Theory of a reconstructive structural transformation in capsids of icosahedral viruses

S. B. Rochal[1,2] and V. L. Lorman[2]
[1]*Physical Faculty, South Federal University, 5 Zorge Str., 344090 Rostov-on-Don, Russia*
[2]*Laboratoire de Physique Theorique et Astroparticules, CNRS–Universite Montpellier 2, Place Eugene Bataillon, 34095 Montpellier, France*

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A theory of a reconstructive structural transformation in icosahedral capsid shells is developed for a whole family of virulent human viruses. It is shown that the reversible rearrangement of proteins during the virus maturation transformation is driven by the variation in the wave number l associated with the protein density distribution function. The collective displacement field of protein centers from their positions in the initial (procapsid) and the final (capsid) two-dimensional icosahderal structures is derived. The amplitude of the displacement field is shown to be small and it minimizes the calculated free energy of the transformation. The theory allows us to propose a continuous thermodynamical mechanism of the reconstructive procapsid-to-capsid transformation. In the frame of the density-wave approach, we also propose to take an equivalent plane-wave vector as a common structural feature for different icosahedral capsid shells formed by the same proteins. Using these characteristics, we explain the relation between the radii of the procapsid and capsid shells and generalize it to the case of the viral capsid polymorphism.

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I. INTRODUCTION

Viruses are nanometer-size highly ordered systems, which combine in their life cycle specific properties encoded in their genome with general physical mechanisms of self-organization. Viral genetic material is protected from external chemical aggressions by a shell (capsid) made of many copies of identical proteins [1]. In addition to the protective function, the viral capsid plays an important role in the transmission of viral genome to an appropriate host cell, i.e., in the way that the virus infects the cell. Extensive studies by means of x-ray diffraction and electron microscopy revealed that the protein organization in almost all small viruses with spherical topology is consistent with the point symmetry of the icosahedron rotational group I [2]. Consequently, the total number of proteins constituting capsid shells is always equal to $|G|N$, where $|G|=60$ is the number of elements in the I group and N is the number of different protein environments in the capsid.

During the last decade, a rapid development of cryoelectron microscopy [3] and tomography [4] brought qualitatively new information about the protein distribution in viral capsids and stimulated a whole series of theoretical works on capsid structure and mechanical properties [5], as well as on thermodynamics [6] and physical mechanisms of the protein shell self-assembly [7]. Advances in experimental techniques have revealed a growing number of capsid structures [8,9], which deviate from the well-known geometrical model of Caspar and Klug (CK) [2]. The CK model considered as a basis of structural virology accounts for the existence of different protein environments for identical proteins by imposing geometrical selection rules on the number N of environments and on their type. According to the CK model $N=h^2+k^2+hk$, where h and k are non-negative integers, and, in addition, all capsids should be constituted by protein pentamers and hexamers. Both conditions are not always satisfied experimentally [8,9].

Recently, we have proposed the density-wave theory of capsid structure and self-assembly [10] for small viruses with spherical topology and icosahedral symmetry based on a generalization of the Landau theory of crystallization. It describes, in a uniform way, both the structures satisfying the CK model and those violating it. The theory deals with the probability density ρ of protein distribution in the procapsid structure presented as $\rho=\rho_0+\Delta\rho$. Here ρ_0 is an isotropic density in the solution and $\Delta\rho$ corresponds to the density deviation induced by the ordering. The critical part $\Delta\rho_l$ of the density is constituted by a system of spherical density waves with the same wave number l: $\Delta\rho_l(\theta,\phi)=\sum_{m=-l}^{m=l}A_{lm}Y_{lm}(\theta,\phi)$. The spherical harmonics Y_{lm} span one irreducible representation (IR) of the SO(3) symmetry group of the disordered state, l is the IR number, and A_{lm} are the amplitudes of the corresponding spherical harmonics. The protein centers in the capsid structure are associated with the positions of maxima of the $\Delta\rho_l$ function. For small icosahedral viruses (with $l\leq 43$), the critical part of the density is reduced to a single irreducible icosahedral function $f_l(\theta,\phi)$, which has no fitting parameter: $\Delta\rho_l(\theta,\phi)=B_l f_l(\theta,\phi)$, where B_l are the amplitudes.

