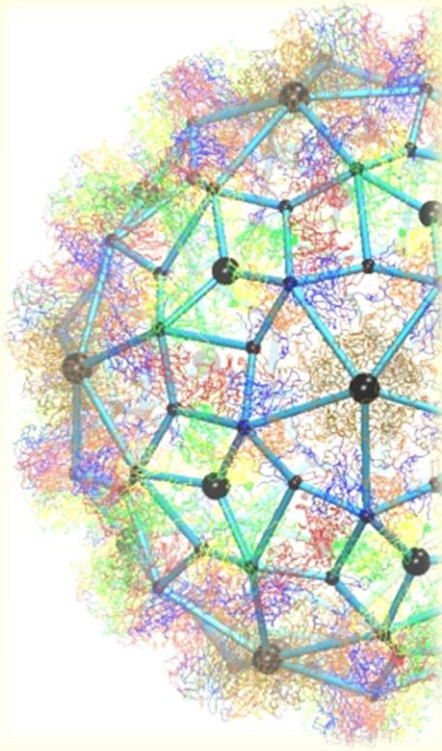
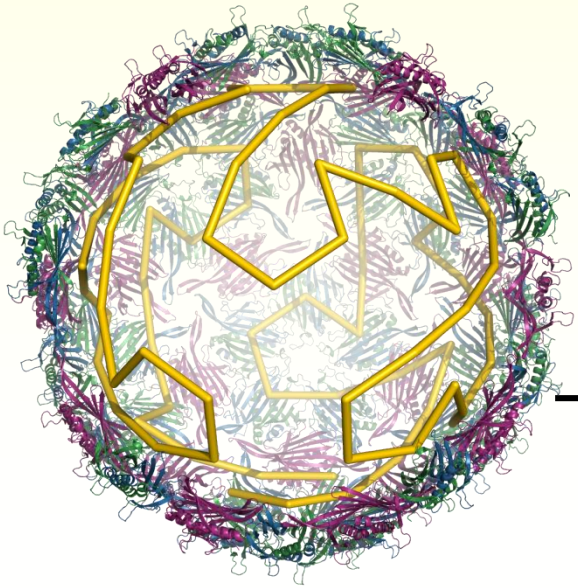
Geometry:

A secret weapon in the fight against viruses





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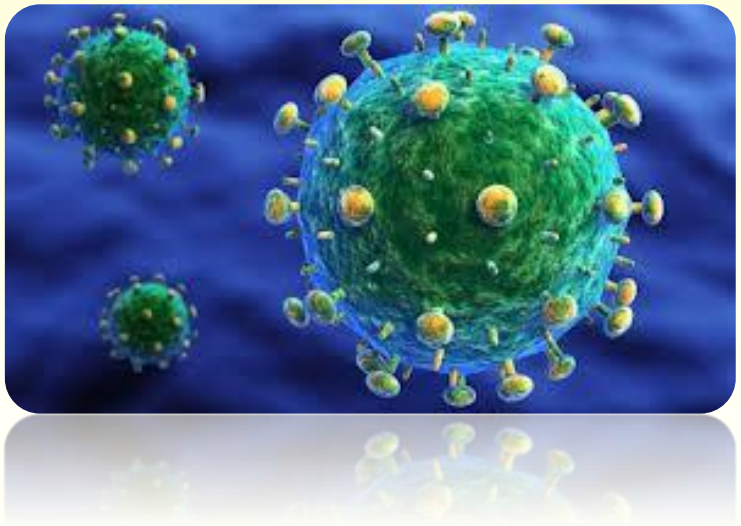
Gresham Lecture 2015

Viruses cause disease

Viruses are responsible for a wide spectrum of devastating diseases in humans animals and plants.

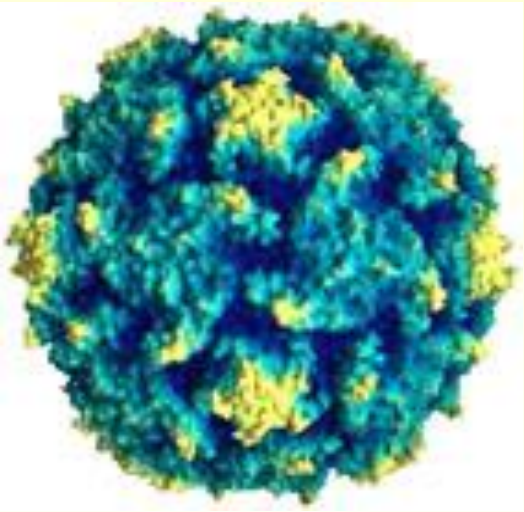
Examples:

- HIV
- Hepatitis C
- Cancer-causing viruses
- Picornaviruses linked with type 1 diabetes



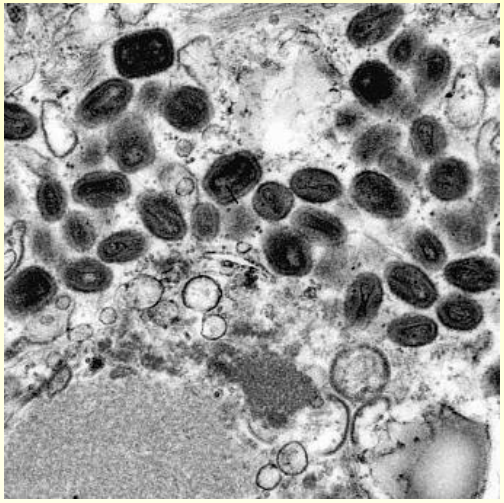
Viruses are also the cause of the common cold!

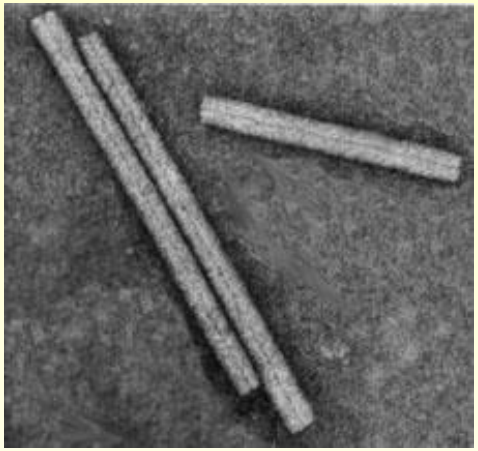
Viruses are known since antiquity…

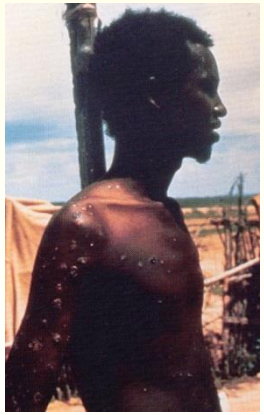


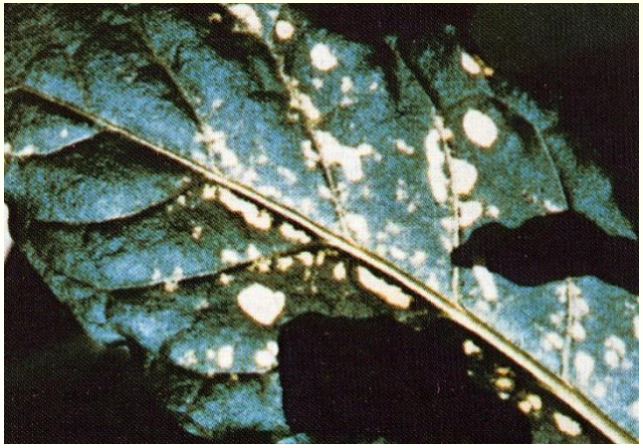
Polio virus

…and affect different kingdoms of life





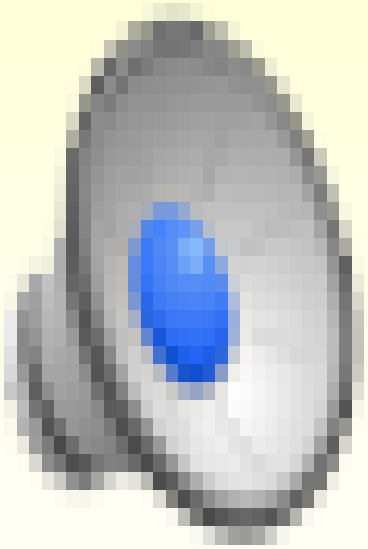




Smallpox infection

Effects of plant viruses of food supply

A bacteriophage infecting a bacterium

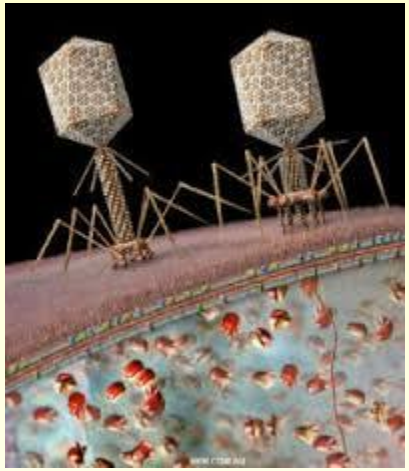


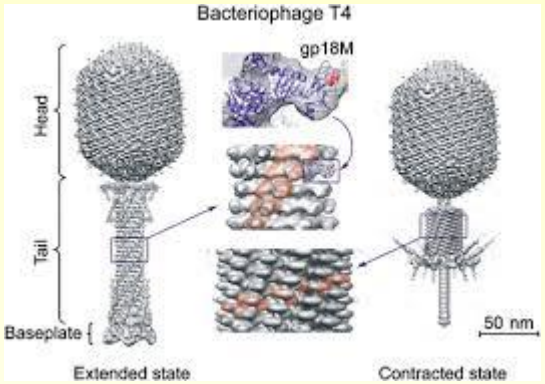
Petr G Leiman

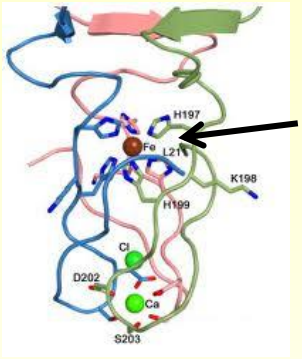
Michael G Rossman,

Purdue University

Viruses are nanoscale machines

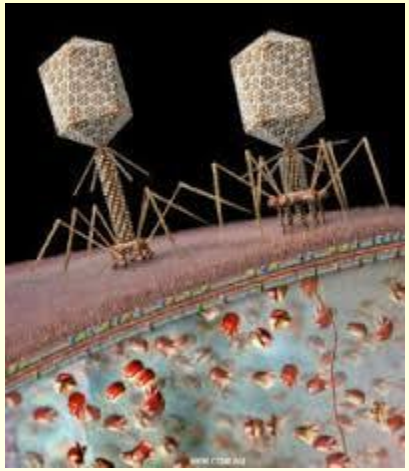


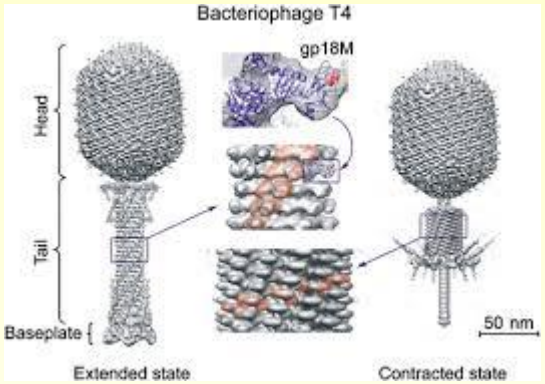


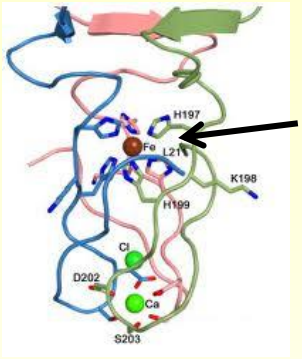


Iron atom

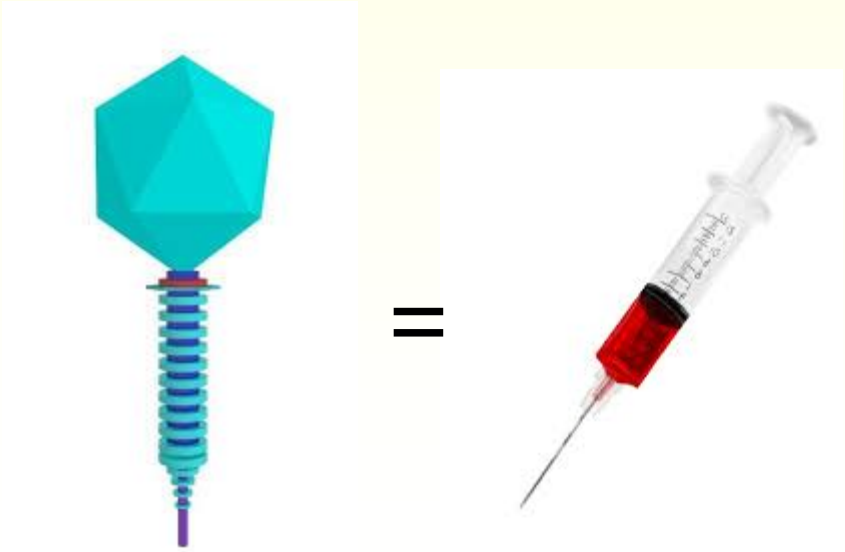
Viruses are nanoscale machines







Iron atom



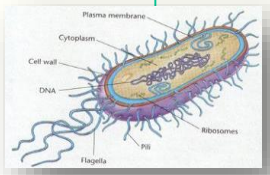
Viruses are very small…

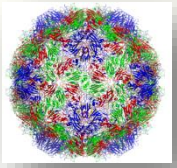
1m $10m^{-1}$ $10m^{-2}$ $10m^{-3}$ $10m^{-4}$ $10m^{-5}$ $10m^{-6}$ $10m^{-7}$ $10m^{-8}$

Eye

Electron Microscope

Light Microscope





... in fact, really tiny!

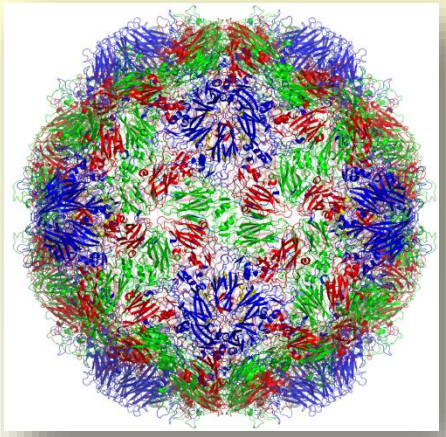
For comparison:

A medium sized virion next to a flea…

…is roughly equivalent to a human next to a mountain twice the size of Mount Everest

Escherichia coli (E. coli)
Infected by the virus
"Coliphage T4", these
bacteria explode, releasing
new viruses

Viruses act like Trojan horses



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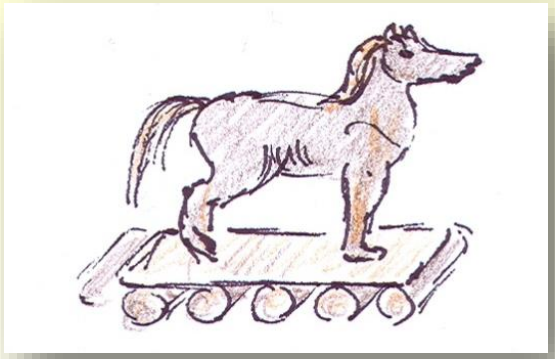
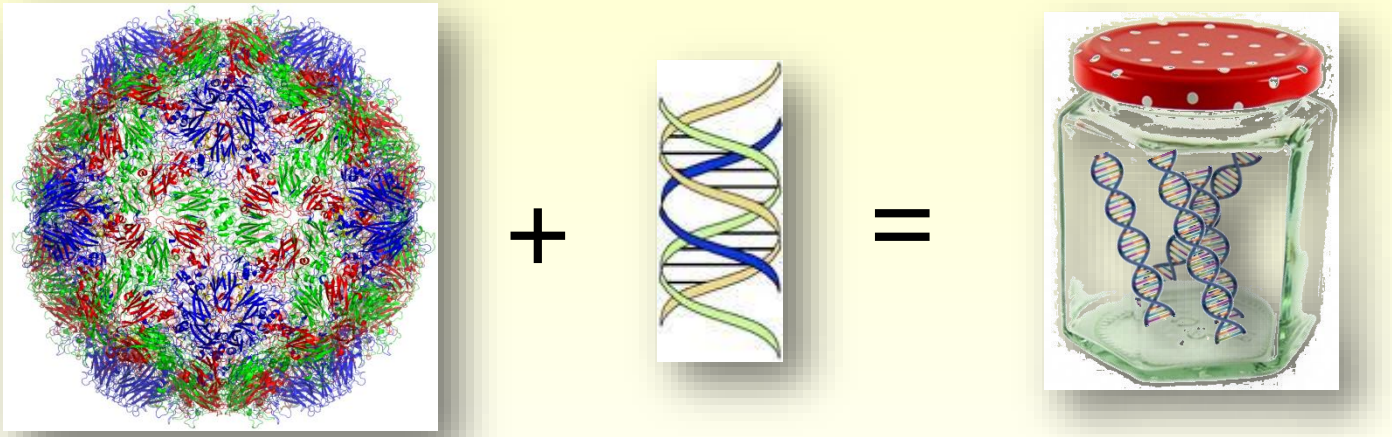


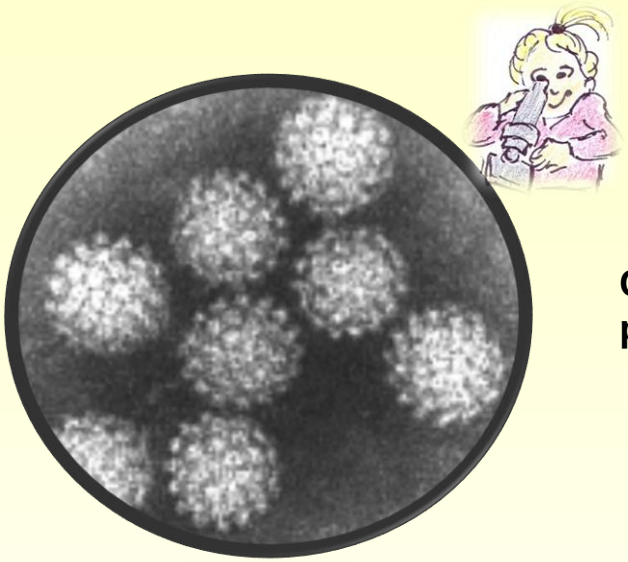
Viral capsids transport genetic material into a host, and thus hijack their hosts machinery to produce new progeny virus

