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The Influence of Type III Antifreeze Protein and its Mutants on Methane Hydrate Adsorption-Inhibition: A Molecular Dynamics Simulation Study†

Mitra Maddah,[a] Mina Maddah,[b] and Kiana Peyvandi *[a]

Supplementary Information

S1 Force Field Parameter

The standard AMBER force field, which is attributable to Kollman and coworkers [1,2] is parameterized and defined for proteins (amino acids) and DNA (nucleotides) and supported by Gromacs package. protein parameters are available in AMBER99SB force field, and we just apply them in our simulation. [3] Methane molecule was optimized and then its parameters were generated with ANTECHAMBER program [3] associated with the general AMBER force field (GAFF). [4] Finally, these parameters were adapted to add into the AMBER99SB force field for the simulation of methane molecules. It was found by structural analysis that these parameters give an accurate reproduction of properties of methane hydrate.

Notes and references

1 T. E. Cheatham, P. Cieplak and P. A. Kollman, *J. Biomol. Struct. Dyn.*, 1999, **16**, 845–862.

2 S. Weiner, P. Kollman, D. Nguyen and D. Case, *J. Comput. Chem.*, 1986, **7**, 230–252.

3 J. Wang, W. Wang, P. Kollman and D. Case, *J. Am. Chem. Soc.*, 2001, **222**, U403.

4 J. Wang, R. Wolf, J. Caldwell, P. Kollman and D. Case, *J. Comput. Chem.*, 2004, **25**, 1157–1174.

5 Z. F. Brotzakis, I. K. Voets, H. J. Bakker and P. G. Bolhuis, *Phys. Chem. Chem. Phys.*, 2018, **20**, 6996–7006.

Table S1 Number of water and methane molecules in hydrate and liquid phase of each simulation set.

System	No. water molecules in SI	No. methane molecules in SI	No. water molecules in liquid	No. methane molecules in liquid
Pure Hydrate	2204	384	7008	420
Hydrate+AFP III	2204	384	6894	405
Hydrate+N14S	2204	384	6861	402
Hydrate+T18N	2204	384	6858	402
Hydrate+Q44T	2204	384	6859	403
Hydrate+AAA	2204	384	6864	403

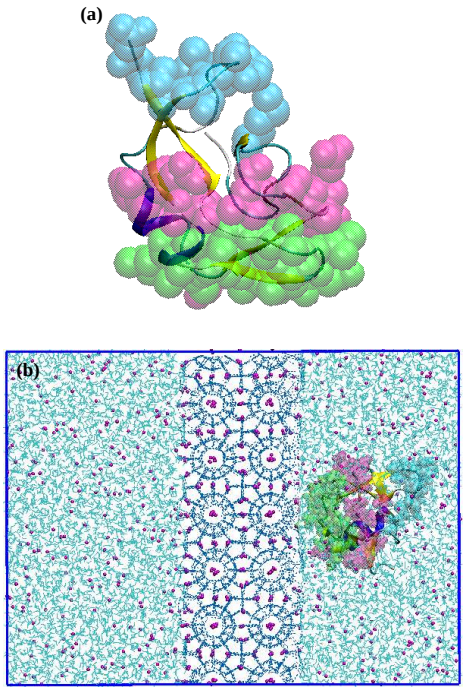

Fig. S1 (a) Three distinct regions of type III antifreeze protein: The IBS region color is denoted by green consists of residues 9, 10, 12, 13, 14, 15, 16, 18, 19, 20, 21 and 44. Vicinity region of IBS is denoted by magenta color consists of residues 8, 23, 37, 39, 42, 43, 46, 47, 48, 50, 51, and 61. Opposite region of IBS is denoted by cyan color of 1, 2, 26, 27, 28, 29, 30 and 56.[5] (b) The orientation of protein and IBS residues respect to hydrate slab, XZ plane of the simulated system is displayed.

