Supporting information

Dynamics of Hydration Water Around Native and Misfolded α-Lactalbumin

Z. F. Brotzakis,[†] C.C.M. Groot,[‡] W.H. Brandeburgo,[†] H.J.Bakker,[‡] and

P. G. Bolhuis[*,†]

Van 't Hoff Institute for Molecular Sciences, Universiteit van Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands, and FOM Institute AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

E-mail: p.g.bolhuis@uva.nl

[*]To whom correspondence should be addressed

[†]Van 't Hoff Institute for Molecular Sciences, Universiteit van Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

[‡]FOM Institute AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

Table S1: Simulation: Average protein water and bulk water hydrogen bond lifetimes using no recrossing time criterion for six different systems: 1) 5% SPC/E 2) 8.5% SPC/E 3) misfolded #1 4) misfolded #2 5) 5% TIP4P/2005 6) 8.5% TIP4P/2005.

system #	1	2	3	4	5	6
t_{bulk}	0.93_1	0.93_1	0.92_1	0.93_4	1.04_1	1.05_1
t_D	1.09_2	1.14_2	1.11_2	1.15_3	1.24_2	1.21_1
t_A	1.23_2	1.25_3	1.20_2	1.22_2	1.51_2	1.46_4
t_{D+A}	1.18_2	1.24_2	1.16_2	1.19_3	1.39_2	1.35_2
$t_{directD}$	0.54_1	0.46_2	0.59_1	0.58_1	0.514_1	0.50_1
S_{HB}	1.38	1.33	1.25	1.28	1.33	1.28

Table S2: Simulation: Average protein water and bulk water hydrogen bond lifetimes using a recrossing time tbuffer=400 fs for six different systems: 1) 5% SPC/E 2) 8.5% SPC/E 3) misfolded #1 4) misfolded #2 5) 5% TIP4P/2005 6) 8.5% TIP4P/2005.

system #	1	2	3	4	5	6
t_{bulk}	3.19_2	3.21_2	3.19_2	3.21_2	3.75_2	3.82_3
t_D	4.53_6	4.73_{17}	4.77_{11}	5.04_{22}	5.38_6	5.30_6
t_A	7.01_{10}	7.08_{22}	6.87_{27}	7.10_{20}	8.50_{12}	8.44_{28}
t_{D+A}	5.79_7	6.47_{14}	5.84_{16}	6.09_{22}	6.89_8	6.83_9
$t_{directD}$	3.64_8	2.96_7	3.92_3	3.92_8	3.67_{10}	3.53_6
S_{HB}	1.81	2.01	1.82	1.90	1.88	1.78

