SCAR-DRIVEN SHAPE-CHANGES OF VIRUS CAPSIDS

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Abstract

We propose that certain patterns (scars) – theoretically and numerically predicted to be formed by electrons arranged on a sphere to minimize the repulsive Coulomb potential (the Thomson problem) and experimentally found in spherical crystals formed by self-assembled polystyrene beads (an instance of the generalized Thomson problem) – could be relevant to extend the classic Caspar and Klug construction for icosahedrally-shaped virus capsids. The main idea is that scars could be produced on the capsid at an intermediate stage of its evolution and the release of the bending energy present in scars into stretching energy could allow for shape-changes. The conjecture can be tested in experiments and/or in numerical simulations.

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1 Introduction

Understanding virus structure is not only of great relevance for human health but it could as well shed light on the origin of life itself. A virus – “the smallest of all self-replicating organisms in nature” – is invariably a single piece of nucleic acid (DNA or RNA) – usually very small – surrounded by proteins encoded by the nucleic acid. These proteins form a protective coat called capsid sometimes cased into a lipidic membrane called envelop. The self-replication is parasitic and happens only with the help of a host cell that provides the necessary organic material to the price of its own death. Viral nucleic acid encodes very few (in many cases only one) types of proteins. These proteins either assemble to form the capsid (coating) or disassemble to release the genome within the host cell (uncoating), depending on the stage of the virus life cycle. Capsids’ shapes are important for the ability of the virus to infect. For instance, HIV-1 is only infective when the shape of its capsid has changed from spherical to conical (a phenomenon called maturation). It is shape-changes of virus capsids that we intend to discuss in this paper.

Viral capsids come in three classes of shapes: helical (the proteins spiralize counter-clockwise around the genetic material), icosahedral or simple (the proteins, arranged in groups of 5 and 6, following precise geometrical/topological prescriptions, as we shall soon recall, make an icosahedron), complex (sphero-cylindrical, conical, tubular or even more complicated shapes, i.e. without a precise resemblance to any particular regular polyhedron, like, e.g., certain bacteriophages). As for the HIV-1, viruses may change their shape. When this happens they are called polymorphic.

In 1956 Crick and Watson proposed that small viruses have capsids with the proteins (or subunits) arranged into morphological units called capsomers with the shape of hexagons and pentagons, called hexamers and pentamers, respectively. These capsomers form icosadeltahedrons, with a fixed number, 12, of pentamers and a variable number of hexamers. Following Crick and Watson’s seminal idea, Caspar and Klug (CK) later extended the class of viruses to which this construction applies to what they called “simple viruses”, i.e. still roughly spherical but not necessarily small viruses. The CK model for the construction of icosadeltahedral capsids is nowadays an established paradigm among virologists. Nonetheless, various modifications/generalizations of this model have been proposed to include (for a review see [7]): spherical viruses that do not respect the CK prescription - e.g. the Papovaviruses capsids, made exclusively of pentamers; polymorphic viruses that, although evolving into non-spherical morphologies, have capsids that respect the CK ‘counting’ of 12 pentamers and 10(T − 1) hexamers - where T = 1, 3, 4, 7,..., see later - [9][11]; other shapes obtained in vitro when proteins self-assemble [9] (see also [10]). For instance, the model proposed in Ref. [11] - based on the continuum elastic
theory of large spherical viruses of Ref. [12] - the authors address the problem of understanding the formation of spherocylindrical and conical virus capsids with 12 pentamers and 10\((T−1)\) hexamers. Here we shall show that, if a change in the texture of the arrangement of proteins takes place, a variety of non-spherical shapes that respect the CK counting could be obtained through a mechanism that we shall call the “scar formation-annihilation mechanism”. Let us now review the CK construction.

