The Principles of Ligand Specificity on beta-2-adrenergic receptor

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Supporting Information

Table Suppl. 1

Figure Suppl. 1-5

Table Suppl. 1a| The average root-mean-square-fluctuations (RMSFs) of the 16 residues responsible for protein-ligand interactions, in the presence of agonists, antagonists and inverse agonists.

		Average RMSFs (Å)		
Residues	Backbone atoms	Agonists	Antagonists	Inverse agonists
W109$^{3.28}$	N	0.640	0.517	0.524
	Cα	0.599	0.488	0.490
	C	0.569	0.458	0.454
D113$^{3.32}$	N	0.493	0.407	0.405
	Cα	0.500	0.414	0.407
	C	0.504	0.421	0.416
V114$^{3.33}$	N	0.485	0.391	0.395
	Cα	0.497	0.401	0.404
	C	0.500	0.415	0.414
V117$^{3.36}$	N	0.524	0.441	0.433
	Cα	0.544	0.456	0.440
	C	0.535	0.448	0.426
F193^{ECL2}	N	0.819	0.692	0.655
	Cα	0.824	0.674	0.638
	C	0.800	0.674	0.640
Y199$^{5.38}$	N	0.720	0.731	0.702
	Cα	0.696	0.698	0.681
	C	0.692	0.635	0.641
S203$^{5.42}$	N	0.713	0.573	0.568
	Cα	0.719	0.568	0.552
	C	0.707	0.549	0.542
S204$^{5.43}$	N	0.698	0.540	0.539
	Cα	0.715	0.564	0.568
	C	0.735	0.578	0.578
S207$^{5.46}$	N	0.801	0.607	0.589
	Cα	0.811	0.623	0.604
	C	0.751	0.618	0.595
W286$^{6.48}$	N	0.664	0.528	0.507
	Cα	0.666	0.525	0.505
	C	0.679	0.544	0.531
F289$^{6.51}$	N	0.680	0.582	0.576
	Cα	0.642	0.553	0.554
	C	0.630	0.535	0.543
F290$^{6.52}$	N	0.644	0.537	0.544
	Cα	0.663	0.550	0.556
	C	0.728	0.588	0.599
N293$^{6.55}$	N	0.760	0.673	0.691
	Cα	0.826	0.724	0.741
	C	0.882	0.743	0.783

Table Suppl. 1a (Cont'd)

Residues	Backbone atoms	Average RMSFs (Å)		
		Agonists	Antagonists	Inverse agonists
Y308$^{7.35}$	N	0.859	0.722	0.732
	Cα	0.831	0.680	0.692
	C	0.804	0.628	0.634
I309$^{7.36}$	N	0.841	0.639	0.646
	Cα	0.848	0.632	0.638
	C	0.791	0.589	0.595
N312$^{7.39}$	N	0.626	0.504	0.512
	Cα	0.639	0.484	0.497
	C	0.625	0.482	0.495

Table Suppl. 1b| The results of two-tailed t-tests assuming equal variances at $p < 0.01$.

	Agon vs. Anta		Agon vs. iAgo		Anta vs. iAgo	
Data Statistics	Agon	Anta	Agon	iAgo	Anta	iAgo
Mean	0.685682	0.56288	0.685682	0.559682	0.56288	0.559682
Variance	0.012928	0.009618	0.012928	0.009831	0.009618	0.009831
Observations	48	48	48	48	48	48
Pooled Variance	0.011273		0.01138		0.009725	
Hypothesized Mean Difference	0		0		0	
t Stat	5.666115		5.786397		0.158865	
P(T<=t) two-tail	1.59E-07		9.41E-08		0.874116	
t Critical two-tail	2.629148		2.629148		2.629148	

* Agon, Anta and iAgo stand for agonists, antagonists, and inverse agonists.

