Combinatorial rules
of icosahedral capsid growth

Richard KERNER∗

∗ Address : LPTMC, Université Paris-VI - CNRS UMR 7600 ,
Tour 24, 4-ème , Boite 121, 4 Place Jussieu, 75005 Paris, France
Tel.: 33 1 44 27 72 98, Fax: 33 1 44 27 51 00, email : rk@ccr.jussieu.fr

Abstract: A model of growth of icosahedral viral capsids is proposed. It
takes into account the diversity of hexamers’ compositions, leading to definite
capsid size. We show that the observed yield of capsid production implies
a very high level of self-organization of elementary building blocks. The
exact number of different protein dimers composing hexamers is related to
the size of a given capsid, labeled by its $T$-number. Simple rules determining
these numbers for each value of $T$ are deduced and certain consequences are
discussed.

Keywords: Capsid growth; Self-organized agglomeration; Symmetry

1 Introduction

Just like the world of planets and stars, the world of viruses is ruled by
numbers. This is particularly true in the case of the numerous group of
spherical viruses, whose protective protein shells called “capsids” display
perfect icosahedral symmetry [1]. It is amazing that these structures, known
to mathematicians since Coxeter’s classification [2], are also observed in the
so-called fullerenes, huge molecules composed exclusively of carbon atoms,
predicted by Smalley and Kroto, and discovered in the eighties.
Since Caspar and Klug \[3\] introduced simple rules predicting a sequence of
observed viral capsids, several models of growth dynamics of these structures
have been proposed, e.g. A. Zlotnick’s model \[4\] published in 1994.

The common geometrical feature of many viral capsids and fullerenes is
their icosahedral shape, with twelve pentagons found on the opposite sides
of six five-fold symmetry axes, and an appropriate number of hexagons in
between. The number of hexagons is given by the following simple formula:

\[ N_6 = 10 (T - 1), \]

where \( p \) and \( q \) are two non-negative integers \[2\].

In capsids, the building blocks made of coat proteins are called monomers,
dimers, trimers, pentamers and hexamers, according to their shape, the bigger
ones usually being assembled from smaller ones prior to further agglom-
eration into capsid shells \[8\]. Sometimes pentameric or hexameric symmetry
is displayed despite the direct construction from 60 or 180 smaller subunits,
like in the Cowpea mosaic virus and the Cowpea chlorotic mottle virus,
respectively \[5\]. Although certain virus species grow medium-size capsids cor-
responding to \( N_6 = 20 \) (like in the \( C_{60} \) fullerene molecule), or \( N_6 = 30 \) and
\( N_6 = 60 \), some of them form pure dodecahedral capsids (with exclusively
pentamers as building blocks), like certain Comoviridae or Cowpea virus \[7\]),
while some others, like human Adenovirus \[6\], form very huge capsids with
\( N_6 = 240 \), corresponding to \( p = 5, \ q = 0 \).

In some cases, the similarity with the fullerene structure is striking: for
example, the TRSV capsid is composed of 60 copies of a single capsid protein
(56 000 Da, 513 amino acid residues) \[10\], which can be put in a one-to-one
correspondence with 60 carbon atoms forming a fullerene \( C_{60} \) molecule; the
aforementioned Cowpea viruses provide another example of the same type.

The process of building the icosahedral viral capsids differs quite essen-
tially from the fullerene formation: fullerenes are formed from carbon atoms
and small carbon molecules like \( C_2, C_3 \), up to \( C_9 \) or \( C_{10} \), etc., in a hot plasma
around electric arc between two graphine electrodes, whereas capsids are built
progressively in liquid medium, from agglomerates of giant protein molecules
displaying pentagonal or hexagonal symmetry, or directly from smaller units
(\textit{monomers} or \textit{dimers}). It also seems that there is no such thing as universal
assembly kinetics: the way the capsids are assembled differs from one virus
to another. The \( T = 7 \) phage HK47 appears to build pentamers and hexam-
ers first, then assemble these capsomers to form the final capsid structure,
whereas another \( T = 7 \) phage labeled P22 appears to assemble its capsids
directly from individual coat proteins (see \[9\] and the references within).
The common point is the presence of pentagons and hexagons in the resulting structure, and the strict topological rules that result from Euler’s theorem on convex polyhedra: \( V - E + F = 2 \), with \( V \) number of vertices, \( E \) number of edges, and \( F \) number of faces. From this one derives the fact that when only pentagonal and hexagonal faces are allowed, the number of pentagons is always \( N_5 = 12 \), while the hexagon number is \( N_6 = 10(T - 1) \).