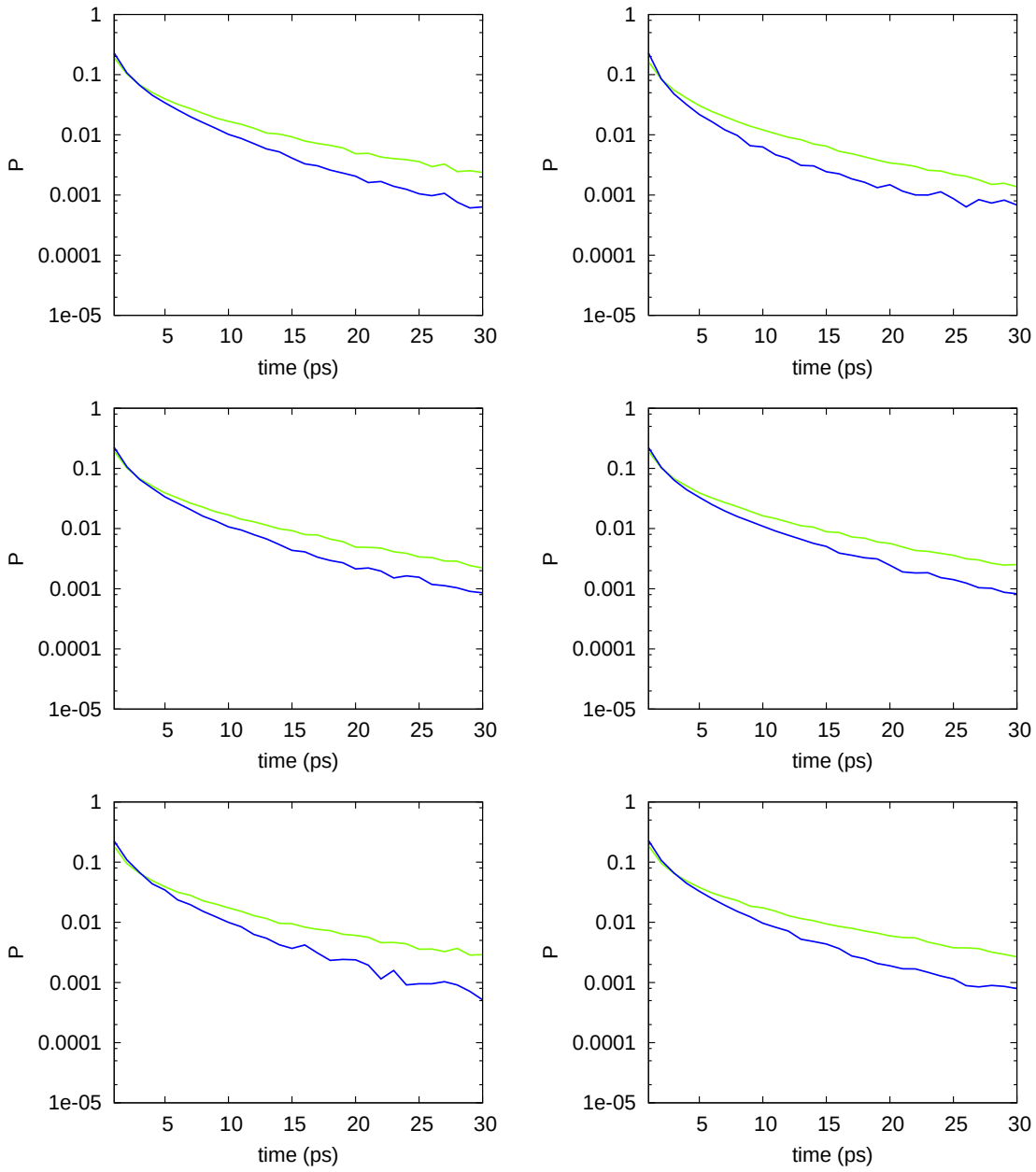


Figure S1: Simulation: Probability distribution of protein-water H-bond lifetimes for the six different systems: a) 5% SPC/E (top left) b) 8.5% SPC/E (top right) c) misfolded #1 (middle left) d) misfolded #2 (middle right) e) 5% TIP4P/2005 (bottom left) f) 8.5% TIP4P/2005 (bottom right). Lifetime distributions of H-bonds accepted by protein (t_A) are depicted in green, while lifetime distribution of H-bonds donated by proteins (t_D) are blue.

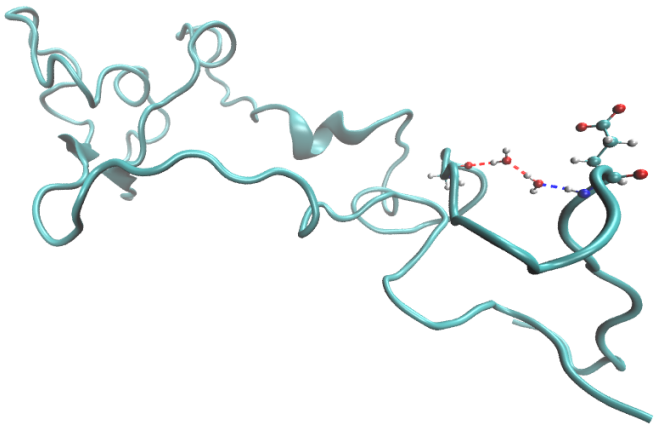


Figure S2: Simulation: Water mediated protein interaction. Here we illustrate how a water configuration containing hydrogen bond types directD, D, and A is mediating the contact of two protein residues.

