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PLYMOUTH

Mathematical and computational modelling in  
Mathematical Virology  
Plymouth, December 3, 2020

Pierre-Philippe Dechant

work with R Twarock and Y-H He

School of Science, Technology & Health, York St John University  
York Cross-disciplinary Centre for Systems Analysis, University of York  
Department of Mathematics, University of York

# Overview

## Mathematical Modelling

- Watson & Crick: Icosahedral and helical symmetry
- Caspar & Klug: Triangulations
- Twarock: More general surface tilings
- Affine symmetry: genome and capsid

## Computational Modelling

- Bioinformatics: packaging signals
- Gillespie stochastic simulations: epidemiological, infection, assembly
- Machine learning: fitness landscape

## Main references

### Models of Viral Capsid Symmetry as a Driver of Discovery in Virology and Nanotechnology

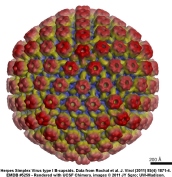
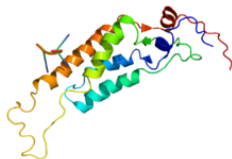
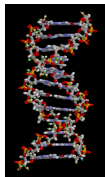
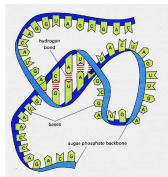
P-P Dechant, R Twarock, The Biochemist, 2021

### Machine-learning a virus assembly fitness landscape

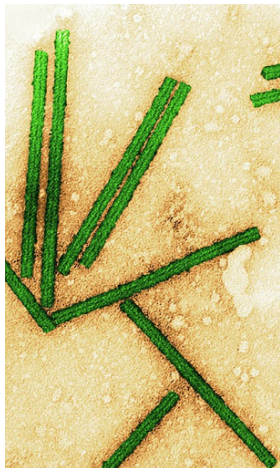
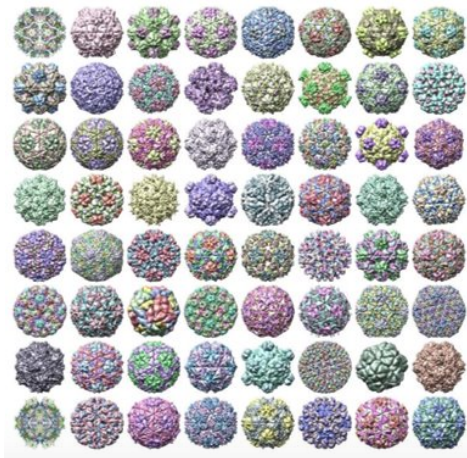
P-P Dechant, Y-H He, PLOS One, arXiv preprint  
arXiv:1901.05051, 2021

# What is a Virus?

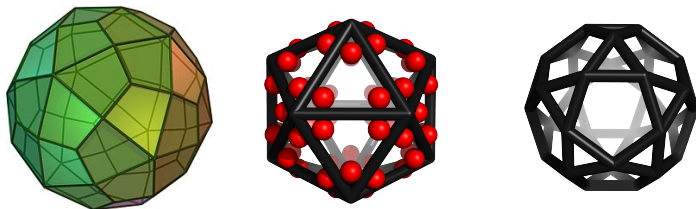
- Transported piece of **genetic information** that e.g. can run a programme in a host cell
- **Genome**: RNA or DNA – single- or double-stranded
- Fragile – needs to be protected by a **protein shell**: **capsid**
- **Gene** → mRNA → **protein** (transcription and translation)
- Each **protein** = amino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



# Many viruses are icosahedral – others helical

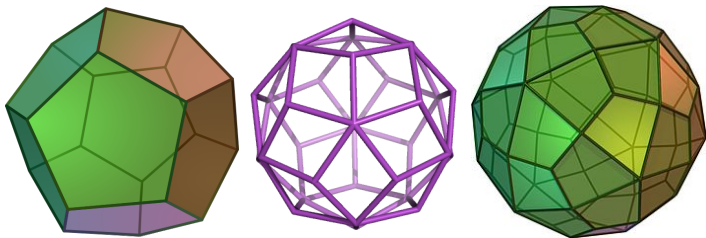


# Watson and Crick: Principle of Genetic Economy



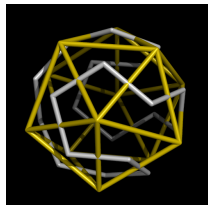
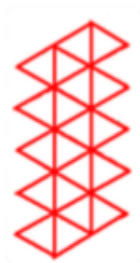
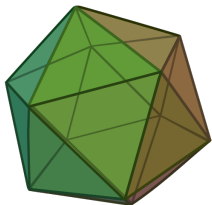
- **Watson & Crick:** Genetic economy  $\rightarrow$  symmetry  $\rightarrow$  icosahedral is largest
- **Rotational** icosahedral group is  $I = A_5$  of order **60**
- **Full** icosahedral group is the **Coxeter group  $H_3$**  of order **120** (including reflections/inversion); generated by the **root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

# Icosahedral solids



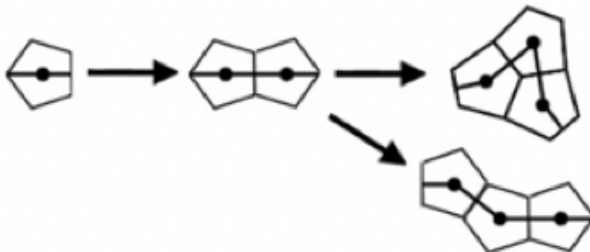
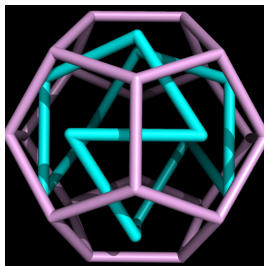
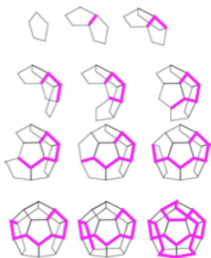
Other **tile shapes** can also give icosahedral tilings: **pentagons** (dodecahedron), **rhombuses** (rhombic triacontahedron), **kites** (deltoidal hexecontahedron)

# Assembling an Icosahedron



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

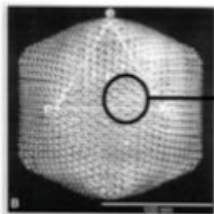
# Assembly and thermodynamics – Hamiltonian paths



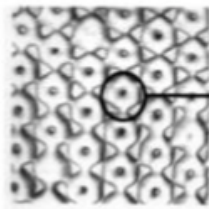
# More than just icosahedral symmetry?

Solved the original problem

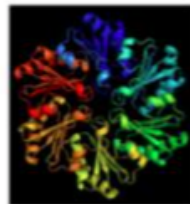
But with that solution (triangular building blocks), can viruses do better?



Protein shell  
(viral **capsid**)



Protein clusters  
(**capsomeres**)

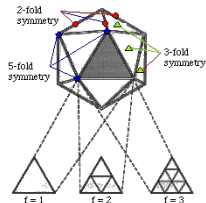
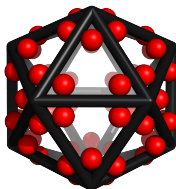
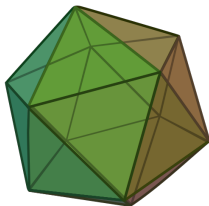


a cluster of 6  
proteins  
(**hexamer**)

# Caspar and Klug: Triangulations

A compromise between mathematics & biology: quasi-equivalence

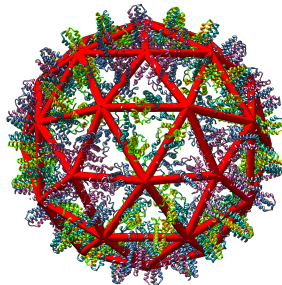
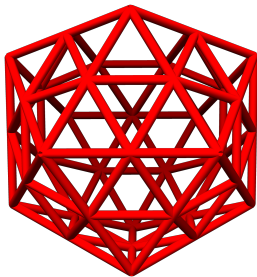
- Mathematical upper limit of **60** for **equivalent** subunits, but biologically want to do better!
- Gene  $\rightarrow$  can already make a **triangle**  $\rightarrow$  might as well make **many!** Triangles are **distinguished** in that they can be **decomposed** into smaller triangles.
- Caspar-Klug ideas of quasi-equivalence and **triangulations**



