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Elasticity theory of the maturation of viral capsids

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ABSTRACT

Many viral capsids undergo a series of significant structural changes following assembly, a process known as *maturation*. The driving mechanisms for maturation usually are chemical reactions taking place inside the proteins that constitute the capsid ("subunits") that produce structural changes of the subunits. The resulting alterations of the subunits may be directly visible from the capsid structures, as observed by electron microscopy, in the form of a shear shape change and/or a rotation of groups of subunits. The existing thin shell elasticity theory for viral shells does not take account of the internal structure of the subunits and hence cannot describe displacement patterns of the capsid during maturation. Recently, it was proposed for the case of a particular virus (HK97) that thin shell elasticity theory could in fact be generalized to include transformations of the constituent proteins by including such a transformations as a *change of the stress-free reference state* for the deformation free energy. In this study, we adopt that approach and illustrate its validity in more generality by describing shape changes occurring during maturation across different T-numbers in terms of subunit shearing. Using phase diagrams, we determine the shear directions of the subunits that are most effective to produce capsid shape changes, such as transitions from spherical to facetted capsid shape. We further propose an equivalent stretching mechanism offering a unifying view under which capsid symmetry can be analyzed. We conclude by showing that hexamer shearing not only drives the shape change of the viral capsid during maturation but also is capable of lowering the capsid elastic energy in particular for *chiral* capsids (e.g., $T = 7$) and give rise to pre-shear patterns. These additional mechanisms may provide a driving force and an organizational principle for virus assembly.

1. Introduction

X-ray crystallography and electron microscopy (EM) have revealed that the protein shells (capsids) of most spherical viruses are assembled into lattices of five- and six-fold tiles (pentamers and hexamers) that have the symmetries of an icosahedron, the platonic solid formed from 20 (three-fold symmetric) equilateral triangular faces connected by 30 (two-fold symmetric) edges and 12 (five-fold symmetric) vertices (see Fig. 1). For all but the smallest and simplest of these shells,

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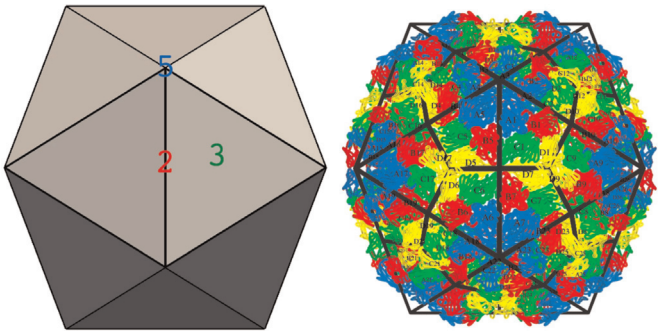

Fig. 1. (Left) Icosahedron two, three and five folds symmetry sites. (Right) Structure of NωV virus, containing four distinct quasi-equivalent subunits (red, green, blue, yellow) in each symmetry-equivalent icosahedral crystallographic "asymmetric" unit. NωV image from VIPERdb (Carrillo-Tripp et al., 2009). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

the icosahedral lattice tiling scheme, first discovered by Caspar and Klug (1962), places the individual proteins (often all chemically identical) in distinct local symmetry environments (see Fig. 1). Based on this fact, Caspar and Klug anticipated that the proteins in different symmetry positions would have similar but slightly different shapes—i.e., they are "quasi-equivalent." They argued that the assembly of the capsid structure would be guided not by purely geometric principles, but rather by physics—specifically, by minimization of the deformation energy cost. X-ray and EM measured structures have confirmed that distinct quasi-equivalent proteins often differ in atomic structure by small "conformational" deformations.

