, behave smoothly, tending to a characteristic constant value when the growing system attains its (first but late) stationary state. Our working assumption now is going to be that in late-stage (slow; damped) growing conditions of the spherical prerequisite of the crystal (or, aggregate), being represented by a nonzero set of stationary states both c_0 as well as Δr may virtually attain their constant limits, so that $c_0/\Delta r \rightarrow \text{const.}$ —perhaps except of possible but small changes due to some fluctuations of the $\partial\Omega$ -domain medium's composition, coming from proteins rare-event actions close to the surface. Which is the nature of such a dynamic fluctuation itself, proposed to be quantified by $\kappa_R = d\Delta r/dR$, will be developed in what follows, and has been associated tightly with the least action principle.

There should be no doubt that the real thermodynamic–kinetic conditions for the formation are of inherently stochastic nature (Luczka et al., 2002; Gadomski et al., 1993), thus leaving the above quiescent-state (deterministic and phenomenological) picture as being not fully satisfied. The stochastic nature of the formation, in turn, would mostly imply a time-correlational statistics being suitably manifested by the velocity field \vec{v} , designated now in a scalar form by a v_{rand} . Certainly, also this way the picture looks far from being complete (Siódmiak et al., 2007; Luczka et al., 2002), especially when consequently neglecting so far the envelope's concentration variations in the (radial) space domain, represented by the concentration gradients (Gadomski and Siódmiak, 2005).

¹ It contains a signature of biomolecule's persistence length and mass too.

So far, however, it is known that when such time-correlational statistics is properly chosen for a new stochastic problem such as the one stated below

$$\frac{dR}{dt} = v_{\text{rand}} \times \frac{\sigma R + R_c}{R - R_c}, \quad (8)$$

where v_{rand} constitutes a stationary Gaussian, algebraically correlated (in time t) multiplicative noise, selected as the most appropriate (Gadomski, 2007) noise source.

The above stochastic equation in its Stratonovich representation has a Fokker–Planck, cf. Luczka et al. (2002) “substitute” which is commonly termed the Smoluchowski equation. This Smoluchowski equation, in turn, can also be derived from the Gibbs’ entropy-production equation coming from nonequilibrium mesoscopic thermodynamics (Gadomski, 2007). The most striking result appears to be a possibility of deriving the Gibbs’ free energy (herein, as $-TS$, with S —the Boltzmann–Gibbs entropy, being widely recognized as a measure of (dis)order and/or information loss/gain, respectively) in a Boltzmann-type (say, traditional) logarithmic form, such as $-k_B T \ln A$ —the argument A , in turn, involves a principal competition effect between the solubility σ^{-1} and the velocity field v_{rand} (Gadomski, 2007; Luczka et al., 2002; Gadomski and Siódmiak, 2005). This way, however, the whole loop seems to be closed in the sense that under reflecting boundary conditions for the protein-matter flux (characteristic of a Kramers type barrier to surmount; Hänggi et al., 1990), and when assuming linear (near-equilibrium) flux–force relations, as well as a proportionality between two main Onsager’s coefficients (diffusion and drift “constants”), one arrives unambiguously at a conclusion: Entropy production (or, dissipation rate) (Glansdorff and Prigogine, 1970; Gambár and Márkus, 2003) and (global) mass conservation law, namely Eq. (5)(Gadomski et al., 1993) are exactly the same powerful machines driving such incredibly entropic system! At this point, let us mention formally that from Sobolev’s inequality, being a mathematical fingerprint of the Gibbs’ entropy-production rate (Dłotko, 1987) it follows that for the Smoluchowski equation, with the corresponding (boundary) conditions mentioned, the entropy production is always positive, and tends to zero when the system approaches the thermodynamic equilibrium (Gambár and Márkus, 2003; Glansdorff and Prigogine, 1970).