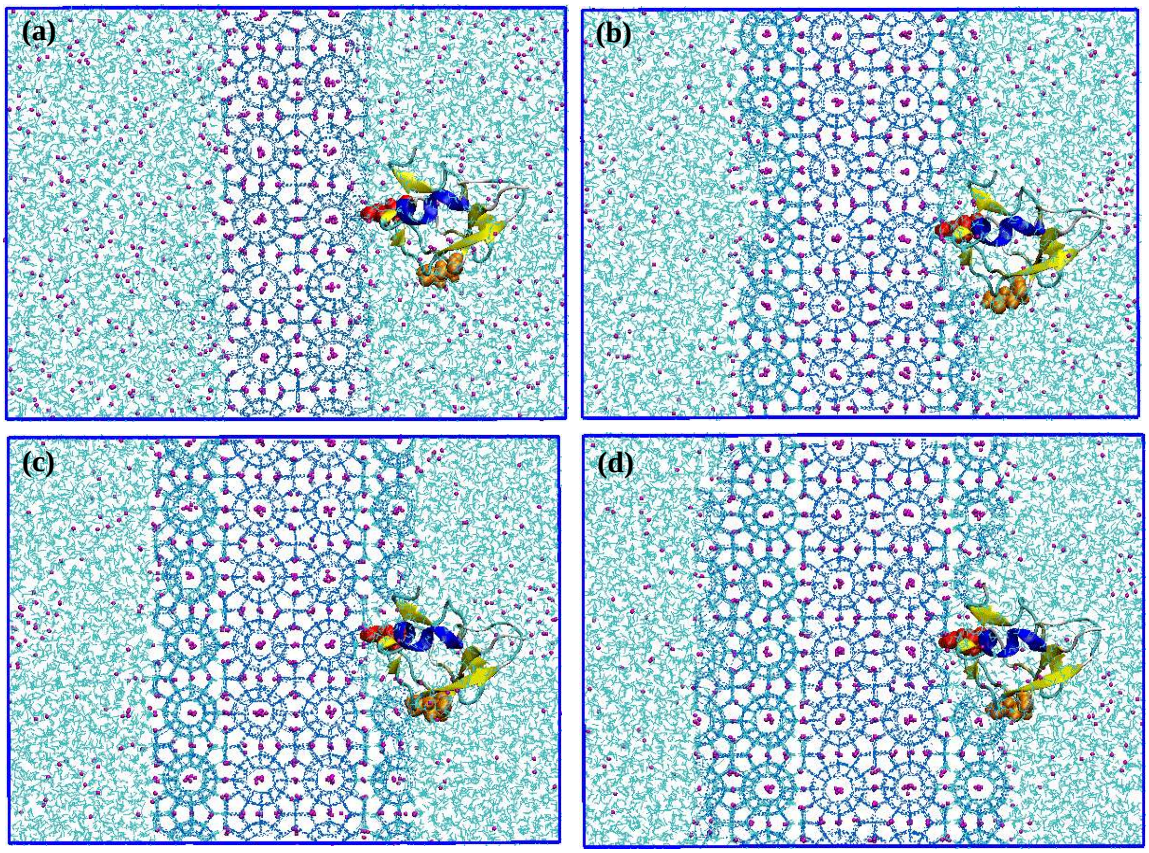

Fig. S2 The XZ-projection of the simulation box of hydrate + AFP III which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. System consists of the hydrate phase and the liquid phase of methane/water. The water and methane molecules are represented by blue lines and purple spheres, respectively. Hydrogen bonds are shown as dark blue dotted lines in the hydrate. Gln9 and Gln44 as first and final residues of IBS are distinguished by orange and red color, respectively.