It follows from the Caspar–Klug (CK) argument that the deformation of quasi-equivalent capsid protein subunits will generally produce a state of pre-stress within the icosahedral shell. A theory based on Kirchhoff–Love thin shell elasticity was constructed by Lidmar et al. (2003) (LNM) for icosahedral capsids and later generalized for non-icosahedral shells, predicts the emergence of pentamers as disinclination defects in an otherwise hexagonal lattice of capsid proteins. Compressive eigen-stresses from the CK lattice construction act as a driving force for outward "buckling" of the pentamers found at the five-fold icosahedral vertices. In this telling, the overall shape of an icosahedral capsid is determined by the dimensionless Föppl von Kármán (FvK) number $\gamma = YR^2/\kappa_C$, which defines the ratio between stretching (Y) and bending stiffness (κ_C) through the capsid radius R. Below a critical value of $\gamma \approx 150$, the bending energy dominates and the virus shell is close to a sphere, while above this value the stretching energy dominates and the capsid becomes more faceted, in closer resemblance to a perfect icosahedron. These predictions are consistent with a trend observed in X-ray and EM structures—larger capsids tend to be more faceted than smaller capsids. Likewise this theory has been successful in explaining the formation of conical capsid shapes (Nguyen et al., 2005), capsid polymorphism (Zandi et al., 2004), and the nonlinear mechanical response under atomic force microscopy (AFM) loading (Klug et al., 2006, 2012; Roos et al., 2010).

Shape transitions are known to occur in particles of many virus types during 'maturation' events, in which the proteins in the capsid assembly undergo significant conformational changes, often yielding a final mature head configuration that is more faceted than the initial prohead configuration, as exemplified by the well-studied bacteriophage HK97 (cf. Ross et al., 2005 and Fig. 2). Maturation can be initiated by a cleavage chemical reaction or it may be induced by changes in the physicochemical environment, such as a change in pH or the insertion of the genome into the capsid.

Within LNM theory, a change of the capsid shape during maturation must be interpreted as a buckling transition driven by changes in the effective mechanical parameters (such as Y and κ_C) of the protein shells, perhaps linked to changes in the effective thickness or bonding structure due to the local conformational changes. However, experimental measurements of elastic properties of HK97 by AFM (Roos et al., 2012) suggest such changes are likely not large enough to produce the

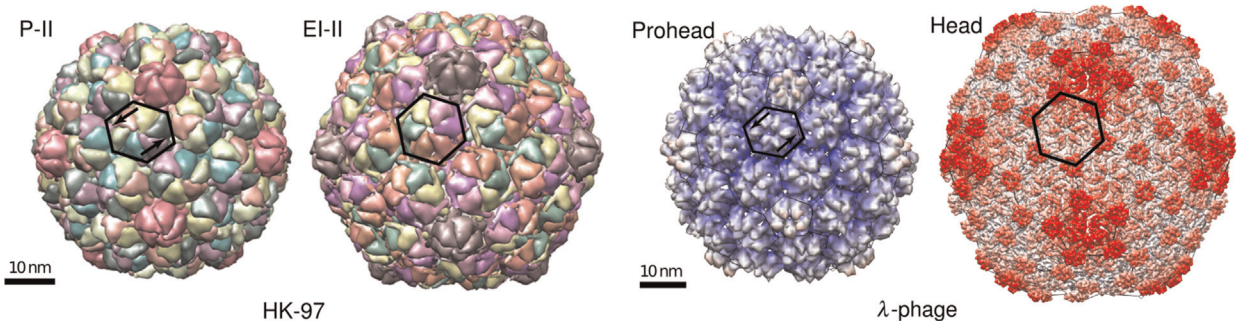

Fig. 2. (Left) Maturation of bacteriophage HK97 from prohead "P-II" state to head "EI-II" state involves unshearing of skewed hexamers to symmetric conformations. (Right) Similar to the HK97 maturation process, λ-phage virus changes from prohead state to head state involve unshearing of skewed hexamers to symmetric conformations. Coordinates obtained from ViperDB (Shepherd et al., 2006) and EMDB (Kinjo et al., 2012) and rendered in Chimera (Pettersen et al., 2004).