

Supporting information

**Synergistic Regulation Mechanism of Iperoxo and
LY2119620 for Muscarinic Acetylcholine M2
Receptor**

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The authors declare that there is no conflict of interest.

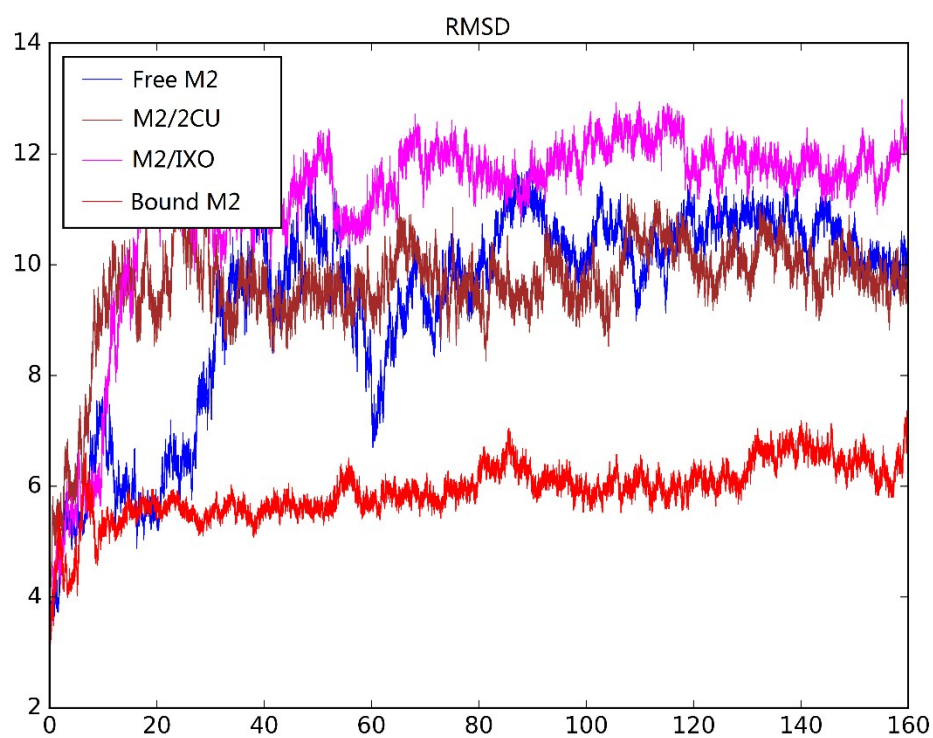


Figure S1. Root mean squared fluctuations of $C\alpha$ atom for four systems.

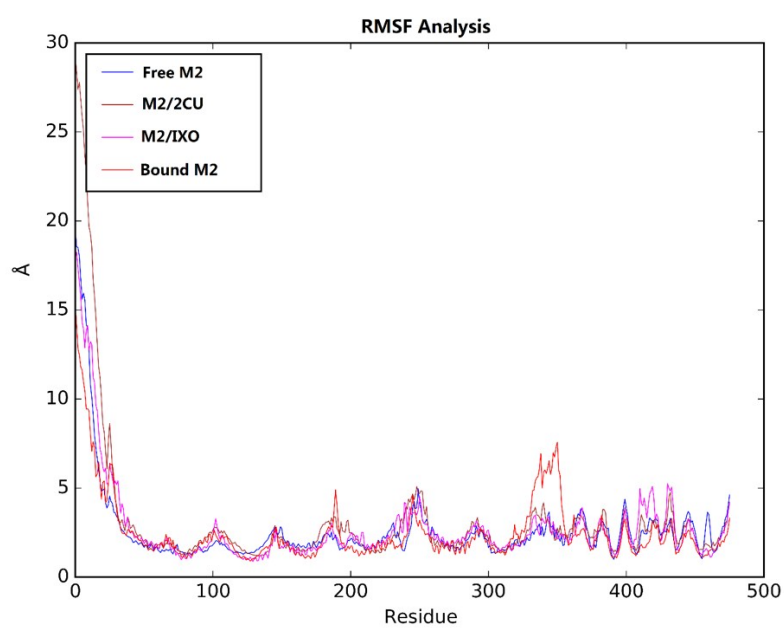


Figure S2. Average fluctuations of C α atoms for four systems.

