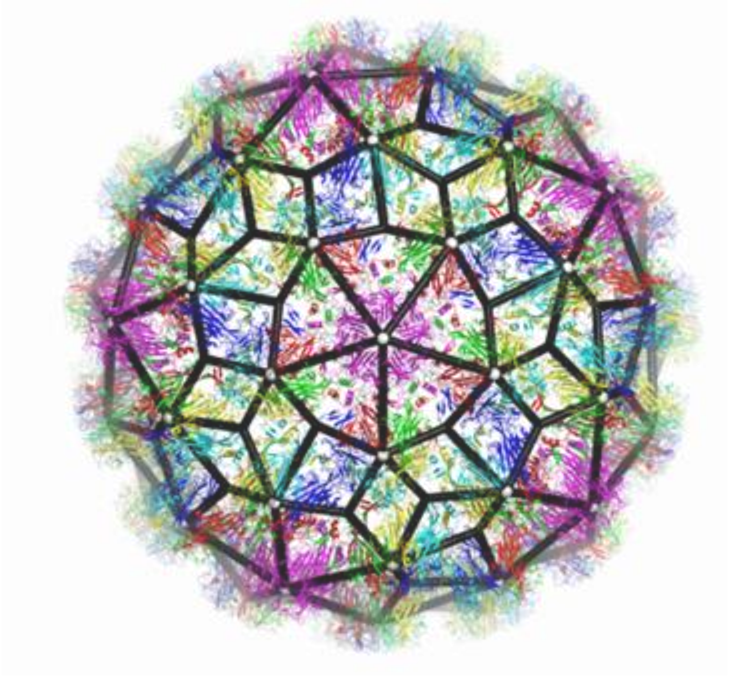
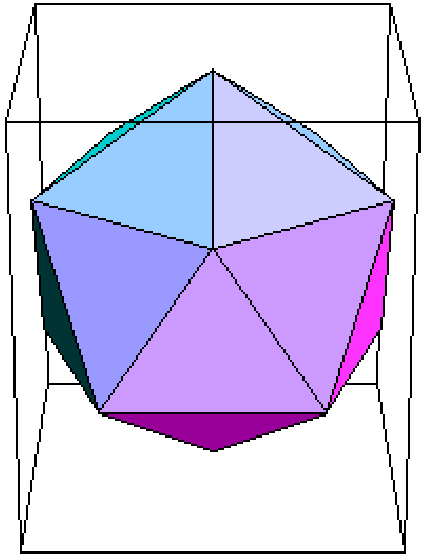
Viruses under the mathematical microscope: viral geometry as a key to understanding viral infections



Reidun Twarock

Departments of Mathematics and Biology

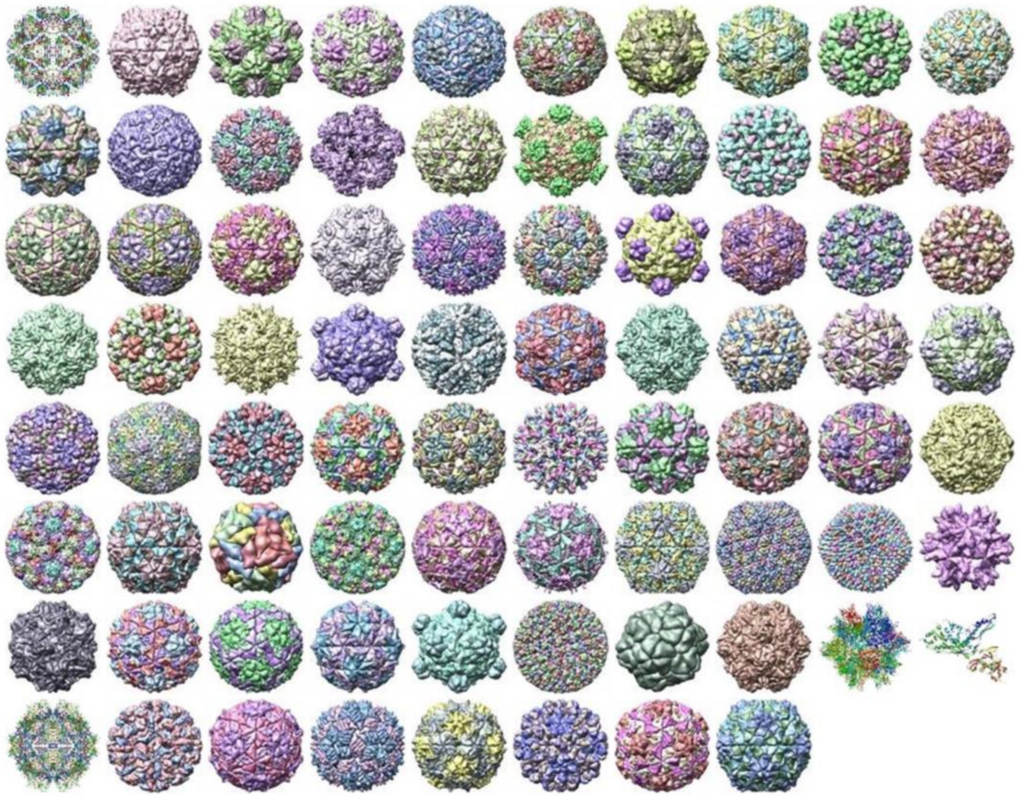
University of York



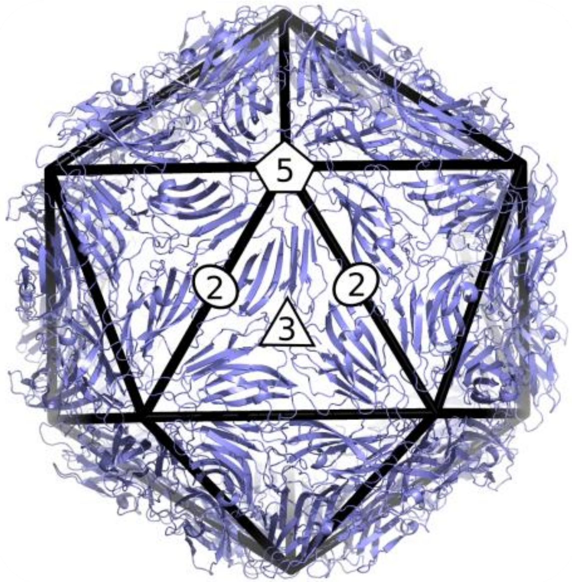
NITMB MathBio Convergence Conference

12th August 2025

Symmetry in Virology



Icosahedral Symmetry



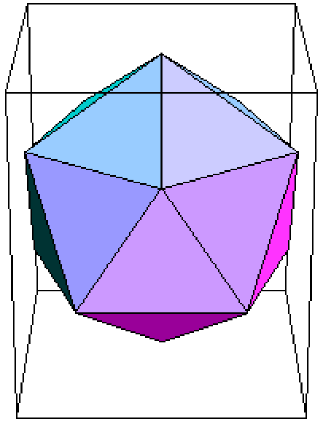
What are the mathematical principles underpinning virus architecture?

The Origin of Symmetry in Virology

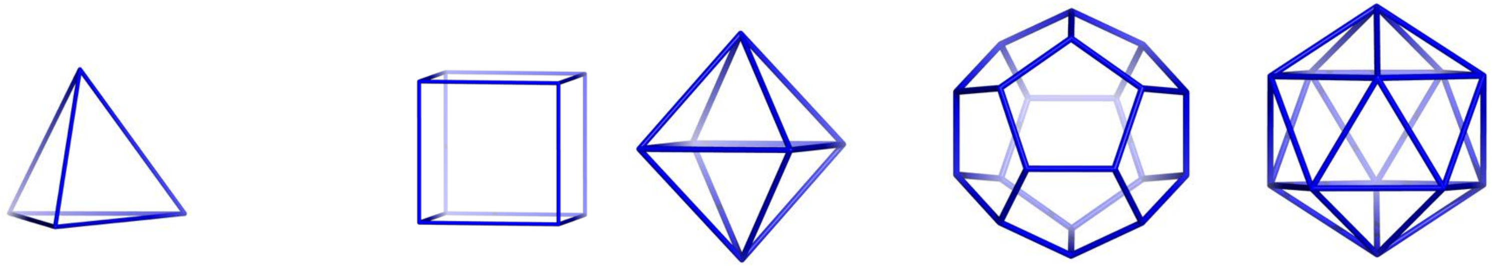
Crick and Watson:

The Principle of Genetic Economy

By synthesizing multiple copies of the capsid building blocks from the same genomic fragment, genome length is minimized, and capsid volume maximized.

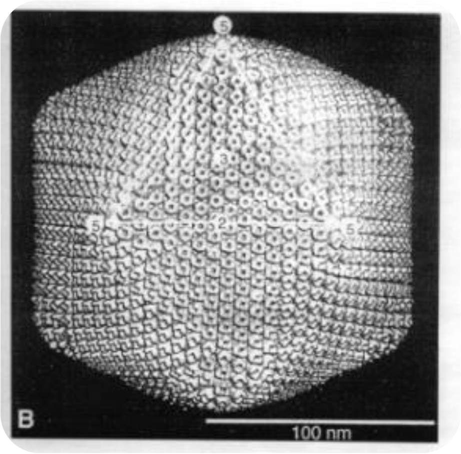


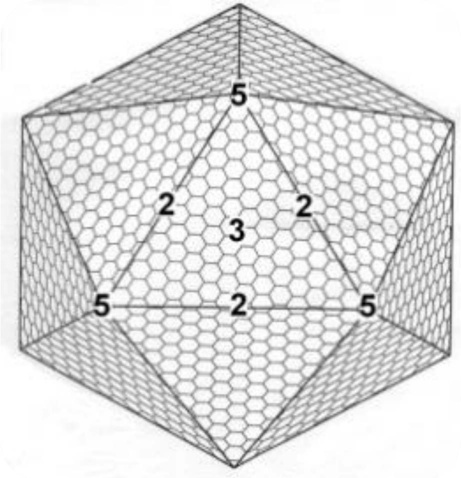
The Platonic solids:



tetrahedral symmetry **octahedral symmetry** **icosahedral symmetry**

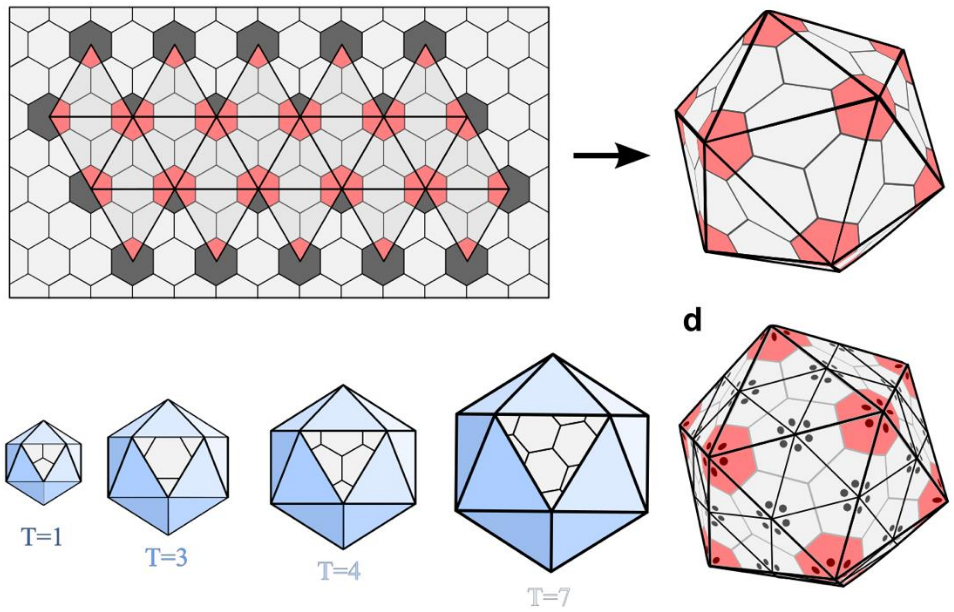
Early Models of Viral Geometry

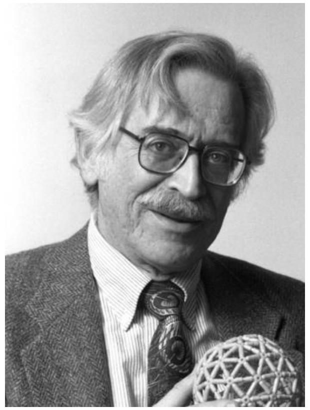




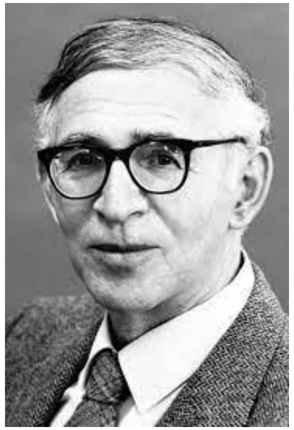
Caspar-Klug theory:

A construction principle for viruses





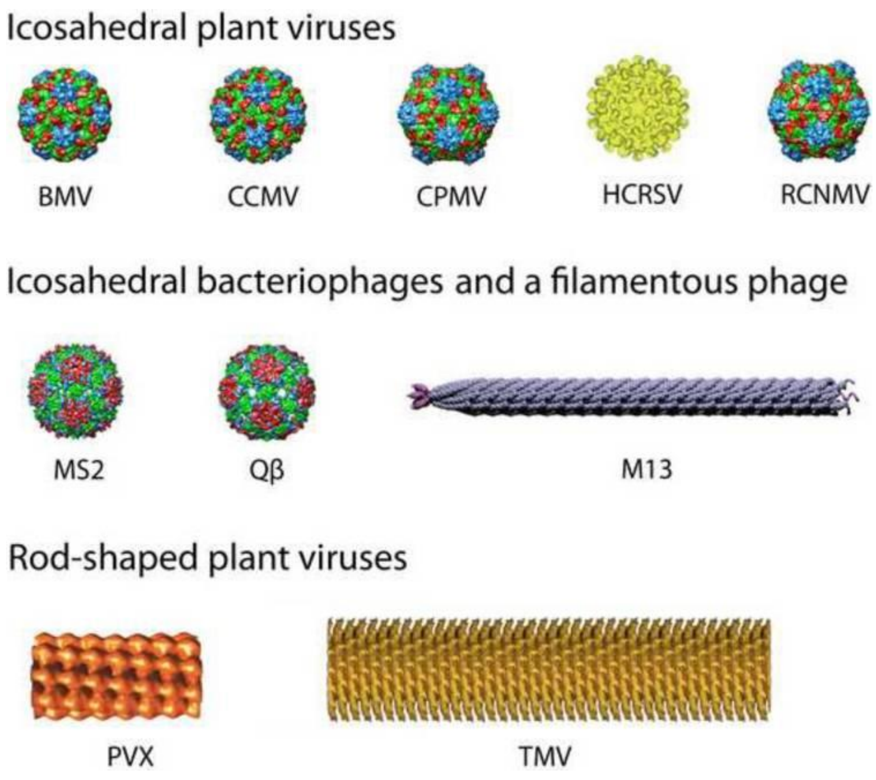
Don Caspar



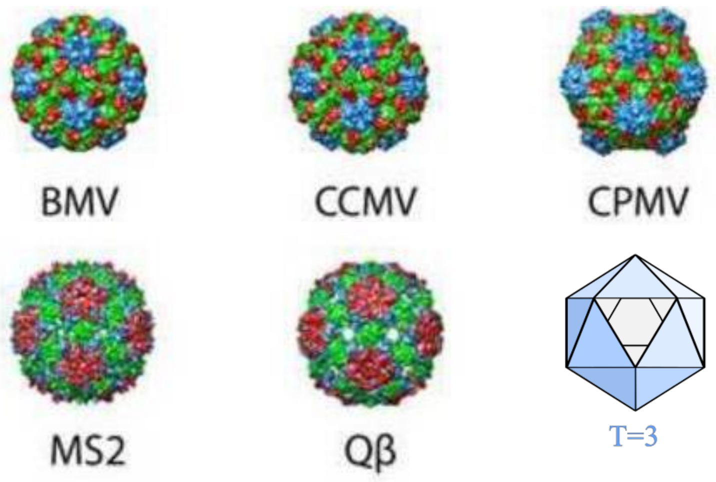
Aaron Klug

A Mathematical Challenge in Virus Nanotechnology

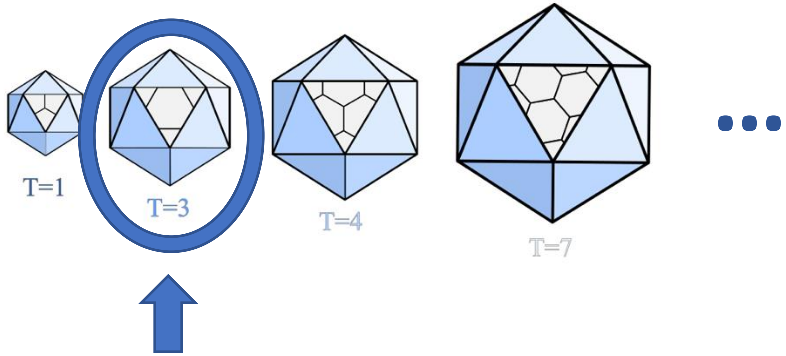
Virus Nanotechnology



Nicole Steinmetz (2010) Viral nanoparticles as platforms for next-generation therapeutics and imaging devices *Nanomedicine* 6(5): 634–641.

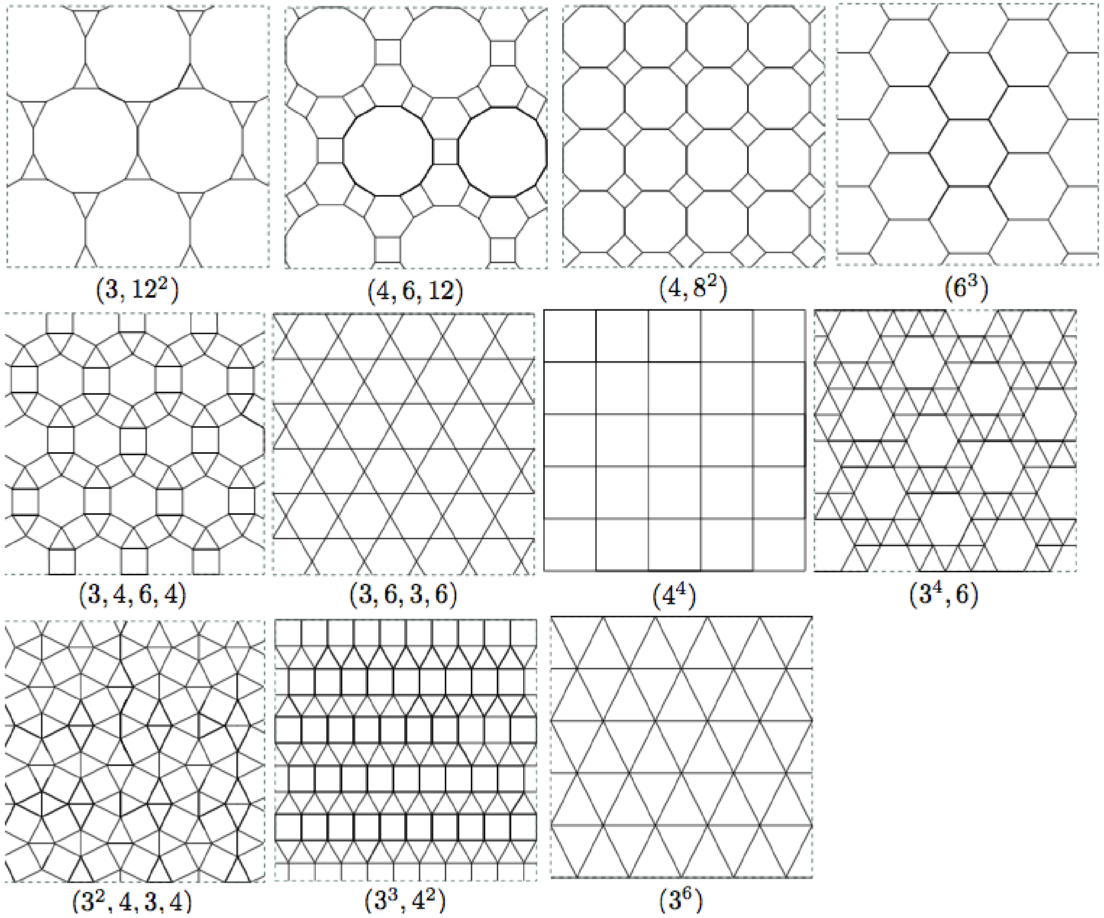


These particles are all classed as *T*=3 in Caspar and Klug's approach



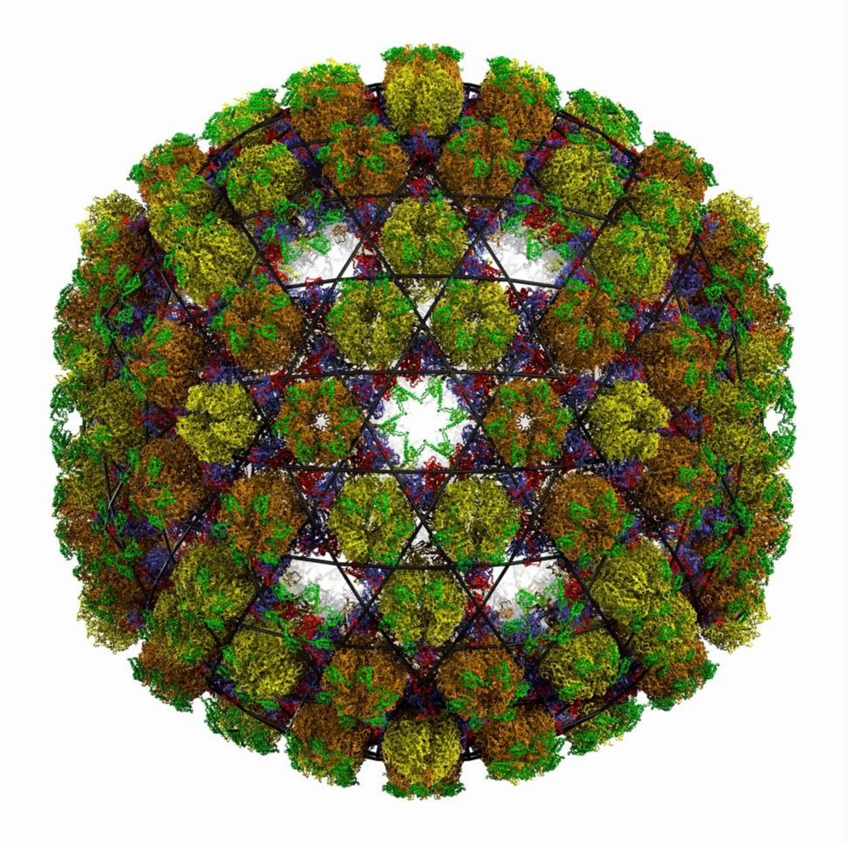
These viruses are all modeled by the same tiling in Caspar Klug theory

Revisit Lattice theory: Archimedean Lattices in Virology



Archimedean lattices are vertex transitive.

