

# Development of HPC Facilities in Nepal

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*Tribhuvan University Kirtipur Kathmandu Nepal*

June 10, 2024



# ■Outline

- Developing HPC lab at CDPTU
- Impact of the lab...
- Recent trend in Computational physics at CDPTU: ML, thermoelectric materials, biophysics - DNA/Protein interaction, Protein/Protein interactions
- Recent results of Protein/Protein interactions

# ■Tribhuvan University (TU)

- The university was established mainly to focus on teaching. However many students/professors are heavily involved in research too nowadays
- The number of students is huge but lacks other required resources
- Government support for research is not significant
- Before 2018 TU was not ranked in World University Ranking. Now the situation is changing/improving
- The Times higher Education (THE)'s ranking shows TU within 801-1000th

Nepal

Tribhuvan University

801-  
1000<sup>th</sup>

World University Rankings  
2023

201-  
250<sup>th</sup>

Asia University Rankings  
2022

## ■ Recent years my experiences ...



*Central Department of physics, Tribhuvan University*

The main goal of university was (is) to teach. Research is just the interest of faculties/students. Professors need to teach large number of courses... So research is not in priority

## ■ Start Up ...

- 2009 - ICTP provided us support to purchase a Desktop and printer...
- We started classical MD simulation of simple systems like oxygen in water apart from study of simple systems by DFT
- 2011 - ICTP started giving more support, we purchased a few more PCs and a Generator too
- The World Academy of Sciences supported for computing facilities

## ■Further support ....



Figure: KASSAISS 2013



Figure: MD School 2014  
6

## ■Support ...?

- At the mean time NAST and UGC provided some support ...  
(i3,i5)
- $\sim 10$  PCs
- We got further support from TWAS/ICQ13

# ■ Computational Physics Lab (Present)



Figure: Computational physics lab @CDPTU. Recent GPUS not seen. We have 2 more GPU servers over there.

# ■ Computational Physics Lab (Present)



Figure: Computational physics lab



Figure: Solar panel for the lab

Figure

# ■ Systems ..

Of course our systems had to be small due to limitations of computational facilities

- **HF/DFT:** Small systems - atoms to molecules, methane clathrates to 2D heterostructures
- **MD Simulations:**
- Environmentally significant – ozone, oxygen, water ...
- Biologically significant – water, amino acids...
- Physics significant – inert gases like Ne, Ar, Kr ...
- Daily life – Polymers, Biopolymers like : DNA/RNA, Protein etc.
- Our current interest: DNA/Protein, Protein/Protein interactions - Interaction of SARS - CoV 2 virus and human ACE2

# ■Impact...(Collaboration to ICTP)



High Pressure Research >

An International Journal

Volume 35, 2015 - Issue 3

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## Decomposition of methane hydrate density-functional theory study

Nurapati Pantha Narayan Prasad Adhikari & Sandro Scandolo

Pages 231-238 | Received 27 Oct 2014, Accepted 20 Apr 2015, Published online: 27 May 2015

[Download citation](#)

<https://doi.org/10.1080/08957959.2015.1043912>



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### Abstract

The high pressure properties of methane hydrates have been the subject

Journal of Molecular Liquids 167 (2012) 34–39



Contents lists available at SciVerse ScienceDirect

## Journal of Molecular Liquids

journal homepage: [www.elsevier.com/locate/molliq](http://www.elsevier.com/locate/molliq)



## Molecular dynamics study of diffusion of heavy water in normal water at different temperatures

Uday Dahal <sup>a</sup>, Narayan P. Adhikari <sup>a,b,\*</sup>

<sup>a</sup> Central Department of Physics, Tribhuvan University, Kathmandu, Nepal

<sup>b</sup> The Abdus Salam International Center for Theoretical Physics, Trieste, Italy

## Study of structural and transport properties of argon, krypton, and their binary mixtures at different temperatures

Sunil Ghimire<sup>1</sup> · Narayan Prasad Adhikari<sup>1</sup>

Received: 2 June 2016 / Accepted: 30 January 2017 / Published online: 28 February 2017  
© Springer-Verlag Berlin Heidelberg 2017

**Abstract** Molecular dynamics simulation of argon, krypton, and their binary mixtures were performed at different temperatures and constant pressure ( $P = 1.013 \text{ bar}$ ) using GROMACS - Groningen Machine for Chemical Simulations. The gases are modeled by Lennard-Jones pair potential, with parameters taken from the literature. The study of radial distribution functions (RDFs) shows a single peak which indicates that there is no packing effect in gaseous state for argon, krypton, and their binary mixtures. The self-diffusion coefficients of argon and krypton is determined by using mean-square displacement (MSD) method and the mutual diffusion coefficients of binary mixtures are determined using Darken's relation. The values of simulated diffusion coefficients are compared with their corresponding theoretical values, numerical estimation, and experimental data. A good agreement between these sets of data is found. The diffusion coefficients obey Arrhenius behavior to a good extent for both pure components and binary mixtures. The values of simulated diffusion coefficient are used to estimate viscosities and thermal conductivities which agrees with theoretical values, numerical estimation, and

### Introduction

The study of transport properties of fluid is important to explain many physical and chemical processes. They are important parameters needed in engineering application such as numerical analysis of fluid flow and heat transfer [1]. The subject of transport phenomena describes the transport of momentum, energy, and mass in the form of mathematical relations [2]. The rapid increase in available computing power allows molecular dynamics simulation to be the best alternative for describing transport properties where experimental data are not available or not accessible [3]. The experimental measurement of diffusion coefficient is very difficult [4]. Therefore, we use molecular dynamics as the best alternative. The transport coefficients can be obtained by both equilibrium molecular dynamics (EMD) and non-equilibrium molecular dynamics (NEMD). In the present work, EMD is chosen.

The study of transport properties of noble gases has become significant to study their physiological exchange and the permeability of tissues to them [5]. Many works



Solid State Communications

Volume 340, December 2021, 114526

## First-principles study of pressure dependence superconductivity in technetium and tantalum

Amit K. Shah <sup>a</sup>, Ramila Khatiwada <sup>a</sup>, Narayan P. Adhikari <sup>a</sup>  , Rajendra P. Adhikari <sup>b</sup>

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International Journal of Modern Physics B  
Vol. 27, No. 8 (2013) 1350023 (18 pages)  
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DOI: 10.1142/S0217979213500239



## A MOLECULAR DYNAMICS STUDY OF OXYGEN GAS IN WATER AT DIFFERENT TEMPERATURES

S. K. THAPA\* and N. P. ADHIKARI\*,†

\**Central Department of Physics, Tribhuvan University,  
Kirtipur, Kathmandu, Nepal*

†*The Abdus Salam International Center for Theoretical Physics, Trieste, Italy  
npadhikari@tucdp.edu.np*

## A 5'-Flanking C/G Pair at the Core Region Enhances the Recognition and Binding of Kaiso to Methylated DNA

Bidhya Thapa, Narayan P. Adhikari,\* Purushottam B. Tiwari,\* and Prem P. Chapagain\*



Cite This: *J. Chem. Inf. Model.* 2023, 63, 2095–2103



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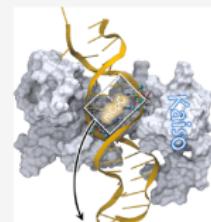
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**ABSTRACT:** Methyl CpG binding proteins (MBPs) are transcription factors that recognize the methylated CpG sites in DNA and mediate the DNA methylation signal into various downstream cellular processes. The C2H2 zinc finger (ZF) protein, Kaiso, also an MBP, preferentially binds to two symmetrically methylated CpG sites in DNA sequences via C-terminal C2H2 ZF domains and mediates the transcription regulation process. Investigation of the molecular mechanism of the recognition of methylated DNA (meDNA) by Kaiso is important to understand how this protein reads and translates this methylation signal into downstream transcription outcomes. Despite previous studies in Kaiso-meDNA interactions, detailed structural investigations on the sequence-specific interaction of Kaiso with the meDNA sequence are still lacking. In this work, we used molecular modeling and molecular dynamics (MD) simulation-based computational approaches to investigate





## OPEN ACCESS

## PAPER

# Binding of SARS-CoV-2/SARS-CoV spike receptor

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26 February 2021

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**Keywords:** spike, SARS-COV-2, hACE2, SARS-COV, Umbrella Sampling, F1  
Supplementary material for this article is available [online](#)

[Home](#) > [Applied Physics Letters](#) > [Volume 104, Issue 7](#) > [10.1063/1.4866383](#)

No Access • Submitted: 29 October 2013 • Accepted: 30 January 2014 •

## Band gap tuning in BN-doped graphene mobility

*Appl. Phys. Lett.* **104**, 073116 (2014); <https://doi.org/10.1063/1.4866383>

T. P. Kaloni<sup>1</sup>, R. P. Joshi<sup>2</sup>, N. P. Adhikari<sup>2</sup>, and U. Schwingenschlögl<sup>1,2</sup>

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ABSTRACT

FULL TEXT

### TOPICS

- Carbon based materials
- Semiconductors
- Intermolecular forces
- Graphene
- Doping
- Electronic transport
- Density functional theory

## ABSTRACT

Using density functional theory, the electronic properties of BN-doped graphene nanoribbons are studied. The band gap of the nanoribbons is found to address a superlattice of 10 nm and 75% are considered,

# ■ Impact...

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Electric field and strain-induced band-gap engineering manipulation of the Rashba spin splitting in Janus van heterostructures

Shubham Patel, Urmimala Dey, Narayan Prasad Adhikari, and A. Taraphder  
Phys. Rev. B **106**, 035125 – Published 18 July 2022

Article References No Citing Articles Supplemental Material PDF

ABSTRACT

The compositional as well as structural asymmetries in Janus transition metal dichalcogenides (TMDs) and their van der Waals heterostructures (vdW HSs) induce an intrinsic Rashba effect (RE). We investigate the variation of band gaps and the Rashba parameter in three different heterostructures having AB-stacked Mo<sub>X</sub>XY/w<sub>X</sub>YY' (X, Y = S, Se, Te; X ≠ Y) interface, using first-principles calculations. We consider the effect of external electric field and biaxial strain in tuning the strength of the intrinsic electric field, which leads to renormalization of the band gap and the Rashba spin splitting. In particular, it is found that the compressive in-plane biaxial strain can lead to a notable increase in the Rashba spin splitting. Moreover, our ab initio density functional theory calculations reveal the existence of a type-II band alignment in these heterostructures, which remains robust under

Received 15th October 2023, Accepted 7th February 2024

## PCCP

### PAPER



Cite this: *Phys. Chem. Chem. Phys.*, 2024, 26, 8794

## Insights from *in silico* study of SARS-CoV-2 variants†

Lokendra Singh Dhami,<sup>ID</sup>‡ Prabin Dahal,<sup>L</sup>‡ Bidhya Thapa,<sup>L</sup> Nurapati Pantha,<sup>A</sup> Rameshwar Adhikari<sup>D</sup> and Narayan Prasad Adhikari<sup>E</sup>

The emergence of new variants of the novel coronavirus SARS-CoV-2 has raised concerns about increased virulence, high transmissibility, and unmatched immune escape due to the evolutionary fitness of the virus. The subject of relative order of variants with the human ACE2 (hACE2) receptor is hotly debated in drug design and development. In this work, we have investigated the receptor binding domain (RBD) of SARS-CoV-2 variants of (B.1.617.2), Omicron (B.1.1.529), variant of interest (VOI); Kappa variant with the human ACE2 receptor by using the umbrella sampling method. The results show that Delta and Delta Plus variants have greater values of the US E

The main results presented in this work are from PCCP papers.

## ■ Impact...

- Provided idea of Molecular Dynamics Simulation and ab initio simulation of solids to huge number of students from Nepal
- Of course quality of the work must be enhanced

# ■Impact...

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**Narayan Prasad Adhikari** 

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 Nurapati Pantha Faculty, Central Department of P...
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Of course these numbers are not only from Computational CMP group but significant numbers come from the group.

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[Published: 19 November 2014](#)

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[Katia Moskitch](#)

[Nature](#) 515, 330–333 (2014) | [Cite this article](#)

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**The International Centre for Theoretical Physics was set up to seed science in the developing world; 100,000 researchers later, it is still growing.**

The dust in Kathmandu cloaks everything. It carpets the streets with a dingy layer. Women cutting waist-high grass are wearing face masks to keep it out. And it settles on the dilapidated buildings of Tribhuvan University (TU) – the biggest scientific establishment in Nepal.

