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Classification of capped tubular viral particles in the family of Papovaviridae

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Abstract

A vital constituent of a virus is its protein shell, called the viral capsid, that encapsulates and hence provides protection for the viral genome. Viral capsids are usually spherical, and for a significant number of viruses they exhibit overall icosahedral symmetry. The corresponding surface lattices, that encode the locations of the capsid proteins and intersubunit bonds, can be modelled by viral tiling theory. It has been shown *in vitro* that under a variation of the experimental boundary conditions, such as the pH value and salt concentration, tubular particles may appear instead of, or in addition to, spherical ones. In order to develop models that describe the simultaneous assembly of both spherical and tubular variants, and hence study the possibility of triggering tubular malformations as a means of interference with the replication mechanism, viral tiling theory has to be extended to include tubular lattices with end caps. We focus here on the case of Papovaviridae, which play a distinguished role from the viral structural point of view as they correspond to all pentamer lattices, i.e. lattices formed from clusters of five protein subunits throughout. These results pave the way for a generalization of recently developed assembly models.

1. Introduction

Viruses are fascinating simple organic systems, consisting of a very compact genome and a protective protein shell or capsid, which hijack host cells typically between one hundred or one thousand times their size in animals and plants, and which have the potential to kill. Advances in virology and the design of anti-viral therapeutics rely strongly on an understanding of the viral replication cycle, and, in particular, of the structure of capsids as well as of the mechanisms which trigger their assembly and disassembly.

The importance of mathematical models for the structure of viral capsids and their assembly has been recognized for decades and is demonstrated by the significance of the 40-year-old Caspar–Klug theory of quasi-equivalence [1] for the classification of viral capsids and for the three-dimensional reconstructions of viral capsids from experimental data [2]. However, the existing models do not account for important classes of viruses including families of cancer-causing viruses whose study is of prime importance for the health sector.

A very promising approach to solve the classification puzzle and yield a brand new perspective on viral structure is viral tiling theory (VTT). It was recently developed by Twarock [3], initially in an attempt to address some of the shortcomings of the Caspar–Klug theory regarding viruses in the family of Papovaviridae. The distinctive feature of the latter is the fact that the surface lattices of their large icosahedral viral capsids are composed of clusters of five proteins only, while the Caspar–Klug theory predicts the presence of pentamers and hexamers. Within the VTT approach, the protein subunits composing the capsids are located in the corners of the tiles that meet at global and local symmetry axes. For viruses in the family of Papovaviridae such as SV40, the tiles are kites and rhombs, and the global five-fold symmetry axes are located at vertices where five kites meet while the local five-fold symmetry axes are located at vertices where two kites and three rhombs meet, as illustrated in figure 2 of [4]. This reproduces the observed arrangements of protein subunits as pentamers. Crucially, VTT exploits the concept of symmetry to the full, and its group theoretical roots lie in the classification of all local symmetry axes of icosahedral structures, which are determined via the affinization of the non-crystallographic Coxeter group H_3 using a method inspired by the projection formalism known from the theory of quasicrystals and Penrose tilings [5, 6]. It is well-suited to the description of the capsid structure of Papovaviridae while still reproducing the tessellations relevant to the description of the viruses in the Caspar–Klug classification. Its predictive power is significantly enhanced, in comparison with the Caspar–Klug theory, through its ability to locate the *bonds* between protein subunits, and not only the location of the protein subunits themselves.

Interestingly, VTT is also appropriate for the description of tubular variants of spherical capsids, whether they are capped or not. This confirms the suggestion by Caspar and Klug that there should exist structural similarities between the surface lattices of tubular and spherical particles as the former occur alongside spherical shells during self-assembly [7]. While spherical particles can package the viral genome and are hence infectious, capped and non-capped tubular variants contain little or no DNA [8]. It is therefore therapeutically desirable to derive an integrated model for assembly of spherical and tubular structures and track down which factors favour non-infectious malformations.

A first step in this direction is to classify tubular structures using VTT. Tubular capsid-like particles can be thought of as rolled sheets of lattices formed from capsomeres, i.e. from clusters of protein subunits. There exists an abundance of tubular structures with open ends and these have been classified for Papovaviridae [9]. On the other hand, tubular structures with end caps are more rare, as their existence places constraints on the possible surface structures of the tubes. It is the purpose of this paper to classify capped tubular structures and enumerate all possibilities for the family of Papovaviridae as an example. This is important because, *in experiments*, capped rather than open tubes are usually observed [8]. The classification derived here is a crucial input for assembly models which consider a scenario where both spherical capsids and tubes occur as products of assembly. It hence paves the way for a generalization of the assembly models in [4, 10].

