Peer-Review

Chang, Ethan. 2026. “Why Viruses Build Icosahedra: A Quantitative Framework for Capsid Architecture and Nanocage Design.” *Journal of High School Science* 10 (3): 461–83. https://doi.org/10.64336/001c.168714.

The central weakness of the manuscript is not the correctness of the geometric analysis itself, but the disconnect between the question posed in the title and the scope of the analysis. The title asks Why Viruses Build Icosahedra, which is fundamentally an evolutionary and mechanistic question requiring comparison against alternative architectural solutions. However, the manuscript explicitly excludes elasticity, energetics, and assembly kinetics and therefore restricts itself almost entirely to topology and geometry. Under such a framework, the manuscript can demonstrate why twelve pentagonal defects are required to close a hexagonal lattice, but it cannot explain why evolution repeatedly selected pentamer–hexamer architectures rather than other possible solutions. The current argument establishes a geometric constraint, not an evolutionary explanation.

The manuscript would be substantially strengthened by reframing the discussion around the advantages of the pentamer–hexamer architecture itself rather than around Euler’s theorem alone. At present, pentagons are treated primarily as curvature-generating elements required for closure. However, the more biologically meaningful observation is that the pentamer–hexamer arrangement separates two otherwise competing design requirements: shell closure and shell size. Pentamers provide the fixed positive curvature required for closure, while hexamers act as curvature-neutral expansion units. Once the twelve pentameric positions are established, shell volume can vary dramatically through the addition or rearrangement of hexameric positions without altering the underlying closure topology. This decoupling of closure from volume is arguably one of the most important properties of icosahedral capsids and may provide a genuine explanation for their evolutionary success.

Related to this point, the manuscript currently misses an opportunity to discuss why hexagonal packing may naturally emerge in self-assembling protein systems. Hexagonal lattices maximize local neighbor contacts and represent a common packing solution throughout nature. From this perspective, hexamers are not arbitrary geometric choices but may arise because they provide efficient local packing and favorable interaction networks. Pentagons then emerge as the minimal positive-curvature defects necessary to close an otherwise hexagonal assembly. Such an argument would connect topology to assembly principles and provide a more mechanistic explanation for the prevalence of pentamer–hexamer architectures.

The manuscript should also consider the possibility that pentamers and hexamers constitute a near-minimal architectural alphabet for constructing closed protein shells. Evolution frequently favors systems that generate enormous structural diversity from a small number of reusable components. Just as four nucleotides generate all genomes and twenty amino acids generate the immense diversity of proteins, pentamers and hexamers may represent a minimal set of assembly motifs capable of generating a large family of capsid sizes and shapes. In this framework, pentamers encode closure while hexamers encode scale. A small number of local assembly rules therefore generate extensive global architectural diversity.

An important comparison missing from the manuscript concerns alternative curvature-generating units. The current discussion notes that triangles, squares, and pentagons can all satisfy closure requirements, but the implications are not explored. A potentially valuable argument is that pentamers may occupy a favorable intermediate position between closure efficiency and assembly complexity. Triangle-based architectures concentrate curvature at only four sites, square-based architectures at six sites, whereas pentamers distribute curvature across twelve locations. More importantly, pentamer–hexamer architectures provide a scalable system in which shell volume can be modified through the addition of hexamers while preserving the same closure framework. Architectures based on smaller curvature-generating units may provide less flexibility, require more extensive redesign for volume changes, and couple closure more tightly to shell size. Even if

qualitative, such comparisons would move the discussion beyond topology and toward a genuine explanation of why evolution may prefer pentamer–hexamer systems.

The manuscript would further benefit from discussing quasi-equivalence and protein versatility. One of the remarkable features of many viral capsids is that the same protein can participate in both pentameric and hexameric environments. This means that evolution can generate a wide range of shell sizes without inventing entirely new structural proteins. The pentamer–hexamer system therefore provides exceptional architectural economy. Closure, expansion, and structural variation can all be achieved through limited modifications of a common assembly framework.

Another important observation that deserves emphasis is that the pentamer–hexamer architecture appears compatible with a wide range of protein folds and interaction chemistries. Icosahedral capsids occur in viruses built from jelly-roll β-barrel proteins, HK97-fold proteins, papillomavirus capsid proteins, and double-jelly-roll proteins, among others. These proteins differ substantially in sequence, fold, and interface chemistry, yet converge on similar global architectures. Such convergence suggests that the pentamer–hexamer solution is not tied to a particular molecular implementation but instead occupies a broadly accessible region of protein design space. This may provide a stronger explanation for its repeated evolutionary emergence than topology alone.

The manuscript should also directly address the question "why not something else?" Why not all-pentamer architectures? Why not tetrahedral or octahedral solutions? Why not lipid vesicles, which can also form closed compartments? Why not highly elongated tubular architectures? At present, alternatives are discussed primarily in terms of geometric permissibility rather than evolutionary tradeoffs. A paper seeking to explain the prevalence of icosahedral capsids should compare competing architectural strategies and identify the advantages that make pentamer–hexamer systems attractive.

Finally, I do not find the nanotechnology section compelling in its current form. The manuscript argues that topology-aware design strategies may improve computational protein cage design, but no evidence is presented that failure to enforce global closure constraints is currently a major limitation of modern nanocage design pipelines. No specific design failures are analyzed, no alternative algorithms are proposed, and no quantitative evidence is presented demonstrating that topology-aware approaches outperform existing methods. As a result, the nanotechnology discussion reads as speculative extrapolation rather than a natural consequence of the preceding analysis. Because the central contribution of the manuscript is the geometric discussion of viral capsids, the paper would likely be stronger, more focused, and more coherent if the nanotechnology section were substantially reduced or removed entirely.

In summary, the manuscript is strongest as a pedagogical review of geometric and topological principles underlying capsid closure. However, if the author wishes to retain the title Why Viruses Build Icosahedra, the discussion must move beyond demonstrating that twelve pentagons are required by Eulerian topology and instead address why pentamer–hexamer architectures may represent an evolutionarily attractive solution. Concepts such as scalable volume control, architectural economy, quasi-equivalence, efficient local packing, compatibility with diverse protein folds, and comparison with alternative assembly strategies would substantially strengthen the manuscript and bring it much closer to answering the question posed by its title.

