Interpreting a point mutation using NMR-derived structural ensembles



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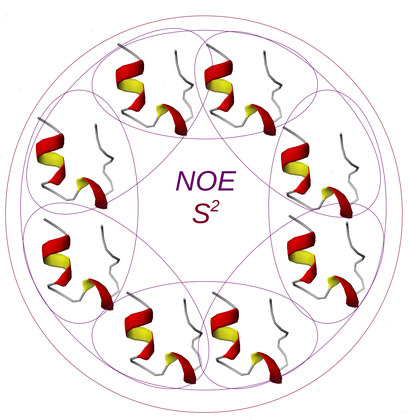
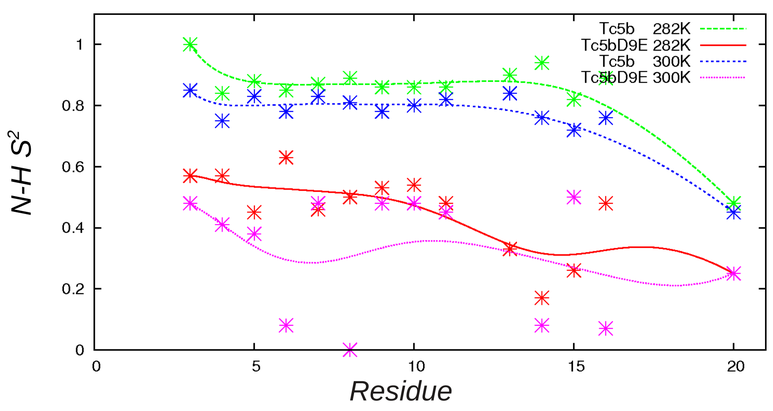
Calculations



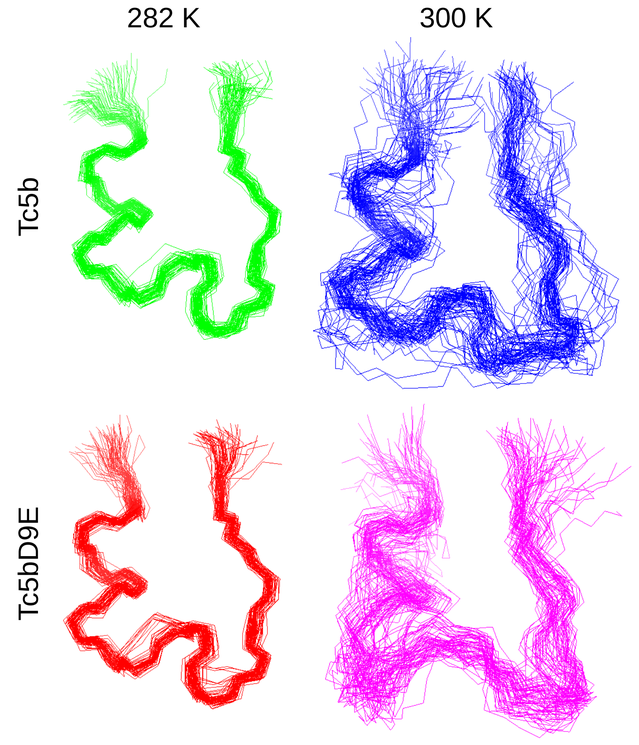
- MUMO method [1]
- As implemented in GROMACS 3.3.1 [2,3]

Experimental data

Tc5b 313 NOE (83 long-range) 174 NOE (29 long-range)
Tc5bD9E 435 NOE (141 long-range) 254 NOE (68 long-range)



Calculated ensembles (64 conformers each)



