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Dissecting the chiral recognition of TLR4/MD2 with Neoseptin-3 enantiomers by molecular dynamics simulations

Cong Zhang[1,2], Siru Wu[1,2], Mingqi Li[1,2], Penghui Li [3], Xiubo Du[3], Yibo Wang[1*], Xiaohui Wang[1,2,4*]

[1]Laboratory of Chemical Biology, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, China
[2]School of Applied Chemistry and Engineering, University of Science and Technology of China, Hefei, 230026, China
[3]Shenzhen Key Laboratory of Marine Biotechnology and Ecology, College of Life Sciences and Oceanography, Shenzhen University, Shenzhen, 518060, China
[4]Beijing National Laboratory for Molecular Sciences, Beijing, 100190, China

*Corresponding authors: Yibo Wang (yibo.wang@ciac.ac.cn); Xiaohui Wang (xiaohui.wang@ciac.ac.cn)

Supporting Information

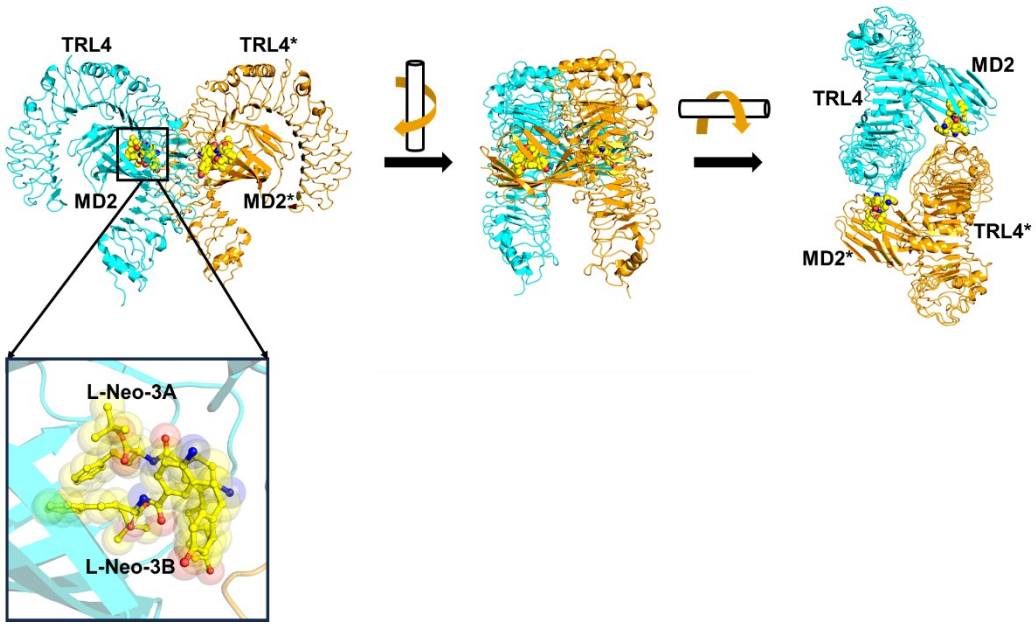


Figure S1. Structural details of the $(2*\text{Neo-3/TLR4/MD2})_2$ complexes. TLR4/MD2 and TLR4*/MD2* proteins are represented with cartoons and colored cyan and bright orange respectively. Neo-3 is represented with yellow sticks and spheres (taking L-Neo-3 as an example).

