Supporting Information for:

Probing early stage of Prion Protein (PrP) aggregation with atomistic molecular dynamics simulations

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Methods

The box for the molecular dynamics simulations is prepared as follow: 18 miniPrPs (β-rich H2H3-Ov PrP^{Sc}) are placed on a grid (3 x 3 x 2) with random orientations (Figure SI-1). The distance among each miniPrPs in every direction is initially fixed at 3 nm. The box is then solvated with SPC waters[1] to obtain an orthorhombic Bravais lattice having edge lengths of 14.5 nm, 14 nm and 10 nm respectively. This leads to a box cell containing approximately 200000 atoms (Figure SI-1). 18 Na+ have been added to neutralize the total charge. The Gromos53a6 force field[2] and the Gromacs package[3] have been chosen for running the molecular dynamics simulations. Cys182 and Cys217 have been connected with a disulphide bond because this is the case in the ovine prion proteins[4]. The PME method has been used for the calculation of the electrostatic contributions to the non-bonded interactions[5]. The equilibration phase consisted in raising the temperature from 50 K to 300 K with steps of 50 K having each a simulation time of 50 ps. The final structure of the equilibration phase has been used as the initial structure for the production phase. Starting from the equilibrated structure we have run 11 replicas with different initial velocities. The v-rescale thermostat algorithm[6] with a τ_t=0.1 ps at 300 K and the isotropic Parrinello-Rahman barostat algorithm[7] with τ_p=0.1 ps and P=1 atm have been used in the production phase that lasted 200 ns. The total cumulative simulation time among the 11 replicas is therefore 2.2 μs saving 1 structure every 5 ps. The analysis of secondary structure elements has been performed with the DSSP package[8]. The most present residues in the interaction between miniPrPs have been identified with POPS[9]. The solvation properties of miniPrPs have been investigating using our in-house method[10;11].

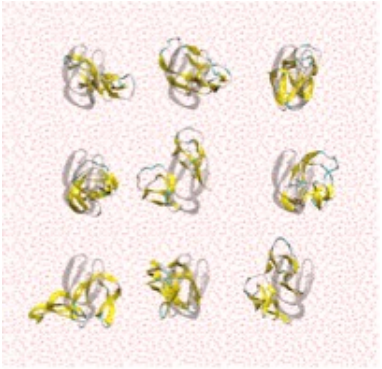

Figure 1: Simulation box: 18 miniPrPs (β-rich H2H3-Ov PrP^{Sc}) placed on a grid (3 x 3 x 2) with distances among them in every direction initially fixed at 3 nm, random orientations and solvated with 63668 water molecules.

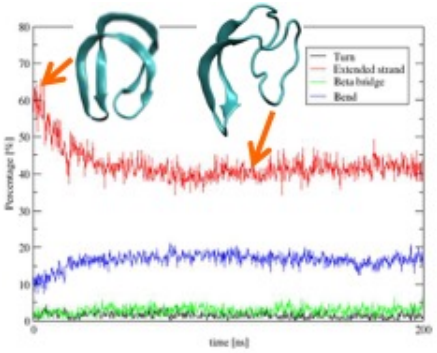

Figure 2: Evolution of the secondary structure elements of the miniPrPs during the aggregation process as calculated with DSSP. The percentage has been calculated counting the ratio between the number of residues of all the miniPrPs being in a specific secondary structure element and the total number of residues.

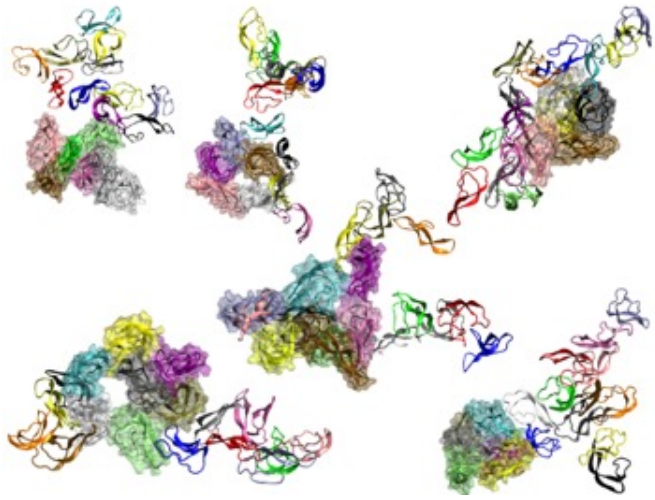

Figure 3: Final complexes for the replicas 5, 6, 7, 8, 9 and 10 with the miniPrPs belonging to the core represented with an opaque surface.

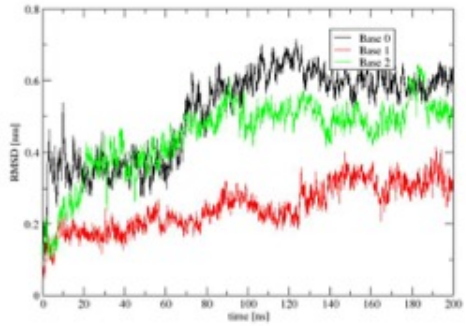

Figure 4: Root Mean Square Deviation (RMSD) of the simulated bases respect to the starting structure.