Viruses look like containers

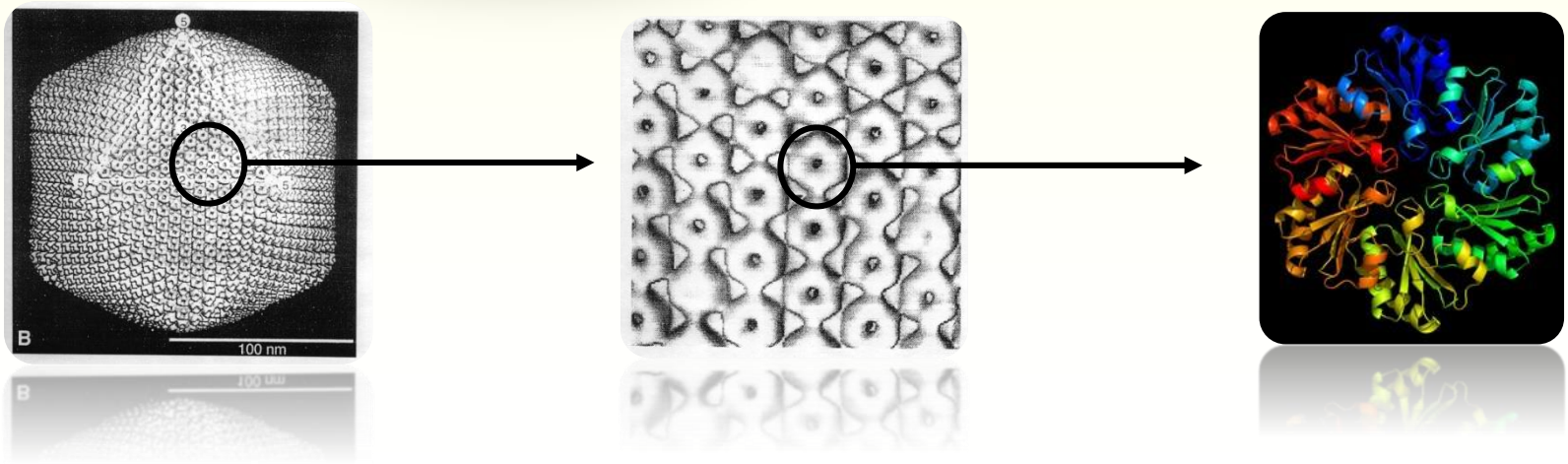


Viruses are containers formed from protein that contain the genetic material

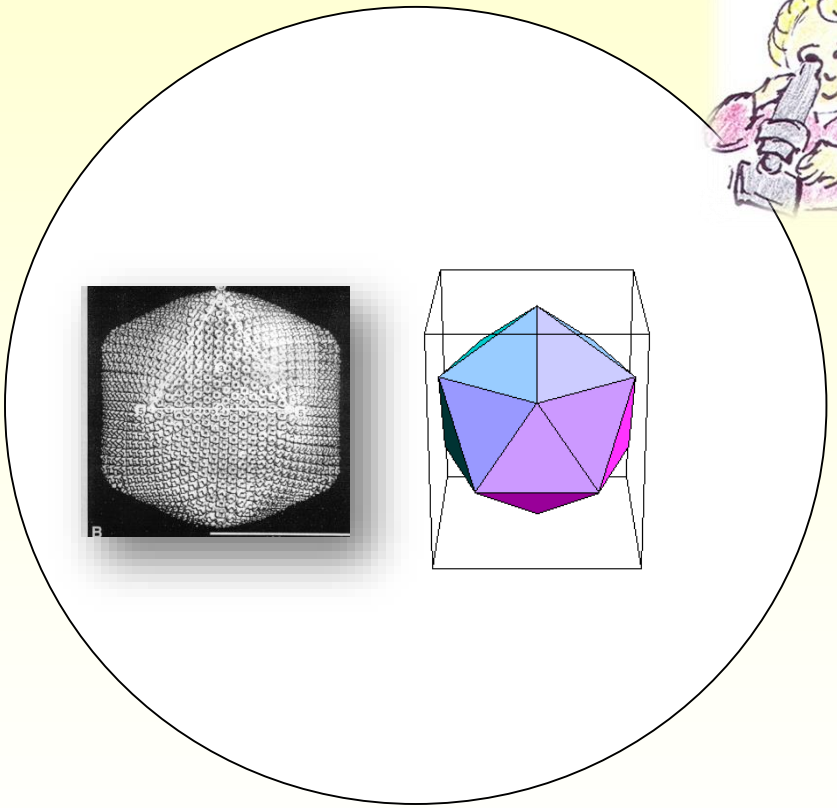
Under the electron microscope



Cryoelectron microscopy pictures of viral particles

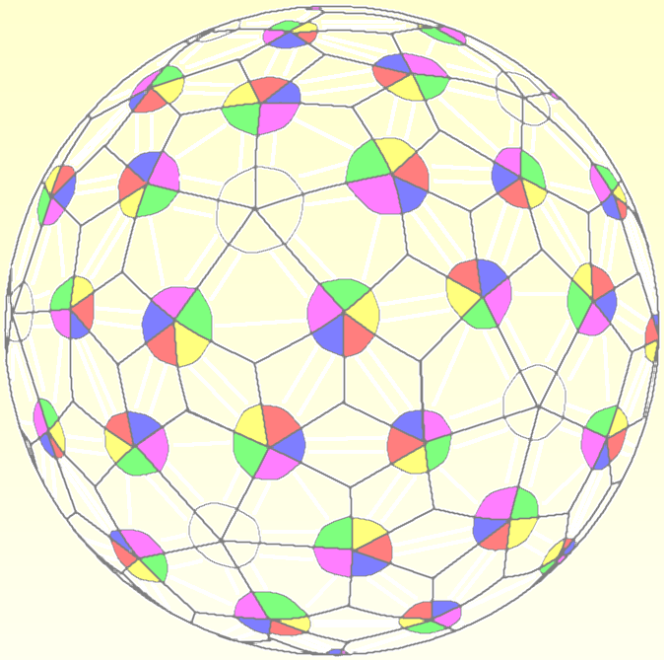


Under the mathematical microscope



Using mathematics it is possible to better understand virus structure and formation.

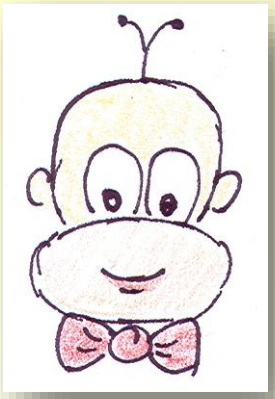
These insights have allowed us to develop new anti-viral strategies.



Geometry & Viruses

The language of symmetry

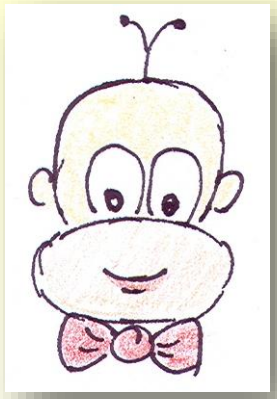
Reflection:



Axis of symmetry: mirror

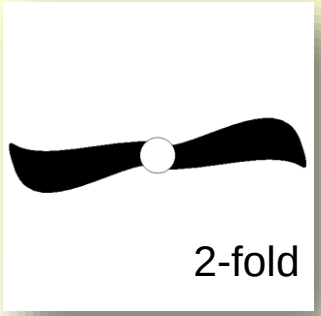
The language of symmetry

Reflection:



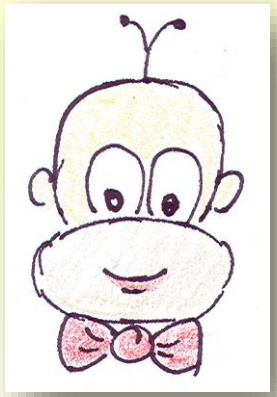
Axis of symmetry: mirror

Rotation:



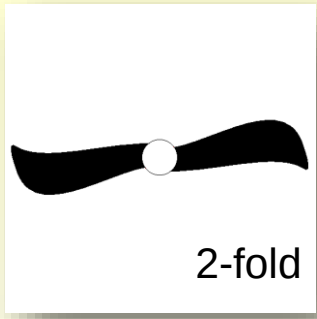
The language of symmetry

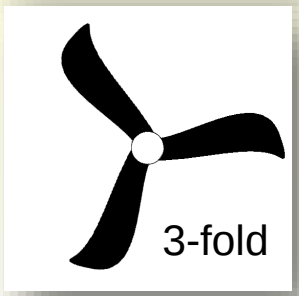
Reflection:



Axis of symmetry: mirror

Rotation:





The language of symmetry

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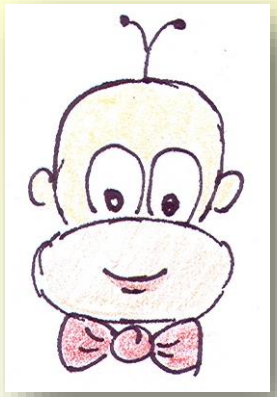

Axis of symmetry: mirror

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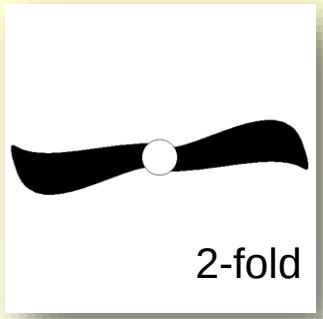
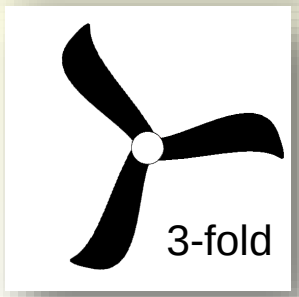
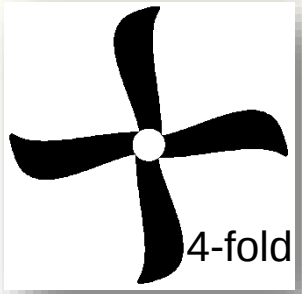
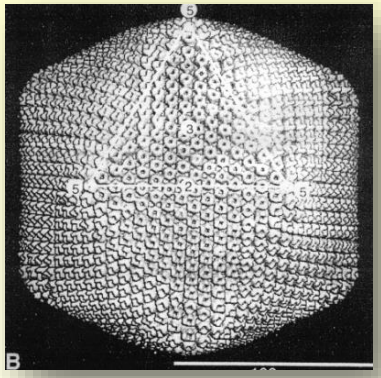
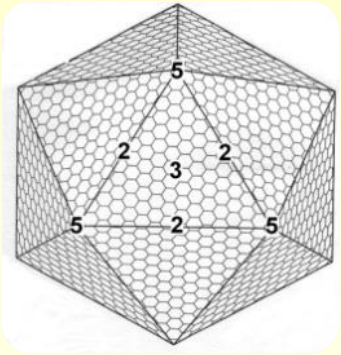


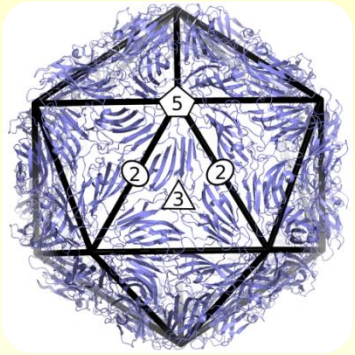


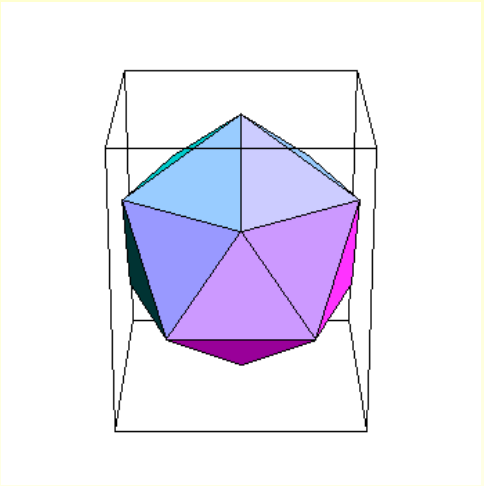


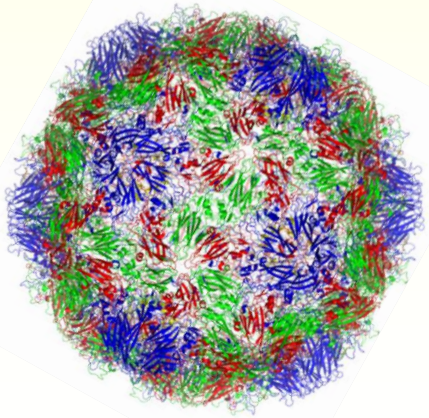
Viral symmetry







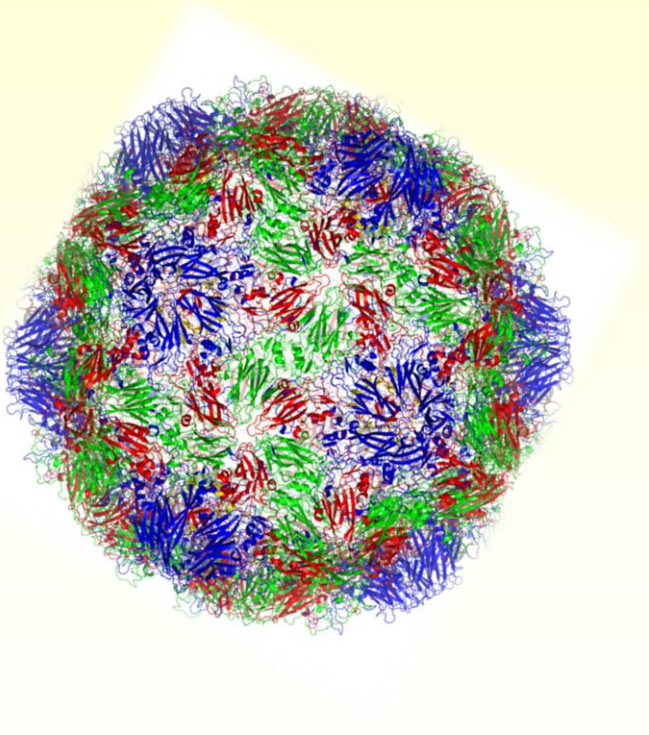




The **icosahedron** has

- 6 axes of 5-fold symmetry
- 10 axes of 3-fold symmetry
- 15 axes of 2-fold symmetry

Viruses look like tiny footballs



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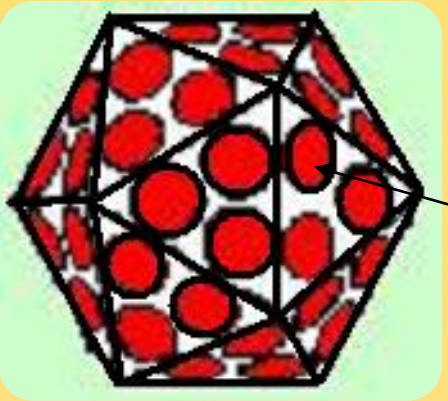
Why do viruses use symmetry?

Crick and Watson, 1956: The principle of genetic economy

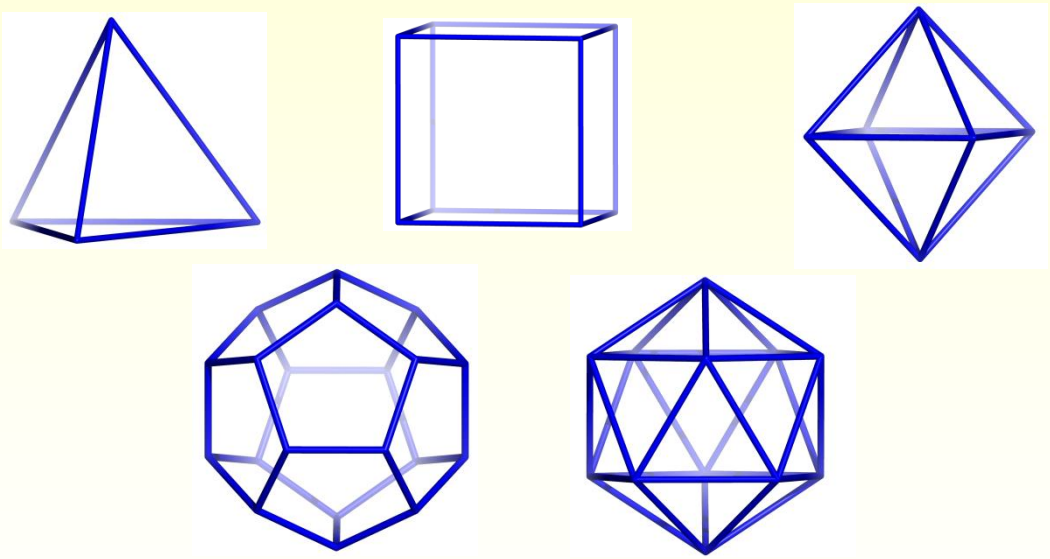
Viruses code for a small number of building blocks that are repeatedly used to form containers with symmetry. Containers with icosahedral symmetry are largest given fixed protein size.



If the position of one red disk is known, then the positions of all others are implied by symmetry.

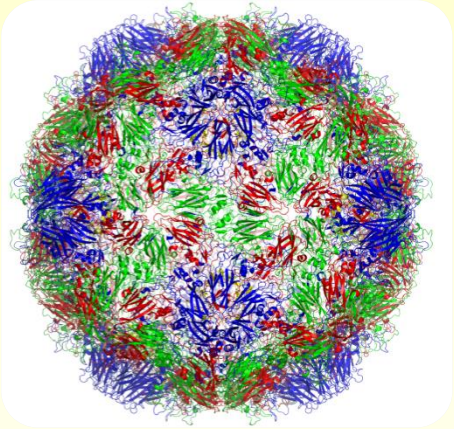
Viral symmetry is special!

One can show that icosahedral symmetry corresponds to the largest symmetry group in 3 dimensions

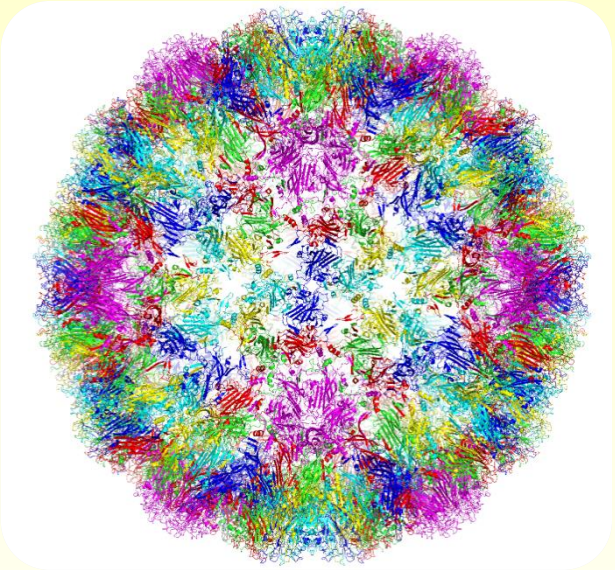


The Platonic solids

Viruses come in different forms and sizes



Common Cold



Viruses causing cervical cancer

?

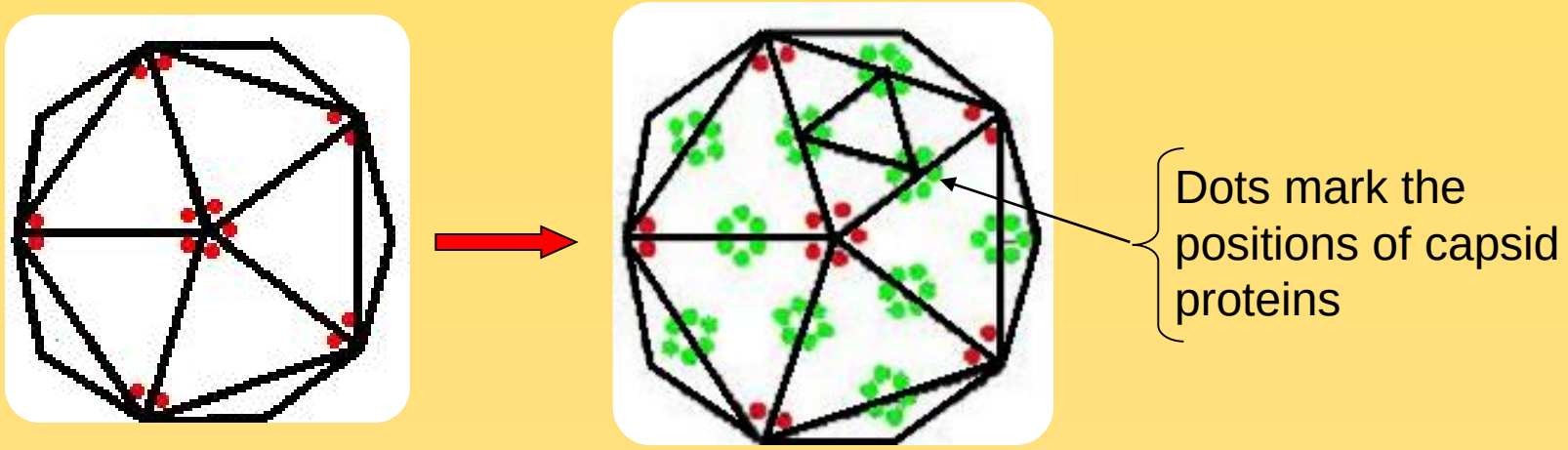
www.giantmicrobes.com

They share the same symmetry properties!

