Supporting Information

Tau R3-R4 Domain Dimer of the Wild Type and Phosphorylated Ser356 Sequences. I. In Solution by Atomistic Simulations

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(A) REMD Simulation Results

β-sheet locations and secondary structure compositions of the five clusters (centroids) predicted by REMD simulations at 305 K

S1 centroid:

β-sheet 1: residues 308-309, β-sheet 2: 313-314, β-sheet 3: 323-330, β-sheet 4: 336-339, β-sheet 5: 343-347, β-sheet 6: 359-362, β-sheet 7: 371-376.
β-sheet : 41.1%, turn : 10.3%, and coil : 48.6%.

S2 centroid:
β-sheet 1: residues 307-310, β-sheet 2: 313-314, β-sheet 3: 326-330, β-sheet 4: 337-339, β-sheet 5: 344-347, β-sheet 6: 351-352, β-sheet 7: 356-362, β-sheet 8: 371-376.
β-sheet : 43.8%, turn : 18.5%, and coil : 37.7%.

S3 centroid:
β-sheet 1: residues 307-310, β-sheet 2: 313-318, β-sheet 3: 326-330, β-sheet 4: 337-339, β-sheet 5: 344-345, β-sheet 6: 350-352, β-sheet 7: 368-376.
β-sheet: 42.5%, turn : 21.2%, coil : 36.3%.

S4 centroid:
β-sheet 1: residues 307-310, β-sheet 2: 313-314, β-sheet 3: 326-328, β-sheet 4: 336-339, β-sheet 5: 344-347, β-sheet 6: 354-362, β-sheet 7: 370-376.
β-sheet : 42.5%, turn : 14.4%, coil : 43.1%

S5 centroid
β-sheet 1: residues 308-311, β-sheet 2: 327-328, β-sheet 3: 343-346, β-sheet 4: 358-362, β-sheet 5: 371-376.
β-sheet : 27.4%, turn : 25.3%, coil : 47.3%.