Narayan Adhikari, however, has managed to stay clean. Clad in an impeccable white shirt and black trousers, he adds his motorbike to a

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## ■Current Interest

- Understanding binding mechanism of SARS-CoV-2: wild type and other mutated variants
- Tuning band gap and other properties of 2D heterostructures - keeping one of them as "GRAPHENE"
- Thermoelectric materials

# ■Current Interest

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Volume 39, June 2024, 108853

## Mechanical and thermoelectric response of 18-valence electron half-Heusler tellurides XFeTe (X=Ti, Hf): A theoretical perspective

Prakash Khatri<sup>a b</sup>, Narayan Prasad Adhikari<sup>a</sup>  

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# ■ Binding of SARS-CoV-2 with hACE2

COVID-19 CORONAVIRUS PANDEMIC

Last updated: August 13, 2023, 01:35 GMT

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Coronavirus Cases:

**693,186,371**

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Deaths:

**6,907,147**

# ■ Binding of SARS-CoV-2 with hACE2

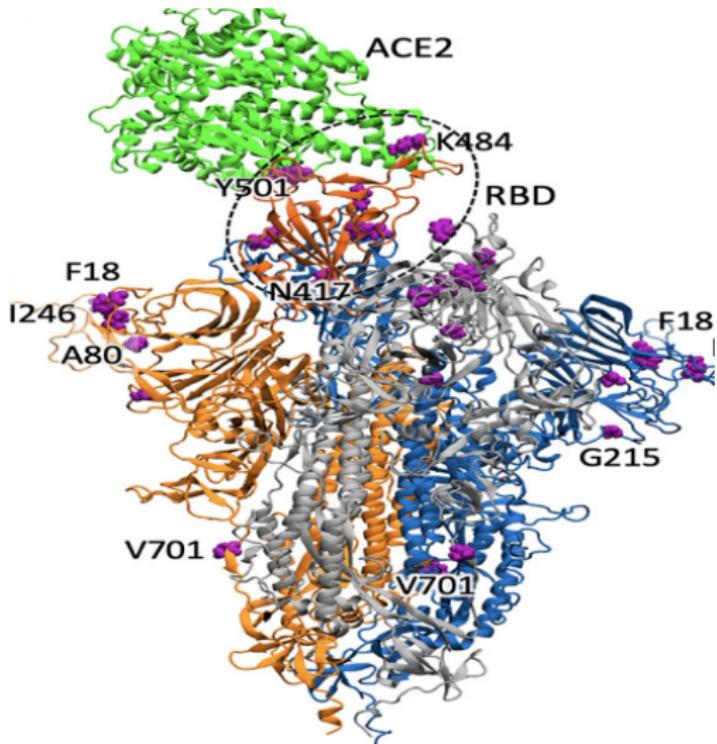
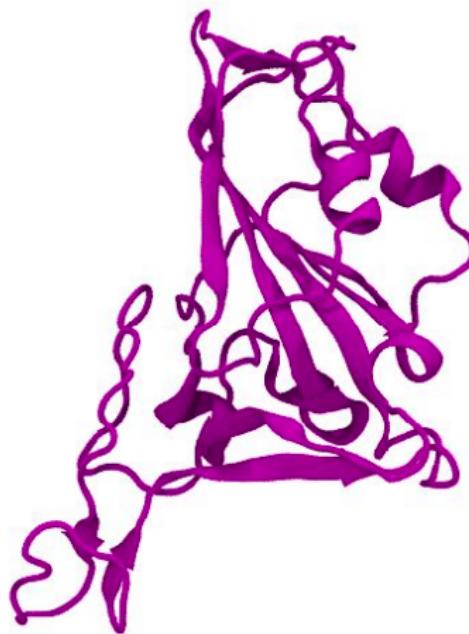


Figure: Binding of spike protein of SARS-CoV-2 and human angiotensin converting enzyme 2 (hACE2)

## ■ Receptor-binding domain (RBD)

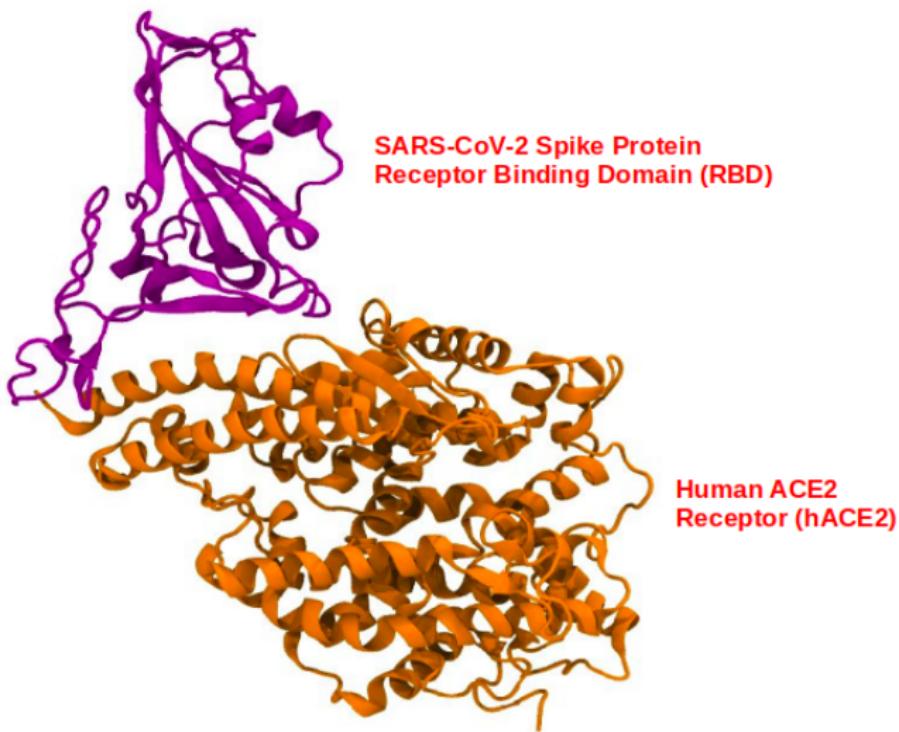


**Figure:** A receptor-binding domain (RBD) is a key part of a virus located on its 'spike' domain that allows it to dock to body receptors to gain entry into cells and lead to infection

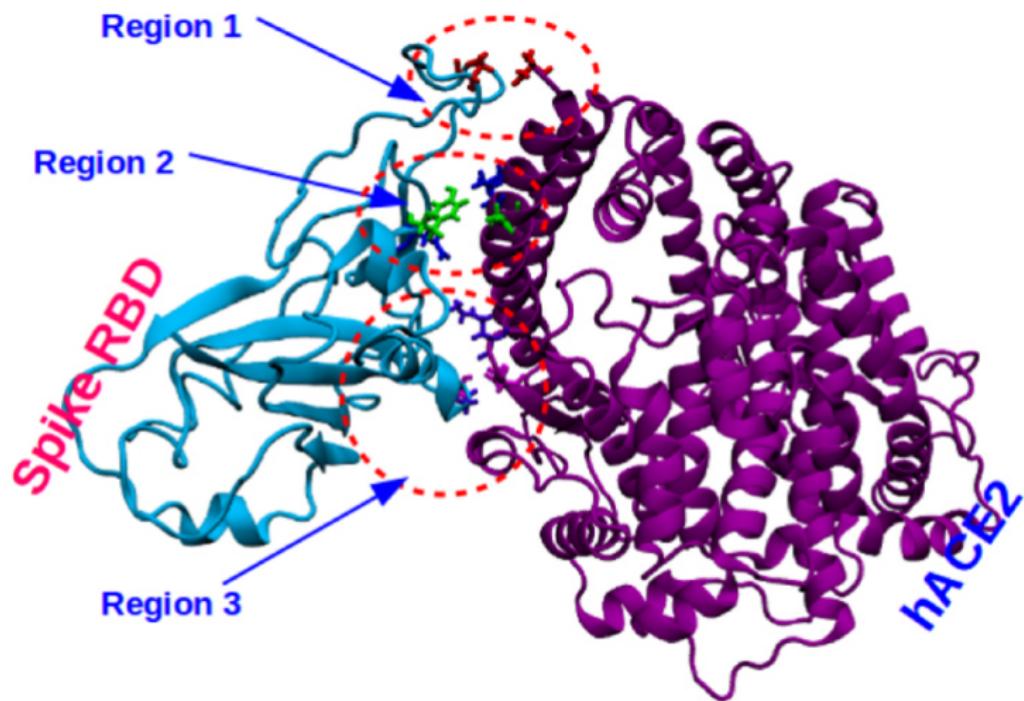
## ■ Human Angiotensin-converting enzyme 2



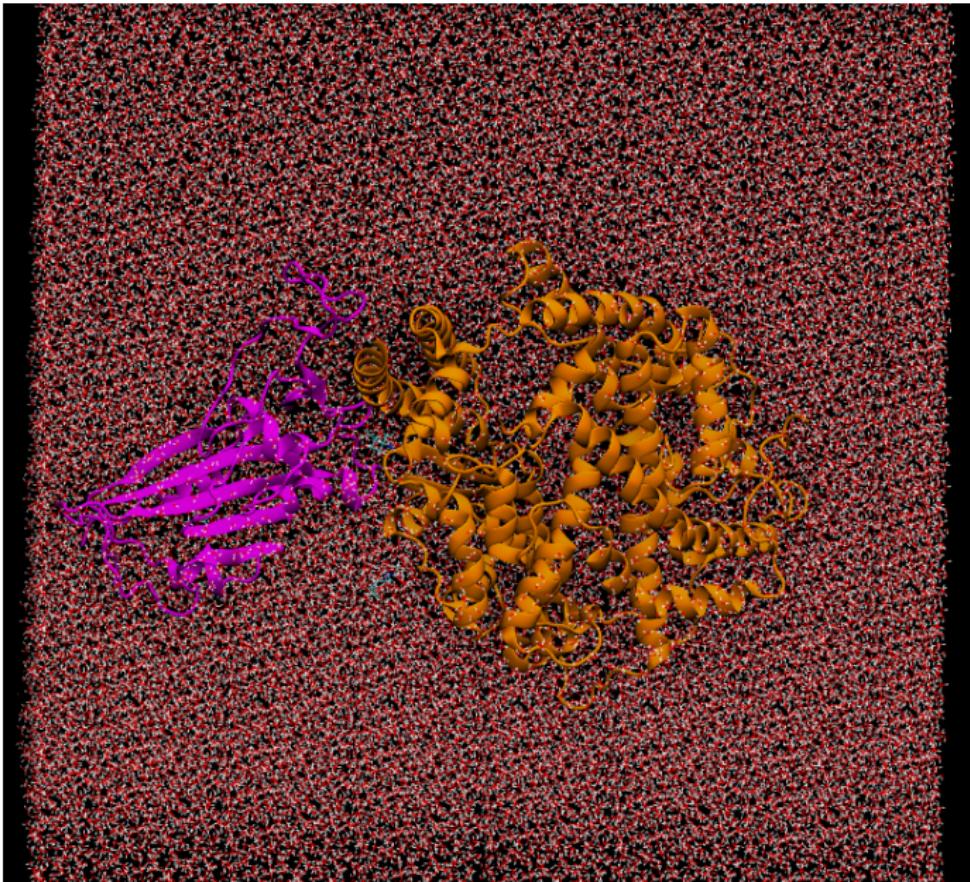
## ■ Binding of SARS-CoV-2 with hACE2



# ■Interacting Regions



## ■ Simulation Box



# ■ Simulation Details

Variants	System Size ( $\text{\AA}^3$ )	Ions Added (0.15 M conc.)	Simulation Time (ns)	Total Atoms
Wild type	133 X 133 X 133	220 $\text{Na}^+$ and 197 $\text{Cl}^-$	100	222,735
Beta	133 X 133 X 133	219 $\text{Na}^+$ and 197 $\text{Cl}^-$	100	222,749
Delta	133 X 133 X 133	222 $\text{Na}^+$ and 119 $\text{Cl}^-$	100	222,758
Mu	133 X 133 X 133	197 $\text{Na}^+$ and 218 $\text{Cl}^-$	100	222,658
Omicron	133 X 133 X 133	224 $\text{Na}^+$ and 202 $\text{Cl}^-$	100	227,029

Total number of particles in box  $\sim 222,700$

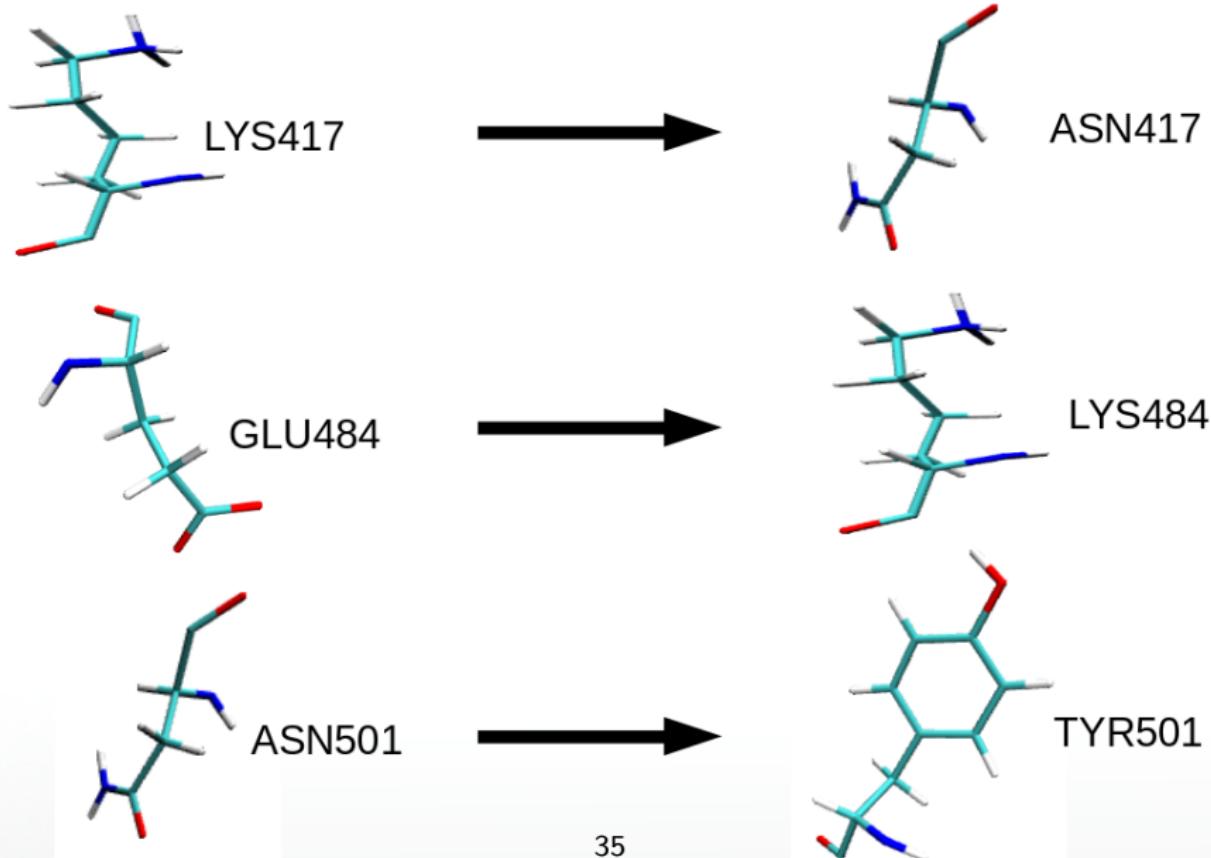
# ■Variants of Concern

Variants	Mutation	Variants of Concern	PDB ID
<b>Wild type</b>	-	-	-
<b>Beta</b>	LYS417-ASN417, GLU484-LYS484, ASN501-TYR501	Dec, 2020	6LZG
<b>Delta</b>	LEU452-ARG452, THR478-LYS478	May, 2021	6LZG
<b>Mu</b>	ARG346-LYS346, GLU484-LYS484, ASN501-TYR501	Aug, 2021	6LZG

