Supplementary Materials

Title: A rational design of α-helix-shaped peptides employing the hydrogen-bond surrogate approach: a modulation strategy for Ras-RasGRF1 interaction in neuropsychiatric disorders

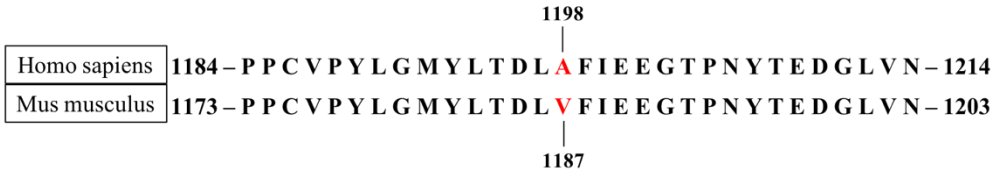


Figure S1. FASTA sequence alignment between RasGRF1 interacting region from two different organisms (*homo sapiens* and *mus musculus*)

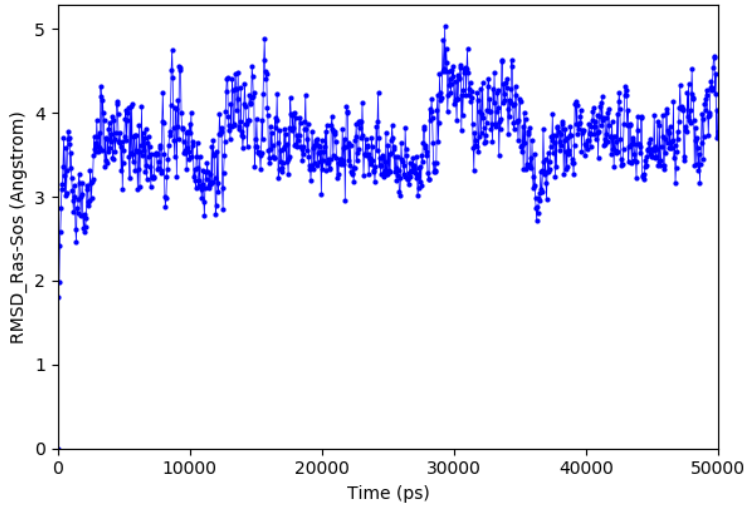
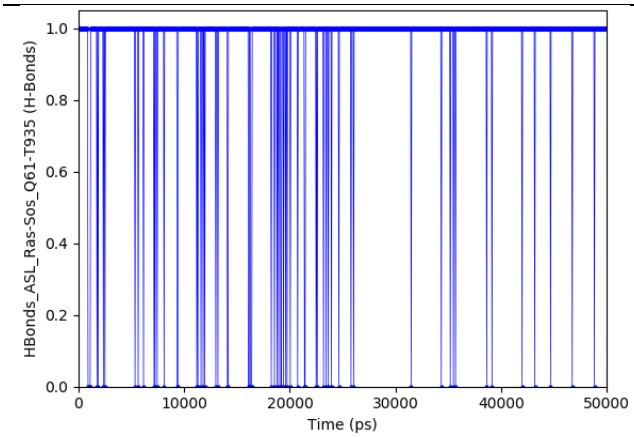
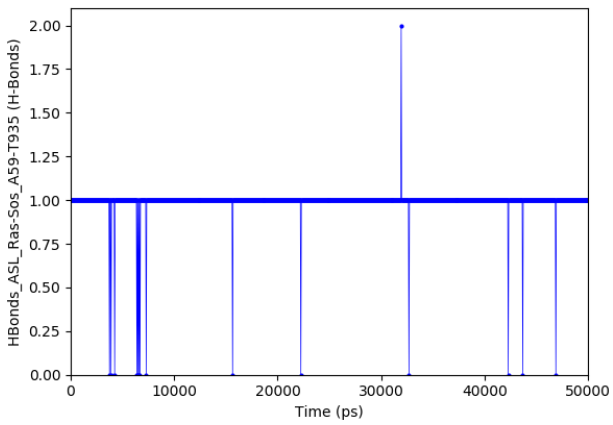


Figure S2. RMSD plot of MD simulation performed on Ras-Sos complex (PDB 1XD2)

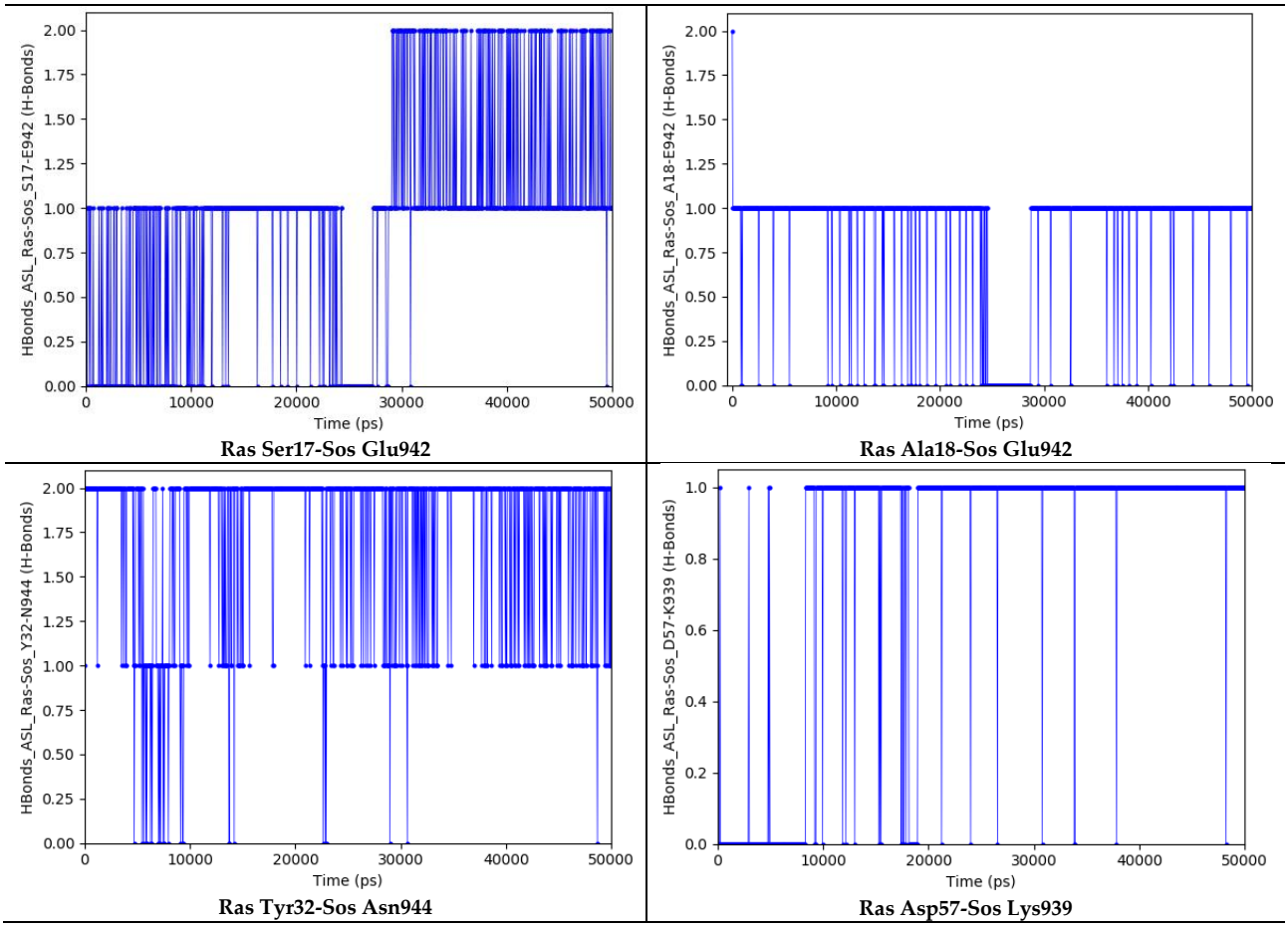
Table S1. Plots of the H-bonds established between Ras and Sos during the MD simulation.



Ras Gln61-Sos Thr935



Ras Ala59-Sos Thr935



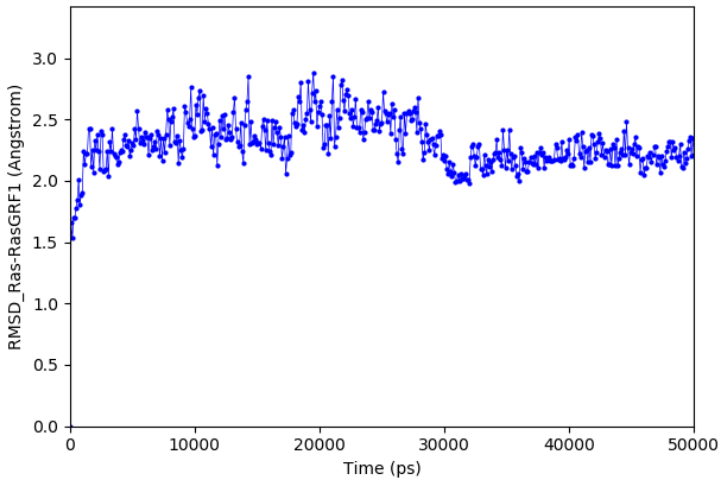
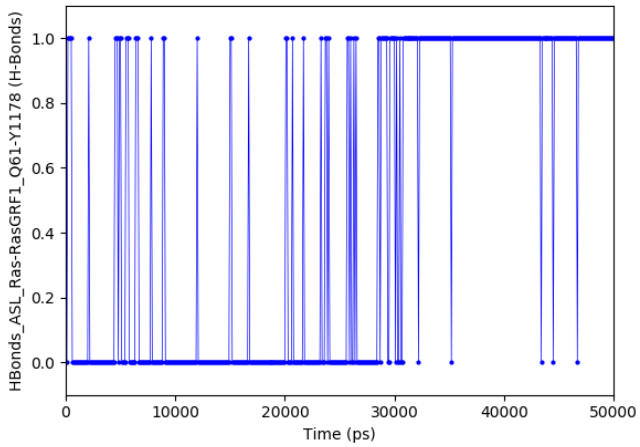
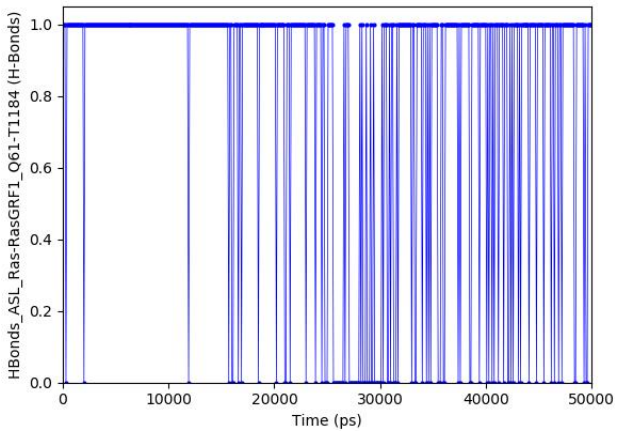


Figure S3. RMSD plot of MD simulation performed on Ras-RasGRF1 complex

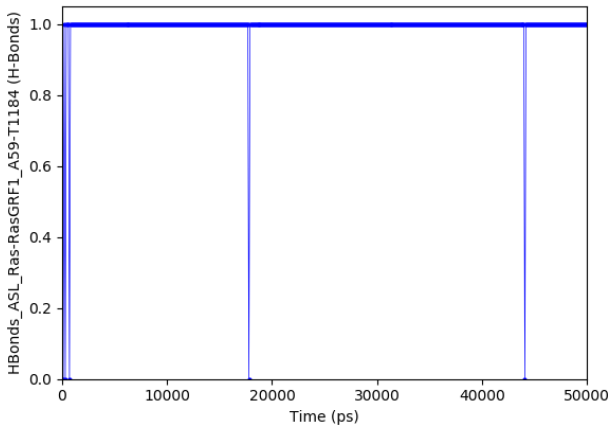
Table S2. Plots of the H-bonds established between Ras and RasGRF1 during the MD simulation.