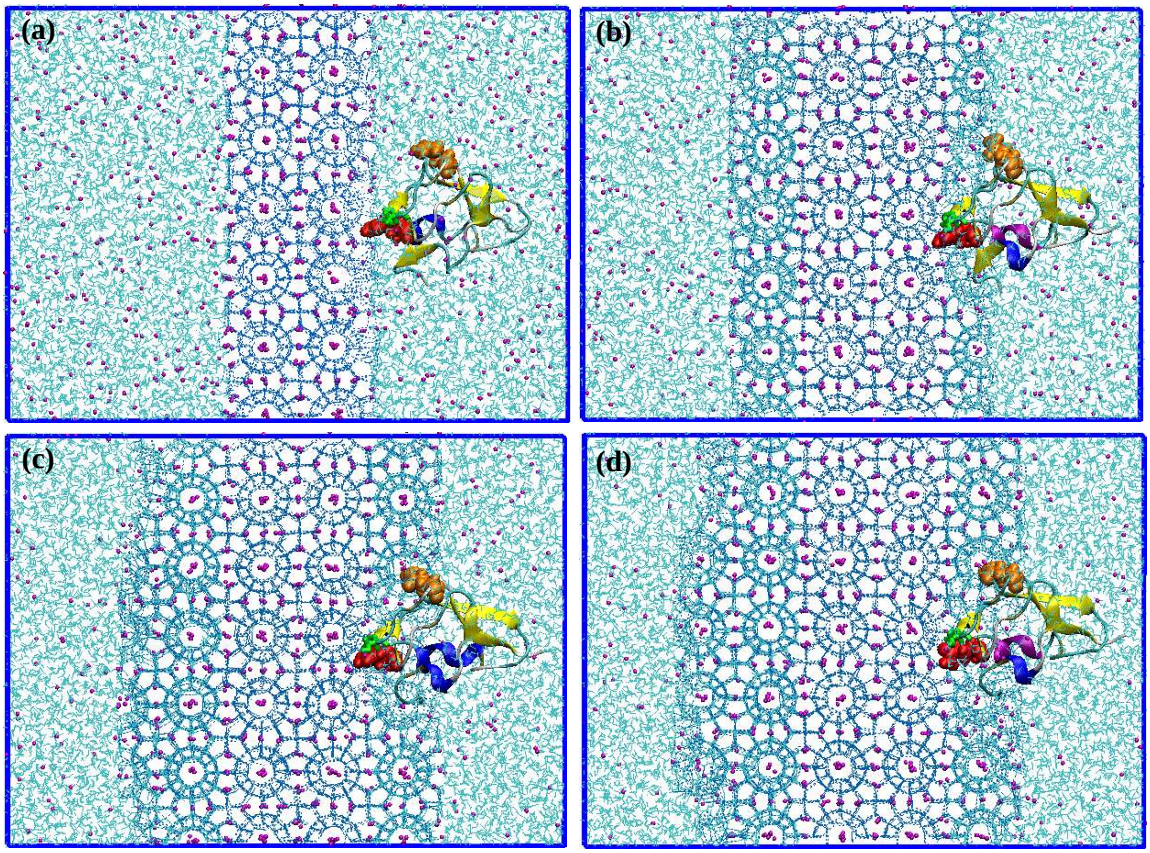

Fig. S3 The XZ-projection of the simulation box of hydrate + N14S which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. The color keys of snapshots are similar to Figure S2. Ser14 is depicted by green color in licorice model.

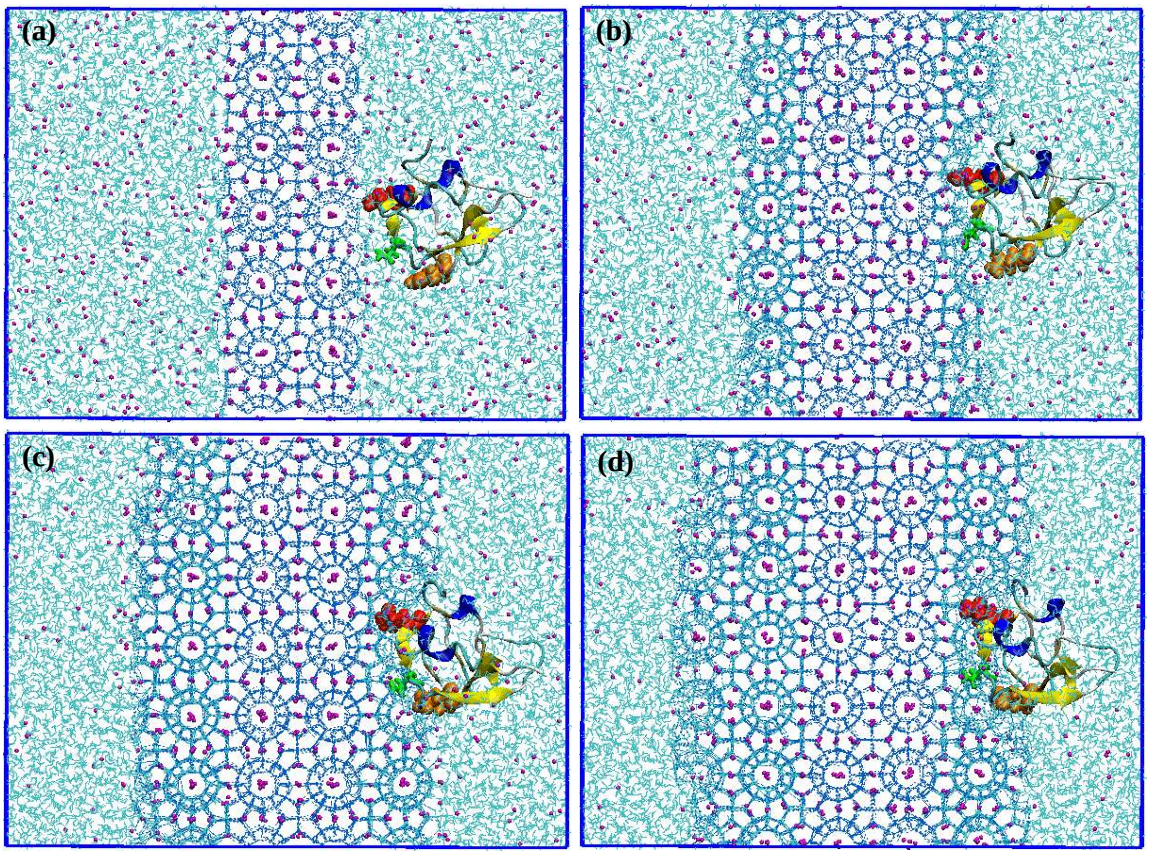

Fig. S4 The XZ-projection of the simulation box of hydrate + T18N which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. The color keys of snapshots are similar to Figure S2. Asn18 is depicted by green color in licorice model.