In the light of what has been rationalized above a legitimate question can be posed: Close to late(st) stage of the spherical nucleus’ formation is there a certain expected interesting “unification” of thermally versus dynamics-driven (pre)ultimate formation’s conditions to occur? If so, could they be stated while based upon a variational principle, pointing univocally to a (Mau-pertuis) least action conditions that appear to prevail usually in such a non-quiescent (local-spatially perturbed²) state, or virtually, a finite system of such states? Our answer, though approximate, ultimately becomes positive, and can be presented as follows. First, note that in our case, i.e. while based on Eqs. (1)–(6) one could generally accept to identify the kinetic energy in terms of the “envelope” (protein-field) concentration source, $c(\bar{r})$. In the same vein, the “potential” (dissipation) energy of the system (we expect that our approximation goes for relatively big viz inertia-feeling aggregates and crystals being formed) could be identified with the nucleus’ density $C(\bar{r})$. The difference of the former and the latter, the envelope’s minimalistic “Lagrangian” prerequisite, L , cf. Eq. (5), could be taken at first sight as the most relevant dynamic observ-

able, namely

$$L[c(\bar{r}), C(\bar{r})] = \lambda[c(\bar{r}) - C(\bar{r})], \quad (9)$$

with λ being a real-value (energy density) constant, responsible mainly for keeping track of appropriate physical units, and then, for posing some limit of our approximation.

Second, if the above would be accepted there existed a (near) late-stage ‘spherical-symmetrical’ limit of the “Lagrangian” prerequisite, namely some $L[c(\bar{r}), C(\bar{r})]$, defined so far as

$$L_{l-s}[c(R), C] = \lambda[c(R) - C], \quad (10)$$

with C —a constant (as above) or an active-concentration shift, wherein the active-concentration means of course $c(R)$, especially when compared to C . But this activity pre-condition stated in terms of $c(R)$ alone is, unfortunately, insufficient, because within the envelope of width Δr , $c(R)$ might experience some accidentally occurring local changes, due to medium’s composition inhomogeneities (Haas and Drenth, 1998), that are proposed to be assumed as nonlinear in $dc(R)/dR$, such that $c(R)$ should be replaced by some $c_2(R)$, where

$$c_2(R) = c(R) + \left(\frac{dc(R)}{dR}\right) \Delta r + \left[\left(\frac{1}{2}\right) \left(\frac{dc(R)}{dR}\right)^2\right] (\Delta r)^2, \quad (11)$$

i.e. being expanded in a power form up to the second term. Note right now that the quadratic term at the r.h.s. of Eq. (11) is necessary to assure somehow the existence of a pressure within the domain $\partial\Omega$. (One could also recall a quadratic term of such a type in the famous Kardar–Parisi–Zhang/KPZ parabolic equation (Dłotko, 1987), describing the surface-growth dynamics under random-force field: in KPZ it is always attributed to a lateral shift of the surface profile, experienced in reality in such field applied.) Moreover, let us anticipate the respective change in notation of $L_{l-s}[c(R), C]$ by $L_{l-s}[c_2(R), C]$. Actually, the change in our notation implies that from now on we would like to opt for having the Lagrangian $L_{l-s}[c_2(R), C]$ as being ultimately proposed for describing the inhomogeneity, κ_R , dynamics readily. Finally, let us claim that indeed a stationarity condition within the envelope is to be satisfied, namely that $d^2c(R)/dR^2 = 0$ —the latter stands for the well-known stationary-diffusion condition within $\partial\Omega$ narrow domain. This is fairly plausible since the balance condition, represented by $dH_{l-s}/dc(R) = -d^2c(R)/dR^2$ (Gumiński, 1980; Natanson, 1896), experiences very negligible changes when the system prefers to sit close-to-equilibrium, cf. Eq. (14), so that the Laplace stationary-diffusion condition seems to hold ultimately. Bear in mind that the local-spatial “fluctuation” (inhomogeneity) dynamics will be described in terms of variational language of the thermodynamics.³ At this stage of our presentation it should suffice to mention that the conventional time operator in Hamilton dynamics, namely d/dt will be replaced by our desired local-spatial operator d/dR , designated for conciseness by ∇_R , thus the substitution $d/dt \rightarrow \nabla_R$ applies. The most important conceptual message