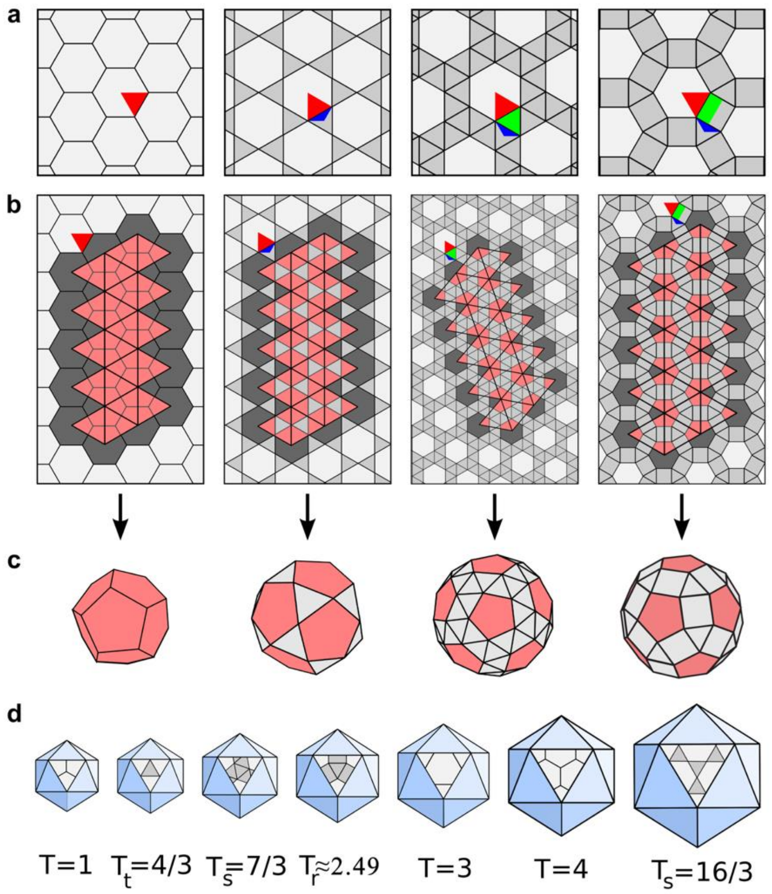
Archimedean lattices are also known as **uniform tilings**



Herpes Simplex Virus

Viral Tiling Theory Refines Models of Virus Architecture

A generalized principle of icosahedral virus architecture:

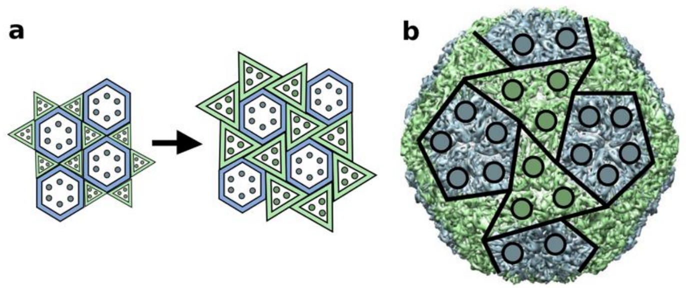


- Caspar-Klug theory is a special case of this overarching theory
- There are capsid layouts with different protein numbers, filling gaps in the evolutionary history of viruses.
- **There are distinct geometric layouts for a given *T*-number**

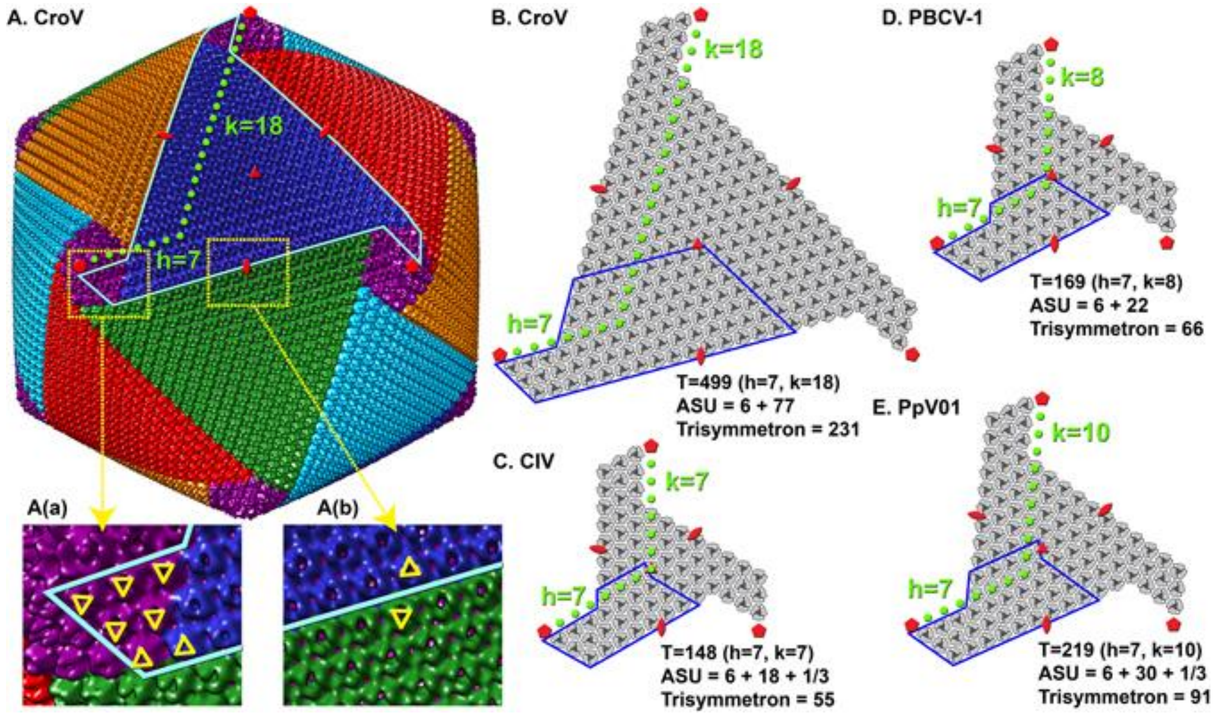
R Twarock & A Luque, Novel icosahedral designs explain structural puzzles in virology, 2019, *Nature Communications 10:* 4414

Viral Tiling Theory Reveals a Novel Degree of Freedom

Gyrated lattice architectures

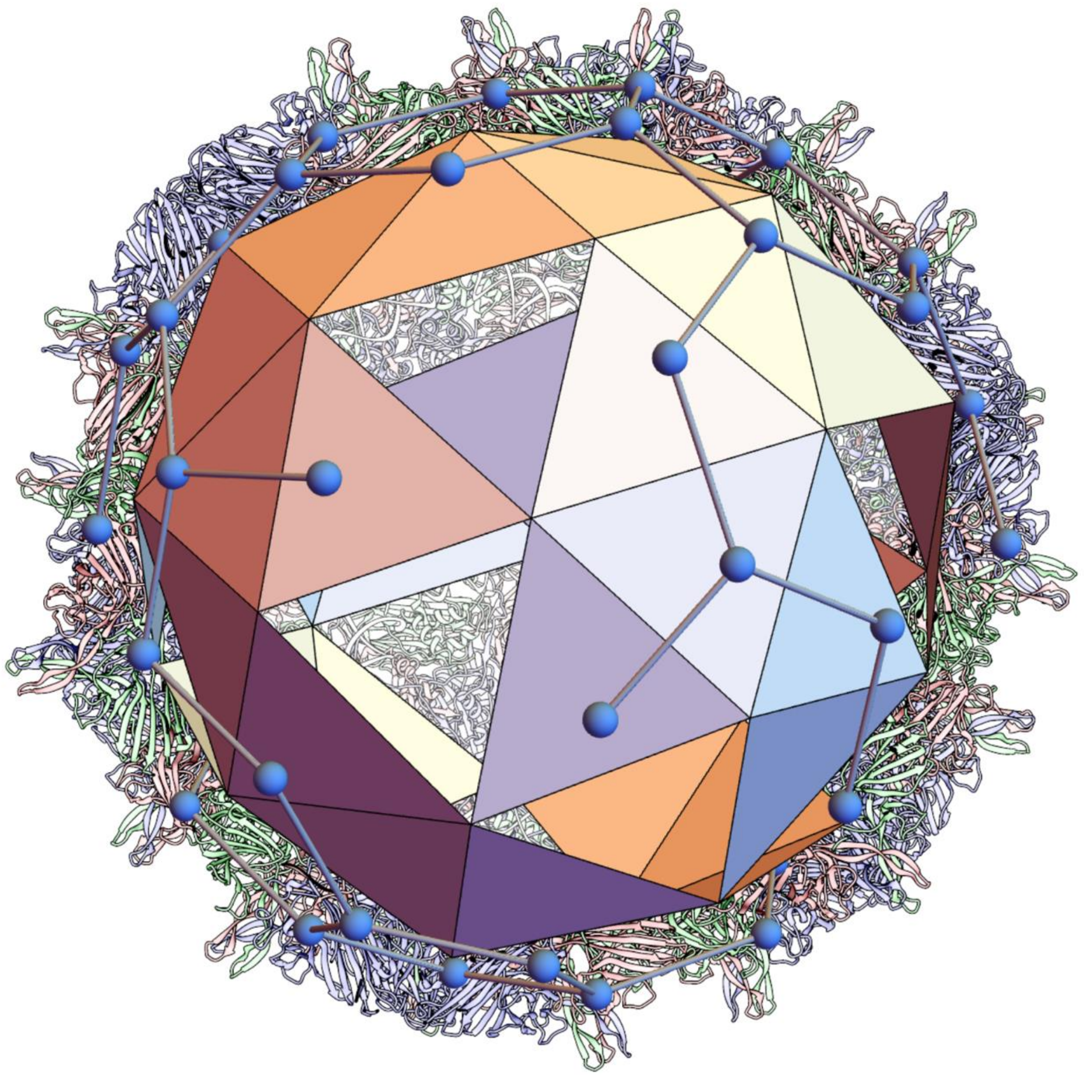


Gyrated lattice architectures: giant phages

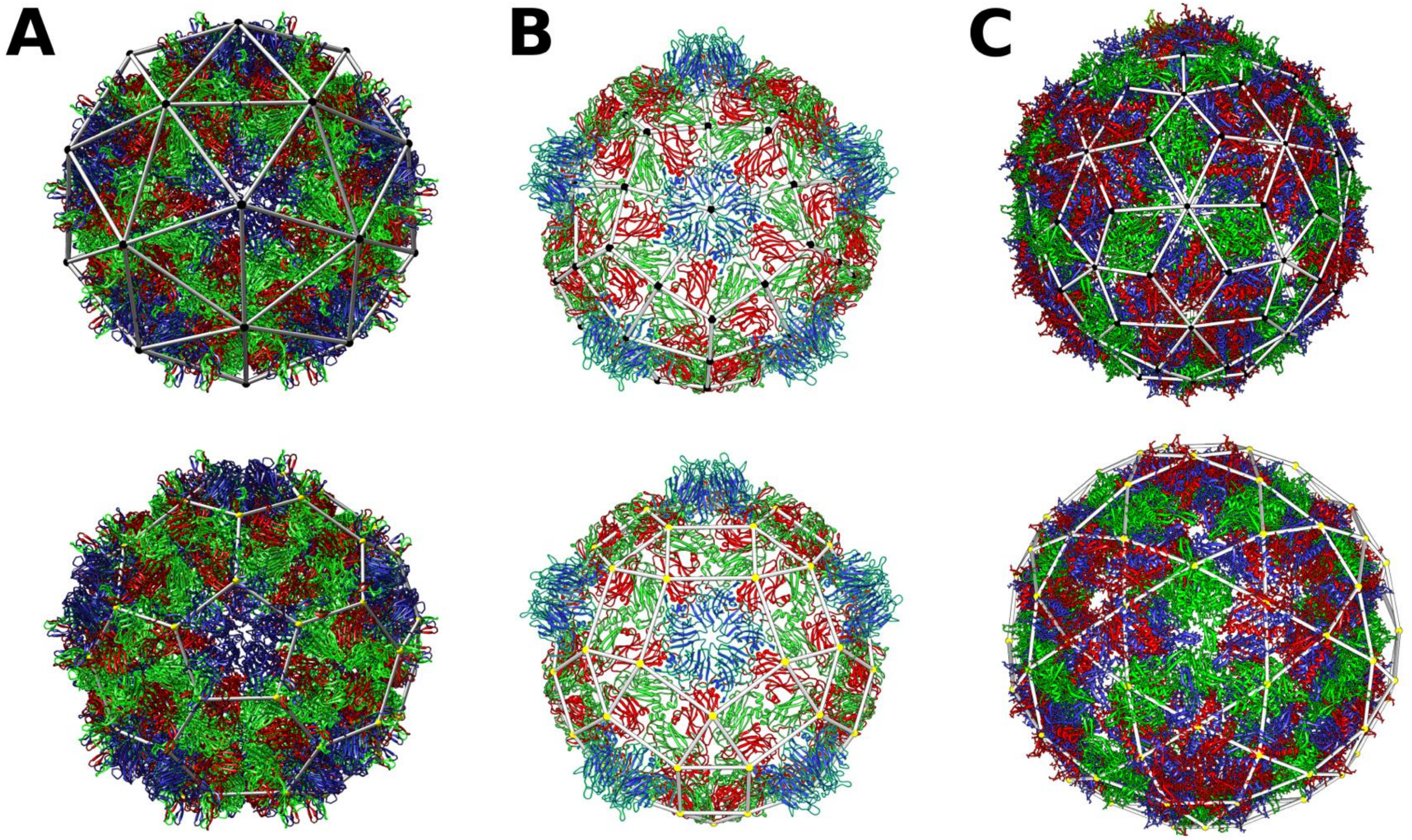


R Twarock & A Luque, Novel icosahedral designs explain structural puzzles in virology, 2019, *Nature Communications 10:* 4414

In silico virus disassembly experiments



From Structure to Function: Capsid Disassembly



Pariacoto Virus

Tobacco Ringspot Virus

Bacteriophage MS2

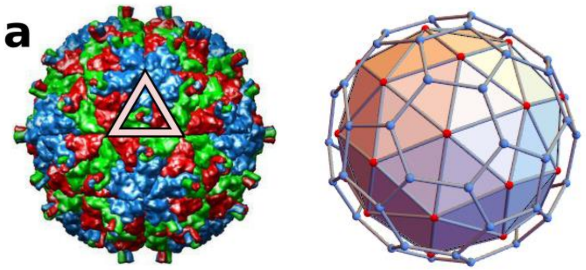
← The **tiling** models the positions and shapes of the distinct capsomer types

← The **dual tiling** is a topological descriptor of the interaction network between capsomers

Percolation Theory & Tiling Theory in Virus Disassembly

triangular

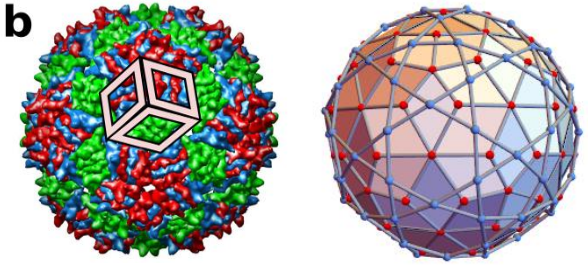
a



60 tiles 3 edges/tile

rhombic

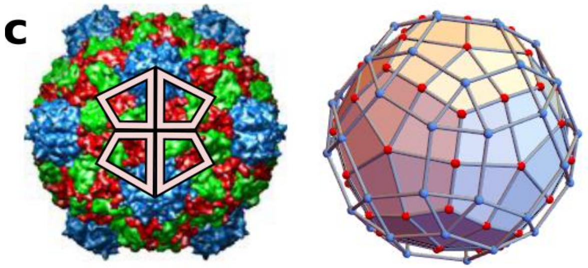
b



90 tiles 4 edges/tile

kite

c



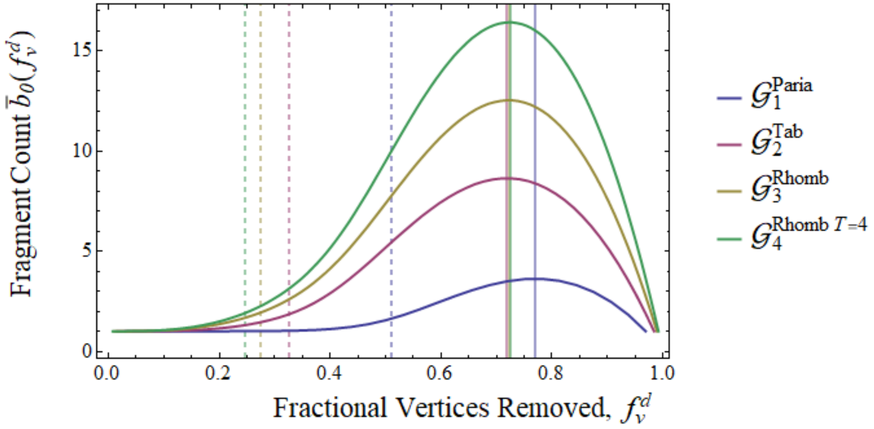
60 tiles 4 edges/tile

← tiling type

← tiling descriptor

Different lattice types result in different biophysical properties:

How many capsomers/tiles can be randomly removed before the capsid fragments into two disconnected components?



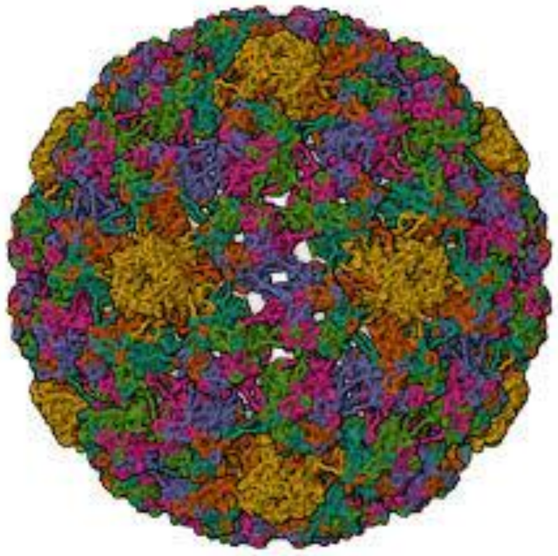
Fragmentation thresholds:

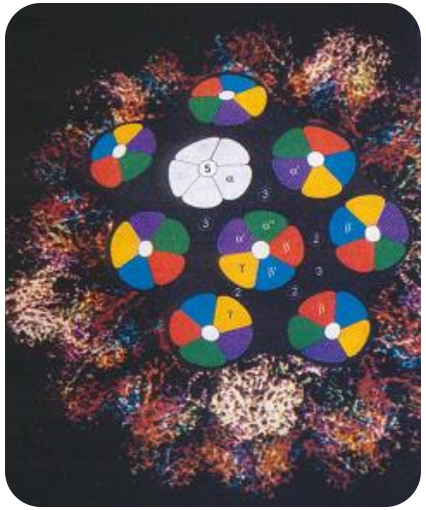
- **Triangular: 0.226**
- **Rhombic: 0.278**
- **Kite: 0.331**

N. Brunck & R. Twarock, Percolation Theory Reveals Biophysical Properties of Virus-like Particles, 2021, *ACS Nano* 15,8, 12988-12995.