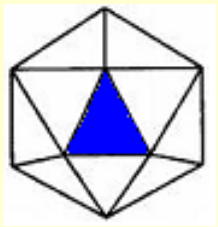
The architecture of larger viruses

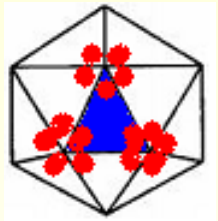
Caspar and Klug discover quasi-equivalence (1962):

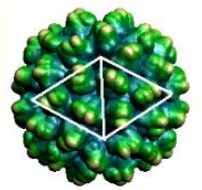
``The local environments of all capsid proteins look similar.''

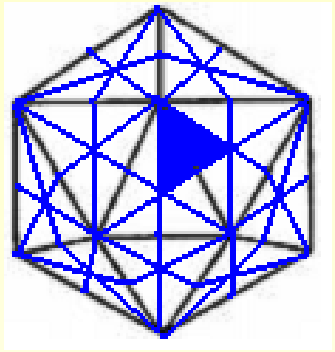


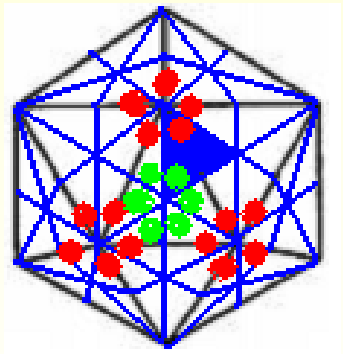
Viral Geometry - triangulations

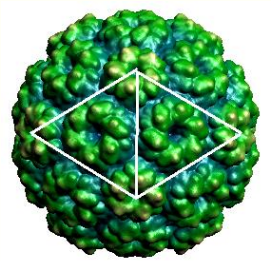


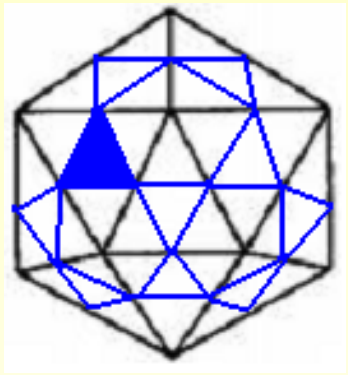


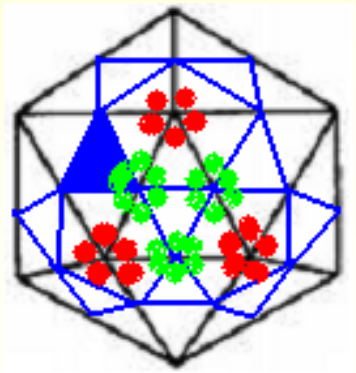


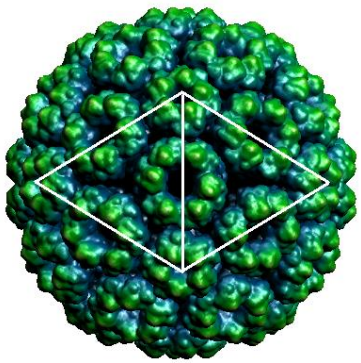


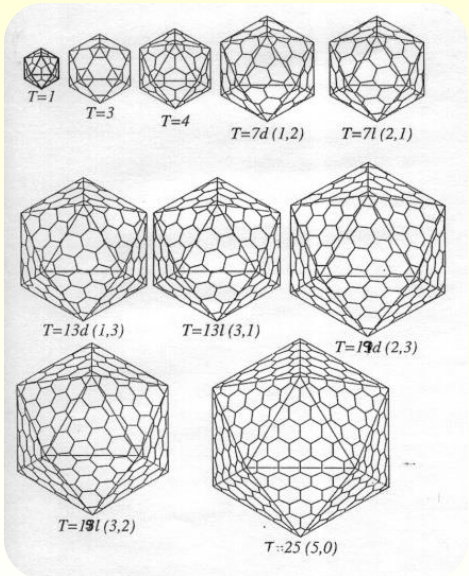






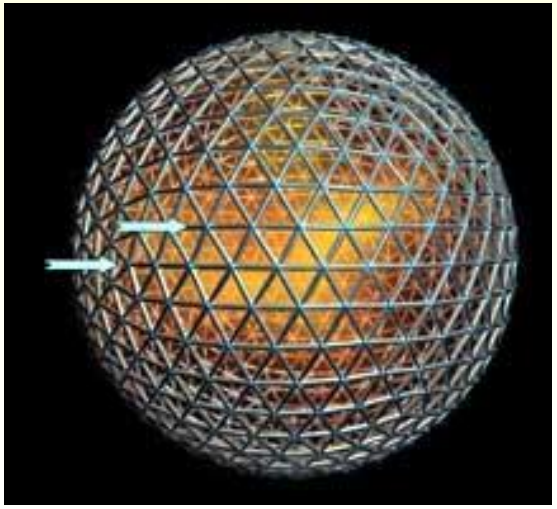


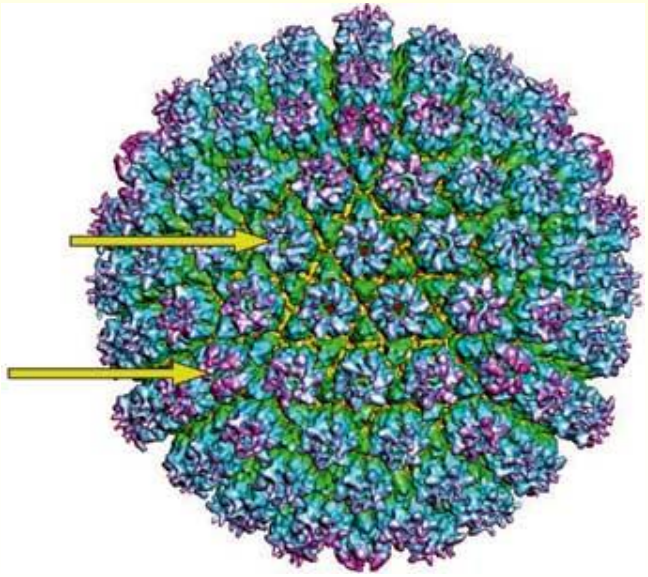


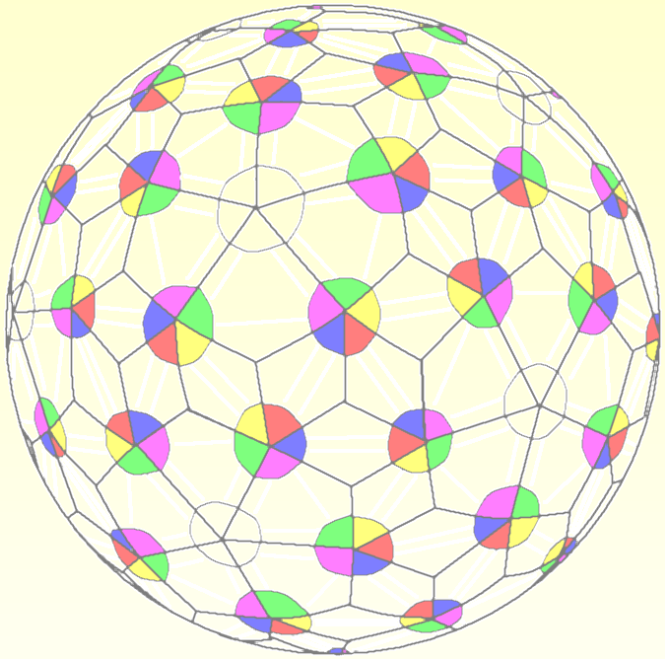


Buckminster Fuller Domes

Large viruses look like Buckminster Fuller's Domes



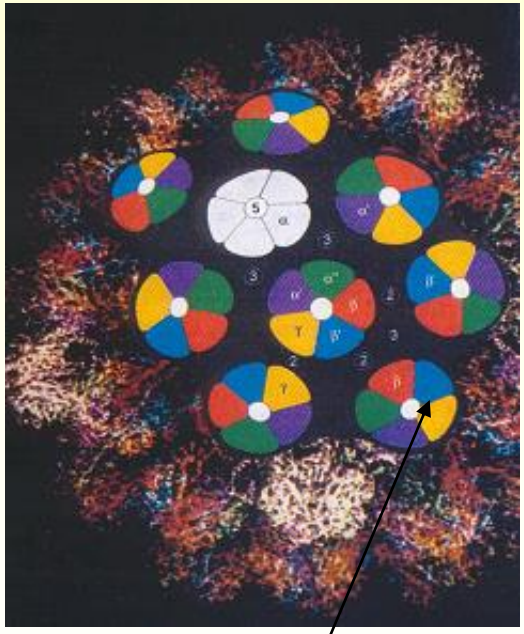




New mathematics is necessary to solve open problems

A structural puzzle in virology

The layouts of some viruses do not correspond to triangulations



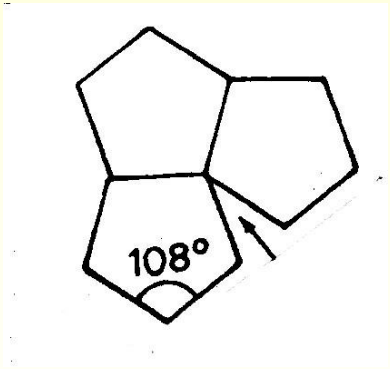
Pentamer: pentagonal cluster

Rayment et al. (Nature, 1982) and Liddington et al. (Nature, 1991) discover viruses with 72 pentagonal clusters

These viruses are of particular interest because some of them (such as papillomavirus) are cancer-causing.

So, what's the problem?

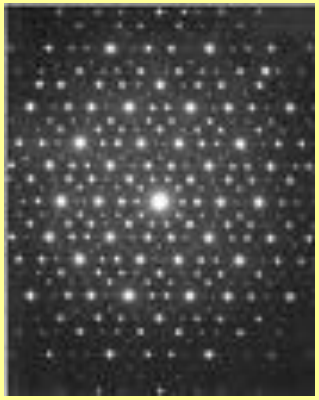
You cannot tile your bathroom with pentagons without gaps and overlaps

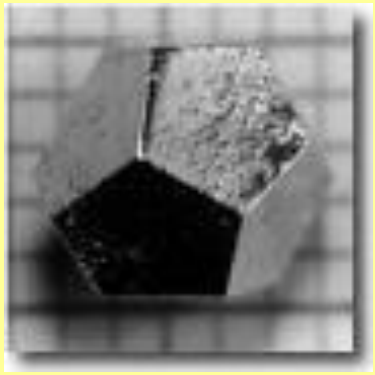


There are no lattices with 5-fold symmetry!

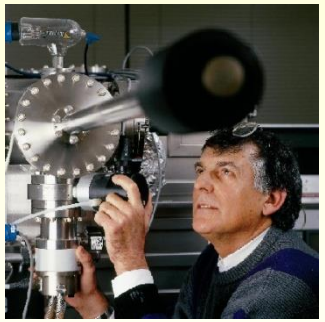
Nature has the answer: Quasi-lattices

A similar puzzle occurred in physics





The diffraction pattern (left) of a quasicrystals (right)



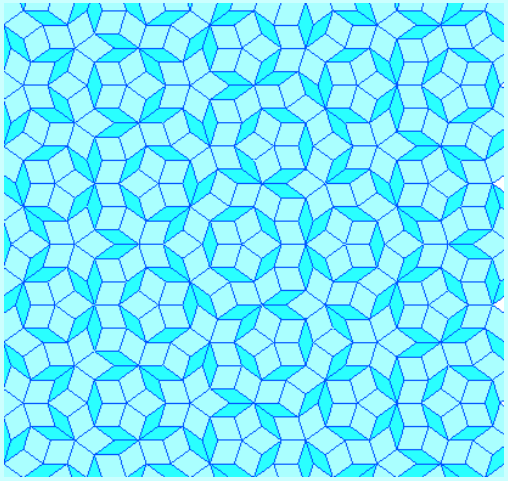
Dan Shechtman et al.

Discovery of quasicrystals in 1984

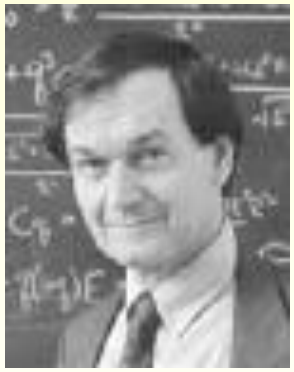
Nobel Prize in Chemistry 2011

Quasi-lattices

Aperiodic structures with long-range order have been studied by Roger Penrose.



A patch of a Penrose tiling

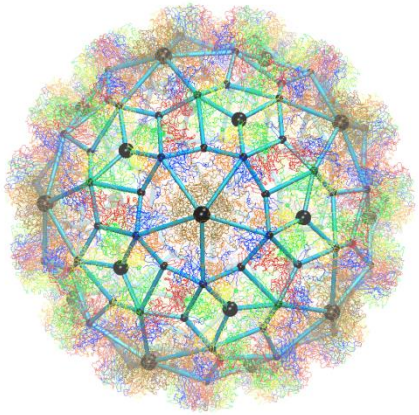


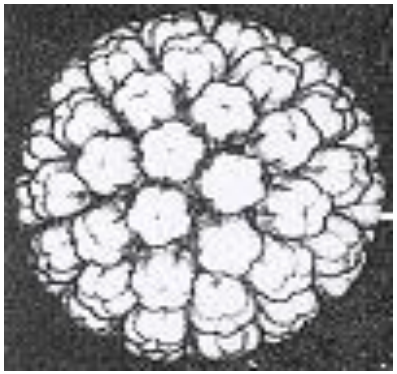
Sir Roger Penrose

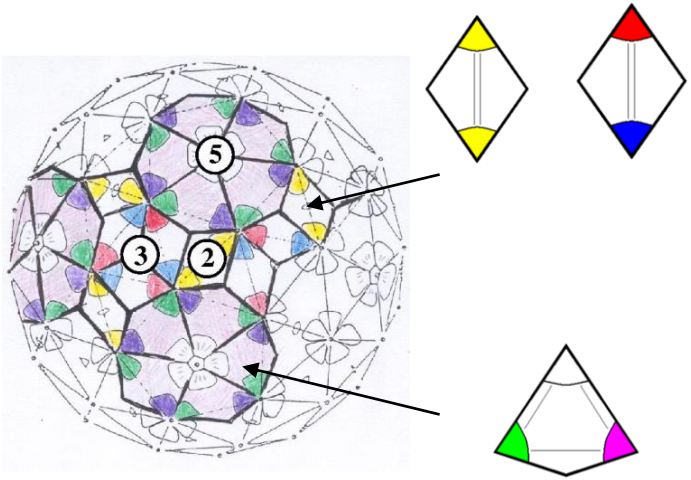
Mathematician from Oxford

Puzzle solved!

