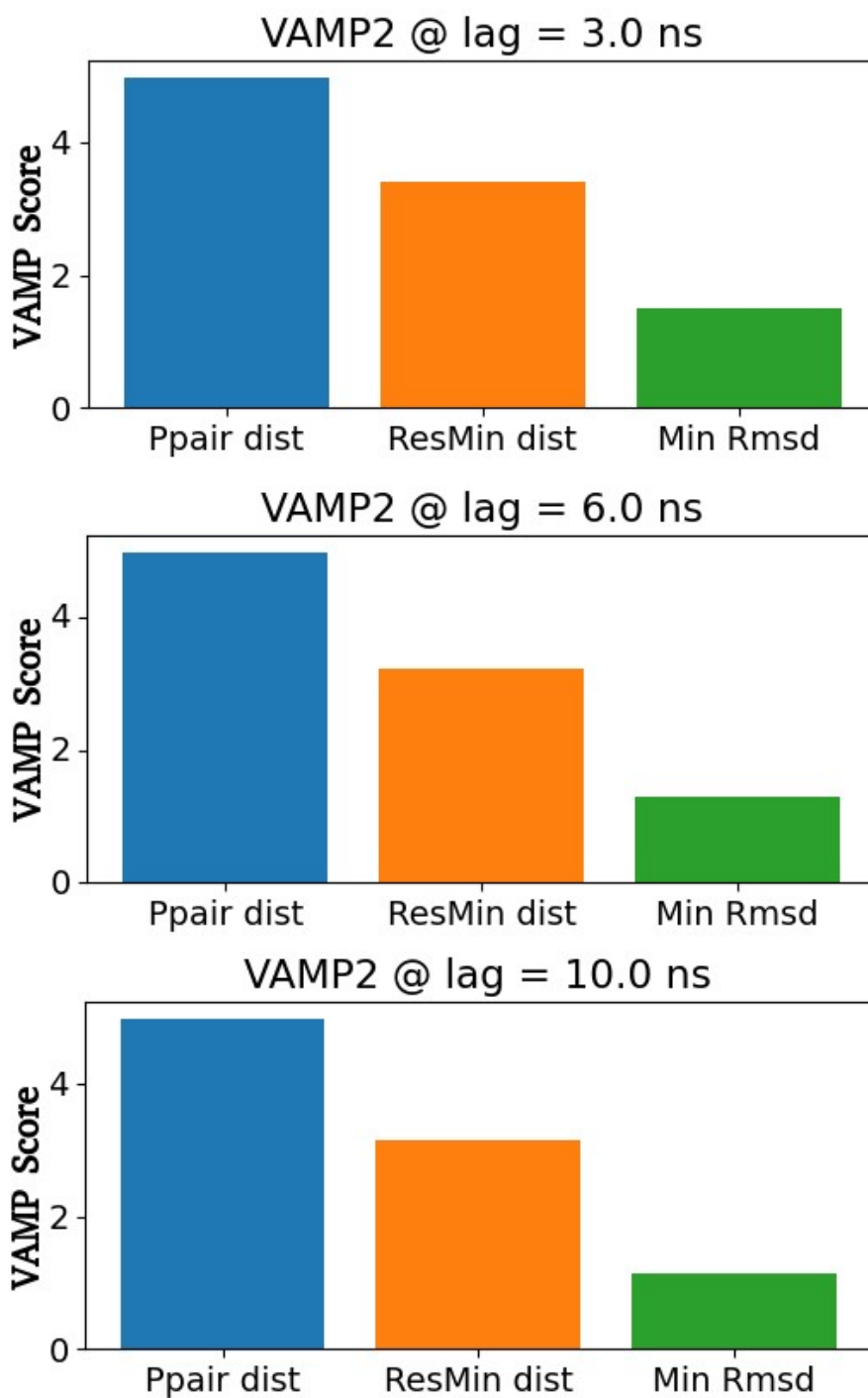


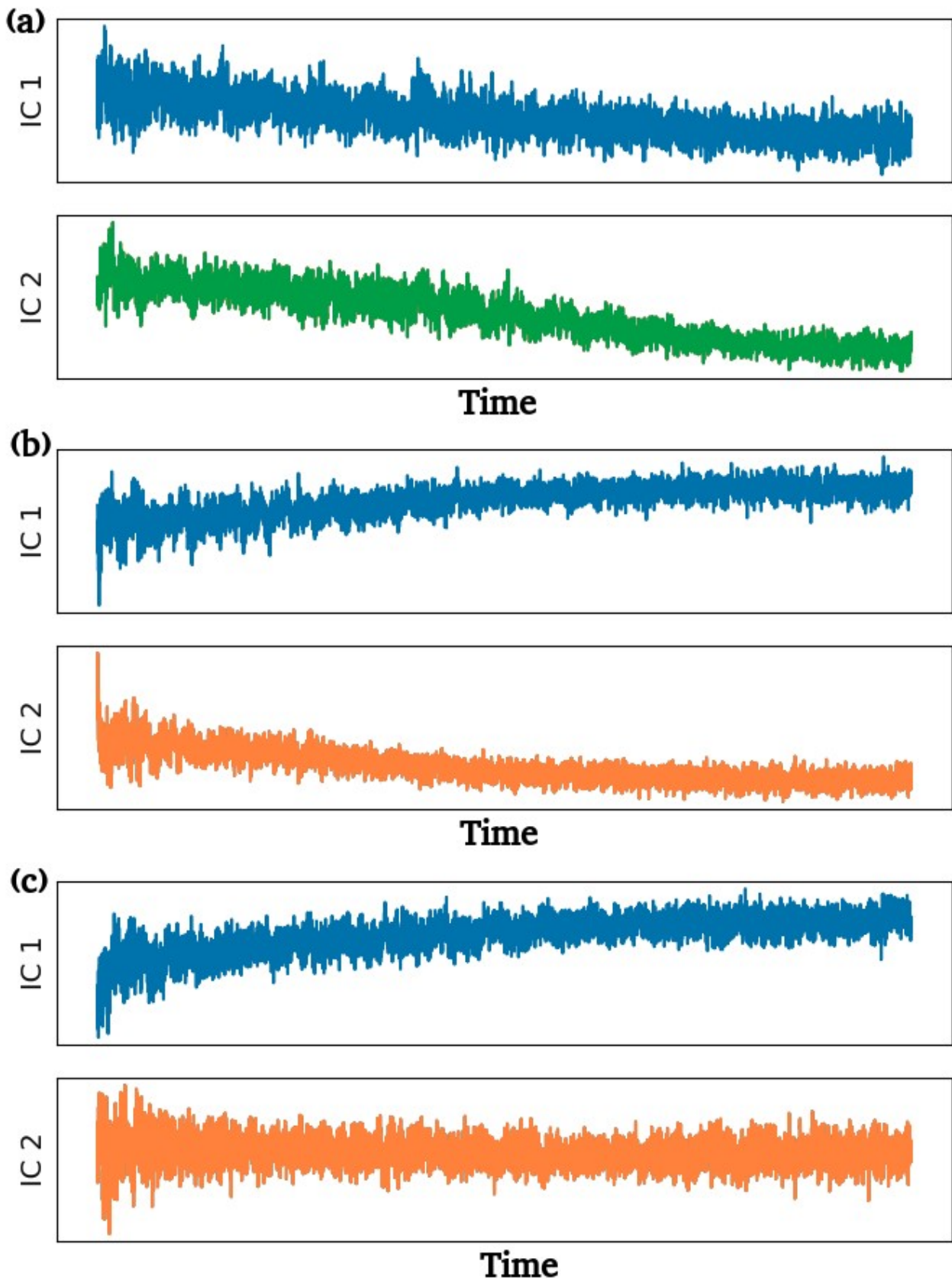
Probing the Structure of human tRNA₃^{Lys} in presence of ligands using docking, MD simulations and MSM analysis