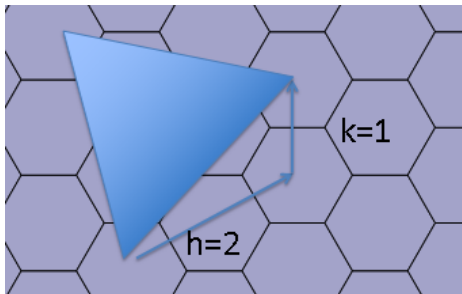
# Caspar-Klug Triangulations

## Triangulation number $T$

- Counts the number of small triangles per icosahedral face
- E.g. Hepatitis B virus (only one structural gene) has  $T = 4$



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



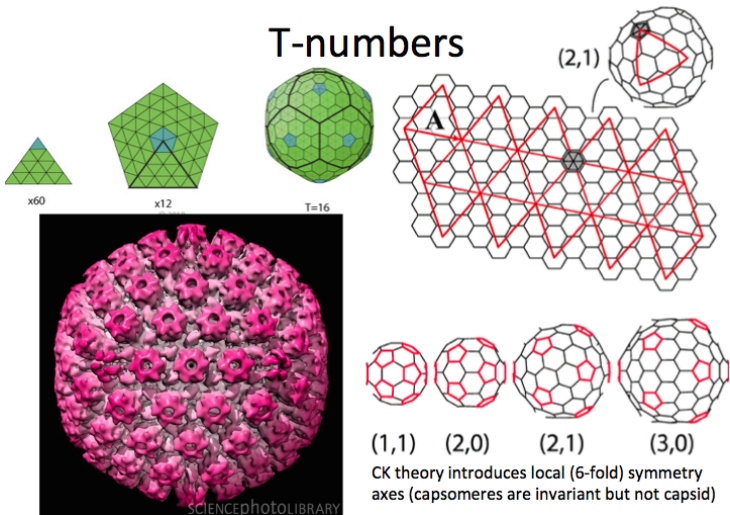
Integer steps  $h$  and  $k$  in hexagonal directions

give allowed triangulation numbers  $T = h^2 + hk + k^2$ .

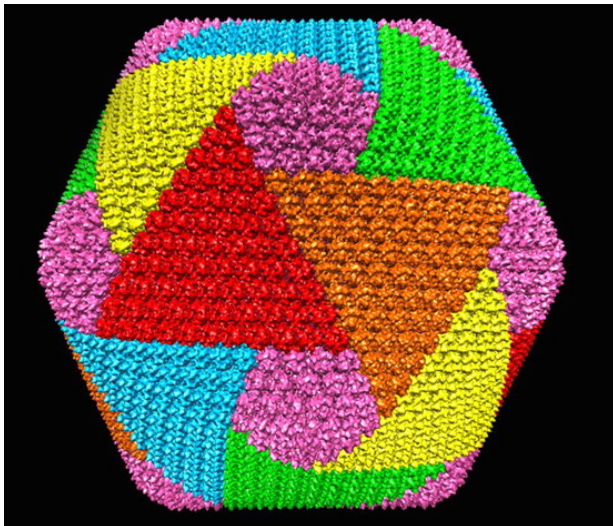
$T$  orbits so  $60T$  proteins

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

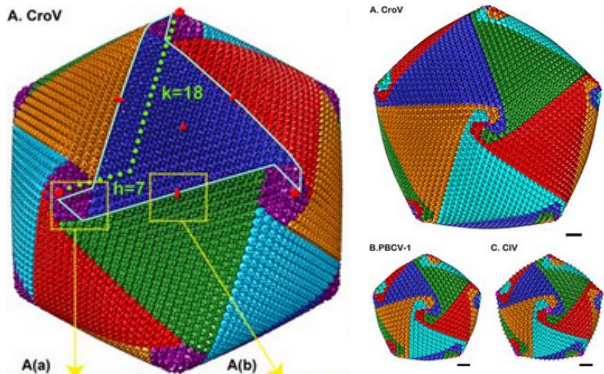
# Viruses: Caspar-Klug $T = h^2 + hk + h^2$ triangulations



# A recent discovery: Giant viruses

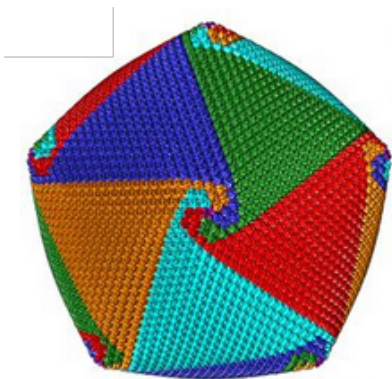


# A family of cages with a common approach – little hooks



Pentasymmetrons and trisymmetrons

## A common approach – little hooks

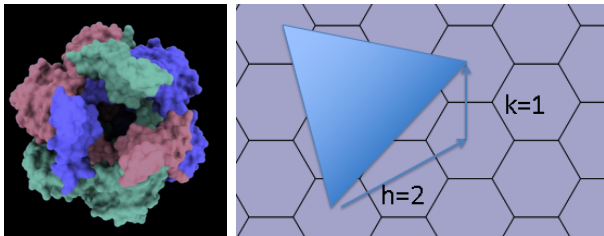


Pentasymmetrons and trisymmetrons

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

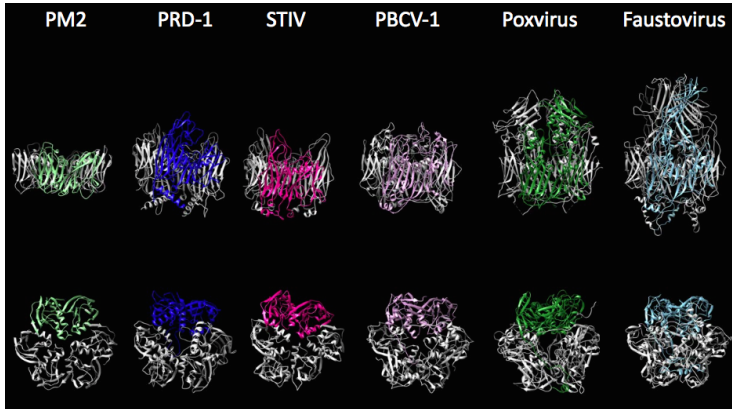
- Chilo iridescent virus:  $T = 147$ ,  $h = 7$  and  $k = 7$
- Paramecium bursaria Chlorella virus 1:  $T = 169$ ,  $h = 7$  and  $k = 8$
- Phaeocystis pouchetti virus:  $T = 219$ ,  $h = 7$  and  $k = 10$
- Faustovirus:  $T = 277$ ,  $h = 7$  and  $k = 12$
- Pacman virus:  $T = 309$ ,  $h = 7$  and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

# Major capsid protein



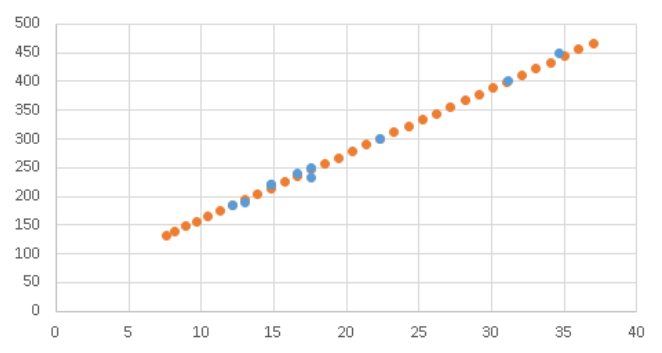
$T$  is an **area**, so  $\sqrt{T}$  gives **size** of triangle and thus also **particle diameter**