After a brief overview of the Caspar–Klug theory and the discussion of generic features of capped tubular viral particles in section 2, a summary of the viral tiling theory as applied to spherical capsids in the family of Papovaviridae is presented in section 3. It provides the

necessary tools for the classification of capped tubular structures for Papovaviridae, which is organized according to the structures of the end caps and given in section 4. In section 5 we provide a comparison with experimental results, and in section 6 we conclude by discussing how these results can be implemented in the framework of assembly models.

2. Icosahedral viral particles: generic features

The capped tubular variants of a given type of icosahedral virus are modelled as tubes with half of an icosahedral capsid closing each end. Their systematic classification may therefore be organized according to the type of end cap and tubular lattice compatible with the symmetries and the tessellation of the corresponding spherical capsid considered. The size of the latter is characterized by a T-number introduced by Caspar and Klug [1]. In the first subsection we briefly review the ingredients of their classification system necessary to our purpose. We then discuss possible end caps given an icosahedral protein shell with a certain T-number.

2.1. Caspar–Klug spherical structures

Spherical viral capsids with icosahedral symmetry possess six five-fold, ten three-fold and fifteen two-fold global rotation axes. Small capsids are organized in clusters of protein subunits centred on the global symmetry axes of the icosahedral structure. But these symmetry axes are not sufficient to accommodate the protein subunits of larger spherical viruses, which occur in multiples of 60. The *quasi-equivalence* theory advocated by Caspar and Klug consists in organizing the protein clusters around the global symmetry axes, but also around some *local* symmetry axes (six-fold) of the icosahedral capsid. The underlying rule for the structural organization of large icosahedral capsids is as follows: the building blocks are *pentamers* and *hexamers*, which are regular polygonal groupings of five and six individual capsid proteins. Pentamers are located on each vertex of the icosahedron's six five-fold symmetry axes (this accounts for $5 \times 6 \times 2 = 60$ individual subunits), while the space between pentamers is filled with hexamers of the same side length. The bigger the capsid, the more hexamers occur, but only in the proportion of 12 to $10(T-1)$, where T is called the *triangulation number*. This terminology stems from the fact that large capsids may be obtained by sub-triangulation of each face of the icosahedron in T smaller facets, producing a shell geometrically equivalent to truncated icosahedra with $12+10(T-1)$ faces. The total number of protein subunits per capsid is therefore $12\times5+10(T-1)\times6 = 60T$. T may be written as $T = h^2+k^2+hk$ where the two non-negative integers h and k encode how to get from one pentamer to its nearest neighbour on the surface lattice that represents the organization of the capsid. Low T-numbers are therefore $T = 1, 3, 4, 7, 9, \ldots$. According to the above classification system, large icosahedral capsids can be thought of as subdivisions of a basic $T = 1$ capsid.

As already pointed out in the introduction, not all spherical icosahedral capsids exhibit the pattern of pentamers and hexamers predicted by Caspar and Klug. A prototype of such non-generic structures are viruses in the family of Papovaviridae, whose capped tubular variants may be classified using viral tiling theory as described in section 4. The classification of tubular variants of generic spherical particles is straightforward, and is given in the following subsection.

2.2. Capped tubular variants of Caspar–Klug spherical viruses

In classifying possible end caps, we find it convenient to consider first a $T = 1$ capsid, and use its dual representation—the dodecahedron—whose twelve pentagonal faces represent the Caspar–Klug pentamers. There are as many types of end caps as there are inequivalent ways of

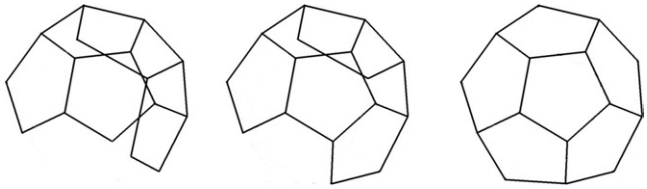

Figure 1. Half capsids cut about the two-, three-, and five-fold axes.

cutting icosahedral capsids into equal halves, given the following two constraints. First of all, each half-spherical capsid must contain one end of each of the six global five-fold symmetry axes in order to ensure that curvature is equally distributed over the end caps. This requirement stems from the fact that the capsid protein subunits cluster in groups of five around these symmetry axes to form the twelve curvature-generating pentamers of icosahedral capsids in the Caspar–Klug theory. It is analogous to pentagons providing curvature in capped carbon nanotubes [11].