Viral Tiling Theory: designed for viruses that are not quasi-equivalent

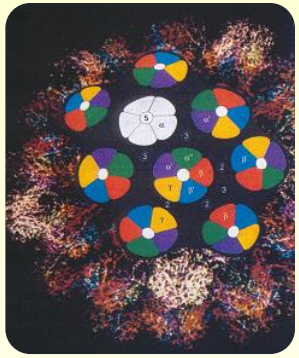


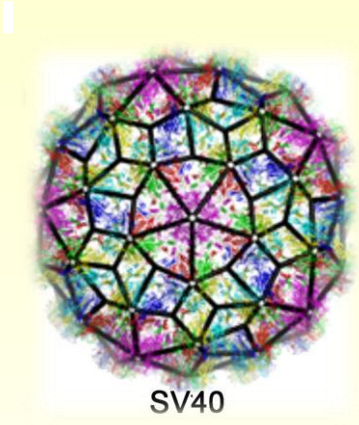


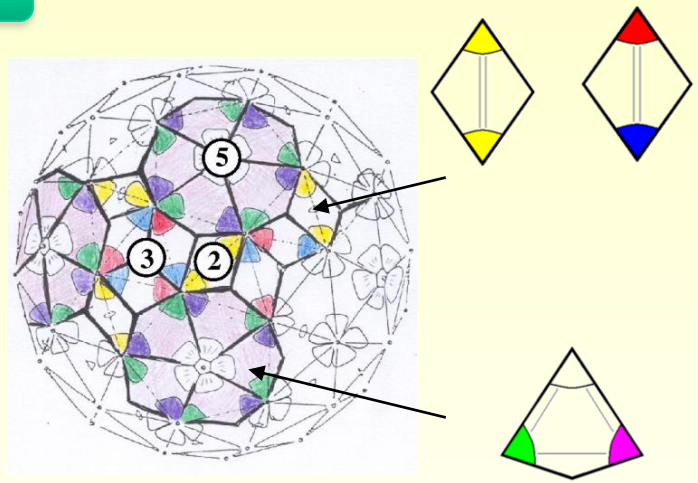


Viral tiling theory

2D

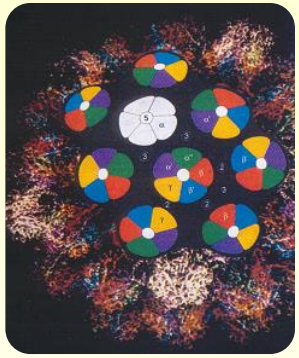


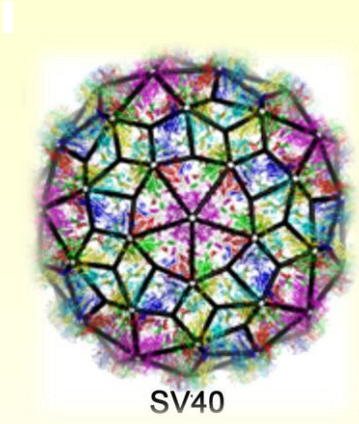


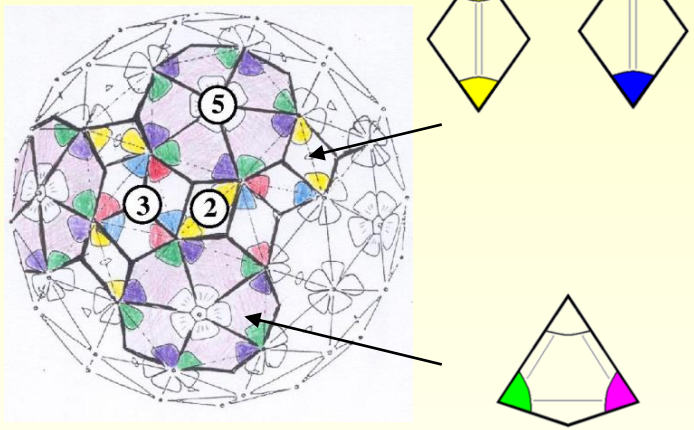


Viral tiling theory

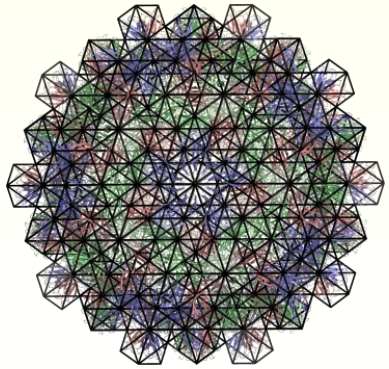
2D

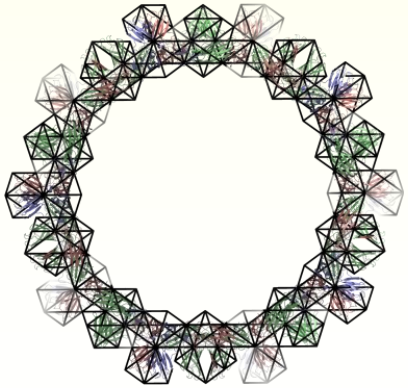


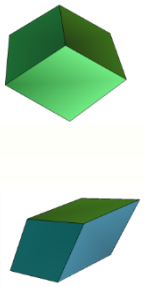


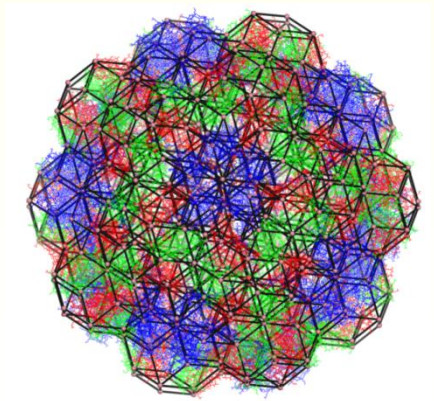


3D

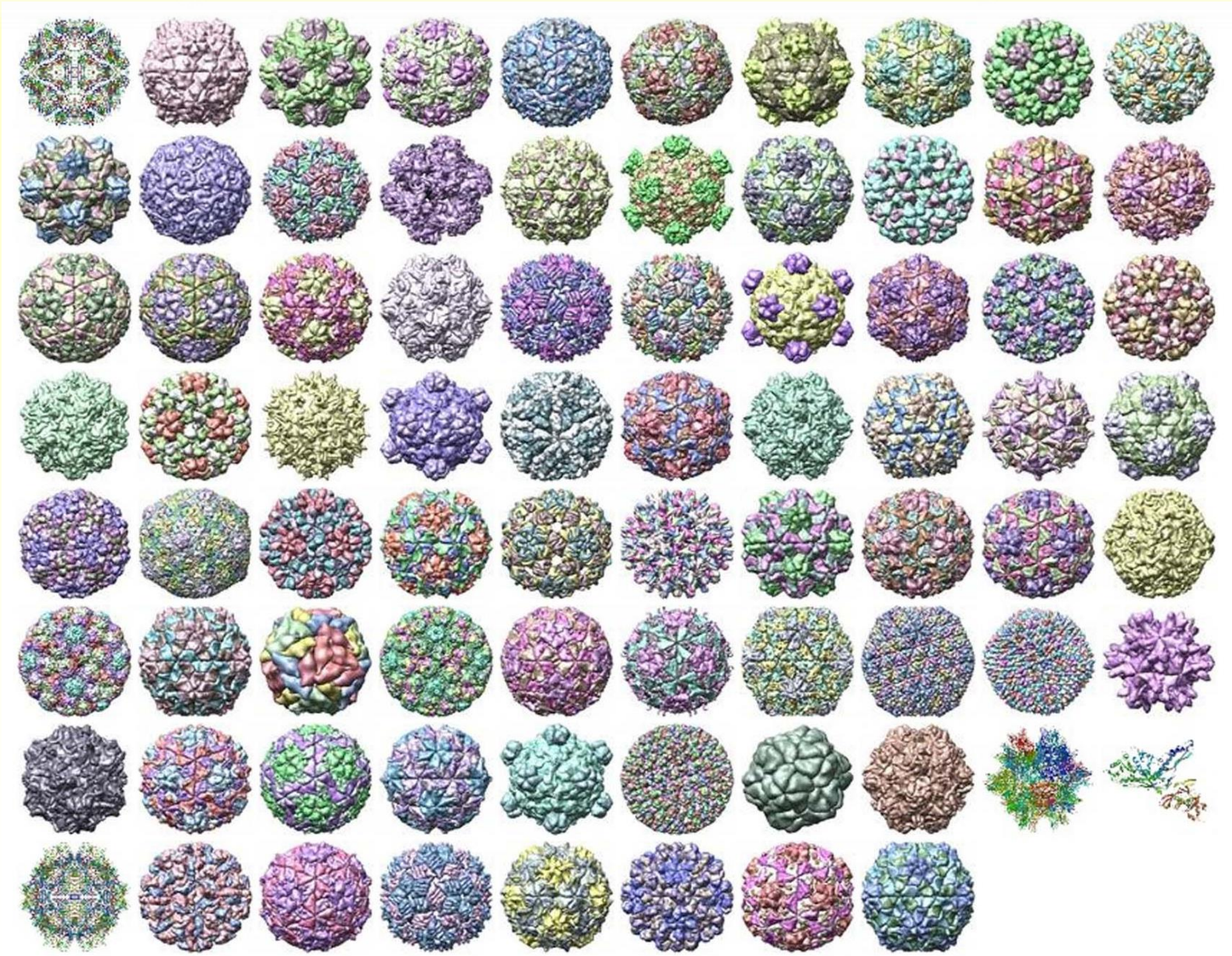








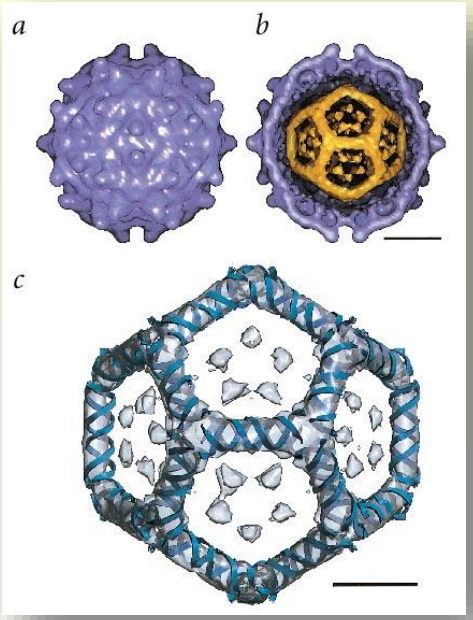
X-ray structures of viral capsids…



...but little information on the genome cargoes being delivered.

Question

Are there other hidden constraints that can only be seen through the mathematical lens?



Pariacoto virus

Is it possible to predict the existence of the characteristic polyhedral cage structure of the viral genome?

Pariacoto virus

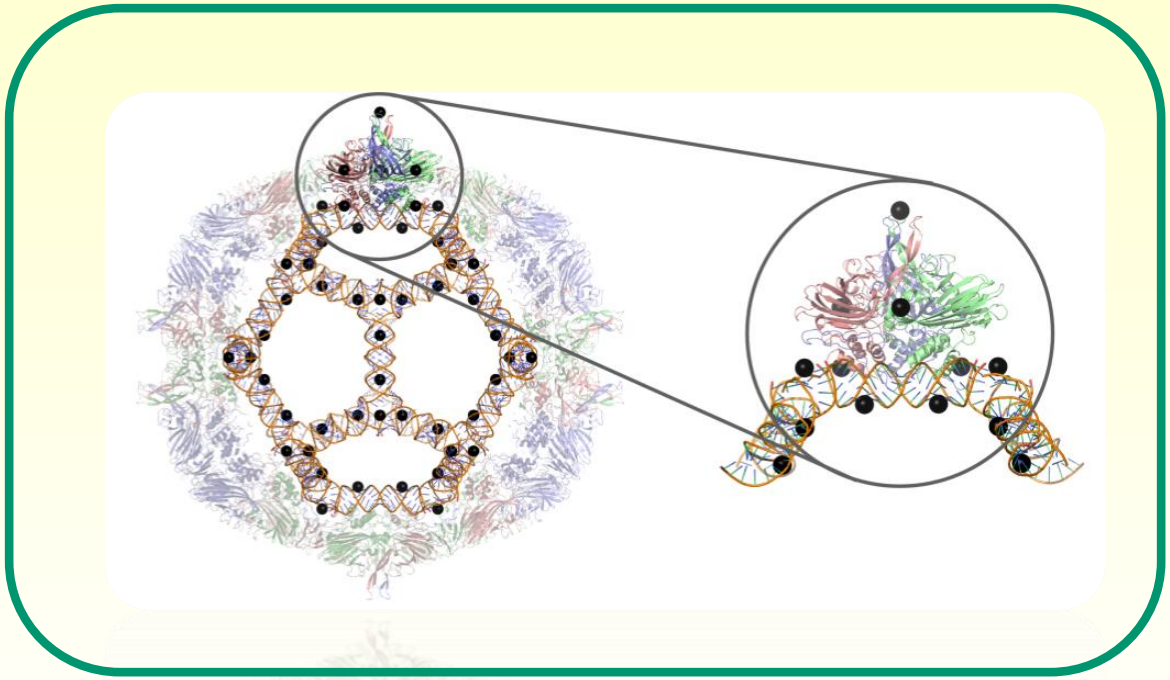
Pariacoto virus

Artist's impression of Pariacoto virus ☺

New insights into genome organisation

Peter Stockley

Neil Ranson



New molecular scaling principle discovered!

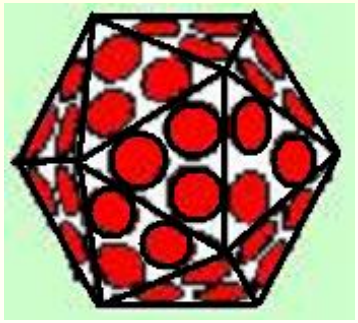
Tom Keef

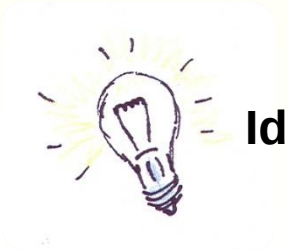
Jess Wardman

Symmetry Groups

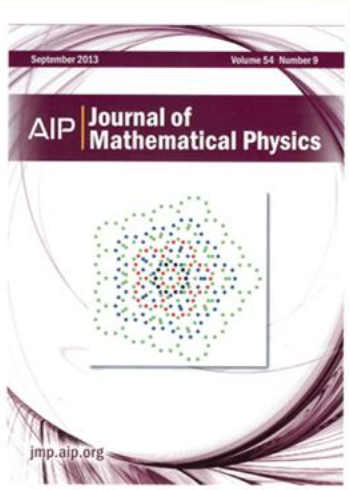
The rotations encoding the symmetries of the football form a group (**symmetry group)**.

The symmetry group of the icosahedron is called the **icosahedral group.** It has 60 elements (group members).





Idea: Classify extensions of the icosahedral group



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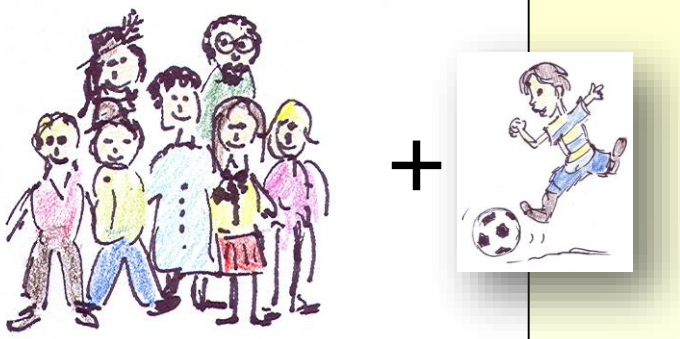

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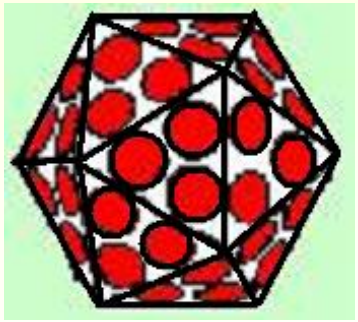

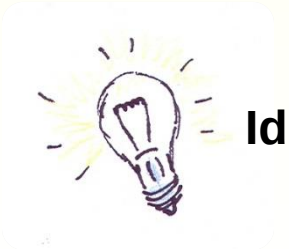

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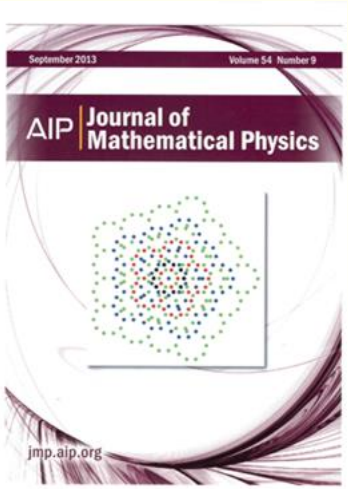
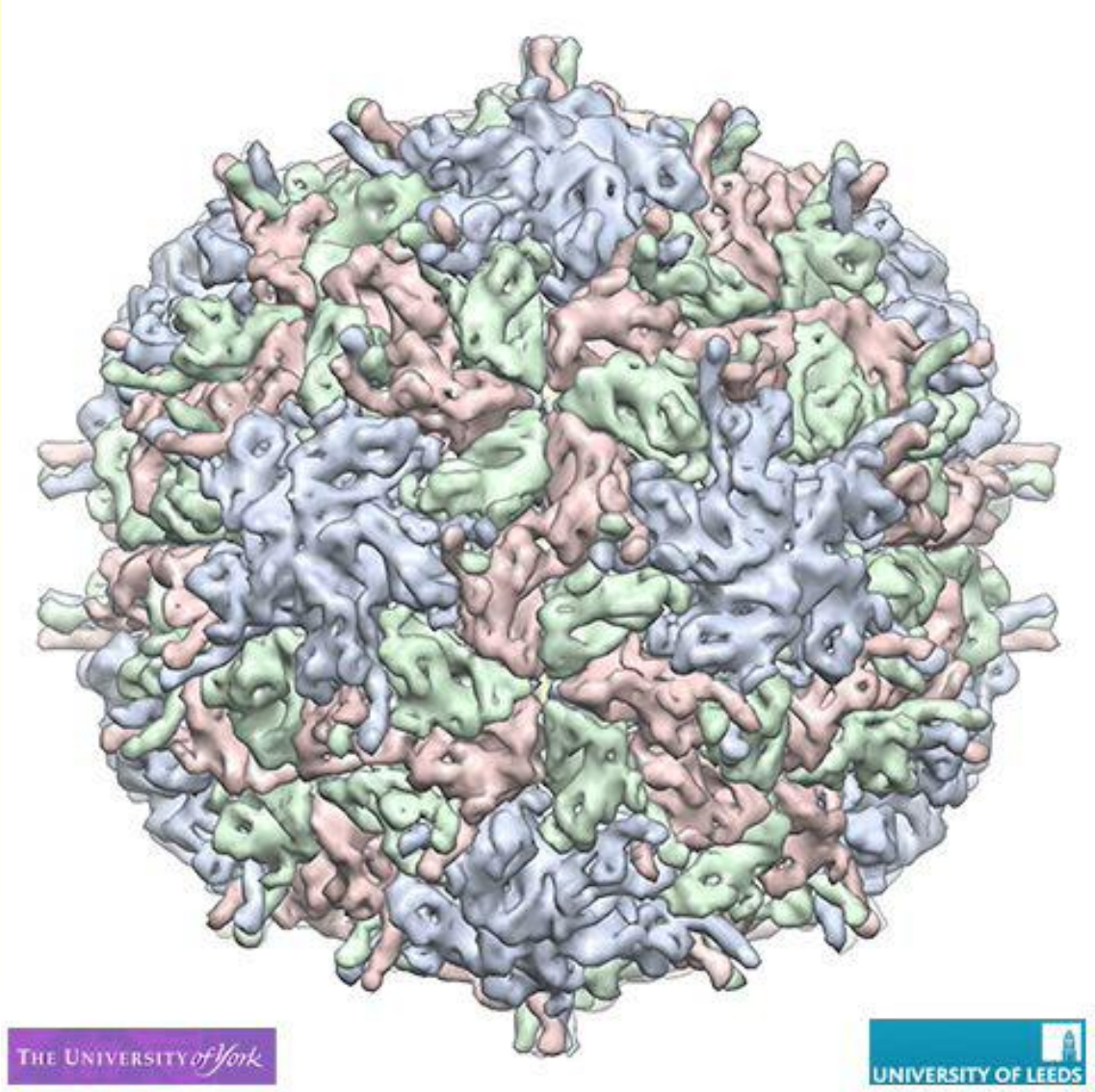
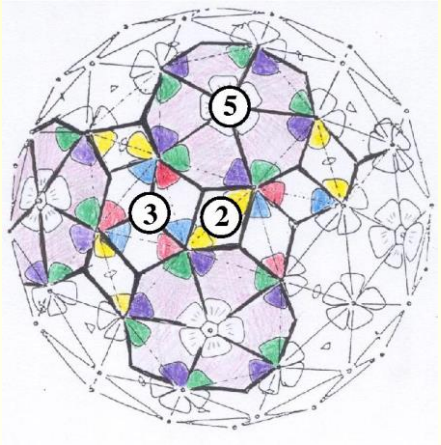