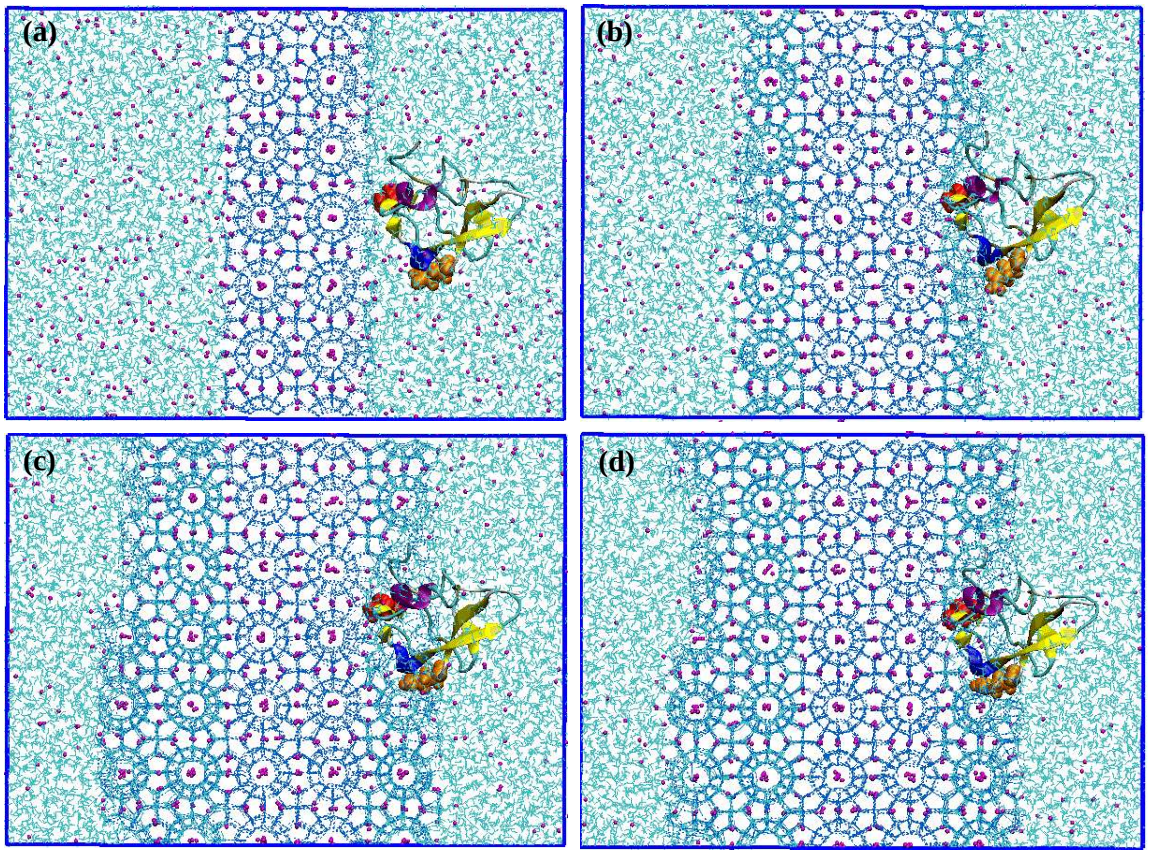

Fig. S5 The XZ-projection of the simulation box of hydrate + Q44T which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. The color keys of snapshots are similar to Figure S3. Thr44 is depicted by red color.

