Molecular Insight into the Interaction between the Spike Protein of the Wildtype, Delta and Omicron SARS-CoV-2 and the Human Angiotensin Converting Enzyme 2 (hACE2): Potential for the Design of Fusion Inhibitors

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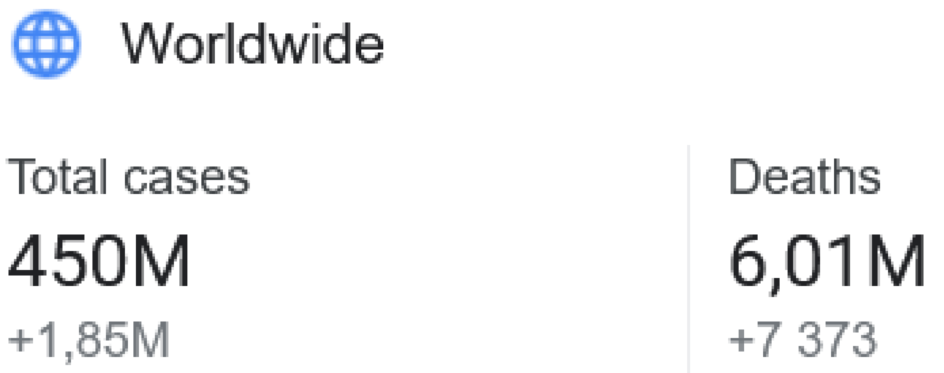
COVID-19 Global Statistics

Covid-19 is the infectious disease caused by the most recently discovered coronavirus (SARS-CoV-2).

Worldwide

Total cases 21 819 827
(23 February – 8 March)

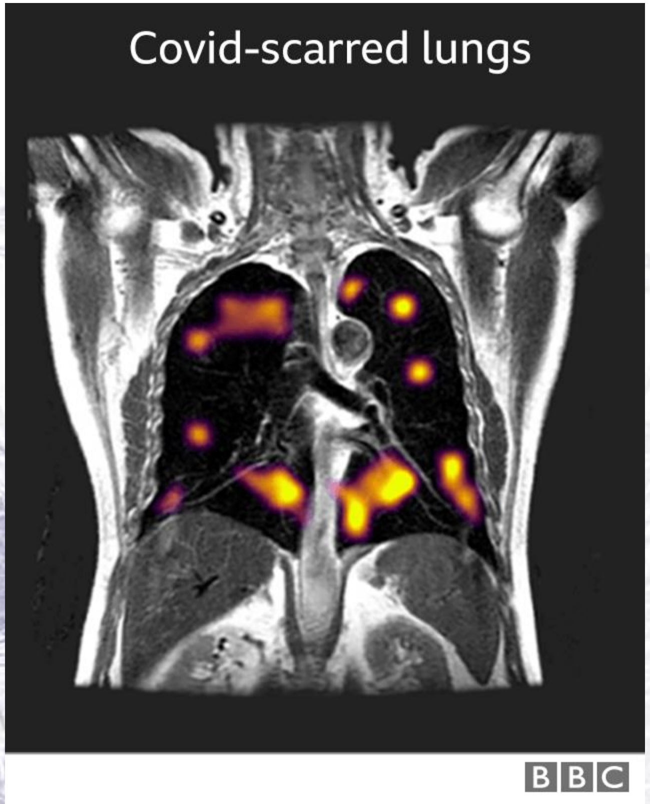


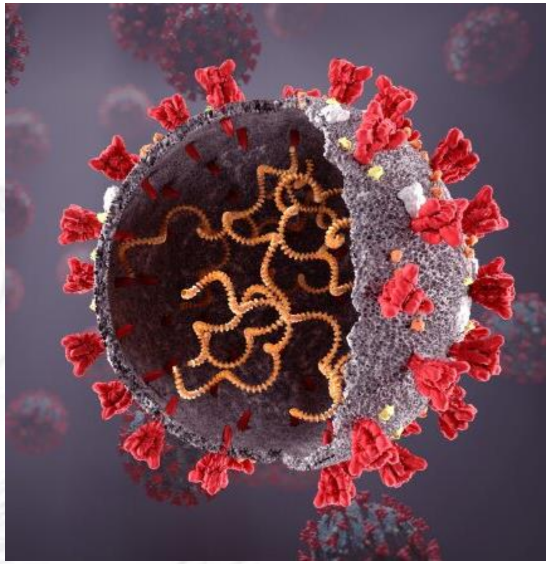
Worldwide

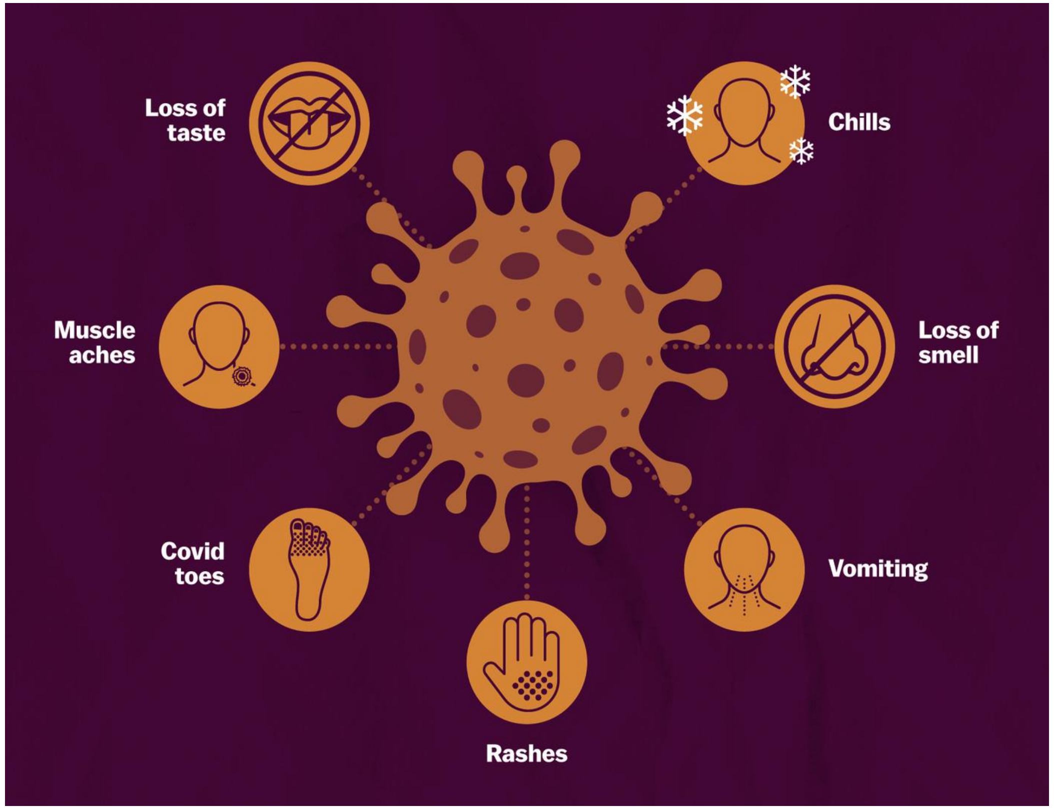
Total cases	Deaths
450M	6,01M
+1,85M	+7 373

SARS-CoV2 and COVID-19

- Signs and Symptoms



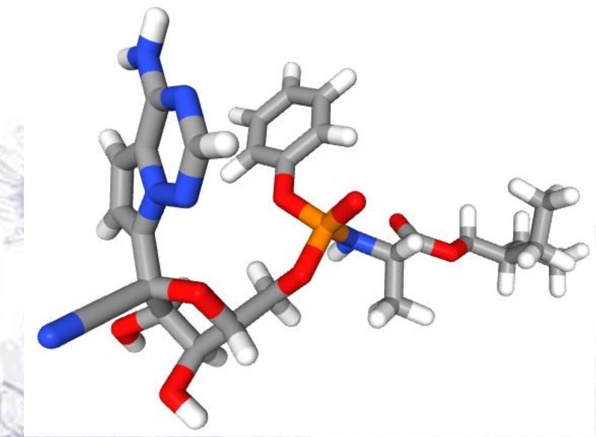




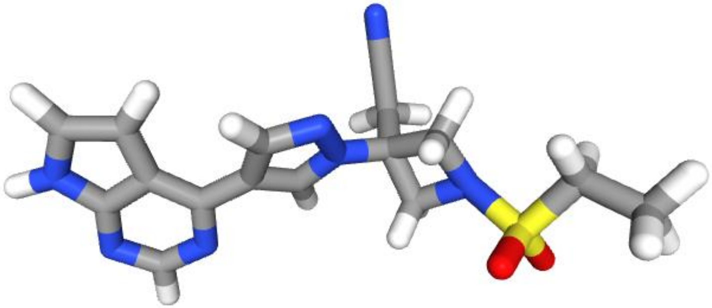
(https://sacoronavirus.co.za/2021/09/12/update-on-covid-19-sunday-12-september/).

Vaccines and Drugs for Covid-19

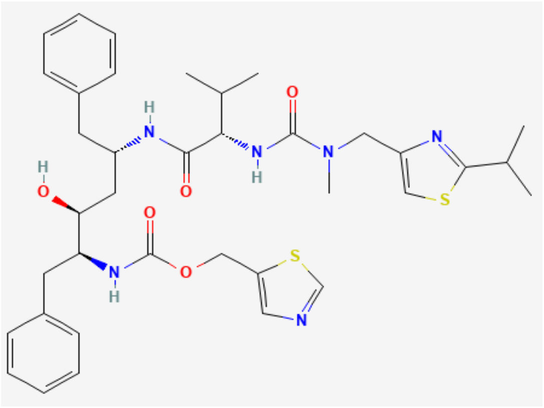
There is a global effort from academic and non-academic groups to evaluate and develop an effective treatment for COVID-19.



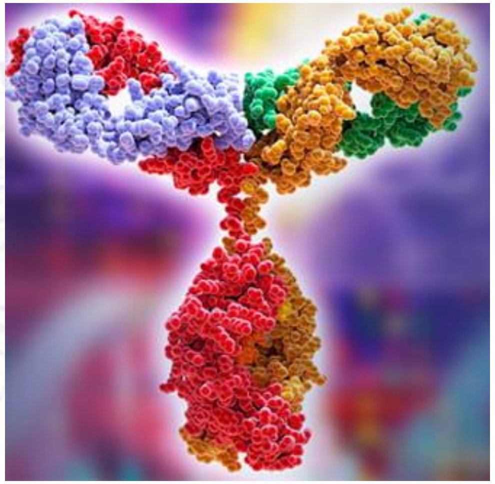
Remdesivir (an antiviral nucleotide analogue)



Baricitinib (Interleukin-6 receptor blockers)



PAXLOVID™ (PF-07321332; ritonavir)



Bebtelovimab works by binding to the spike protein

[Johnson & Johnson vaccine](#)
[Oxford, AstraZeneca vaccine](#)
[Sinopharm BBIBP vaccine](#)

[BioNTech, Pfizer vaccine](#)
[CoronaVac vaccine](#)

Our Humble Contribution

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PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