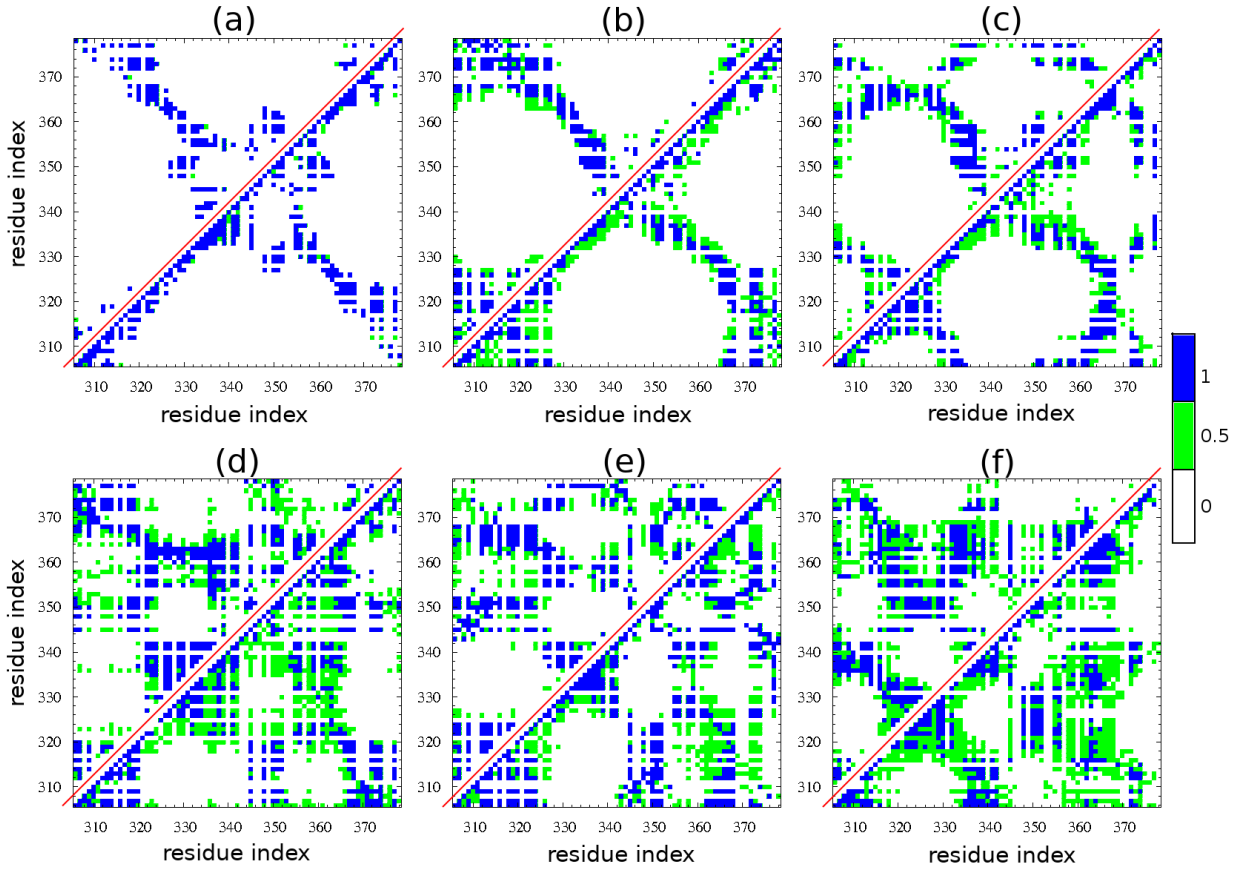

Figure S1. Intra-molecular (upper parts) and inter-molecular (lower parts) side chain - side chain contact maps of tau306-378 dimer in c-EM fibril state (a), and the predicted REMD-centroids S1 (b), S2 (c), S3 (d), S4 (e) and S5 (f) at 305 K. The color code reports the probability. A single conformation is used in all cases.

(B) MD Simulation Results

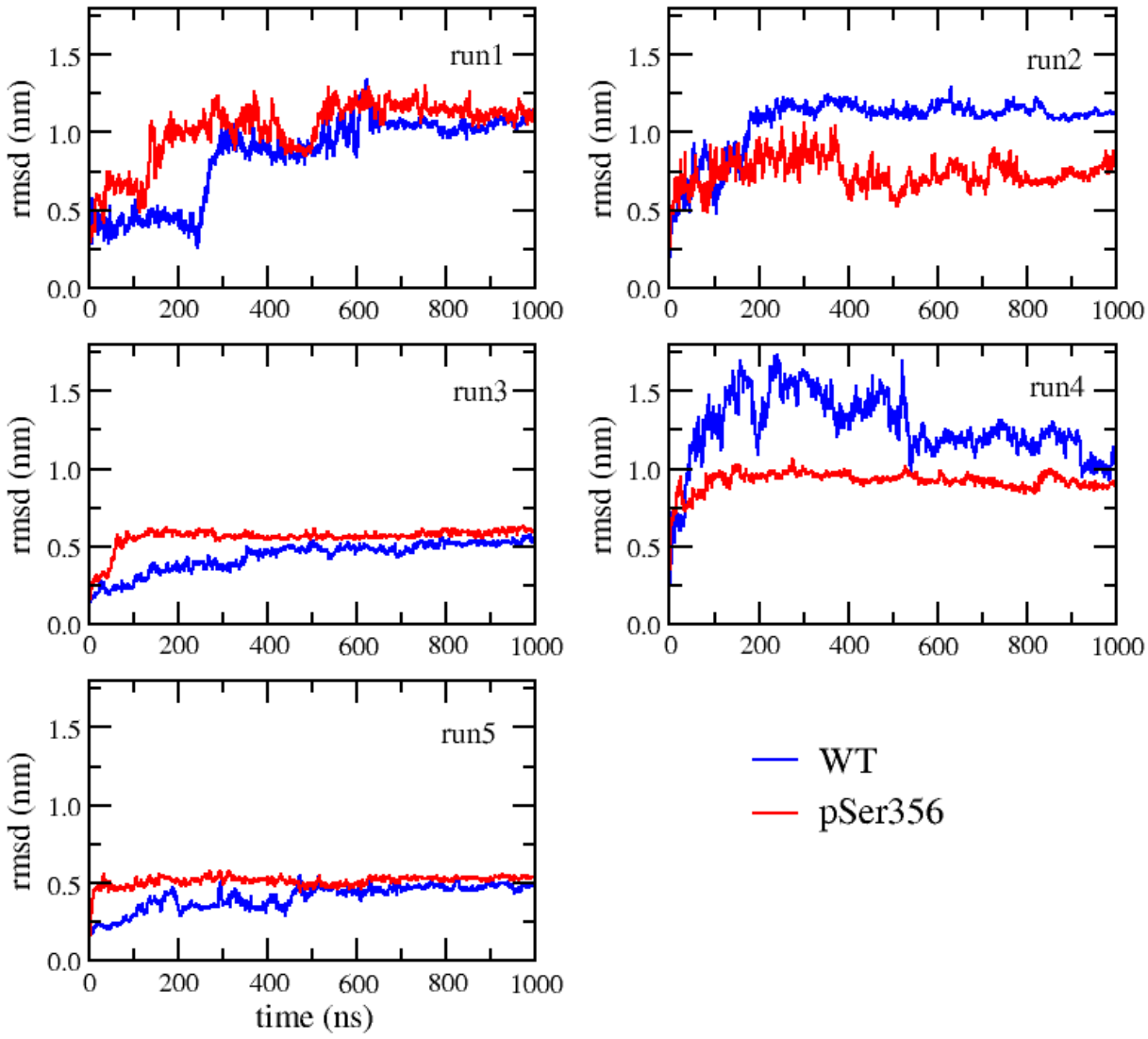

Figure S2. Cα RMSD of the dimer MD simulations starting from the S1 to S5 states of the WT (blue) and pSer356 (red) sequences at 305 K.

