Biology through the Mathematics microscope: new exciting directions of research

Anne Taormina

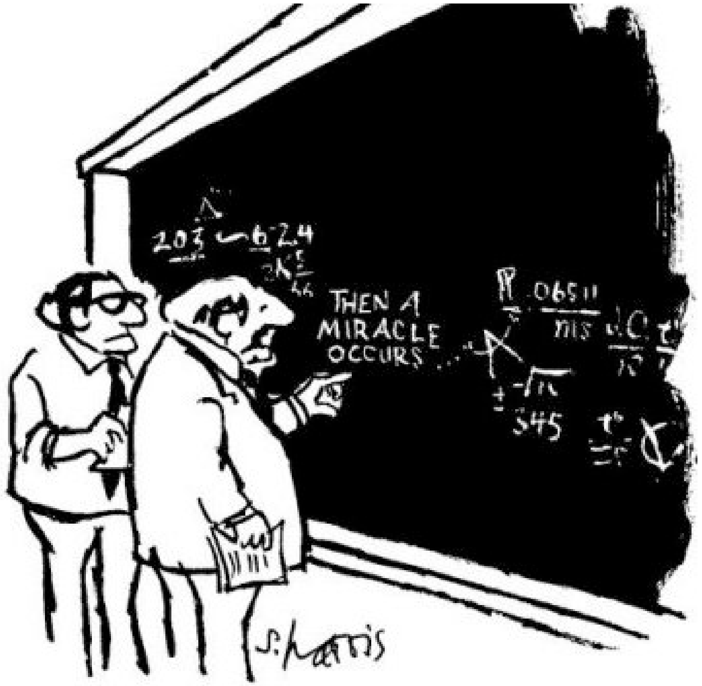
Prospects in Mathematics, 10 January 2009, Durham

What is Mathematical Biology?

- Application of mathematical modelling to solve problems in biology
- One of the fastest growing research areas in mathematics
- Contributes significantly to our understanding of the biological world
- Produces new mathematical questions

Biologists...

- deal with `single problems'
- have intuitive approach to problems
- have excellent technology at their disposal
- can be intimidated by mathematicians



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

Mathematicians...

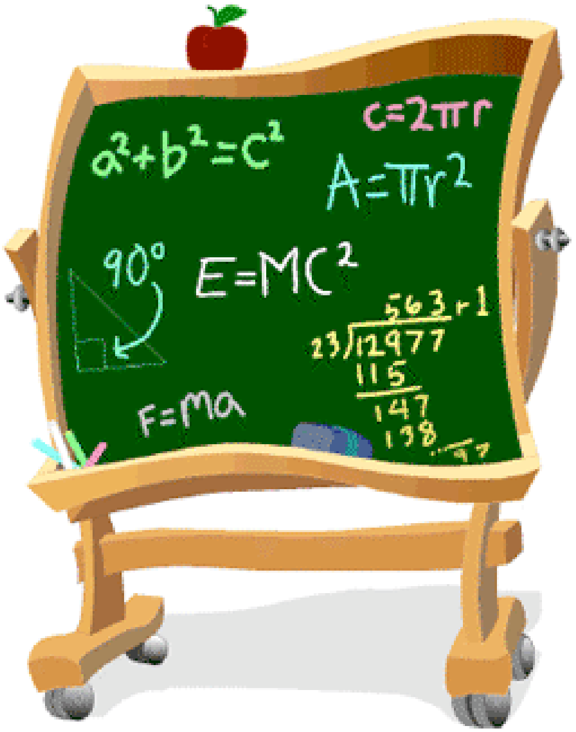
- look for generalisations
- use `noddy' approaches bearing little relevance to the real situation in Biology
- use very brushstroke approaches not specific enough for Biology

Some specific biological problems where new mathematical approaches are needed:

- Cell Signalling
- Reaction – diffusion in cells
- Modelling kinetics
- Spatio-temporal issues in cells
- Self-assembly
- Hierarchy of scales, deterministic vs stochastic
- Cell processes e.g. dynamics of microtubules
- Huge amounts of messy biological data which needs very good statistical methods (data integration that you can have confidence in)
- Neural networks
- Protein structure and folding - conformational changes in viruses
- Mapping phenotype to genotype

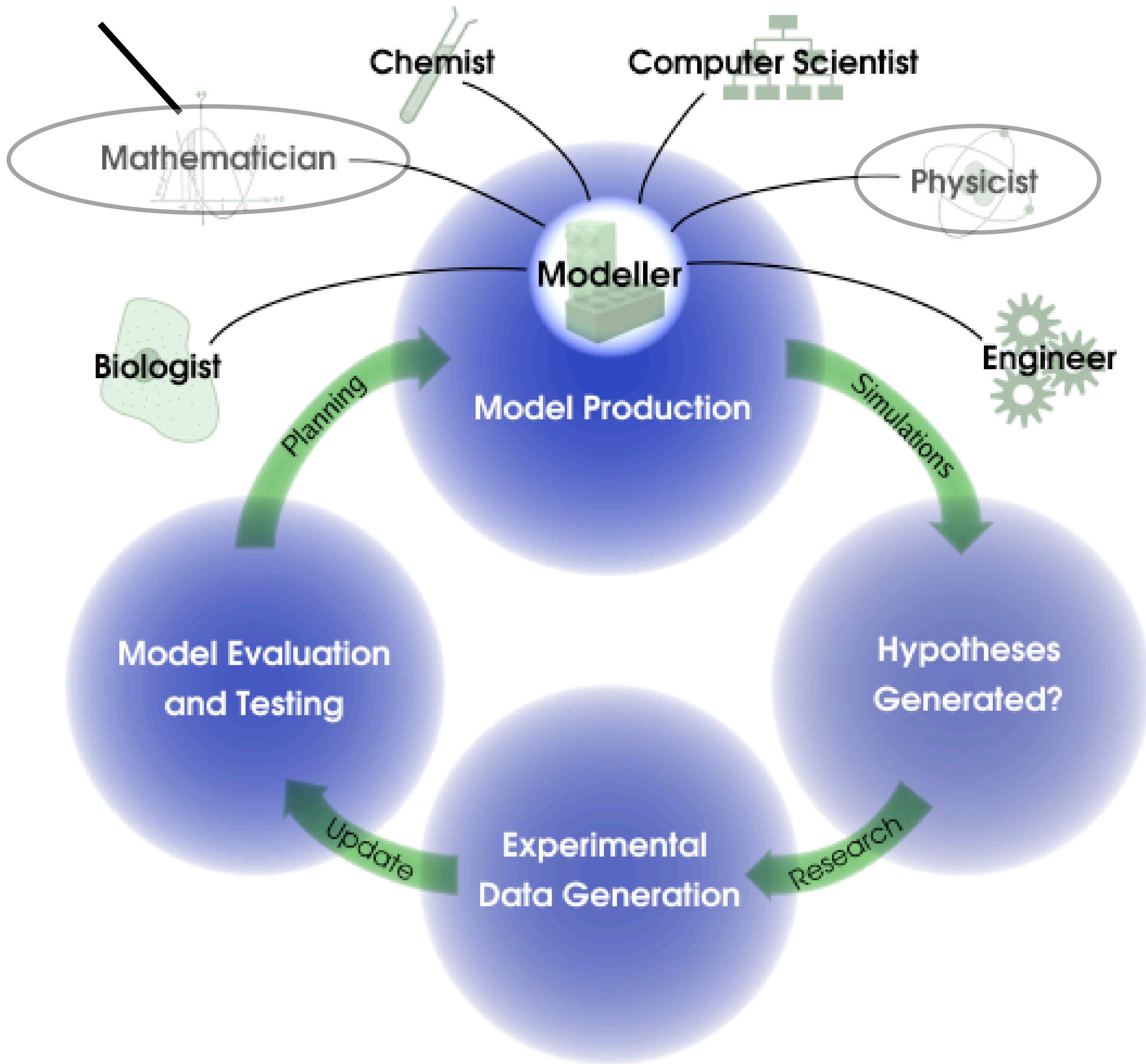
New Mathematics?

- Brand new maths inspired by a biological problem
- Surprising maths - using existing maths techniques you would never expect to be appropriate or relevant, or adapting maths techniques to the scales involved in biology.



New Maths

Integrative biology



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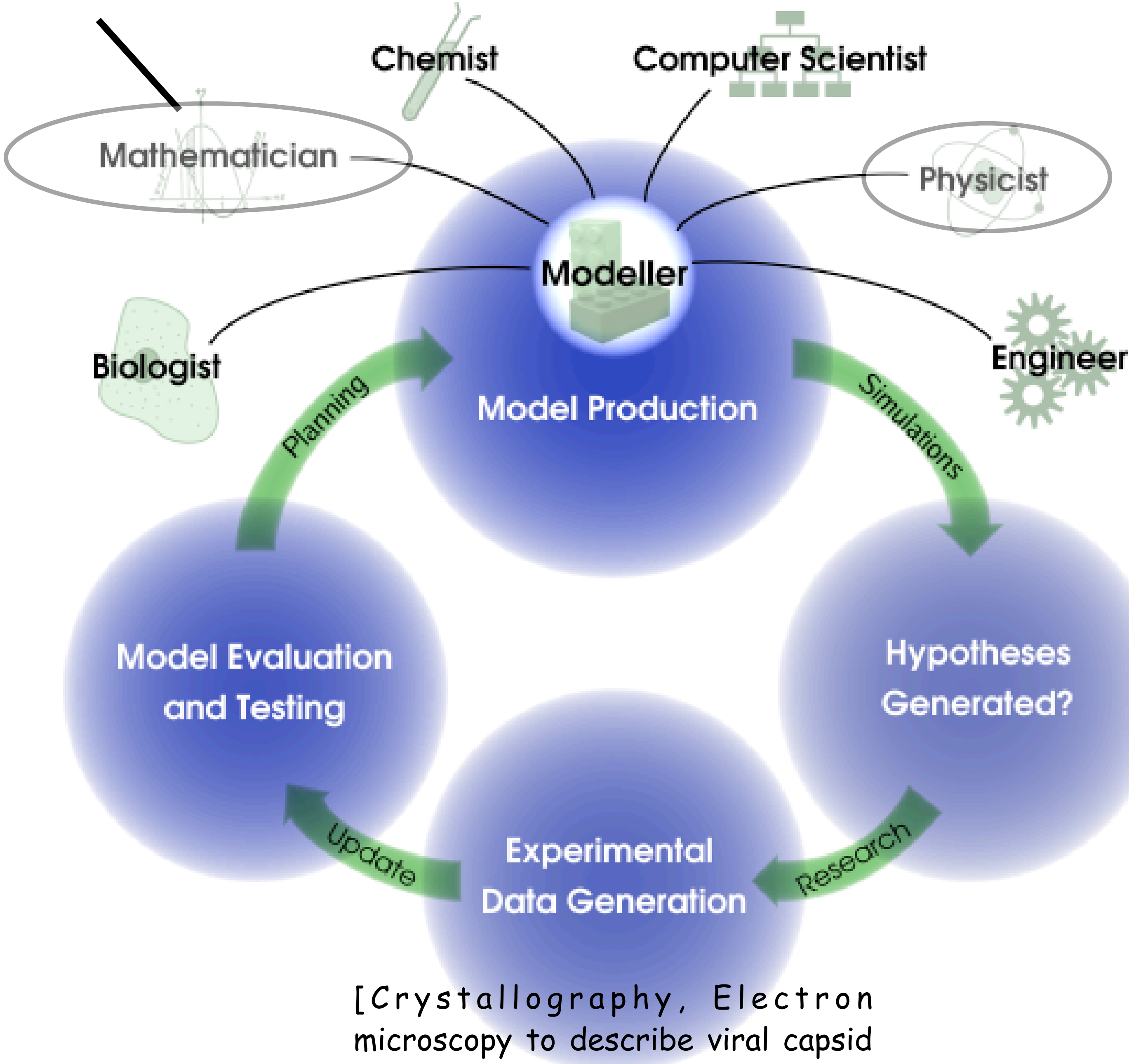

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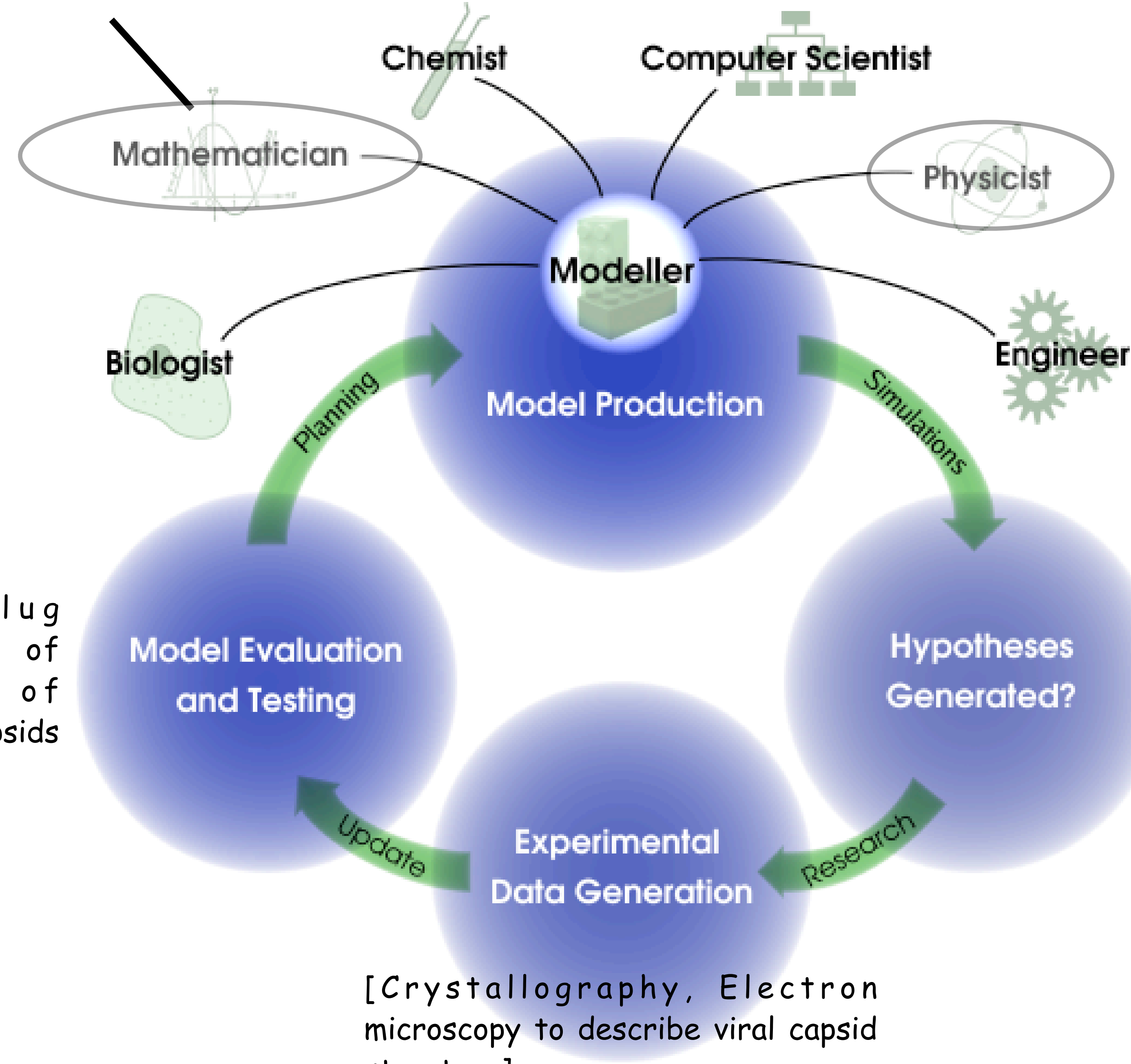

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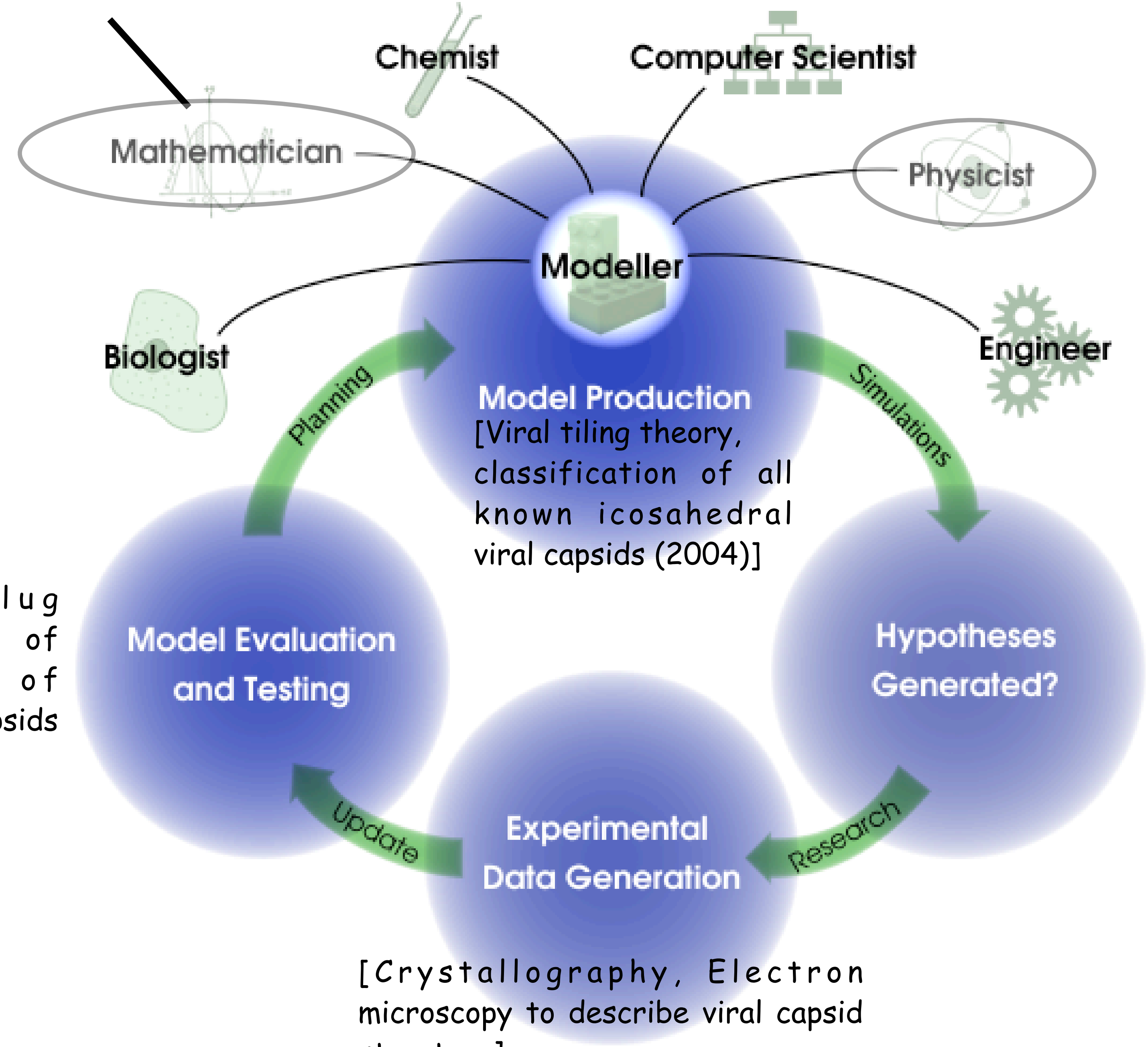

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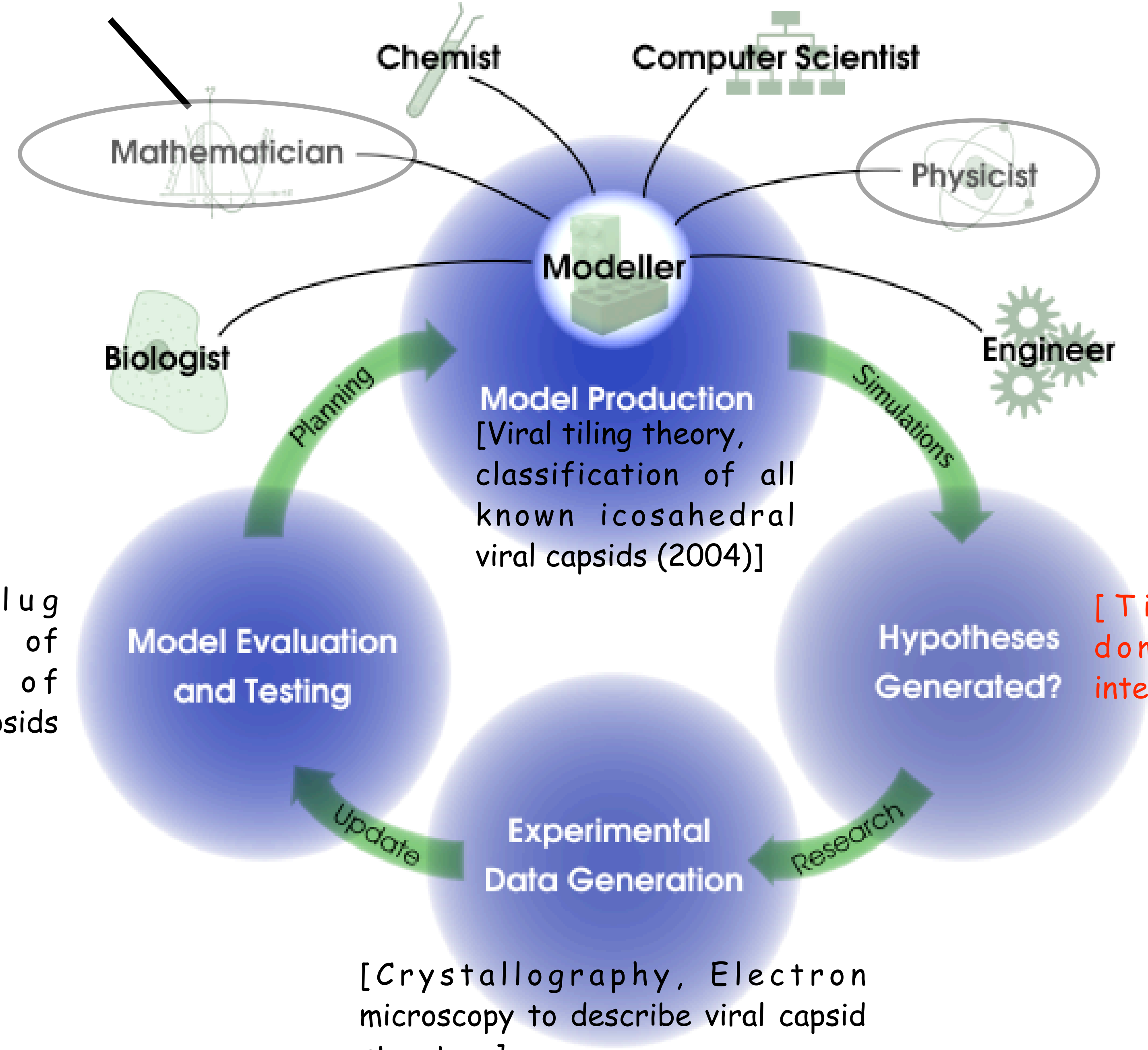

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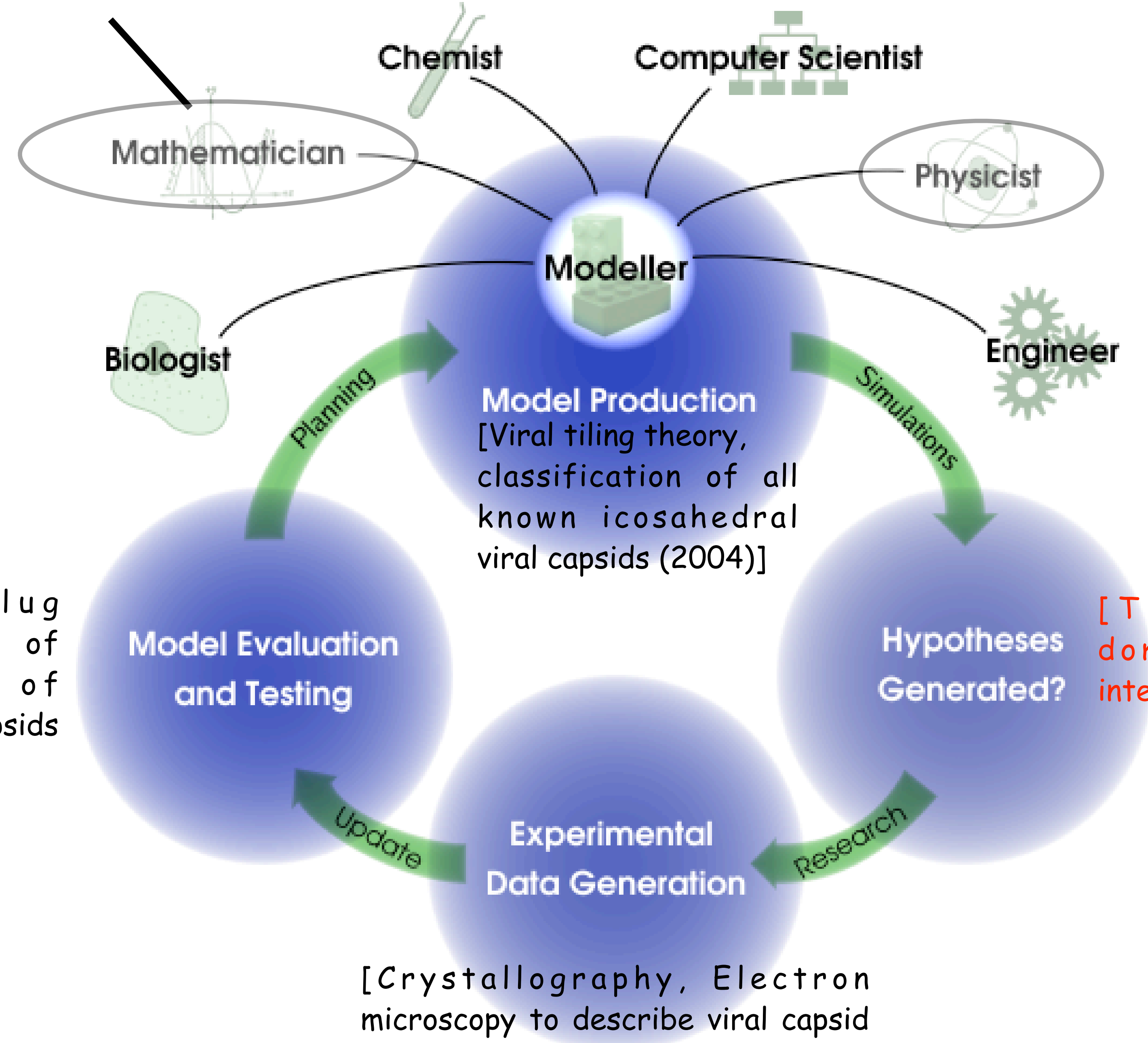

