Reliability and reproducibility checklist for molecular dynamics simulations *All boxes must be marked YES by acceptance unless "Response not needed if No".*	Yes	No	Response (Please state where this information can be found in the text)
1. Convergence of simulations and analysis			
1a. Is an evaluation presented in the text to show that the property being measured has equilibrated in the simulations (*e.g.* time-course analysis)?	☒	☐	RMSD analysis in Fig S2, S3, S5 and S11
1b. Then, is it described in the text how simulations are split into equilibration and production runs and how much data were analyzed from production runs?	☒	☐	Methods section Main Text
1c. Are there at least 3 simulations per simulation condition with statistical analysis?	☒	☐	Trajectories per replica are shown in Fig. S2, S6 and S12
1d. Is evidence provided in the text that the simulation results presented are independent of initial configuration?	☒	☐	NOESY restraints are added
2. Connection to experiments			
2a. Are calculations provided that can connect to experiments (*e.g.* loss or gain in function from mutagenesis, binding assays, NMR chemical shifts, J-couplings, SAXS curves, interaction distances or FRET distances, structure factors, diffusion coefficients, bulk modulus and other mechanical properties, *etc.*)?	☒	☐	The major part of the text deals with Solution NMR evaluation of the mutants identified by simulation
3. Method choice			
3a. Do simulations contain membranes, membrane proteins, intrinsically disordered proteins, glycans, nucleic acids, polymers, or cryptic ligand binding?	☐	☒	
3b. Is it described in the text whether the accuracy of the chosen model(s) is sufficient to address the question(s) under investigation (e.g. all-atom vs. coarse-grained models, fixed charge vs. polarizable force fields, implicit vs. explicit solvent or membrane, force field and water model, etc.)?	☒	☐	Methods section
3c. Is the timescale of the event(s) under investigation beyond the brute-force MD simulation timescale in this study that enhanced sampling methods are needed?	☐	☒	
If **YES**, are the parameters and convergence criteria for the enhanced sampling method clearly stated?	☐	☐	
If **NO,** is the evidence provided in the text?	☒	☐	Network analysis focuses on short-timescale correlations
4. Code and reproducibility			
4a. Is a table provided describing the system setup that includes simulation box dimensions, total number of atoms, total number of water molecules, salt concentration, lipid composition (number of molecules and type)?	☒	☐	In the supplementary information
4b. Is it described in the text what simulation and analysis software and which versions are used?	☒	☐	Method Section
4c. Are other parameters for the system setup described in the text, such as protonation state, type of structural restraints if applied, nonbonded cutoff, thermostat and barostat, etc.?	☒	☐	Method Section

4d. Are initial coordinate and simulation input files and a coordinate file of the final output provided as supplementary files or in a public repository?	☒	☐	
4e. Is there custom code or custom force field parameters?	☐	☒	Response not needed if **No**
If **YES**, are they provided as supplementary files or in a public repository?	☒	☐	