# Major capsid protein – evolutionary conservation



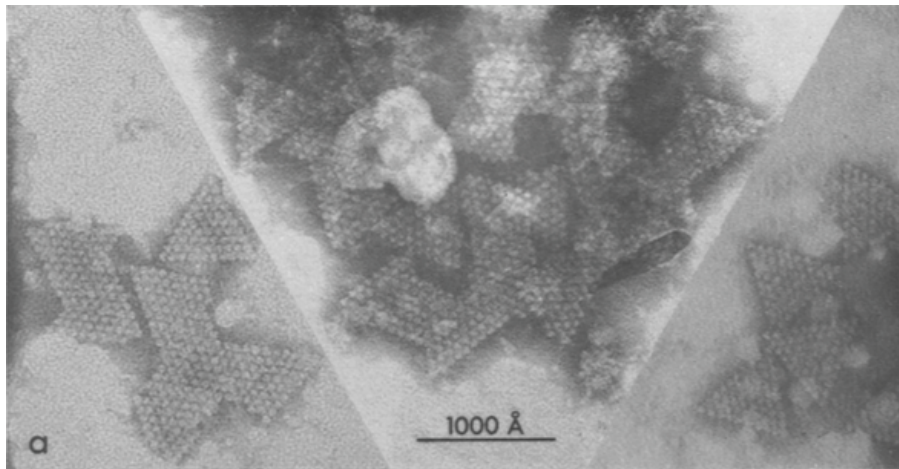
For same size tessellating unit particle size should **scale** as  $\sqrt{T}$

## Predict a scaling relation

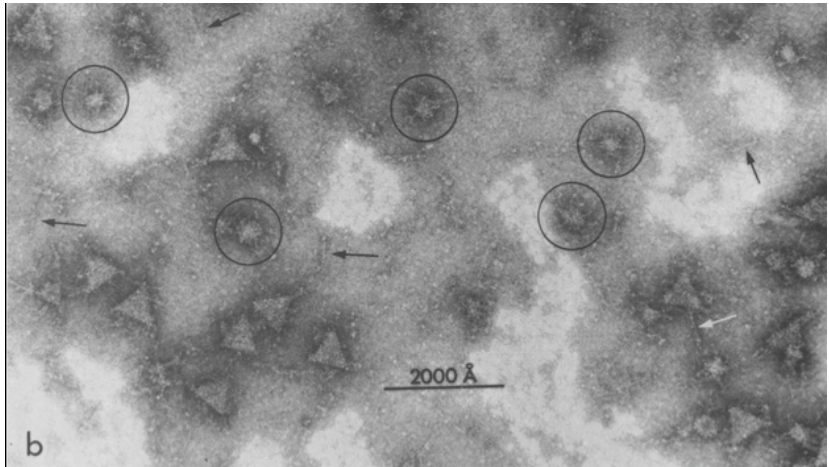


Missing points allowed geometrically but less **stable**? Or just not yet **discovered**? **Predict** Tetraselmis virus 1 TetV-1 of  $257\text{nm} \pm 9\text{nm}$  is exactly  $T = 343$ . **Predict** **holes in family exist** and **sizes** are given by this scaling

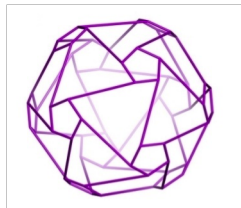
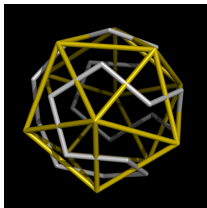
# Trisymmetrons and Pentasymmetrons



# Major capsid protein - trimer, pseudohexamer



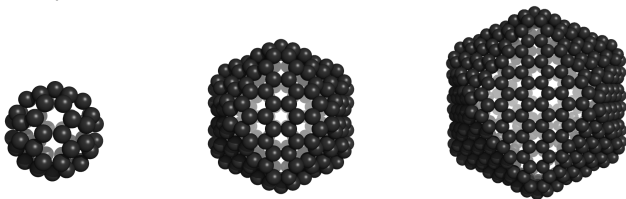
# Build from prearranged blocks? Back to Hamiltonian paths



- 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**

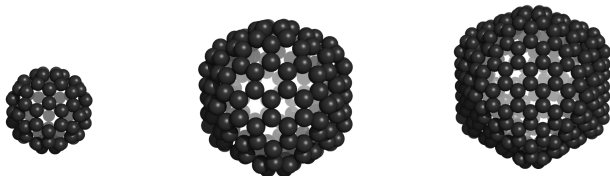
# Other objects made from identical building blocks: Fullerenes

- 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)

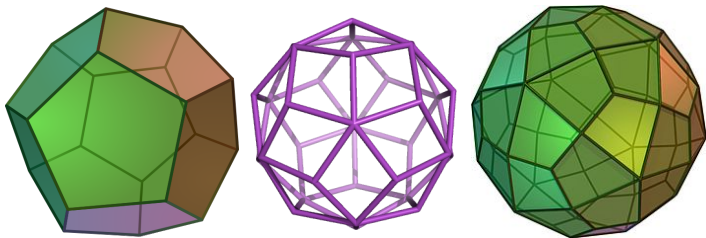


# Fullerenes

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

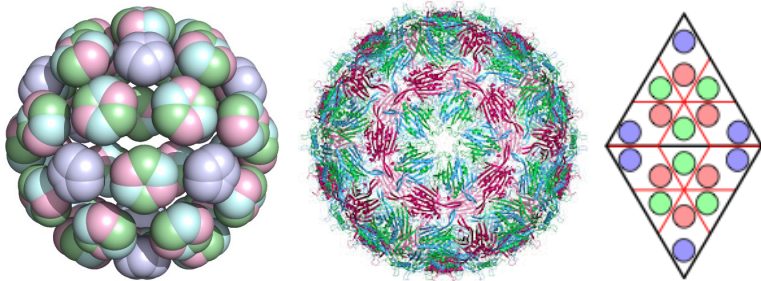


## More general tile shapes from other icosahedral tilings



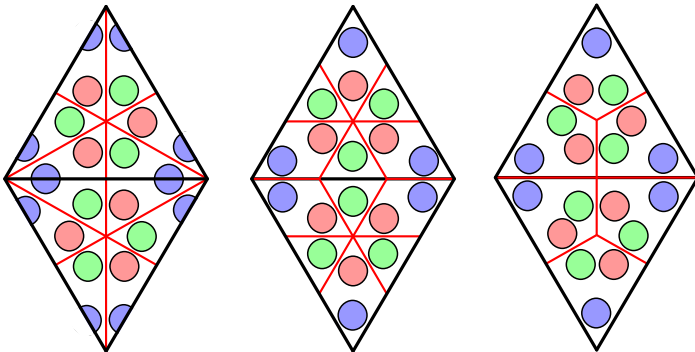
Other **tile shapes** can also give icosahedral tilings: **pentagons** (dodecahedron), **rhombuses** (rhombic triacontahedron), **kites** (deltoidal hexecontahedron)

## triangulations vs other quasi-equivalent tilings



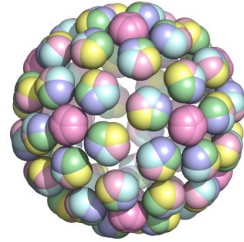
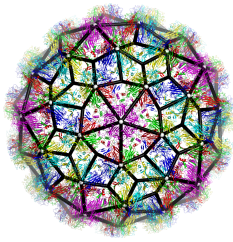
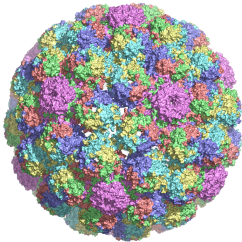
Two **viral surface** layouts: a  $T = 4$  **triangulation** (e.g. HBV) and a **rhombus** tiling (MS2) for a pseudo  $T = 3$  **triangulation**

# Other quasi-equivalent tilings



Three (pseudo)  $T = 3$  capsids: Polio, MS2 and Pariacoto.  
Different building blocks depending on the underlying biology:  
**dimer** vs **trimer** interactions.