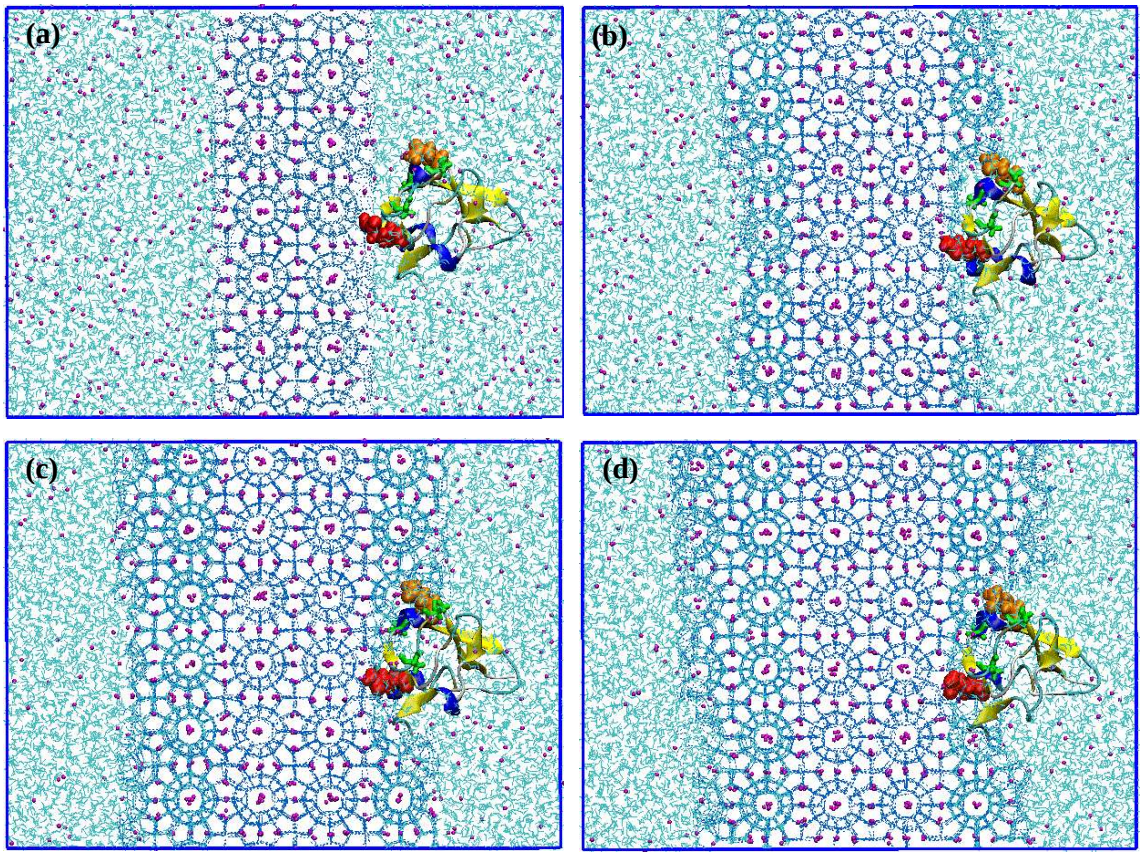

Fig. S6 The XZ-projection of the simulation box of hydrate + AAA which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. The color keys of snapshots are similar to Figure S2. Ala10, Ala13 and Ala19 are depicted by green color.

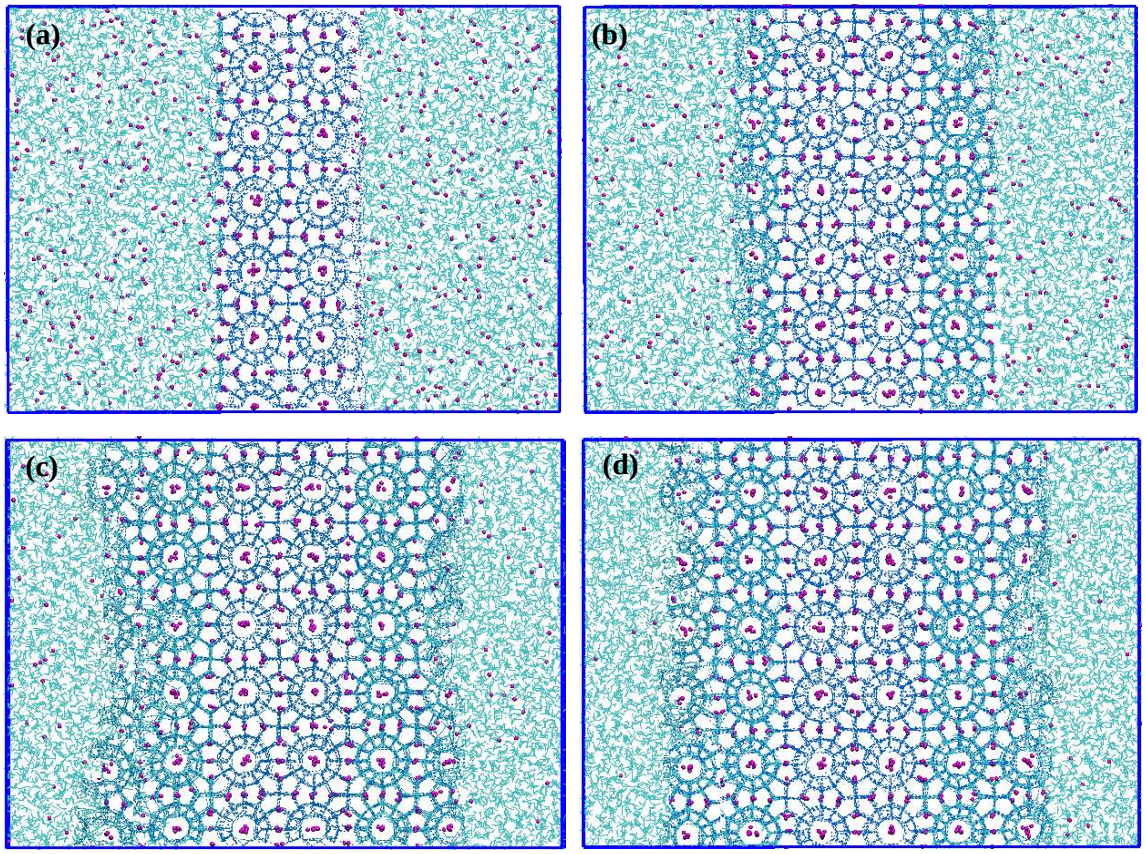

Fig. S7 The XZ-projection of the simulation box of pure hydrate which relates to (a) t=0 ns, (b) t=9 ns, (c) t=20 ns, and (d) t=30 ns. The color keys of snapshots are similar to Figure S2.