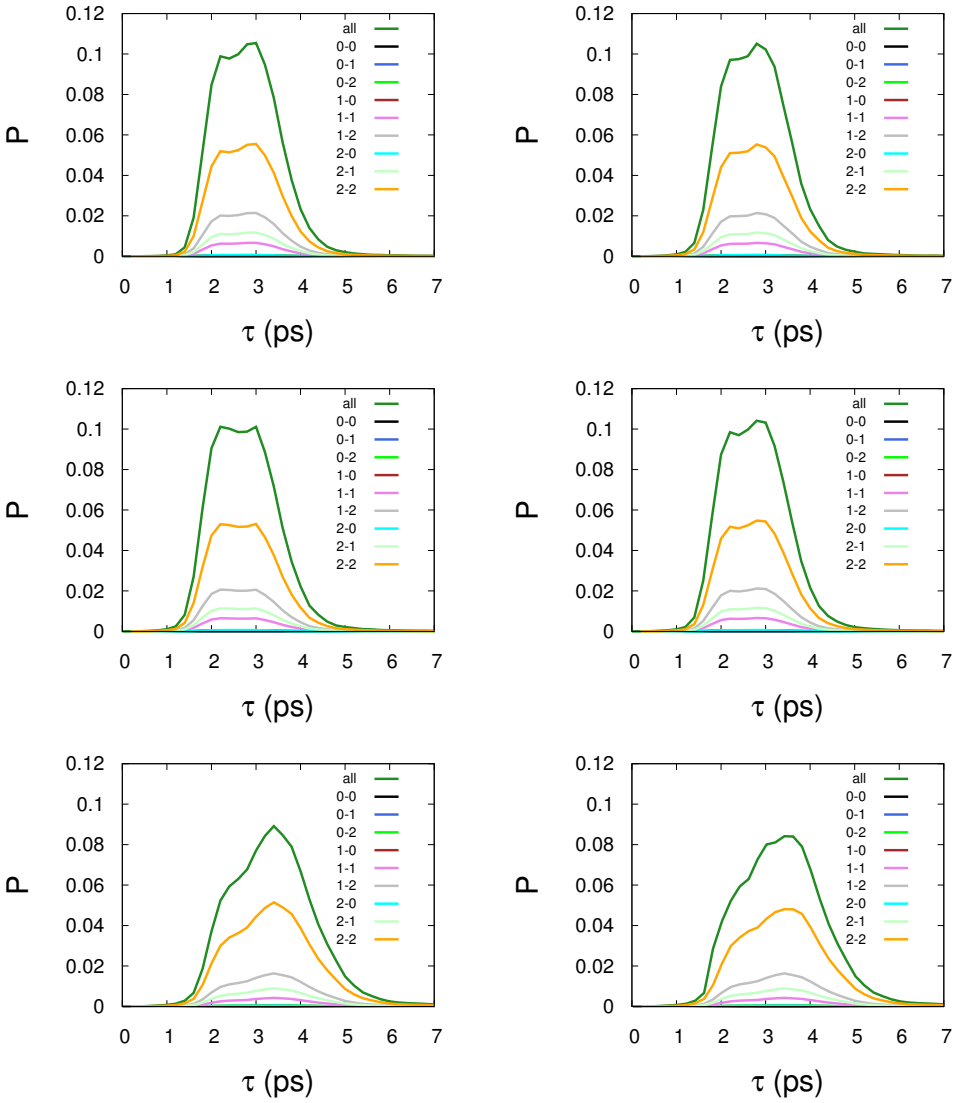


Figure S3: Simulation: Probability distribution of reorientation decay times of the bulk water for the six different systems: a) 5% SPC/E b) 8.5% SPC/E, c) misfolding #1 d) misfolding #2 e) 5% TIP4P/2005 f) 8.5% TIP4P/2005.

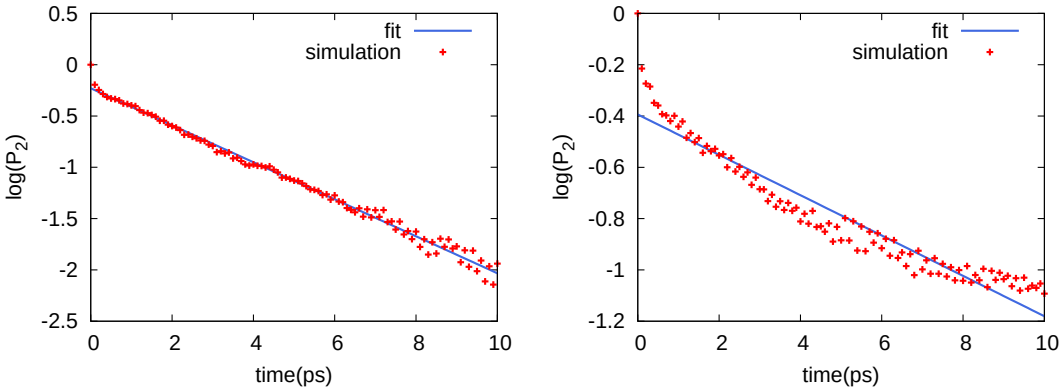


Figure S4: Simulation: Two plots illustrating the reorientation decays ($\log(P_2)$) of a single hydration shell water molecule from the simulation data (red) and the fitted curve (blue).