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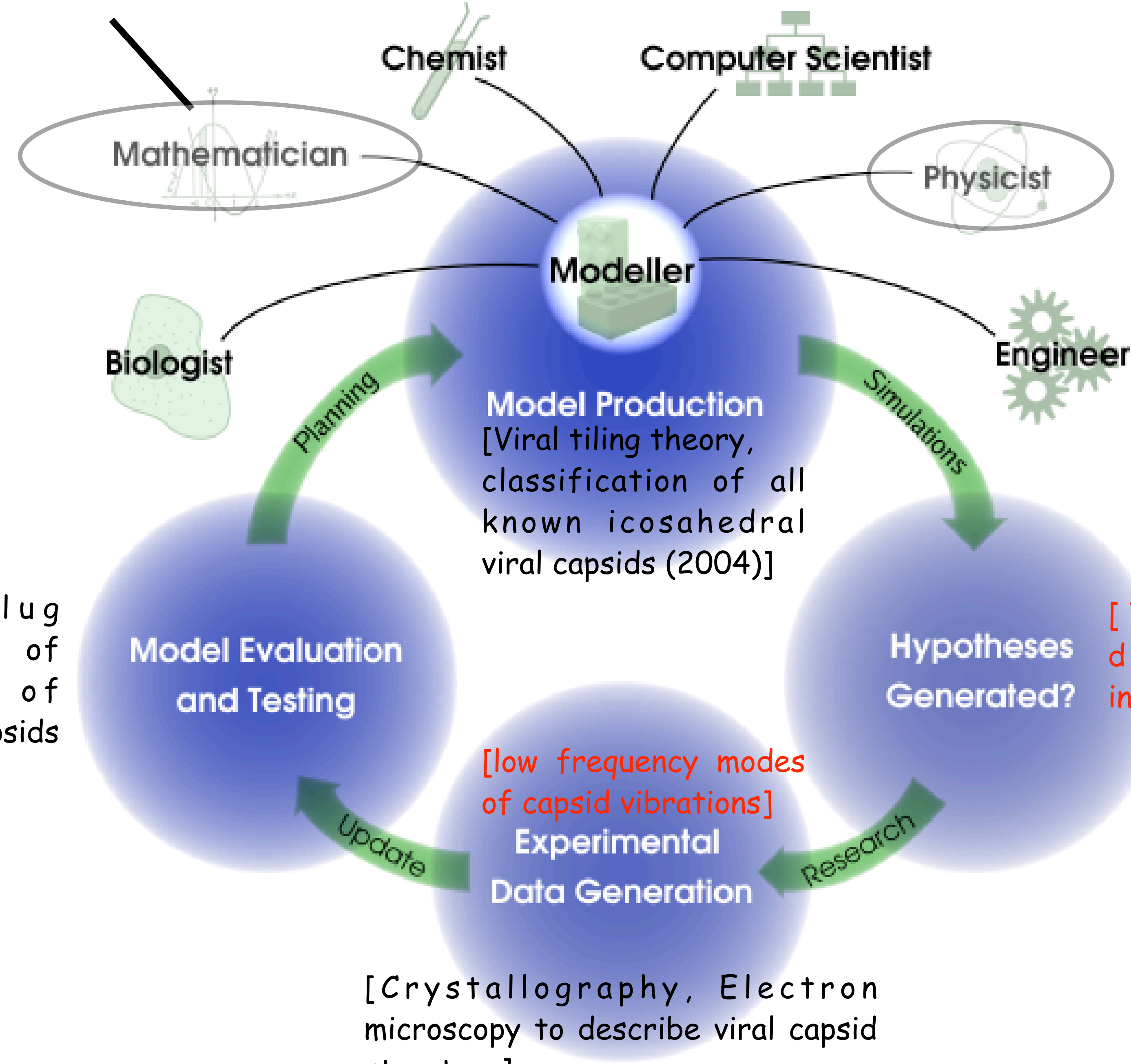

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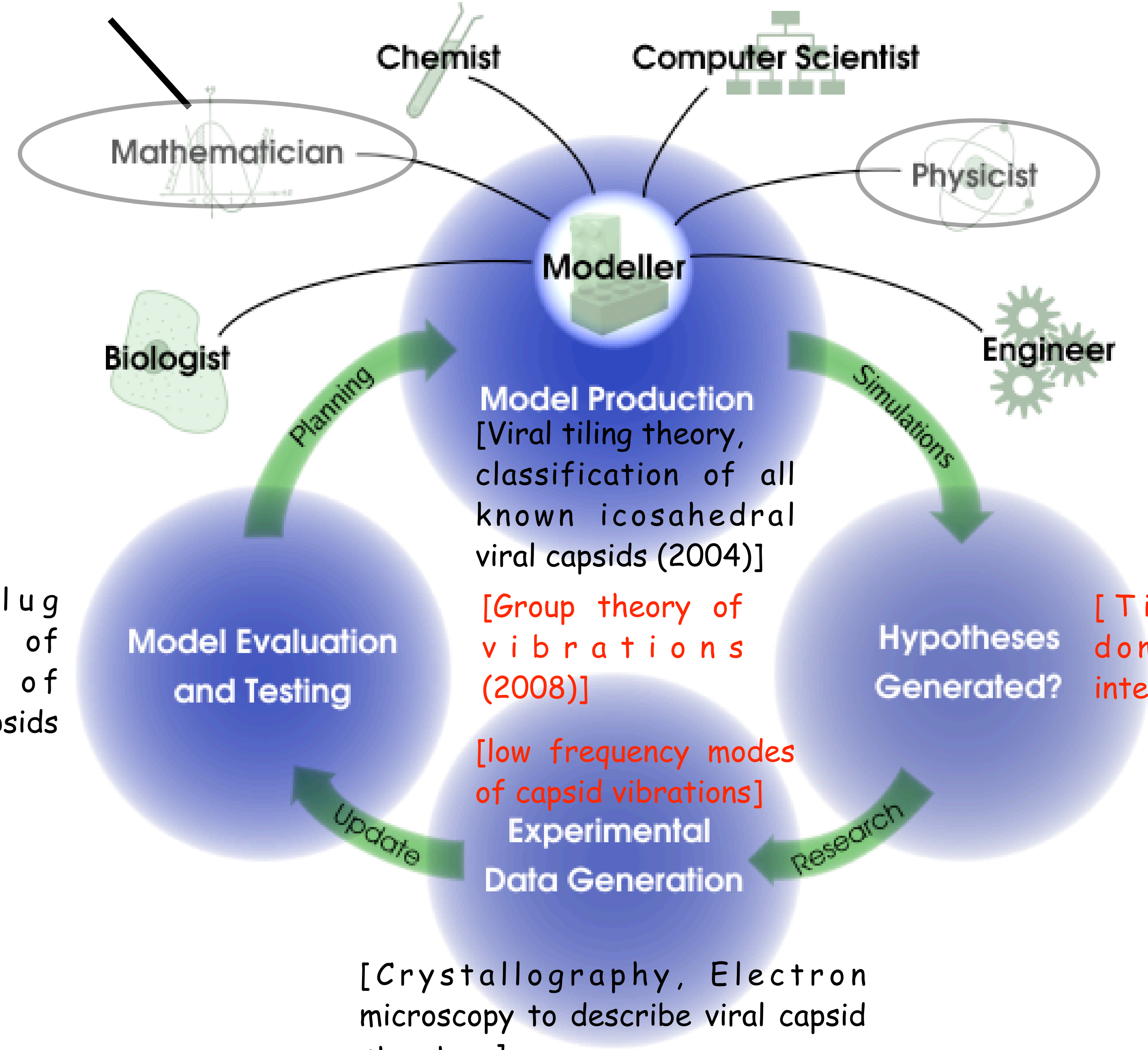

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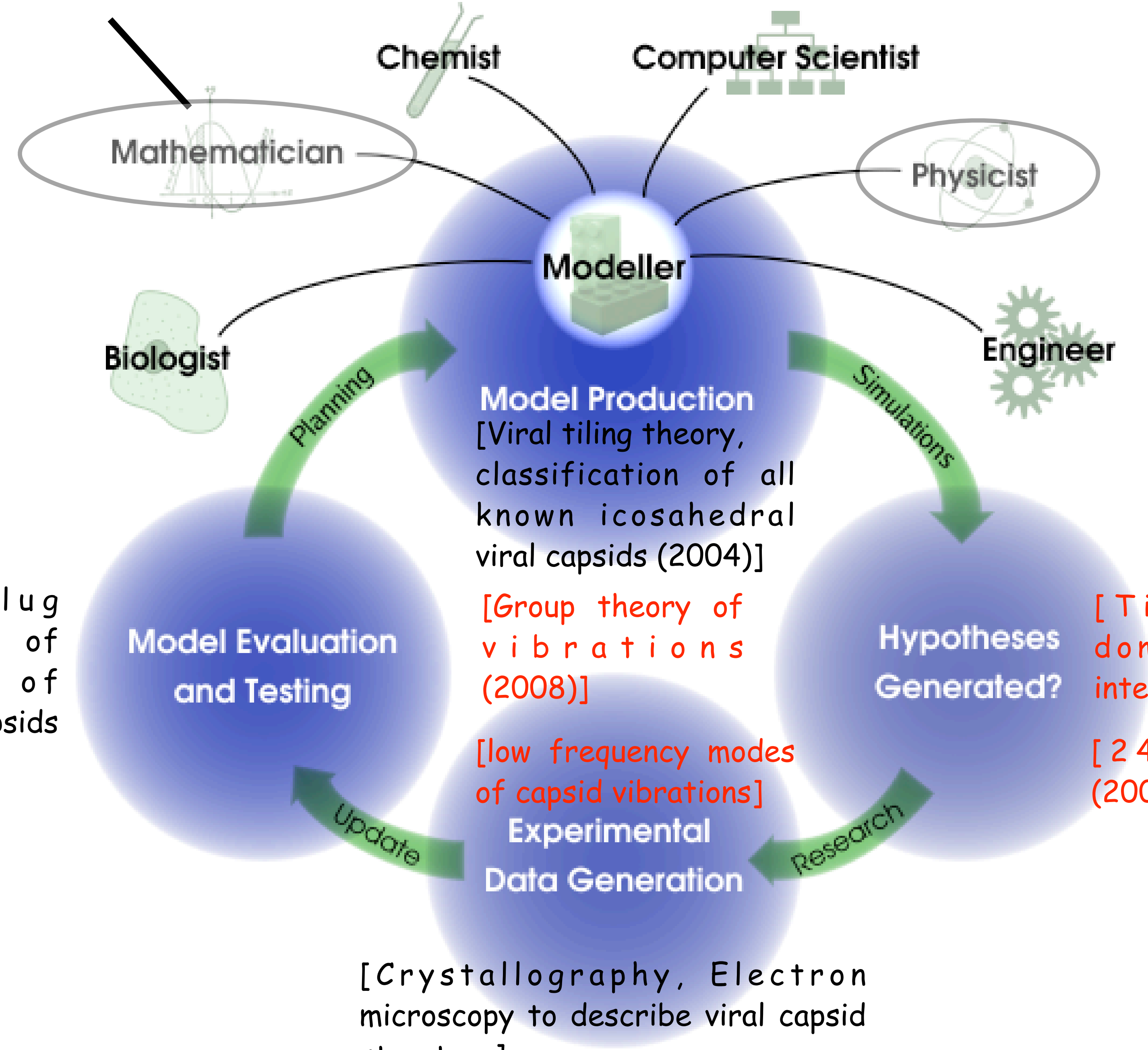

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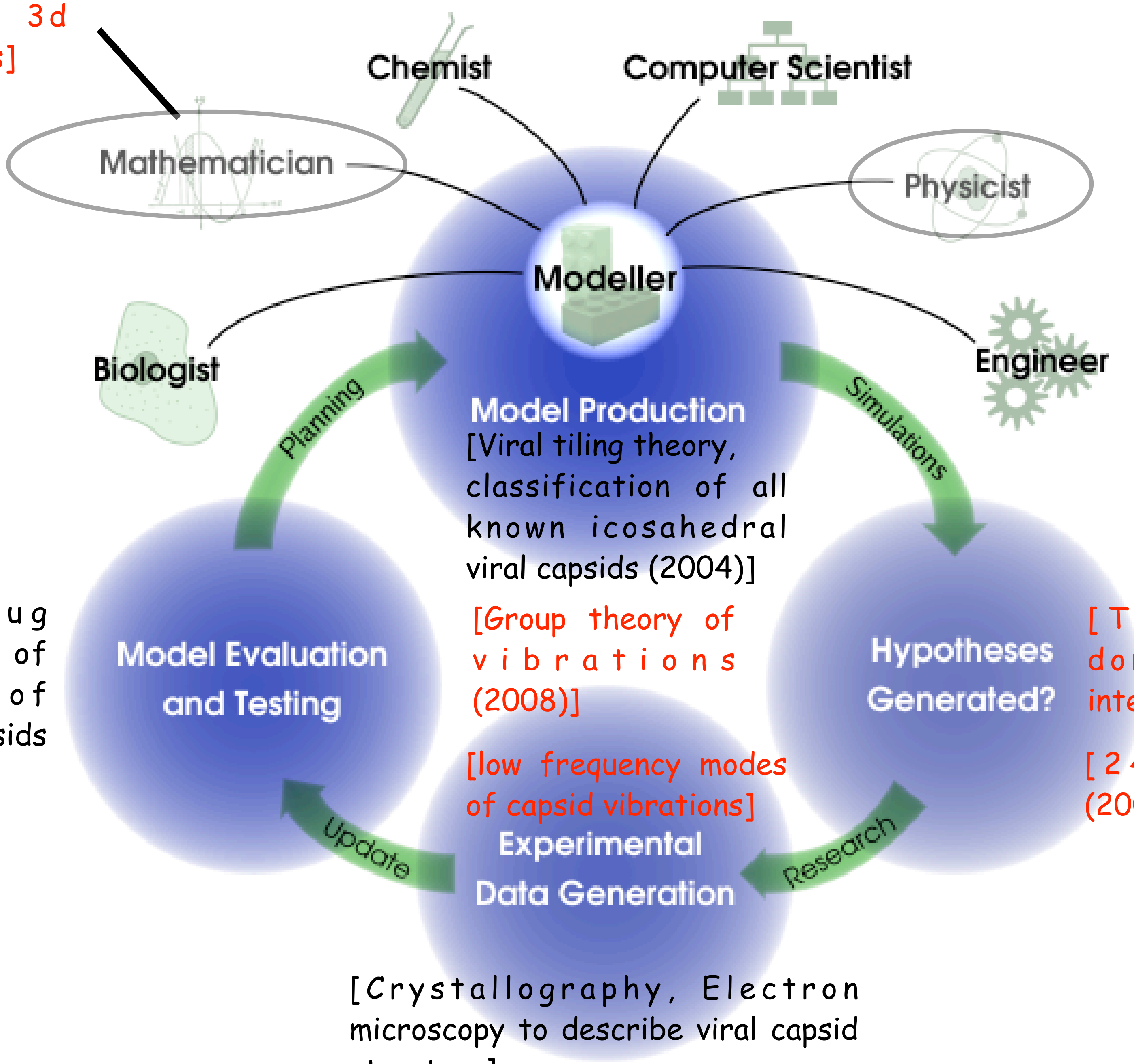

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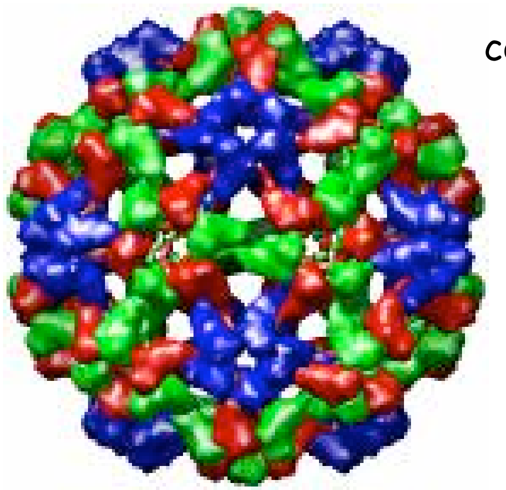


computer model based on crystallographic data

chlorotic cowpea mottle virus
(ccmv)

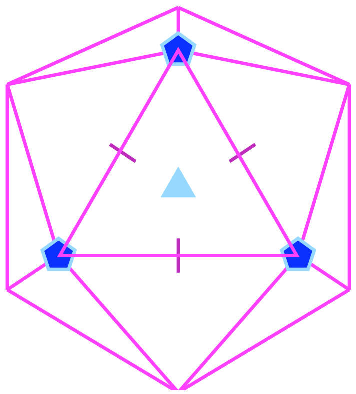
pentamer = cluster of 5 proteins (12)

hexamer = cluster of 6 proteins (3 + 3) (20)

number of proteins on capsid: $5 \times 12 + 6 \times 20 = 180$

(12 → number of vertices; 20 → number of `faces')

Golden rectangles and icosahedra

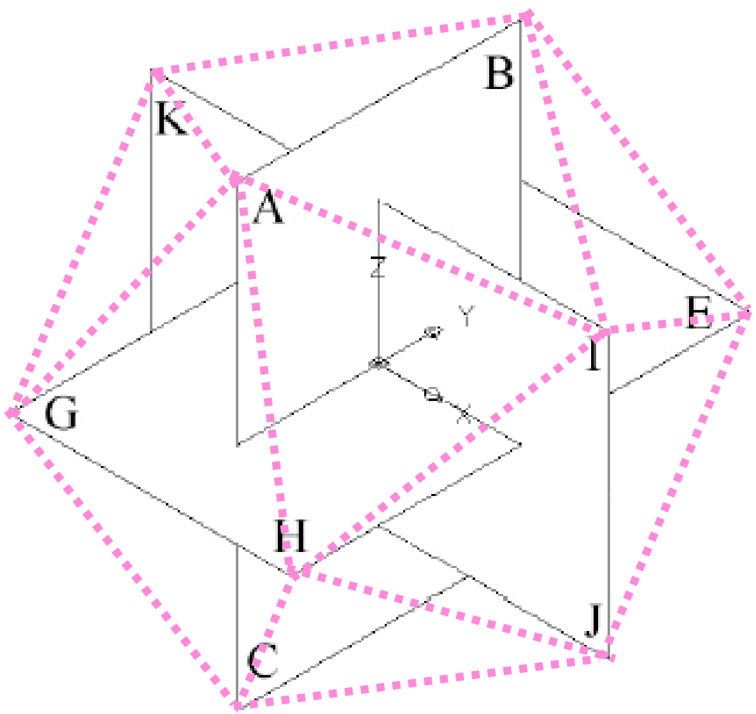


The icosahedron is a Platonic solid with 20 triangular faces and 12 vertices

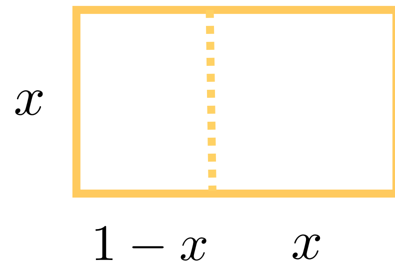
– **2-fold symmetry axis (15 axes)**

▲ **3-fold symmetry axis (10 axes)**

⬟ **5-fold symmetry axis (6 axes)**



Golden ratio : $\tau = \frac{1}{2}(1+\sqrt{5})$

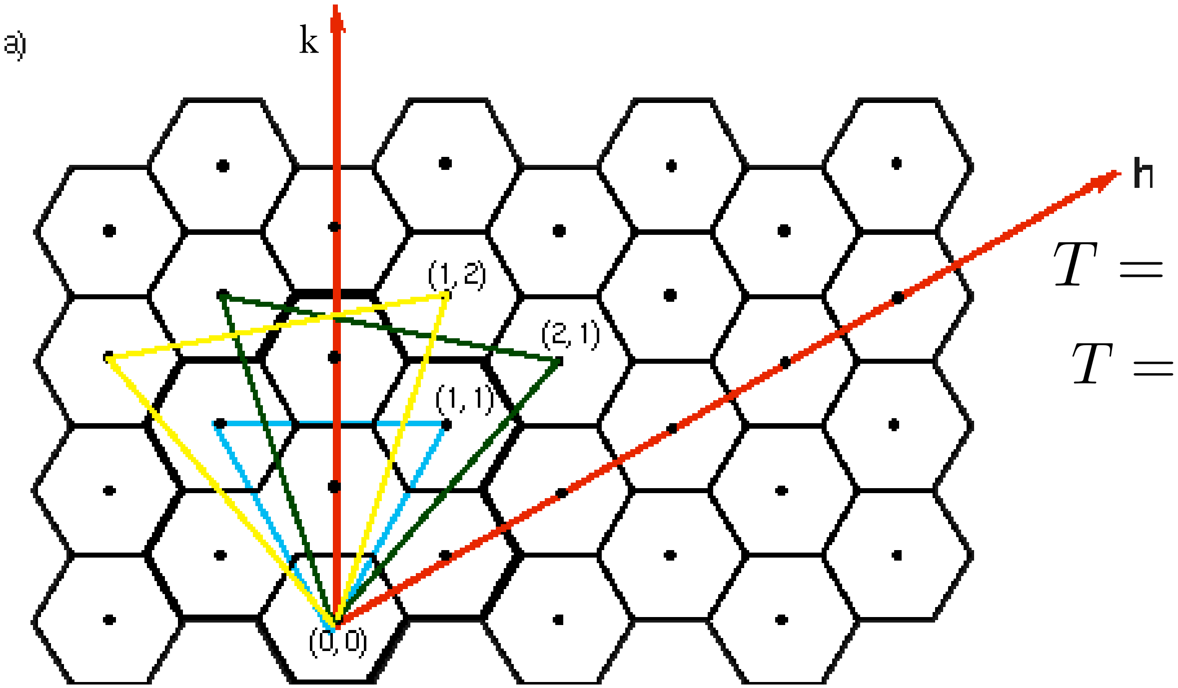


$$\frac{\text{length}}{\text{width}} = \frac{1}{x} = \frac{x}{1-x} \equiv \tau = \text{golden ratio}$$

↓

Defining property

Caspar-Klug classification

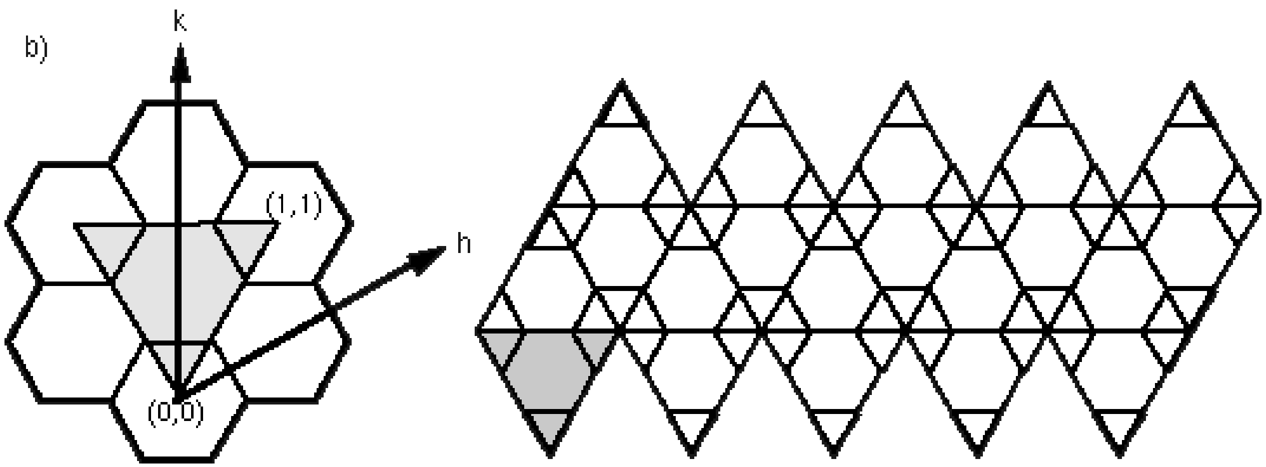


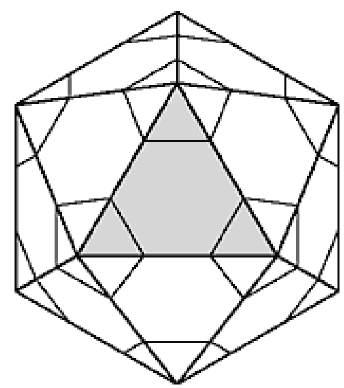
$$T = h^2 + hk + k^2, \qquad h, k \in N \cup \{0\}$$

$$T = 1, 3, 4, 7, 9, 12, 13, \ldots$$

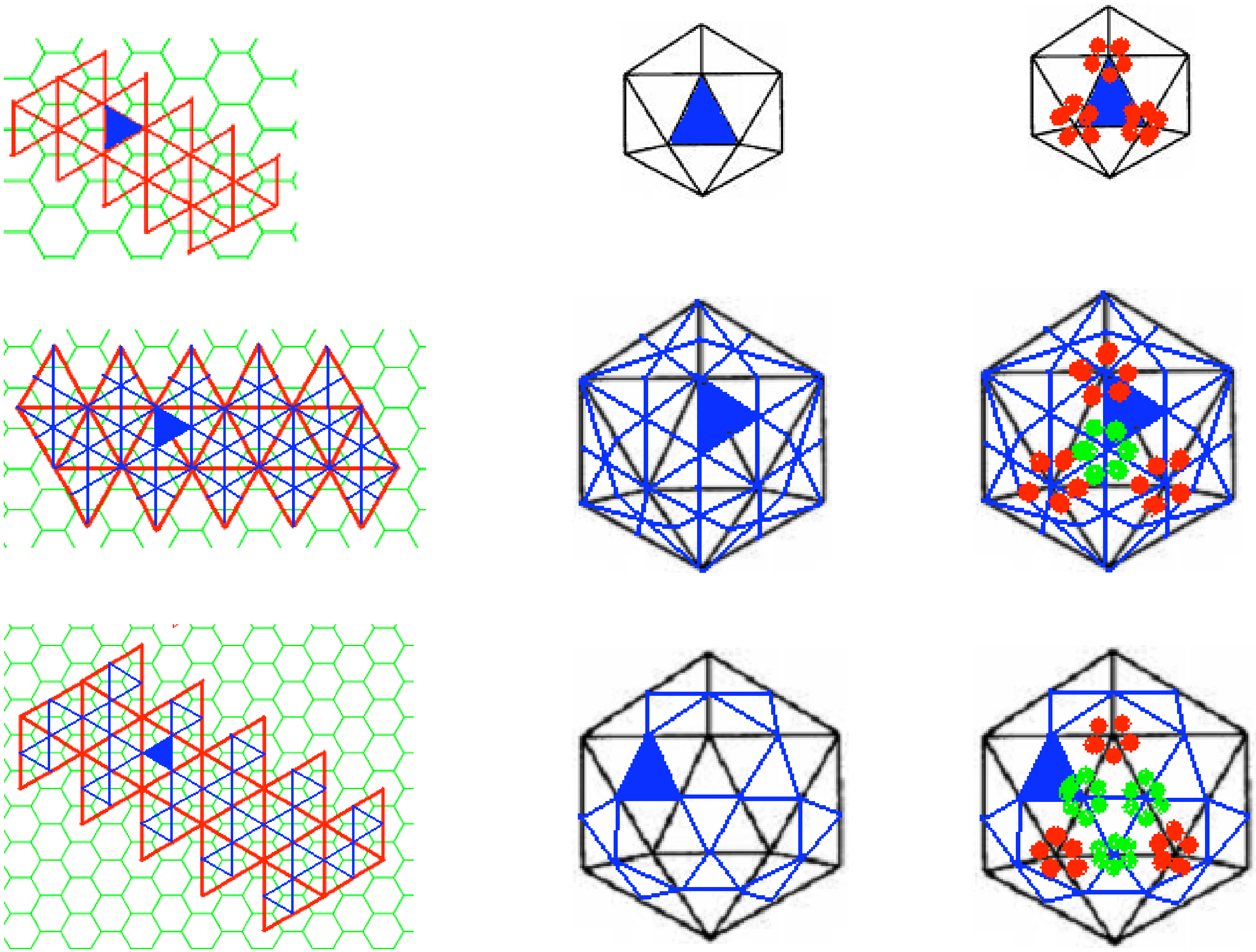
global 3-fold symmetry axis or
local 6-fold symmetry axis

example: T=3 (h=k=1) buckyball





The surface lattices (Caspar-Klug classification)



12 pentagonal clusters
T=1

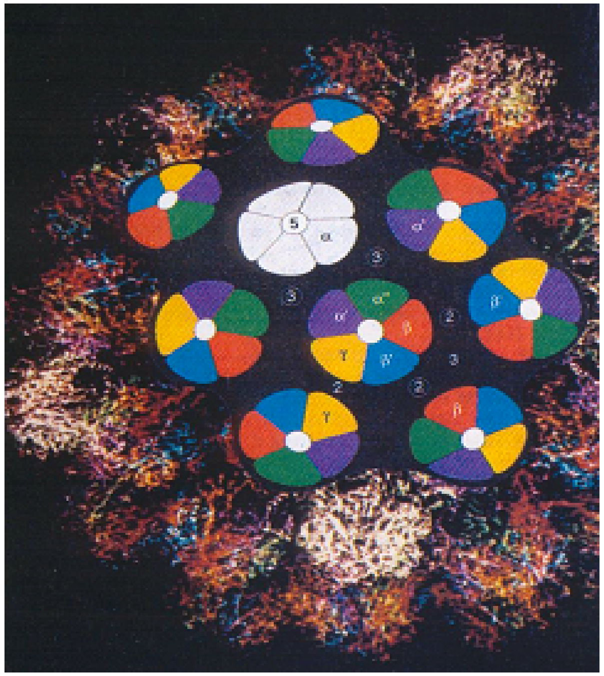
12 pentagonal clusters
20 hexagonal clusters
T=3

12 pentagonal clusters
30 hexagonal clusters
T=4

Viruses following the predicted surface lattices have **subsequently been discovered experimentally.**

However...