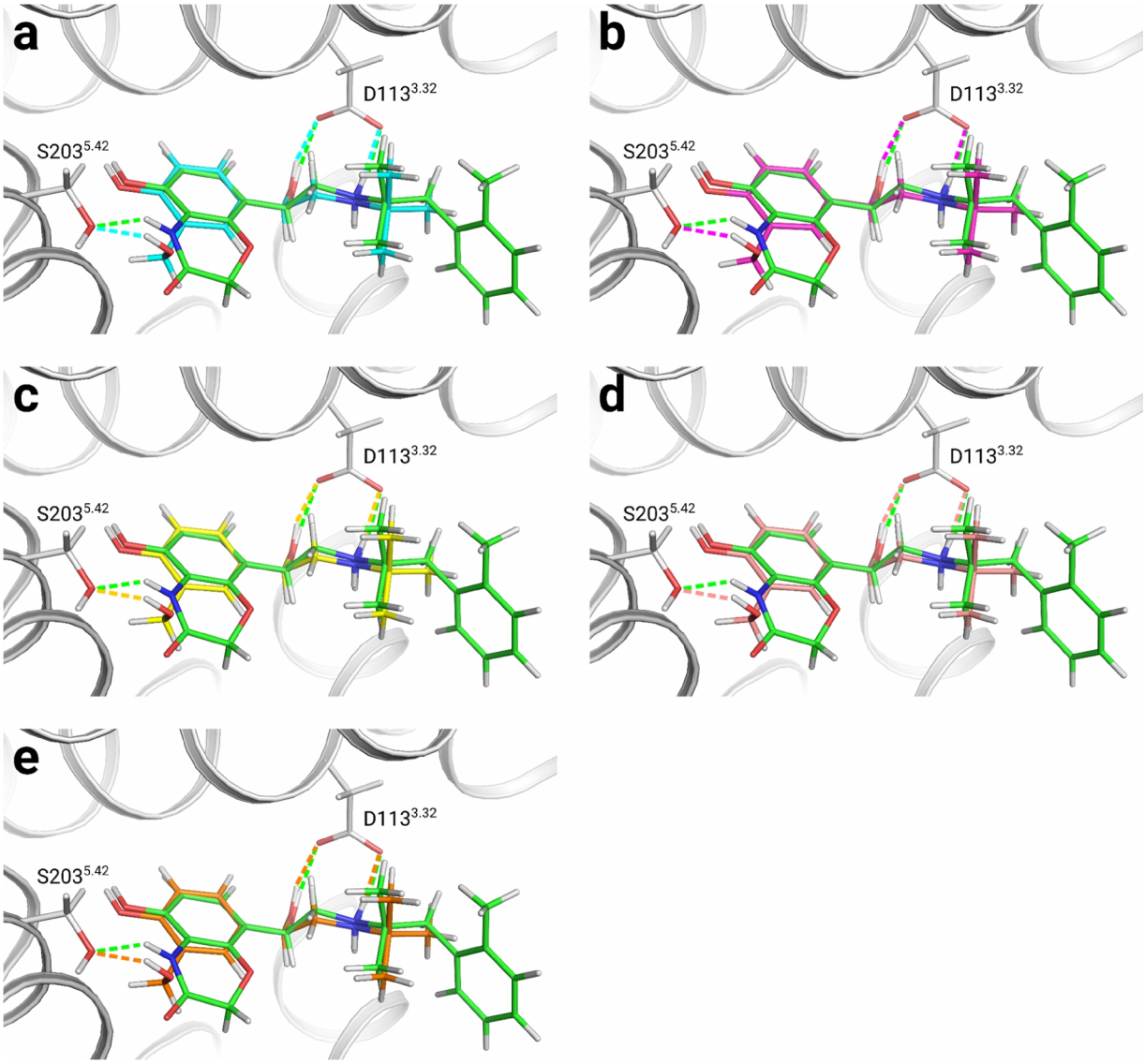

Figure Suppl. 1| The overlays of the best five docking poses of salbutamol (Agon-4) on 4LDE. (a) (green) BI167107 (Agon-1) in 4LDE; (cyan) the rank 1 pose of salbutamol (Agon-4). (b) (green) BI167107 (Agon-1) in 4LDE; (magenta) the rank 2 pose of salbutamol (Agon-4). (c) (green) BI167107 (Agon-1) in 4LDE; (yellow) the rank 3 pose of salbutamol (Agon-4). (d) (green) BI167107 (Agon-1) in 4LDE; (pink) the rank 4 pose of salbutamol (Agon-4). (e) (green) BI167107 (Agon-1) in 4LDE; (orange) the rank 5 pose of salbutamol (Agon-4).