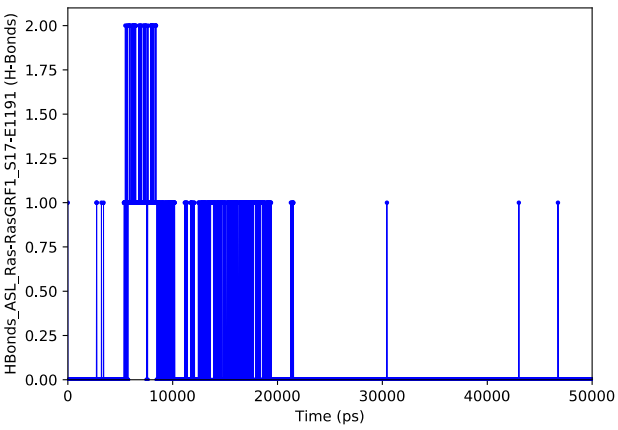
Ras Gln61-RasGRF1 Tyr1178



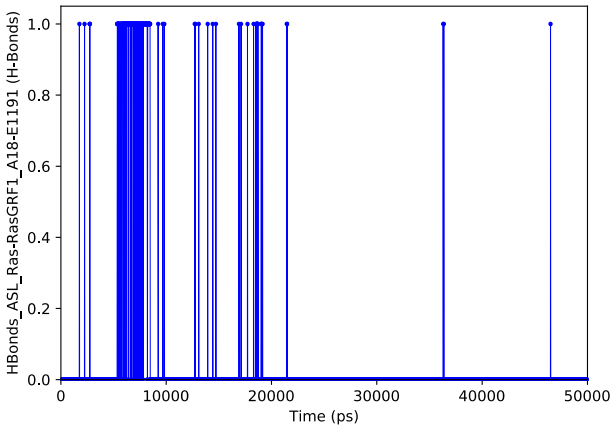
Ras Gln61-RasGRF1 Thr1184



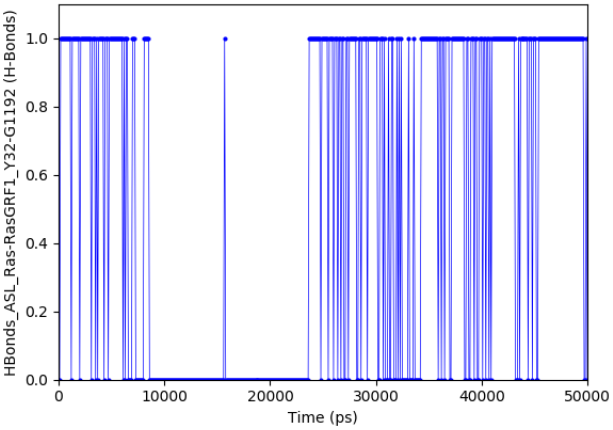
Ras Ala59-RasGRF1 Thr1184



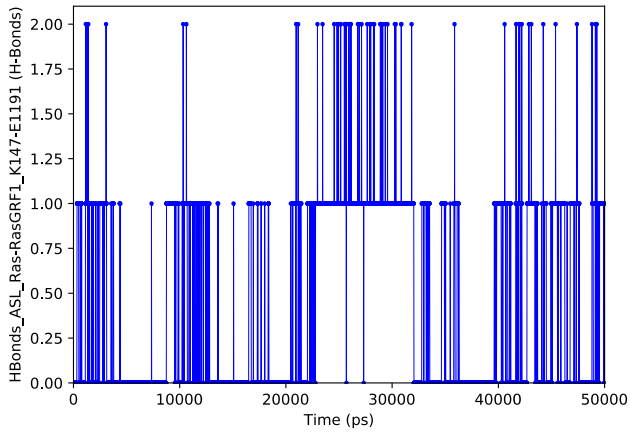
Ras Ser17-RasGRF1 Glu1191



Ras Ala18-RasGRF1 Glu1191



Ras Tyr32-RasGRF1 Gly1192



Ras Lys147-RasGRF1 Glu1191

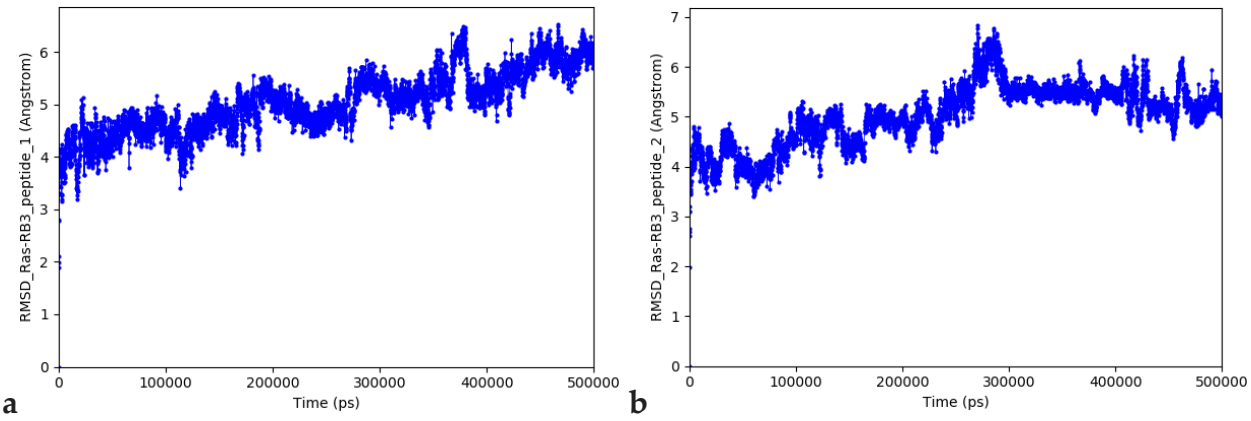


Figure S4. RMSD plots of first **(a)** and second **(b)** MD simulations performed on Ras-RB3 peptide complex

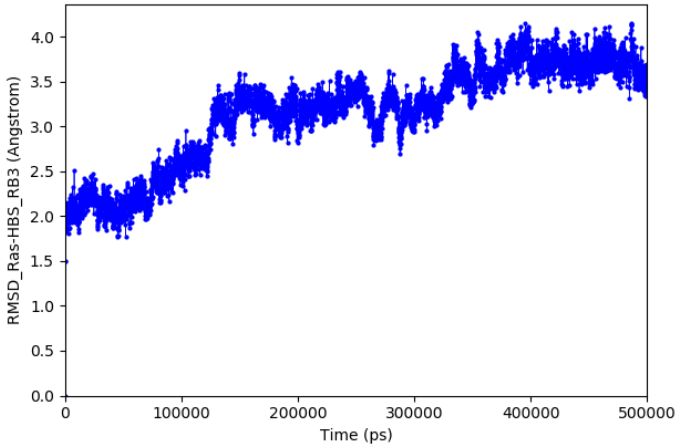


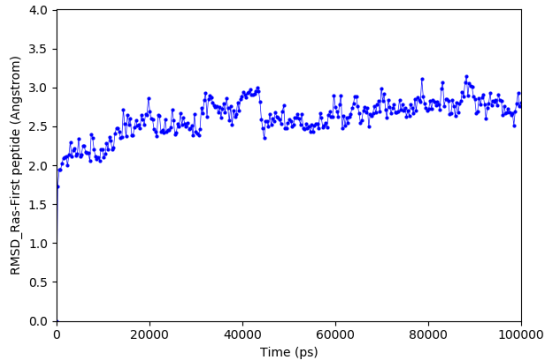
Figure S5. RMSD plot of MD simulation performed on Ras protein in complex with 3_{10}-HBS RB3 peptide

Table S3. $\Delta G_{binding}$ average values of the interaction energies and the Generalized Born solvation energy for the MD trajectories of the complexes Ras-point mutated 3_{10}-HBS RB3 peptides.