Second, the six pentamers within each cap must be arranged symmetrically so that the cap's boundary can fit a tube-generating sheet with two parallel sides. If a cut were made such that structures smaller, respectively larger, than a hemisphere were obtained, then the larger structure could not be continued into a tubular structure without the occurrence of negative curvature at its circular intersection with the tube. However, the occurrence of negative curvature puts more strain on the structure and is hence less likely to occur. Similarly, the smaller structure would first have to be continued to a hemisphere by the addition of further capsomeres and could only then be continued into a tubular structure if a strong increase in curvature at the intersection of the end cap and tube were to be avoided. This latter case is hence equivalent to the cuts we have considered already. However, we remark that even though less probable, such structures may occur, such as, for example, the budding of a tube from a virus shell (see [8], Plate XII).

We therefore focus here on the situation where all end caps are hemispheres, and hence transitions into tubes are flat. For these cases, the constraints listed above yield precisely three types of end cap for each size of icosahedral capsid: they are obtained by cutting the capsid in half about the icosahedral five-, three-, and two-fold vertices, as shown in figure 1. It follows that capped tubular variants can be labelled by the T-number of the spherical particles associated with the end caps and the order $n = 2, 3$ or 5 of the symmetry axis about which the capsid is cut in half. For fixed T, there are therefore *at most* three types of end cap. Whether the three types occur in tubular variants depends on the compatibility of the end caps described above with the structure of the tubular lattice, inherited from the structure of the associated icosahedral capsid. For instance, the second constraint imposed above ensures that the pentamers in the cap can be 'glued' to the ends of *hexagonal* tubes, where the hexagons represent hexamers. Therefore, viruses within the classification of Caspar and Klug at number T (whose capsids possess $10(T - 1)$ hexamers around local six-fold symmetry axes) admit capped tubular variants corresponding to the end caps labelled $(T, 5)$, $(T, 3)$ and $(T, 2)$.

3. Viral tiling theory and spherical particles in the family of Papovaviridae

Since a thorough understanding of some Papovaviridae viruses is extremely desirable in view of their cancer-causing nature, and since the Caspar–Klug theory fails to provide the necessary ingredients to grasp the structure of their capsids and to construct their tubular variants, we

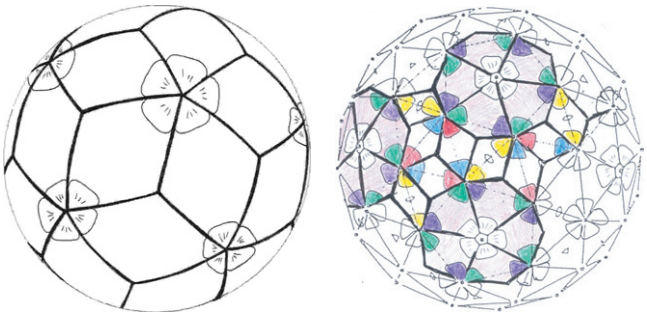

Figure 2. The spherical tiling for a $T = 1$ structure (left) and for a (pseudo-) $T = 7$ capsid (right) representing particles with icosahedral symmetry in the family of Papovaviridae.
(This figure is in colour only in the electronic version)

review here the elements of VTT required for the description of spherical particles in the family of Papovaviridae and, partially, for the discussion of their tubular malformations.

VTT provides a framework for the description of the surface lattices that act as blueprints for the organization of the proteins in viral capsids. In particular, the surface lattices of the spherical particles are modelled as spherical tilings, i.e. tessellations in terms of a set of shapes (called tiles) that cover the sphere without gaps and overlaps. They are obtained via a group theoretical formalism that pinpoints the locations of *local* symmetry axes of order 3, 5 and 6, which mark the locations of the centres of the protein clusters (called trimers, pentamers and hexamers, respectively) that form the capsids.