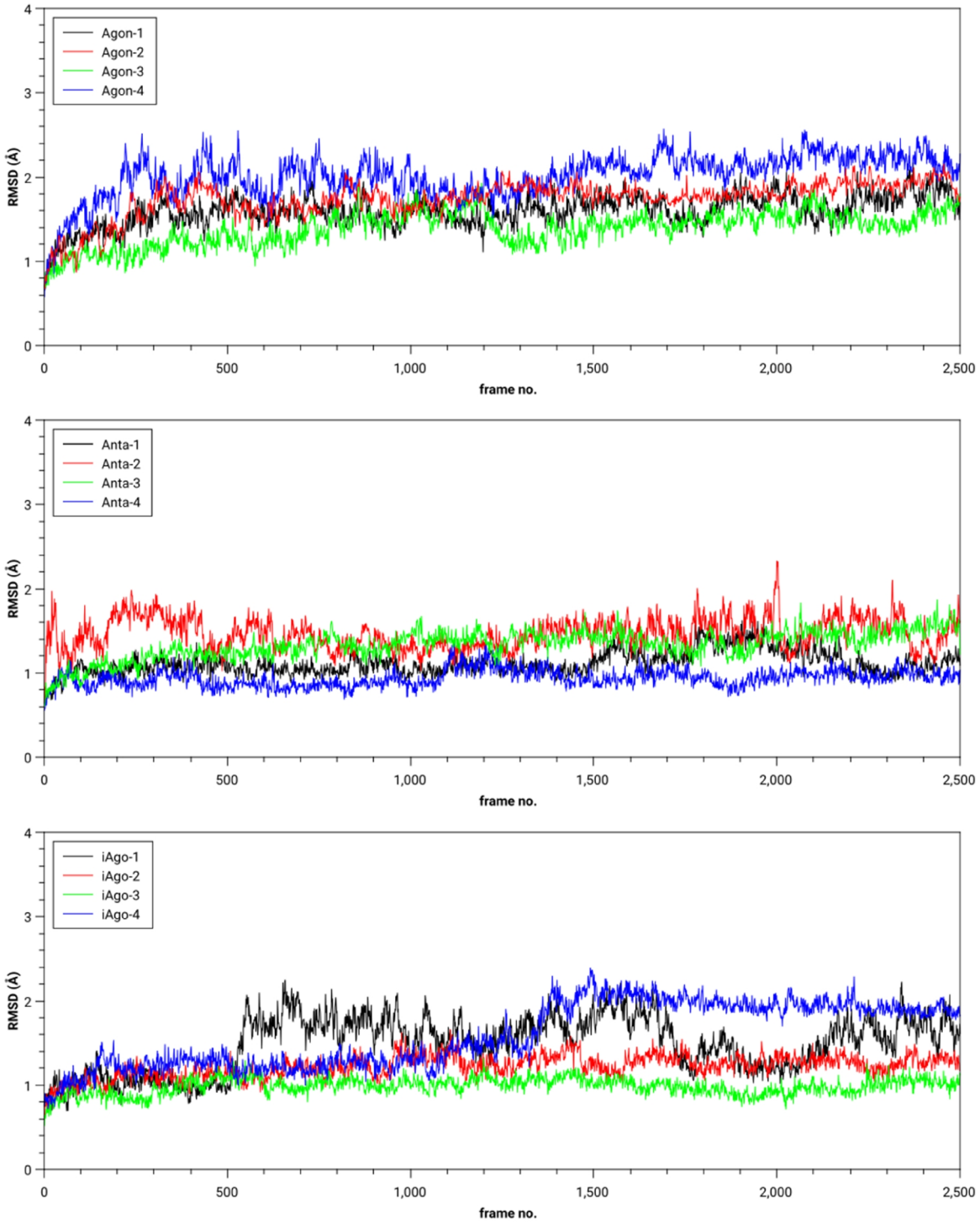

Figure Suppl. 2| The root-mean-square deviations (RMSDs) of the protein helices with respect to the starting frame.

