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Genome Organisation and Assembly of RNA Viruses: Where Structure Meets Function

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This talk covers work is collaboration with (*York/Modelling)* Eric Dykeman, Karim ElSawy, Nick Grayson, Giuliana Indelicato, Tom Keef, German Leonov, David Salthouse, Jess Wardman; (*Leeds/Experiment*) Alison Ashcroft, Victoria Morton, Neil A. Ranson, Nicola Stonehouse, Peter G. Stockley.

Abstract:

Cryo-electron microscopy and X-ray crystallography have revealed ordered features in the genome organisation of a number of ssRNA viruses. These include a dodecahedral cage in Pariacoto virus and a double-shell organisation in bacteriophage MS2. We show here that these ordered features are due to symmetry constraints on the overall organisation of the particles [1], and provide an explanation of the physical reasons underlying these constraints [2]. The latter is based on a series of coarse-grained molecular dynamics simulations of the MS2 genome inside its viral capsid, in which the capsid is represented by the solvent accessible surface of the X-ray structure, and the RNA as a connected string of beads with beads modelling individual nucleotides. We show that the radial distribution of the RNA is due to confinement, whilst the characteristic polyhedral structure of the outer RNA shell is a result of the topography of the inner capsid surface, both confirming predictions of our symmetry approach.

We moreover address the implications of these results for virus assembly. One clue is provided by the allosteric effect by which RNA binding to coat protein dimers results in a conformational change from a symmetric to an asymmetric form of the dimer. We show that this switch is not sequence specific and can therefore be triggered by different stem loops in the genome [3]. We moreover demonstrate that the RNA stem loops impact on assembly pathway selection [4]. This results in an assembly model for viral capsids in which the packaged RNA actively participates by conformer switching of potentially all 60 asymmetric dimers in the capsid [5]. For this to occur, RNA must pass under all 60 dimers, and there are in principle over 40000 pathways that would allow this. We show that in the wild type phage this number is dramatically reduced because of the presence of the maturation protein [6]. These results predict, for the first time, directly how an RNA sequence should be positioned within a viral capsid.

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[2] K.M. Elsawy, L.S.D. Caves & R. Twarock (2010) On the origin of order in the genome organisation of ssRNA viruses, submitted to *J. Mol. Biol.*
[3] Dykeman EC, Stockley PG, Twarock R (2010) Dynamic allostery controls coat protein conformer switching during MS2 phage assembly, *J Mol. Biol.* 395: 916-23; Dykeman EC, Twarock R (2010) All-atom normal-mode analysis reveals a dynamic RNA-induced allostery in a bacteriophage coat protein*, Physical Review E*. 81, 031908.
[4] ElSawy KM, Caves L, Twarock R (2010) The impact of viral RNA on the association rates of capsid protein assembly: bacteriophage MS2 as a case study*, J. Mol. Biol.* 400(4):935-47.
[5] Victoria L. Morton, Eric C. Dykeman, Nicola J. Stonehouse, Alison E. Ashcroft, Reidun Twarock and Peter G. Stockley (2010) The Impact of Viral RNA on Assembly Pathway Selection, *J. Mol. Biol.* 401(2):298-308.
[6] E.C. Dykeman, N. Grayson, N. A. Ranson, P.G.Stockley & R. Twarock, Simple rules for efficient assembly predict the layout of a packaged viral RNA, submitted to *Nat. Struct. Mol. Biol.*