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Machine-learning a virus assembly fitness landscape

SIAM Algebraic geometry, data science and fundamental physics

Bern, July 12, 2019

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work with Y-H He and R Twarock

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Department of Mathematics, University of York

Rationale

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

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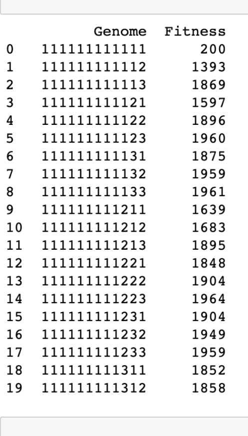

```
         Genome  Fitness
0   111111111111      200
1   111111111112     1393
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```

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

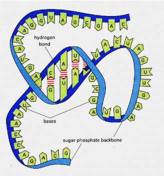
Overview

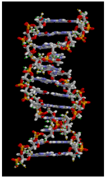
1.
   - Virus structure and assembly
   - Toy model and evolutionary fitness landscape

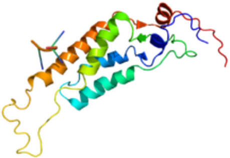
2.
   - Neural networks
   - Predictions

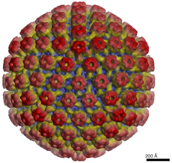
What is a Virus?

- Piece of genetic information in the form of RNA or DNA
