Supplementary Materials for The Energy Landscapes of a Mechanical Prion and their Implications for the Molecular Mechanism of Long-Term Memory

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This PDF file includes:

Details of the Materials and Methods

Description of the AWSEM force field

AWSEM is a predictive coarse-grained protein folding force field. The Hamiltonian is summarized in Eq.1. It consists of a backbone term,$V_{backbone}$, which restricts the chain to having polypeptide like conformations and is mostly sequence independent. The burial term, V_{burial}, attempts to sort each residue into its preferred burial environment - exposed, partially buried or completely buried. The contact term, $V_{contact}$, consists of a direct contact interaction and a water or protein mediated interaction[1] (Papoian et al., 2004). Depending on the instantaneous local density of the interacting residue pair, this terms accounts for the water and protein mediated interactions, respectively. The hydrogen bonding term, V_{HB}, consists of two interactions which favor β-hydrogen bonding geometries. The first one is sequence independent, long range, and favors cooperative formation of β-sheets, and the other is sequence dependent and depends sensitively on the distance and relative orientation of the interacting groups. Finally, the local-in-sequence interactions ($3 \leq |i-j| \leq 9$, i, j are residue indices) are governed by the associative fragment memory term, V_{FM}. In this study, the associative memory term is determined by 20 so-called fragment memories for each segment CPEB-Q sequence with length 9. These fragment memories are sequence homologs found using sequence alignment tool PSI-BLAST searching through the PDB database[2, 3] (Bryngelson et al., 1995; Davtyan et al., 2012).

$$V_{total} = V_{backbone} + V_{contact} + V_{burial} + V_{HB} + V_{FM} \tag{1}$$

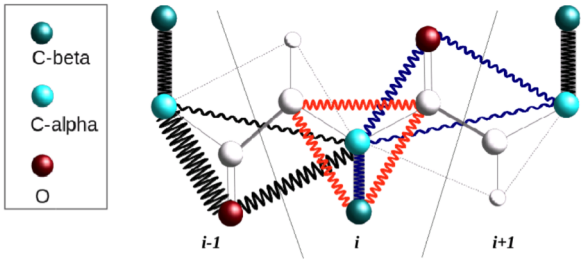

Figure S1: The connectivity of the chain is maintained by a combination of harmonic potentials. The distances constrained by $V_{contact}$ are shown as dashed lines and the distances constrained by V_{chain} are shown as springs.

Description of the All-atom simulations

We used the CHARMM27 parameter set for the protein molecules and salt ions and the CHARMM TIP3P model for water in a cubic box ($5.10nm^3$) containing around 6000 water molecules. The calculation were done with the GROMACS software package. The annealing simulations are performed from 300K to 500K within 200 ns.

Supplementary figures

Tuning the secondary structural parameters in AWSEM for polyQ sequence

The secondary structural weight in AWSEM is associated with a bias for the α-helix conformation and another bias for β-strand hydrogen bond formation. The strength of these terms for normal globular proteins usually is determined from secondary structure prediction. However, in the case of intrinsic disordered proteins like polyQ, secondary structure prediction may not be adequate, but requires a separately tuned secondary structure bias. To test these values, we compare the stability of secondary structures with different secondary structural bias weights, and compare the stability from the AWSEM simulations with the statistics from an All-Atom simulations. When the secondary structural bias is 0.7 for helical structures in AWSEM, α-helix and β-strands have similar stability as is also seen in the All-Atom simulations. This set of secondary structure coefficients was then used in AWSEM simulations for the Q-rich proteins in this study.