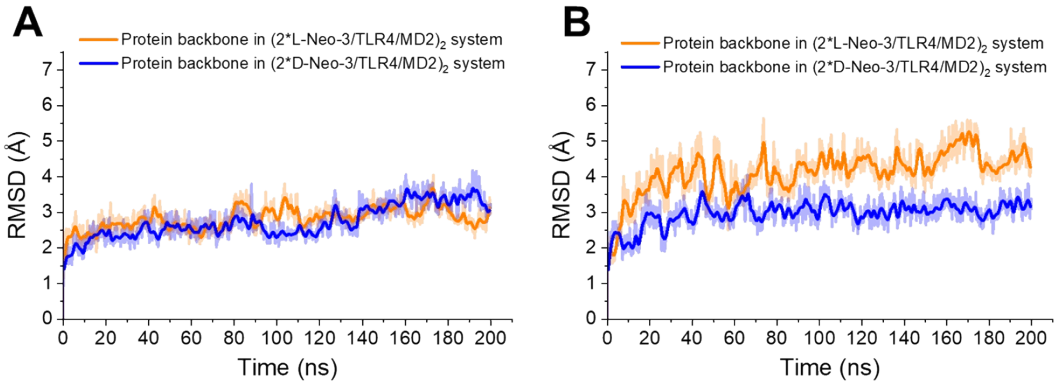


Figure S2. RMSDs of the protein backbone atoms in the second **(A)** and third **(B)** independent repeated simulations of $(2*\text{L-Neo-3/TLR4/MD2})_2$ and $(2*\text{D-Neo-3/TLR4/MD2})_2$ systems.

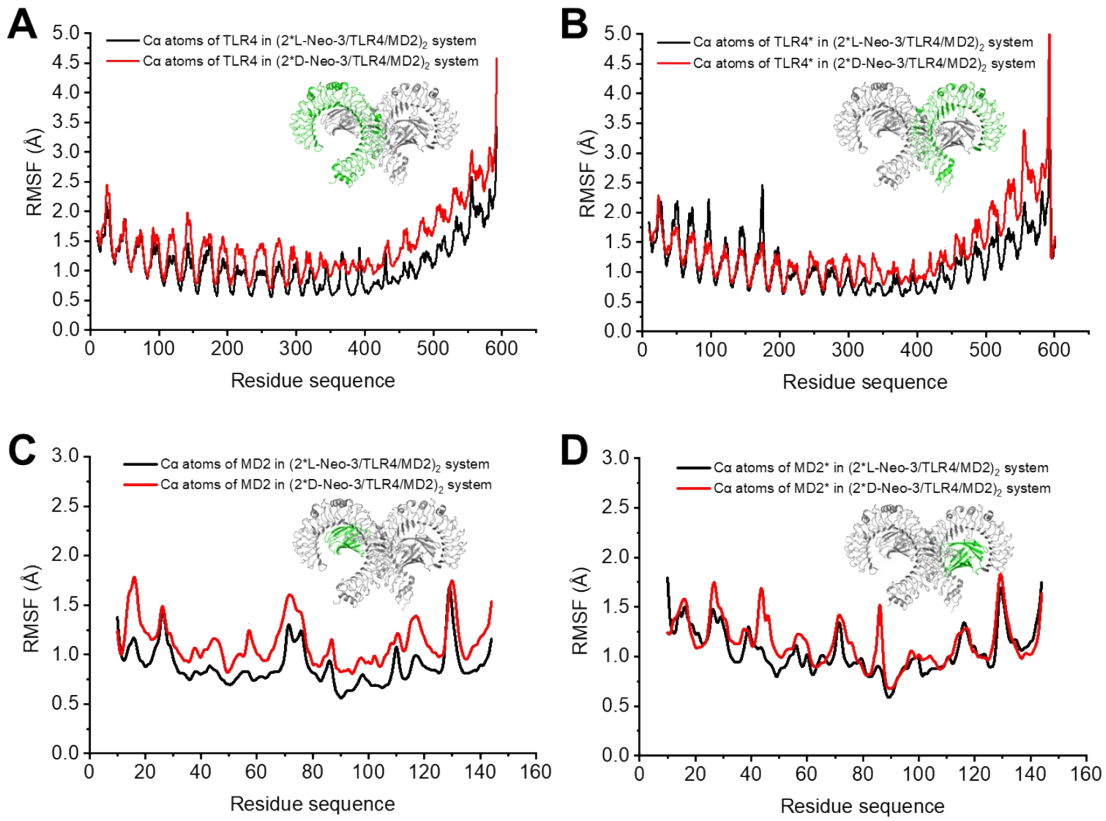


Figure S3. RMSFs of the Cα atoms of TLR4 **(A)**, TLR4* **(B)**, MD2 **(C)**, and MD2* **(D)** during the last 80 ns trajectories in the simulation of $(2*L\text{-Neo-3/TLR4/MD2})_2$ and $(2*D\text{-Neo-3/TLR4/MD2})_2$ systems.

