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Recent developments in mathematical virology

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Non-linear Algebra in Applications, ICERM
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Overview

1. Virus structure and dynamics
   - Icosahedral symmetry
   - Tiling theory
   - Extended structures
   - Giant viruses
2. Virus assembly
   - MS2 and Packaging Signals
   - Virus-like Particles
   - Anti-virals
3. Disease dynamics
   - Intracellular – Replication
   - Immunological – Infection Dynamics
   - Modelling

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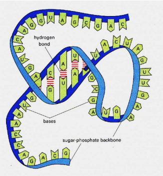
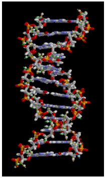
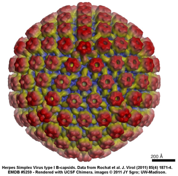
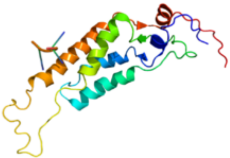
What is a Virus?

- Transported piece of genetic information that e.g. can run a programme in a host cell
- Genome: RNA or DNA
- Fragile – needs to be protected by a protein shell: capsid
- Gene $\rightarrow$ mRNA $\rightarrow$ protein (transcription and translation)
- Each protein $=$ amino acid chain folds into a 3D shape: one geometric building block

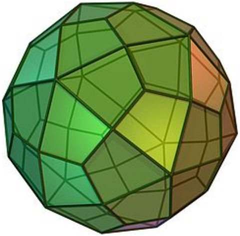


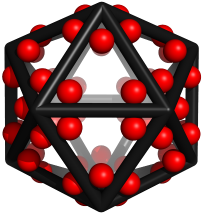


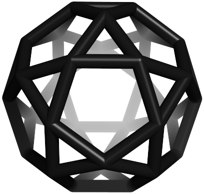




Watson and Crick: The Icosahedron



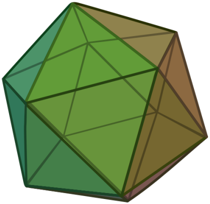


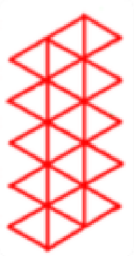


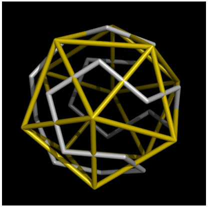
- Crick&Watson: Genetic economy → symmetry → icosahedral is largest
- Rotational icosahedral group is $I = A_5$ of order 60
- Full icosahedral group is the Coxeter group H_3 of order 120 (including reflections/inversion); generated by the root system icosidodecahedron

Many viruses are icosahedral

Assembling an Icosahedron

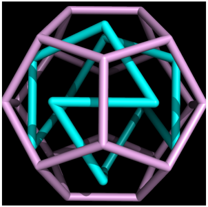


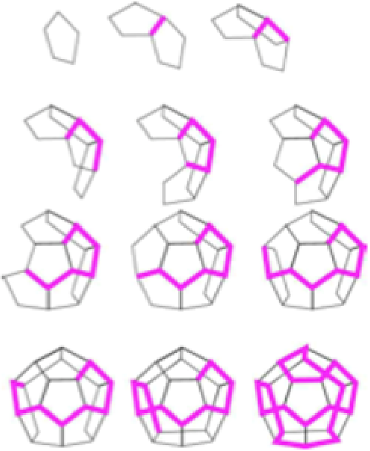




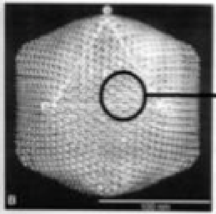
- Assemble from 20 identical triangular building blocks
- The order of addition gives a Hamiltonian path on the dual dodecahedron

Assembling a dodecahedron

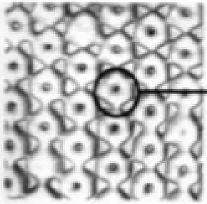




More than just icosahedral symmetry?



Protein shell
(viral capsid)

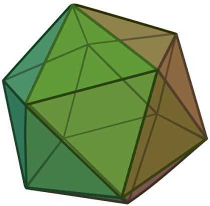


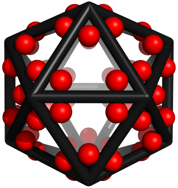
Protein clusters
(capsomeres)

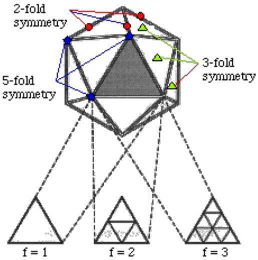
a cluster of 6
proteins
(hexamer)

Caspar and Klug: Triangulations

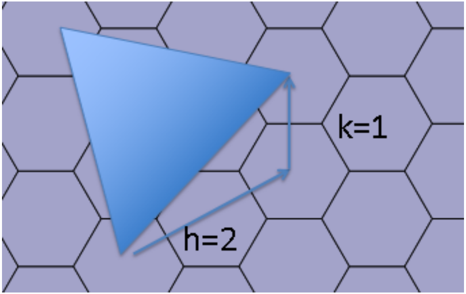
- Mathematical upper limit of 60 for equivalent subunits, but biologically want to do better!
- Gene $\rightarrow$ can already make a triangle $\rightarrow$ might as well make many!
- Caspar-Klug ideas of quasi-equivalence and triangulations







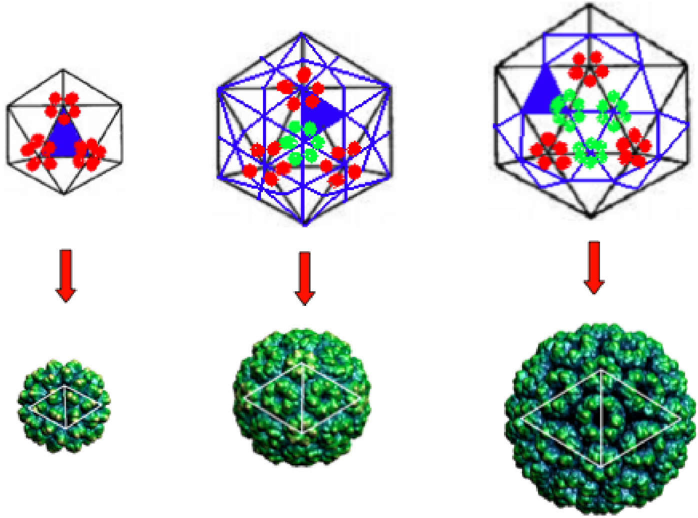
Viruses: Caspar-Klug triangulations $T = h^2 + hk + k^2$



integer steps h and k in hexagonal directions give allowed triangulation numbers $T = h^2 + hk + k^2$

T orbits so $60T$ proteins, 60 of which form 12 pentamers, and $60(T-1)$ form $10(T-1)$ hexamers

Viruses: Caspar-Klug triangulations $T = h^2 + hk + h^2$



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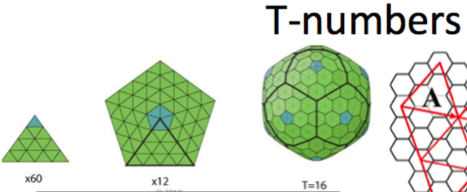
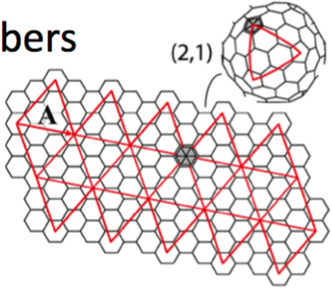
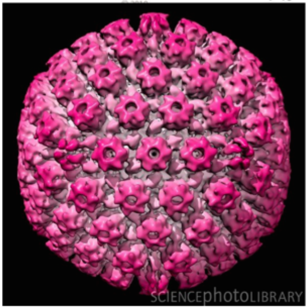
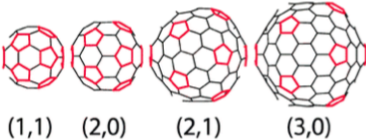








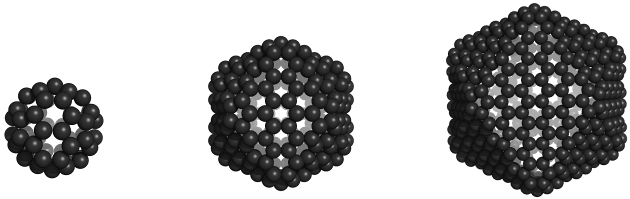
CK theory introduces local (6-fold) symmetry axes (capsomeres are invariant but not capsid)