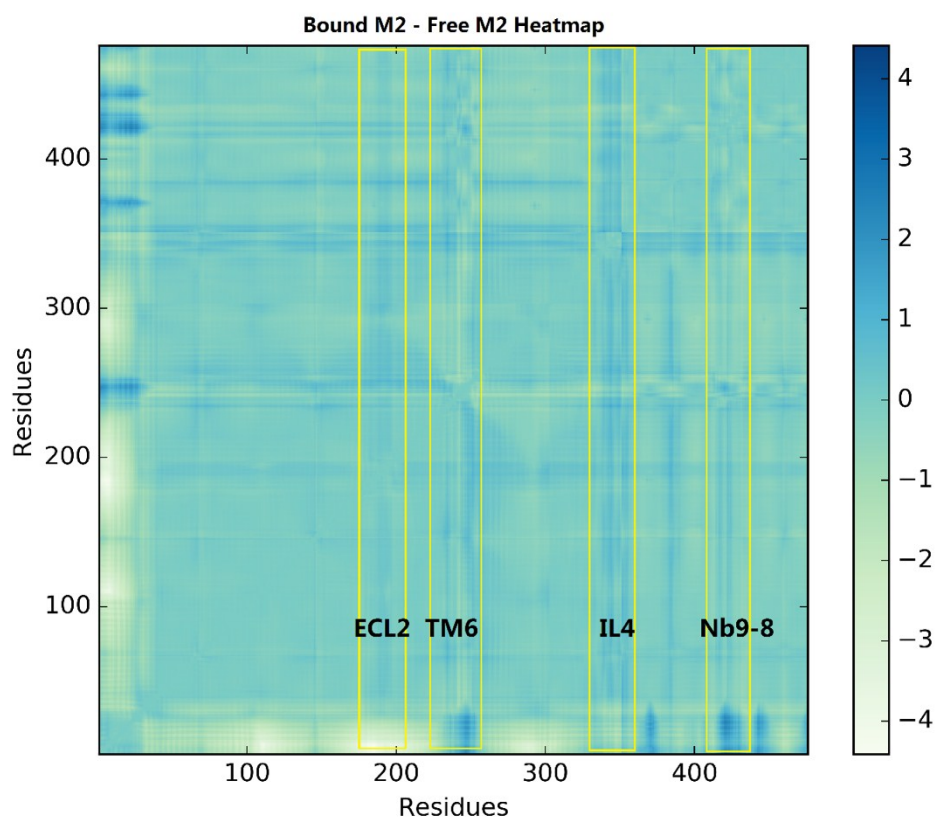


Figure S3. Distance different landscape between bound and free M2.