Secondary structure composition of WT system using the time interval 50-1000 ns of each MD run averaged over the five runs

Averaged over 5 trajectories: beta-sheet = 30.9 ± 6.3, turn = 26.2 ± 5.5, coil = 42.5 ± 5.1, helix= 0.4 ± 0.3.

Run 1: beta-sheet = 35.7 ± 4.2, turn = 22.0 ± 4.6, coil = 42.0 ± 4.7, helix= 0.3 ± 0.2.
Run 2: beta-sheet = 27.4 ± 7.4, turn = 30.0 ± 5.6, coil = 42.5 ± 5.0, helix= 0.1 ± 0.1.
Run 3: beta-sheet = 35.4 ± 3.6, turn = 26.2 ± 3.9, coil = 38.3 ± 3.5, helix= 0.1 ± 0.1.
Run 4: beta-sheet = 28.1 ± 5.5, turn = 25.8 ± 6.1, coil = 45.3 ± 5.0, helix= 0.8 ± 0.5.
Run 5: beta-sheet = 27.9 ± 3.0, turn = 27.0 ± 4.1, coil = 44.6 ± 4.2, helix= 0.5 ± 0.3.

Secondary structure composition of pSer356 system using the time interval 50-1000 ns of each MD run averaged over the five runs

Averaged over 5 trajectories: beta-sheet = 27.6 ± 5.0, turn = 25.4 ± 5.8, coil = 46.6 ± 5.5, helix= 0.4 ± 0.2.

Run 1: beta-sheet = 26.5 ± 6.9, turn = 26.8 ± 8.8, coil = 46.4 ± 5.6, helix= 0.3 ± 0.2.
Run 2: beta-sheet = 26.8 ± 5.5, turn = 23.8 ± 4.2, coil = 49.2 ± 5.1, helix= 0.2 ± 0.1.
Run 3: beta-sheet = 30.7 ± 3.3, turn = 27.9 ± 3.7, coil = 41.0 ± 4.0, helix= 0.4 ± 0.3.
Run 4: beta-sheet = 27.5 ± 3.7, turn = 22.5 ± 4.1, coil = 49.1 ± 4.3, helix= 0.9 ± 0.7.
Run 5: beta-sheet = 26.5 ± 3.1, turn = 26.2 ± 4.9, coil = 47.2 ± 4.3, helix= 0.1 ± 0.1.