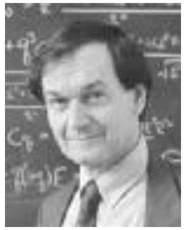
All-pentamer Capsid Architectures & Aperiodic Tilings

All-pentamer Capsid Architectures



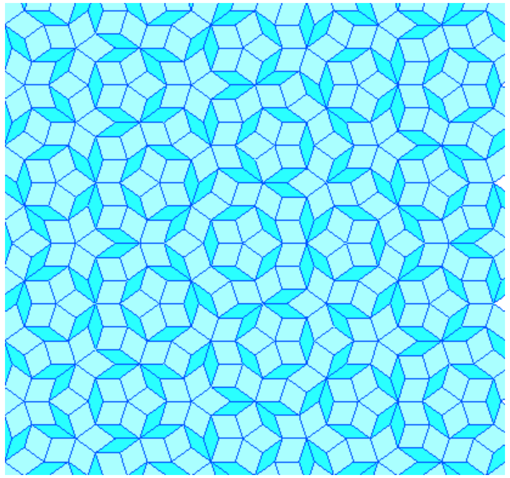


The cancer-causing papillomaviruses



Sir Roger Penrose

Oxford



Penrose tiling

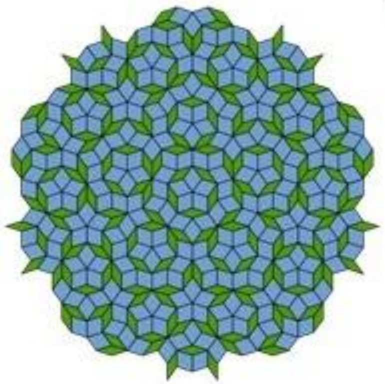
Does this organization confer specific biophysical properties to these capsid architectures?

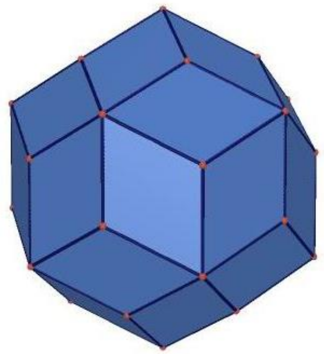
Virus Architecture & Quasilattices: all-pentamer architectures

5D Lattice

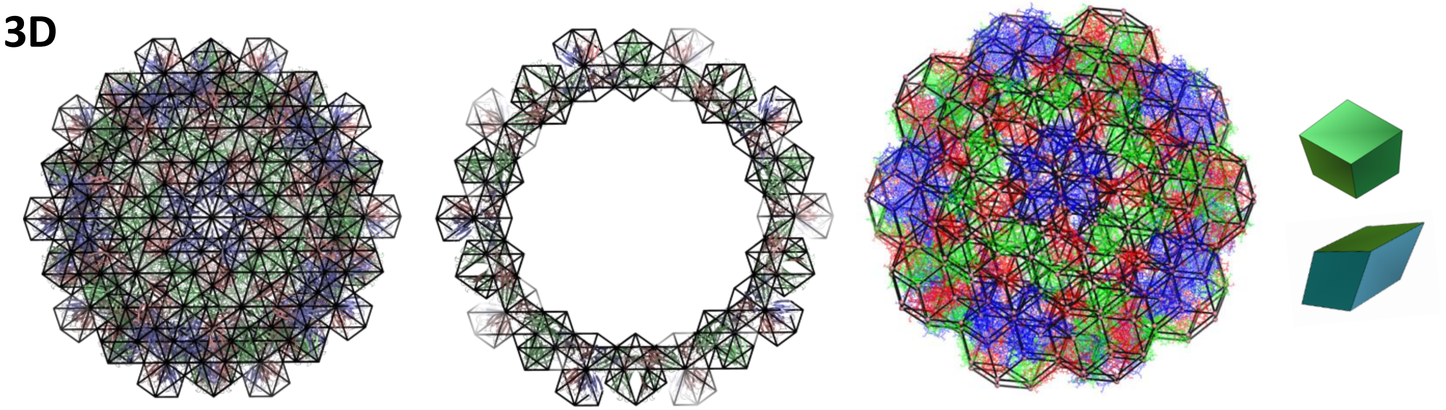
2D Quasilattice

3D “Control Space”

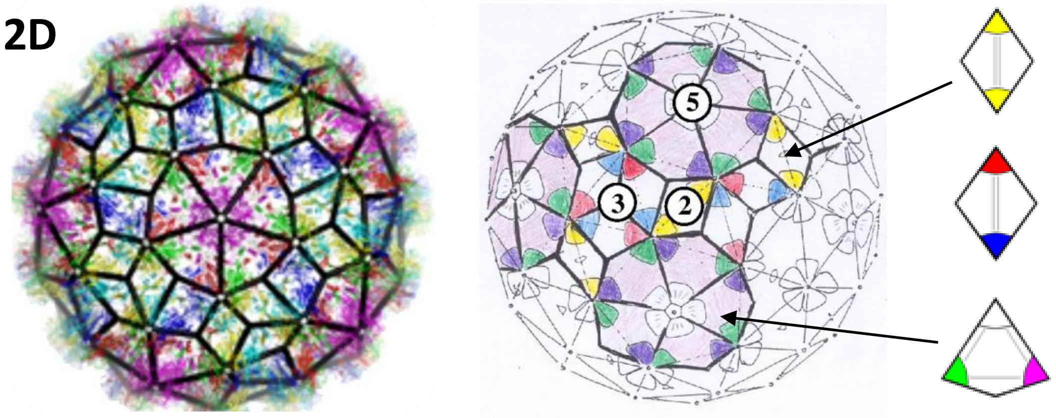




3D

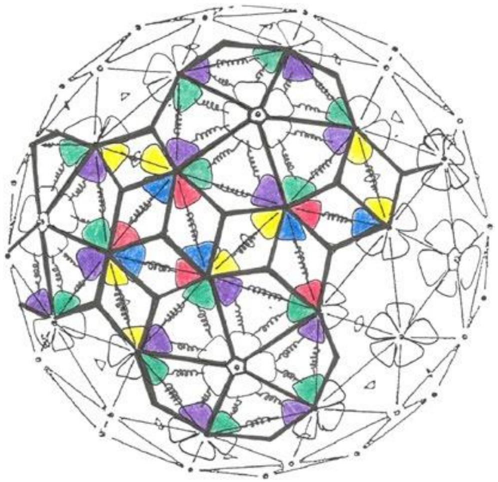


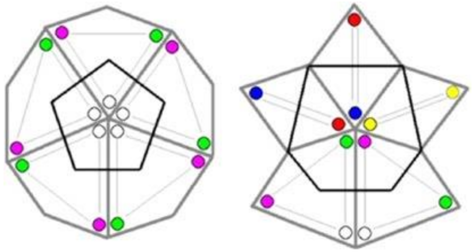
2D

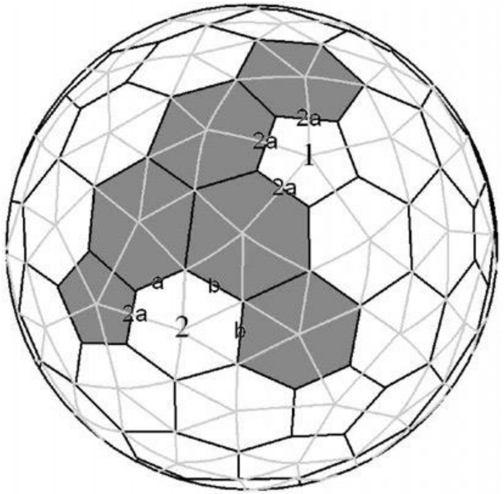


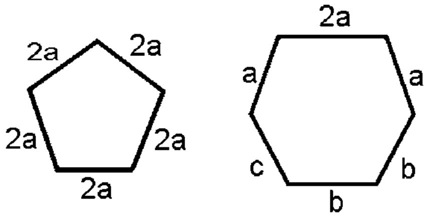
Two distinct environments of bonds around the two types of pentamer

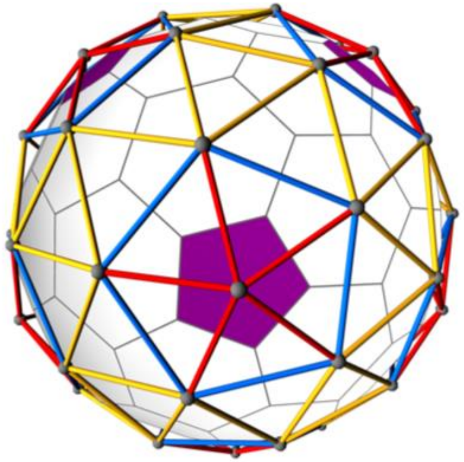
An Assembly Model Based on Tiling Theory

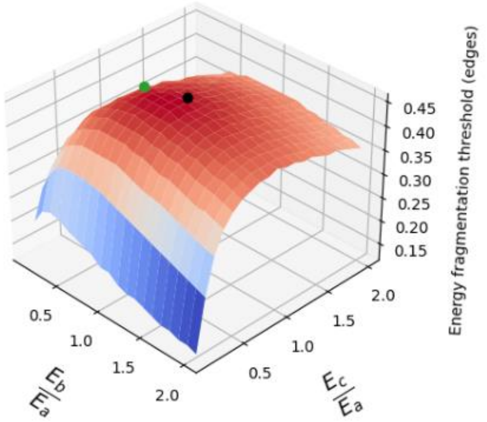


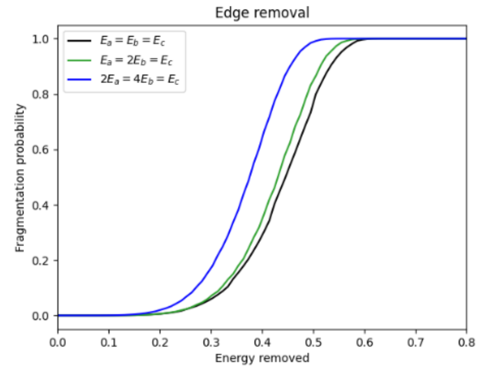










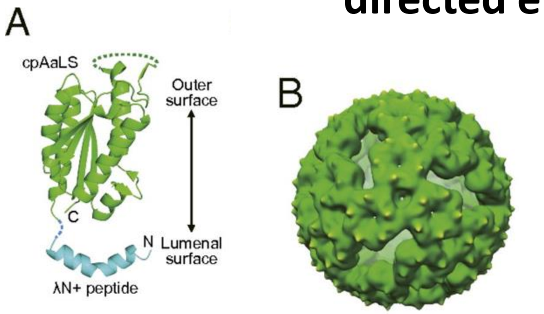


Weights impact on resilience to fragmentation

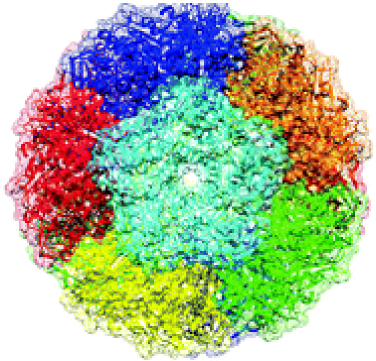
Q. Roussel, S. Benbedra & R. Twarock, Protein container disassembly pathways depend on geometric design, under review

Compare With Other All-Pentamer Container Architectures

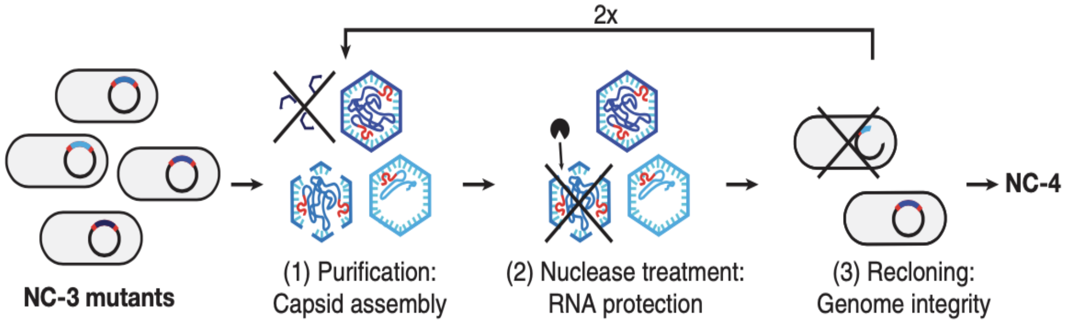
Evolve nanocontainers from nonviral proteins via directed evolution

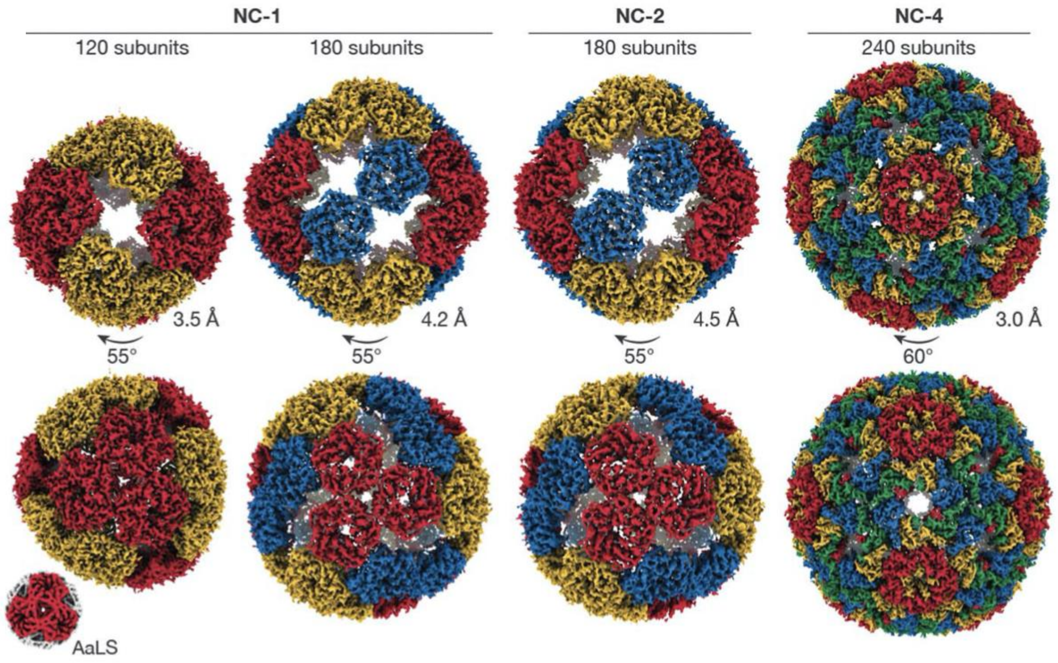


A bacterial protein can be engineered to package its own coding sequence.



dodecahedron
formed from 12 pentamers
Aquifex aeolicus

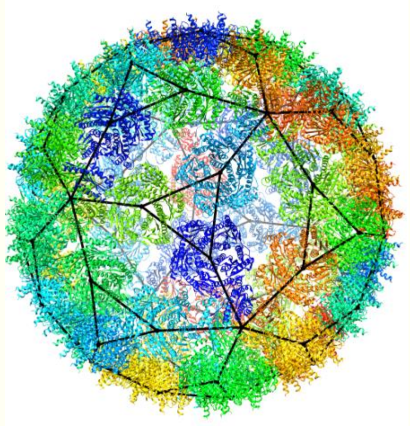




Increase in capsid size under directed evolution

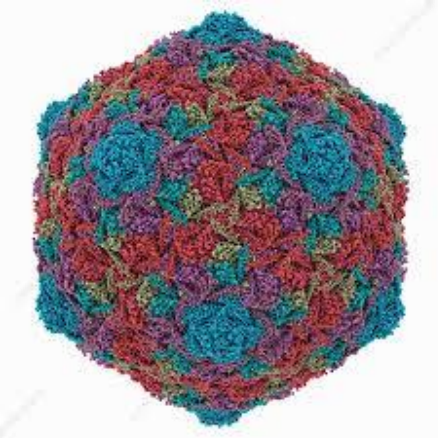
S. Tetter, N. Terasaka, A. Steinauer, R.J. Bingham, S. Clark, A.P. Scott, N. Patel, M. Leibundgut, E. Wroblewski, N. Ban, P.G. Stockley ,R. Twarock & D. Hilvert (2021) Evolution of a virus-like architecture and packaging mechanism in a repurposed bacterial protein, *Science* 372(6547):1220-1224.

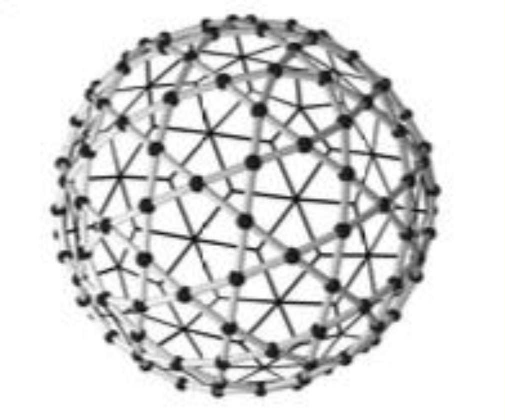
AaLS nanoparticle



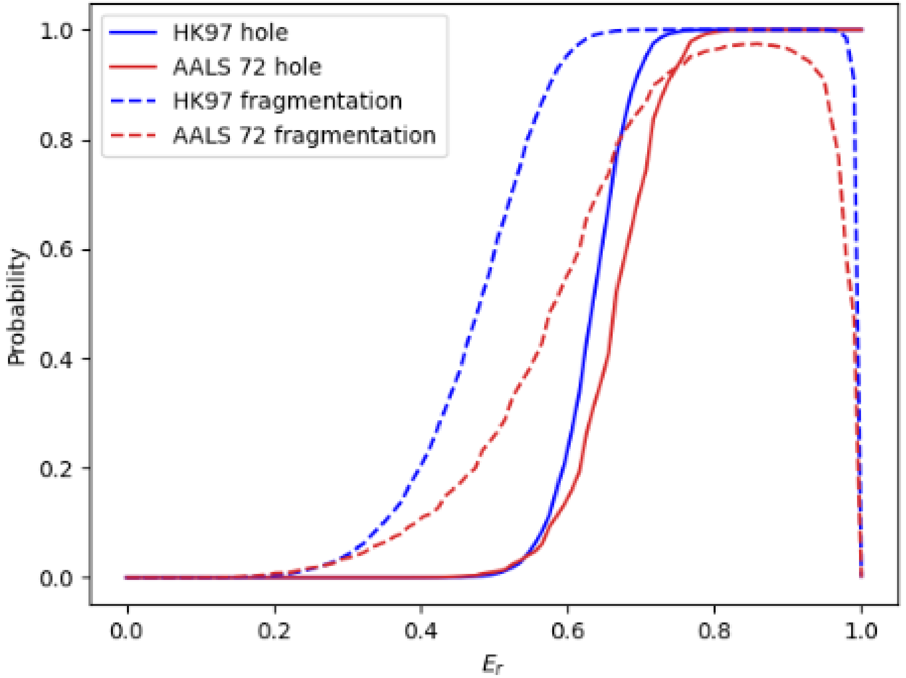
72 pentamers

Bacteriophage HK97





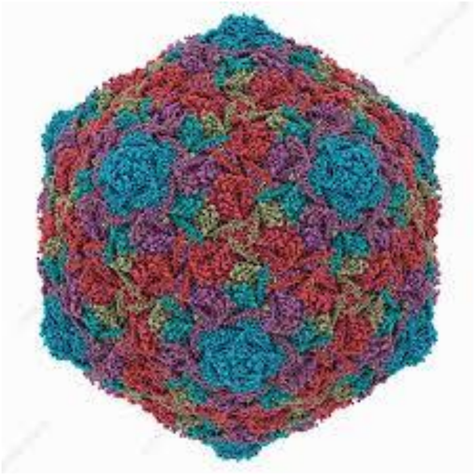
12 pentamers
&
60 hexamers

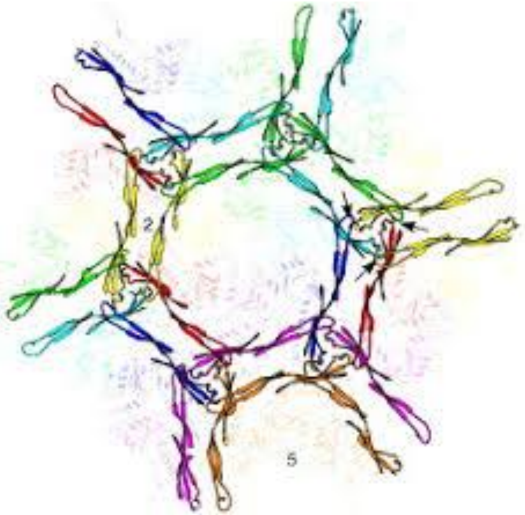


- HK97 and AaLS fragment before hole formation
- AaLS is more stable despite its porous nature

Biological Implications

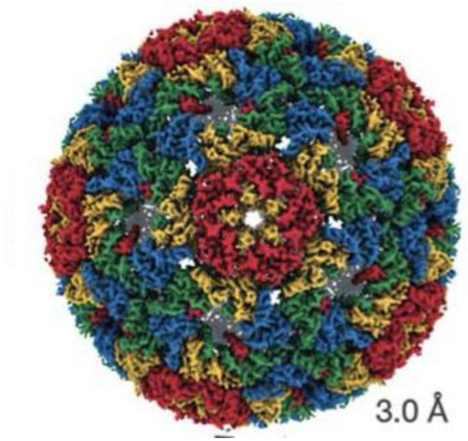
Insights into mechanisms:





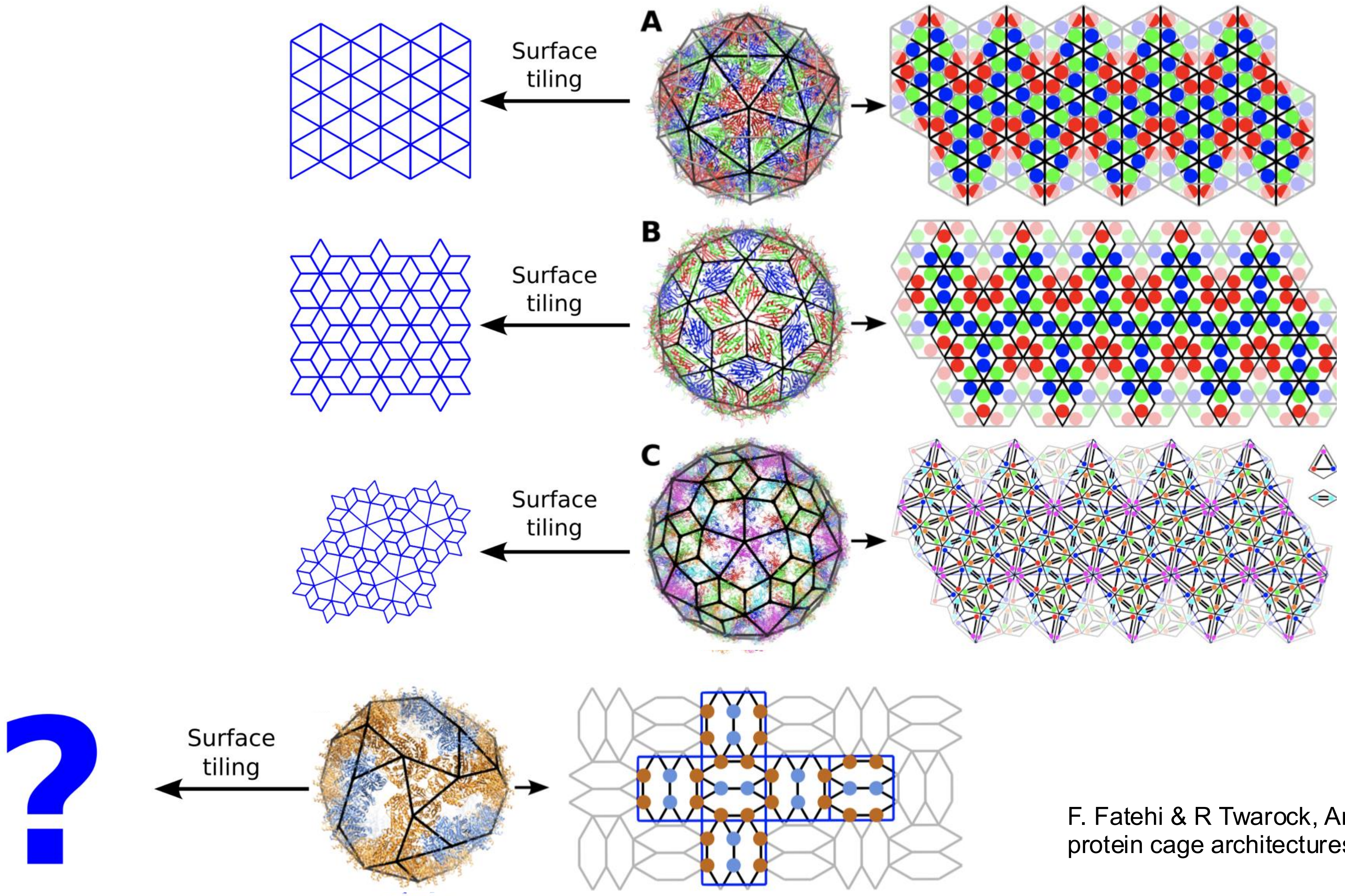
Additional capsid components are required to stabilize the capsid

A basis for exploitation in nanotechnology:



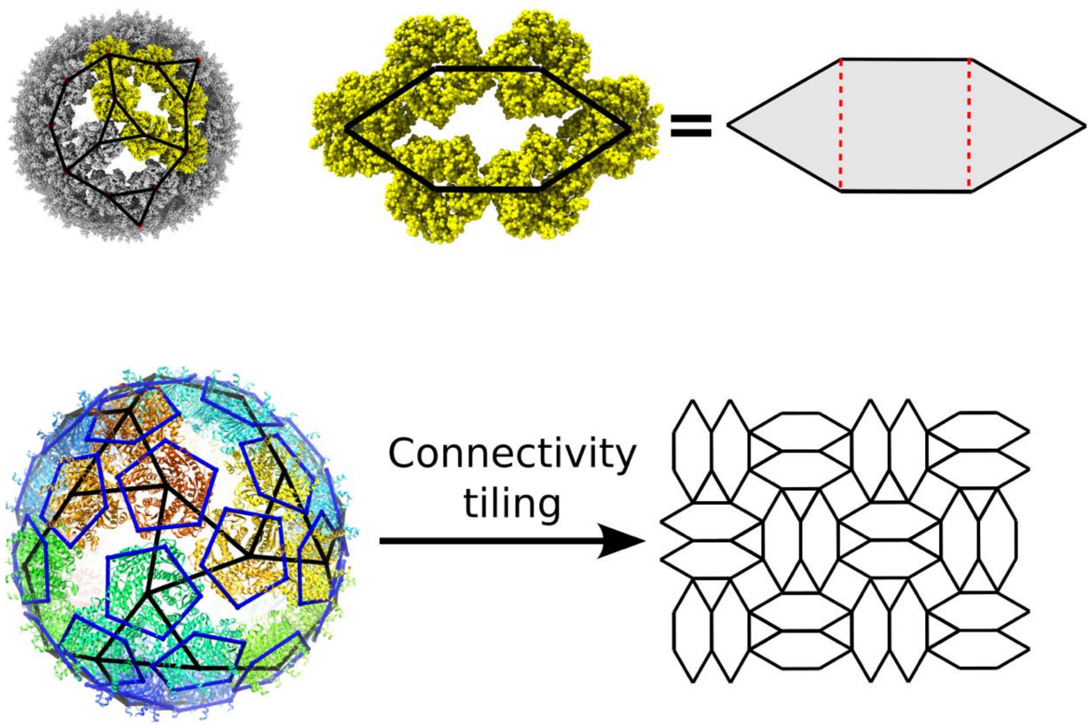
Protein-engineered capsids for applications

An interaction network approach to protein container structure prediction

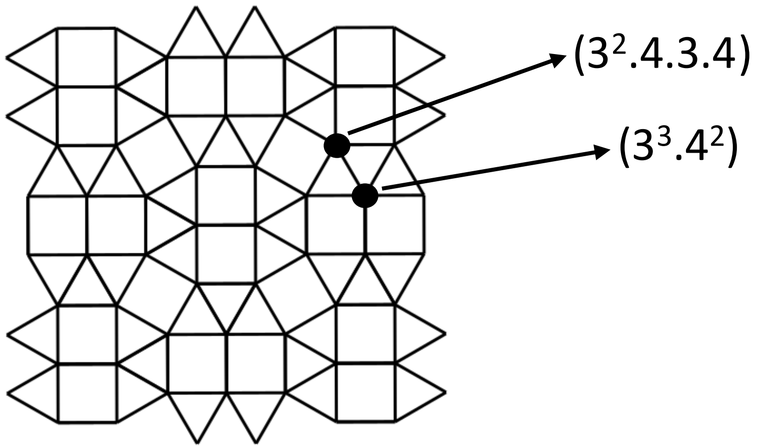


F. Fatehi & R Twarock, An interaction network approach predicts protein cage architectures in bionanotechnology, *PNAS*, 2023

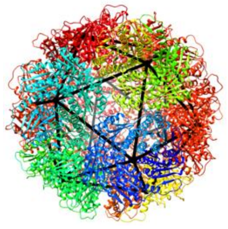
The Interaction Network Approach is Predictive



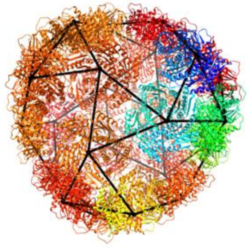
***k*-uniform tilings are required:** tilings of the plane by convex regular polygons, connected edge-to-edge, with *k* types of vertices.



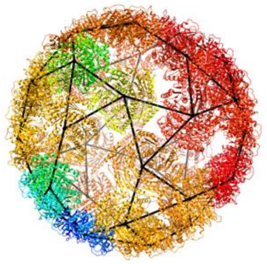
$(3^3.4^2,3^2.4.3.4)$ tiling



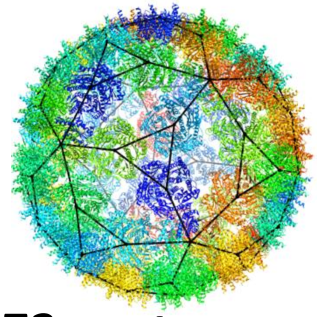
12 pentamers



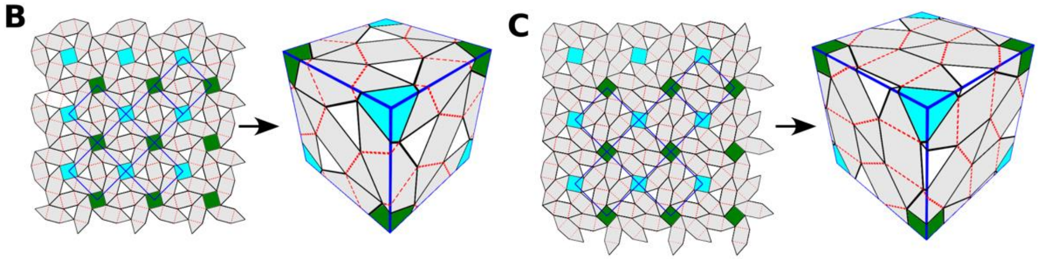
24 pentamers



36 pentamers

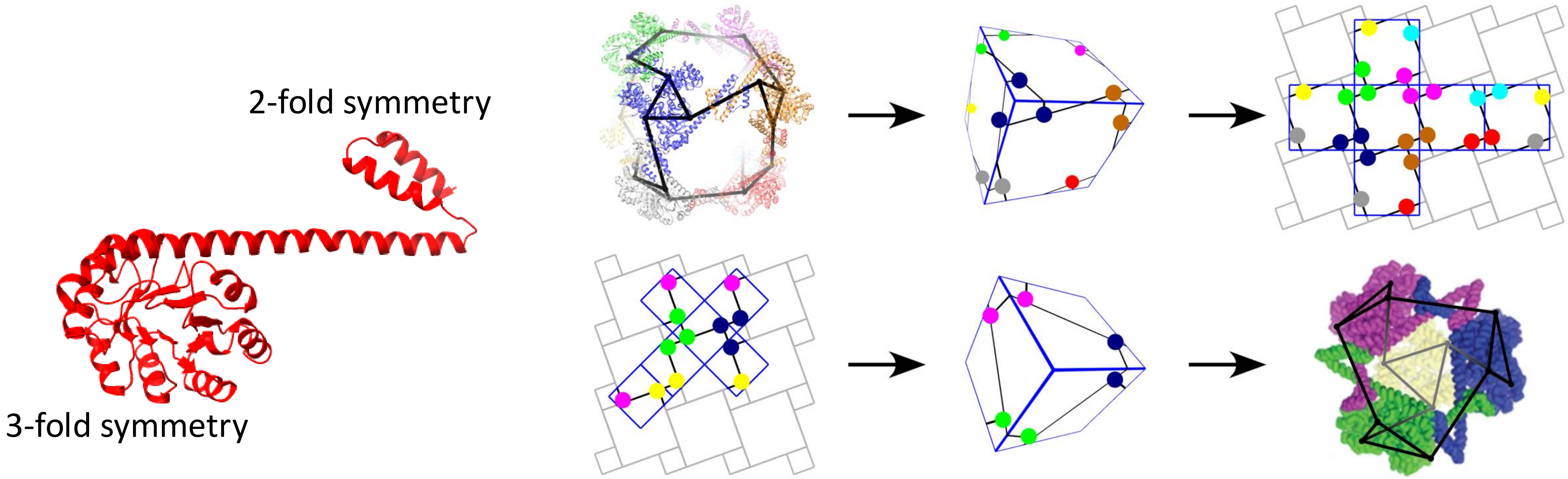


72 pentamers



Particle architectures that have not yet been observed.

Predictive Power of the Approach



- An interaction network can be associated with a tiling (connectivity tiling).
- Connectivity tilings can be used to predict other cage structures.

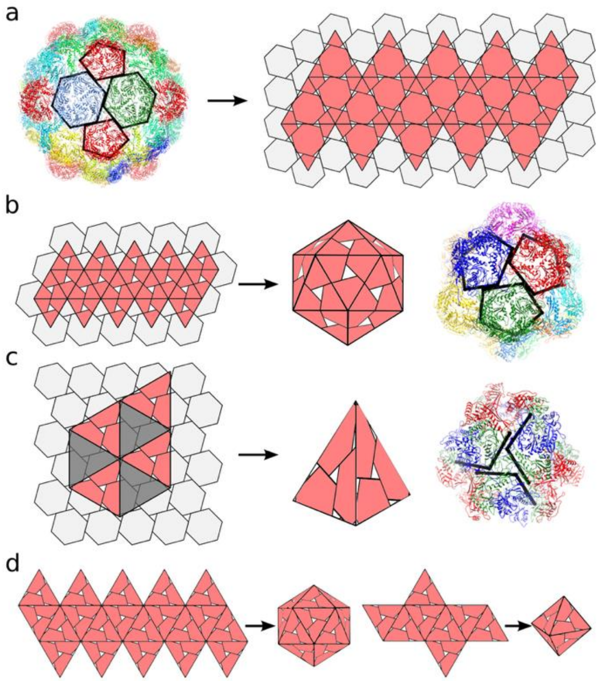
Lai et al, Nat Chem 2014: fusing two natural protein oligomers using a continuous alpha-helical linker to design a novel protein that self assembles into a 750 kDa, 225 Å diameter, cube-shaped cage

YT Lai, et al., Designing and defining dynamic protein cage nanoassemblies in solution. Sci. 415 Adv. 2, e1501855 (2016).

Virus-like Protein Cages in Nanotechnology

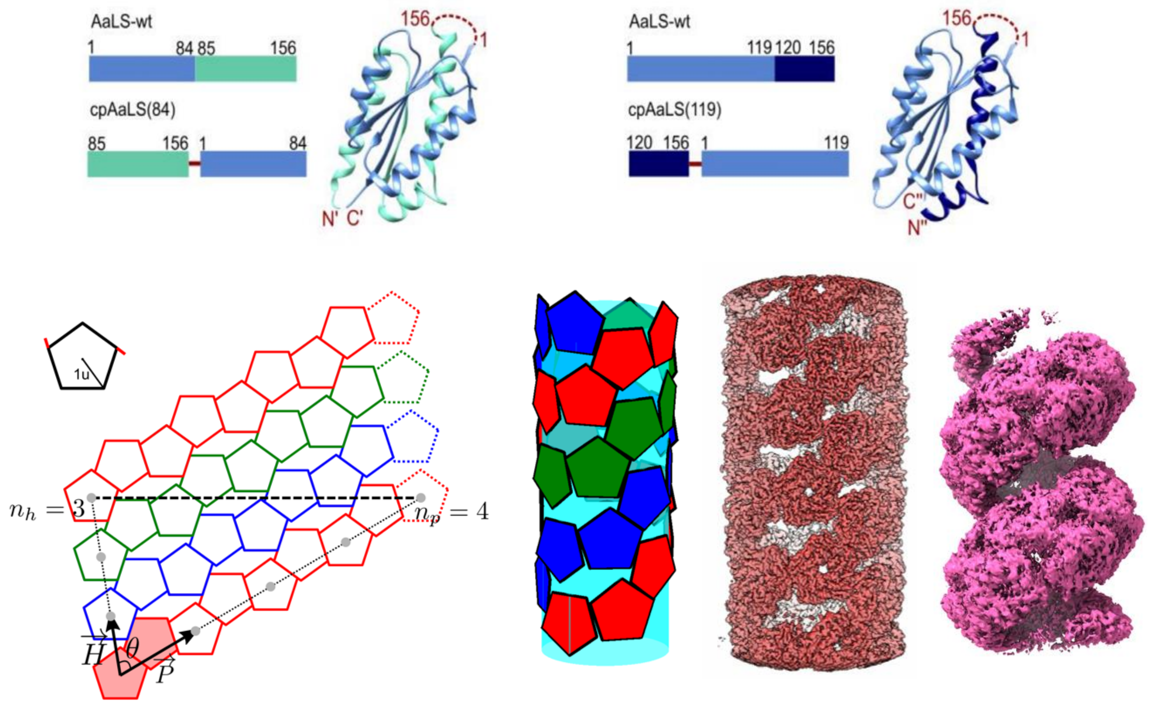
Point mutations in a virus-like capsid can drive the assembly of novel symmetry-reduced structures.

Triple mutant of an encapsulin (*Myxococcus xanthus),* a 180-mer bacterial capsid that adopts the viral HK97 fold, results in a tetrahedral particle.



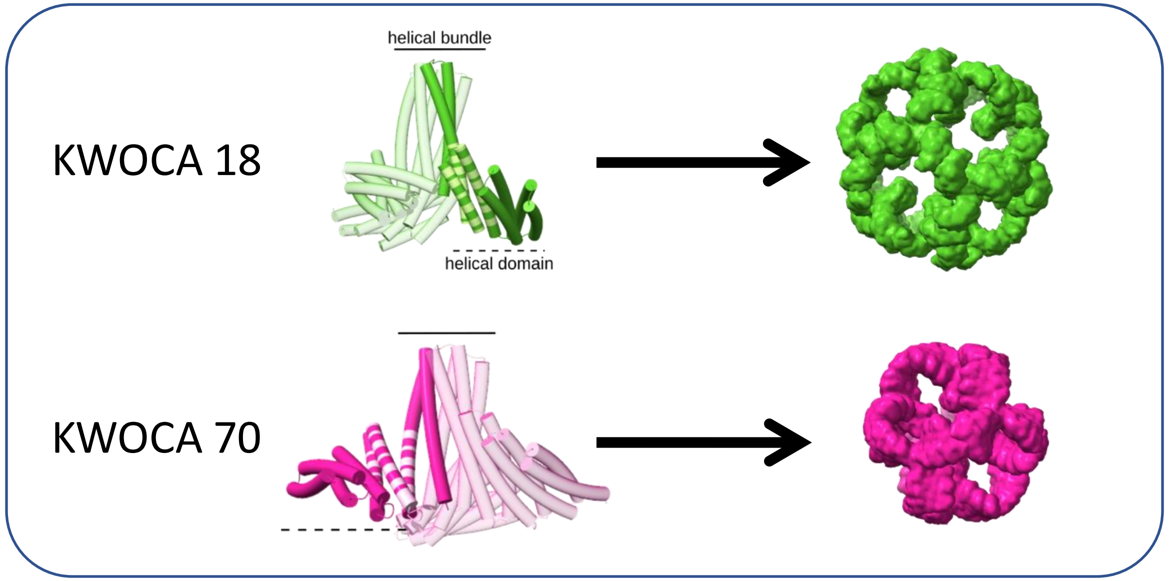
Taylor N. Szyszka et al. (2024) “Point mutation in a virus-like capsid drives symmetry reduction to form tetrahedral cages”, PNAS 121 (20) e2321260121.