The manuscript currently treats the pentamer–hexamer architecture primarily as a geometric consequence of Eulerian topology. However, if the goal is to explain why evolution repeatedly converged on this architecture, I encourage the author to consider a broader framework in which the pentamer–hexamer system is viewed as an exceptionally efficient architectural solution. In particular, the following five concepts could provide a more compelling explanation for the prevalence of icosahedral capsids:

1.Local packing efficiency (hexamers).

Hexagonal packing is one of the most efficient local packing arrangements observed in nature and maximizes the number of nearest-neighbor contacts. In self-assembling protein systems, this may provide favorable interaction networks, structural stability, and efficient use of interface area.

Hexamers may therefore emerge not merely because they are geometrically convenient, but because they represent a natural local packing optimum.

2.Closure capability (pentamers).

A purely hexagonal lattice remains flat and cannot close. Pentamers provide the minimal positive-curvature defects necessary to transform a flat hexagonal network into a closed shell. Rather than viewing pentagons simply as topological requirements, they can be interpreted as the specific structural elements that solve the closure problem while minimally disrupting efficient hexagonal packing.

3.Quasi-equivalence (same protein in multiple environments).

One of the most remarkable features of many viral capsids is that the same protein can participate in both pentameric and hexameric assemblies. This dramatically reduces the number of distinct structural components required for shell construction. The ability of a single protein to occupy multiple local environments may be one of the key innovations underlying the success of icosahedral capsids and deserves greater emphasis.

4.Scalability (variable T numbers).

Once the closure problem is solved by the fixed set of pentameric positions, shell volume can vary through the addition of hexameric positions. This allows the same architectural framework to generate a wide range of capsid sizes and genome capacities. In this sense, pentamers determine closure while hexamers determine scale. The resulting decoupling of shell closure from shell volume may be one of the most important evolutionary advantages of the pentamer–hexamer architecture.

5.Evolutionary economy (minimal set of building blocks).

The pentamer–hexamer system may represent a near-minimal architectural alphabet capable of generating enormous structural diversity. Just as four nucleotides generate all genomes and twenty amino acids generate the diversity of proteins, a small set of assembly motifs can generate a large family of capsid architectures. This architectural economy provides substantial evolutionary flexibility while minimizing the need for additional structural innovations.

Collectively, these five principles may offer a more biologically meaningful explanation for the repeated emergence of icosahedral capsids than topology alone. They move the discussion from the question of what geometries are possible to the more important question of why evolution may have repeatedly selected this particular solution from among many geometrically permissible alternatives.

Finally, I encourage the author to substantially expand the reference list. The current manuscript relies heavily on a limited set of classical geometric and virological sources. Additional references covering quasi-equivalence, capsid assembly, viral evolution, structural convergence, protein self-assembly, elastic shell theory, and comparative viral architectures would considerably strengthen the scholarly foundation of the manuscript and better place the proposed ideas within the broader literature.

The closest thing to a publishable new idea would be to elevate those points into a formal hypothesis:

Pentamer–hexamer systems represent a near-minimal architectural alphabet that maximizes the ratio of accessible enclosed volume, shape diversity, and assembly robustness to the number of required building-block classes.

That is not proven in the manuscript, but it is at least a new conceptual claim that could generate predictions and be tested against alternative architectures. Without something of that sort, the paper remains primarily a pedagogical synthesis of existing ideas.

Better yet, quantify (at least rough calculations) so you can prove “Pentamer–hexamer systems maximize architectural versatility per unit assembly investment.” see attached chat-gpt file. That now beccomes genuinely publishable as a significant contribution to the corpus of knowledge in the field.

Reviewer 1 Critiques and Responses

The central weakness of the manuscript is not the correctness of the geometric analysis itself, but the disconnect between the question posed in the title and the scope of the analysis. The title asks Why Viruses Build Icosahedra, which is fundamentally an evolutionary and mechanistic question requiring comparison against alternative architectural solutions. However, the manuscript explicitly excludes elasticity, energetics, and assembly kinetics and therefore restricts itself almost entirely to topology and geometry. Under such a framework, the manuscript can demonstrate why twelve pentagonal defects are required to close a hexagonal lattice, but it cannot explain why evolution repeatedly selected pentamer–hexamer architectures rather than other possible solutions. The current argument establishes a geometric constraint, not an evolutionary explanation.

Response: I thank the reviewer for the thoughtful critiques and insightful suggestions. The comments helped improve the manuscript and my understanding of the topic.

I agree that topology alone cannot provide a complete evolutionary explanation for the repeated emergence of icosahedral capsids. The original manuscript focused primarily on the geometric and topological constraints governing shell closure, emphasizing why twelve pentagonal defects are required within a hexagonal lattice. In response to the comments, I expanded the discussion to examine potential advantages of pentamer–hexamer architectures beyond topology. The revised discussion includes efficient local packing, quasi-equivalence, scalability, architectural economy, comparisons with alternative structural strategies, and evidence of structural convergence across diverse viral lineages.

I also revised the Abstract, Introduction, and Conclusion to reflect this broader perspective. The revised Abstract now presents pentamer–hexamer organization not only as a topological solution for shell closure but also as a potentially advantageous architectural framework. The revised Conclusion emphasizes that these proposed advantages are intended as interpretations and hypotheses rather than definitive evolutionary mechanisms.

The revised manuscript now more explicitly acknowledges the roles of elasticity, energetics, and assembly kinetics in shaping viral capsid evolution. These additions help place the geometric analysis in a broader biological context and better address why pentamer–hexamer architectures may have been repeatedly favored during viral evolution.

