Supplementary Material

Probing Conformational Landscapes of Binding and Allostery in the SARS-CoV-2 Omicron Variant Complexes Using Microsecond Atomistic Simulations and Perturbation-Based Profiling Approaches: Hidden Role of Omicron Mutations as Modulators of Allosteric Signaling and Epistatic Relationships

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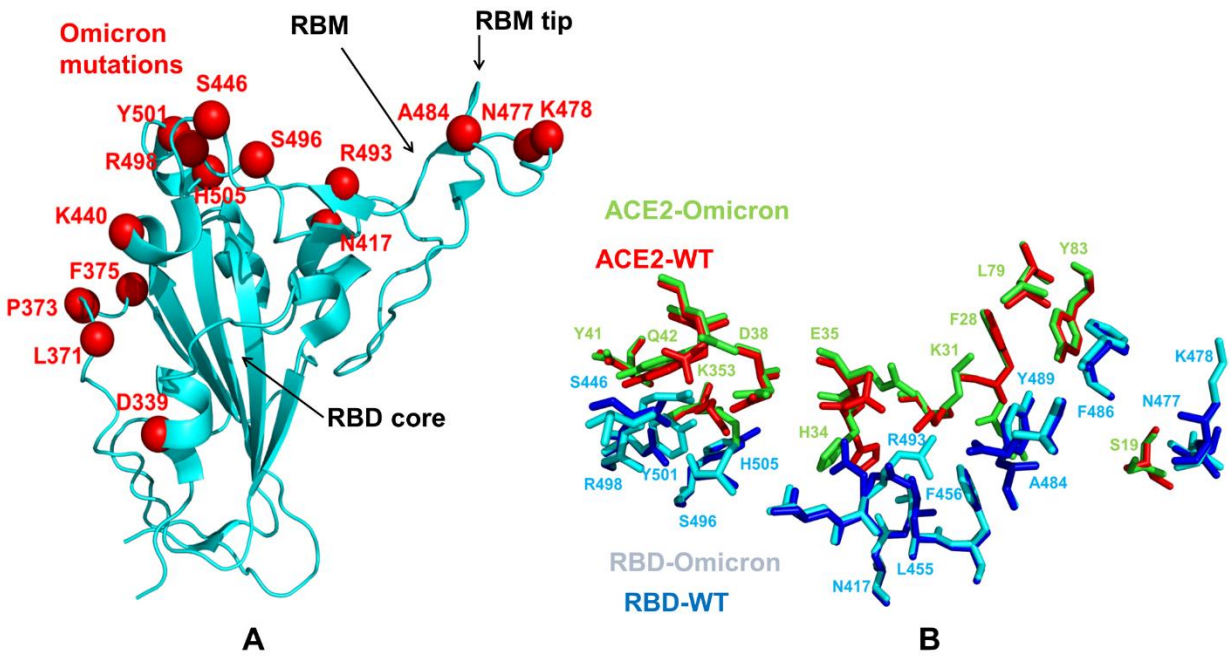

Figure S1. The SARS-CoV-2 RBD structure and binding interface residues in the RBD-ACE2 complexes. (A) The structure of the S-RBD (in ribbons) with Omicron mutations shown in red spheres. The RBD core region, the RBM region and the RBM tip motif are indicated by arrows. (B) Superposition of the RBD-ACE2 binding interface residues for the WT RBD-ACE2 complex (pdb id 6M0J) and Omicron BA1 RBD-ACE2 (pdb id 7WBP).