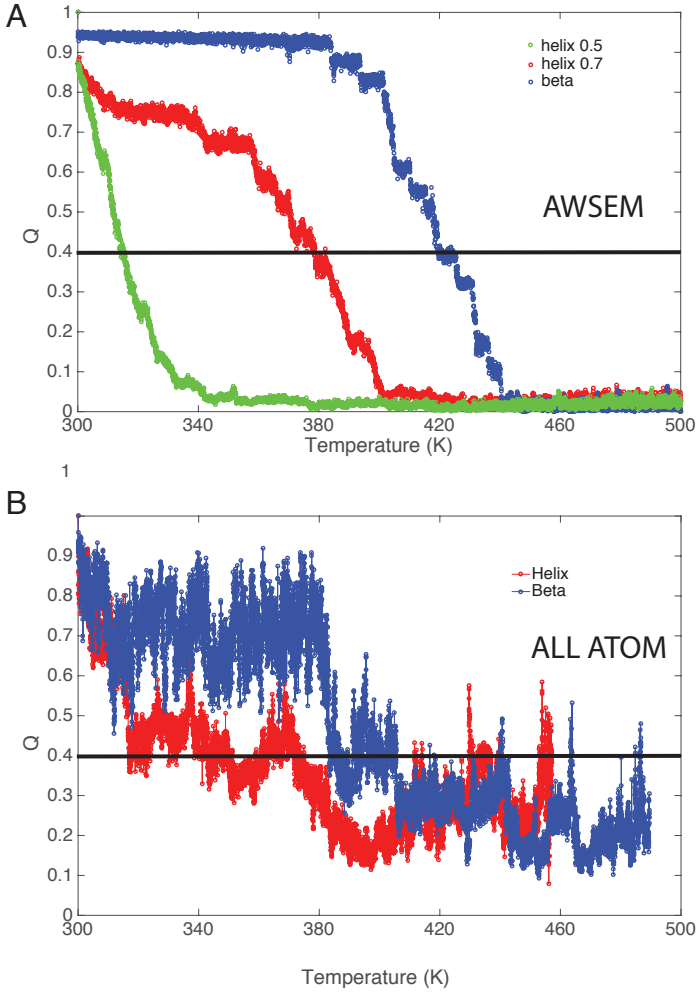

Figure S2: The stability of different secondary structures in AWSEM is in harmony with those from All-Atom simulation. (A): Thermal stability of α-helix and β-strands in AWSEM simulation using Q as a measurement; the blue curve is the melting curve starting from β-strand hairpin, while the red and green are melting curves starting from α-helices. The melting temperature for β-strands is around 420K, and is around 380K for helices. (B): Thermal stability of α-helix and β-strands in All-Atom simulation using Q as a measurement; the blue curve starts with a β-hairpin, while the red starts with α-helices. The melting temperature for β-strands is around 410K, and around 370K for the helices.