The manuscript would be substantially strengthened by reframing the discussion around the advantages of the pentamer–hexamer architecture itself rather than around Euler's theorem alone. At present, pentagons are treated primarily as curvature-generating elements required for closure. However, the more biologically meaningful observation is that the pentamer–hexamer arrangement separates two otherwise competing design requirements: shell closure and shell size. Pentamers provide the fixed positive curvature required for closure, while hexamers act as curvature-neutral expansion units. Once the twelve pentameric positions are established, shell volume can vary dramatically through the addition or rearrangement of hexameric positions without altering the underlying closure topology. This decoupling of closure from volume is arguably one of the most important properties of icosahedral capsids and may provide a genuine explanation for their evolutionary success. Related to this point, the manuscript currently misses an opportunity to discuss why hexagonal packing may naturally emerge in self-assembling protein systems. Hexagonal lattices maximize local neighbor contacts and represent a common packing solution throughout nature. From this perspective, hexamers are not arbitrary geometric choices but may arise because they provide efficient local packing and favorable interaction networks. Pentagons then emerge as the minimal positive-curvature defects necessary to close an otherwise hexagonal assembly. Such an argument would connect topology to assembly principles and provide a more mechanistic explanation for the prevalence of pentamer–hexamer architectures.

Response: This comment led me to revise the manuscript to focus more on the architectural advantages of pentamer–hexamer systems rather than Eulerian topology alone.

I expanded the sections on hexagonal packing, polygonal substitutions, capsid variation, and the conclusion to emphasize three related concepts: (1) hexamers provide efficient local packing and favorable interaction networks, (2) pentamers provide the minimal positive-curvature defects required for shell closure, and (3) the combination of fixed pentameric positions and variable hexameric positions separates shell closure from shell expansion. Together, these revisions highlight how pentamer–hexamer architectures provide an efficient and scalable assembly framework. This may help explain their repeated evolutionary emergence across diverse viral lineages. The relevant additions are discussed in greater detail in the responses to Reviewer's Major Points 1, 2, 4, and 5 below.

The manuscript should also consider the possibility that pentamers and hexamers constitute a near-minimal architectural alphabet for constructing closed protein shells. Evolution frequently favors systems that generate enormous structural diversity from a small number of reusable components. Just as four nucleotides generate all genomes and twenty amino acids generate the immense diversity of proteins, pentamers and hexamers may represent a minimal set of assembly motifs capable of generating a large family of capsid sizes and shapes. In this framework, pentamers encode closure while hexamers encode scale. A small number of local assembly rules therefore generate extensive global architectural diversity.

Response: In response to this comment, I expanded the conclusion section to discuss pentamers and hexamers as complementary assembly motifs that collectively provide closure, expansion, and structural adaptability. The revised text now emphasizes the architectural economy of the pentamer–hexamer framework and discusses how a wide range of capsid architectures can emerge from only two recurring assembly motifs. This concept is further developed in the response to Reviewer's Point 5 (Evolutionary Economy) below.

An important comparison missing from the manuscript concerns alternative curvature-generating units. The current discussion notes that triangles, squares, and pentagons can all satisfy closure requirements, but the implications are not explored. A potentially valuable argument is that pentamers may occupy a favorable intermediate position between closure efficiency and assembly complexity. Triangle-based architectures concentrate curvature at only four sites, square-based architectures at six sites, whereas pentamers distribute curvature across twelve locations. More importantly, pentamer–hexamer architectures provide a scalable system in which shell volume can be modified through the addition of hexamers while preserving the same closure framework. Architectures based on smaller curvature-generating units may provide less flexibility, require more extensive redesign for volume changes, and couple closure more tightly to shell size. Even if qualitative, such comparisons would move the discussion beyond topology and toward a genuine explanation of why evolution may prefer pentamer–hexamer systems.

Response: This comment included several of the concepts later summarized in the reviewer's five-point framework, particularly closure capability (Point 2) and scalability (Point 4). In response, I addressed the critiques in the following three sections: "Polygonal Substitutions and Curvature Distribution," "Design Options for Viral Capsids," and "Conserved Geometry and Capsid Variation" on pages 5–8.

The revised manuscript compares triangles, squares, and pentagons in terms of curvature distribution. It also discusses how pentamer–hexamer architectures uniquely separate shell closure from shell expansion. These additions emphasize that pentamer–hexamer systems not only satisfy topological

requirements but also provide a scalable architectural framework that may help explain their repeated evolutionary emergence.

The manuscript would further benefit from discussing quasi-equivalence and protein versatility. One of the remarkable features of many viral capsids is that the same protein can participate in both pentameric and hexameric environments. This means that evolution can generate a wide range of shell sizes without inventing entirely new structural proteins. The pentamer–hexamer system therefore provides exceptional architectural economy. Closure, expansion, and structural variation can all be achieved through limited modifications of a common assembly framework.

Response: This is an important point closely related to the discussion of quasi-equivalence and architectural economy addressed in the response to Reviewer's Point 3 below. I added a new paragraph in the "Conserved Geometry and Capsid Variation" section (page 7, paragraph 6). This paragraph emphasizes how identical capsid proteins can participate in both pentameric and hexameric assemblies, thereby enabling scalable shell architectures without requiring entirely new structural proteins.

Another important observation that deserves emphasis is that the pentamer–hexamer architecture appears compatible with a wide range of protein folds and interaction chemistries. Icosahedral capsids occur in viruses built from jelly-roll β-barrel proteins, HK97-fold proteins, papillomavirus capsid proteins, and double-jelly-roll proteins, among others. These proteins differ substantially in sequence, fold, and interface chemistry, yet converge on similar global architectures. Such convergence suggests that the pentamer–hexamer solution is not tied to a particular molecular implementation but instead occupies a broadly accessible region of protein design space. This may provide a stronger explanation for its repeated evolutionary emergence than topology alone.

Response: This was a helpful observation. To address this point, I expanded the Conclusion and added new references discussing structural convergence (references 10, 27–29). The revised text now proposes that the pentamer–hexamer framework may represent a broadly accessible architectural solution compatible with diverse protein folds and interaction chemistries. This helps explain why evolutionary convergence repeatedly favors this design.

