Analysing UK SARS-CoV-2 spike protein mutations via t-SNE paired with K-means clustering

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Context & Aims

COVID-19 pandemic:

- 770,000,000 infections[1]
- Estimated death toll: 18,000,000 – 32,000,000[2]

Spike glycoprotein:

- Receptor binding motif (RBM) residues bind directly to ACE2[3]
- Receptor binding domain (RBD), two regions S1 & S2[4]

Infectivity:

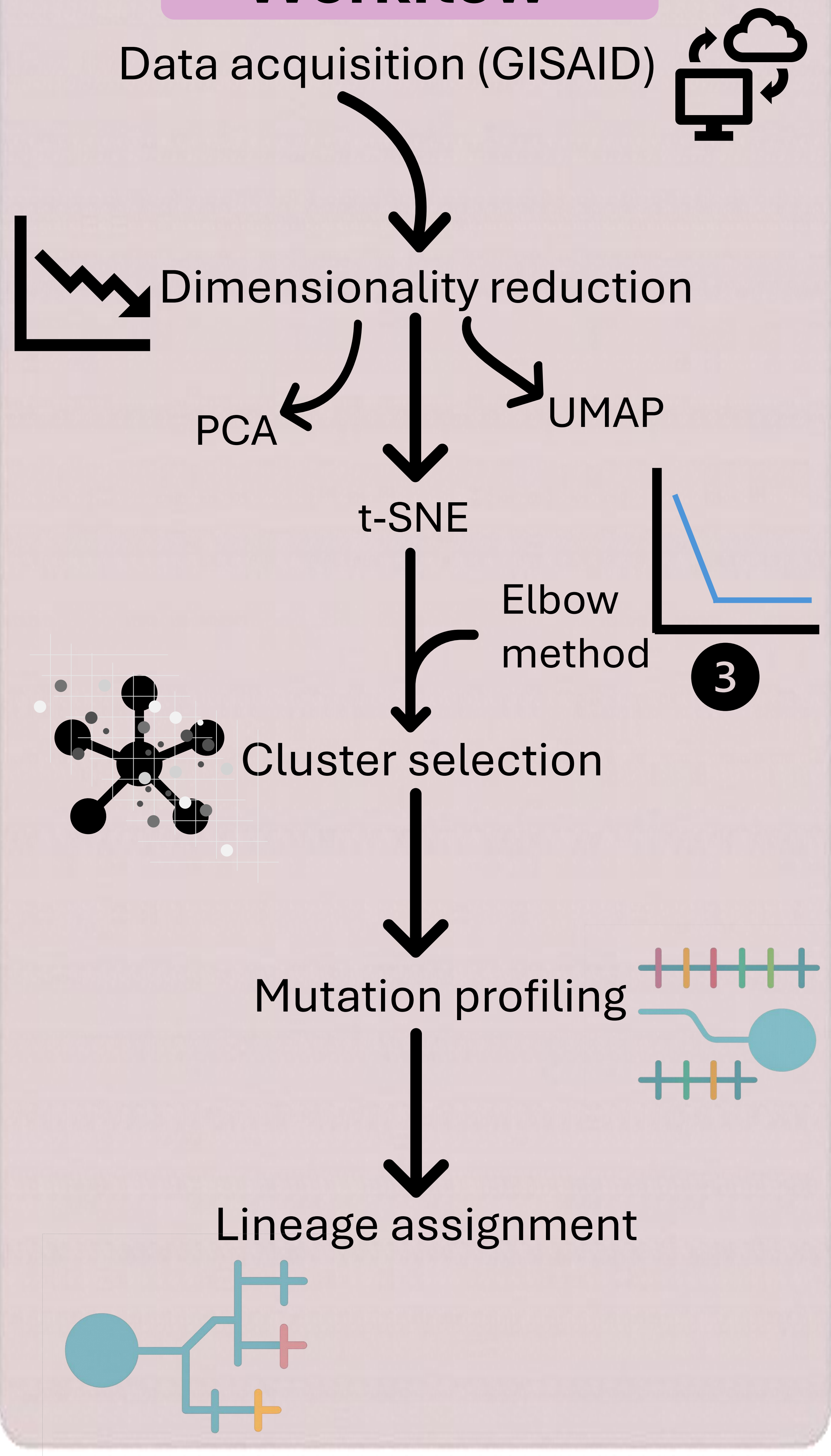
- RBD/RBM mutations modulate infectivity[5]
- Examples: N501Y & D614G enhance affinity and stability changes[6]
- How many key mutations occur in these regions may infer infectivity?