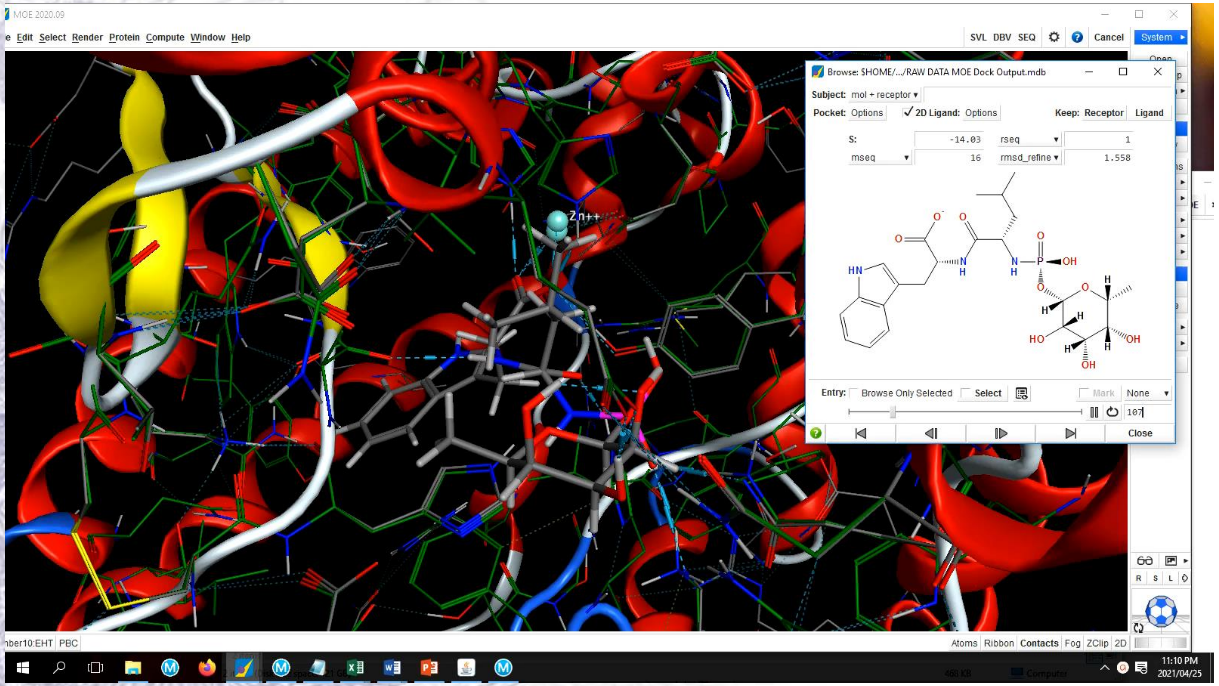
Computational drug repurposing strategy predicted peptide-based drugs that can potentially inhibit the interaction of SARS-CoV-2 spike protein with its target (humanACE2)

Samuel Egieyeh ✉, Elizabeth Egieyeh co, Sarel Malan ✱, Alan Christofells co, Burtram Fielding ✱

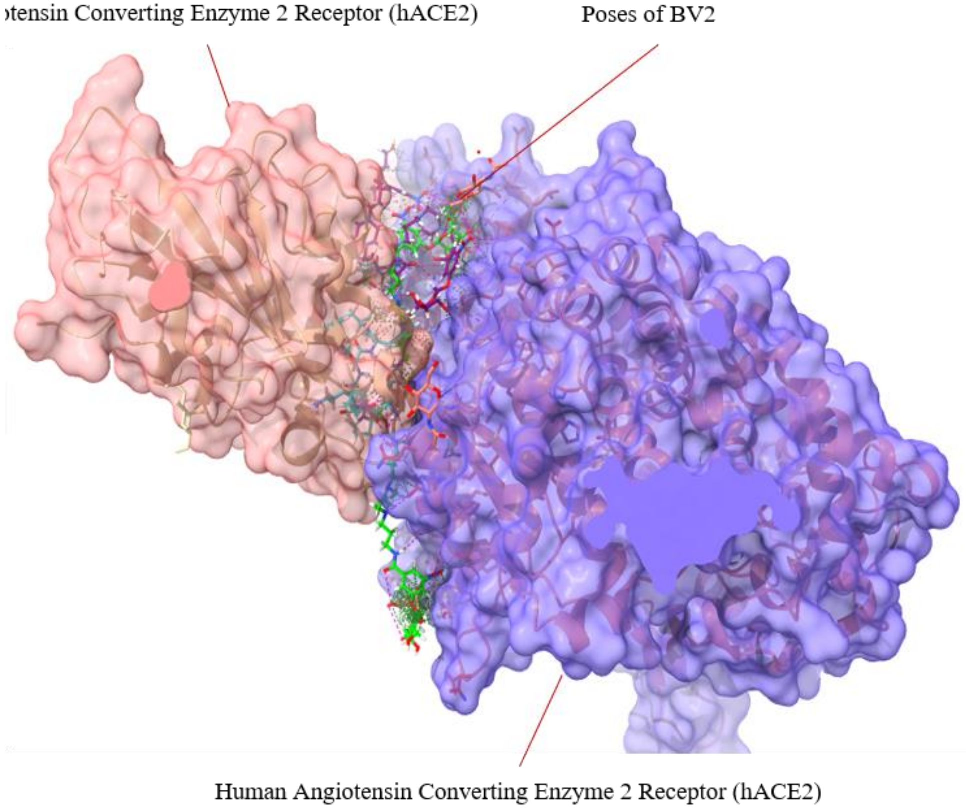
Egieyeh S, Egieyeh E, Malan S, Christofells A, Fielding B (2021) Computational drug repurposing strategy predicted peptide-based drugs that can potentially inhibit the interaction of SARS-CoV-2 spike protein with its target (humanACE2). PLoS ONE 16(1): e0245258. https://doi.org/10.1371/journal.pone.0245258

Computational Drug Repurposing Strategy

- There is a global effort from academic and non-academic groups to evaluate and develop an effective treatment for COVID-19.

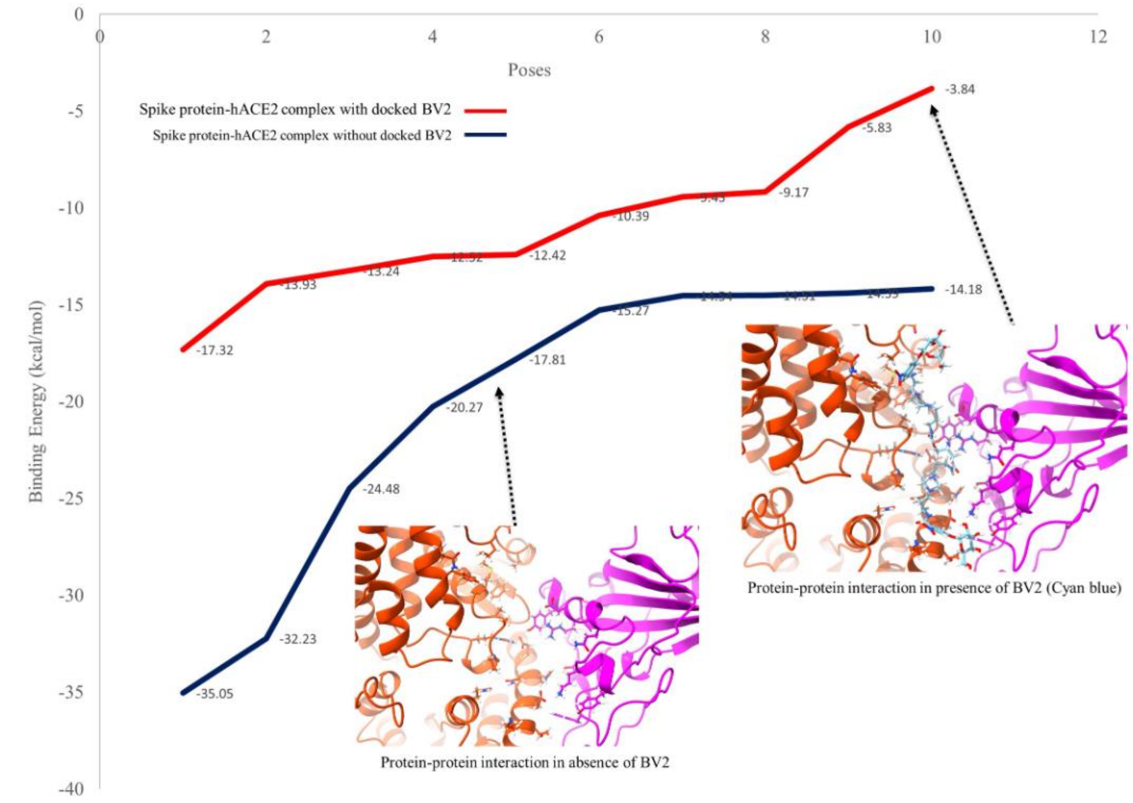


S: -14.03 rseq 1
mseq 16 rmsd_refine 1.558



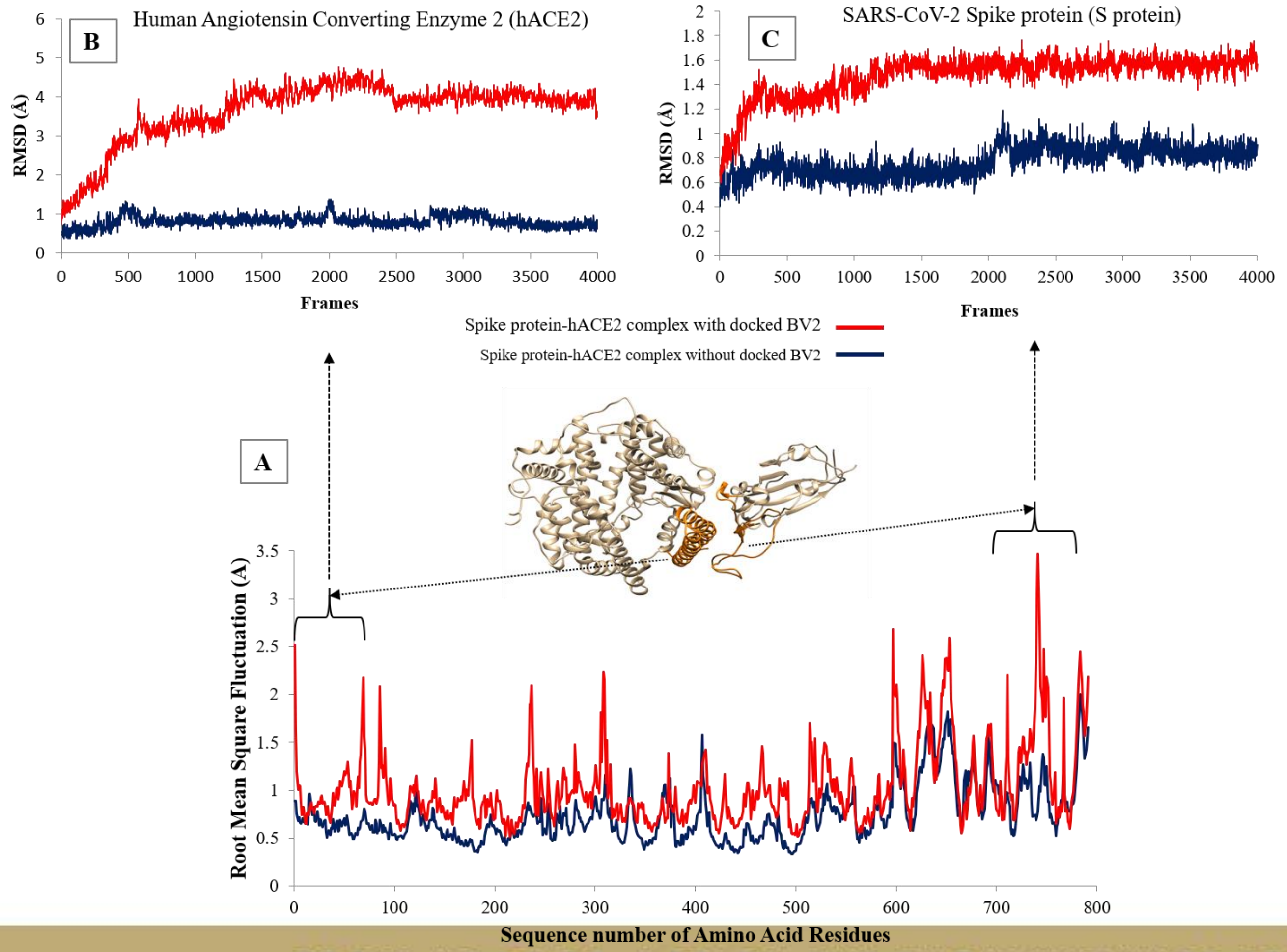
Egieyeh S, Egieyeh E, Malan S, Christofells A, Fielding B (2021) Computational drug repurposing strategy predicted peptide-based drugs that can potentially inhibit the interaction of SARS-CoV-2 spike protein with its target (humanACE2). PLoS ONE 16(1): e0245258. https://doi.org/10.1371/journal.pone.0245258

