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Supplementary Information

Molecular Dynamics Simulations Elucidate Conformational Selection and Induced Fit Mechanisms in the Binding of PD-1 and PD-L1

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Table S1. Key contacts between PD-1 (excluding the CC' loop) and PD-L1

No	Name	Type	Distance (Å)[#]	
			open-liganded	closed-liganded
1	LYS131NZ-GLN66NE2	hydrogen bond	3.26	2.80
2	ASN66ND2-ALA121O	hydrogen bond	3.05	2.85
3	ALA132N-GLN66OE1	hydrogen bond	3.53	2.90
4	GLU136-ARG125	salt bridge	2.71	2.45

[#] A hydrogen bond or salt bridge is formed when the distance is below 3.5 Å.

Table S2. Mean donor-receptor distances (Å) and survival ratios of Hydrogen bonds during MD simulations

Interaction residues		Open-unliganded		Closed-unliganded		Open-liganded		Closed-liganded	
		Mean distance	Survival ratio	Mean distance	Survival ratio	Mean distance	Survival ratio	Mean distance	Survival ratio
$MET70_N$	*$THR120_O$*	*2.84±0.01*	*1.00±0.00*	*2.93±0.02*	*0.99±0.01*	*2.84±0.02*	*1.00±0.00*	*2.93±0.09*	*0.97±0.05*
$SER71_O$	*$THR120_N$*	*4.08±0.34*	*0.21±0.07*	*6.89±0.38*	*0.00±0.00*	*3.92±0.64*	*0.27±0.36*	*7.66±0.51*	*0.00±0.00*
$SER71_N$	*$THR120_{OG1}$*	*3.57±0.34*	*0.53±0.23*	*6.41±0.36*	*0.00±0.00*	*4.25±0.56*	*0.28±0.21*	*7.32±0.27*	*0.00±0.00*
$SER73_{OG}$	$ASP26_{OD1}$	-	-	-	-	7.53±2.38	0.12±0.13	6.74±2.52	0.13±0.15
$ASN74_{OD1}$	$VAL23_N$	-	-	-	-	12.44±3.41	0.11±0.15	14.00±4.41	0.00±0.00
$ASN74_{ND2}$	$THR22_{OG1}$	-	-	-	-	13.96±4.05	0.05±0.07	17.26±6.72	0.00±0.00
$GLN75_{OE1}$	$ARG125_N$	-	-	-	-	13.07±4.99	0.08±0.13	2.98±0.03	0.98±0.01
$GLN75_{OE1}$	$ARG125_O$	-	-	-	-	12.56±4.52	0.06±0.09	3.57±0.11	0.45±0.16
$GLN75_{OE1}$	$TYR123_{OH}$	-	-	-	-	15.3±5.03	0.02±0.03	8.65±3.15	0.00±0.00
$GLN75_{NE2}$	$ARG125_O$	-	-	-	-	12.57±4.81	0.00±0.00	2.89±0.02	1.00±0.00
$GLN75_{NE2}$	$ASP26_{OD1}$	-	-	-	-	10.48±2.36	0.02±0.03	3.88±0.31	0.39±0.21
$THR76_{OG1}$	$ARG125_{NH1}$	-	-	-	-	11.56±1.54	0.00±0.00	3.76±0.26	0.42±0.17
$THR76_O$	$LYS124_{NZ}$	-	-	-	-	4.34±0.94	0.30±0.31	4.16±0.34	0.21±0.19
$ASP77_{OD2}$	$LYS124_{NZ}$	-	-	-	-	4.92±1.95	0.45±0.47	6.71±2.88	0.00±0.00

Intramolecular between MET70 and SER71 of the C strand and THR120 of the F strand of PD-1 are shown in italic. Other bonds exist in the interface between PD-1 and PD-L1. The values were presented as means ± SD of three different values measured from three independent simulations with duration of 50ns for each system.