Not all viruses follow these predictions



Rayment et al. (Nature, 1982) and Liddington et al. (Nature, 1991) observe a virus with 72 pentamers

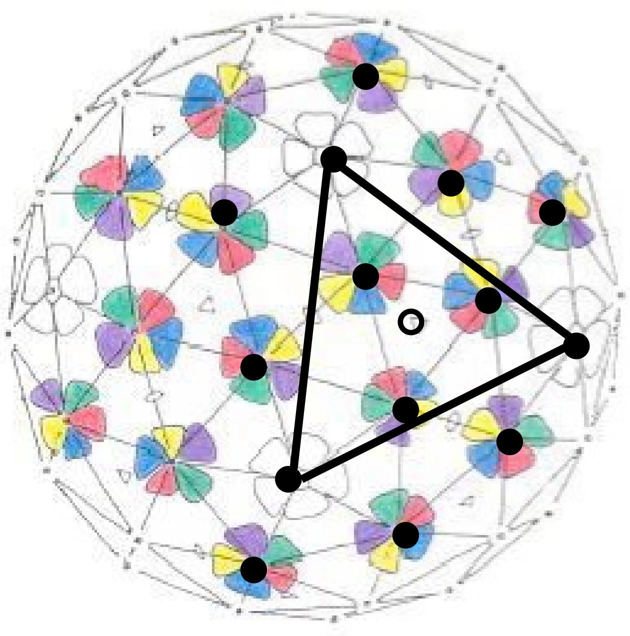
Example:
Cancer-causing viruses, such as Human Papilloma virus.
It causes cervical cancer which represents 10% of all cancers in women

All clusters are pentamers, meaning:

1. **existence of local 5-fold symmetry axes**
2. **they can not be modelled via hexagonal lattices**

Adapted maths: Viral Tiling Theory

Puzzle of all-pentamer viruses like SV40

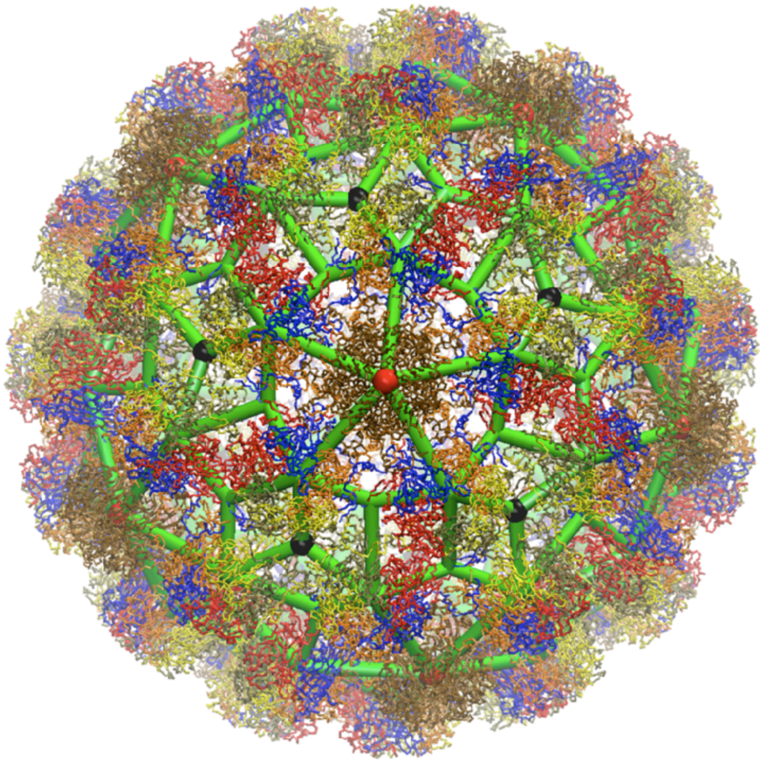


Patera and Twarock, 2002

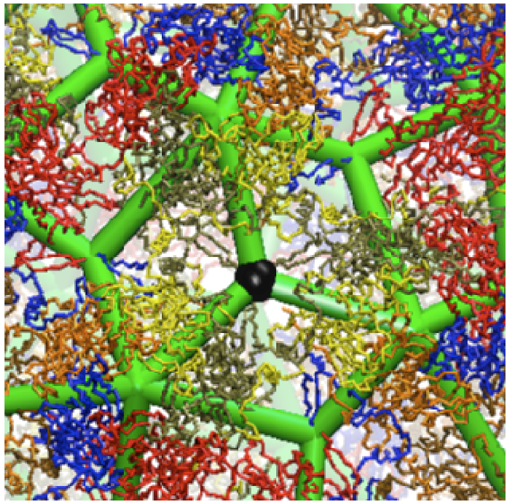
Twarock, 2004

Technique providing fragments of aperiodic tilings

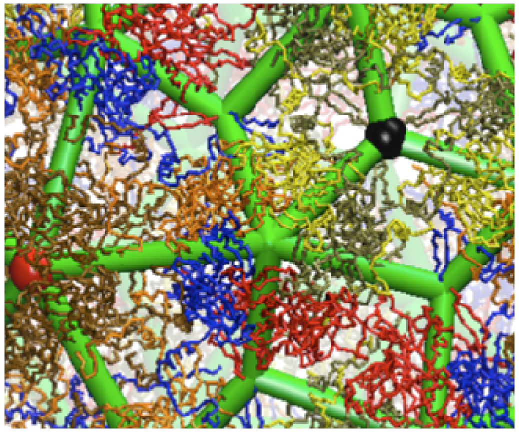
Tiling of SV40: Rhombs and kites



5-fold axis



3-fold axis



Pentamer not located at 5-fold axis

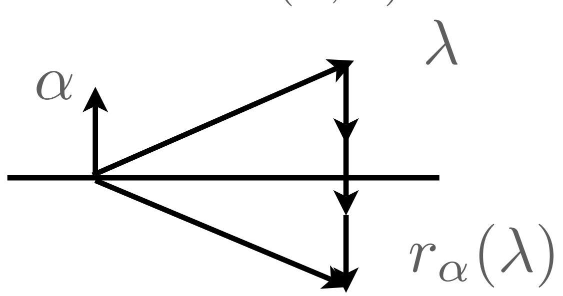
Courtesy K. ElSawy, T. Keef and R. Twarock

New Maths: 3d implications of non-crystallographic properties

Finite crystallographic vs non-crystallographic Coxeter groups

- Finite crystallographic Coxeter groups
- Weyl groups associated with simple Lie algebras (Ex: W(A2) of order 6)
- generated by reflections

$$r_\alpha \lambda = \lambda - 2\frac{(\lambda,\alpha)}{(\alpha,\alpha)}\alpha, \quad 2\frac{(\lambda,\alpha)}{(\alpha,\alpha)} \in Z$$



- admit a unique affine extension (infinite-dim)
- root lattice generated via translation by the highest root and reflections

- Finite non-crystallographic Coxeter groups
- Symmetry groups of regular polygons with any number of vertices but 2, 3, 4, 6 (Ex: H2 - pentagons/decagons; order 10);

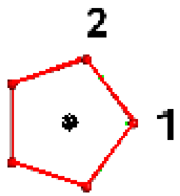
  H3 - icosahedral group, order 120;

  H4 - order 14400
- generated by reflections

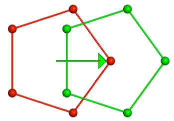
$$2\frac{(\lambda,\alpha)}{(\alpha,\alpha)} \in Z[\tau], \ \tau = \frac{1}{2}(1+\sqrt{5})$$

- admit a unique affine extension (infinite-dim)
- application of reflections and translation by the highest root produces a dense point set

Non-dense point sets



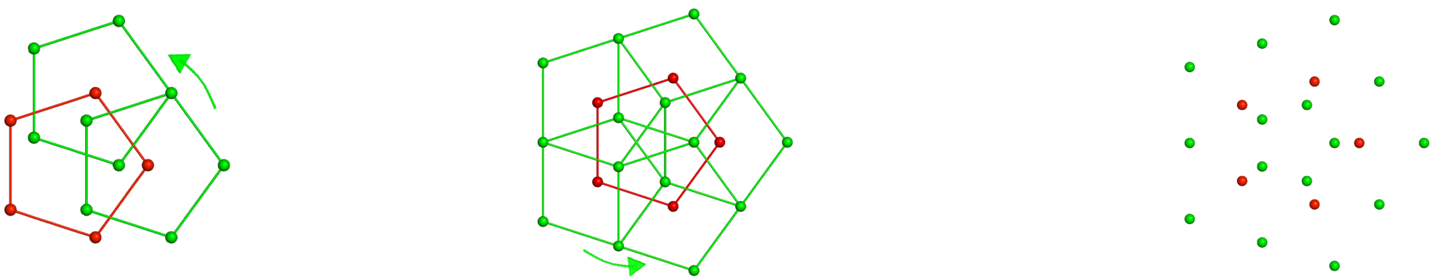
5-fold rotation by 72 degrees, called R



a translation called T

The extended group contains every possible combination of R and T:

R, RR, RRR, RRRR, T, RT, RRT, RRRT, etc…



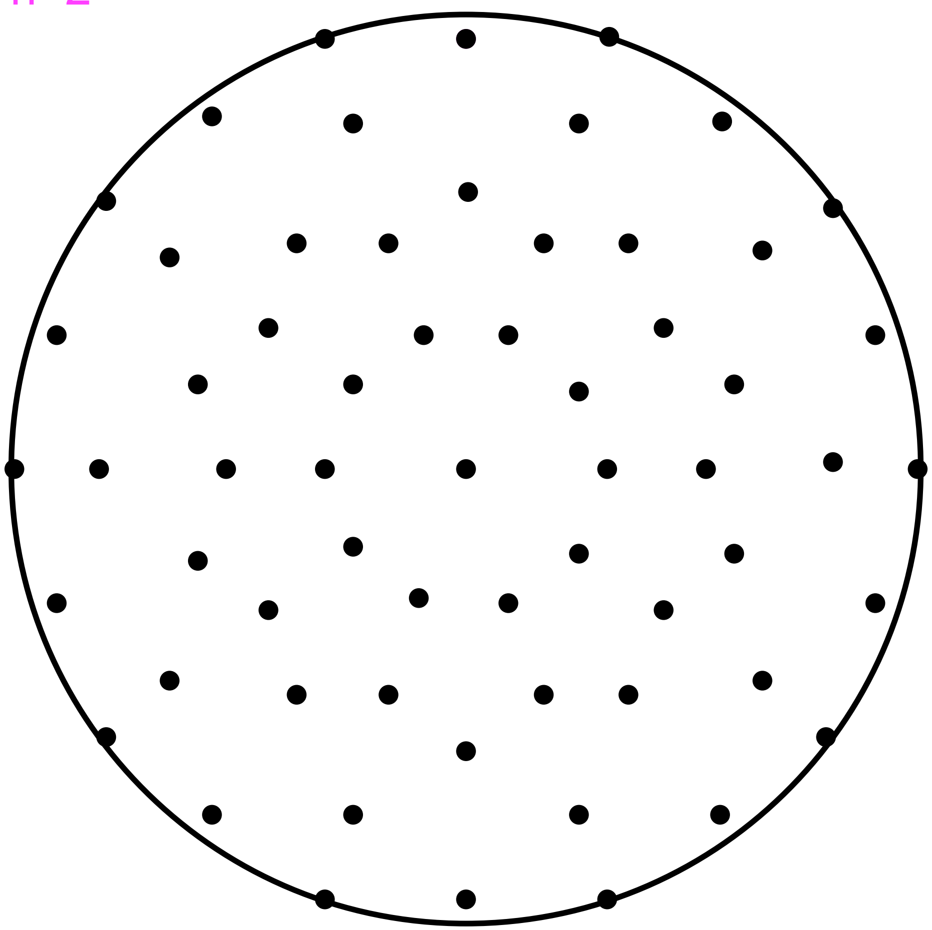
$$Q_2(n) = \{s^m(T,R)O : m \leq n\},\ n \in N$$

Non-dense point sets

Introduce a **cut-off** (T only acts n times, reflections are unrestricted) to obtain point sets S(n) that are subsets of the vertex sets of Penrose tilings.

$$Q_2(n) = \{s^m(T, r_{\alpha_1}, r_{\alpha_2})O : m \leq n\} = \left\{ \sum_{\alpha \in \Phi} n_\alpha \alpha : n_\alpha \in \mathbf{N} \cup \{0\}, \sum_{\alpha \in \Phi} n_\alpha \leq n \right\}$$

n=2



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$$\tau^2 = \tau + 1$$

$$\alpha_1 = 1, \; \alpha_2 = e^{4i\pi/5}$$

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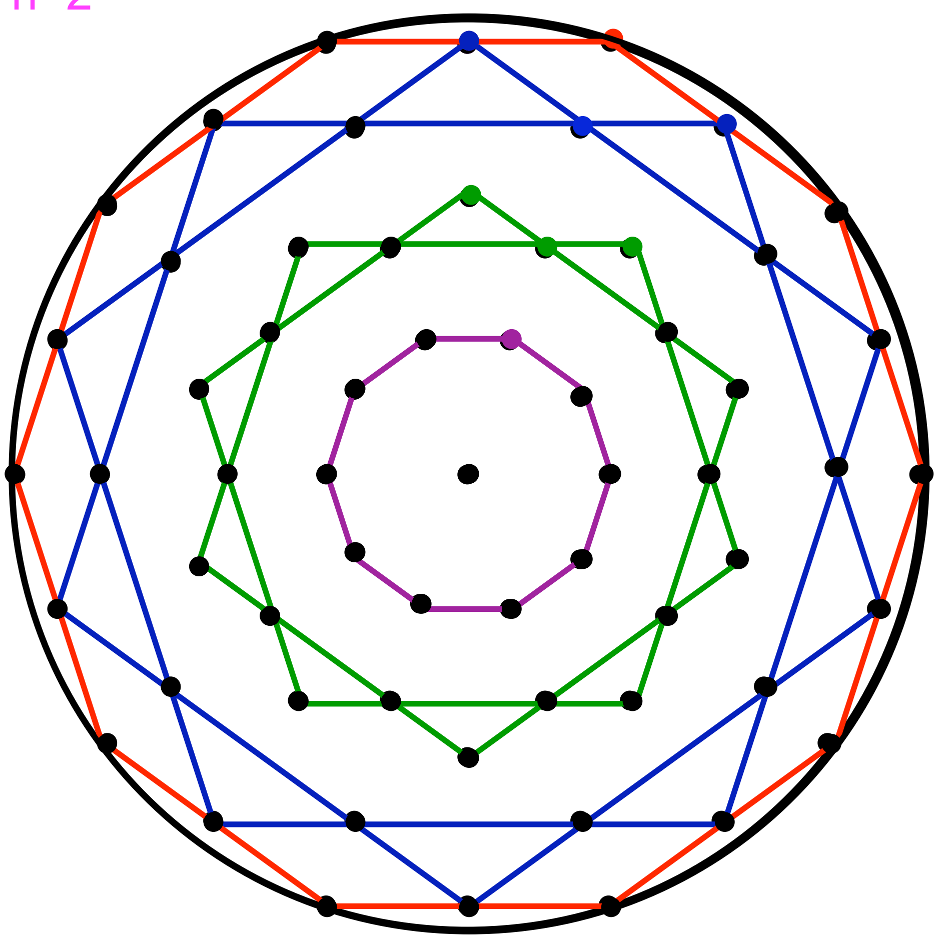

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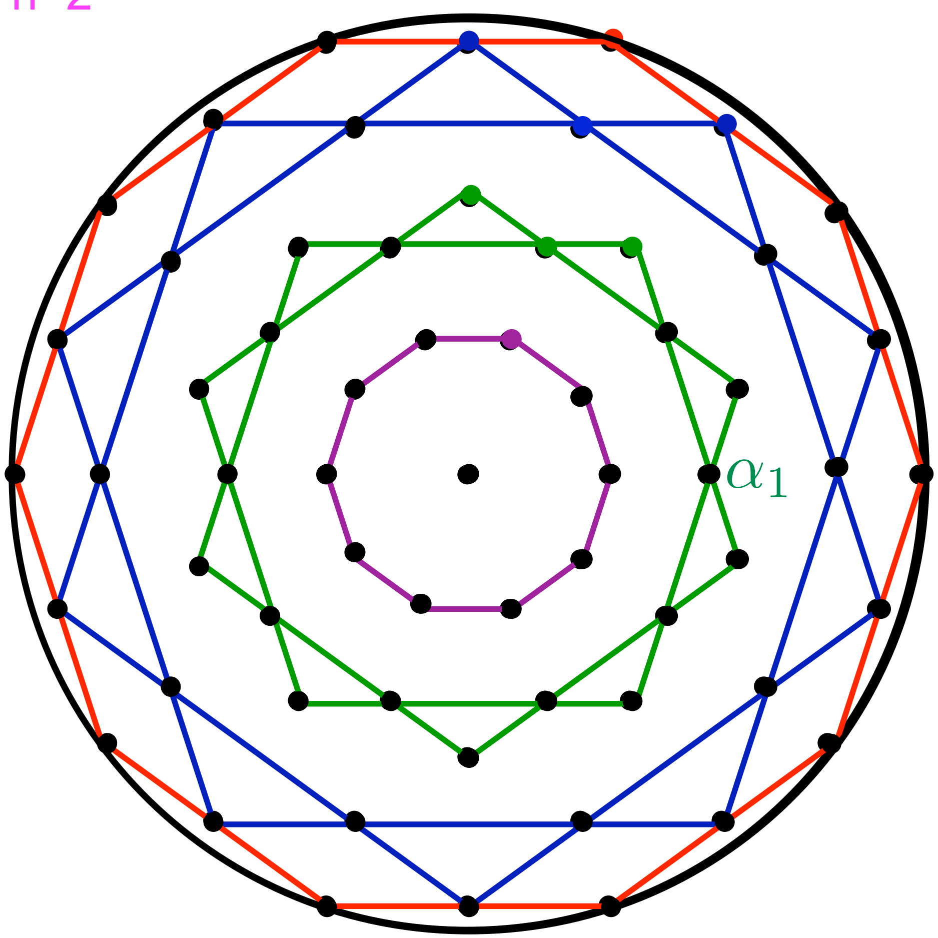

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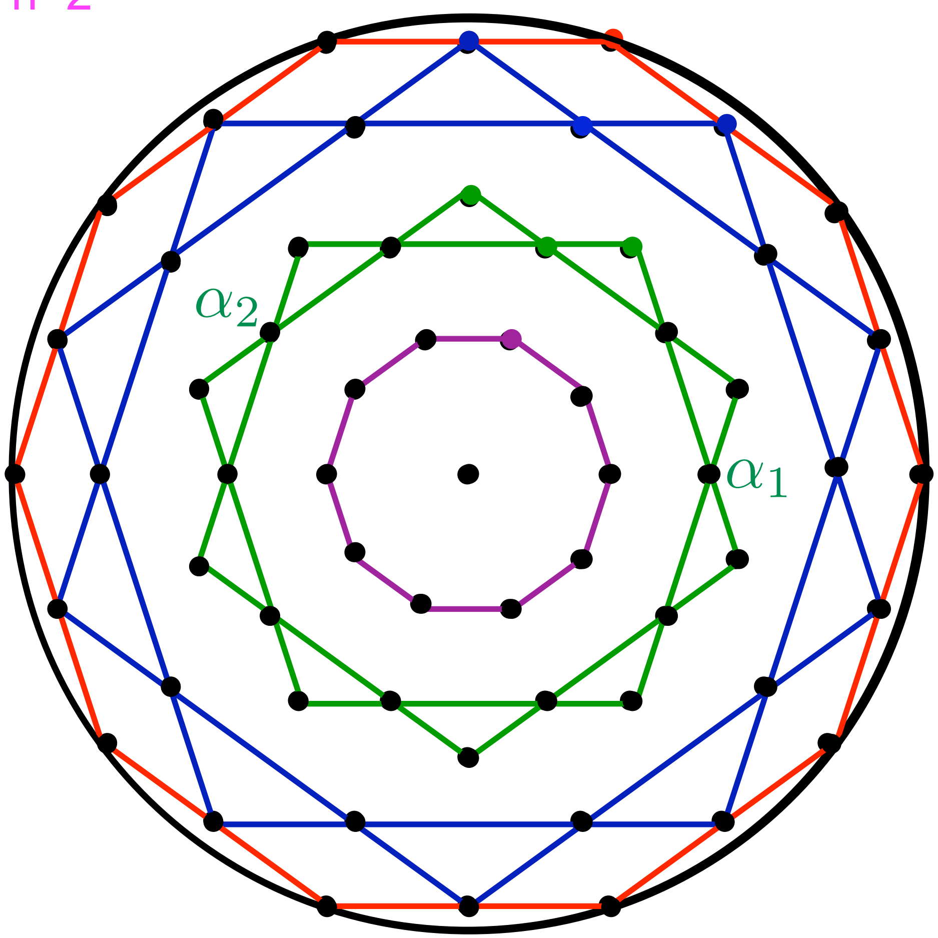

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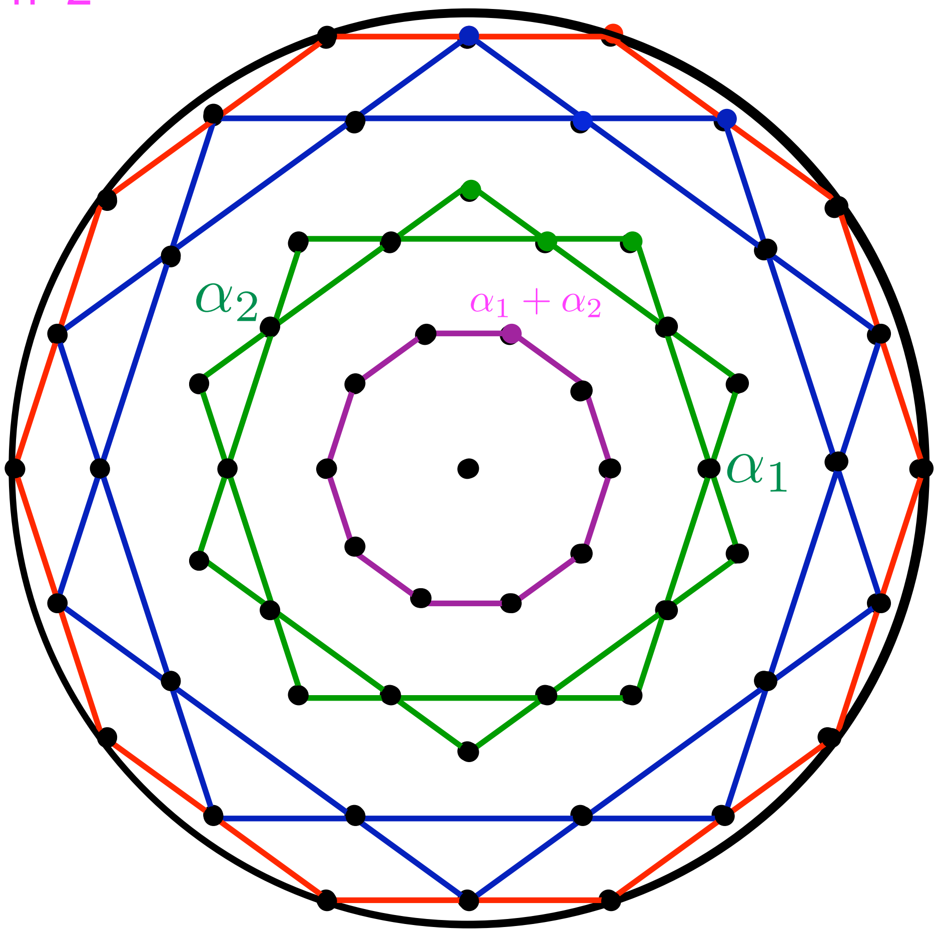