Computational Drug Repurposing Strategy



Protein-protein interaction in presence of BV2 (Cyan blue)

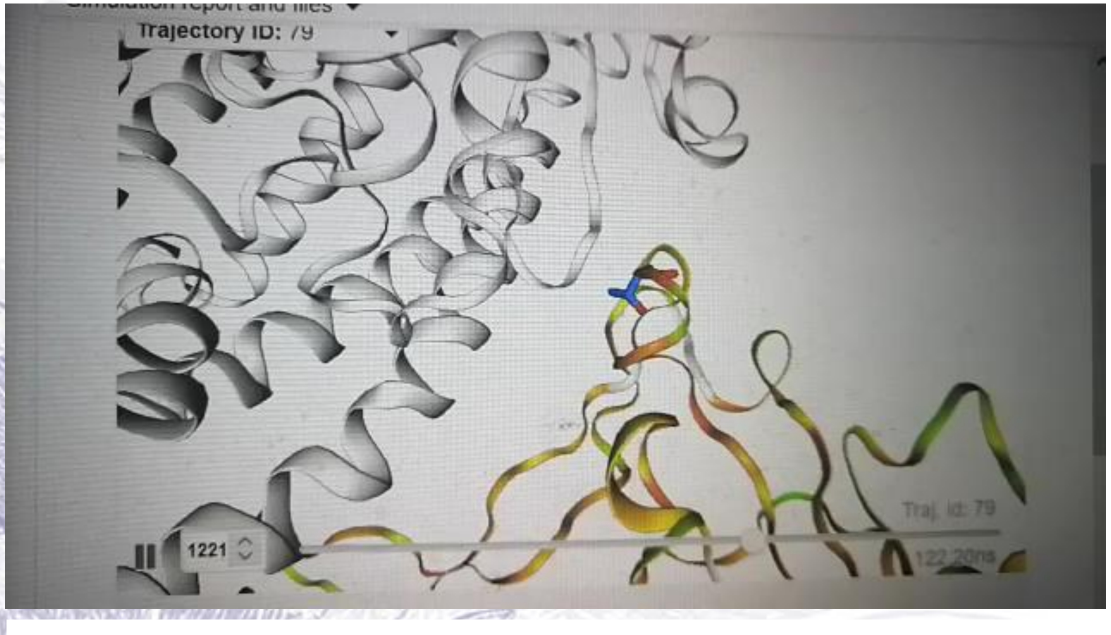
Protein-protein interaction in absence of BV2



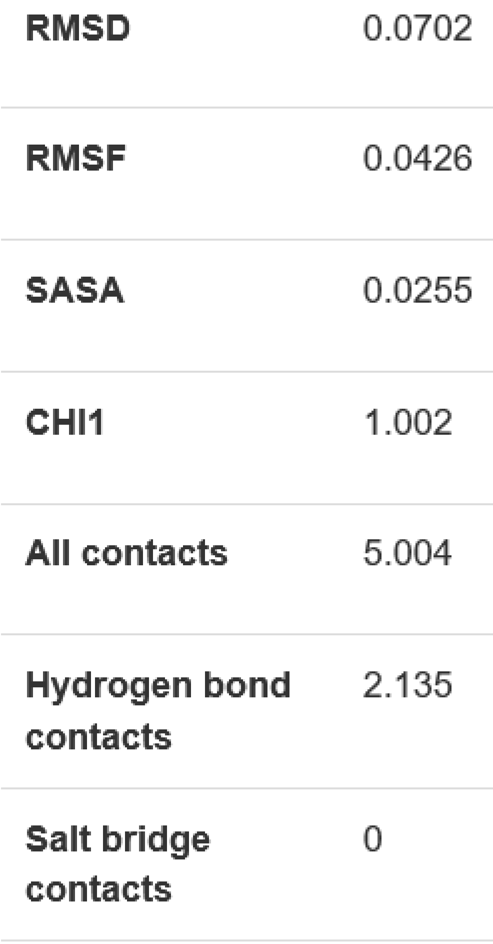
Accounting for mutations

SCoV2-MD: a database for the dynamics of the SARS-CoV-2 proteome and variant impact predictions

SCoV2-MD

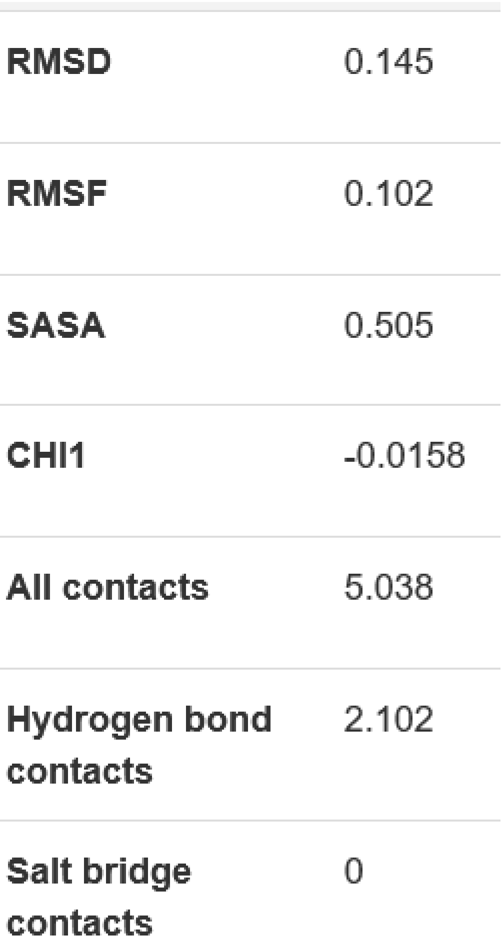


The mutations in S protein could have profound impacts on diagnostic detection, antiviral immunity, and virus infectivity



RMSD	0.0702
RMSF	0.0426
SASA	0.0255
CHI1	1.002
All contacts	5.004
Hydrogen bond contacts	2.135
Salt bridge contacts	0

N501Y



RMSD	0.145
RMSF	0.102
SASA	0.505
CHI1	-0.0158
All contacts	5.038
Hydrogen bond contacts	2.102
Salt bridge contacts	0

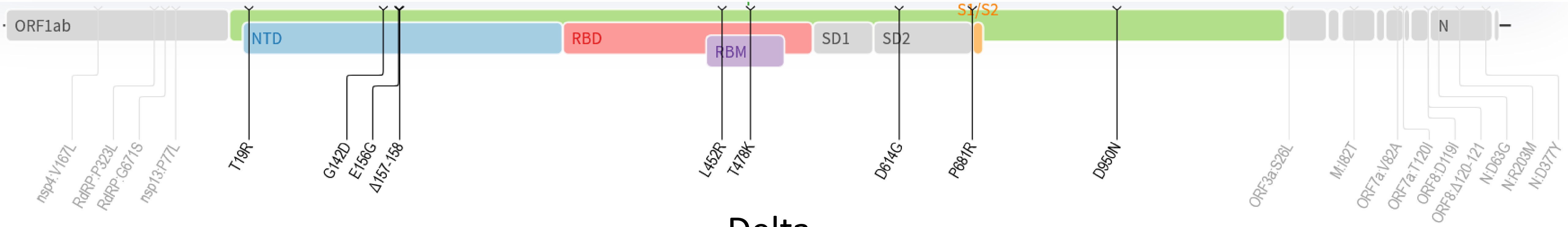
K417N

https://www.nature.com/articles/s41418-021-00846-4.pdf

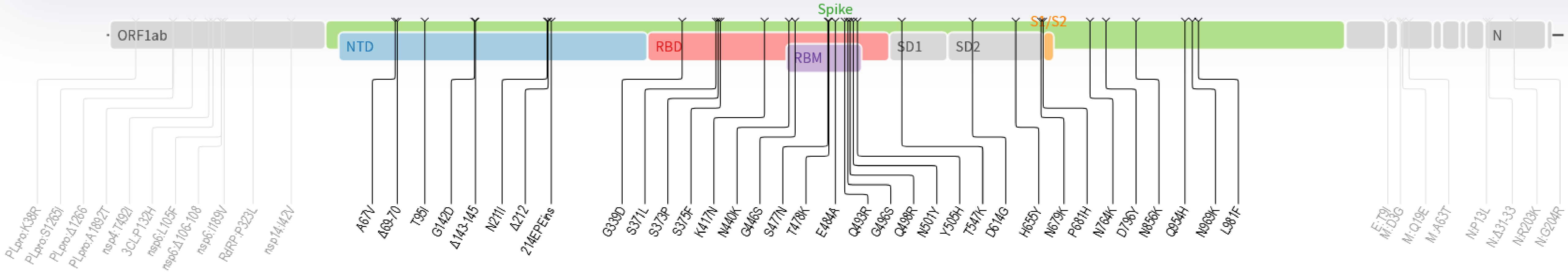
Objectives

- Predict effect of mutations on dynamics of the interaction of the receptor binding motif of the spike protein with its host receptor (hACE2)
- Characterize the wildtype and variant forms of the receptor binding motif of the Spike protein
- Generate pharmacophore model for the wildtype and variant forms of the receptor binding motif of the Spike protein
- Use the pharmacophore model to screen a natural product database

Mutations in Delta and Omicron variants



Delta

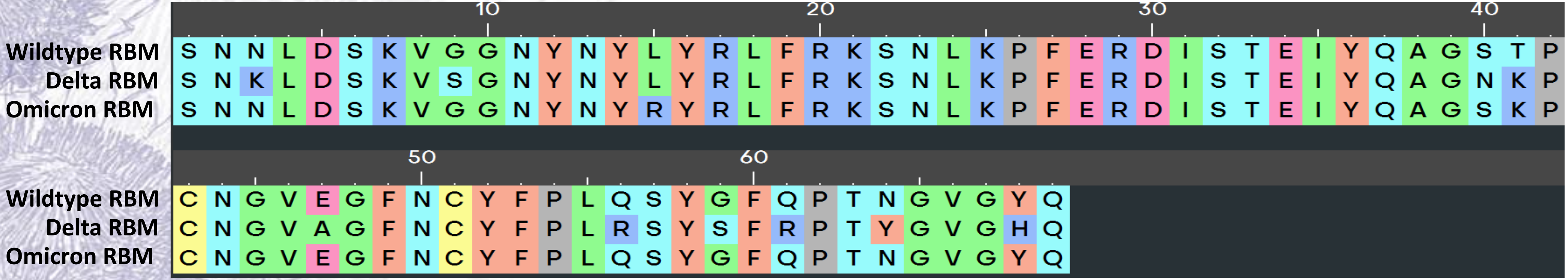


Omicron

https://covdb.stanford.edu/page/mutation-viewer

Modelling and superimposition of receptor binding motif of wildtype, Delta and Omicron variants of SARS CoV-2 spike protein