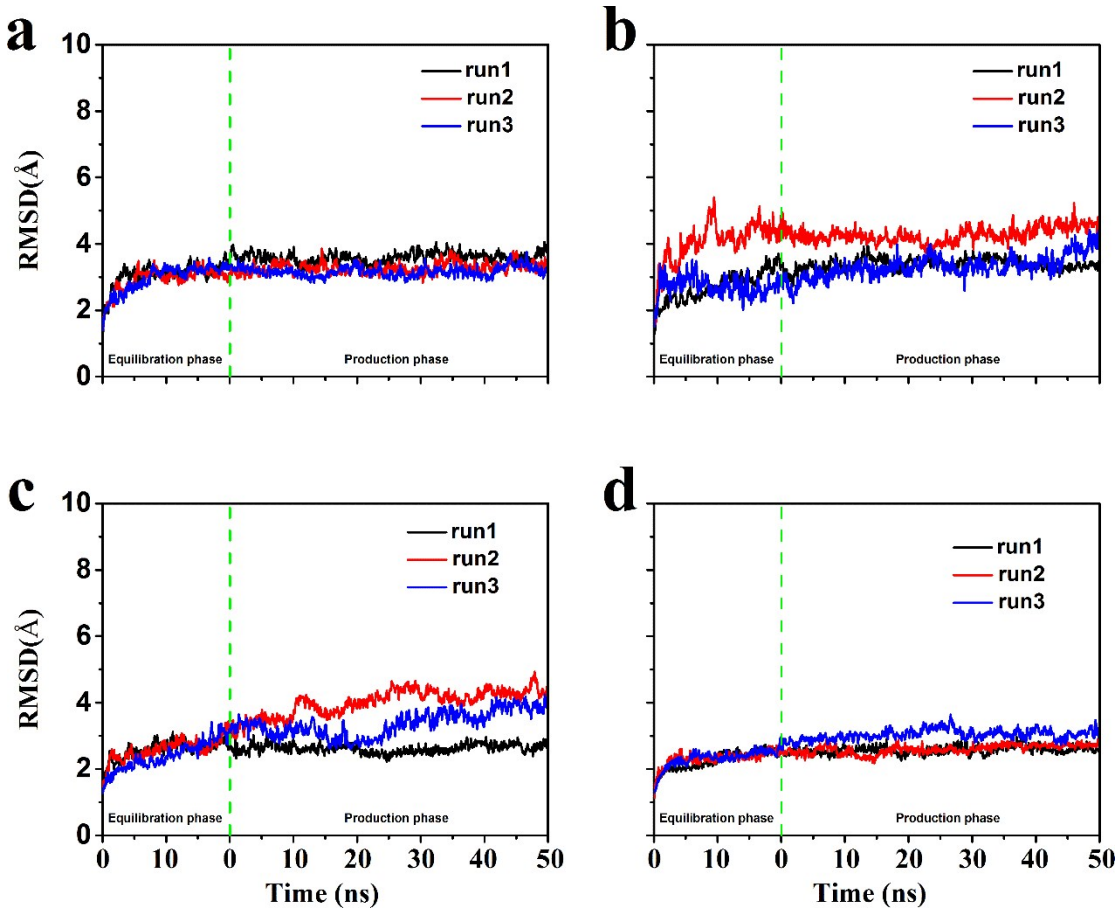

Figure S1. Stability of the four simulated systems. (**a**) RMSD of heavy atoms for the open-unliganded PD-1 in three runs. (**b**) RMSD of heavy atoms for open-liganded PD-1/PD-L1 complex in three runs. (**c**) RMSD of heavy atoms for closed-unliganded PD-1 in three runs. (**d**) RMSD of heavy atoms for closed-liganded PD-1/PD-L1 complex in three runs.