Revised Text: Page 9, paragraph 2
Support for this hypothesis comes from the observation that evolution has repeatedly converged on pentamer–hexamer architectures across diverse viral lineages. Notably, the convergence is observed among viruses built from structurally distinct capsid proteins (4,10,27–29). This suggests that the pentamer–hexamer framework is not tied to a particular molecular implementation but instead represents a broadly accessible architectural solution that can be realized by diverse protein folds and interaction chemistries. Such convergence may reflect the evolutionary advantages of pentamer–hexamer systems, including efficient packing, scalability, quasi-equivalent assembly, and compatibility with diverse protein folds. Future computational and comparative studies may help determine whether the geometric and architectural advantages discussed here are sufficient to account for the repeated emergence of this solution in nature.

The manuscript should also directly address the question "why not something else?" Why not all-pentamer architectures? Why not tetrahedral or octahedral solutions? Why not lipid vesicles, which can also form closed compartments? Why not highly elongated tubular architectures? At present, alternatives are discussed primarily in terms of geometric permissibility rather than evolutionary tradeoffs. A paper seeking to explain the prevalence of icosahedral capsids should compare competing architectural strategies and identify the advantages that make pentamer–hexamer systems attractive.

Question: Why pentamer–hexamer architectures rather than tetrahedral, octahedral, all-pentamer, or highly elongated alternatives?

Response: The manuscript discussed geometric differences among tetrahedral, octahedral, and icosahedral architectures in the sections "Polygonal Substitutions and Curvature Distribution," "Efficiency of Icosahedral Enclosure: A Spherical Approximation," "Design Options for Viral Capsids," and "Conserved Geometry and Capsid Variation." (Pages 5–8)

Furthermore, I strengthened these comparisons and added new discussion emphasizing the architectural advantages of pentamer–hexamer systems. In particular, the revised manuscript now discusses how tetrahedral and octahedral architectures concentrate curvature at relatively few locations, coupling shell closure more tightly to shell size. By contrast, pentamer–hexamer architectures separate closure from scale, allowing shell volume to expand through the addition of hexamers without altering the underlying topology (page 7, paragraphs 4 and 5).

The manuscript also discusses atypical architectures such as the all-pentamer capsid of Human Papillomavirus 16 and elongated bacteriophage capsids. It shows that these alternative solutions remain constrained by the same geometric principles while sacrificing some scalability or simplicity of the canonical pentamer–hexamer framework (page 8 and paragraph 1).

Revised Text**:** Page 7, paragraphs 4 and 5
Beyond curvature distribution, the icosahedral geometry also provides a unique degree of scalability. In tetrahedral and octahedral geometries, shell closure and size are more tightly coupled because curvature is concentrated at relatively few locations (four and six sites, respectively). In pentamer–hexamer systems, a fixed set of twelve pentamers provides the curvature required for closure, while additional hexamers can be incorporated to increase shell size without altering the underlying topology (Figure 5). This closure-scale decoupling enables a common geometric design to support capsids of widely varying dimensions.

Icosahedral symmetry reflects an evolutionary convergence toward a common capsid geometry. This geometry allows shell closure, distributes curvature evenly, and encloses volume efficiently. Pentamers determine closure; hexamers scale. This principle is exemplified by the Caspar–Klug triangulation-number (T-number) system, in which progressively larger capsids are generated by adding increasing numbers of hexameric positions while retaining the same twelve pentamers required for shell closure (3).

Page 8 and paragraph 1
Some viral lineages depart from the typical pentamer–hexamer lattice. Human Papillomavirus 16, for example, is built entirely from pentamers (4). In these capsids, twelve pentamers occupy the vertices, and the remaining pentamers occupy positions surrounded by six neighboring units, analogous to those normally filled by hexamers. This arrangement is possible because of flexible protein–protein interfaces. Later tiling analyses (15,16) show that even these "atypical" structures still follow the same geometric rules for icosahedral closure. These examples illustrate that alternative architectural solutions are possible, but they often require additional structural adaptations to preserve the underlying requirements for icosahedral closure. Such adaptations may involve tradeoffs in assembly simplicity, structural regularity, or scalability relative to the canonical pentamer–hexamer framework.

Question: Why not lipid vesicles?
Response: To address the question of membrane-based alternatives, I added a new section entitled "Diversified Strategies Beyond Icosahedra: Enveloped Viruses with Variable Shapes." This new section emphasizes that lipid-enveloped viruses represent an alternative evolutionary strategy. The lipid membrane offers increased structural flexibility but reduced mechanical stability. The

comparison helps place icosahedral capsids within a broader landscape of viral architectural solutions. It highlights the tradeoffs that may contribute to the repeated emergence of rigid pentamer–hexamer capsids.

Revised Text: Page 9, paragraph 3

Diversified Strategies Beyond Icosahedra: Enveloped Viruses with Variable Shapes

Not all viruses adopt rigid icosahedral structures. Enveloped viruses (e.g., influenza A virus and human immunodeficiency virus) are surrounded by lipid membranes and can exhibit substantial variation in shape and size (30,31). This flexibility may facilitate processes such as membrane fusion, host-cell entry, and immune evasion (32,33). However, membrane-based architectures are generally less mechanically stable and more sensitive to environmental disruption than rigid protein capsids. These contrasting strategies illustrate that viral evolution balances multiple functional requirements rather than optimizing a single geometric property.

Finally, I do not find the nanotechnology section compelling in its current form. The manuscript argues that topology-aware design strategies may improve computational protein cage design, but no evidence is presented that failure to enforce global closure constraints is currently a major limitation of modern nanocage design pipelines. No specific design failures are analyzed, no alternative algorithms are proposed, and no quantitative evidence is presented demonstrating that topology-aware approaches outperform existing methods. As a result, the nanotechnology discussion reads as speculative extrapolation rather than a natural consequence of the preceding analysis. Because the central contribution of the manuscript is the geometric discussion of viral capsids, the paper would likely be stronger, more focused, and more coherent if the nanotechnology section were substantially reduced or removed entirely.

Response: To address this comment, I substantially revised and shortened this section. I removed discussion of current computational design pipelines failing to achieve shell closure, deleted the associated Figure 7A, and eliminated speculative proposals involving curvature penalties and topology-enforcement strategies.

