

Studies of Stability of H1 Helix in the Prion Protein

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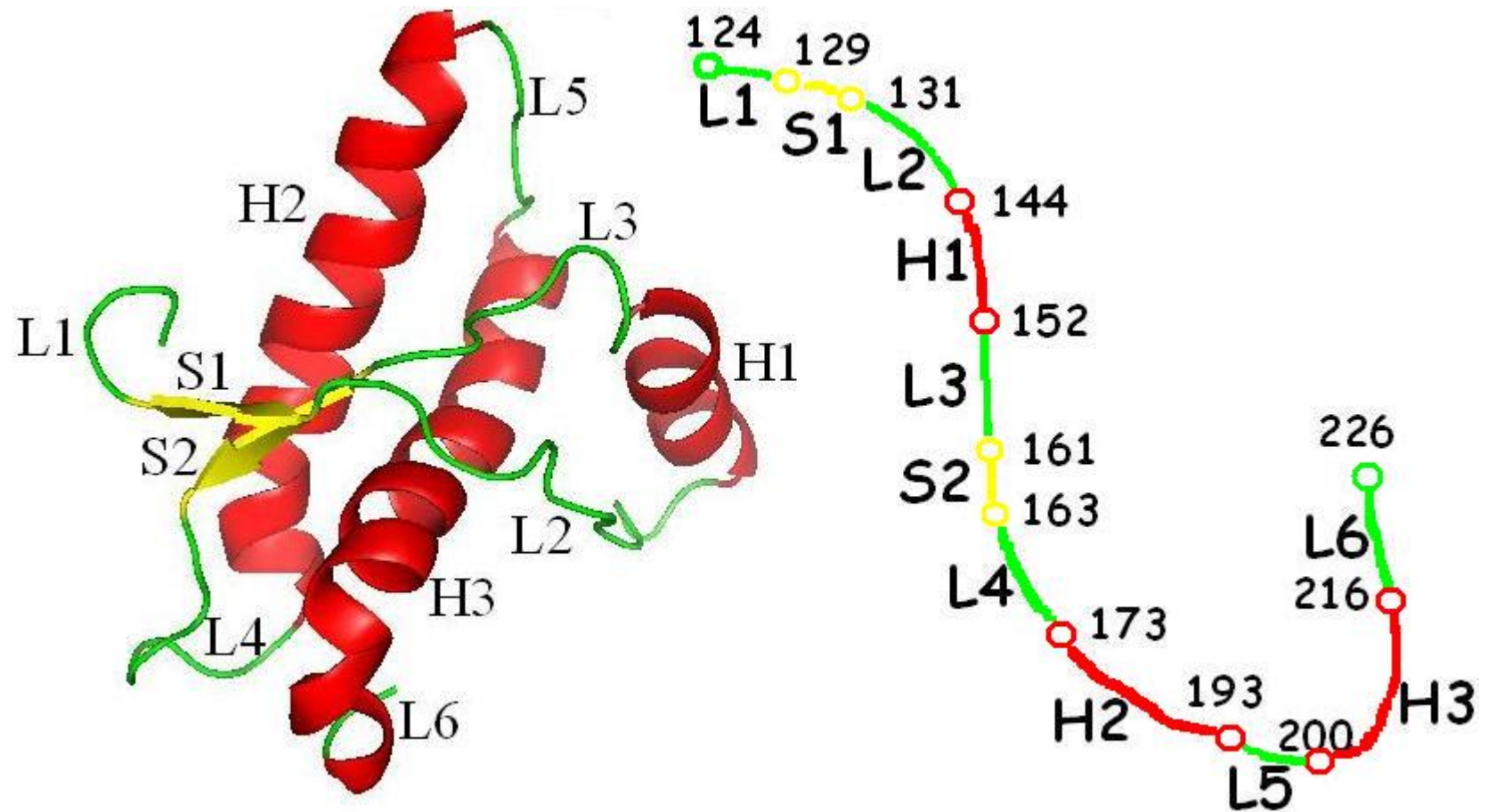
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Misfolding of prion protein is cause of an encephalopathy

- Misfolding of prion protein from its normal conformation (PrPC) to its disease form (PrPSc) is the cause of a number of human and animal encephalopathies: CJD in human, BSE in cow, Scrapie in sheep.
- Misfolding is believed to be conversion of a helix in PrPC into β -sheet.
- PrPSc aggregates to β -amyloid (starch-like fiber)