Aims:

Gaps remain in our understanding of SARS-CoV-2 clustering patterns in the UK and extracting meaningful information from large-scale datasets

1. **Divulge temporal and general trends**
2. **Identify which dimensionality reduction technique best pairs with K-means clustering regarding efficiency and cluster clarity**
3. **Reveal dominant clusters and explore their infectivity & potential lineage from their centroids**

Workflow



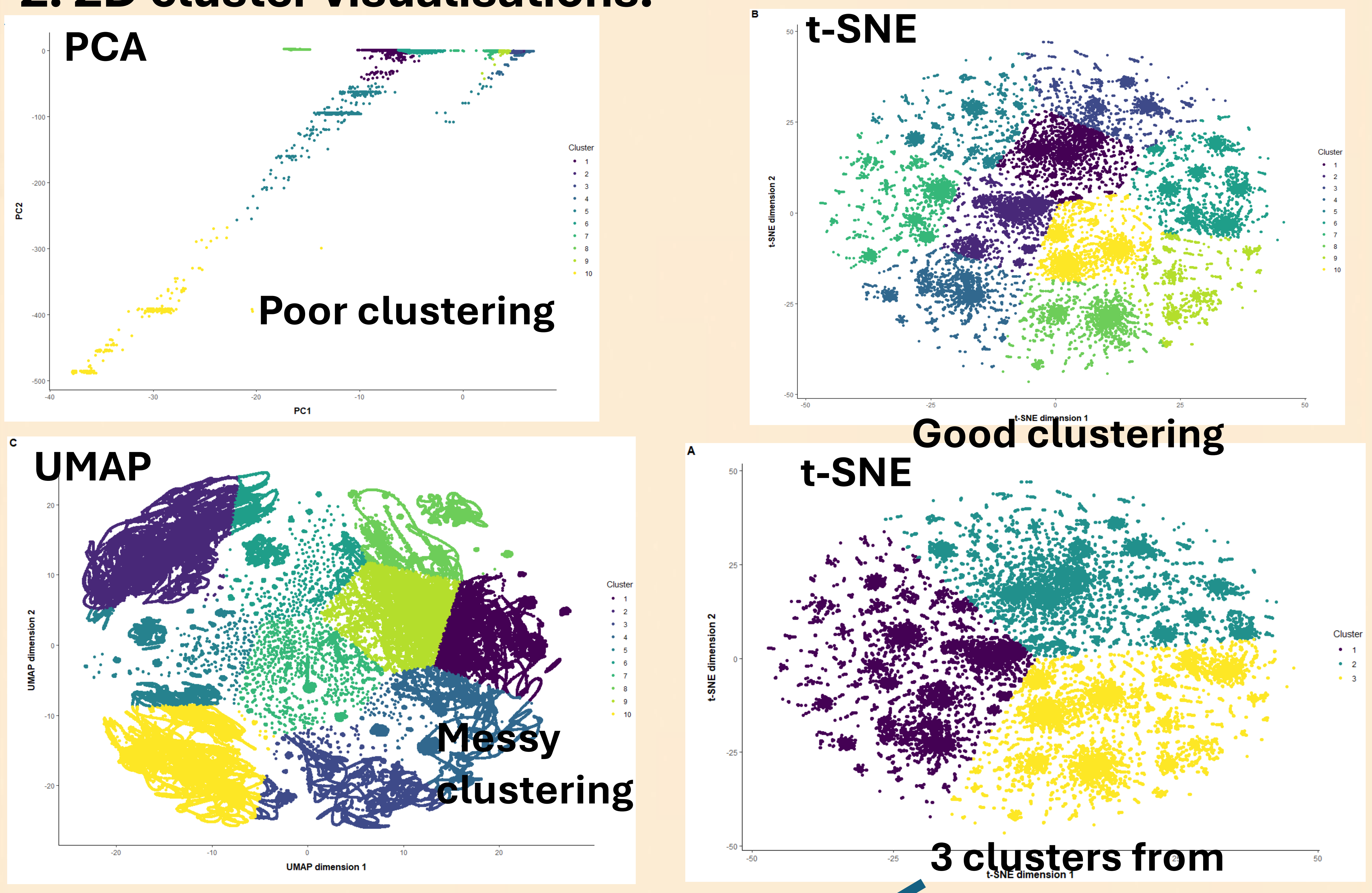
Key results

Over 6 hours

1. Efficiency comparison:

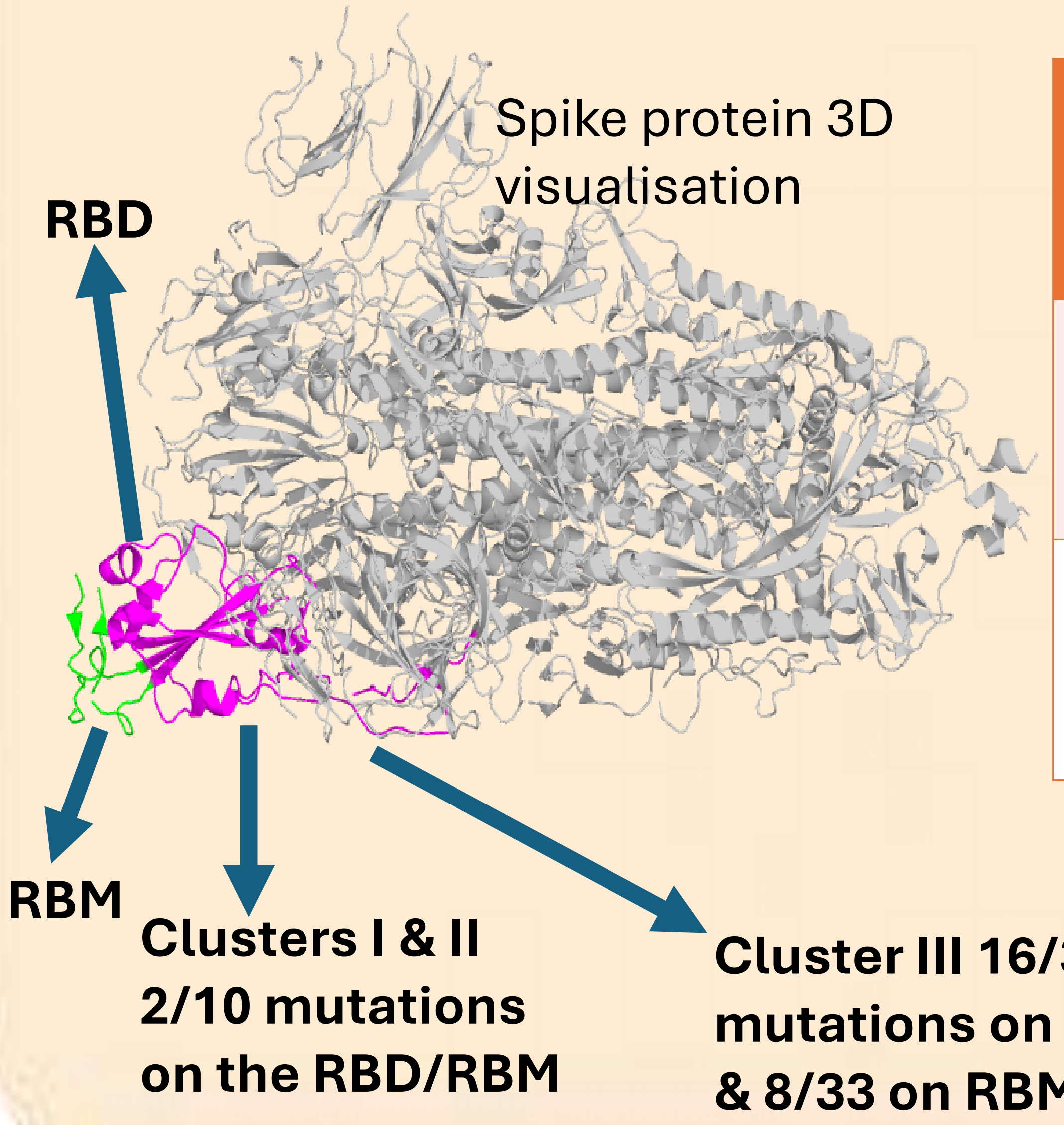
Techniques	Reduction time	Clustering time (seconds)	Efficiency increase compared to K-means alone
Principal Component Analysis (PCA)	1 hour 28 minutes	69.98	x4
t-distributed stochastic neighbour embedding (t-SNE)	**4 minutes**	**3.60**	**X1000**
Uniform Manifold Approximation and Projection (UMAP)	37 minutes	36	X9

2. 2D cluster visualisations:



3 clusters from elbow method

3. Mutation profiling & lineages:



Spike protein 3D visualisation
RBD
RBM
Clusters I & II 2/10 mutations on the RBD/RBM
Cluster III 16/33 mutations on RBD & 8/33 on RBM

Cluster	Key mutations	Infectivity	Lineage
I & II	L452R, P681R	Moderate	Delta
III	N501Y, D614G, E484A	High	Omicron

4. Temporal & General trends:

- 15,213 unique mutations
- Sequences accumulated mutations over time, 3 (2020) to 65 (2024) → Muller's ratchet[7]
- Strong positive correlation, $\rho=0.895$, $p \ll 0.001$

Conclusions and future work

- **t-SNE paired with K-means most efficient & most clear cluster visualisation**
- **3 major cluster groups, I & II likely share a common ancestor**
- **Cluster III highest proportion of RBD/RBM mutations, potentially the most infectious**
- **Cluster & mutation profiling can guide future vaccine development**
- **t-SNE assisted K-means clustering has the potential method to deal with large-scale SARS-CoV-2 datasets**

Acknowledgements & References

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(2) COVID-19 cases [Internet]. datadot. [cited 2025 Feb 21]. Available from: https://data.who.int/dashboards/covid19/cases?n=c

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(4) McCallum M, Walls AC, Bowen JE, Corti D, Veesler D. Structure-guided covalent stabilization of coronavirus spike glycoprotein trimers in the closed conformation. Nat Struct Mol Biol [Internet]. 2020 Oct 4 [cited 2025 Feb 23];27(10):942–9. Available from: https://www.nature.com/articles/s41594-020-0483-8?fromPaywallRec=false

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