The revised section now focuses on how viral capsid geometry may provide conceptual insights for protein-cage design rather than proposing specific computational solutions. In particular, it highlights the ability of a limited set of recurring structural motifs to generate diverse nanoscale architectures. The section concludes with an open question regarding future topology-aware design strategies rather than a claim about current methodological limitations. The revised section appears on pages 9 and 10.

In summary, the manuscript is strongest as a pedagogical review of geometric and topological principles underlying capsid closure. However, if the author wishes to retain the title Why Viruses Build Icosahedra, the discussion must move beyond demonstrating that twelve pentagons are required by Eulerian topology and instead address why pentamer–hexamer architectures may represent an evolutionarily attractive solution. Concepts such as scalable volume control, architectural economy, quasi-equivalence, efficient local packing, compatibility with diverse protein folds, and comparison with alternative assembly strategies would substantially strengthen the manuscript and bring it much closer to answering the question posed by its title.

Response: I thank the reviewer for the thoughtful summary and constructive assessment. The revisions described above and below were made to address these concerns. In particular, I expanded the discussion of scalable volume control, architectural economy, quasi-equivalence, structural convergence, compatibility with diverse protein folds, and alternative architectural strategies. I also revised the Abstract and Conclusion to place the geometric analysis within a broader biological and evolutionary context.

The manuscript currently treats the pentamer–hexamer architecture primarily as a geometric consequence of Eulerian topology. However, if the goal is to explain why evolution repeatedly converged on this architecture, I encourage the author to consider a broader framework in which the pentamer–hexamer system is viewed as an exceptionally efficient architectural solution. In particular, the following five concepts could provide a more compelling explanation for the prevalence of icosahedral capsids:

1. Local packing efficiency (hexamers).

Hexagonal packing is one of the most efficient local packing arrangements observed in nature and maximizes the number of nearest-neighbor contacts. In self-assembling protein systems, this may provide favorable interaction networks, structural stability, and efficient use of interface area. Hexamers may therefore emerge not merely because they are geometrically convenient, but because they represent a natural local packing optimum.

Response: I expanded the discussion of the hexagonal lattice to emphasize the potential functional advantages of hexameric organization beyond its geometric role (page 3, paragraph 4). The revised text now discusses how hexagonal packing maximizes nearest-neighbor contacts, minimizes unused space, reduces assembly free energy, and distributes mechanical stress evenly. These properties suggest that hexamers serve as an efficient structural framework for capsid organization.

Revised Text: Page 3, paragraph 4

Hexagonal packing represents one of the most efficient local packing arrangements found in nature. It maximizes the number of nearest-neighbor contacts and minimizes unused space (11,12), while reducing assembly free energy and distributing mechanical stress evenly (13,14). In viral capsids, hexameric organization provides a stable and efficient interaction network that can be assembled from repeated protein subunits. These properties suggest that hexamers may represent more than a geometric convenience; they serve as an efficient structural framework for capsid organization.

2. Closure capability (pentamers).

A purely hexagonal lattice remains flat and cannot close. Pentamers provide the minimal positive-curvature defects necessary to transform a flat hexagonal network into a closed shell. Rather than viewing pentagons simply as topological requirements, they can be interpreted as the specific structural elements that solve the closure problem while minimally disrupting efficient hexagonal packing.

Response: To address this point, I addressed pentamers as curvature-generating elements that have the smallest angular deficits in the “Polygonal Substitutions and Curvature Distribution” section (pages 5 and 6, Table 1) and further emphasized their architectural role in the conclusion section.

The revised manuscript now discusses how pentamers provide the smallest positive-curvature contribution among the polygonal alternatives capable of closing a hexagonal lattice. This allows shell closure while distributing curvature more evenly than triangles or squares. The conclusion further emphasizes that pentamers solve the closure problem while minimally disrupting efficient hexagonal packing. Together, these revisions extend beyond topological necessity and highlight the functional role of pentamers as the structural elements that enable shell closure.

Revised Text: Page 8, paragraph 4

Viewed more broadly, pentamers and hexamers do more than satisfy geometric constraints. Hexamers provide efficient local packing and extensive neighbor contacts, promote structural stability. By contrast, pentamers provide the smallest positive-curvature contribution among the polygonal alternatives capable of closing a hexagonal lattice. They therefore solve the closure problem while minimizing disruption of efficient hexagonal packing. Together, these complementary structural

motifs form a simple yet versatile architectural strategy that supports shell closure, scalable growth, and structural adaptability.

3. Quasi-equivalence (same protein in multiple environments).
One of the most remarkable features of many viral capsids is that the same protein can participate in both pentameric and hexameric assemblies. This dramatically reduces the number of distinct structural components required for shell construction. The ability of a single protein to occupy multiple local environments may be one of the key innovations underlying the success of icosahedral capsids and deserves greater emphasis.

Response: To address this point, I added a new paragraph to further emphasize the significance of quasi-equivalence. The revised text now discusses how the same capsid protein can participate in both pentameric and hexameric assemblies, reducing genetic complexity while preserving structural versatility.

Revised Text: Page 7, paragraph 6
The scalability is complemented by quasi-equivalence (3,4), in which identical protein subunits adopt slightly different conformations to form both pentameric and hexameric assemblies. By allowing the same protein to occupy multiple structural roles, quasi-equivalence provides architectural economy. As a result, larger and more diverse capsids can be constructed from the same capsid proteins rather than requiring entirely new structural components. Quasi-equivalence thus reduces genetic complexity while preserving structural versatility, enabling diverse capsid architectures to emerge from a limited set of recurring building blocks.

4. Scalability (variable T numbers).
Once the closure problem is solved by the fixed set of pentameric positions, shell volume can vary through the addition of hexameric positions. This allows the same architectural framework to generate a wide range of capsid sizes and genome capacities. In this sense, pentamers determine closure while hexamers determine scale. The resulting decoupling of shell closure from shell volume may be one of the most important evolutionary advantages of the pentamer–hexamer architecture.