³ In Hamilton–Jacobi, also Lagrange and Newton customary used language of dynamics, our present (thermo)dynamic proposal given by Eq. (11), and its context explored thereafter, should perhaps be rewritten as $L_{l-s}[c_2(R), C] = T_{\text{kin}} - U_{\text{pot}}$, wherein $T_{\text{kin}} \simeq c(R) + (dc(R)/dR)\Delta r + [(1/2)(dc(R)/dR)^2](\Delta r)^2$, and $U_{\text{pot}} \simeq C$, with accuracy depending on the magnitude of constant λ from Eq. (10). Note, however, that $L_{l-s}[c_2(R), C] \equiv (dc(R)/dR)\Delta r + [(1/2)(dc(R)/dR)^2](\Delta r)^2 - [C - c(R)]$ holds, which would suggest a splitting of the energy difference, measured by Lagrangian L_{l-s} to fast-changing and slow-changing energetic modes given by two last terms put before and after the subtraction sign, respectively. To construct properly the Hamiltonian, cf. Eq. (14), to the latter the (supremum) double layer concentration $2c(R)$ should be added, which finally would make some inconsistency when applying it right in this form—therefore so designing the Lagrangian is forbidden.

² Such tacitly taken postulate about this spatial rare-event and regressive perturbation of the homogeneity of the $\partial\Omega$ -domain medium’s composition is quantified by local concentration gradient.

appears to be that the customary used Lagrange–Hamilton action operator, taken over the whole time domain, will be formally substituted into a dissipation volume integral. For both operators analogous minimum conditions, such as the one stated below, can be considered (Gumiński, 1980; Natanson, 1896). Then, one is able to write down formally the least action variational principle as the minimum condition applied to Eq. (5), in its late stage of constant and very slow formation pace $dR/dt \rightarrow \text{const.}$ emphasized above, as follows (notice: the below written integral is formally called the dissipation volume integral; Natanson, 1896)

$$\delta \iiint_{V_{\text{sphere}} = \left(\frac{4}{3}\right)\pi R^3} L_{I-s}[c_2(R), C] dV = 0, \quad (12)$$

(by the way, involving, as expected, no time integration due to reduction of our exploration interest up to stationarity conditions, only) which results in a novel, quasi-dynamic Newton-type analogous (thermodynamic) law, such as

$$\nabla_R \frac{\delta L_{I-s}[c_2(R), C]}{\delta \nabla_R c(R)} - \frac{\delta L_{I-s}[c_2(R), C]}{\delta c(R)} = 0, \quad (13)$$

wherein $\nabla_R c(R) \equiv dc(R)/dR$, cf. Eq. (11). Bear in mind that now, in contrast to the Hamilton mechanics, the partial differentiation in Eq. (13), representing the (dis)orderly aggregation late-stage dynamics in terms of κ_R -inhomogeneity development, is performed over the prior-to-use preselected intensive variable, herein $c(R)$ (and its gradient, $\nabla_R c(R)$) of course, thus one has to associate it with its transportation (process) property, i.e. with a local flux, which in our case looks plausible while based upon the local mass conservation in the domain $\partial\Omega$, cf. Eq. (16) beneath. In what follows one would be curious to see at which point our formal preference of the dynamic part over its thermodynamics reminder would arrive in case of late-stage growth of interest? Next, the system, when entering the late stage is expected naturally to be conservative in terms of energy, so that its “Hamiltonian”, linked generally to the “Lagrangian” by a Legendre transform, fairly conforms to

