Supporting Information

Detailed method for model construction and differences between models

The heterogeneous Aβ-tau mixtures were constructed based on Lührs ssNMR model of $A\beta_{17-42,}$ which protein data bank (PDB) ID is 2BEG for Aβ monomer and mutated $A\beta_{17-42}$ for tau monomers. Lühr's Aβ model has 10 different coordinates in one PDB file, because of the fluctuation of atoms. That fluctuation induces the different compositions of residues, so it can change the interior feature of monomer. To consider that impact, we used 2 types of tau models which are mutated Lühr's Aβ models. They are called as WT1 and WT2 in the main paper. The different conformation of those is that the Valine (VAL) residue is located at different side. V287 (VAL) of WT1 is located at the outside of the loop and that of WT2 is at inside of the loop. Other mutated models are prepared by replace the residues of Aβ into tau's residues. Since K280 (LYS) residue is deleted and the other residues are shifted to fill the empty place, so each models have different interior conditions from that of WT models.

Characters of binding interactions for each models

Composed amino acids for each models have four main features that are hydrophobic, hydrophilic, polar uncharged and special cases. For intuitive insights of binding features, direct interacting features are organized at table S2. Every possible combinations are considered and represented with various colors. Especially, complementary interactions between Aβ and tau layers seem to initiate the breakage of interactions and allow water molecules to access into the interior regions.

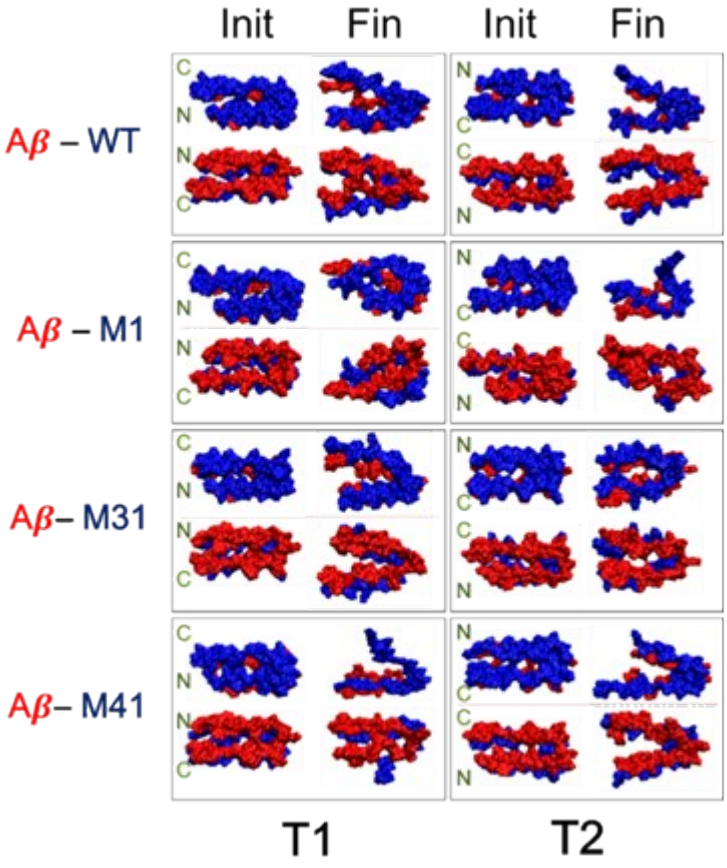

Fig S1. Different configurations at initial steps and final steps for each models are represented after the stabilizing simulations were performed. Blue layers are representing the Tau proteins and red layers represent Aβ proteins.