	Wildtype RBM	Delta RBM	Omicron RBM
Wildtype RBM	0	0.09	0.16
Delta RBM	0.09	0	0.21
Omicron RBM	0.16	0.21	0



										10										20										30										40		
Wildtype RBM	S	N	N	L	D	S	K	V	G	G	N	Y	N	Y	L	Y	R	L	F	R	K	S	N	L	K	P	F	E	R	D	I	S	T	E	I	Y	Q	A	G	S	T	P
Delta RBM	S	N	K	L	D	S	K	V	S	G	N	Y	N	Y	L	Y	R	L	F	R	K	S	N	L	K	P	F	E	R	D	I	S	T	E	I	Y	Q	A	G	N	K	P
Omicron RBM	S	N	N	L	D	S	K	V	G	G	N	Y	N	Y	R	Y	R	L	F	R	K	S	N	L	K	P	F	E	R	D	I	S	T	E	I	Y	Q	A	G	S	K	P

								50										60									
Wildtype RBM	C	N	G	V	E	G	F	N	C	Y	F	P	L	Q	S	Y	G	F	Q	P	T	N	G	V	G	Y	Q
Delta RBM	C	N	G	V	A	G	F	N	C	Y	F	P	L	R	S	Y	S	F	R	P	T	Y	G	V	G	H	Q
Omicron RBM	C	N	G	V	E	G	F	N	C	Y	F	P	L	Q	S	Y	G	F	Q	P	T	N	G	V	G	Y	Q

Dynamics of the interaction

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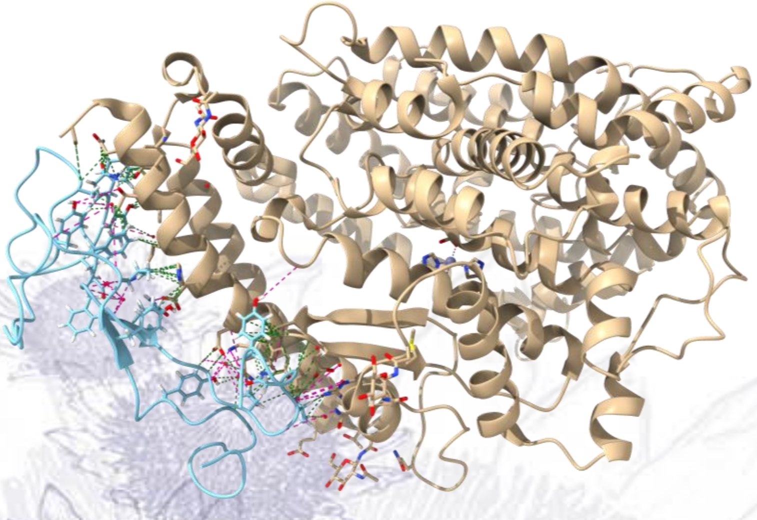
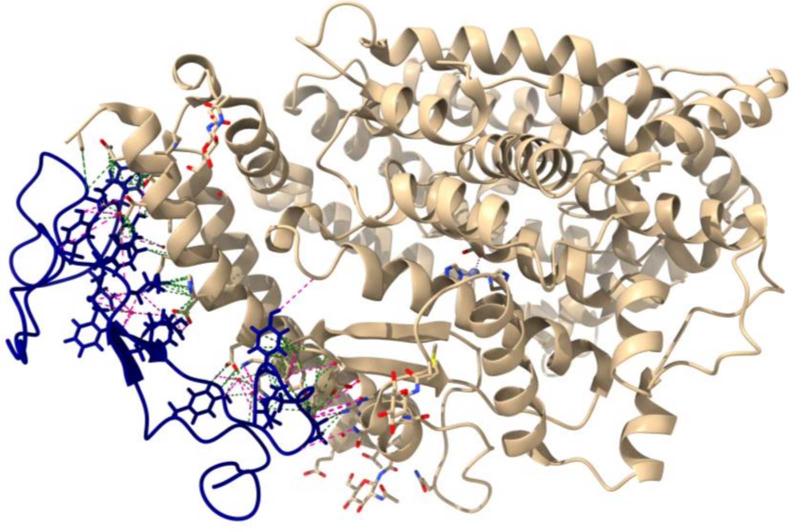
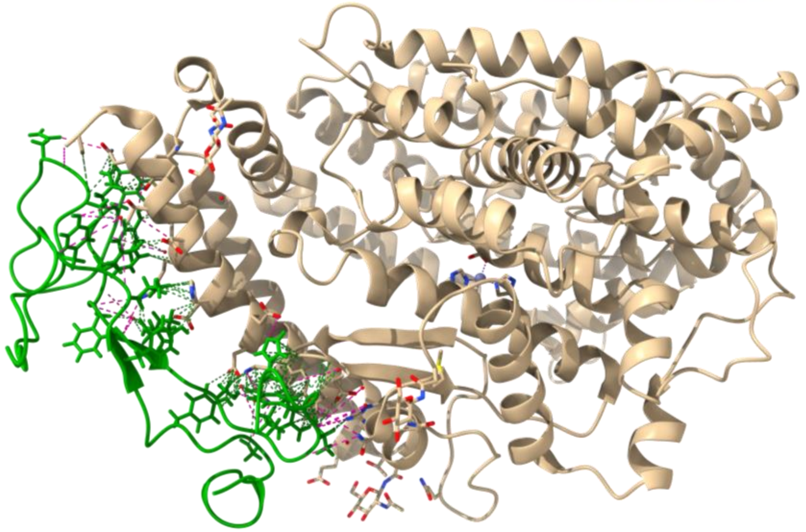
Residue Interaction with ChimeraX 1.2.4



Wildtype RBM: 35 Hbond, 118 VDW



Delta RBM 41 Hbond, 119 VDW

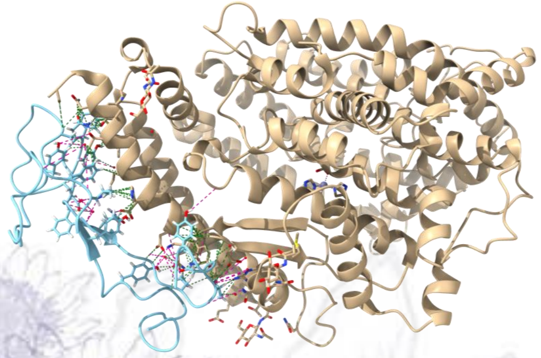


Omicron RBM 36 Hbond, 192 VDW

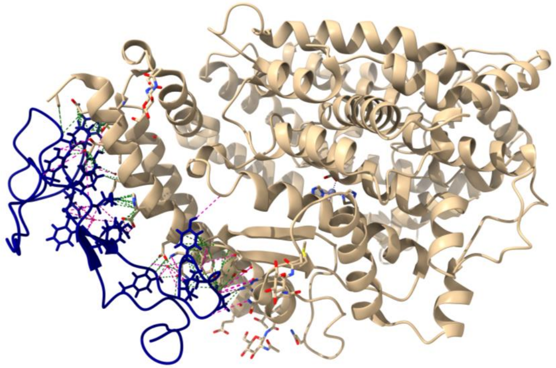
Protein-protein complex	ΔG (kcal mol^{-1})
wildtypeRBD-hACE2	-12.6
deltaRBD-hACE2	-12.7
OmnicronRBD-hACE2	-11.8

Prediction of protein-protein binding affinity implemented in PRODIGY (PROtein binDIng enerGY prediction) web server

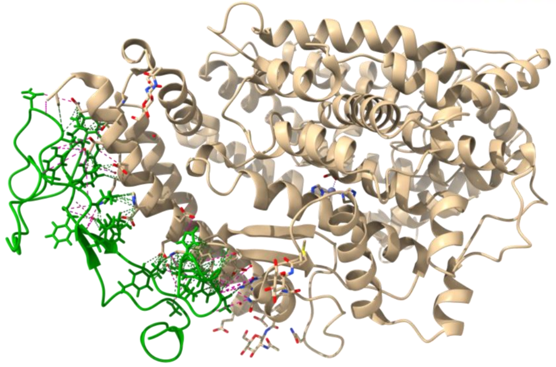
Dynamics of the interaction



Wildtype RBM: 35 Hbond, 118 VDW



Delta RBM 41 Hbond, 119 VDW



Omicron RBM 36 Hbond, 192 VDW

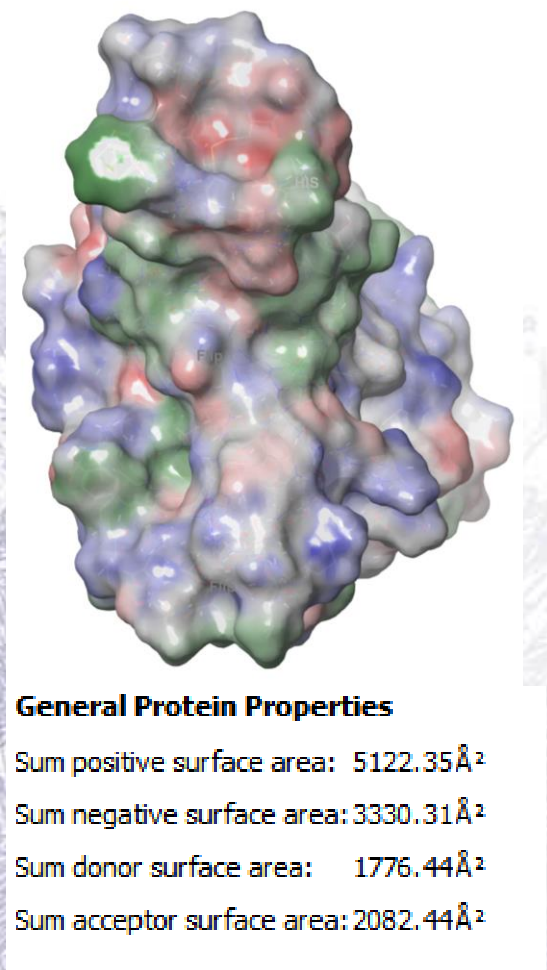
Number of Interfacial Contacts (ICs) per property:
ICs charged-charged: 3
ICs charged-polar: 10
ICs charged-apolar: 19
ICs polar-polar: 5
ICs polar-apolar: 24
ICs apolar-apolar: 10
Non Interacting Surface (NIS) per property:
NIS charged: 25.52%
NIS apolar: 34.55%

Number of Interfacial Contacts (ICs) per property:
ICs charged-charged: 3
ICs charged-polar: 10
ICs charged-apolar: 20
ICs polar-polar: 5
ICs polar-apolar: 24
ICs apolar-apolar: 11
Non Interacting Surface (NIS) per property:
NIS charged: 25.91%
NIS apolar: 34.43%

Prediction details
Number of Interfacial Contacts (ICs) per property:
ICs charged-charged: 7
ICs charged-polar: 7
ICs charged-apolar: 19
ICs polar-polar: 6
ICs polar-apolar: 20
ICs apolar-apolar: 10
Non Interacting Surface (NIS) per property:
NIS charged: 25.96%
NIS apolar: 34.84%

Patch surface analysis

Implemented in Maestro (Schrodinger)