2 Caspar-Klug construction

The fact that exactly 12 pentamers are necessary is easily understood if we look at this problem as the analogue problem of tiling a sphere with pentagons and hexagons and we take into account the topological properties of the sphere (Euler theorem, see, e.g., [13]). The precise number of hexagon is not fixed by this argument and needs further assumptions that we shall later discuss. The argument goes like this:

Suppose that the polygons’ edges join three at the time. If \(N_p\) is the number of \(p\)-gons used to tile a unit sphere, i.e. \(N_5\) pentagons and \(N_6\) hexagons, the resulting polyhedron \(P\) has \(V_P = 1/3 \sum_N N_p\) vertices, \(E_P = 1/2 \sum_N N_p\) edges, and \(F_P = \sum_N N_p\) faces, giving for the Euler characteristic \(\chi = V_P - E_P + F_P\), the following expression

\[
\sum_N (6-p)N_p = 6\chi = 12 ,
\]

since for a sphere \(\chi = 2\). Explicitly Eq. (1) reads

\[
(6 - 5) N_5 + (6 - 6) N_6 = 12
\]

(2)

hence to tile a sphere \(N_5 = 12\) is required, but \(N_6\) can be arbitrary. As said, for icosahedrons (the case of virus capsids) \(N_6\) is not arbitrary but must be a specific number that we shall soon obtain. For the mathematical problem of tiling the sphere one might also imagine to use heptagons. In that case the Euler formula (1) gives

\[
N_5 - N_7 = 12 .
\]

(3)

Thus, starting from the tiling of the sphere with exactly 12 pentagons (and an arbitrary number of hexagons) one can add pairs pentagon-heptagon, but not a pentagon or a heptagon separately. Note that this is only a mathematical consideration and its relevance for virus structure is all to be proved.

\footnote{That virus capsids’ construction and tiling theory are strictly related has been shown in detail in Ref.[8]. There a more general analysis than the one presented here is carried on giving the opportunity to include capsids entirely made of pentamers. Those configurations do not violate Euler’s theorem because certain pentamers interact with 6 nearest neighbors and certain with 5 nearest neighbors, the latter being 12 in number.}
The geometric interpretation of the Euler formula (1) is that a unit sphere has curvature $R_{\text{sphere}} = +1$ and each polygon contributes to this curvature with $R_p = (6 - p)/12$: a hexagon with $R_6 = 0$, a pentagon with $R_5 = +1/12$, a heptagon with $R_7 = -1/12$. This can be understood by constructing hexagons, pentagons and heptagons out of equilateral triangles of paper. A hexagon is obtained by joining together 6 triangles: they all stay in a plane. Take one triangle out and join what is left to make a pentagon and the resulting figure will bend outwards, while adding one triangle to the hexagon to make a heptagon results into an inward bending. This also tells us that a certain amount of bending energy $E_b$ is necessary to convert a hexagon into a pentagon or into a heptagon. How big is $E_b$ depends on the elastic properties of the material used.

Suppose now that the proteins are arranged on a plane to form the hexagonal lattice of Fig.1. An edge shared by two hexagons counts for two proteins. The vector $\vec{A} = h\vec{a} + k\vec{b}$ corresponds to $h = 1$ and $k = 3$.

This does not affect the part of the proof of Euler's theorem (1) based on $E_P = 1/2 \sum_{p} N_{p,p}$ because for the purpose of tiling the sphere it is correct to think of each edge shared by two polygons as contributing 1 and not 2 to the formula. On the other hand, real capsomers (pentamers or hexamers) are individual entities that cluster to make the icosahedron. Hence, on real capsids, two hexamers that ‘neighbor on one edge’, say, have 12 proteins and not 11.
Icosahedral Virus &  $N_{\text{proteins}}$ & $T$
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Feline Panleukopenia Virus & 60 & 1
Human Hepatitis B & 240 & 4
Infectious Bursal Disease Virus (IBDV) & 780 & 13
**General** & $60T$ & $h^2 + k^2 + hk$

Table 1: Examples of viruses that follow the CK classification taken from Ref. [6].