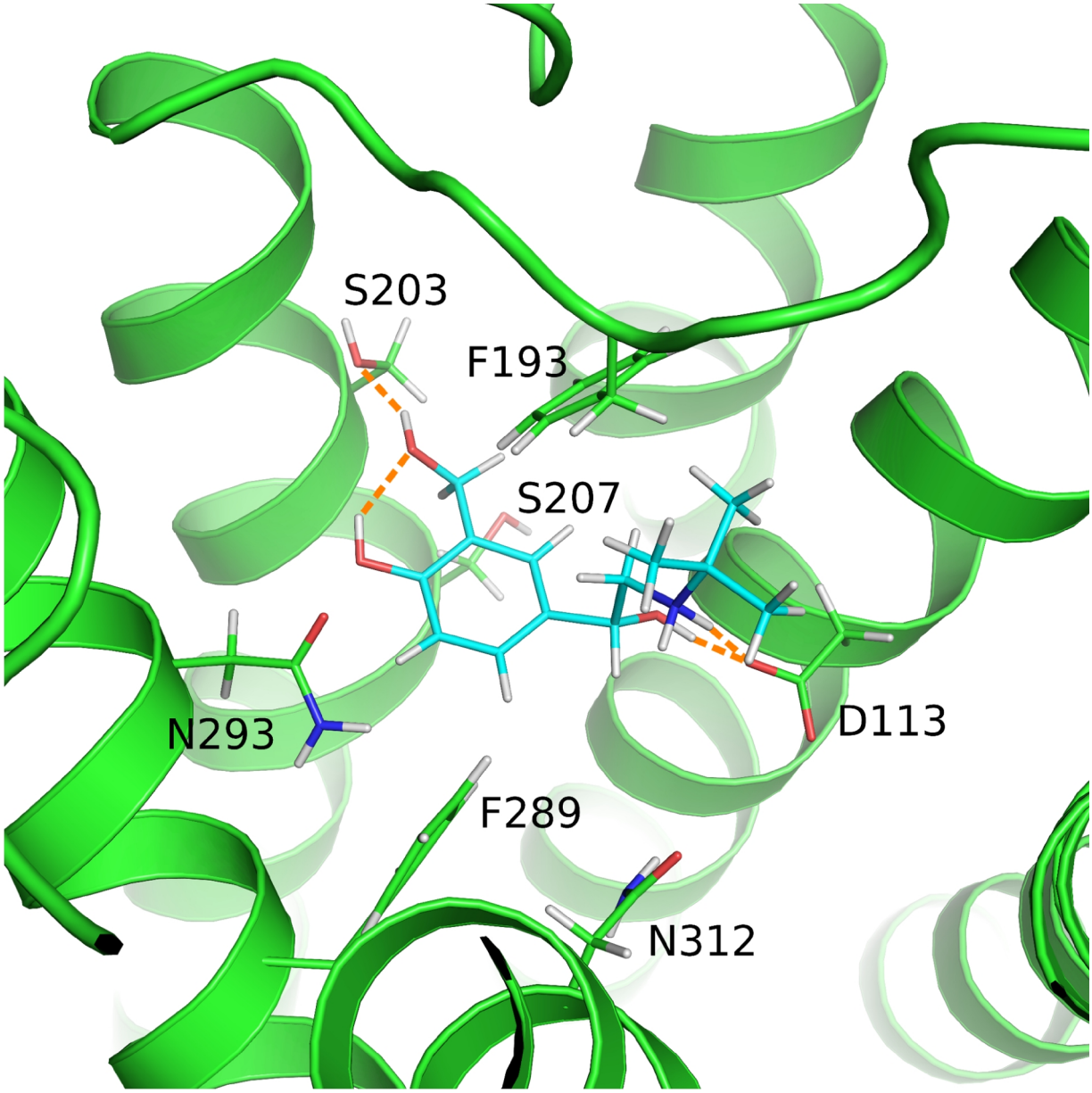

Figure Suppl. 3| The docking pose of salbutamol (Agon-4).