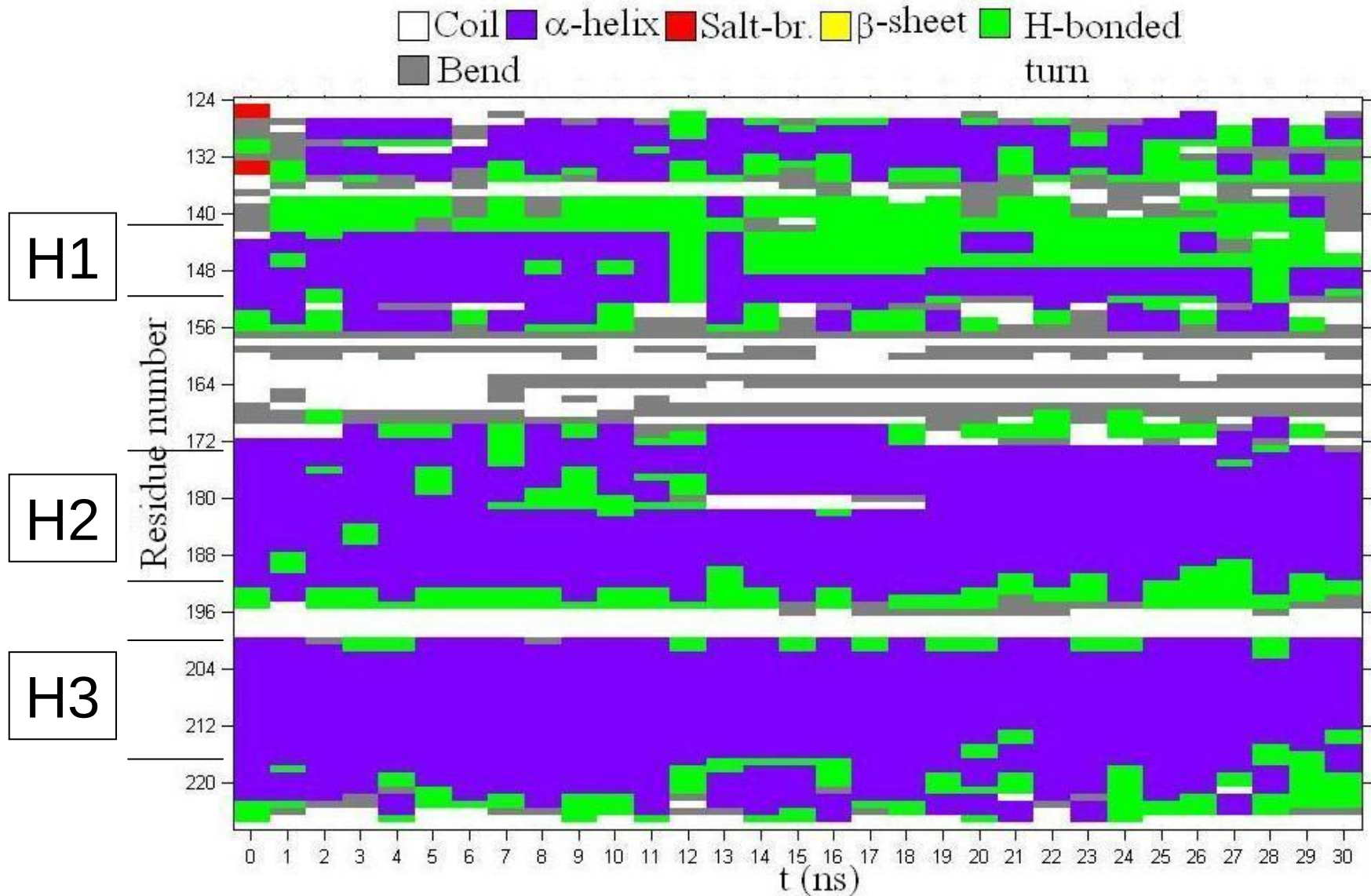
Secondary and tertiary structure of PrPC



Some premises

- H2-H3 appear to stable in experimental and theoretical studies
- Unraveling of H1 appears to be key to PrPC to PrPSc conversion
- Presence of PrPSc in the vicinity of PrPC appears to induce conversion of latter
- Template-assistance model: PrPC to PrPSc conversion induced by catalytic interaction between PrPC and PrPSc