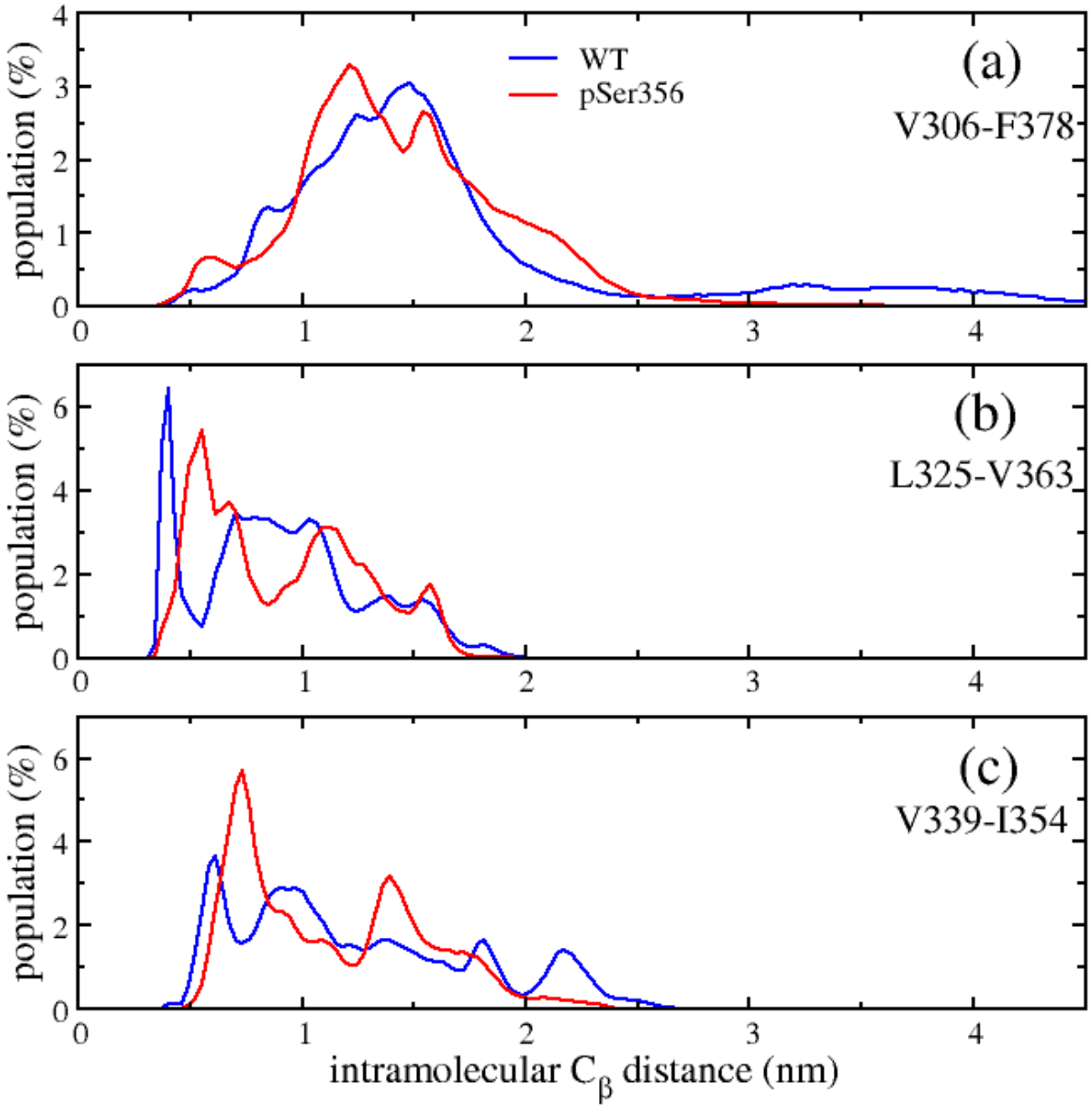

Figure S3. Distributions of intramolecular distances between the Cβ atoms of two specific residues averaged over the two chains and the five MD trajectories for the WT and pSer356 sequences. For each simulation we considered the time interval 50-1000 ns. The intra-molecular distances between Cβ atoms of V306-F378, L325V363 and V339-I354 are 1.0, 0.66 and 0.57 nm in the cryo-EM structure of fibril.