The status quo for 40 years

- New insights in the 2000s from Reidun Twarock who essentially founded the field and other mathematical physicists (e.g. Anne Taormina etc)

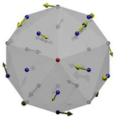
Fullerenes

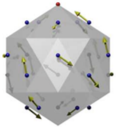
- other icosahedral objects in nature: football-shaped fullerenes
- Different shells with icosahedral symmetry: e.g. C_{60}, C_{240}, C_{540}
- Follow Caspar-Klug-like layouts (e.g. $T = h^2$ and $T = 3h^2$ families)

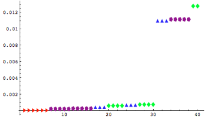


Vibrations of capsids and fullerenes

- Normal modes/vibrations of icosahedral capsids given by representation theory of the icosahedral group
- E.g. $\Gamma^{\mathrm{disp}}_{\mathrm{Icos}} = \Gamma^{1} + 3\Gamma^{3} + \Gamma^{3'} + 2\Gamma^{4} + 3\Gamma^{5}$
- Pioneered by Anne Taormina, Kasper Peeters and Francois Englert







I	1	$20C_3$	$15C_2$	$12C_5$	$12C_5^2$
1	1	1	1	1	1
3	3	0	−1	τ	σ
$\bar{3}$	3	0	−1	σ	τ
4	4	1	0	−1	−1
5	5	−1	1	0	0
Icos perm	12	0	0	2	2
$\chi^{\mathrm{disp}}_{\mathrm{Icos}}$	36	0	0	2τ	2σ
Dodec perm	20	2	0	0	0
$\chi^{\mathrm{disp}}_{\mathrm{Dodec}}$	60	0	0	0	0
IDD perm	30	0	2	0	0
$\chi^{\mathrm{disp}}_{\mathrm{IDD}}$	90	0	−2	0	0
tr Icos perm	60	0	0	0	0
$\chi^{\mathrm{disp}}_{\mathrm{trIcos}}$	180	0	0	0	0

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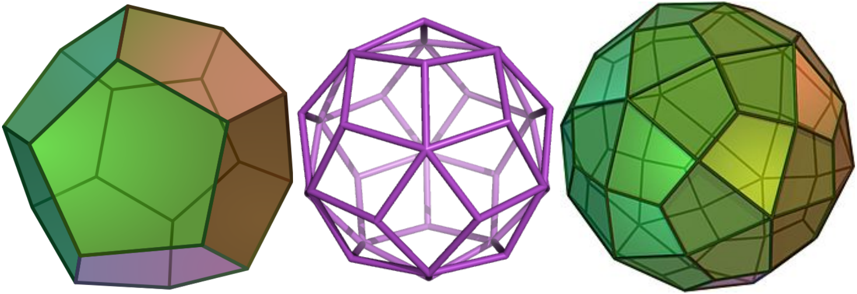
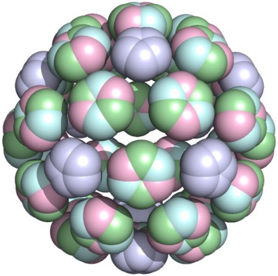
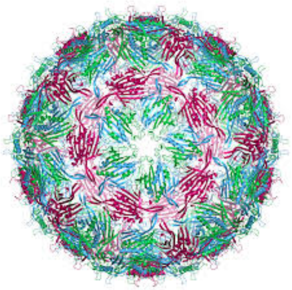
More general icosahedral tilings

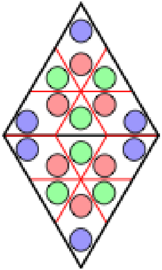


Other tile shapes can also give icosahedral tilings: pentagons (dodecahedron), rhombuses (rhombic triacontahedron), kites (deltoidal hexecontahedron)

triangulations vs other quasi-equivalent tilings

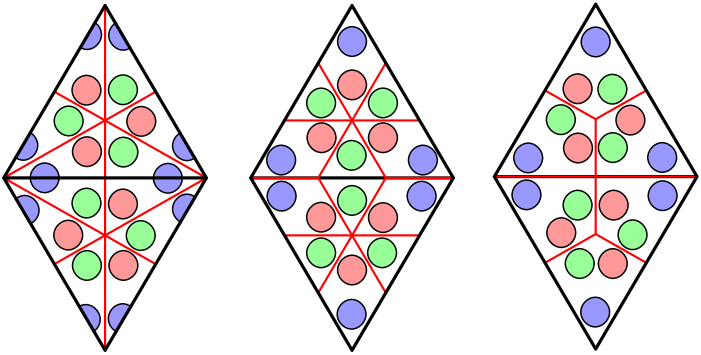






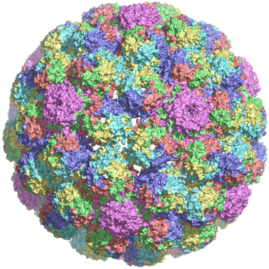
Two viral surface layouts: a $T = 4$ triangulation (e.g. HBV) and a rhombus tiling (MS2) for a pseudo $T = 3$ triangulation

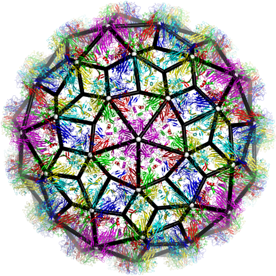
Other quasi-equivalent tilings

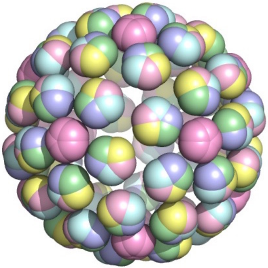


Three $T = 3$ capsids: Polio, MS2 and Pariacoto

A puzzle: non-quasiequivalent tilings – Penrose



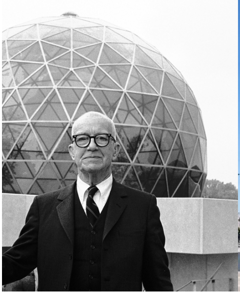




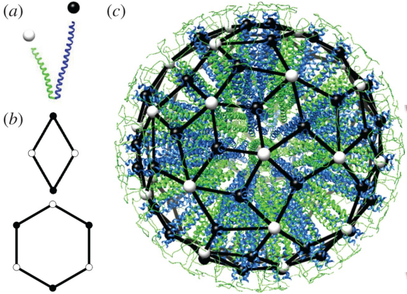
More general icosahedral tilings: Cryo-EM reconstruction of HPV, a kite-rhombus tiling and a pseudo $T = 7$ triangulation.

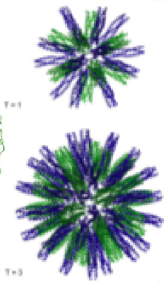
Architecture

- Triangulations: Buckminster Fuller geodesic domes
- kite-rhombus tiling: the new Amazon HQ



Self-assembling protein nanoparticles



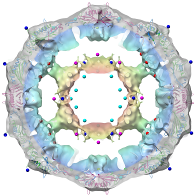
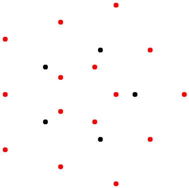
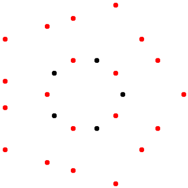


Giuliana Indelicato

Quantized e.g. in mass spec - predict units by symmetry. Particles eg. for vaccine design

More general symmetry still?

- Improves the limit to $60T$, but only in terms of surface structures (12 pentagons and rest hexagons).
- Making the symmetry non-compact might allow more general symmetry, simultaneously constraining different 'radial levels'
- Non-compact generator is a translation – motivates looking into affine extensions of icosahedral symmetry
- There is an inherent length scale in the problem – given by size of nucleic acid/protein molecules

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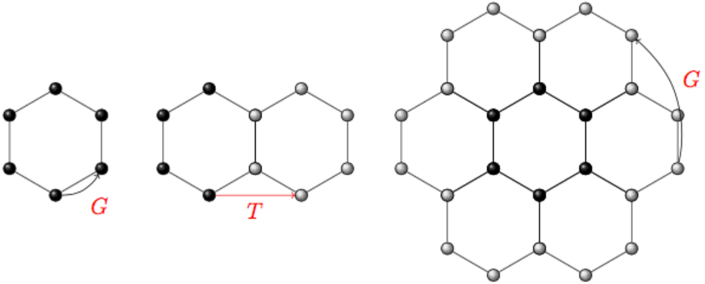
Affine extensions - A_2

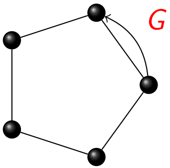
Unit translation along a vertex of a unit hexagon



A random translation would give 6 secondary hexagons, i.e. 36 points. Here we have degeneracies due to 'coinciding points', and building up the hexagonal lattice.