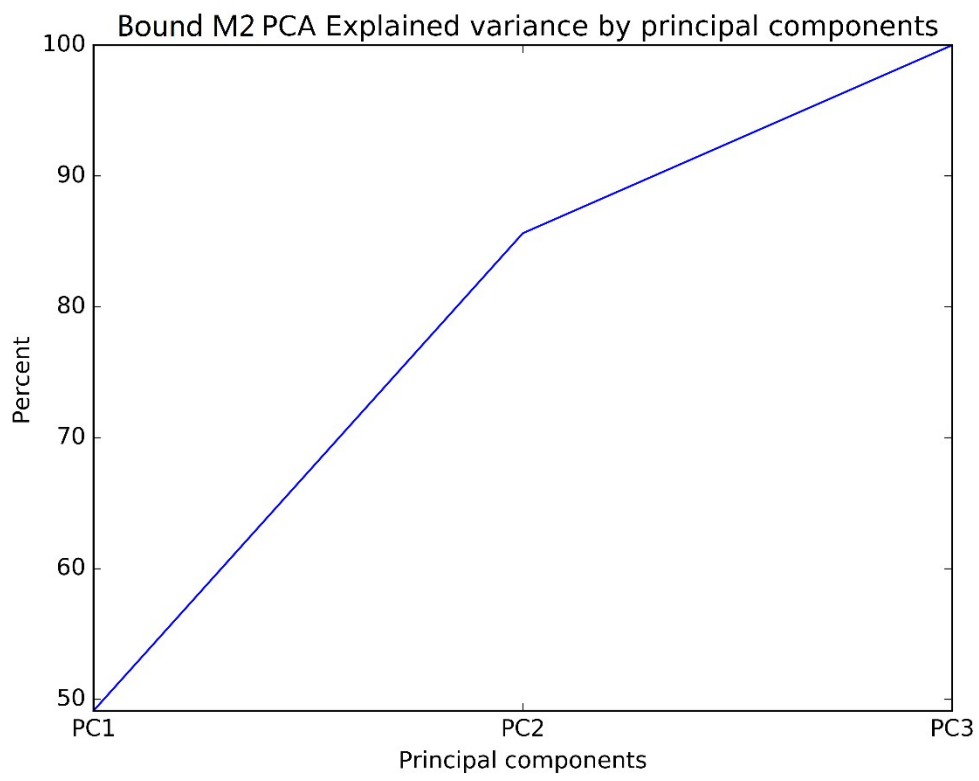


Figure S4. PCA Explained variance by principal components

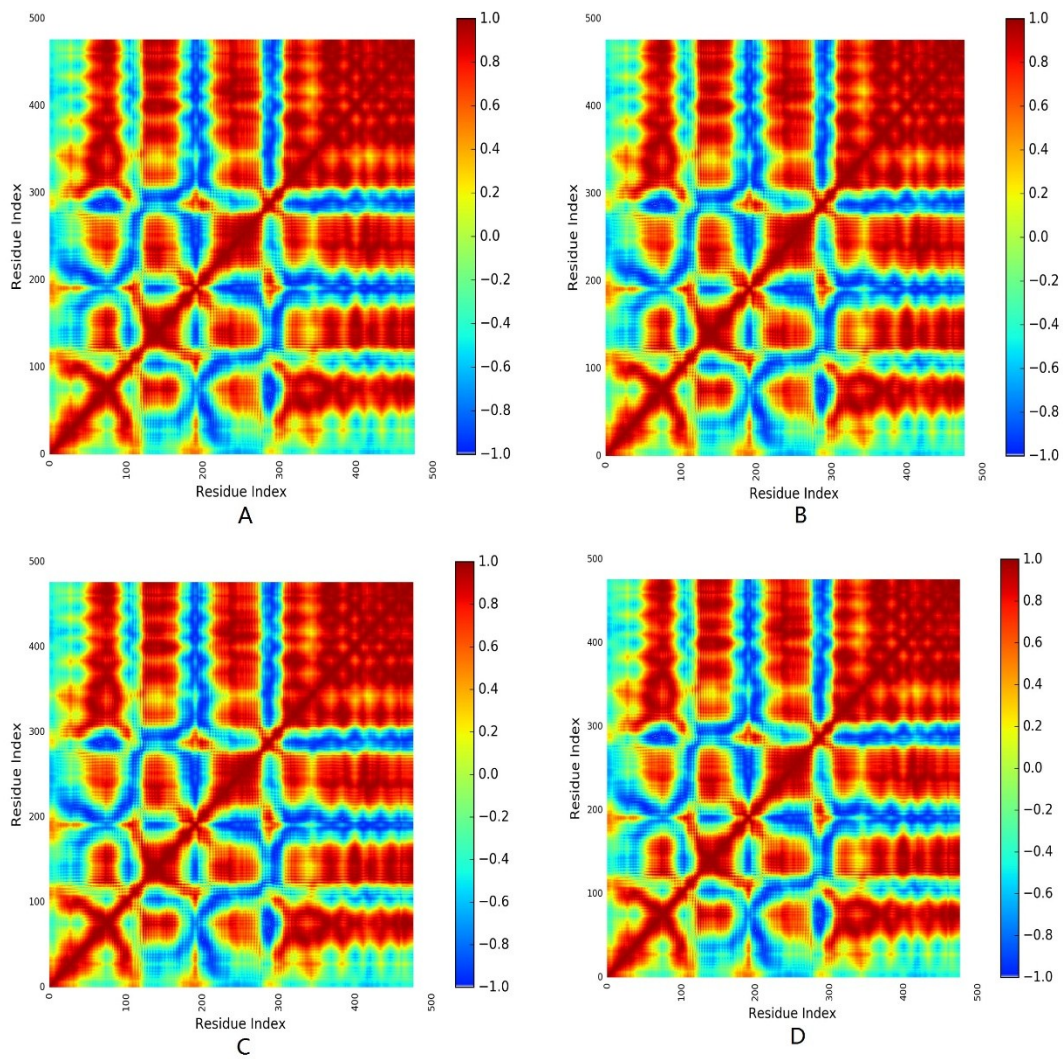
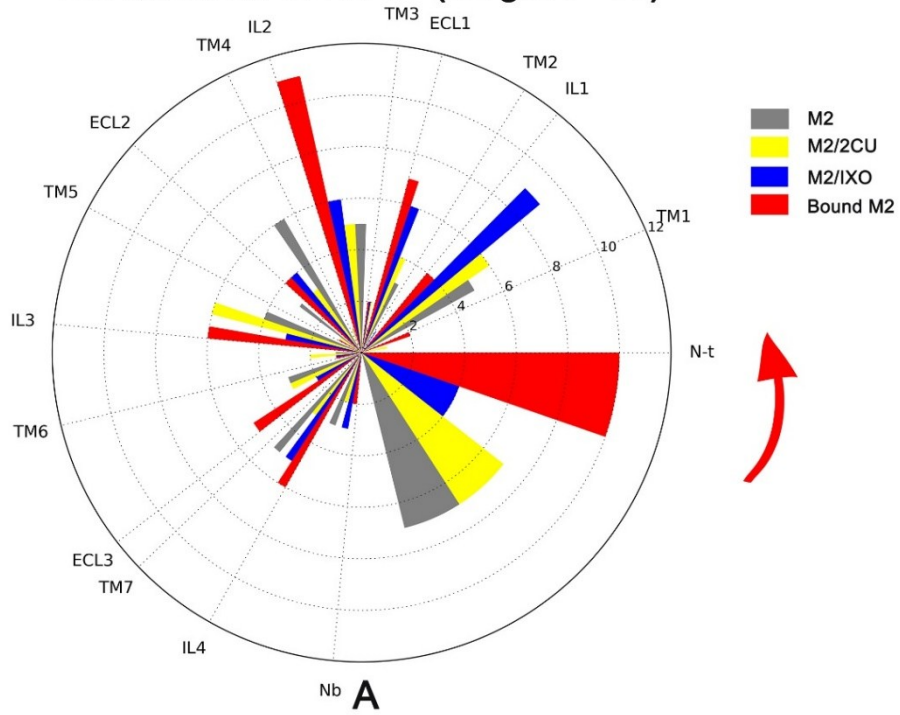


Figure S5. Dynamic Cross-Correlation Maps for each system. A: Free M2. B: M2/IXO. C: M2/2CU. D: Bound M2.

Distribution of Node (Degree>10)



Distribution of Node (Betweenness>0.02)

