Fine-tuning the spike: Rebuilding glycosylation from structure to function by high performance computing

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The extensive glycosylation of fusion proteins, known as glycan shield, is a trademark feature of enveloped viruses, which use it used to hide from the hosts' immune system, facilitating viral pathogenesis. The SARS-CoV-2 spike (S) protein provides a very particular case within this context. S is heavily shielded, yet, because of its mechanism of action, not as effectively as fusion glycoproteins of "evasion strong" enveloped viruses, dangerously exposing its receptor binding domain (RBD) for binding the main receptor ACE2[1].

Understanding the specific functions of the SARS-CoV-2 S unique glycosylation pattern is tricky because the glycans' intrinsic conformational disorder prevents structural characterisation. In this talk I will focus primarily on how we used high-performance computing (HPC) molecular simulations to advance our knowledge on the role of glycosylation in the SARS-CoV-2 infection [2,3]. I will focus in particular on how we identified the unique functional role of the glycan shield in the activation of the S glycoprotein, and on how specific changes in the nature and topology of the glycan shield affect fusion, fine-tuning the S. Furthermore, I will discuss how changes in the glycan shield topology are intertwined with the S evolution [3,4], and have and are increasing SARS-CoV-2 infectivity along the phylogenetic tree by enhancing viral evasion and S fitness or both.

Bibliographic references:
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