Characterizing flexibility and mobility in the natural mutations of the SARS-CoV-2 spikes

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✓Abstract

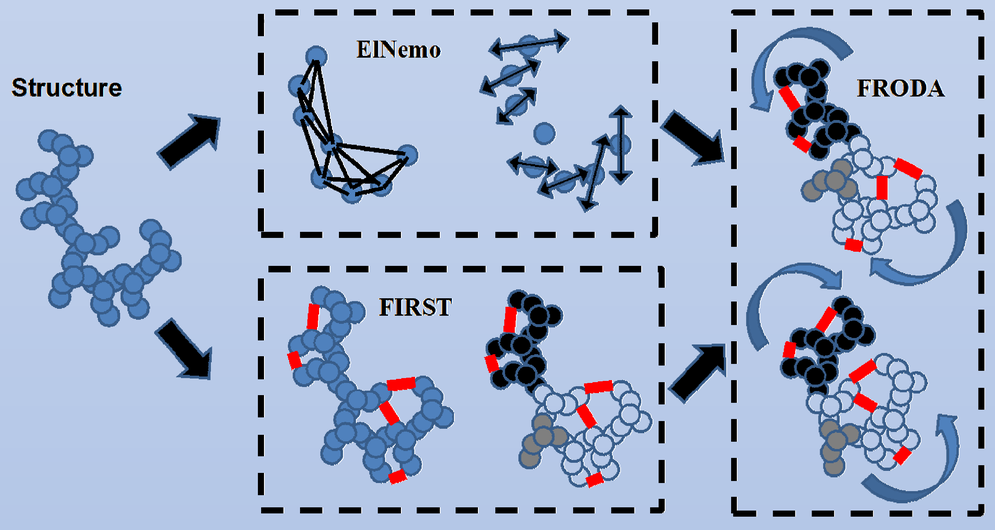
We perform in-silico modelling of the SARS-CoV-2 spike protein and its mutations, using structures from the Protein Data Bank (PDB), to ascertain their dynamics, flexibility and rigidity. Identifying the precise nature of the dynamics for the spike proteins enables, in principle, the use of further in-silico design methods to quickly screen both existing and novel drugs that may hinder these natural dynamics. We use a recent protein flexibility modelling approach, combining methods for deconstructing a protein structure into a network of rigid and flexible units with a method that explores the elastic modes of motion of this network, and a geometric modelling of flexible motion. We also conduct this analysis on synthetic structures of some newer variants (α, β, γ).

✓ Protein selection

- We use PDB structures of wild (6VYB, etc. [1]) and mutated SARS-CoV-2 spike proteins (7LWI, ..., 7YLP [2]) as deposited in the PDB.
- This trans-membrane spike glycoprotein mediates entry into host cells.
- It is a "main target for neutralizing antibodies upon infection and the focus of therapeutic and vaccine design".
- It forms homotrimers protruding from the viral surface.
- Observed in closed and open states.

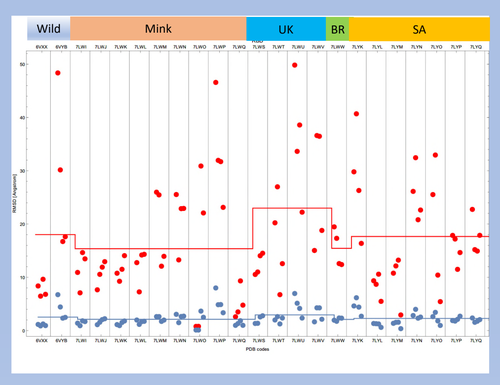
✓Flexibility modelling

- Use coarse-grained molecular dynamics which is sped up by prior calculation of rigid and flexible sub-units in given protein chain.
- See [3] for details.

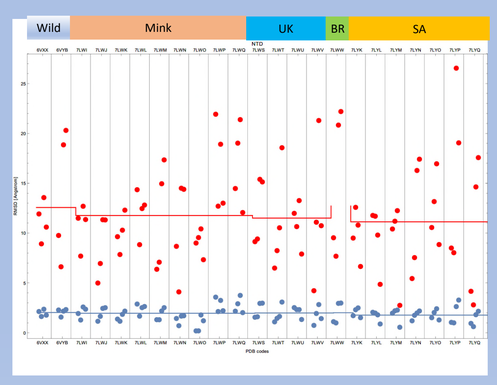


✓ Summary of flexibility/mobility results

Receptor binding domain



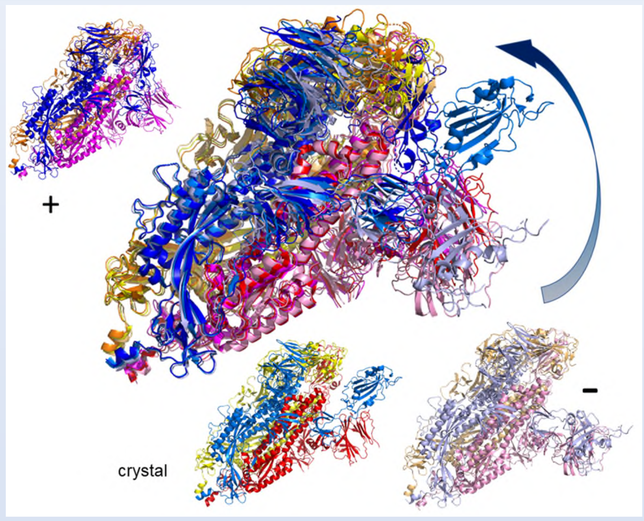
N terminal domain



✓References:

[1] Walls, A. C., Park, Y.-J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell, 181(2), 281-292.e6. https://doi.org/10.1016/j.cell.2020.02.058
[2] Gobeil, S. M.-C., Janowska, K., Mcdowell, S., Mansouri, K., Parks, R., Stalls, V., Kopp, M. F., Manne, K., Saunders, K., Edwards, R. J., Haynes, B. F., Henderson, R. C., & Acharya, P. (2021). Effect of natural mutations of SARS-CoV-2 on spike structure, conformation and antigenicity. BioRxiv, 2021.03.11.435037. https://doi.org/10.1101/2021.03.11.435037
[3] Römer, R. A., Römer, N. S., & Wallis, A. K. (2021). Flexibility and mobility of SARS-CoV-2-related protein structures. Scientific Reports, 11, 4257. https://doi.org/10.1101/2020.07.12.199364
[4] Panayis, J., Roemer, N. S., Bellini, D., Wallis, K., & Roemer, R. A. (2021). Characterizing flexibility and mobility in the natural mutations of the SARS-CoV-2 spikes. BioRxiv, 2021.09.14.460264. https://doi.org/10.1101/2021.09.14.460264

✓ Results for wild-type SARS-CoV-2 spike protein (6VYB)



Large flexibility in RBD:

- Clear hinge movement of the RBD domain in the open configuration (6VYB)
- RBD domain moving between open and closed configuration (6VXX) .
- range of movement measured to be quite large (~60A)
- flexibility within the RBD domain itself during the hinge movement also considerable.
- findings suggest that RBD domain has necessary flexibility to attach to human ACE2
- to our knowledge, the first time the hinge motion of the RBD domain has been predicted solely based on the dynamics of structure.
- See [3]

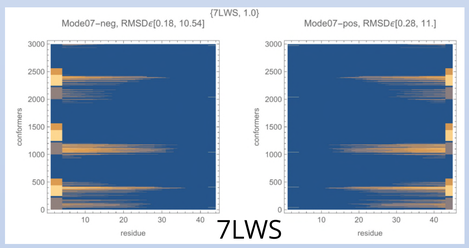
✓ Results for mutations of SARS-CoV-2 spike protein

✓ α-variant (UK detection)

7LWS 7LWT 7LWU 7LWV

Summary of whole spike flexibility:

- Overall, most movement on **top of spike**
- **Closing and opening** movements of RBD regularly *go together* with NTD moves
- QR code visualization via [5]

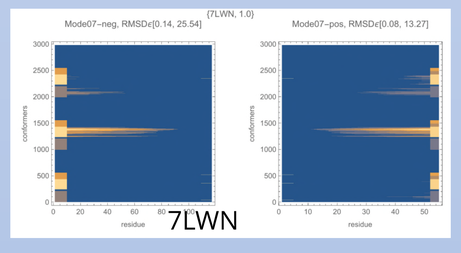


✓ β-variant (SA detection)

7LWL 7LWN 7LWM 7LWO 7LWP 7LWQ

Summary of whole spike flexibility:

- **Closing and opening** movements of RBD regularly *go together* with NTD moves
- Somewhat less movement of NTD

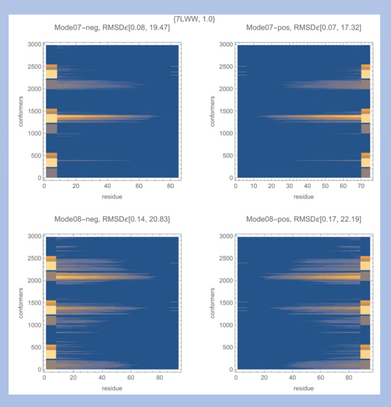


✓ γ-variant (BR detection)

7LWW

Summary of whole spike flexibility:

- **Closing and opening** movements of RBD regularly *go together* with NTD moves
- Higher modes (here 8) show similar levels of flexibility



✓Conclusions

- differences in flexibility/mobility between wild-type structures and mutated structures exist
  - these are of similar magnitude as variations between identical mutations
  - no easy discernible overall trend
- quick method to determine conformational movements as long as structure is know (and given in .pdb file)
- happy to discuss any possible follow-ups along these lines ...
- combination with MD possible (as likely next step ...)

[5] AniMol Web Viewer, https://animol.warwick.ac.uk, @AniMolWebApp