Supplementary Information

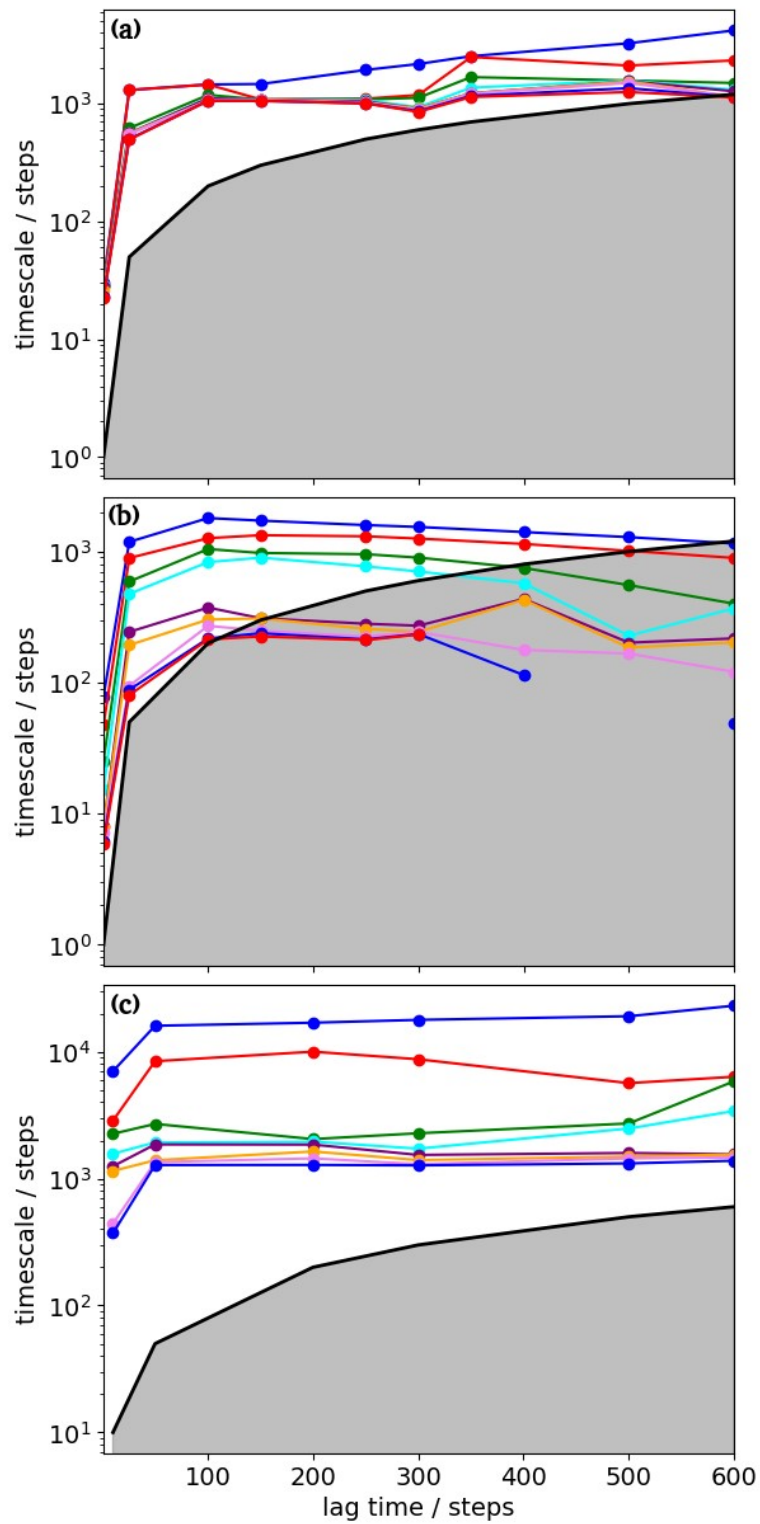
Supplementary Figure S1: VAMP score calculated for different features at various lag times.



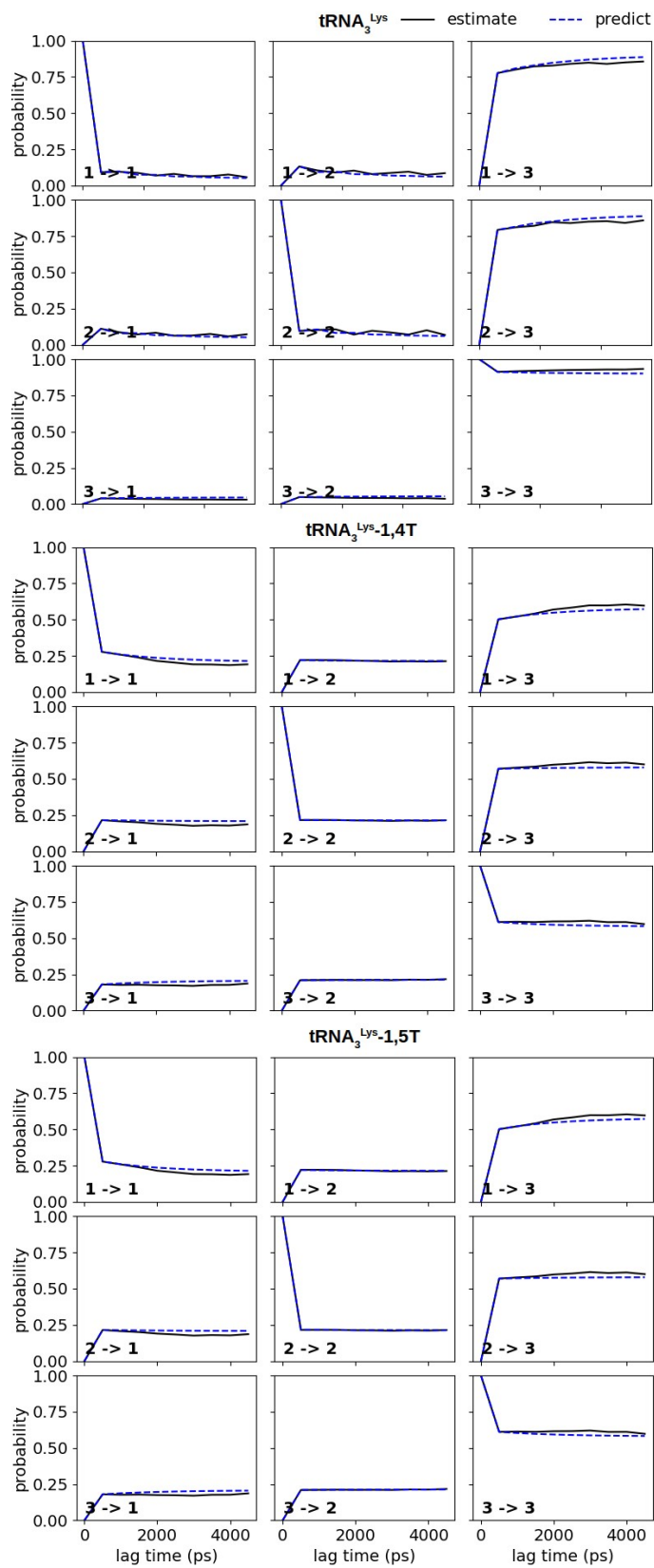
Supplementary Figure S2: Lag time for all the systems.