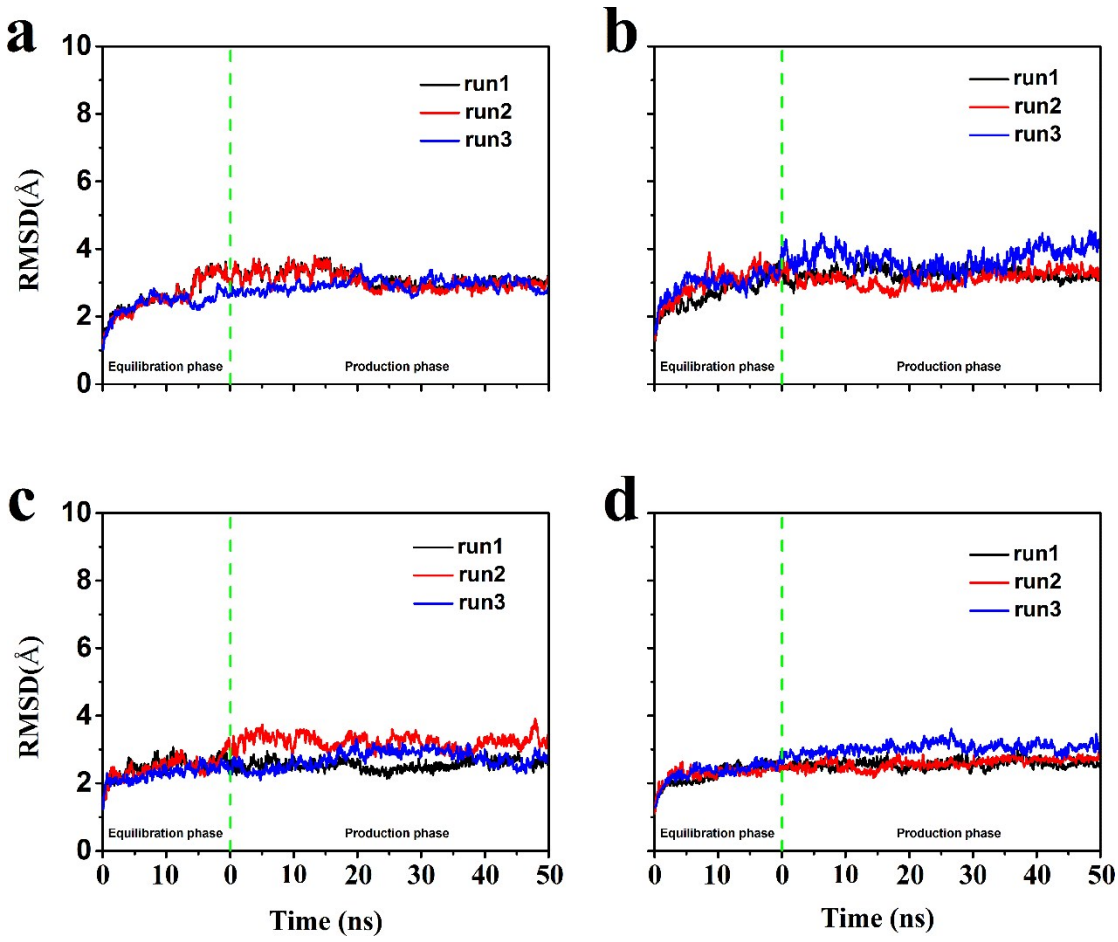

Figure S2. Stability of the four simulated systems excluding the CC' loop of PD-1. (**a**) RMSD of heavy atoms for the open-unliganded PD-1 in three runs. (**b**) RMSD of heavy atoms for open-liganded PD-1/PD-L1 complex in three runs. (**c**) RMSD of heavy atoms for closed-unliganded PD-1 in three runs. (**d**) RMSD of heavy atoms for closed-liganded PD-1/PD-L1 complex in three runs.

