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Supporting Information

Discovery of cryptic allosteric sites using reversed allosteric communication by a combined computational and experimental strategy

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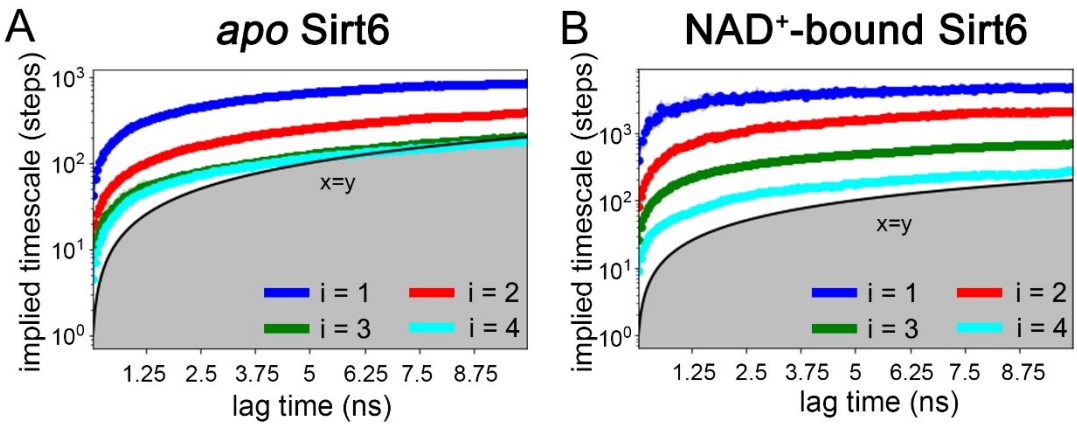

Figure S1. The result of implied timescale test for *apo* (**A**) and *holo* (**B**) Sirt6. Blue, red, green, and cyan lines show the timescale τ_1, τ_2, τ_3, and τ_4 as a function of lag times. Black lines represent x=y in logarithmic coordinates.

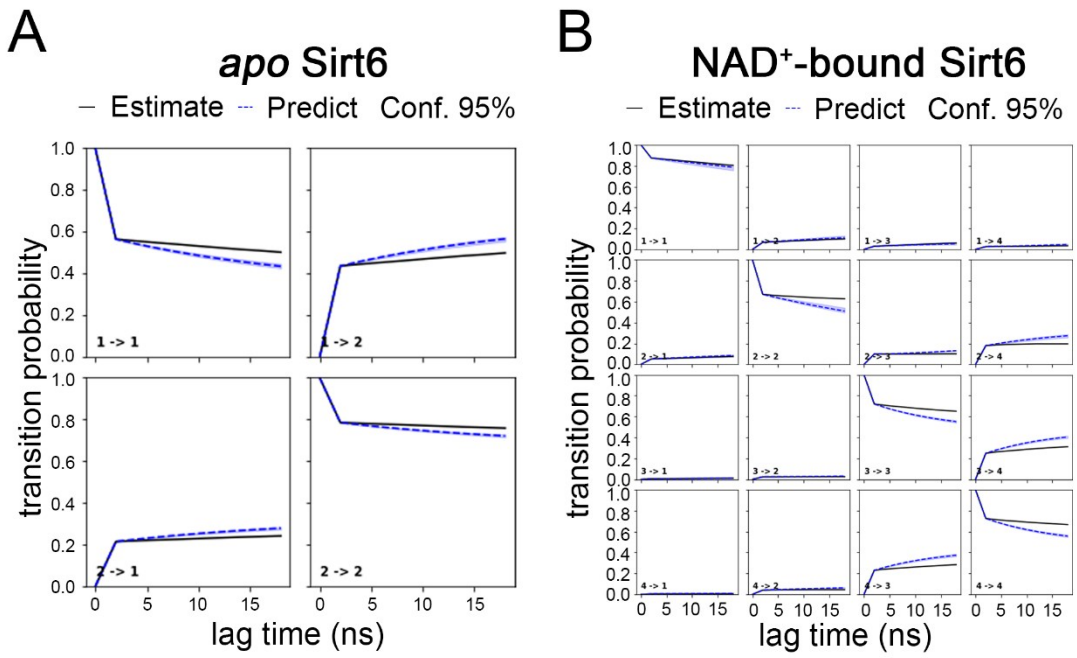

Figure S2. The result of the Chapman-Kolmogorov test for 2 metastable states in *apo* Sirt6 (**A**) and 4 metastable states in *holo* Sirt6 (**B**). The solid estimate lines are the transition probability calculated by MSMs, while the dotted predict lines are practical transition probability observed in trajectories.