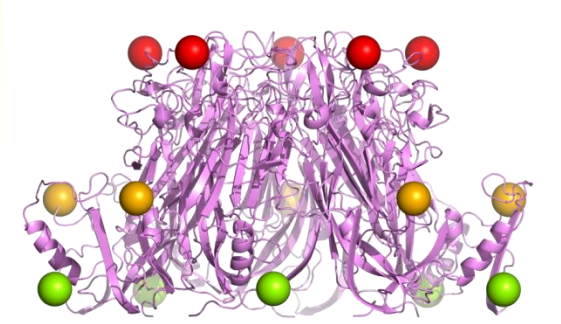
Pariacotovirus

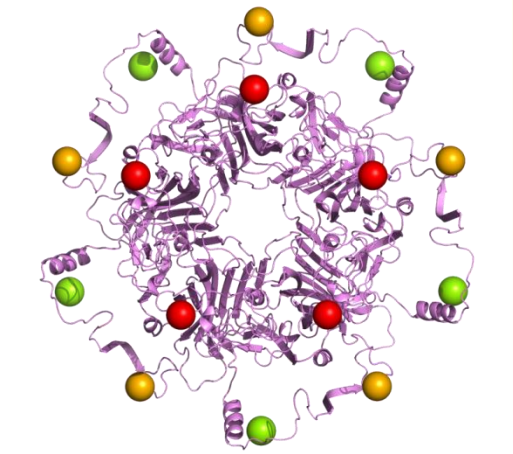


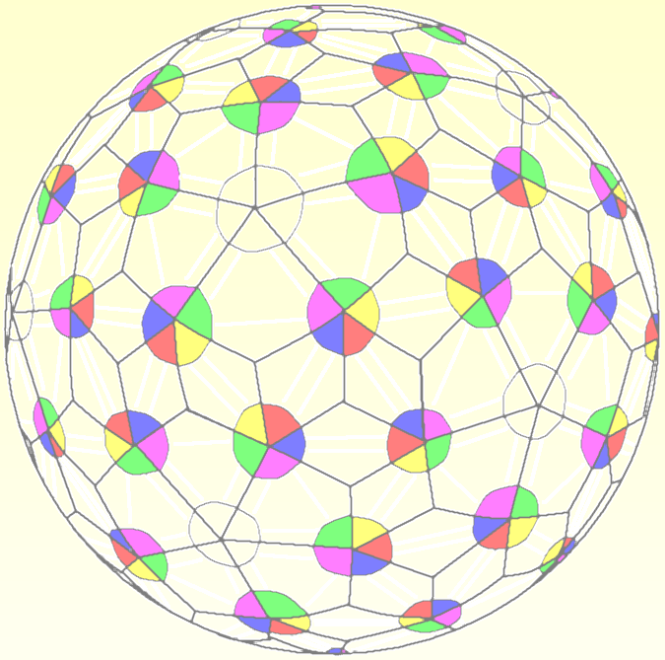
Cancer-causing viruses

New insights into structural constraints on virus architecture





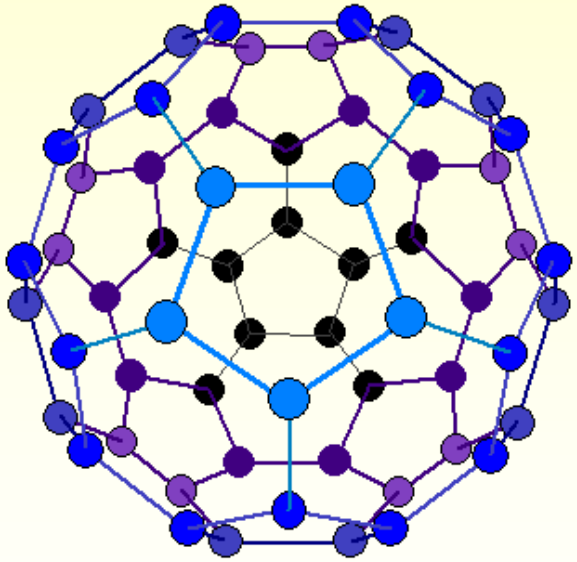




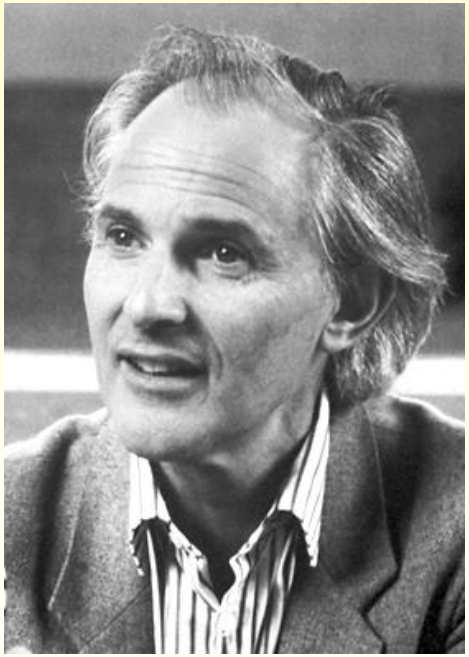
New insights in other areas of Science

Fullerenes – carbon cages

Buckminster fullerene

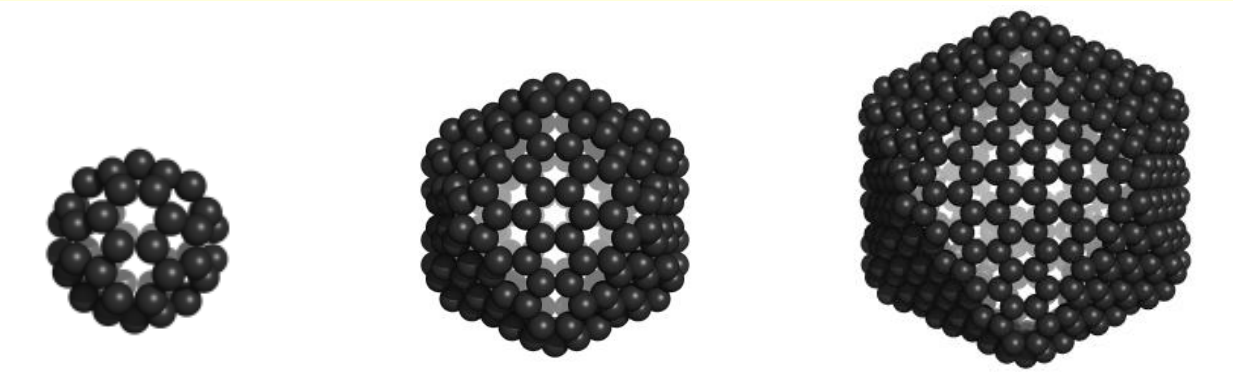


Buckyball C_{60}

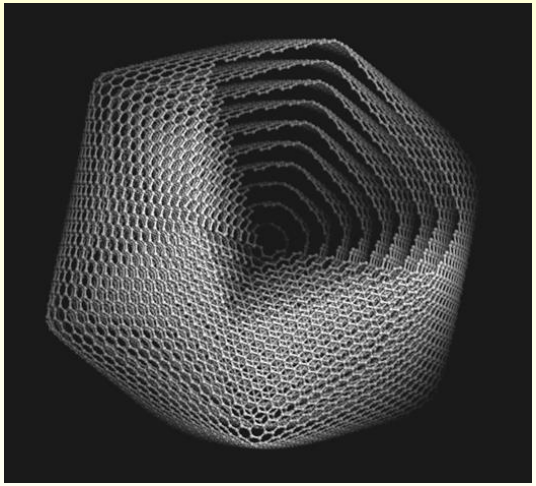


Sir Harald Kroto
Nobel Prize in Chemistry 1996

Carbon onions: nested carbon cages

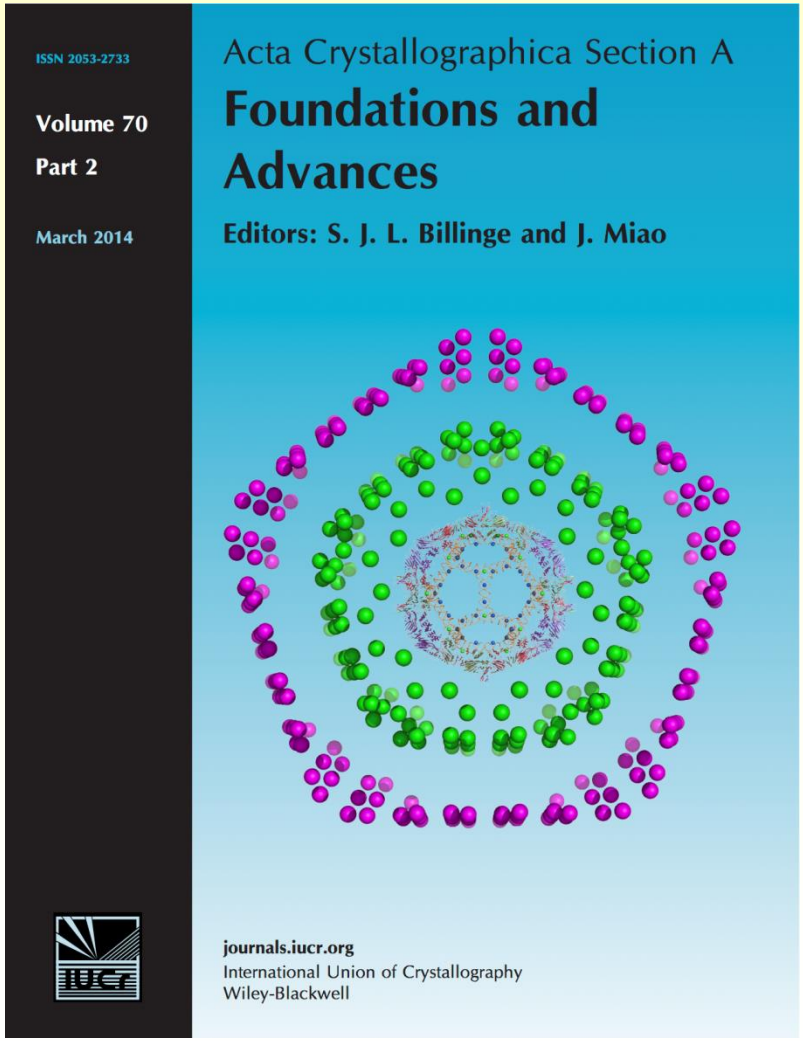


C_{60} C_{240} C_{540}

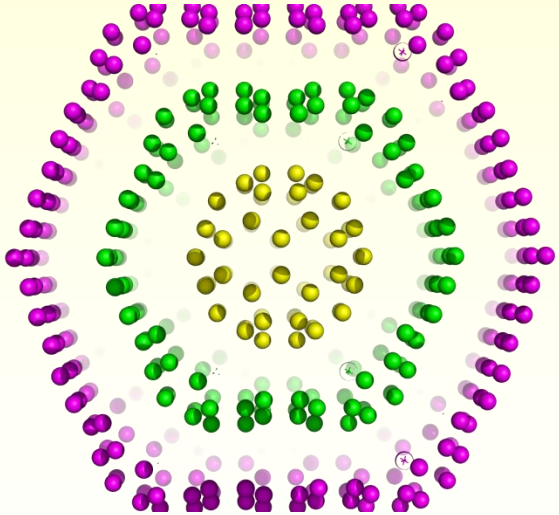


Adapted from Chemistryworld (June 2014)

The same mathematics works for fullerenes

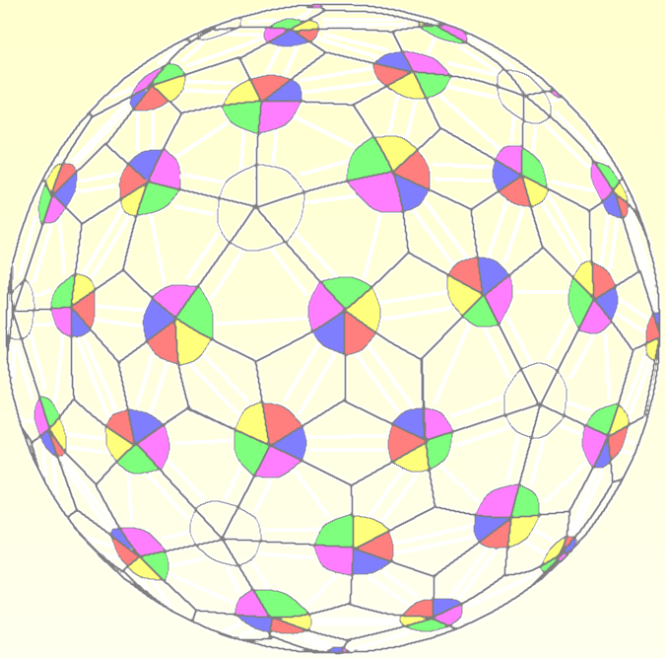


The atomic positions of the C_{60}-C_{240}-C_{540} carbon onion also follow the same mathematical structures



with Pierre Dechant, Tom Keef & Jess Wardman

Featured as a research highlight in Nature Physics 2014 (“Know your onions”)

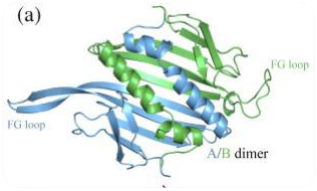


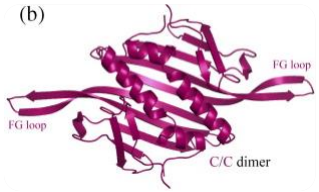
Viral Geometry

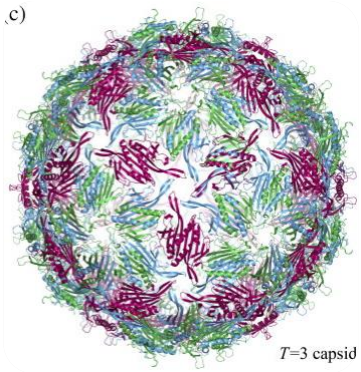
and

Code Breaking

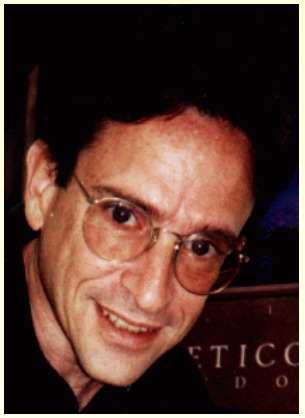
How do viruses form?

60 

+ 30 

= 

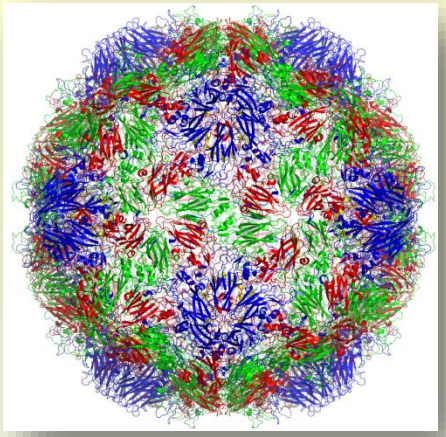
Virus assembly – the viral production line



Movie curtesy of
Arthur J Olson

(Scripps)

Remember:



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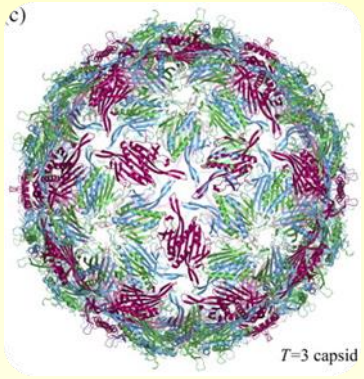
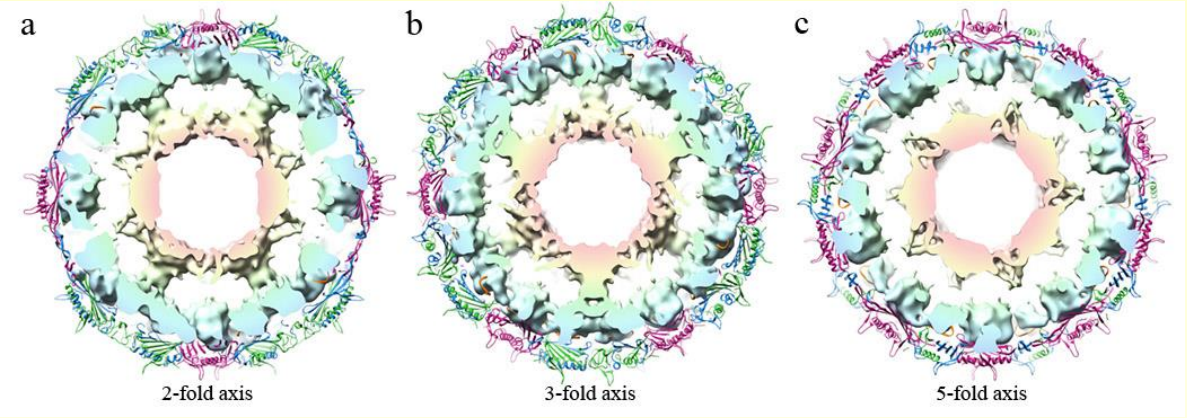
Viruses are containers formed from protein that contain the genetic material