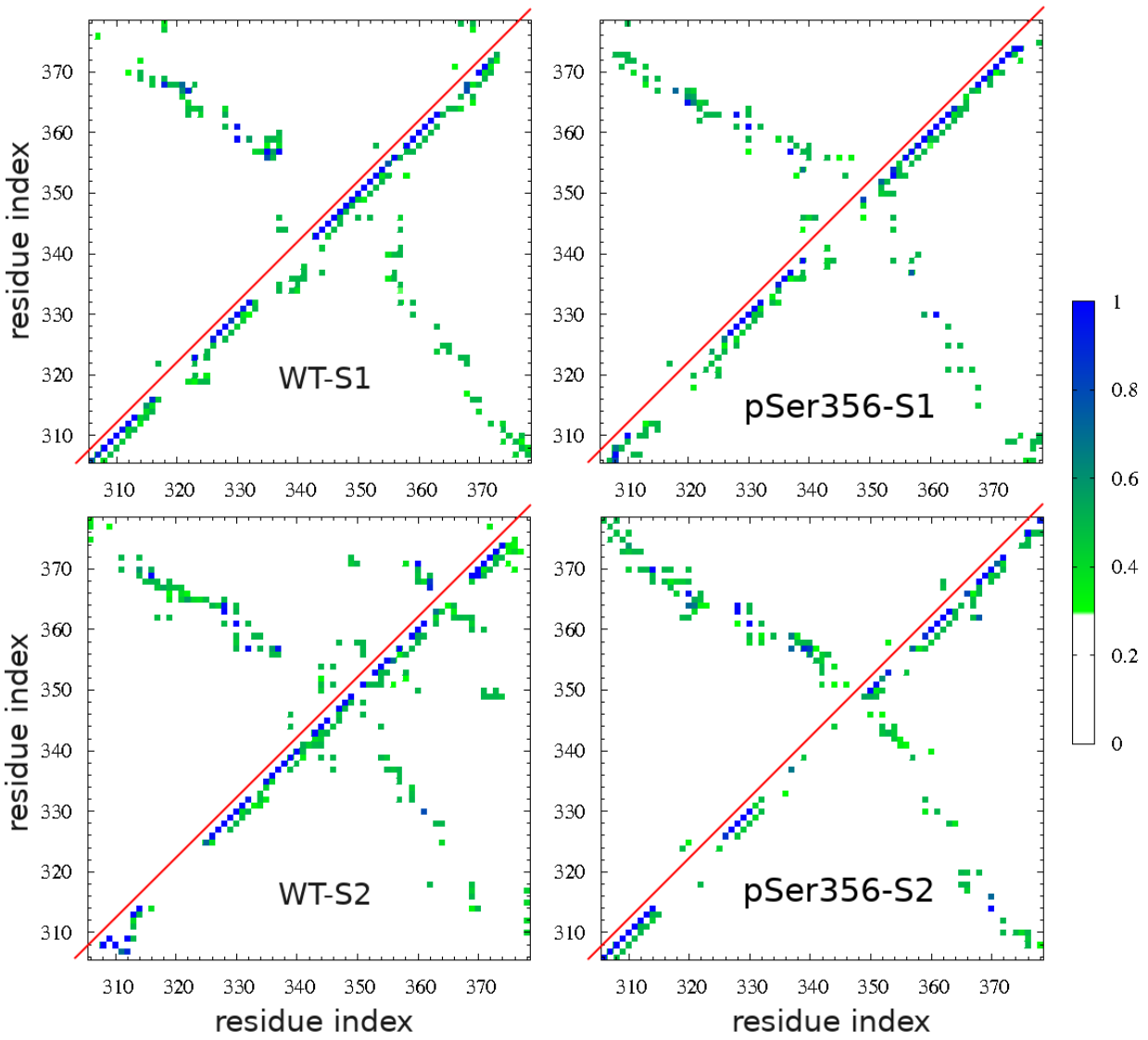

Figure S4. Intra-molecular (upper parts) and inter-molecular (lower parts) side chain-side chain probability contact maps of tau306-378 dimer using the time interval 950-1000 ns of the MD runs starting from S1 and S2 for the WT and pSer356 sequences. For clarity, all probabilities < 0.3 are not shown.

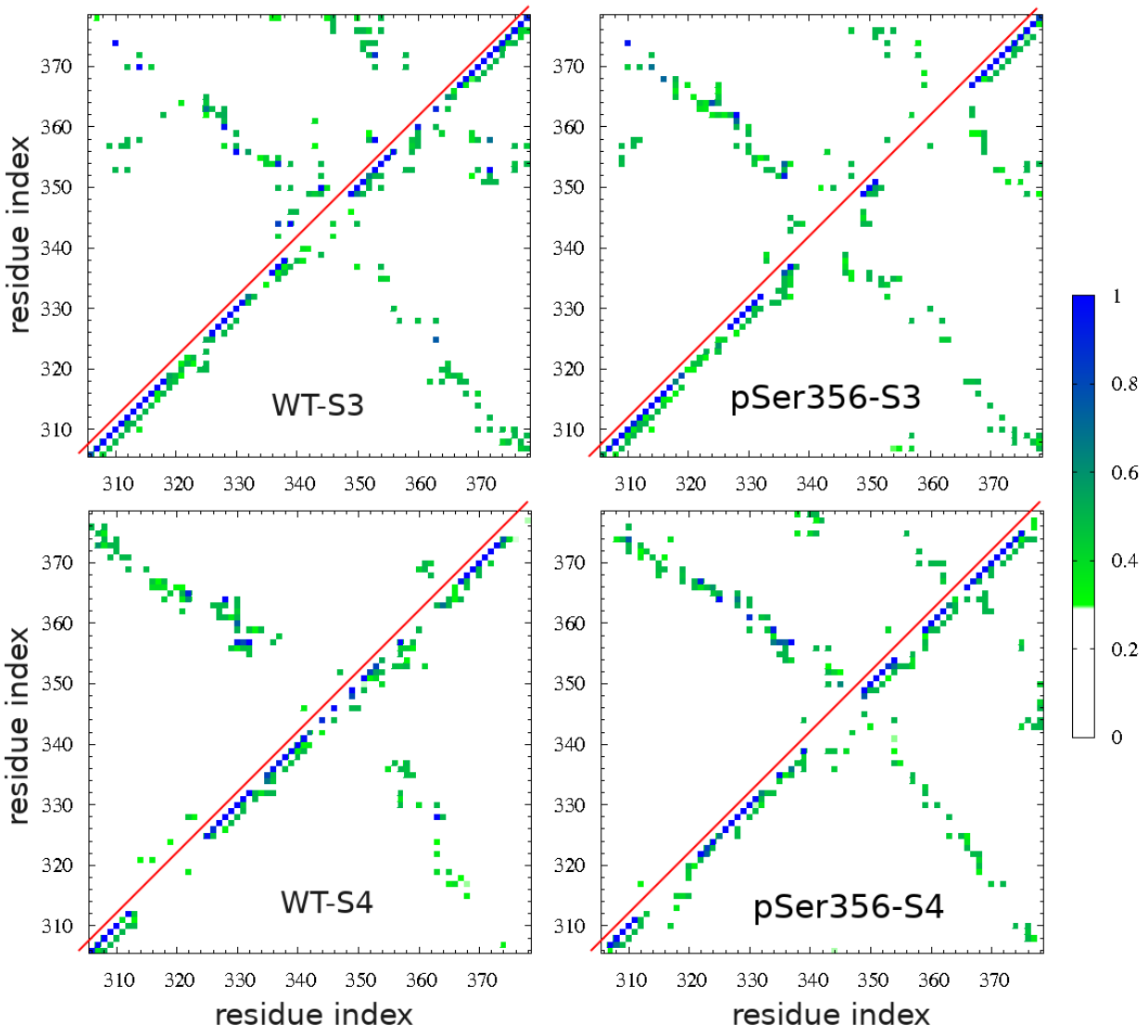

Figure S5. Intra-molecular (upper parts) and inter-molecular (lower parts) side chain - side chain probability contact maps of tau306-378 dimer using the time interval 950-1000 ns of the MD runs starting from S3 and S4 for the wild type and phosphorylated Ser356 sequences. All probabilities < 0.3 are not shown.