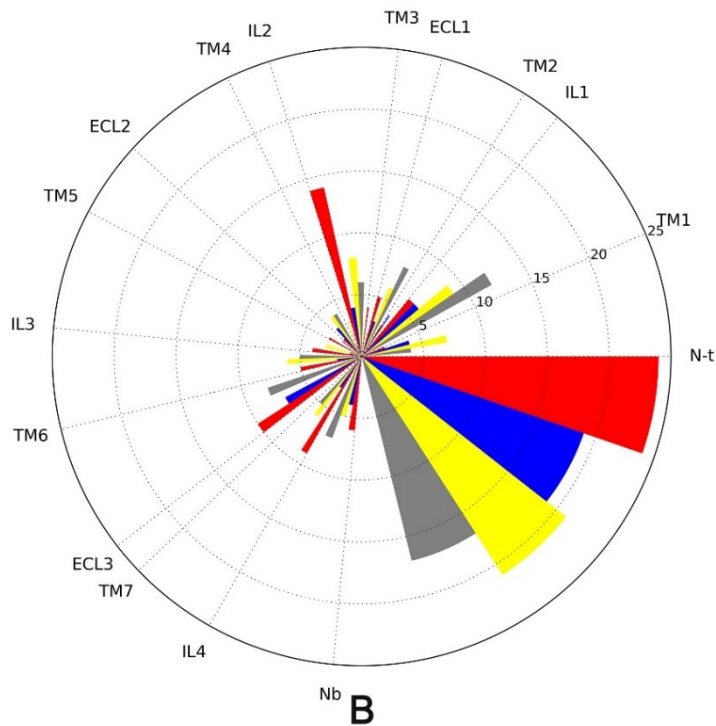


Figure S6. The distribution of nodes with weighted degree (>10) and weighted betweenness (>0.02). A: Distribution of node (degree >10). B: Distribution of node (betweenness >0.02).

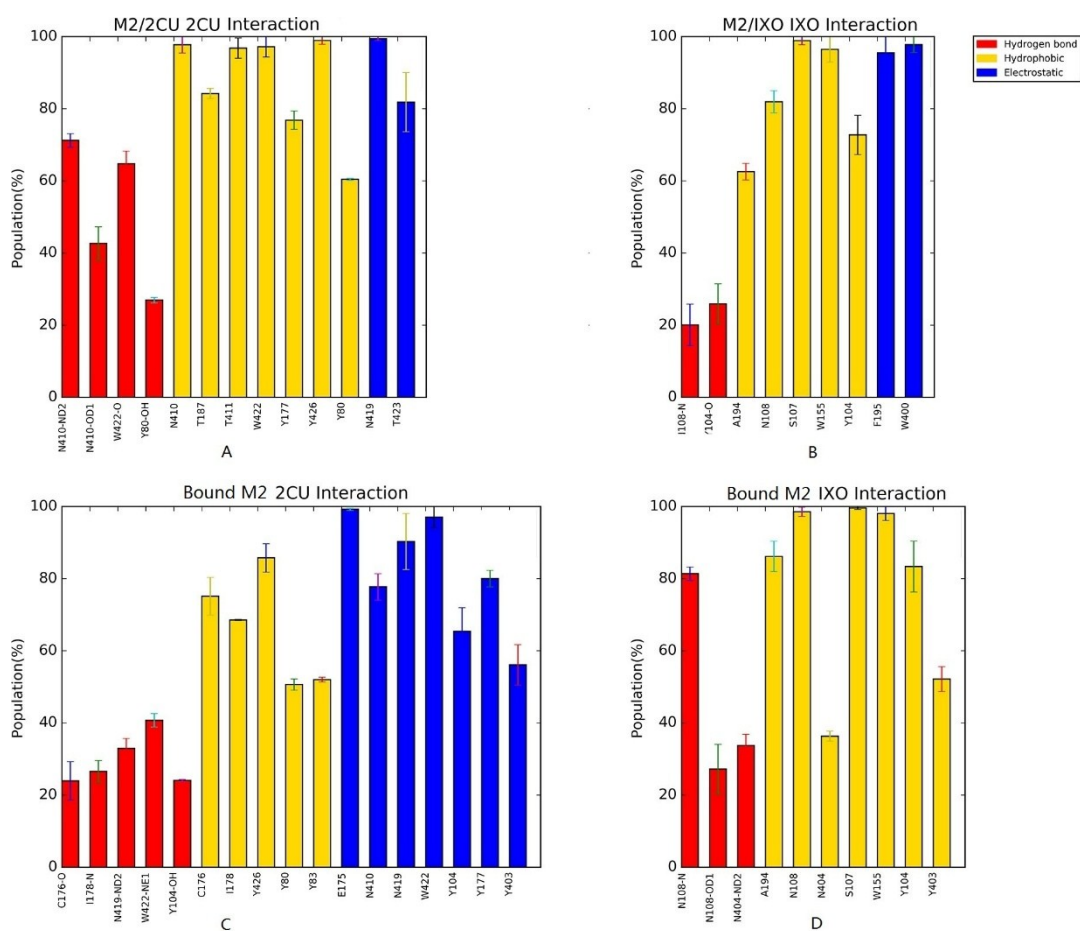


Figure S7. Interaction between M2 and ligand for four system. A: Interaction between 2CU and M2 for M2/2CU. B: Interaction between IXO and M2 for M2/IXO. C: Interaction between 2CU and M2 for Bound M2. D: Interaction between IXO and M2 for Bound M2.