Contrary to the case of fullerene molecules, whose yield from the hot plasma is in the best case no higher than 10% of total mass of carbon sooth, viruses use almost 100% of pentamers and hexamers at their disposal to form perfect icosahedral capsid structures, into which their DNA genetic material is densely packed once the capsid is complete.

This means that the initial nucleation ratio of pentamers versus hexamers is very close to its final value in capsids in order to minimize the waste. Secondly, the final size of the capsid must depend on particular assembly rules, which can be fairly well deduced from the statistical weights of various agglomeration steps, found by maximizing the final production rate. Let us investigate the rules that define the type and the size of capsids, simultaneously optimizing the production rate.

2 Probabilistic analysis of agglomeration

The simplest stochastic model of growth successfully applied to fullerene formation \cite{11} is based on the assumption that the dominant agglomeration processes consist of forming new polygons in the cavities between two polygons on the border of the existing cluster, by adjoining a \( C_2 \) or a \( C_3 \) molecule to a cavity found in a cluster already formed. One of such processes is shown in Fig.1 below.

It is clear that the resulting (666) cluster is wasted for further fullerene formation, whereas a (656) cluster can be used in the next agglomeration step. Because the (666) clusters are also absent in final fullerene cage, it is easy to see that at each of consecutive agglomeration steps the yield of ”proper” clusters, useful for further fullerene construction, is exactly \( 1/2 \). After about 23 to 24 steps leading from the initial three-polygon structure to an almost finished fullerene cage with 27 to 28 (out of total of 32) polygons already in place, the total yield would approach \( 2^{-24} \approx 10^{-8} \) instead of observed \( 10^{-1} \), i.e. \( 10\% \) ! This means that there is a mechanism that favours the creation of “correct” structures versus the “wrong” ones, so that the average yield of
clusters proper for further fullerene construction becomes close to $q = 0.957$ at each agglomeration step, ensuring $q^{24}$ of order of $10^{-1}$.

In the case of fullerenes, the correction is due to the Boltzmann-Gibbs factors reflecting the energy differences between four basic processes: creating a new pentagon in a $(6,6)$ cavity, or creating a new hexagon in a $(5,6)$ or in a $(6,6)$ cavity, assuming that the energy barrier against creation of two or three pentagons sticking together is so big that the corresponding Boltzmann factor is close to 0. These factors could be evaluated by requiring that the successive probabilities of finding pentagons among all polygons in clusters of given size (after an n-th agglomeration step) and the corresponding yields form a geometric progression [11].

In the case of the icosahedral capsid formation the building process is not random at all. One can be convinced that a high degree of self-organization is involved by considering what would happen if even a small amount of randomness was present. Let us exclude from our considerations the capsids formed exclusively by pentamers; i.e. pure dodecahedral structures, and look at the build-up of bigger capsids involving twelve pentamers and the necessary number of hexamers.

Let us denote the concentration (or the nucleation rate) of pentamers by $x$, that of hexamers by $(1-x)$. Then the probabilities of doublets are readily calculated as follows:

$$P_{56} = 2 \cdot W_{56} x(1-x)/Q; \quad P_{66} = W_{66} (1-x)^2/Q,$$  \hspace{1cm} (1)

where $W_{j,k}$, $j, k = 5, 6$ are the statistical weights depending on the virus type and on the chemical barriers between various sides, and

$$Q = 2 \cdot W_{56} x(1-x) + W_{66} (1-x)^2$$

Figure 1: Creation of a new polygon in a cavity between two polygons
Figure 2: Adding a pentamer or a hexamer to an existing doublet