In [10], we focused only on the first step of the self-assembly process, which is usually called a procapsid formation [1]. However, in a large number of viruses, the step of a procapsid formation is followed by a maturation phenomenon. The latter process is accompanied by collective rearrangements of protein positions, resulting in a *reconstructive structural transformation* of the capsid. It also involves different specific (and often irreversible) biochemical features [11] such as large conformational changes in proteins, protein cleavage, and elastic instabilities of the global shape [5]. In contrast to the procapsid formation, which displays universal properties, biochemical changes during maturation are not the same for different virus families. The results of [12] have shed a new light on this problem. It was proved that in the Flavivirus family (Dengue virus, West Nile virus, Yellow

Fever virus, etc.) immature capsids undergo *first* reversible structural changes that *then* render them accessible to irreversible protein cleavage. Thus, in this family the structural transformation of the procapsid shell into the capsid one is a reversible physical process. This fact leads to two preliminary physical conclusions. On one hand, the reversibility of the process suggests that the phenomenon can be understood in rather simple terms of the theory of phase transitions. But on the other hand, due to the absence of a simple group-subgroup relationship between the procapsid and capsid structures, the corresponding transition is reconstructive. Generally, reconstructive solid-solid transformations have no simple and universal description. However, as it is shown in the following sections, the reconstructive phase transition in the capsids of the Flavivirus family [i.e., the particular class of icosahedral two-dimensional (2D) nanocrystals with spherical topology] can be described by a simple collective displacement field of all proteins with small amplitude minimizing the global free energy of the system. From a physical point of view, a continuous thermodynamical description of a reconstructive transformation in a capsid nanocrystal is a new and unconventional development of the theory of phase transitions. In structural virology, it helps to understand the mechanisms of virus maturation.

The main aim of the present work is to extend further the Landau theory of phase transitions in order to give a simple and clear explanation of the reversible reconstructive structural transformation in the Flavivirus family. In the frame of the density-wave approach, we show that the transformation is associated with the variation in the protein density distribution wave number l and is intimately related to the procapsid self-assembly transition preceding the reconstructive procapsid-to-capsid transition.

The paper is organized as follows. In Sec. II the Landau free energy of the procapsid-to-capsid phase transformation in Dengue virus is derived together with the collective displacement field of all proteins constituting the shell. In Sec. III we discuss capsid radius variation during the maturation phase transformation in terms of protein density waves. Possible polymorphism of viral capsid forms is also discussed. Section IV is devoted to the conclusions.

II. STRUCTURAL TRANSFORMATION IN FLAVIVIRUSES

The choice of the Flavivirus family is motivated by several reasons. On one hand, though the virulent human viruses belonging to this family are extremely important for biology, the structural data on their organization were acquired only quite recently [9]. On the other hand, the structure of mature Flaviviruses violates the CK geometrical model but is perfectly consistent with the predictions of the density-wave theory [10].

A constructive comparison of the procapsid and capsid structures of Flaviviruses became possible due to an important result obtained in [10]: there exist *qualitatively different* structures induced by irreducible icosahedral functions $f_l(\theta,\phi)$ with different l but with the *same number* N of inequivalent protein positions. It is, in particular, the case of capsids constituted by 180 proteins located in $N=3$ different

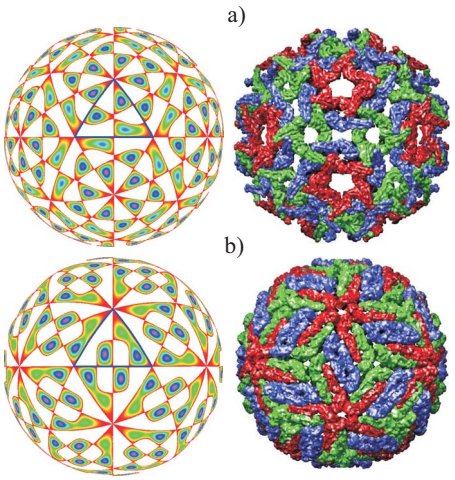

FIG. 1. (Color online) Procapsid (a) and capsid (b) structures of the Dengue virus. Protein density distribution induced by the irreducible icosahedral function f_l with (a) $l=27$ and (b) $l=25$ (left panel). Experimental viral structures [14] (right panel).

