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Supramolecular self-assembly: molecular dynamics modeling of polyhedral shell formation

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Abstract

The self-assembly of polyhedral virus shells (capsids) provides a fascinating example of the complex processes that occur in the simplest of organisms. Little is known about the assembly mechanism, but the fact that different viruses adopt similar structures hints at common design principles and suggests that simplified models ought to be helpful in understanding the assembly process. In order to establish the viability of this approach we have carried out exploratory MD simulations that demonstrate the self-assembly of pentakisdodecahedral (60-faced) shells.

Keywords:

1. Introduction

The formation of supramolecular protein assemblies – a common element of many biological processes – is of great interest because it lies at the interface of chemistry and biology. The assembly of certain small virus particles provides a particularly accessible example for elucidating the principles of macromolecular organization because the process is reversible and readily analyzed [1,2]. Although there are many possible geometrical forms that the capsid – the protein coat encasing the viral genome – could have adopted, nature appears to have utilized only two basic package types, namely helical tubes and near-spherical shells exhibiting icosahedral symmetry. In many instances, e.g., [3], viral subunits assemble *in vitro* even without the presence of genetic material. Simple virus particles are often stabilized almost exclusively by protein-protein interactions; hence the study of assembly of just the protein subunits, as described here, is a realistic approximation to the assembly of significant classes of viruses.

The genetic information required for capsid construction is minimized by using multiple copies of the same protein subunit (or a very small number of different subunits); symmetry is a natural consequence of such an approach since the same subunits appear throughout the structure. What limits the amount of genetic information an icosahedral virus is capable of carrying is the internal volume of the capsid. A near-spherical shape provides maximal size for a given surface area, and the symmetry minimizes the "engineering" design information needed for construction. In the smallest viruses of this type, each triangular face of the underlying icosahedron consists of three smaller protein subunits.

While there are viruses with capsids consisting of 60 subunits, the volume is insufficient for substantial amounts of nucleic acid, and larger shells are found

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with multiples of 60 units, i.e., 60 T, with T as large as 25. These shells have the same icosahedral symmetry, but since 60 subunits is the maximum possible under conditions of complete equivalence, the concept of quasi-equivalence [4,5] – inspired by Fuller's geodesic domes – was introduced to explain how such globally symmetric structures might be constructed with only minimal departure from an identical local environment for each subunit.

A great deal is known about assembled capsid structure and the nature of the stabilizing interactions, but since partially assembled intermediates are highly transient little is known about the mechanism of assembly [2]. The fact that self-assembly is so robust [5], not to mention the ubiquity of the icosahedral motif, suggests that the molecular dynamics (MD) simulation of low resolution models emphasizing "shape" – which are independent of the molecular details of particular viruses [6] – might capture the essence of the process. While simple mechanical models have been used to explore steric aspects of assembly [5], the MD approach ought to permit exploration of the assembly pathways themselves. Despite an enormous range of applications, e.g., [7], MD has not been used to model capsid assembly; here we report on the first application of MD to the self-assembly problem.

2. Methodology

Given that this is the first attempt to study capsid self-assembly the model has deliberately been kept as simple as possible. We consider a system of rigid triangular subunits designed to assemble – at least in principle – into pentakisdodecahedral (60-faced) shells. Each triangular subunit is represented by a rigid planar assembly of spheres as shown in Fig. 1. The larger spheres produce the overall shape of the subunit, and spheres in different subunits interact by means of a short-range repulsion (the repulsive part of the Lennard-Jones interaction) that prevents overlap. The small spheres signify attraction sites; corresponding pairs of attraction sites on different subunits attract by means of a $1/r$ potential; at short range this interaction smoothly merges into a narrow harmonic well. A permanent bond forms whenever a pair of attraction sites comes within a predetermined bonding range; bonding is accomplished by replacing the attractive potential by just its harmonic component. Two subunits are regarded as fully bonded when all three pairs of attraction sites are mutually bonded; the planes formed by the triplets of attraction sites dictate the dihedral angles between bonded subunits, and these are chosen to be those of the desired polyhedral structure. (In addition to the present simulations, the same approach has been used to construct smaller polyhedra, as well as 32-faced "soccer balls".)