# A puzzle: non-quasiequivalent tilings – Penrose



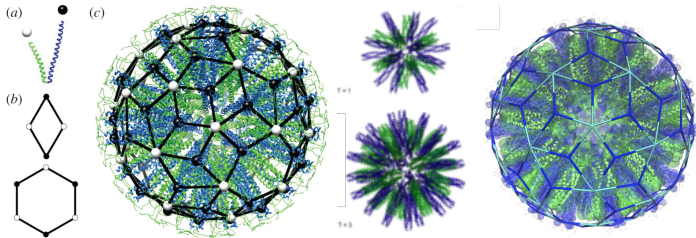
More general icosahedral tilings: Cryo-EM **reconstruction** of Human Papillomavirus (HPV), a **kite-rhombus** tiling and a pseudo  $T = 7$  **triangulation** (but only 6 orbits).  
Reidun Twarock: Viral Tiling theory

# Architecture

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



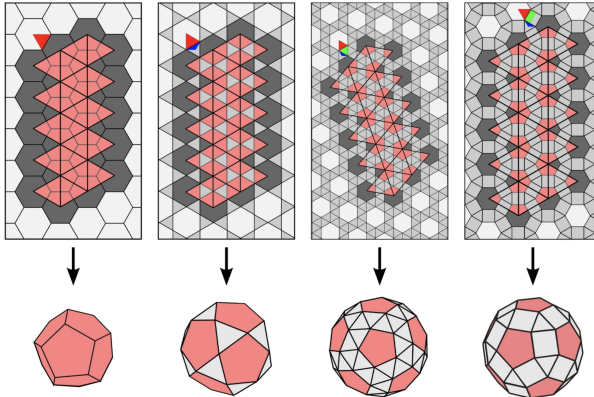
# Nanotech 1: Self-assembling protein nanoparticles



**De novo** design of nanoparticles from identical building blocks.

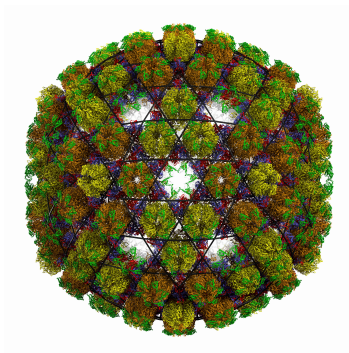
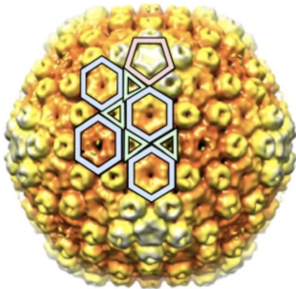
**Quantised** number of building blocks (e.g. in mass spec) - mathematically predict structure and properties. Particles used for vaccine design (malaria).

# More generalised: Archimedean tilings



Reidun Twarock & Antoni Luque: Put an icosahedral net on more general hexagonal tilings.

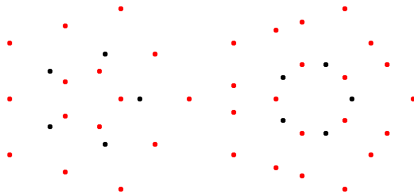
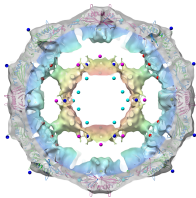
# Beyond quasi-equivalence: Archimedean tilings



More general surface tilings e.g. for phage Basilisk and Herpes Simplex Virus.

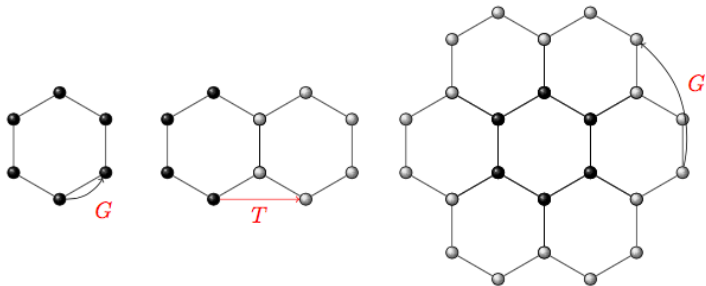
# More general symmetry still? Affine symmetry ideas.

- Description only in terms of **surface structures**.
- 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



Affine extensions -  $A_2$ 

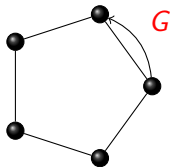
Unit translation of a unit hexagon



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.

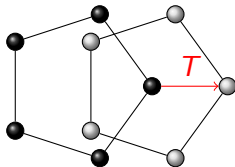
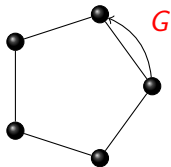
# Affine extensions of non-crystallographic groups?

Unit translation along a vertex of a unit pentagon



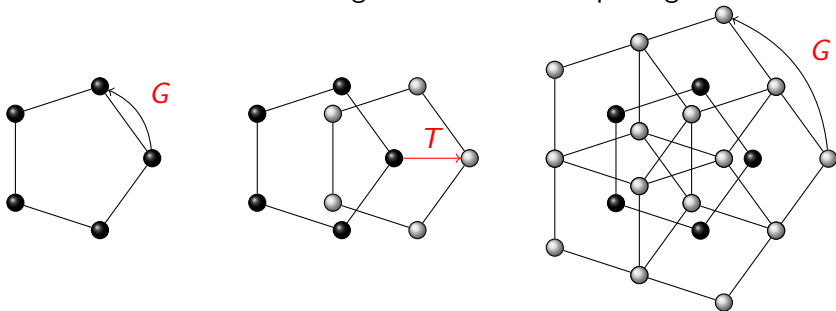
# Affine extensions of non-crystallographic groups?

Unit translation along a vertex of a unit pentagon



## Affine extensions of non-crystallographic groups?

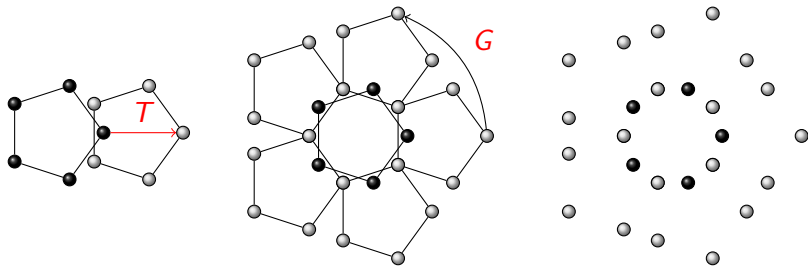
Unit translation along a vertex of a unit pentagon



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?

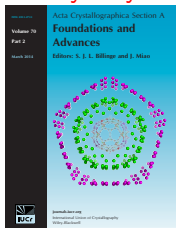
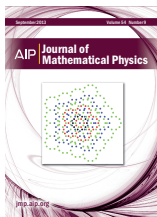
Translation of length  $\tau = \frac{1}{2}(1 + \sqrt{5}) \approx 1.618$  (golden ratio)



Cartoon version of a **virus** or **carbon onion**. Would there be a **biological 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 polye 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  $72^\circ$  about the midpoint of the original pentagon. This results in a new set of points obeying five-fold symmetry, set 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 Pentacoronavirus.

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  $C_{60} @ C_{120} @ C_{180}$ .