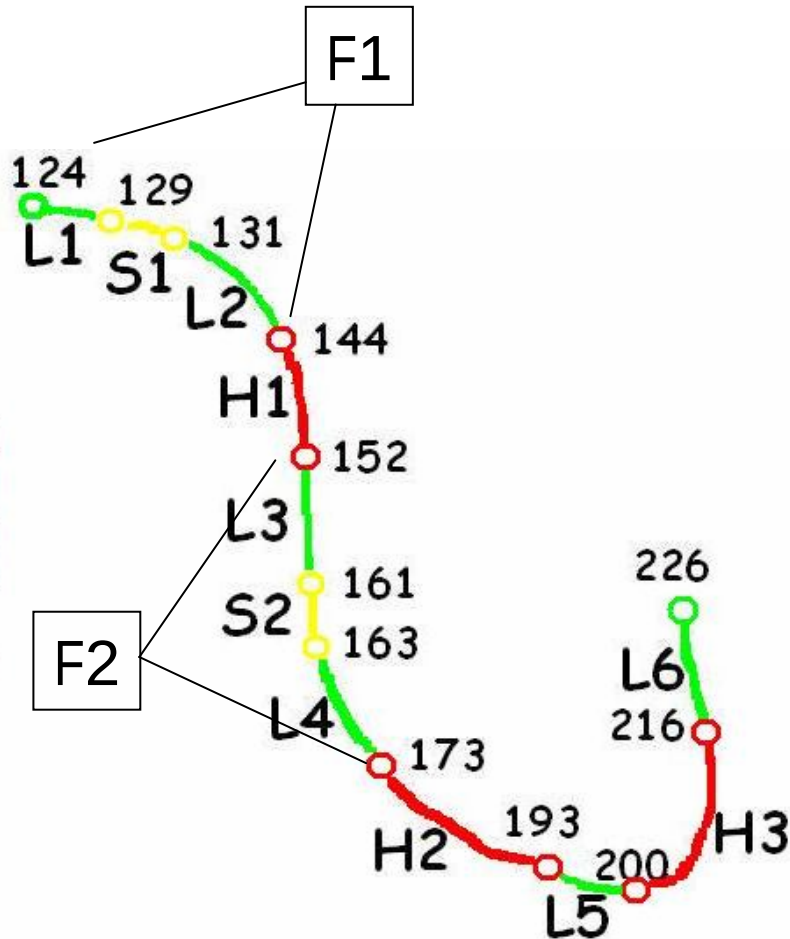
H2 and H3 are structurally robust; H1 less so