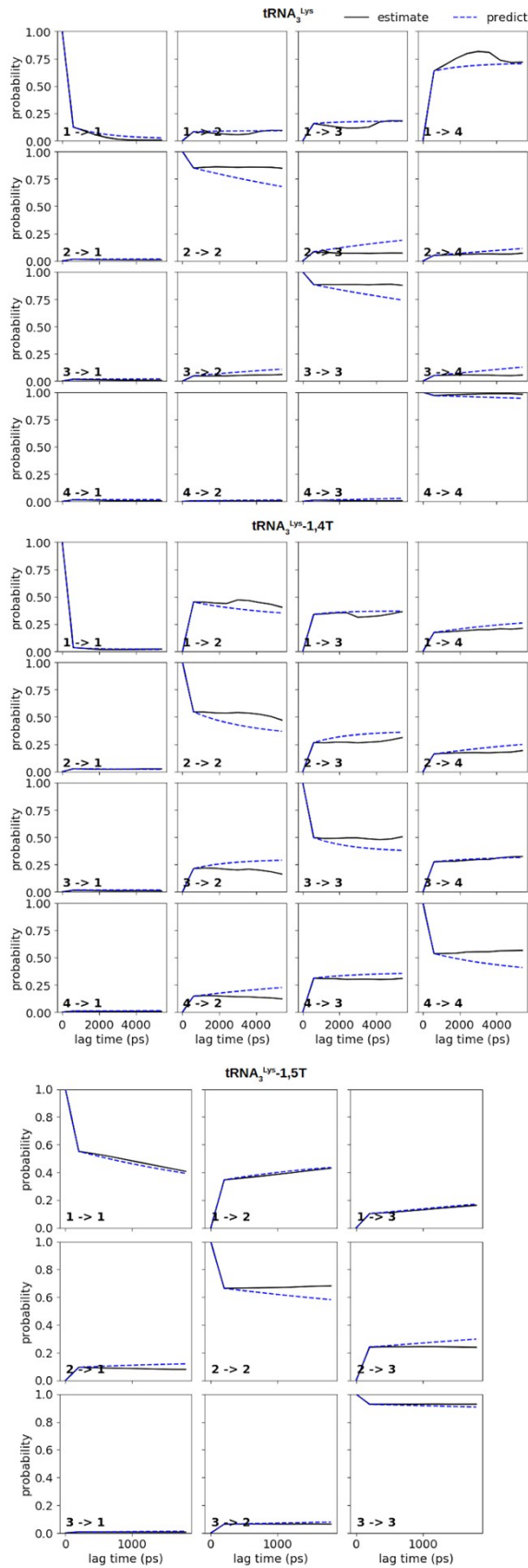
Supplementary Figure S3: Lag time calculation for (a) apo tRNA₃^{Lys}, (b) tRNA₃^{Lys}-1,4T and (c) tRNA₃^{Lys}-1,5T.



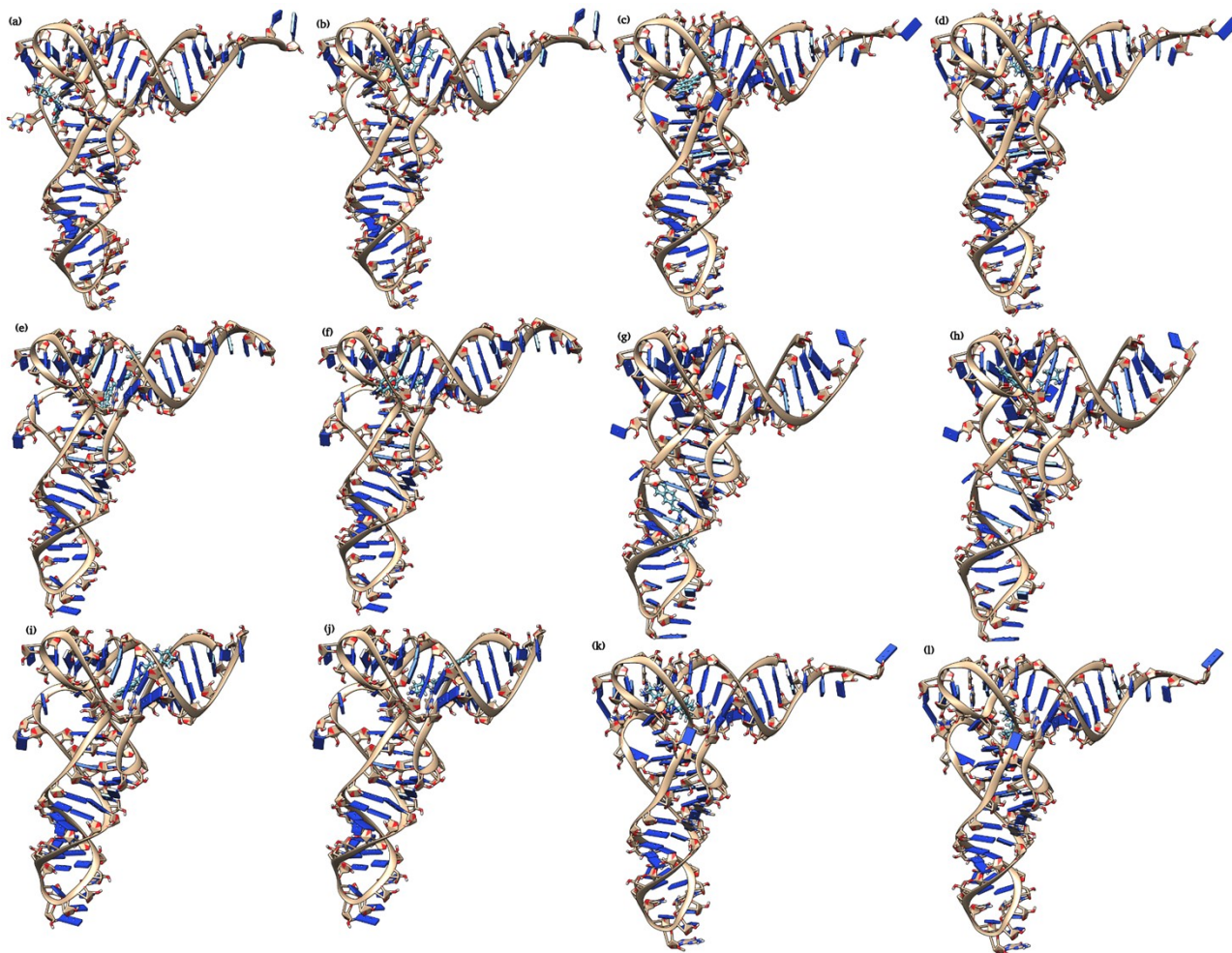
Supplementary Figure S4: Chapman Kolmogorov test for whole structure of apo $\text{tRNA}_3^{\text{Lys}}$, $\text{tRNA}_3^{\text{Lys-1,4T}}$ and $\text{tRNA}_3^{\text{Lys-1,5T}}$.



Supplementary Figure S5: Chapman Kolmogorov test for DT loop structure of apo tRNA₃^{Lys}, tRNA₃^{Lys}-1,4T and tRNA₃^{Lys}-1,5T.



Supplementary Figure S6: Docking images of 14T and 15T ligands against different tRNA crystal structures (a) 1FIR-14T, (b) 1FIR-15T, (c) 1EHZ-14T, (d) 1EHZ-15T, (e) 1VTQ-14T, (f) 1VTQ-15T, (g) 3L0U-14T, (h) 3L0U-15T, (i) 4TNA-14T, (j) 4TNA-15T, (k) 3TRA-14T and (l) 3TRA-15T.