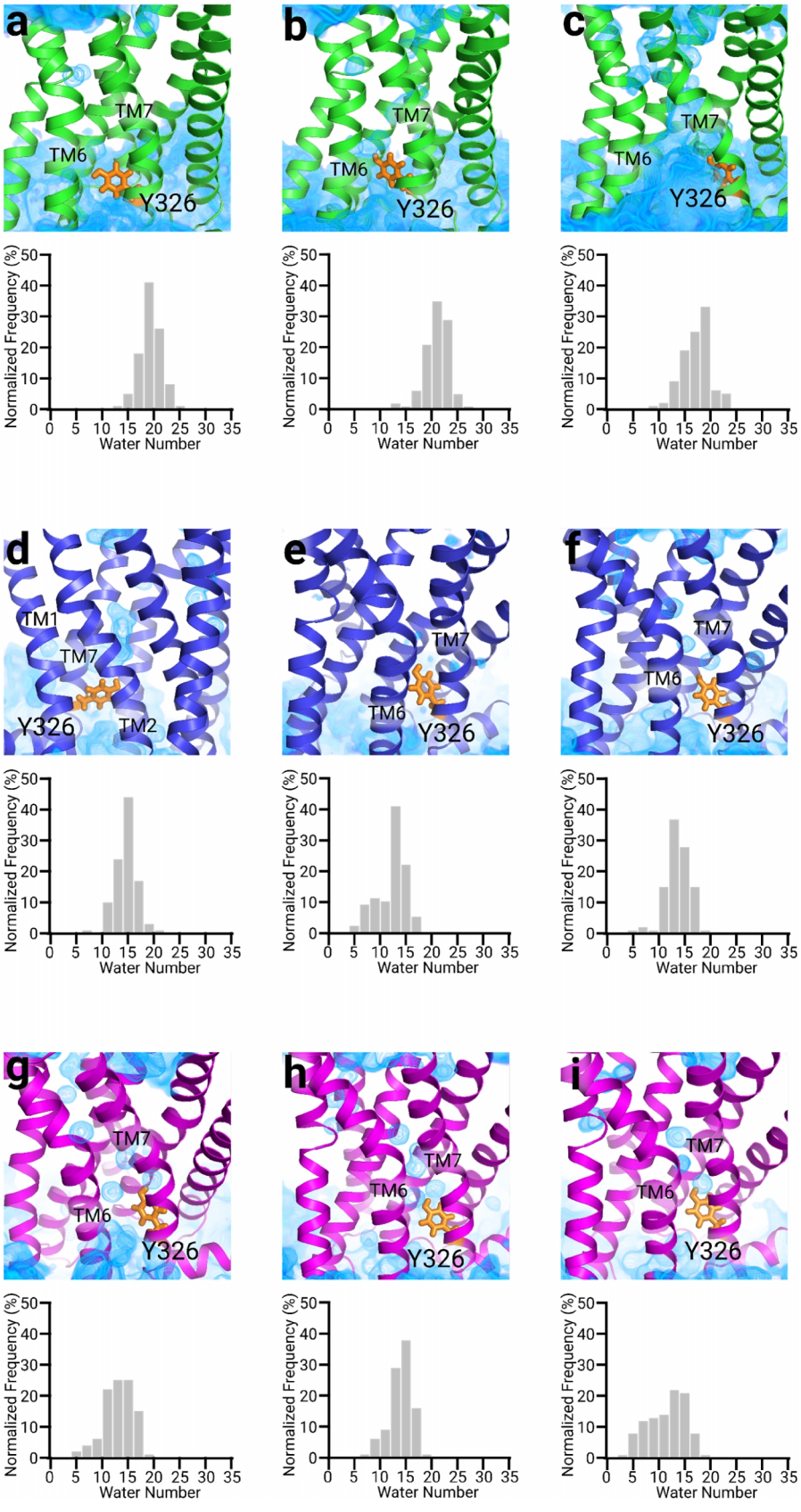
a
TM7
TM6
Y326
b
TM7
TM6
Y326
c
TM7
TM6
Y326
Normalized Frequency (%)
Water Number
d
TM1
TM7
Y326
TM2
e
TM7
TM6
Y326
f
TM7
TM6
Y326
g
TM7
TM6
Y326
h
TM7
TM6
Y326
i
TM7
TM6
Y326

Figure Suppl. 4| The number of water molecules next to Y326$^{7.53}$. (a) Top: water density of Agon-2 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Agon-2 bound β_2AR. (b) Top: water density of Agon-3 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Agon-3 bound β_2AR. (c) Top: water density of Agon-4 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Agon-4 bound β_2AR. (d) Top: water density of Anta-2 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Anat-2 bound β_2AR. (e) Top: water density of Anat-3 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Anat-3 bound β_2AR. (f) Top: water density of Anat-4 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in Anat-4 bound β_2AR. (g) Top: water density of iAgo-2 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in iAgo-2 bound β_2AR. (h) Top: water density of iAgo-3 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in iAgo-3 bound β_2AR. (i) Top: water density of iAgo-4 bound β_2AR in the final 100 frames. Bottom: The number of water molecules within 4 Å of Y326$^{7.53}$ in iAgo-4 bound β_2AR.