Goal of this study

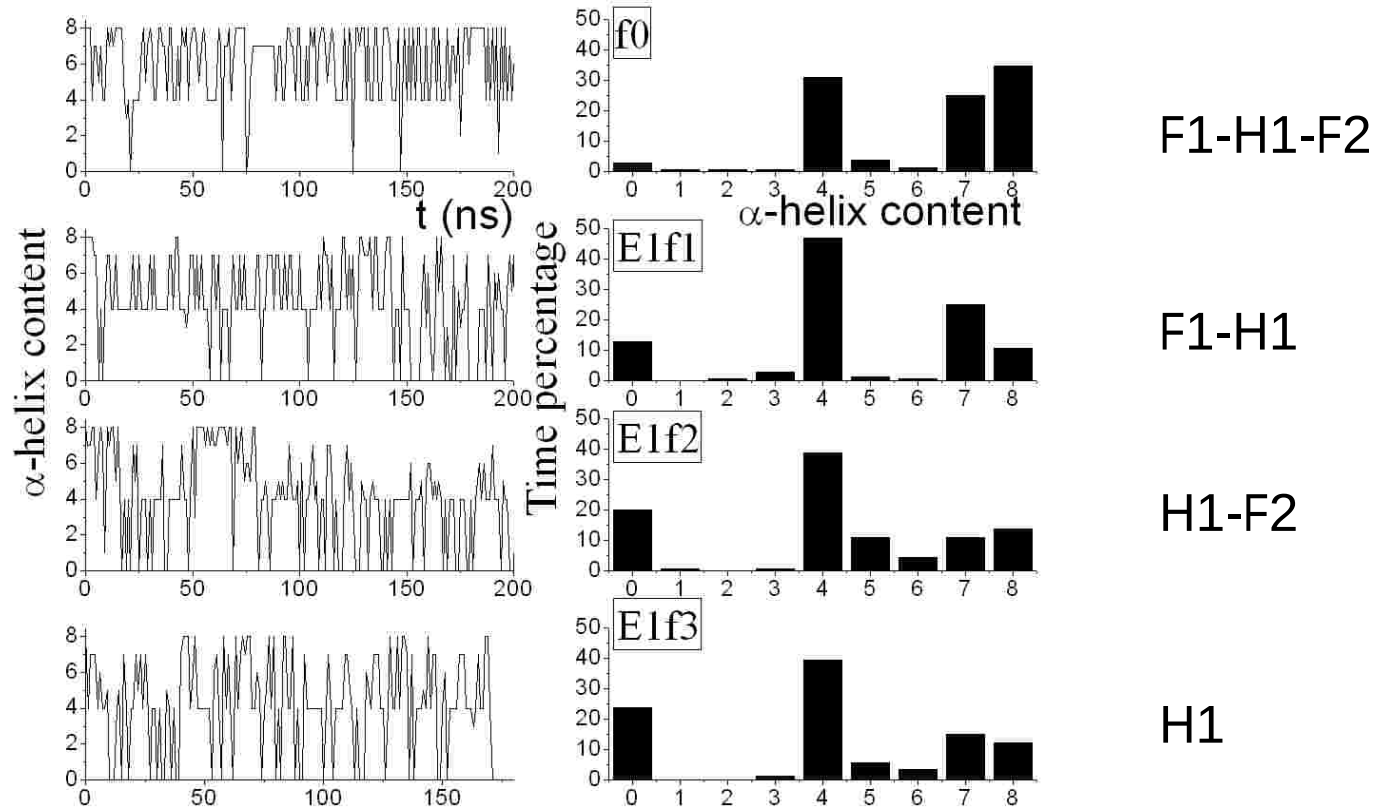
- Verify a simplified version of template-assistance model by MD simulation
 - 3D structure of PrPSc not yet known
- Emulate the effect of would-be catalytic interaction by artificially induced changes in PrPC
- Examine H1 stability under such changes and identify factors that most affect the integrity of H1

Stability of H1: dependence on existence of flank



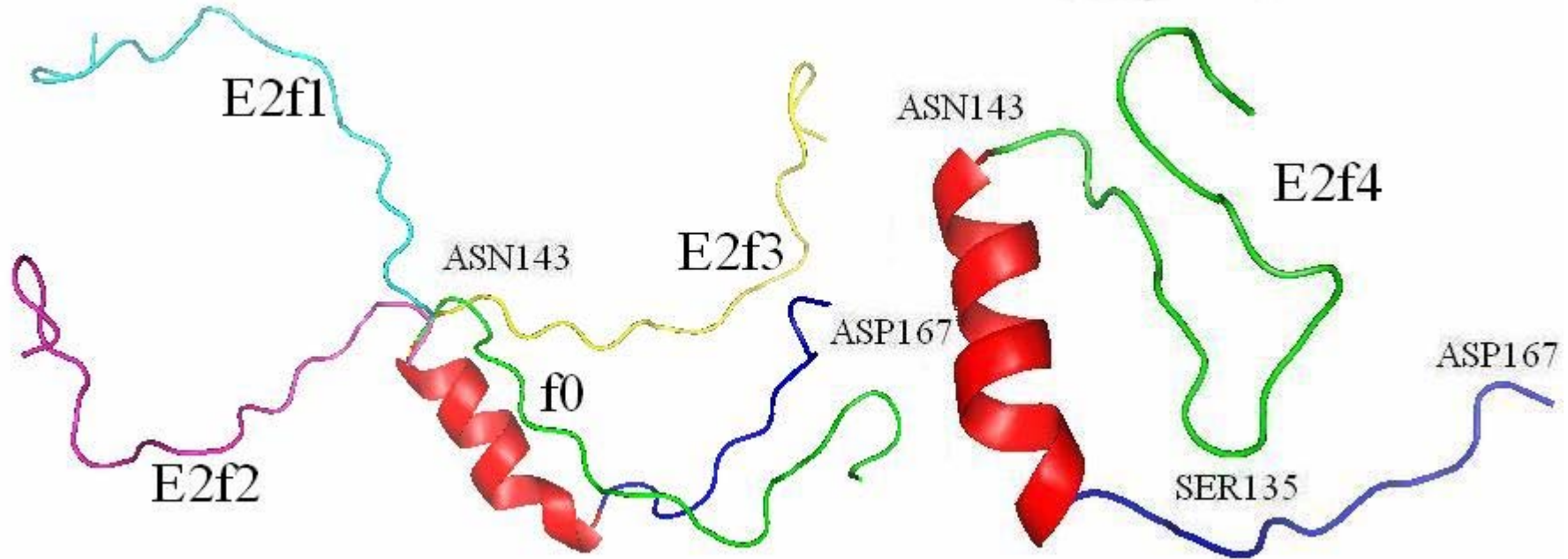
- H2 to L6 excluded from simulation
- $F1 = L1 + S1 + L2$
- $F2 = L3 + S2 + L4$
- Simulations (AMBER 8 ff03)
 - E1f1: H1+F1
 - E1f2: H1+F2
 - E1f3: H1