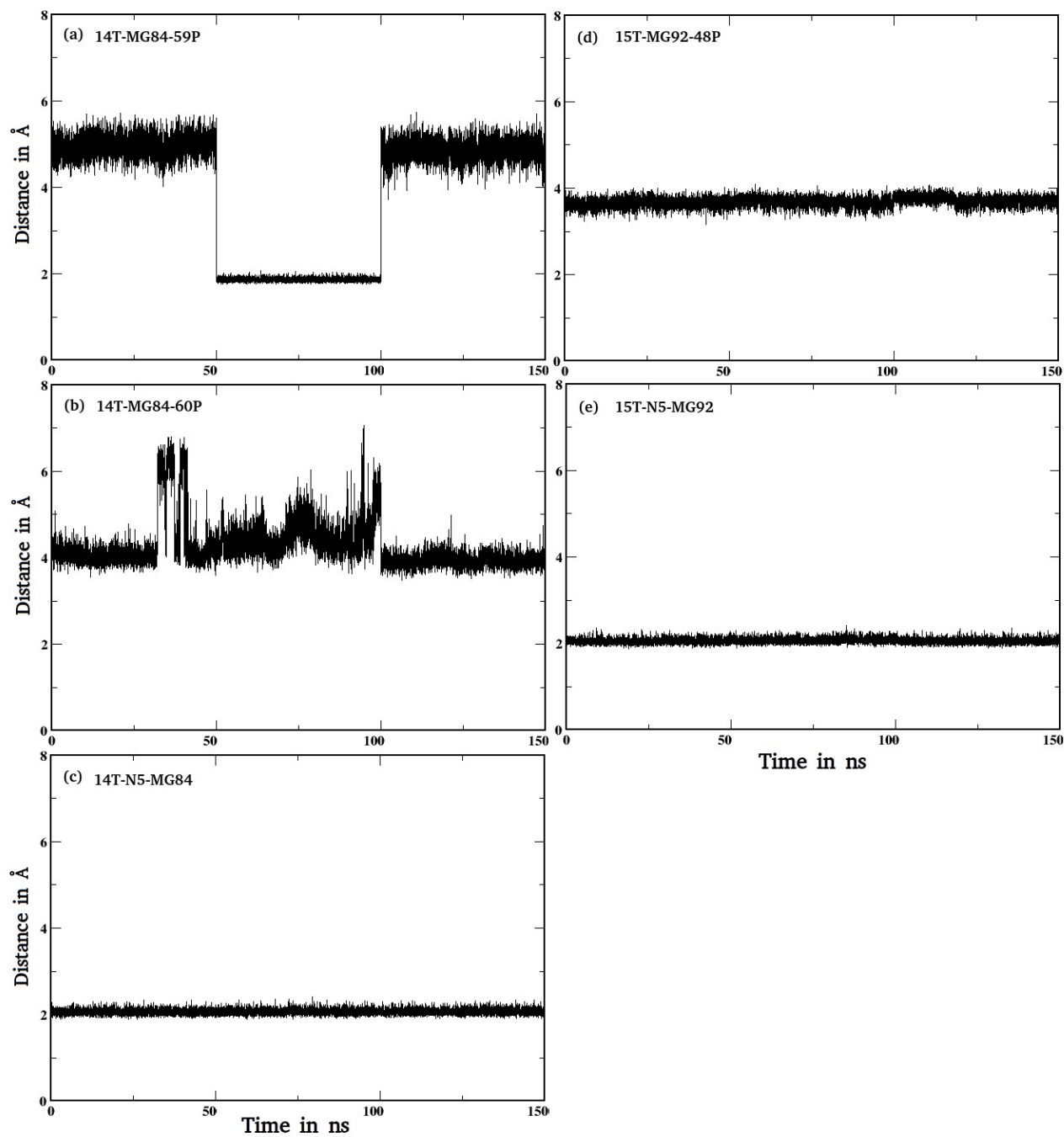
Supplementary Table S7: Area under the curve values for three sets of simulations of three complex systems (tRNA₃^{Lys} system, tRNA₃^{Lys}-1,4T system and tRNA₃^{Lys}-1,5T system).

	tRNA₃^{Lys} system	tRNA₃^{Lys} - 1,4T system	tRNA₃^{Lys} - 1,5T system
Set – 1	4480.26	4351.5	3753.42
Set – 2	3771.87	4743.03	3334.4
Set – 3	4053.13	4802.13	3176.96

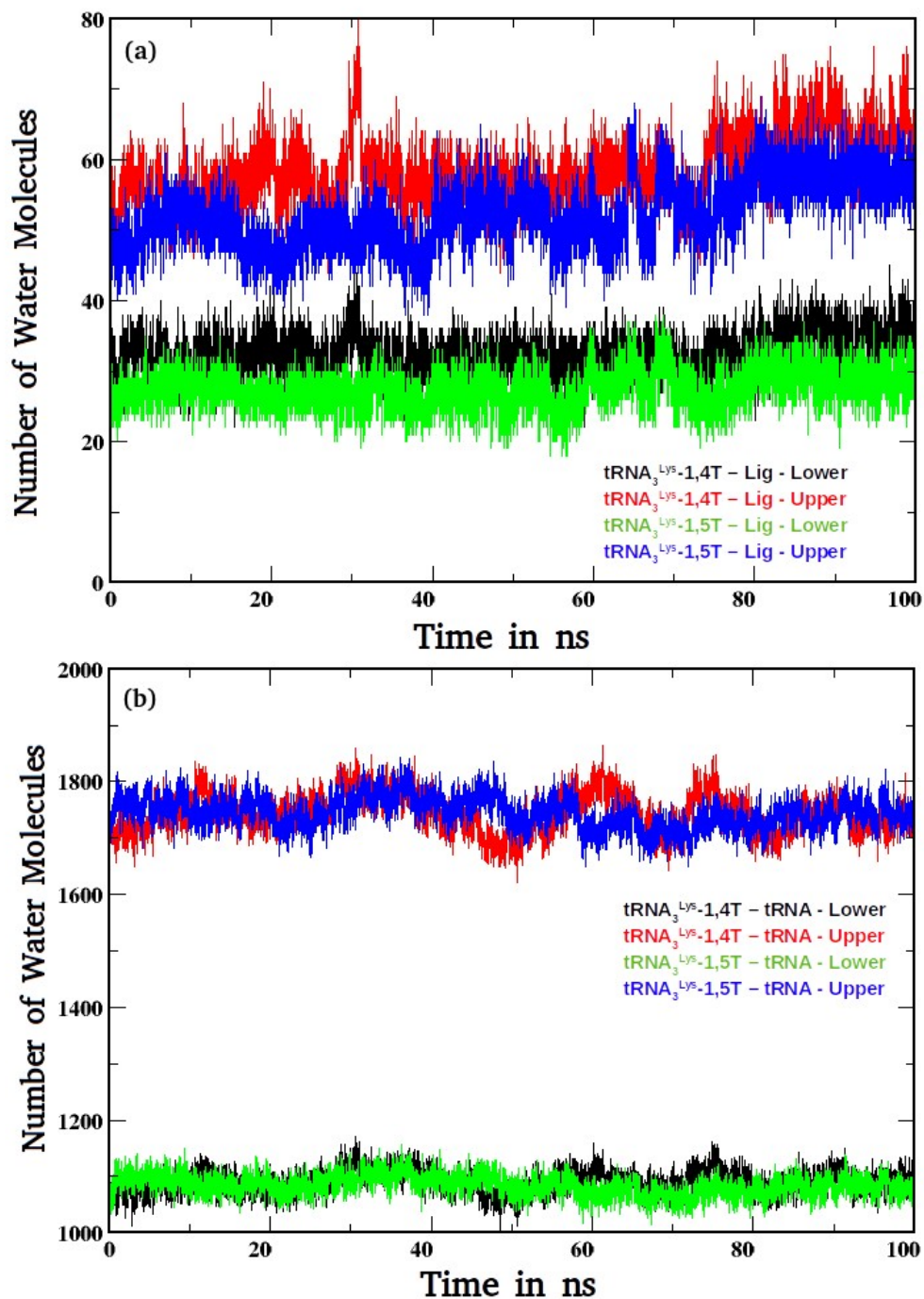
Supplementary Table S8: Interactions of 1,4T and 1,5T ligands with tRNA₃^{Lys} for three runs of simulations.