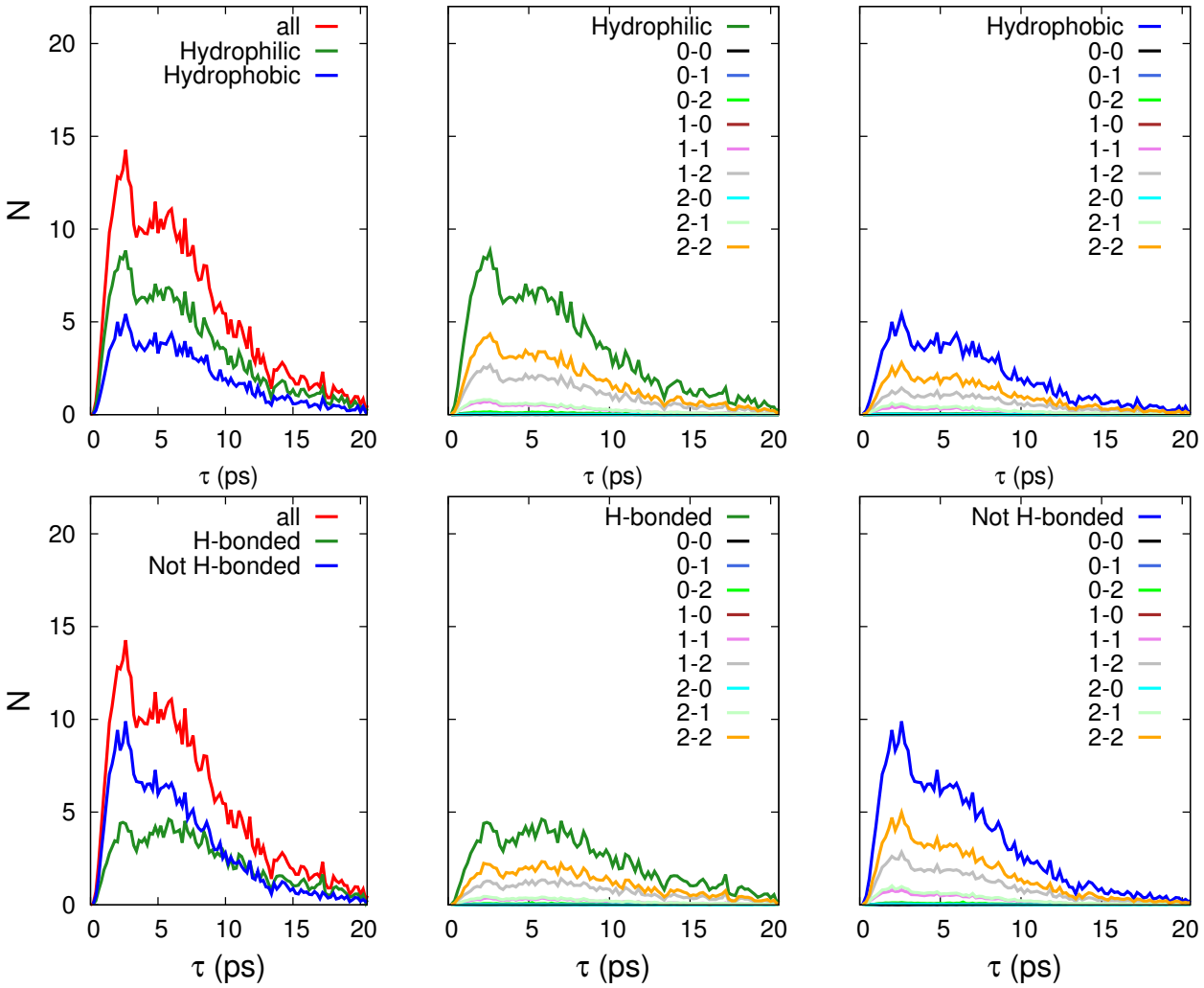


Figure S5: Simulation: Number distributions of reorientation decay times of the hydration water for 5 % SPC/E system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.