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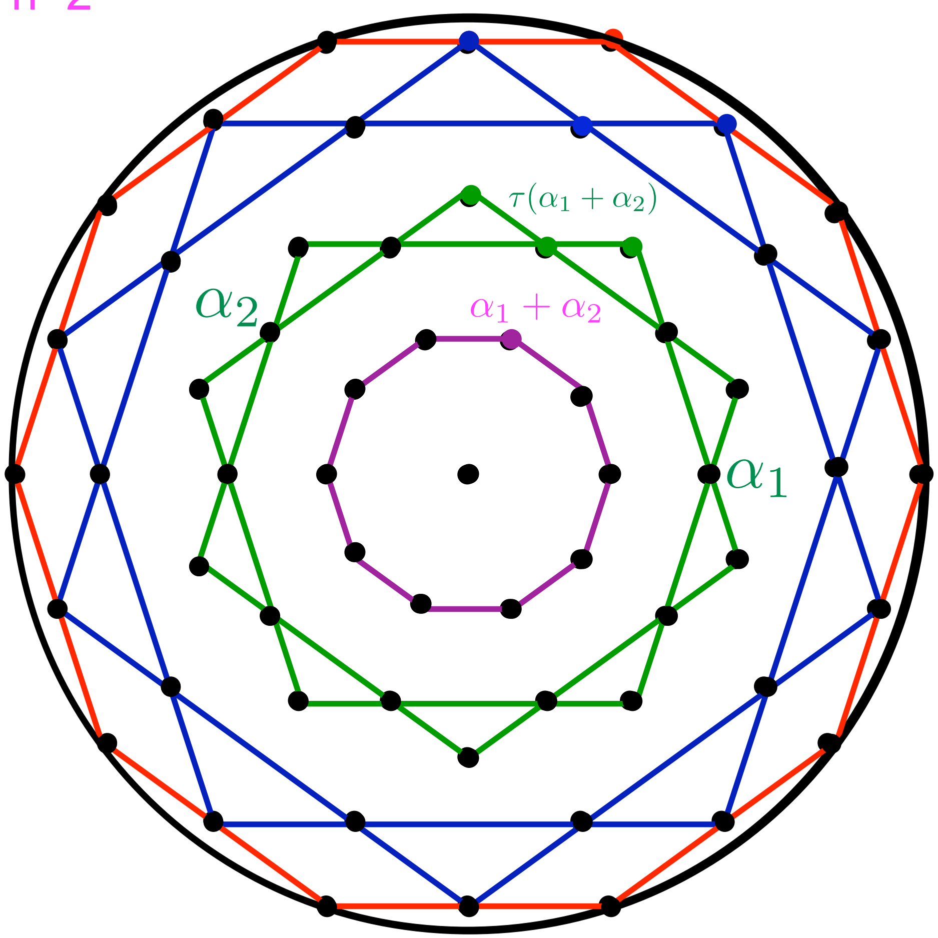

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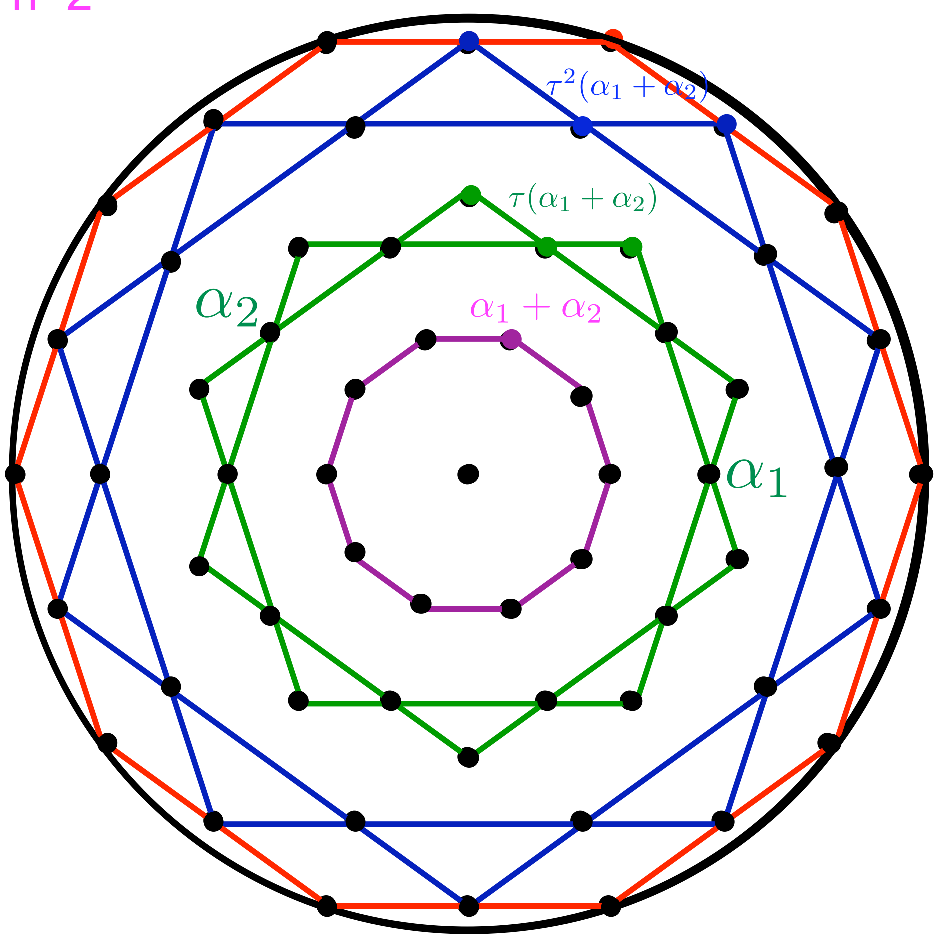

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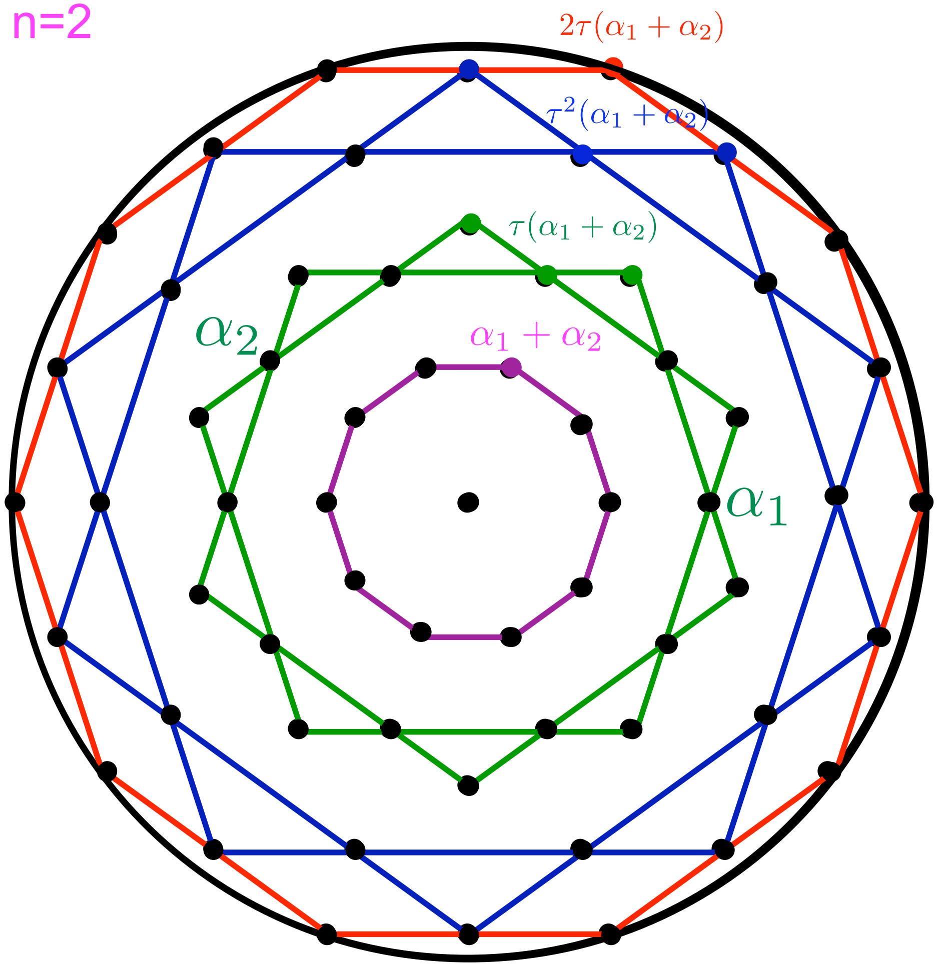

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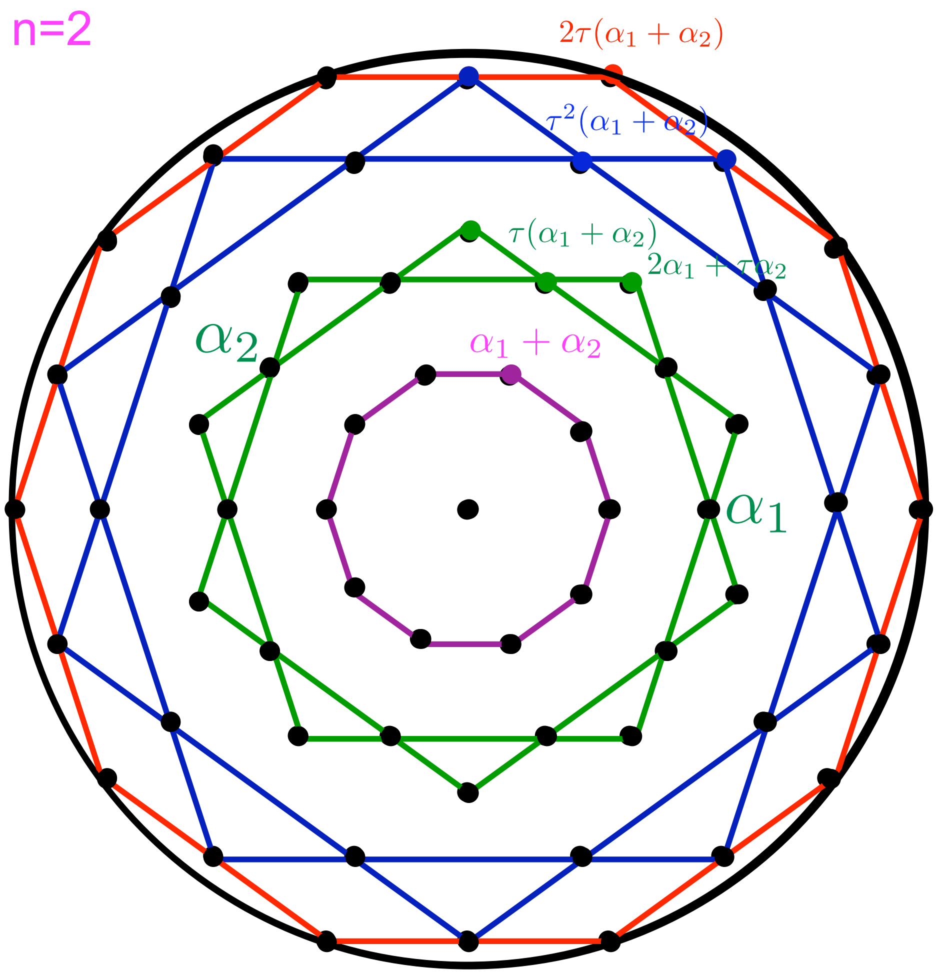

$$\Phi = \{\pm\alpha_1, \pm\alpha_2, \pm(\alpha_1+\tau\alpha_2), \pm(\tau\alpha_1+\alpha_2), \pm(\tau\alpha_1+\tau\alpha_2)\}$$

$$\tau^2 = \tau + 1$$

$$\alpha_1 = 1,\ \alpha_2 = e^{4i\pi/5}$$

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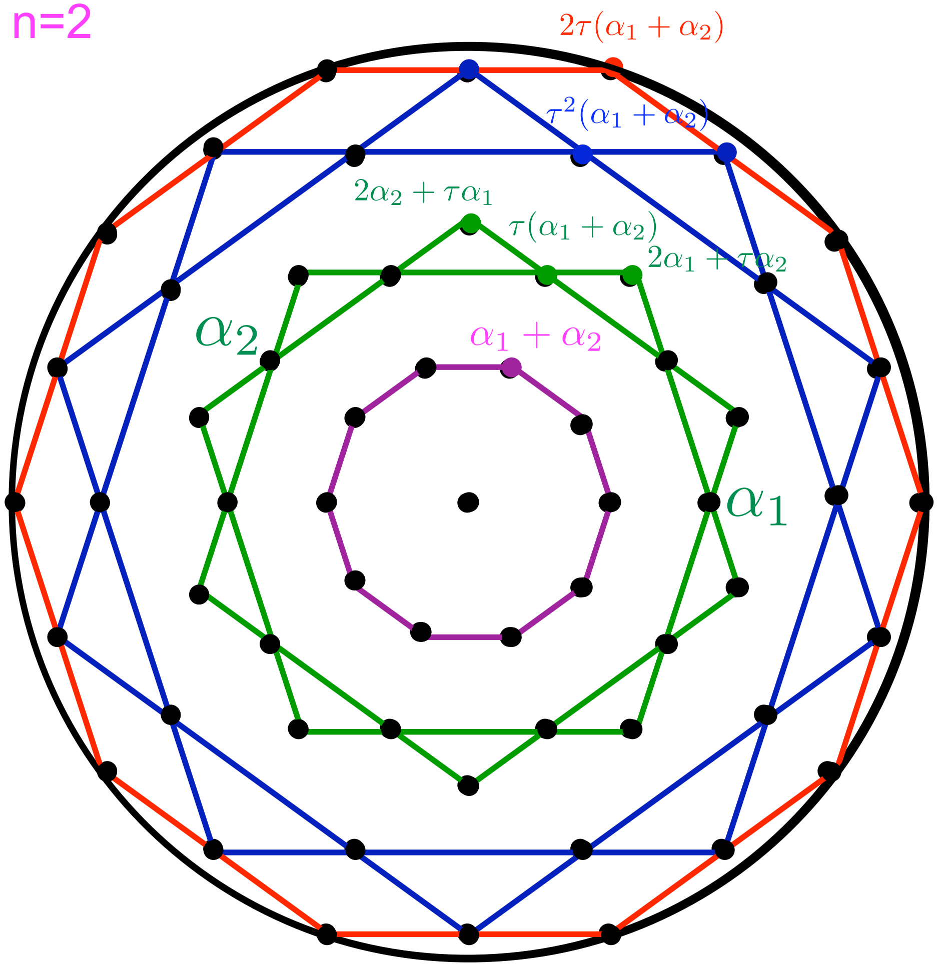
n=2



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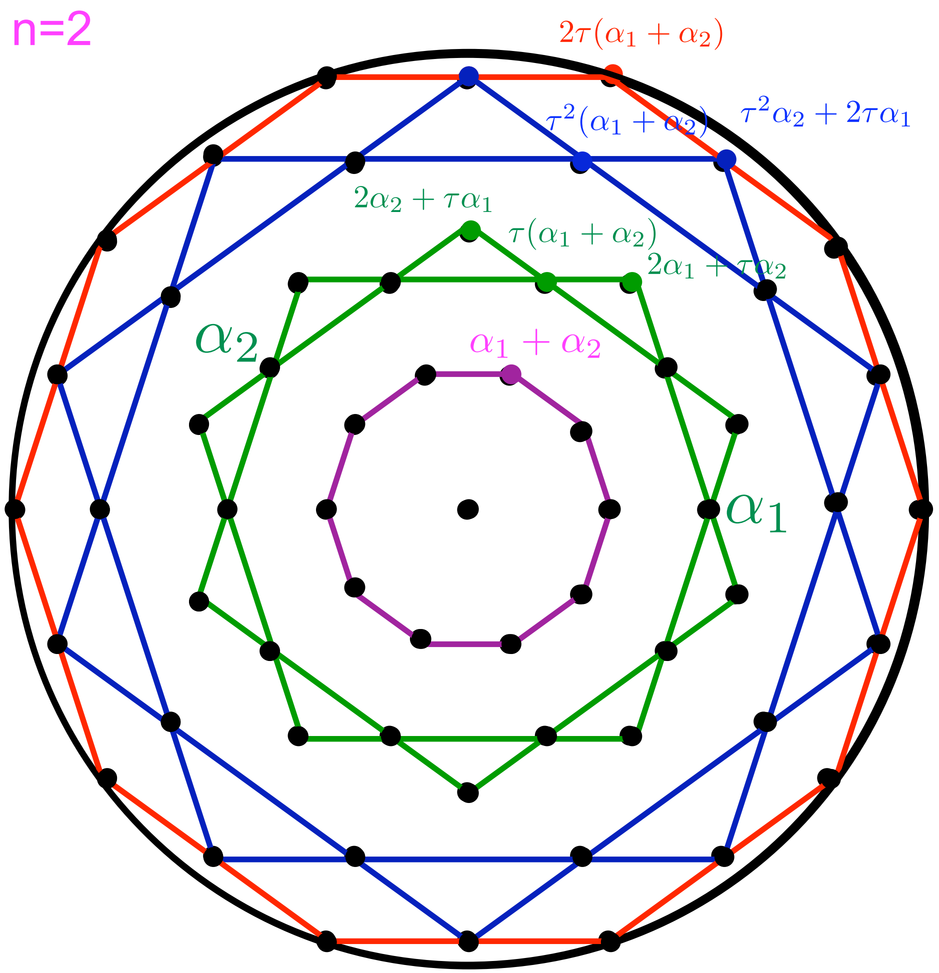

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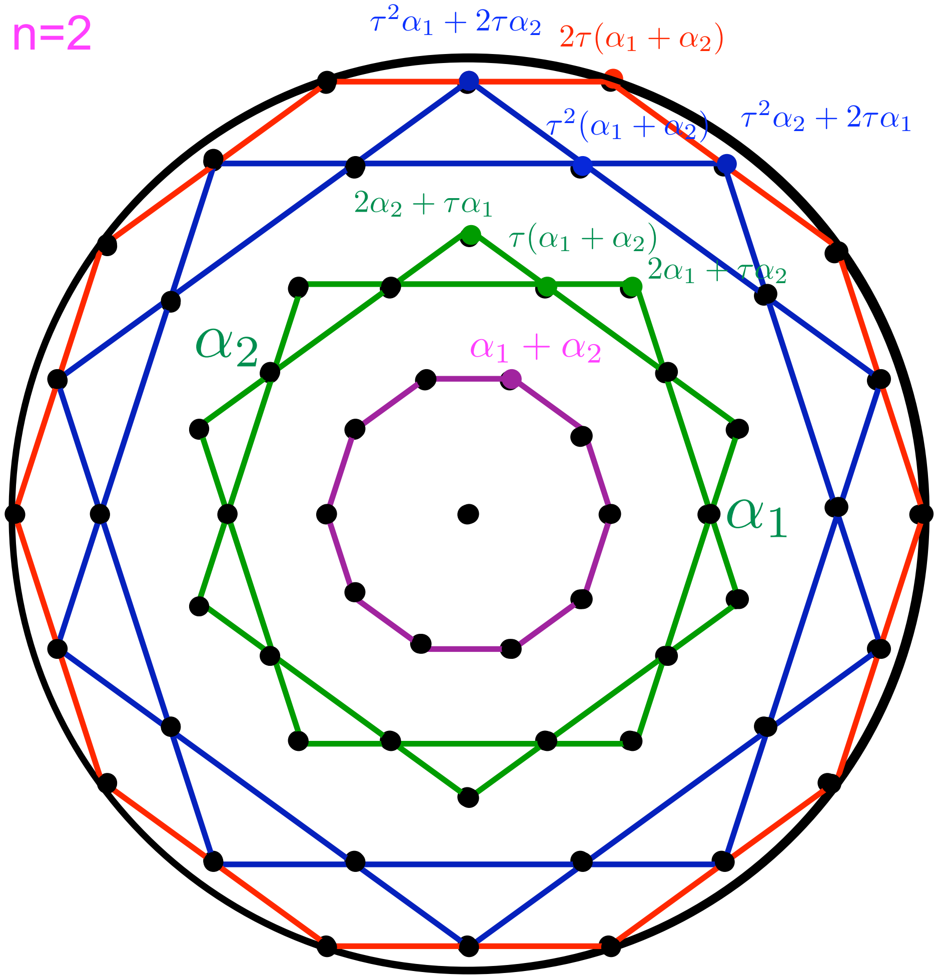

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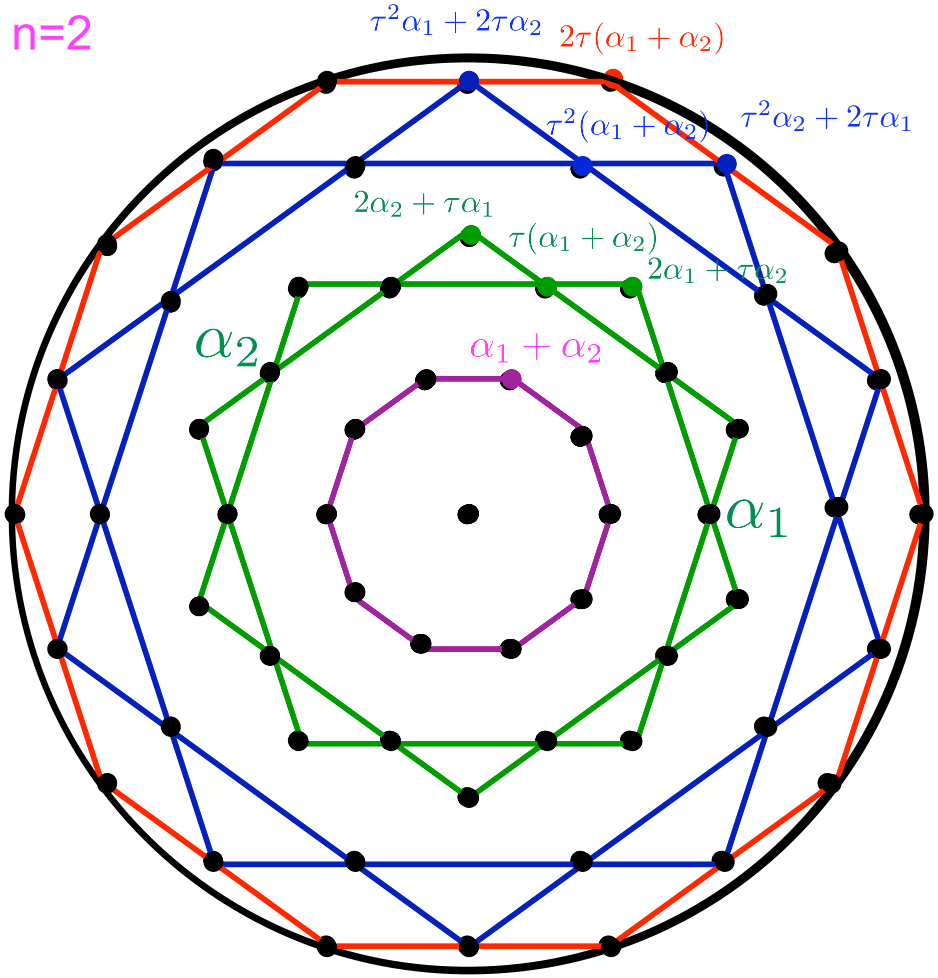

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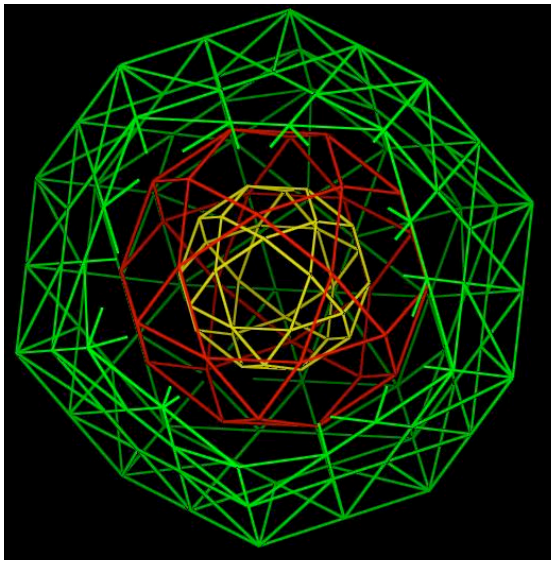
Nested decagons and pentagons

Solving the puzzle of Papovaviridae

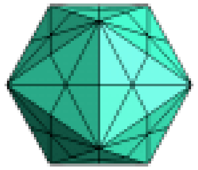
The 3d point set S(5) of H3 is dense enough to contain the vertices of polyhedra representing the all-pentamer capsids observed so far.