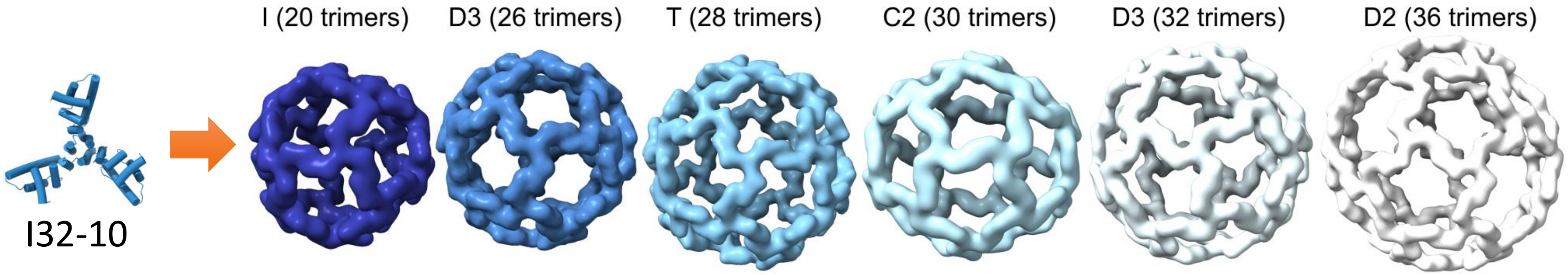
Controlled geometry of a non-quasi-equivalent all-pentamer protein cage



L. Koziej, F. Fatehi, M. Aleksejczuk, M. Byrne, N. Ranson, J.G. Heddle, R. Twarock & Y. Azuma (2025) “Controlled geometry of non-quasi-equivalent all-pentamer protein cage.”, *ACS Nano.*

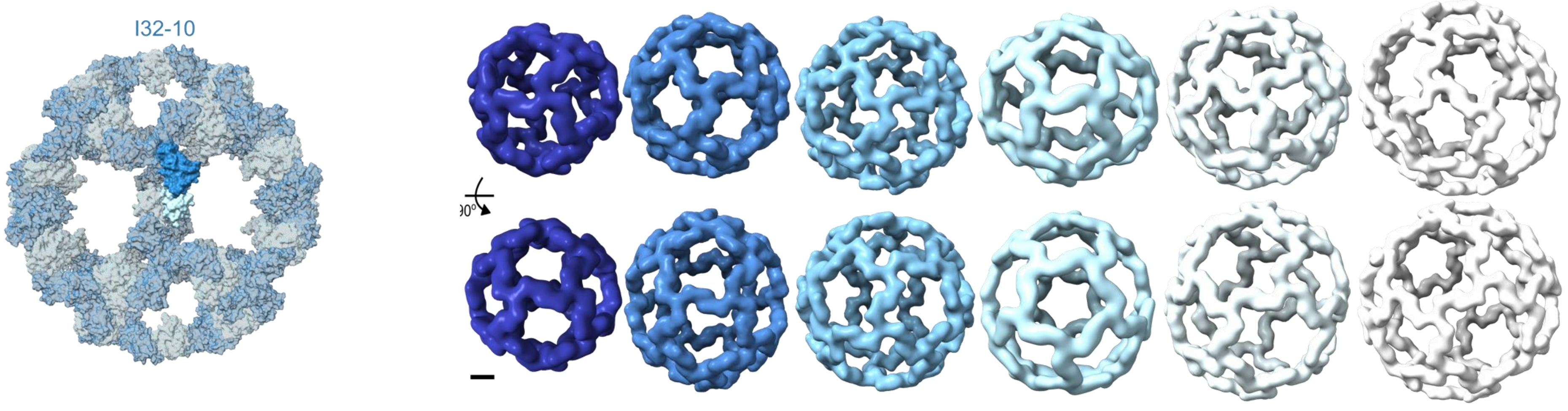
Polymorphism in *de novo* designed protein cages

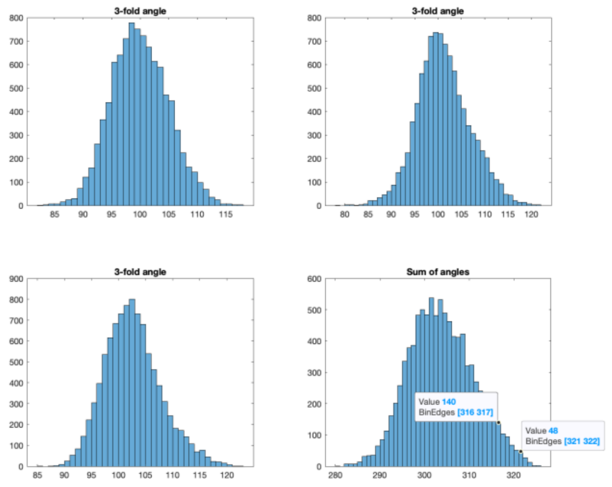


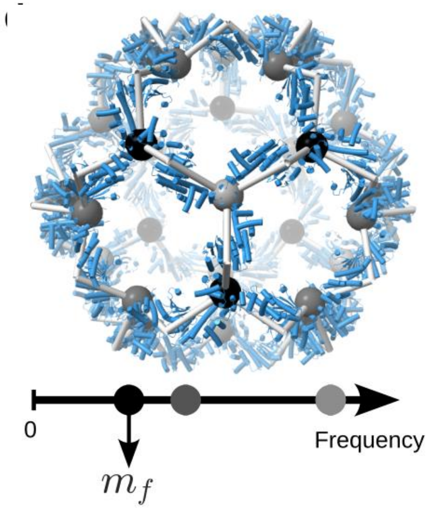


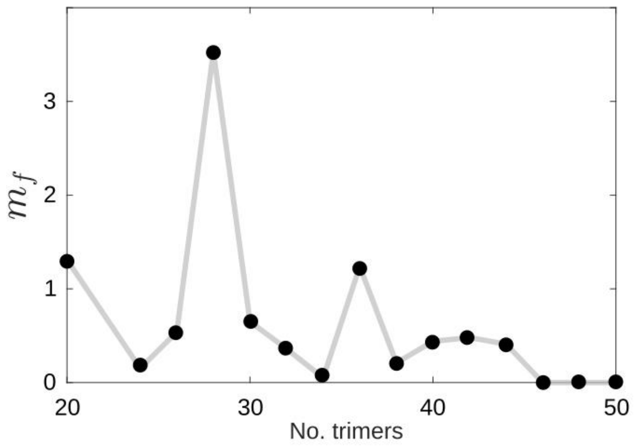
A. Khmelinskaia, N.P. Bethel, F. Fatehi, A. Antanasijevic, A.J. Borst, S.H. Lai, J.Y.J. Wang, B.B. Mallik, M.C. Miranda, A.M. Watkins, C. Ogohara, S. Caldwell, M. Wu, A.J.R. Heck, D. Veesler, A.B. Ward, D. Baker, R. Twarock, N.P. King (2025) “Local structural flexibility drives oligomorphism in computationally designed protein assemblies.” *Nature Structural Molecular Biology*

Predictive Control of Cage Geometry

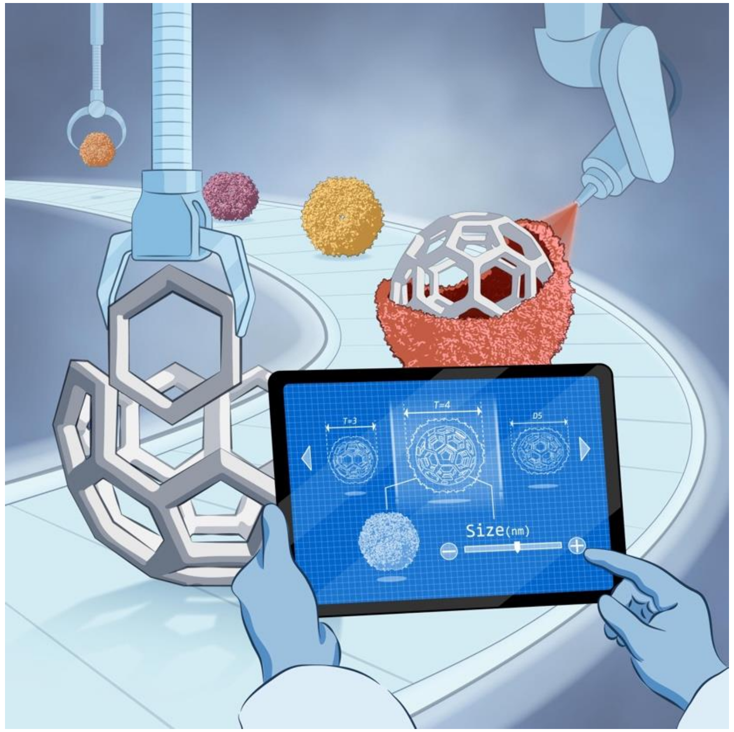








We have come a long way in controlling particle morphology…

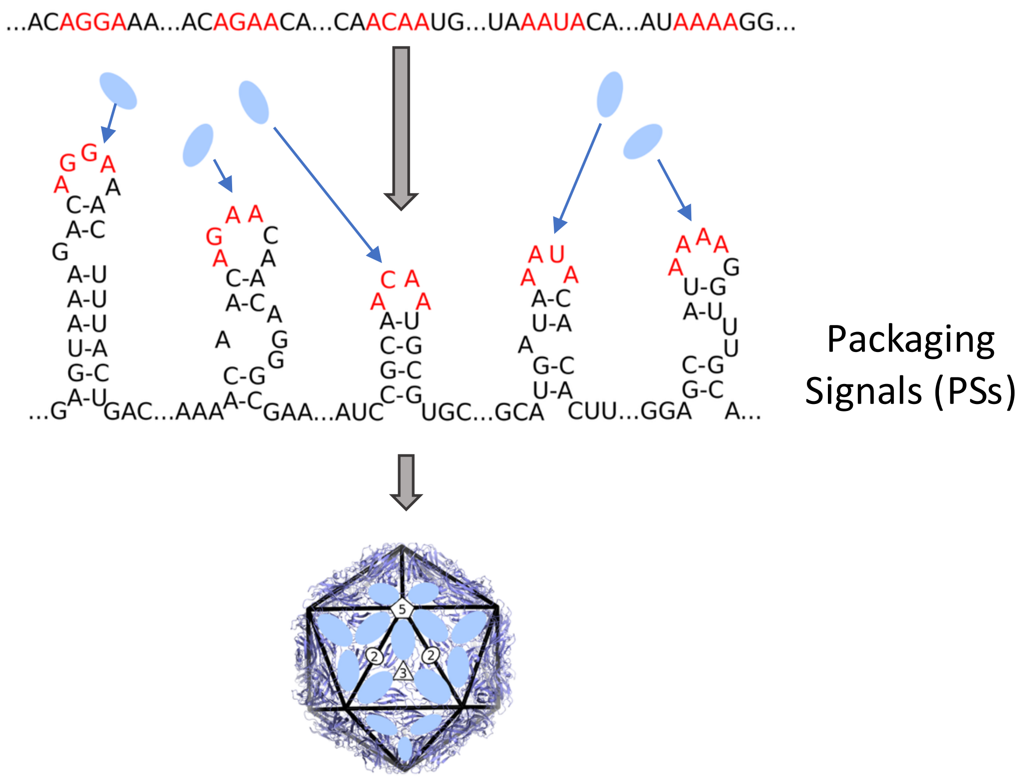


…but this is not the whole story:

Viral genomes play cooperative roles in virus assembly

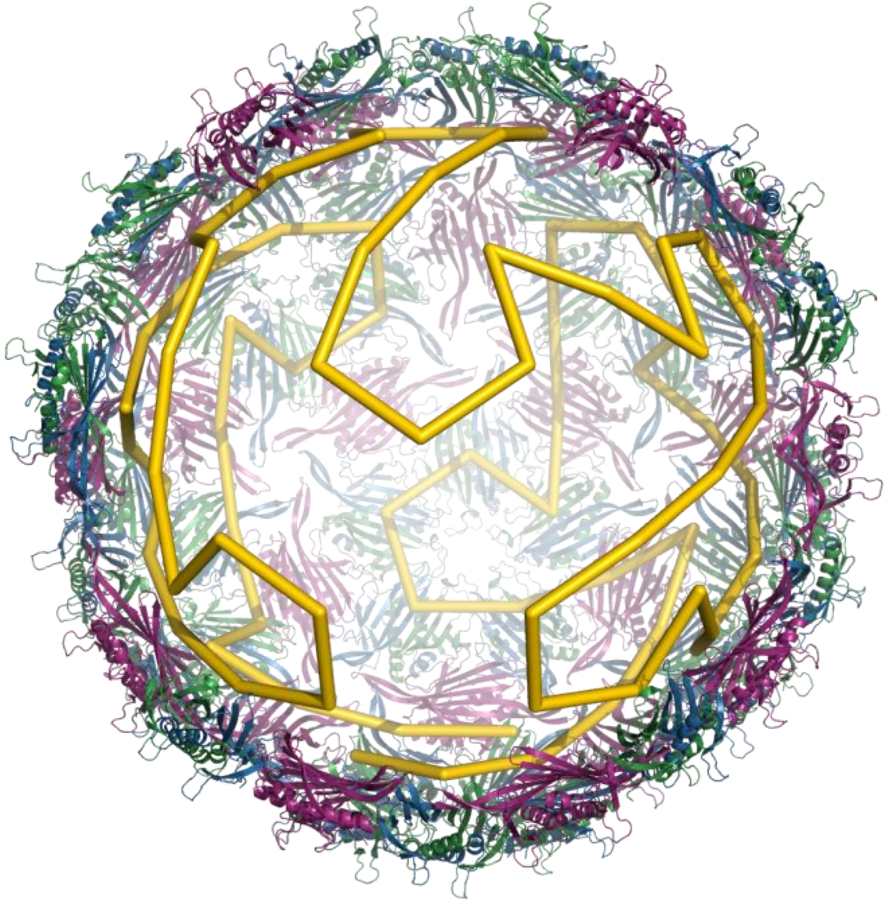
Biela, A.P., Naskalska, A., Fatehi, F. *et al.* Programmable polymorphism of a virus-like particle. *Commun Mater* 3, 7 (2022).

Discovery of a virus assembly mechanism

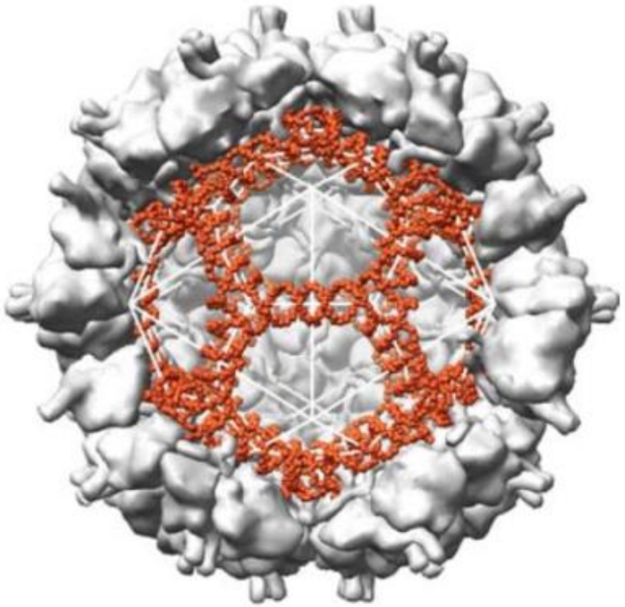


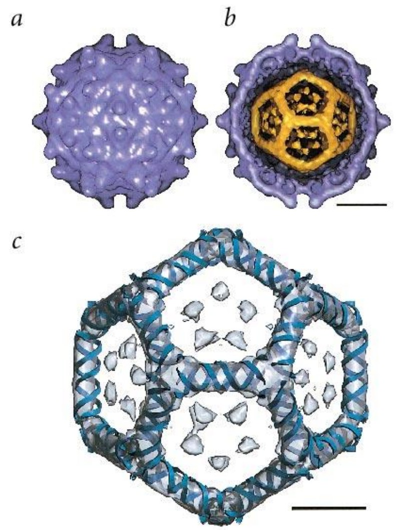
- R. Twarock, R.J. Bingham, E.C. Dykeman & P.G. Stockley (2018) A modelling paradigm for RNA virus assembly, *Curr. Opin. Virol.* 30, 1.
- R. Twarock & P.G. Stockley, RNA-Mediated Virus Assembly: Mechanisms and Consequences for Viral Evolution and Therapy, Annu. Rev. Biophys., 2019

Viral Geometry Informed Data Analysis



The Mathematical Challenge





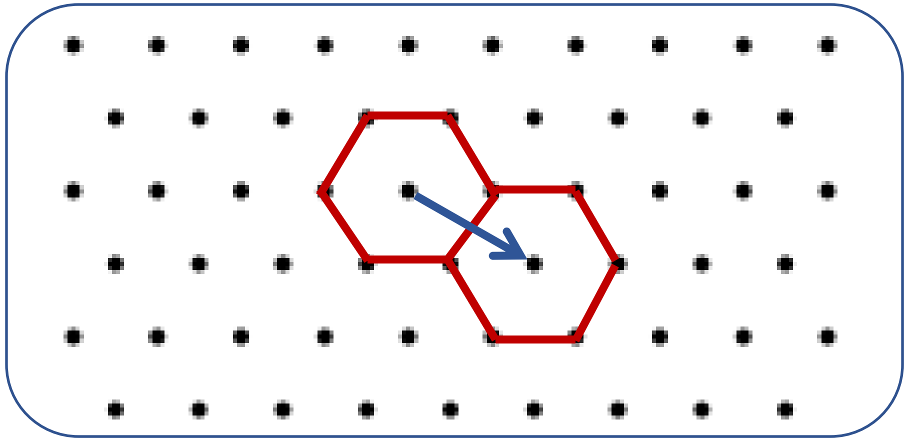
Pariacoto virus

We need to understand virus architecture in 3 dimensions:

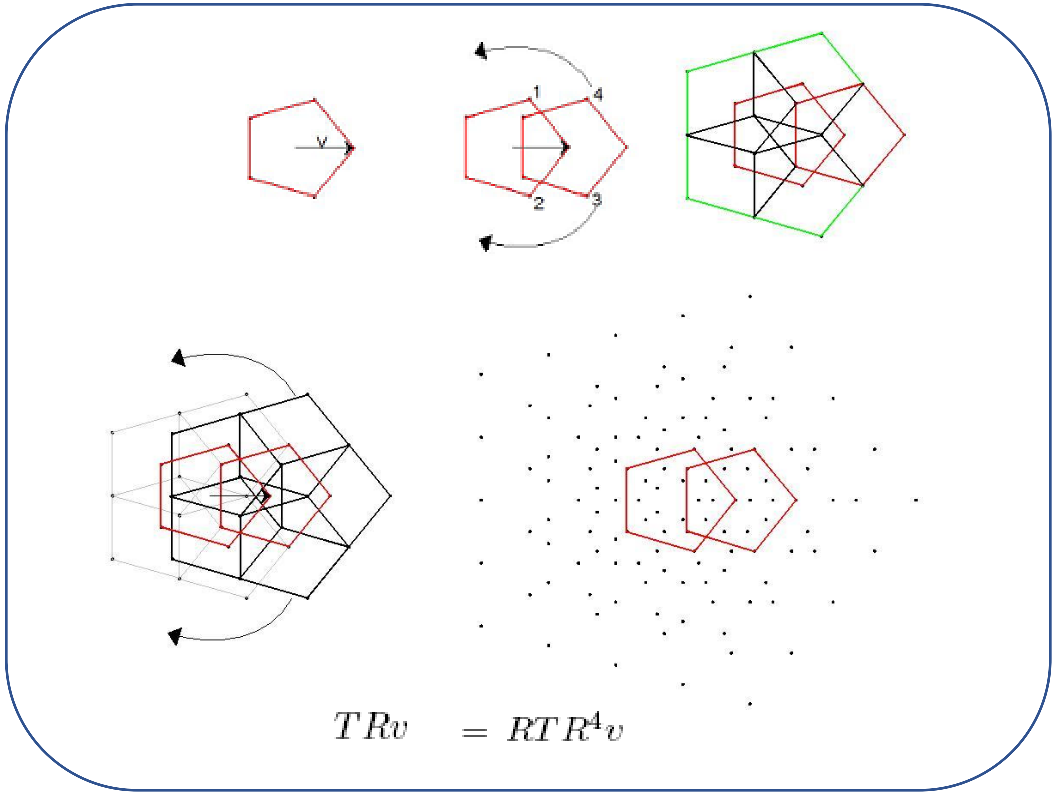
Surface lattices are insufficient!