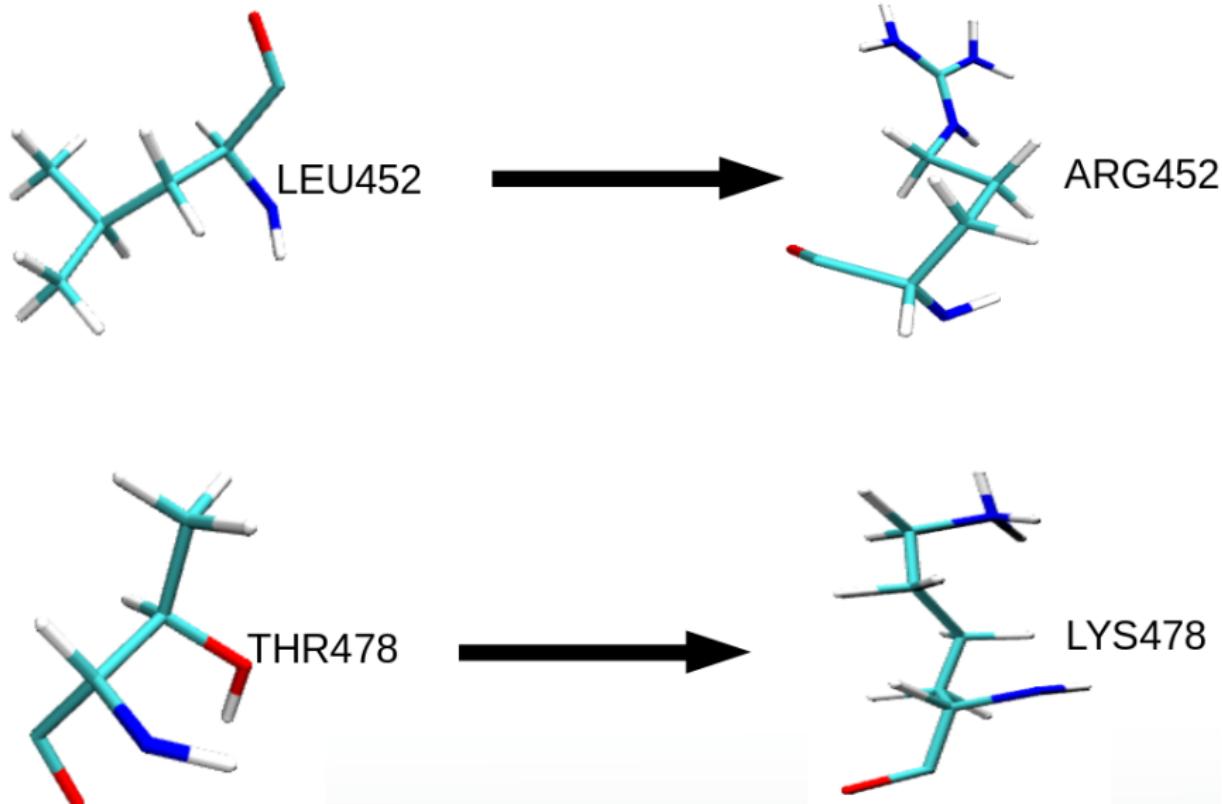
## ■Variants of Concern

Variants	Mutation	Variants of Concern	PDB ID
<b>Omicron</b>	LYS417-ASN417, GLY446-SER446, GLU484-ALA484, GLN493-ARG493, GLY496-SER496, GLN498-ARG498, ASN501-TYR501, TYR505-HIS505, SER477-ASN477, GLY339-ASP339, SER371-LEU371, SER373-PRO373, SER375-PHE375, ASN440-LYS440, THR478-LYS478	Nov, 2021	6WBP

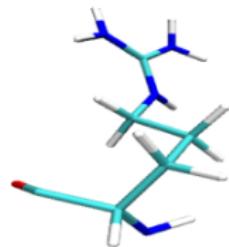
## ■Variants of Concern- $\beta$



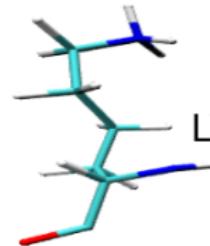
## ■Variants of Concern- δ



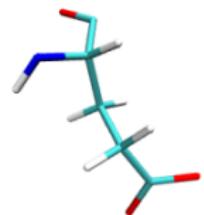
## ■Variants of Concern- $\mu$



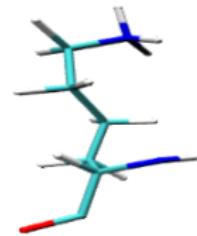
ARG346



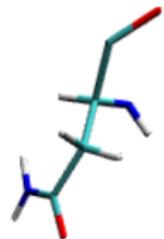
LYS346



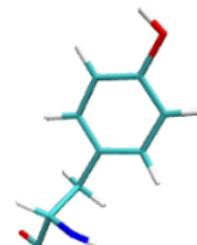
GLU484



LYS484

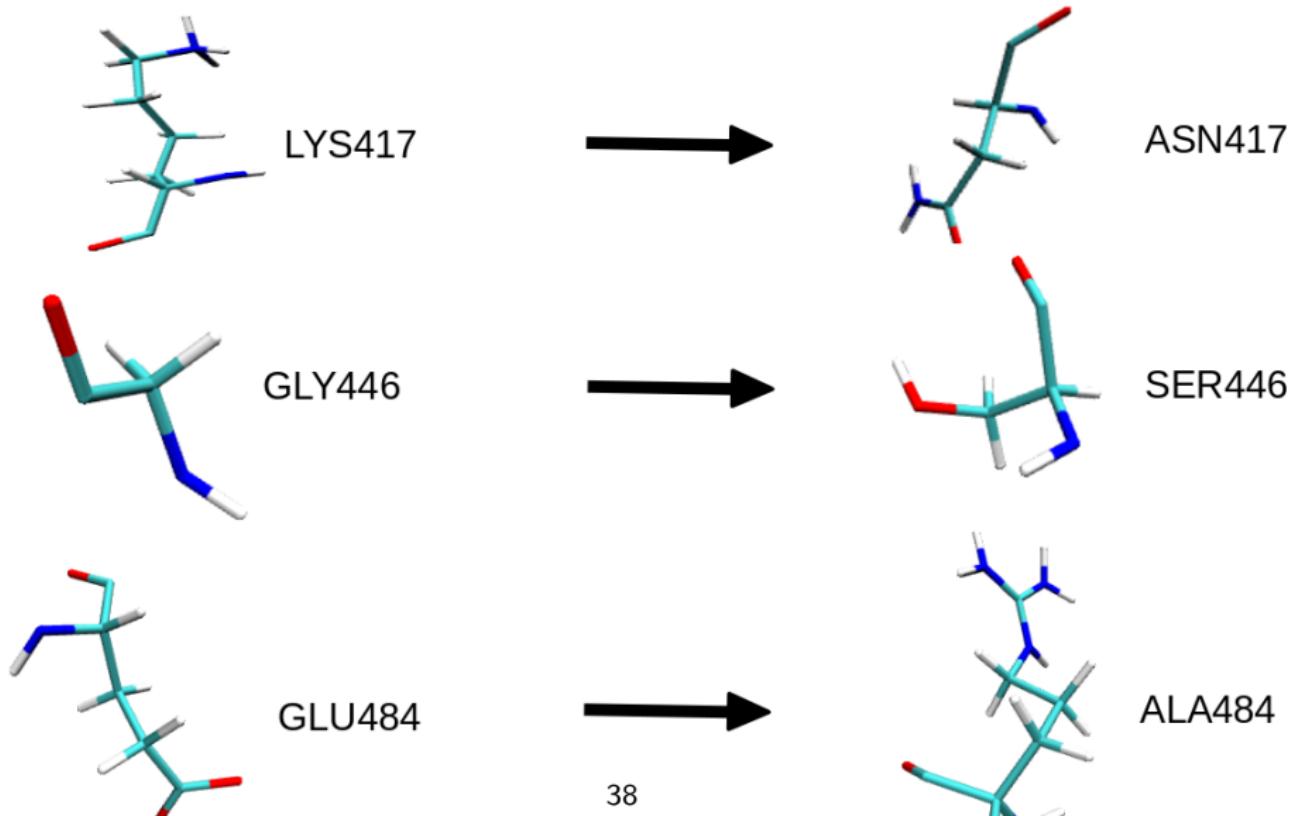


ASN501

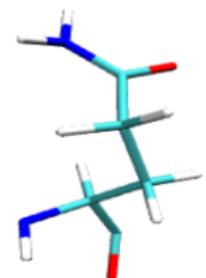


TYR501

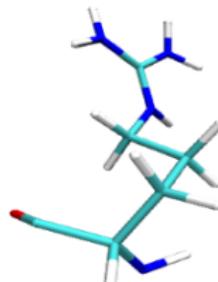
## ■Variants of Concern- Omicron



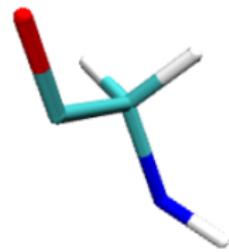
## ■Variants of Concern- Omicron



GLN493



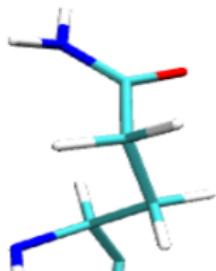
ARG493



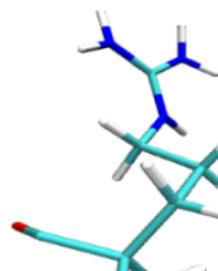
GLY496



SER496

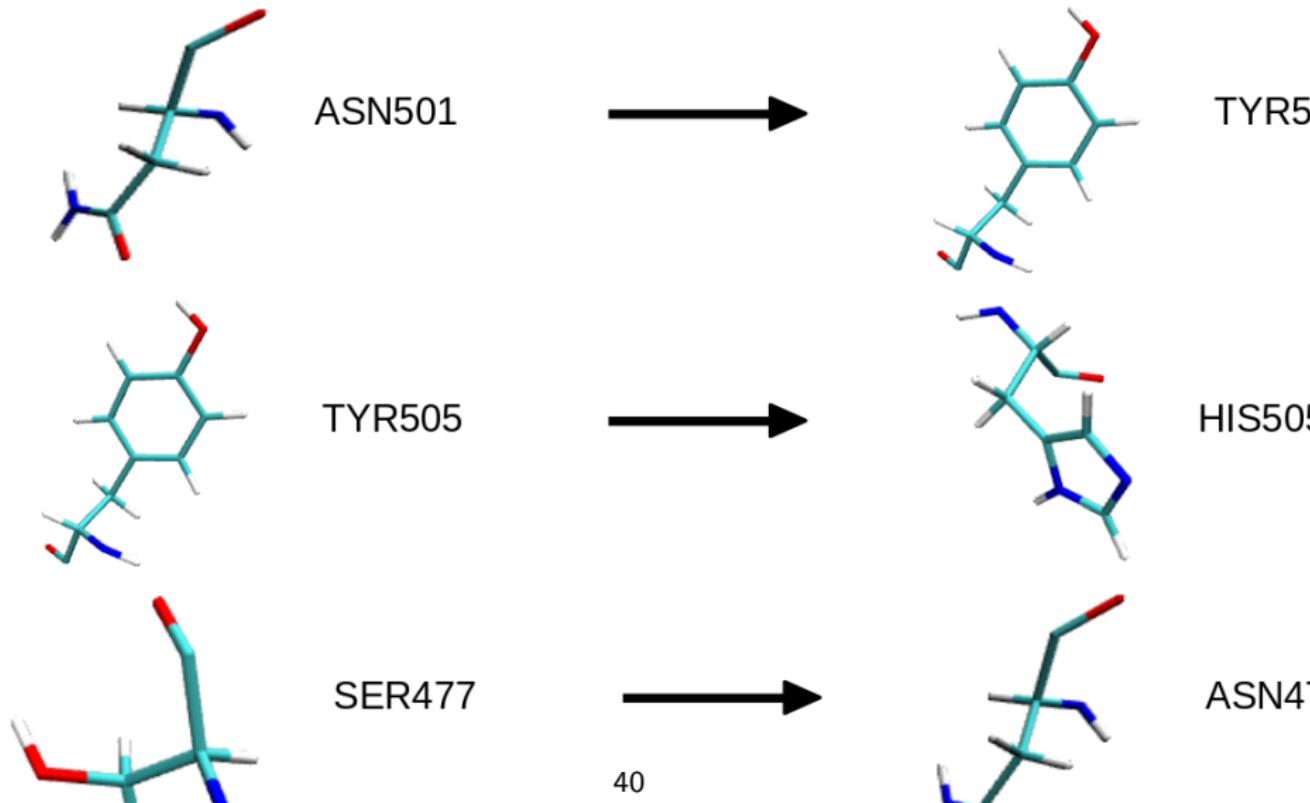


GLN498

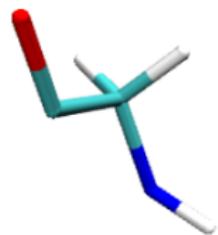


ARG498

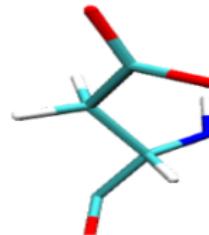
## ■Variants of Concern- Omicron



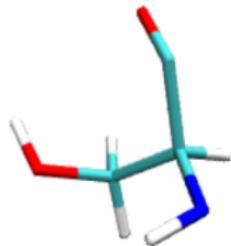
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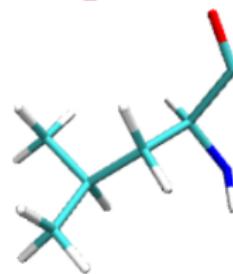
GLY339