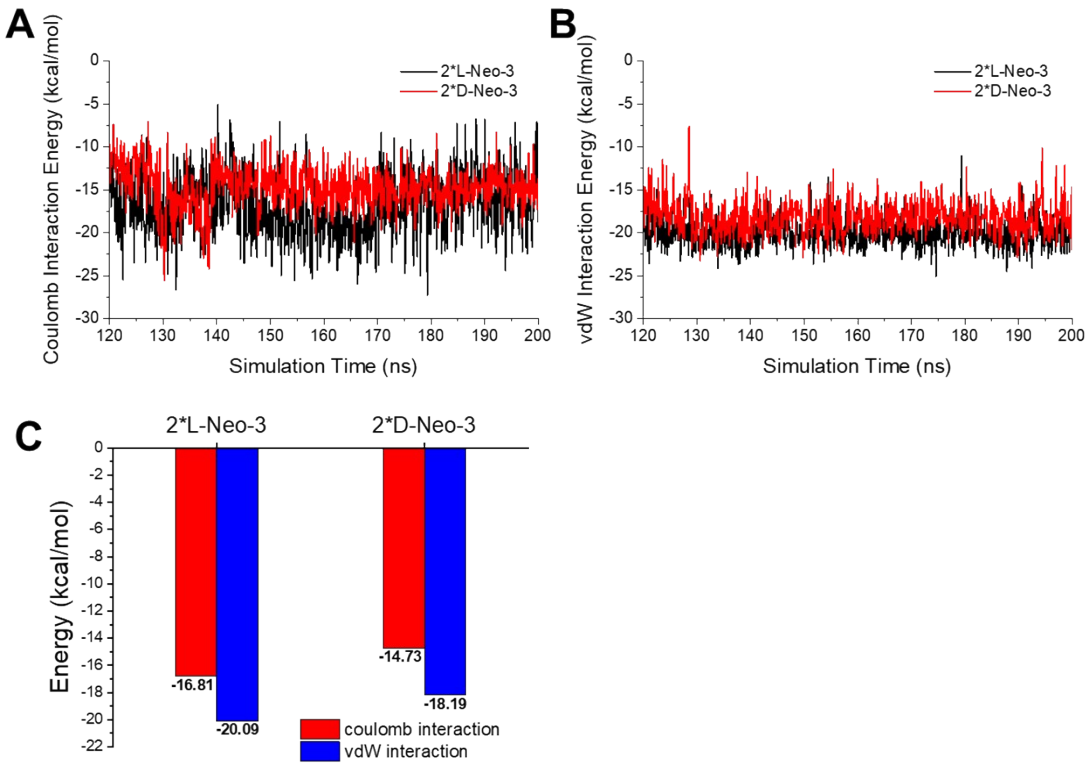


Figure S4. (**A**, **B**) Changes in Coulomb interaction energy (**A**) and van der Waals (vdW) interaction energy (**B**) between two L-Neo-3 or two D-Neo-3 molecules within the cavity of MD2 during the last 80 ns of MD trajectories; (**C**) The average Coulomb interaction energy (red) and vdW interaction energy (blue) between two L-Neo-3 or two D-Neo-3 molecules within the cavity of MD2 over the last 80 ns of MD trajectories.