General Protein Properties

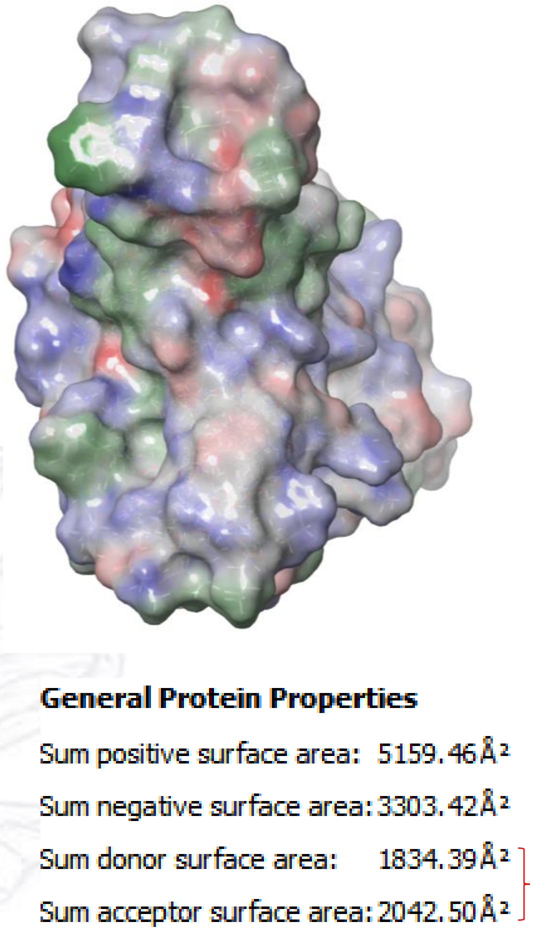
Sum positive surface area: 5122.35Å²

Sum negative surface area: 3330.31Å²

Sum donor surface area: 1776.44Å²

Sum acceptor surface area: 2082.44Å²

Wildtype RBM



General Protein Properties

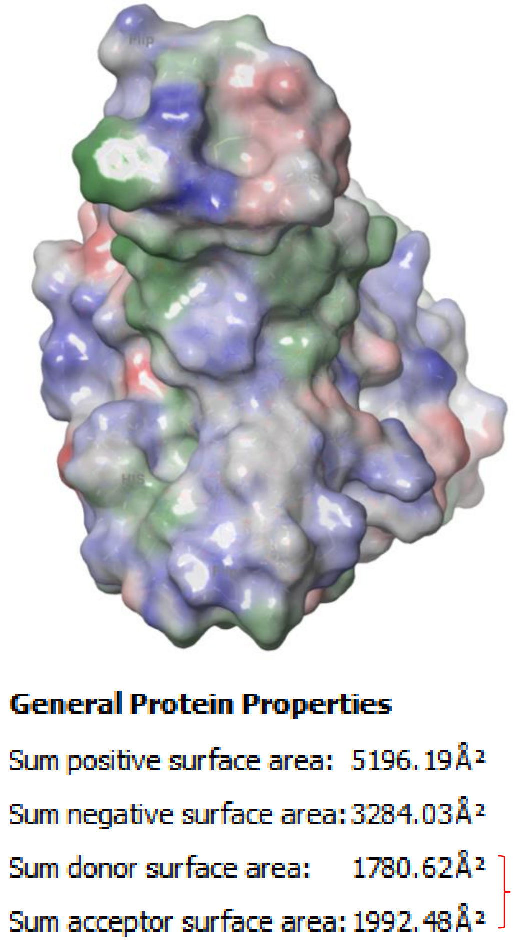
Sum positive surface area: 5159.46Å²

Sum negative surface area: 3303.42Å²

Sum donor surface area: 1834.39Å²

Sum acceptor surface area: 2042.50Å²

Delta RBM



General Protein Properties

Sum positive surface area: 5196.19Å²

Sum negative surface area: 3284.03Å²

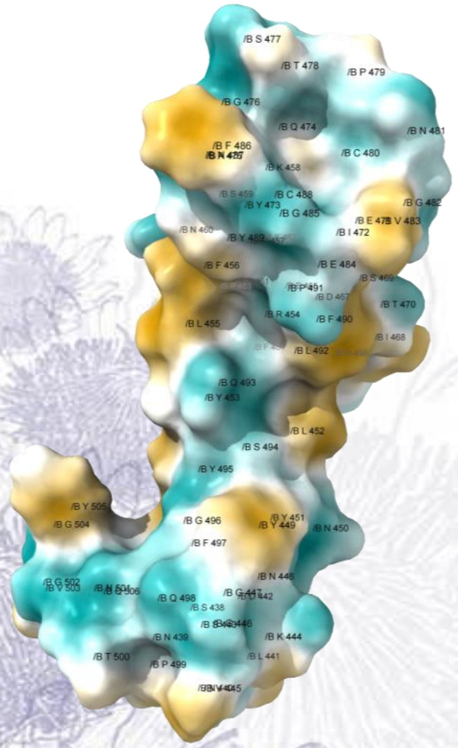
Sum donor surface area: 1780.62Å²

Sum acceptor surface area: 1992.48Å²

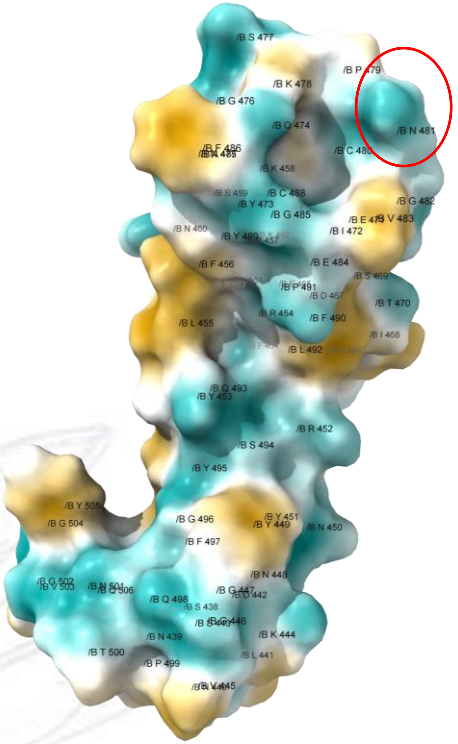
Omicron RBM

Molecular lipophilicity potential (MLP) maps

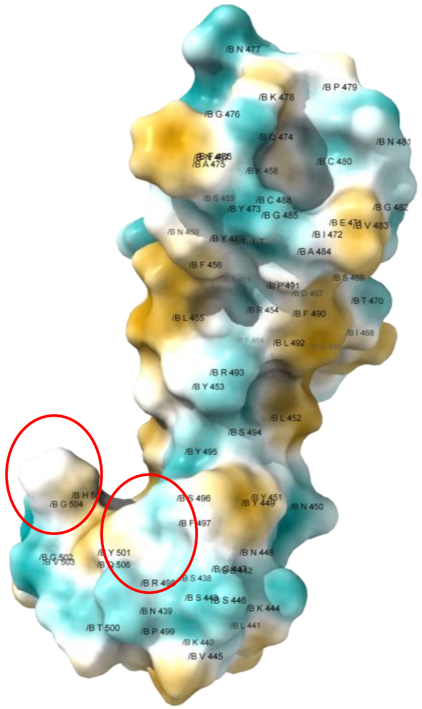
dark cyan (most hydrophilic) to white to dark goldenrod (most lipophilic)



