Important validation of 3D models of HIV-1 matrix shells

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Our efforts to improve a model of the HIV-1 virus structure led us to the development of software to validate hypothetical versions of the HIV-1 matrix shell. In this manuscript we reconstruct a full model of the HIV-1 envelop protein and predict its interaction with a previously published matrix shell structure. The evidence generated suggests a role of the HIV-1 matrix shell in viral entry.[b]

In 2021 we developed a software that challenged published structures of the HIV-1 matrix shell [1]. Over the years, numerous papers have appeared in the literature claiming various hexagon-based configurations of the HIV-1 matrix shell depicting their hypothetical structures with connected hexagons or triangles. As a prove of concept, for our validation software, we processed the coordinates of one of the postulated HIV-1 matrix structures published by Kun Qu et al. in the prestigious journal *Science* [2] and showed structural abnormalities that such model contained (Fig 1). We are currently developing an open-source version of this software to aid the structural biology community validate their HIV-1 3D matrix shells prior to publication.

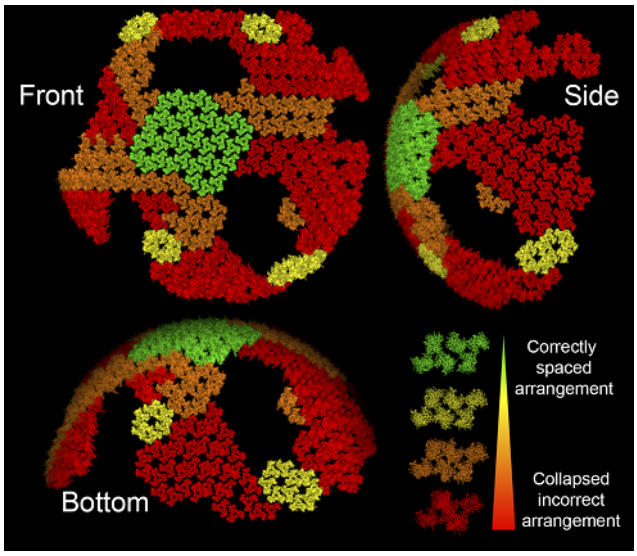

Figure 1: Reconstruction of a published HIV-1 matrix shell. The structure is rotated 90° to the left to show the side view (Side) or 90° upwards to show the bottom view. The color scale legend indicates correct positioning of adjacent HIV-1 matrix trimers in green. The color transition to yellow, orange, and red indicate increasingly more collapsed and thus inadequate matrix trimer positions.

To model a complete matrix shell, we needed an atomically complete model of the envelop (Env) glycoprotein (gp120/41). The structure of the Env complex and has not been fully determined by X-ray crystallography or cryoEM. Thus, we reconstructed the Env glycoprotein using available crystal structures for the external domains of gp120/41 (PDB ID: 4ZMJ), the transmembrane domain (PDB ID: 6E8W), the amphipathic lentiviral lytic peptide domain (PDB ID: 5VWL). The structure of the remaining 40 residues was predicted in silico and the model was fitted in the cryoEM structure (EMDB ID: EMD-1814) using PowerFit.

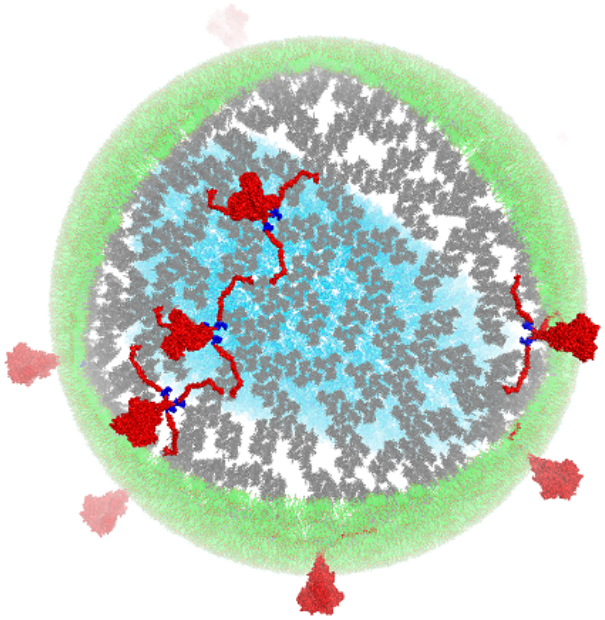

Figure 2: Full reconstruction of the HIV-1 viral particle. In light blue the viral core is shown withing a full HIV-1 matrix shell (grey) without hexagonally arranged structures. The envelop proteins are shown in red, with their KS domain in dark blue. A lipid bilayer is depicted in light green.

With the structure of Env at hand, we were then able to improve our previous model of the HIV-1 shell [3] by including the Env proteins, thus considering the cytoplasmic domain of Env interacting with the matrix shell. Such interaction suggests a role of the matrix shell in facilitating viral entry by guiding the clustering of envelop proteins. By developing a mathematically possible arrangement for the matrix shell and

an atomic resolution HIV-1 Env glycoprotein, we were able to build an updated model of the HIV-1 particle (Fig 2) [1]. Our model highlights the critical interaction between the CT domain of clustered Env glycoproteins and points towards a model in which adjacent Env CT domains could interact to retain the necessary clusters of Env proteins for viral entry.

Notes

a. Email: marcelo@ualberta.ca

b. Original version of this article is Ref. [1]

References

[1] Santos J.R.L., et al., *Viruses* 2021 **13**(8):1515

[2] Kun Qu, et al., *Science* 2021 **373**(6555):700-704

[3] Weijie Sun, et al., *POLS* 2019 **14**(11):e0224965