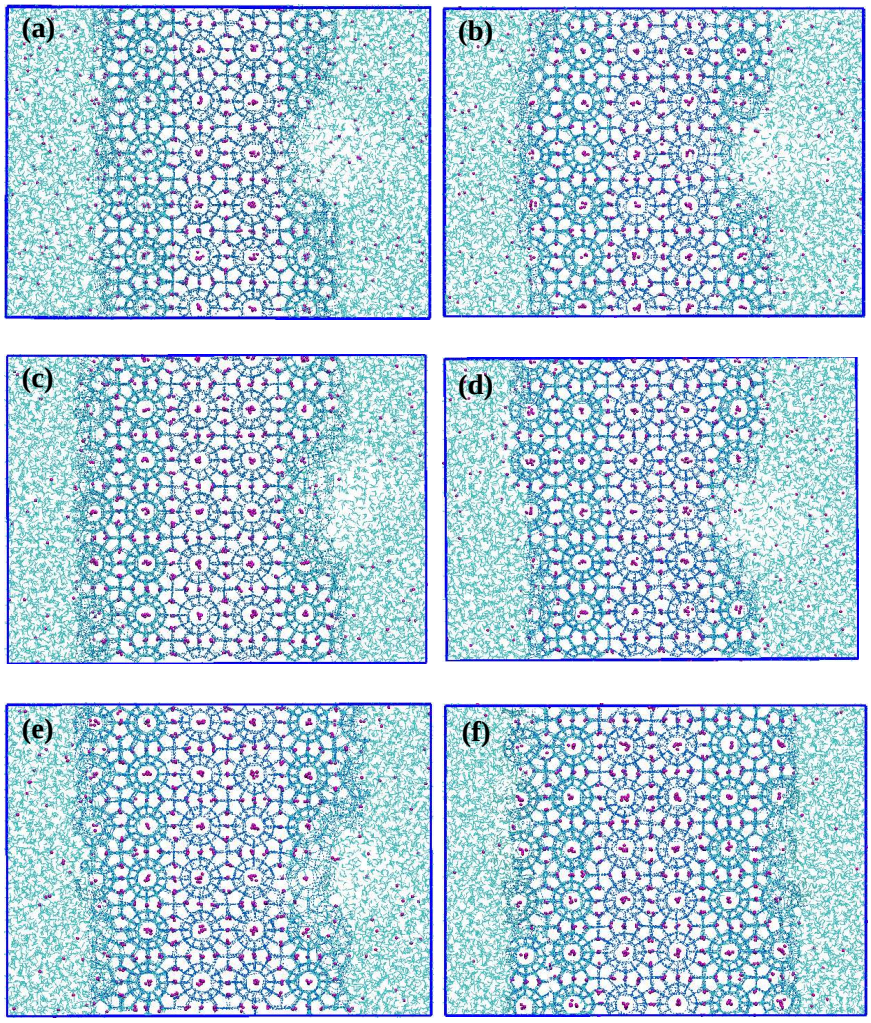

Fig. S8 The final configuration of the simulation box at t= 30 ns for (a) hydrate + AFP III, (b) hydrate + N14S, (c) hydrate + T18N, (d) hydrate + Q44T, (e) hydrate + AAA, and (f) pure hydrate. Protein is not shown to better representation of curvature. The color keys of figures are similar to Figure S2.

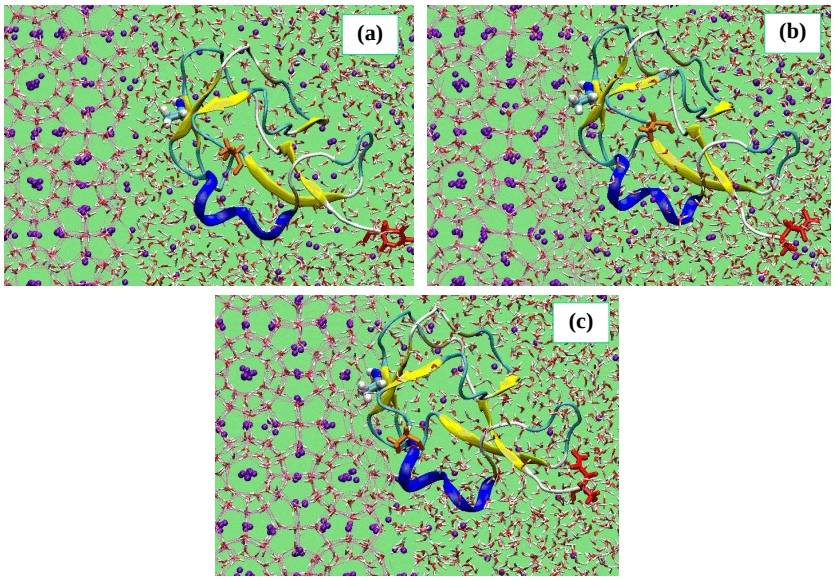

Fig. S9 Three snapshots of AFP III simulation at (a) t=0 ns, (b) t=5 ns, and (c) t=30 ns which display the entrapment of Ala16 inside a half-cage by hydrate growth. Projection are capured at XZ plane. The initial and final residues are represented by red and orange color, respectively. Water molecules, methane molecules, and hydrogen bonds are displayed by licorice model, purple spherical model, and pink crossed line, respectively.