Residues	H-bond	tRNA ₃ Lys-1,4T system			tRNA ₃ Lys-1,4T system		
		Traj1	Traj2	Traj3	Traj1	Traj2	Traj3
53-Lig	O6...H23-N5	91.07					
60-Lig	O2...H22-N5	77.92					
60-Lig	O2P...H22-N5		75.15	56.94			
52-Lig	O6...H23-N5			54.37			
53-Lig	O6...H23-N5		19.86				
59-Lig	O2P...H22-N5			8.87			
60-Lig	O2P...H23-N5		8.35				
51-Lig	N7...H20-N4			6.32			
49-Lig	O1P...H21-N4			4.79			
58-Lig	O3'...H23-N5			4.69			
58-Lig	O3'...H22-N5			4.68			
50-Lig	N6-H62...O1					46.77	
50-Lig	N6-H61...O1					45.98	
50-Lig	N6-H62...N1				4.66		44.58
50-Lig	N6-H62...N3				8.32		37.20
50-Lig	N6-H61...N1				4.86		35.81
50-Lig	N6-H61...N3				7.69		29.34
50-Lig	N6-H62...O1				27.90		
50-Lig	N6-H61...O1				27.72		
61-Lig	N4-H42...N3				23.21		
61-Lig	N4-H42...N1				23.17		
50-Lig	O5'...H22-N5					19.36	21.63
61-Lig	N4-H41...N1				15.06		
61-Lig	N4-H41...N3				8.57		
51-Lig	O2P...H22-N5					7.71	
64-Lig	N3-H3...O1					3.96	
61-Lig	N4-H42...O1				3.11		
62-Lig	N4-H41...N1						2.95

Supplementary Figure S9: Distances of Mg^{++} ion interactions with the ligands 1,4T and 1,5T from the respective systems.



Supplementary Figure S10: The number of water molecules present within the close proximity of the ligand bound tRNA₃^{Lys} systems. The distance between solute molecules and the water considered for lower is ≤ 3.4 Å and for upper is ≤ 5 Å.



Supplementary Table S11: Water mediated interactions in three systems (tRNA₃^{Lys} system, tRNA₃^{Lys}-1,4T system and tRNA₃^{Lys}-1,5T system) above 40% of residence time from all the three trajectories.

tRNA₃^{Lys} system

Donor	Acceptor H	Acceptor	Traj-1	Traj-2	Traj-3
2MG_6@O2P	WAT@H1	WAT@O	60.12		
RG_5@O2P	WAT@H2	WAT@O	57.53		
RG_15@N7	WAT@H2	WAT@O	50.34	42.47	42.52
RG_53@O6	WAT@H2	WAT@O	49.07		44.88
RG_53@O6	WAT@H1	WAT@O	48.59		46.40
RG_15@N7	WAT@H1	WAT@O	48.42	52.57	46.53
H2U_47@O1P	WAT@H1	WAT@O	45.87		
2MG_6@O1P	WAT@H2	WAT@O	42.52		
2MG_6@O1P	WAT@H1	WAT@O	41.27		
5MC_48@O2'	WAT@H2	WAT@O	40.52		
RA_7@O2P	WAT@H2	WAT@O	40.01		
WAT@O	RC_61@H42	RC_61@N4	41.24		
RC_62@O2P	WAT@H1	WAT@O		50.03	47.84
RU_8@O4	WAT@H2	WAT@O		44.44	
RG_15@O6	WA@H2	WAT@O		43.99	45.59
RC_62@O2P	WAT0@H2	WAT@O		43.88	49.20
RG_15@O6	WAT@H1	WAT@O		42.48	42.93
12A_37@O2P	WAT@H2	WAT@O		40.09	
RU_66@O4	WAT@H2	WAT@O			49.38
RU_66@O4	WAT@H1	WAT@O			45.75
RC_3@O1P	WAT@H1	WAT@O			42.86
RC_4@O2P	WAT@H1	WAT@O			41.03

tRNA₃^{Lys} - 1,4T system

Donor	Acceptor H	Acceptor	Traj-1	Traj-2	Traj-3
WAT@O	RC_13@H41	RC_13@N4	77.85		
WAT@O	RG_59@H1	RG_59@N1	55.51		
1MA_58@O3'	WAT@H1	WAT@O	63.22		
RG_59@O2P	WAT@H1	WAT@O	58.36		

RG_24@O2P	WAT@H2	WAT@O	45.67		
RG_53@N7	WAT@H1	WAT@O	45.48		
RG_53@N7	WAT@H2	WAT@O	44.23		
RA_9@O2P	WAT@H1	WAT@O	43.79		
RU_12@O2P	WAT@H2	WAT@O	43.62		
5MC_48@N3	WAT@H1	WAT@O	41.93		
RC_68@N3	WAT@H1	WAT@O	41.33		
RA_9@O2P	WAT@H2	WAT@O	41.17		
RU_12@O2P	WAT@H1	WAT@O	40.88		
5MC_48@N3	WAT@H2	WAT@O	40.38		
RU_8@O1P	WAT@H1	WAT@O		41.95	
RG_24@O2P	WAT@H1	WAT@O		61.65	
RC_11@O1P	WAT@H2	WAT@O		44.94	
RU_8@O1P	WAT@H2	WAT@O		42.75	
RC_11@O1P	WAT@H1	WAT@O		46.06	
PSU_55@O4	WAT@H2	WAT@O		41.71	
PSU_55@O4	WAT@H1	WAT@O		41.27	
1MA_58@O3'	WAT@H2	WAT@O			47.21
RA_9@O2P	WAT@H1	WAT@O			41.78
RU_12@O2P	WAT@H2	WAT@O			41.19
RG_59@O2P	WAT@H2	WAT@O			40.98
RA_9@O2P	WAT@H2	WAT@O			40.23
WAT@O	RC_13@H41	RC_13@N4			76.13

tRNA₃^{Lys} - 1,5T system

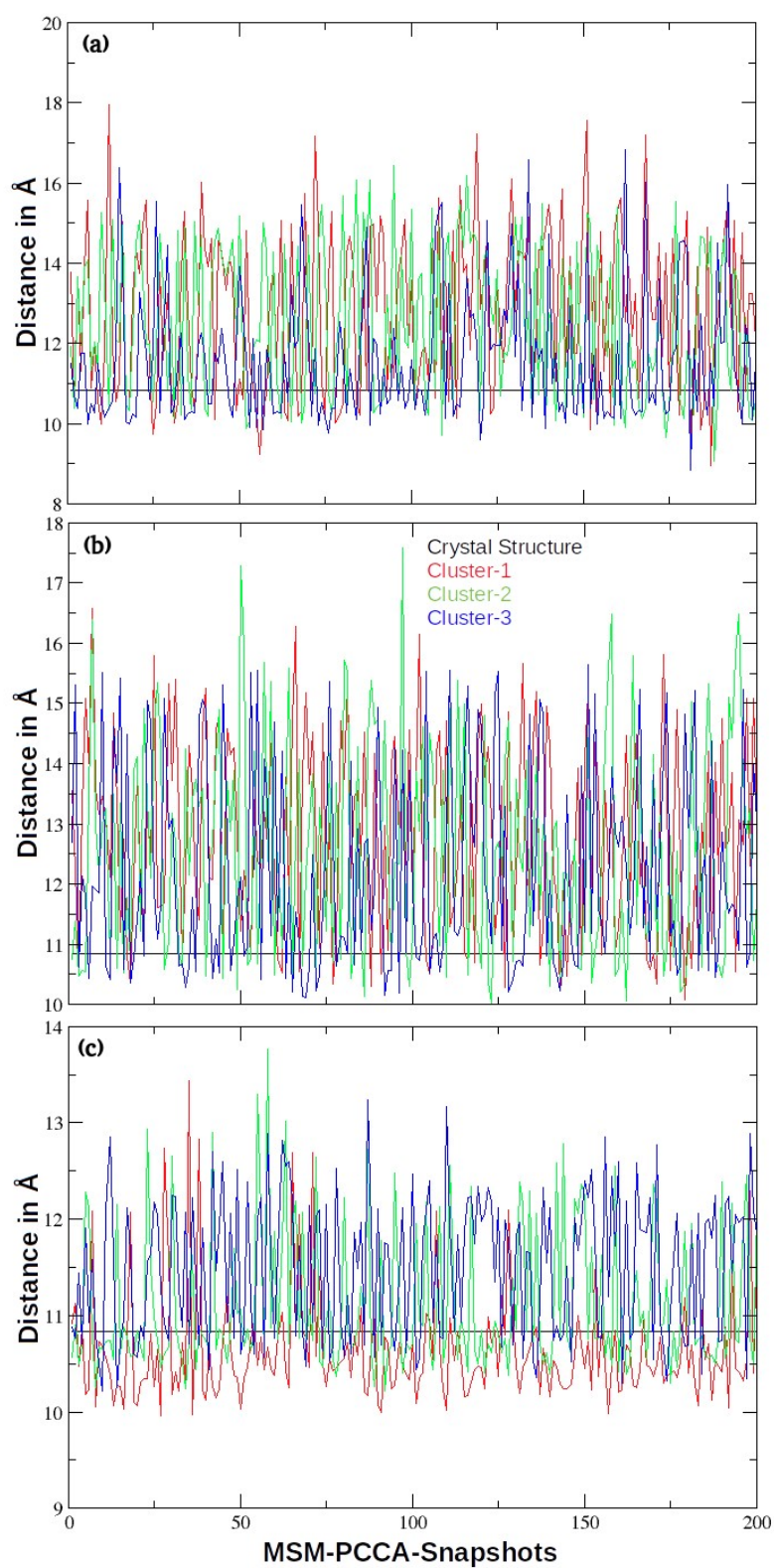
Donor	Acceptor H	Acceptor	Traj-1	Traj-2	Traj-3
1MA_58@O3'	WAT@H2	WAT@O	54.41		
2MG_6@O2P	WAT@H2	WAT@O	47.51		
RG_59@O2P	WAT@H2	WAT@O	47.05		
RG_59@N7	WAT@H2	WAT@O	45.21		
1MA_58@O1P	WAT@H1	WAT@O	44.89		
2MG_6@O2P	WAT@H1	WAT@O	42.95		
RG_15@N7	WAT@H2	WAT@O	41.87		
RG_59@N7	WAT@H1	WAT@O	41.30		