is the normalizing factor. Note that we exclude two pentamers coming together, i.e. \( W_{55} = 0 \). Similarly, the probabilities of three admissible "triplets" in the next agglomeration step displayed in Fig. 3 are given by:

\[
P_{566} = P_{56} + 2 \cdot P_{66} W_{665} x / Q_2, \quad P_{666} = 2 \cdot P_{66} W_{666} (1 - x) / Q_2,
\]

where \( W_{665} \) and \( W_{666} \) denote the statistical weights of corresponding agglomeration processes, and \( Q_2 = W_{665} x + W_{666} (1 - x) \). Now we can evaluate the average pentamer rate \( x^{(k)} \) in clusters of given size, after \( k \)-th agglomeration step. The first three values are given by:

\[
x^{(1)} = \frac{1}{2} P_{56}, \quad x^{(2)} = \frac{1}{3} P_{656}, \quad x^{(3)} = \frac{1}{4} (2 P_{5656} + P_{6566} + P_{5666}), \text{ etc}
\]

(In the expression for \( x^{(3)} \) we use the probabilities for three different allowed clusters, which are not discussed in detail here, but can be quite easily obtained using the appropriate statistical weights and Boltzmann-Gibbs factors).

We can use these formulae in two different ways. Either we impose the statistical weights \( W_{ij} \) and \( W_{ij,k} \), and determine the consecutive pentamer concentrations in growing clusters, starting from a given initial concentration \( x \); or treat the statistical weights as unknowns and determine them from self-similarity equations for successive pentamer concentrations:

\[
\frac{x^{(n+2)} - x^{(n+1)}}{x^{(n+1)} - x^{(n)}} = \frac{x^{(n+1)} - x^{(n)}}{x^{(n)} - x^{(n-1)}} \quad n = 2, 3, 4...
\]
The resulting solutions for the limit values of $x$ and for auxiliary variables $\xi = (W_{56})/(W_{66})$, $\eta = (W_{56,6})/(W_{66,5})$, $\zeta = (W_{66,6})/(W_{66,5})$, etc., although usually not in the form of simple fractions, give very good hints concerning the assembly rules leading to particular capsid structures.

Now, as the capsid production rate from initial protein material is close to 100%, for fullerene-like ($T = 3$) capsids we should have the initial rate of pentamers versus all capsomers as 3 : 8. In order to keep the same ratio in the grown-up capsids, simple “sticking rules” will suffice.

Let us denote pentamers’ sides by symbol $p$, whereas two different kinds of sides on hexamers’ edges will be called $a$ and $b$ (Fig. 4). Suppose that a hexamer can stick to a pentamer with only ($p + a$)-combination; then two hexamers must stick to each other only through a ($b + b$) combination, with both ($p + b$) and ($a + b$) combinations being forbidden by chemical potential barrier. With these assumptions we get the following statistical factors: $W_{56} = 15$, $W_{66} = 9$, $W_{56,6} = 3$, $W_{66,5} = 5$ and $W_{66,6} = 0$. With these rules the statistics in clusters will converge to the final value $x = 3/8$ as shown in Fig. 4 below:

Similarly, with a more differentiate hexamer scheme, ($abcabc$), and with the assembling rules allowing only associations of $p + a$ and $b + c$, we get with a 100% probability the $T = 4$ capsid, with $x = 2/7$, as shown in Fig. 5.
Note that in both cases we show only one of the “basic triangles” forming the capsid, which is always made with 20 identical triangles sticking together to form a perfect icosahedral shape.

These examples suggest that strict association rules may exist providing precise agglomeration pathways for each kind of icosahedral capsid. Let us analyze these rules in more detail.

3 Combinatorics of icosahedral capsids growth

The virus capsid growth differs essentially from the fullerene agglomeration. Taking into account the complexity of interactions between various proteins forming hexamers and pentamers, the Boltzmann factors resulting from the energy barriers should reduce to simple dichotomy: certain agglomerations are allowed, whereas some others (like binding two pentamers together) are
just forbidden. In contrast, the Boltzmann factors resulting from energy barriers between the allowed processes should not be very different at temperatures between 20° and 37° C.