Response: To address this point, I expanded the discussion of scalability in both the “Design Options for Viral Capsids” section and the “Conserved Geometry and Capsid Variation” section. The revised manuscript highlights the complementary roles of pentamers and hexamers, in which pentamers determine closure whereas hexamers determine scale. It further discusses how this decoupling of shell closure from shell volume provides a scalable architectural framework capable of accommodating genomes of widely varying sizes. This may help explain the evolutionary convergence of pentamer–hexamer capsid architectures.

Revised Text:
Design Options for Viral Capsids: Page 7, paragraph 4
Beyond curvature distribution, the icosahedral geometry also provides a unique degree of scalability. In tetrahedral and octahedral geometries, shell closure and size are more tightly coupled because curvature is concentrated at relatively few locations (four and six sites, respectively). In pentamer–hexamer systems, a fixed set of twelve pentamers provides the curvature required for closure, while additional hexamers can be incorporated to increase shell size without altering the underlying topology (Figure 5). This closure-scale decoupling enables a common geometric design to support capsids of widely varying dimensions.

Conserved Geometry and Capsid Variation: Page 7, paragraphs 5 and 6

Icosahedral symmetry reflects an evolutionary convergence toward a common capsid geometry. This geometry allows shell closure, distributes curvature evenly, and encloses volume efficiently. Pentamers determine closure; hexamers scale. This principle is exemplified by the Caspar–Klug triangulation-number (T-number) system, in which progressively larger capsids are generated by adding increasing numbers of hexameric positions while retaining the same twelve pentamers required for shell closure (3).

The scalability is complemented by quasi-equivalence (3,4), in which identical protein subunits adopt slightly different conformations to form both pentameric and hexameric assemblies. By allowing the same protein to occupy multiple structural roles, quasi-equivalence provides architectural economy. As a result, larger and more diverse capsids can be constructed from the same capsid proteins rather than requiring entirely new structural components. Quasi-equivalence thus reduces genetic complexity while preserving structural versatility, enabling diverse capsid architectures to emerge from a limited set of recurring building blocks.

5. Evolutionary economy (minimal set of building blocks).
The pentamer–hexamer system may represent a near-minimal architectural alphabet capable of generating enormous structural diversity. Just as four nucleotides generate all genomes and twenty amino acids generate the diversity of proteins, a small set of assembly motifs can generate a large family of capsid architectures. This architectural economy provides substantial evolutionary flexibility while minimizing the need for additional structural innovations.

Response: To address this point, I expanded the Conclusion to emphasize the complementary roles of pentamers and hexamers as recurring assembly motifs. The Conclusion further proposes the hypothesis that pentamer–hexamer architectures may represent a near-minimal architectural framework for closed protein shells, capable of generating substantial structural diversity from a limited set of recurring assembly motifs.

Revised Text: Page 8, paragraph 4; page 9, paragraphs 1 and 2
Viewed more broadly, pentamers and hexamers do more than satisfy geometric constraints. Hexamers provide efficient local packing and extensive neighbor contacts, promote structural stability. By contrast, pentamers provide the smallest positive-curvature contribution among the polygonal alternatives capable of closing a hexagonal lattice. They therefore solve the closure problem while minimizing disruption of efficient hexagonal packing. Together, these complementary structural motifs form a simple yet versatile architectural strategy that supports shell closure, scalable growth, and structural adaptability.

Conceptually, this framework resembles other biological systems in which a limited set of building blocks generates substantial diversity. For example, four nucleotides encode genomes, and twenty amino acids generate the diversity of proteins. Similarly, two recurring assembly motifs can generate a large family of capsid architectures while maintaining a common organizational scheme. One hypothesis emerging from these observations is that pentamer–hexamer architectures represent a near-minimal architectural framework for closed protein shells. By combining a fixed closure mechanism with flexible expansion, this arrangement may provide an unusually favorable balance between simplicity and versatility. Such a framework can accommodate a wide range of capsid geometries while preserving efficient packing and reliable shell closure. Combined with quasi-equivalence, it may enable diverse capsid architectures to be constructed from a limited set of protein subunits.

Support for this hypothesis comes from the observation that evolution has repeatedly converged on pentamer–hexamer architectures across diverse viral lineages. Notably, the convergence is observed among viruses built from structurally distinct capsid proteins (4,10,27–29). This suggests that the

pentamer–hexamer framework is not tied to a particular molecular implementation but instead represents a broadly accessible architectural solution that can be realized by diverse protein folds and interaction chemistries. Such convergence may reflect the evolutionary advantages of pentamer–hexamer systems, including efficient packing, scalability, quasi-equivalent assembly, and compatibility with diverse protein folds. Future computational and comparative studies may help determine whether the geometric and architectural advantages discussed here are sufficient to account for the repeated emergence of this solution in nature.

Collectively, these five principles may offer a more biologically meaningful explanation for the repeated emergence of icosahedral capsids than topology alone. They move the discussion from the question of what geometries are possible to the more important question of why evolution may have repeatedly selected this particular solution from among many geometrically permissible alternatives.

Response: This framework helped me expand the discussion beyond geometric necessity to include potential evolutionary advantages of pentamer–hexamer architectures. I included new discussions of local packing efficiency, closure capability, quasi-equivalence, scalability, architectural economy, alternative architectural strategies, and structural convergence. While the review remains focused on geometric principles, these additions help connect topology to the broader question of why evolution may have converged on pentamer–hexamer capsid architectures.

Finally, I encourage the author to substantially expand the reference list. The current manuscript relies heavily on a limited set of classical geometric and virological sources. Additional references covering quasi-equivalence, capsid assembly, viral evolution, structural convergence, protein self-assembly, elastic shell theory, and comparative viral architectures would considerably strengthen the scholarly foundation of the manuscript and better place the proposed ideas within the broader literature.

