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Viral evolution through the lens of geometry: new routes for antiviral therapy

Genetic changes occur rapidly in a viral population due to error-prone replication. This makes viruses ideal biological systems in which to study the laws of evolution. One of the important selective pressures on viral evolution is the need to guarantee swift formation of virus particles of the correct geometry, which relies on two types of codes: the *genetic code* that encodes viral proteins, and an *assembly code* that provides an instruction manual for the assembly of viral components [1-4]. As both codes are superimposed along the viral genomic sequence [5-7], structure and function are intertwined at the genetic level and simultaneously impose selective pressures on viral evolution.

In this talk I will demonstrate how insights in the genetic and assembly code can be used to define new types of genotype-phenotype-fitness maps for the study of viral evolution [8]. Coupled with models of a viral infection [9], this approach can be used to assess the merits of different forms of anti-viral intervention targeted at the assembly code. I will also demonstrate that the assembly code is evolutionarily robust, and is shared by different strain variants, thus opening up the opportunity for broad-spectrum antiviral therapy.

- [1] Twarock R, Bingham RJ, Dykeman EC, Stockley PG: **A Modelling Paradigm for RNA virus assembly**. *To appear in Current Opinion in Virology* 2018.
- [2] Dykeman EC, Stockley PG, Twarock R: **Solving a Levinthal's paradox for virus assembly identifies a unique antiviral strategy**. *Proc Natl Acad Sci U S A* 2014, **111**:5361–6.
- [3] Prevelige PE: **Follow the Yellow Brick Road: A Paradigm Shift in Virus Assembly**. *J Mol Biol* 2016, **428**:416–418.
- [4] Twarock R, Leonov G, Stockley PG: **Hamiltonian Path Analysis of Viral Genomes**. *To Appear in Nat Comms* 2018.
- [5] Shakeel S, Dykeman EC, White SJ, Ora A, Cockburn JJB, Butcher SJ, Stockley PG, Twarock R: **Genomic RNA folding mediates assembly of human parechovirus**. *Nat Commun* 2017, **8**:5.
- [6] Patel N, White SJ, Thompson RF, Bingham R, Weiß EU, Maskell DP, Zlotnick A, Dykeman EC, Tuma R, Twarock R, et al.: **HBV RNA pre-genome encodes specific motifs that mediate interactions with the viral core protein that promote nucleocapsid assembly** Nikesh. *Nat Microbiol* 2017, **17098**.
- [7] Patel N, Dykeman EC, Coutts RH a., Lomonosoff GP, Rowlands DJ, Phillips SE V., Ranson N, Twarock R, Tuma R, Stockley PG: **Revealing the density of encoded functions in a viral RNA**. *Proc Natl Acad Sci* 2015, **112**:201420812.
- [8] Dykeman EC: **A Model for Viral Assembly around an Explicit RNA Sequence Generates an Implicit Fitness Landscape**. *Biophys J* 2017, **113**:506–516.
- [9] Bingham RJ, Dykeman EC, Twarock R: **RNA virus evolution via a quasispecies-based model reveals a drug target with a high barrier to resistance**. *Viruses* 2017, **9**.