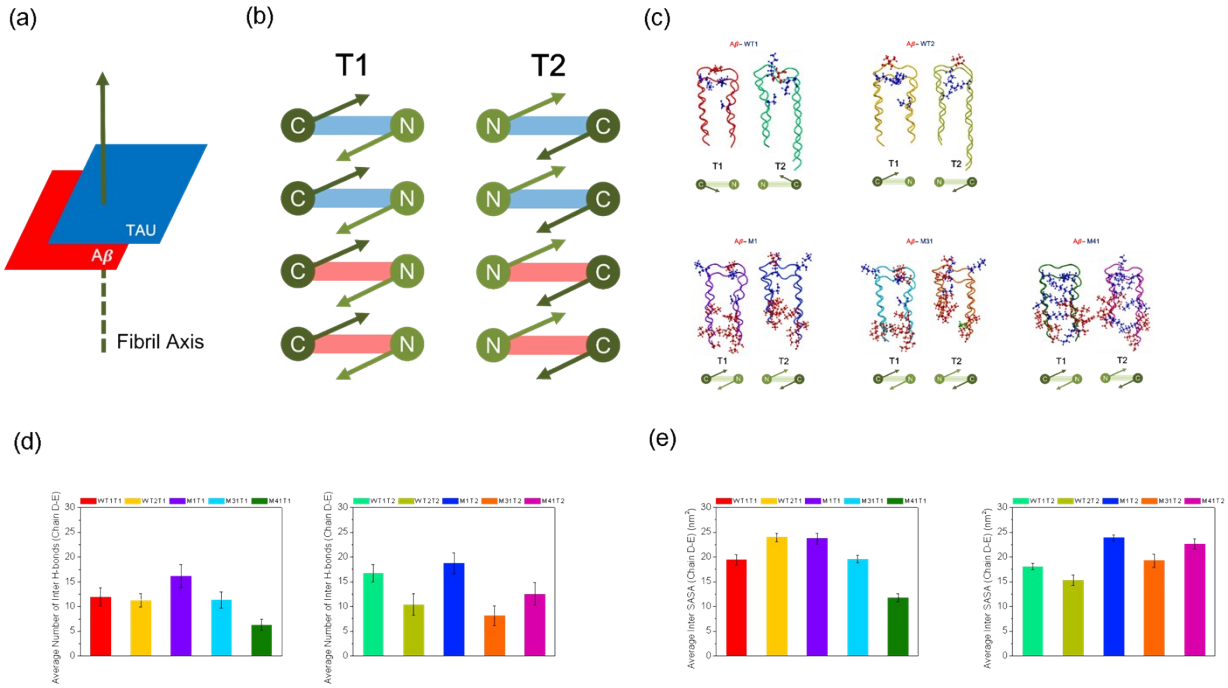

Fig S2. Different arrangement of oligomers which are stacked with the different directions. (a) A scheme of oligomer. Arrows show directions of tilted interior residues. (b) shows interacting features between Tau (blue) and Aβ (red) layers. (c) Inter and inter salt-bridge interactions between Aβ and tau mixtures for each model. (d) Average number of hydrogen bonds between Aβ and tau mixture interfaces from last 5 ns. (e) Average SASA between Aβ and tau mixture interfaces from last 5 ns.