A peculiarity of Papovaviridae lies in the fact that all protein clusters are pentamers, i.e. are arranged about local or global symmetry axes of order five. The icosahedral spherical particles in this family correspond to either configurations of 12 pentamers arranged around the symmetry axes of an icosahedron, or to configurations with 60 additional pentamers located around further local symmetry axes. The former are called $T = 1$ structures according to the classification of Caspar and Klug, and the latter (pseudo-) $T = 7$ structures because they share certain properties with $T = 7$ geometries in their classification. The corresponding tilings are shown in figure 2. The tiling corresponding to the (pseudo-) $T = 7$ particle has been derived in [3] and corresponds to a tessellation in terms of kites and rhombs. It describes the surface structure of viruses such as polyomavirus, that has been a structural puzzle for a decade in view of Caspar–Klug theory [12].

Tiles can be interpreted from a biological point of view as representing interactions between the protein subunits located on the tiles. For example, in the case of the kite and rhomb tiling, kites correspond to the trimer interactions, that is interactions between three protein subunits, and rhombs to dimer interactions, that is interactions between two protein subunits. The geodesics (arc) between the protein subunits on the tile in the spherical tiling mark the locations of the C-terminal arm extensions that form these bonds, as corroborated by the results in [13].

4. Capped structures for pentagonal tubes: Papovaviridae variants

Pentagonal tubes are known to occur, for example, in the family of Papovaviridae, which we are discussing in this paper. Different types of tubes occur predominantly for different viruses in this family. For example, human wart infection seems to be accompanied mostly by narrow tubes, and polyomavirus infection mostly by wide tubes, whereas preparations from rabbit

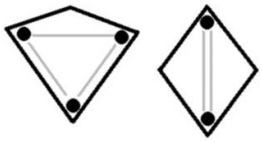

Figure 3. Tiles for models in the Papovaviridae family.

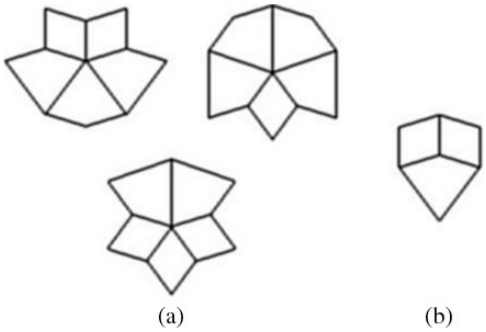

Figure 4. (a) The three allowed vertex stars with the vertex located on a pentamer. (b) The only other allowed vertex star.

papilloma infected tissue have been shown to contain both kinds of tube [14]. We focus here in particular on polyomavirus, which is a (pseudo-) $T = 7$ viral capsid whose capsid proteins form three capsid-like polymorphs as well as tubular structures [15]. The capsid-like polymorphs are a 72-capsomere (pseudo-) $T = 7$ capsid, a 12-capsomere $T = 1$ capsid and a 24-capsomere octahedral particle [16]. A mathematical model for the collective description of the surface structures of all particles in the family has been derived in [6]. Since the particles with octahedral symmetry are usually observed only *in vitro*, we are focusing on the icosahedral cases here.

All capsomeres are pentamers built from five VP1 protein subunits. The surface structures of these polymorphs and all possible non-capped tubes may be described using VTT [3, 9] as discussed in section 3. The relevant tiles are kites and rhombs, with protein subunits located at some specific vertices of each tile as shown in figure 3: the kites represent trimer interactions and the rhombs represent dimer interactions between the individual subunits. The tiles can meet according to two simple rules, which were originally based on biologic assumptions.

- *Rule 1*. Edges may only meet if they are of the same length. This means that rhomb tiles may only meet kite tiles at the shorter edges of the kite tiles.
- *Rule 2*. If a vertex is decorated (has a protein subunit) then it may only meet another decorated vertex. Similarly, undecorated vertices may only meet other undecorated vertices. Partially decorated vertices cannot occur.

From a combinatorial point of view there are only a few possibilities for assembling tiles around a vertex according to these rules. These configurations are called *allowed vertex stars*. They are shown in figure 4, bar the vertex stars which are only found in spherical caps. Consequently, any tiling obtained from kites and rhombs with the above matching rules has a periodic structure of ribbons of kites and rhombs[4]. For classification purposes, we introduce

[4] Periodicity is a consequence of the matching rules; otherwise, aperiodic structures could also be constructed with this set of tiles.