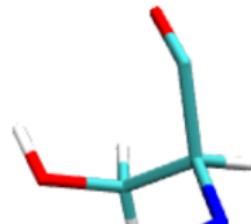
ASP339



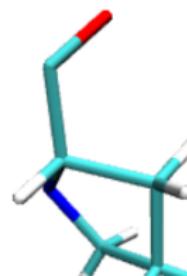
SER371



LEU371

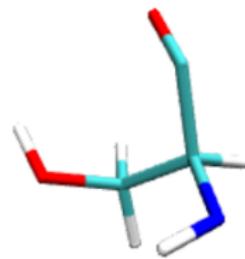


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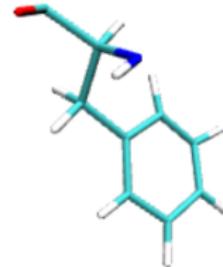


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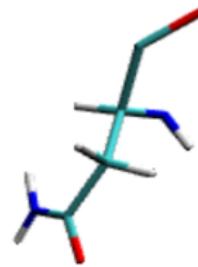
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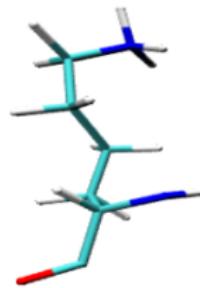
SER375



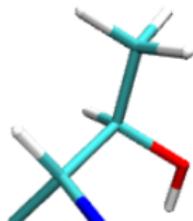
PHE375



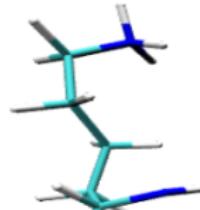
ASN440



LYS440



THR478



LYS478

# ■Are the VoC stable?

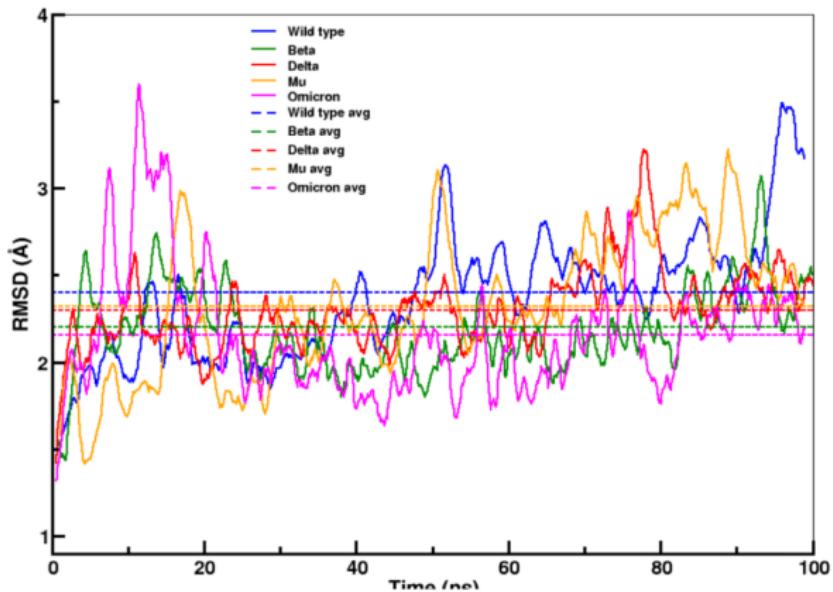
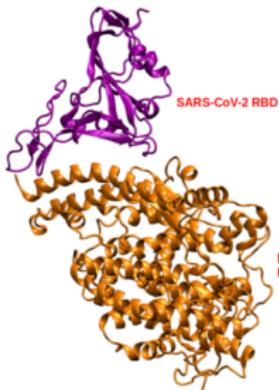
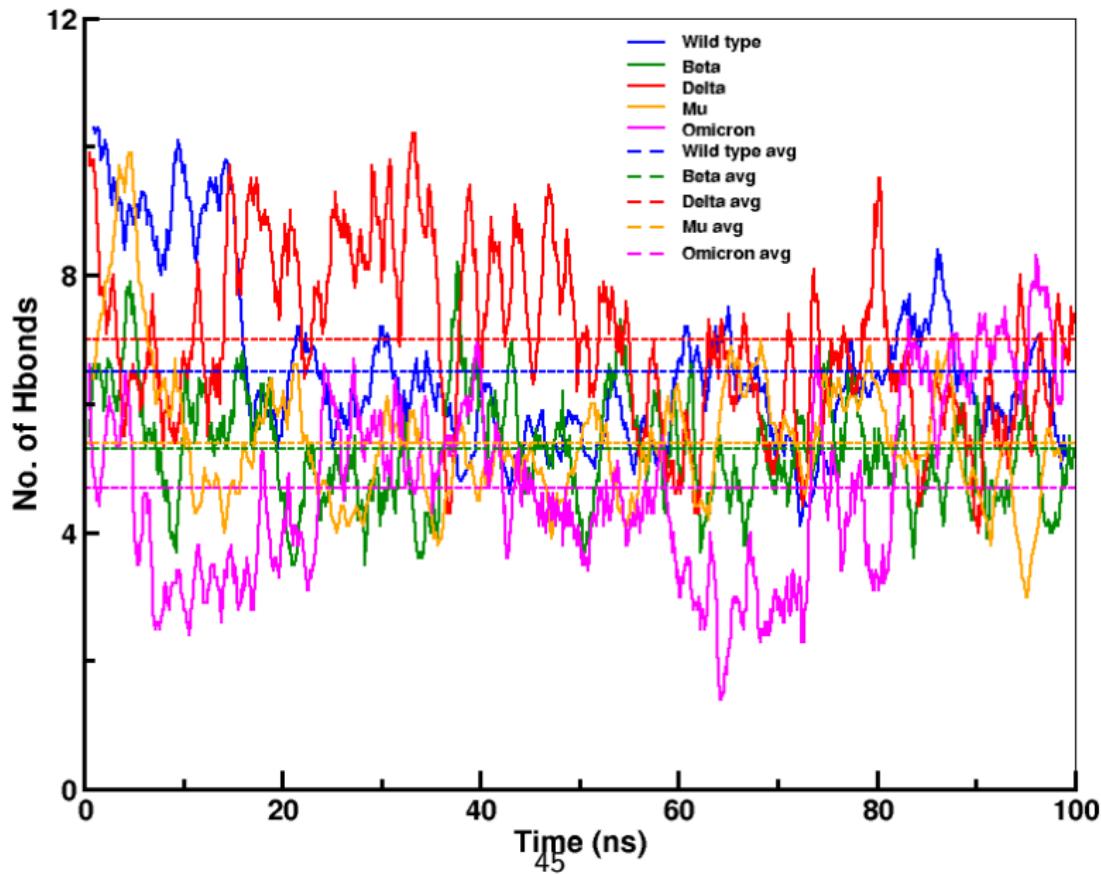


Figure: RMSD of all the variants

## ■ Major Binding Factors in Protein-Protein

- Hydrogen bonds
- Salt bridge interaction
- Hydrophobic interactions
- Non bonded interactions - vdW and Electrostatic Interactions
- Binding free energy by Umbrella Sampling

# ■ Hydrogen Bonds



## ■ Hydrogen Bonds

<b>Variants</b>	<b>Average Number of Hbonds</b>
<b>Wild type</b>	$6.5 \pm 0.10$
<b>Beta</b>	$5.3 \pm 0.03$
<b>Delta</b>	$7.0 \pm 0.04$
<b>Mu</b>	$5.4 \pm 0.05$
<b>Omicron</b>	$4.7 \pm 0.04$

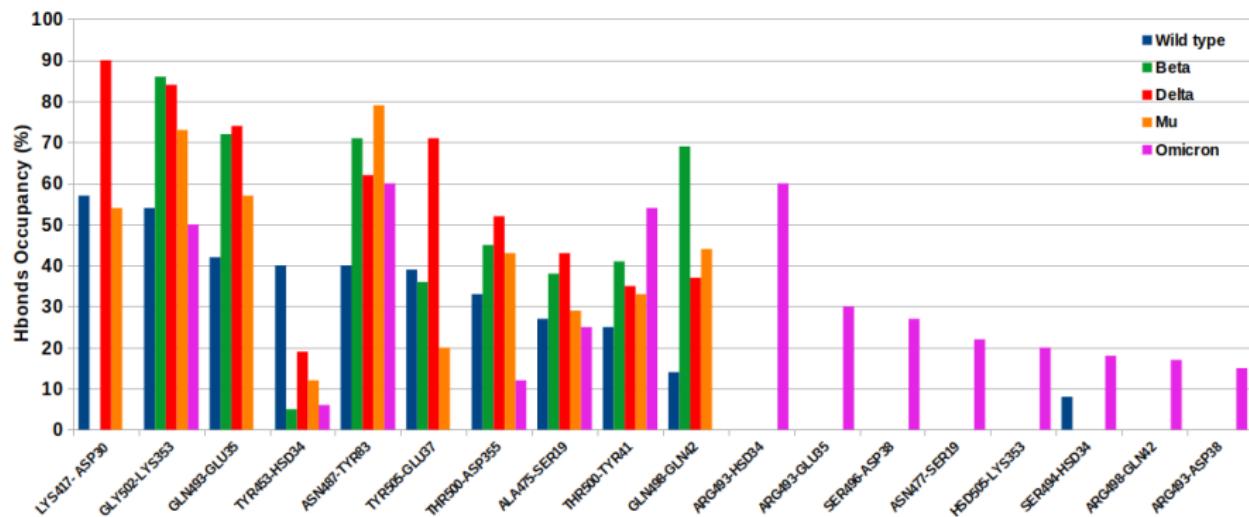
# ■Hydrogen Bonds Occupancy

Hydrogen Bonds		Wild type	Beta	Delta	Mu	Omicron
Donor	Acceptor	Occupancy				
LYS417-Side	ASP30-Side	57.00%	-	90.08%	54.31%	-
GLY502-Main	LYS353-Main	54.12%	86.30%	84.13%	73.35%	49.50%
GLN493-Side	GLU35-Side	41.56%	71.50%	74.01%	57.31%	30.02%
HSD34-Side	TYR453-Side	39.88%	-	18.65%	-	-
TYR83-Side	ASN487-Side	39.40%	70.80%	61.81%	76.35%	60.24%
TYR505-Side	GLU37-Side	38.72%	36.25%	71.33%	19.64%	-
THR500-Side	ASP355-Side	32.96%	44.79%	52.08%	43.29%	11.55%
SER19-Side	ALA475-Main	27.04%	11.92%	33.23%	-	-
THR500-Side	TYR41-Side	25.08%	40.91%	35.32%	32.87%	53.71%
GLN498-Side	GLN42-Side	-	35.65%	20.24%	27.25%	16.87%
GLN42-Side	GLN498-Side	-	33.76%	16.47%	16.43%	-
LYS31-Side	GLN493-Side	12.92%	12.71%	15.48%	13.03%	-
LYS353-Side	GLN498-Side	-	-	14.68%	-	-
GLN498-Side	ASP38-Side	-	-	13.49%	-	-
ASN487-Side	GLN24-Side	-	12.41%	10.32%	-	-
SER19-Main	ALA475-Main	-	25.92%	10.12%	20.64%	19.08%
GLN24-Side	ALA475-Main	-	-	-	15.83%	-
ARG493-Side	HSD34-Side	-	-	-	-	59.94%
SER496-Side	ASP38-Side	-	-	-	-	26.51%
SER19-Main	ASN477-Side	-	-	-	-	22.39%
LYS353-Side	HSD505-Side	-	-	-	-	18.67%
HSD34-Side	SER494-Main	-	-	-	-	17.97%
ARG493-Side	ASP38-Side	-	-	-	-	14.76%