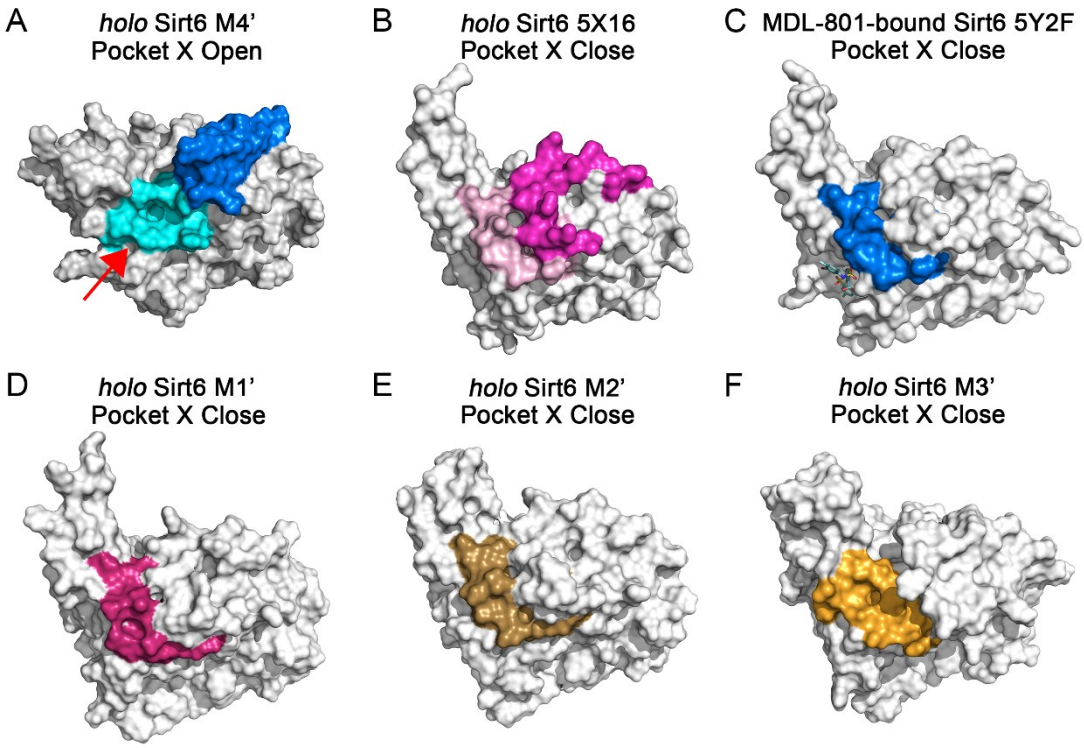

Figure S3. Pocket X emerged only in *holo* Sirt6 M4' metastable state (**A**), while was invisible in crystal structures 5X16 (**B**), 5Y2F (**C**), and *holo* Sirt6 M1'-M3 metastable states (**D**-**F**).

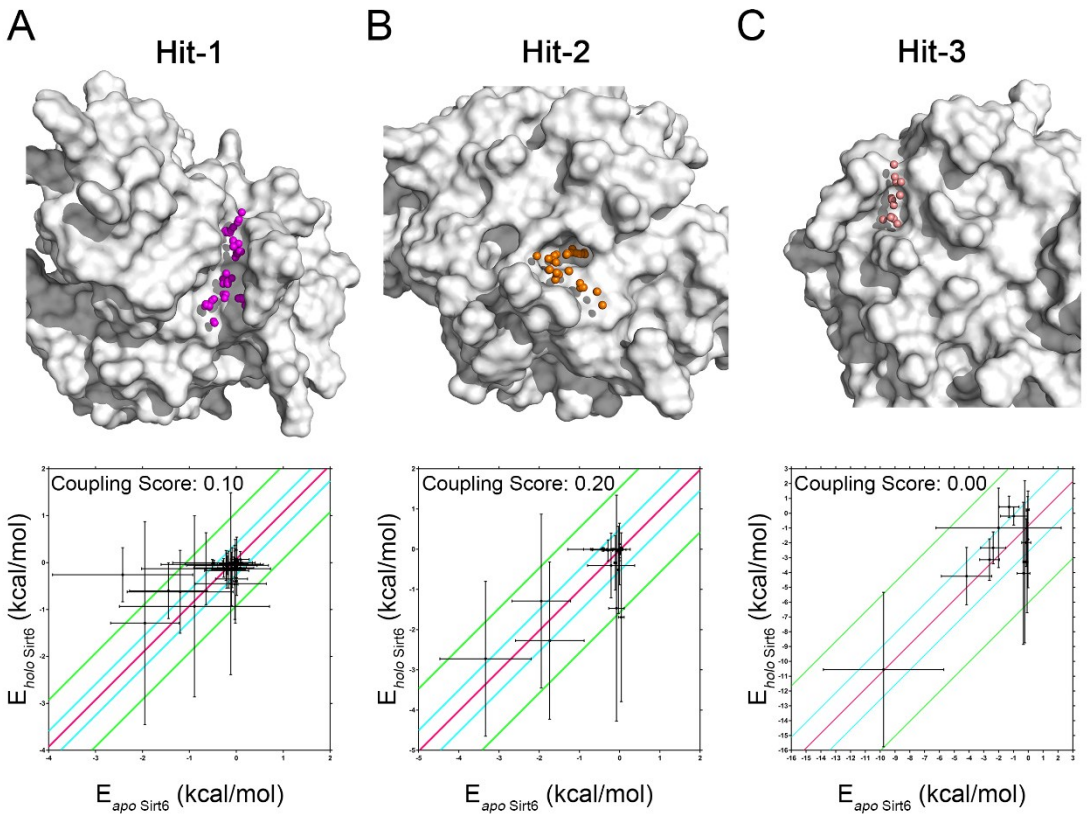

Figure S4. Representative Fpocket hits (**A-C**) failed to pass energy coupling score analyses for allosteric signal testing.