Frustration analysis of oligomers with low molecular weight

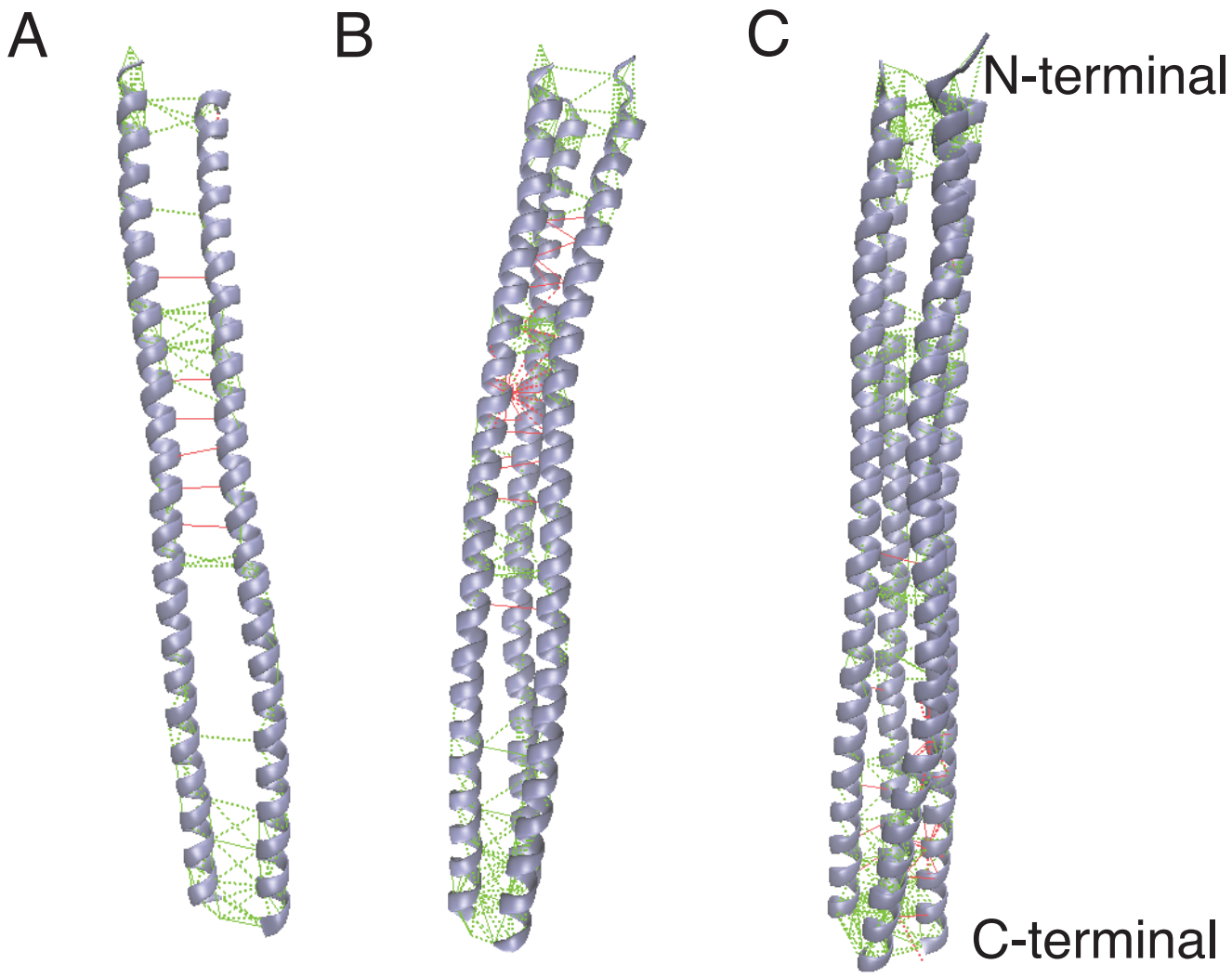

Figure S3: The frustratograms show calculated the configurational frustration of the CPEB-Q dimer, trimer and tetramer. Minimally frustrated contacts are shown in green and highly frustrated contacts are shown in red. As indicated from analysis, the three oligomeric species are overall only weakly frustrated, and most of the interactions are minimally frustrated[4](Ferreiro et al., 2014). Taken together, the coiled-coil oligomers are stable.