Affine extensions of non-crystallographic groups?

Unit translation along a vertex of a unit pentagon



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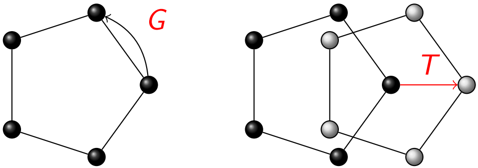

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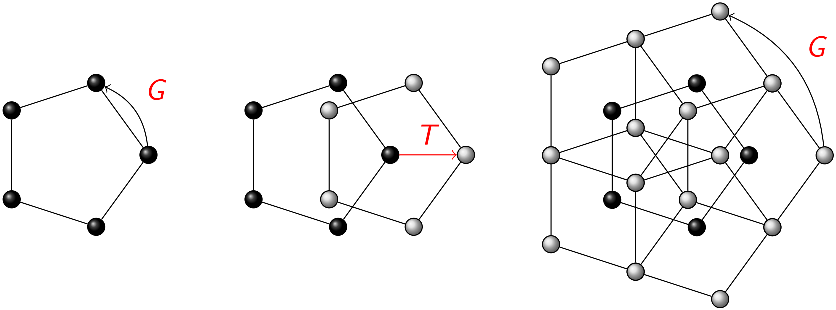
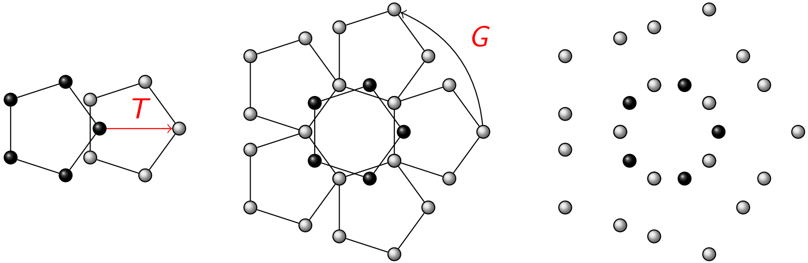


A random translation would give 5 secondary pentagons, i.e. 25 points. Here we have degeneracies due to 'coinciding points'.

Affine extensions of non-crystallographic root systems?

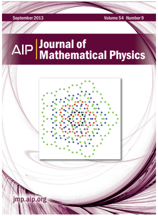
Translation of length $\tau = \frac{1}{2}(1+\sqrt{5}) \approx 1.618$ (golden ratio)

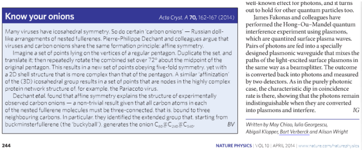


Cartoon version of a virus or carbon onion. Would there be an evolutionary benefit to have more than just compact symmetry? The problem has an intrinsic length scale.

Affine extensions of non-crystallographic Coxeter groups

- 2D and 3D point arrays for applications to viruses, fullerenes, quasicrystals, proteins etc
- Two complementary ways to construct these





Know your onions *Acta Cryst. A* **70**, 162–167 (2014)

Many viruses have icosahedral symmetry. So do certain 'carbon onions' — Russian doll-like arrangements of nested fullerenes. Pierre-Philippe Dechant and colleagues argue that viruses and carbon onions share the same formation principle: affine symmetry.

Imagine a set of points lying on the vertices of a regular pentagon. Duplicate the set, and translate it; then repeatedly rotate the combined set over 72° about the midpoint of the original pentagon. This results in a new set of points obeying five-fold symmetry, yet with a 2D shell structure that is more complex than that of the pentagon. A similar 'affinization' of the (3D) icosahedral group results in a set of points that are nodes in the highly complex protein network structure of, for example, the Pariacoto virus.

Dechant *et al.* found that affine symmetry explains the structure of experimentally observed carbon onions — a non-trivial result given that all carbon atoms in each of the nested fullerene molecules must be three-connected, that is, bound to three neighbouring carbons. In particular, they identified the extended group that, starting from buckminsterfullerene (the 'buckyball'), generates the onion $C_{60}@C_{240}@C_{540}$. *BV*

well-known effect for photons, and it turns out to hold for other quantum particles too.

James Fakonas and colleagues have performed the Hong–Ou–Mandel quantum interference experiment using plasmons, which are quantized surface plasma waves. Pairs of photons are fed into a specially designed plasmonic waveguide that mixes the paths of the light-excited surface plasmons in the same way as a beamsplitter. The outcome is converted back into photons and measured by two detectors. As in the purely photonic case, the characteristic dip in coincidence rate is there, showing that the photons remain indistinguishable when they are converted into plasmons and interfere. *IG*

Written by May Chiao, Iulia Georgescu, Abigail Klopper, Bart Verberck and Alison Wright

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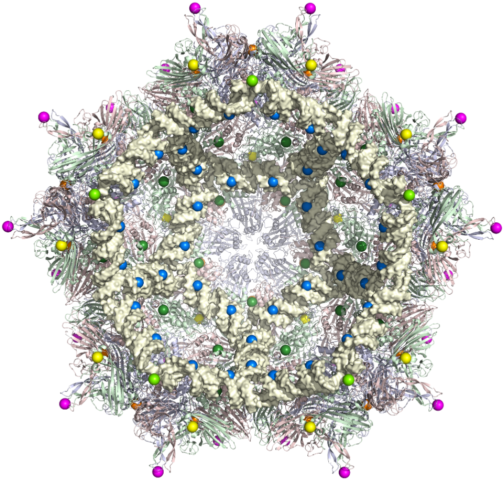
Other ideas

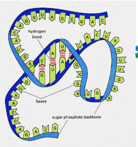
- Project symmetry orbits in 6D to get finite extended icosahedral point arrays (Emilio Zappa)
- Use projection to find 3D tiles to model viruses (David Salthouse)
- Use projection to model transitions between capsids via lattice transitions in 6D (Giuliana Indelicato)

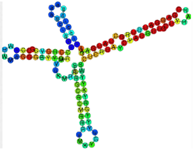
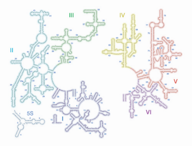
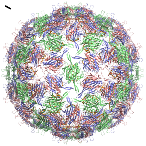
Use in Mathematical Virology



New insight into RNA virus assembly

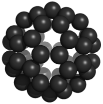
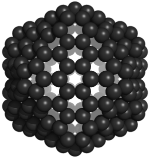
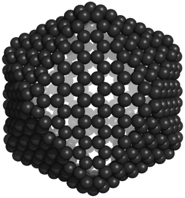
- There are specific interactions between RNA and coat protein (CP) given by icosahedral symmetry axes
- Essential for assembly, as only this RNA-CP interaction turns CP into right geometric shape for capsid formation
- Hamiltonian cycle visiting each RNA-CP contact once – dictated by symmetry
- Even the RNA has an icosahedrally ordered component



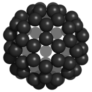
Extension to fullerenes: carbon onions

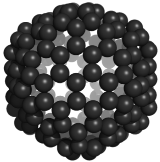
- Extend idea of affine symmetry to other icosahedral objects in nature: football-shaped fullerenes (with Jess Wardman)
- Recover different shells with icosahedral symmetry from affine approach: carbon onions ($C_{60} - C_{240} - C_{540}$)

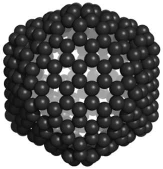





Extension to fullerenes: carbon onions

- Extend idea of affine symmetry to other icosahedral objects in nature: football-shaped fullerenes
- Recover different shells with icosahedral symmetry from affine approach: carbon onions ($C_{80} - C_{180} - C_{320}$)

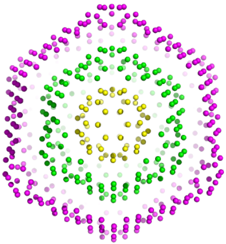


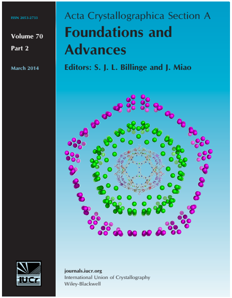


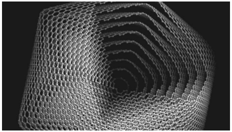


Viruses and fullerenes – symmetry as a common thread?