- Protected by a protein shell: capsid made of geometric protein building block



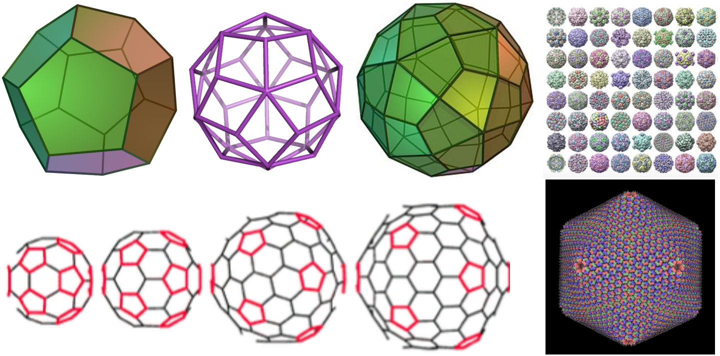






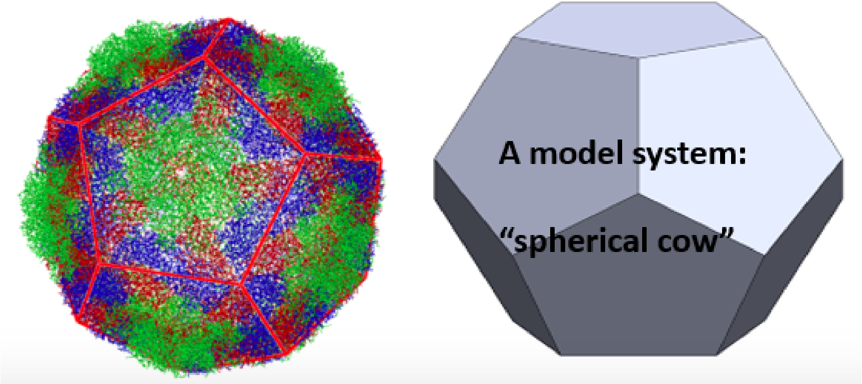
Herpes Simplex Virus type I B-capsids. Data from Rochat et al. J. Virol (2011) 85(4) 1871-4.
EMDB #5259 - Rendered with UCSF Chimera. images © 2011 JY Sgro; UW-Madison.

Most viruses are icosahedral



- Highly developed structure theory
- Nucleic acid component thought to be disordered

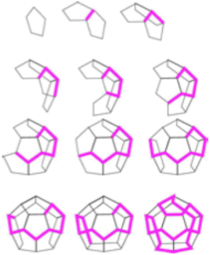
Simplest model: a dodecahedron



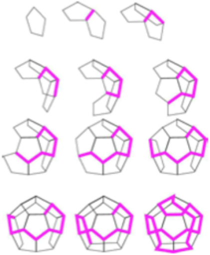
A model system:

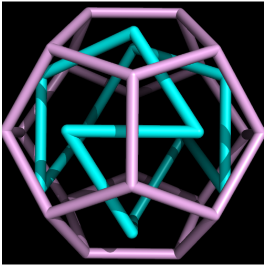
“spherical cow”

Assembly and thermodynamics – Hamiltonian paths



Assembly and thermodynamics – Hamiltonian paths





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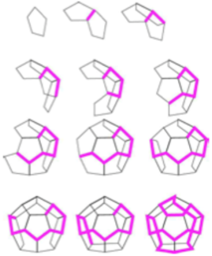
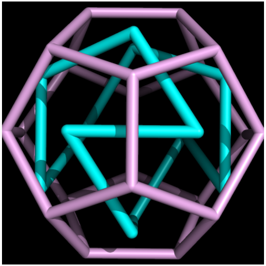
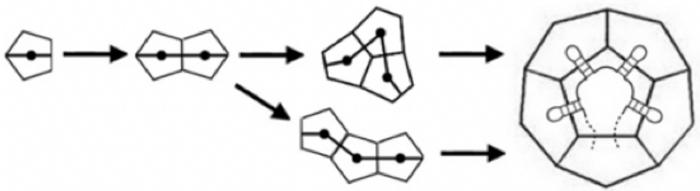
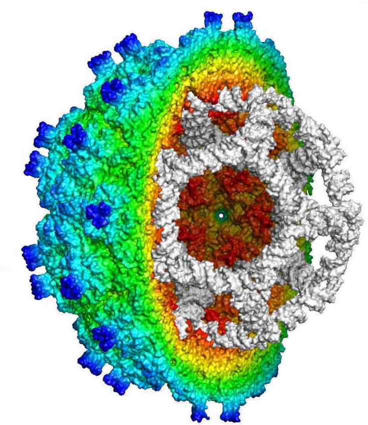




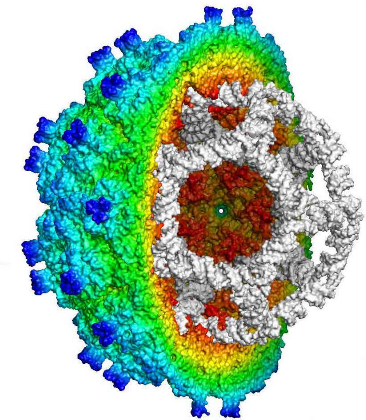


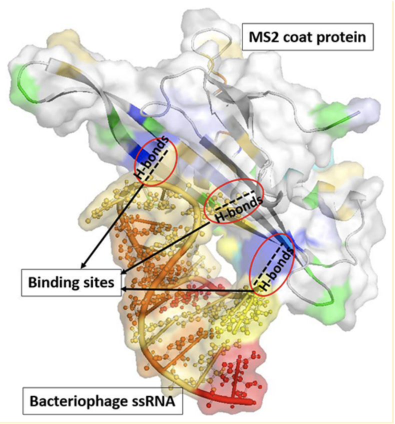
3D distribution: RNA-CP contacts