$A^2 = a^2(h^2 + k^2 + 2hk \cos \varphi) = a^2(h^2 + k^2 + hk) \equiv a^2T(h,k)$, with $T(h,k) = 1, 3, 4, 7, \ldots$. Being the area of the triangle given by $\alpha_A = (\sqrt{3}/4)a^2T(h,k)$ and the area of one hexagon $\alpha_6 = (\sqrt{3}/2)a^2$, the number of hexagons per triangle is $n_6 = \alpha_A/\alpha_6 = [T/2]$. The total number of subunits is obtained by counting the total number of hexagons used for the planar lattice of Fig.1, which is $N_6 = 20(T/2) = 10T$, then multiplying by 6 (the number of edges of the hexagon): $N_{\text{proteins}} = 60T$. On the real 3-dimensional solid (that one one might think of obtaining by folding the planar template) the $60T$ proteins are arranged as: i) 60 form 12 pentamers; ii) $60(T - 1)$ form $10(T - 1)$ hexamers, for a total number of morphological units of $N = 10T + 2$. The figures obtained are icosadeltahedrons characterized by the pair of integers $(h,k)$ which not only are related to the total number of proteins, but also give the “chirality” of the polyhedron. Viruses belonging to this class follow these prescriptions with great accuracy and they are classified according to the values of $T$ (see Table 1 for some examples and Ref. [6] for an exhaustive database on icosahedral virus structures). As recalled above, recently there have been various attempts to generalize the CK model to include other
morphologies [11, 9]. Later we shall show that, if a change in the texture of the CK arrangement of proteins takes place under certain conditions, then a great variety of morphologies could be naturally obtained.

3 Lessons from the Thomson Problem

Let us now turn our attention to a different but geometrically related physical set-up from which we would like to gain some insights for the generalization of the CK construction we are looking for: the Thomson problem [14]. It consists of determining the minimum energy configuration for a collection of electrons constrained to move on the surface of a sphere and interacting via the Coulomb potential. This old (and largely unsolved) problem has many generalizations for more general repulsive potentials as well as for topological defects rather than unit electric charges [15], [16]. The fact that the two problems (virus capsids construction and equilibrium configurations for charges on a sphere) are intimately related can be seen from the numerical results for the Thomson problem that have been obtained over the years.

In Ref. [17] the authors proposed as solution of the problem an arrangement of \( N \) electrons on the sphere into a triangular lattice where each electron has 6 nearest neighbors sitting at the vertices of an hexagon, with the exception of 12 locations where the nearest neighbors are only 5 sitting at the vertices of a pentagon and \( N = 10T + 2 \), with \( T = h^2 + k^2 + hk \): that is the icosadeltahedron. Note that in this case the electrons are constrained to be on the surface of the sphere, e.g. imagining the sphere as a metal, while the proteins have not such constraint. Furthermore, the polygons here are “imaginary”, in the sense that only the vertices are real particles, while the edges are not.

Further studies [18] have shown that, even for \( N = 10T + 2 \) electrons, when \( N \) is large enough (of the order of 500), configurations which differ from the icosadeltahedron have lower energy than the corresponding icosadeltahedron. That is, when near one of the 12 pentagons two hexagons (let us call this a 5-6-6 structure) are replaced by a pair heptagon-pentagon (let us call this a 5-7-5 structure) to form a linear pattern called scar, the energy is lower than that of a configuration of 12 pentagons and all the rest hexagons. This indeed happens in numerical simulations for \( N > N_{scar} \sim 500 \), where the scars become longer (e.g. 5-7-5-7-5, etc.), always respect the topological/geometrical constraint of Eq. (3), can spiralize or might even form exotic patterns like two nested pentagonal structures with five pentagons placed at the vertices of the outer pentagonal structure, five heptagons at the vertices of the inner pentagonal structure, and a heptagon in the common center (the vertex of the icosadeltahedron) (see, e.g., [15] and references therein). The latter patterns are called pentagonal buttons and an explanation of their origin can be found in Ref.[13]. Apparently, even more complicated structures
can appear in numerical simulations \[15\]. Scars have been experimentally found to be formed in spherical crystals of mutually repelling polystyrene beads self-assembled on water droplets in oil \[19\]. The repulsive potential there is not the Coulomb potential, hence that is a particular instance of the generalized Thomson problem. These experimental findings confirm that, at least in the case of scars, things go along the lines of the above outlined analysis.