Wildtype RBM:
minimum -25.18,
mean -2.864,
maximum 23.38

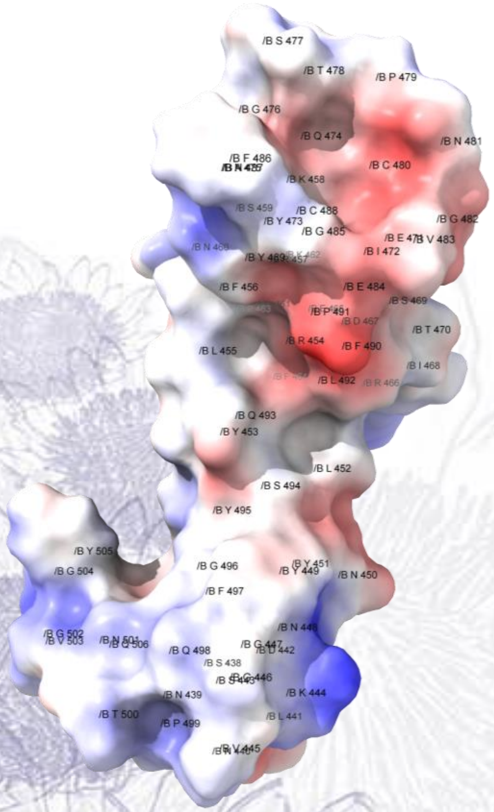


Delta RBM:
minimum -25.32,
mean -3.015,
maximum 23.22

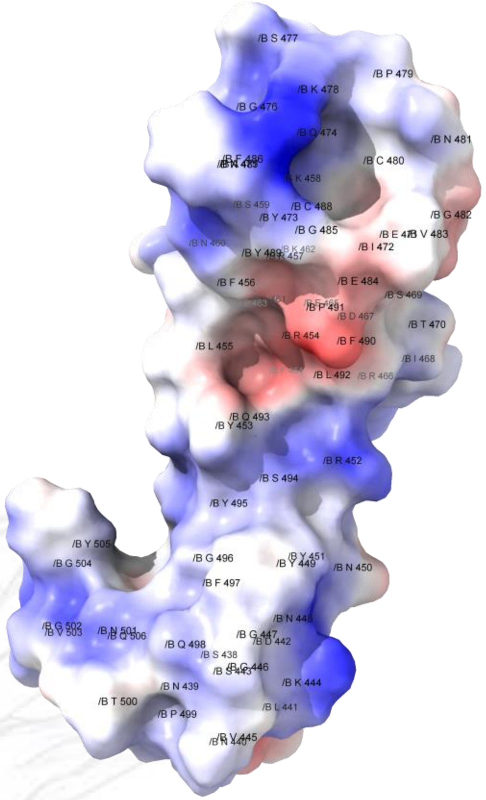


Omicron RBM:
minimum -25.45,
mean -2.545,
maximum 24.04

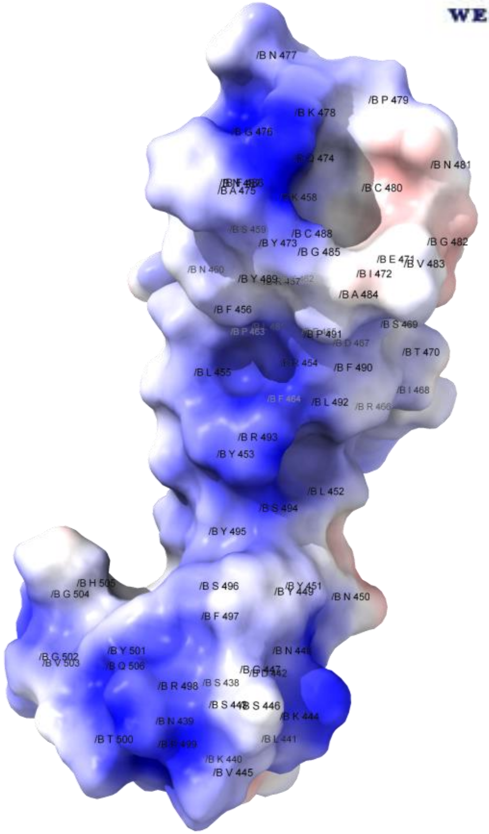
Coulombic electrostatic potential



Wildtype RBM:
minimum, -9.15,
mean 0.69,
maximum 9.73

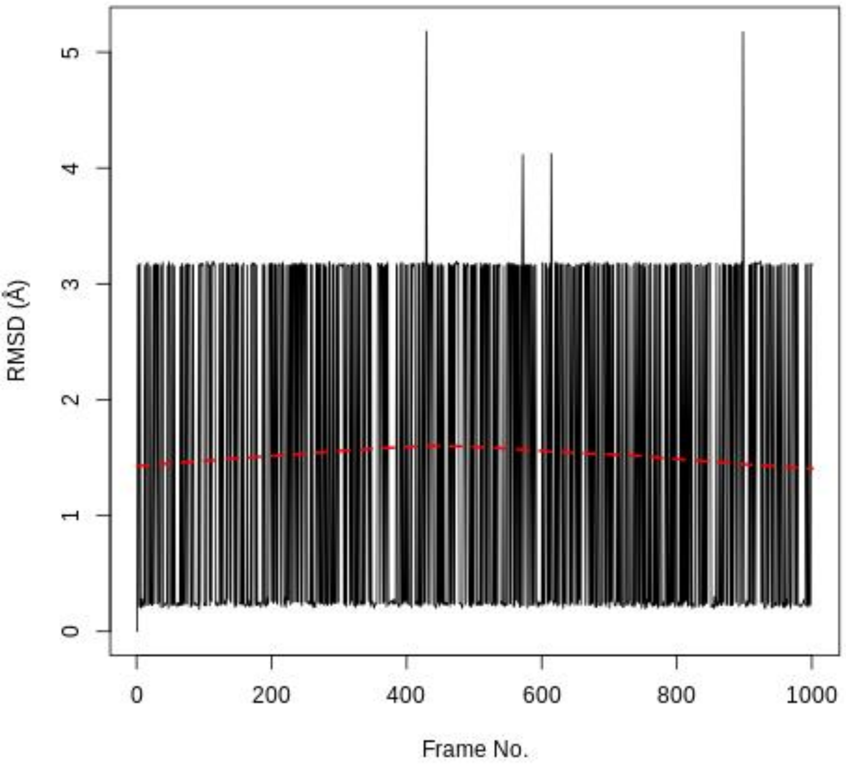


Delta RBM:
minimum, -8.51,
mean 1.64,
maximum 10.35

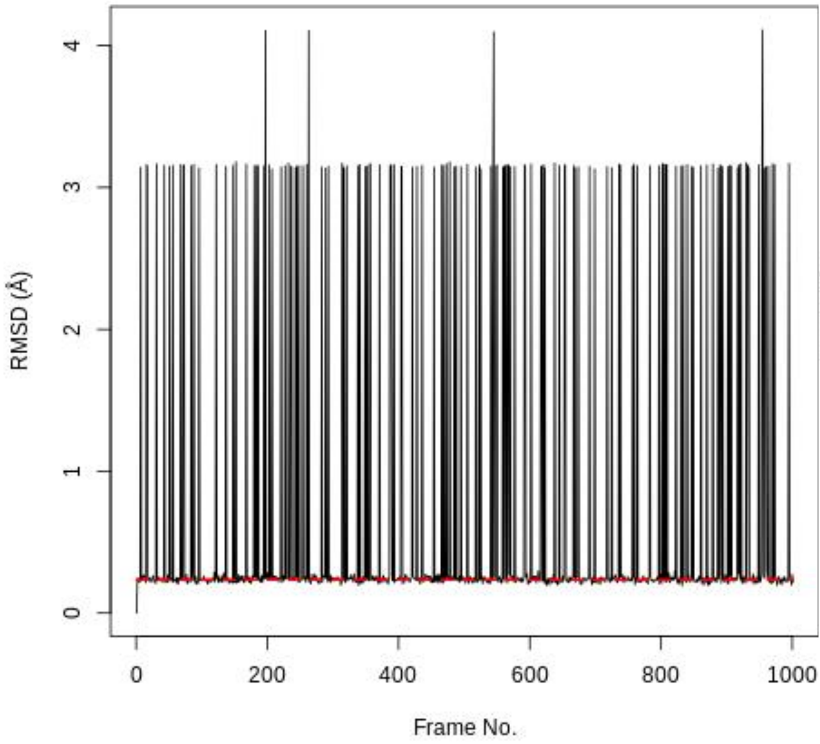


Omicron RBM:
minimum, -5.58,
mean 3.02,
maximum 13.16

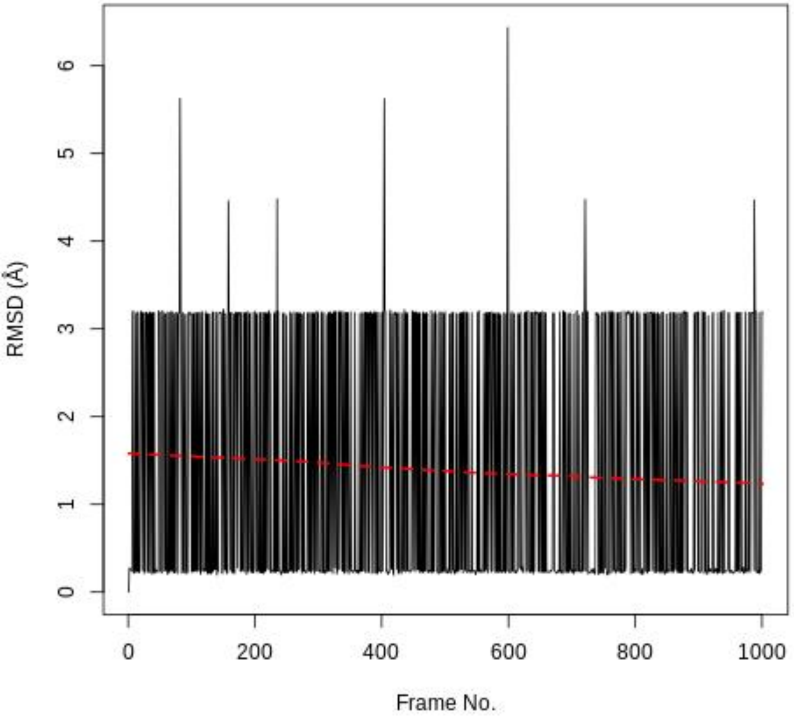
Molecular Dynamics of the receptor binding motif of wildtype, Delta and Omicron variants of SARS CoV-2 spike protein



Wildtype RBM

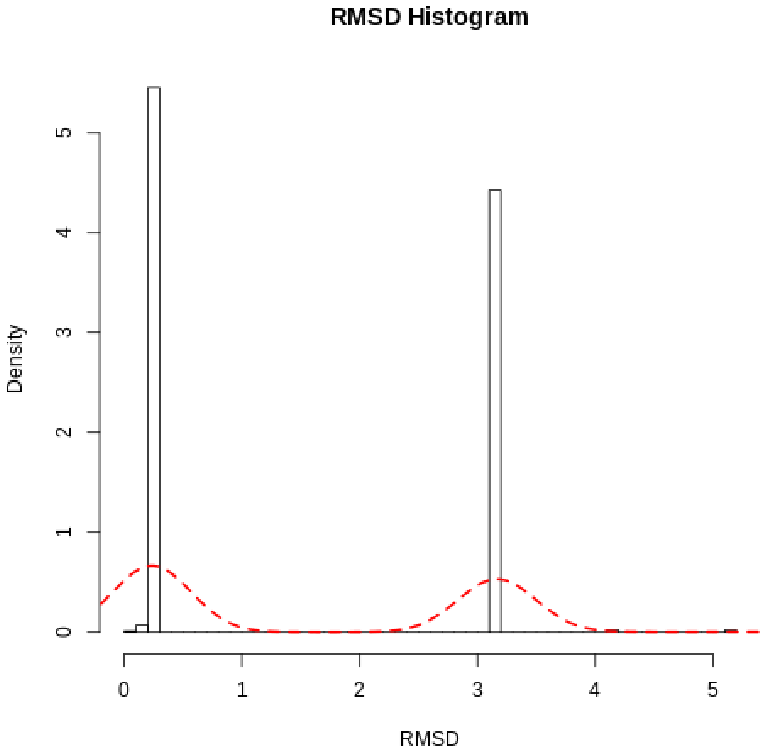


Delta RBM

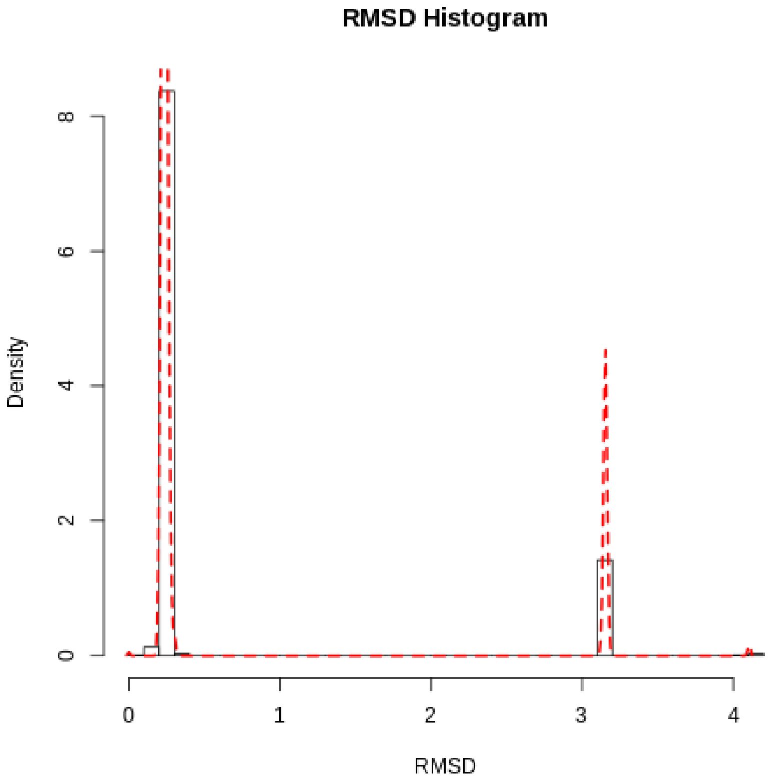


Omicron RBM

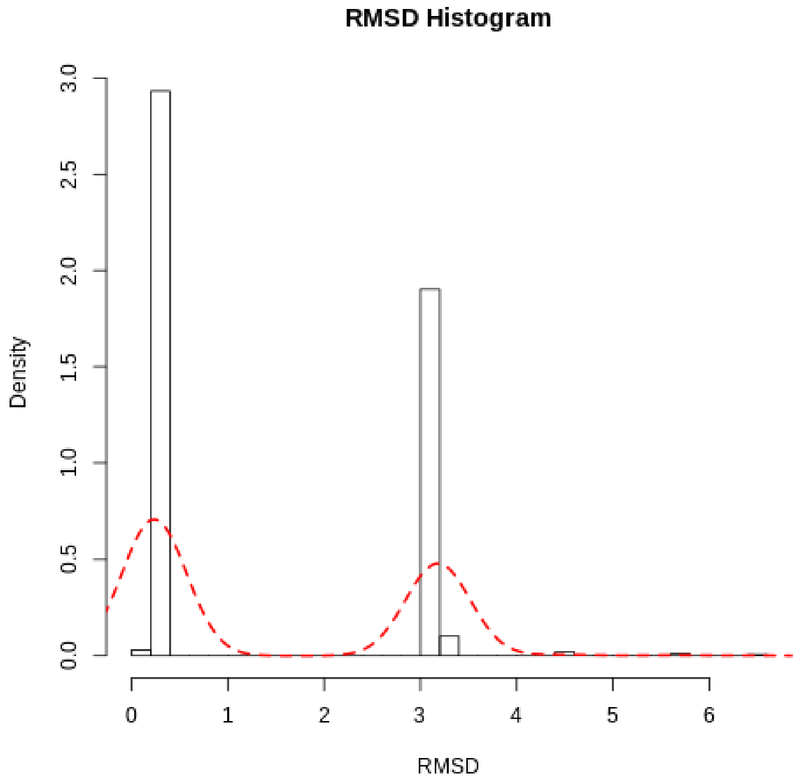
Molecular Dynamics of the receptor binding motif of wildtype, Delta and Omicron variants of SARS CoV-2 spike protein



