An interdisciplinary approach to virus structure and assembly

Case study: Statistical Mechanics of Molecular and Cellular Biological Systems

It was Francis Crick and James Watson who in 1956 suggested that viruses exhibit symmetry for reasons of genetic economy. If that is the case one might think that mathematicians who study symmetry should be able to provide new insights into virus structures and mechanisms in the viral life-cycle that depend on these symmetries. Moreover structural insights developed by mathematicians working in collaborations with experimental biologists might even have the potential to trigger new advances in anti-viral therapies in medicine.

With this in mind, it was during an interdisciplinary programme, *Statistical Mechanics of Molecular and Cellular Biological Systems*, at the Isaac Newton Institute in 2004 that Reidun Twarock, a mathematician from York, and Peter Stockley, an experimental biologist from Leeds, began to collaborate on a mathematical theory of the structure of viruses. For both, the Institute's programme was a transformative experience since which, with their research teams, they have developed a distinctive integrative interdisciplinary approach to problems that neither discipline could have solved if working in isolation.

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Mathematical techniques

Reidun and her group have developed new mathematical techniques to characterise and predict the structural properties of viruses. Additionally, they have discovered how to use these results to elucidate mechanisms such as virus assembly and structural transitions of the viral capsids, which are important for the understanding of infections. They use viral tiling theory to model the surface structures of protein containers (capsids) that encapsulate and protect the viral genomes.

Their recent mathematical contributions include the first prediction of structural constraints on the full 3D architecture of viruses via a classification of new affine extensions of the icosahedral group and non-crystallographic Coxeter groups. Among other things this has led to the discovery of a previously unrecognised molecular scaling principle in virology.

In a pioneering interdisciplinary study of viruses based on a combination of graph theory, biochemistry and kinetic modeling, Stockley and Twarock were first to predict the asymmetric configuration of the linear viral RNA sequence within the observed (averaged) RNA density in any virus.

Their joint work has initiated a paradigm shift in our understanding of the RNA virus assembly: they have shown that the viral genomes in RNA viruses play a number of co-operative roles during the

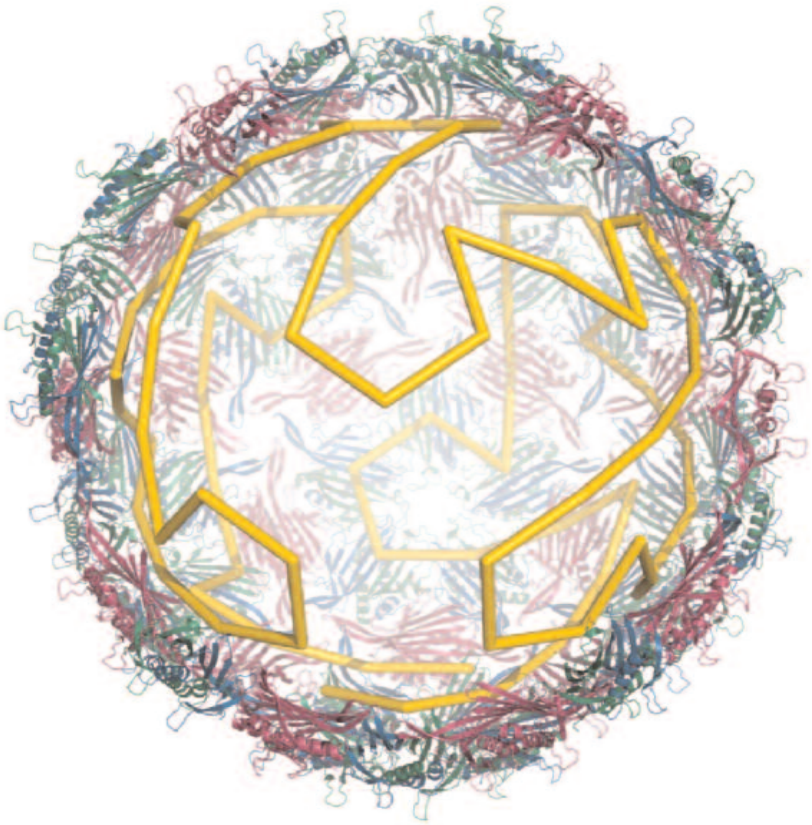
formation of the protective protein containers that had previously been overlooked. This work also showed that a protein-centric view of assembly is inappropriate for RNA viruses, the largest group of all viruses including a number of important human, animal and plant pathogens. Instead, such viral assemblies follow a set of simple rules that crucially depend on interactions between capsid protein and genomic RNA, hence providing an explanation for the high efficiency of e RNA virus assembly.

Research highlight

This work was chosen as a research highlight by the *Journal of Molecular Biology* in Spring 2011, and featured by *Global Medical Discovery* [1], a website specialised in publishing medically important basic research. It could be a first important step towards the development of drugs that inhibit virus assembly by exploiting these vital co-operative roles of the genomic RNA. Moreover, the work on virus structure has paved the way for current research efforts to better understand viral evolution and in particular the ability of viruses to evade therapy via mutation. This research could lead to novel strategies for mutation-proof therapeutics.

Workshops and publications

In addition to the 2004 satellite workshop in the framework of the Newton Institute programme, Stockley and Twarock have organised a further two workshops on *Mathematical Virology* (2007, 2010). They have edited two special issues on mathematical virology in the journal *Computational and Mathematical Methods in Medicine* and one on virus assembly in *Physical Biology*. They have also published a book on *Emerging Topics in Physical Virology*, Imperial College Press, 2010.



A Hamiltonian path indicating the location of the genomic RNA molecule in the capsid (R Twarock)

Economic and social impact and implications

The economic and social impact of theoretical work on viruses cannot be overestimated. For example, the eradication of foot-and-mouth disease in the UK cost about eight billion pounds [2] and the cost to the public health sector, never mind the human cost, of viral infections such as HIV, Hepatitis, and the cancer-causing Papilloma viruses, is even larger. It is therefore of paramount importance to develop new anti-viral therapeutics.

We see that work begun at the Isaac Newton Institute has spawned research at this rich interface between mathematics and the life sciences, and through it the Institute has made significant contributions to the economy, public health and national well being.

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Reidun Twarock is Professor of Mathematical Biology, a joint appointment in Mathematics and Biology at the University of York. Her research group currently is comprised of 4 postdoctoral research assistants, 3 PhD students and a Marie Curie Fellow.

Peter Stockley is Professor of Biological Chemistry at the Astbury Centre for Structural Molecular Biology in Leeds and was involved in establishing the Astbury Centre where he was Director for many years. He was also involved in establishing the Leeds Centre for Bionanosciences.

References

Isaac Newton Institute programme: *Statistical Mechanics of Molecular and Cellular Biological Systems*, January to July 2004. Organisers: T Duke, J Molloy, T McLeish, W Poon, P Stockley and J Trinick.

Programme webpage: www.newton.ac.uk/programmes/SMC/

Final scientific report: www.newton.ac.uk/reports/0304/smc.html

[1] globalmedicaldiscovery.com/?s=Twarock

[2] Rowlands, DJ *Foot-and-Mouth Disease* Elsevier, 2003