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

3D distribution: RNA-CP contacts





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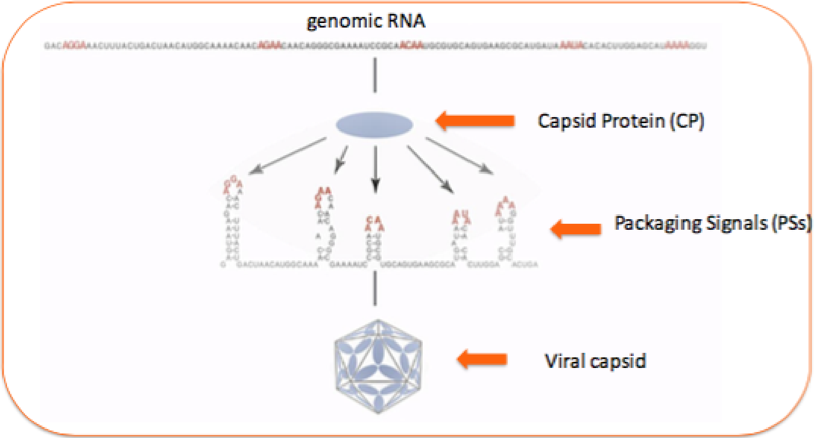
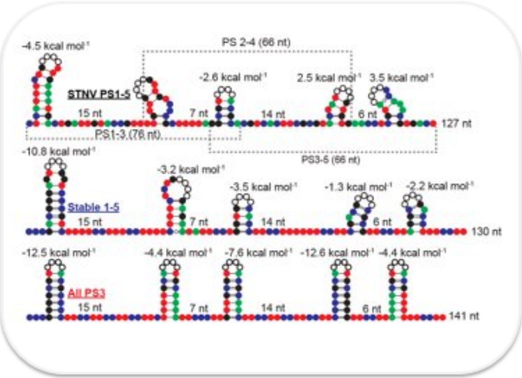
Packaging signal-mediated assembly

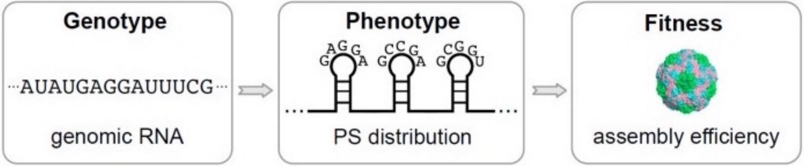


Engineering Packaging Signals to make VLPs



Virus-like particles with improved PS sequences assemble twice as efficiently. Potential applications to vaccines or drug delivery.

Genotype – Phenotype – Fitness map



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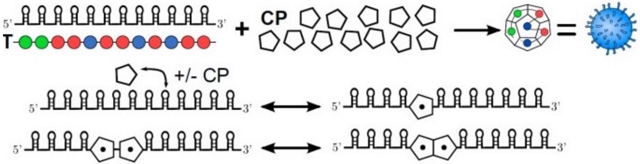
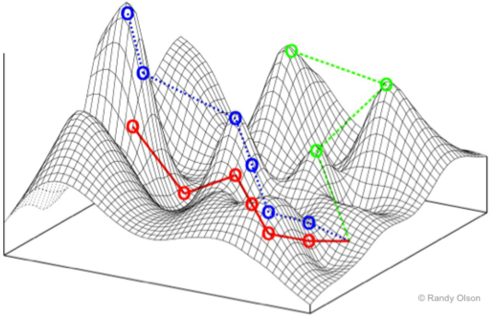


- 12 PSs in 3 bands (strong/intermediate/weak, 12/8/4, 3/2/1, green/blue/red)
- Molecular dynamics simulation: stochastically select one possible reaction at a time
- Enough resources for 2000 virus capsids

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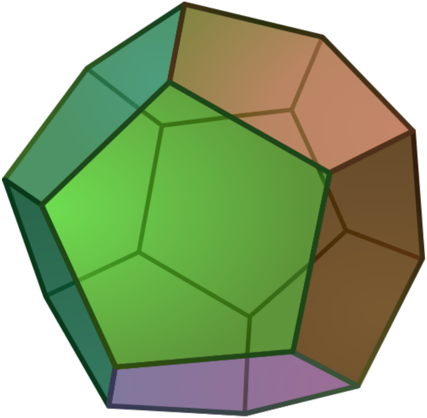
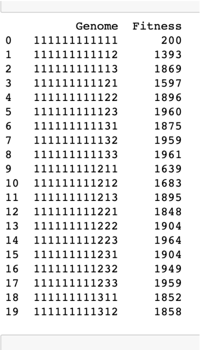
Generally messy (many contributions) and difficult to quantify.