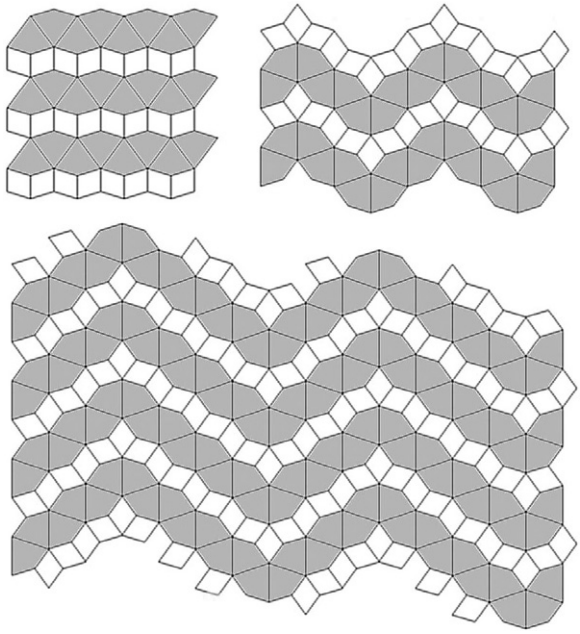

Figure 5. Three possibilities for lattices based on kites and rhombs, following the allowed tiling rules. Ribbons of kites have been highlighted to show the periodic structure.

the terminology *tube of ribbon number N* for a tube that, when cut parallel to the tube axis, transforms into a flat sheet consisting of N such ribbons. Some examples of allowed tilings are shown in figure 5. In the following subsections we discuss which capped tubular structures can be associated with each spherical capsid in the family of Papovaviridae. We denote by (T, n, N) the capped tubular variant associated with an icosahedral capsid of triangulation number T, whose end caps are obtained by cutting the capsid around a global n-fold symmetry axis and whose tubular section has ribbon number N.

4.1. $T = 1$ capped tubes

$T = 1$ particles formed from the polyomavirus capsid protein VP1 exhibit a structure with dimer interactions between protein subunits and therefore, according to VTT, may be tessellated by rhombs (see figure 2). The surface lattice of such particles can be represented in planar geometry as shown in figure 6, where we display the three ways of cutting the particles into halves according to the three options discussed in section 2. For each of them we must check whether the two halves can be completed to a tube by adding kite and rhomb tiles according to the allowed rules.

For $T = 1$ particles, capped tubular variants can be constructed for any of the three types of end caps. Samples of the corresponding tubes are shown in figure 7. The $(1, 5, N)$ capped tubular structure exhibits a total number of $12 + 10N$ pentamers as there are ten in each highlighted ribbon and six in each end cap. The $(1, 3, N)$ capped tubular structure contains 12 pentamers per ribbon and therefore a total of $12(N + 1)$ pentamers, whereas the $(1, 2, N)$ capped tubular structure has 14 pentamers per ribbon and a total of $12 + 14N$ pentamers. It follows that the number of protein subunits in each are $5(12+10N)$, $60(N+1)$ and $5(12+14N)$, respectively.

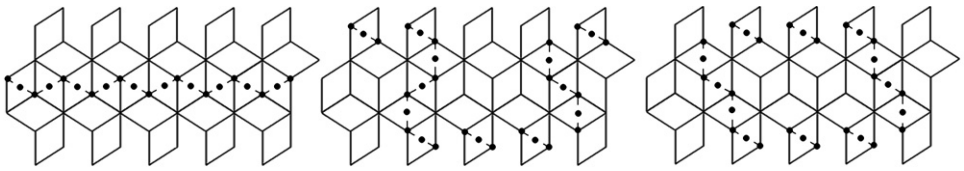

Figure 6. $T = 1$ capsid-like particle made with rhombs only. The three ways of cutting the particle in half. From left to right: $(1, 5)$, $(1, 3)$ and $(1, 2)$. This is a planar representation of a spherical capsid, so it can only be used as a qualitative diagram.

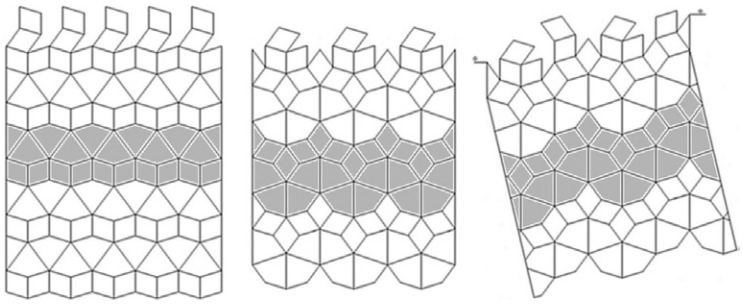

Figure 7. Nets for the three possible $T = 1$ tubes corresponding to a rhomb tiling (triacontahedron). (a) $(1, 5)$, (b) $(1, 3)$, (c) $(1, 2)$, where the stars show where to join the sides of the tube together. The highlighted bands show the repeated sections.