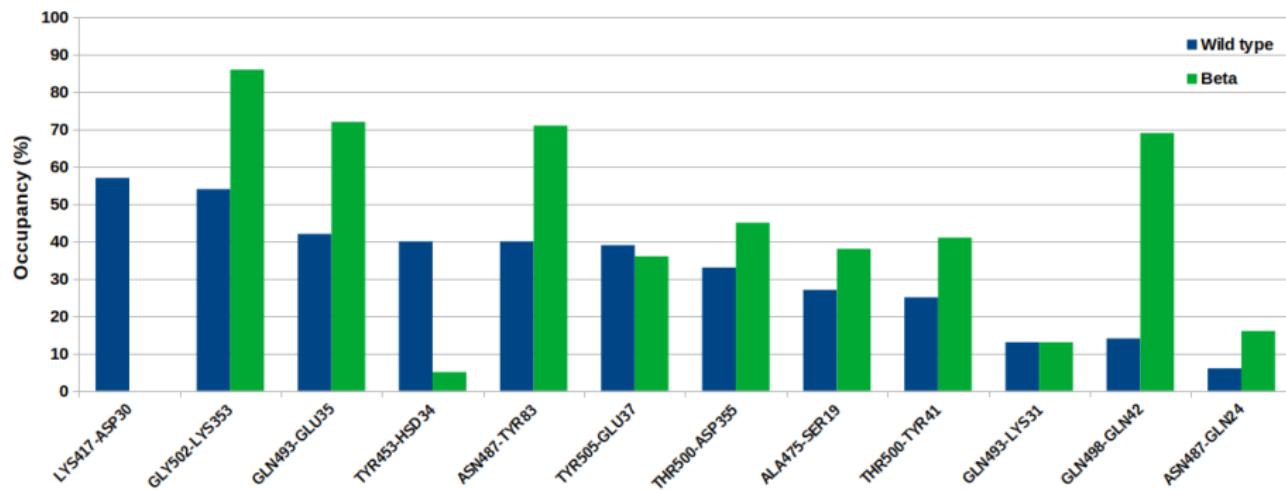
# ■Hydrogen Bonds Occupancy

RBD-hACE2	Wild type	Beta	Delta	Mu	Omicron
	Occupancy (%)				
LYS417-ASP30	57	-	90	54	-
GLY502-LYS353	54	86	84	73	50
GLN493-GLU35	42	72	74	57	-
TYR453-HSD34	40	5	19	12	6
ASN487-TYR83	40	71	62	79	60
TYR505-GLU37	39	36	71	20	-
THR500-ASP355	33	45	52	43	12
ALA475-SER19	27	38	43	29	25
THR500-TYR41	25	41	35	33	54
GLN493-LYS31	13	13	15	13	-
GLN498-GLN42	14	69	37	44	-
GLN498-LYS353	3	-	15	-	-
GLN498-ASP38	3	-	13	-	-
ASN487-GLN24	6	16	14	12	9
ALA475-GLN24	3	5	7	16	7
ARG493-HSD34	-	-	-	-	60
ARG493-GLU35	-	-	-	-	30
SER496-ASP38	-	-	-	-	27
ASN477-SER19	-	-	-	-	22
HSD505-LYS353	-	-	-	-	20
SER494-HSD34	8	-	-	-	18
ARG498-GLN42	-	-	-	-	17
ARG493-ASP38	-	-	-	-	15
ARG498-ASP38	-	-	48	-	7

# ■Hydrogen Bonds Occupancy Comparison



# ■Hydrogen Bonds: $\beta$ and Wild Type



## ■ Hydrogen Bonds: $\beta$ and Wild Type

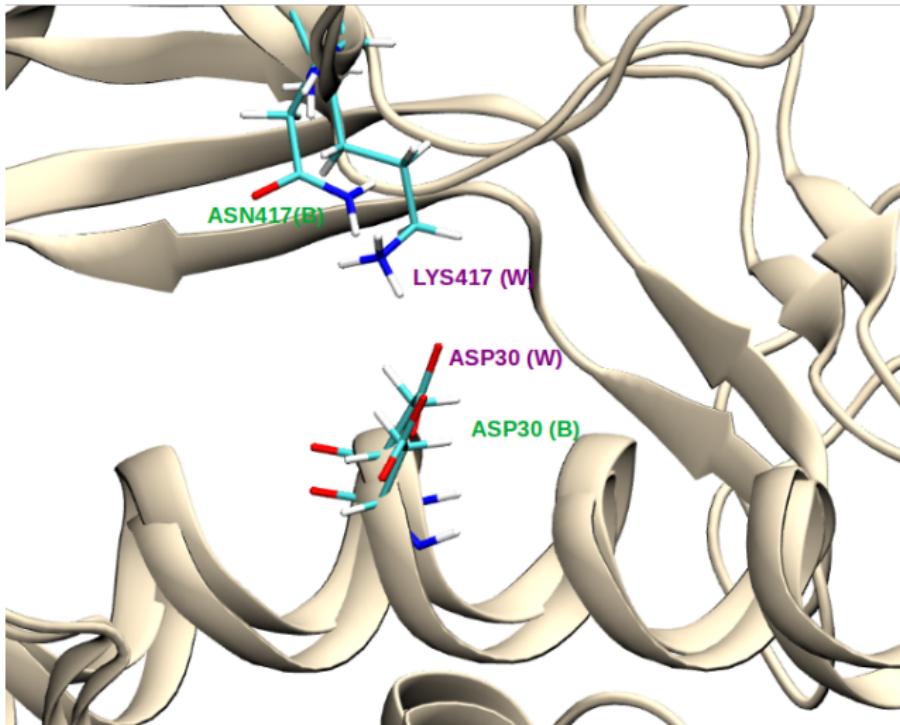
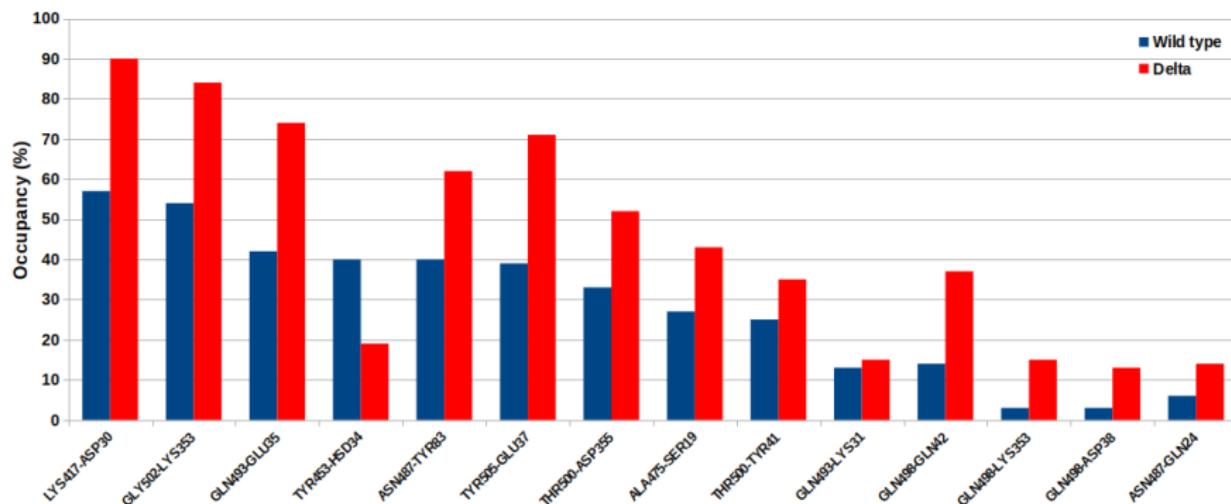
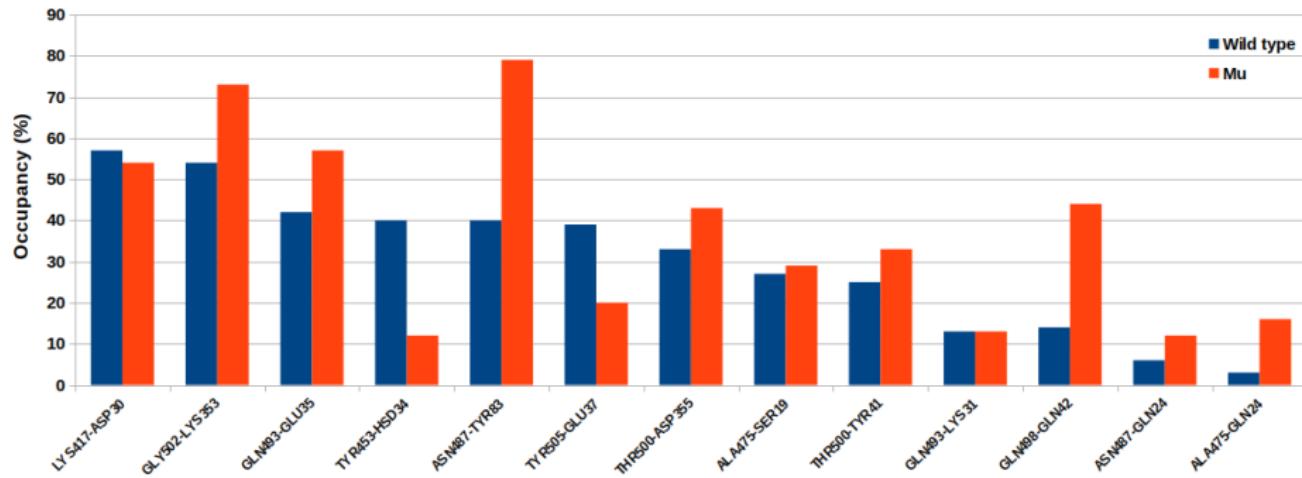


Figure: K417N Mutation in  $\beta$  variant

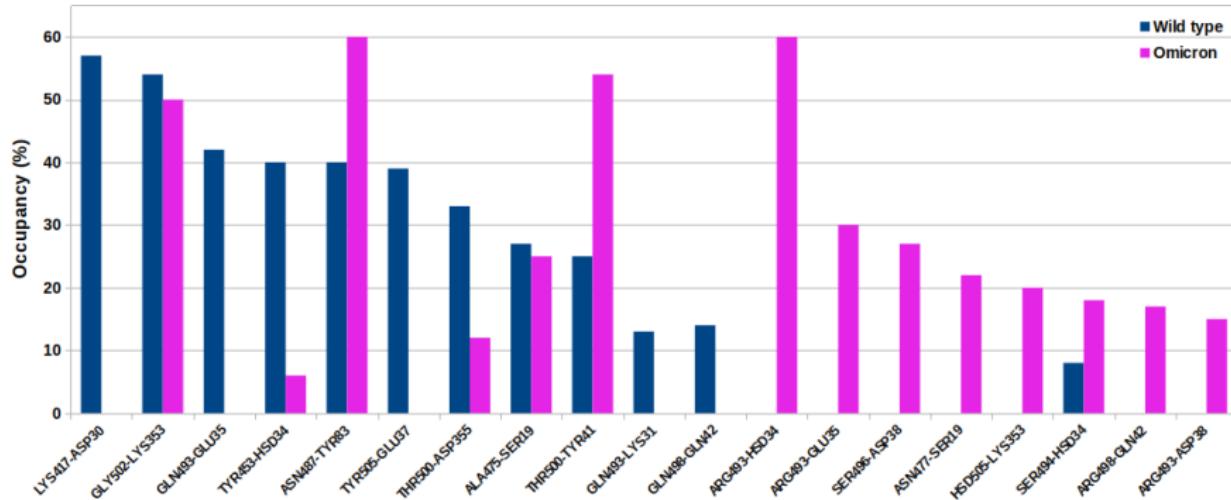
# ■Hydrogen Bonds: $\delta$ and Wild Type