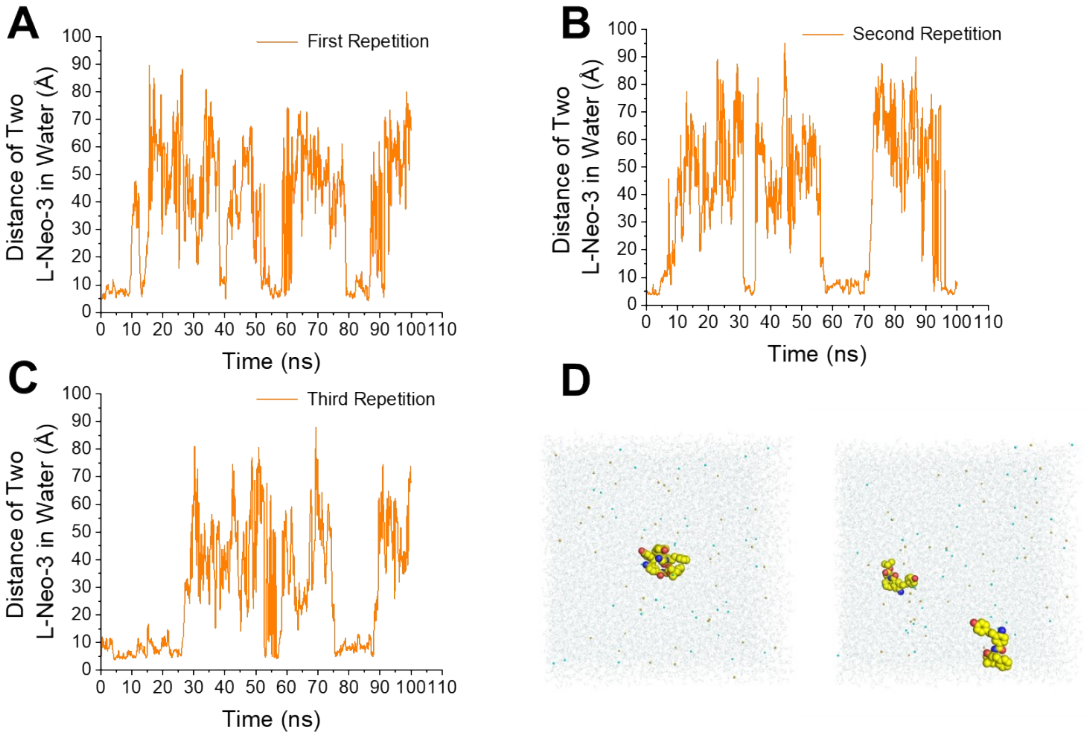


Figure S5. (A-C) Time evolution of distance between two L-Neo-3 molecules in three independent repeated simulations; **(D)** The relative position of two L-Neo-3 at the beginning (left) and ending (right) in the first simulation.

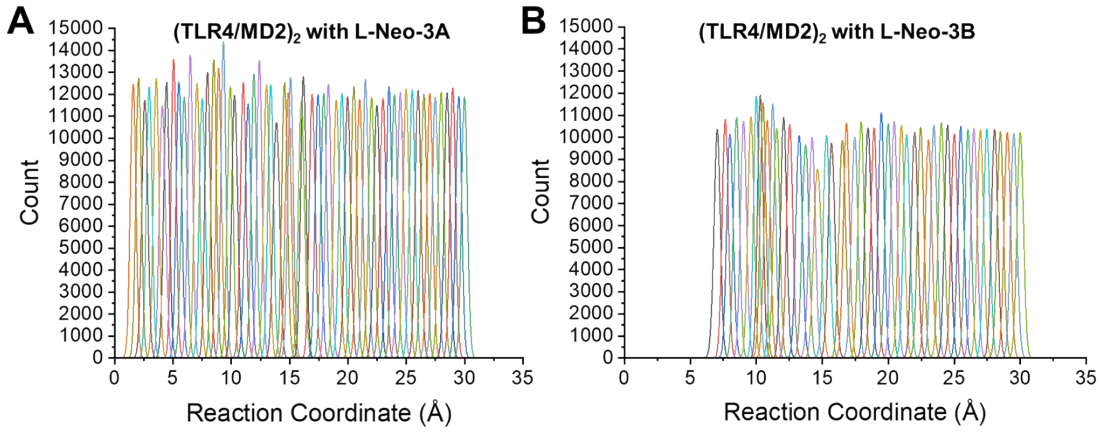
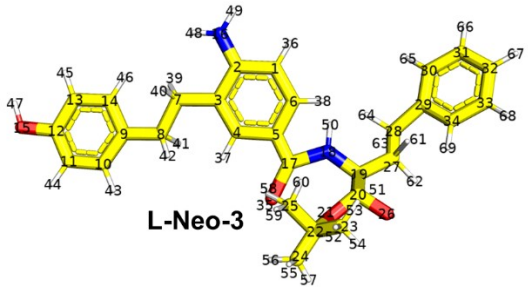
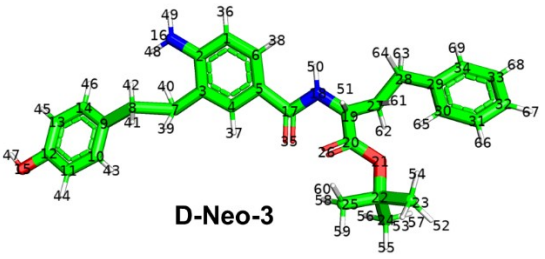