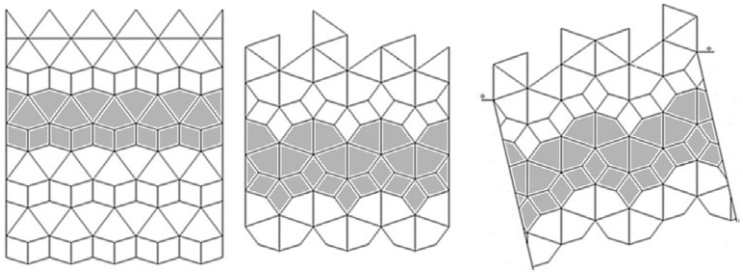

Figure 8. Nets for the three possible $T = 1$ tubes corresponding to a triangulation (icosahedron).

A similar lattice is obtained for $T = 1$ particles with trimer interactions throughout that are represented by icosahedra. The surface lattices of the tubes coincide with those in figure 7, and the only difference consists in the caps as shown in figure 8.

4.2. (Pseudo-) $T = 7$ capped tubes

The second type of spherical icosahedral particles in the family of Papovaviridae is the (pseudo-) $T = 7$ capsids in figure 2, section 3. We represent the corresponding tiling, again in planar geometry, in figure 9. The three different ways of cutting the lattices in half according to the options discussed in section 2 are indicated by ribbons of highlighted rhombs, with cuts running through the centres of the rhombs. For each case one has to check whether these configurations can be continued into a tube using the vertex stars in figure 4. This is possible for the (7, 5) cut, and the corresponding tube is shown in figure 10, where periodically repeated sections have been highlighted.

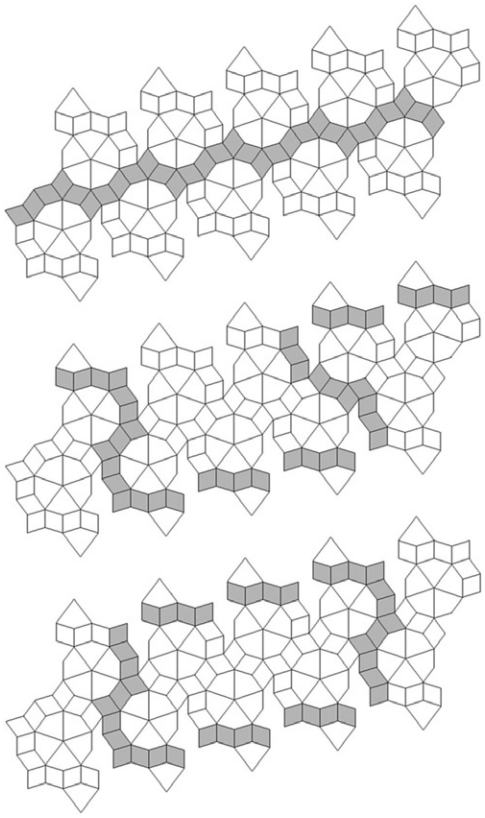

Figure 9. A $T = 7$ lattice with rhombs highlighted to show the three possible ways of cutting it in half. The cuts run through the centres of the highlighted rhombs so that one half of each rhomb is contained in each cap. The configurations correspond to the (7, 5) cut (top), (7, 3) cut (middle) and (7, 2) cut (bottom) respectively.

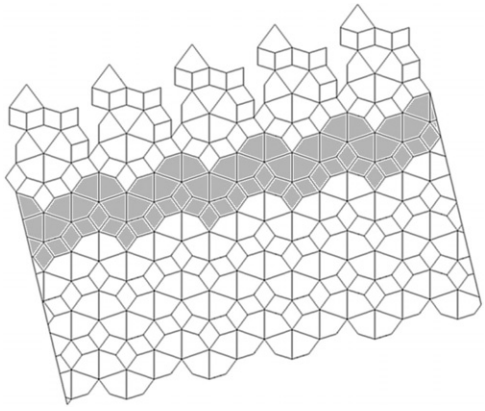

Figure 10. Net for the (7, 5) tube.

There are 30 pentamers per repeated section and thus, for a tube with N repeated sections, there are $6(12 + 5N)$ pentamers in the complete shell.

