Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information:

In silico decryption of serotonin-receptor binding: Local non-covalent interaction and long-range conformational changes

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I. COMPARISON OF QM AND MM INTERACTION ENERGY BETWEEN AROMATIC RESIDUES AND SEROTONIN

The comparison of average stacking interaction energy from quantum mechanical (QM) calculations using ωB97XD and molecular mechanical (MM) interaction energy are given in Table S1. The average QM interaction energy is calculated by taking the average of each interaction energy trajectory in Figure 5 in the main manuscript. The MM non-bonded interaction energy (based on CHARMM22/CMAP force fields) between serotonin and the particular residue is calculated using Gromacs software by specifying the particular energy group. Qualitatively, the trend in interaction energy remain the same using QM or MM methods. Quantitatively, the MM interaction energy consistently underestimates the QM interaction energy for all the residues except for Phe217 where it reproduces the QM interaction energy. For Phe330, the underestimation of interaction energy from MM force fields is quite significant. The reason could be either (i) underestimation of attractive electrostatic energy which occurs due to T-type stacking[1,2] or (ii) neglected long-range dispersion force by MM force fields or both.

II. WATER-MEDIATED PROTEIN-LIGAND HYDROGEN BONDS

Figure S1a shows the time-evolution of the distance between the HN of serotonin and oxygen of water (black) and backbone oxygen of Ala216 and hydrogen of water (red). It is evident from the figure that a strong water mediated hydrogen bond is formed between Ala and serotonin around 1 ns which is retained until 35 ns contributing to the stability of the serotonin-receptor complex. On the other hand, formation of a direct hydrogen bond (contributing to the between the serotonin (NH_3^+) and COO^- of ASP129 is evident from the plot of distance between O1 (of $CO1O2^-$) of Asp129 and N of serotonin and O2 (of $CO1O2^-$) of Asp129 and N of serotonin (Figure S1b).

Figure S2 shows the decay of H-bond correlation function between the receptor protein and water (black) and between serotonin and water (red) calculated using Gromacs software. The fitting of the decay curves with mono-exponential functions (dashed green and blue lines,