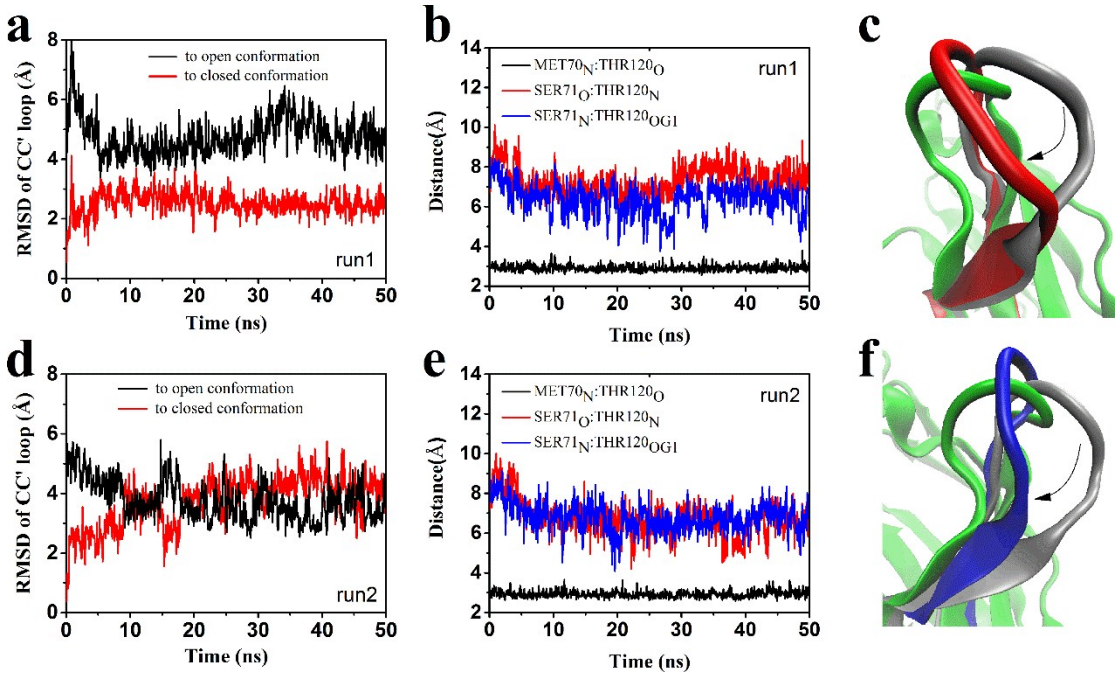

Figure S3. Structural fluctuations in the closed-unliganded system. (**a,d**) RMSD of the CC' loop relative to the open (black) and closed (red) conformation in run1 and run2, respectively. (**b,e**) Donor-receptor distances for three hydrogen bonds between MET70, SER71 and THR 120 in run1 and run2. (**c,f**) The averaged structures of the CC' loop in run1 (red) and run2 (blue), which were aligned to crystal structures of the open (green) and closed (silver) forms.

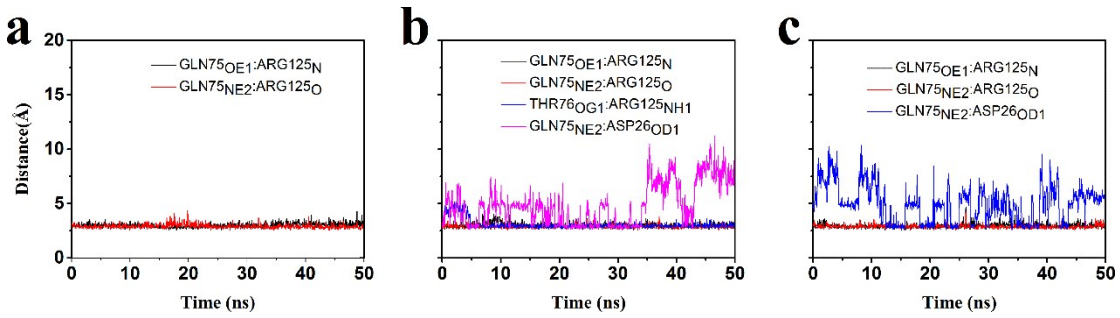

Figure S4. Stability of the hydrogen bonds between the CC' loop and PD-L1 in the closed-liganded system. (**a**). Donor-receptor distances for two hydrogen bonds in run1. (**b**). Donor-receptor distances for four hydrogen bonds in run2. (**c**). Donor-receptor distances for three hydrogen bonds in run3.