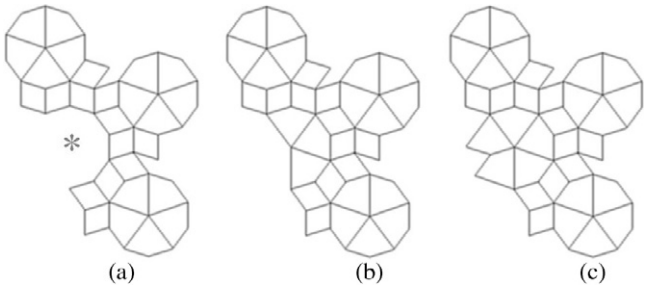

Figure 11. (a) ∗ shows the untilable boundary section where the only possible choice is to add three kites as in (b). This implies the addition of two more kites. If all of the kites are pointing inwards, this configuration necessarily leads to a spherical capsid when continuing according to the rules. Otherwise, one obtains the untilable region shown in (c).

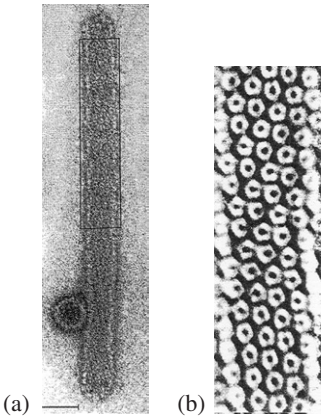

Figure 12. (a) Experimental data for a capped tube and (b) a filtered image of a portion of that tube, both adapted from [15].

For the other two cuts, it is not possible to extend the end caps to tubes, because for both the (7, 3) cut and the (7, 2) cut there exists an area along the cut that corresponds to the scenario depicted in figure 11(a).

The only possible way to complete this configuration based on rule 1 above is to add three kite tiles as shown in figure 11(b). According to rule 1, this configuration has to be continued with two further kite tiles. If these are pointing inwards, any continuation of this configuration according to the rules necessarily leads to a spherical capsid. The alternative is to insert them pointing outwards as shown in figure 11(c). However, according to rule 2, this is an untilable configuration, i.e. it cannot be completed with the set of tiles according to the rules: the only geometrically possible tile for this gap would be a rhomb, but this leads to a configuration that does not correspond to any of the allowed vertex stars in figure 4 and is hence excluded.

5. Comparison with experimental results

The surface structures of tubular particles in the family of Papovaviridae have been investigated by cryo-electron microscopy. For example, capped tubular particles with a diameter of 400–450 Å have been considered in [15]. In order to analyse these data, which are shown in figure 12(a) (adapted from figure 2A in [15]), the diffraction pattern has been used to create a

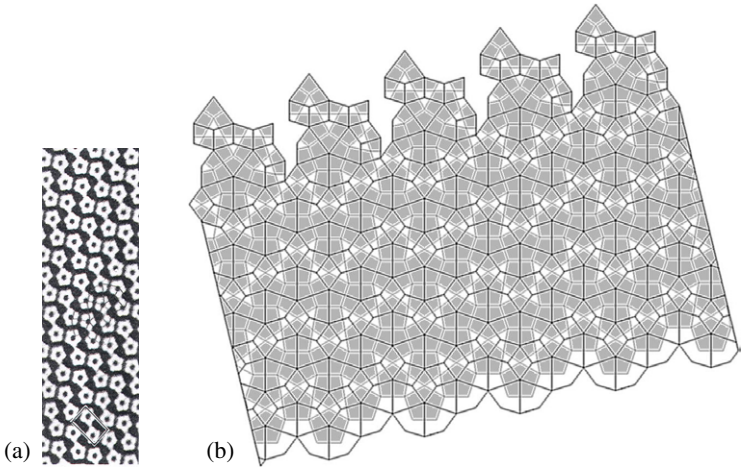

Figure 13. (a) The surface lattice suggested in [15] compared with (b) the lattice implied by the tiling in figure 10.