BY

well-known effect for photons, and it turns out to hold for other quantum particles too. James Falconer and colleagues have performed the Hong-Ou-Mandel quantum interference experiment using plasmons, which are quantized surface plasmon waves. Pairs of photons are fed into a specially designed photonic waveguide that mixes the paths of the light-excited surface plasmons in the same way as a beam splitter. 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 intercede. **DO**

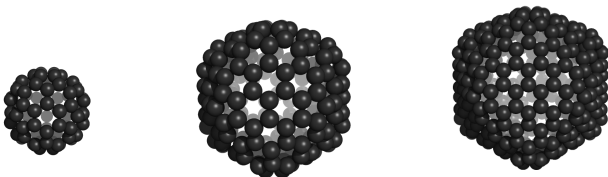
Written by Amy Chew, Min Gong, Albert Polman, Ben Lohr and Klaus Wiggler

NATURE PHYSICS | VOL 10 | APRIL 2014 | www.nature.com/naturephysics

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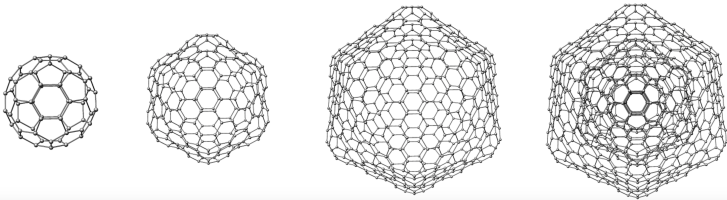
# Extension to fullerenes: carbon onions

- 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** ( $C_{80} - C_{180} - C_{320}$ )

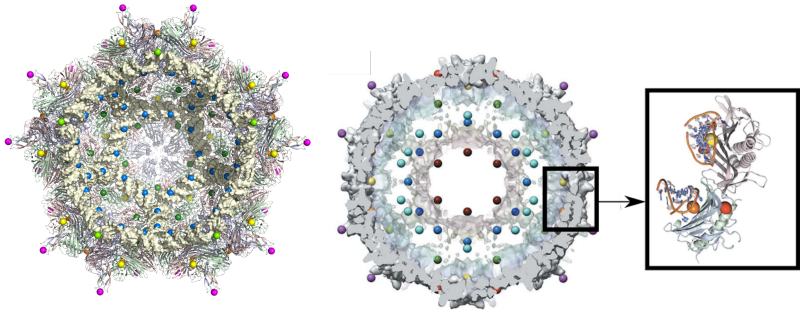


# Extension to fullerenes: carbon onions

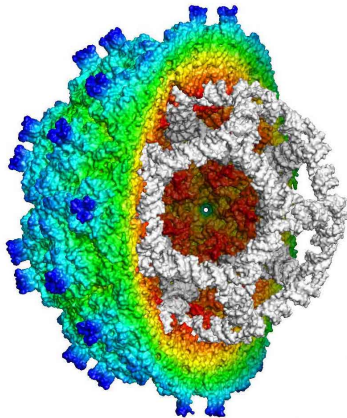
- Extend idea of affine symmetry to other icosahedral objects in nature: football-shaped **fullerenes**
- Recover different shells with icosahedral symmetry from affine approach: **carbon onions** ( $C_{60} - C_{240} - C_{540}$ )



# Use in Mathematical Virology

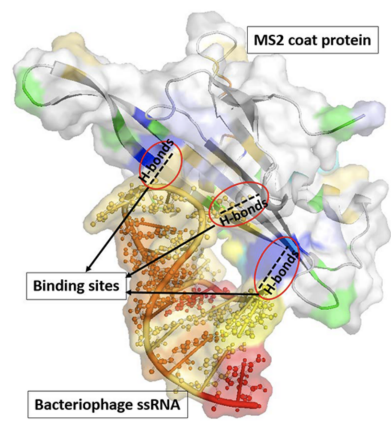
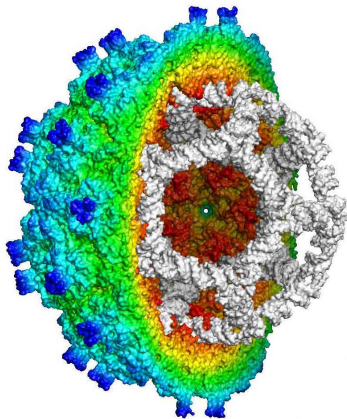


## 3D distribution: RNA-CP contacts



There are **specific interactions** between **RNA** and coat protein (**CP**) given by icosahedral **symmetry** axes

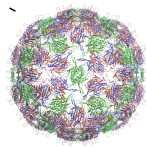
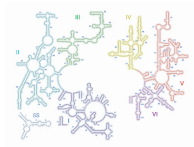
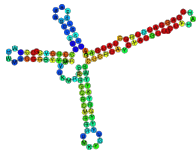
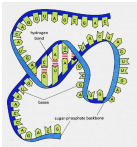
## 3D distribution: RNA-CP contacts



There are **specific interactions** between **RNA** and coat protein (**CP**) given by icosahedral **symmetry** axes

# New insight into RNA virus assembly

- There are **specific interactions** between **RNA** and inner (**capsid**) surface
- Essential for **(co-)assembly**, as only this RNA-CP interaction turns CP into **right geometric** shape for **capsid formation** for MS2
- **Hamiltonian cycle** visiting each RNA-CP contact once – dictated by symmetry
- Even the RNA has an **icosahedrally ordered component**



# RNA is involved in a co-assembly process through packaging signals



These **packaging signals** help recruit coat protein (CP) in a **co-assembly** process.

# Overview

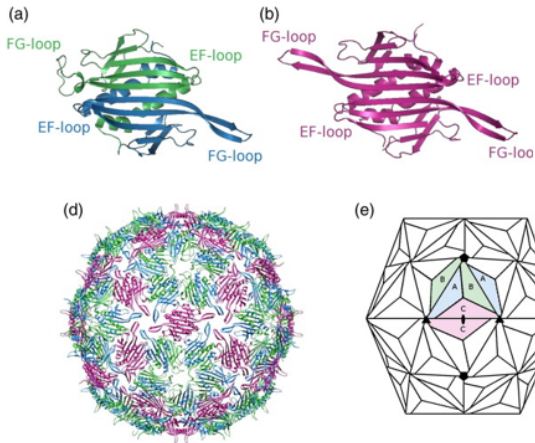
## Mathematical Modelling

- Watson & Crick: Icosahedral and helical symmetry
- Caspar & Klug: Triangulations
- Twarock: More general surface tilings
- Affine symmetry: genome and capsid

## Computational Modelling

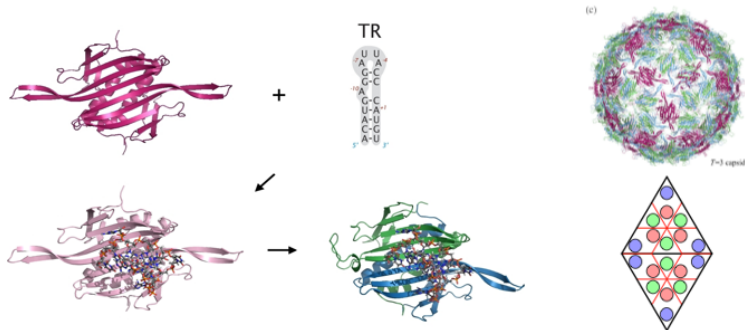
- Bioinformatics: packaging signals
- Gillespie stochastic simulations: epidemiological, infection, assembly
- Machine learning: fitness landscape

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



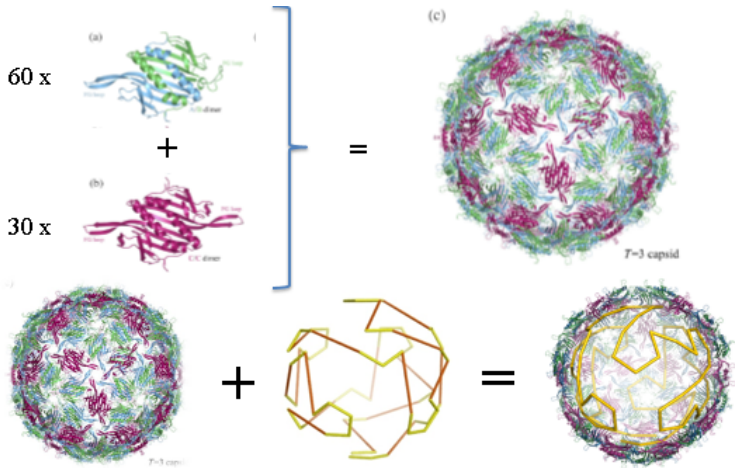
## Need to bind RNA in 60 places

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).