# ■Hydrogen Bonds: $\mu$ and Wild Type



# ■Hydrogen Bonds: in Omicron & Wild Type



# ■Hydrogen Bonds: Omicron and Wild Type

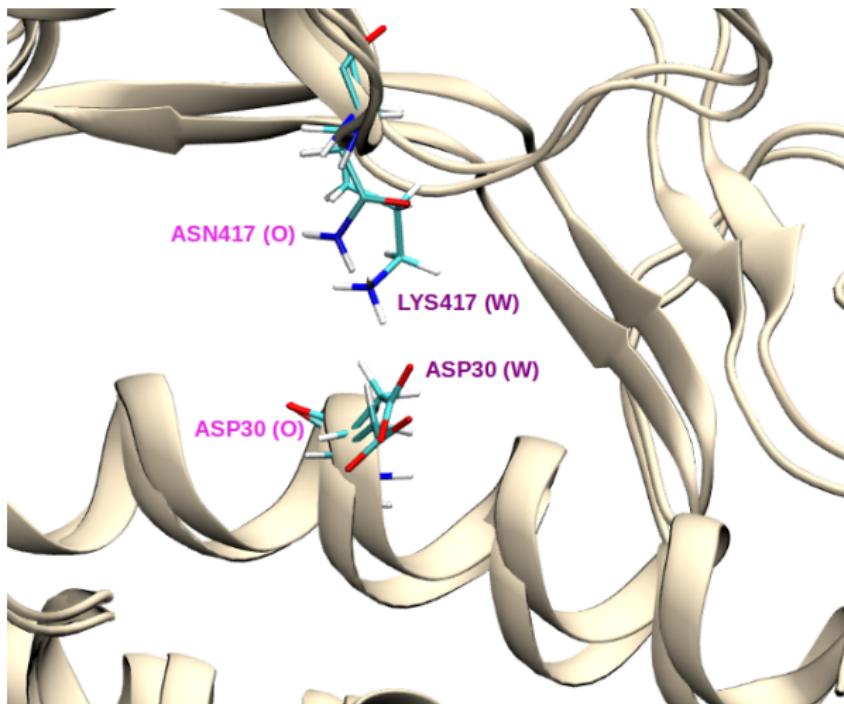


Figure: K417N Mutation in Omicron variant

# ■ Hydrogen Bonds: Omicron and Wild Type

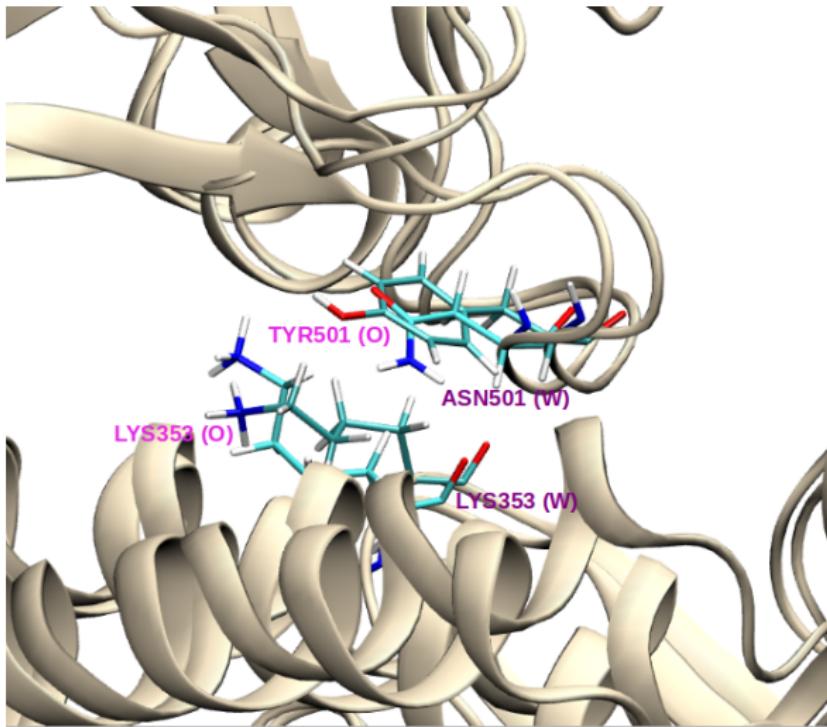


Figure: N501Y Mutation in Omicron variant

# ■Hydrogen Bonds: Omicron and Wild Type

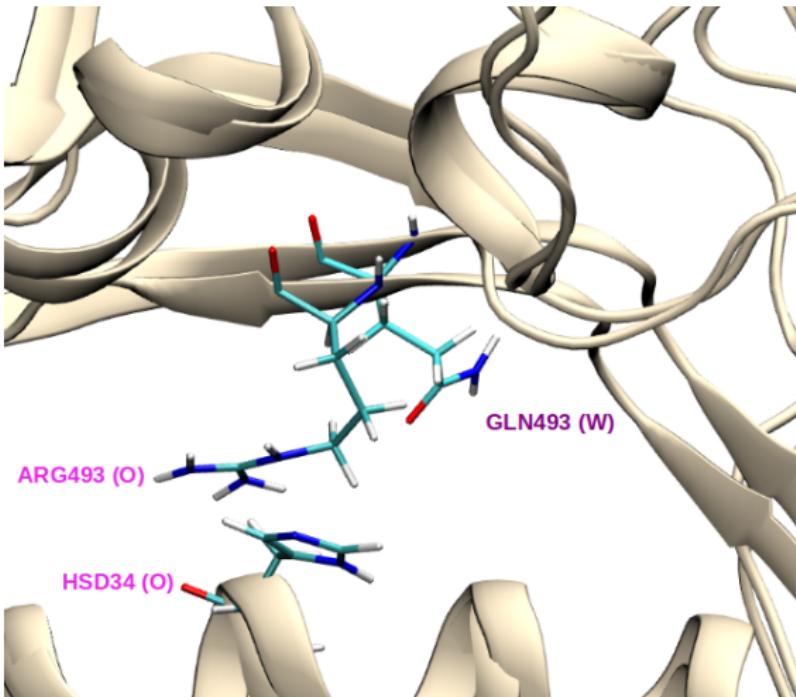
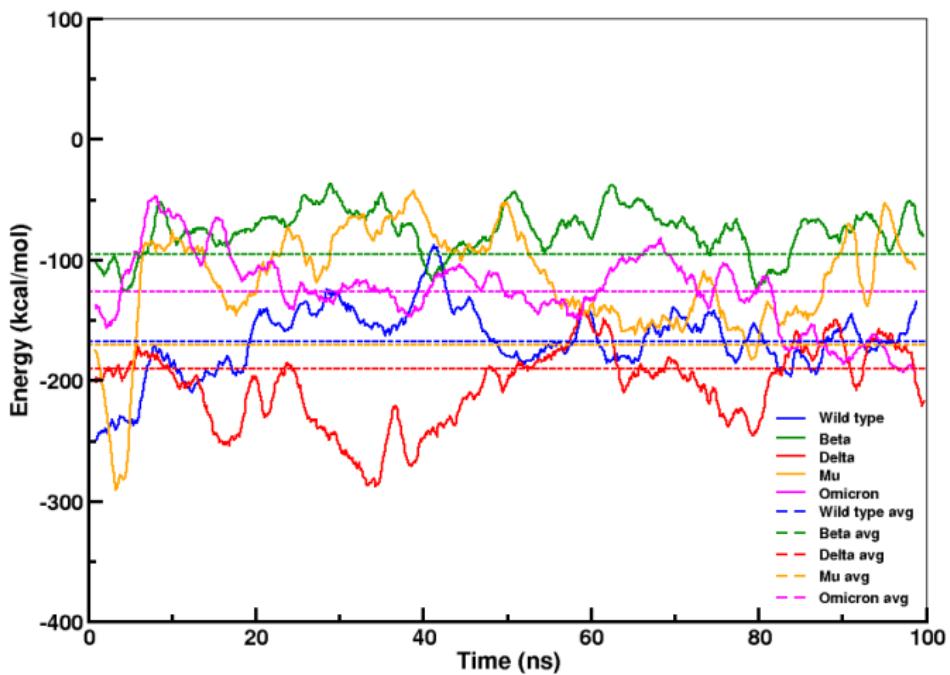
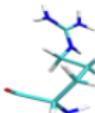
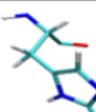
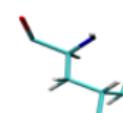
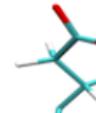


Figure: Q493R Mutation in Omicron variant

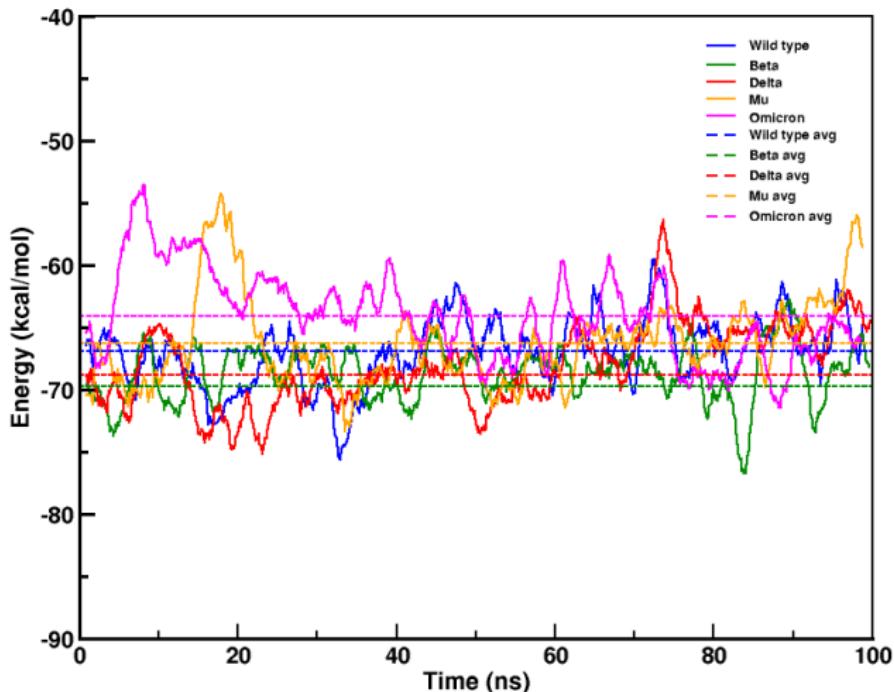
## ■Electrostatic Interactions in variants



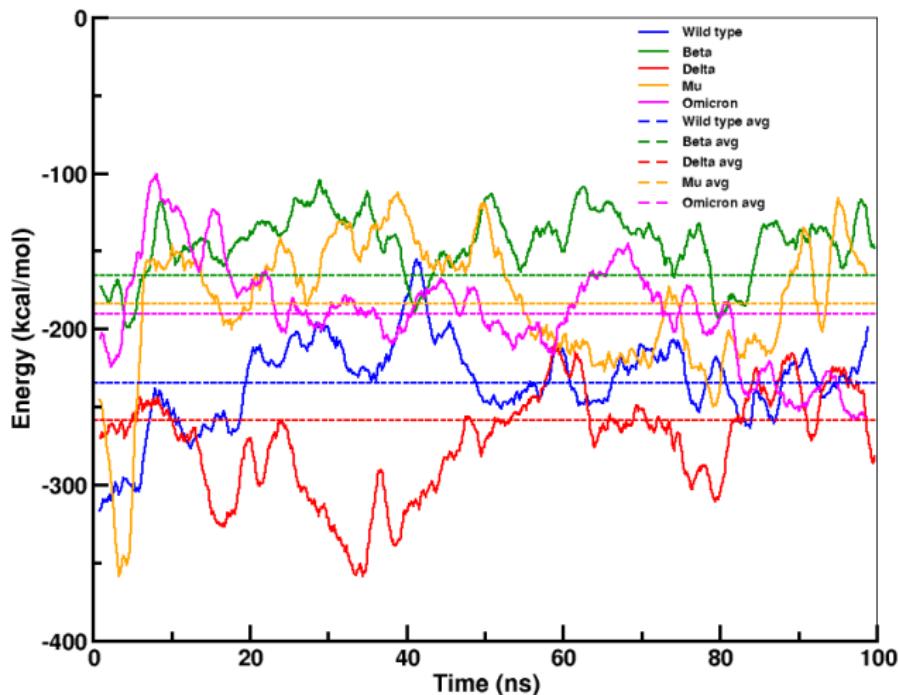
# ■Electrostatic Interactions in variants

Amino Acid Residues	
+ve Charged	-ve Charged
ARG	
LYS	
HIS	
GLU	
ASP	
	-

# ■ van der Waals Interactions in variants



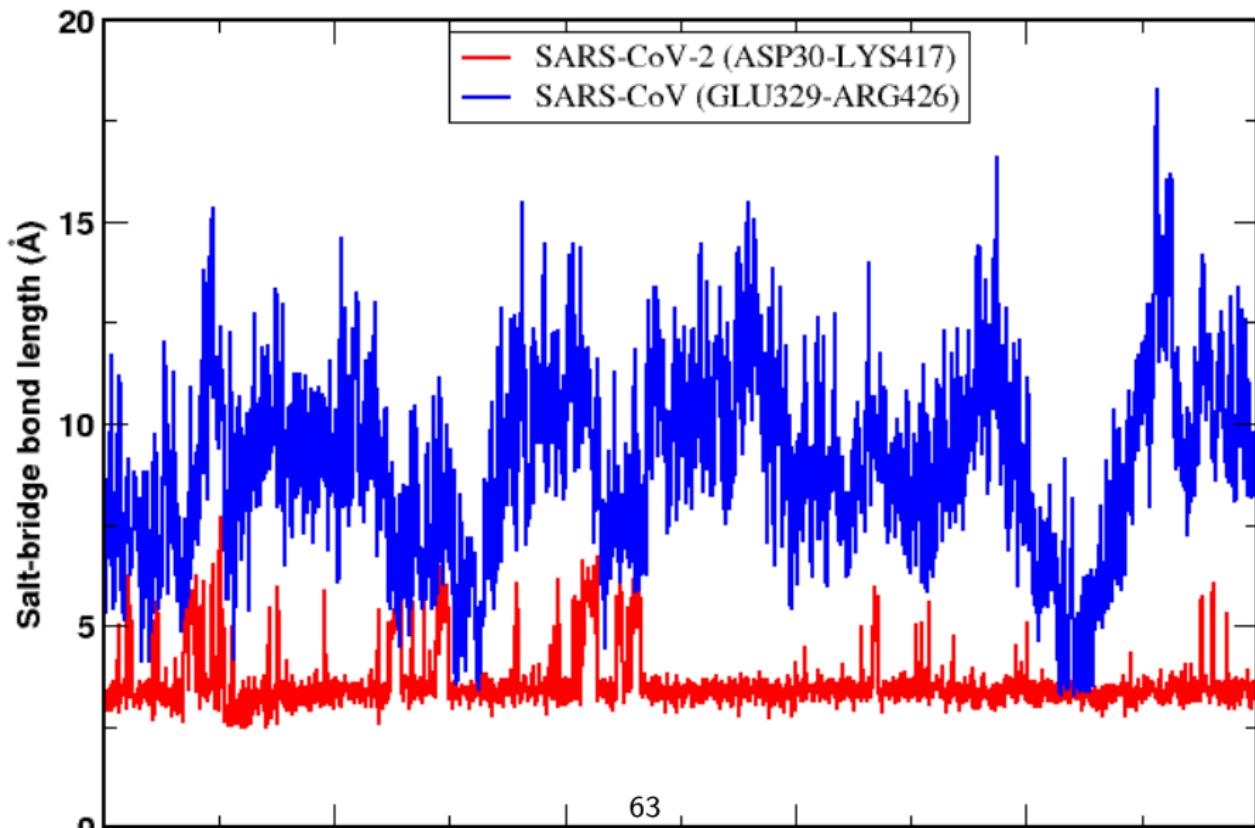
# ■nonbonded Interactions in variants



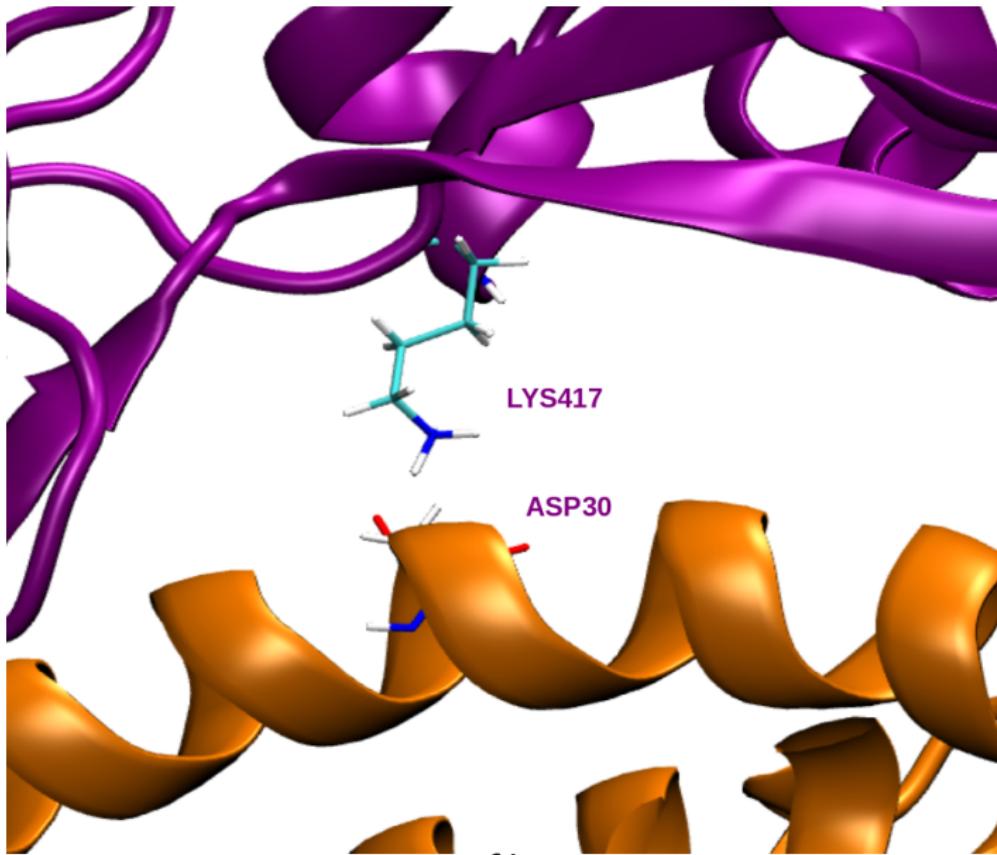
# ■Electrostatic & vDW Interactions in variants