Linking Lattices with Symmetry Groups

Affine extended symmetry groups generate lattices:



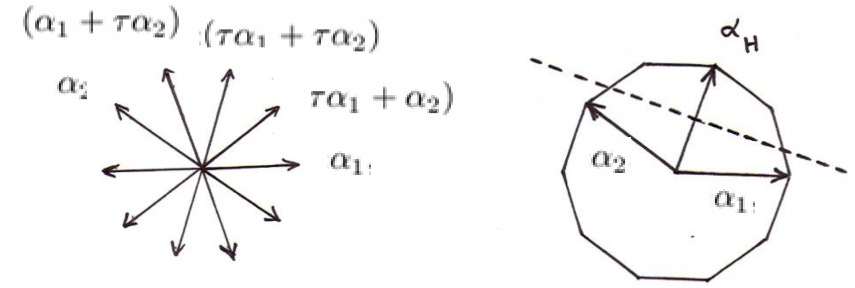
By analogy: Construct affine extensions of noncrystallographic symmetry groups



The Noncrystallographic Coxeter Group H_2: Tilings & Affine Extensions

The root system of H_2 encoding reflections:

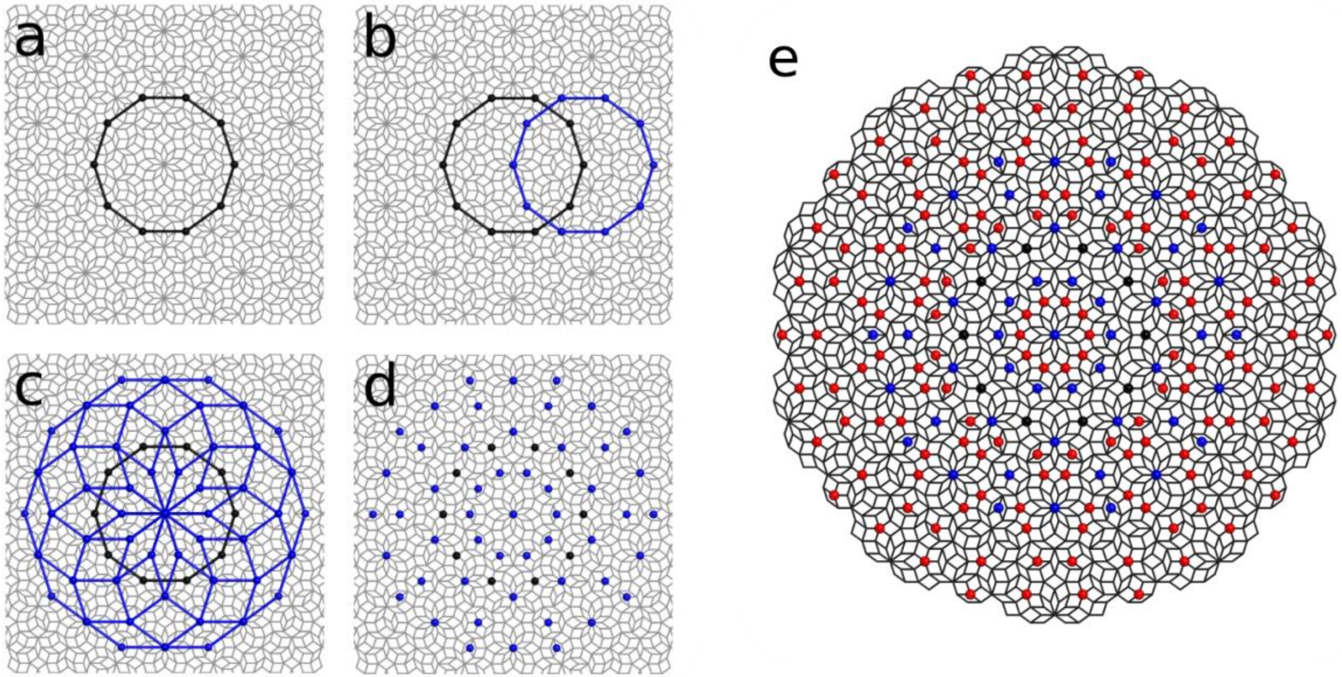
$$\{\pm\alpha_1,\ \pm\alpha_2,\ \pm(\alpha_1+\tau\alpha_2),\ \pm(\tau\alpha_1+\alpha_2),\ \pm(\tau\alpha_1+\tau\alpha_2)\}$$



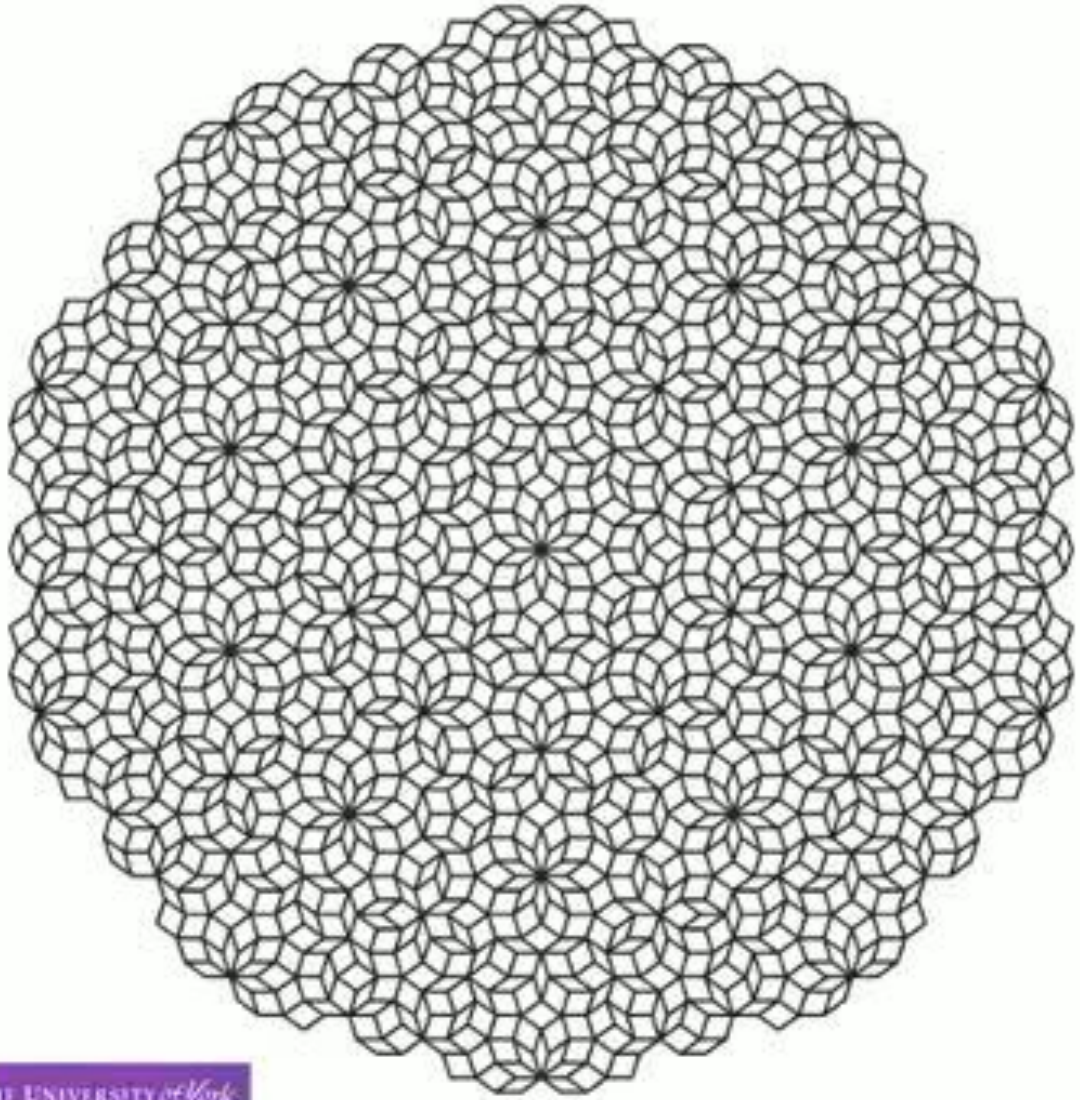
$$\tau := \frac{1}{2}(1+\sqrt{5}) \qquad \mathbb{Z}[\tau] := \{a+\tau b\,|\,a,b\in\mathbb{Z}\}\,.$$

The Kac-Moody formalism gives an additional affine reflection

$$\begin{pmatrix} 2 & \tau \\ \tau & 2 \end{pmatrix} \longrightarrow \begin{pmatrix} 2 & \tau' & \tau' \\ \tau' & 2 & -\tau \\ \tau' & -\tau & 2 \end{pmatrix}$$



Affine Extensions of Decagonal Symmetry



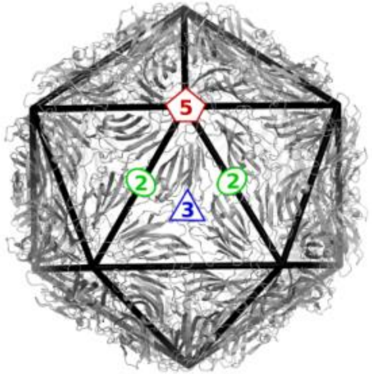
Here we display a Penrose tiling generated via the canonical projection.

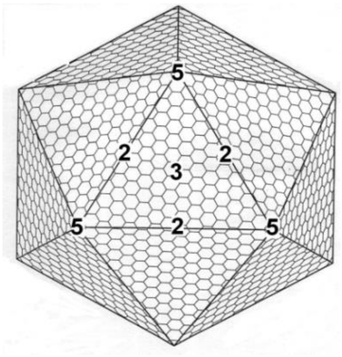
THE UNIVERSITY of York

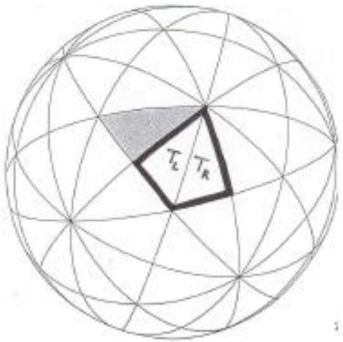
UNIVERSITY OF LEEDS

The Noncrystallographic Coxeter Group H_3

We are interested in icosahedral symmetry: $I = \langle r_5, r_2 | r_5^5 = r_2^2 = (r_5 r_2)^3 = id \rangle$

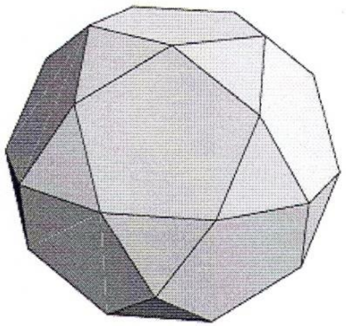


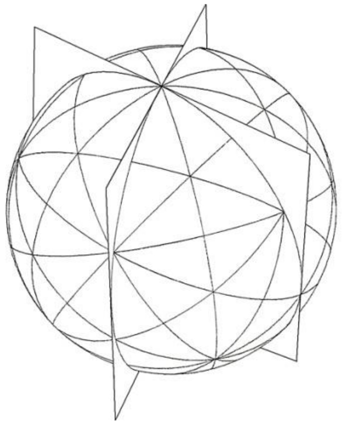




The reflections generating the rotations of icosahedral symmetry are encoded by the 30 vectors pointing to the vertices of an icosidodecahedron:

$$\Delta_3 = \left\{ \begin{array}{ll} (\pm 1, 0, 0) & \text{and all permutations} \\ \frac{1}{2}(\pm 1, \pm\tau', \pm\tau) & \text{and all even permutations} \end{array} \right.$$

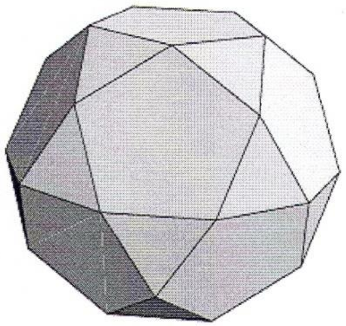


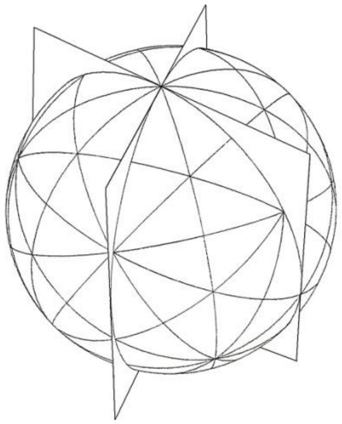


Affine Extended Symmetry Groups

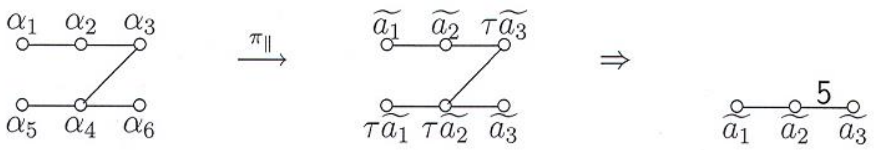
The reflections generating the rotations of icosahedral symmetry are encoded by the 30 vectors pointing to the vertices of an icosidodecahedron:

$$\Delta_3 = \left\{ \begin{array}{cl} (\pm 1, 0, 0) & \text{and all permutations} \\ \frac{1}{2}(\pm 1, \pm\tau', \pm\tau) & \text{and all even permutations} \end{array} \right.$$





The projection in terms of Dynkin diagrams:

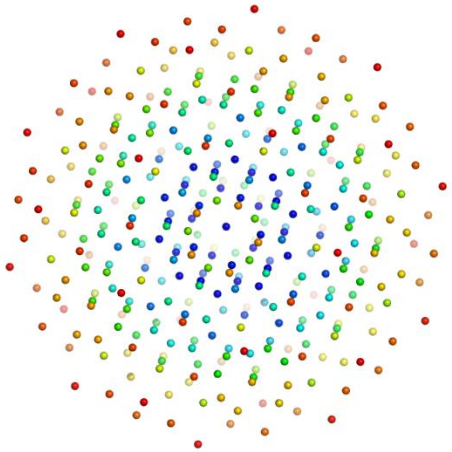


With $\tau = \frac{1}{2}(1+\sqrt{5})$ and $\tau' = \frac{1}{2}(1-\sqrt{5})$:

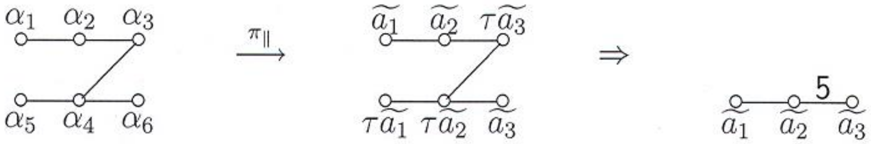
$$\begin{array}{lll} \alpha_1 \mapsto \widetilde{a_1} = \frac{1}{2}(-\tau', 1, -\tau) & & \alpha_2 \mapsto \widetilde{a_2} = \frac{1}{2}(1, -\tau, -\tau') \\ \alpha_3 \mapsto \tau\widetilde{a_3} = \frac{1}{2}(-\tau, -\tau^2, 1) & & \alpha_4 \mapsto \tau\widetilde{a_2} = \frac{1}{2}(\tau, -\tau^2, 1) \\ \alpha_5 \mapsto \tau\widetilde{a_1} = \frac{1}{2}(1, -\tau, -\tau^2) & & \alpha_6 \mapsto \widetilde{a_3} = \frac{1}{2}(-1, \tau, -\tau') . \end{array}$$

$$\begin{pmatrix} 2 & -1 & 0 \\ -1 & 2 & -\tau \\ 0 & -\tau & 2 \end{pmatrix} \longrightarrow \begin{pmatrix} 2 & 0 & \tau' & 0 \\ 0 & 2 & -1 & 0 \\ \tau' & -1 & 2 & -\tau \\ 0 & 0 & -\tau & 2 \end{pmatrix}$$

The standard formalism determines the translation to be a translation by the highest root vector. An iterative application leads to nested point sets.



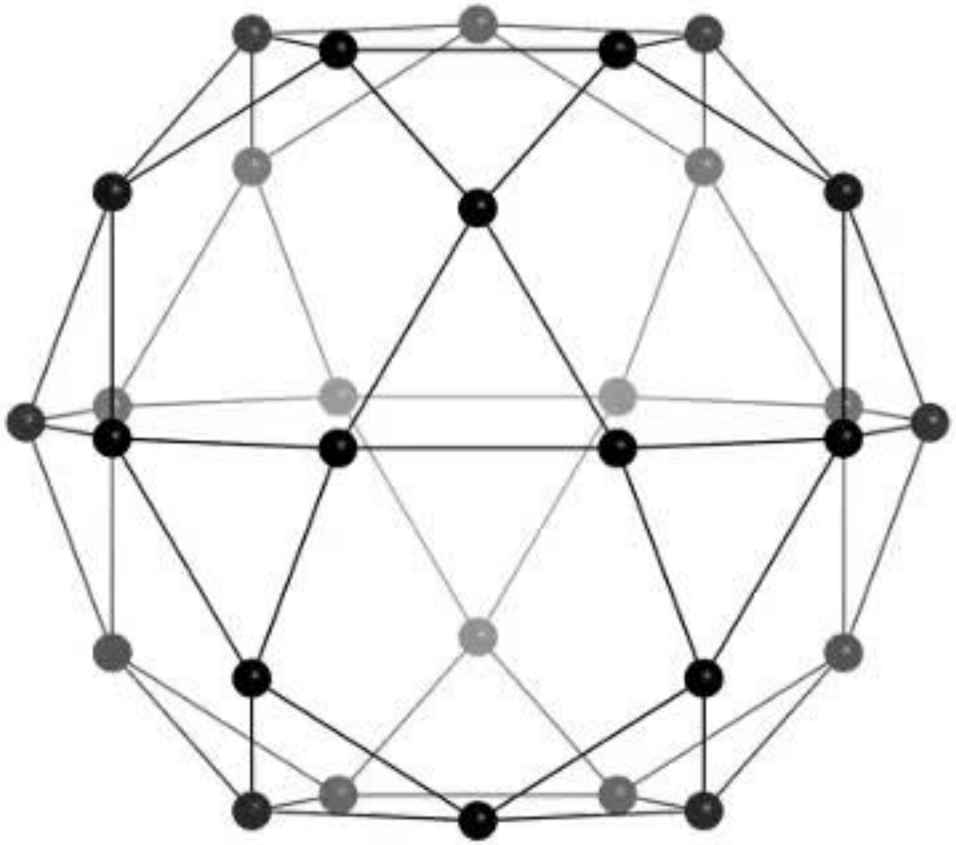
In terms in terms of Dynkin diagrams:



With $\tau = \frac{1}{2}(1+\sqrt{5})$ and $\tau' = \frac{1}{2}(1-\sqrt{5})$:

$$\begin{aligned} \alpha_1 &\mapsto \widetilde{a_1} = \tfrac{1}{2}(-\tau', 1, -\tau) & \alpha_2 &\mapsto \widetilde{a_2} = \tfrac{1}{2}(1, -\tau, -\tau') \\ \alpha_3 &\mapsto \tau\widetilde{a_3} = \tfrac{1}{2}(-\tau, -\tau^2, 1) & \alpha_4 &\mapsto \tau\widetilde{a_2} = \tfrac{1}{2}(\tau, -\tau^2, 1) \\ \alpha_5 &\mapsto \tau\widetilde{a_1} = \tfrac{1}{2}(1, -\tau, -\tau^2) & \alpha_6 &\mapsto \widetilde{a_3} = \tfrac{1}{2}(-1, \tau, -\tau') . \end{aligned}$$

Affine Symmetry



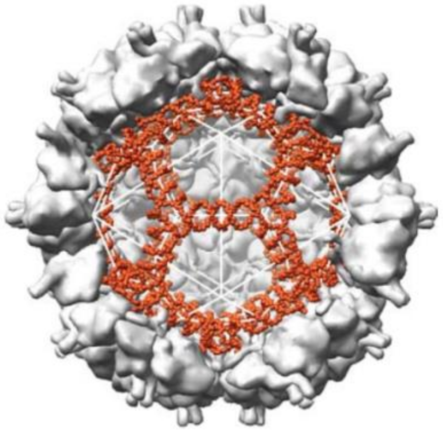
The icosidodecahedral start configuration:

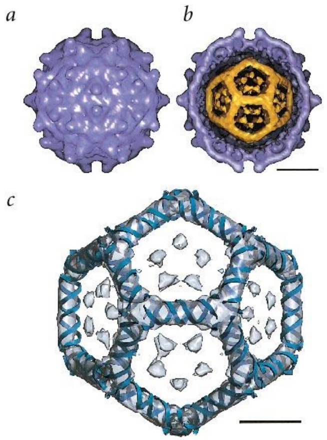
An Archimedean solid with icosahedral symmetry, composed of 12 pentagons and 20 triangles with vertices at two-fold symmetry axes.