- Get nested arrangements like Russian dolls: carbon onions (e.g. Nature 510, 250253)

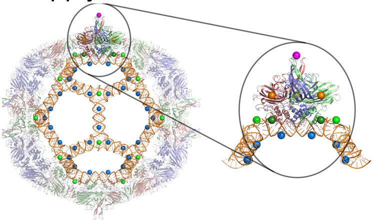


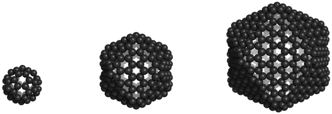




Two examples

- Non-compact symmetry that relates different structural features in the same polyhedral object when there is an additional length scale
- Novel symmetry principle in Nature, shown that it seems to apply to at least fullerenes and viruses





Overview

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   - Icosahedral symmetry
   - Tiling theory
   - Extended structures
   - Giant viruses
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   - Anti-virals
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   - Intracellular – Replication
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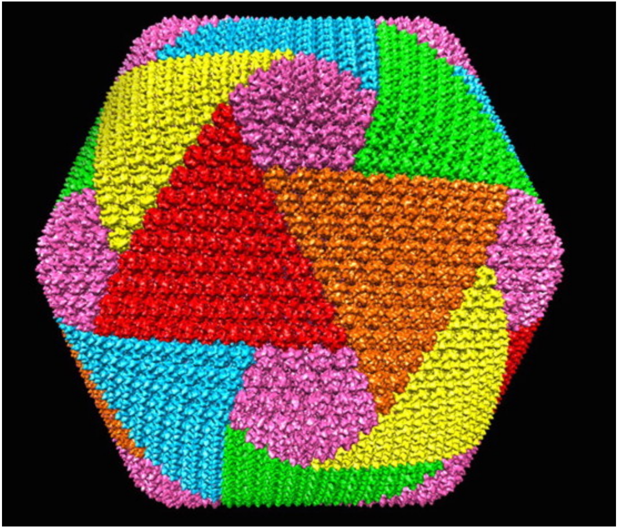
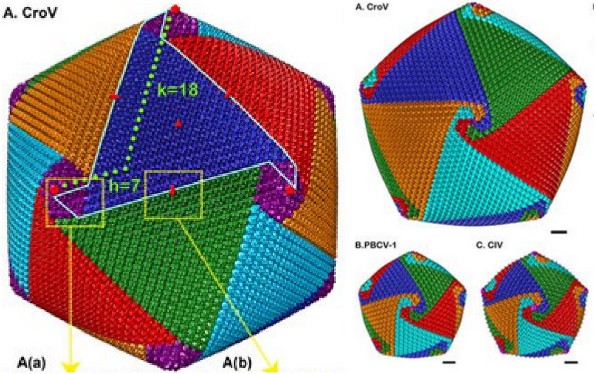
   - Modelling

Giant viruses

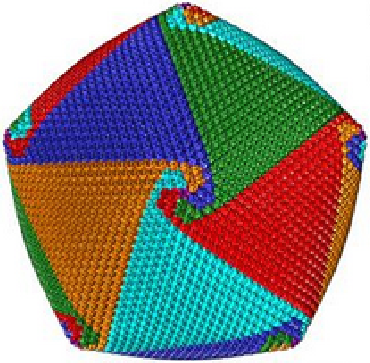


A common approach – little hooks



Pentasymmetrons and trisymmetrons

A common approach – little hooks

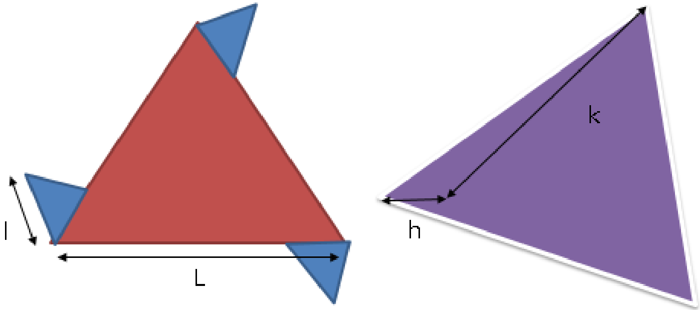


Pentasymmetrons and trisymmetrons

A family of solutions: $h = 7$ – and some gaps

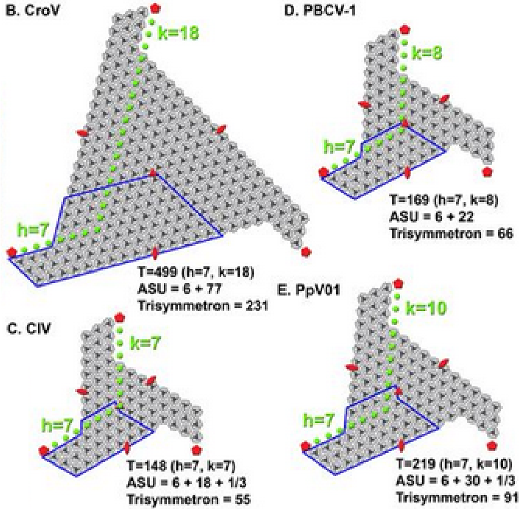
- Chilo iridescent virus: $T = 147$, $h = 7$ and $k = 7$
- Paramecium bursaria Chlorella virus 1: $T = 169$, $h = 7$ and $k = 8$
- Phaeocystis pouchetti virus: $T = 219$, $h = 7$ and $k = 10$
- Faustovirus: $T = 277$, $h = 7$ and $k = 12$
- Pacman virus: $T = 309$, $h = 7$ and $k = 13$
- Cafeteria roenbergensis: $T = 499$, $h = 7$ and $k = 18$

Count areas?

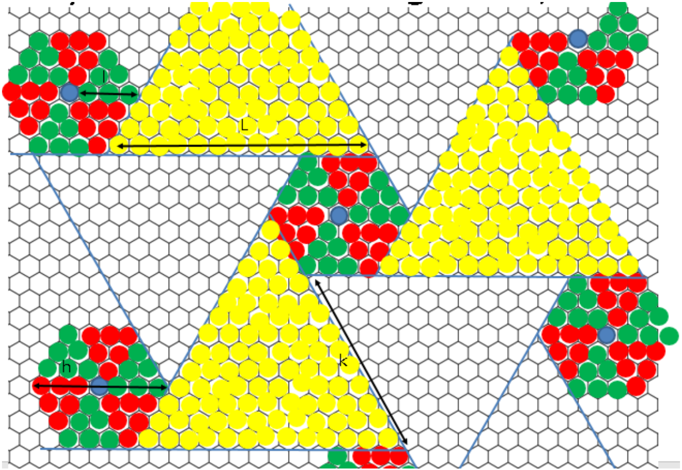


When is there an equivalent description in terms of Caspar-Klug h and k?

Count hexagons



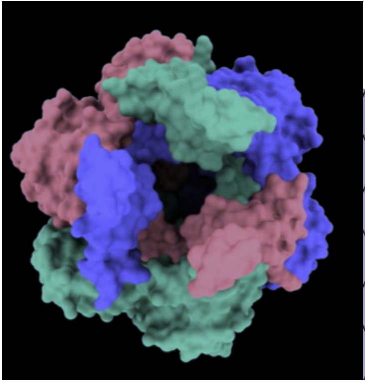
Trisymmetrons and Pentasymmetrons – how to count

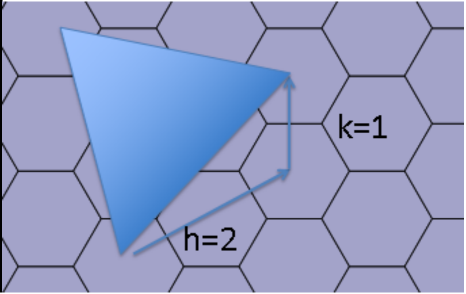


Trisymmetrons and Pentasymmetrons – how to count

- Each has $l(l+1)/2$ or $L(L+1)/2$ hexamers
- So in total $20(3l(l+1)/2 + L(L+1)/2)$
- Caspar-Klug theory predicts $10(T-1) = 10(h^2 + hk + k^2 - 1)$
- So for which h, k, l, L can there be equality?
- Turns out for $h = 2l + 1$ and $k = L - l$ this holds identically
- So can have odd h and any k