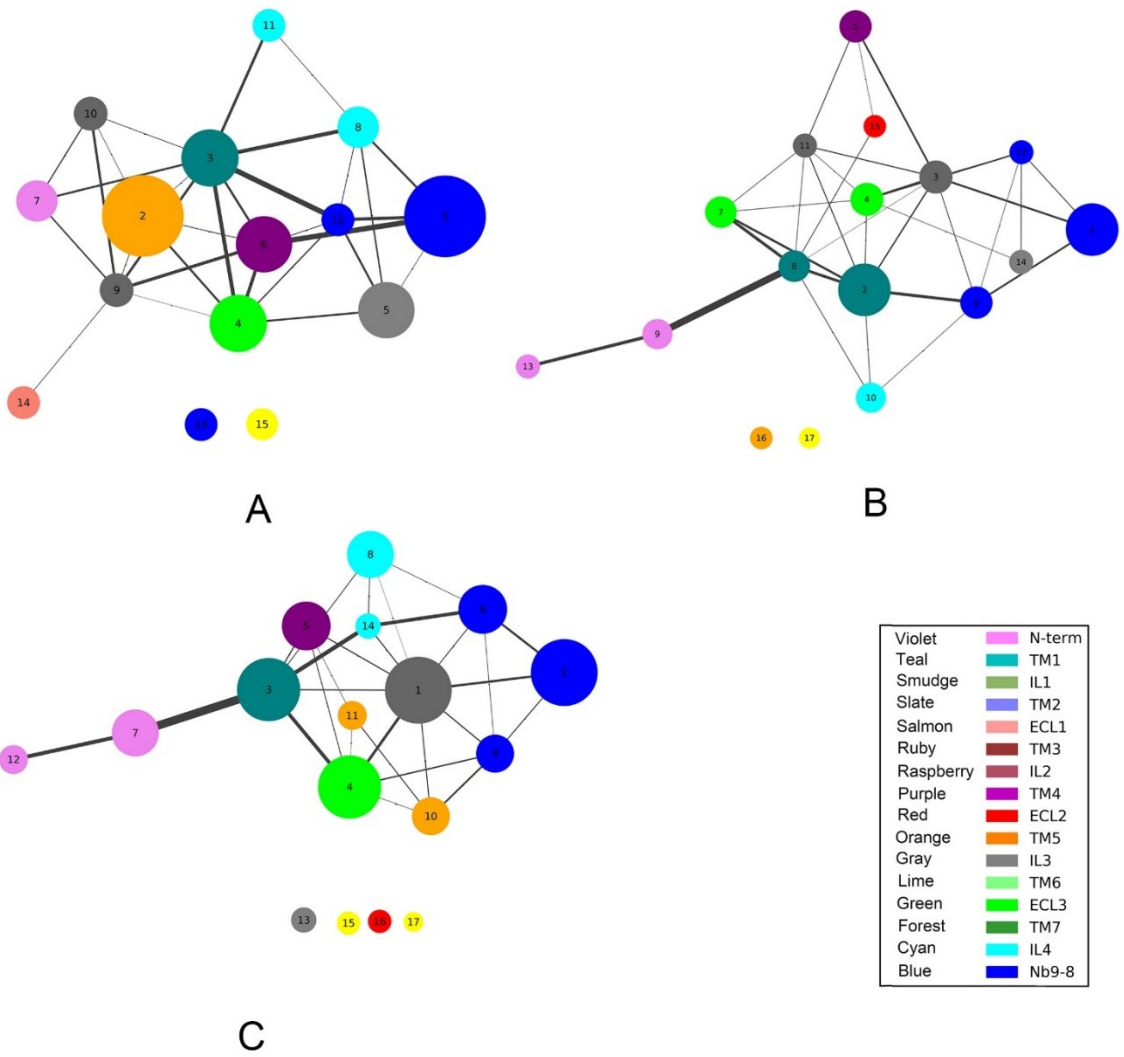


Figure S8. Modifications to perturb the community network for Bound M2. A: IXO-weakened. B: 2CU-weakened. C: IXO&2CU-weakened.

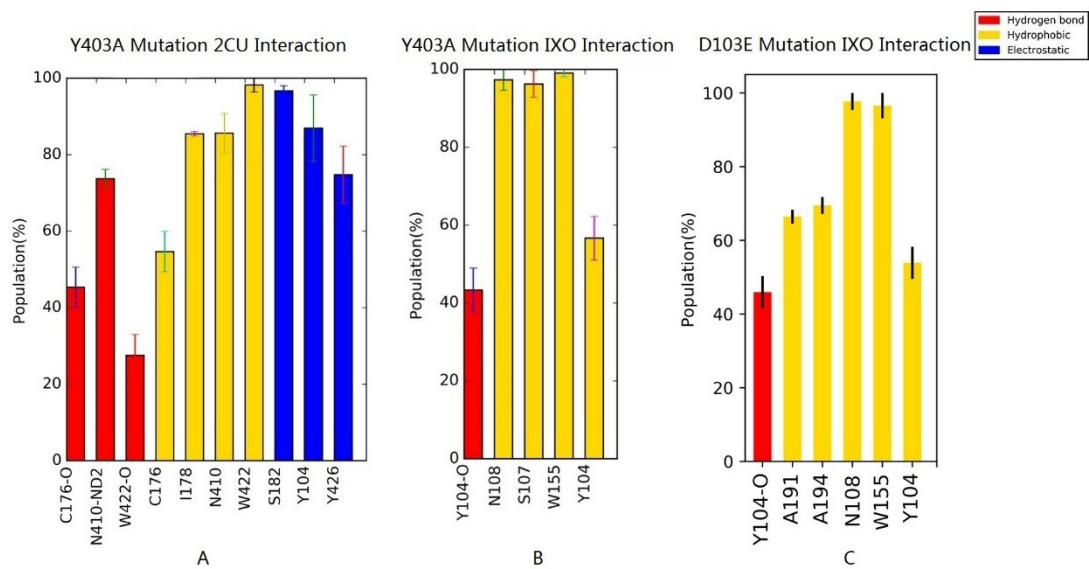


Figure S9. Interaction between M2 and ligand for Y403A and D103E mutant. A: Interaction between 2CU and M2 for Bound M2. B: Interaction between IXO and M2 for Bound M2. C: Interaction between IXO and M2 for D103E.