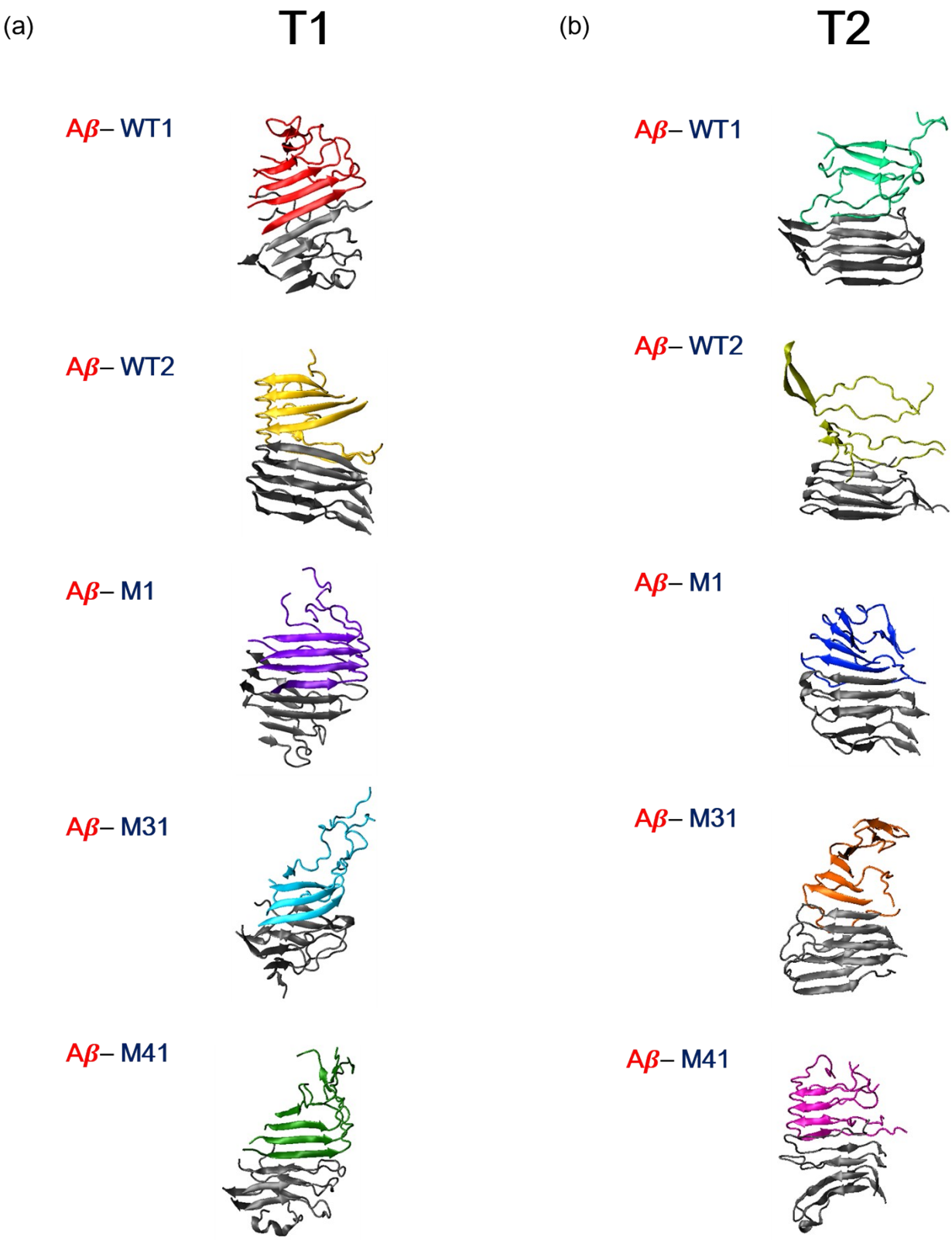

Fig S3. Final configurations for mixtures after the 20ns MD simulations were performed. (a) binding type 1 models are represented. (b) binding type 2 models are described

Hydrophobic	A	V	I	L	M	F	Y	W
Hydrophilic	R	H	K	D	E			
Uncharged	S	T	N	Q				
Special cases	C	U	G	P				

ABETA	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	ResID
ABETA	I	O	I	O	I	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T1
WT1	I	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	I	O	I	O	I	O	I	O	I	
ABETA	I	O	I	O	I	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T2
WT1	I	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	I	O	I	O	I	O	I	O	I	
ABETA	I	O	I	O	I	O	I	O	O	O	O	I	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T1
WT2	I	O	I	O	I	O	I	O	I	O	O	I	O	O	O	I	O	I	O	I	O	I	O	I	O	I	
ABETA	I	O	I	O	I	O	I	O	O	O	O	I	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T2
WT2	I	O	I	O	I	O	I	O	I	O	O	I	O	O	O	I	O	I	O	I	O	I	O	I	O	I	
ABETA	I	O	I	O	I	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T1
M1	I	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	O	O	I	O	I	O	I	O		
ABETA	I	O	I	O	I	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	O	T2
M1	I	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	I	O	I	O	I	O	I	O		
ABETA	I	O	I	O	I	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	O	T1
M31	I	O	I	O	I	O	I	O	I	O	O	O	I	O	O	O	O	I	O	I	O	I	O	O	I	I	
ABETA	I	O	I	O	I	O	I	O	O	O	O	I	O	O	O	I	O	I	O	I	O	O	O	I	O	O	T2
M31	I	O	I	O	I	O	I	O	I	O	O	O	I	I	O	O	O	I	O	I	O	I	O	I	O	O	
ABETA	I	O	I	O	I	O	I	O	O	I	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	I	T1
M41	O	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	O	O	I	O	I	O	O	O	I	
ABETA	I	O	I	I	O	O	I	O	O	O	O	O	O	O	O	I	O	I	O	I	O	O	O	I	O	O	T2
M41	O	O	I	O	I	O	I	O	I	O	O	O	I	O	O	I	O	O	O	I	O	I	O	O	I	O	
TAU	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	ResID

Table S1. Interior and exterior residues are distinguished with their features. The feature of residues are categorized with 4 colors, which are red (hydrophobic residues), blue (hydrophilic residues), dark gray (uncharged residues) and green (special residues, such as Cysteine, Glycine and Proline).

