nature portfolio

Peer Review File



Open Access This file is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to

the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. In the cases where the authors are anonymous, such as is the case for the reports of anonymous peer reviewers, author attribution should be to 'Anonymous Referee' followed by a clear attribution to the source work. The images or other third party material in this file are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <u>http://creativecommons.org/licenses/by/4.0/</u>.

REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

Most of the major issues I raised have now been addressed and I believed the manuscript has now been improved and is almost ready for publication.

The only important issue left is that my comment 3 has been ignored and the old review replaced by a new one that has appeared in the meantime. This is unacceptable -- since the authors want to make a major point about fusion they should really cite the original research in lines 77-83 and in other places throughout the manuscript where they refer to all the spike activities I mentioned rather than just reference a review.

Two more minor comments:

1. line 526 indicates pixel size for a CCD camera with a tenth of picometer precision which seems rather inflated

2. The schematic of the EM data processing (Supp Fig. 1) is lacking some statistical/numerical data processing information: how many micrographs were analysed, how many particles went into each classification etc. etc.

Our response to the reviewer comments are in bold.

Reviewer #1 (Remarks to the Author):

The only important issue left is that my comment 3 has been ignored and the old review replaced by a new one that has appeared in the meantime. This is unacceptable -- since the authors want to make a major point about fusion they should really cite the original research in lines 77-83 and in other places throughout the manuscript where they refer to all the spike activities I mentioned rather than just reference a review.

We have now provided primary references for the SARS-CoV-2 spike activities including furin and TMPRSS cleavage, ACE2-binding and references for the pre-and post-fusion structures (Refs. 6-12) and kept the two reviews we cited in the previous submission; one on CoV fusion in general (Ref. 5) and a comprehensive review on SARS-CoV-2 entry (Ref. 13).

Two more minor comments:

1. line 526 indicates pixel size for a CCD camera with a tenth of picometer precision which seems rather inflated

We have now removed a significant digit and report a 2.06Å pixel size.

2. The schematic of the EM data processing (Supp Fig. 1) is lacking some statistical/numerical data processing information: how many micrographs were analysed, how many particles went into each classification etc. etc.

The revised version of Supplementary Figure 1 now includes a breakdown of the number of particles analyzed and the number of classes analyzed.