Variants	Electrostatic (kcal/mol)	vdW (kcal/mol)	Non-bonded (kcal/mol)
Wild type	-174.83 ± 1.97	-68.72 ± 0.23	-243.55 ± 1.95
Beta	-95.90 ± 0.90	-69.73 ± 0.16	-165.63 ± 0.93
Delta	-190.03 ± 1.33	-68.83 ± 0.18	-258.85 ± 1.35
Mu	-177.33 ± 2.33	-66.23 ± 0.26	-183.55 ± 2.32
Omicron	-126.06 ± 1.21	-64.10 ± 0.19	-190.16 ± 1.28

# Salt Bridge Interactions in variants



## ■ Salt Bridge Interactions in variants



## ■ Salt Bridge Interactions in variants

Variants	Average Distance (Å)
Wild type	$3.59 \pm 0.03$
Delta	$3.49 \pm 0.02$
Mu	$5.22 \pm 0.10$

## Solvent accessible surface area - RBD

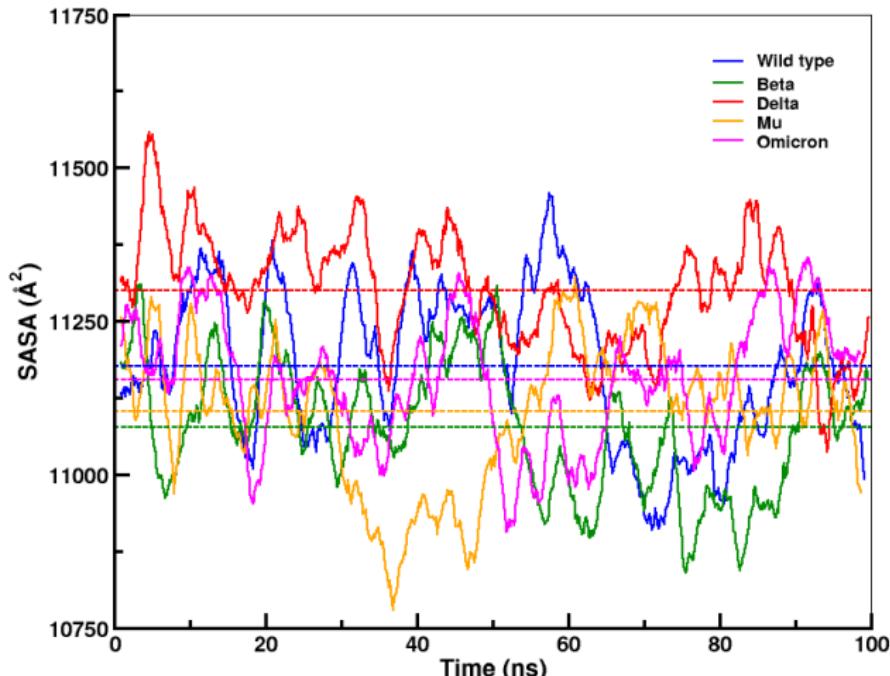


Figure: SASA of RBD

## Solvent accessible surface area - hACE2

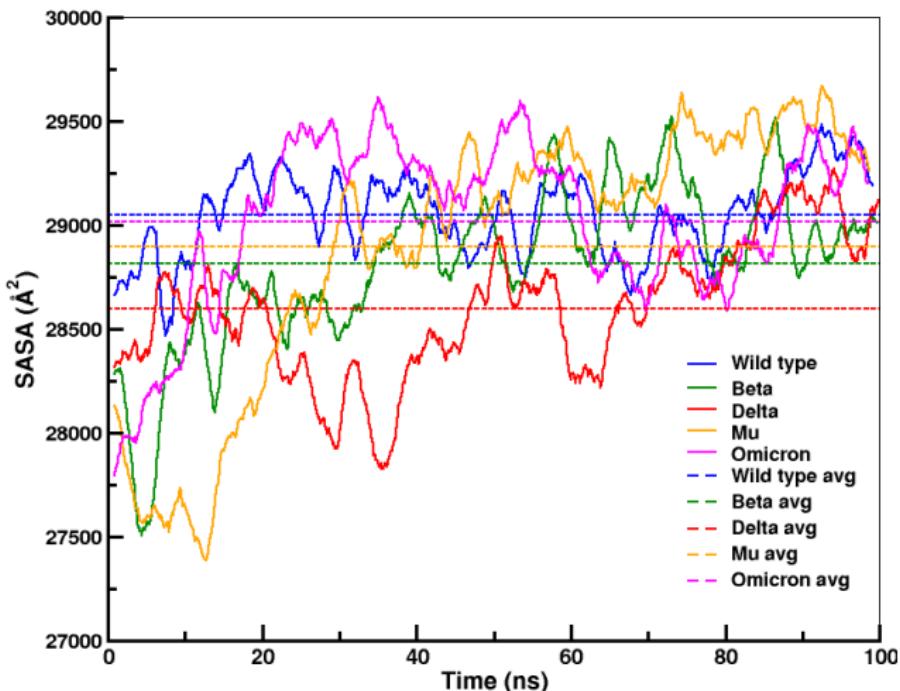


Figure: SASA of hACE2

# SASA - RBD/hACE2

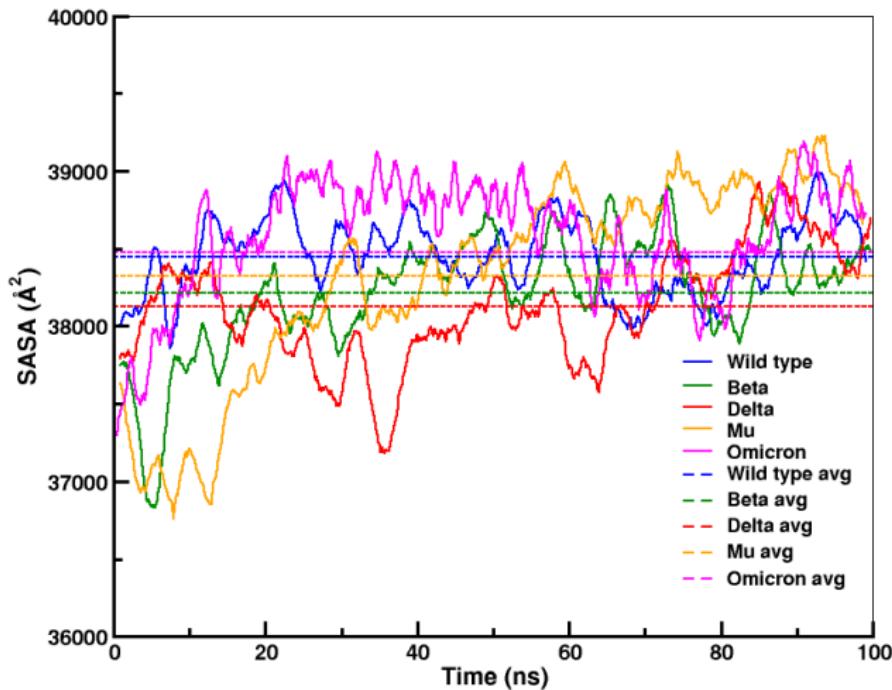


Figure: SASA of RBD/hACE2 Complex

# SASA - RBD/hACE2

Variants	Solvent Accessible Surface Area ( $\text{\AA}^2$ )			Net Contact Area ( $\text{\AA}^2$ )
	hACE2	RBD	Complex	
Wild type	29046.90 $\pm$ 12.65	11177.93 $\pm$ 7.46	38447.53 $\pm$ 15.10	888.65 $\pm$ 10.53
Beta	28810.64 $\pm$ 14.03	11078.36 $\pm$ 4.96	38212.08 $\pm$ 14.46	838.46 $\pm$ 10.37
Delta	28595.04 $\pm$ 12.35	11299.79 $\pm$ 4.79	38123.39 $\pm$ 13.90	885.72 $\pm$ 9.61
Mu	28892.39 $\pm$ 29.85	11102.94 $\pm$ 7.23	38322.84 $\pm$ 30.66	836.25 $\pm$ 21.69
Omicron	29011.01 $\pm$ 14.88	11154.45 $\pm$ 4.86	38575.04 $\pm$ 14.13	795.21 $\pm$ 10.54

Figure: SASA of RBD/hACE2 Complex

# ■Hydrophobic Interaction

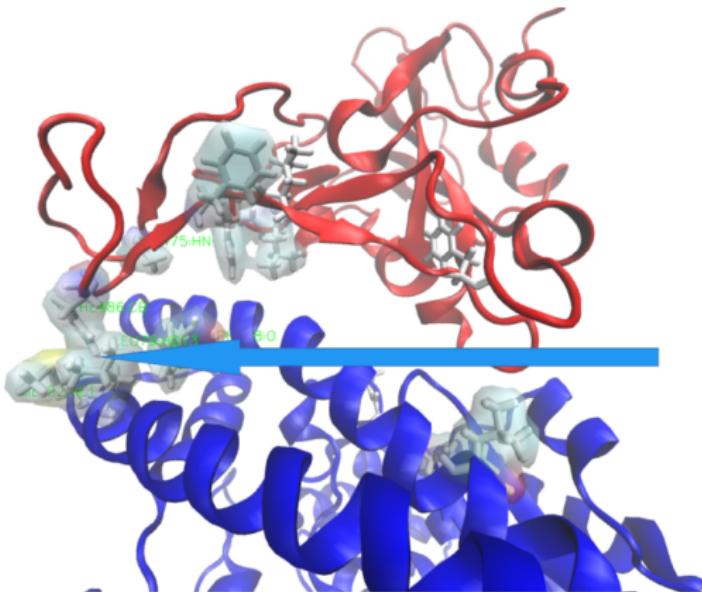


Figure: Phenylalanine486 in RBD inserts into the hydrophobic groove created by phenylalanine28, L79 and Methionine82 in hACE2

# ■Hydrophobic Interaction

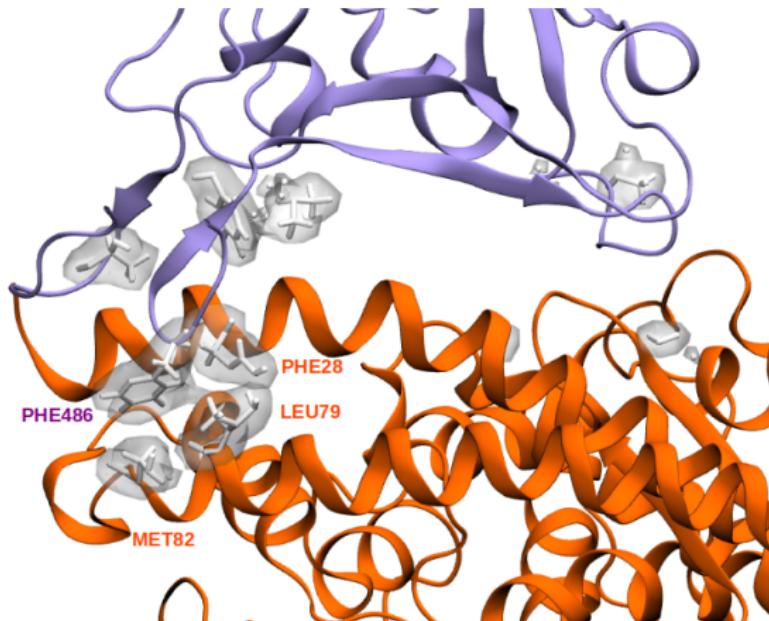


Figure: F486 in RBD inserts into the hydrophobic groove created by F28, L79 and M82 in hACE2

## ■Umbrella Sampling

- It is useful to sample easily unreachable phase points
- We need to use first a biasing potential (we use harmonic one) to sample such points in phase space
- Then to estimate the binding free energy we apply WHAM (Weighted Histogram Analysis Method)