The lesson we learn from the Thomson problem is that the total energy of the system is the sum of bending energy and stretching energy, \( E_t = E_b + E_s \), and that the two energy types compete for the minimization of the total energy \[15\]. Below the threshold for the scar production \( N_{\text{scar}} \), \( E_b \) is provided by the 12 pentagons, while the hexagons contribute to \( E_s \) only. When \( N > N_{\text{scar}} \) it becomes energetically favorable to convert a pair 6-6, with zero total and local curvature \((0 = 0 + 0)\) and zero bending energy, into a pair 5-7, again with zero total curvature but with nonzero local curvature \((0 = +1/12 - 1/12)\) hence with nonzero bending energy given by \( 2E_b \). Here \( E_b \) is the energy necessary to convert a 6 into a 5 (or into a 7) that, in the application to virus capsids we shall shortly discuss, should be thought of as the conformational switching energy \[20\] (for the conformational switching energy in HIV-1’s capsid see, e.g., Ref.\[21\]).

4 Scars on Virus Capsids

What we propose here is that: scars of pentamers and heptamers can appear on icosahedral virus capsids at an intermediate stage of their evolution towards a non-spherical shape and can actually drive such shape-change. The idea is that scars can appear on the intermediate spherical capsid in two ways: either because they minimize the total energy \( E_t \) or via an external modification, that we generically call the “interaction with the environment”. In the first case we expect this to happen for \( N > N_{\text{scar}} \); in the second case \( N \) can be smaller than \( N_{\text{scar}} \). In both cases the spherical configuration with scars is supposed to have higher total energy than the non-spherical configuration without scars:

\[
E_{t}^{\text{Spherical + Scars}} > E_{t}^{\text{Non-Spherical}} ,
\]

or

\[
E_{t}^{\text{Spherical + Interaction}} \leftrightarrow E_{t}^{\text{Spherical + Scars}} > E_{t}^{\text{Non-Spherical}} ,
\]

hence the net effect of the scar formation is a shape-change from spherical to non-spherical. Both instances take into account the differences between

\[\text{For the Thomson problem it is found (see, e.g., } 22\text{) that heptagons (and even squares) appear even for } N < N_{\text{scar}}.\text{ For instance, already for } N = 71,123 \text{ the heptagon-pentagon scars are present, while for } N = 141,172 \text{ a square surrounded by 8 pentagons appear. Note that here the CK counting for } N, N = 10T + 2, \text{ is not at work.}\]
the physics of the Thomson problem and the physics of viral capsid. For the (generalized) Thomson problem, the electrons (or, generically, the repelling particles) are constrained on the surface of a sphere and no interaction with the external environment takes place. Both these constraints are not at work in the case of viral capsids, hence in some cases it might be energetically favorable for the capsid to first produce the scars and then get rid of them by changing shape.

Our conjecture needs to be tested in experiments and/or in numerical simulations based on some particular model. Nonetheless, its strength is that it would explain at once two experimental facts: that scars have not been seen on spherical virus capsids as yet and that many examples of non-spherical capsids that, although non-spherical, respect the CK counting of 12 pentamers and 10\((T - 1)\) hexamers, are found in nature and/or in artificial capsids assembly\(^4\) ("bucky-tubes" shaped, bacteriophages' heads, retroviruses, etc.). Our hypothesis does not exclude the possibility that scars could be present in the final (stable) capsid of some large virus, it ascribes to scars the responsibility for shape-change of spherical capsids.

The way we postulate the scar-driven shape-change mechanism to take place is as follows: i) At first the proteins start assembling to make an icosadeltahedron following the CK prescription. ii) At an intermediate stage, due to the interaction with the environment and/or to the reach of the threshold \(N_{\text{scar}}\), they form scars near the location of one or more of the 12 pentamers at the vertices of the icosadeltahedron. The needed extra bending energy \(2E_b\) in the case of the formation of what we might call a “simple” scar: 5-7-5 \(E_b\) has to be identified with the conformational switching energy \(20\). iii) Eventually, the capsid changes shape, from spherical to non-spherical via the release of the bending energy into stretching energy at the location of the scar with the consequent “annihilation” of the 5-7 pair into a 6-6 pair. The resulting capsid has the usual morphological units, pentamers and hexamers, but not the spherical shape. Note that for us in the presence of scars, the total number of proteins needed is the same as for the icosadeltahedral case without scars (this follows from 6 + 6 = 5 + 7) while the number and type of morphological units changes (for one simple scar: 13 pentamers, 1 heptamer, 10\((T - 1)\) hexamers, etc.).