181 nested shells of radii between 0.236 and 5

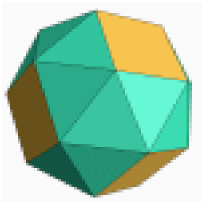


Courtesy T. Keef and R. Twarock

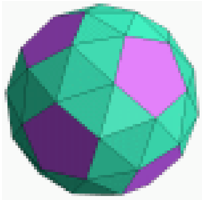
templates (5-coordinated vertices)



icosahedron
R=1.17; S(3)



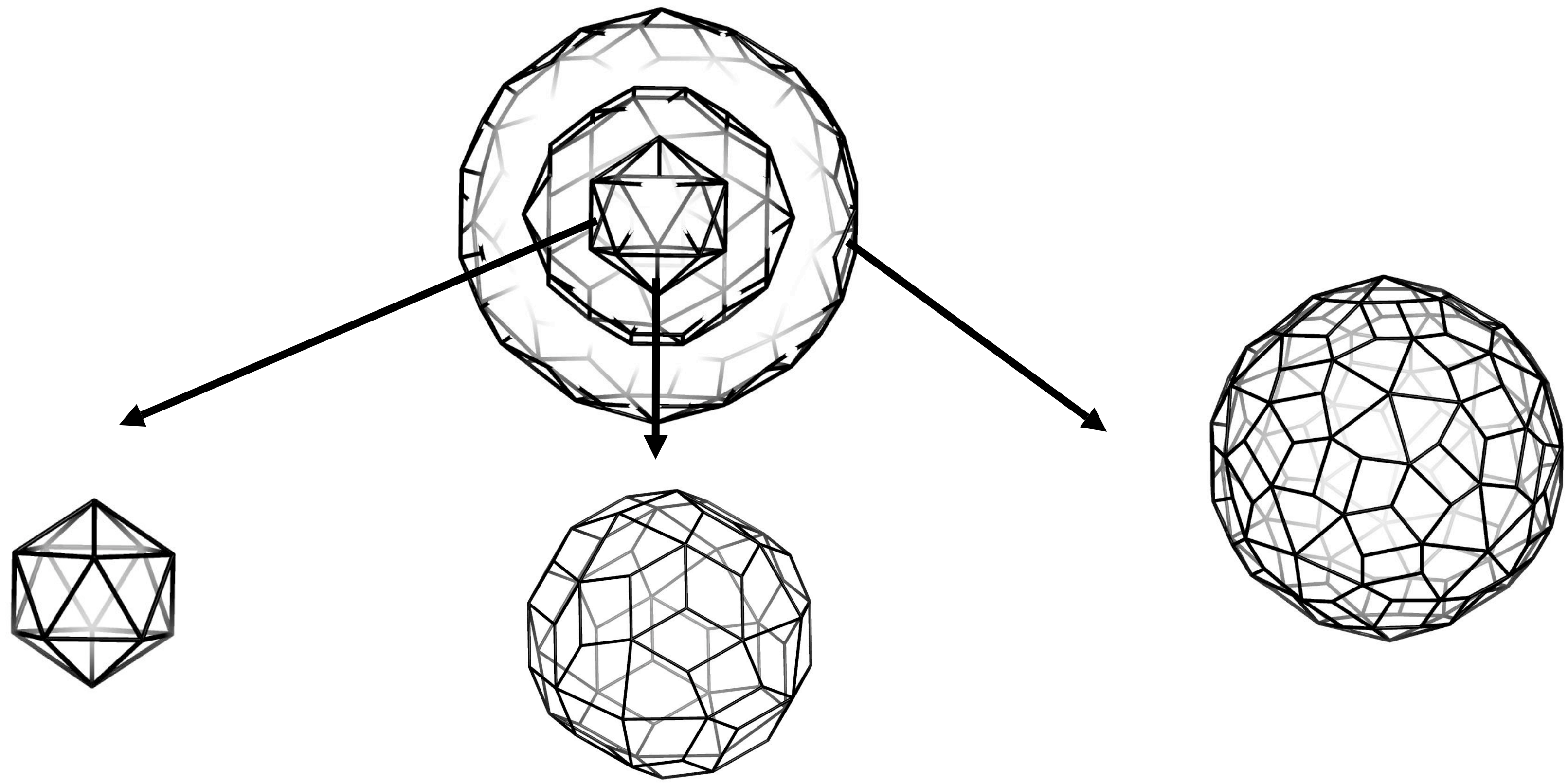
snub cube
R=2.32; S(4)



snub dodecahedron
R=3.12; S(5)

Keef & Twarock, q.bio.BM/0512047

Prediction: relative sizes



Predictions are in good agreement with experiments (Kanesashi et al.)

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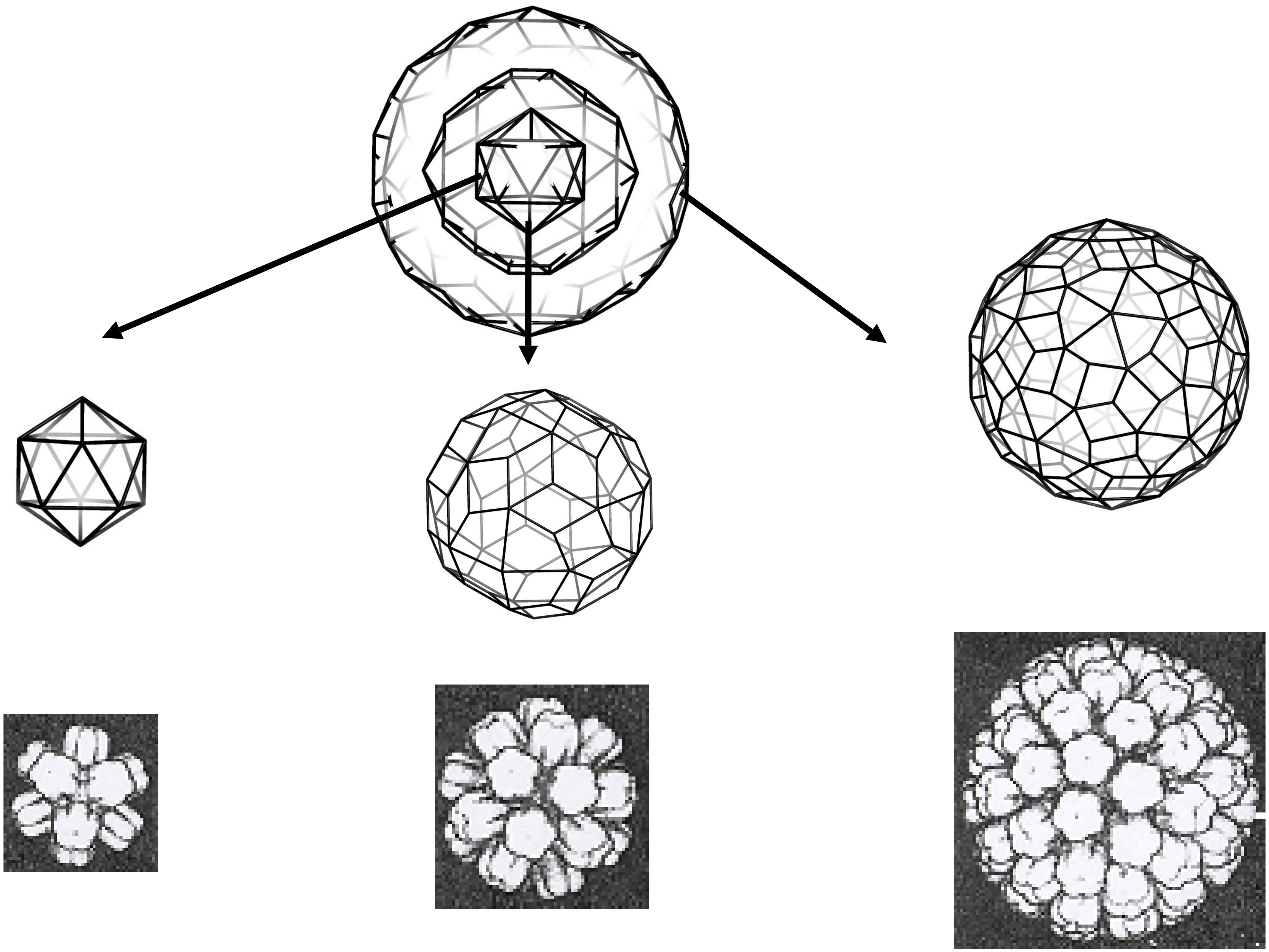

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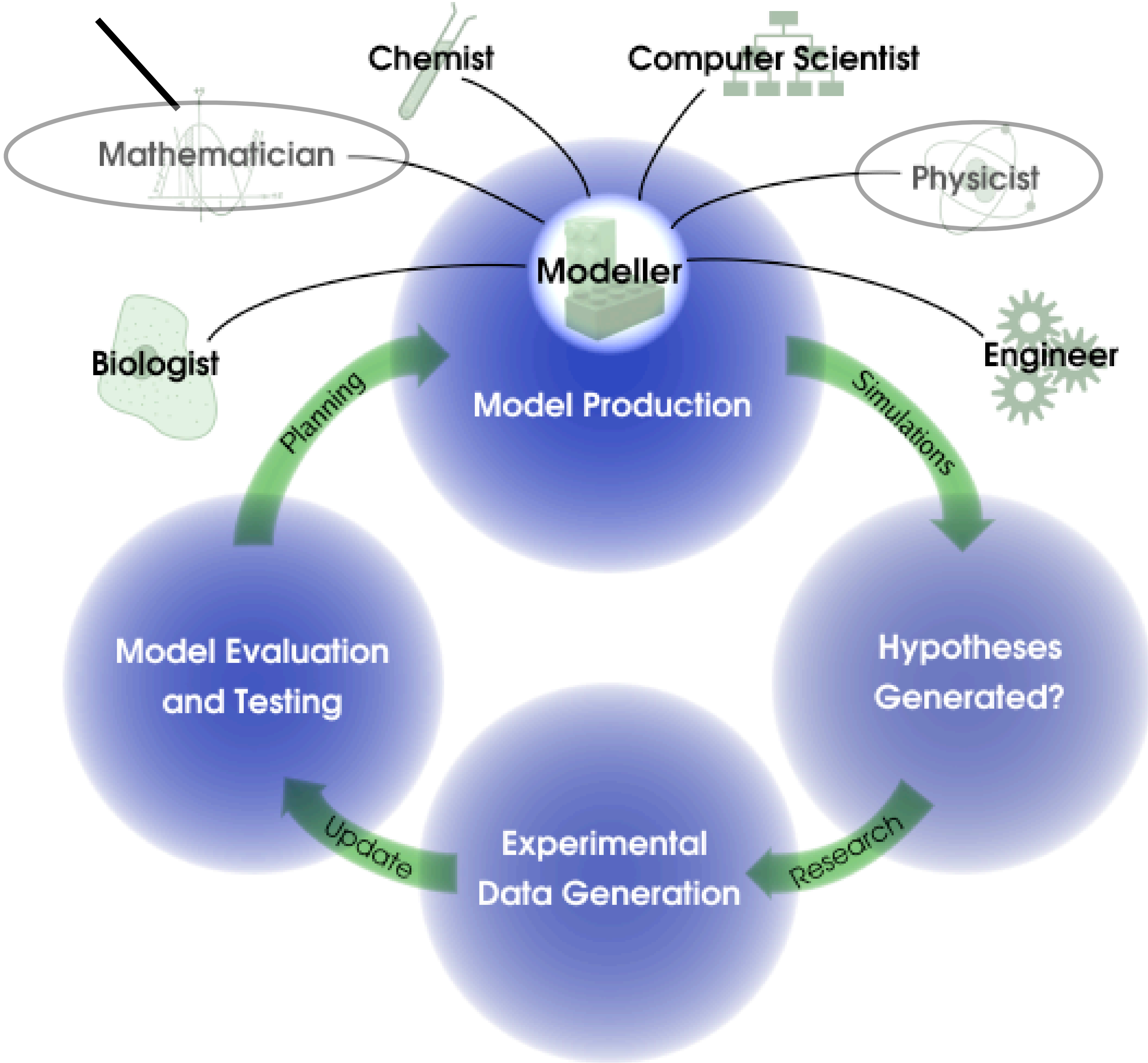
New Maths

Integrative biology



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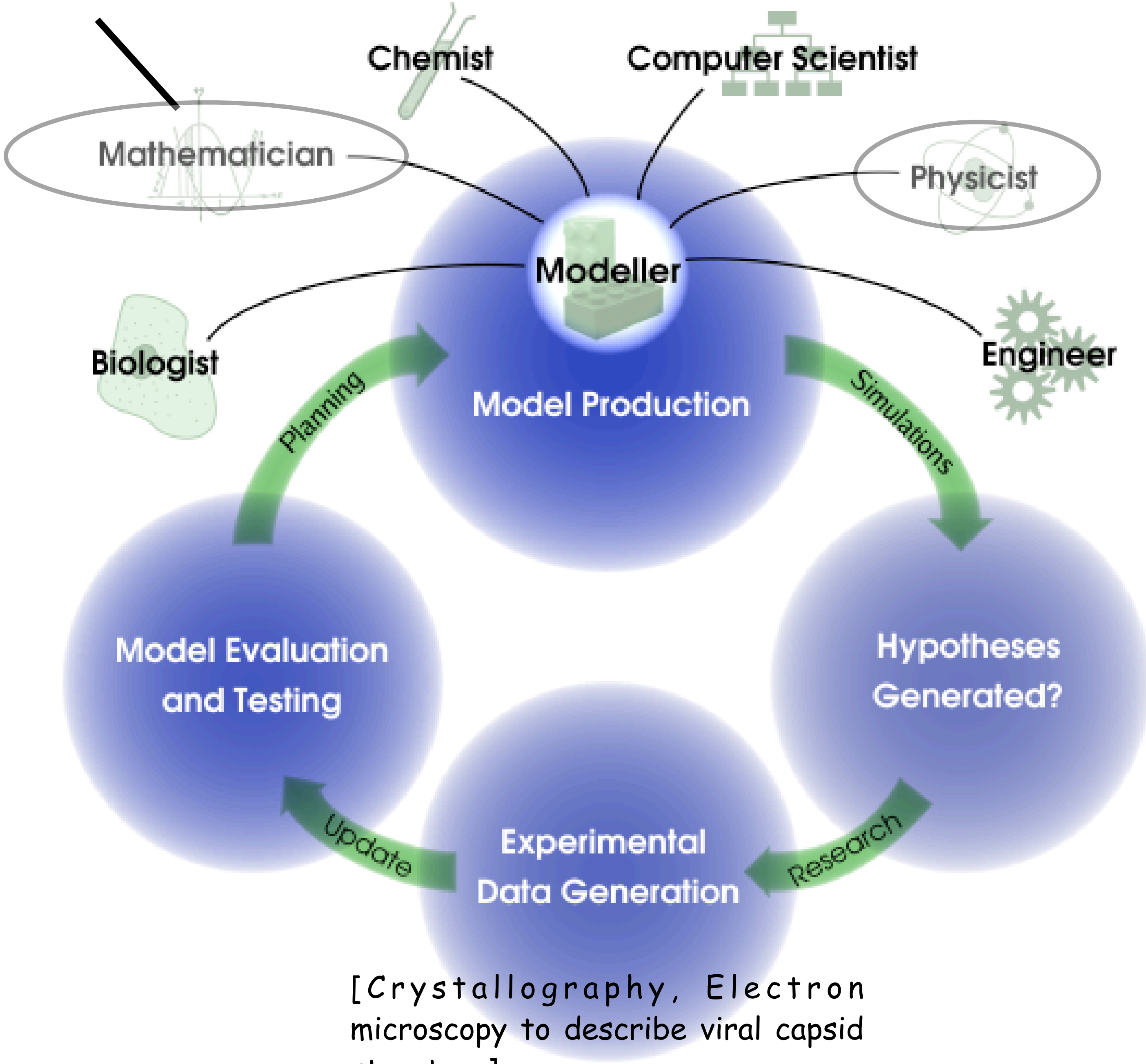

[Crystallography, Electron microscopy to describe viral capsid structure]

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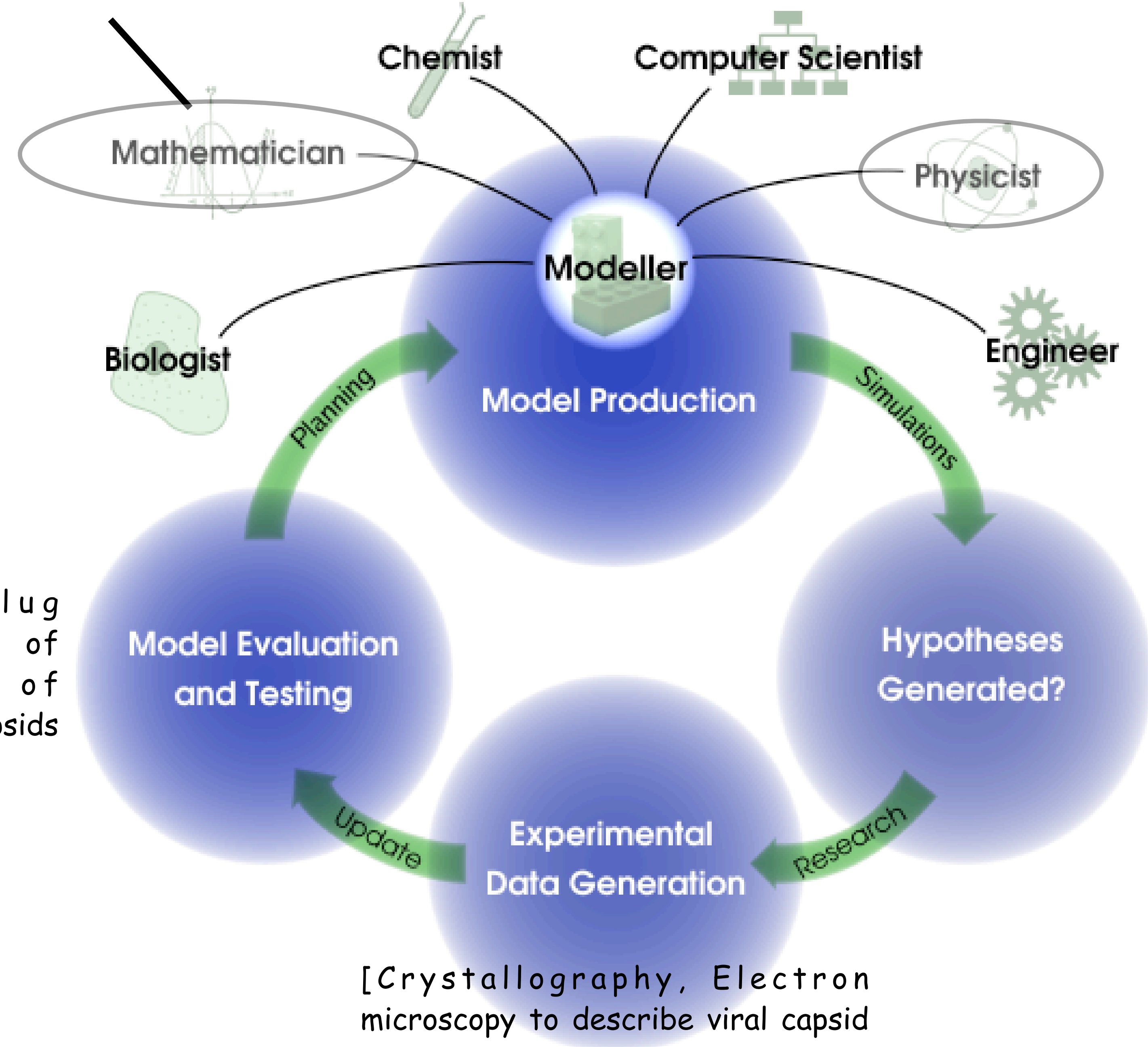

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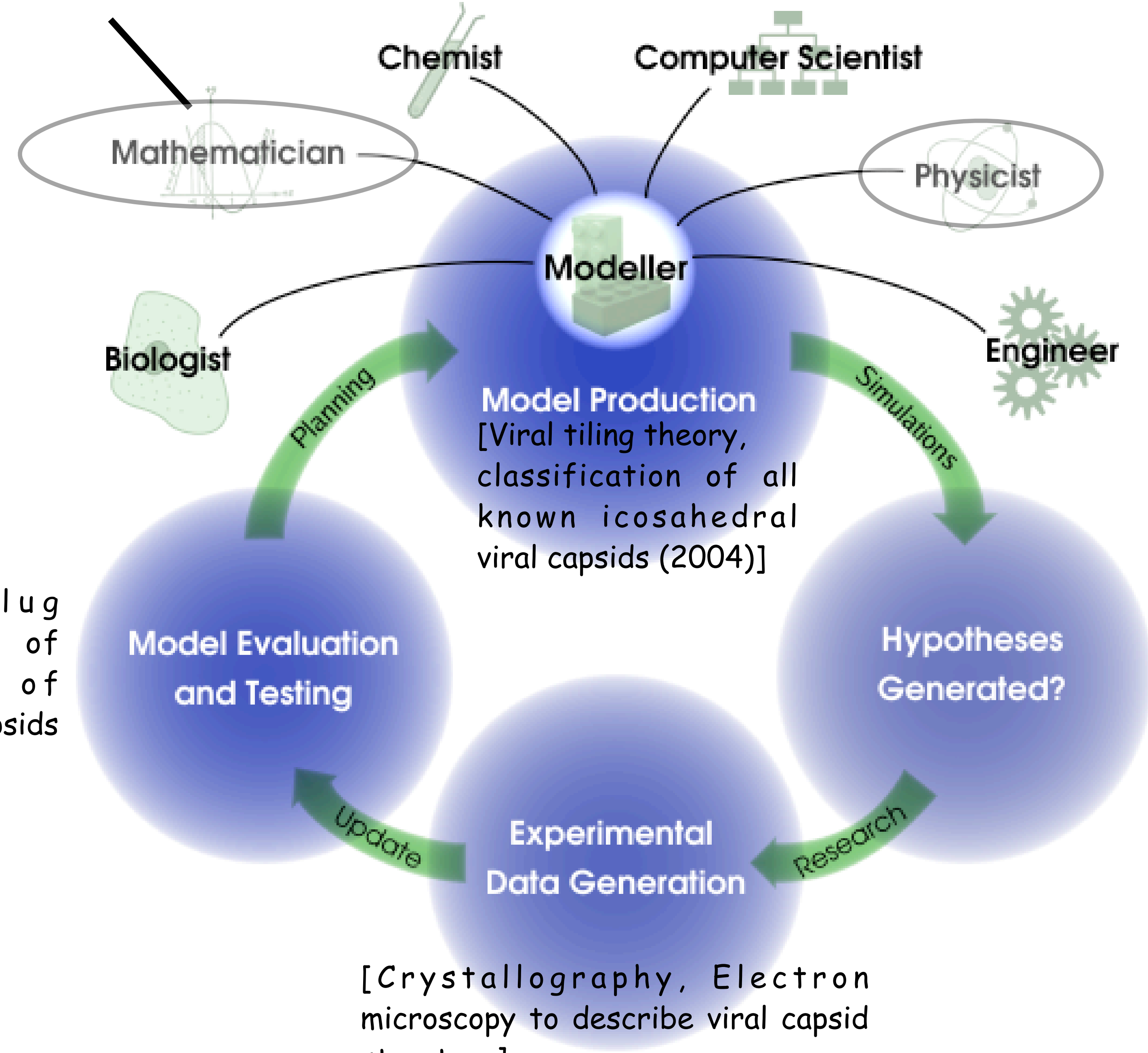

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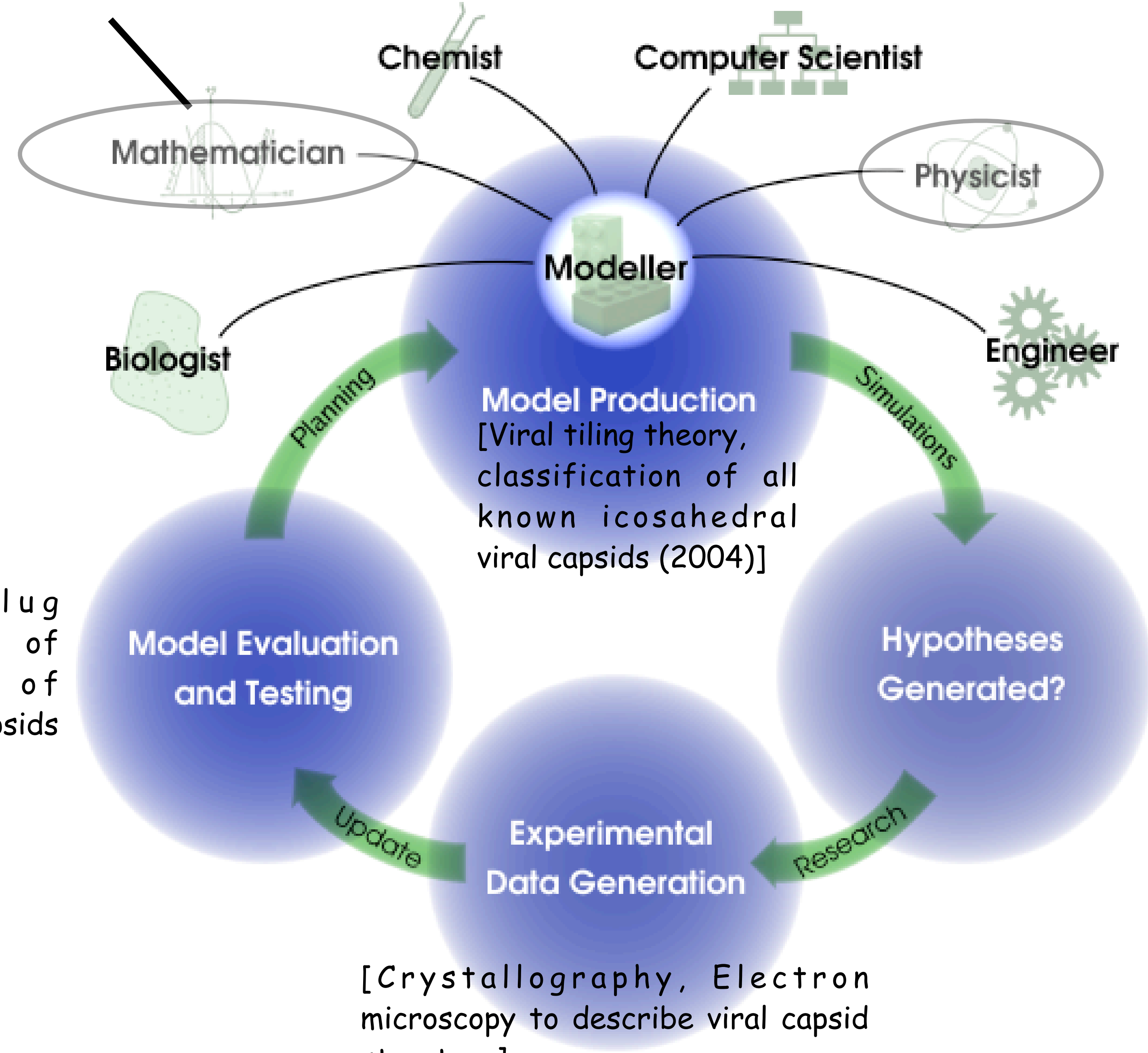