RG_15@N7	WAT@H1	WAT@O	40.95	
RU_33@O4	WAT@H1	WAT@O		41.16
RU_33@O4	WAT@H2	WAT@O		40.42
WAT@O	RC_11@H42	RC_11@N4	44.92	
RG_15@N7	WAT@H2	WAT@O		51.55
RU_8@O4	WAT@H1	WAT@O	51.43	44.98
RG_15@N7	WAT@H1	WAT@O		47.63
RU_8@O4	WAT@H2	WAT@O		47.57
PSU_27@O4	WAT@H2	WAT@O		43.35
PSU_27@O4	WAT@H1	WAT@O		41.91
RA_57@O2P	WAT@H2	WAT@O		41.52
RG_15@O6	WAT@H1	WAT@O		40.93
WAT@O	PSU_27@H5	PSU_27@N5		52.41
PSU_27@O2P	WAT@H1	WAT@O		58.19
RC_11@O1P	WAT@H2	WAT@O		49.39
2MG_6@O1P	WAT@H2	WAT@O		45.63
RA_57@O1P	WAT@H1	WAT@O		43.12
RC_11@O1P	WAT@H1	WAT@O		42.09
RA_7@O5'	WAT@H2	WAT@O		41.77
PSU_27@O2P	WAT@H2	WAT@O		41.67
RC_28@O2P	WAT@H1	WAT@O		41.66
RA_7@O5'	WAT@H1	WAT@O		41.31
RA_57@O1P	WAT@H2	WAT@O		40.02

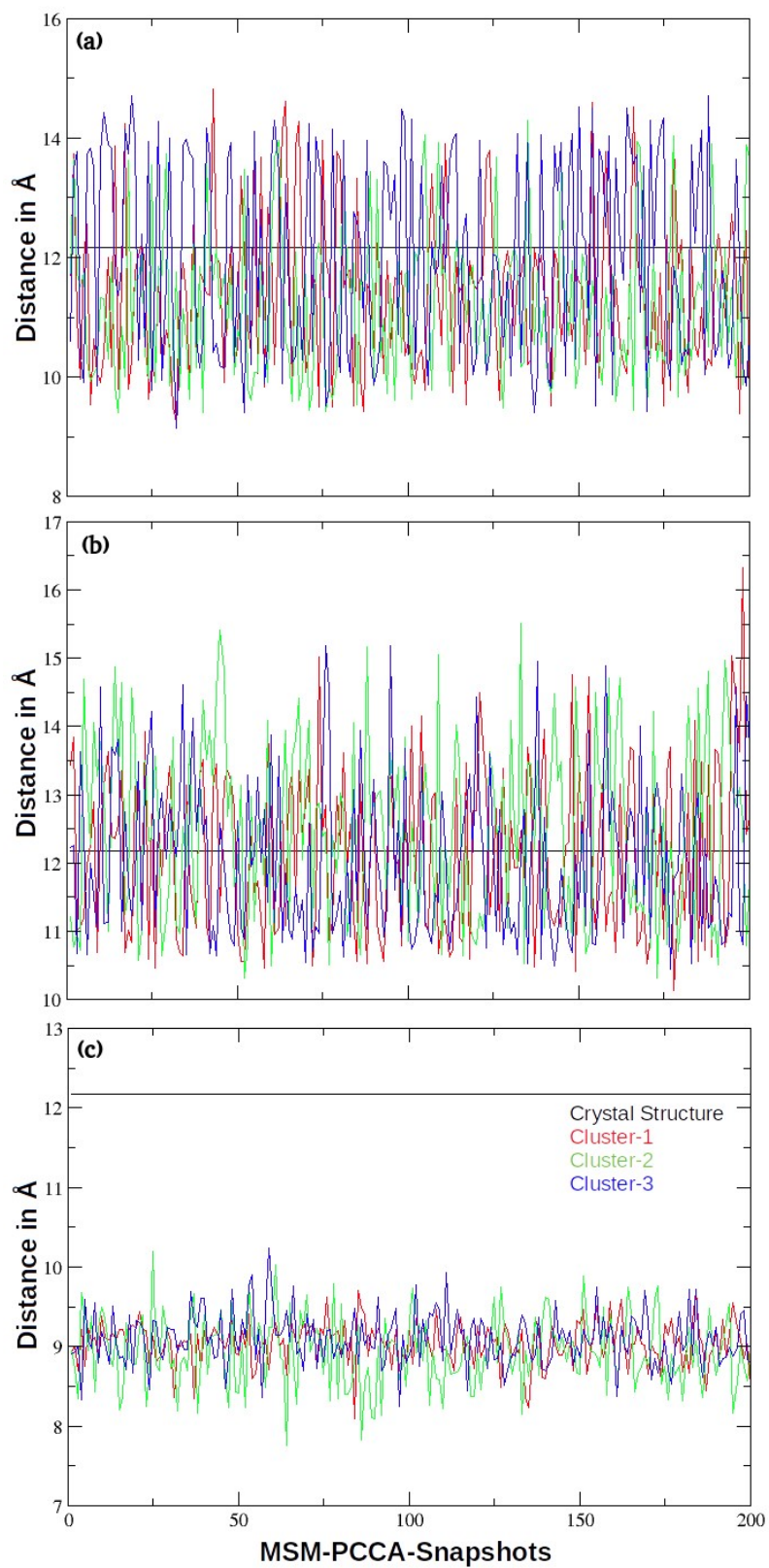
Supplementary Table S12: MMGBSA free energy components of tRNA₃^{Lys}-14T and tRNA₃^{Lys}-15T system for three sets of MD simulations.