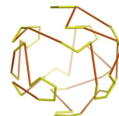
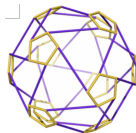
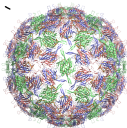
Peter Stockley (Leeds), Neil Ranson (Leeds), Eric Dykeman (York)  
et al

# MS2 Hamiltonian path

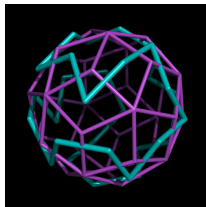
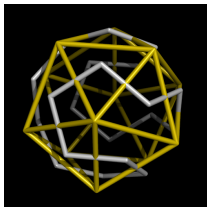
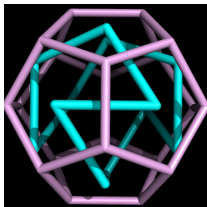


# New insight into RNA virus assembly

- Example of 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** identified an **evolutionarily conserved** cycle
- **Patents** for new **antiviral strategies** and **virus-like nanoparticles** e.g. for **drug delivery** (Twarock group)

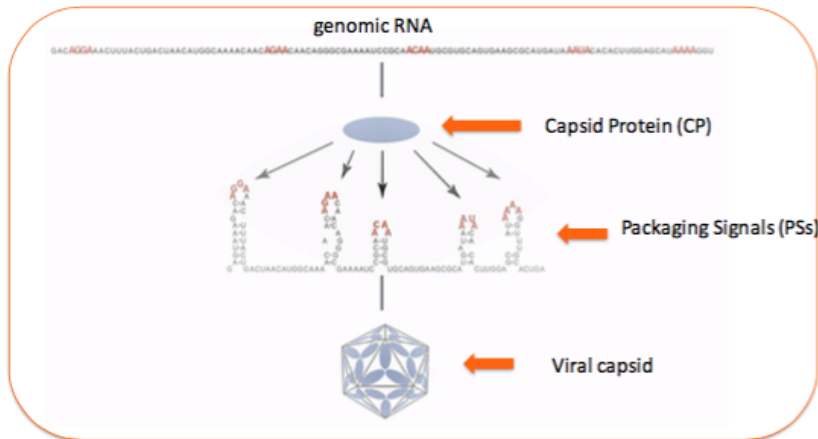


# Hamiltonian cycles on icosahedral solids



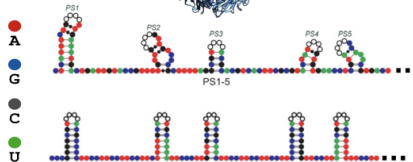
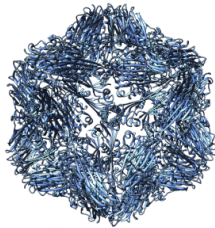
- So **interaction contacts** are given by the **symmetry**
- Orbits of the interaction points have to be visited by the **RNA exactly once**
- Even the RNA has an **icosahedrally ordered component**
- **Hamiltonian cycles** for dodecahedron, icosahedron and rhombic triacontahedron

# Assembly via Multiple dispersed Packaging Signals



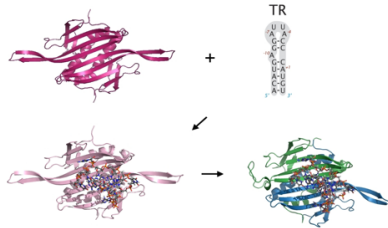


# Nanotech 2: Engineering Packaging Signals to make VLPs



**Repurpose:** Improved sequences optimised for assembly efficiency (e.g. STNV). Potential applications to vaccines or drug delivery.

# Antivirals: Understanding assembly allows one to interfere



- target **RNA**
- target **CP**
- introduces **competitors**
- this might still drive **evolution** due to exerting selection pressures but less so than biochemical antivirals

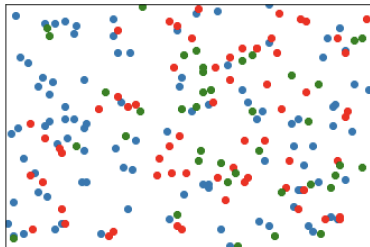
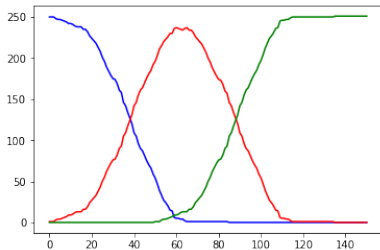
# Simulations

## Stochastic simulations

rather than ODE models because of discrete nature and low numbers: Gillespie-type algorithms that select a random reaction to occur

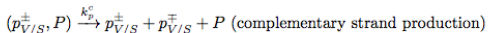
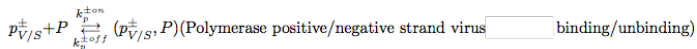
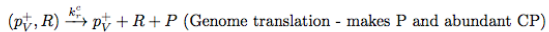
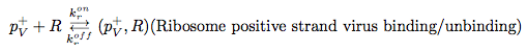
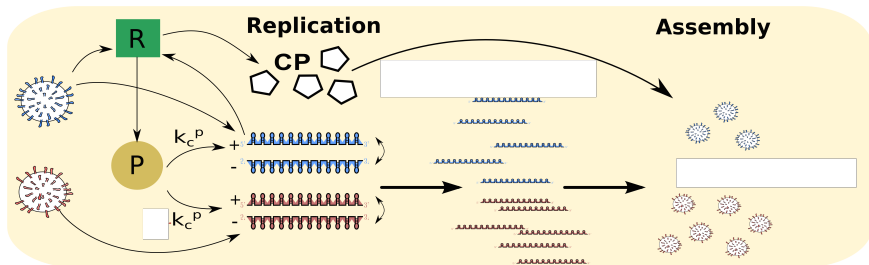
- SIR and spatial modelling (epidemiology)
- Multi-scale model coupling of an intracellular model with an immune system (infection model)
- Assembly toy model simulations

# Basic epidemiological simulations

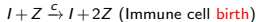
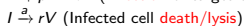
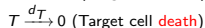
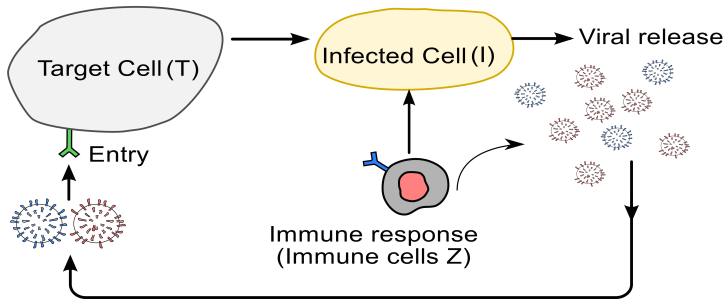


Gillespie **SIR model** and **spatial/movement model**.