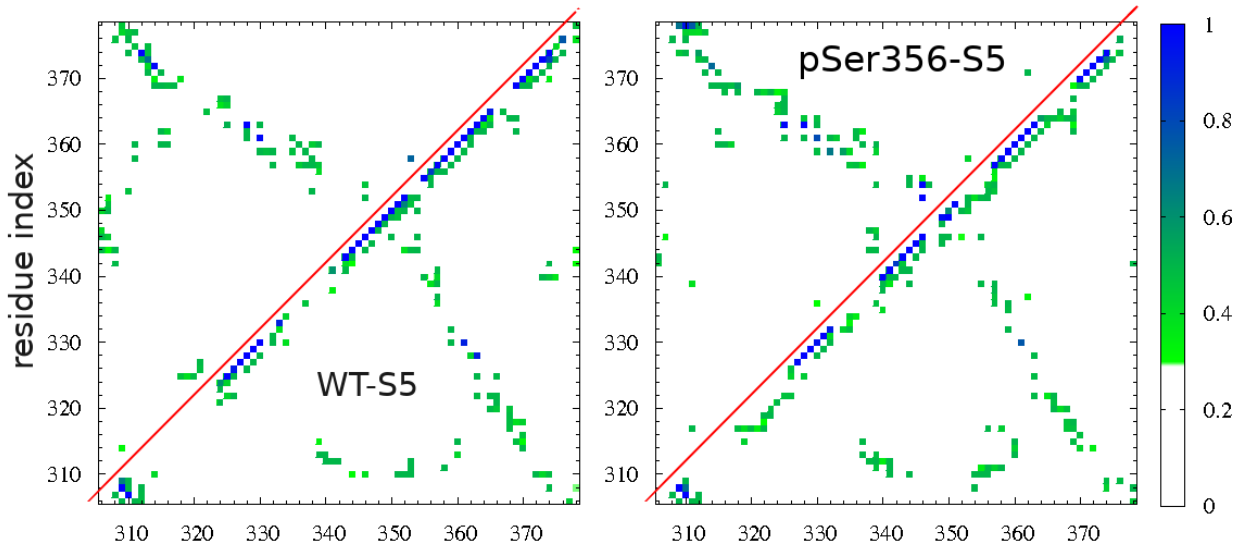

Figure S6. Intra-molecular (upper parts) and inter-molecular (lower parts) side chain-side chain probability contact maps of tau306-378 dimer using the time interval 950-1000 ns of the MD run starting from S5 for the wild type and phosphorylated Ser356 sequences. All probabilities < 0.3 are not shown.