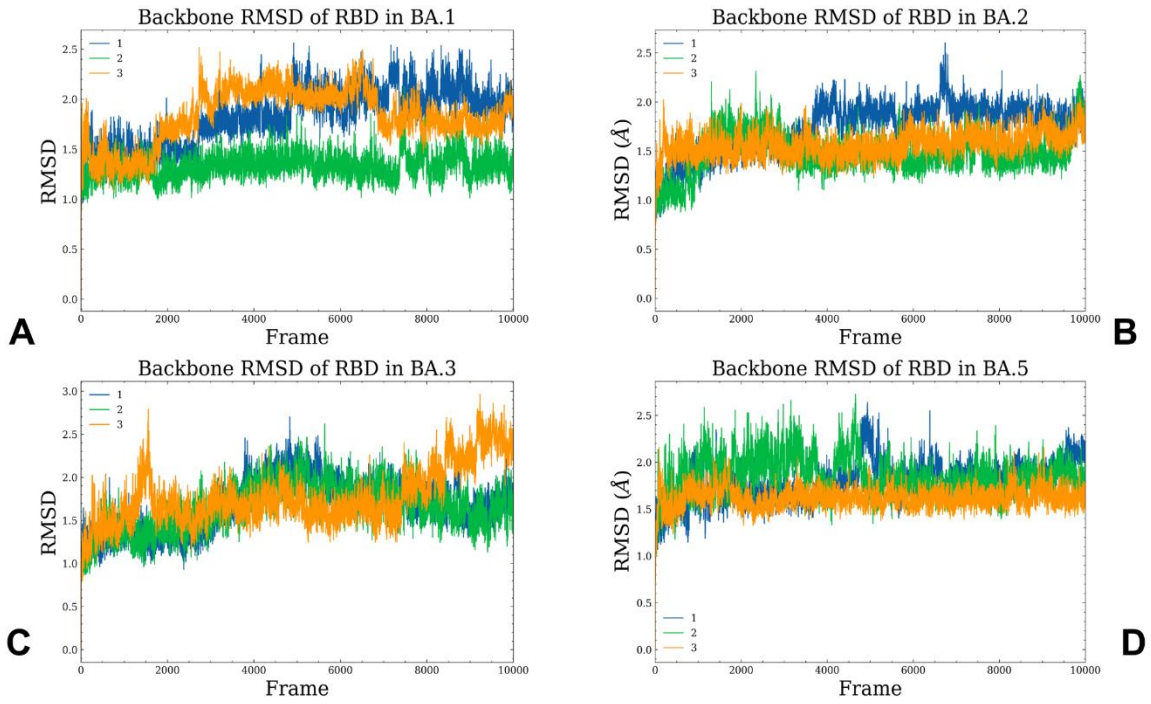

Figure S2. Conformational dynamics profiles obtained from all-atom MD simulations of the Omicron RBD BA.1, BA.2, BA.3 and BA.4/BA.5 complexes with hACE2. The RMSD profiles for the RBD residues obtained from 3 microsecond MD simulations of the Omicron RBD BA.1-hACE2 complex, pdb id 7WBP (A), Omicron RBD BA.2-hACE2 complex, pdb id 7XB0 (B), Omicron RBD BA.3-hACE2 complex, pdb id 7XB1 (C) and Omicron RBD BA.4/BA.5-hACE2 complex, pdb id 7XWA (D).

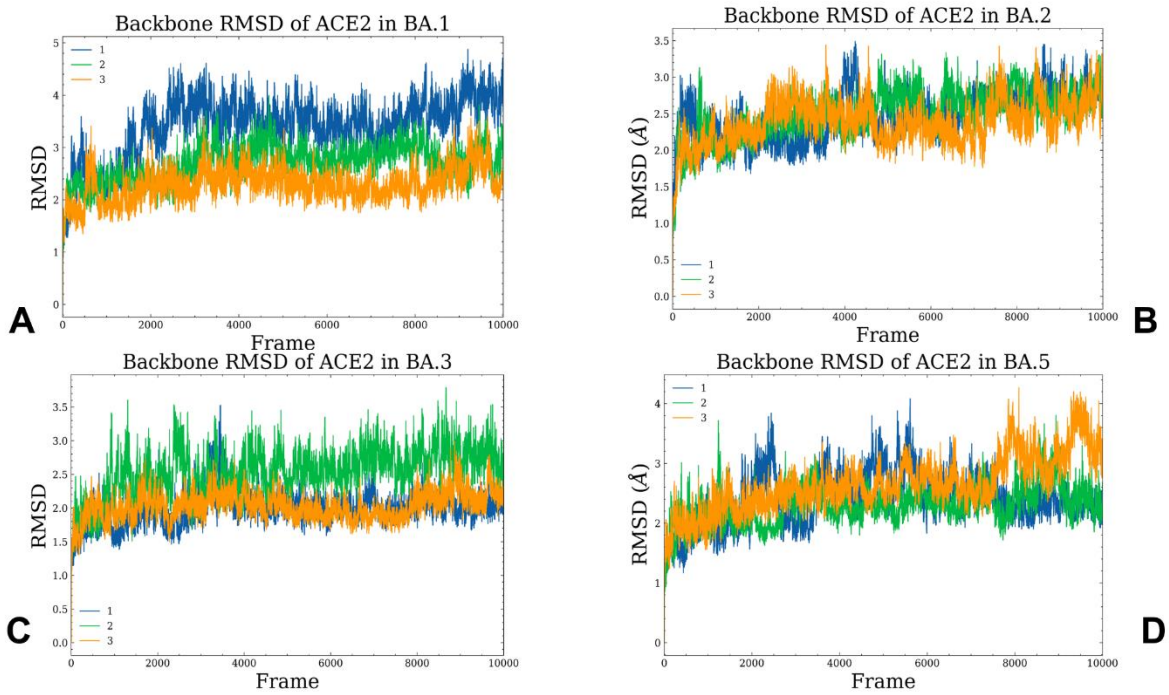

Figure S3. Conformational dynamics profiles of the ACE2 residues obtained from MD simulations of the Omicron RBD BA.1, BA.2, BA.3 and BA.4/BA.5 complexes with hACE2. The RMSD profiles for the ACE2 residues obtained from 3 microsecond MD simulations of the Omicron RBD BA.1-hACE2 complex, pdb id 7WBP (A), Omicron RBD BA.2-hACE2 complex, pdb id 7XB0 (B), Omicron RBD BA.3-hACE2 complex, pdb id 7XB1 (C) and Omicron RBD BA.4/BA.5-hACE2 complex, pdb id 7XWA (D).