environments. The positions of protein centers induced by the f_{27} [left panel in Fig. 1(a)] form local pentamers and hexamers and thus satisfy the CK model, while the positions generated by the f_{25} [left panel in Fig. 1(b)] violate the CK rules. To very good accuracy, they correspond to the experimental protein distributions in the Dengue virus procapsid and capsid [9,12,14] presented in the right panel of Figs. 1(a) and 1(b), respectively. To facilitate the comparison of the experimental structures with the protein positions induced by the density functions, we show in the left panel of Fig. 1 the so-called asymmetric protein unit (triangle connecting one fivefold axis with two neighboring threefold axes). This is a standard notation in structural virology, which shows different protein environments, existing in a given capsid structure. One can easily compare the positions of the density function maxima, with the protein center positions. It is evident that the density functions presented in Fig. 1 (left panel) have three 60-fold orbits of maxima. Correspondingly, three different maxima (one representative per orbit) find themselves in the asymmetric protein unit. One of the orbits is situated around fivefold axes of the icosahedral symmetry. Proteins situated in the corresponding positions are shown in red in the right panel of Fig. 1. Two other orbits (proteins in the corresponding positions are shown in blue and green) form in the procapsid structure [Fig. 1(a)] nearly regular hexagons around icosahedral threefold axes. In the capsid structure [Fig. 1(b)], it is also very easy to make one-to-one correspondence between the typical rhombus of maxima positions around the icosahedral twofold axis (left panel) and the corresponding rhombus with the herring-bone protein arrangement (right panel).

For the following theory of phase transition between these two structures, it is important to note that the point symmetry of the protein shell remains icosahedral in all intermediate states of the reconstructive structural transformation. This fact was revealed recently [12] by the tracing of viral particles in the host cell secretory pathway and by *in vitro* experiments. Conservation of the icosahedral symmetry during

the Flavivirus structural transformation means that the protein density function in the intermediate states is a combination of f_{27} and f_{25} with the relative weight of these two icosahedral functions being a thermodynamical variable dependent on external parameters such as temperature, concentration, and pH value. Then, the stability of the initial, final, and all intermediate structures is described by the same free energy $F(B_{27},B_{25})$. Here the amplitudes B_{27} and B_{25} play the role of order parameters responsible for both the procapsid formation and the reconstructive procapsid-to-capsid transition in the considered virus family. Note that to obtain the unified description of two processes and the continuous thermodynamical description of the considered reconstructive solid-solid transformation, one has to choose the liquid state as a latent parent phase for both the capsid and the procapsid crystalline structures. Until now the liquid state was considered in the theory of phase transitions to be not informative for such kinds of problems because it was not clear how to relate its characteristics to crystalline (discrete) positions. The density-wave approach gives the answer to this question and makes possible further development of the theory of phase transitions in nanostructures (which is more general than the theory of virus maturation considered here).

The free-energy expansion describing both the assembly and the maturation processes in the Flavivirus family can be taken in a standard form [13], containing successive invariant terms $F=F_0+F_2+F_3+F_4+\ldots$. Due to the asymmetry of capsid proteins, the protein density function $\Delta\rho_l(\theta,\phi)$ contains the odd wave numbers l only and, consequently, the third-order term F_3 is identically zero. The second-order term F_2 is expressed as an invariant quadratic form of the amplitudes $A_{l,m}$. For the description of transitions between the isotropic and different icosahedral states, it can be simplified and expressed in terms of the icosahedral function amplitudes B_l only

$$F_2=\sum_l \alpha(l,R;T,c)\sum_{m=-l}^{m=l} A_{l,m}A_{l,m}^*=\sum_l \bar{\alpha}(l,R;T,c)B_l^2, \quad (1)$$

where $\alpha(l,R;T,c)$ or $\bar{\alpha}(l,R;T,c)$ are temperature- and composition-dependent coefficients of the Landau theory.