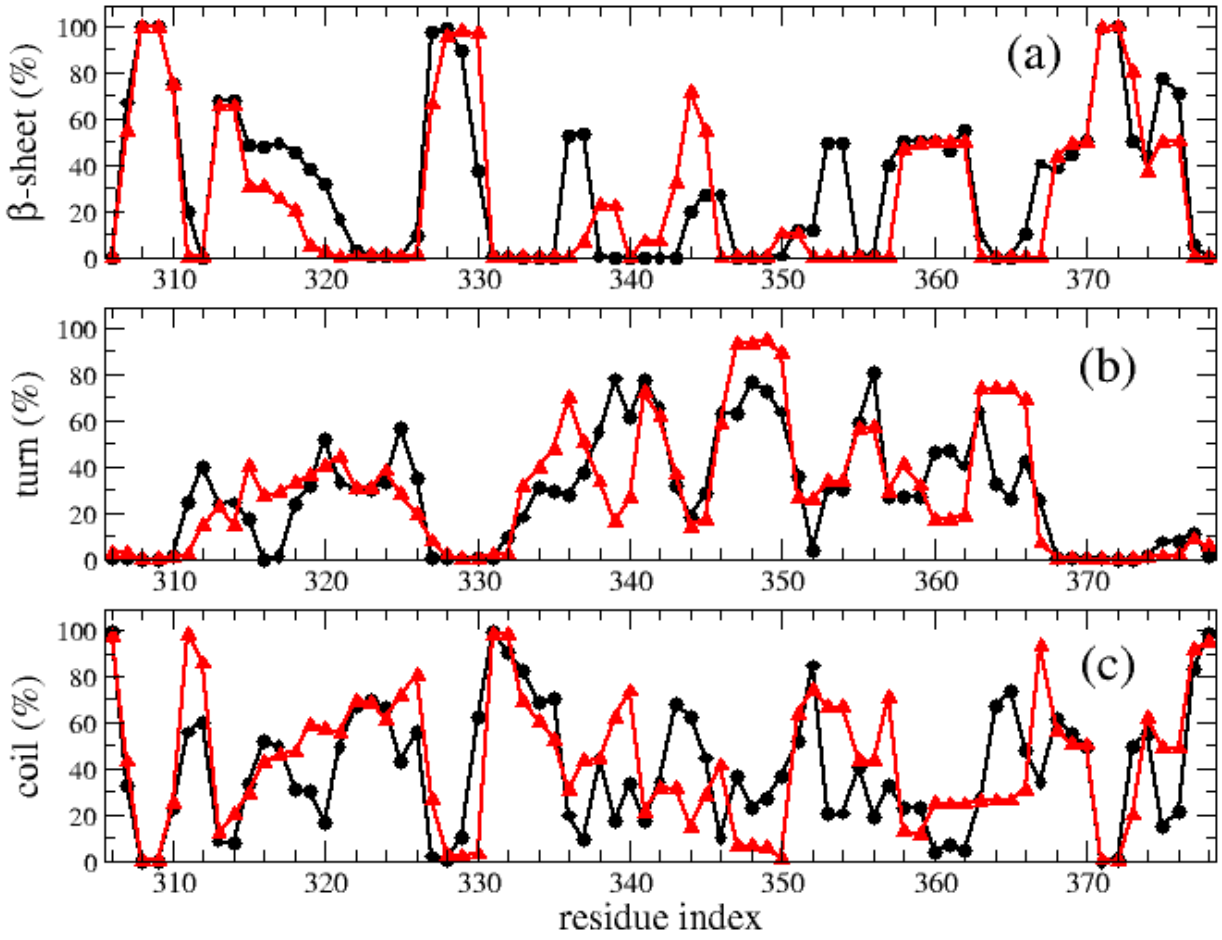

Figure S7. Secondary structure propensities along the sequence of tau306-378 dimer at 305 K averaged over the two chains and the runs S3 and S5 for the WT (black) and pSer356 sequence (red). For each simulation we consider the time interval 50-1000 ns. Very similar results are obtained using the time interval 950-1000 ns.