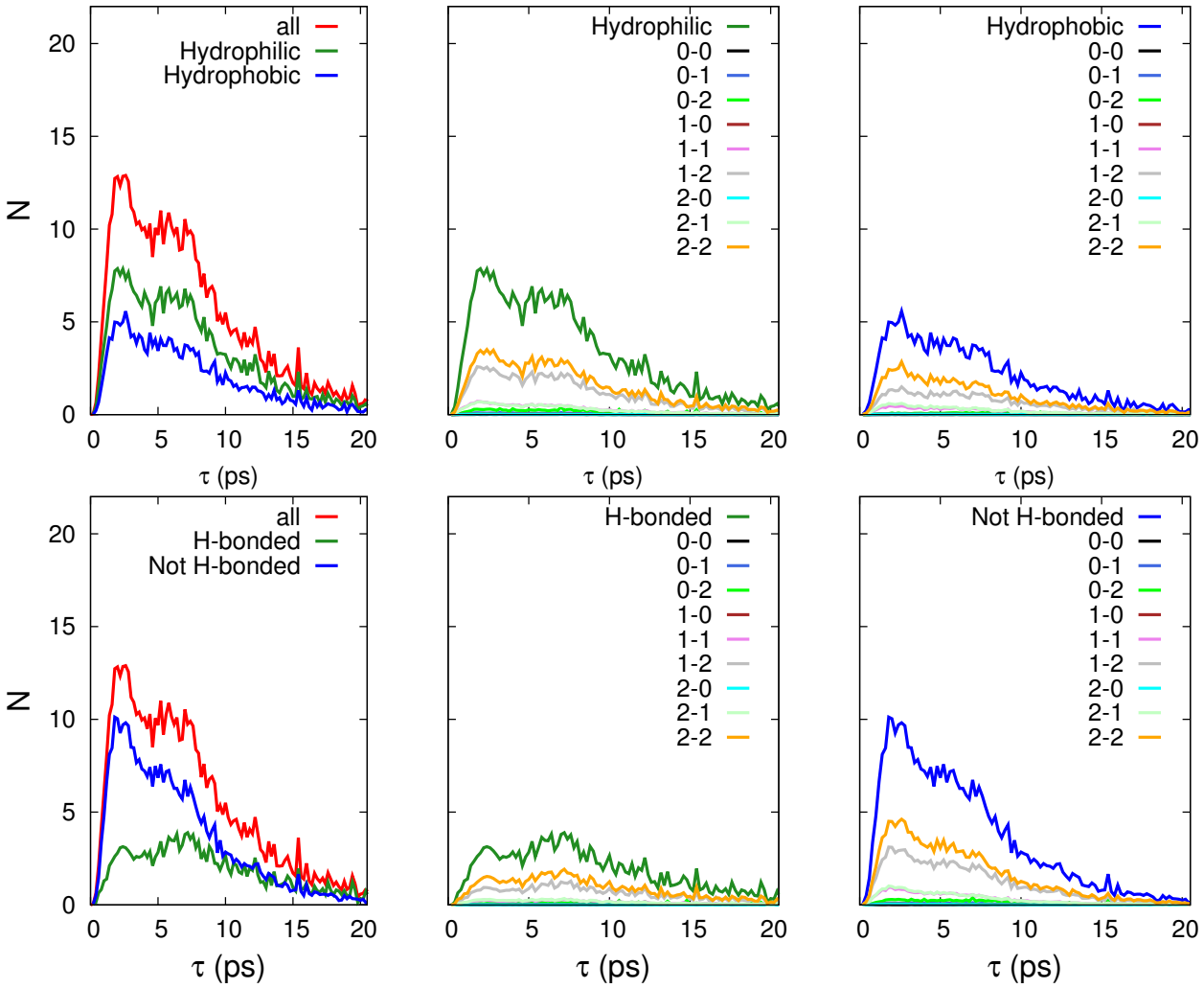


Figure S6: Simulation: Number distributions of reorientation decay times of the hydration water for 8.5 % SPC/E system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.

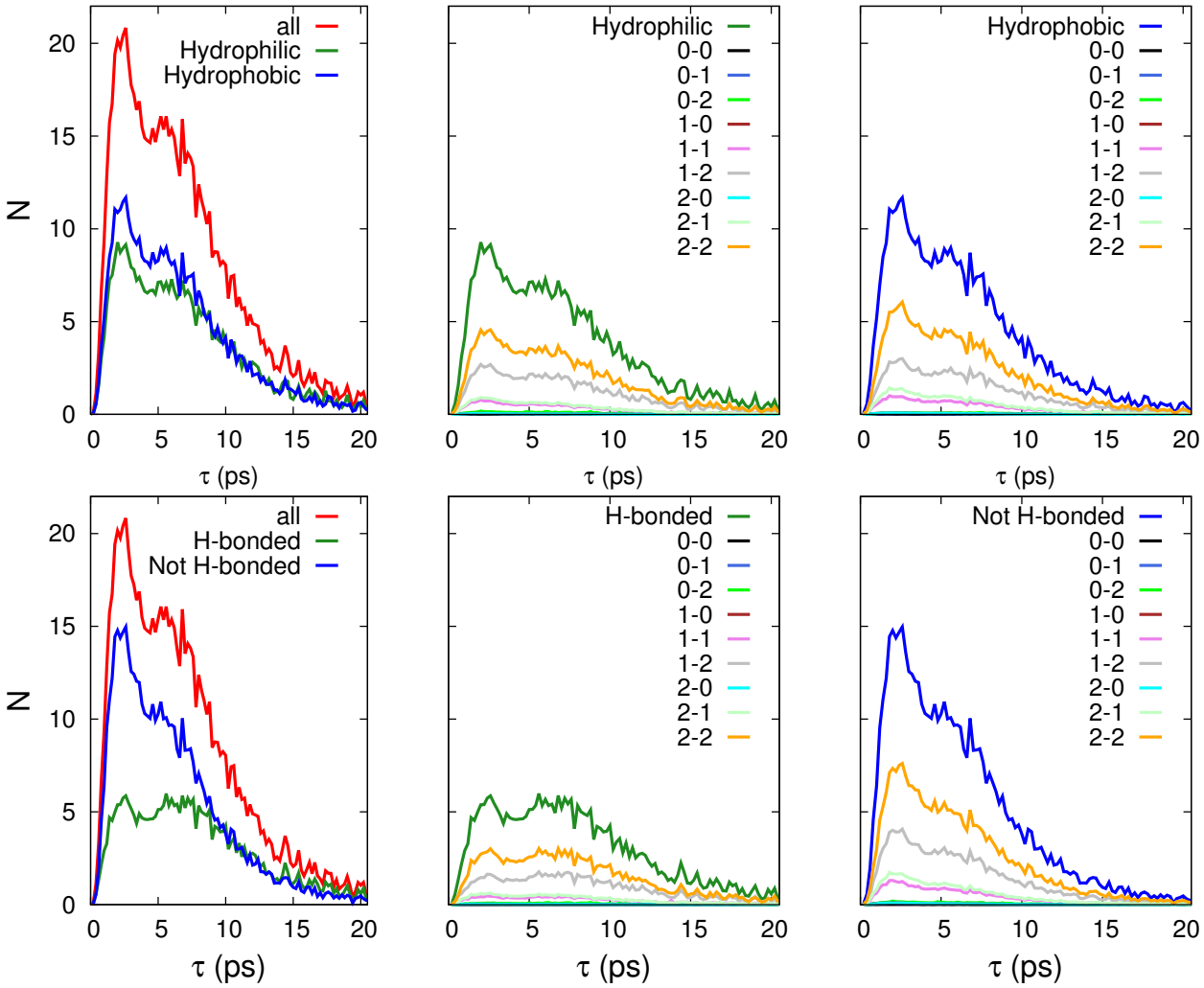


Figure S7: Simulation: Number distributions of reorientation decay times of the hydration water for the misfolded #1 system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.