As said earlier, there is a strong interest today in trying to generalize the CK construction to include non-spherical viruses, important examples being retroviruses that have spherical, spherocylindrical and conical capsids (see, e.g., Ref.\(^{23}\) and references therein). In the work of Ref.\(^{11}\) the proposal that spontaneous curvature of the proteins in the capsids can drive a change in shape from spherical to spherocylindrical or conical shapes is extensively

\(^{4}\)Although we believe that the “scar-driven shape-change mechanism” is of general relevance for many virus capsids, a good candidate for the experimental test of the conjecture is probably HIV-1’s capsid evolution to the mature conical conformation.
studied and the geometric construction of certain capsids (spherocilyndrical and conical) is carried out. The application of that approach to the case of retroviruses is then performed in Ref. [23], where the importance of the environment for the assembly of retrovirus capsids is pointed out. What we conjecture here is that the basis of these phenomena is the formation of scars. Our belief is based on the following observations: i) Scars appear in the geometrically related (generalized) Thomson problem; ii) Their formation/annihilation mechanism here seems to us a natural way to convert bending energy (formation) into stretching energy (annihilation); iii) This way a mechanism for producing a great variety of shapes (not only the spherocilyndrical or conical) is in place: the formation/annihilation of scars (simple or complex) in different locations on the intermediate icosadeltahedron (we suppose that this happens near the vertices).

Other authors have also speculated that scars should occur on virus capsids [19]. They expect scars to be formed only on large viruses and that means that they are expecting scars to be seen on the final capsid. As said, this is an instance that we do not exclude but that is not essential for us as our main proposal is to ascribe the shape-change to the scars formation/annihilation mechanism. More interestingly for us are the conclusions of Ref. [9] on the importance of the conformational switching energy as a second important control parameter (the first being the spontaneous curvature [11]) for capsid shapes. In that work the authors have numerically studied a model based on adherent disks of different diameters and understood that the switching energy plays a crucial role in the determination of which shape the capsid will eventually prefer (see also the related work of Ref. [10]).

Let us now focus on the kind of shapes one can obtain via the scar formation/annihilation mechanism. It is easy to convince oneself that indeed a great variety of shapes could be obtained: At the site on the intermediate icosadeltahedron where the scar is formed and then annihilated the sphere gets stretched. The amount of stretching depends on the complexity of the

Figure 3: The intermediate spherical (icosadeltahedral) capsid with the $C_5$-symmetric distribution of simple scars.
The scars could be formed symmetrically (as we shall soon see, for a particular symmetry of formation of scars we shall naturally obtain the spherocylindrical shape) or asymmetrically hence giving rise to regular or irregular shapes. Of all these very large number of shapes only a subset will describe real virus capsids. A systematic study can be carried out using this method and case by case it could be seen whether it fits with the elastic properties of the virus capsids and with the constraints coming from the environment [23]. What we shall do now is to construct, within our framework, one particular shape, the spherocylindrical. This will give us the opportunity to show how the method of construction works in a case that is known to correspond to, e.g., certain bacteriophages.

Suppose that the intermediate icosadeltahedron is formed. We can then refer to the hexagonal lattice and to the template of Fig.1 and Fig.2. Let us imagine that the scars, e.g., all simple, are created only near the 10 inner vertices via a mechanism that respects the $C_5$ rotation symmetry around the north pole-south pole axis. In Fig.3 the vertices where the scars are formed are indicated with •, while the other two are indicated with ◦. Take a pair of the equilateral triangles of that template: any one from one of the outer layers of five triangles (e.g. the layer of triangles that correspond to the north pole) and the one from the inner layer that shares an edge with it. In Fig.4 of such pairs is shown and the different nature of the vertices is represented like in Fig.3. The scars are distributed in a way that is asymmetric with respect to the two triangles, hence the net effect of their formation/annihilation mechanism will deform them differently. Depending on the actual orientation of the scar around the given vertex the deformation will be different. To obtain the spherocylindrical capsid the three scars should make the lower triangle thinner and longer (they stretch the area and make it bigger) and this has the effect of shrinking the upper triangle by making the common edge shorter. Due to the symmetry of the location of scars the two edges of the new lower triangle have to be the same. If this mechanism takes place in the same fashion for all the ten pairs of triangles of the template of Fig.1 the resulting new template is the one given in Fig.4. We require that this mechanism is area preserving, i.e. that the total number