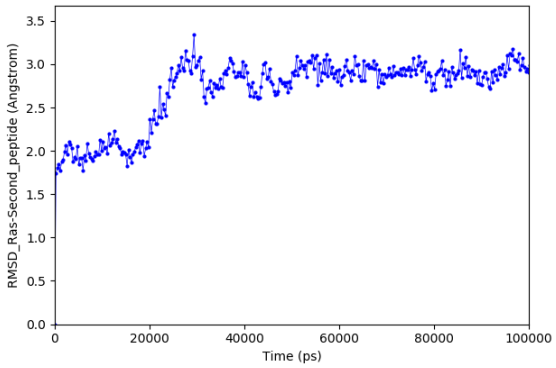
	First Peptide	**Second Peptide**	**Third Peptide**
Point mutation	T1184R	T1184M	D1185W
$\Delta G_{binding}$ – average interaction energy	-98.85 kcal/mol	-48.00 kcal/mol	-98.57 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	9.36 kcal/mol	-44.76 kcal/mol	-4.93 kcal/mol
	Fourth Peptide	**Fifth Peptide**	**Sixth Peptide**
Point mutation	D1185Y	D1185F	D1185L
$\Delta G_{binding}$ – average interaction energy	-101.10 kcal/mol	-84.63 kcal/mol	-78.69 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	-1.38 kcal/mol	-10.19 kcal/mol	-3.38 kcal/mol
	Seventh Peptide	**Eighth Peptide**	**Ninth Peptide**
Point mutation	F1188R	F1188H	I1189M
$\Delta G_{binding}$ – average interaction energy	-47.97 kcal/mol	-8.58 kcal/mol	-34.55 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	-39.52 kcal/mol	-60.99 kcal/mol	-48.57 kcal/mol
	Tenth Peptide	**Eleventh Peptide**	**Twelfth Peptide**
Point mutation	E1190H	E1191I	E1191L
$\Delta G_{binding}$ – average interaction energy	-36.69 kcal/mol	-44.44 kcal/mol	-53.27 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	-36.68 kcal/mol	-34.21 kcal/mol	-41.85 kcal/mol
	Thirteenth Peptide	**Fourteenth Peptide**	**Fifteenth Peptide**
Point mutation	E1191V	E1191T	T1193R
$\Delta G_{binding}$ – average interaction energy	-53.11 kcal/mol	-42.78 kcal /mol	-45.44 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	-41.30 kcal/mol	-41.72 kcal/mol	-44.74 kcal/mol

	Sixteenth Peptide
Point mutation	T1193N
$\Delta G_{binding}$ – average interaction energy	-51.05 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	-46.10 kcal/mol

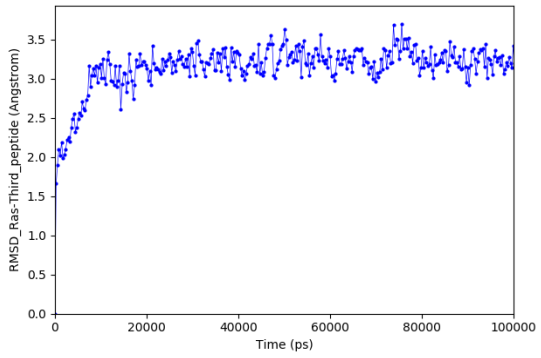
Table S4. RMSD plots of 100 ns-long MD simulations performed on Ras protein in complex with the sixteen point-mutated 3_{10}-HBS RB3 peptides