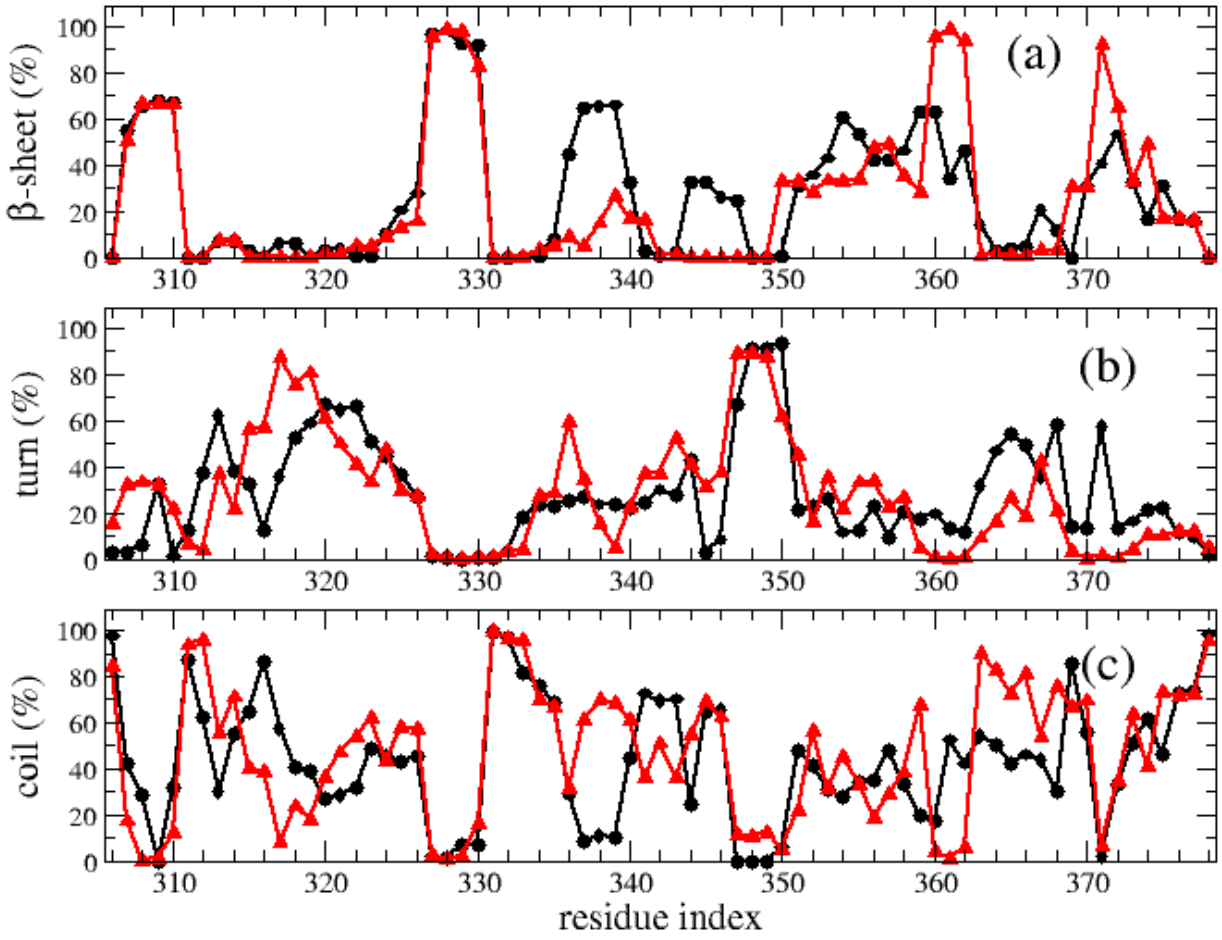

Figure S8. Secondary structure propensities along the sequence of tau306-378 dimer at 305 K averaged over the two chains and the runs S1, S2 and S4 for the WT (black) and pSer356 sequence (red). For each simulation we consider the time interval 50-1000 ns. Very similar results are obtained using the time interval 950-1000 ns.

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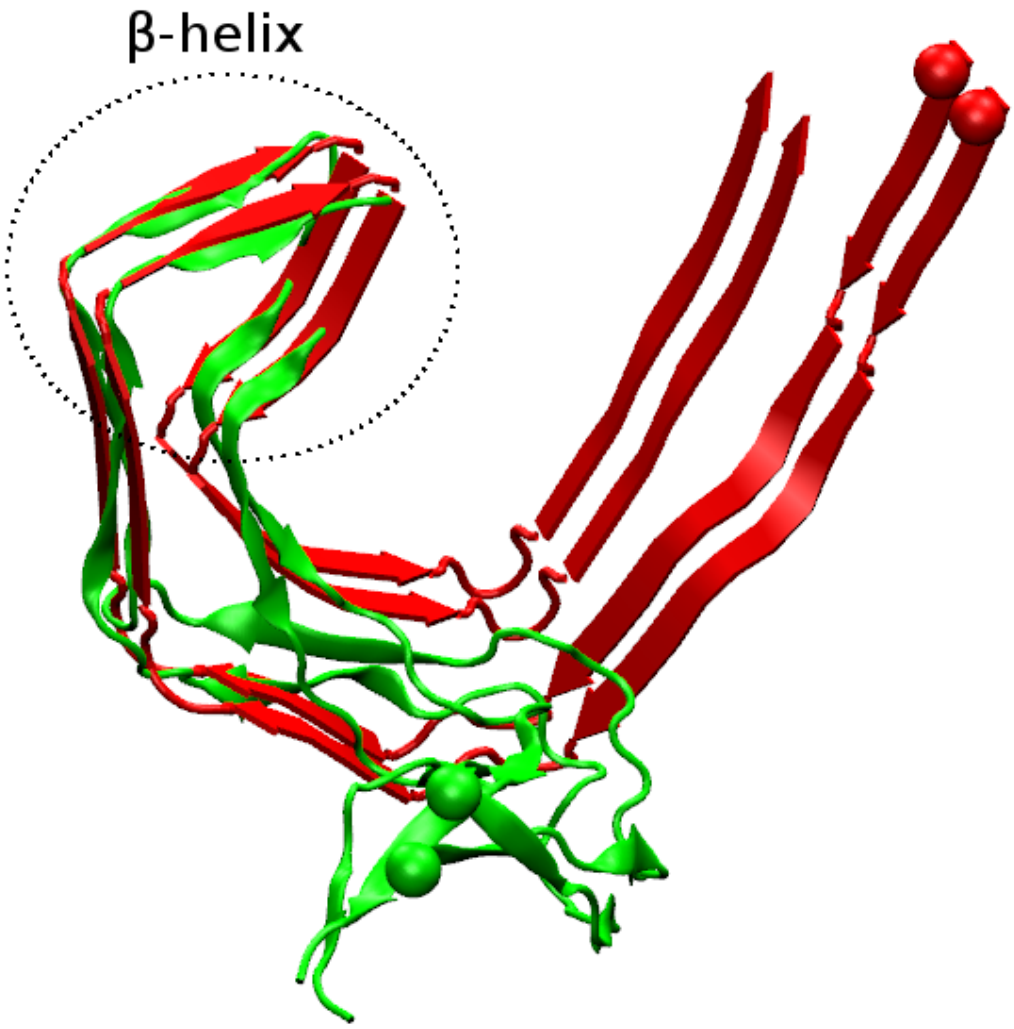

Figure S9. Representative MD structure (green) superposed on the cryo-EM structure of tau306-378 dimer at 305 K showing the high conservation of the ß-helix motif. Balls locate the N-termini.