Figure S6. Histogram analysis of the overlap between umbrella windows along the reaction coordinates of L-Neo-3A(**A**) and L-Neo-3B(**B**) binding to TLR4/MD2. Each window consistently overlaps with its neighboring windows.

Table S1. RESP charges of all atoms of L-Neo-3 and D-Neo-3 molecules. (e = 1.602176×10^{-19} C).





Atom index	Atom type	L-Neo-3 RESP charge (e)	D-Neo-3 RESP charge (e)	Atom index	Atom type	L-Neo-3 RESP charge (e)	D-Neo-3 RESP charge (e)
1	C	-0.253542	-0.23047	36	H	0.139383	0.132874
2	C	0.376439	0.405284	37	H	0.142317	0.152758
3	C	0.025192	0.048769	38	H	0.128338	0.153559
4	C	-0.25267	-0.235421	39	H	0.020216	0.04282
5	C	0.029439	-0.04222	40	H	0.020216	0.04282
6	C	-0.212705	-0.248908	41	H	0.067573	0.061056
7	C	0.123748	-0.048803	42	H	0.067573	0.061056
8	C	-0.176916	-0.042412	43	H	0.146684	0.141066
9	C	0.159446	0.090866	44	H	0.152252	0.150045
10	C	-0.250805	-0.221753	45	H	0.152252	0.150045
11	C	-0.204099	-0.206394	46	H	0.146684	0.141066
12	C	0.362112	0.367569	47	H	0.368103	0.375482
13	C	-0.204099	-0.206394	48	H	0.386652	0.402695
14	C	-0.250805	-0.221753	49	H	0.376652	0.352695
15	O	-0.581886	-0.592086	50	H	0.313926	0.300725
16	N	-0.915712	-0.981363	51	H	0.160165	0.178078
17	C	0.634421	0.7044	52	H	0.03283	0.112679
18	N	-0.864813	-0.687066	53	H	0.03283	0.112679
19	C	0.392859	0.120197	54	H	0.03283	0.112679
20	C	0.292193	0.652868	55	H	0.03283	0.112679
21	O	-0.473368	-0.625392	56	H	0.03283	0.112679
22	C	0.998173	0.956254	57	H	0.03283	0.112679
23	C	-0.295653	-0.519383	58	H	0.03283	0.112679
24	C	-0.295653	-0.519383	59	H	0.03283	0.112679
25	C	-0.295653	-0.519383	60	H	0.03283	0.112679
26	O	-0.380974	-0.541226	61	H	0.000455	-0.096873
27	C	0.082506	0.421155	62	H	0.000455	-0.096873
28	C	-0.089115	-0.108226	63	H	-0.006231	0.013829
29	C	0.10885	0.050153	64	H	-0.006231	0.013829
30	C	-0.145715	-0.143113	65	H	0.112335	0.117475
31	C	-0.151992	-0.133848	66	H	0.116916	0.115157
32	C	-0.093748	-0.093547	67	H	0.103083	0.105441
33	C	-0.151992	-0.133848	68	H	0.116916	0.115157
34	C	-0.145715	-0.143113	69	H	0.112335	0.117475
35	O	-0.532239	-0.629581				