While these interactions are, in principle, sufficient to ensure assembly – although the growth dynamics of the model can only be established empirically – additional assembly rules are required to prevent the appearance of incorrect structures. After a bond has formed the sites involved no longer attract other subunits, otherwise an amorphous globule can form. Attraction of unbounded subunits is only allowed when there is no risk of forming an incompatible bond; if two subunits in a partially assembled structure are incompletely bonded no other free subunits are attracted to a subunit already in the structure. Another

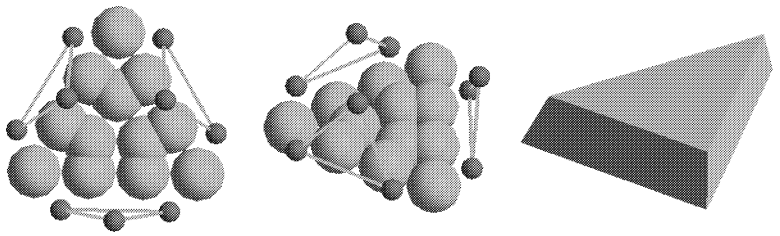

Fig. 1. Details of the capsid subunit showing the large spheres that provide the excluded volume and the small spheres denoting attraction sites; an alternative view shows the lateral faces of the equivalent triangular block bevelled so that it can be used repeatedly to build a 60-hedron.

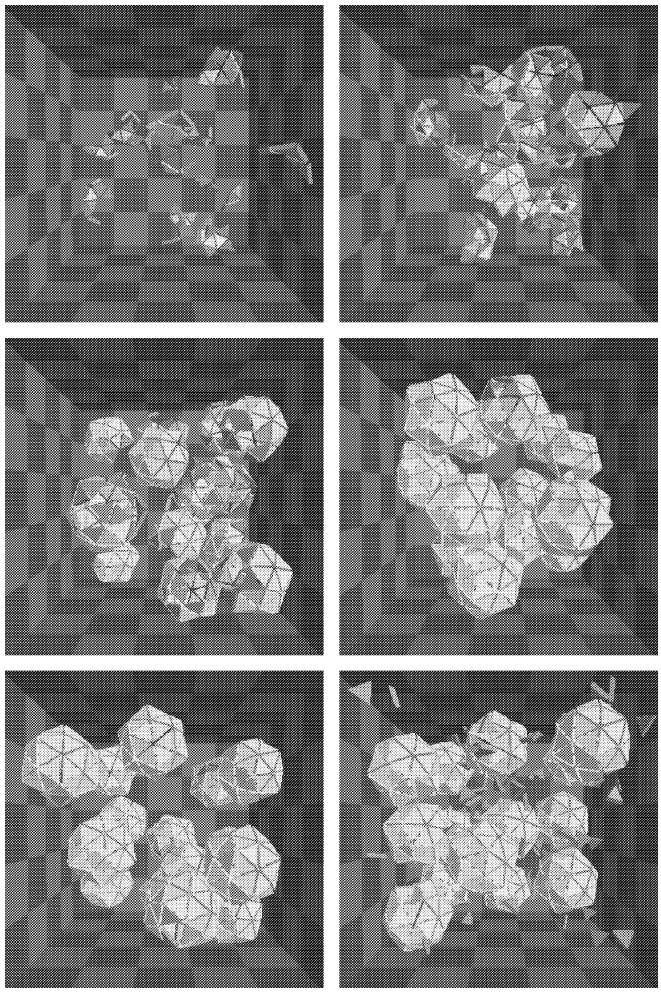

Fig. 2. Snapshots showing several stages of the self-assembly process; unattached subunits are omitted for clarity except in the final frame.

assumption, introduced purely for computational convenience, is that attraction only occurs between partially formed structures and monomers, but not between pairs of partial polyhedra, because of the difficulty of ensuring the structures mesh correctly; the extent to which nature also adopts this policy remains to be seen. Finally, since there is only a limited supply of monomers, the number of subassemblies allowed to nucleate is restricted.