The $\bar{\alpha}(l,R;T,c)$ phenomenological coefficient in the second-order term (1) is minimal with respect to the discrete wave number l and goes through zero at the self-assembly transition from the isotropic phase [13] [curve 2 in Fig. 2(a)]. Further variation in external parameters can induce a small continuous shift of the $\bar{\alpha}(l,R;T,c)$ minimum position as a function of l. In icosahedral shells, this process takes place only for some families of viruses. In certain viruses, a shift of the $\bar{\alpha}(l,R;T,c)$ minimum can induce a bifurcation of the density function maxima, thus, making this thermodynamical process improbable. For example, for $l=27$, the protein density function has 180 maxima, while for $l=31$ (which is the next wave-number value allowed by the selection rules [10]) the number of density maxima becomes 240. On the contrary, for viruses with $N=3$, the continuous variation in the $\bar{\alpha}$ minimum position between $l=27$ and $l=25$ [curve 3 in Fig. 2(a)] does not change the number of the density function maxima and leads to the correlated collective shift of the 180

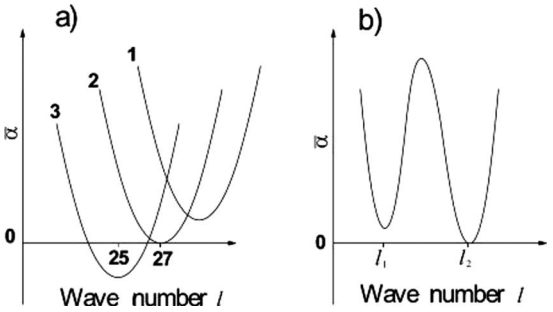

FIG. 2. Dependence of the $\bar{\alpha}(l,R;T,c)$ phenomenological coefficient in the second-order term [Eq. (1)] of the free energy on the wave number l. The $\bar{\alpha}(l,R;T,c)$ value is given in arbitrary units. In the vicinity of the capsid self-assembly and reconstructive procapsid-to-capsid transition (a): in the isotropic state (curve 1), in the self-assembly transition point (curve 2), and after the structure reconstruction (curve 3). For the capsid shells, which show structural polymorphism (b).

protein center positions. The corresponding collective displacement field (Fig. 3) is a continuous function depending on external thermodynamical parameters. The displacement field preserves the icosahedral symmetry of the shell in all intermediate states (Fig. 4) of the process and its amplitude minimizes the Landau free energy with the second-order term given by Eq. (1). The procapsid self-assembly transition is driven by the B_{27} order parameter. Its relative weight with respect to that of B_{25} is maximal in the procapsid state [Fig. 4(a)], then decreases with the shift of the $\bar{\alpha}(l,R;T,c)$ minimum position during the reconstructive structural transformation process [Figs. 4(b)–4(e)], and finally locks in the capsid structure characterized by the maximal contribution of B_{25} to the capsid density function [Fig. 4(f)].

Let us also show that the reconstructive transformation in the considered system can take place continuously, without jumps of B_{27} and B_{25} order parameters. Symmetry analysis

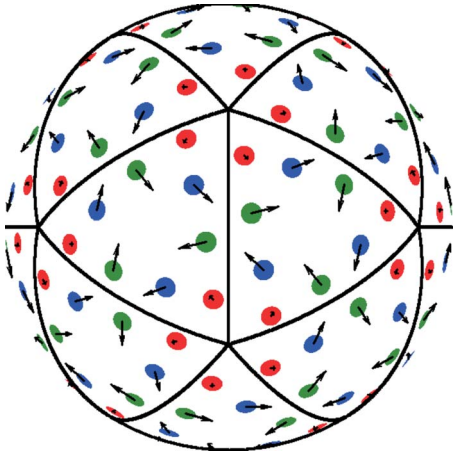

FIG. 3. (Color online) Calculated collective displacement field of protein centers in viruses of the Flavivirus family during the reconstructive procapsid-to-capsid transformation. The positions in the initial procapsid structure are given by circles. The directions and the amplitudes of protein displacements to their final positions in the capsid structure are given by arrows.