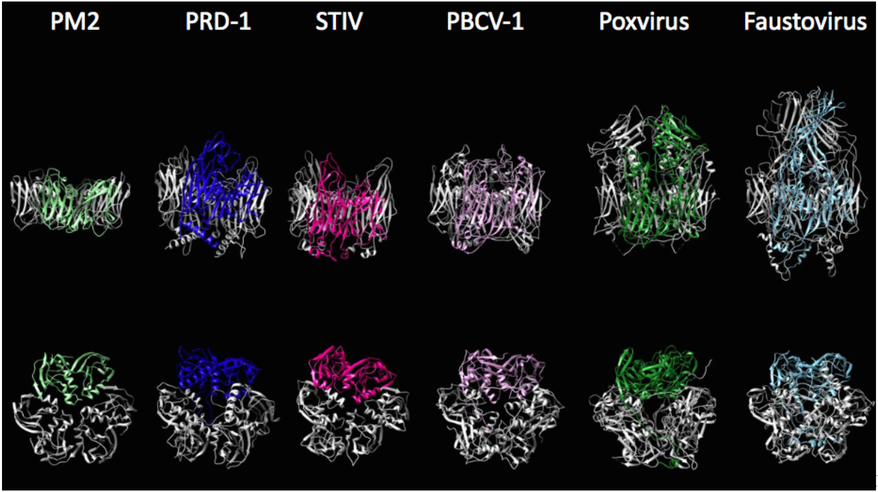
Major capsid protein



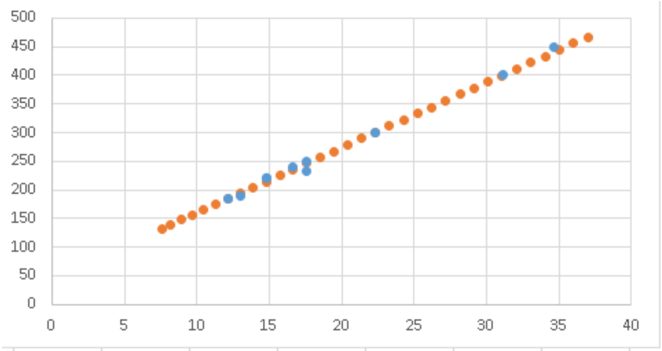


T is an area, so $\sqrt{T}$ gives size of triangle and thus also particle diameter

Major capsid protein – evolutionary conservation

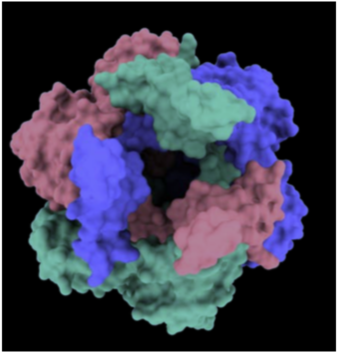


Scaling

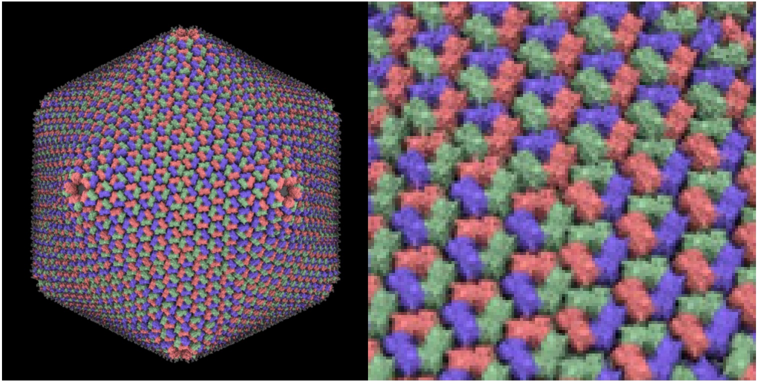


Missing points allowed geometrically but less stable? Or just not yet discovered? Predict Tetraselmis virus 1 TetV-1 of $257nm \pm 9nm$ is exactly $T = 343$. Predict holes in family exist and sizes given by this scaling

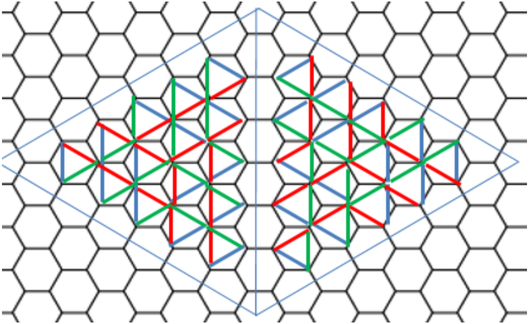
Major capsid protein – trimer / pseudohexamer



Decorations – threefold and giants



Decorations – threefold and giants

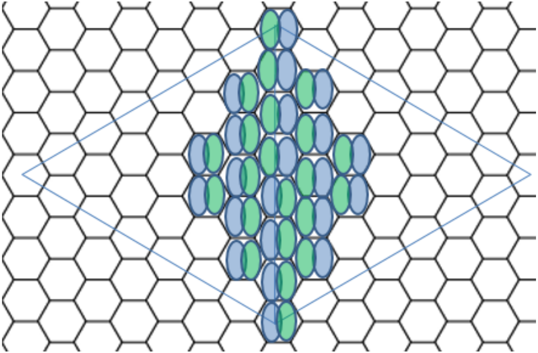


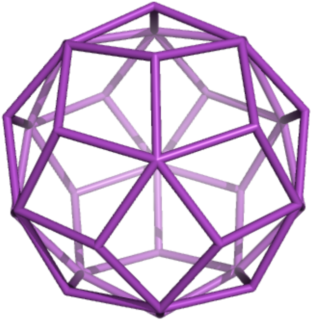
Use hexagonal tiling unit with decorations that partially break the symmetry: 6, 3, 2, 1

If respect the 3-fold axis, then still have partial lattice symmetry!

Defects/domain walls at the other symmetry axes

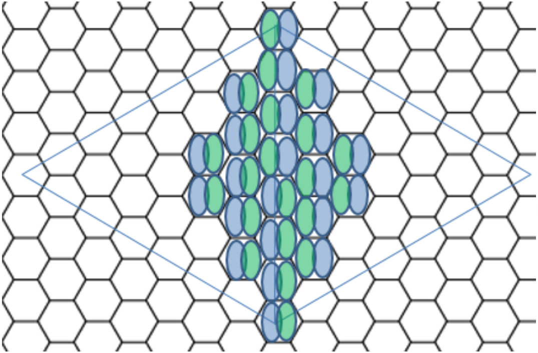
Decorations – twofold case

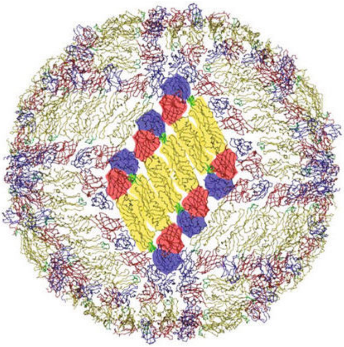




Symmetric with respect to 2-fold axis – quasi-lattice symmetry
Looks like a rhombic triacontahedron all over again