Stability of different oligomers

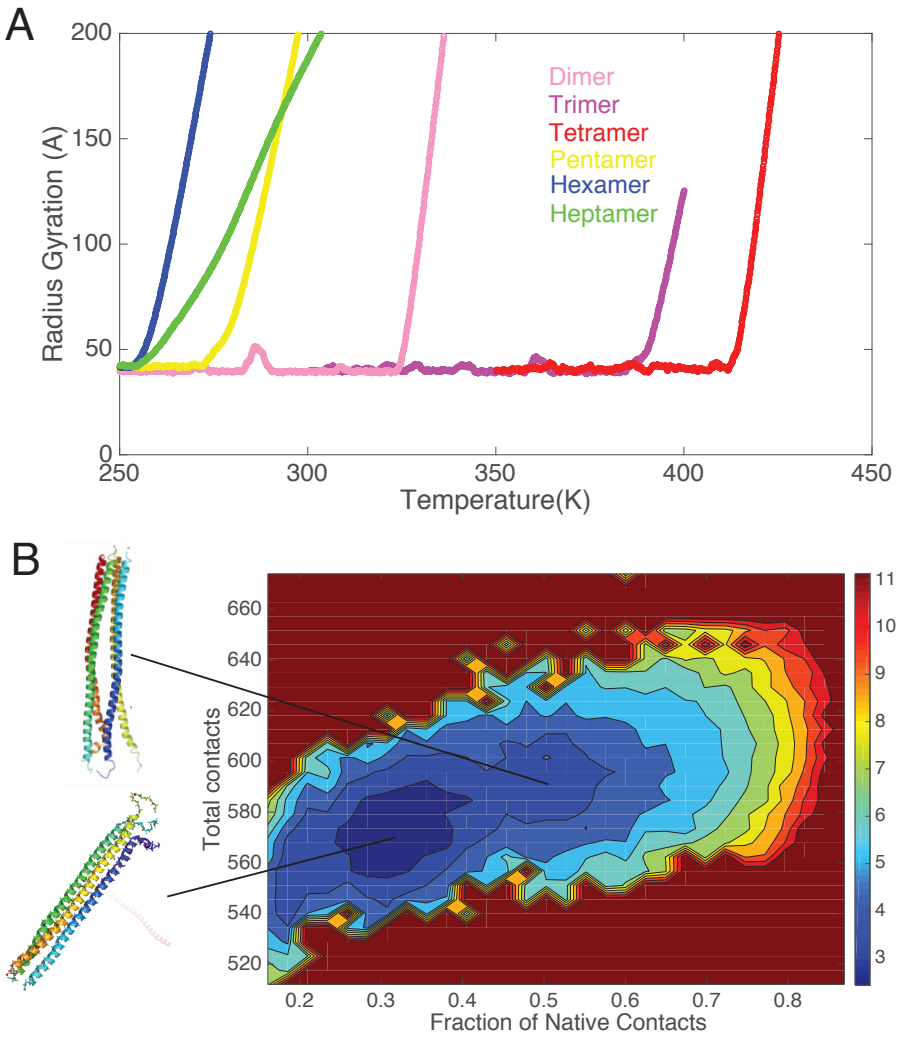

Figure S4: Simulated melting and free energy profile quantify the relative stability of different coiled-coil oligomers. (A): Simulated melting of different oligomers reveals their thermal stability. The radius of gyration is plotted as a function of temperature for each oligomer in different colors. (B): 2D Free energy landscape as a function of fraction of native contacts (Qw) and the total number of total contacts is shown.

Simulated structures of higher oligomers

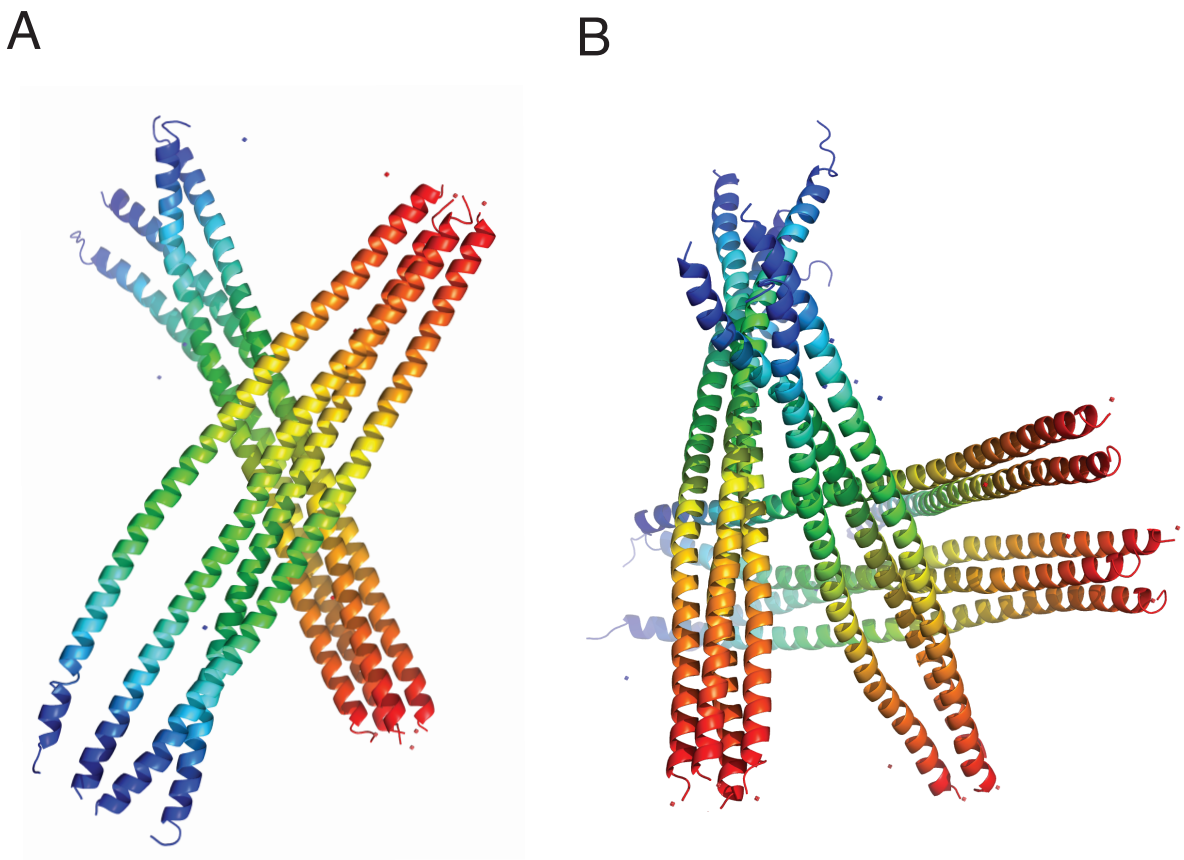

Figure S5: Simulated oligomeric structures of the CPEB-Q with higher molecular weight. A: In this structure, the antiparallel orientation of an octameric CPEB-Q is evident; The N-terminal of CPEB-Q is colored orange, and the C-terminal blue. B: The structure of a decamer of CPEB-Q; The N-terminal of CPEB-Q is colored orange, and the C-terminal blue.