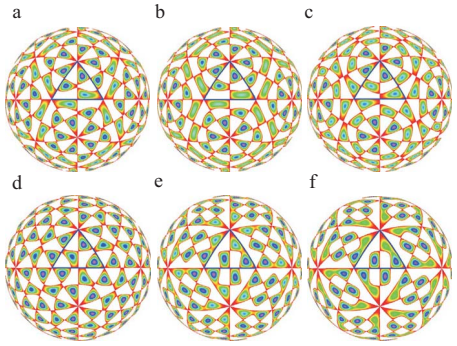

FIG. 4. (Color online) Variation (a)–(f) in the protein density function in intermediate states of the reconstructive procapsid-to-capsid transformation in Flavivirus family. Density function is chosen in the normalized form: $\Delta\rho_l = b_{27}f_{27} + b_{25}f_{25}$ with $b_{27} + b_{25} = 1$. Density distributions with the following b_{25} values are presented: (a) 0; (b) 0.2; (c) 0.4; (d) 0.6; (e) 0.8; and (f) 1.

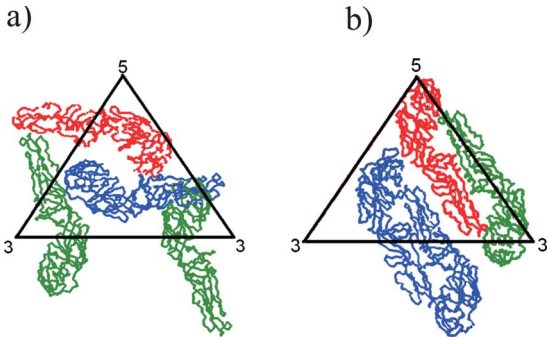

FIG. 5. (Color online) Evolution of protein positions in the asymmetric protein unit of the Flavivirus corresponding to the collective displacement field (Fig. 3) between (a) procapsid and (b) capsid. The asymmetric unit is presented by the triangle connecting one fivefold axis of the structure with two neighboring threefold axes. Three different positions of identical proteins are given (to compare with Fig. 3 and with [9,12]). Protein positions remain in the vicinity of the same symmetry axes both in the procapsid and the capsid structures.

demonstrates that there exist two invariant coupling terms between B_{27} and B_{25} in the fourth degree. The total free energy of the system has then the form

$$F_{tot} = F_{27}(B_{27}) + F_{25}(B_{25}) + \beta_1(T,c)B_{27}^3B_{25} + \beta_2(T,c)B_{27}B_{25}^3. \tag{2}$$

Here the first term is the free-energy part dependent on the B_{27} order parameter only, the second term stands for the contribution of the B_{25}, while the two last terms, expressing the coupling of the order parameters $\beta_1(T,c)$ and $\beta_2(T,c)$, are the temperature- and concentration-dependent coupling constants. The equations of state of the system are then given by

$$\partial F_{tot}/\partial B_{27} = 0; \quad \partial F_{tot}/\partial B_{25} = 0. \tag{3}$$

The solutions of the equations of state [Eq. (3)] determine the equilibrium dependence of B_{27} and B_{25} on temperature, concentration, and pH values. Minimization of free energy (2) with respect to both order parameters shows that a nonzero value of B_{27} induces a nonzero value of B_{25} and vice versa. This fact makes possible a continuous thermodynamical path from the procapsid state to the capsid one.