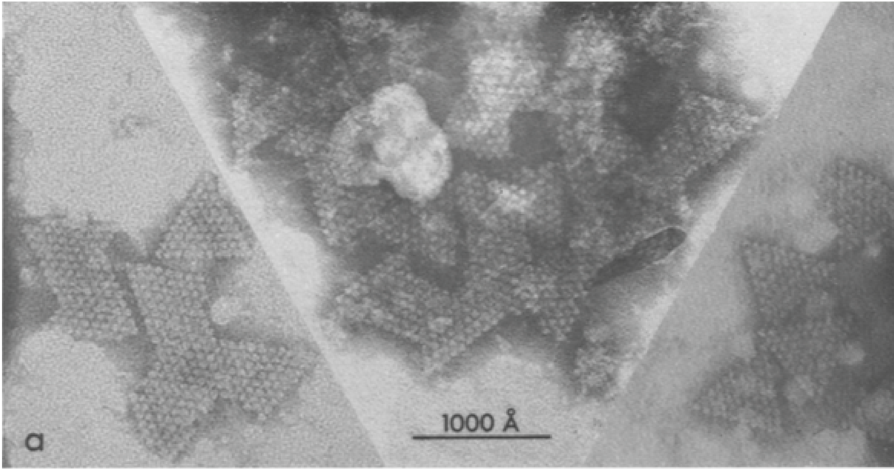
Decorations – twofold and Zika



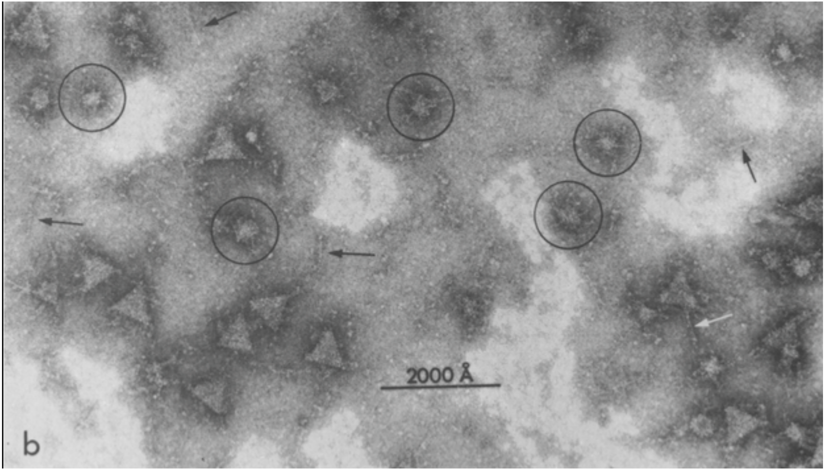


This is exactly what Zika looks like

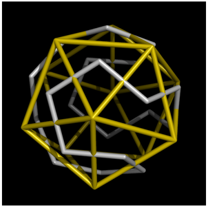
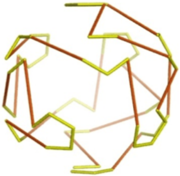
Trisymmetrons and Pentasymmetrons



Major capsid protein - trimer, pseudohexamer



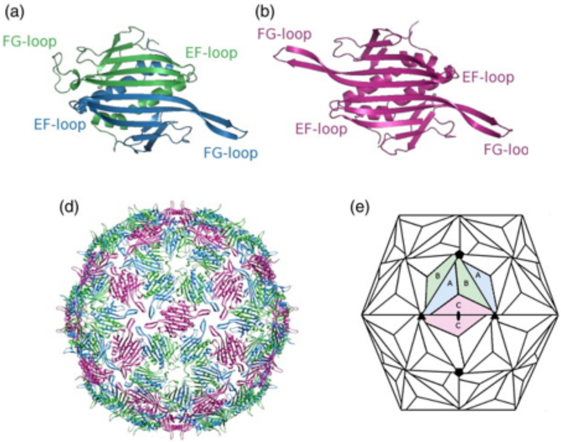
Build from prearranged blocks? Back to Hamiltonian paths


- Are the trisymmetrons and pentasymmetrons preformed? (or is that just what virions fall apart into?)
- If trisymmetrons are assembled then we're back to a Hamiltonian path for the icosahedron
- If pentasymmetrons then get a slightly new polyhedron

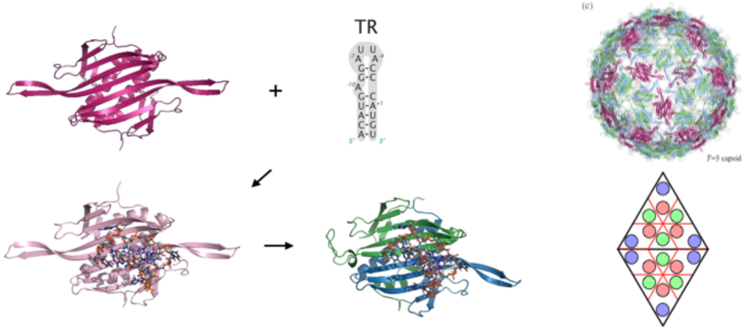
Overview

MS2 tiling and dimeric building blocks: A/B and C/C



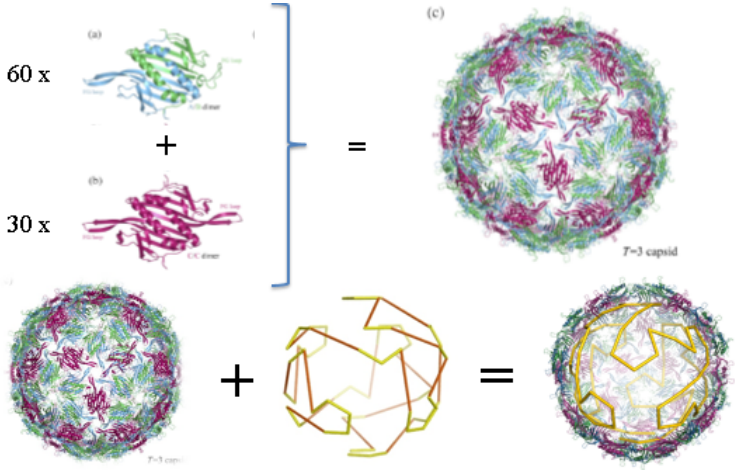
Need to bind RNA in 60 places

The TR sequence is known to initiate assembly by associating with the maturation protein. It forms a stemloop and it has been shown that the stemloop changes the conformation of the symmetric C/C dimer to the asymmetric A/B dimer (allosteric switch).



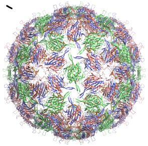
Peter Stockley (Leeds), Neil Ranson (Leeds), Eric Dykeman (York)

MS2 Hamiltonian path

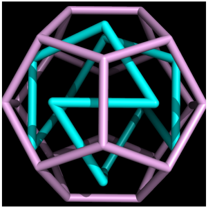
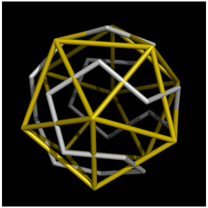
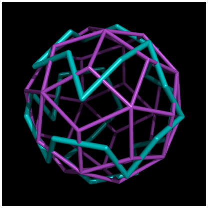


New insight into RNA virus assembly

- More realistic examples for MS has 60 vertices with $41,000$ paths
- The RNA is actually circularised by Maturation Protein: only 66 cycles
- With thermodynamical assembly kinetics and 5-fold averaging experiments uniquely idenfied an evolutionarily conserved cycle
- Patents for new antiviral strategies and virus-like nanoparticles e.g. for drug delivery (Twarock group)

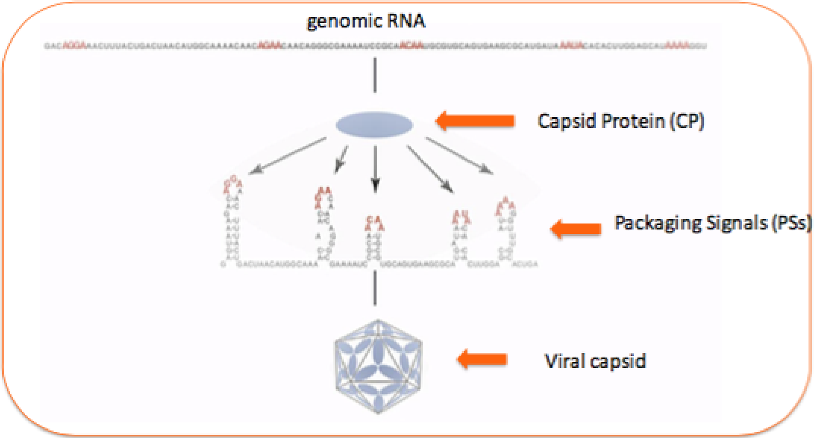
Hamiltonian cycles on icosahedral solids

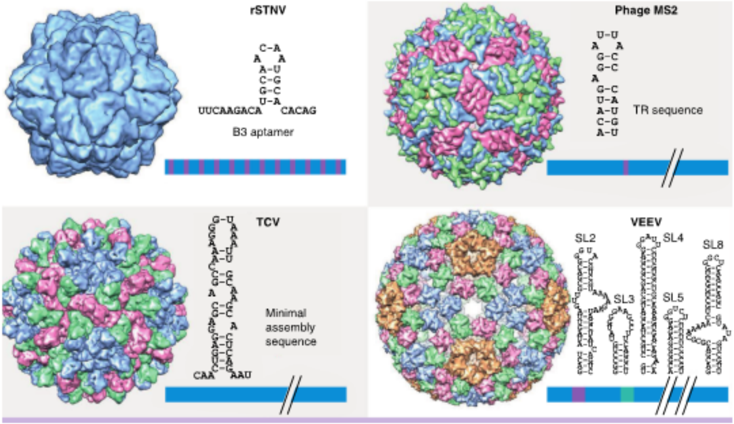
- So interaction contacts are given by the symmetry
- Orbits of the interaction points have to be visited by the RNA exactly once
- Even the RNA has an icosahedrally ordered component
- Hamiltonian cycles for dodecahedron, icosahedron and rhombic triacontahedron

Overview

Multiple dispersed Packaging Signals paradigm



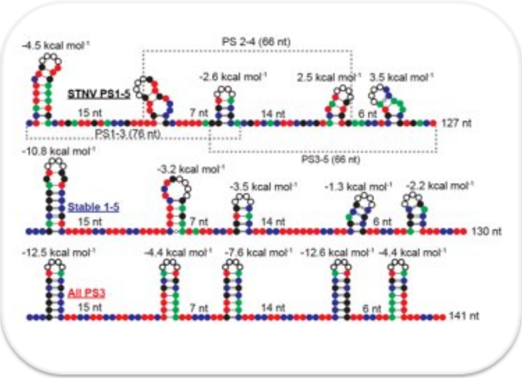
Common Mechanism across groups of viruses



German Leonov, Richard Bingham

Overview

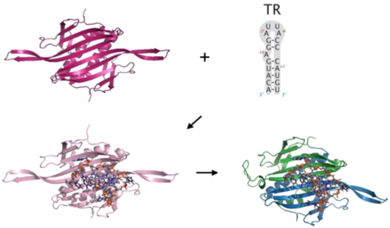
Engineering Packaging Signals to make VLPs



Improved sequences assemble twice as efficiently (Nikesh Patel).
Potential applications to vaccines or drug delivery.

