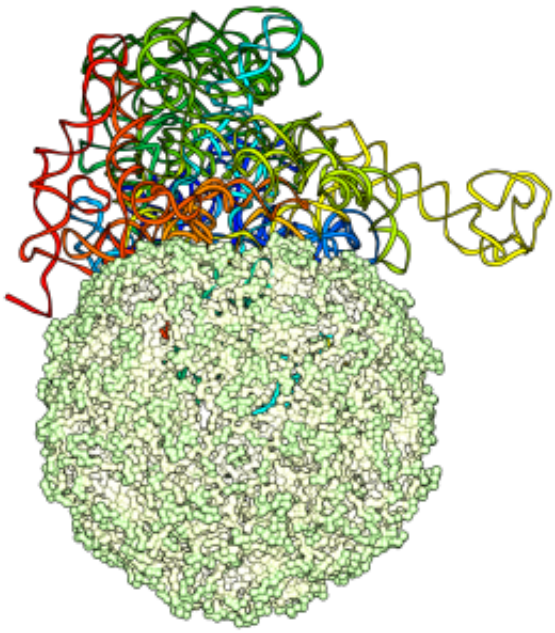
Tightly packed in its shell: Even minimal mutations stop viruses from packing RNA into capsids

January 6 2015



RNA in capsid. Credit: SISSA

A study, in which the International School for Advanced Studies collaborated with the Josef Stefan Institute of Ljubljana, analyzed how genome mutations of RNA viruses tend to be lethal for these infectious agents. It takes very little to make the RNA too messy and bulky to fit into the capsid—the shell that contains the viral genome—and by doing

so disrupt the reproductive process.

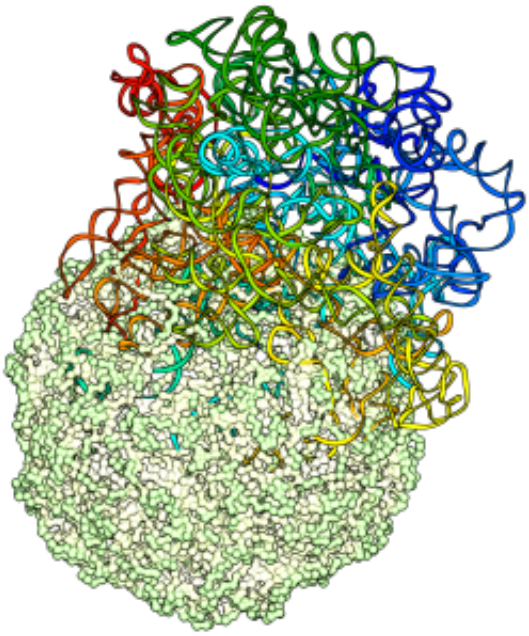
To get into the capsid, the "exoskeleton" of viruses, RNA must be well combed and "packed", because otherwise it won't fit. The packing of RNA is governed by the genome itself. Based on previous research that demonstrated that viral RNA is normally optimized for packing (outside the capsid it is only slightly bigger than the capsid itself), a Italian-Slovenian research team, including Cristian Micheletti of SISSA, verified what types of genome alterations preserve the optimization and which instead render the RNA too bulky. The result? "Even small mutations have a dramatic effect that causes the mass of genetic material to expand", explains Micheletti, "and this prevents the virus from replicating".

"The starting idea is that there are at least two types of developmental drives acting on RNA: one acts on the proteins synthesized by the virus, determining its infectious potential, and the other optimizes its packaging" explains Luca Tubiana, first author together with Anže Lošdorfer Božič, second author of the study, former SISSA student and now postdoc in Rudolf Podgornik's group in Ljubljana. "We asked ourselves to what extent mutations at the level of protein synthesis - which are required by the virus to survive the contrasting action of the host's immune system (and more recently of drugs) - interfered with packaging".

The scientists expected a fairly mild effect but their observations demonstrated the opposite. "Using computer simulations, we produced what might be considered minor mutations, known as 'synonymous' mutations, and so we were expecting them to have a small effect on packaging", explains Tubiana.

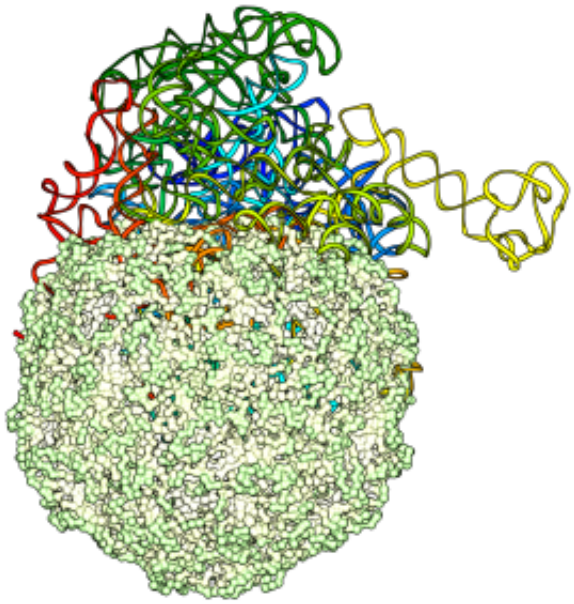
Synonymous mutations change the composition of RNA but not the proteins it synthesizes. These mutations cause changes in a codon, the

sequence inside the gene that chooses which amino acid to insert into the chain that forms the protein, but the amino acid remains the same, since it can be coded by several codons. "Even with mutations having such a limited effect the consequences on packing are dramatic", continues Tubiana. In most cases the RNA mass becomes too bulky and no longer fits into the capsid.



RNA in capsid. Credit: SISSA

The study, which made the cover of the January 6th 2015 issue of *Biophysical Journal*, helps to better understand the mechanisms of viral replication and the conditions under which this is blocked.



RNA in capsid. Credit: SISSA

How does a virus reproduce? "Viruses are strange things, half-living and half-dead", explains Micheletti. "They aren't able to reproduce by themselves, as other pathogens like bacteria, for instance, do. Viruses are basically tiny vessels with a stiff shell that contains a certain amount of genetic material, sometimes DNA, in other cases RNA, as in our recent study". The vessel, continues Micheletti, enter the cells and infects them, it penetrates their nucleus and attaches itself to their DNA forcing the cells to synthesize its own genetic material and the proteins that make up the viral capsid. "In practice, it's as if the virus were some kind of criminal that hijacks a factory's assembly line making the workers mass produce and assemble its own pieces. The cell produces new viruses until it is so full that it explodes, releasing the viruses into the environment where they are ready to infect new cells".

More information: arxiv.org/pdf/1410.7836.pdf