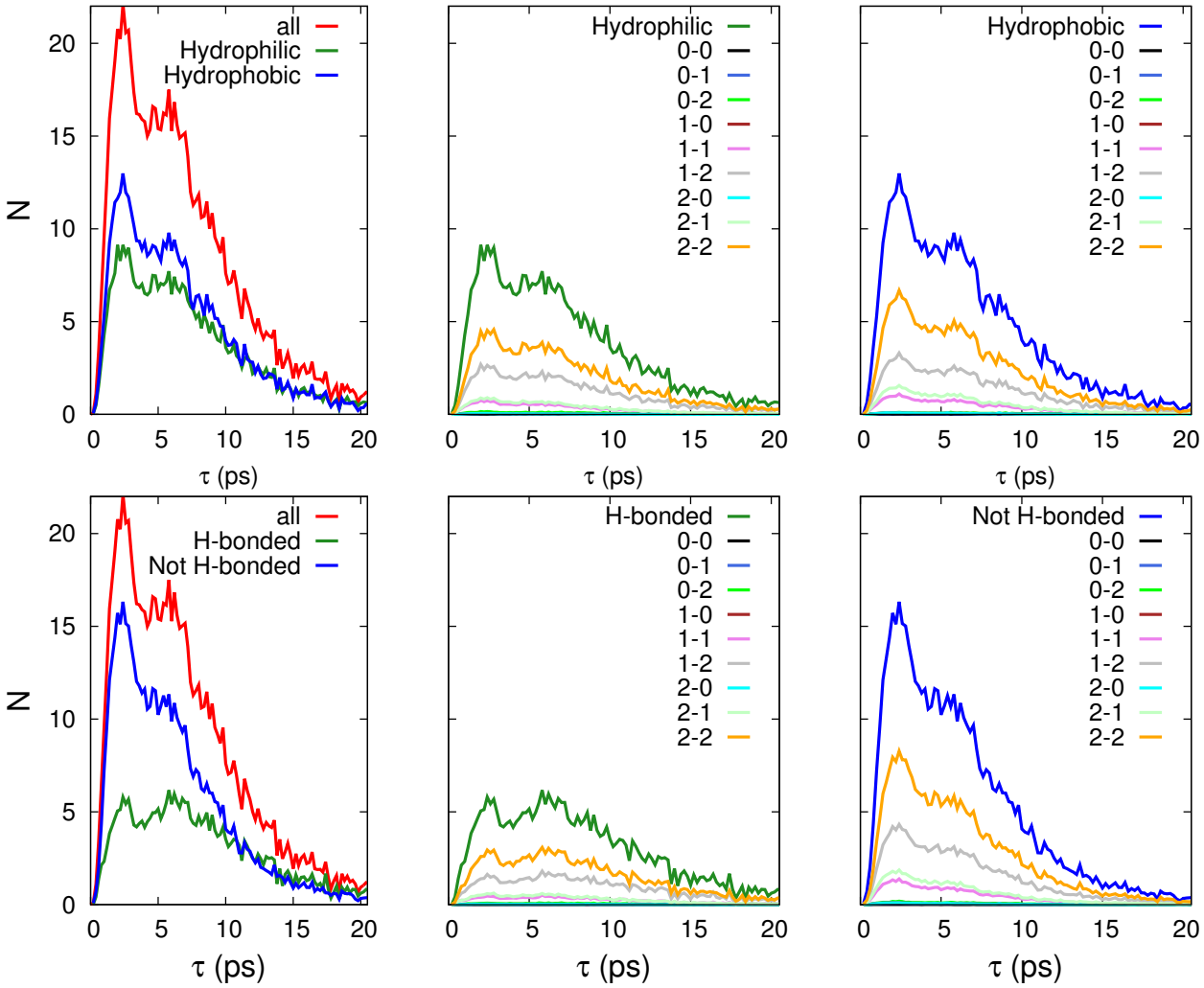


Figure S8: Simulation: Number distributions of reorientation decay times of the hydration water for the misfolded #2 system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.