Genome organisation in MS2

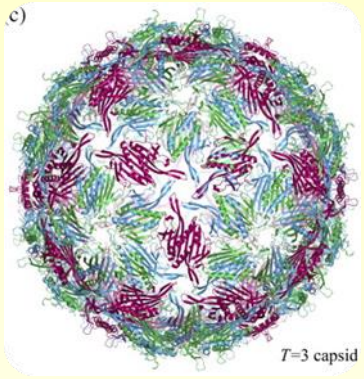


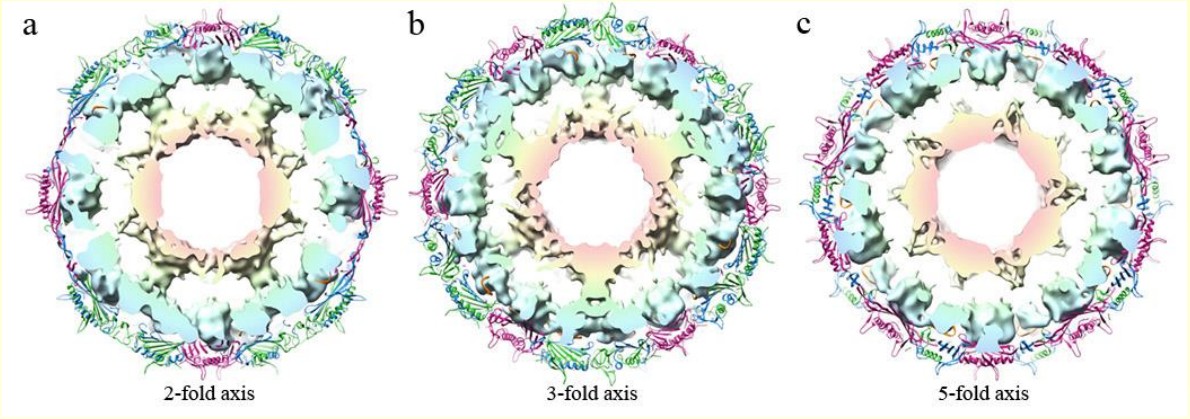
outside view



cross section revealing inside view

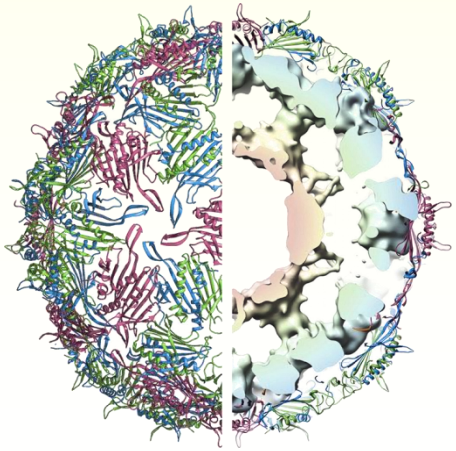
Genome organisation in MS2



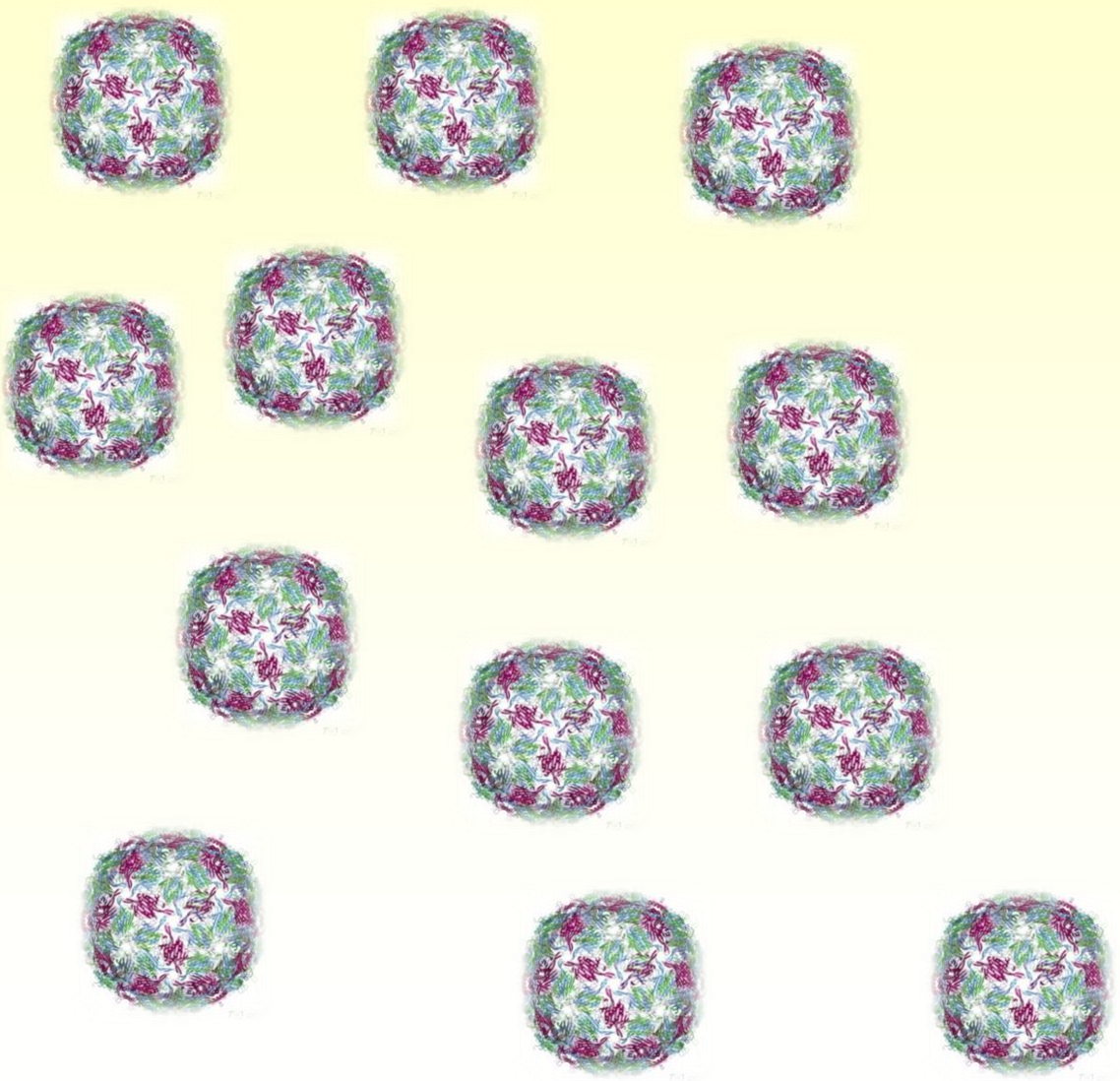


outside view

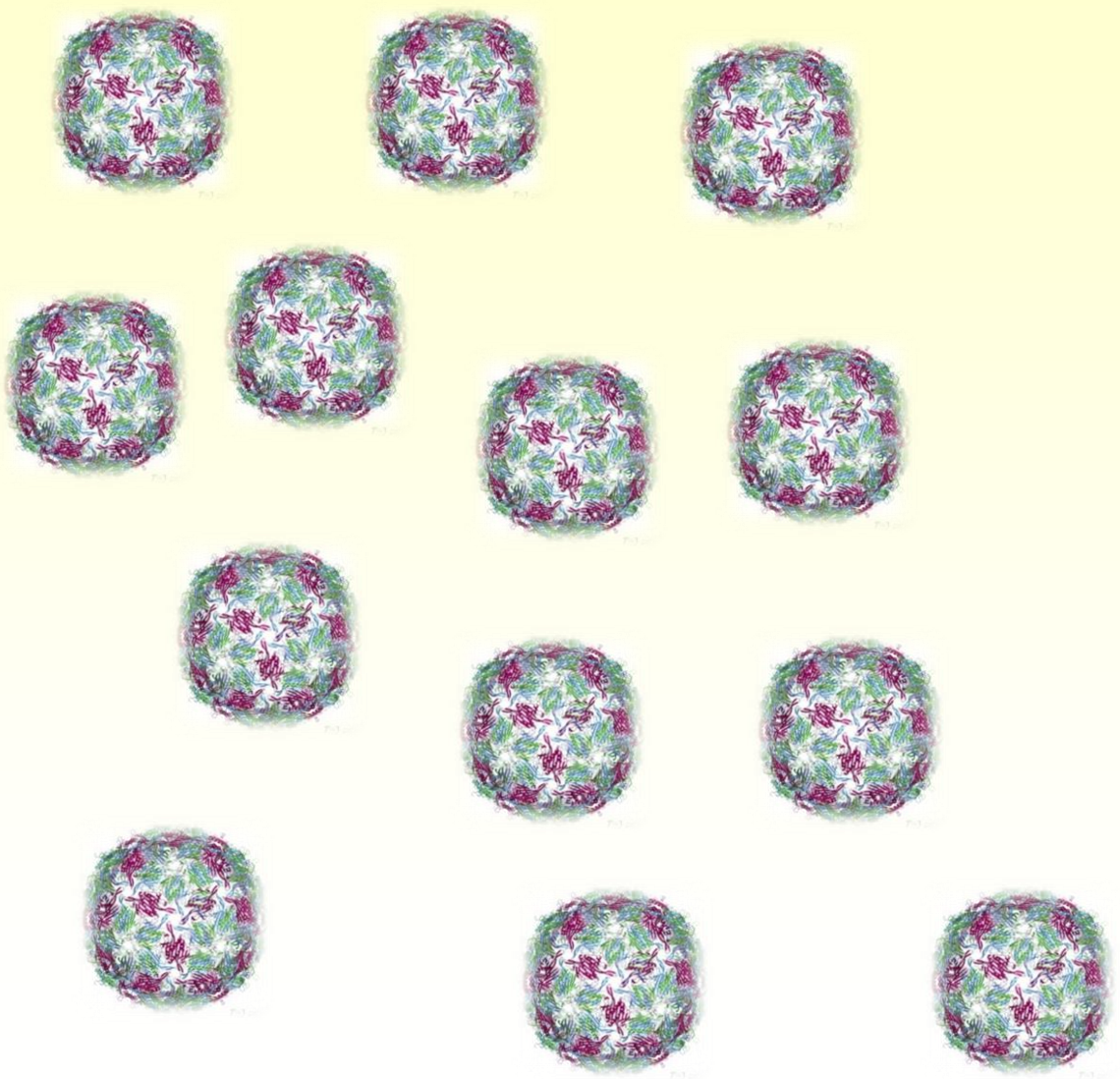
cross section revealing inside view

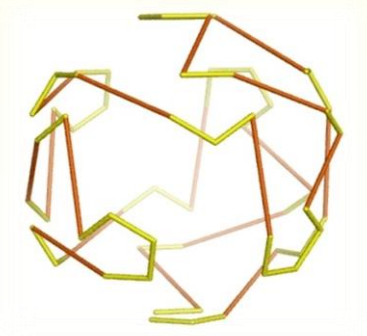


Genome organisation in MS2

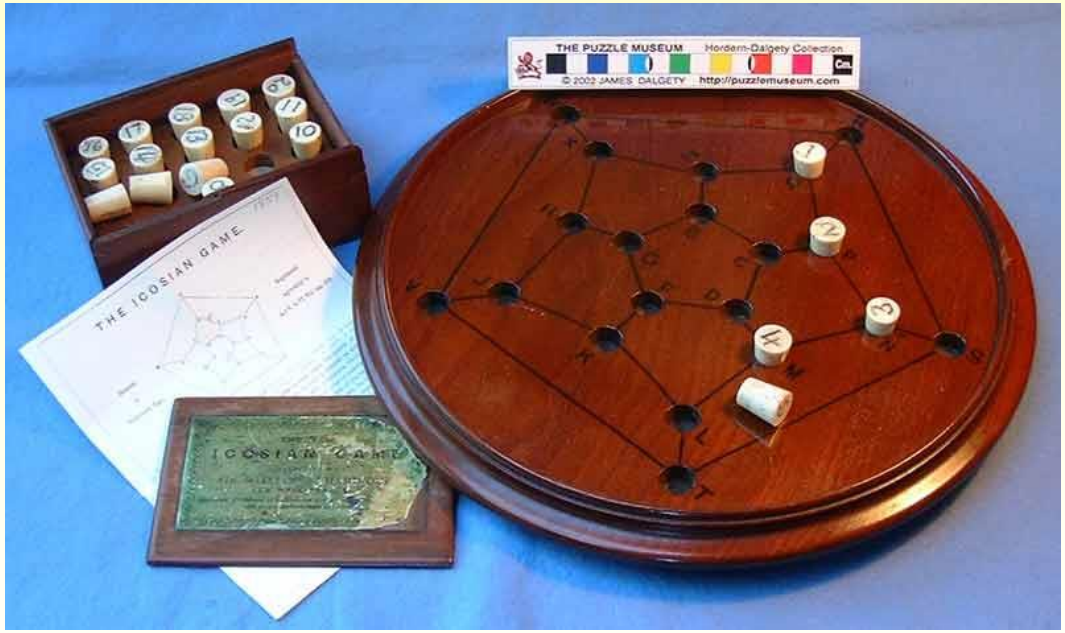


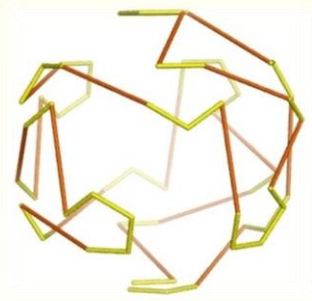
Genome organisation in MS2





The icosian game

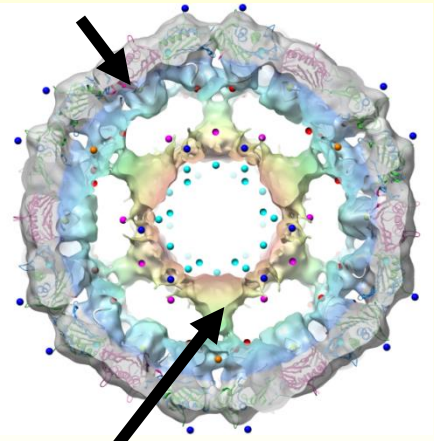




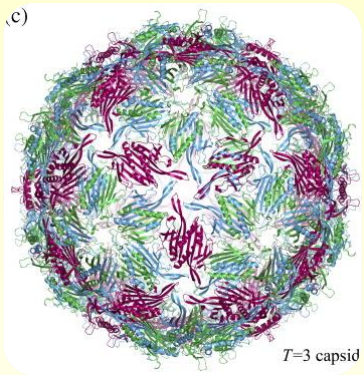
A board game designed by Hamilton based on the concept of Hamiltonian circuit (cycle)

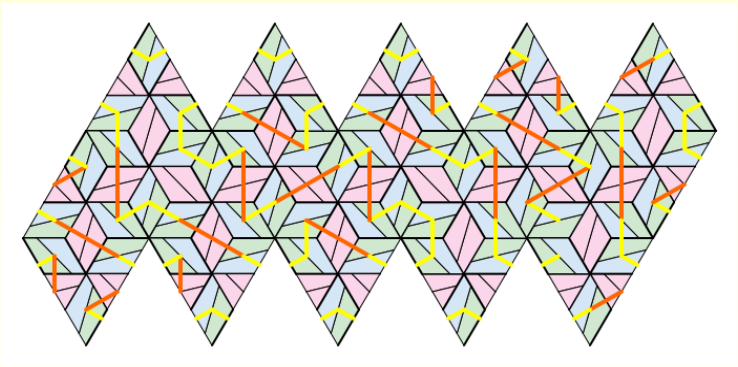
Genome organisation provides clues on virus assembly

Outer Shell



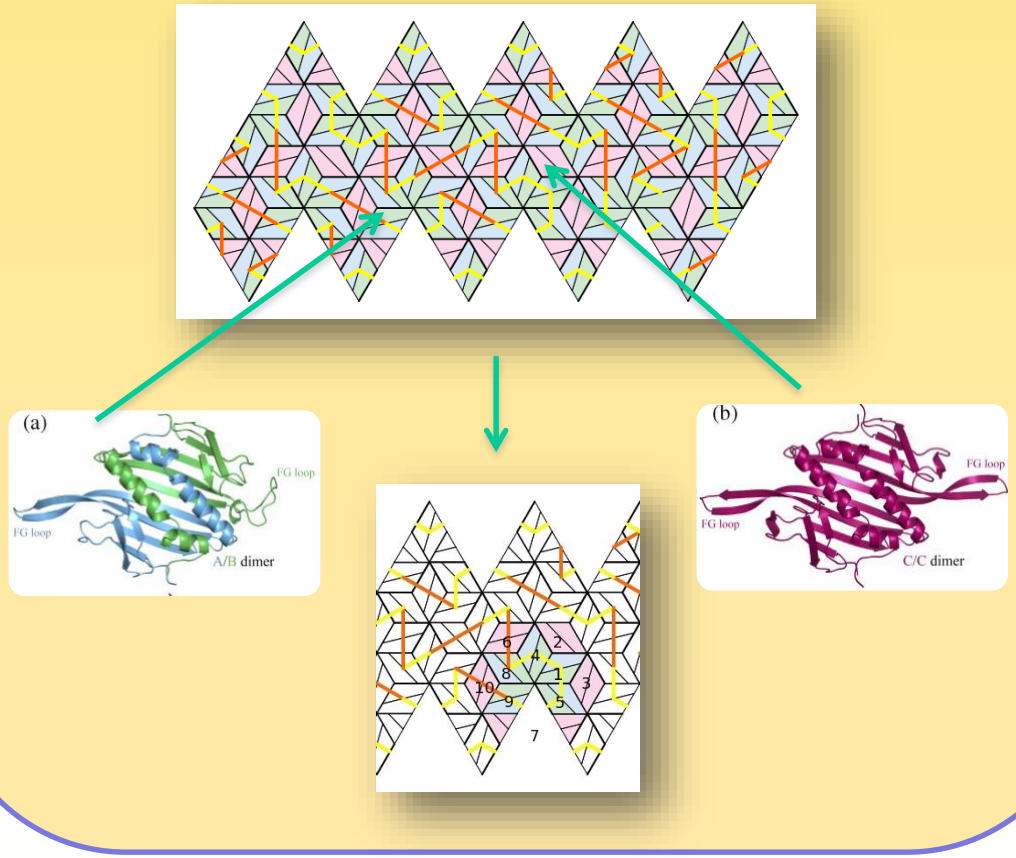
Inner Shell



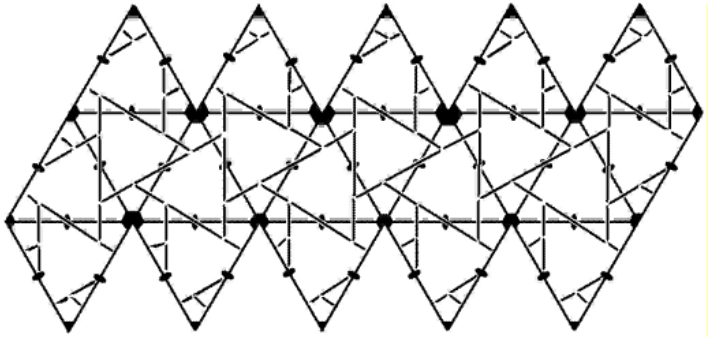


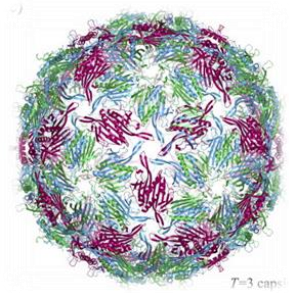
Assembly pathways – the viral production line

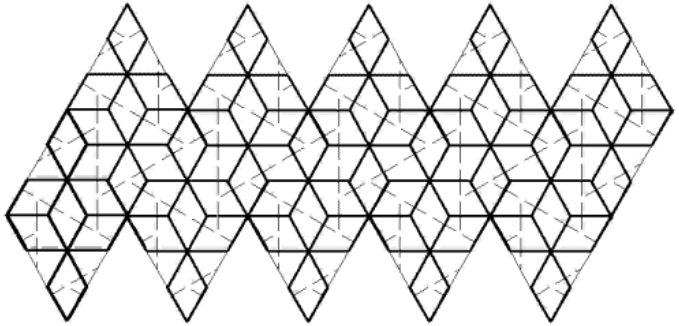
A Hamiltonian Path encodes the order of sequential dimer addition:



Hamiltonian paths are the instruction manual

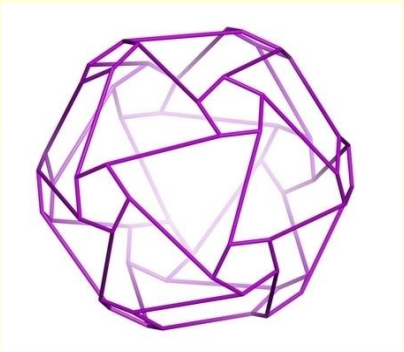


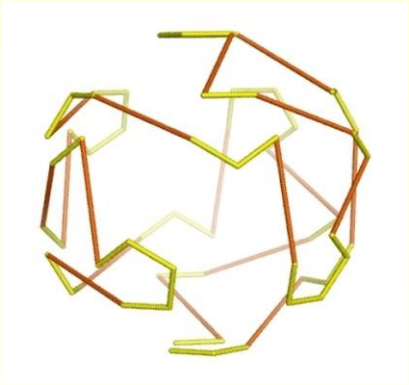


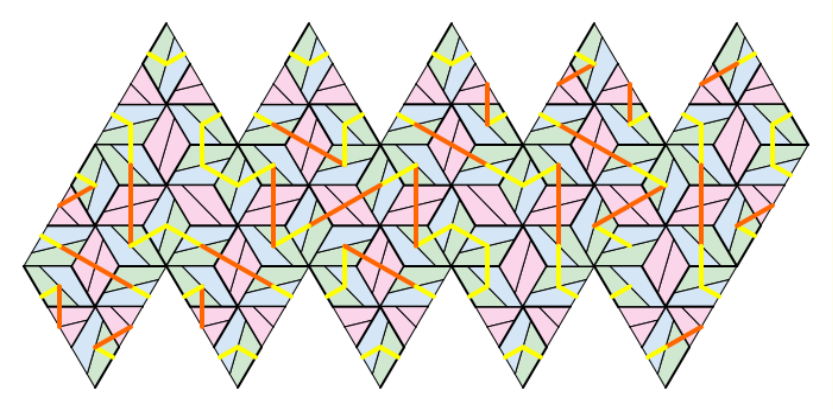


Enumerate assembly pathways

How many Hamiltonian paths are possible?





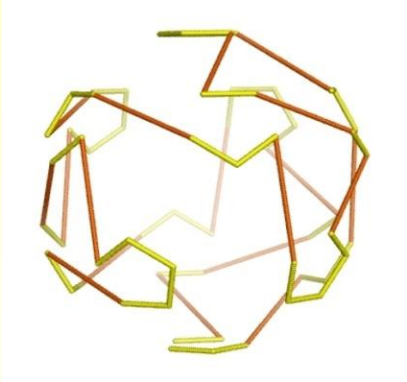


There are over 40,500 such paths for MS2!

Striking conclusion

RNA configuration within the particle is more constrained than previously appreciated!