The amplitudes of protein center displacements obtained in the present work by the free-energy minimization are much smaller than those induced by all previously proposed empirical mechanisms [9,12]. Figure 5 shows the evolution of $N=3$ protein positions, corresponding to the collective displacement field (Fig. 3) between procapsid [Fig. 5(a)] and capsid [Fig. 5(b)] structures. The result is presented in usual for the structural virology terms of an asymmetric protein unit. Three different positions of identical proteins are given in red, blue, and green. It is easy to follow the evolution of each protein position during the procapsid-to-capsid structural transformation. We would like to stress, however, that in addition to the protein center displacements, the protein molecules in the considered viral capsid participate in the complex rotational motion in the direction perpendicular to the capsid surface (Fig. 4(B) in [12]). This motion leads to the changes in the apparent projection of the protein molecule on the capsid surface. As for the protein center positions, it is easy to see by a direct comparison that the evolution obtained in the present work is quite different with respect to the mechanisms of [9,12]. The simplest way to do it is to follow the evolution of protein positions given by the same color in Figs. 5(a) and 5(b) [and in Figs. 1(a) and 1(b)] and then to compare it with the corresponding evolution presented in [9,12,14]. Namely, in Fig. 5, the pentamers, which are already formed in the procapsid, are not destroyed during the transformation. The corresponding proteins (shown in red in Fig. 5) located in the vicinity of the fivefold axis of the protein shell are shifted very slightly. Their positions remain in the very vicinity of the fivefold axes. Two other types of protein positions (blue and green in Fig. 5) also remain in the vicinity of the same symmetry axes both in the procapsid and the capsid structures though the displacements of these positions are more important than those of the "pentameric" ones. In their turn, the mechanisms proposed in both [9,12] show important exchanges between the protein positions situated around fivefold, threefold, and twofold axes and imply large displacements of protein centers.

Finally, note that in all types of phase transformations, smaller displacements of particle centers correspond usually to smaller energy costs. This fact makes the mechanisms involving small displacement fields much more probable with respect to those with larger displacements. In the present state of the experimental technique, it is difficult to trace the path of an individual protein on the capsid surface during the maturation transformation. Thus, the protein paths predicted by our model based on the collective displacement field with the small amplitude and minimizing the global free energy of the system become important for further biological applications (e.g., for the relation between the protein path and the infectivity acquired by the capsid after the maturation transition).

III. DISCUSSION

The thermodynamics of capsid self-assembly and maturation processes depends not only on the characteristic wave

number l but also on the capsid radius R. However, this variable is not completely independent of l. The wave number l determines the number of proteins in the shell [10], while the capsid radius R is related to the protein size and their packing. In particular, in the Dengue virus, the protein packing in the capsid state (which looks locally like a hexagonal close packing) is more dense than the packing in the procapsid state. Correspondingly, the capsid shell radius decreases through the procapsid-to-capsid reconstructive phase transition. Different packings result in qualitatively different structures (see Fig. 1). Nevertheless, it is possible to find an average common feature for different packings of the same proteins using the well-known relations between the spherical and the plane waves. Note that local packing is not strongly dependent on the capsid curvature and can be thus considered in the plane-wave approximation. Spherical waves on the shell surface are well approximated by the plane waves in the case $R \gg \lambda$, where λ is the plane wavelength. For the waves with high l participating in the icosahedral protein density function $\Delta\rho_l(\theta,\phi)$, this approximation is reasonable. More rigorously, to attain the plane-wave limit in the equations of spherical dynamics, it is necessary to replace the ratio l/R by the magnitude q of an effective wave vector $\boldsymbol{q}$ and then to tend R to infinity [15].

In the frame of the unified density-wave mechanism of the procapsid self-assembly and the reconstructive procapsid-to-capsid transformation in the Flavivirus family, the ratio l/R can vary only slightly around some average value determined by the individual protein size. The following estimations confirm the theoretical arguments. Namely, for the Dengue virus procapsid, $l=27$ and the diameter is $\simeq 60$ nm [12], i.e., $l/R \simeq 0.90$ nm^{-1}. For the capsid, $l=25$ and the diameter is $\simeq 53$ nm [12], which gives $l/R \simeq 0.94$ nm^{-1}. Along this reconstructive transition related to the l change, the average wave vector length $q=l/R$ varies only slightly (less than 4.5%), while the capsid radius R undergoes an apparent jump of more than 13%. Thus, we propose to take the average plane-wave vector length $q=l/R$ as a common feature for all capsids constituted by the same proteins. Furthermore, in the isotropic protein solution before the assembly transition, the density fluctuations with maximal amplitude should also correspond to wave vectors with the length $q \simeq l/R$. This remark suggests a new type of comparative experiments: the results of a simple x-ray scattering on the viral coat protein solutions can be compared with the small-angle x-ray scattering on the processed capsids or with the capsid images reconstructed from the cryoelectron microscopy.