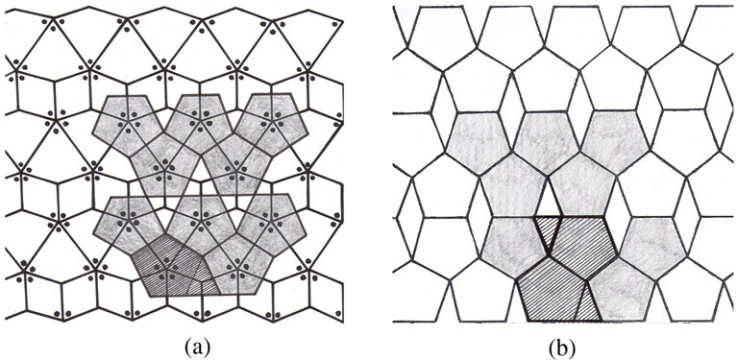

Figure 14. The lattice implied by the tiling approach (a) compared with the surface lattice in [8] (b).

filtered image of the data (see figure 12(b) adapted from figure 2B in [15]). For an interpretation of these filtered images, surface lattices in terms of pentagons have been suggested. These lattices differ from the lattices that we have obtained via our approach. In particular, the lattice in [15] is shown in figure 13(a) in comparison with our lattice, that is shown superimposed on the tiling in figure 13(b).

However, it seems to us that the fit of the lattice suggested in [15] is qualitative only, and that it is not clear—especially in view of the quality of the initial data, as well as the subsequent application of a filtering procedure—whether this is indeed the correct description of the data. For example, if, when computer-generating the picture in figure 12(b) based on the diffraction data, a too small sized unit cell had been assumed, a lattice like the one derived here would have automatically been excluded *a priori*.

A similar phenomenon occurred for the usual (non-capped) tubes. In an earlier paper [9] we have derived a surface lattice from first mathematical principles based on the tiling approach (see figure 14(a)) that differs from the lattices used by Klug and collaborators in [8] to explain their experimental data (see figure 14(b)). An analysis of the bonding structure implied by these

lattices shows that the lattice obtained via the tiling approach describes a more stable structure. Indeed, while a pentamer is connected to only three others in the lattice suggested in [8], it is connected to six others in ours. It is hence a more likely candidate for the surface structure of the tubes. A comparison with the corresponding experimental data had shown that, as in the present case, factoring in the quality of the initial (unfiltered) data it is an equally plausible alternative. It would hence be interesting to investigate this issue experimentally in more detail, especially since the available resolution has dramatically improved since the time when these experiments had been carried out.

6. Conclusion

In this paper, we have extended viral tiling theory to tubular structures with end caps for the scenario that the transition between end caps and tubes occurs without generation of extra curvature. Four different tubular lattices have been derived—three of them with $T = 1$ end caps and one with a (pseudo-) $T = 7$ end cap.

Papovaviridae are distinguished from other families of viruses by the fact that the surface lattices of both spherical and tubular particles are formed from pentamers throughout, that is from protein clusters of five individual protein subunits. In this respect, Papovaviridae are different not only from the Caspar–Klug cases but also from fullerenes, i.e. cages formed from carbon atoms that have a structure similar to the lattices occurring in the Caspar–Klug theory. For fullerenes, it is known that tubular lattices with end caps occur as well as the spherical lattices. They are called carbon nanotubes, and a classification of these may be found in [17]. Viruses described by the Caspar–Klug theory have associated tubular structures that have the same surface lattices as carbon nanotubes, and a classification of these structures can hence be inferred from the literature on carbon nanotubes. We have therefore focussed in this paper on Papovaviridae, which fall out of the scope of the Caspar–Klug classification.

While fullerenes also exist in spiral and toroidal conformations (see for example chapter 7 in [17]), such structures have not been observed in viruses. A reason for this may be the fact that heptagonal rings are needed in addition to the pentagonal and hexagonal ones in order to create the negative curvature necessary to form spiral and toroidal shapes. Heptagonal ring structures can be formed from carbon atoms, but capsid proteins of viruses have never been observed in clusters of seven or with a local bonding structure corresponding to seven-fold local symmetry. Therefore, unless such clusters can be enforced by protein engineering, analogues to spiral and toroidal fullerene lattices are unlikely to exist in viruses. In any case, they are impossible in the framework of all-pentamer lattices, which correspond to the case of Papovaviridae.

The classification of capped tubular structures for Papovaviridae derived here together with the classification of the spherical particles in this family obtained in earlier work can be used to construct assembly models that take the simultaneous formation of spherical and tubular capsid structures into account. The derivation of extensions of the models in [4, 10] is planned along these lines. We shall use such models to investigate how realistic it is to trigger the formation of tubular (rather than spherical) structures and hence influence the viral replication cycle. Since Papovaviridae contain cancer-causing viruses this research may benefit the development of anti-viral drugs in the long term.

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