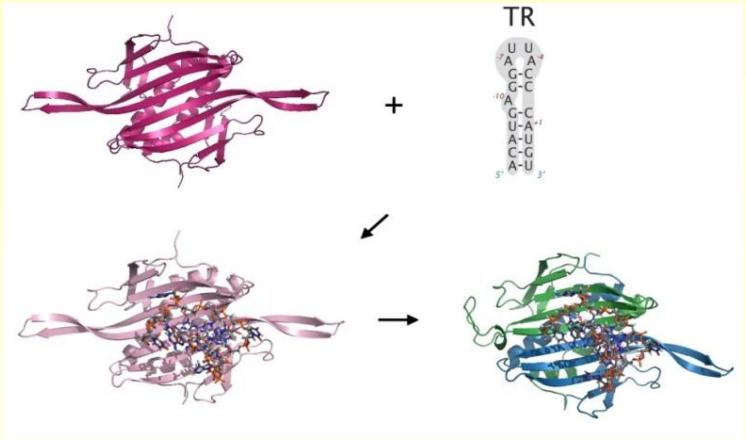
=

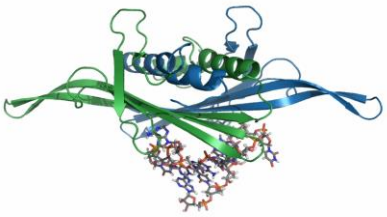


Confirmed via three different methods:

- Kinetic modeling
- Bioinformatics analysis
- Analysis of cryo-EM tomogram

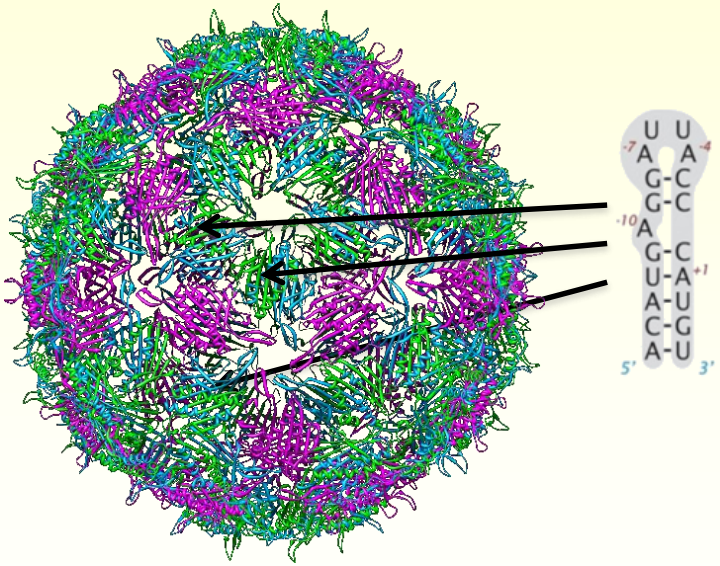
The Packaging Signal Hypothesis





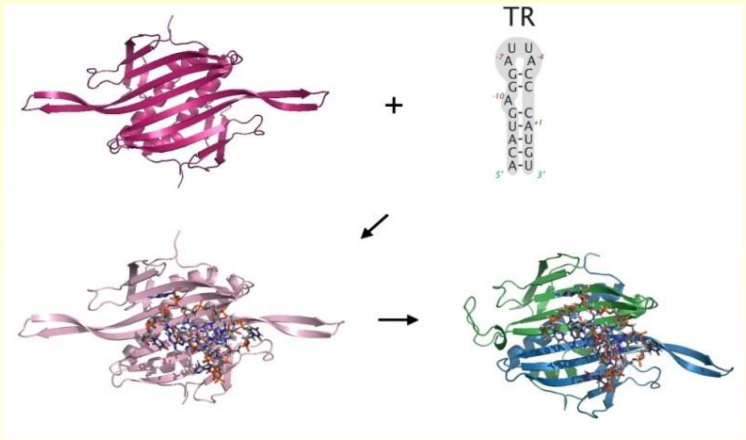
Hypothesis:

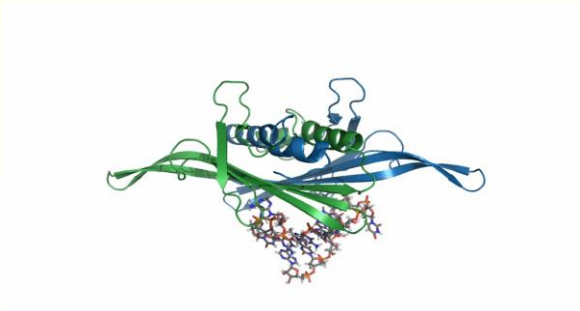
RNA stem-loops are located (ideally) at **all** vertex positions



“Packaging signals”

The Packaging Signal Hypothesis





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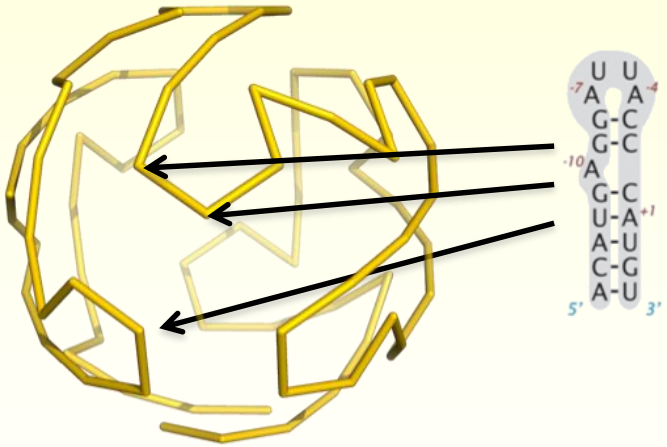
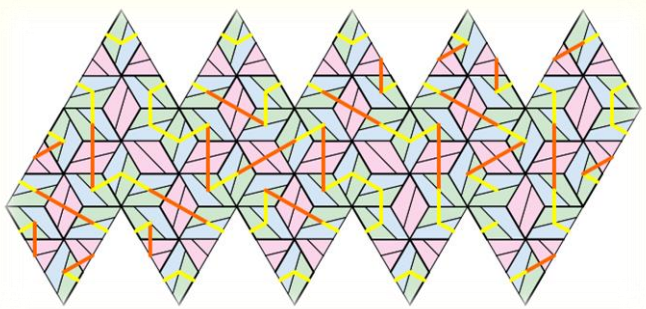


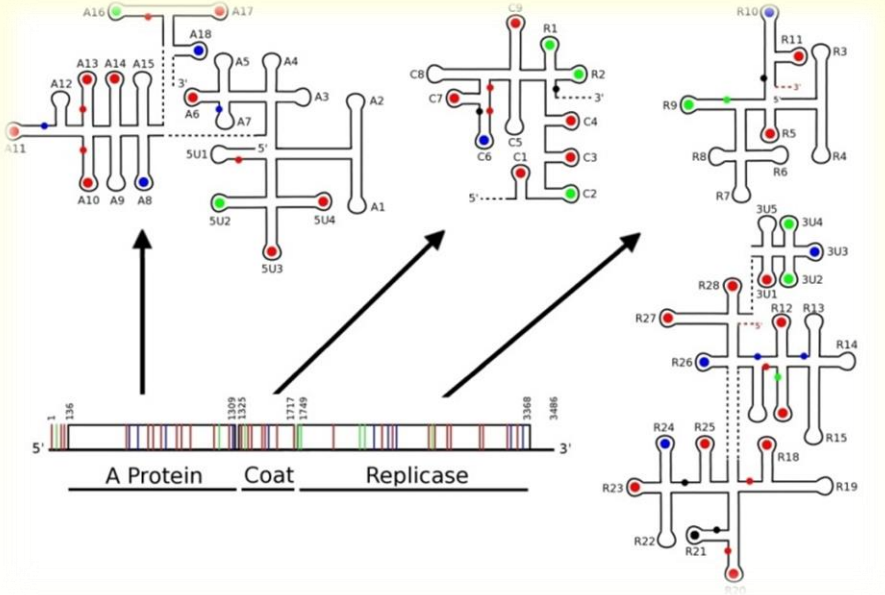
“Packaging signals”

The packaging signal paradigm

Multiple dispersed interactions with capsid protein are essential for efficient capsid formation

Graph Theory
&
Bioinformatics

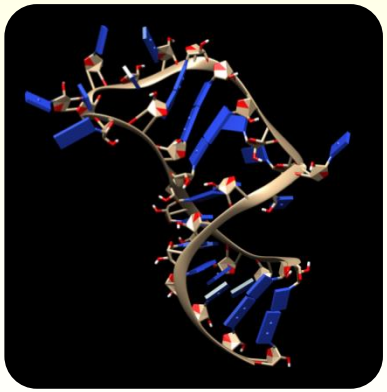


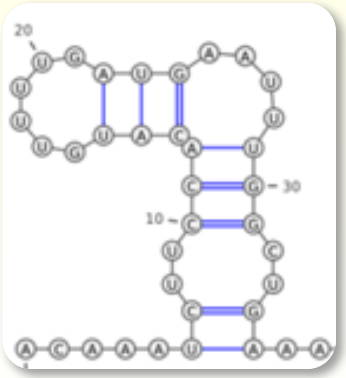


Viral geometry and code breaking

The challenge:

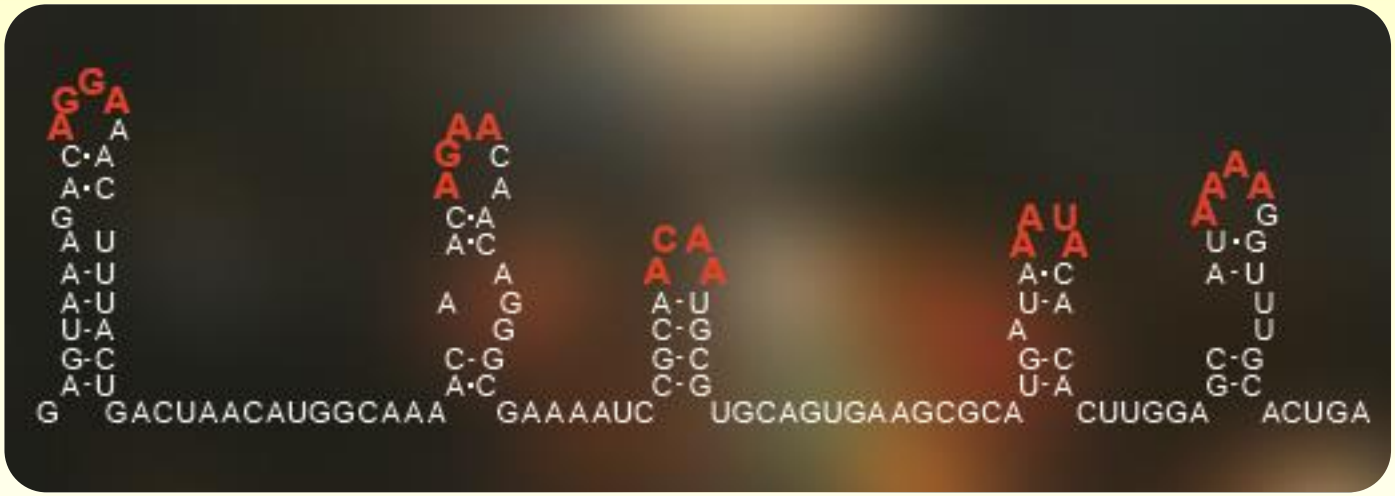
Identify packaging signals in a wide range of viruses





Viral Enigma Machine

Researchers discover viral "Enigma machine"
Published Wednesday 4 February 2015



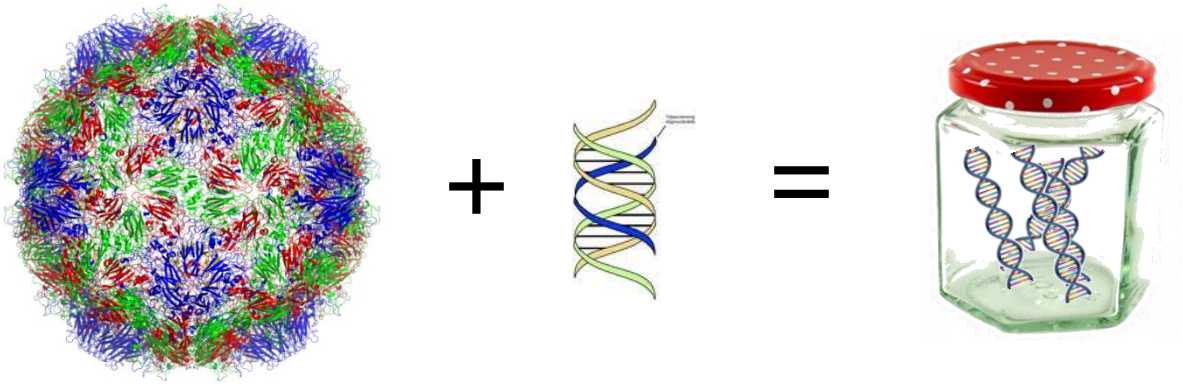
“Researchers have **cracked a code** that governs infections by a major group of **viruses including the common cold and polio**.

Until now, scientists had not noticed the code, which had been hidden in plain sight in the sequence of the ribonucleic acid (RNA) that makes up this type of viral genome.”

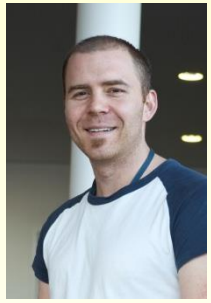
A paradigm shift in virus assembly

Long-standing hypothesis: Virus capsid assembly can be understood by studying the assembly of the capsid proteins in isolation

We have shown: Viral genomes play essential roles in capsid assembly



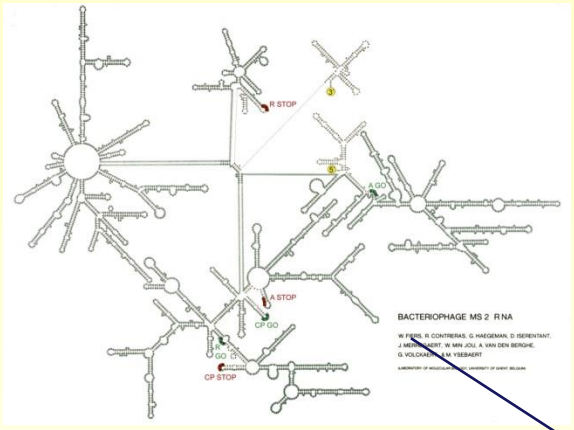
In collaboration with experimental groups at:
- **the Astbury Centre for Structural Molecular Biology in Leeds**
- **the University of Helsinki**

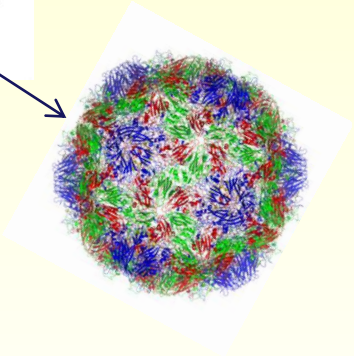


Eric Dykeman

Peter Stockley

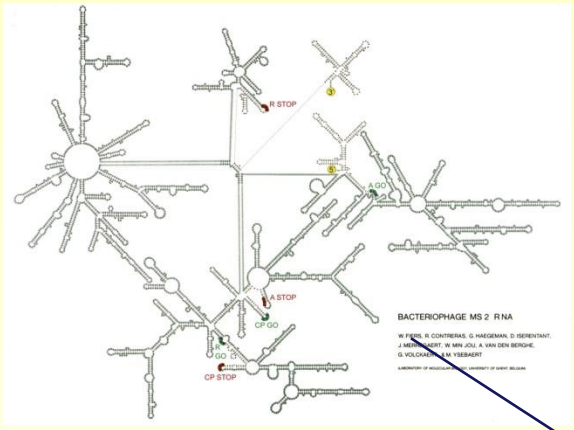
The mechanism: Viruses behave like “self-packing suitcases”

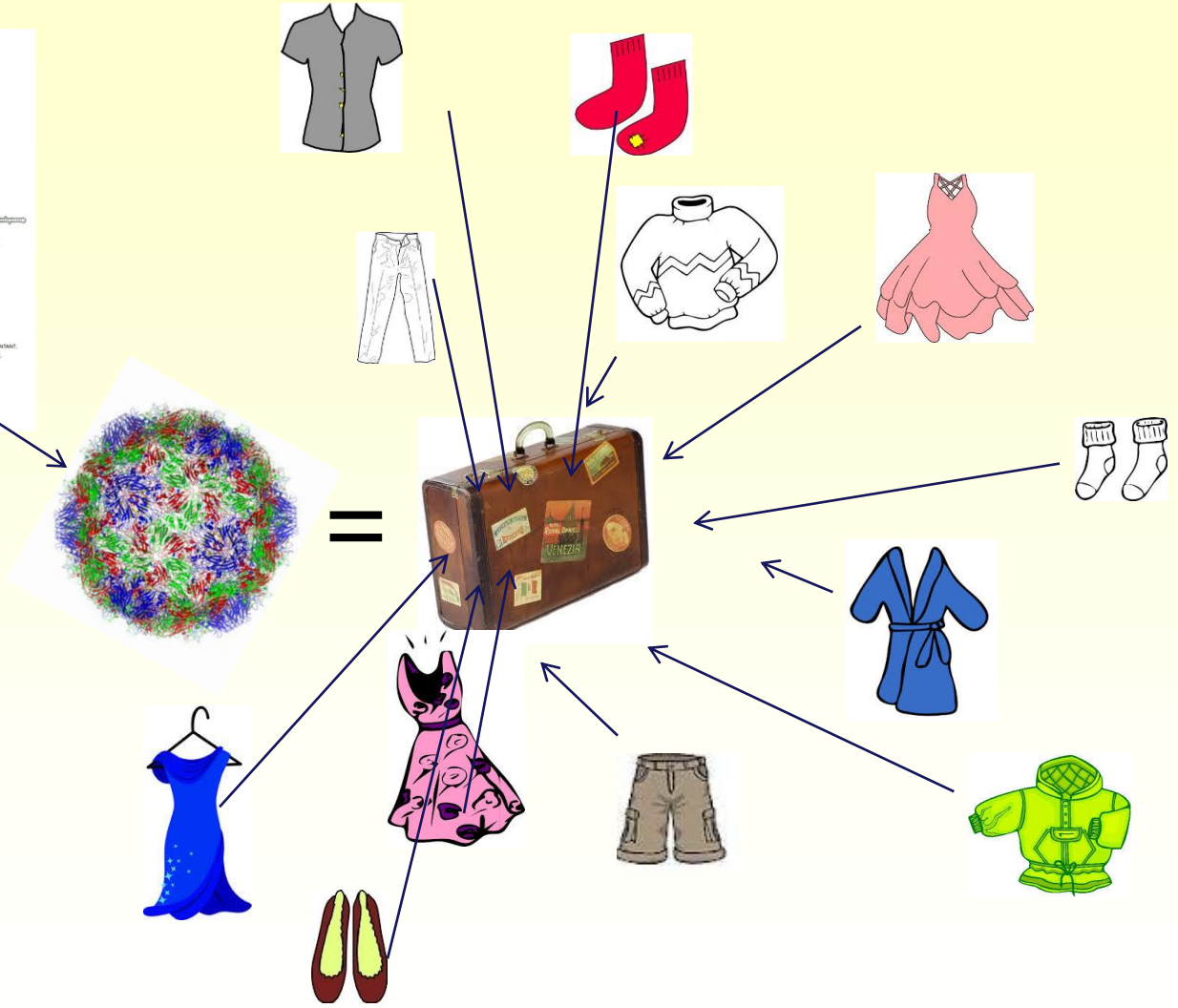




Article by Prof Peter Stockley, Leeds – Huffington Post

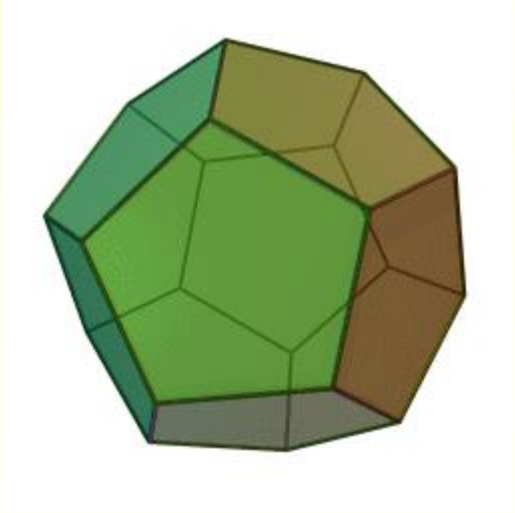
The mechanism: Viruses behave like “self-packing suitcases”