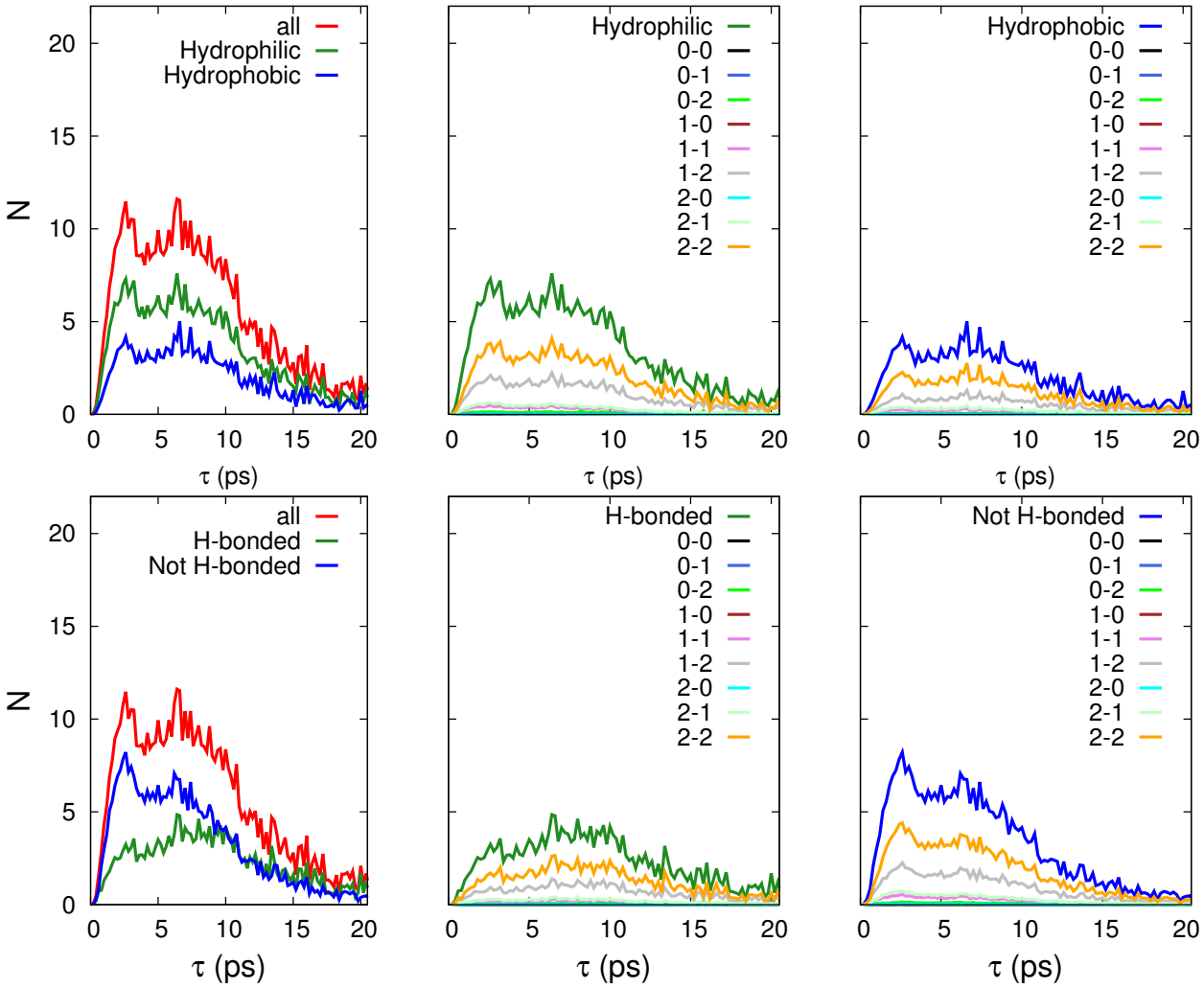


Figure S9: Simulation: Number distributions of reorientation decay times of the hydration water for 5.5 % TIP4P/2005 system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.