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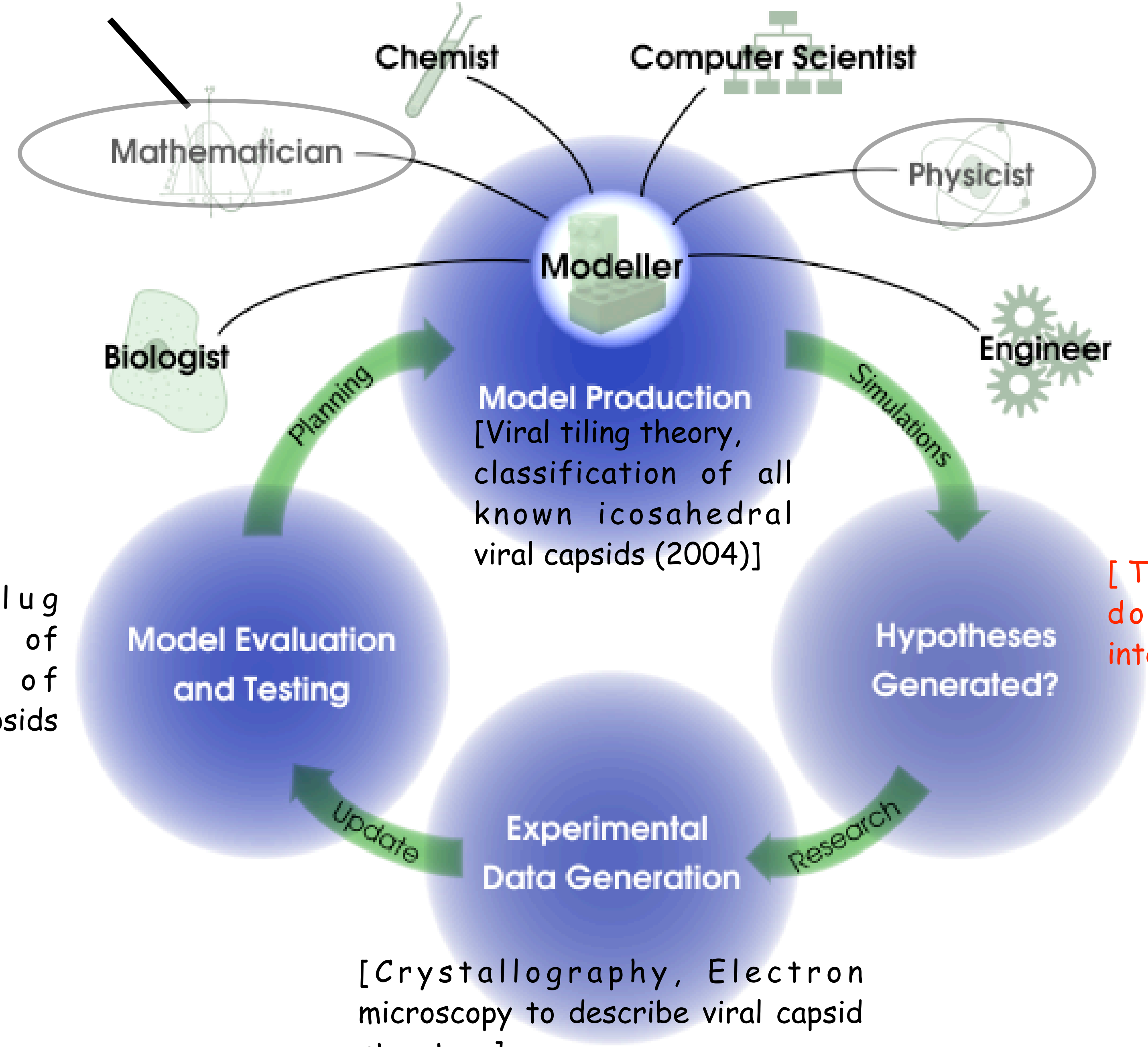

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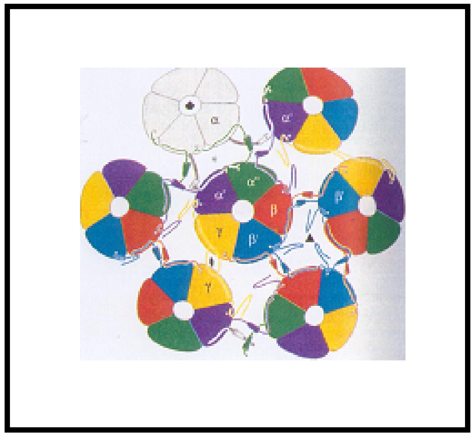
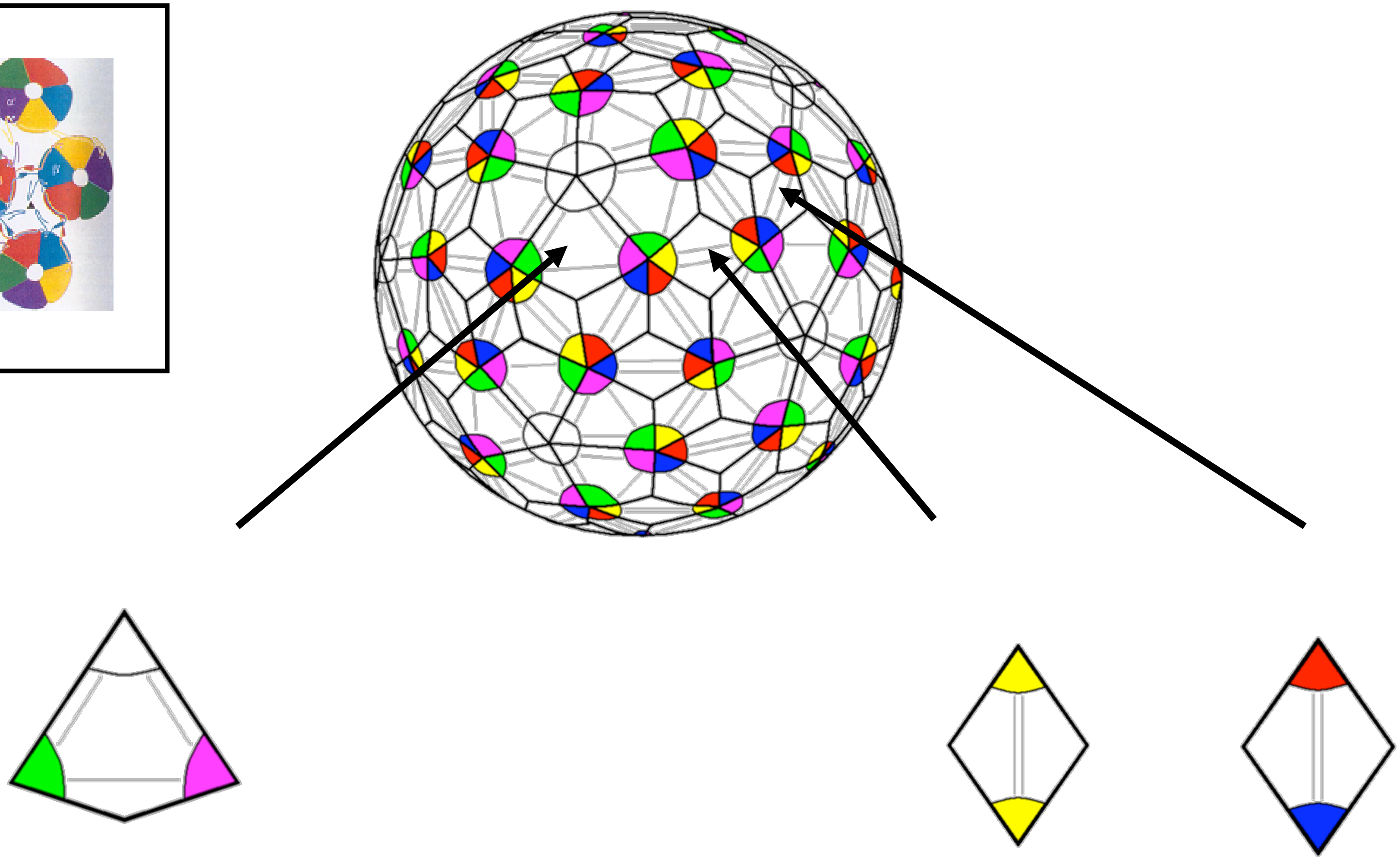
Adapted Maths: Vibrations of viral capsids

Integrative biology: Prediction of Bonding structure

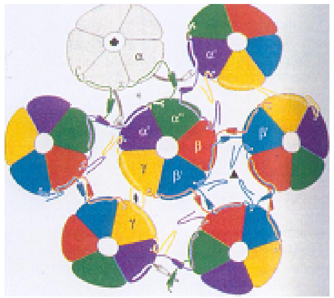


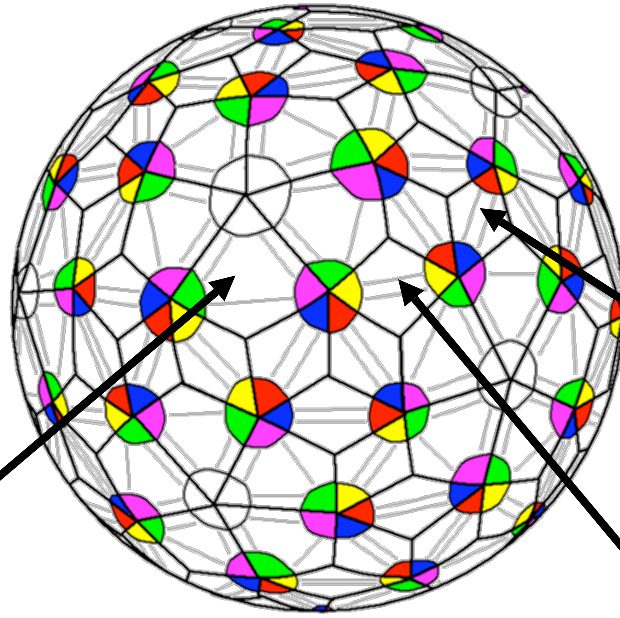


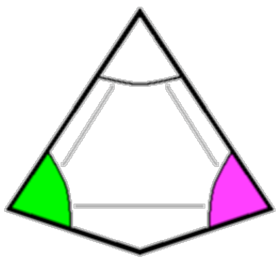
Trimer interaction

Two types of dimer interaction

Integrative biology: Prediction of Bonding structure







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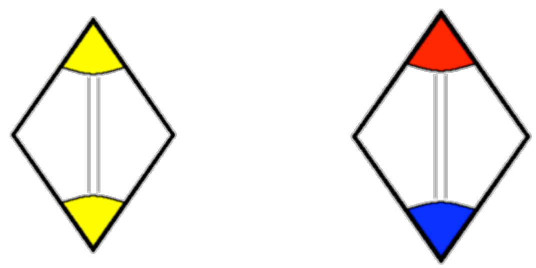
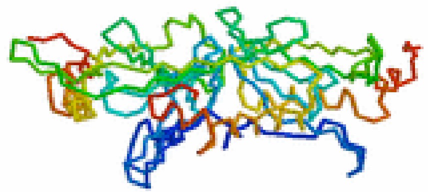
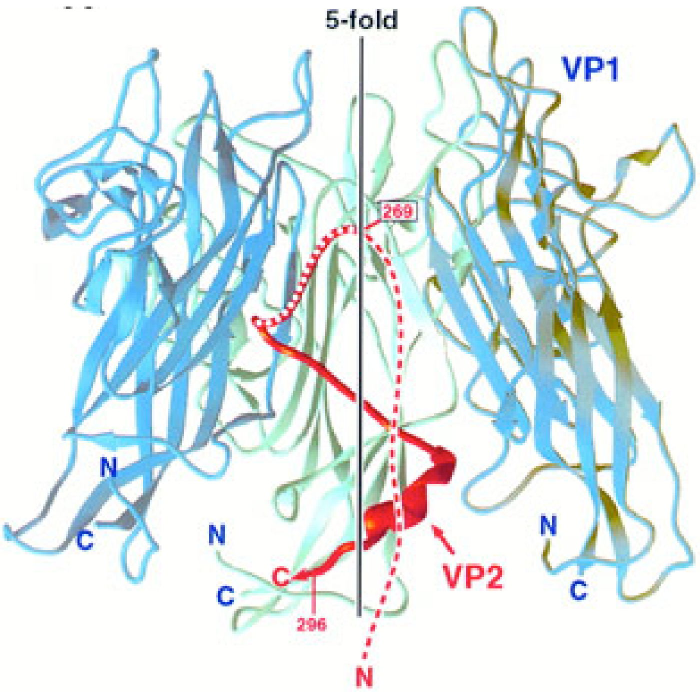


Two types of dimer interaction

Capsid structure : Huge number of degrees of freedom



vibration of protein



Ex: The capsid protein VP1 exhibits 361 residues, and the capsid of SV40 is formed with 360 such proteins

D = 360 x 361 x A x 3 = 129,960 x A x 3

Degrees of freedom:

D = P x R x A x 3 = 3n

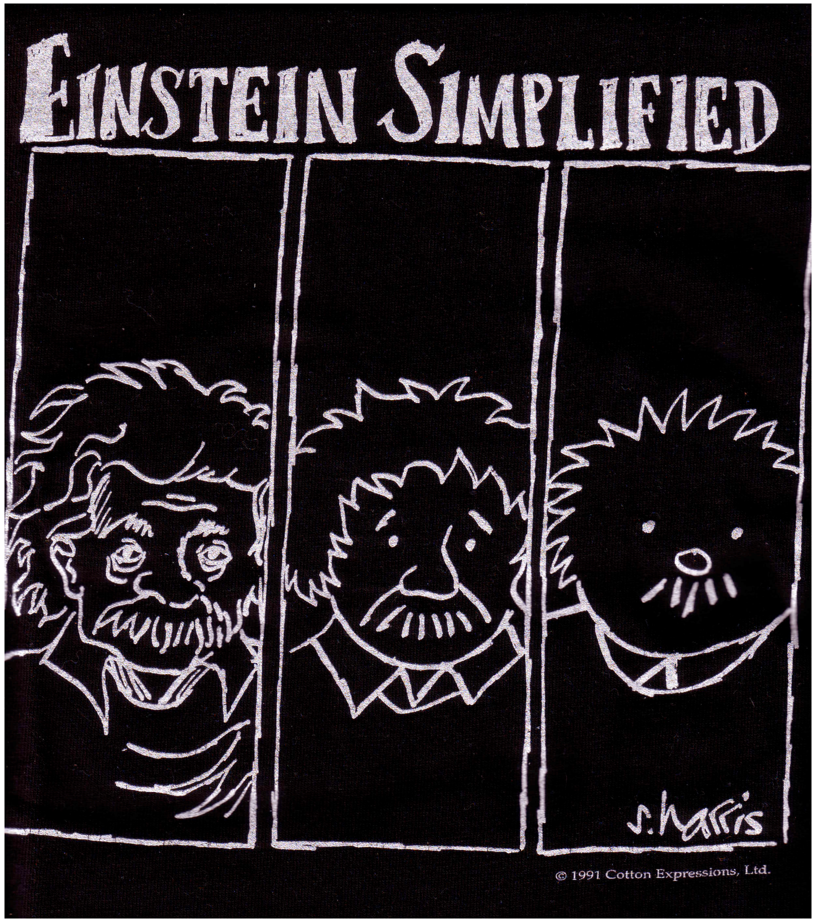
- P: number of proteins
- R: number of residues
- A: number of atoms per residue
- 3: spatial d.o.f. per atom

Capsid structure : Coarse-Graining

Reduced number of d.o.f.

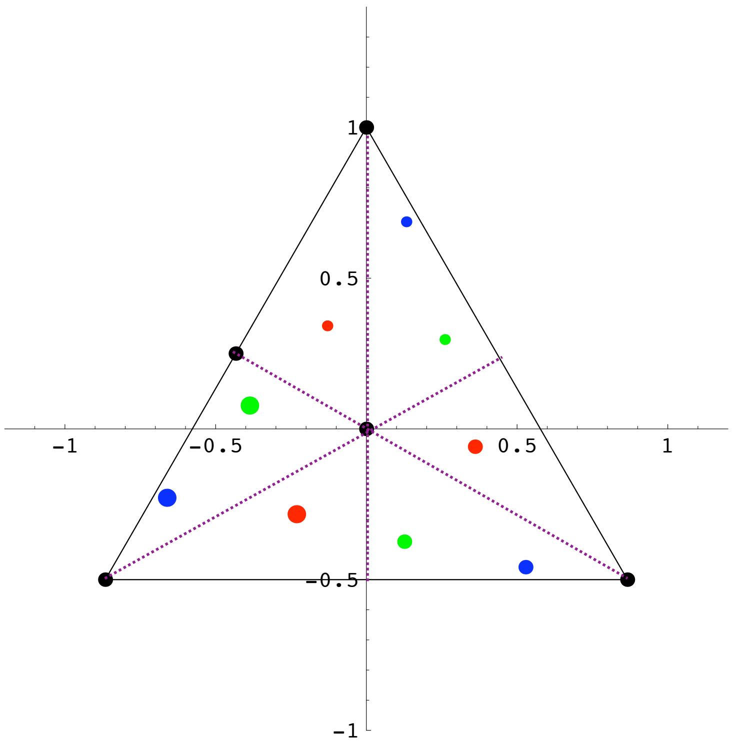
Insight in *systematics* of capsid dynamics

Each capsid protein is replaced by its centre of mass calculated from all its constituent atoms



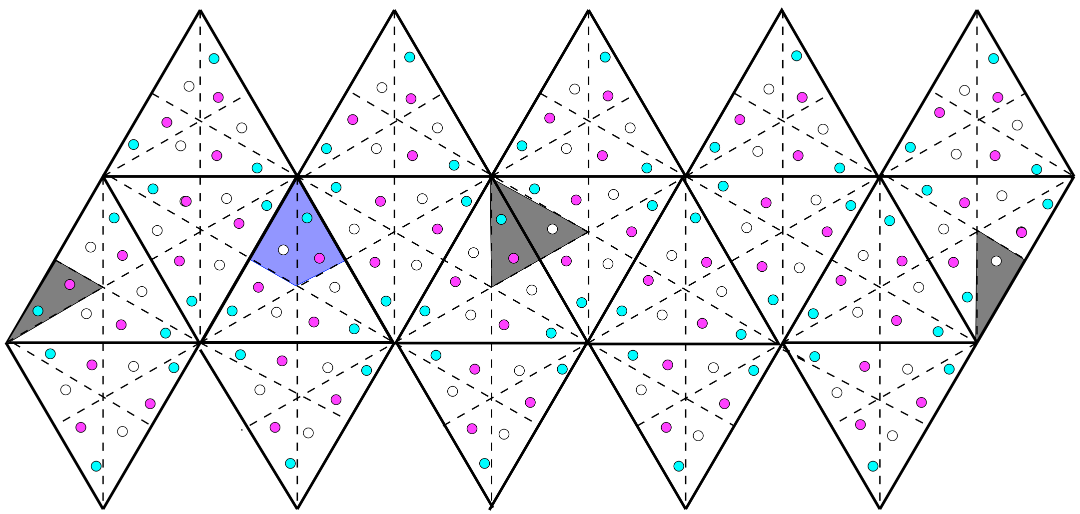
The equilibrium positions of proteins are taken from the VIPER website and are assumed to respect icosahedral symmetry

Typical example: Rice Yellow Mottle Virus



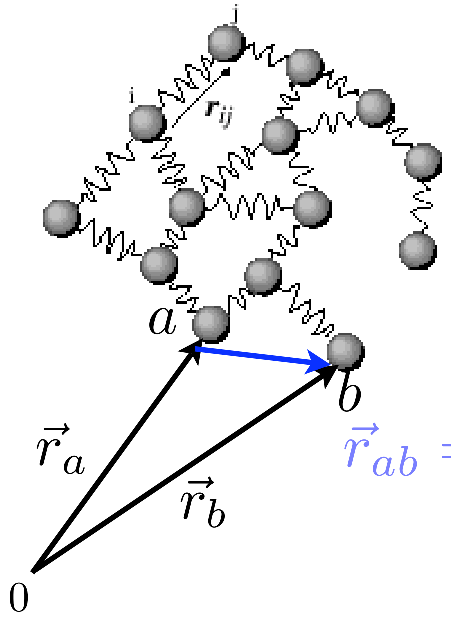
T=3 virus

Caspar-Klug tiling (triangles)



experimental data on proteins positions

Potential : Harmonic approximation



$$V(x_a^i, x_b^j) = \sum_{a,b=1}^{N} \frac{k_{ab}}{2} \left(|\vec{r}_{ab}| - |\vec{r}_{ab}^{\,0}|\right)^2$$

$$\vec{r}_{ab} = \vec{r}_b - \vec{r}_a$$

spring-mass model

small deviations from equilibrium

$$V = \sum_a \frac{\partial V}{\partial x_a^i}\Big|_{x=x_0} (x_a^i - x_b^{0i}) + \sum_{a,b} \frac{1}{2} \frac{\partial^2 V}{\partial x_a^i \partial x_b^j}\Big|_{x=x_0} (x_a^i - x_a^{0i})(x_b^j - x_b^{0j}) + \ldots$$

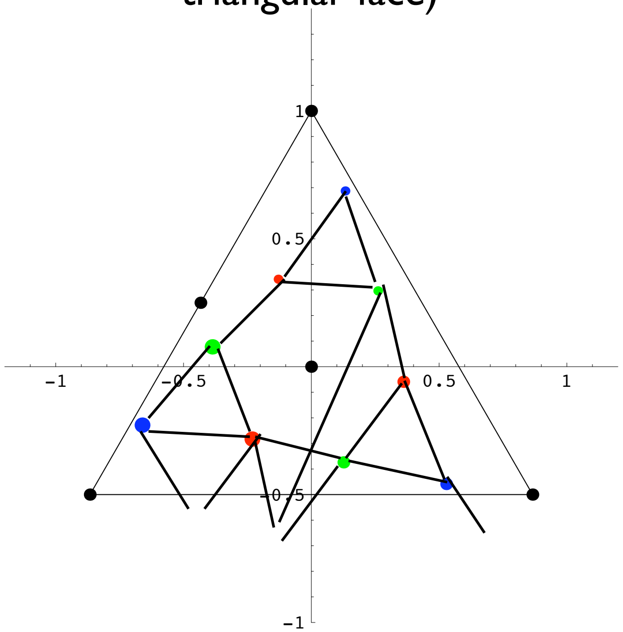
$$\frac{d^2}{dt^2}(x_a^i - x_a^{0i}) + F_{ab}^{ij}(x_b^j - x_b^{0j}) = 0$$

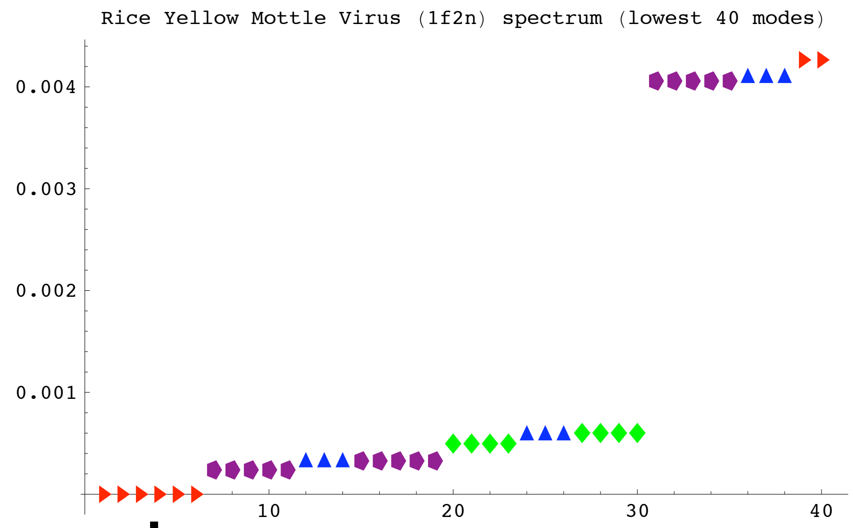
equations of motion for deviations from equilibrium

force matrix whose eigenvalues are the frequencies of the normal modes of vibration

Example: Low-frequency spectrum of RYMV

180 proteins (9 per triangular face)





6 trivial zero modes

$$\Gamma^{displ}_{540} = 9\,[\Gamma^{1+} + 3\Gamma^{3+} + 3\Gamma^{3'+} + 4\Gamma^{4+} + 5\Gamma^{5+}]$$

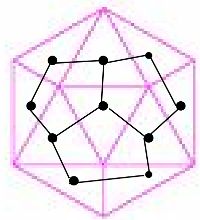
24 near zero-modes

$$2[\Gamma^{3'+} + \Gamma^{4+} + \Gamma^{5+}]$$

recurrent pattern in all Caspar-Klug viruses

Why 24?