Response: I expanded the reference list from 30 to 43 references. Several new references were added to address the specific topics identified by the reviewer. They include viral evolution and structural convergence (Bamford et al., 2005; Abrescia et al., 2012), comparative viral architectures (Baker et al., 1999), protein self-assembly and capsid assembly dynamics (Zlotnick, 1994; Mateu, 2013; Whitesides & Grzybowski, 2002), and elastic shell theory (Nelson, 2002). These references were incorporated into relevant sections. Together, these additions provide broader literature support while maintaining the manuscript's focus on the geometric principles underlying viral capsid organization.
The closest thing to a publishable new idea would be to elevate those points into a formal hypothesis: Pentamer–hexamer systems represent a near-minimal architectural alphabet that maximizes the ratio of accessible enclosed volume, shape diversity, and assembly robustness to the number of required building-block classes. That is not proven in the manuscript, but it is at least a new conceptual claim that could generate predictions and be tested against alternative architectures. Without something of that sort, the paper remains primarily a pedagogical synthesis of existing ideas. Better yet, quantify (at least rough calculations) so you can prove “Pentamer–hexamer systems maximize architectural versatility per unit assembly investment.” see attached chat-gpt file. That now beccomes genuinely publishable as a significant contribution to the corpus of knowledge in the field.

Response: I agree that the observations discussed throughout the manuscript can be synthesized into a broader conceptual hypothesis regarding the evolutionary success of pentamer–hexamer architectures. In response, I expanded the Conclusion to propose that pentamer–hexamer systems may represent a near-minimal architectural framework for closed protein shells. Specifically, a fixed set of twelve pentamers provides shell closure, whereas a variable number of hexamers enables substantial variation in capsid size and geometry. This arrangement may provide a favorable balance between architectural simplicity, scalability, and structural versatility (page 9, paragraphs 1 and 2).

I also agree that this hypothesis generates testable predictions and may be useful for comparing pentamer–hexamer architectures with alternative capsid designs. The revised Conclusion now explicitly identifies this hypothesis as a potential direction for future computational, theoretical, and comparative studies.

A quantitative analysis of architectural versatility per unit assembly investment would require additional assumptions and comparative modeling that were beyond the scope of this review. I therefore present this idea as a hypothesis for future study rather than as a demonstrated conclusion.

Reviewer 2 Critiques and Responses
Please verify that all links to the references point to the correct source.

Response: All references, links, and DOIs were reviewed and verified to ensure that they correspond to the correct sources.

The authors must disclose and acknowledge any assistance received in the preparation of this manuscript, including but not limited to editorial, technical, analytical, or writing support. All such contributions must be clearly stated in the Acknowledgments section.

Response: The Acknowledgments section was updated to recognize individuals who provided editorial, technical, or other assistance (page 10, paragraph 4).

Include enough recent references along with foundational ones. Ensure references directly support your claims. Avoid "padding." Use credible sources (peer-reviewed journals, reputable books, official reports).

Response: The reference list was expanded and updated to include additional peer-reviewed sources covering capsid assembly, quasi-equivalence, structural convergence, viral evolution, physical virology, elastic shell theory, and protein nanocage design. Citations were also reviewed to ensure that each reference supports the associated statement, and unnecessary references were removed where appropriate.

All assumptions (including implicit assumptions) must be explicitly stated and clearly justified. The authors should explain why each assumption is reasonable and discuss its impact on the results and conclusions.

Response: The "Theoretical Framework for Capsid Architecture Analysis" section was expanded to explicitly state the assumptions underlying the geometric model, including the treatment of capsids as idealized closed polyhedral shells composed of regular polygons with equal edge lengths and three faces meeting at each vertex. The manuscript now further clarifies that elasticity, bending energy, assembly kinetics, and other physical factors are not included in the model and discusses how these assumptions affect interpretation of the conclusions.

Avoid overreaching conclusions that extend beyond what is supported by the data and analysis.

Response: The Abstract, Conclusion, and nanotechnology discussion were revised to use more cautious language and to distinguish between geometric conclusions supported by the analysis and broader interpretations regarding viral evolution and nanocage design. In the revised manuscript, terms such as "may help explain," "suggest," "may represent," and "may provide" are used where appropriate to avoid conclusions that extend beyond the scope of the evidence.

Verify that you have used past perfect tense and third person throughout the manuscript wherever applicable.

Response: The manuscript was reviewed for consistency of tense, grammar, and point of view. Revisions were made where necessary to improve consistency and maintain an appropriate academic writing style throughout the manuscript.

The central conceptual claim of the manuscript is that pentamer–hexamer architectures represent an evolutionarily favored or near-optimal solution because they simultaneously maximize packing efficiency, scalability, structural economy, and adaptability. However, these remain qualitative assertions. Although the manuscript discusses several desirable properties of the pentamer–hexamer architecture, it never operationalizes these properties into a quantitative framework that allows comparison with alternative architectures (e.g., tetrahedral, octahedral, all-pentamer, elongated, or enveloped systems). Consequently, the proposed evolutionary explanation remains an opinion or conceptual hypothesis rather than a demonstrated scientific conclusion. Without defining explicit optimization criteria and evaluating competing architectures under a common mathematical framework, there is no objective basis for concluding that the pentamer–hexamer solution is evolutionarily superior rather than merely possessing several appealing characteristics. Without this step, the manuscript offers a plausible conceptual synthesis of existing knowledge rather than a publishable advance beyond the current literature.

Although the author argues that quantitative comparison would require additional assumptions, this does not adequately address the reviewer's suggestion. The objective was not to establish an absolute measure of evolutionary fitness but to develop a comparative framework in which alternative capsid architectures are evaluated under identical simplifying assumptions. Because those assumptions would be applied uniformly across all competing geometries, the resulting comparisons would still be scientifically meaningful. Even a preliminary, dimensionless optimization index integrating enclosure efficiency, scalability, architectural economy, and protein reuse would substantially strengthen the manuscript by transforming the central hypothesis into a quantitative and testable framework. In its current form, the manuscript remains largely qualitative and therefore stops short of making the conceptual advance proposed during review.
For example, one could define a dimensionless "architectural utility" index such as
U=(Building Block Classes×Assembly Complexity) divided by
(Enclosed Volume×Scalable Configurations×Protein Reuse)

The precise formula is not important. The important point is that all architectures (tetrahedral, octahedral, all-pentamer, pentamer–hexamer, elongated, etc.) would be evaluated under the same assumptions.
The question would not be "Is this the true evolutionary fitness?" Instead it would be "Under identical geometric assumptions, which architecture performs best?" Those are fundamentally different questions.
Likewise, one could imagine a multi-objective score
F=w1E+w2S+w3R+w4V
where
E = enclosure efficiency
S = scalability
R = robustness or redundancy
V = versatility
Even if the weights are initially set equal, the framework becomes testable because one can perform a sensitivity analysis by varying the weights. If the pentamer–hexamer architecture consistently ranks highest across a broad range of weightings, that would provide much stronger support for the manuscript's central thesis.