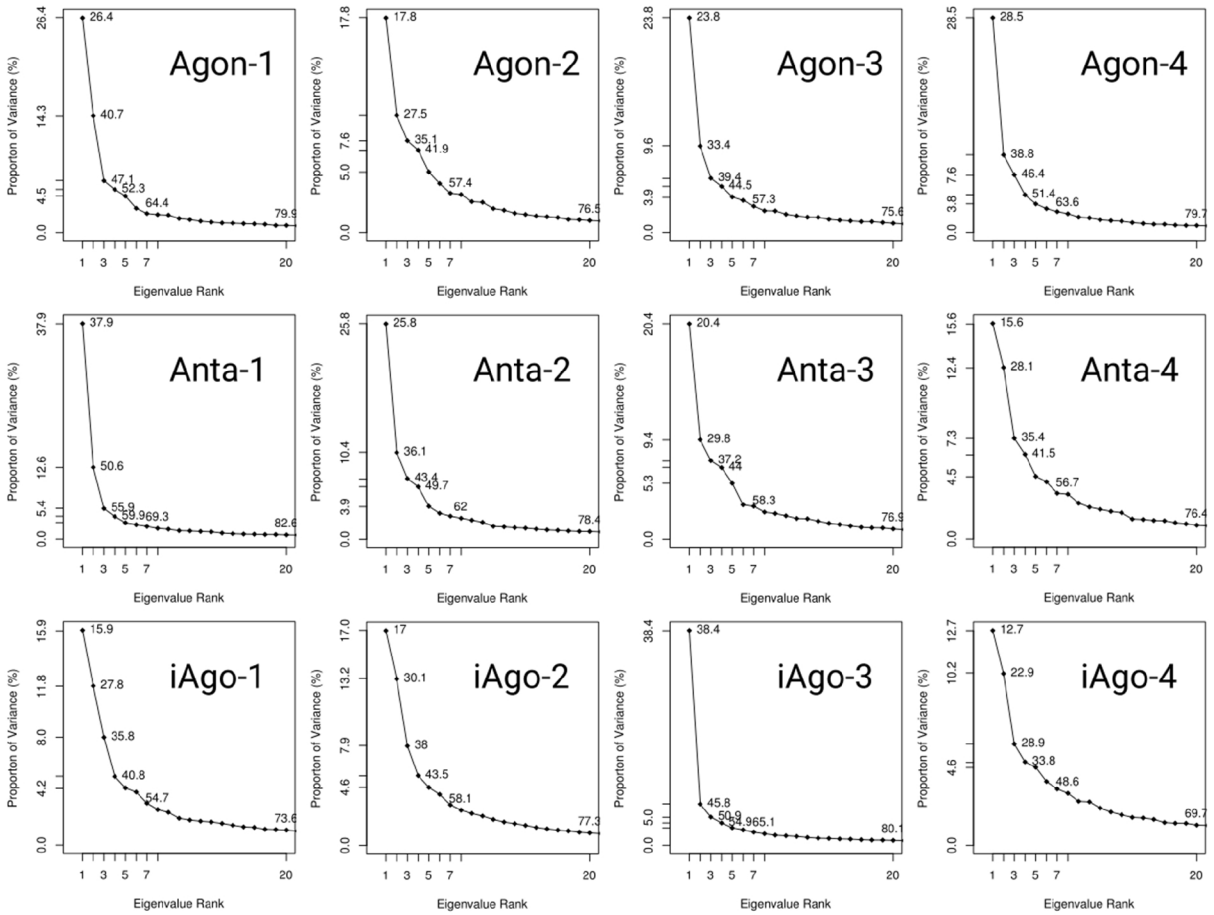

Figure Suppl. 5 | The proportion of mean square displacements (or variance %) of atoms' positional fluctuations versus their corresponding eigenvalue rank in all 12 systems.