$$H_{I-s}[c_2(R), C] = \lambda[c_2(R) + C], \quad (14)$$

which provokes when keeping it fairly conserved, $dH_{I-s}/dt \approx 0$, that if $R \gg R_c$ readily, than the total mass contained in the double layer (“envelope”), denoted by $m_{\Delta r}$, does not change appreciably any more, so that $dm_{\Delta r}/dt \approx 0$ preferentially applies. Notice that if $R \gg R_c$ is fulfilled than $c_2(R) \rightarrow c_0$ holds, which means that our simple minded H_{I-s} from Eq. (14) tends really to a constant, since $\nabla_R c(R) \rightarrow 0$ should apply ultimately. This further implies, because of the volume of the spherical nucleus, $V_{\text{sphere}} = (4/3)\pi R^3 \sim \text{const.}$, being fairly preserved too, that within the (quasi-adiabatic⁴) “envelope” one provides, within the above juxtaposed accuracy limits, that also very likely

$$\frac{dc(R)}{dt} = 0, \quad (15)$$

which straightforwardly means that the local (within-envelope) mass conservation law holds, namely that

$$\frac{\partial c(R)}{\partial t} = -\text{div}[c(R)v(R)\vec{e}_R] = -\vec{\nabla}_R c(R) \cdot \vec{e}_R v(R) = \frac{dc(R)}{dR} v(R), \quad (16)$$

with \vec{e}_R , a corresponding unit-vector acting outwards along radial direction (Gadomski et al., 1993). Note that, in general, the velocities v_{rand} from Eq. (8) as well as $v(R)$ from Eq. (16), the former formally associated with time- and the latter with local-spacial changes are

for sure interrelated, but in general, they should be considered as different. It seems, however, legitimate to ascertain that the quantity $v(R)$ can be associated with local flickering changes within the field $c_2(R)$, the latter being prompted mainly by protein motions within $\partial\Omega$. The motions, when the protein is considered as neutral molecule, could be associated with local diffusive concentration gradients. When, in turn, the protein is considered as macroion, thus as a charged particle, $v(R) \simeq v_{\text{rand}}$, wherein v_{rand} should follow an “intermittent” time statistics, coming from electrostatic interactions and water-caused screening effects of the macroions with the surface. For such a case, Eq. (16) instead of first Fick’s law has to be applied locally in $\partial\Omega$ (Gadomski and Siódmiak, 2005; Siódmiak et al., 2007). Summing up in part, one can say that Eq. (16), or equivalently Eq. (15), both of them support well the overall mass- and total-energy conservative scenario within the envelope $\partial\Omega$.

Turning back to Eq. (13), anticipated univocally as the analog of the Newton’s law, one finally arrives within by λ imposed accuracy at a Vojta-type (Gumiński, 1980) “envelope’s momentum”, i.e. the generalized variational-principle thermodynamic momentum

$$\Pi(R) = \frac{\delta L_{I-s}[c_2(R), C]}{\delta \nabla_R c(R)} \simeq \Delta r[1 + \Delta r \nabla_R c(R)], \quad (17)$$

defined in the same manner as provided by Vojta many years ago (Gumiński, 1980), and being a central result of the thermodynamic approach invented. To fulfil linear thermodynamics conditions (Gadomski, 2007; Gambár and Márkus, 2003), stated on the Onsager’s flux–force basis (Glandsdorff and Prigogine, 1970), one has to pose a limit on its validity, namely that $|\vec{\nabla}_R c(R)| \gg \lambda^{-1/2}$ should work. (A precursor of such variational approach was W. Natanson, a physicist from Jagellonian University, Cracow (Natanson, 1896).) Notice that the generalized thermodynamic momentum is given in terms of the double layer width Δr , as well as its corrections due to existence of the local-spacial gradients, causing some micro-flows in $\partial\Omega$ zone. Be aware that these local gradients do vanish at any local equilibrium, thus $dc(R) = 0$ is established. Interestingly, there exists, cf. Eq. (17), the Vojta-type momentum at such equilibrium, namely

$$\Pi_{\text{eq}}(R) \simeq \Delta r. \quad (18)$$

This would imply that according to Eq. (18) the Vojta-type momentum $\Pi_{\text{eq}}(R)$ is about for being conserved when the width $\Delta r \rightarrow \text{const.}$ Otherwise, it is not conserved even at equilibrium.