F1 is crucial to stability of H1



Simulation	Zero turn (%)	One turn (%)	Two turns (%)
f0	3	32	60
E1f1	13	50	35
E1f2	20	38	25
E1f3	23	40	27

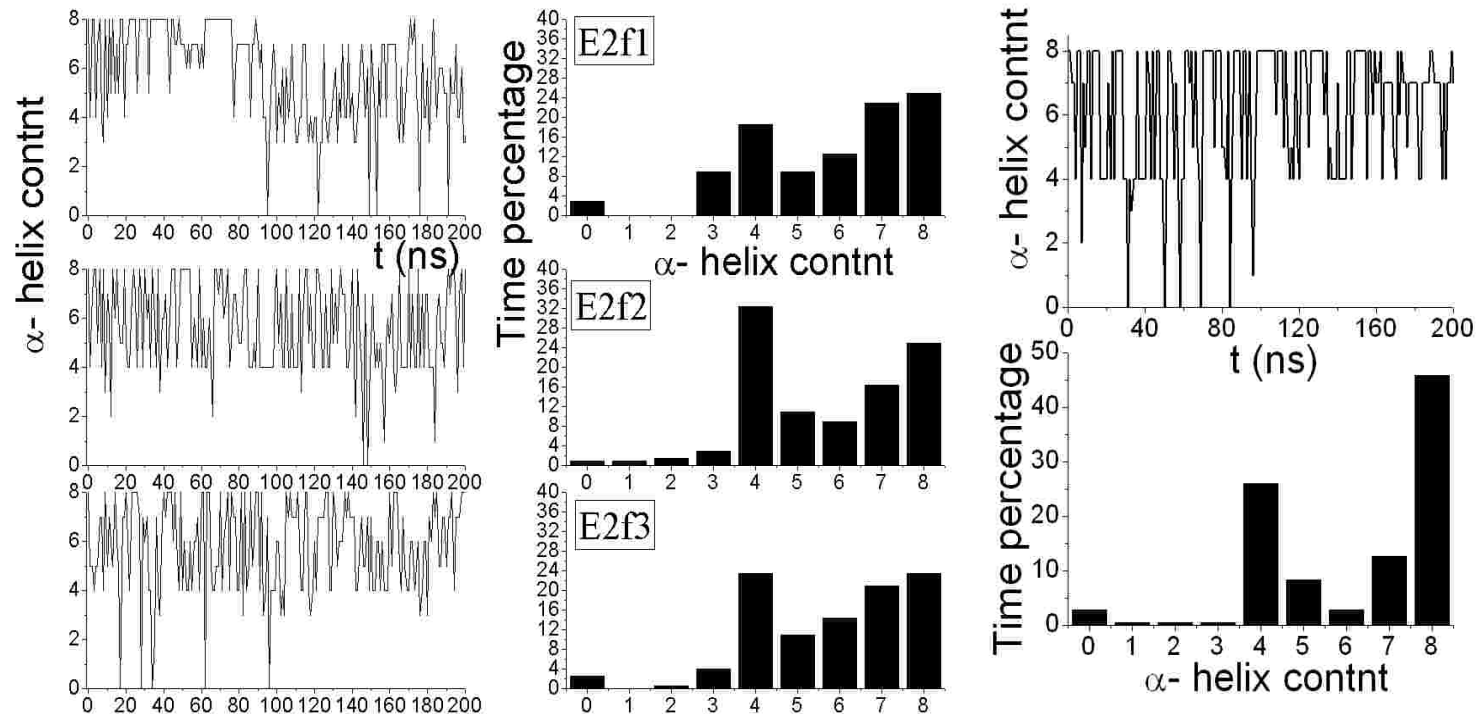
Stability of H1: dependence on Conformation of F1