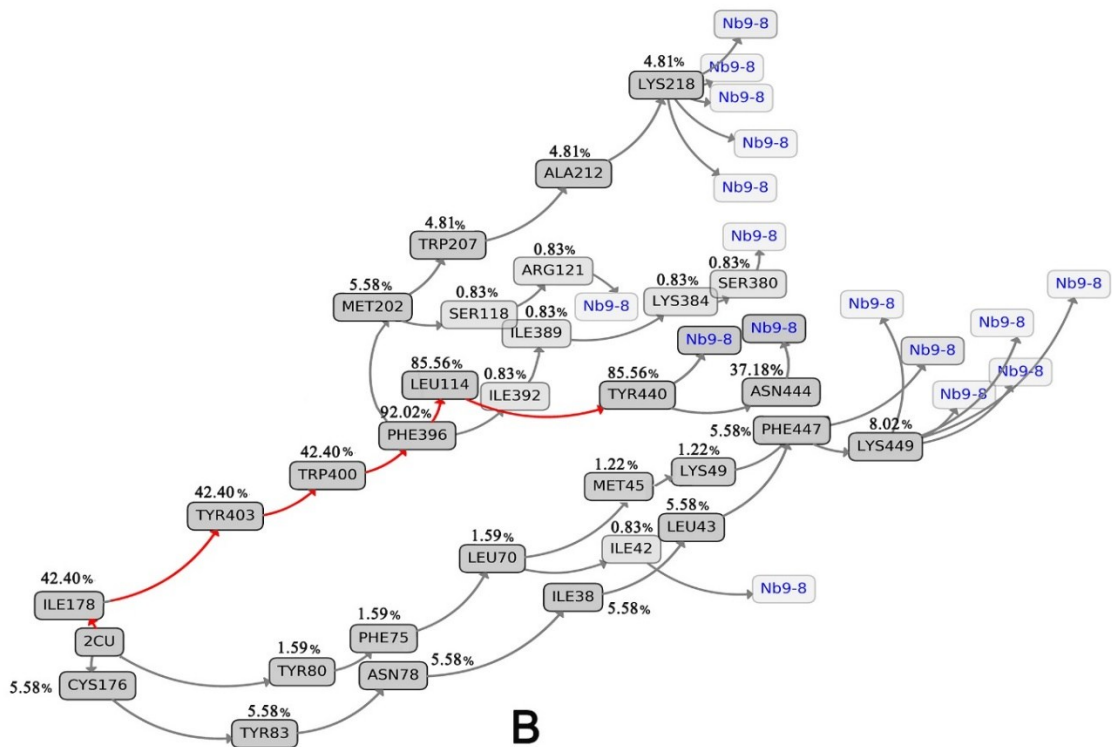
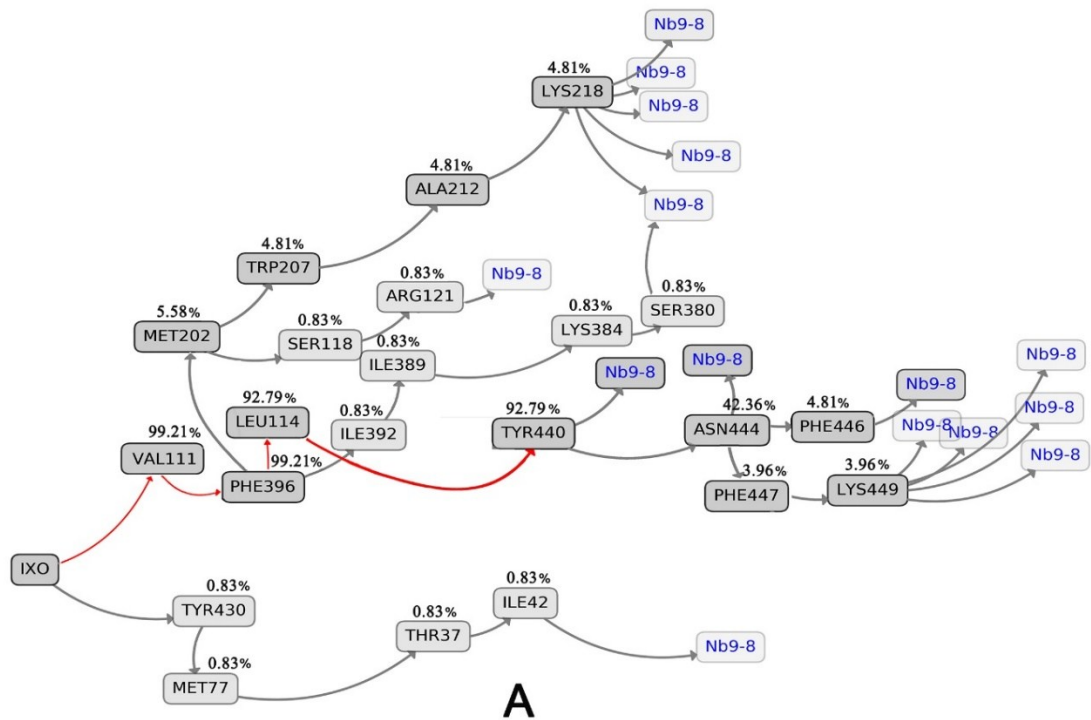


Figure S10. Allosteric regulation pathways of bound M2. A: IXO regulation pathway. B: 2CU regulation pathway.