What remains then are pure statistical factors, which must play the decisive role in order to ensure that the "correct" configurations are produced at each consecutive step almost without exception, i.e. practically with a 100% yield. Let us show now how these statistical factors can be evaluated, and what constraints they imply on the capsomer structure.

From symmetry considerations (and confirmed by chemical analysis) it results that the pentamers are composed from five identical dimers, so that their five edges are perfectly equivalent, and that they possess a defined orientation, i.e. it is known which one of the two faces will be on the outer side of the capsid. All the five sides of a pentamer should be equivalent (identical), because 5 is a prime number, and any division into parts will break the symmetry. Concerning the hexamers, as 6 is divisible by 2 and 3, one can have the following four situations:

- All 6 sides equivalent, (aaaaaa)
- Two types of sides, disposed as (ababab)
- Three types of sides, disposed as (abcabc)
- Six different sides, (abcdef)

The hexamers are also oriented, with one face becoming external, and the other one turned to the interior of the capsid. The three differentiated hexamers are represented in Figure 6 below.

Figure 6: Three differentiations of hexamers

If the viruses were using undifferentiated hexamers with all their sides equivalent, then there would be no reason for not creating any kind of structures as shown in Fig. 6, and the final yield would be very low (at best
like in the fullerenes, less than 10%). But with differentiated hexamers of the (ababab) type simple selection rules excluding the (p − b) and (ab) associations while letting the creation of (p − a) and of (b − b) links, we have seen that the issue becomes determined with practically 100% certainty, as it follows from the Fig. 4.

These sticking rules can be summarized up in a table that we shall call the “affinity matrix”, displayed in the Table 1 below:

|   | p | a | b |
|---|---|---|---|
| p | 0 | 1 | 0 |
| a | 1 | 0 | 0 |
| b | 0 | 0 | 1 |

Table I: Affinity matrix for the $T = 3$ capsid construction

Here a “0” is put at the crossing of two symbols whose agglomeration is forbidden, and a “1” when the agglomeration is allowed. By construction, a “1” can occur only once any line or in any column. The next case presents itself when one uses the next hexamer type, with a two-fold symmetry: (abcabc). Again, supposing that only a-sides can stick to pentamers’ sides p, there is no other choice but the one presented in Fig. 5. The corresponding affinity matrix is as follows:

|   | p | a | b | c |
|---|---|---|---|---|
| p | 0 | 1 | 0 | 0 |
| a | 1 | 0 | 0 | 0 |
| b | 0 | 0 | 0 | 1 |
| c | 0 | 0 | 1 | 0 |

Table II: Affinity matrix for the $T = 4$ capsid construction

Finally, let us use the most highly differentiated hexamers of the (abcdef)-type. Starting with pentamers surrounded by the hexamers sticking via the (p − a)-pairing, we discover that now two choices are possible, leading to left- and right-hand sided versions, as shown in the following Fig. 7.

The corresponding affinity matrices are given below:
Figure 7: The building formulae for the $T=7$ capsids; left and right

|   | p | a | b | c | d | e | f |
|---|---|---|---|---|---|---|---|
| p | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| a | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| b | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| c | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| d | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| e | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| f | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Table III (a): Affinity matrix for the $T = 7$ (left) capsid construction

|   | p | a | b | c | d | e | f |
|---|---|---|---|---|---|---|---|
| p | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| a | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| b | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| c | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| d | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| e | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| f | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Table III (b): Affinity matrix for the $T = 7$ (right) capsid construction
Now a natural question can be asked: what comes next? In order to grow capsids with $T$-numbers greater than 7, one has to introduce new types of hexamers that would never stick to pentamers, but being able to associate themselves with certain sides of the former maximally differentiated hexamers. The result is shown in the Fig. 8 below:

![Figure 8: The building formula for the T=9 capsid](image)

The corresponding affinity table is given below:

|   | p | a | b | c | d | e | f | $n_a$ | $n_b$ |
|---|---|---|---|---|---|---|---|-------|-------|
| p | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0     | 0     |
| a | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0     | 0     |
| b | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0     | 0     |
| c | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0     | 0     |
| d | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0     | 0     |
| e | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0     | 0     |
| f | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0     | 0     |
| $n_a$ | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0     | 0     |
| $n_b$ | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0     | 0     |