E2f1-f3: change relative orientation of H1 and F1(change dihedral angle of Asn143)

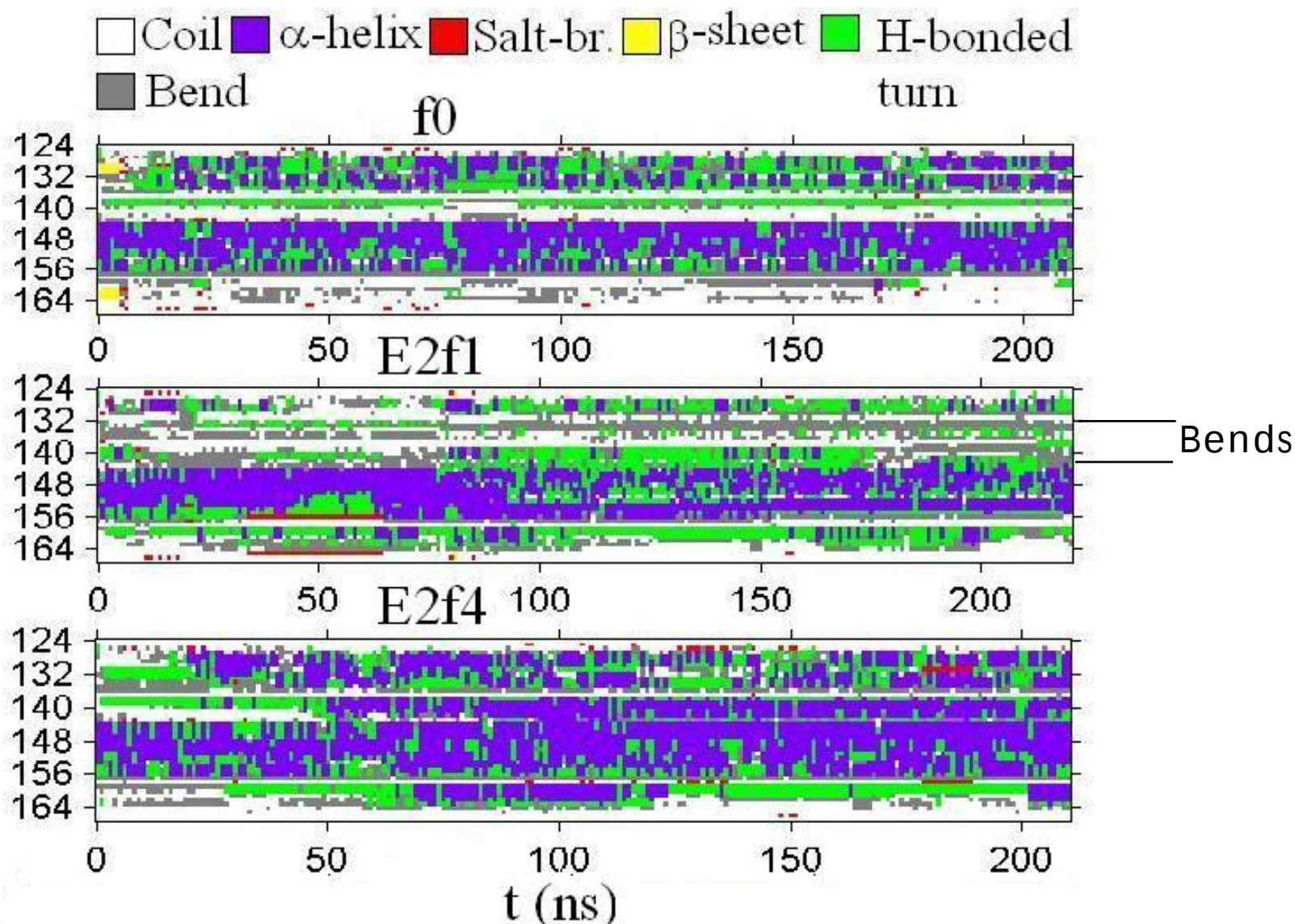
E2f4: change internal conformation of F1 (dihedral angles of Ser135)