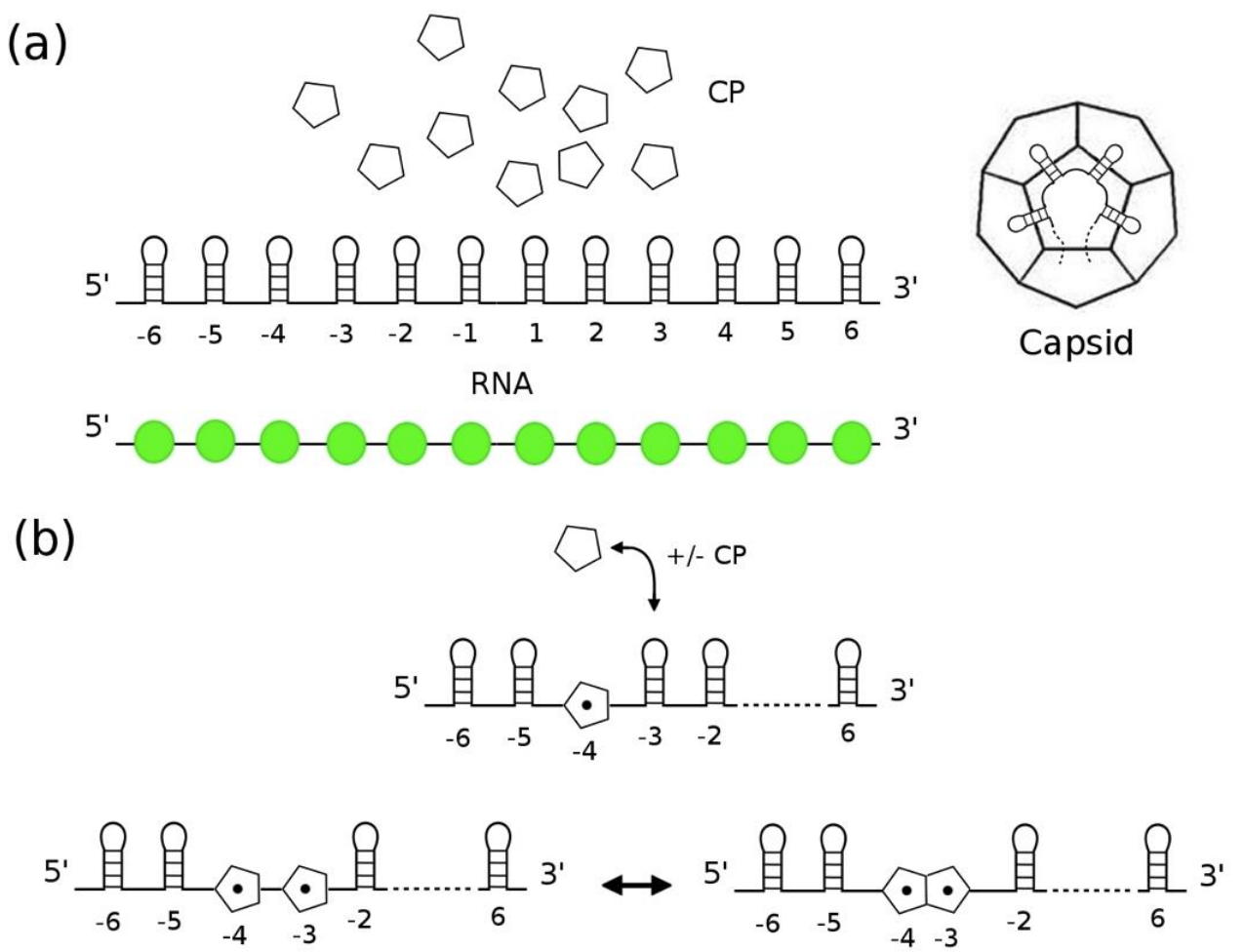
Article by Prof Peter Stockley, Leeds – Huffington Post

How does that work?



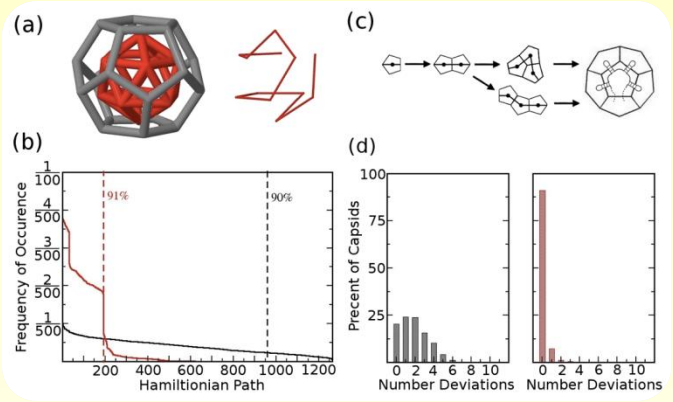
Study formation of a dodecahedral shell from pentagonal building blocks

Assembly models



EC Dykeman, PG Stockley & R Twarock (2014) PNAS

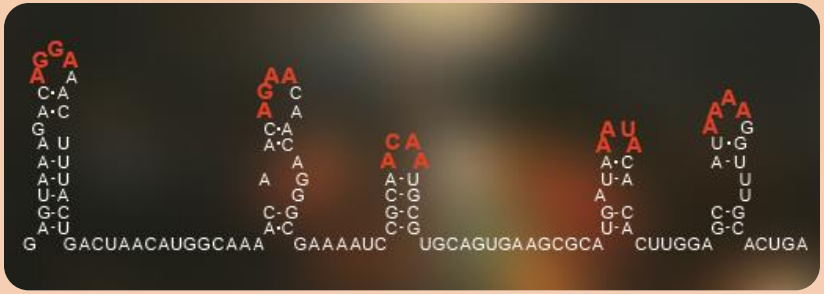
A solution to Levinthal's paradox in virology

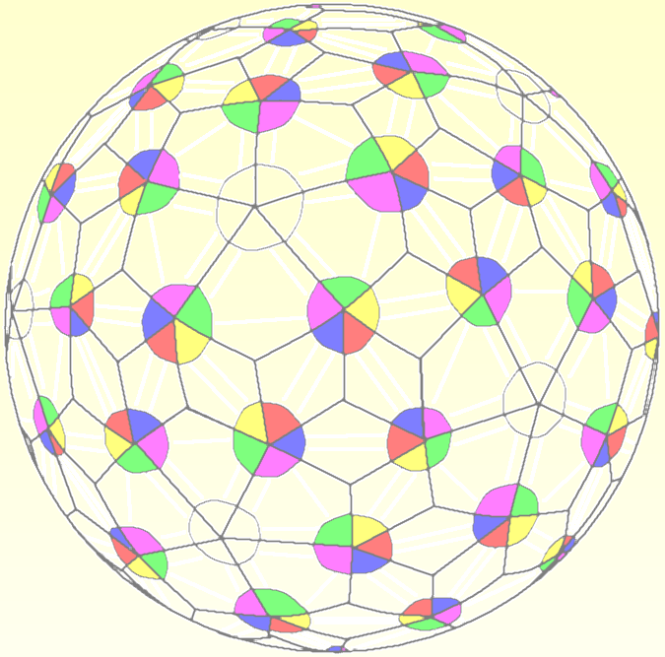


Reduction to only a small number of all possible assembly pathways

These are the (energetically) favourable ones

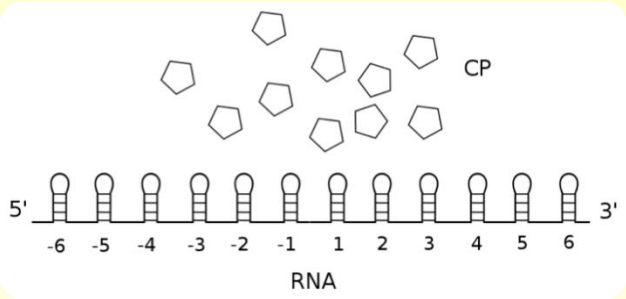
Packaging signals are the code that enables efficient virus assembly



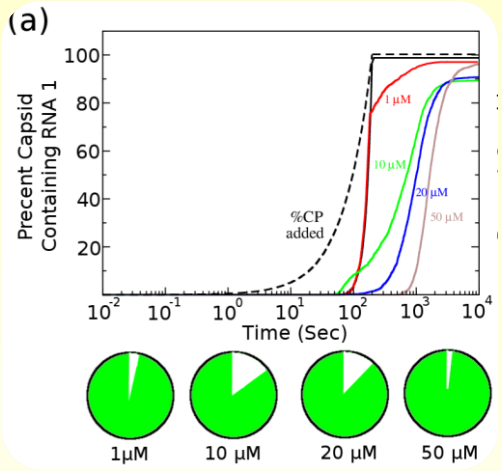


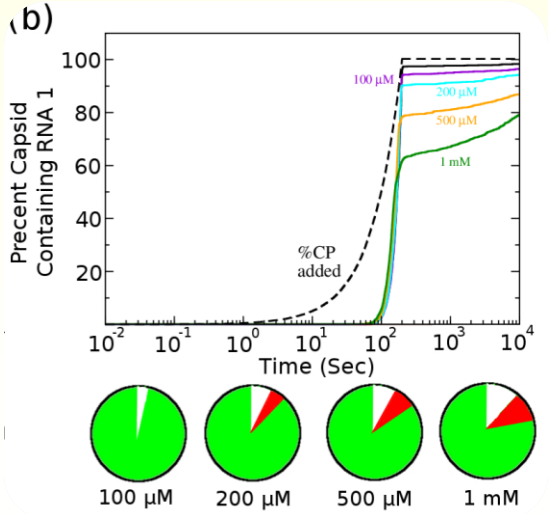
Mathematics underpins the discovery of new drugs

New avenues in drug design



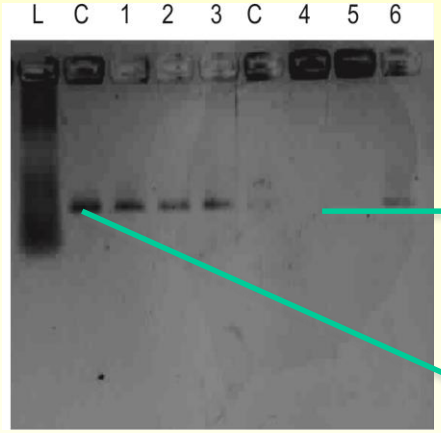
+ drug molecules



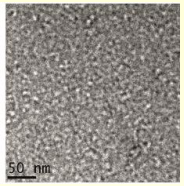


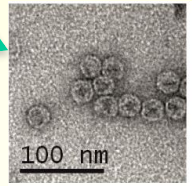
It works!

MS2 TR [1 µM] CP_2 [3.5 µm] reassemblies with various ligands [1 µM].



MS2 VLP

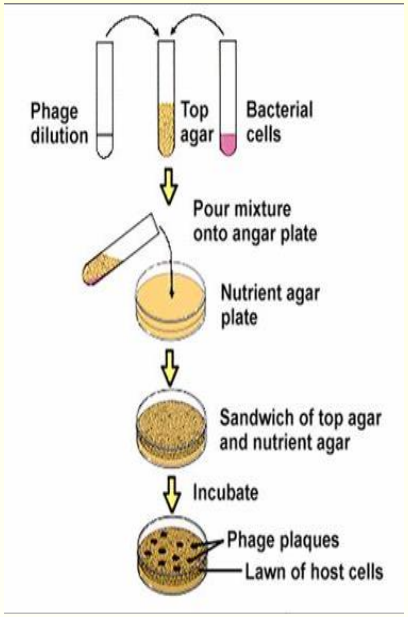


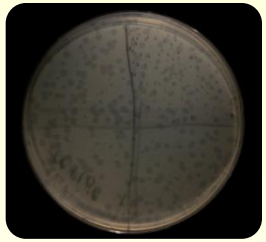


Control

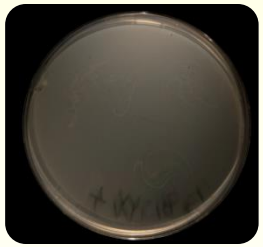
Peter Stockley

Amy Barker

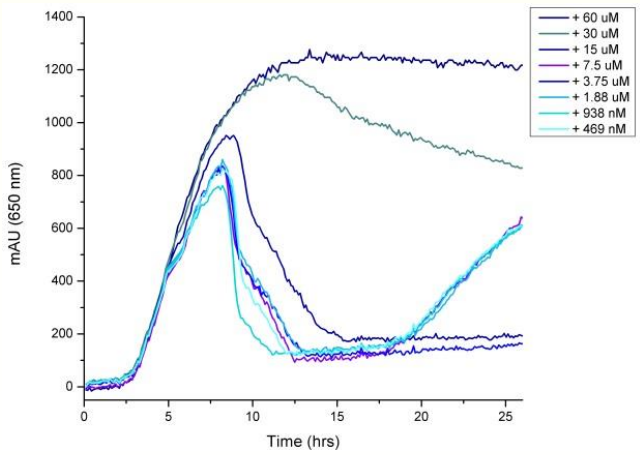




No drug



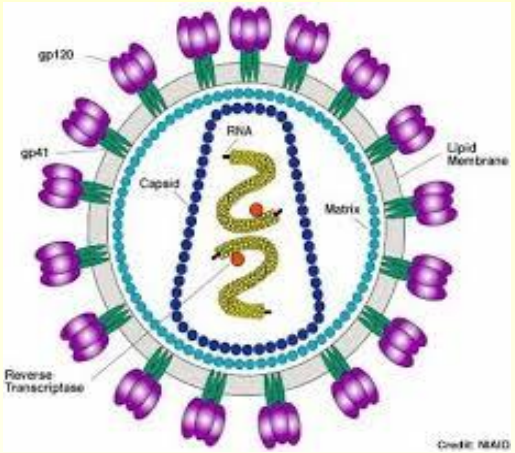
60 µM



Solution to a fundamental problem

• Escape mutants can occur when viruses are challenged by a drug;

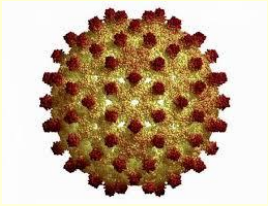
•small changes in capsid structure make drugs less likely to bind (problems with the “key-lock” principle).

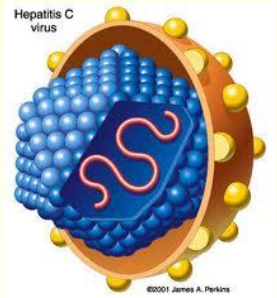


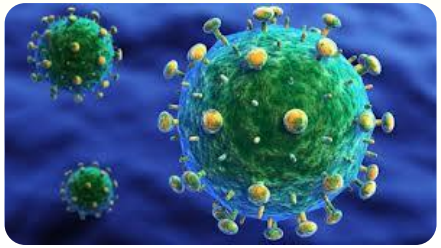
The solution:

Our mechanistic insights provide a new solution, because they allow us to target evolutionarily stable features.

A new anti-viral approach







A patent

University of York, in collaboration with the Universities of Leeds and Helsinki, has **filed a patent in September 2013, proposing a novel anti-viral strategy in RNA viruses** based on these discoveries.

We have exemplifying this strategy in a wide range of viral systems, including:

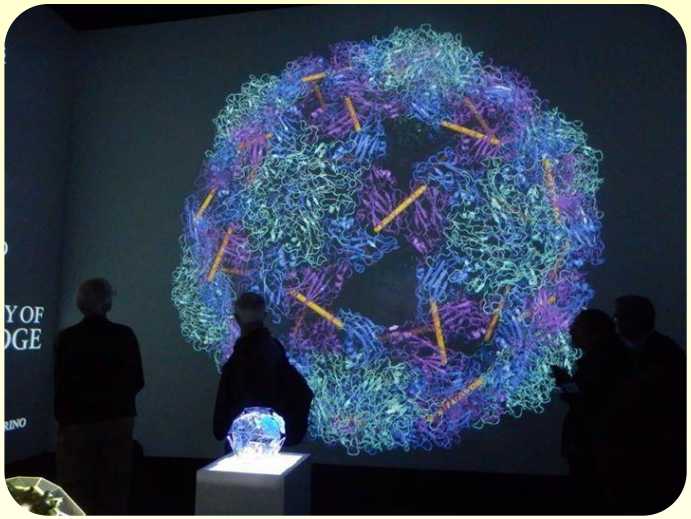
- Hepatitis B and C
- HIV

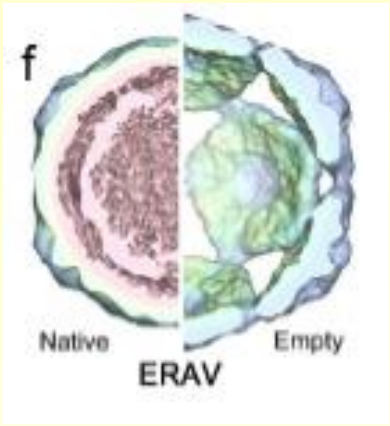
=> New opportunities also for vaccine design

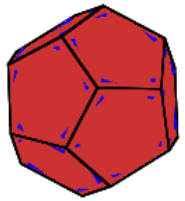
Mathematics and Design in Dialogue

Viral geometry and design:
Collaboration with Briony Thomas, Leeds

Art inspired by virus dynamics





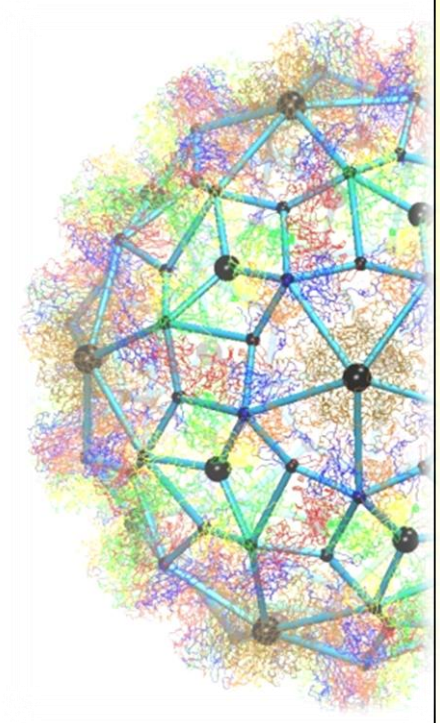


Festival of Ideas – York – June 2015

Summary

Mathematics provides fundamental new insights into virus architecture.

These results can then be used to investigate how viruses form, evolve, and infect their hosts.



Our highly interdisciplinary approach has resulted in a new anti-viral strategy that avoids the problem of escape mutants.

Mathematics has played a key role in these discoveries

Thanks

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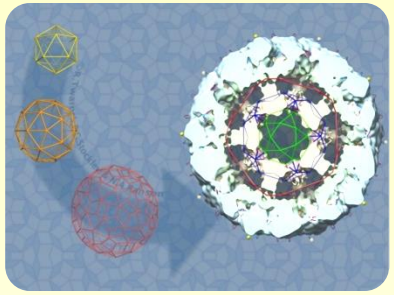

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