Table S1. Statistical analysis of the intermolecular contact residues in Omicron RBD-hACE2 complexes.*

ACE2	BA.1 RBD	BA.2 RBD	BA.3 RBD	BA.4/5 RBD
S19	A475, G476,N477	A475, G476,N477	A475, G476,N477	A475, G476,N477
T20		N477	A475,N477	N477
Q24	A475, G476,N477 F486, N487, Y489	A475, G476,N477 F486,N487, Y489	A475, G476,N477 F486,N487, Y489	A475, G476,N477, N487, Y489
T27	F456, Y473, A475,Y489	F456, Y473, A475,Y489	F456, Y473, A475,Y489	F456,Y473, A475,Y489
F28	N487,Y489	N487,Y489	Y489	F456, N487,Y489
F30	L455, F456	N417, L455, F456	L455, F456	L455, F456, Q493
K31	L455, F456, Y489,R493	L455, F456, G485,Y489, R493	L455, F456, Y489,R493	L455, F456, Y489,Q493
H34	Y453, L455, R493, S494, Y495	R403, N417, Y453, L455, R493	N417, Y453, L455, R493	N417, Y453, L455, R493
E35	R493	R493	R493	Q493
E37	H505	H505	H505	H505
D38	Y449, S496, R498, Y501	Y449, Y495, G496, R498, Y501	Y449, Y495, R498, Y501	Y449, Y495, G496, R498, Y501
Y41	R498, T500, Y501	R498, T500, Y501	R498, T500, Y501	R498, T500, Y501
Q42	S446, Y449, R498	Y449, R498	Y449, R498	Y449, R498
L45	R498,T500	V445, R498,T500	V445, R498,T500	V445, R498,T500
L79	F486	G485, F486	F486	V486
M82	F486	F486	F486	V486

Y83	F486, N487, Y489	F486, N487, Y489	F486, N487, Y489	N487, Y489
Q325	V593	Q506	V503, Q506	
G326			T500	T500
N330	T500	P499,T500	P499,T500	P499,T500
G352		Y501,G502	Y501,G502	Y501
K353	R403, Y495, S496, T500, Y501, G502, H505	R403,Y495, T500,Y501, G502,V503, H505	R403, Y495, T500,Y501, G502,V503, H505	Y495, T500,Y501, G502, H505
G354	T500,Y501, G502,V503, H505	T500,Y501, G502,V503, H505	T500,Y501, G502,V503, H505	Y501, G502,V503, H505
D355	T500, Y501,G502	T500, Y501,G502	T500, Y501,G502	T500, Y501,G502
R357		T500		T500

*Two residues are defined in contact if any of their heavy atom is within a distance of 5.0 Å

Table S2. The Occupancy of the Pairwise Interactions in the Omicron RBD-hACE2 Complexes

	Interaction	BA.1-ACE2	BA.2-ACE2	BA.3-ACE2	BA.4/BA.5-ACE2
Salt bridges	R403-E37	65%	73%	73%	62%
	K440-E329	31%	54%	54%	53%
	R493-E35	77%	92%	99%	
	R493-D38	26%	89%	89%	
	R498-D38	59%	95%	83%	78%
Hydrophobic Interactions	F456-T27	95%	96%	88%	57%
	Y473-T27	92%	89%	85%	72%
	A475-T27	88%	93%	83%	66%
	F486-F28	78%	97%	90%	54%
	F486/V486-L79	85%	89%	82%	57%
	F486/V486-M82	85%	96%	90%	62%
	F486/V486-Y83	90%	95%	87%	53%
	Y489-F28	97%	94%	95%	86%
	Y489-L79	90%	95%	86%	72%
	Y489-Y83	96%	82%	88%	77%
Hydrogen Bonds	Y453-H34	66%	82%	92%	52%
	Y449-D38	65%	82%	58%	60%
	A475-S19	60%	95%	85%	82%
	N477-S19	58%	97%	97%	69%
	N487-Q24	62%	92%	92%	71%
	N487-Y83	76%	92%	90%	54%
	Y489-F28	82%	86%	80%	68%
	T500-D355	82%	77%	90%	72%
	T500-Y41	72%	80%	95%	54%
	G502-K353	78%	84%	78%	67%
	Y501-K353	86%	90%	84%	77%
	Q493-K31				87%
	Q493-H34				90%