Structural transition dynamics from α-helix to β-strands in a trimer

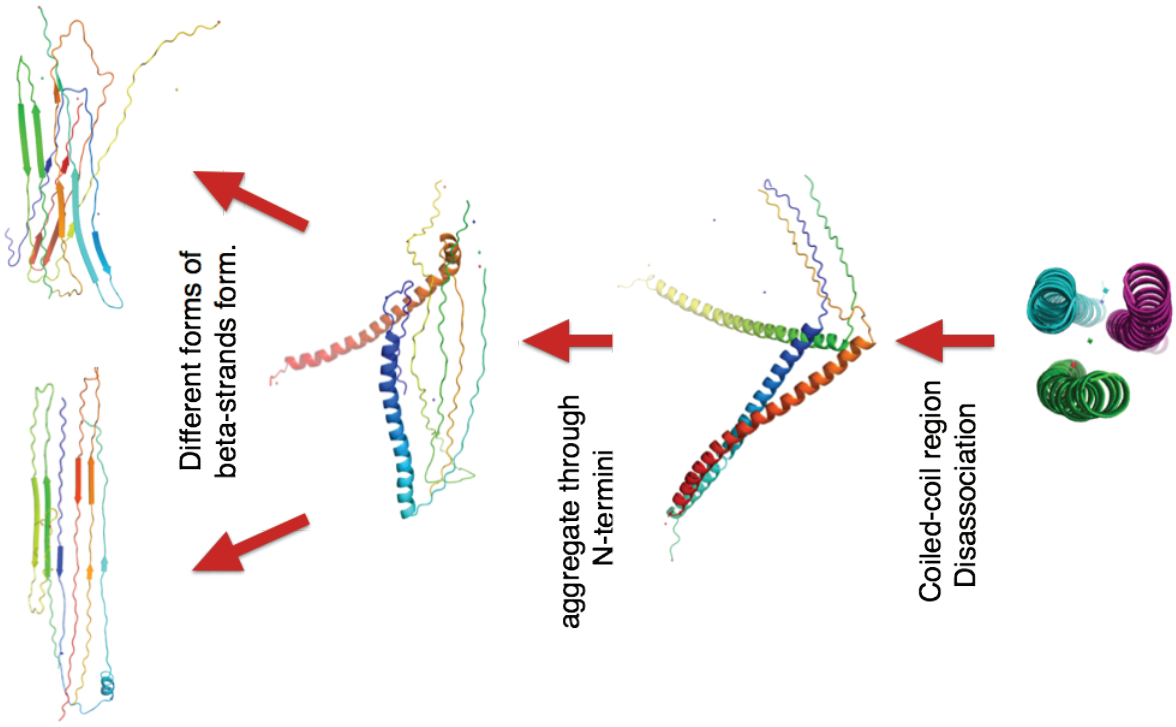

Figure S6: Structural transition dynamics of the CPEB-Q trimer. The N-terminal amyloid forming region undergoes the structural transition first and mediates structural transition for the remainder of the chains.

References

[1] G. A. Papoian, J. Ulander, M. P. Eastwood, Z. Luthey-Schulten, and P. G. Wolynes, "Water in protein structure prediction," *Proceedings of the National Academy of Sciences*, vol. 101, pp. 3352–3357, Mar. 2004.

[2] J. D. Bryngelson, J. N. Onuchic, N. D. Socci, and P. G. Wolynes, "Funnels, pathways, and the energy landscape of protein folding: a synthesis," *Proteins*, vol. 21, pp. 167–195, Mar. 1995.

[3] A. Davtyan, N. P. Schafer, W. Zheng, C. Clementi, P. G. Wolynes, and G. A. Papoian, "AWSEM-MD: Protein Structure Prediction Using Coarse-Grained Physical Potentials and Bioinformatically Based Local Structure Biasing," *The Journal of Physical Chemistry B*, vol. 116, pp. 8494–8503, July 2012.

[4] D. U. Ferreiro, E. A. Komives, and P. G. Wolynes, "Frustration in biomolecules," *Quarterly Reviews of Biophysics*, vol. 47, pp. 285–363, Nov. 2014.