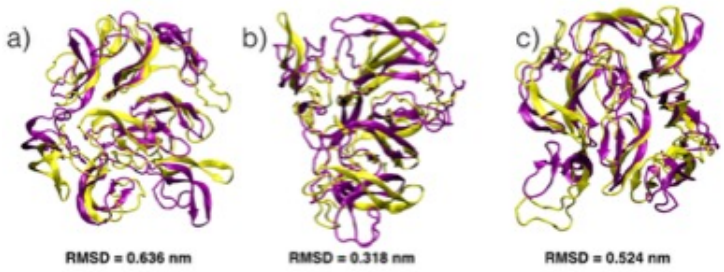

Figure 5: Superimposition of the first (purple) and last (yellow) structure from the simulation of the bases: (a) base of the replica 0, (b) base of the replica 1 and (c) base of the replica 2.

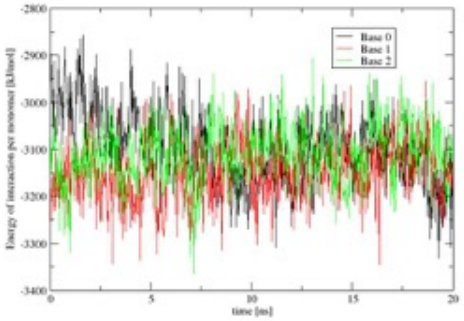

Figure 6: Energy of interaction per miniPrPs within the bases for the last 20 ns of simulation.

Table 1: a) Ranking order of the 15 most present residues in interaction between the miniPrPs of the bases. b) Ranking order of the 15 most present residues in interaction between the miniPrPs of the branches.

a		b	
Res	%	Res	%
LYS 197	7.2	LYS 197	7.2
THR 195	4.5	LYS 207	4.9
ARG 211	4.5	GLN 215	4.7
LYS 188	4.4	LYS 188	4.6
LYS 207	4.1	ASN 184	4.5
MET 209	4.1	THR 195	3.8
HIS 190	4.0	ARG 211	3.8
ASN 184	4.0	MET 209	3.8
THR 196	3.8	MET 216	3.7
ASN 200	3.7	ASN 200	3.5
GLN 215	3.6	CYS 217	3.4
MET 216	3.2	HIS 190	3.4
THR 202	3.1	THR 196	3.2
THR 186	2.8	CYS 182	3.2
GLN 189	2.7	VAL 183	3.0

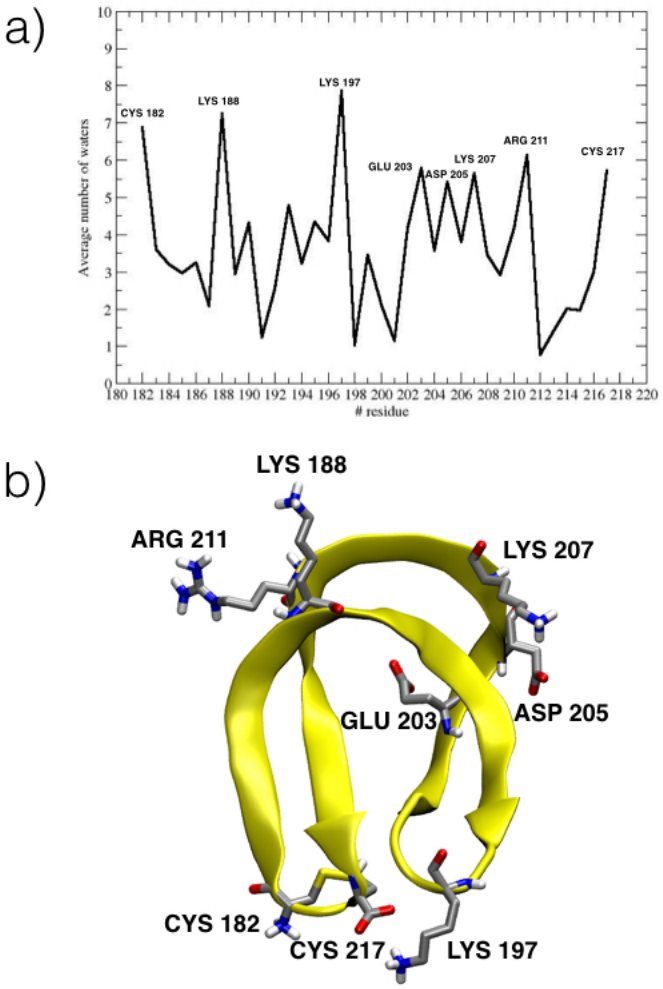

Figure 7: Solvation properties of the final complexes. a) Average number of waters visiting each residues; b) Rank of the first eight residues that, on average, are visited by a higher number of water molecules.

Figure 8: Two movies are available for the reader to watch the aggregation process as obtained with the atomistic molecular dynamics. The miniPrPs belonging to the core represented with an opaque surface.

References

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