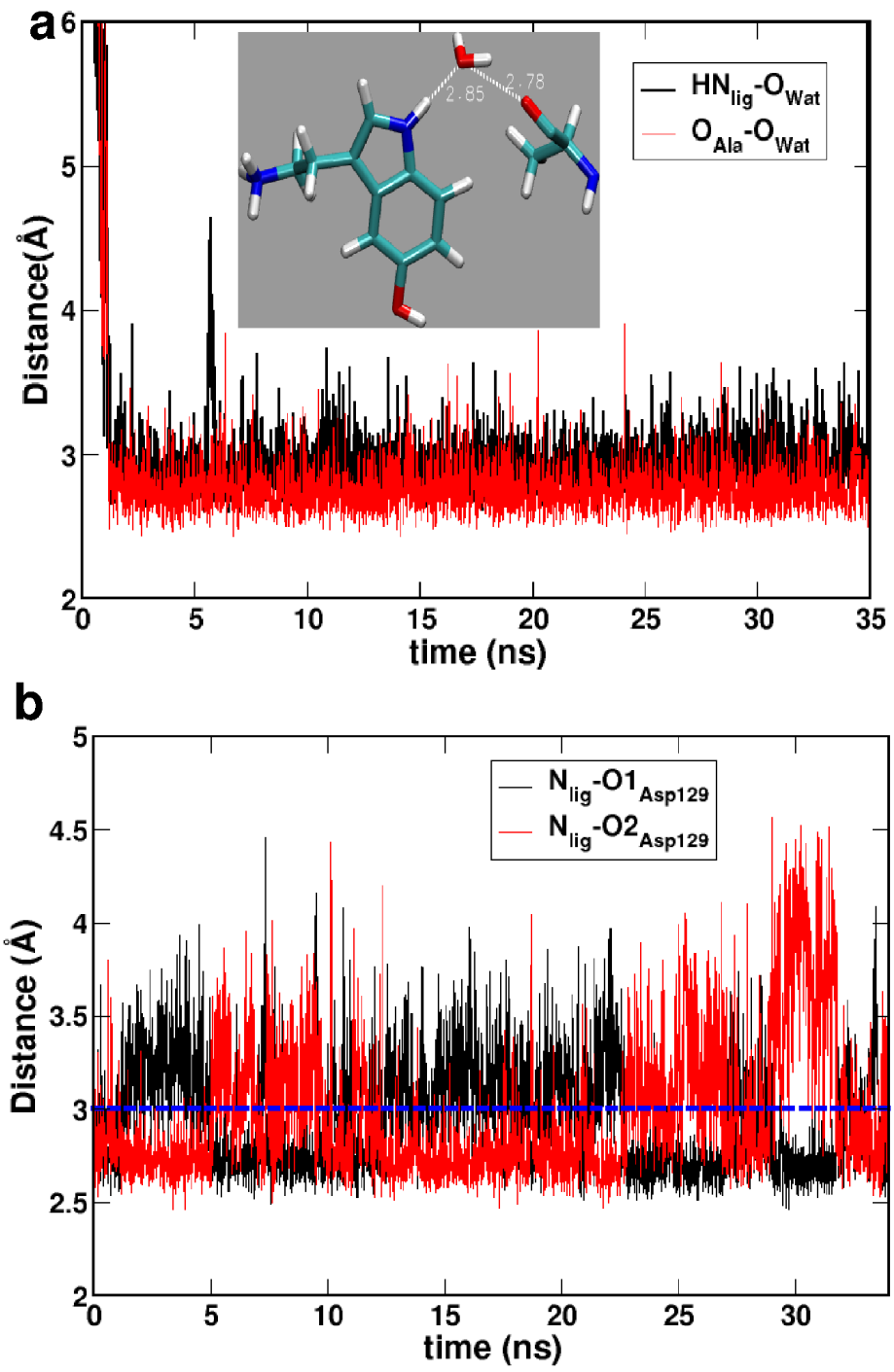

FIG. S1. (a) Time-evolution of the HN-O_{water} (black) and O_{water}-O_{ala} (red) hydrogen bonding distances. Inset shows a snapshot with the two hydrogen bonds. (b) Time-evolution of distances between nitrogen of NH_3^+ of serotonin and two oxygens (O1 and O2) of COO^- Asp129. The blue dashed line indicates the reference donor-acceptor distance for a typical hydrogen bond.

respectively) yield receptor-water H-bond lifetime of 12 ps and serotonin-water lifetime of 6.8 ps.

III. GRAPHICAL REPRESENTATION OF DYNAMIC CROSS CORRELATION MATRIX

Figure S3 and S4 shows the dynamic cross correlation (DCC) matrix of serotonin-receptor complex and apo-receptor, respectively in the range [-1.0:1.0] with color map. While Figure S3 indicates strong positive correlation between TM3 and TM5/mini-G_0/TM6, strong negative and positive correlation between TM5 and mini-G_0/TM6, respectively and strong negative correlation between TM6 with mini-G_0 region in serotonin-receptor complex. Figure S4 indicates strong positive correlation between TM7 with TM1/TM3 and strong negative correlation between TM7 and TM5/mini-G_0 as well as strong negative TM1/TM3 with mini-G_0.

To investigate the effect of temporal resolution of the data on the quality of DDCC, the same DDCC were also calculated for snapshots in 100 ps (1000 snapshots from 100 ns data) interval and the DCC plots and DDCC plot remain almost the same (within error bar of ± 0.06).