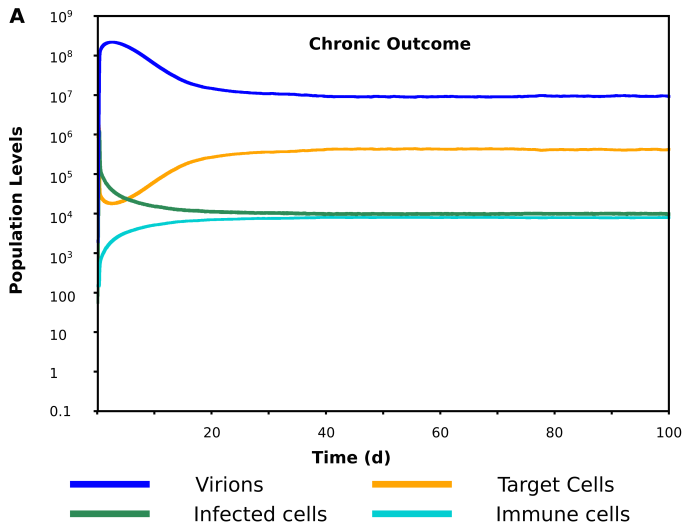
# Infection model: intracellular model



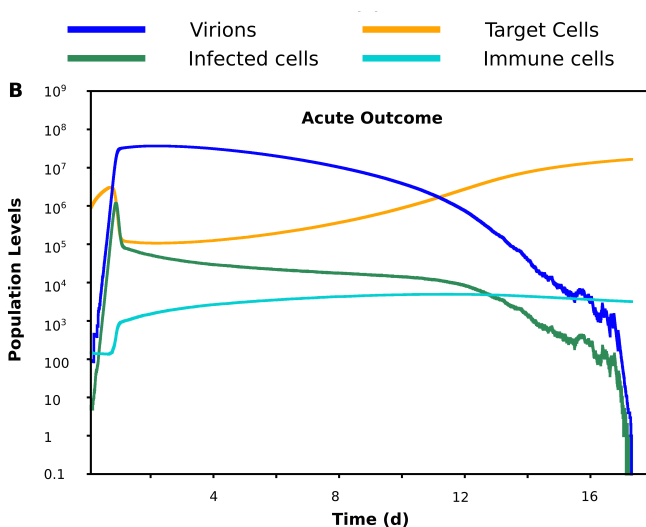
# Infection model: immune system



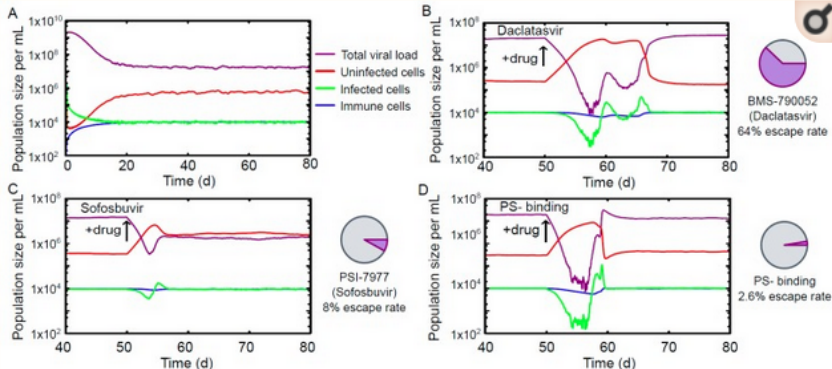
# Chronic infections



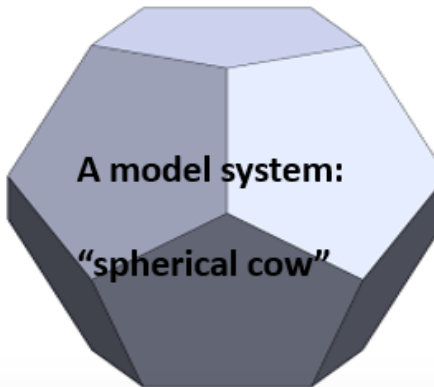
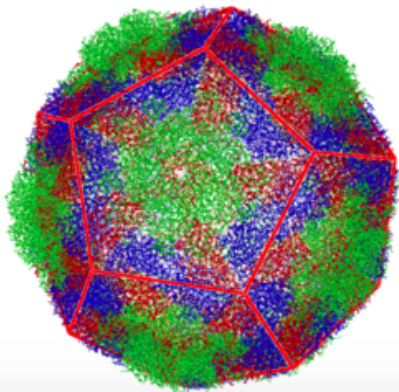
# Acute infections



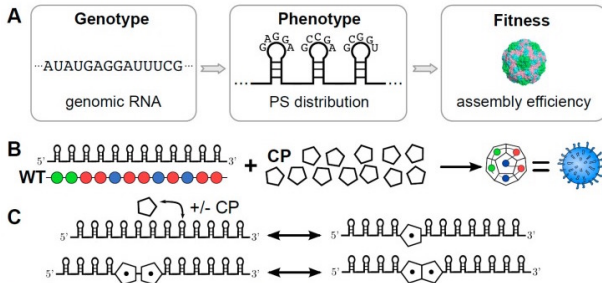
# Antivirals: Evolutionarily stable drugs



# Simulating an assembly toy model: Dodecahedral cow

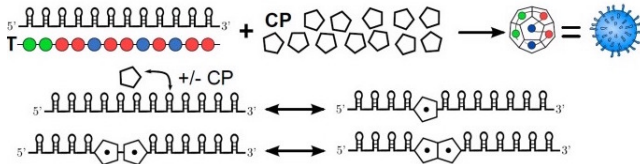


## A mathematical and biophysical assembly toy model



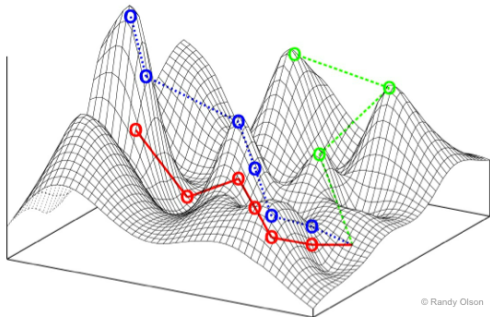
A **phenomenological** genome space of 12 packaging signals with 3 binding **affinity** bands (weak, medium, strong). Can compute the **whole** space explicitly in terms of **assembly efficiency**.

## Simplest model: the dodecahedron



- 12 PSs in 3 bands (strong/intermediate/weak, 3/2/1, green/blue/red)
- Gillespie molecular **simulation**: stochastically select one possible reaction at a time
- Enough **resources for 2000** virus capsids
- Computed fitness landscape in 4 weeks on a supercomputer

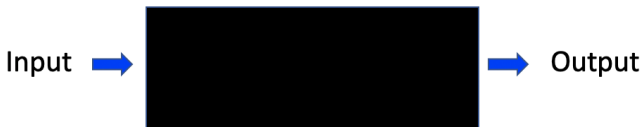
# Fitness Landscape



© Randy Olson

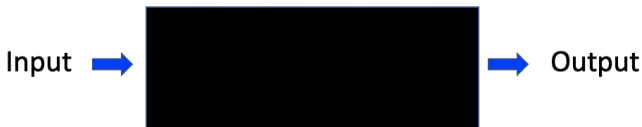
Generally **messy** (many contributions) and difficult to quantify.  
Here capture the **assembly** contribution for the phenotype space of  $3^{12}$  points with (stochastic) assembly **efficiency** ( $< 2000$ ).

# A prime machine learning example



- **Input vector:** Genotype/Phenotype of length 12 (packaging signal strengths in 3 bands): 12D vector
- **Output vector:** Assembly efficiency (out of 2000 possible capsids): scalar
- **Black box:** Expensive map: Molecular dynamics simulations (computationally very costly)

# A prime machine learning example



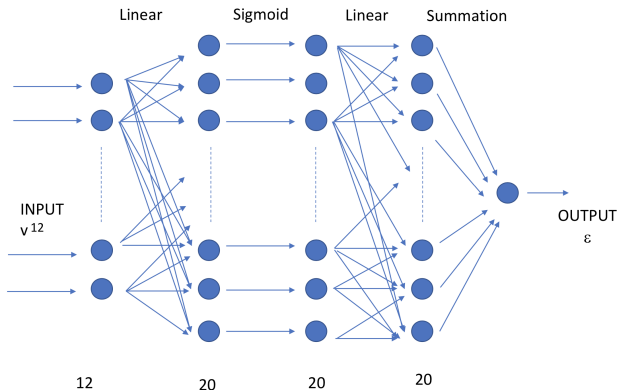
- **Input vector:** Genotype/Phenotype of length 12 (packaging signal strengths in 3 bands): 12D vector
- **Output vector:** Assembly efficiency (out of 2000 possible capsids): scalar
  
- **Black box:** Cheap approximation of map: Machine learning via a neural network