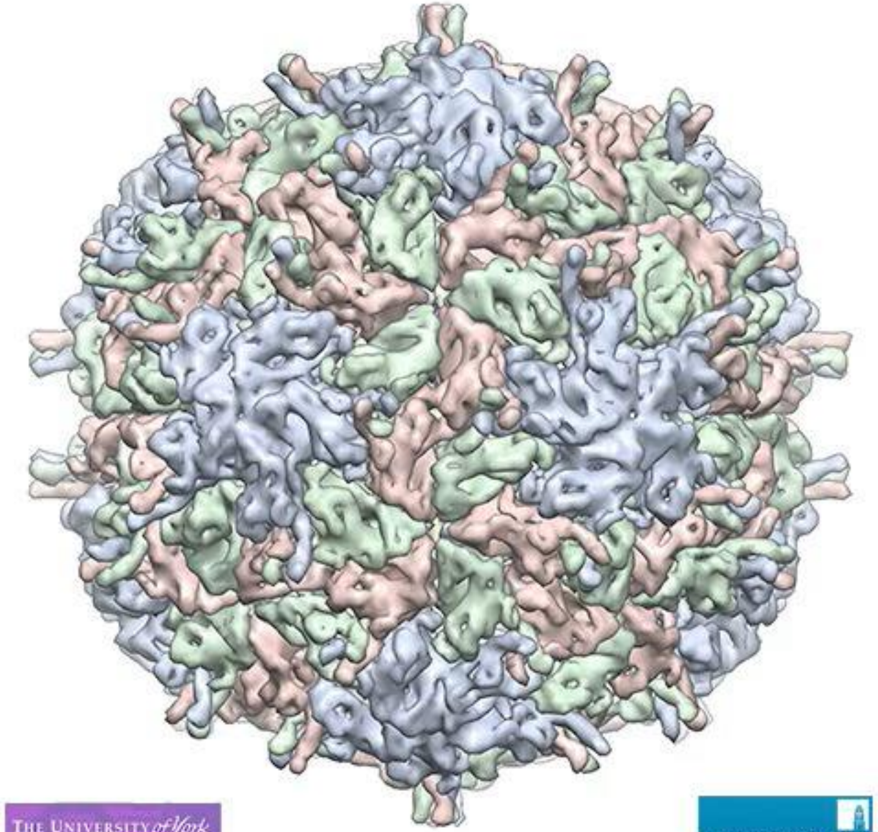
THE UNIVERSITY of York

UNIVERSITY OF LEEDS

Application to Paricoto virus





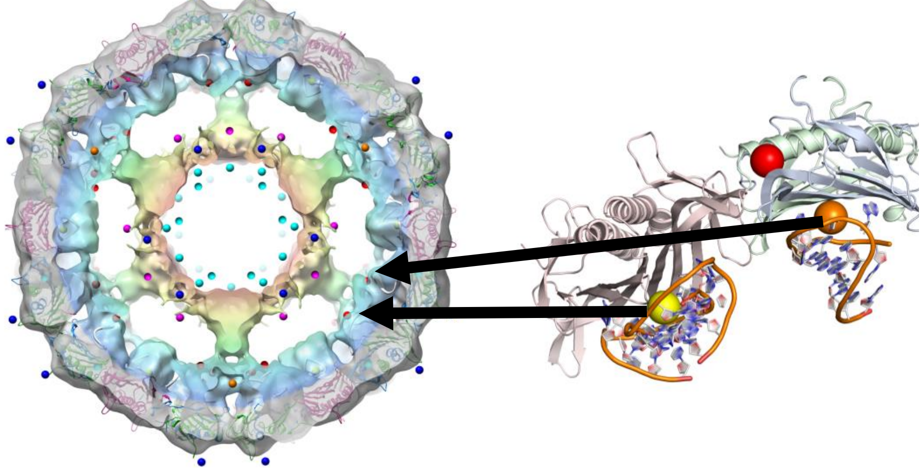


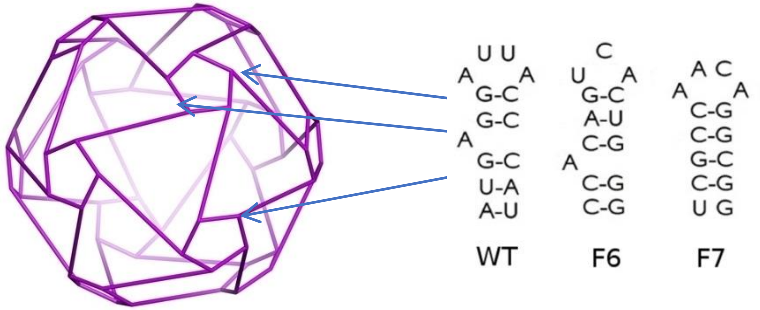
THE UNIVERSITY of York

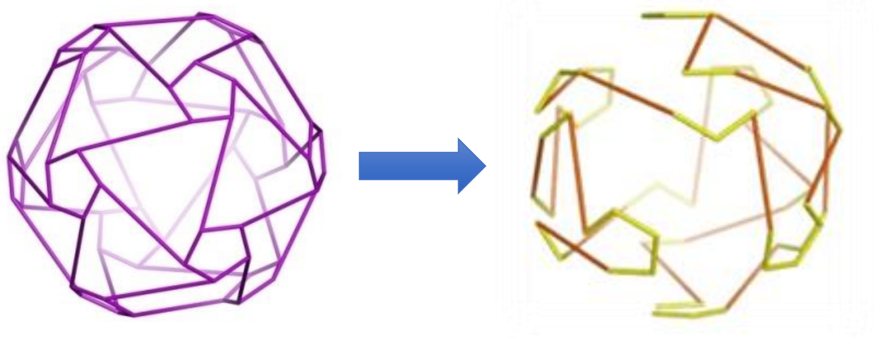
UNIVERSITY OF LEEDS

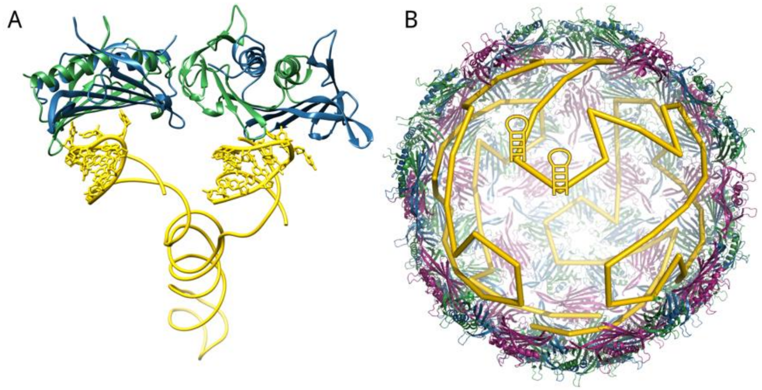
Hamiltonian Path Analysis: Decrypting Viral Genomes

Connect vertices at the binding sites into a polyhedral shape:





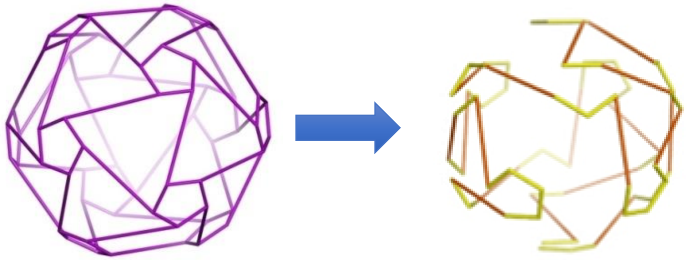




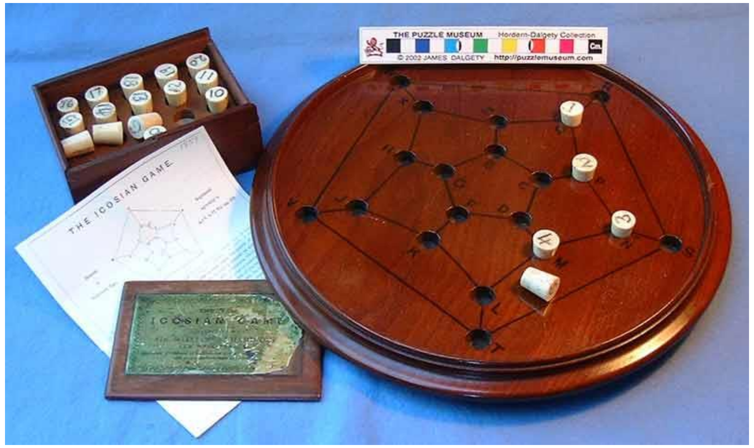
R. Twarock, G. Leonov & P.G. Stockley (2018) Hamiltonian Path Analysis of Viral Genomes, *Nature Comms.* 9, 2021.

Viruses Play the Icosian Game

There are geometric constraints on the organization of the viral genome inside the capsid:



In each particle, the RNA in proximity to capsid forms (part of) a **Hamiltonian path.**

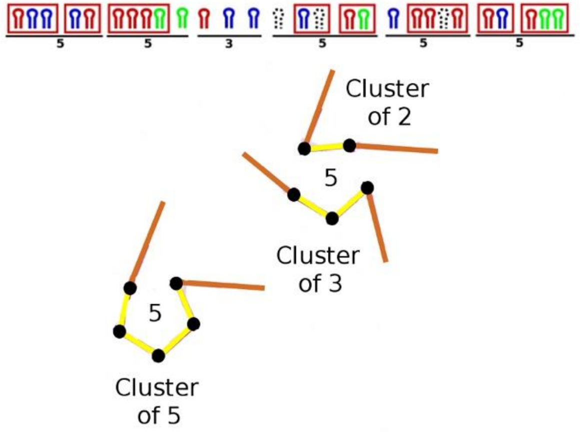


The icosian game: A board game designed by Hamilton based on the concept of Hamiltonian circuit (cycle)

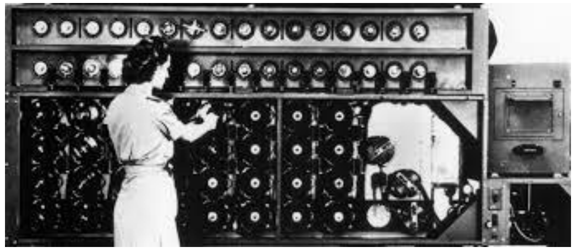
Viral Geometry & Code Breaking

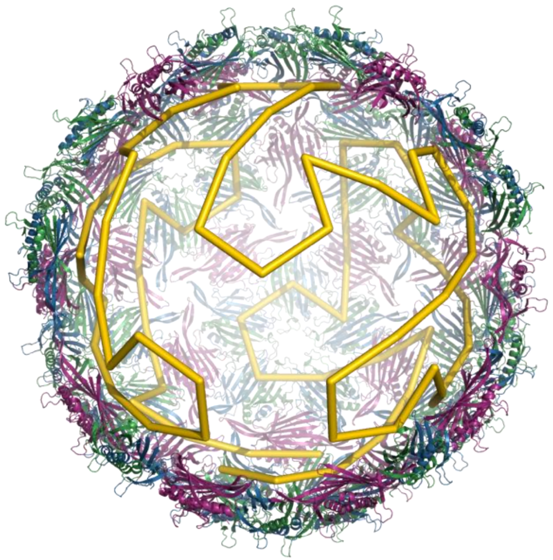
Hamiltonian Path Analysis:

Use the Hamiltonian path constraint:



PSs cluster in groups of 5, 3 or 2





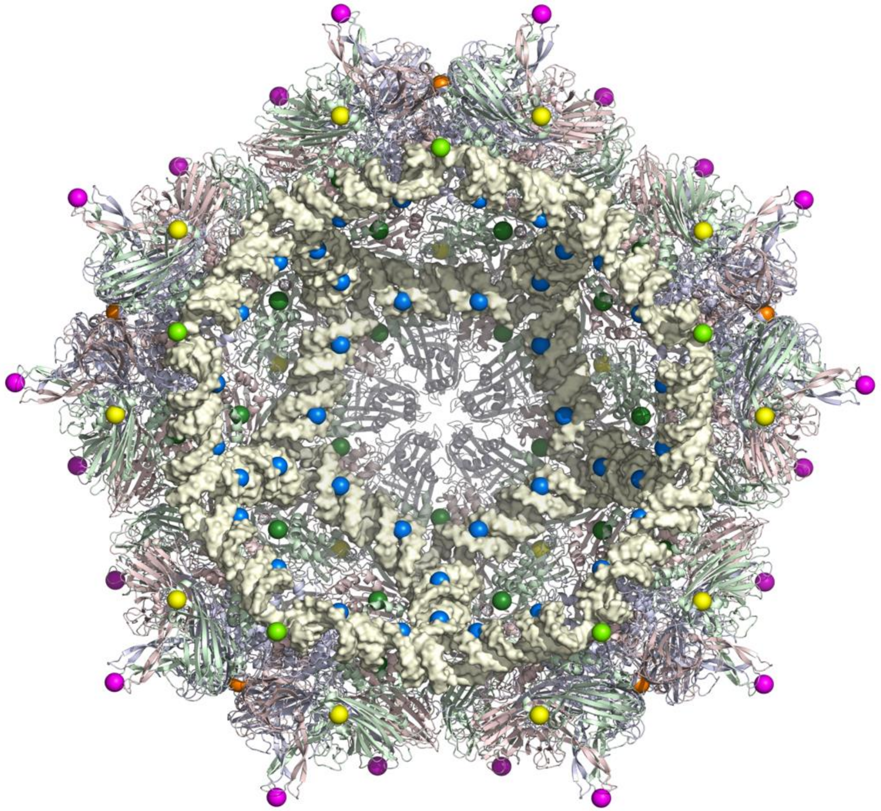
The Mathematical Microscope
enables code breaking

We have characterized the mechanism in different viruses, including:

- Hepatitis B virus
- Corona viruses
- Picornaviruses

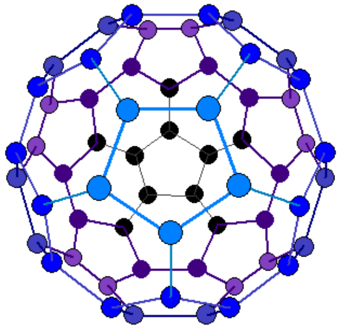
R. Twarock, G. Leonov & P.G. Stockley (2018) Hamiltonian Path Analysis of Viral Genomes, *Nature Comms.* 9, 2021.

Affine extended symmetry groups in biology and chemistry

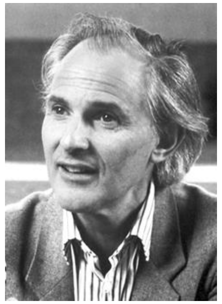


Applications in Chemistry

Fullerenes – carbon cages



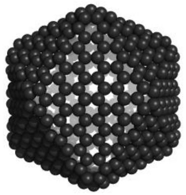
Buckyball C_{60}



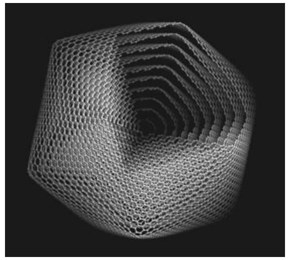
Sir Harald Kroto
Nobel Prize in
Chemistry 1996

C_{60}

C_{240}

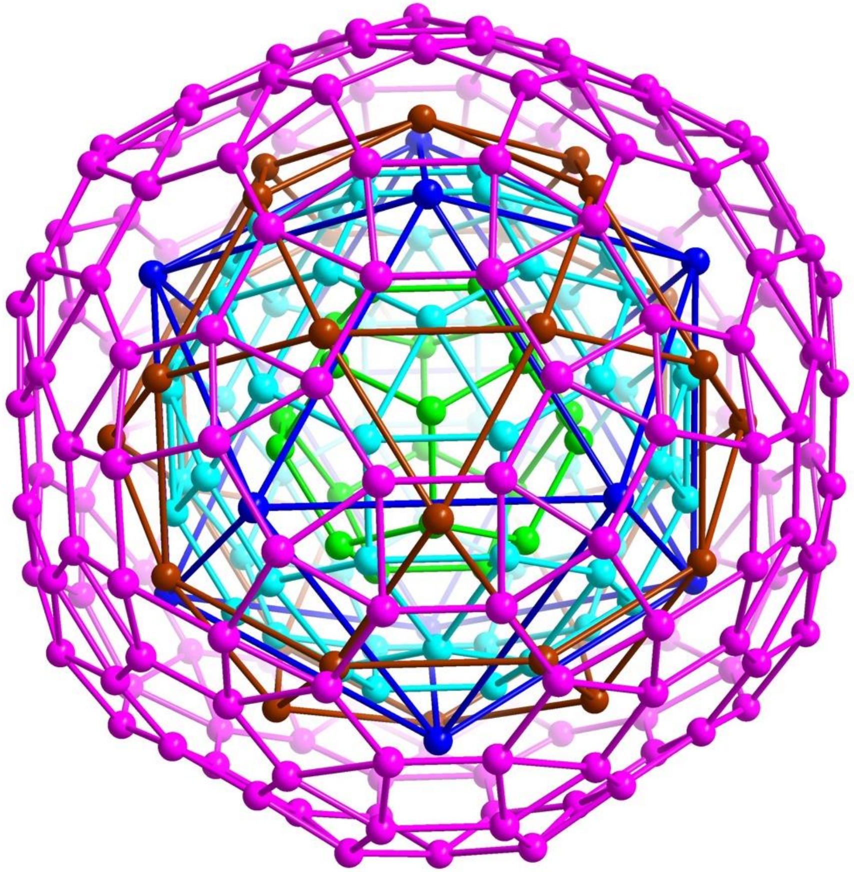


C_{540}



Adapted from
Chemistryworld

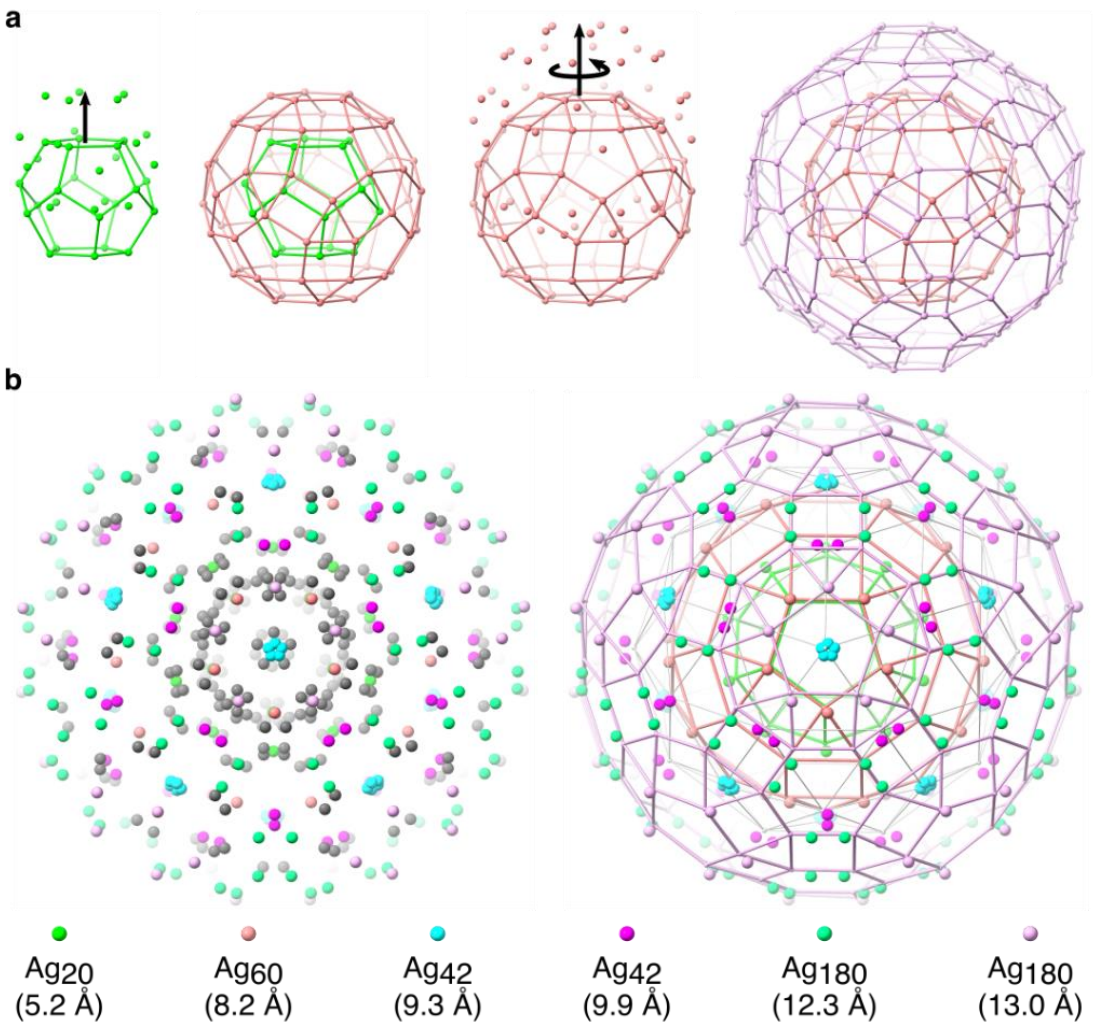
Current research: clusters of silver atoms



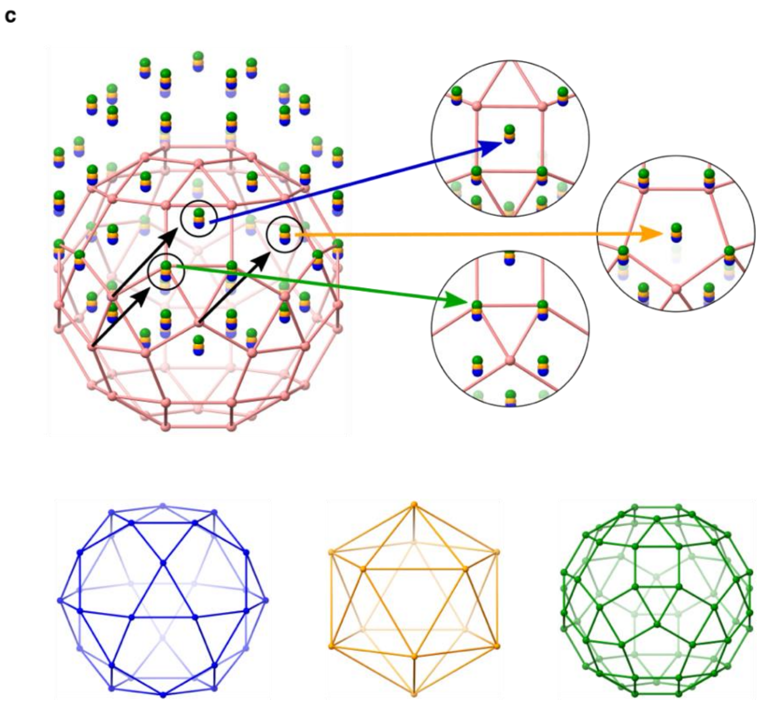
with Di Sun,
School of Chemistry and Chemical Engineering, Shandong University