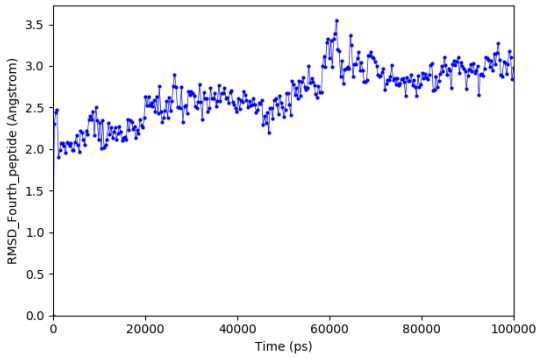
Ras-First Peptide



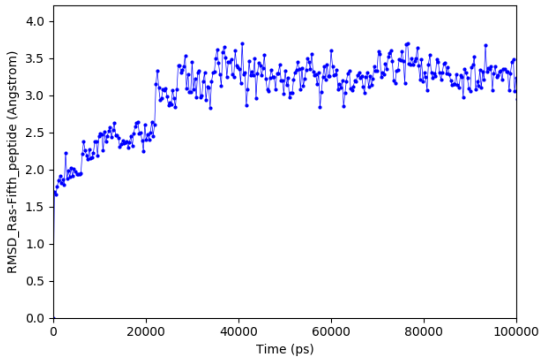
Ras-Second Peptide



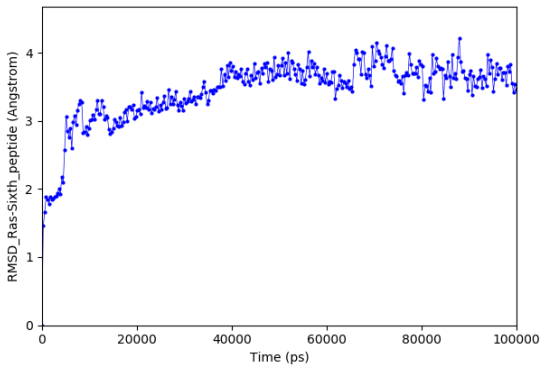
Ras-Third Peptide



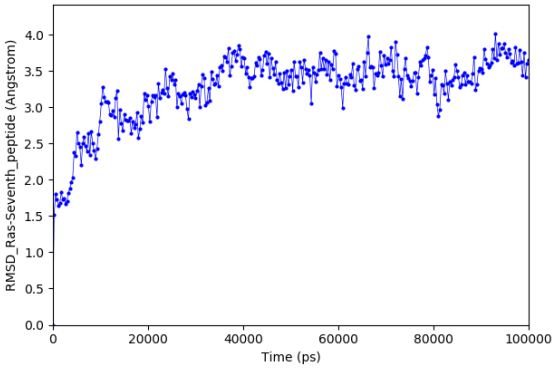
Ras-Fourth Peptide



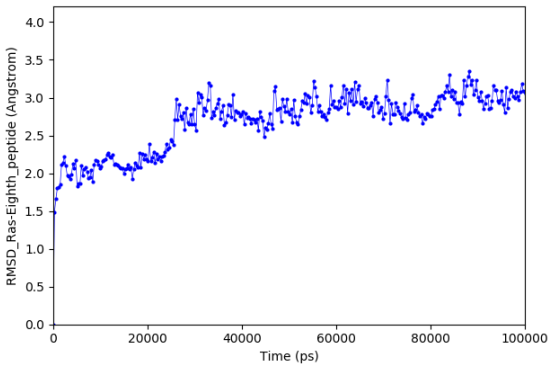
Ras-Fifth Peptide



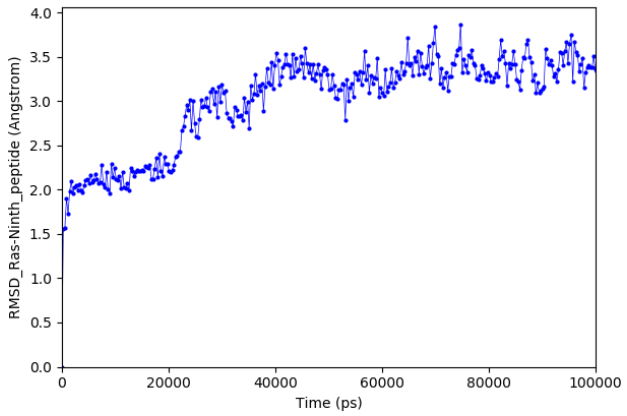
Ras-Sixth Peptide



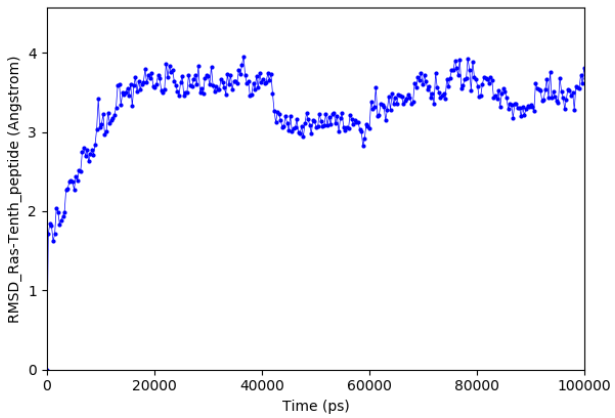
Ras-Seventh Peptide



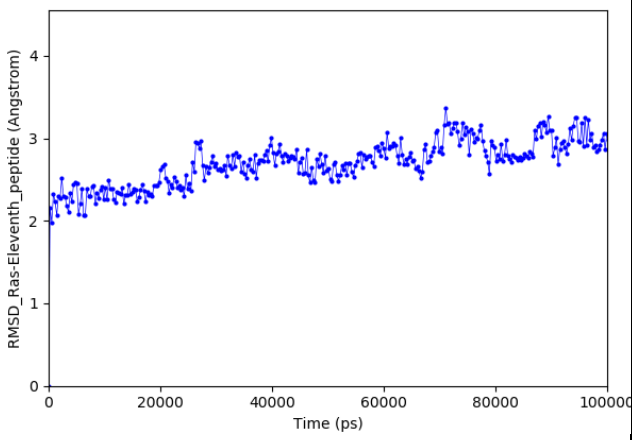
Ras-Eighth Peptide



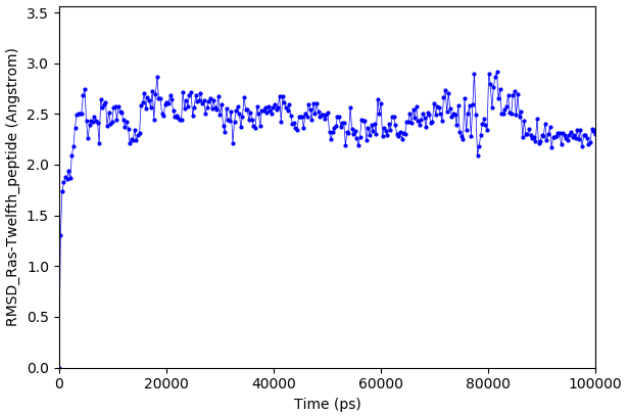
Ras-Ninth Peptide



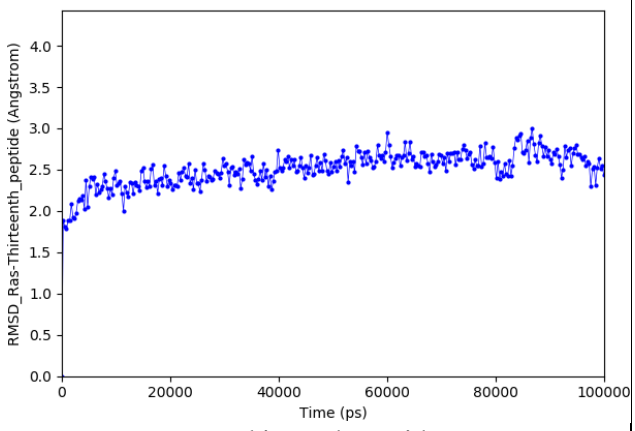
Ras-Tenth Peptide



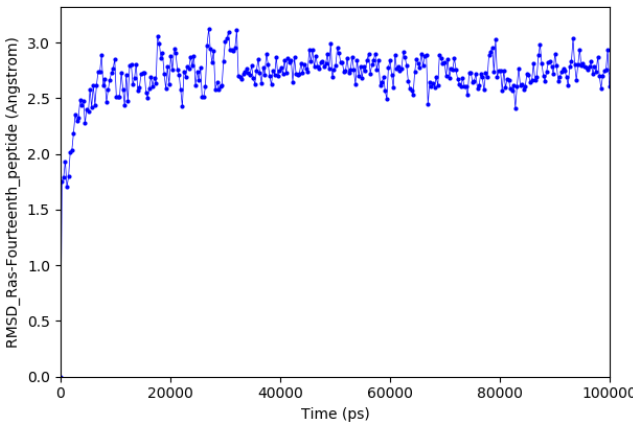
Ras-Eleventh Peptide



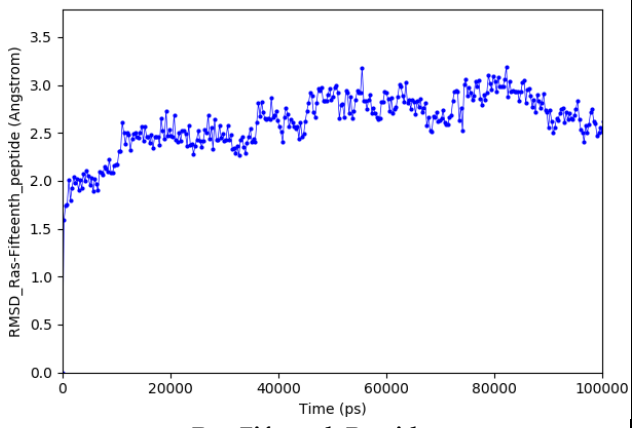
Ras-Twelfth Peptide



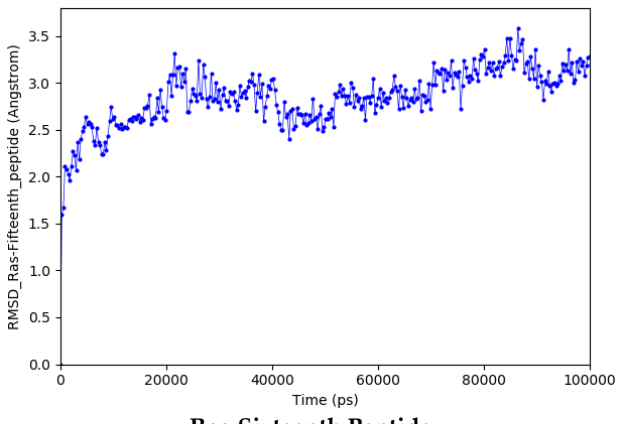
Ras-Thirteenth Peptide



Ras-Fourteenth Peptide



Ras-Fifteenth Peptide

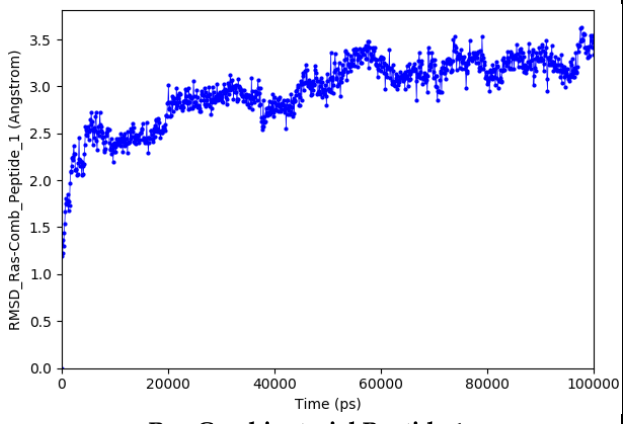


Ras-Sixteenth Peptide

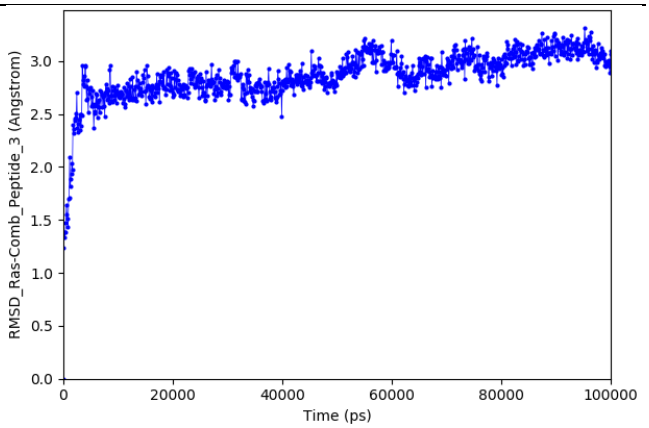
Table S5. $\Delta G_{binding}$ average values of the interaction energies and the Generalized Born solvation energy for the MD trajectories of the complexes Ras-combinatorial peptides.

	First Peptide	Third Peptide	Eleventh Peptide
Peptide sequence	YLGMYLRWLVRMELGR	YLGMYLRYLVRMELGR	YLGMYLRFLVRMEVGR
$\Delta G_{binding}$ – average interaction energy	-217.54 kcal/mol	-251.32 kcal/mol	-233.65 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	134.08 kcal/mol	154.52 kcal/mol	142.26 kcal/mol
	Twelfth Peptide	**Fifteenth Peptide**	**Sixteenth Peptide**
Peptide sequence	YLGMYLRLLVRMEVGR	YLGMYLMFLVRMEVGR	YLGMYLMLLVRMEVGR
$\Delta G_{binding}$ – average interaction energy	-252.46 kcal/mol	-176.32 kcal/mol	-166.15 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	159.96 kcal/mol	96.53 kcal/mol	73.61 kcal/mol
	Eighteenth Peptide	**Nineteenth Peptide**	**Twentieth Peptide**
Peptide sequence	YLGMYLRYLVRMETGR	YLGMYLRFLVRMETGR	YLGMYLRLLVRMETGR
$\Delta G_{binding}$ – average interaction energy	-283.21 kcal/mol	-262.47 kcal/mol	-217.80 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	182.87 kcal/mol	159.85 kcal/mol	129.08 kcal/mol
	Twenty-third Peptide	**Twenty-fourth Peptide**	**Twenty-fifth Peptide**
Peptide sequence	YLGMYLMFLVRMETGR	YLGMYLMLLVRMETGR	YLGMYLRWLVRMELGN
$\Delta G_{binding}$ – average interaction energy	-195.79 kcal/mol	-163.02 kcal/mol	-153.99 kcal /mol
$\Delta G_{binding}$ – average GB solvation energy	110.27 kcal/mol	80.71 kcal/mol	56.75 kcal/mol
	Twenty-ninth Peptide	**Forty-second Peptide**	**Forty-third Peptide**
Peptide sequence	YLGMYLRFLVRMELGN	YLGMYLRYLVRMETGN	YLGMYLRFLVRMETGN
$\Delta G_{binding}$ – average interaction energy	-174.73 kcal/mol	-194.94 kcal/mol	-247.51 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	88.17 kcal/mol	105.36 kcal/mol	124.01 kcal/mol
	Forty-fourth Peptide	**Forty-fifth Peptide**	**Forty-eighth Peptide**
Peptide sequence	YLGMYLRLLVRMETGN	YLGMYLMWLVRMETGN	YLGMYLMLLVRMETGN
$\Delta G_{binding}$ – average interaction energy	-219.53 kcal/mol	-150.62 kcal/mol	-145.62 kcal/mol
$\Delta G_{binding}$ – average GB solvation energy	123.22 kcal/mol	64.59 kcal/mol	53.81 kcal/mol

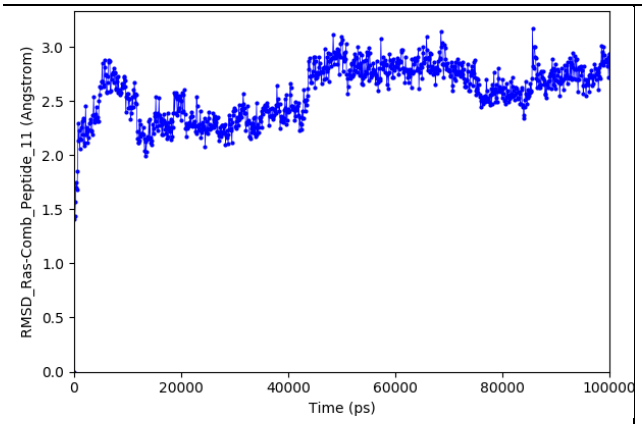
Table S6. RMSD plots of 100 ns-long MD simulations performed on Ras protein in complex with the selected eighteen 3_{10}-HBS RB3 combinatorial peptides