Icosahedron



The vibrations of the icosahedral cage induce vibrations of the dodecahedral cage

$$\Gamma^{displ}_{ICO} = \Gamma^{1+} + (\Gamma^{3+} + \Gamma^{3-}) + \Gamma^{3-} + \Gamma^{3'-} + \Gamma^{4+} + \Gamma^{4-} + 2\Gamma^{5+} + \Gamma^{5-} \quad (36)$$

degrees of freedom: 12 x 3 = 36
non-genuine vibrations: 3 + 3 = 6 (rotations + translations of whole capsid)
number of constraints: 30 (springs along edges of icosahedron)

number of zero modes: 36 - 6 - 30 = 0	stable capsid

Dodecahedron

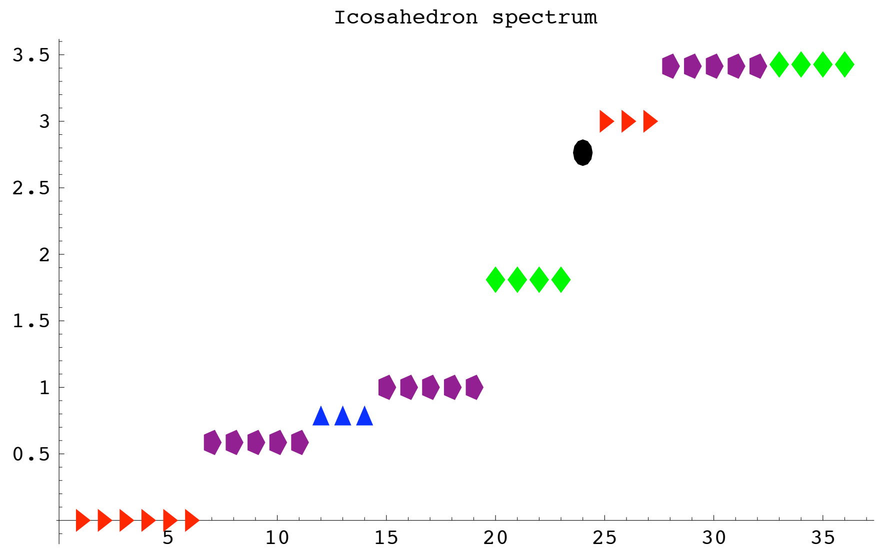
The vibrations of the dodecahedral cage induce vibrations of the icosahedral cage

$$\Gamma^{displ}_{DODE} = \Gamma^{1+} + (\Gamma^{3+} + \Gamma^{3-}) + \Gamma^{3-} + \Gamma^{3'-} + \Gamma^{4+} + \Gamma^{4-} + 2\Gamma^{5+} + \Gamma^{5-} \quad (36)$$
$$+\Gamma^{3'+} + \Gamma^{3'-} + \Gamma^{4+} + \Gamma^{4-} + \Gamma^{5+} + \Gamma^{5-} \quad (24)$$

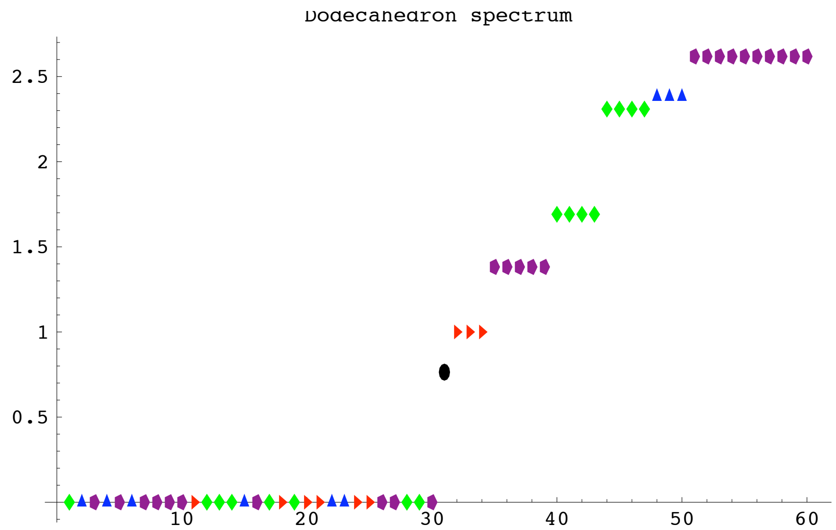
degrees of freedom: 20 x 3 = 60
non-genuine vibrations: 3 + 3 = 6 (rotations + translations of whole caspid)
number of constraints: 30 (springs along edges of dodecahedron)

number of zero modes: 60 - 6 - 30 = 24	unstable capsid

Spectrum within spring-mass model



stable capsid



unstable capsid (24 zero-modes)

Map between representations in icosahedron and dodecahedron cases

$$\Gamma^{displ}_{ICO} = \Gamma^{1+} + (\Gamma^{3+} + \Gamma^{3-}) + \Gamma^{3-} + \Gamma^{3'-} + \Gamma^{4+} + \Gamma^{4-} + 2\Gamma^{5+} + \Gamma^{5-}$$

$$\downarrow \qquad \downarrow \qquad \downarrow$$

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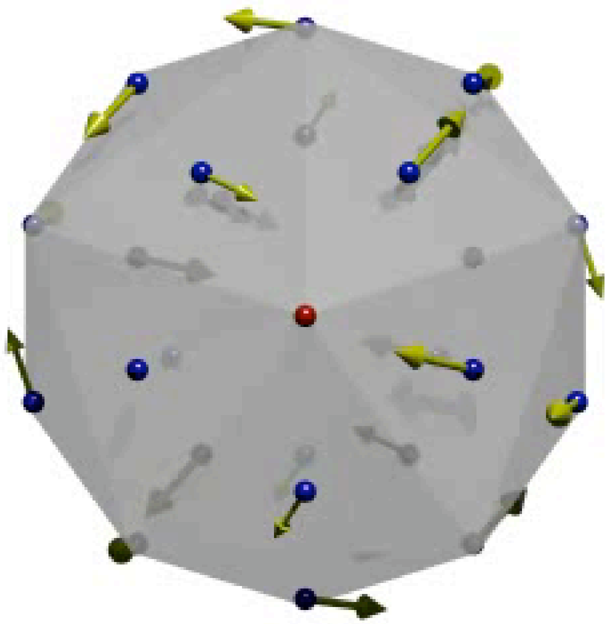
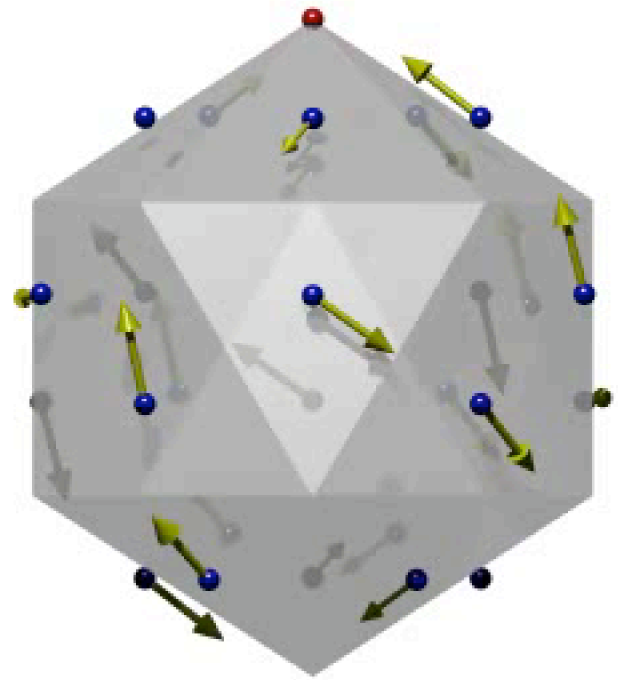
$$+\Gamma^{3'+} + \Gamma^{3'-} + \Gamma^{4+} + \Gamma^{4-} + \Gamma^{5+} + \Gamma^{5-}$$

$$\downarrow$$

$$0$$

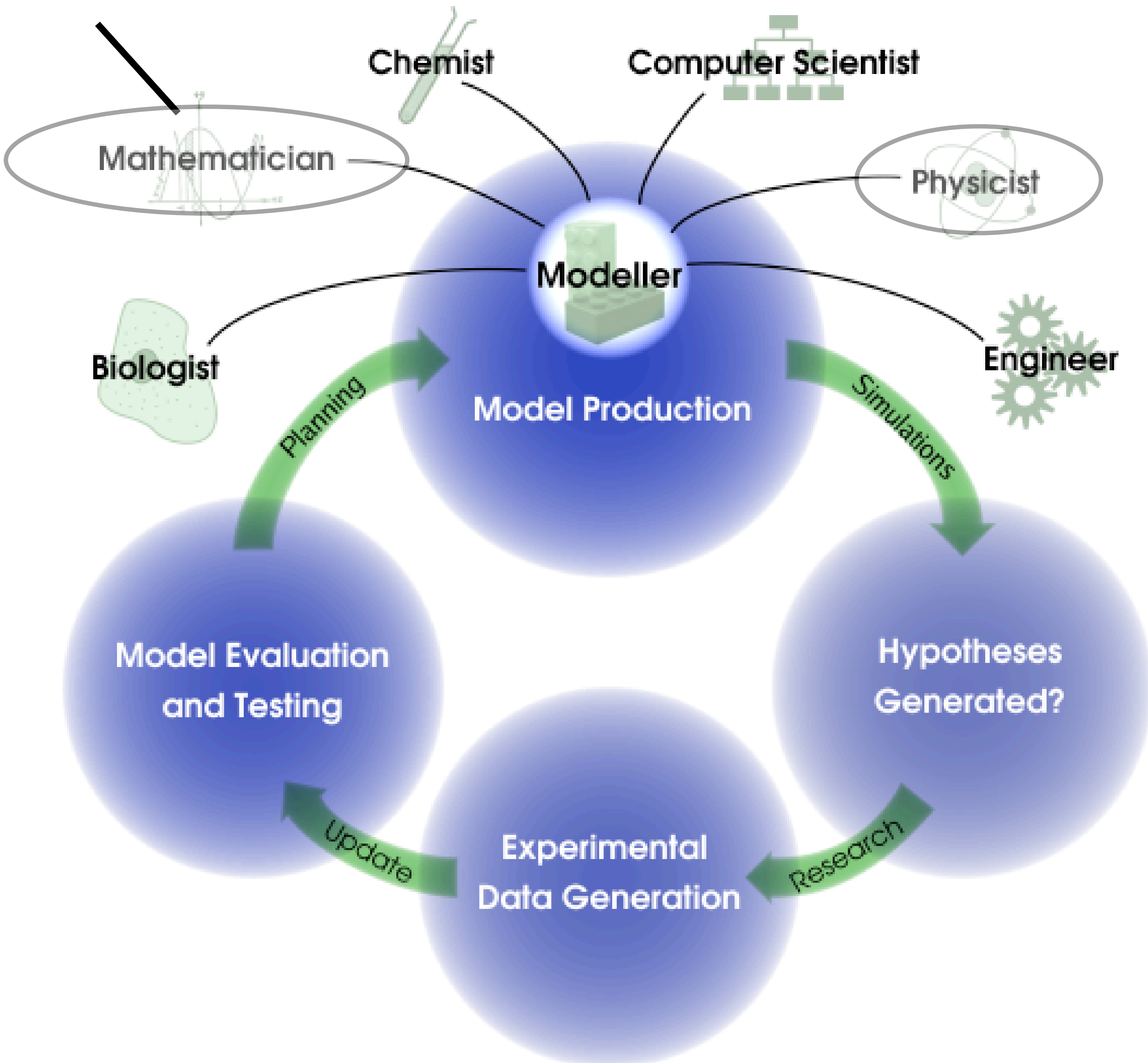




Dodecahedron zero mode 3'+

New Maths

Integrative biology



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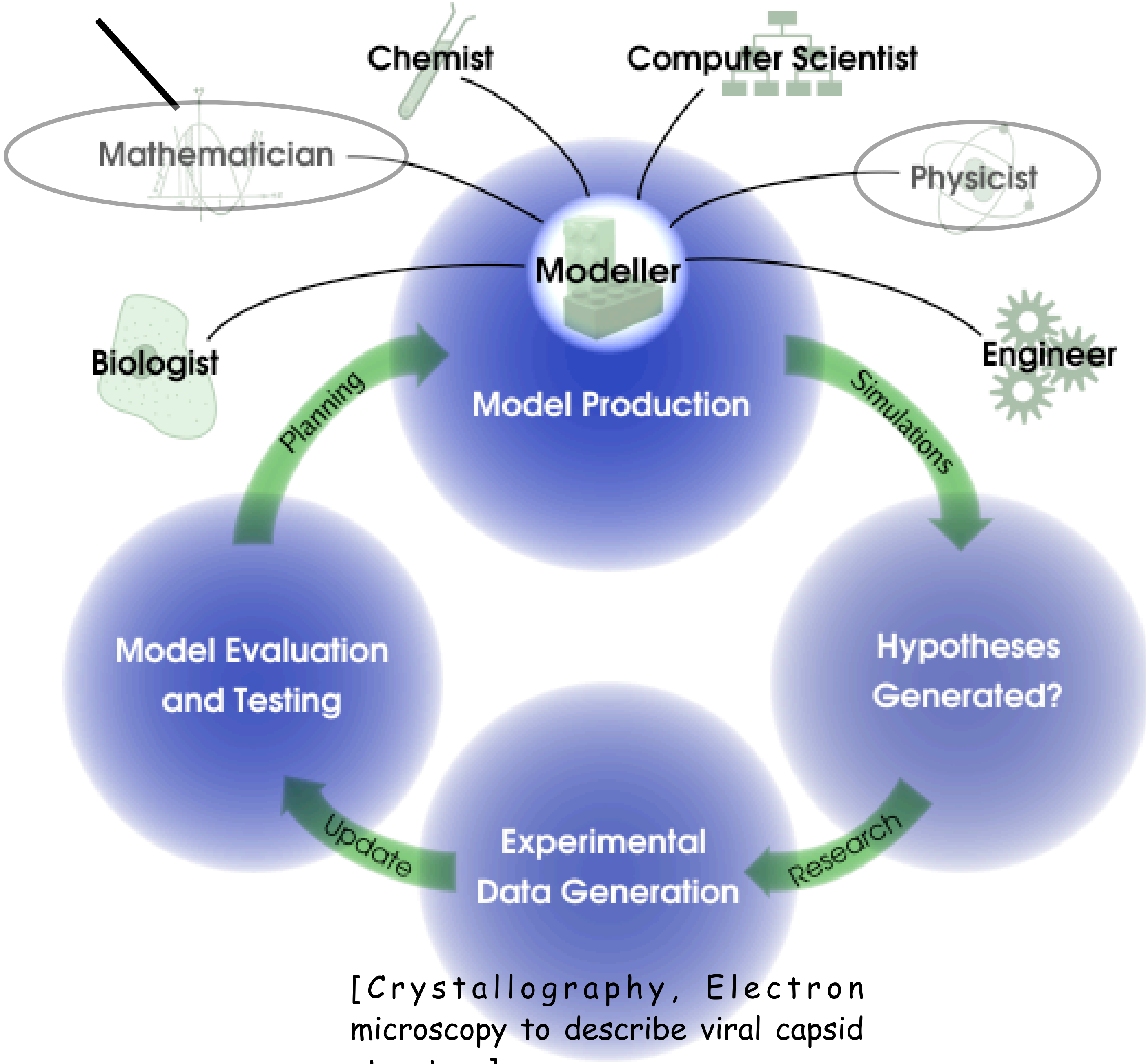

[Crystallography, Electron microscopy to describe viral capsid structure]

New Maths

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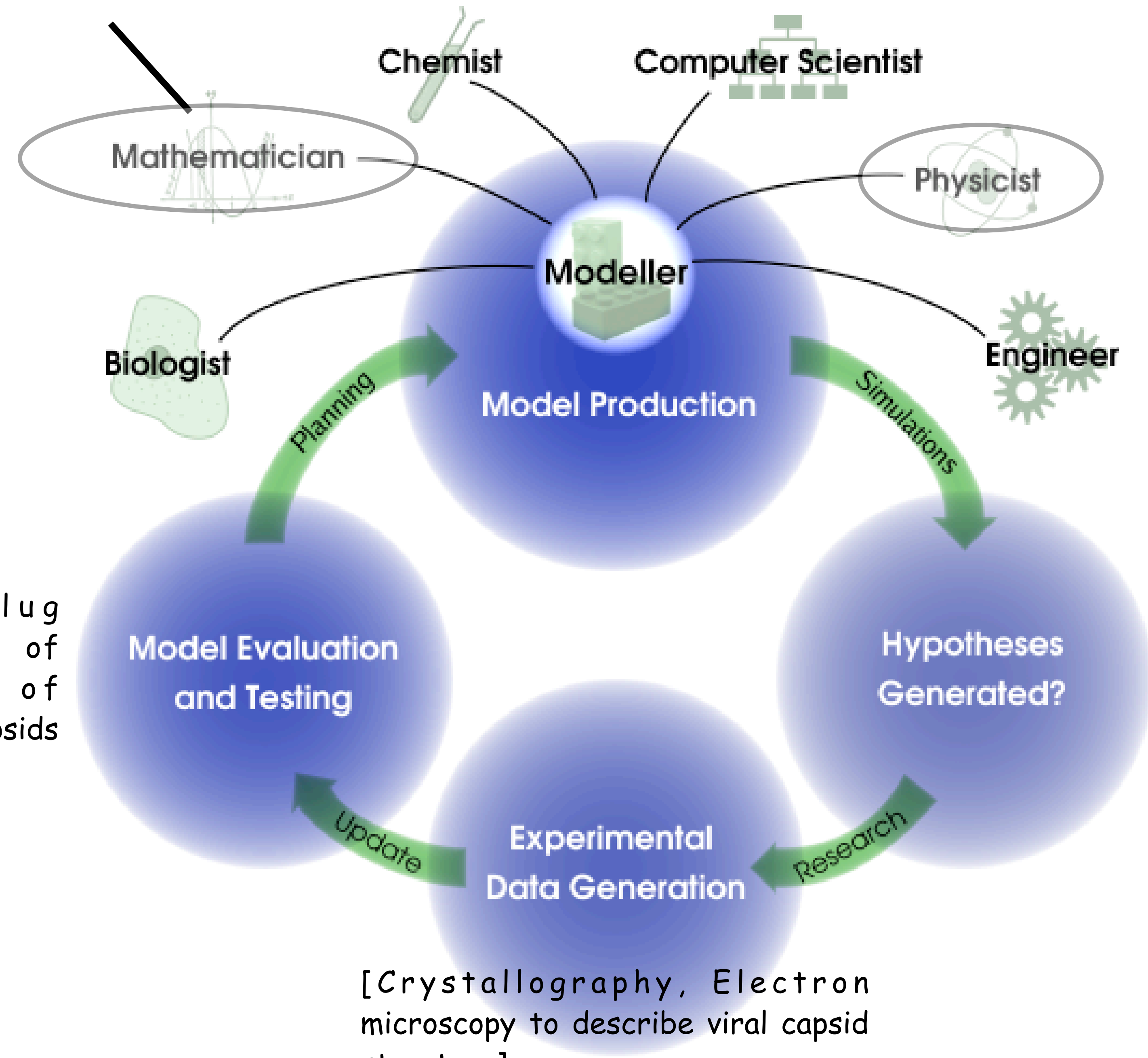

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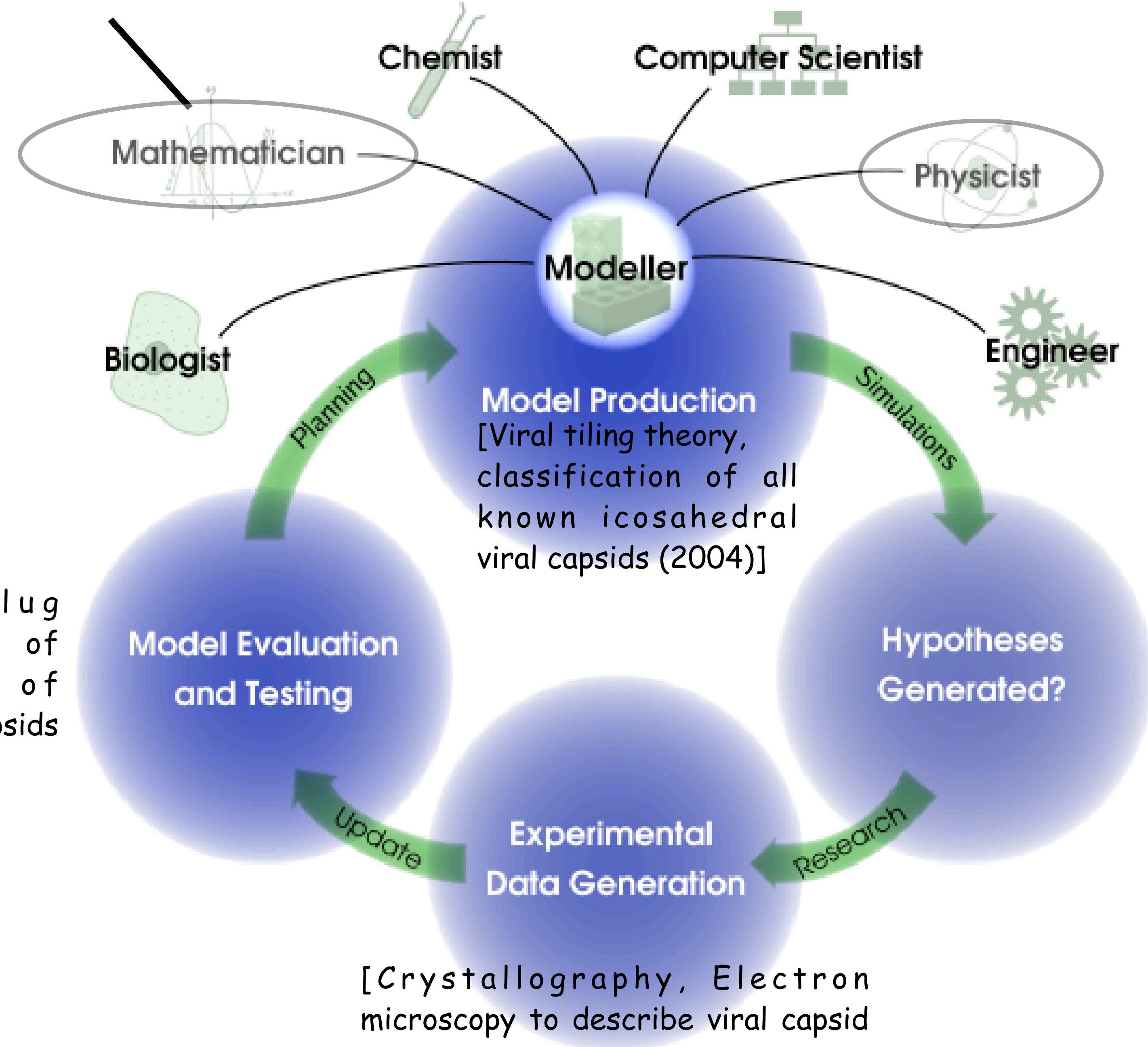

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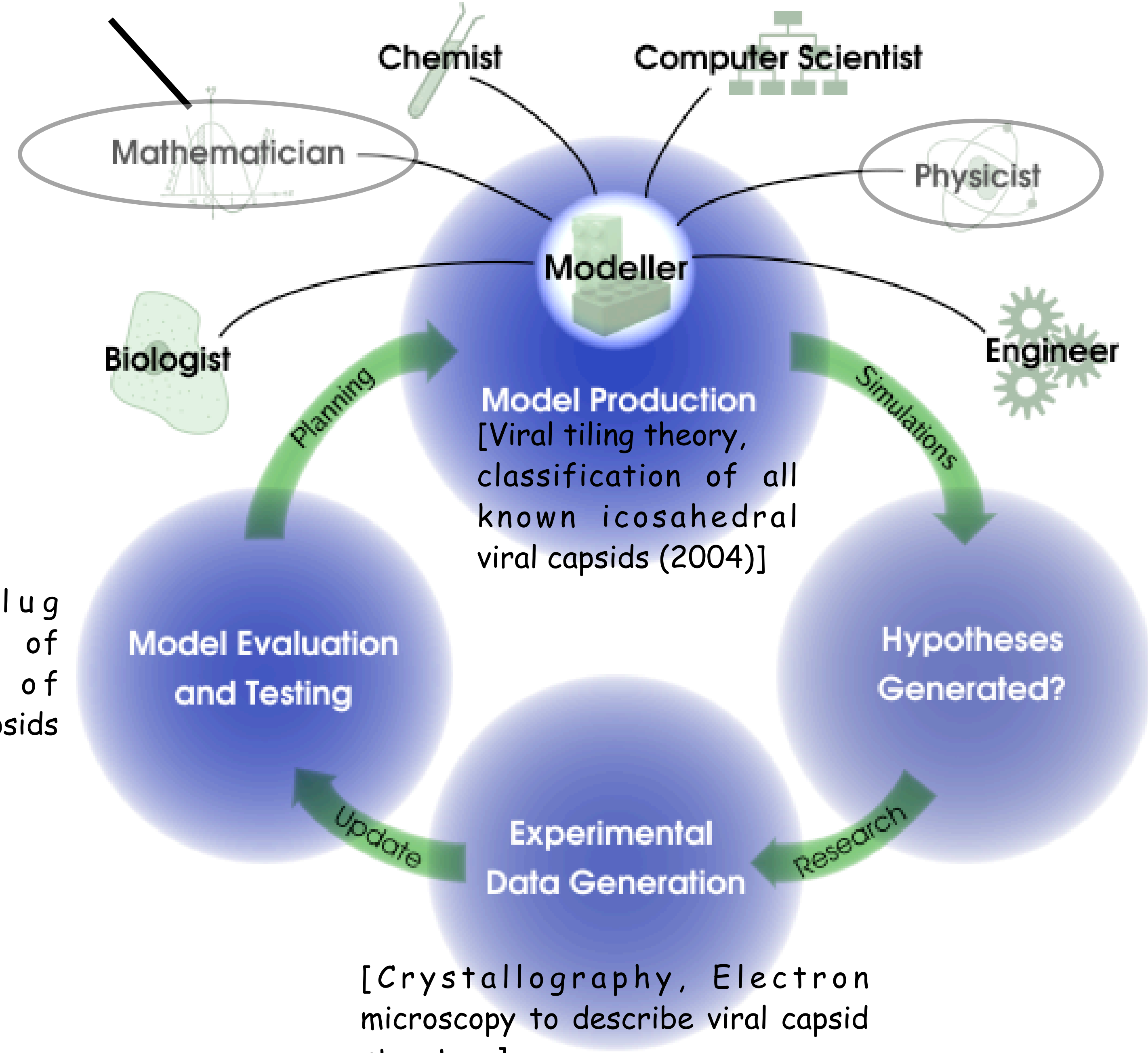

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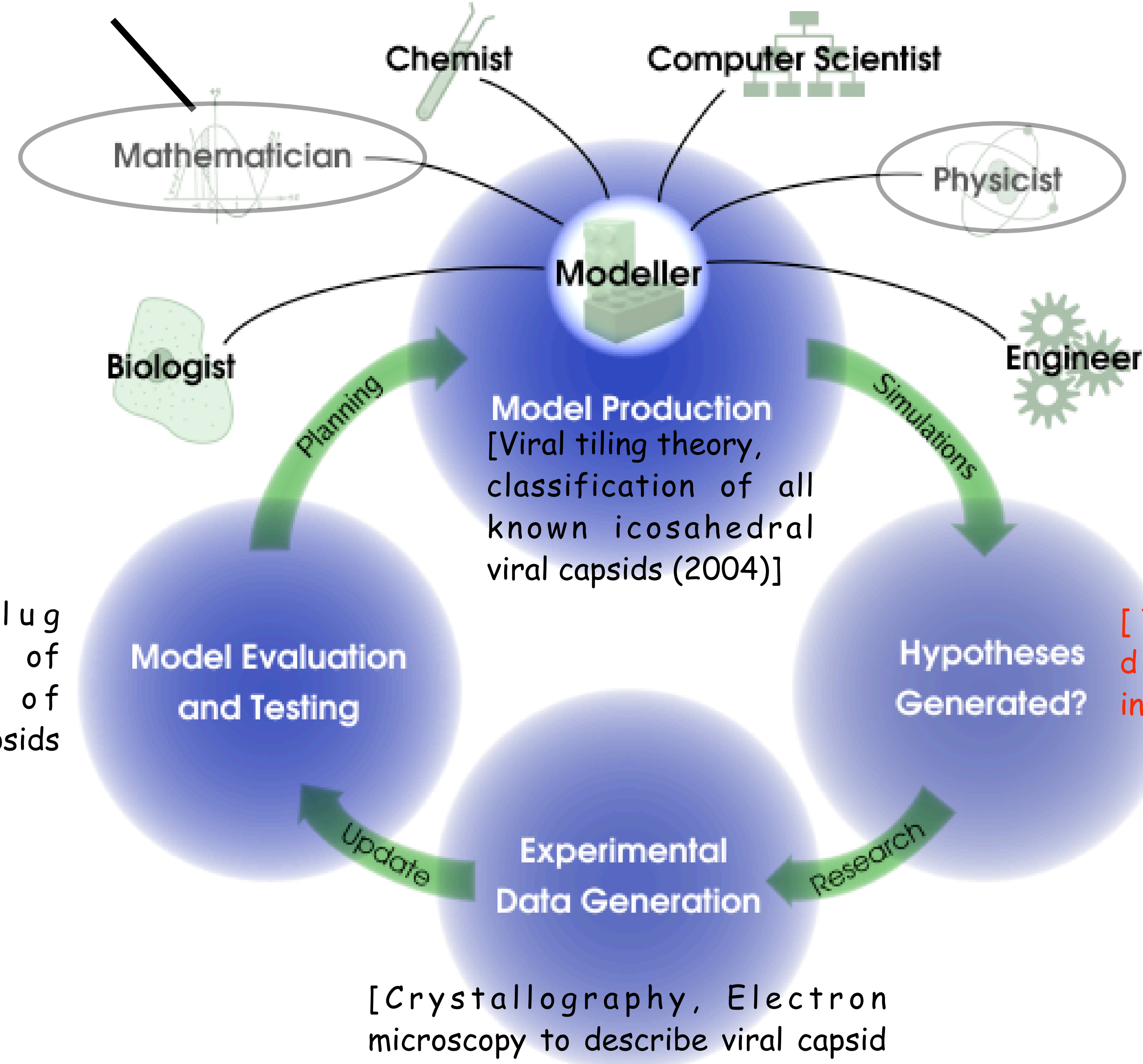