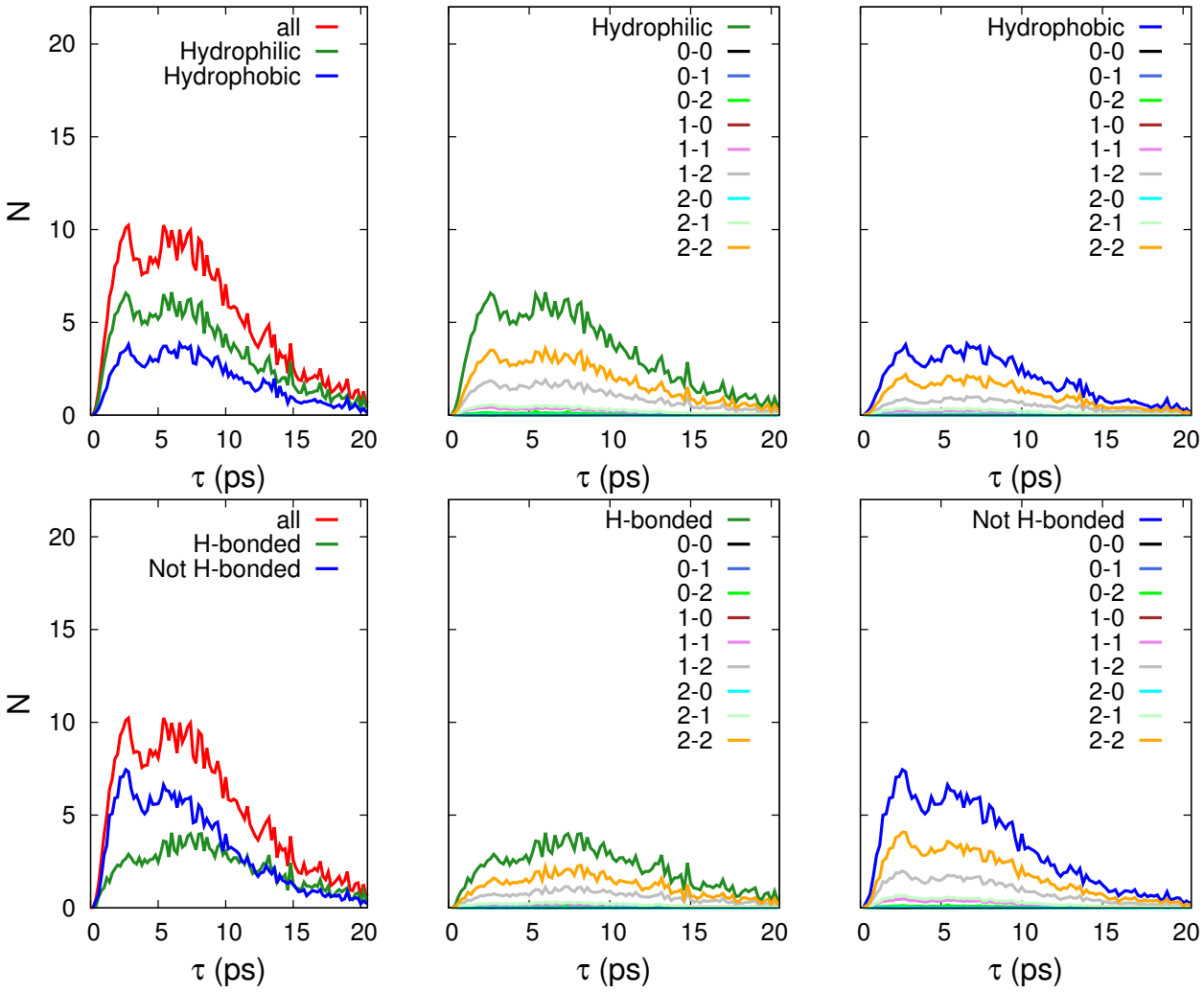
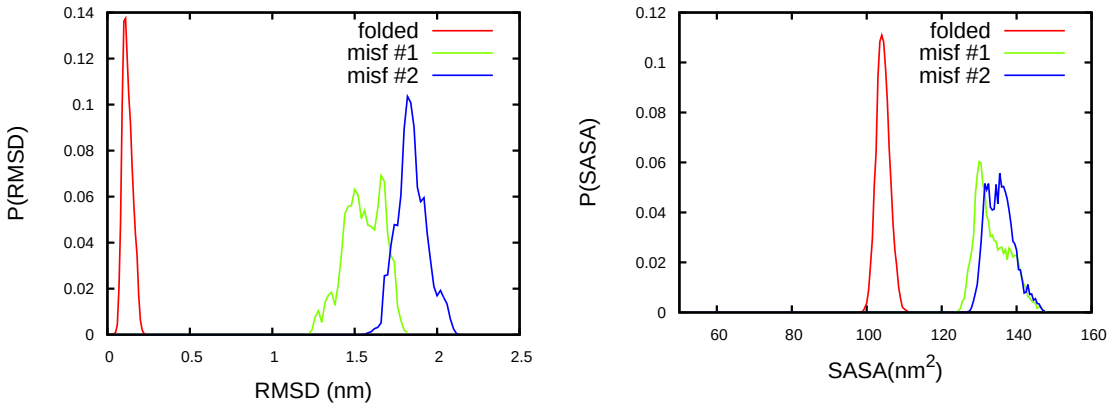


Figure S10: Simulation: Number distributions of reorientation decay times of the hydration water for 8.5 % TIP4P/2005 system. For the first row, the first column depicts the overall hydration water, and its subdivision into molecules hydrating hydrophilic and hydrophobic groups. The second column depicts the subdivision of hydrophilic population according to the hydrogen bond coordination. The third column depicts the subdivision of hydrophobic population according to hydrogen bond coordination. For the second row the first column depicts the overall hydration water, and subdivision into molecules that are hydrogen bonded to the protein (green) and molecules that are not (blue). The second column depicts the subdivision of h-bonded coordination according to hydrogen bond coordination. The third column depicts the subdivision of non-bonded population according to hydrogen bond coordination.



(a) (b) (c) (d)

Figure S11: Structural analysis of the misfolded state. a) Root mean square deviation (RMSD) of the C_α atoms of the protein with respect to the native structure b) Total solvent accessible surface area (SASA), c) SASA for hydrophilic (HF) and hydrophobic (HP) residue of 5% SPC/E folded system and d) SASA for hydrophilic (HF) and hydrophobic (HP) residues of the misfolded systems