Here capture the assembly contribution for the phenotype space of 3^{12} points with (stochastic) assembly efficiency (< 2000).

Fundamental Physics



Genotype–fitness map



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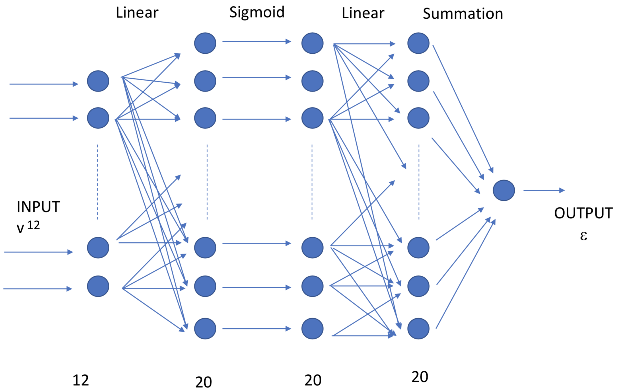
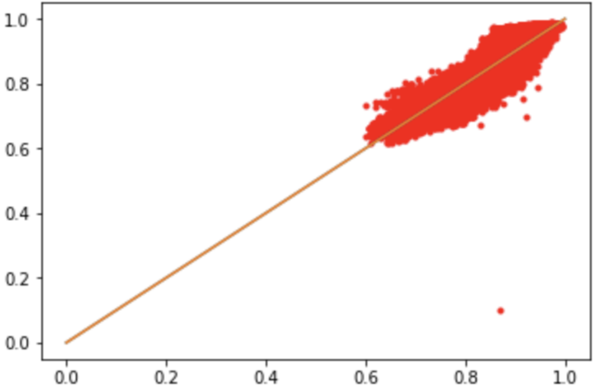
Machine Learning with a Neural Network

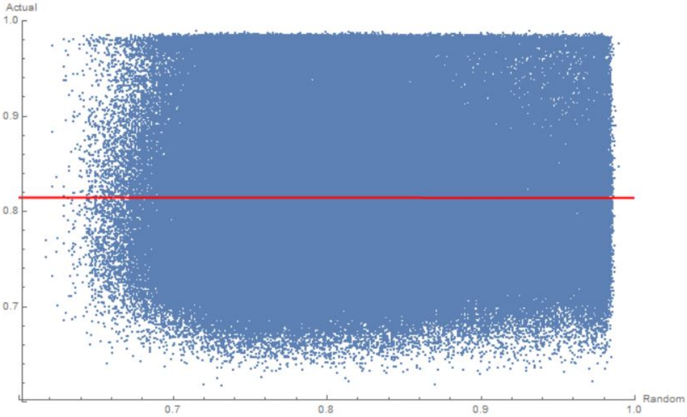


Predictions



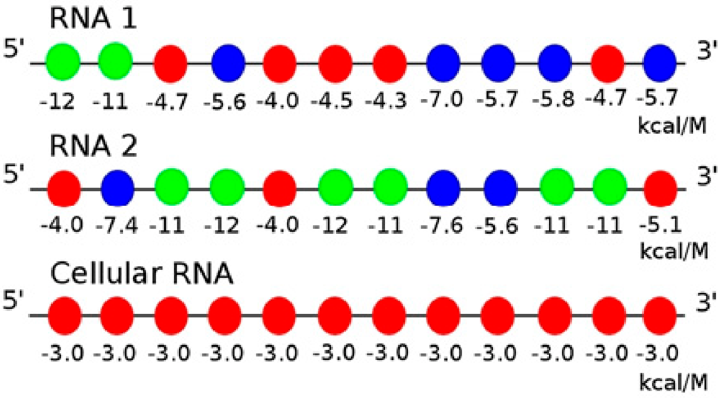
predicted vs actual value of assembly efficiency

Predictions



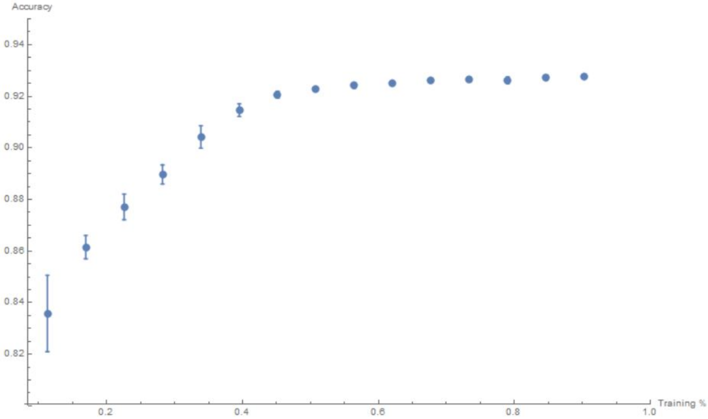
vs random assignments of assembly efficiency

Not just random, intrinsic features?

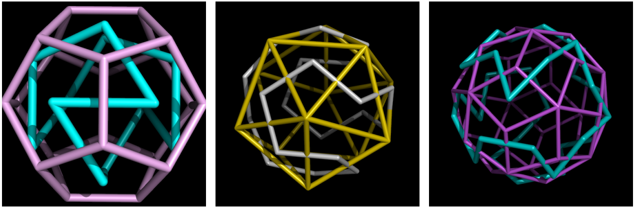


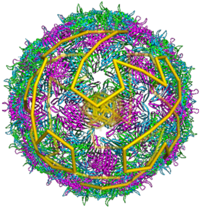
Definite starting point with strong binding, then weaker binding in an error-correcting bit, driven to completion by thermodynamics

Learning Curve



Conclusions





Do more realistic models in future – geometry, binding gradation.
Partially explore the landscape and predict the rest (procedurally)?

Thank you!

Machine-learning a virus assembly fitness landscape
P-P Dechant, Y-H He, arXiv preprint arXiv:1901.05051, 2019