Table IV: Affinity matrix for the $T = 9$ capsid construction

For bigger capsids, in which the rate of pentamers is lower, one cannot obtain proper probabilities unless more than one type of hexamers is present, out of which only one is allowed to agglomerate with pentamers. In the case of two different hexamer types one obtains either the $T = 9$ capsid, or, with
more exclusive sticking rules, the \( T = 12 \) capsid. Finally, in order to get the \( T = 25 \) adenovirus capsid, one must introduce no less than four hexamer types, out of which only one type can agglomerate with pentamers.

Figure 9: The \( T=12 \) capsid’s basic triangle

The affinity matrix for \( T = 12 \) capsid is as follows:

\[
\begin{array}{ccccccccccc}
\text{p} & \text{a} & \text{b} & \text{c} & \text{d} & \text{e} & \text{f} & \text{n}_a & \text{n}_b & \text{n}_c & \text{m}_c & \text{m}_d \\
p & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
a & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
b & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
c & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
d & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
e & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
f & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
n_a & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
n_b & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
n_c & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
m_c & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
m_d & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
\end{array}
\]

Table V: Affinity matrix for the \( T = 12 \) capsid construction
Now we can organize all these results in a single table that follows. To each value of triangular number $T$ corresponds a unique partition into $1 + (T - 1)$, where the “1” represents the unique pentamer type and $(T - 1)$ is partitioned into a sum of certain number of different hexamer types, according to the formula

$$(T - 1) = \alpha 6 + \beta 3 + \gamma 2$$

with non-negative integers $\alpha$, $\beta$ and $\gamma$.

| Type $(p,q)$ | $T = p^2 + pq + q^2$ | $N_6 = 10(T - 1)$ | $T$ decomposition |
|-------------|-------------------|-----------------|------------------|
| (1,1)       | 3                 | 20              | $1 + 2$          |
| (2,0)       | 4                 | 30              | $1 + 3$          |
| (2,1)       | 7                 | 60              | $1 + 6$          |
| (3,0)       | 9                 | 80              | $1 + 6 + 2$      |
| (2,2)       | 12                | 110             | $1 + 6 + 2 + 3$  |
| (3,1)       | 13                | 120             | $1 + 6 + 6$      |
| (4,0)       | 16                | 150             | $1 + 6 + 6 + 3$  |
| (3,2)       | 19                | 180             | $1 + 6 + 6 + 6$  |
| (4,1)       | 21                | 200             | $1 + 6 + 6 + 6 + 2$ |
| (5,0)       | 25                | 240             | $1 + (4 \times 6)$ |
| (3,3)       | 27                | 260             | $1 + (4 \times 6) + 2$ |
| (4,2)       | 28                | 270             | $1 + (4 \times 6) + 3$ |
| (5,1)       | 31                | 300             | $1 + (5 \times 6)$ |
| (6,0)       | 36                | 350             | $1 + (5 \times 6) + 2 + 3$ |

Table VI: Classification of icosahedral capsids. The last column gives the number and type of hexamers needed for the construction.
The inspection of Table VI leads to the following simple rules:

1) For the construction of a capsid with given triangular number $T$ one needs exactly $T$ different proteins (or at least, $T$ different types of sticking sides) - because the affinity matrix has the dimension $T \times T$, as easily seen in the examples.

2) By definition, the “affinity matrices” have only one non-zero item in each row and in each column; moreover, they are symmetric. This means that all capsid protein types (or more exactly, all different sticking sides) encountered in a complete icosahedron appear with the same frequency: 60 times each. This can be most easily seen for the $p$-type forming a pentamer: there are 12 of them in each pentamer, and there are 12 pentamers in any icosahedral capsid. But then each $p$ sticks to an $a$, and exclusively to it: therefore, there must be also 12 $a$-type proteins in the complete capsid, and so on, for each different protein. This means that all the subunits that assemble in pentamers and hexamers later on have to be produced at exactly the same rate in order to optimize capsid production.