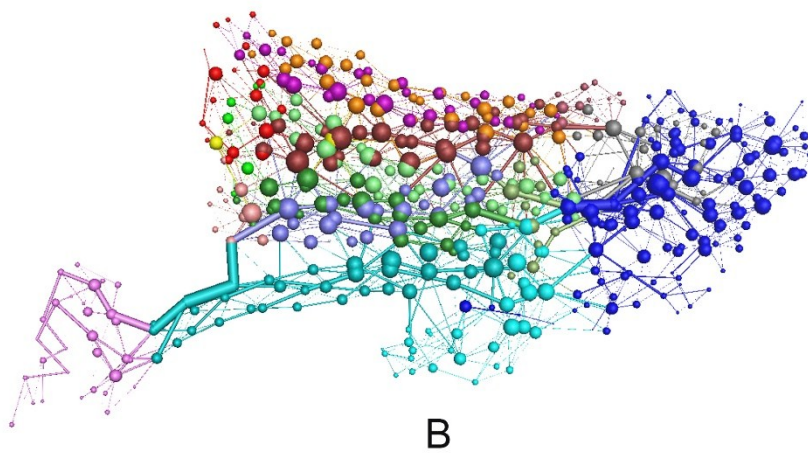
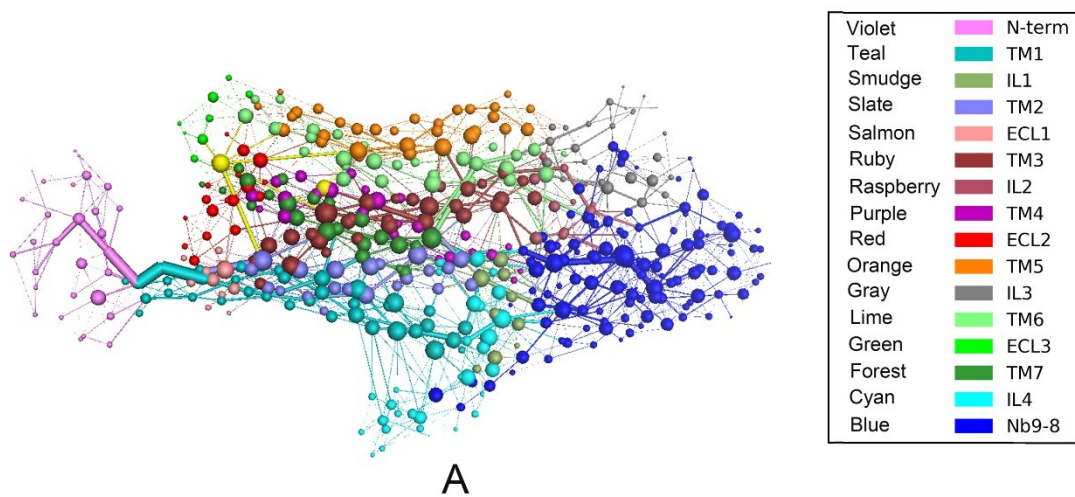


Figure S11. Dynamics network for Y403A and F396A mutant. A: Network for Y403A mutant. B: Network for F396A mutant.

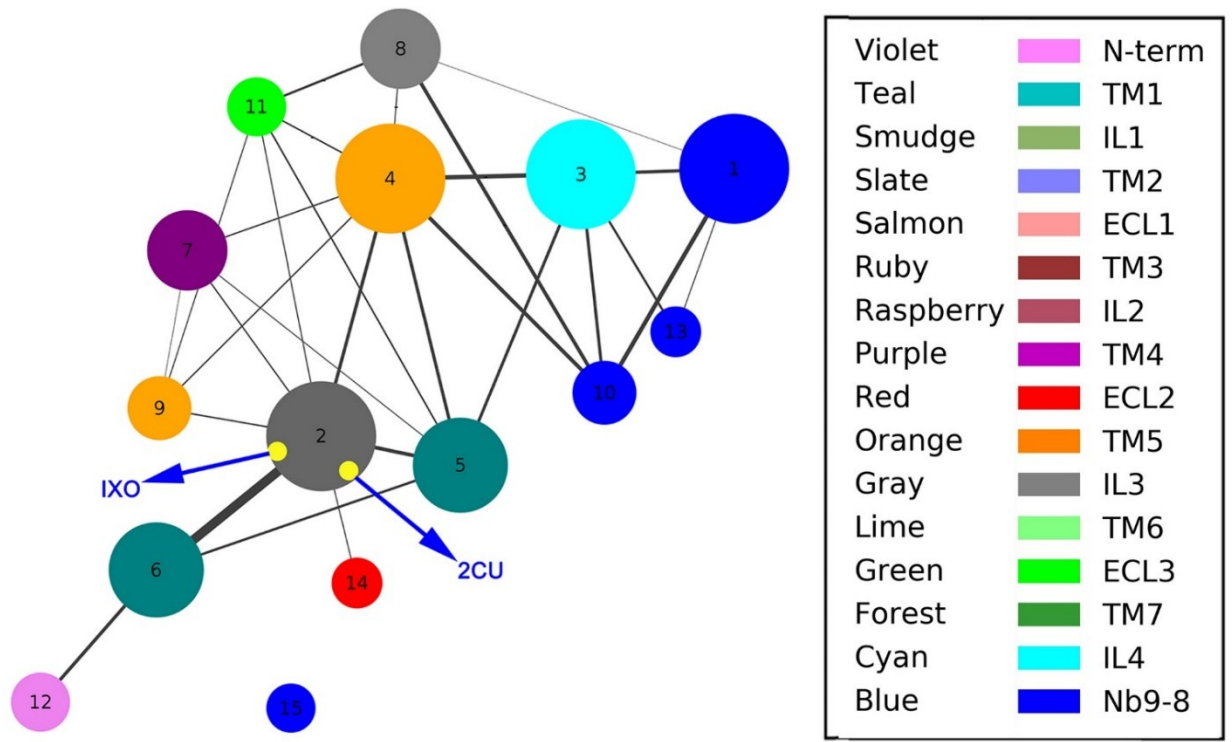


Figure S12. Community Network for F396A mutant.