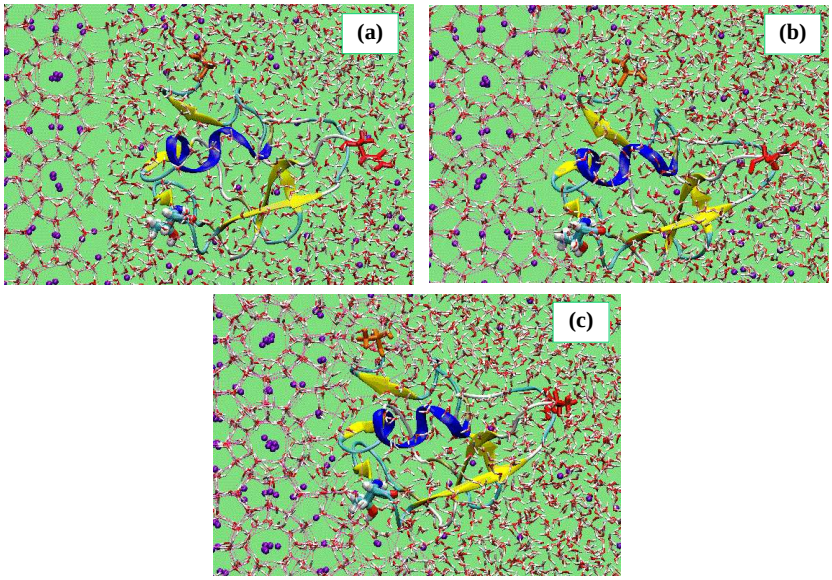

Fig. S10 Three snapshots of AFP III simulation at (a) t=0 ns, (b) t=5 ns, and (c) t=30 ns which display the entrapment of Thr18 inside a half-cage by hydrate growth. Projection are capured at XZ plane. The color keys of snapshots are similar to Figure S9.

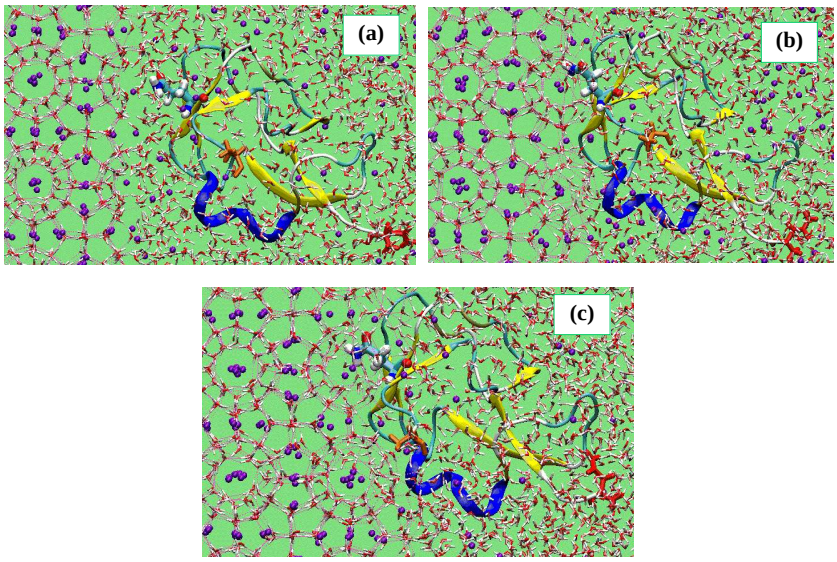

Fig. S11 Three snapshots of AFP III simulation at (a) t=0 ns, (b) t=5 ns, and (c) t=30 ns which display the entrapment of Gln44 inside a half-cage by hydrate growth. Projection are capured at YZ plane. The color keys of snapshots are similar to Figure S9.