TABLE S1. Comparison of average quantum mechanical and average molecular mechanical interaction energy (in kcal/mol) for serotonin-residue pairs from 35 ns simulation

Method	ΔE_{327}	ΔE_{330}	ΔE_{331}	ΔE_{359}	ΔE_{217}
QM	-6.50	-6.00	-3.02	-0.30	-0.73
MM	-4.21	-2.39	-2.41	2.03	-0.75

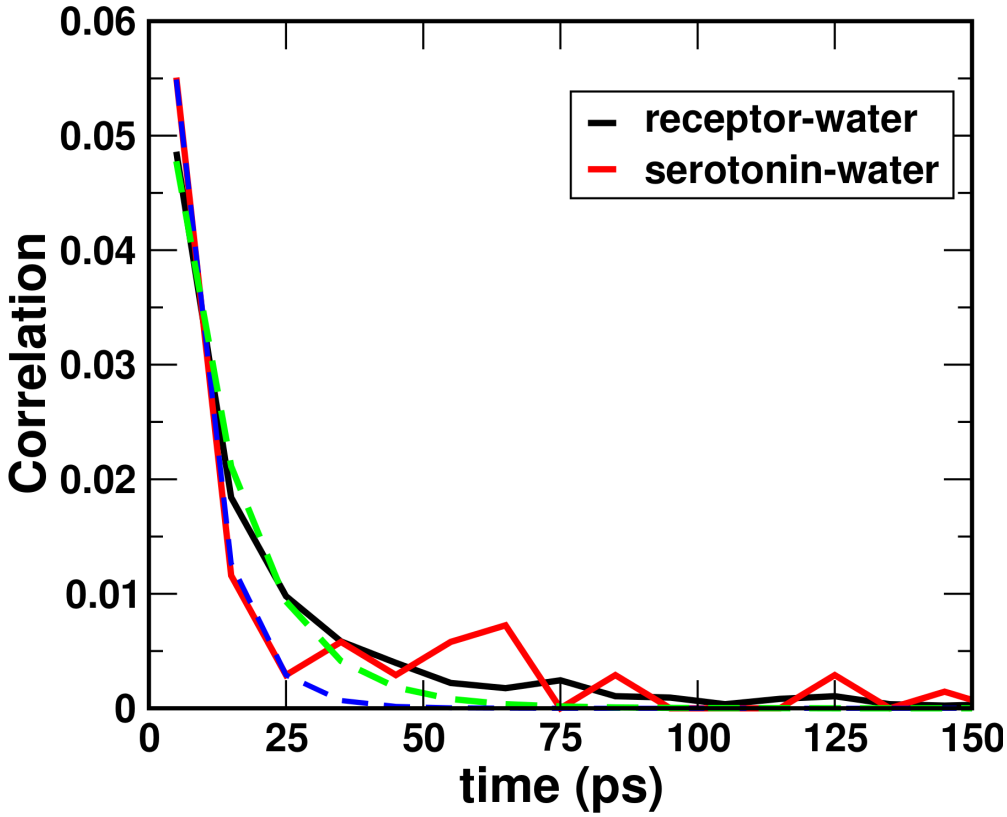

FIG. S2. Decay of hydrogen(H) bond correlation function for receptor-water (black) and serotonin-water (red) H-bonding. The dashed green and blue lines represent their mono-exponential fitting, respectively.