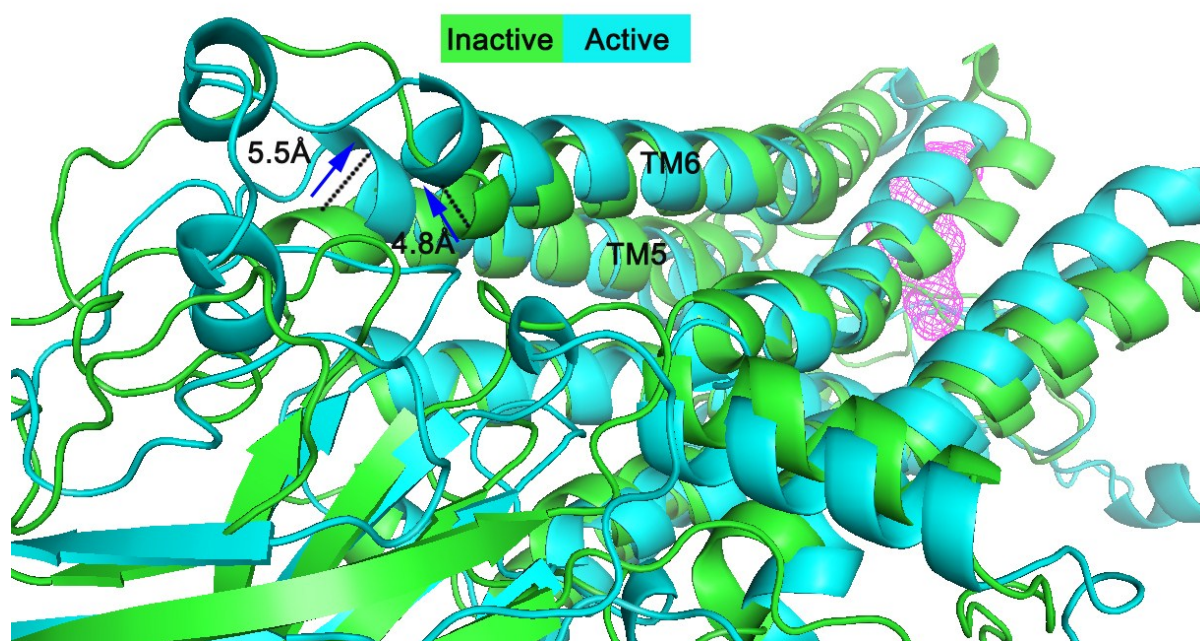


Figure S13. Alignment between inactive and active states. TM5 and TM6 are closer in M2-Active crystal structures of GPCRs reveal a network of hydrogen bonding interactions that extend from the binding pocket to the cytoplasmic surface.

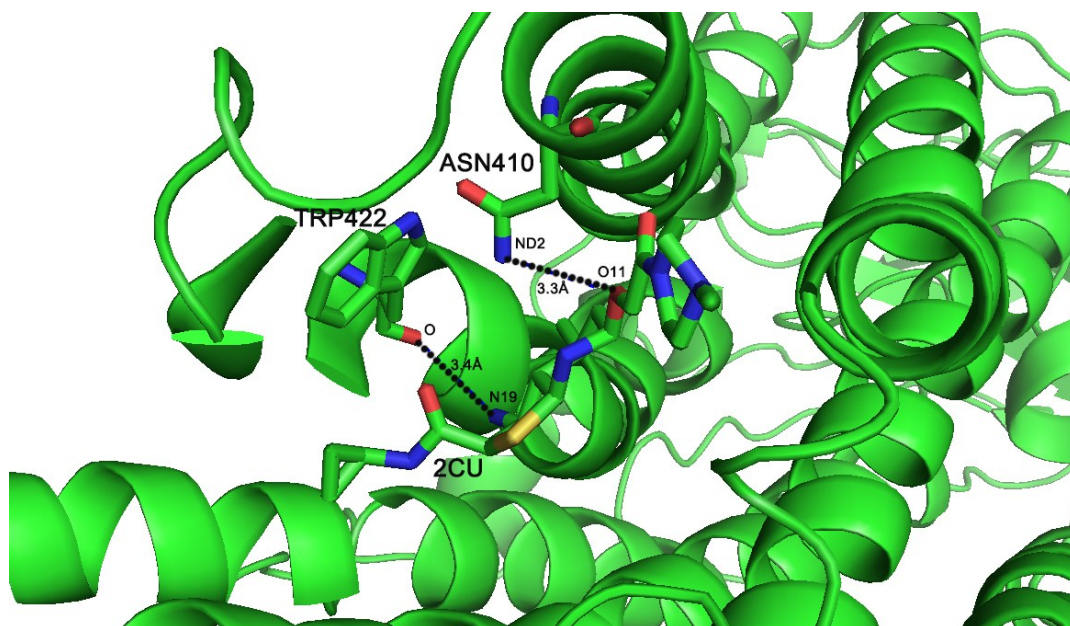


Figure S14. Two hydrogen bonds with TRP422 and ASN410.