As an additional remark, let us stress that the density-wave theory can also explain the polymorphism of viral capsid forms. Frequently observed during *in vitro* assembly of capsids formed by mutant proteins [16] or in viruslike particles [17], the polymorphism consists in the formation of different icosahedral shells by the same proteins. The $\bar{\alpha}(l,R;T,c)$ phenomenological coefficient in Eq. (1) has in this case two (or sometimes more) minima [see Fig. 2(b)] situated at different permitted values of the wave number l and separated by rather high-energy barriers. Variation in the assembly conditions chooses the minimum for which the density function goes through zero and, consequently, the number of proteins and their type of organization in the shell. For the Hepatitis B virus (HBV) capsid proteins [18], two possible forms with $N=4$ and $N=3$ correspond to the minima with $l=31$ and $l=27$, respectively. For mutant Cowpea Chlorotic Mottle Virus (CCMV) proteins [16], the shells are associated with $l=15$, $N=1$, $l=21$, $N=2$, and $l=27$, $N=3$ values. In the viruslike particles [17], these values are $l=21$, $N=2$ and $l=27$, $N=3$. As in the theory of reconstructive procapsid-to-capsid structural transition, the difference in capsid radii in the case of capsid forms polymorphism can be understood in terms of the average $q=l/R$ value. For the HBV, the shell diameters $D_4=30$ nm and $D_3=26$ nm correspond to $q_{31}=2.067$ nm^{-1} and $q_{27}=2.077$ nm^{-1}, respectively, with the difference making less than 0.5%. The diameters $D_2=25$ nm and $D_1=18$ nm of the CCMV shells also lead to a very small q difference (less than 0.8%). For the viruslike particles [17], the diameters $D_2=21.5$ nm and $D_3=27.3$ nm correspond to $q_{21}=1.954$ nm^{-1} and $q_{27}=1.978$ nm^{-1}, respectively, thus, confirming the small difference in $q=l/R$ between polymorphic states.

IV. CONCLUSION

The theory of the reconstructive structural transformation between the icosahedral 2D nanocrystals with spherical topology developed in the present work allows to describe in a simple way structural changes during the maturation process from the procapsid to the capsid state in a whole family of viruses. The example of Flavivirus was chosen because of its complexity for a conventional structural description in terms of the CK geometrical model and its high biological relevance. We based the proposed approach on the Landau density-wave theory and on the choice of the liquid state as a common latent parent phase for both the procapsid and the capsid icosahedral structures. This unconventional approach to the classical theory of phase transitions allowed us to describe the reconstructive procapsid-to-capsid transition in a continuous way. In the frame of our theory, the reconstructive procapsid-to-capsid transformation in the Flavivirus family was successfully related to the thermodynamical variation in the equilibrium wave number l of the protein density function from $l=27$ to $l=25$. The collective displacement field of protein centers from their positions in the procapsid structure to their final positions in the capsid structure was calculated. Its amplitude related to the order parameter of the procapsid-to-capsid transformation is a small parameter and minimizes the free energy of the system. The displacement field obtained suggests a new structural mechanism of the transition. The resulting amplitudes of protein center displacements are much smaller than the displacement amplitudes in all previously proposed mechanisms. We proposed also to take the average plane vector $q=l/R$ as a universal feature for different capsid shells constituted by the same proteins. The equivalent average plane-wave vector allowed us to compare the capsid shell radii before and after the maturation transition in the Flavivirus family and to relate the radii of different polymorphic states of mutant viruses and viruslike particles.

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