# Input and Output dataset

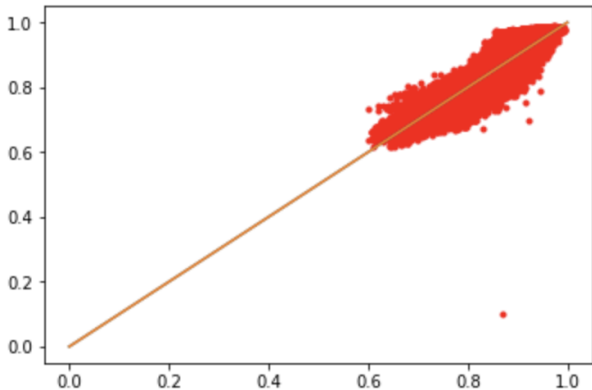
	Genome	Fitness
0	111111111111	200
1	111111111112	1393
2	111111111113	1869
3	111111111121	1597
4	111111111122	1896
5	111111111123	1960
6	111111111131	1875
7	111111111132	1959
8	111111111133	1961
9	111111111211	1639
10	111111111212	1683
11	111111111213	1895
12	111111111221	1848
13	111111111222	1904
14	111111111223	1964
15	111111111231	1904
16	111111111232	1949
17	111111111233	1959
18	111111111311	1852
19	111111111312	1858

$3^{12} \sim \frac{1}{2}$  Million data points

# Machine Learning with a Neural Network

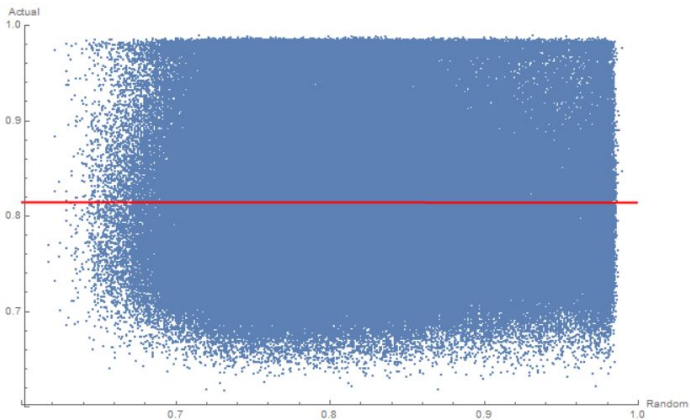


# Predictions



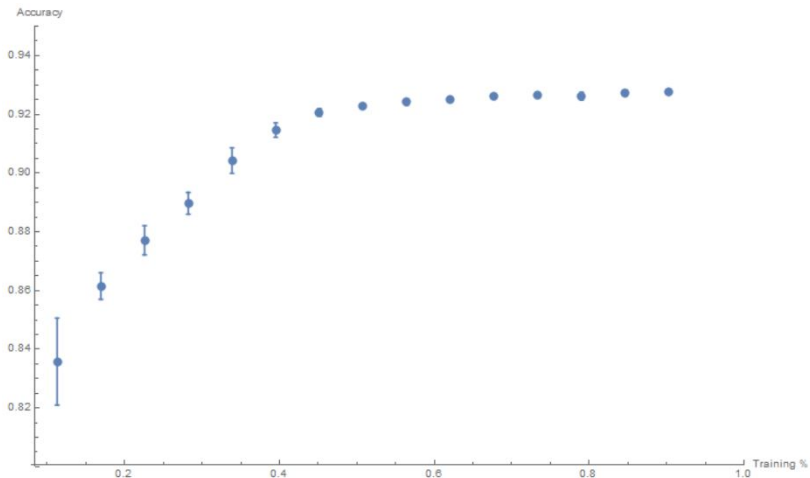
predicted vs actual value of assembly efficiency

# Predictions

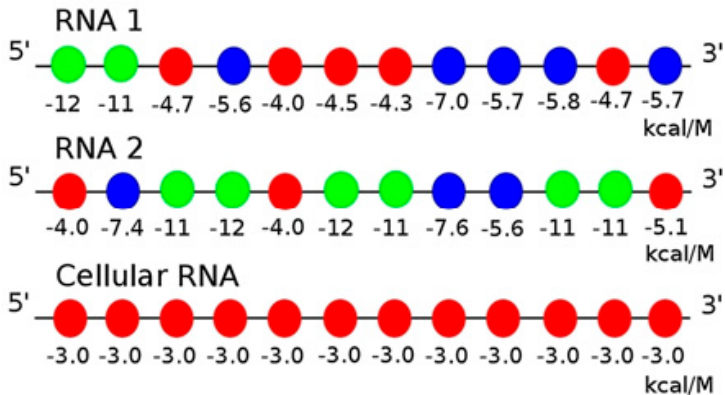


vs **random** assignments of assembly efficiency

# Learning Curve

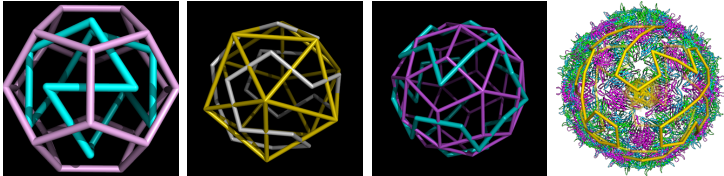


## Not just random, intrinsic features?



Definite **starting point** with strong binding, then weaker binding in an **error-correcting** bit, driven to completion by **thermodynamics**

# Conclusions: Mathematical and Computational Virology



ML might allow us to do more **realistic** models in future – geometry, binding strength **gradation**. **Partially** explore the landscape and predict the rest (procedurally)?

*Insights into **mathematical and biophysical** design principles open up novel directions for **biomedicine and nanotechnology**.*

# Overview

## Mathematical Modelling

- Watson & Crick: Icosahedral and helical symmetry
- Caspar & Klug: Triangulations
- Twarock: More general surface tilings
- Affine symmetry: genome and capsid

## Computational Modelling

- Bioinformatics: packaging signals
- Gillespie stochastic simulations: epidemiological, infection, assembly
- Machine learning: fitness landscape

# Further references

- [1] F. Crick, J. Watson, *Nature* 177, 1956, 473.
- [2] D. Caspar, A. Klug, *Cold Spring Harb. Symp. Quant. Biol.* 27, 1962, 1.
- [3] R. Twarock, A tiling approach to virus capsid assembly explaining a structural puzzle in virology, *J. Theor. Biol.* 226, 477-482 (2004)
- [4] R. Twarock & A. Luque, Structural puzzles in virology solved with an overarching icosahedral design principle, *Nature Comms* 10.1 (2019): 1-9
- [5] P-P. Dechant, C. Boehm & R. Twarock, Novel Kac-Moody-type affine extensions of non-crystallographic Coxeter groups, *J. Phys A*, 285202 (2012)
- [6] T. Keef, J.P. Wardman, N.A. Ranson, P.G. Stockley & R. Twarock, Structural constraints on the three-dimensional geometry of simple viruses: case studies of a new predictive tool. *Acta Cryst A*. 69, 2013, 140-50
- [7] P. Dechant, J. Wardman, T. Keef & R. Twarock, Viruses and fullerenes - symmetry as a common thread? *Acta Cryst A* 70, 2014, 162-7|
- [8] R. Twarock, G. Leonov & P.G. Stockley, Hamiltonian Path Analysis of Viral Genomes, *Nature Communications* 9, 2018, 2021
- [9] R. Twarock & P.G. Stockley, RNA-Mediated Virus Assembly: Mechanisms and Consequences for Viral Evolution and Therapy, *Annu Rev Biophys.* 48, 2019, 495-514
- [10] G. Indelicato, N. Wahome, P. Ringler, S. A. Müller, M.-P. Nieh, P. Burkhard & R. Twarock, Principles Governing the Self-Assembly of Coiled-Coil Protein Nanoparticles, *Biophys J.* 110, 2016, 646-60

## Main references

### Models of Viral Capsid Symmetry as a Driver of Discovery in Virology and Nanotechnology

P-P Dechant, R Twarock, The Biochemist, 2021

### Machine-learning a virus assembly fitness landscape

P-P Dechant, Y-H He, PLOS One, arXiv preprint  
arXiv:1901.05051, 2021

### Topical Collection: Machine-learning mathematical structures

Editors: Y-H He, P-P Dechant, A Kasprzik, A Lukas  
Advances in Applied Clifford Algebras, August 2021

# Algebraic interests

Thank you!

- **Exceptional** root systems/geometries ( $H_4$ ,  $E_8$  etc)
- **Clifford** algebras
- **ADE** correspondences
- (Reflexive) **polytopes**