Overview

Understanding assembly allows one to interfere



- target RNA
- target CP
- introduces competitors
- this might drive evolution due to exerting selection pressures

Overview

1. Virus structure and dynamics
   - Icosahedral symmetry
   - Tiling theory
   - Extended structures
   - Giant viruses
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   - Immunological – Infection Dynamics
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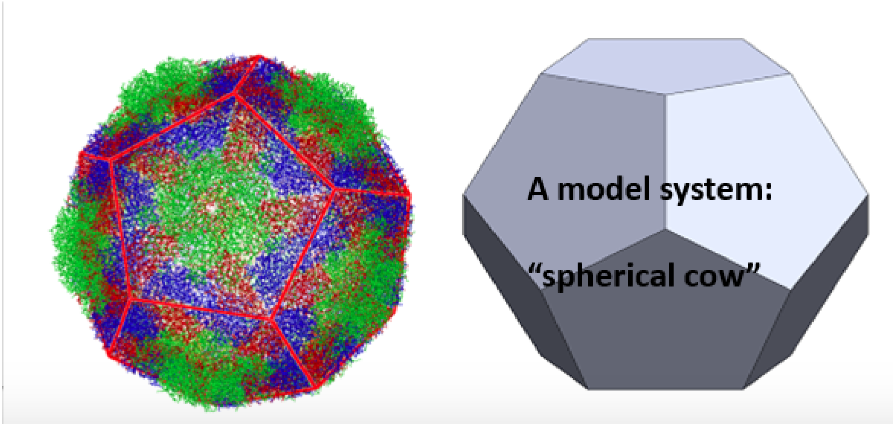
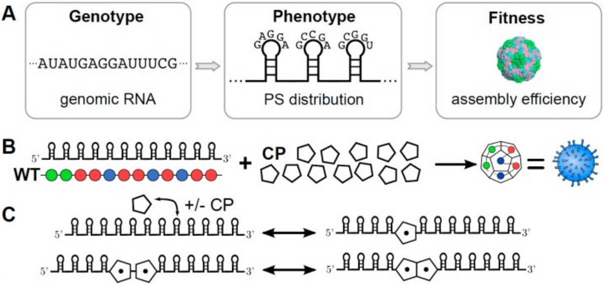
Dodecahedral cow (Rich Bingham)



Viral evolution and quasispecies

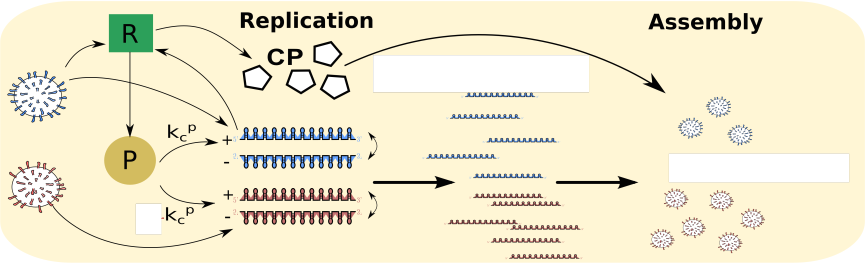


A phenomenological genome space of 12 packaging signals with 3 binding affinity bands (weak, medium, strong). Can compute the whole space explicitly in terms of assembly efficiency.

Simulations

- Stochastic simulations rather than ODE models because of discrete nature and low numbers
- Gillespie algorithm that selects a random reaction to occur (Eric Dykeman)
- Couple an intracellular model (replication) with an infection model (immune system)

Intracellular model: replication



Intracellular reactions

$$p_V^+ + R \underset{k_r^{off}}{\overset{k_r^{on}}{\rightleftarrows}} (p_V^+, R) \text{(Ribosome positive strand virus binding/unbinding)}$$

$$(p_V^+, R) \xrightarrow{k_r^c} p_V^+ + R + P \text{ (Genome translation - makes P and abundant CP)}$$

$$p_{V/S}^{\pm} + P \underset{k_p^{\pm off}}{\overset{k_p^{\pm on}}{\rightleftarrows}} (p_{V/S}^{\pm}, P) \text{(Polymerase positive/negative strand virus binding/unbinding)}$$

$$(p_{V/S}^{\pm}, P) \xrightarrow{k_p^c} p_{V/S}^{\pm} + p_{V/S}^{\mp} + P \text{ (complementary strand production)}$$

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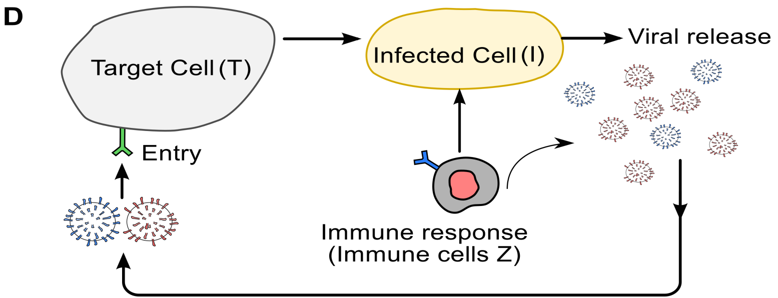
Infection model: immune system



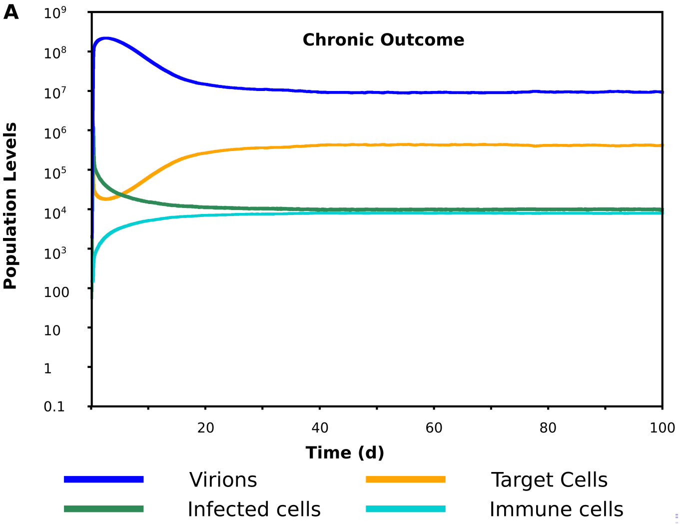
Immune cell reactions

$$T \xrightarrow{\lambda} 2T \text{ (Target cell birth)}$$
$$T \xrightarrow{d_T} 0 \text{ (Target cell death)}$$
$$T + pV + qS \xrightarrow{\beta} I \text{ (Infection of target cell)}$$
$$I \xrightarrow{a} rV + sS \text{ (Infected cell death/lysis, if } p > 0\text{)}$$
$$I + Z \xrightarrow{\pi} Z \text{ (Infected cell removal by immune system)}$$
$$V + Z \xrightarrow{u} Z \text{ (Virion removal by immune system)}$$