Wildtype RBM

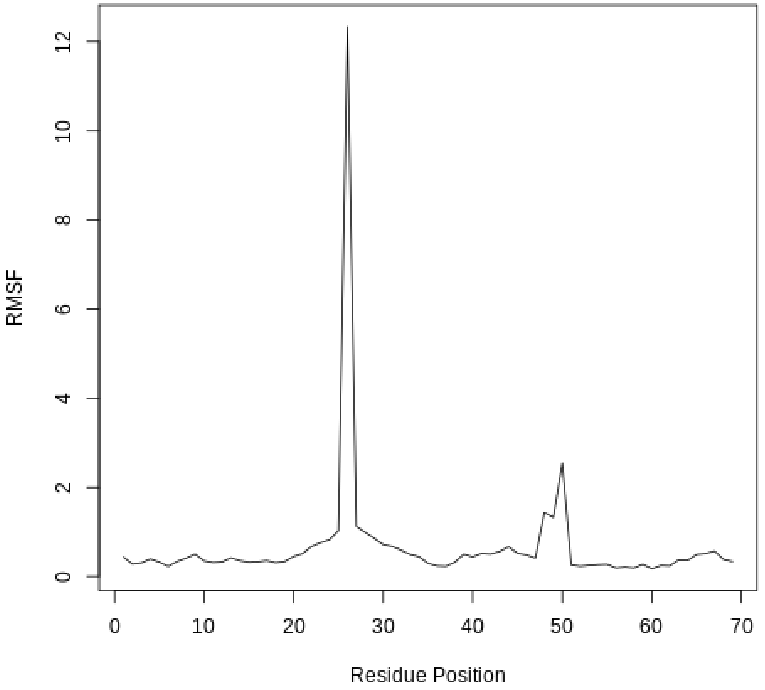


Delta RBM

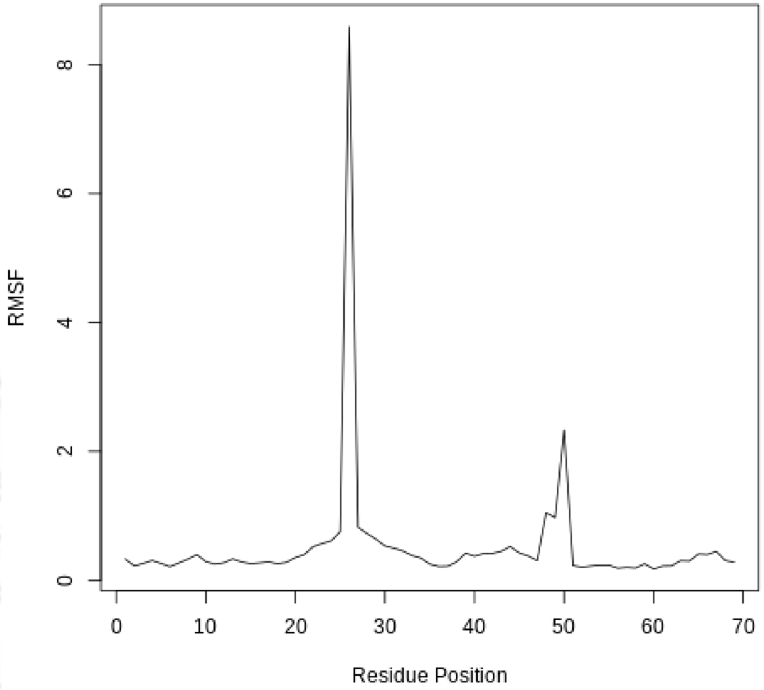


Omicron RBM

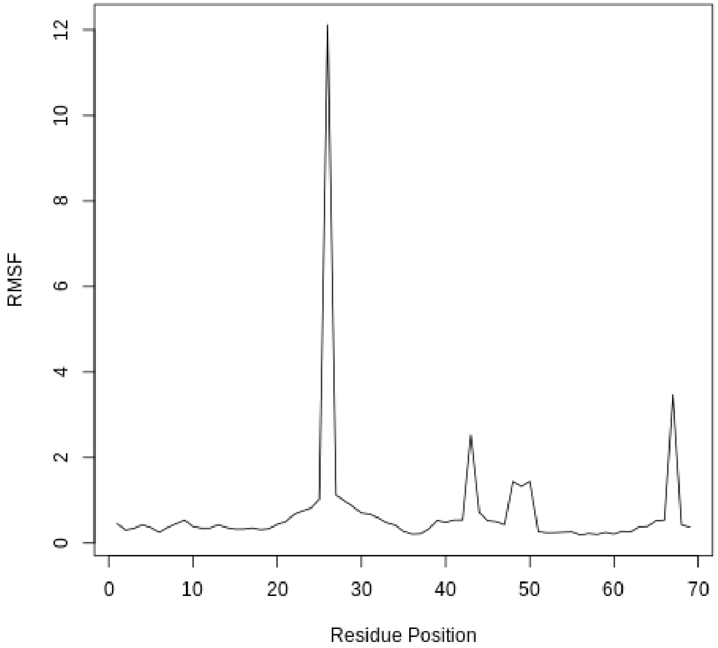
Molecular Dynamics of the receptor binding motif of wildtype, Delta and Omicron variants of SARS CoV-2 spike protein



Wildtype RBM



Delta RBM



Omicron RBM

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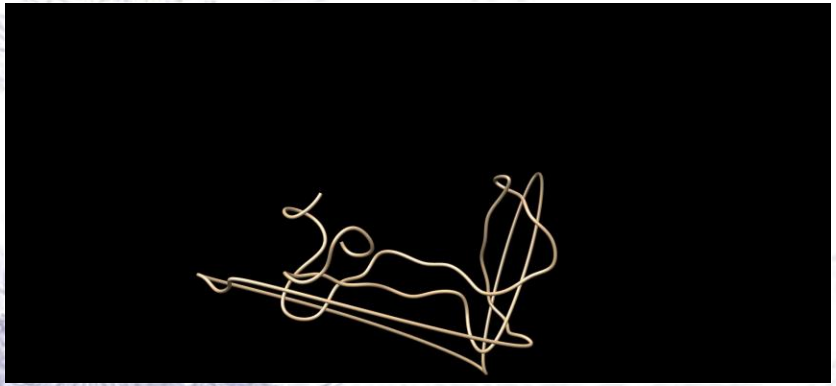
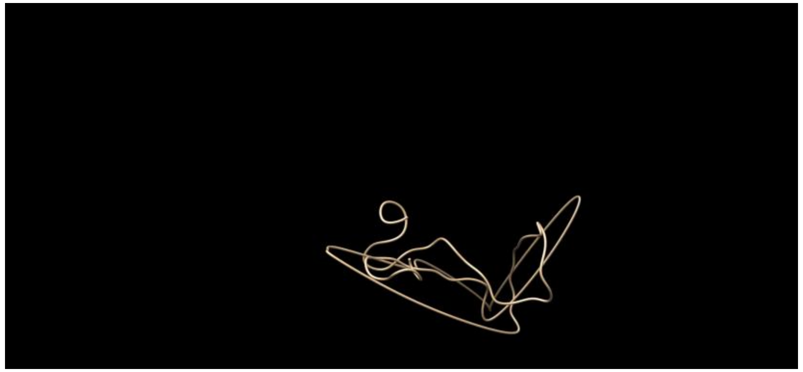