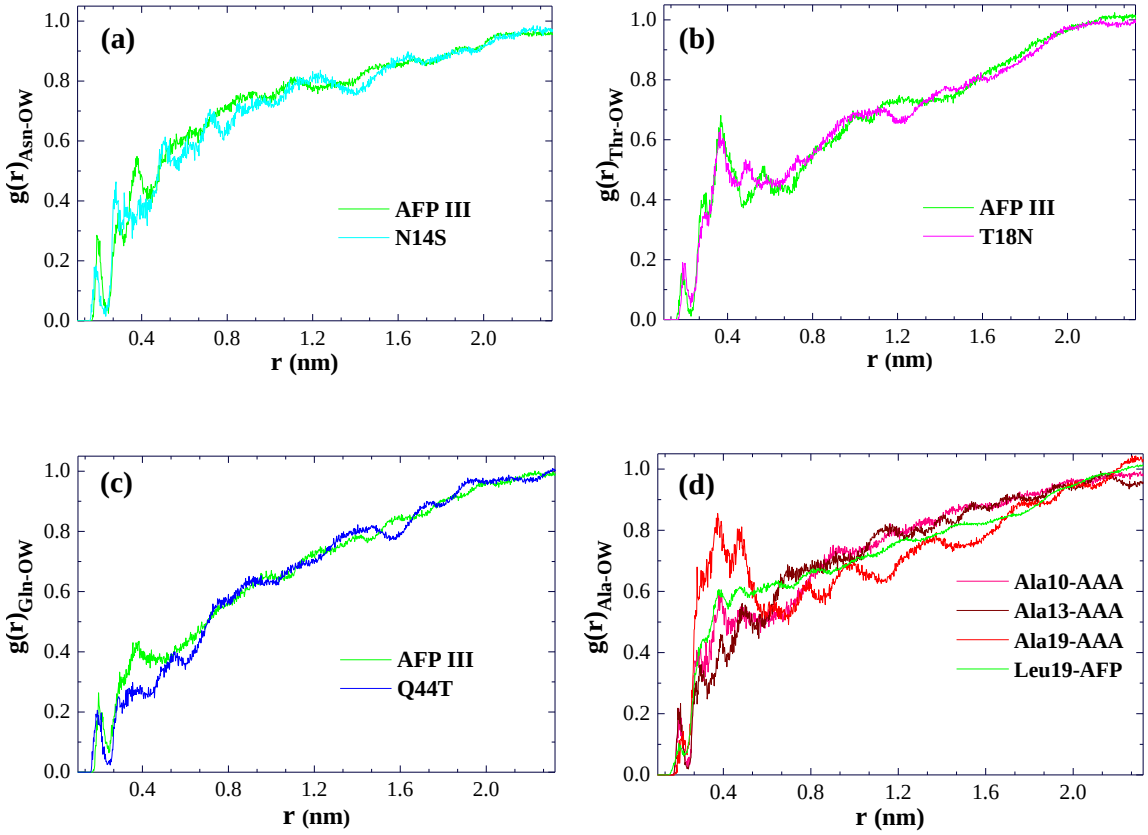

Fig. S12 Radial distribution function (RDF) of oxygen atom of water molecules around the (a) Asn14 in wild type AFP III and Ser14 in N14S, (b) Thr18 in wild type AFP III and Asn18 in T18N (c) Gln44 in wild type AFP III and Thr44 in Q44T, and (d) Leu19 in wild type AFP III and Ala10, 13, and 19 in AAA during simulation time.

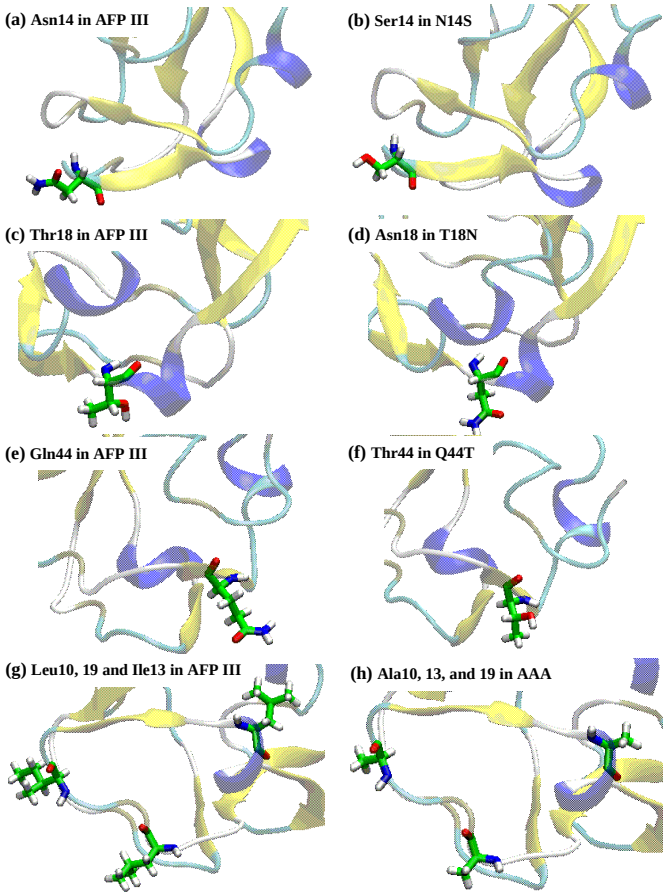

Fig. S13 The structure of the wild type AFP III and each of the mutant proteins are compared. Mutated residues are shown by licorice model. Carbon, oxygen, nitrogen, and hydrogen atoms are colored by green, red, blue, and white, respectively.

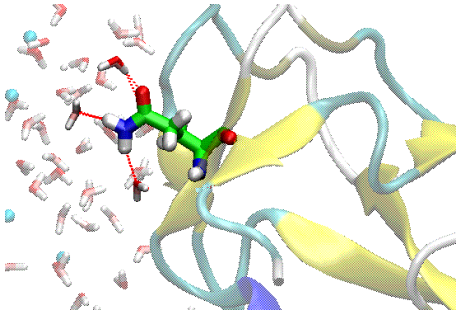

Fig. S14 Displaying of formed hydrogen bond between Gln44 with water molecules in wild type AFP III at 30 ns. The red dotted lines represent the hydrogen bonds.