As a consequence, and within by λ imposed accuracy, the nonequilibrium (but close-to-equilibrium) thermodynamic “force” (outflow), F_{th} , possibly acting on the object’s surface, this way exerting virtually a pressure on it, looks like

$$F_{\text{th}} = \frac{\partial \Pi(R)}{\partial \nabla_R c(R)} \simeq \Delta r^2, \quad (19)$$

i.e. it is given entirely in terms of the envelope’s width Δr but squared, cf. Eq. (19). Notice that very close-to-equilibrium this force may equilibrate due to $\Delta r \rightarrow \text{const.}$ but otherwise it does not.

The osmotic-type pressure can then be estimated as the force F_{th} acting on the fixed surface area of the sphere at some $R \gg R_c$; this area $a_{\text{sph}} = 4\pi R^2$, thus the osmotic-type pressure, when undergoing a standard pressure’s definition, namely $\pi_{\text{osm}} = F_{\text{th}}/a_{\text{sph}}$, reads

$$\pi_{\text{osm}} \simeq \frac{1}{4\pi} \left(\frac{\Delta r}{R}\right)^2, \quad (20)$$

thus, being fully derivable by the nested sphere two attributes: its radius R and envelope’s width Δr . Thus, it is shown that such momentum $\Pi(R)$, given by Eq. (17), when subjected to the nucleus’ surface upon its respective changes, may contribute markedly to the osmotic-type pressure near interface. It seems that this quantity, in general, would bear a signature of the second virial coefficient, the

⁴ Since the process that we study though globally isothermal, may locally, which means in the “envelope”, deviate slightly from such a quite “stiff” and experimentally justified condition of $T = \text{const.}$ (Chernov, 1997), where T —the temperature.

value of which helps to decide whether the biomolecular aggregation is orderly, even though being of non-Kossel crystalline output (Chernov, 1997), or not (Haas et al., 1999).

Finishing this section, let us come back to the (analogous to Newton's law) dynamics of the $\partial\Omega$ -domain medium's inhomogeneity κ_R . From Eq. (13) it clearly follows that in the stationary-diffusion condition, $d^2c(R)/dr^2 = 0$, this inhomogeneity $\kappa_R = d\Delta r/dR$ develops according to a quantitative recipe given by

$$\kappa_R(1 + 2\Delta r \nabla_R c(R)) \approx 1. \quad (21)$$

It results in having, thanks to the above mentioned Laplacian-field stationarity (energy balance) condition, the inhomogeneity of interest as fairly uniquely determined, namely

$$\kappa_R \approx \frac{1}{[1 + 2\Delta r \nabla_R c(R)]}. \quad (22)$$

Realize that very nearly to the equilibrium κ_R is defined as $\kappa \approx 1$, i.e. constant. It is possible only when the object at equilibrium, no matter whether the finally grown spherical crystal or not, stands itself for the (biggest) inhomogeneity, since $\Delta r \approx R$ holds. Otherwise, κ_R , as is seen from Eq. (22) takes on fractional, even very small values. It could also be mentioned that from Eq. (22) one may easily recover the width of the $\partial\Omega$ domain in terms of the local-spatial gradient $\nabla_R c(R)$ and the fluctuation κ_R , namely

$$\Delta r \approx \frac{1}{2\nabla_R c(R)} \left(\frac{1}{\kappa_R} - 1 \right). \quad (23)$$

As noted above the limit of $\kappa_R \approx 1$ results in $\Delta r \approx 0$. This implies again that at the (true) equilibrium there is no special reason for speaking about the existence of our $\partial\Omega$ domain anymore.