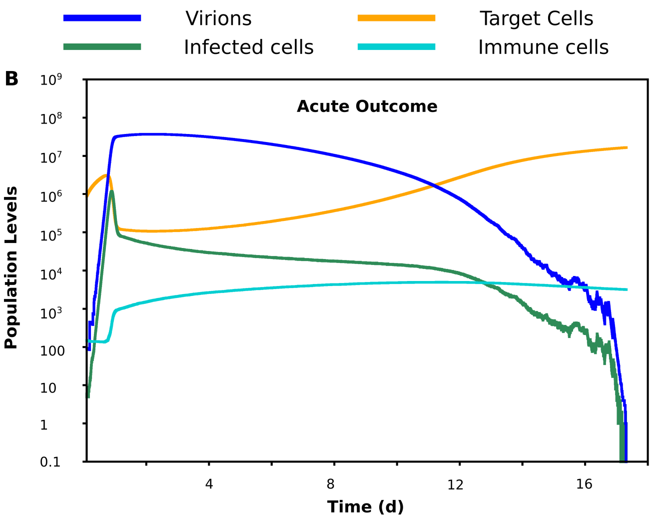
$$I + Z \xrightarrow{c} I + 2Z \text{ (Immune cell birth)}$$
$$Z \xrightarrow{b} 0 \text{ (Immune cell death)}$$

Overview

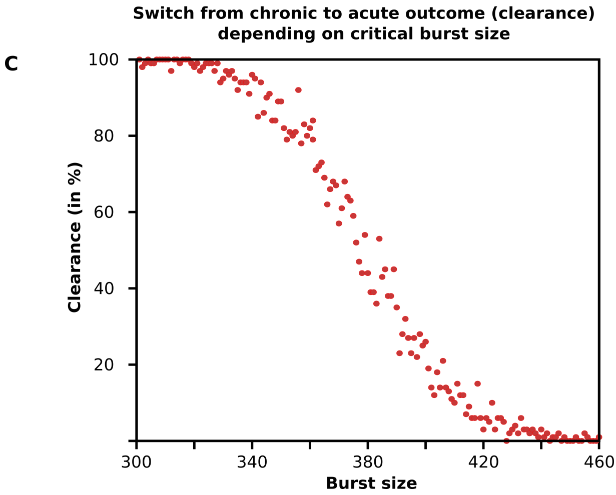
Chronic infections



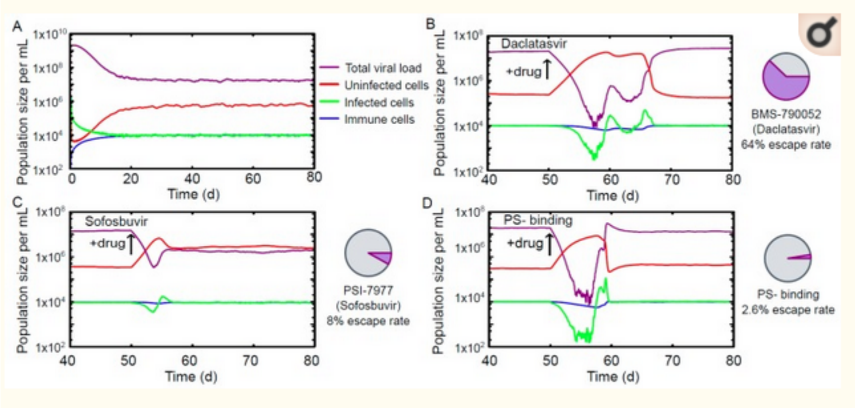
Acute infections



Transition between chronic and acute



Evolutionarily stable drugs



Summary of mathematical virology

- a truly diverse interdisciplinary endeavour: group theory, tiling theory, dynamical systems, graph theory, computational modelling, biophysics, bioinformatics, biochemistry, cell biology, structural biology, immunology
- curiosity-driven and impactful: from understanding a structural puzzle to a new generation of anti-virals – by accident

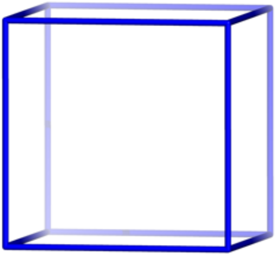
Other algebraic interests

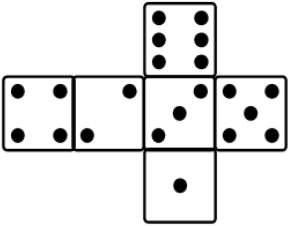
- exceptional root systems/geometries
- (reflexive) polytopes
- Clifford algebras
- ADE correspondences

Thank you!
LGBTQ+ lunch at 1pm.

Symmetry averaging

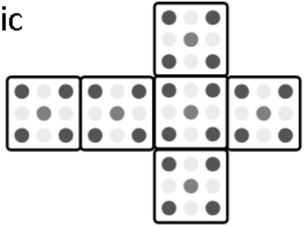
- As an example use the symmetry of a cube
- (axes of 4-fold, 3-fold and 2-fold symmetry)
- Dice have approximately cubic symmetry, but have slightly asymmetric features (the faces)





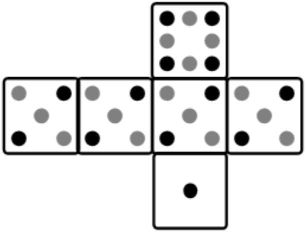
Symmetry averaging

- As an example use the symmetry of a cube
- Approximately cubic symmetry, but have slightly asymmetric features (the faces)
- Experiment averages over all orientations
- Washes out all asymmetric features

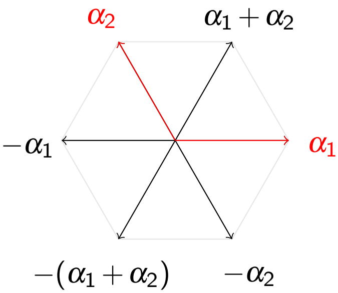


Symmetry averaging

- Assume we have a distinguished face, e.g. 1 is always at the bottom
- The 6 can be in two configurations
- Average over the other 4 faces



Root systems



Root system Φ: set of vectors α in a vector space with an inner product such that

1. $\boxed{\Phi \cap \mathbb{R}\alpha = \{-\alpha, \alpha\} \;\forall\, \alpha \in \Phi}$
2. $\boxed{s_\alpha \Phi = \Phi \;\forall\, \alpha \in \Phi}$

Simple roots: express every element of Φ via a $\mathbb{Z}$-linear combination.

reflection/Coxeter groups $\boxed{s_\alpha : v \to s_\alpha(v) = v - 2\frac{(v|\alpha)}{(\alpha|\alpha)}\alpha}$

Affine extensions

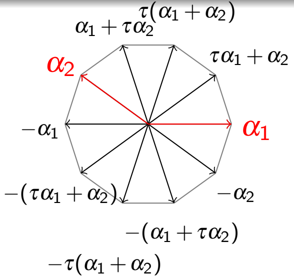
An affine Coxeter group is the extension of a Coxeter group by an affine reflection in a hyperplane not containing the origin $s^{aff}_{\alpha_0}$ whose geometric action is given by

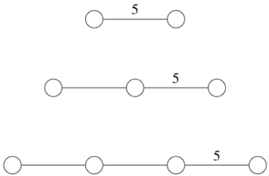
$$\boxed{s^{aff}_{\alpha_0} v = \alpha_0 + v - \frac{2(\alpha_0|v)}{(\alpha_0|\alpha_0)}\alpha_0}$$

Non-distance preserving: includes the translation generator

$$\boxed{Tv = v + \alpha_0 = s^{aff}_{\alpha_0} s_{\alpha_0} v}$$

Non-crystallographic Coxeter groups $H_2 \subset H_3 \subset H_4$





$$A = \begin{pmatrix} 2 & -\tau \\ -\tau & 2 \end{pmatrix}$$

$$A = \begin{pmatrix} 2 & -1 & 0 \\ -1 & 2 & -\tau \\ 0 & -\tau & 2 \end{pmatrix}$$

$$A = \begin{pmatrix} 2 & -1 & 0 & 0 \\ -1 & 2 & -1 & 0 \\ 0 & -1 & 2 & -\tau \\ 0 & 0 & -\tau & 2 \end{pmatrix}$$

$H_2 \subset H_3 \subset H_4$: 10, 120, 14,400 elements, the only Coxeter groups that generate rotational symmetries of order 5

linear combinations now in the extended integer ring

$$\boxed{\mathbb{Z}[\tau] = \{a + \tau b | a, b \in \mathbb{Z}\}}$$ golden ratio $$\boxed{\tau = \frac{1}{2}(1+\sqrt{5}) = 2\cos\frac{\pi}{5}}$$

$$\boxed{x^2 = x + 1} \quad \boxed{\tau' = \sigma = \frac{1}{2}(1-\sqrt{5}) = 2\cos\frac{2\pi}{5}} \quad \boxed{\tau + \sigma = 1, \tau\sigma = -1}$$