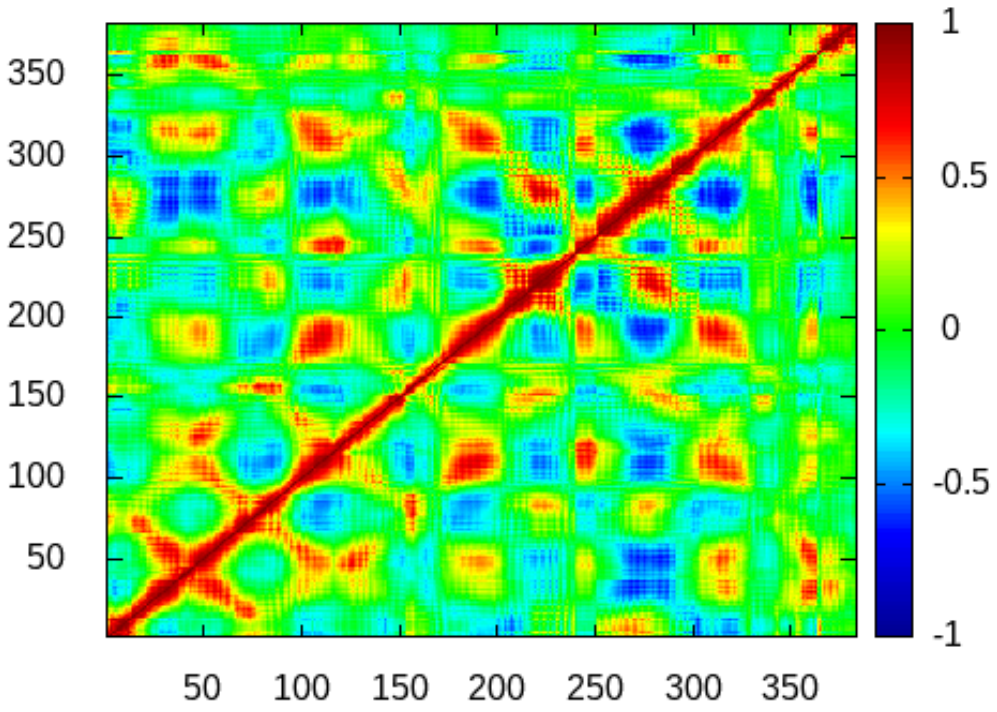

FIG. S3. Dynamic cross correlation matrix for the serotonin-receptor complex in the range [-1.0:1.0] with color map for C_α of receptor for 10000 snapshots from 100 ns trajectory.

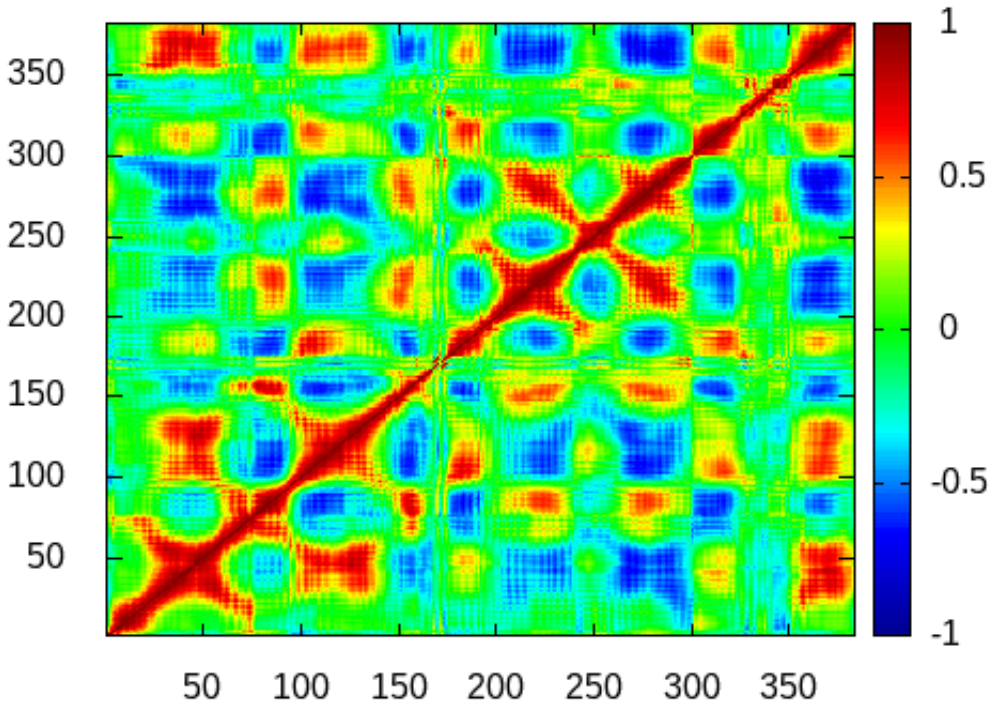

FIG. S4. Dynamics cross correlation matrix for the apo-receptor in the range [-1.0:1.0] with color map for C_α of receptor for 10000 snapshots from 100 ns trajectory.

REFERENCES

[1]R. P. Matthews, T. Welton and P. A. Hunt, *Phys. Chem. Chem. Phys.*, 2014, **16**, 3238–3253.

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