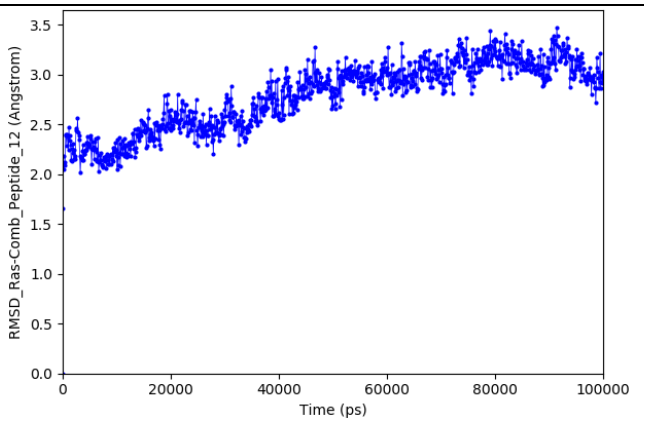
Ras-Combinatorial Peptide 1



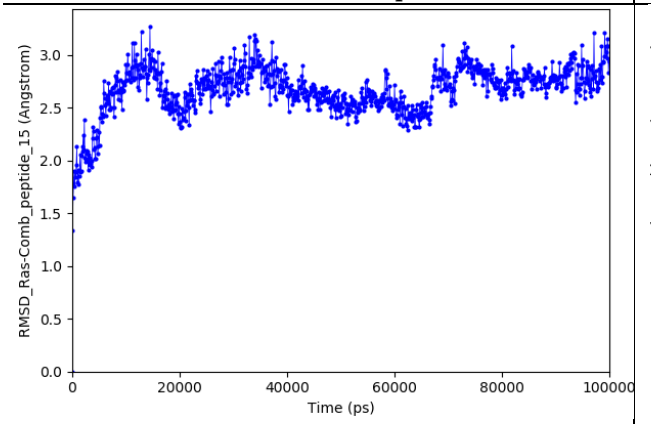
Ras-Combinatorial Peptide 3



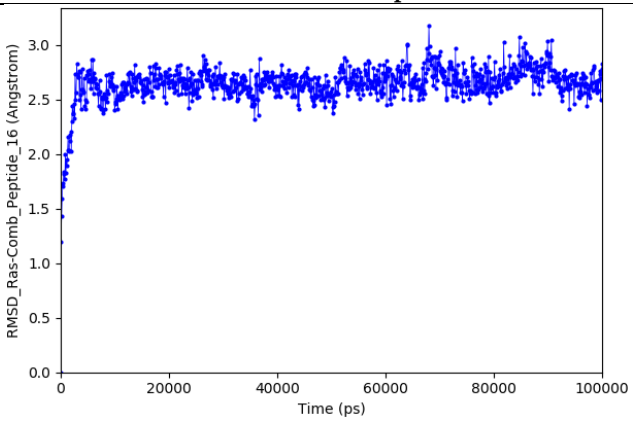
Ras-Combinatorial Peptide 11



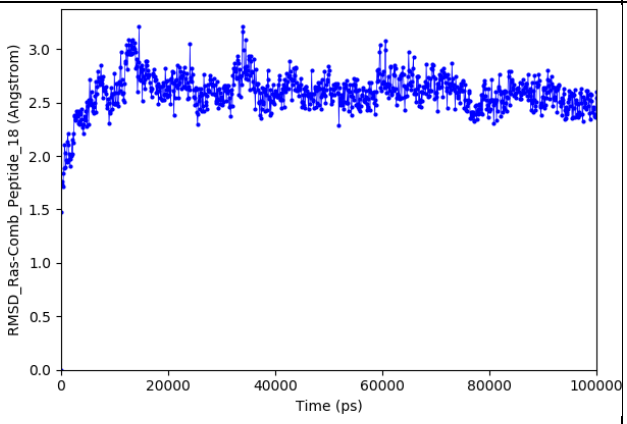
Ras-Combinatorial Peptide 12



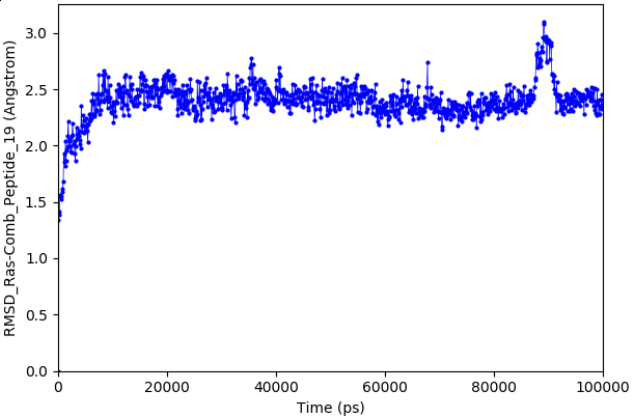
Ras-Combinatorial Peptide 15



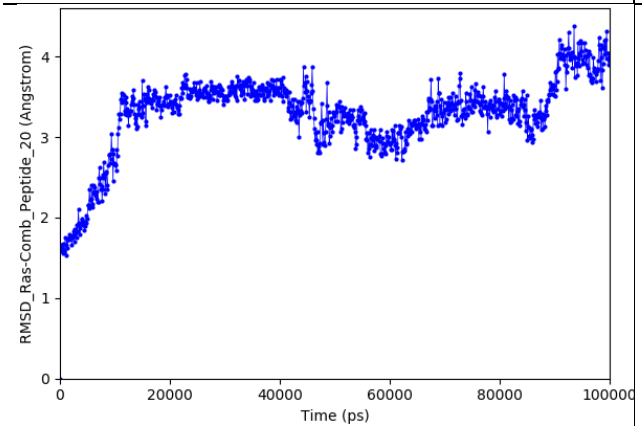
Ras-Combinatorial Peptide 16



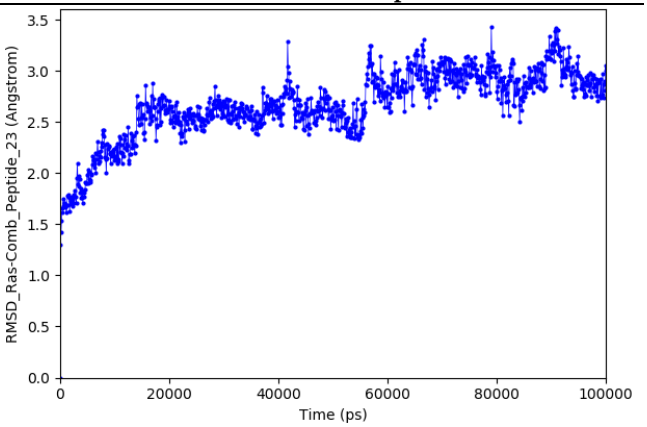
Ras-Combinatorial Peptide 18



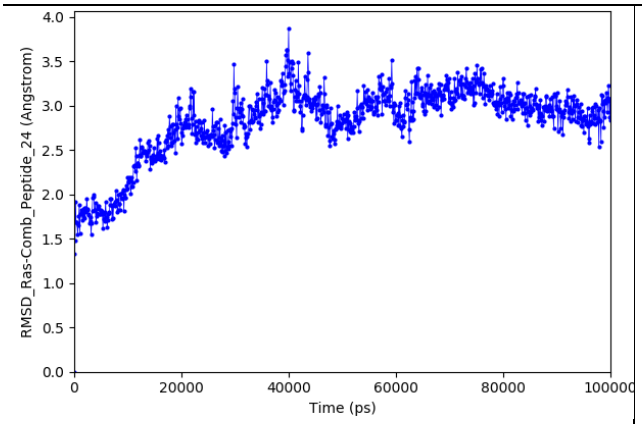
Ras-Combinatorial Peptide 19



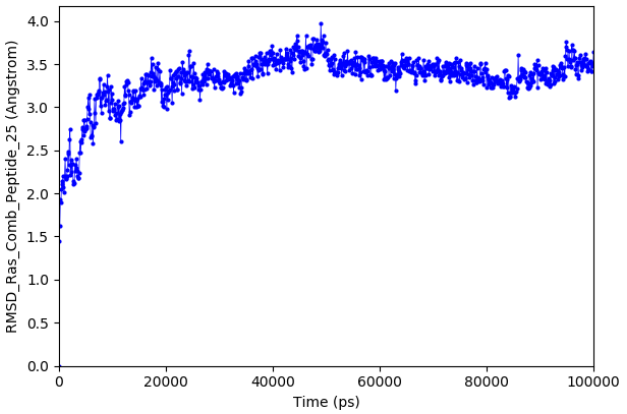
Ras-Combinatorial Peptide 20



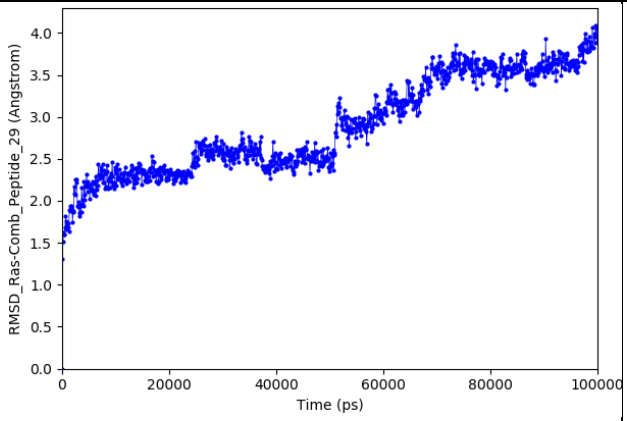
Ras-Combinatorial Peptide 23



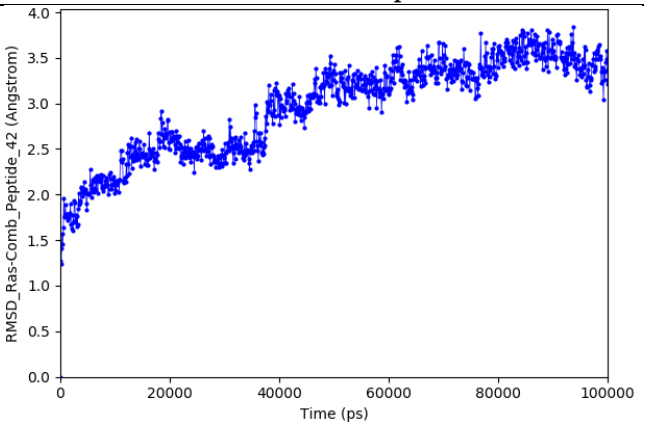
Ras-Combinatorial Peptide 24



Ras-Combinatorial Peptide 25



Ras-Combinatorial Peptide 29



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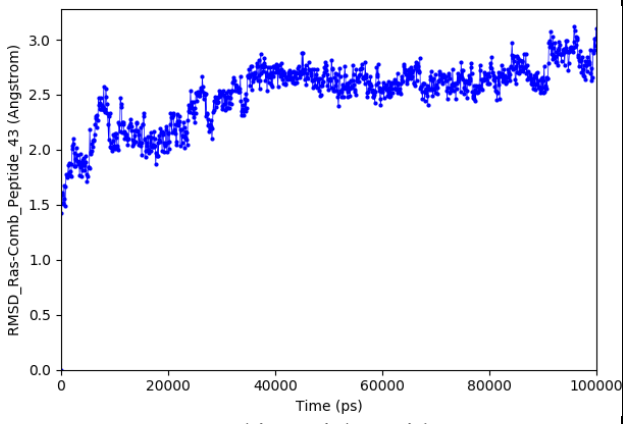

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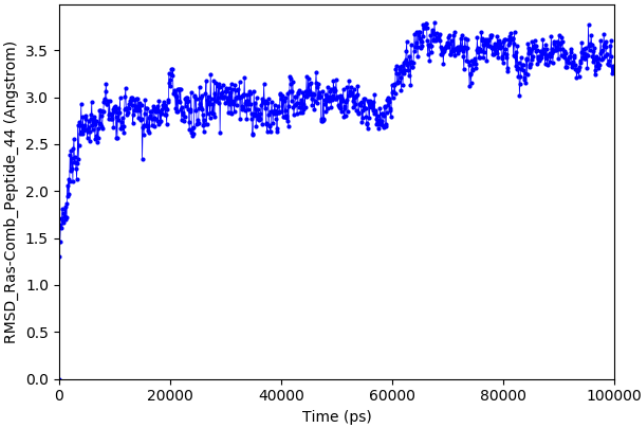