3) The capsomers composing a given capsid should be produced at different rates, with a very simple rule: for every dozen of pentamers, one should have 60 maximally diversified hexamers of the type $(abcdef)$, (and of each different type, like the $(n_an_bn_cn_dn_en_f)$ in the $T = 9$ capsid); then 30 hexamers of each $(ababab)$ type; and 20 hexamers of the $(abcabc)$ type. This rule can be easily seen upon inspection of Figures 4 – 8.

4) In order to know how many (and of which kinds) hexamers should be used, the $T$-number should be partitioned into $1+ “the rest”, the “1” staying for the unique type of pentamers’ side, while “the rest” must be decomposed into a sum of numbers 2, 3 or 6, according to the simple factors of 6. This is shown in the last column of Table I: we see that $T = 3 = 1 + 2$; $T = 4 = 1 + 3$; then the next cases decomposes as $T = 7 = 1 + 6$; $T = 9 = 1 + 6 + 2$ (by the way, with this scheme in mind there is no point in trying to build a capsid with $1 + 6 + 3 = 10$ because 10 cannot be found among the triangular numbers!).

5) There is a clear ”evolutionary” pattern in the last table - meaning that every next (bigger) type of capsid uses the previous construction, just adding a minimal amount of novelty: and it is clear most of the time which kind of new hexamer one must add, just looking at the differences between
the consecutive T-numbers - e.g. if they differ by 2 or by 3, one should add one new hexamer type, ababab or abcabc, respectively; but if they differ by 4 (e.g. from T=21 to T=25) or by 5 (from T=31 to T=36); one must add two new types of (ababab), or one (ababab) and one (abcabc) type.

6) Finally, one should apply these reasonings also to capsids that are not built with classical hexamers and pentamers. One may introduce a “dual” picture in which not the sides, but the vertices of capsomers correspond to real proteins’ extremities. The examples of the alternative realisation of $T = 3$ and $T = 4$ capsids with pentamers and dimers only are shown in the Fig. 11 below.

![Figure 10: Alternative realizations of $T = 3$ and $T = 4$ capsids](image)

It can be easily deduced from these figures that the $(p-a)$-dimers composing pentamers occur 60 times in each capsid, whereas the $(b-b)$-dimers occur only 30 times in a complete $T = 3$ capsid, but the $(b-c)$-dimers occur 60 times in each $T = 4$ capsid. In some cases in a $T = 4$ capsid the triplets of $(b-c)$-dimers are replaced either by hexamers (then we obtain again a $T = 3$ capsid), or by star-like trimers which will then occur 20 times. Whatever the decoration, each different letter symbol occurs with the same frequency, i.e. 60 times in each capsid independently of the value of $T$. This suggests that all dimer proteins are produced at the same rate, and the differentiation process that leads to exclusion rules for subsequent agglomeration occurs later on. These realizations of capsid structure are akin to the decoration rules for curved Penrose-like tilings introduced by R. Twarock.
Conclusion: how to hinder capsid production?

Capsids are a vital part of viral life cycle, protecting its most essential and the most vulnerable part, which is their genetic code. We need to consider that viruses can have DNA or RNA genomes and the latter are especially sensitive to degradation (by nucleases). In other words, without the capsid, the genomes exposed to the hostile external world would be destroyed in a couple of hours by the ultraviolet radiation, or by chemical attacks of $SO_2$, ozone $O_3$, $NO_2$, etc. The efficient protection provided by capsid shell ensures longevity and makes possible long travels from one host to another. Should we know how to hinder capsid assembly, this information would have enormous potential benefit for the development of antiviral therapies.

The existence of a well-defined agglomeration scheme during the capsid production suggests many possibilities of destructive intervention. As a matter of fact, the more complicated the system and the more intricate the laws of its functioning, the more there are ways of hindering it. Let us consider a few examples of how to decrease the efficiency of capsid building.

1) Create seven-sided polygons - heptamers - with the same proteins that usually form pentamers. Such a unit will be also surrounded by hexamers, creating local negative curvature, thus enhancing the proper capsid production. Such an achievement is quite unlikely because of the steric hindrance - there is just not enough place in order to pack seven proteins which usually go in packs by five. Even if there was such a possibility, the heptamers should be created inside the infected cells, or delivered there in some way, which is extremely difficult.