Interaction Types	Color		Combination	
Hydrophobic-Hydrophobic				
Hydrophilic-Hydrophilic				
Hydrophobic-Special				
Hydrophilic-Special				
Hydrophobic-Hydrophilic				
Special-Special				
Hydrophobic-Uncharged				
Hydrophilic-Uncharged				
Uncharged-Uncharged				
Uncharged-Special				
Inside-Outside			I	O

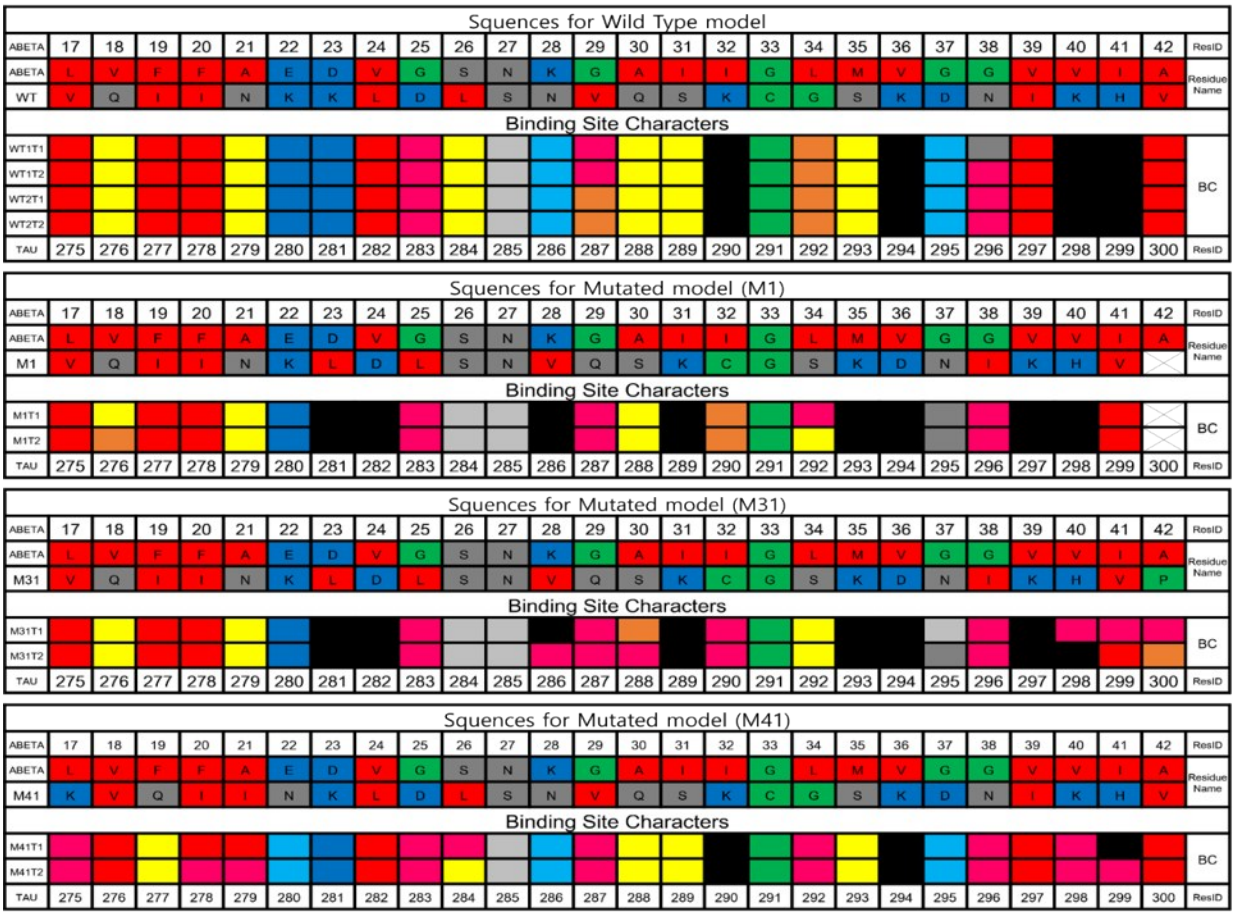

Table S2. The features of binding regions are analyzed with the table. Each colors represents types of interactions.