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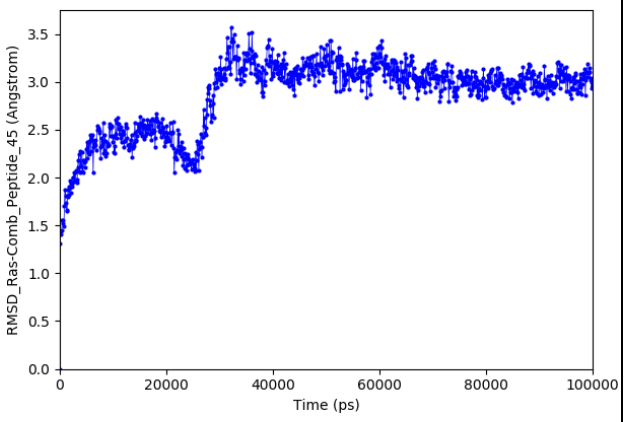

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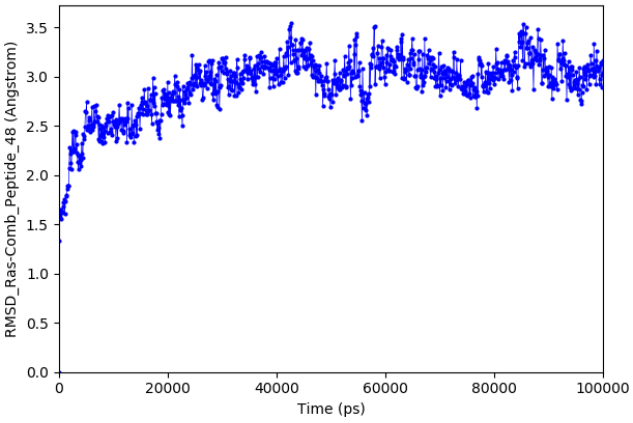
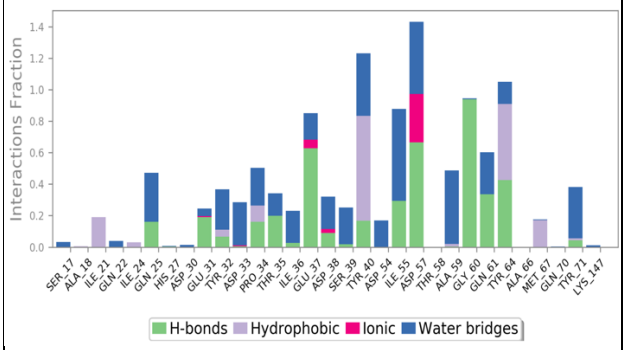
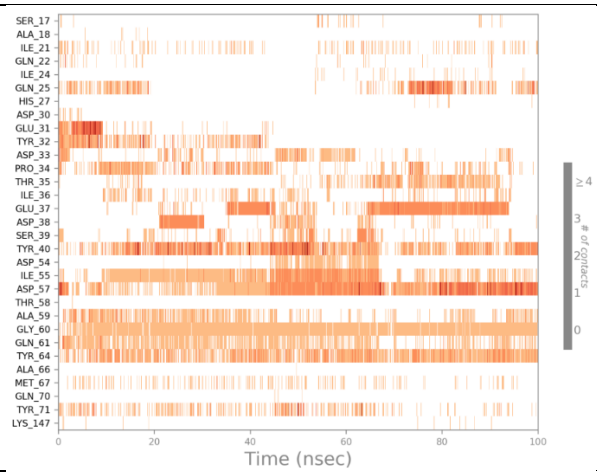
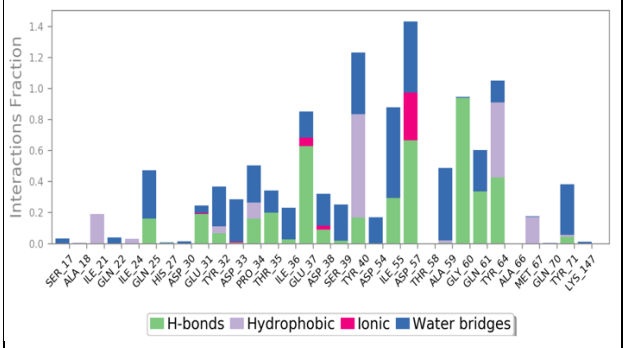
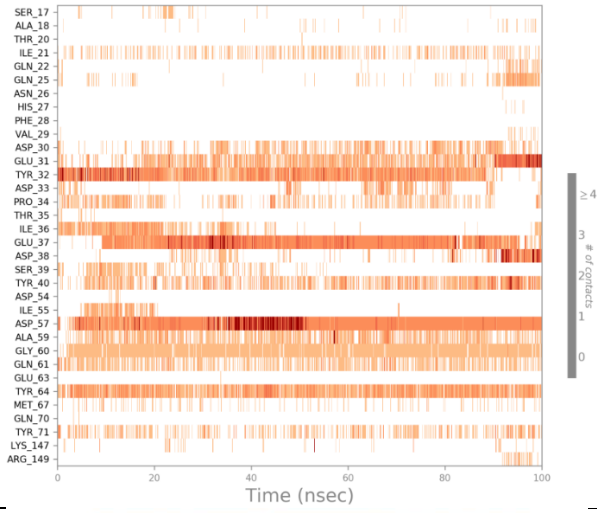
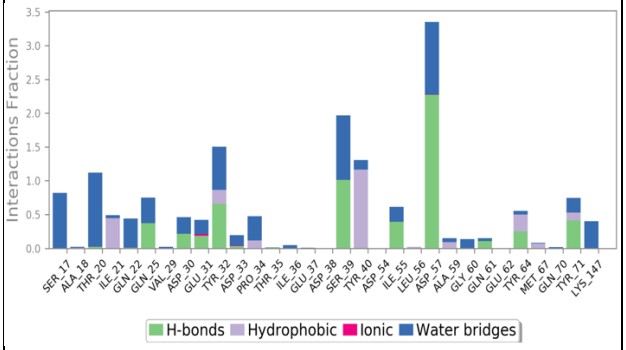
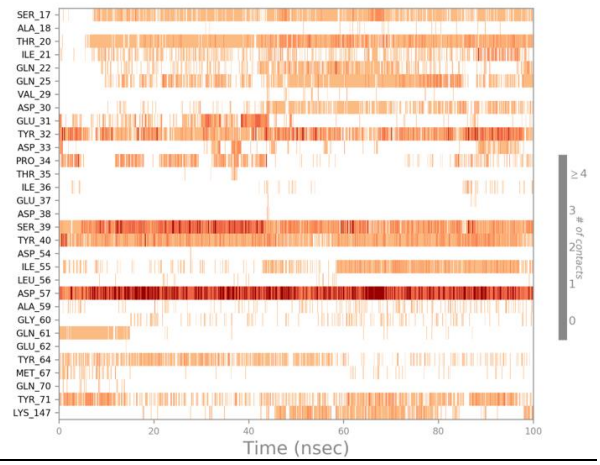
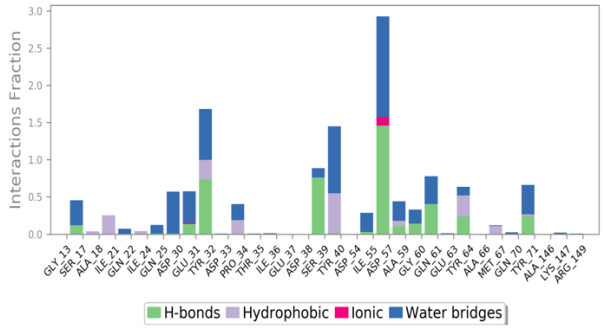
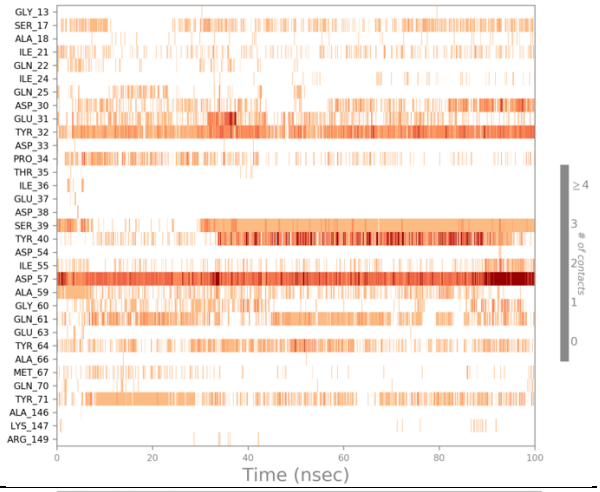
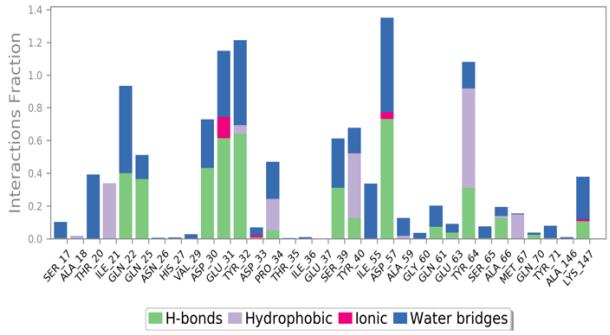
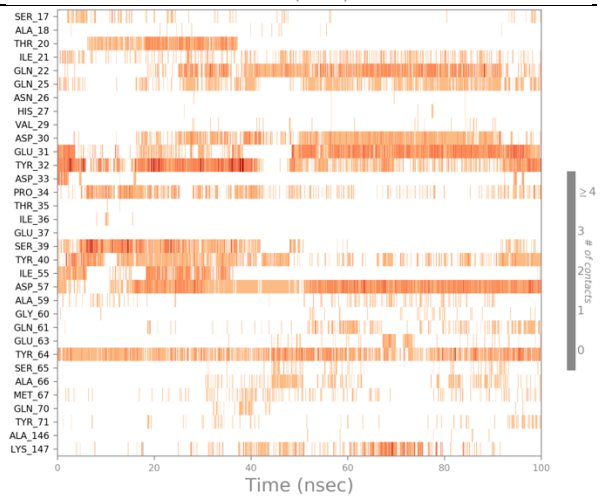
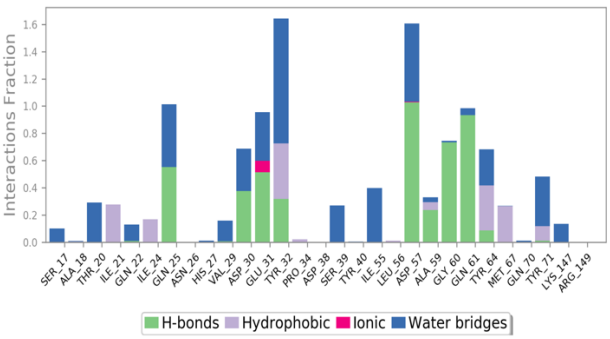
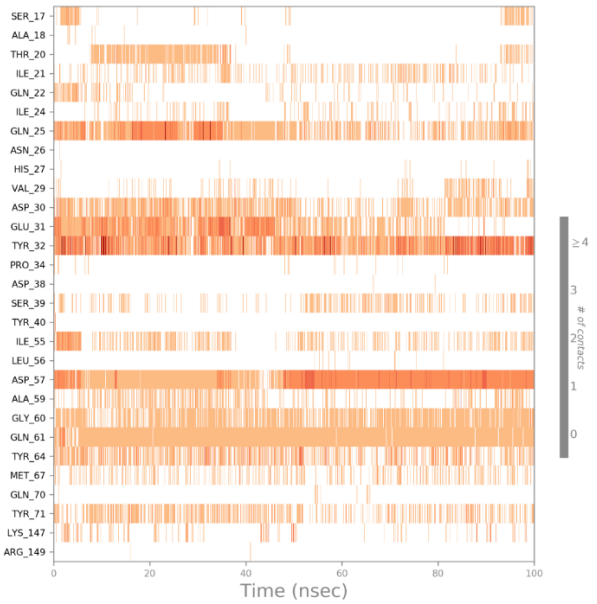
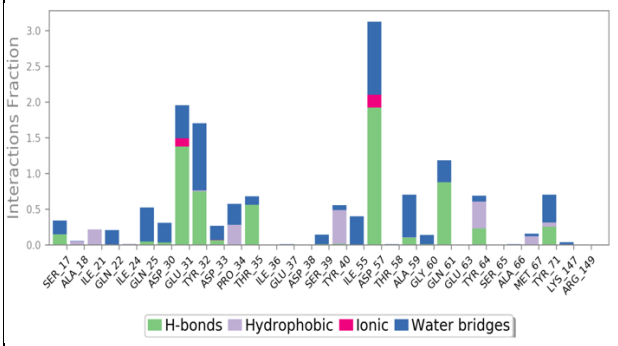
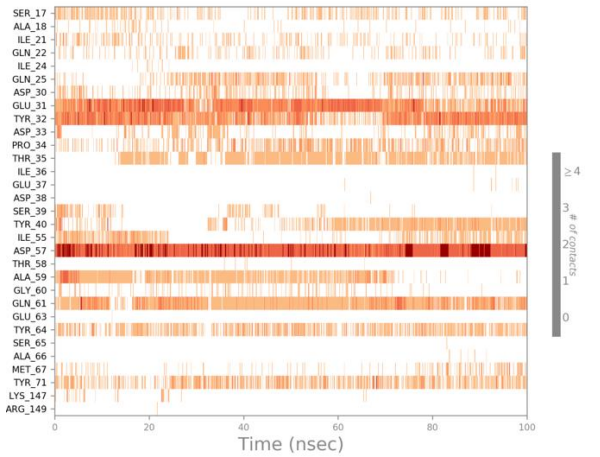
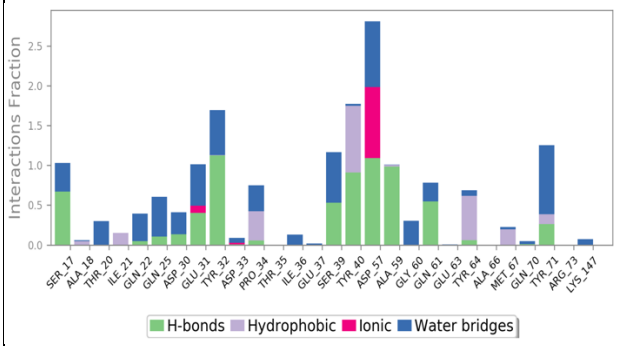
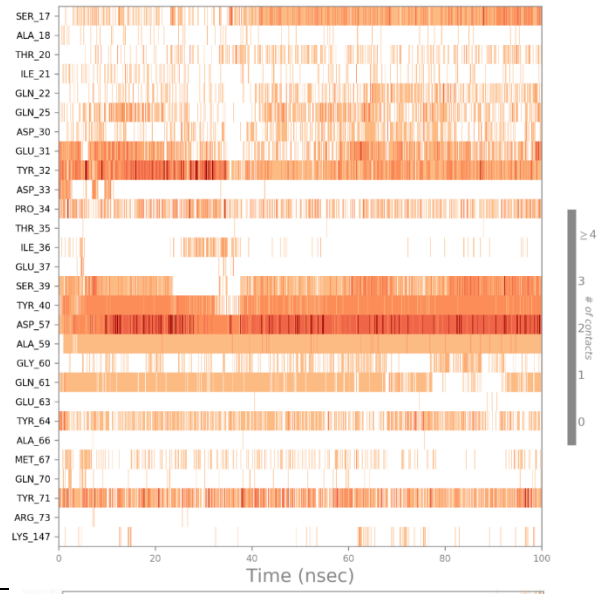
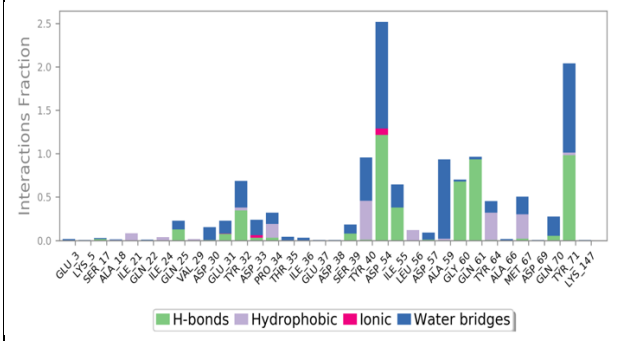
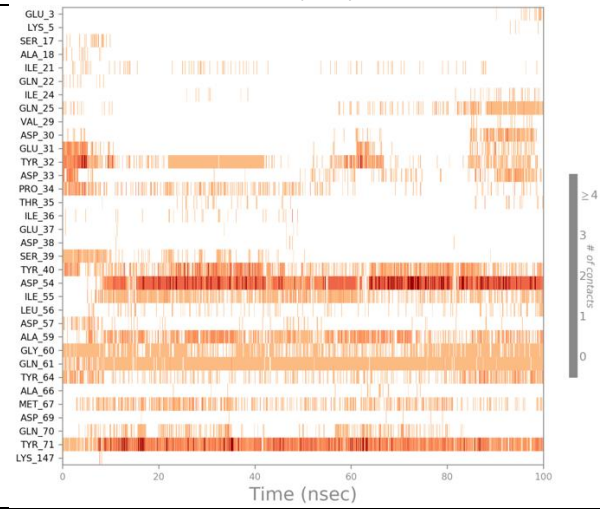