Applications in Chemistry

The construction principle

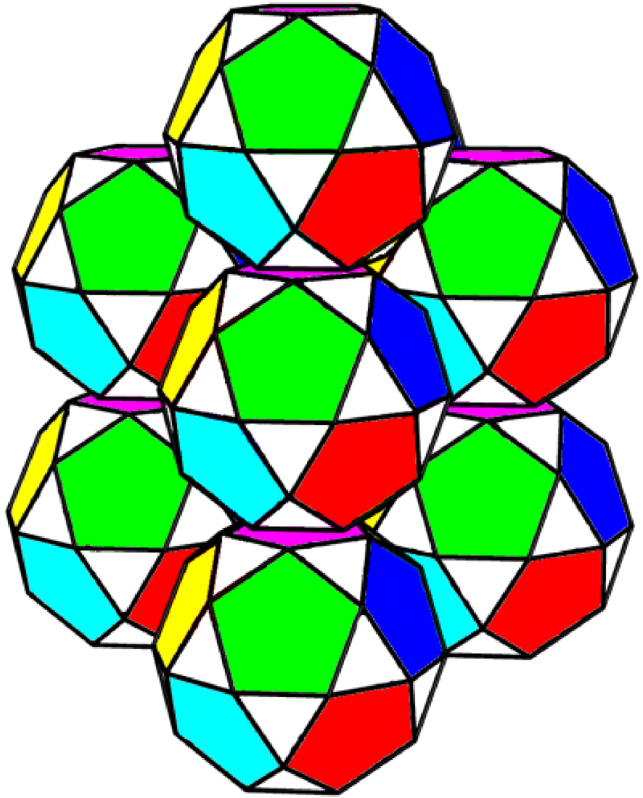


Nested "near-miss" architectures discovered

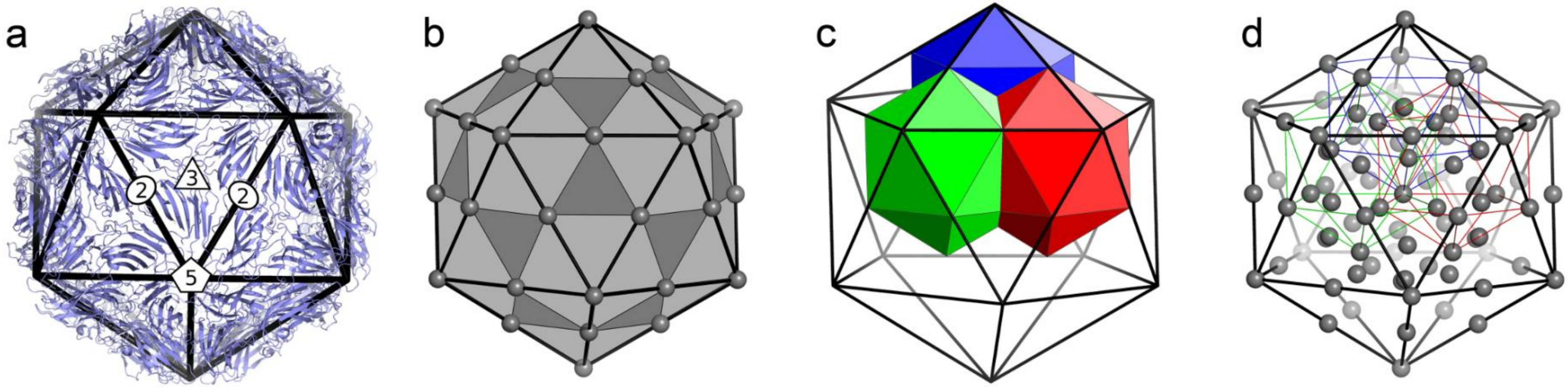


Y. Chen, Z. Wang, K. O'Brien, R Twarock & D. Sun, The Pregnant Ag_{180}: $Ag_{122}Cl_{114}(AsO_4)_{20}$ Fullerene-like Fragment Solid in Buckyball-like Silver Nanocage

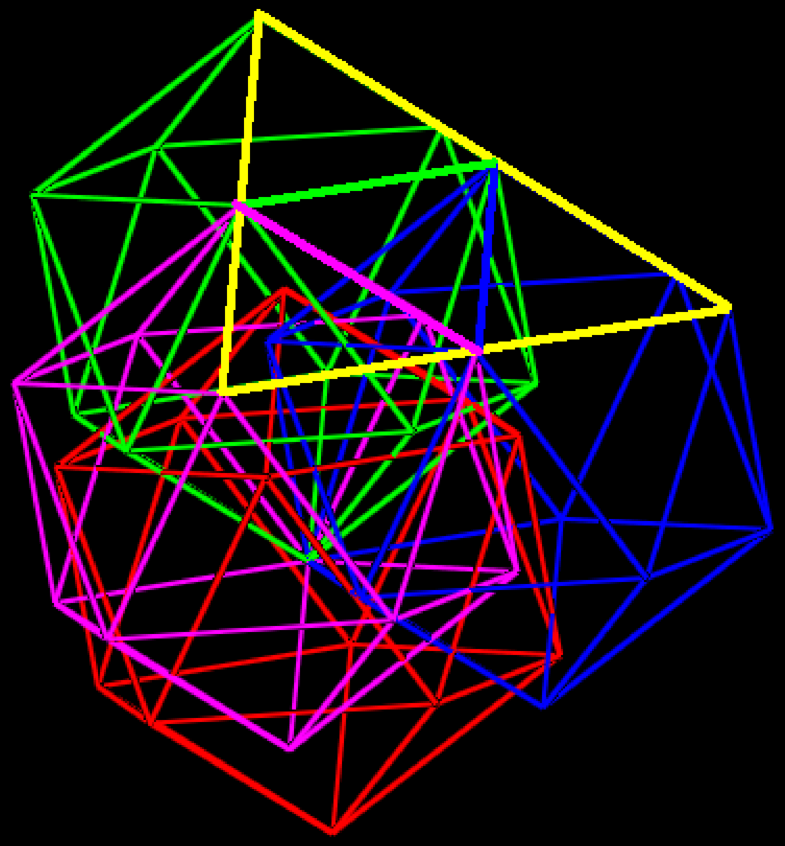
Affine extended symmetry groups and packing problems



From Groups & Symmetries to Packings



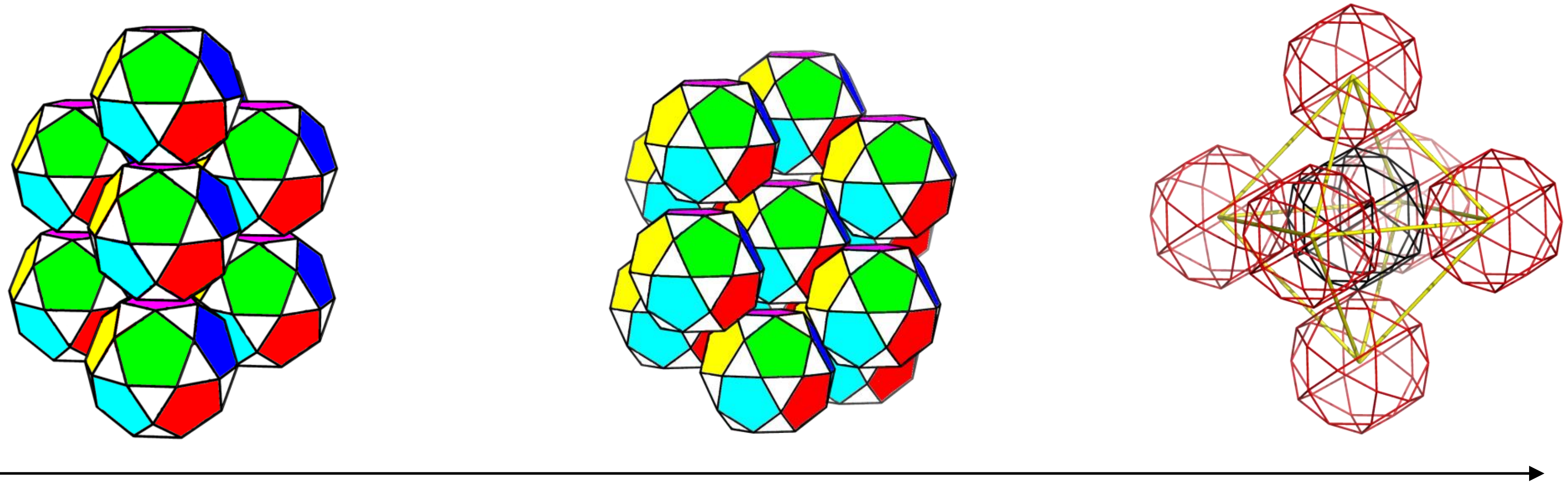
An Example in 3D: the Icosahedron



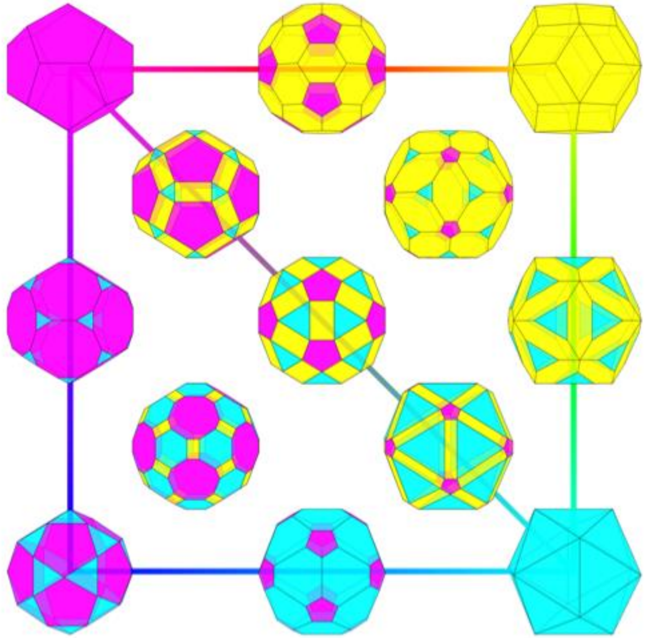
Connections with Packing Problems

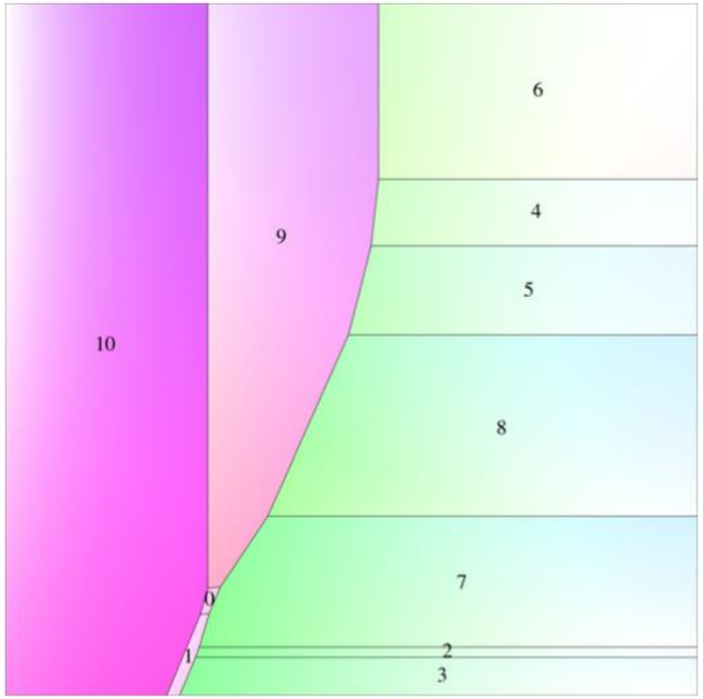
What is the densest packing of icosahedrally symmetric objects?

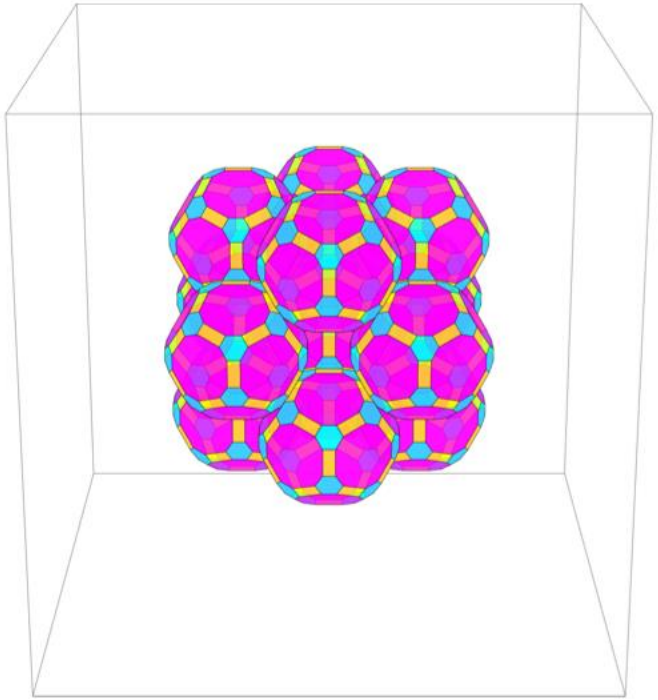
We can determine polyhedral packings via our affine extended symmetry groups



Packing density = 0.864720 0.787 0.408







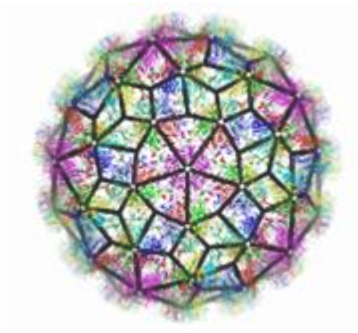
polyhedron	family	n	$\langle a,c \rangle$	ϕ numeric	ϕ analytic	ref
icosi-dodecahedron	523	1	$\langle 1,S^2 \rangle$	0.86471099	0.86472037	[32]
dodecahedron	523	1	$\langle 1,3 \rangle$	0.90448597	0.90450850	[32]
rhombic triacontahedron	523	1	$\langle s\sqrt{5},3 \rangle$	0.80178496	0.80178728	[32]
icosahedron	523	1	$\langle s\sqrt{5},S^2 \rangle$	0.83633257	0.83635745	[32]

0.864720

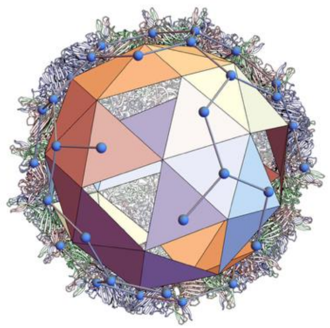
Complexity in Surfaces of Densest Packings for Families of Polyhedra, Elizabeth R. Chen, Daphne Klotsa, Michael Engel, Pablo F. Damasceno, and Sharon C. Glotzer, Phys. Rev. X **4**, 011024

Viruses Under The Mathematical Microscope

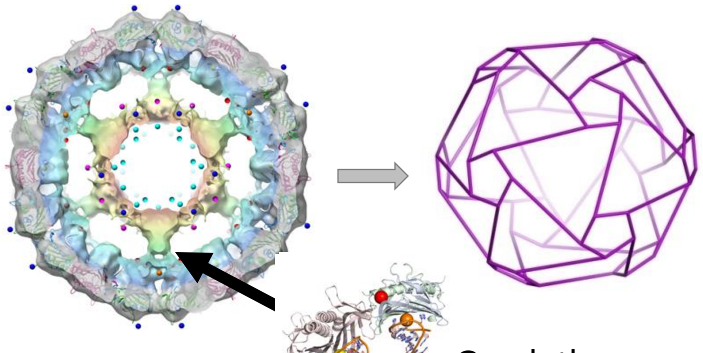
Mathematical models of virus architecture



Viral Tiling theory



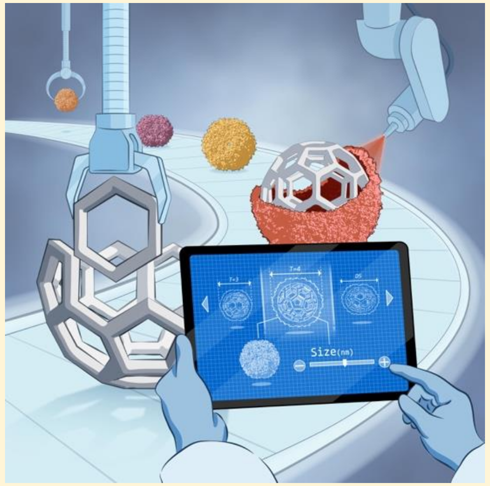
Interaction networks



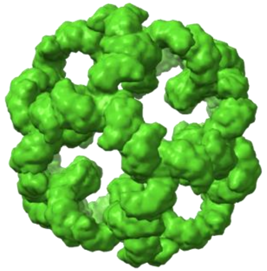
Group theory

Graph theory

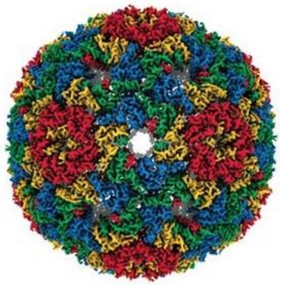
Mission



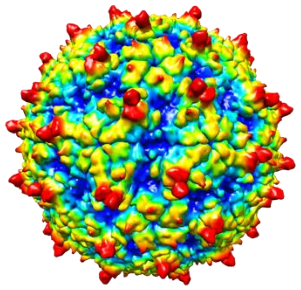
Analyse viral evolution and pathology through the lens of viral geometry



de novo designed particles



Protein engineered nanocages

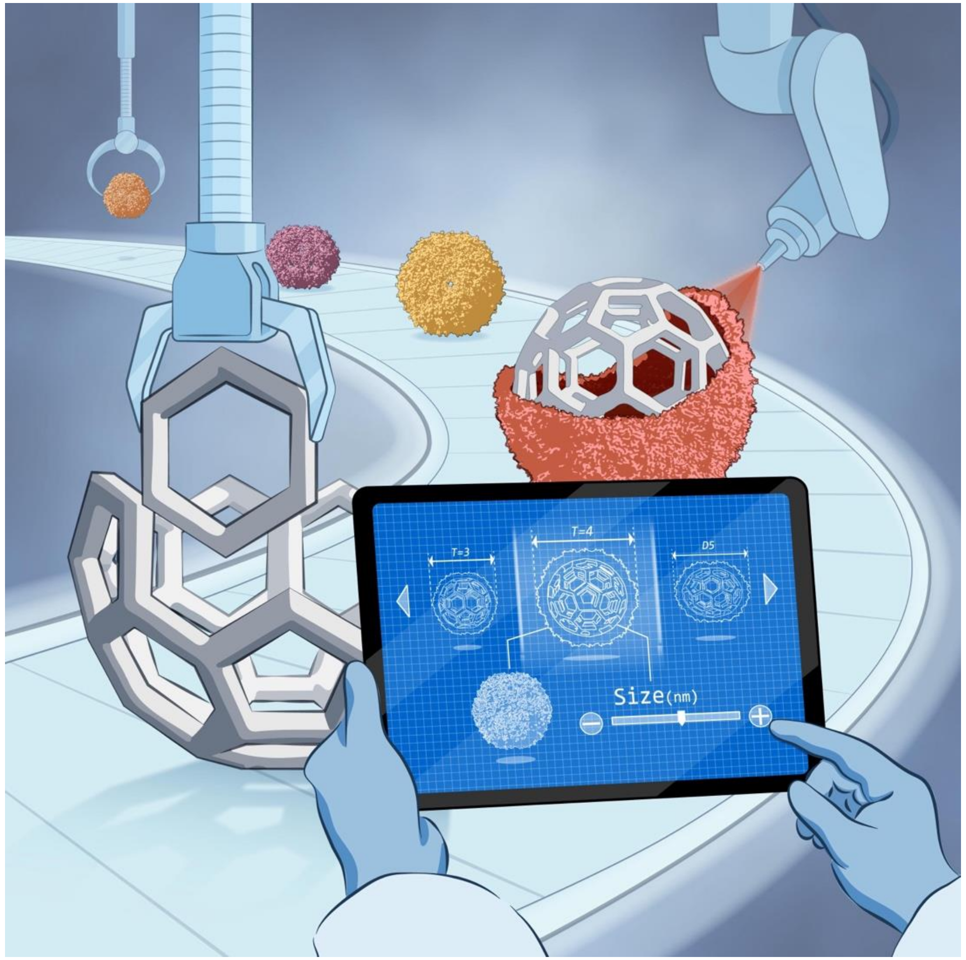


Virus like particles

Applications in Anti-viral Therapy, Gene Therapy & Vaccinology

Geometry-informed mechanistic understanding of viral life cycles provide innovation in:

- **anti-viral therapy** (inhibiting virus assembly);
- **Gene Therapy** (viral vector design);
- **Vaccinology** (VLP assembly/design).



The York team:

Lekshmi Nair

Bhavya Mishra

Wenhan Li

Richard Bingham

Eric Dykeman

and many alumni, in particular:

Sam Clark,

Farzad Fatehi

Pierre Dechant

James Geraets

Sam Hill

Tom Keef

David Salthouse

Jess Wardman

Eva Weiss

Emilio Zappa

Collaborators:

Wellcome Investigator Team at the Astbury Centre in Leeds:

Peter Stockley
Rebecca Chandler-Bostock
Nikesh Patel
Caitlin Simpson

International Collaborations:

ETH Zurich: Don Hilvert, Stephan Tetter (now Cambridge)

Lausanne: Angela Steinauer

Gladstone Institutes: Melanie Ott

University of Sydney: Yu Heng Lau

University of Krakow: Jonathan Heddle, Yusuke Atsuma, Artur Biela, Antonina Naskalska

American Regent: Nicholas Brunk

Munich University: Alena Khmelinskaia, Kevin O'Brien

University of Washington: Neil King, David Baker

Funding is gratefully acknowledged from:

EPSRC

wellcome trust Investigator

The Royal Society

MRC Medical Research Council

The Leverhulme Trust

BBSRC bioscience for the future