In other words, the additional assumptions are not a fatal obstacle. They are part of constructing a model. The scientific value comes from making those assumptions explicit and then asking whether the conclusions are robust to reasonable variations.
A reasonable implementation could probably be accomplished in about a week by:
Defining 4–6 geometric criteria.
Normalizing each criterion to a common scale.
Computing scores for tetrahedral, octahedral, pentamer-only, pentamer–hexamer, and perhaps enveloped architectures.
Performing a simple sensitivity analysis.
Discussing the limitations.
No experiments would be required. The calculations could be approximate, provided the assumptions were stated explicitly and made engineering and evolutionary sense.

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No experiments would be required. The calculations could be approximate, provided the assumptions were stated explicitly and made engineering and evolutionary sense.

Response:

I sincerely thank the reviewer for the thoughtful comment and for providing a clear roadmap for constructing a quantitative comparative framework to strengthen the central hypothesis.
In response, I added a new section entitled "Quantitative Comparison of Representative Capsid Architectures" and three new tables (pages 8–11). Following the reviewer's recommendations, the revised manuscript introduces six explicit evaluation criteria and compares five capsid architectures under a common framework. The revision also includes a sensitivity analysis and discusses the assumptions and limitations.
To strengthen the structural comparison, I also added a new reference and Figure 1F illustrating the all-pentamer architecture of HPV-16. In addition, the Abstract, Introduction, and Conclusion were revised to integrate the quantitative framework and its implications for the central hypothesis.
Consistent with the reviewer's recommendation, the framework is presented as a testable comparative model rather than a quantitative measure of evolutionary fitness. Under these common assumptions, the canonical pentamer–hexamer architecture achieved the highest utility score and remained the highest-ranked architecture across a broad range of criterion weightings.

The author has substantially addressed my previous concern. In particular, the addition of the quantitative comparative framework represents an important improvement over the previous version. The manuscript now defines six architectural criteria, evaluates five representative architectures under a common framework, calculates an overall architectural utility score, performs a sensitivity analysis across alternative criterion weightings, and explicitly discusses the assumptions and limitations of the framework. This directly addresses the central objective of my previous recommendation and transforms the manuscript from a largely qualitative argument into a testable comparative model.
I nevertheless have one remaining concern regarding the quantitative framework. The sensitivity analysis examines the robustness of the result to changes in the weights assigned to the six criteria, but it does not examine the robustness of the result to the scores assigned to the architectures themselves. For example, the pentamer–hexamer architecture receives a score of 2 for all six criteria, whereas the all-pentamer architecture receives scores of 1–2 and the prolate architecture receives scores of 1.5–2. Although the accompanying discussion provides reasonable qualitative arguments for these rankings, it is not always clear why a particular architecture should receive, for example, 1 rather than 1.5, or 1.5 rather than 2. Consequently, some of the conclusion is effectively built into the assigned scores.

I therefore recommend that the author strengthen the operational definition of each scoring category. Wherever possible, scores should be connected to measurable or mathematically defined quantities, analogous to the use of S/(V^2/3) for enclosure efficiency. Where objective numerical quantities are unavailable, the manuscript should provide explicit criteria explaining what distinguishes scores of 0, 0.5, 1, 1.5, and 2. Ideally, the author should also perform a simple score-sensitivity analysis—for example, allowing the less objectively determined scores to vary by ±0.5—to determine whether the pentamer–hexamer architecture remains highest-ranked. Such an analysis would complement the existing weight-sensitivity analysis and demonstrate that the conclusion is not simply a consequence of the particular ordinal scores initially assigned.

Comments to author

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Response

I thank the reviewer for the constructive feedback and for helping improve the quantitative framework. The comments helped me think more deeply and quantitively about the scoring definitions. The revised framework now uses more measurable criteria, explains how each score was assigned, removes overlapping criteria, and shows that the main conclusion remains robust under alternative scores and weights. The revision is described on Pages 9–12 of the manuscript. I revised the framework as follows.

1. The scoring definitions were strengthened. Table 2 now provides numerical, geometric, or structural definitions for each scoring category, as advised.
2. Protein reuse was replaced with vertex coordination. Protein reuse depends on biological factors that cannot be determined consistently from shell geometry alone, and in the previous scheme, protein reuse did not distinguish the representative architectures. I therefore replaced it with vertex coordination, defined as the number of polygons meeting at each vertex. This directly countable property represents a geometric constraint.

3. Architectural economy was renamed polygon-class economy. This new name describes more clearly what the criterion measures. Polygon-class economy is defined by the number of distinct recurring polygon classes used to construct the shell. Table 2 now provides explicit scoring categories for this criterion.
4. Scalability was clarified, and architectural versatility was removed. Architectural versatility was removed because it is an emergent property that overlaps with scalability and economy. Scalability is now defined as the ability to increase shell size while preserving the polygon classes, local vertex relationships, and shell-closure rules. Uniform enlargement without adding or rearranging polygonal units does not count as scalability. The revised framework therefore contains five rather than six criteria.
5. The utility scores were recalculated. All five representative architectures were rescored using the revised five-criterion framework, and the utility scores and rankings in Table 3 were recalculated.
6. The sensitivity analysis was expanded. Three sensitivity tests are now reported in Table 4. First, each criterion was omitted in turn. Second, each criterion weight was increased from 0.20 to 0.40, with the other four weights reduced to 0.15 each. Third, I tested uncertainty in the assigned scalability scores within ±0.5. Scalability was tested because it is the only criterion not based on a measured or counted quantity. The canonical pentamer–hexamer architecture or its prolate variant remained highest or tied for highest in every combination, and no other architecture exceeded either variant.

Thank you for addressing my comments. Accepted.