No other rules are imposed and monomers are free to bond at any available location on a partially formed structure. Torsional interactions help align partially bonded subunits; these are not required once the subunits are completely bonded since the bond forces themselves ensure alignment. Gradual heating of the system by the exothermal bond-formation process is avoided by applying a small velocity-dependent damping interaction along each bond. In other respects the MD computation follows the conventional approach for rigid-body systems – see, e.g., [8]. The parameters used in specifying the interactions are determined empirically to ensure efficient self-assembly, and presently do not bear any relation to experimental quantities. Since visualization is important in this work, hard (elastically reflecting) container walls are used rather than periodic boundaries.

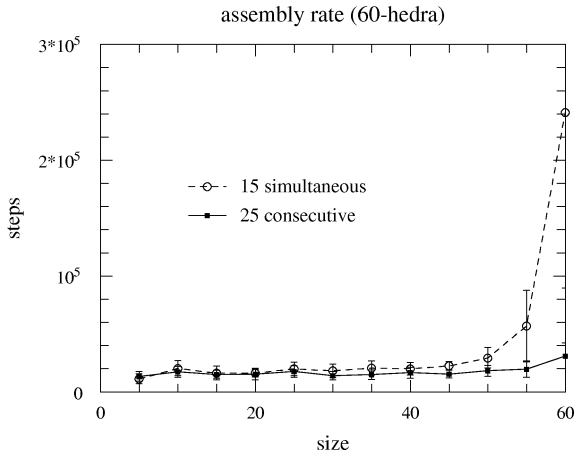

Fig. 3. Measurements of assembly rate for single and multiple polyhedra: the mean numbers of time steps required for successive additions of five subunits are shown (error bars indicate standard deviations).

3. Results

Typically, about a half million integration steps are required to obtain the fully assembled polyhedra. Space allows just a single example of a run consisting of 1000 subunits in which 15 polyhedra are allowed to grow. Fig. 2 presents a series of screen images showing various stages of growth; monomers are removed from all but the final picture for clarity. All the polyhedra that were allowed to nucleate have completely assembled. Color is used to distinguish those facets of the subassemblies that already have their full complement of bonds from those that are only partially bonded. Examination of this run (and others) indicates that subassemblies tend to remain compact, suggesting that incoming subunits seek locations where bonding to more than one attached subunit is possible.

Quantitative estimates of growth rate can be made by measuring the subassembly size as a function of time. Runs such as that shown above – where most monomers are eventually incorporated into the shells – are not suitable for measurements of this kind, because gradual monomer depletion inhibits growth and there is steric hindrance between shells. Instead, just a single polyhedron is allowed to form in an environment containing several times (here 216) the required number of subunits; once complete, all bonds are broken and the process is repeated. Fig. 3 summarizes the construction history by showing the mean number of steps required for each 5-subunit size increase; the growth rate is practically constant, except for the last few subunits. The reason for the slowdown is that some of the bonding sites of a nearly complete structure are less accessible, so that more time is spent searching for the correct monomer alignment. Such behavior may be contrasted with what happens when monomer depletion dominates the final stages of a run with 1000 subunits in which 15 polyhedra form concurrently; here there is substantial retardation of the growth rate. This particular model clearly has no favored intermediate states along the assembly pathway.

4. Conclusion

The simulations described here model the self-assembly of idealized virus capsid subunits into polyhedral shells. Since the model is entirely *ad hoc* we have not attempted to relate it to real viruses; we view these initial results purely as a proof of principle. Such an approach provides, for the first time, a theoretical method for studying assembly pathways; since the simulations make predictions about relative populations of partially formed structures it should eventually be possible to compare such results with experiment. Subsequent work will focus on exploring alternative self-assembly scenarios, and the models will be extended to incorporate quasi-equivalence and other characteristics of real viruses (molecular structure, interactions, and details such as scaffold proteins). General features of self-assembly pathways that might emerge from such simulations could prove important for finding ways to inhibit the assembly process (with possible therapeutic consequences).

Acknowledgments

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