MMGBSA- Free Energy Components			
tRNA₃^{Lys}-14T	Set - 1	Set-2	Set-3
BOND	-5.6183	-6.7418	-6.4972
ANGLE	-6.7446	-6.6416	-6.5458
DIHED	-59.3688	-59.8953	-59.5319
VDWAALS	-30.8807	-31.2762	-30.3163
EEL	-3.3843	4.04	-4.0114
EGB	42.3723	43.8491	41.8662
ESURF	-4.4082	-4.2994	-4.2646
DELTA G gas	-102.1482	-96.6784	-102.9906
DELTA G solv	37.9641	39.5497	37.6015
DELTA TOTAL	-64.1842	-57.1287	-65.3891
tRNA₃^{Lys}-15T	Set - 1	Set-2	Set-3
BOND	-6.5776	-6.8163	-6.7945
ANGLE	-6.9637	-6.8247	-6.7261
DIHED	-60.0581	-59.1454	-59.5388
VDWAALS	-35.852	-30.8996	-41.3142
EEL	-18.1354	0.3625	15.8677
EGB	95.4041	79.9155	64.8676
ESURF	-5.2023	-4.5222	-4.8998
DELTA G gas	-123.7378	-99.4339	-94.686
DELTA G solv	90.2018	75.3933	59.9678
DELTA TOTAL	-33.536	-24.0407	-34.7183

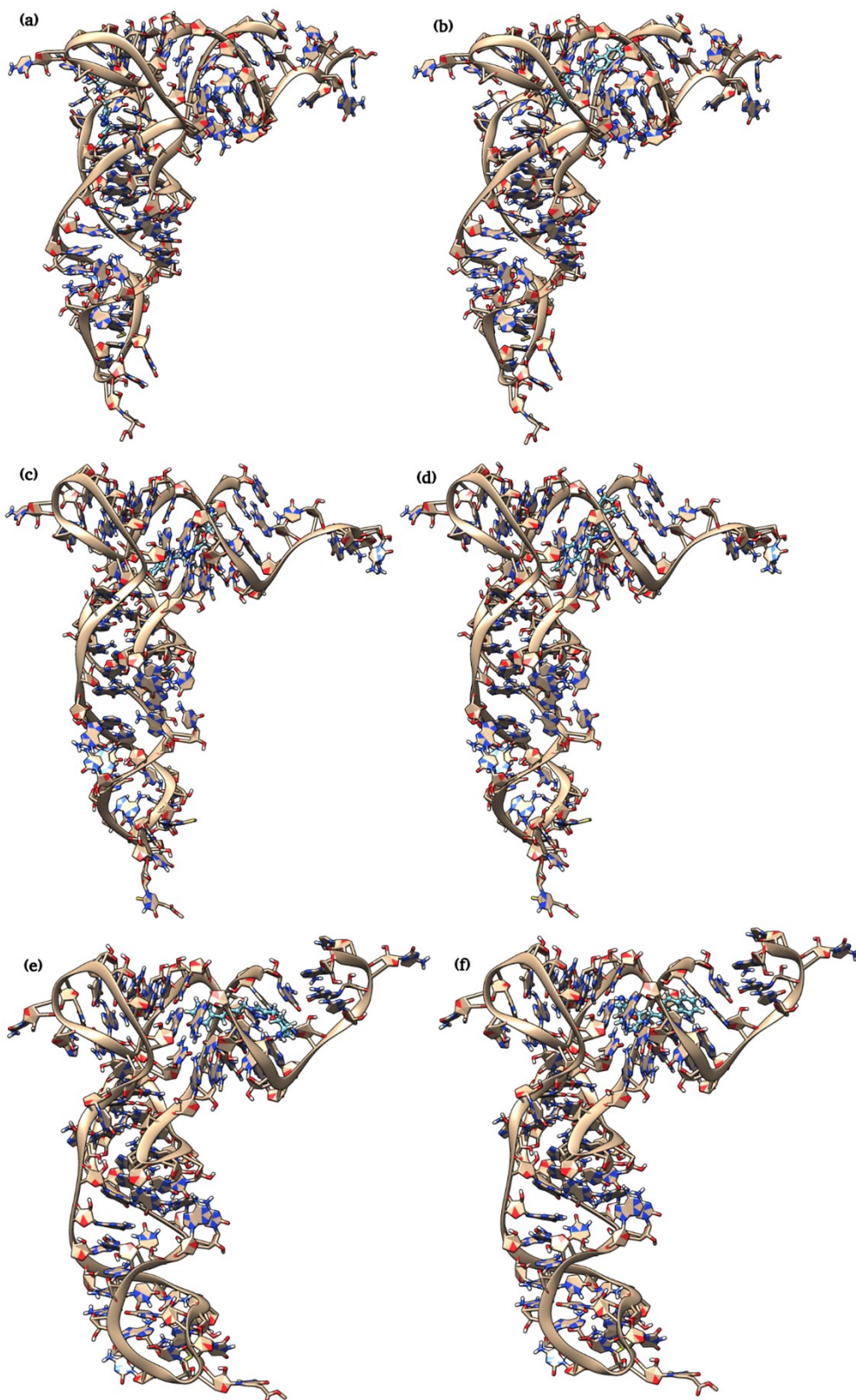
Supplementary Figure S13: The G6-U67 base pair distance for (a) tRNA₃^{Lys}, (b) tRNA₃^{Lys-1,4T} and (c) tRNA₃^{Lys-1,5T}.



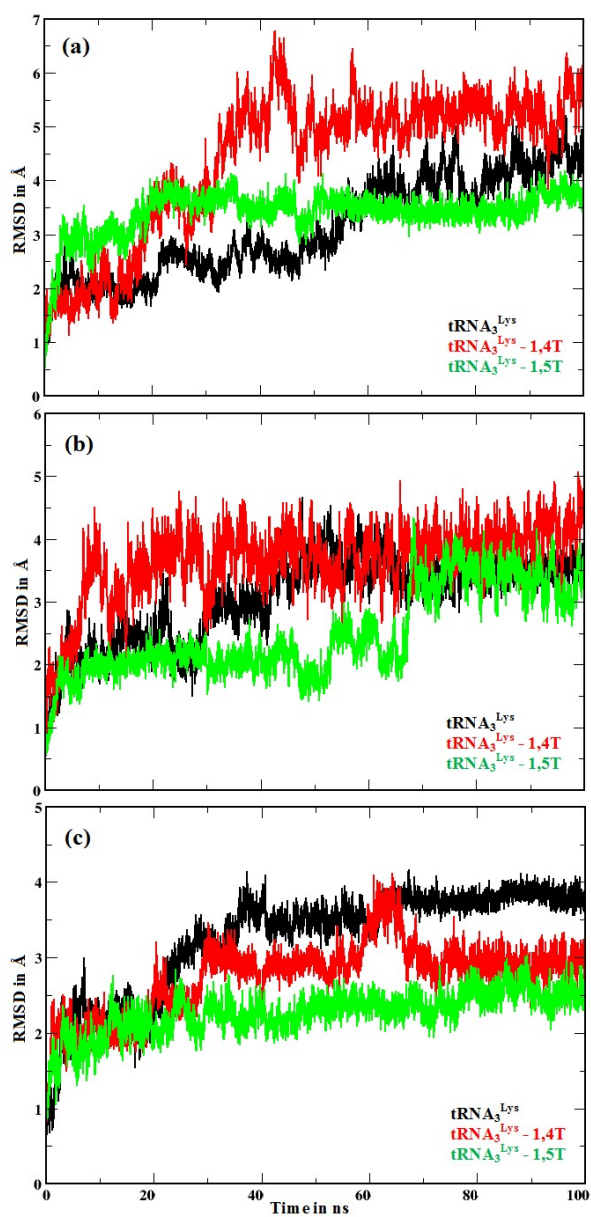
Supplementary Figure S14: The C11-G45 base pair distance for (a) tRNA₃^{Lys}, (b) tRNA₃^{Lys-1,4T} and (c) tRNA₃^{Lys-1,5T}.