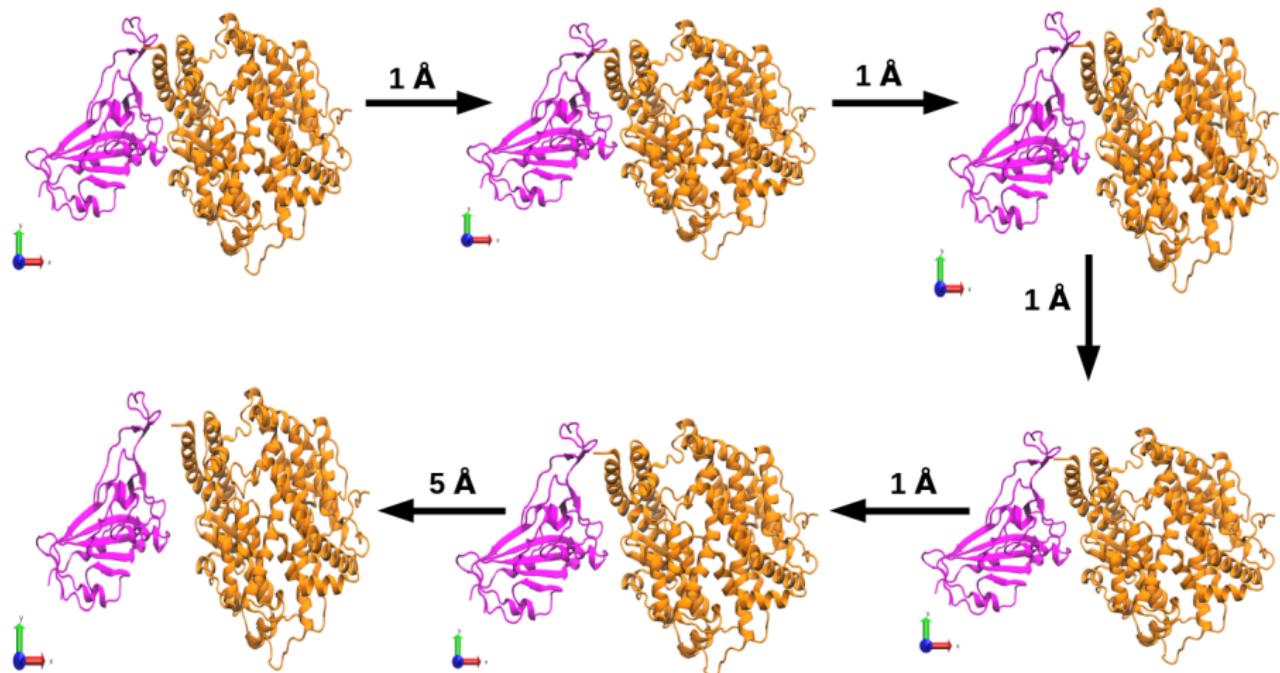
## ■Umbrella Sampling

- One can use various quantities like dihedral angle, distance etc. as reaction coordinates we use distance between COM of RBD and hACE2
- Force constant ( $k$ ) = 1.5 kcal/mol $^{-2}$
- Equilibration: NVT 5 ns (1.0 fs/step)
- Production: NPT 10 ns (2.0 fs/step)

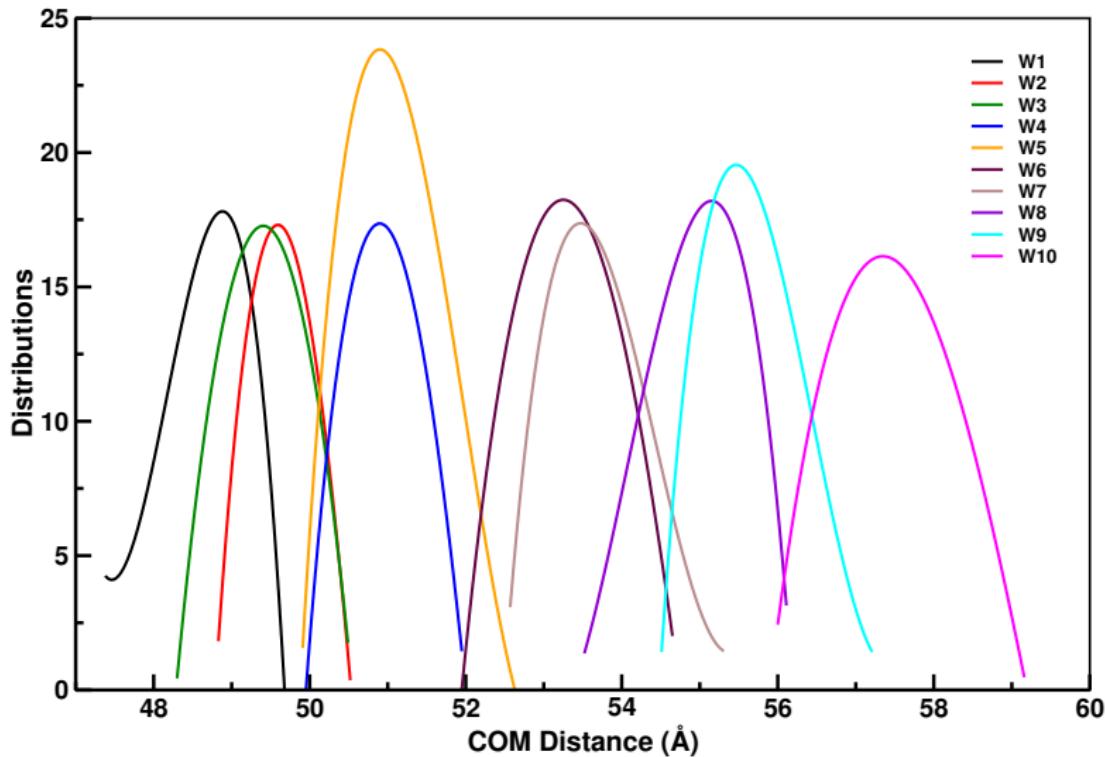
# ■Umbrella Sampling

Variants	System Size ( $\text{\AA}^3$ )	Ions Added (0.15 M conc.)	Simulation Time (ns)
<b>Wild type</b>	250 X 90 X 90	191 $\text{Na}^+$ and 168 $\text{Cl}^-$	10
<b>Beta</b>	250 X 90 X 90	192 $\text{Na}^+$ and 168 $\text{Cl}^-$	10
<b>Delta</b>	250 X 90 X 90	191 $\text{Na}^+$ and 168 $\text{Cl}^-$	10
<b>Mu</b>	250 X 90 X 90	191 $\text{Na}^+$ and 168 $\text{Cl}^-$	10
<b>Omicron</b>	250 X 90 X 90	190 $\text{Na}^+$ and 168 $\text{Cl}^-$	10

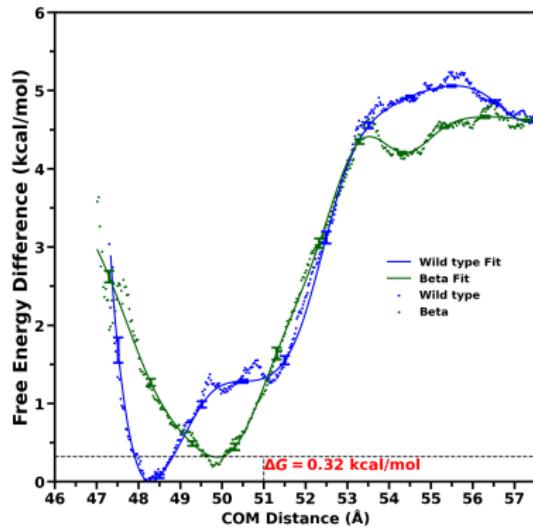
# ■ Umbrella Sampling



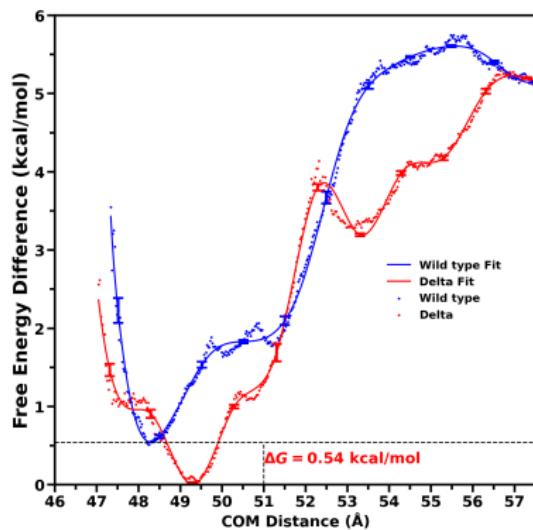
# ■Umbrella Sampling



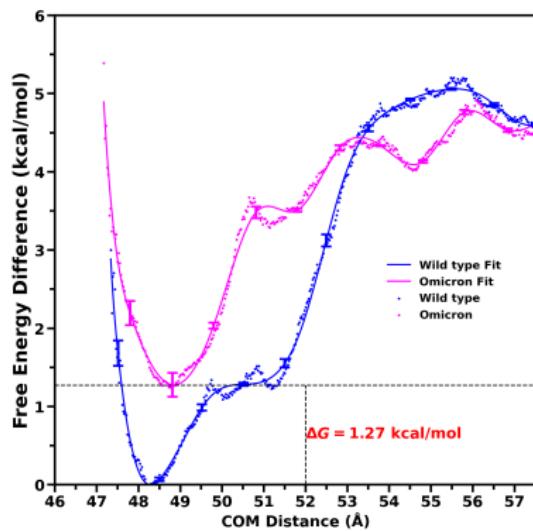
# ■ Umbrella Sampling $\beta$



# ■ Umbrella Sampling $\delta$



# ■ Umbrella Sampling Omicron



# ■ Umbrella Sampling & SMD

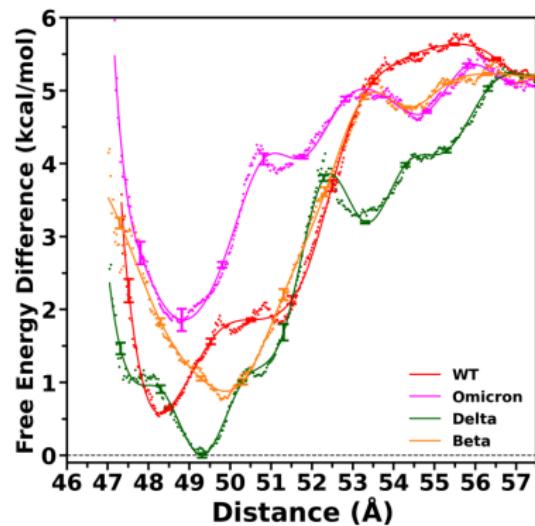
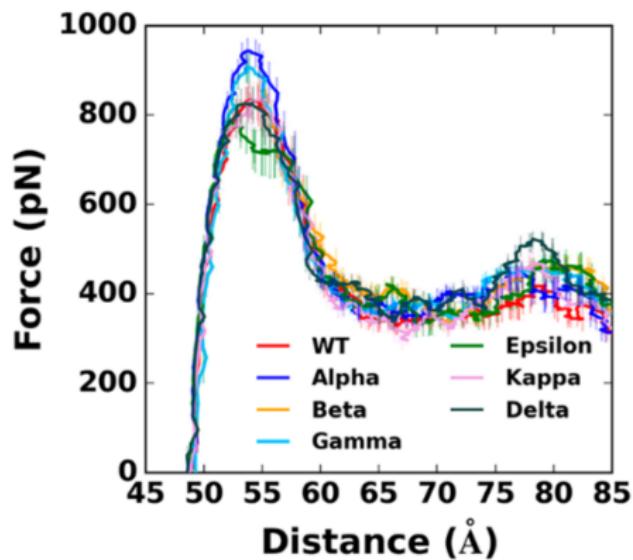


Figure: SMD Kim et al from J. Chem. Theory Comput. 2021, 17, 7070-7070

## ■ MM/GBSA binding Free Energy

- One of the ways to get binding free energy is Molecular Mechanics Generalized Born surface Area (MM/GBSA) method
- In this method we consider all the energy terms and entropic contributions
- In MMGBSA method the free energy of a state that is P1, P2 or P1P2 is estimated from

## ■ MM/GBSA binding Free Energy

$$G = E_{bnd} + E_{el} + E_{vdW} + G_{pol} + G_{np} - TS \quad (1)$$

where the first three terms are standard MM energy terms from bonded (bond, angle and dihedral), electrostatic and van der Waals interactions.  $G_{pol}$  and  $G_{np}$  are the polar and non-polar contributions to the solvation free energies.  $G_{pol}$  is typically obtained by using the generalized Born (GB) model (giving the MM/GBSA approach), whereas the non-polar term is estimated from a linear relation to the solvent accessible surface area (SASA). The last term in above Equation is the absolute temperature, T, multiplied by the entropy, S, estimated by a normal-mode analysis of the vibrational frequencies.

## ■ MM/GBSA binding Free Energy

Variants	MM/GBSA Energy (kcal/mol)
Wild type	- 44.15 ± 8.07
Beta	-38.69± 6.53
Delta	- 44.93 ± 7.69
Mu	- 37.31 ± 7.98
Omicron	-36.2 ± 7.61

## ■Conclusions and Concluding Remarks

- Changes in hydrogen bonds due to mutations in different variants like  $\beta$ ,  $\delta$ ,  $\mu$  and Omicron have been studied
- Similarly changes in salt bridge, hydrophobic, van der Waals Electrostatic interactions have been studied due to mutations
- Our results show that  $\delta$  variants have highest binding free energy.
- Our US Sampling results agree with previously reported results by SMD

# ■Acknowledgement

- Lokendra Singh Dhami
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- Narayan Gautam
- Shyam Khanal
- Rajendra Koirala
- Jhulan Powrel
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- GU: Tiwari
- IITK: Nair
- JNCASR: Narasimhan
- IITKGP: Taraphder
- UM:MacKerrel
- IISER Pune: Ghosh, Singh
- TIFRH: Shenoy
- SNBNCBS: (Late) Mookerjee
- Ph.D. Students: Kaphle, Pantha, Lamichhane, Khanal, Pokhrel, Koirala, Thapa, Khatri, Neupane, Powrel
- M.Sc. Students: > 200...

*Thank  
you!*