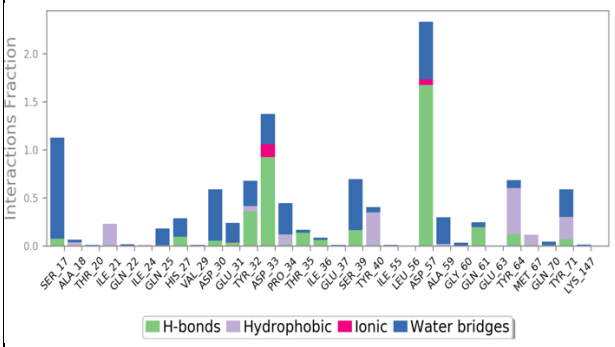
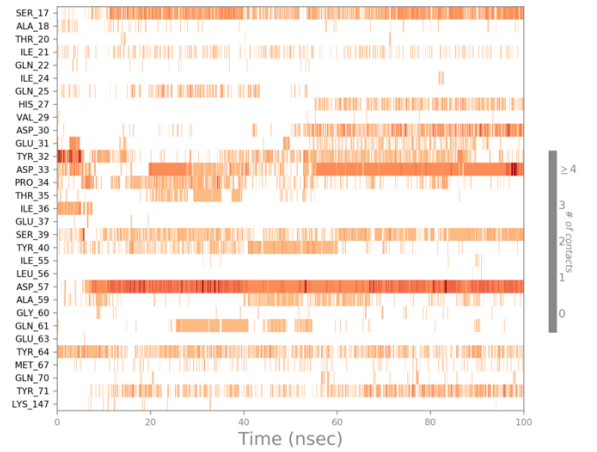
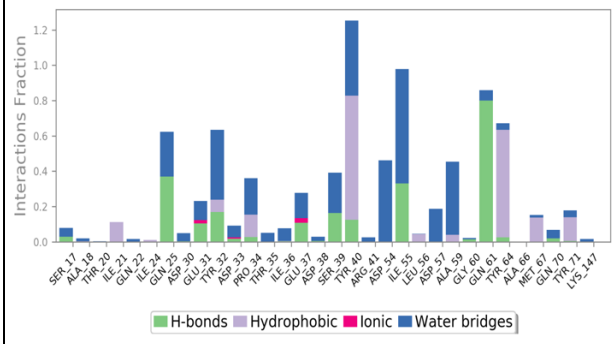
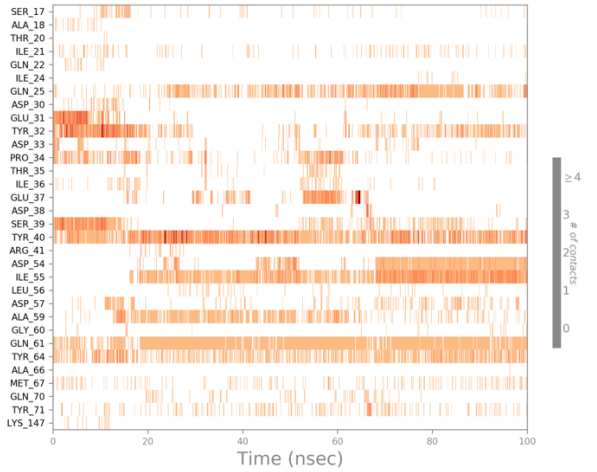
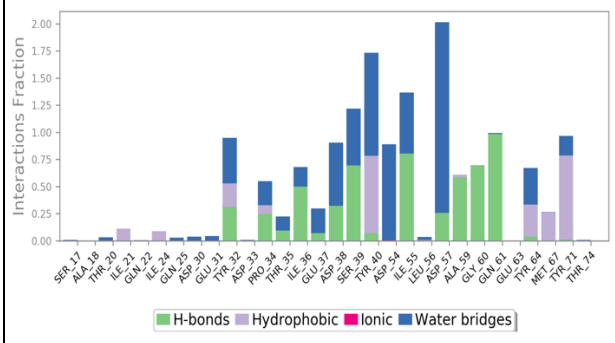
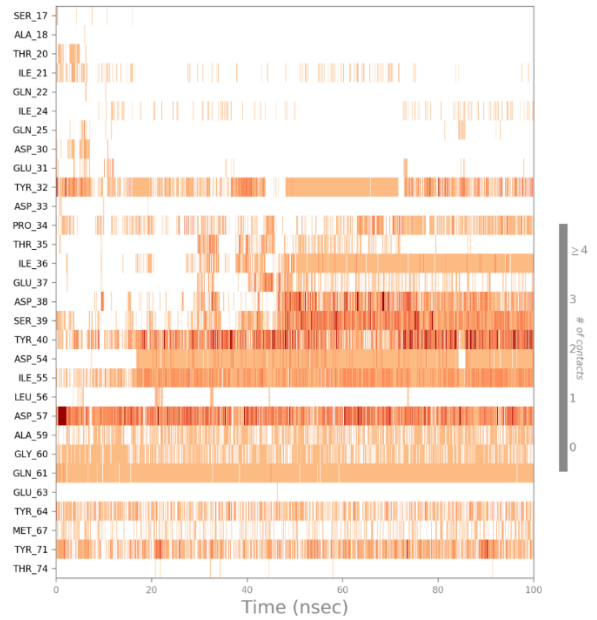
Ras-Combinatorial Peptide 48

