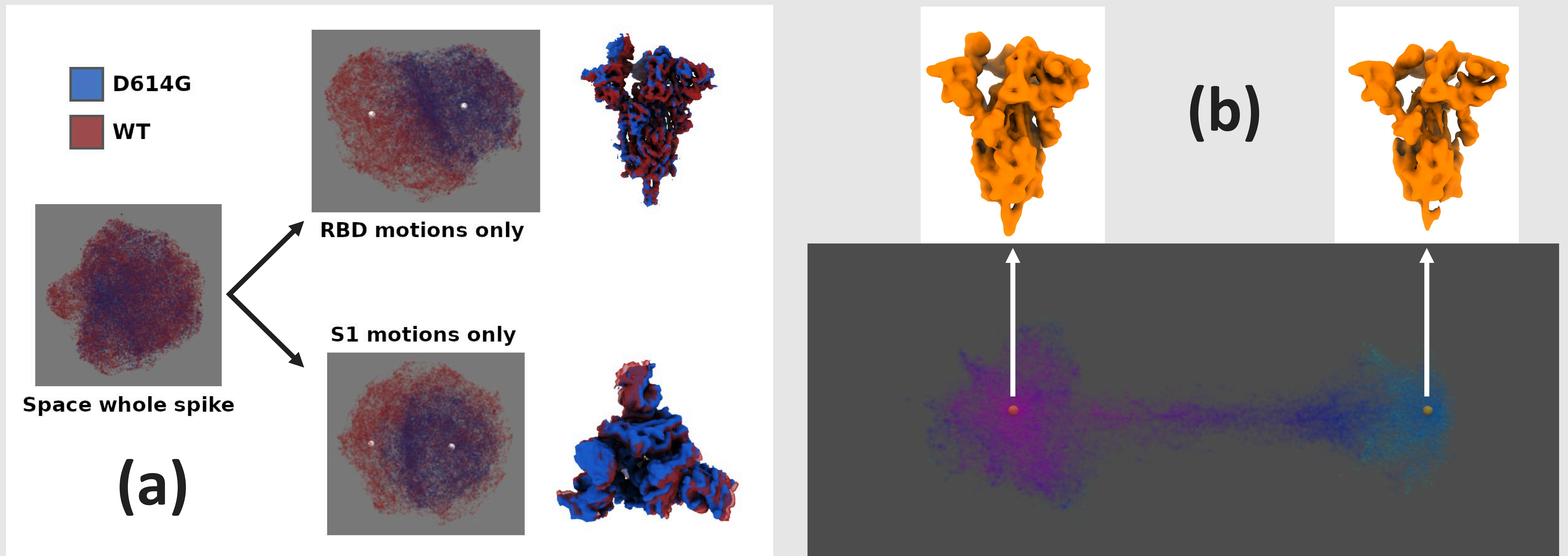


A new tool for the analysis of molecular motions: studying continuous heterogeneity through Zernikes3D

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Introduction

- Continuous flexibility is promoting a paradigm shift in cryoEM. The ability to capture a given macromolecule at different states leads to new and exciting heterogeneity analysis with the potential to uncover structural conformational landscapes from experimental data.
- In this work we present the Zernikes3D, a novel tool to study continuous heterogeneity from maps, structures, and particles

Methods

$$g_L(\vec{r}) = \sum_l \sum_n \sum_m \alpha_{l,n,m} Z(\vec{r})$$

- Coefficients $\alpha_{l,n,m}$ can be masked to focus the deformation field on a region of interest
- Maps, structures, and particles can be translated to a common framework (combined analysis)

Results

(a)

- COVID-19 spike combined analysis (WT + D614G) in 1Up conformation
- The structural effect of the mutation is hidden when the whole spike is considered
- Focused heterogeneity analysis on the RBD shows a clear distinction between the mutations. D614G is more efficient exploring the open state

(b)

- Flexibility analysis for the 1Up and 3Down conformations of the COVID-19 spike
- When classes are clear, the conformational landscape shows a clear distinction of states
- Richer conformational landscapes provide a better understanding of the intraclass and interclass conformational transitions

Conclusions

- Novel approach to extract conformational landscapes from all CryoEM data types (maps, structures, and particles)
- Unique possibilities to perform focused analysis on specific regions of a molecule
- Innovative tools for real time inspection and annotation of conformational spaces
- ZART reconstruction: pushing local resolution of maps by correcting motion blurred artefacts

References

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