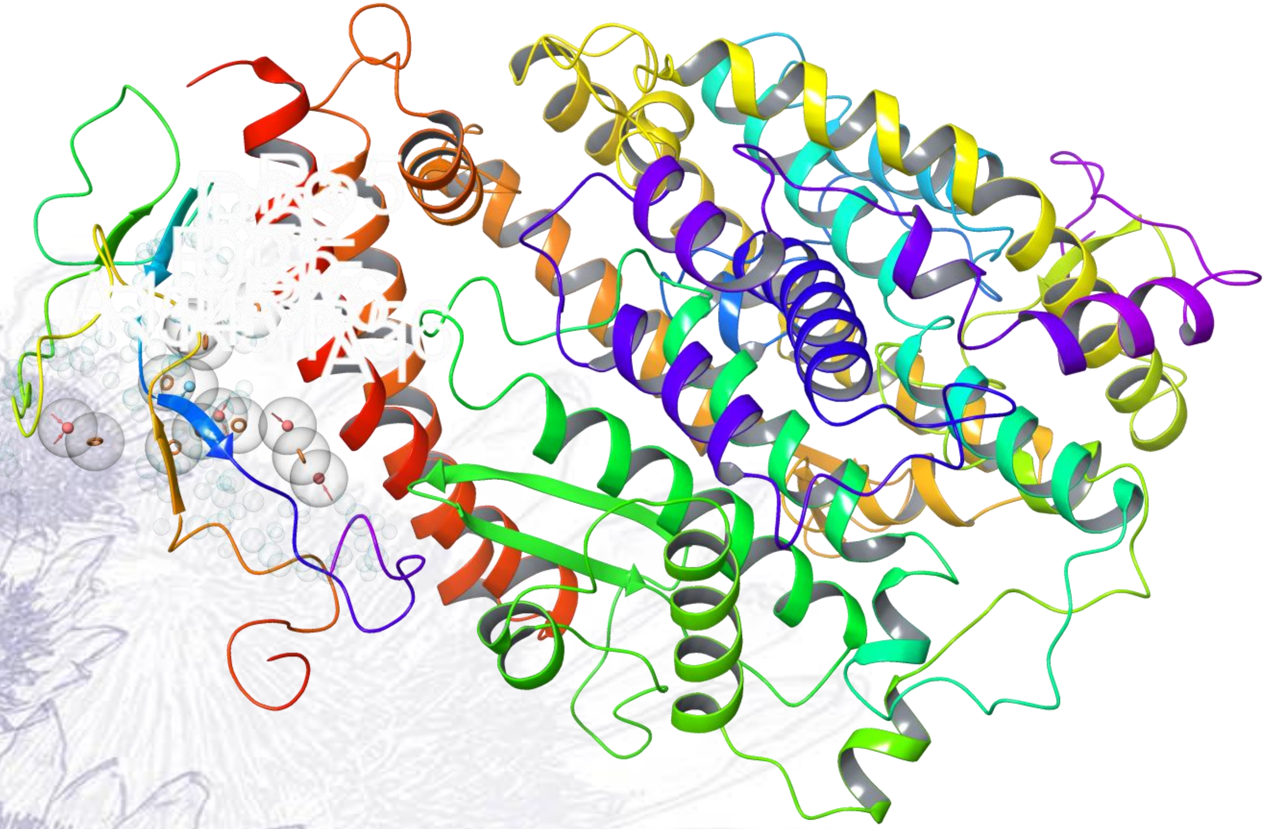
Wildtype RBM

Delta RBM



Omicron RBM

Pharmacophore model of wildtype SARS CoV-2 spike protein



Rank	Feature_label	source
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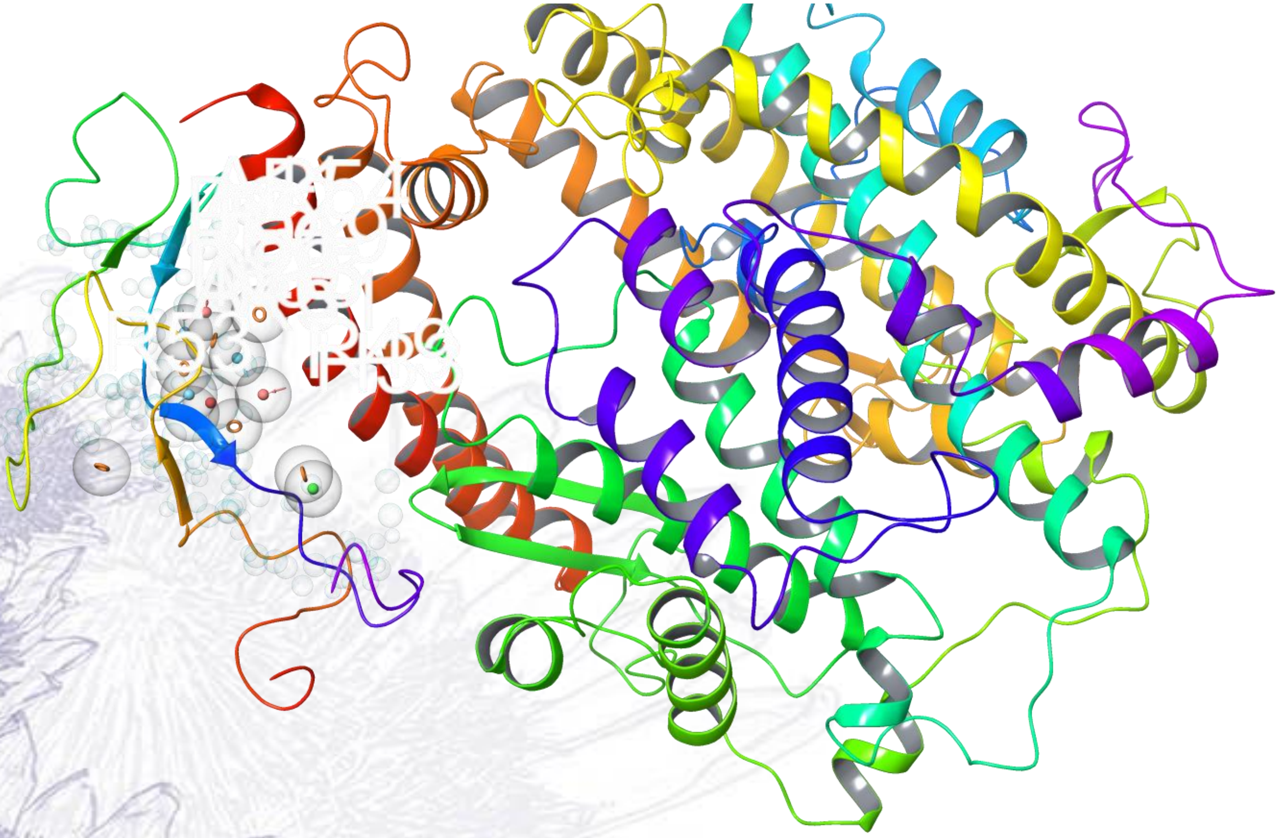
2	R2148	RingChemscoreHphobe
3	R2111	RingChemscoreHphobe
4	R2297	RingChemscoreHphobe
5	A449	HBond
6	A88	HBond
7	D933	HBond
8	D934	HBond
9	N1570	HBond
10	R2287	HBond
11	R2151	RingChemscoreHphobe
12	A418	HBond
13	R2142	RingChemscoreHphobe
14	D967	HBond
15	A16	HBond

Wildtype RBM

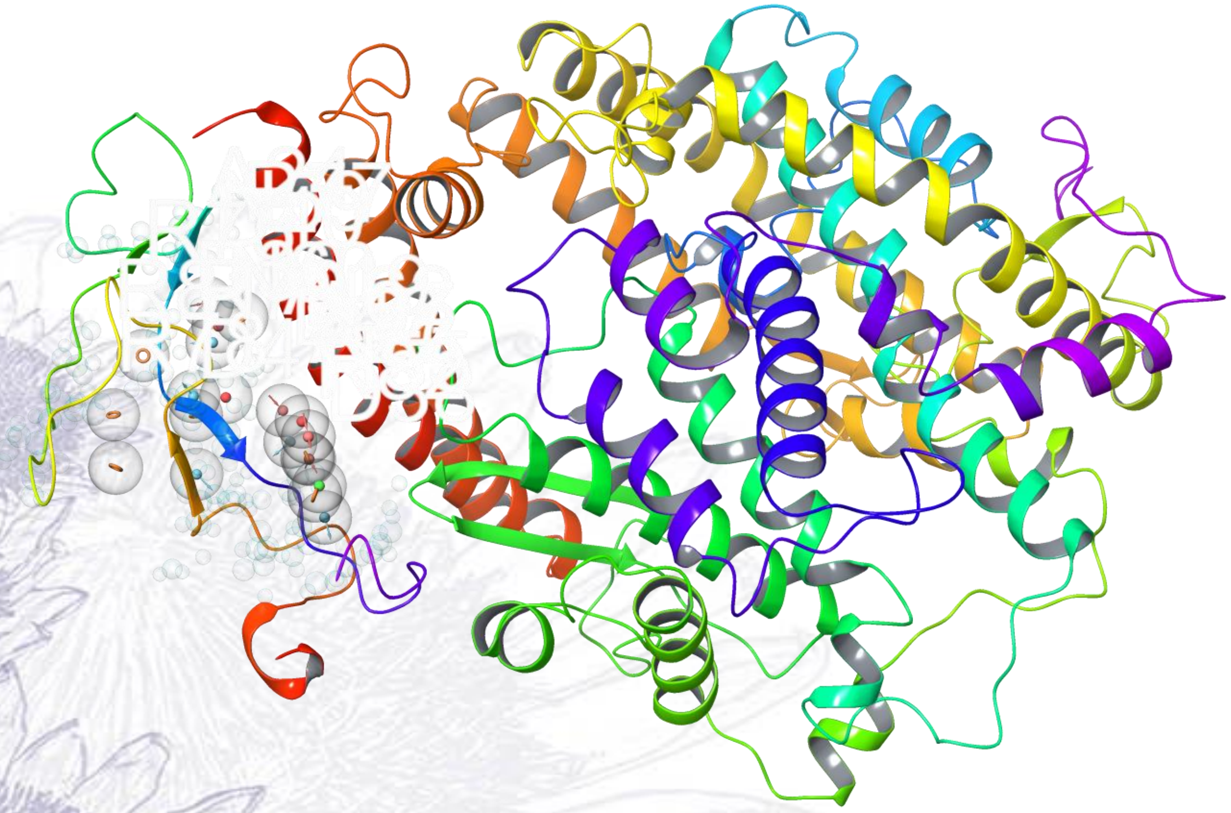
Pharmacophore model of Delta variants of SARS CoV-2 spike protein



Rank	Feature_label	source
1	N1589	HBond
2	R2264	RingChemscoreHphobe
3	H1454	HBond+PhobEn
4	R2282	RingChemscoreHphobe
5	R2186	RingChemscoreHphobe
6	R1945	RingChemscoreHphobe
7	R2331	RingChemscoreHphobe
8	A142	HBond
9	D1015	HBond
10	D1005	HBond
11	A609	HBond
12	R2188	RingChemscoreHphobe
13	D1021	HBond
14	A544	HBond

Delta RBM

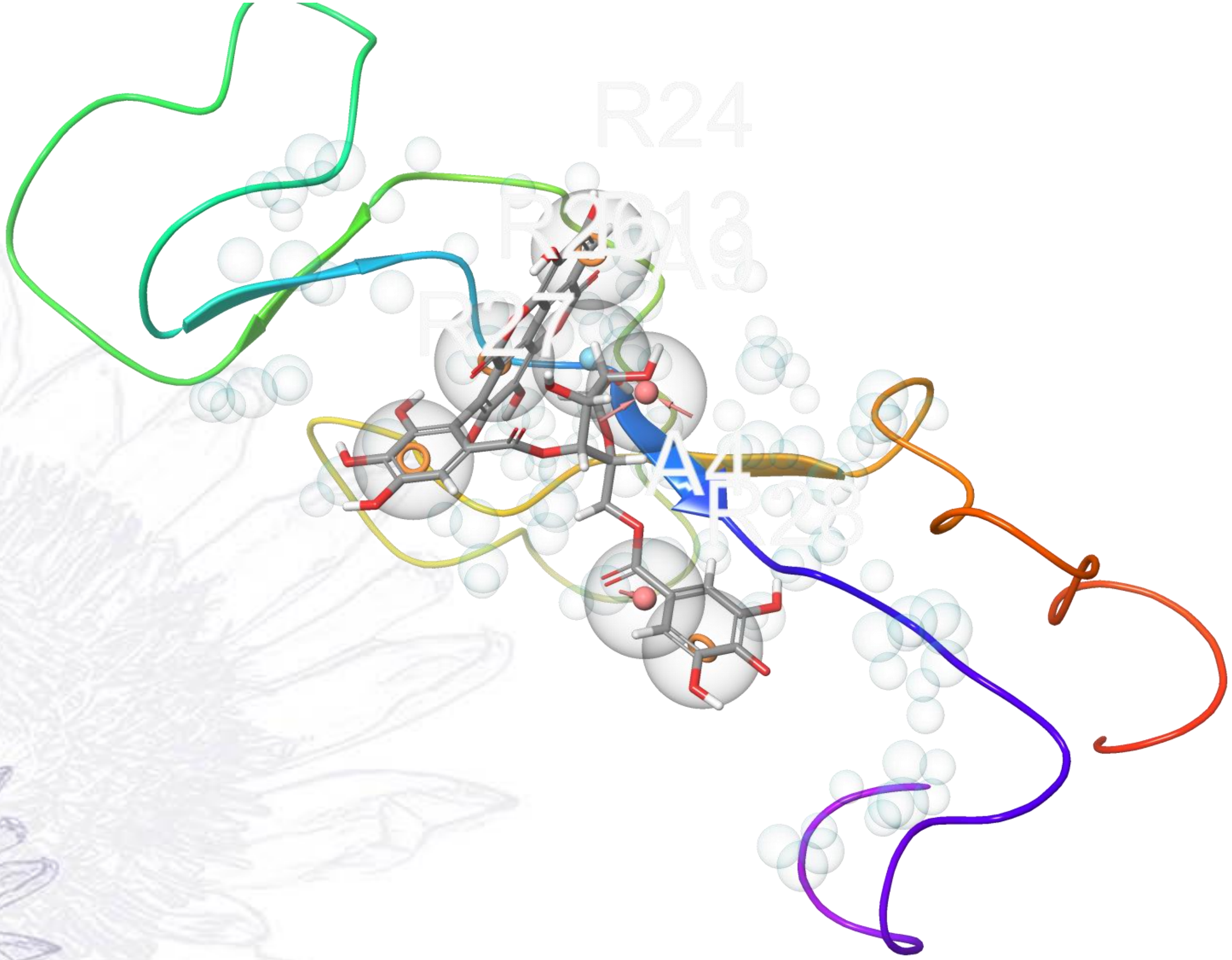
Pharmacophore model of Omicron variants of SARS CoV-2 spike protein



Omicron RBM

Rank	Feature_label	source
1	R2188	HBond+PhobEnPairHB
2	D933	HBond+PhobEnHB
3	N1570	HBond
4	N1568	HBond
5	R2254	RingChemscoreHphobe
6	R2153	RingChemscoreHphobe
7	R2082	RingChemscoreHphobe
8	R2175	RingChemscoreHphobe
9	A532	HBond
10	A522	HBond
11	D996	HBond
12	D942	HBond
13	D1010	HBond
14	D911	HBond
15	R2162	RingChemscoreHphobe
16	N1588	Electro+HBond
17	A510	HBond
18	H1387	PhobEn
19	R2239	RingChemscoreHphobe
20	A581	HBond

Pharmacophore model screening



Conclusions

- Mutations affects dynamics of the interaction of the receptor binding motif of the spike protein with its host receptor (hACE2)

- Characterization revealed significant differences in 3D structures of the wildtype and variant forms of the receptor binding motif of the Spike protein

- Pharmacophore model generated for the wildtype and variant forms of the receptor binding motif of the Spike protein

- Virtual screening of natural product database with pharmacophore models identify potential fusion inhibitors.