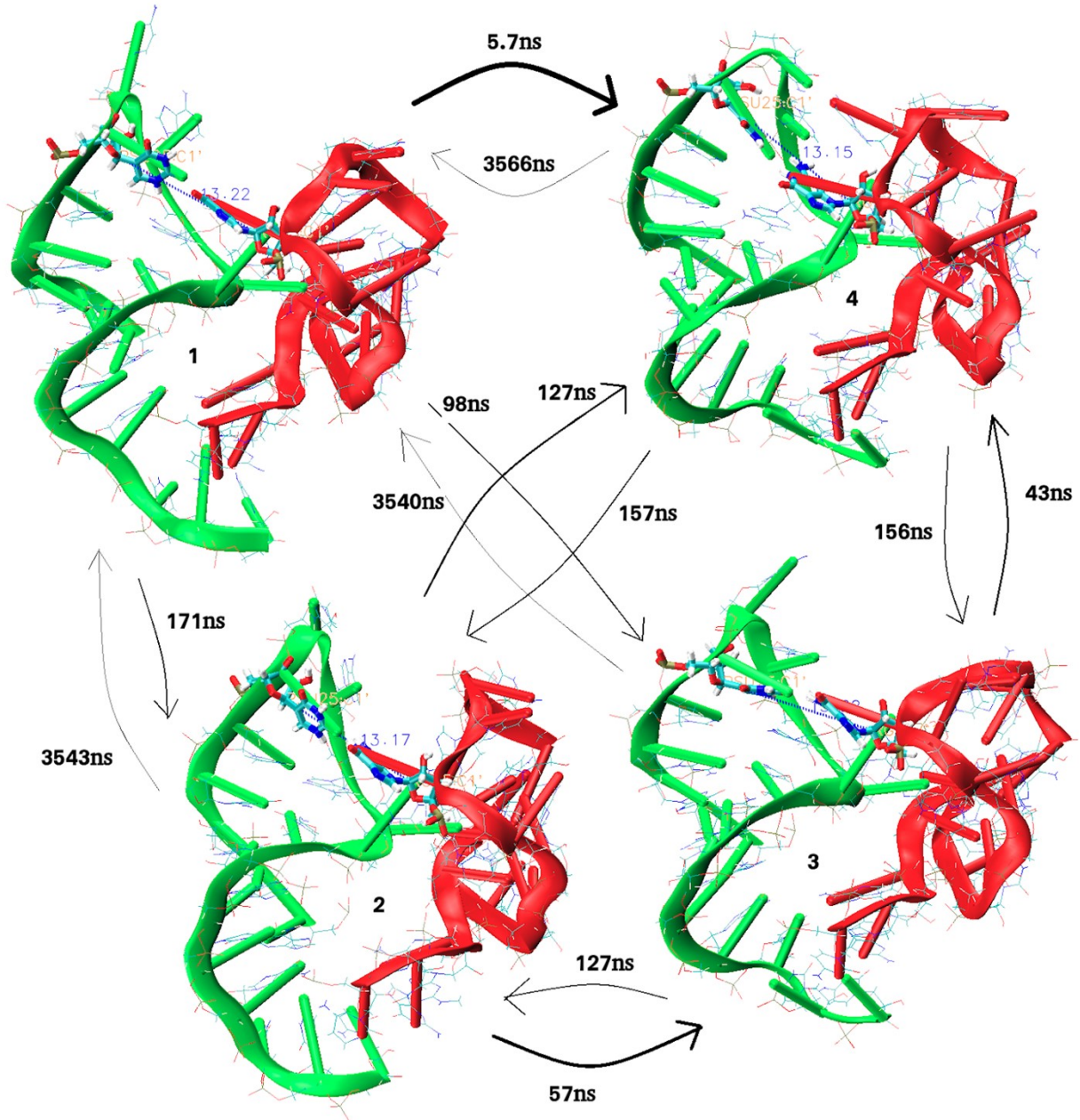
Supplementary Figure S15: The docked poses of 1,4T and 1,5T ligands against three representative structures, one from each MSM macrostate.



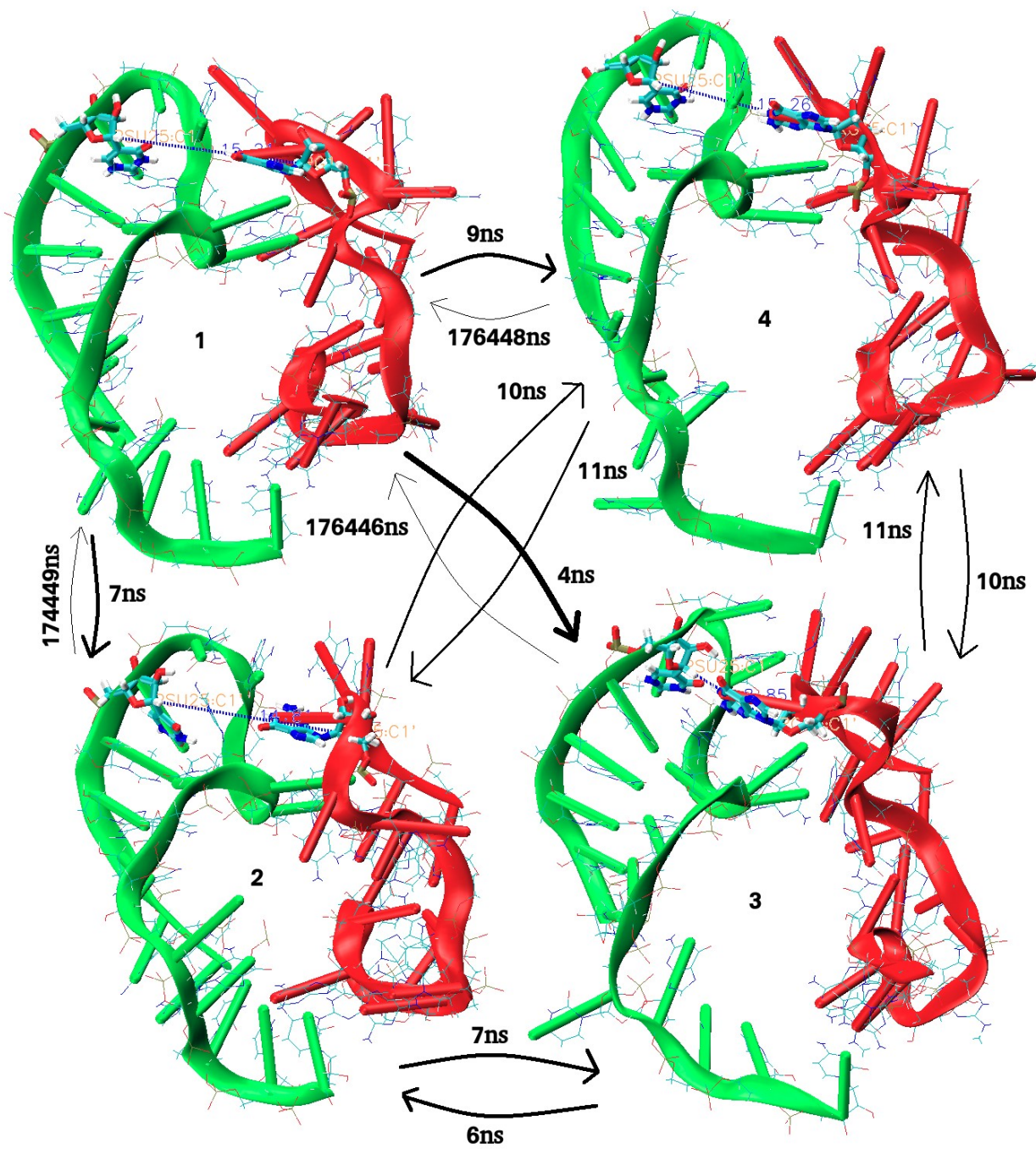
Supplementary Figure S16: The RMSD of anticodon loop region of the tRNA₃^{Lys} for all three systems. (a) Run-1, (b) Run-2 (c) Run-3.



Supplementary Figure S17: MSM macrostates and MFPT rates for D and TΨC loop of apo tRNA₃^{Lys}. The D and TΨC loop are represented in red and green colours respectively.



Supplementary Figure S18: MSM macrostates and MFPT rates for D and TΨC loop of tRNA₃^{Lys}-1,4T.



Supplementary Figure S19: MSM macrostates and MFPT rates for D and TΨC loop of tRNA₃^{Lys}-1,5T.