Relative F1-H1 orientation has larger effect than F1 conformation on stability of H1

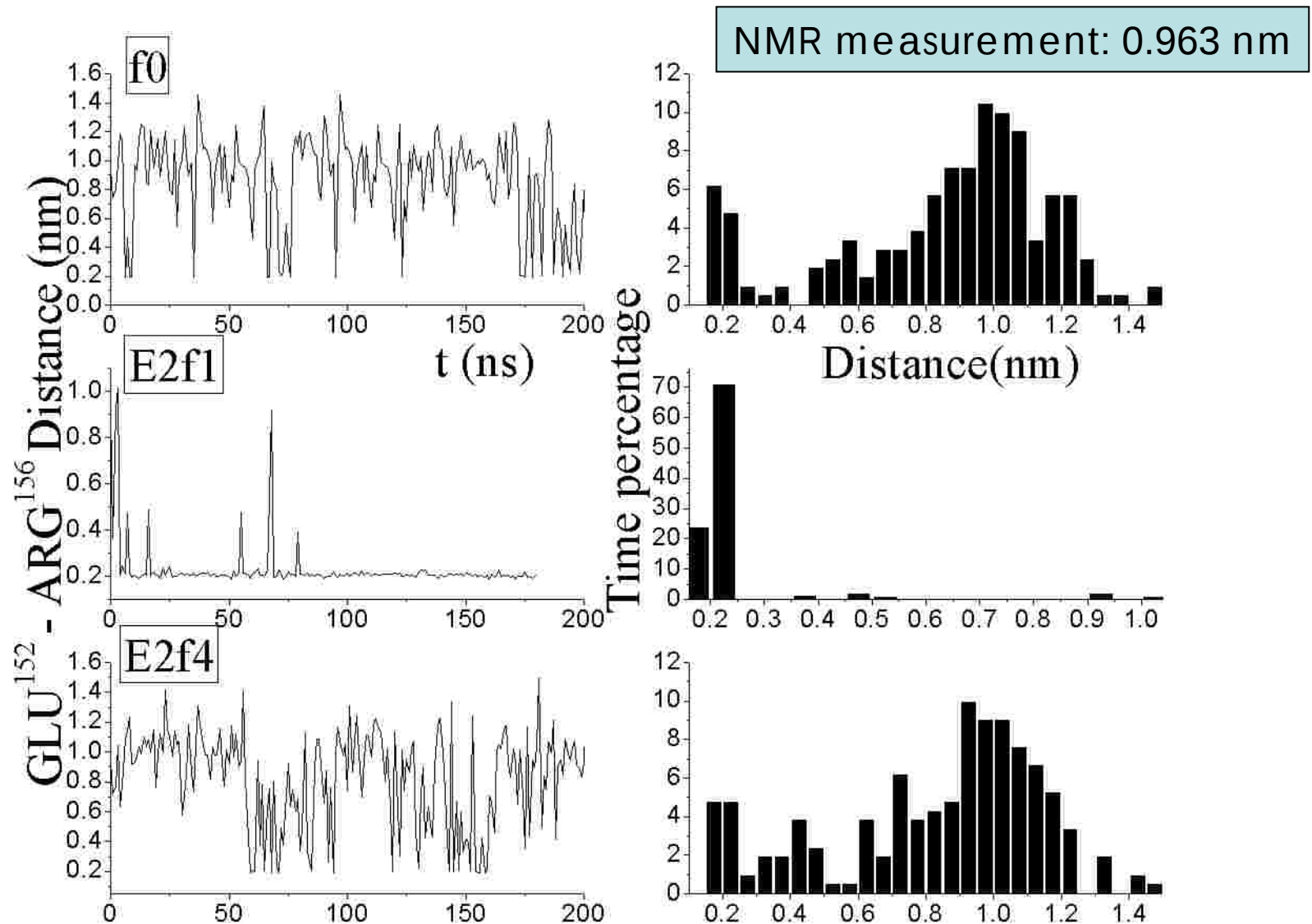


Simulation	Zero turn (%)	One turn (%)	Two turns (%)
f0	3	32	60
E1f2	20	38	25
E2f1	25	25	38
E2f2	3	40	36
E2f3	12	36	30
E2f4	3	27	59

