Geometry: A secret weapon in the fight against viruses

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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
Viruses are nanoscale machines
Viruses are very small…
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

![Diagram: 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
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:

2-fold
Reflection:

Axis of symmetry: mirror

Rotation:

2-fold

3-fold

The language of symmetry
The language of symmetry

**Reflection:**
- Axis of symmetry: mirror

**Rotation:**
- 2-fold
- 3-fold
- 4-fold
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
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

They share the same symmetry properties!

www.giantmicrobes.com
The architecture of larger viruses

Caspar and Klug discover quasi-equivalence (1962):
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The local environments of all capsid proteins look similar.’’
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Dots mark the positions of capsid proteins.
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

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

The layouts of some viruses do not correspond to triangulations.

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.

Pentamer: pentagonal cluster
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
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

SV40

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?

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

Pariacoto virus
Pariacoto virus
Pariacoto virus

Artist’s impression of Pariacoto virus 😊
New insights into genome organisation

New molecular scaling principle discovered!

Peter Stockley

Neil Ranson

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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Idea: Classify extensions of the icosahedral group.
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 carbon cages

Applications

Conclusions

Virus Structure

Fullerenes and Carbon onions

Fullerene cages derived from affine symmetry principles for non-crystallographic systems & applications to viruses/carbon onions

Adapted from Chemistryworld (June 2014)
The same mathematics works for fullerenes

The atomic positions of the $\text{C}_{60}$-$\text{C}_{240}$-$\text{C}_{540}$ 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 =

(a) [Image of a protein structure]

(b) [Image of a protein structure]

(c) [Image of a virus particle]
Virus assembly – the viral production line

Movie courtesy of Arthur J Olson
(Scripps)
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
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”
Multiple dispersed interactions with capsid protein are essential for efficient capsid formation.
Viral geometry and code breaking

The challenge:

Identify packaging signals in a wide range of viruses
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

(a) Percent Capsid Containing RNA 1

(b) Percent Capsid Containing RNA 1
It works!

MS2 TR [1 µM] CP₂ [3.5 µm] reassembles with various ligands [1 µM].

Peter Stockley
Amy Barker
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

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

- Hepatitis B and C
- HIV

=> New opportunities also for vaccine design

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.
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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