4. Late-stage Conservative Conditions for the Nested Sphere: A Hydrodynamic Limit as Revealed by Laminar (Macro)ions' Flow

It can also be seen, and it follows again, from the least action (Maupertuis) principle for the (very slowly) growing object, Eq. (12), especially when confronted suitably with Eq. (5) and Eq. (15), that from a hydrodynamic point of view the late-stage (dis)orderly protein aggregate growth may be characterized by a more or less laminar flow of macroions (i.e., proteins, with their individual, mainly water-based "envelopes" carried with).

From Eq. (12), seen in terms of the (variational) minimum condition to Eq. (5) at $R \gg R_c$, it follows immediately that

$$v(R)\vec{e}_R \cdot \vec{d}S_{\text{sphere}} = 0 \quad (24)$$

applies, which means that because of $\cos[v(R)\vec{e}_R, \vec{d}S_{\text{sphere}}] = 0$ in Eq. (24), the velocity vector-field must be seen to be pointed perpendicularly to the radial direction, thus, in such way as if it was more "swimming" along the nucleus' surface than going to feed it furthermore. Thus, this field is recognized to lose entirely the direction indicated by \vec{e}_R . (From hydrodynamic point of view such boundary conditions are called the slip boundary conditions: thus the laminar flow of proteins immersed in aqueous solution is going to slip along the spherical object's surface.)

This implies ultimately that under the late-stage conditions, as expected, the scenario cannot be fully hydrodynamic (no chance for turbulence for sure!) but it is ought to be smooth enough, thus laminar. In other words, the chance for increasing the nucleus' volume drops down dramatically, except of rare-event "feeding" through regressive ionic-composition (or, water-based restructuring) fluctuations to occur virtually. Thus, one may say that the formation is practically terminated—a relevant observation when concerns technological realizations to become efficient.

5. Final Address and Perspective

In this study, we have developed systematically our type of rationale, starting from a basic physical observation that thermodynamics contains also a dynamic, deeply essential part worth exploring. Therefore, each thermodynamic (or, thermodynamic-kinetic) process (Gadomski, 2007; Siódmiak et al., 2007; Gadomski and Siódmiak, 2005), such as any (dis)orderly aggregate formation can be, must also uncover some interesting dynamic peculiarities, such as those fairly assigned to the quasi-adiabatic system of the nested sphere in late-stage growing conditions, presented throughout.

From the underlying theoretical, and to some extent fairly approximate and stationarity-involving proposal, it clearly follows that the dynamic sub-description (Gambár and Márkus, 2003) conveyed throughout the paper can by itself express some chances as to reveal very interesting, also stability-concerning aspects of the formation, especially the dynamic properties of the inhomogeneity, or (radial) "fluctuation" κ_R —this fact being of special interest from a practical, let us say, mainly technological viewpoint. The biomedical context cannot be omitted as well, cf. Krebs et al. (2005); Gsponer and Vendruscolo (2006), and refs. therein.

Speaking concisely, since in both technological as well as biomedical circumstances the aggregation as a thermodynamic process is rather considered as an undesirable side-effect, therefore all strategy in both seemingly different activity fields should rely on controlling the awkward, possibly defects-causing "fluctuation", in terms of the double layer width Δr , and the gradients $\nabla_R c(R)$ (as well as macroions' velocity statistics; Luczka et al., 2002), emerging therein.