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5 Complex scars might not be that rare as the same amount of energy is needed for the formation of, say, one next-to-simple scar (5-7-5-7-5) and two simple scars, i.e. $4E_b$.  
6 $C_n$ is the finite group of rotations of angles $2\pi/n$, with $n = 1, 2, 3, \ldots$. $C_5$ is one of the subgroups of the icosahedral group, the group of all possible symmetries of the icosahedron. Its relevance for the Thomson problem has been understood in [13] where a mechanism of spontaneous symmetry breaking is seen as the responsible for some of the patterns found in numerical simulations. Here our introduction of the $C_5$ symmetry is motivated solely by the need to build up the spherocylinder.  
7 Of course the axis is completely arbitrary as long as it encompasses two opposite vertices.  
8 Five north pole triangles paired with their common-edge inner triangles and five south pole triangles paired with their common-edge inner triangles.
Figure 4: The generalized CK construction of the template driven by the scars formation-annihilation mechanism.

of proteins needed is the same as the one needed for the icosadeltahedron, they are only rearranged. This is obtained by requiring that $2\alpha_A = \alpha_1 + \alpha_2$, where $\alpha_1$ is the area of the upper new triangle and $\alpha_2$ the area of the lower new triangle in Fig.4. This means that the three quantities must be related as

$$\sqrt{3}A^2 = B \left( \sqrt{A^2 - \frac{1}{4}B^2} + \sqrt{C^2 - \frac{1}{4}B^2} \right), \quad (4)$$

with $B < A$ and $C > A$. Recall that, for $a = 1$, $A^2 = T = h^2 + k^2 + hk$, hence the final capsid, obtained by folding the new template of Fig.4 (see Fig.5), will have (12 pentamers and) the $10(T - 1)$ hexamers distributed differently with respect to the intermediate icosadeltahedron.

Notice that this spherocylinder is slightly different from the one obtained in [11] as the upper and lower half-icosadeltahedrons are not obtained by folding five equilateral triangles but five isosceles triangles (in this sense they are no longer proper half-icosadeltahedrons but a deformation of them). This is an instance that could be experimentally tested.

From this construction it is clear that a variety of shapes could be obtained this way. For instance, if the scars carry a bigger bending energy than the one used above than the final shape is a backy-tube capsid; if the orientation of the scars in the previous setting is such that $C$ shrinks, hence $B$ becomes longer, then a disk-like shape is obtained; etc. Let us stress here again that for these shapes to correspond to real virus capsids one needs more detailed information.

5 Conclusions

In this paper we proposed a mechanism of formation and subsequent annihilation of scars of pentamers-heptamers at an intermediate stage of the evolution of spherical virus capsid as the responsible for a great variety of non-spherical virus shapes. Our conjecture is based on the fact that scars
are found in the (generalized) Thomson problem, in experiments and in numerical simulations, and on the observation that this mechanism would give a simple, plausible and general explanation of changes of capsid’s shape that retain the Caspar-Klug counting for capsomers. The conjecture can be tested, for instance, in experiments where artificial capsids are synthesized and/or in numerical simulations based on available models. Scars should appear on what we called here the intermediate icosadeltahedron, then should drive the change in shape. Capsids that could perhaps be used to this end are those relative to viruses that are known to have non-spherical final shape but still pentamers and hexamers as morphological units, like for instance certain bacteriophages or retroviruses. This conjecture, if experimentally confirmed, would extend the classic Caspar and Klug construction for icosahedral viruses to include viruses that still have pentamers and hexamers as morphological units but no longer are icosadeltahedrons.

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