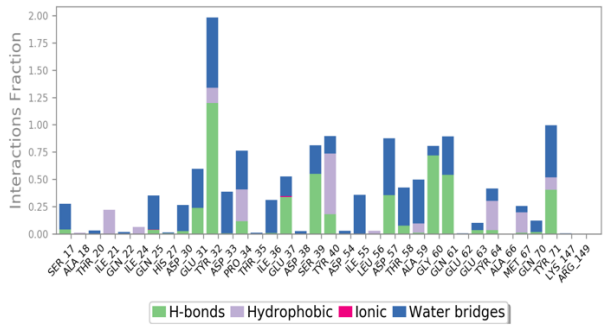
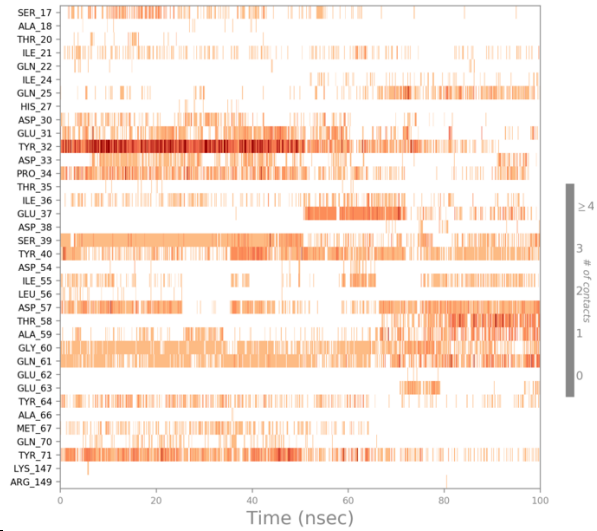
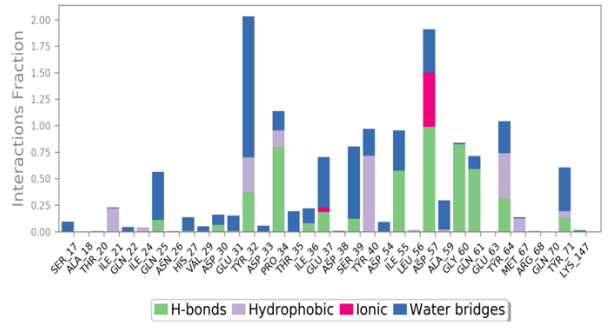
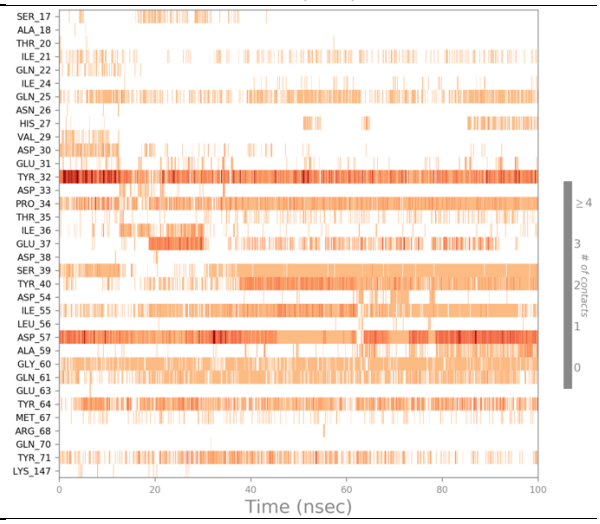
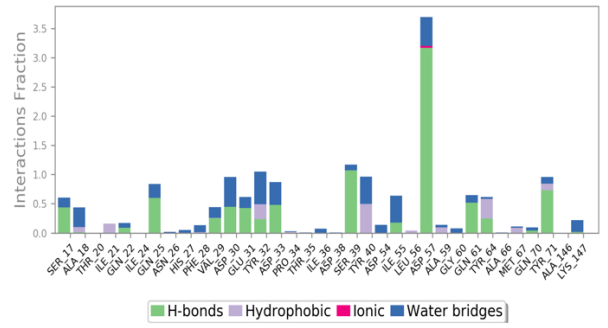
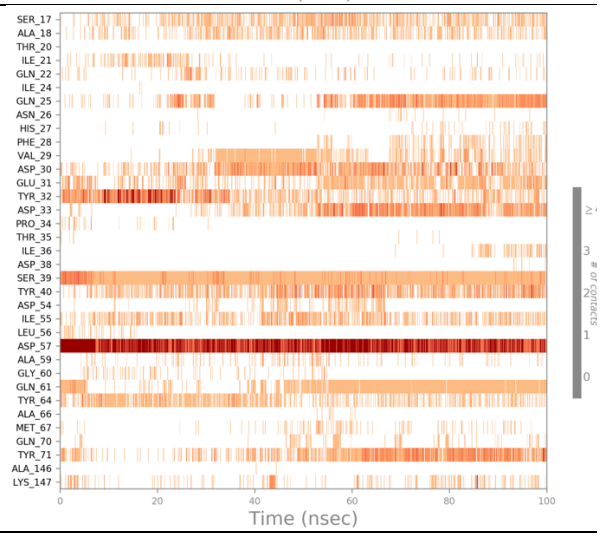
Table S7. The bar charts of protein-ligand interactions for the eighteen 3_{10}-HBS RB3 combinatorial peptides (on the left column); the plots illustrating the frequency of interaction occurrences between the combinatorial peptides and Ras protein (on the right column)

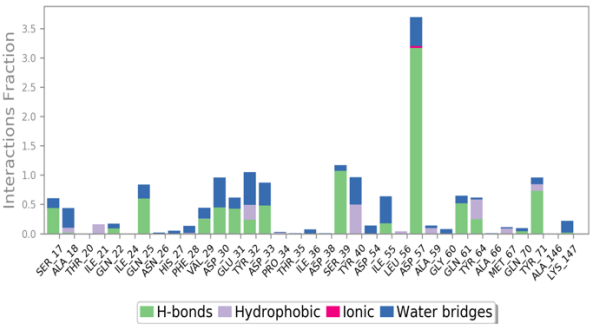
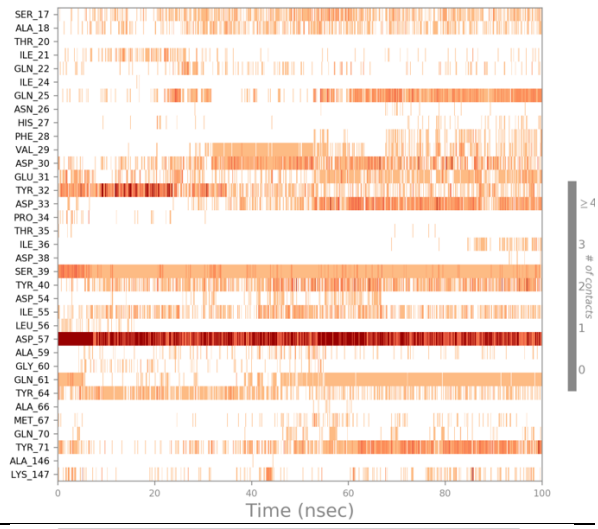
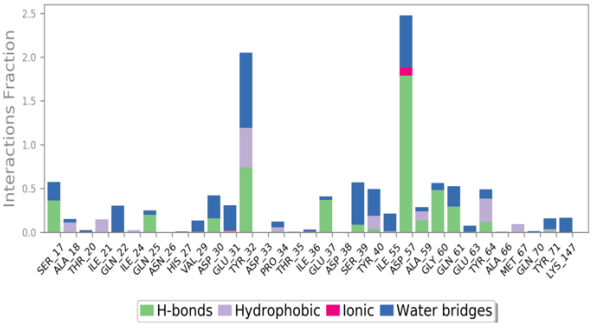
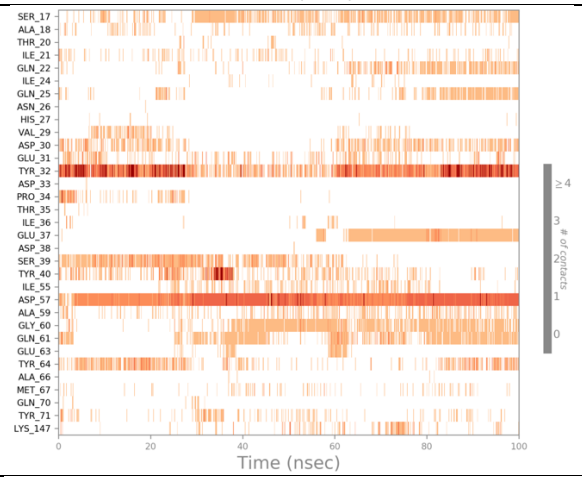
Combinatorial Peptide 1		
Combinatorial Peptide 3		
Combinatorial Peptide 11		

Combinatorial Peptide 12		
Combinatorial Peptide 15		
Combinatorial Peptide 16		

Combinatorial Peptide 18		
Combinatorial Peptide 19		
Combinatorial Peptide 20		

Combinatorial Peptide 23		
Combinatorial Peptide 24		
Combinatorial Peptide 25		

Combinatorial Peptide 29		
Combinatorial Peptide 42		
Combinatorial Peptide 43		

Combinatorial Peptide 44		
Combinatorial Peptide 45		
Combinatorial Peptide 48