The most relevant aspects uncovered can be juxtaposed as follows: (i) in the late-stage conditions, the nested-sphere system in a transient heat bath is about to follow the energy conservation quite likely but cannot be thought of to follow, in general, the (Vojta-type) momentum conservation (Natanson, 1896; Gumiński, 1980)—the interchangeable and nonequibrated (Glansdorff and Prigogine, 1970; Sabater, 2006) action of the osmotic-type pressure is rather expected to manifest instead; note that typically, if the system, for example a diffusion-reaction system "sitting" close-to-equilibrium, obeys the total-energy conservation, it also manifests a Hamilton-Newton total-momentum conservation, at least when examined in an inertial reference frame; (ii) the hydrodynamic aspect of the process, when $R \gg R_c$ readily applies, seems to be of secondary importance from scientific viewpoint but looks promising from technological applications because of its laminar, thus "slippery", character; (iii) the above stated, and shown throughout the paper, appears to be in excellent semi-quantitative accord both with experimental trends (Haas and Drenth, 1998; Haas et al., 1999) as well as with recent description of the process given in terms of the double layer ("envelope") as a (macro)ion channel with its open-close states Fuliński et al. (1998)—here the open state, characteristic of generally non-Markovian dynamics, corresponds to our late-stage crystal-growth conditions, whereas other, transient and long-preserving states far-from-equilibrium (Nicolis et al., 2004), may yield certain (dis)orderly aggregates' formations or cessation-to-growth events Siódmiak et al. (2007). Then, it may lead to fluctuation-induced transitions in protein crystallization and aggregation (Nicolis et al., 2004).

In a final word, it should be emphasized that the so-called metastable demixing (or, liquid-liquid immiscibility) region viz. narrow zone, characteristic of appearance of such an envelope (depletion zone; double layer, as is termed the paper throughout) is an experimentally justified fact (Haas and Drenth, 1998; Haas et al., 1999), to be deciphered from protein-crystal versus aggregate phase diagrams (Bratko and Blanch, 2001)—they are typically solubility against concentration, also osmotic pressure

involving (and, temperature) plots (Chernov, 1997). In the proposed, fairly provocative approach, we are able to offer a (modified) solubility measure by means of the inverse of the supersaturation $\sigma^{-1} = [C/c_2(R)] - 1$, thus having the near-surface concentration not as $c(R) = c_0(1 + (2\Gamma/R) + \Delta\chi)$ (Gadomski, 2007), i.e. by means of a generalized Gibbs-Thomson boundary condition, with some $\Delta\chi$, a mechanism- and temperature-dependent (additional; possibly nonequilibrium (Nicolis et al., 2004)) term (Gadomski and Siódmiak, 2005). We have rather to opt for utilizing $c_2(R)$ (be aware that our results are quite biased by this justifiable presumption, Eq. (11)) for being, in principle, capable of providing such plots (Haas and Drenth, 1998; Chernov, 1997) as well. As has been shown above, a derivative of $\Pi(R)$ such as $\pi_{\text{osm}} = (\delta\Pi(R)/\nabla_R c(R))$ at some $R \gg R_c$, when subjected to the corresponding sphere-surface “test” area $a_{\text{sph}} = 4\pi R^2$, would give rise to the osmotic-type pressure, in the energetic form of

$$\pi_{\text{osm}} \simeq (\Delta r)^2 \approx \Pi^2(R)_{\text{eq}}, \quad (25)$$

cf. Eq. (18), so that the plots solubility vs. osmotic pressure, given in terms of equilibrium Vojta-type momentum (Gumiński, 1980; Natanson, 1896) but squared, seem available too. Since typically expansion of the latter over the concentration (Haas and Drenth, 1998) would allow to extract the second virial coefficient, B_2 , we might also interpret our result in such terms upon realizing that B_2 of our type, avoiding purposely for the moment to speak of its range and sign (Chernov, 1997), would contain the geometrical information about the actual magnitude of the nucleus surface, within spherical approximation given always by a_{sph} used in Eq. (20) for some suitable $R \gg R_c$. Another attractive context, involving the local-spatial inhomogeneity, and its phase-transitive capacity (Nicolis et al., 2004), cf. Eq. (22), an effect to be followed by suitable optical and spectroscopic methods (Krebs et al., 2005; Gsponer and Vendruscolo, 2006) in parallel with Δr -behavior, opens up some emerging practical possibilities too.

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