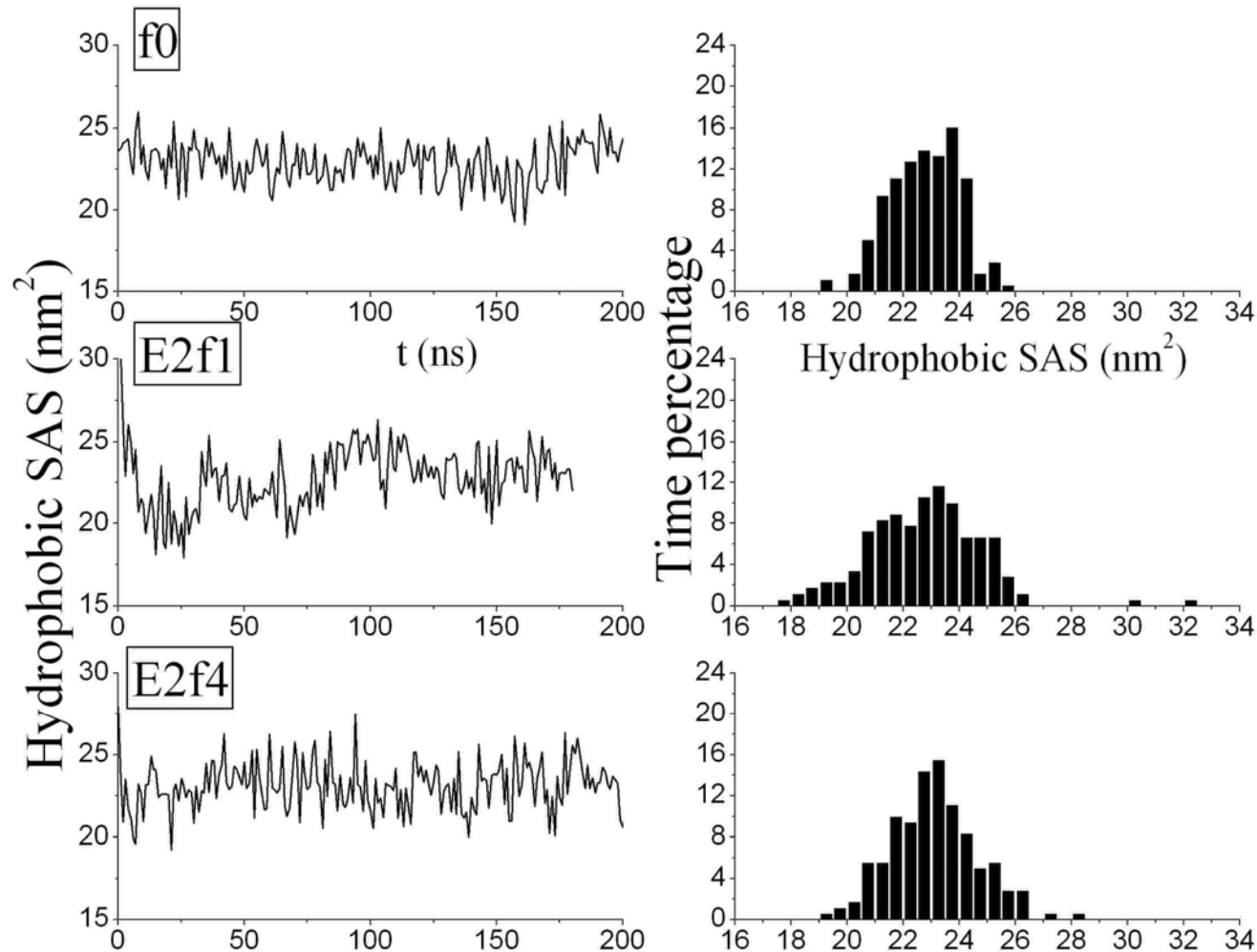
With changed F1-H1 orientation (E2f1) bends appear at residues 126-144



With changed F1-H1 orientation (E2f1) span of salt-bridge Glu152-Arg156 abnormal



Hydrophobicity does not appear to appear to play major role in unfolding of H1 – Surface accessible area (SAS) unchanged



Summary

- Simulations of PrPC by AMBER 8 (force field ff03) conform with other experiment and MD results
- Stability of H1 does not depend on H2 and H3
- The flank L1-S1-L2 (F1) is crucial to integrity of H1; flank L3-S2-L4 less so
- Relative F1-H1 angle crucial to integrity of H1; internal conformation of F1 not so

Thank you!