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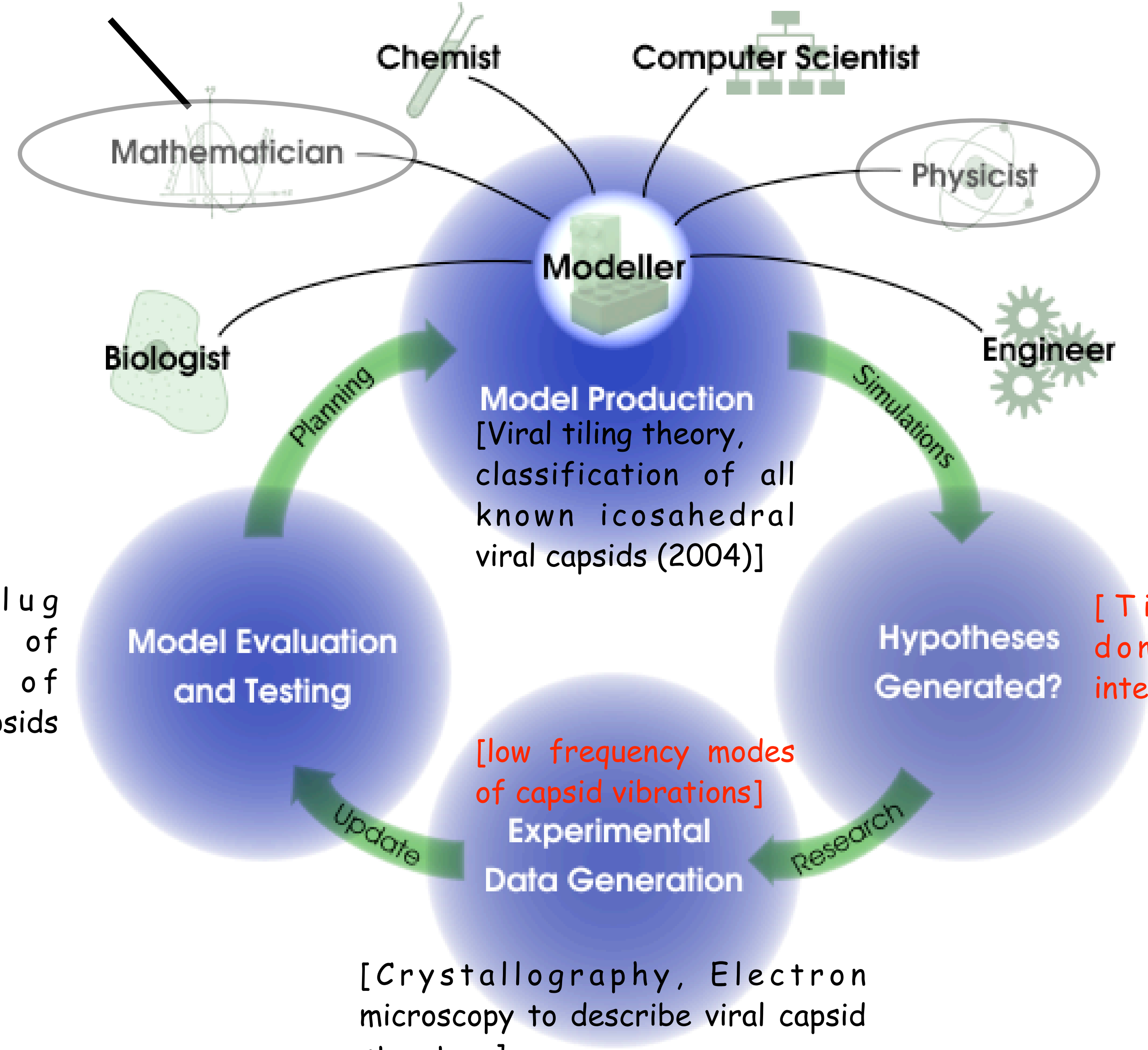

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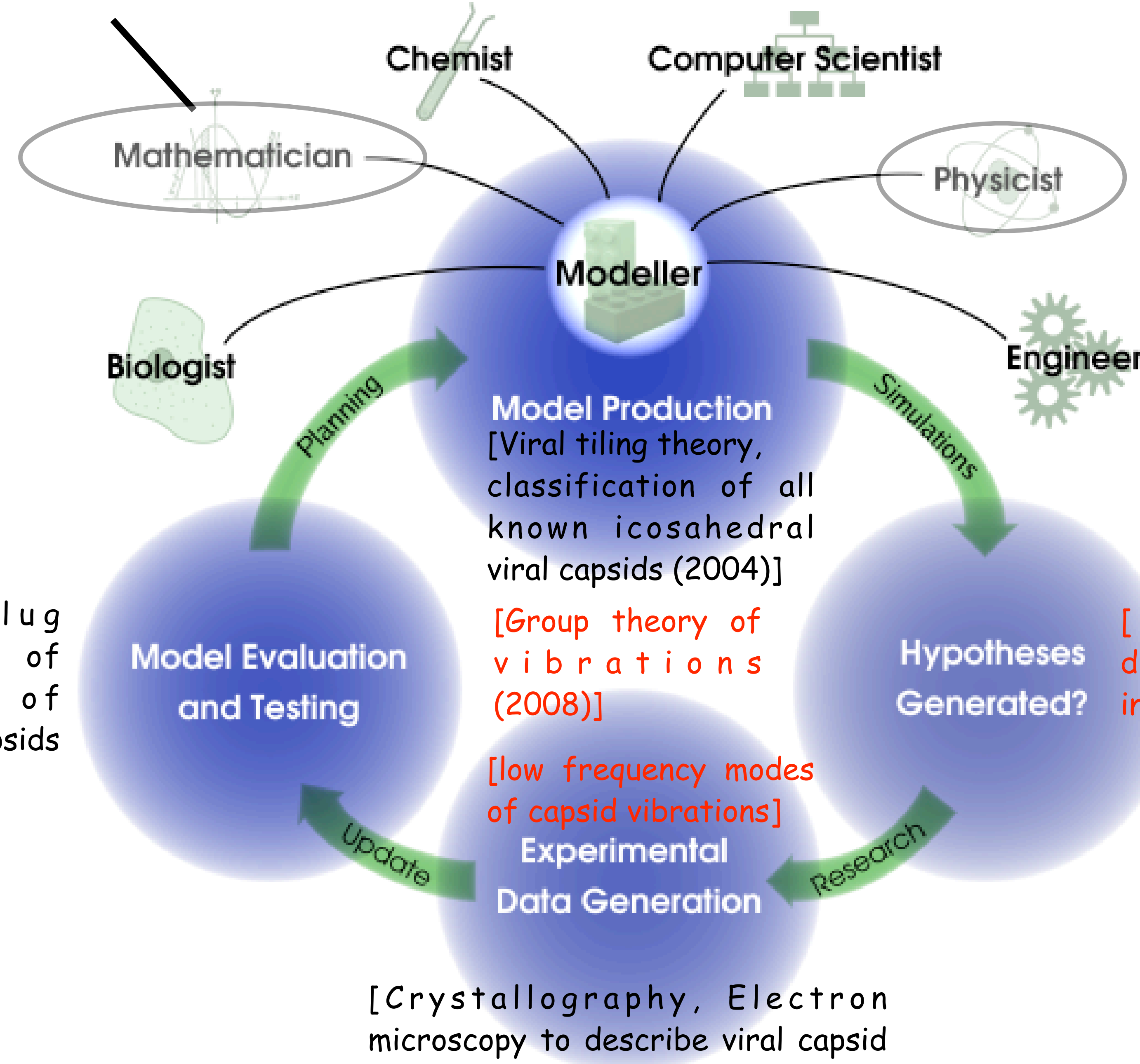

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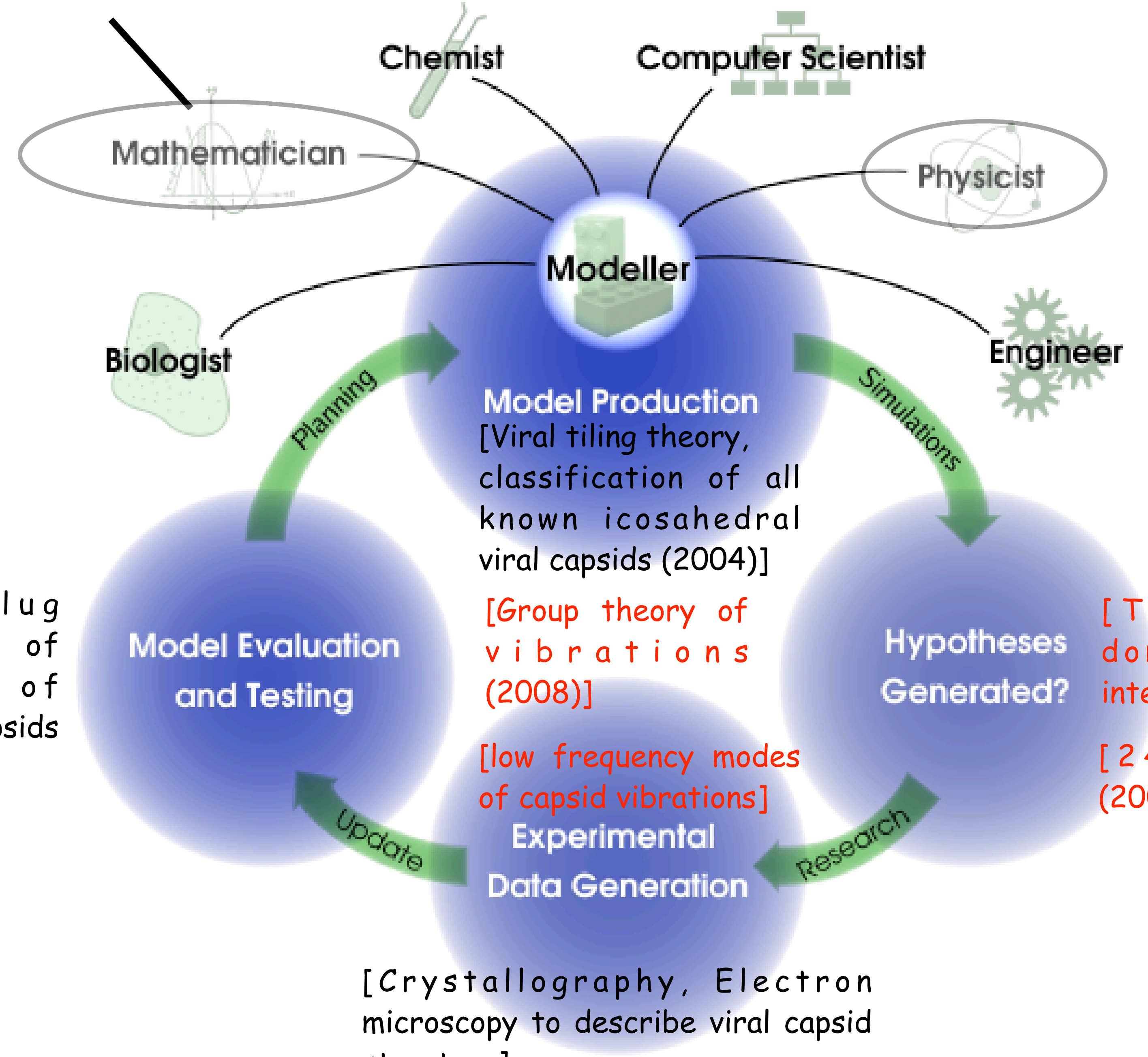
New Maths

[Affine non-crystallographic Coxeter groups]

Integrative biology



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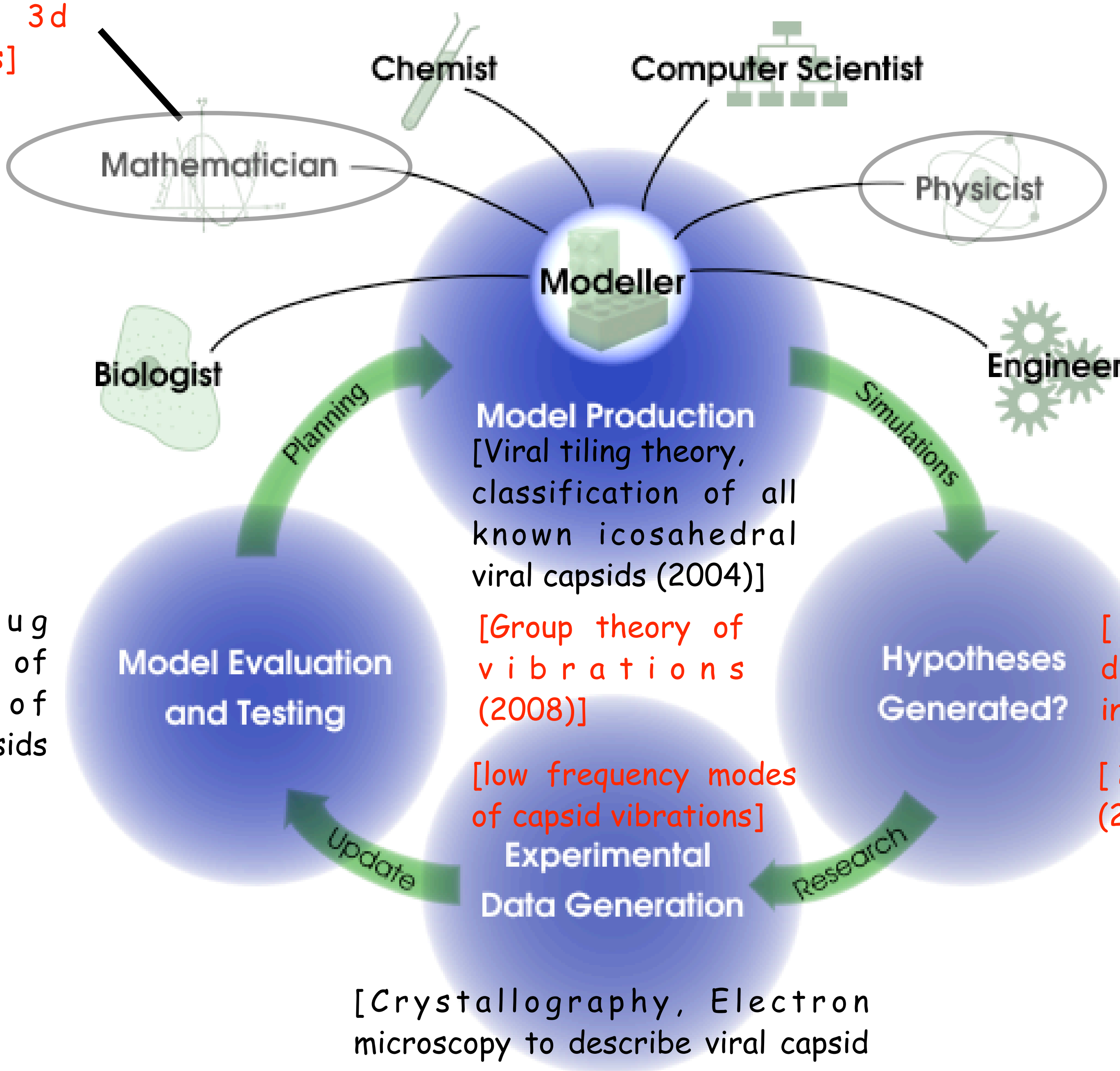
[stability of 3d elastic networks]



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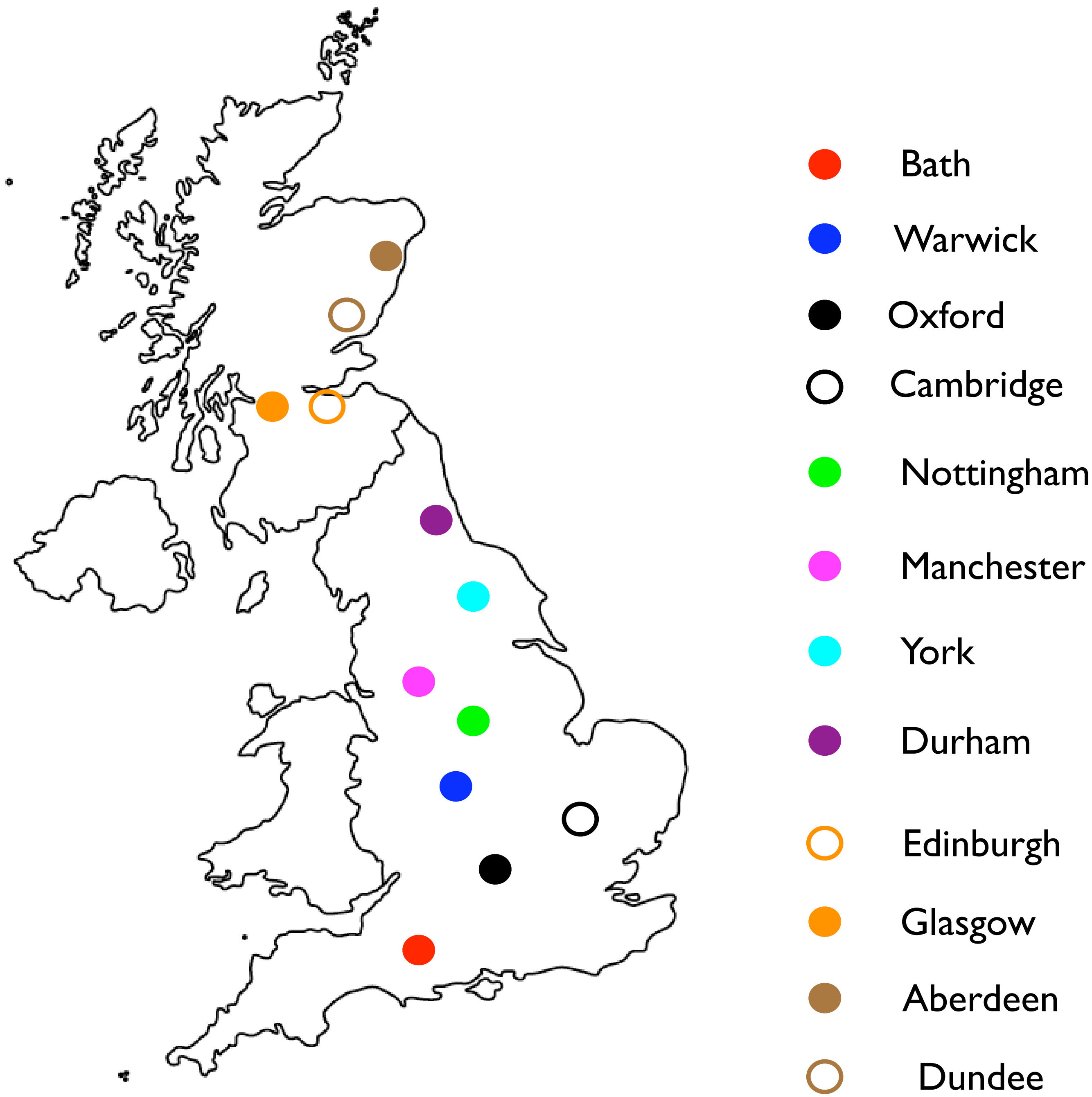
RAE 2008
Sector Overview UoA 21: Applied Mathematics

Mathematical Biology: The sub-panel noted the continued growth in this area. Strong groups were present in 13 submissions and many institutions expressed plans to expand their research in this area; some 13 of the early career researchers were declared in this area. There is a great breadth of coverage, from biology and medicine right through to ecology and epidemiology. A number of groups are involved in large, inter-departmental, multi-disciplinary research efforts. There has been significant growth in applications in medicine. Scope remains for increased attention to problems which lead to significant advances in either science or mathematics, or both.

Mathematical Biology in the UK (not complete)



Centre for Mathematical Biology - Bath University

Biology and Biochemistry	Steve Dorus, evolutionary genetics and genomics. Edward Feil, molecular evolution, recombination and population structure of bacterial pathogens. Laurence Hurst, evolutionary genetics. Alex Jeffries, functional genomics, molecular evolution, and bioinformatics. Robert Kelsh, vertebrate developmental biology, gene regulatory networks, cell migration. Klaus Kurtenbach, genetic epidemiology and evolutionary ecology of vector-borne zoonoses. Mike Mogie, understanding the factors favouring the evolution and maintenance of sexual and asexual reproduction. Alan Rayner, fungi, complexity. Tamas Szekely, evolutionary biology. Matthew Wills, macroevolutionary patterns and the fossil record.
Mathematical Sciences	Nick Britton, ecology and evolution, reaction-diffusion. Ben Adams, host-pathogen systems - epidemiology, evolution, diversity. Merrilee Hurn, Markov chain Monte Carlo methods, including image analysis. Hartmut Schwetlick, analysis, PDEs, applied mathematics, modelling, numerics. Gavin Shaddick, statistics, epidemiology. Vadim Shcherbakov, spatial point processes and interacting particle systems. Jane White, ecology, epidemiology.
Computer Science	Joanna Bryson, understanding natural intelligence, designing intelligent systems. Mariana De Vos, knowledge representation and reasoning, evolutionary game theory.
Management	Neil Allan, disease theory and risk. Christos Ioannidis, linear econometric models; non-linear, and long-memory time series dynamic models. Andreas Krause, networks, agent-based simulations.
Mechanical Engineering	William Megill, biomimetics, comparative biomechanics, behavioural ecology, coastal oceanography.
Pharmacy and Pharmacology	Begona Delgado-Charro, drug delivery, non-invasive monitoring and pharmacokinetic profiling across the skin.
Physics	Dick James, animal aggregation. Alain Nogaret, spiking semiconductor neurons (experimental).
Psychology	Suzanne Skevington, psychosocial aspects of HIV/AIDS, depression, exercise, dementia, etc, especially in relation to quality of life.

Mathematics Institute Warwick - Mathematical Biology

David Rand: Genetic circuits in clocks, pure and applied dynamical systems

Nigel Burroughs: Mathematical immunology, especially control and regulation of the immune system, graph theory and phylogenetics, signalling and gene regulation, statistical methods for gene network inference. Most of my work is a mix of modelling and data analysis.

David Epstein: Phylogenetic tree construction, on the basis of sequence data. Combinatorial, computational and statistical issues which arise in the study of proteins in cell biology.

Ian Stewart: Pattern formation in networks of dynamical systems, with applications to animal locomotion, neuroscience, and ecosystems.

Robert MacKay: Dynamical systems, mathematical physics, and complexity science

Glasgow Department of Mathematics - Mathematical Biology

Martin Bees: Bioconvection. Biological control of pests. Bacterial pattern formation. Plankton patchiness.

Christina Cobbold: Population dynamics. Spatial Ecology. Evolutionary ecology. Arterial disease.

Nick Hill: Arterial disease. Circulation of blood. Bioconvection. Plant population dynamics. Random walks and animal movement.

Kenneth Lindsay: Neuron morphology. Neuron function. Spiking neural networks. Point processes and stochastic differential equations.

Xiaoiu Luo: Arterial disease. Computational Biomechanics. Flow in airways. Fluid/structure interaction (FSI). Gall bladder diseases. Heart valves.

Ray Ogden: Mechanics of biological tissues. Arteries.

Radostin Simitev: Waves in cardiac tissue.

Tianhai Tian: Genetic regulatory networks. Cell signal transduction pathways. Calcium signalling and regulation. Stochastic simulation.

School of Mathematical Sciences Nottingham - Mathematical Medicine and Biology

Helen Byrne: Growth and treatment of solid tumours, tissue engineering and stem cell biology. Mathematical tools: nonlinear dynamics, asymptotic analysis, continuum mechanics and multiscale-hybrid modelling.

Stephen Coombes: Role of branching dendrites with active spines on single neuron output. Effect of cannabinoids on emergent neural network dynamics . Waves and patterns in tissue level models of synaptic and EEG. Mathematical tools: nonlinear dynamics and statistical physics.

Linda Cummings: Growth and treatment of solid tumours, tissue engineering and stem cell biology. Mathematical tools: nonlinear dynamics, asymptotic analysis, continuum mechanics and multiscale-hybrid modelling.

York University: York Centre for Complex Systems

Reidun Twarock: development and application of group theoretical and algebraic methods in mathematical biology, carbon chemistry and mathematical physics.

Jamie Wood: computational and analytic techniques in statistical mechanics to further our knowledge of the stability and robustness of natural systems. Flocking or herding behaviour in animals (network rewiring).

Durham University: Biomathematics group

Kasper Peeters: Dynamical processes within the cell. Protein and virus conformational changes.

Bernard Piette: Dynamical processes within the cell. Cytoskeleton.

Anne Taormina: Protein and virus conformational changes. Viral capsid assembly. Construction of DNA cages.

Ian Vernon: modelling of intracellular chemical reaction networks as stochastic processes, applying Bayesian inference to the rate constants of such reaction networks, and the adaptation of deterministic computer model calibration techniques to the stochastic case, in view of applying them to systems biology models.

Wojtek Zakrzewski: Dynamical processes within the cell. Cytoskeleton.

New lecturer (October 2009)

MSc in Biomathematics

Department of Mathematical Sciences

Durham University

In partnership with the Biophysical Sciences Institute

Courtesy John Attle, Durham Photographic Society

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Regulatory Networks in Biology
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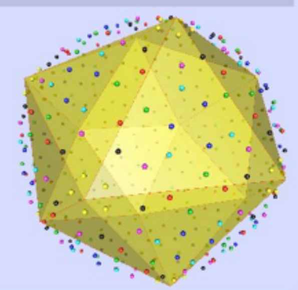
Biological Physics
Quantum Mechanics for Biomaterials
Computational Mechanics

You will have opportunities to take an active part in several events organised by the Biophysical Sciences Institute during the academic year, and to be exposed to a variety of research environments within the Departments of Biological and Biomedical Sciences, Chemistry, Engineering, Mathematical Sciences and Physics.

Apply before July 1st for entry in October 2009

www.dur.ac.uk/mathematical.sciences/biomaths/



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Tel: +44 (0)191 334 3050
Email:P.G.Maths@durham.ac.uk