2) A better way to hinder capsid production would be to produce hexamers or pentamers with “wrong” proteins inserted, or in a wrong order - e.g. (abbaab) or (aaabbb) instead of (ababab) so that they could fit with one side, but then present a wrong protein to next capsomers trying to agglomerate, thus destroying the symmetry and order of the construction. Again, this supposes the creation of modified RNA chains ordering the production of different hexamers, and again, the delivery problem seems very difficult to solve.

3) A more natural way to hinder capsid production may be deduced from the probabilistic analysis of various agglomeration pathways. Each
capsid must contain exactly 12 pentamers and 10 \((T-1)\) hexamers of various kinds. In order to ensure the full use of all these building blocks, their initial ratios should be as close as possible to 12 : \((10(T-1))\). If for some reasons an excess of hexamers were produced, entire capsids still would be completed leaving the extra hexamers unemployed.

But the situation will radically change if an excess of pentamers could be created during capsid assembly phase inside an infected cell. The agglomeration starts around the pentamers, because the probability of a pentamer-hexamer association is much higher than that of a hexamer-hexamer association ([4], [11]). What will happen now can be illustrated on a concrete example. Let us imagine a great number of “kits” with 12 pentamers and 20 hexamers (ababab) each. As we know, with simple matching rules allowing associations \((p+a)\) and \((b+b)\) and forbidding the associations \((p+b)\) and \((a+a)\), a complete capsid can be constructed. Suppose now that many such “kits” have been dropped on the ground, and many people are trying simultaneously to build \(T=3\) capsids. The rules of the game being that once a person grabs a capsomer and sticks it to the partially built capsid, the capsomer can not be removed. After some time everybody will succeed in constructing an entire full capsid, with no extra capsomers left.

Suppose now that someone had thrown in some extra hexamers. After a while some of the hexamers will be left out - but if there were 12\(N\) pentamers and more than 20\(N\) of hexamers, there will be still \(N\) full capsids completed at the end of the day.

The situation would be totally different had someone poured in an excess of pentamers. Supposing that people grab capsomers one by one at random, there will be hardly one or two full capsids completed.

This comes out from simple probability calculus. Let us start with the simplest example, 20 hexamers \((ababab)\) and 13 pentamers \((ppppp)\). Of course, if the things were not happening at random, but in an organized way, one can construct a complete \(T=3\) capsid and leave the extra pentamer alone. There are exactly 13 ways of doing it - just taking the decision which one among the 13 pentamers should be chosen to be dropped out. But if the agglomeration happens at random, there is no reason that one of the pentamers should wait until the 12 others are incorporated in a capsid. People acting randomly would rather pick up as many hexamers as they can; and there is an enormous number of ways of doing it (with all possible permutations taken into account), so the probability of this to happen is orders of magnitude higher than the probability of the happy issue described above.
For example, there are $13 \times 20$ different ways of producing two incomplete capsids: a pentamer-hexamer doublet and an incomplete $T = 3$ capsid with one hexamer missing; and there are $13 \times 20 \times 19$ different ways of producing a $5-6-6$ agglomerate and an incomplete capsid with two hexamers missing, and so on.

This means that as a result, we shall have in the best case two uncomplete capsids, and most probably even a higher number of incomplete, unfinished structures.

This is what would happen to people trying to pick up spare parts at a car cemetery, full of naked car frames and spare wheels, and to make up a complete car. “Complete” meaning four wheels in one car - with three wheels only no car will ever roll out. But if the number of wheels is not 4 times $N$ ($N$ being the number of car frames with no wheels), but only half of it, say, then what would most probably happen is that almost everybody would end up with a car with 3 or 2 wheels, and almost nobody with a complete car.

In other words, if we could incite some cells to produce exclusively pentamers of the virus by which it is attacked, - this has to happen inside the cell, where the capsids are being produced - then there will be an excess of pentamers, and almost no complete capsid will be produced. And with no complete capsids viruses will be much less obnoxious.

To implement such a scenario is certainly a challenge for molecular biology and nano-technology.

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