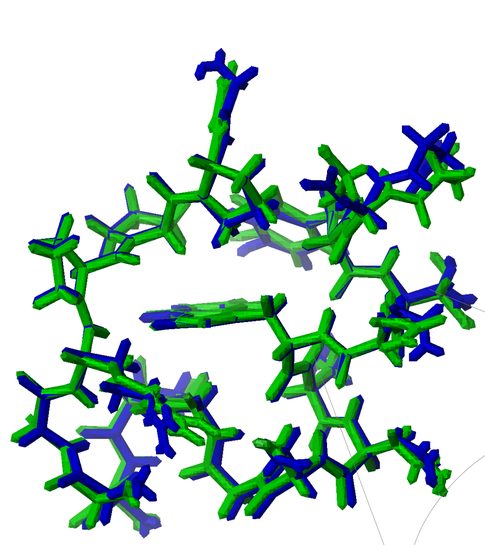
Conclusions

- Atomic-level picture of dynamics
- Pronounced differences at higher temperature
- D9E mutation decreases helicity
- D9E mutation affects contacts between N- and C-terminus

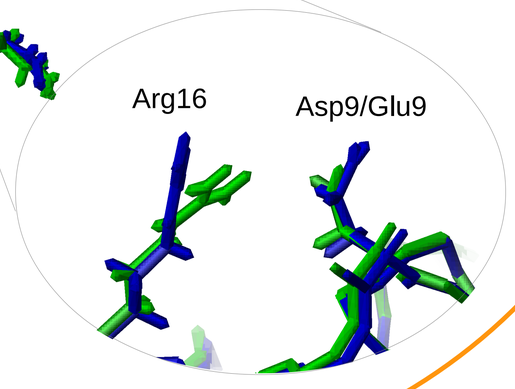
Plans & ongoing research

- Larger ensembles to address correlated motions
- Efforts to make ensembles more complient with experimental data
- Analyse the changes in residue-residue contacts in more detail

- Tc5b: 20-residue Trp-cage structure
- Trp6 + Tyr3: ”hydrophobic core”
- D9E mutation perturbs the Asp9-Arg16 salt bridge



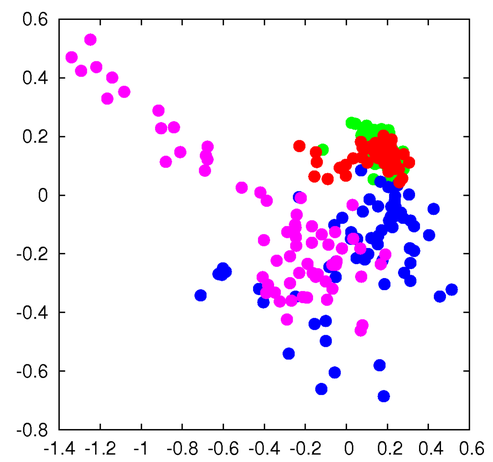
Tc5b
Tc5bD9E
Average NMR structures at 282K: minute changes only



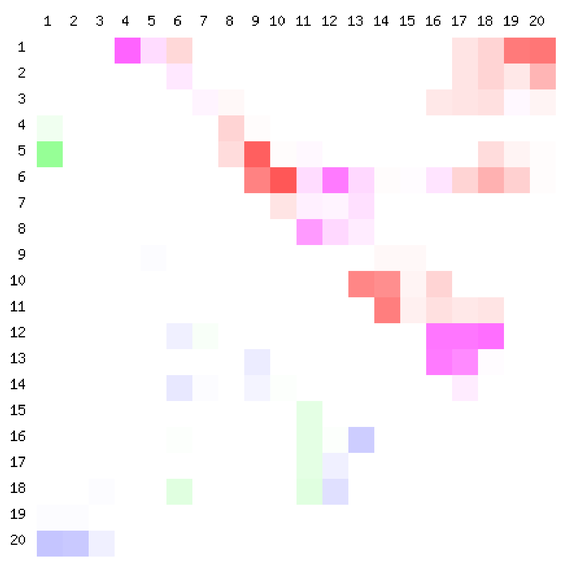
Correspondence to experimental data [4]

S^2: 0,96	S^2: 0,97
δHα: 0,91	δHα: 0,68
S^2: 0,91	S^2: 0,96
δHα: 0,85	δHα: 0,50

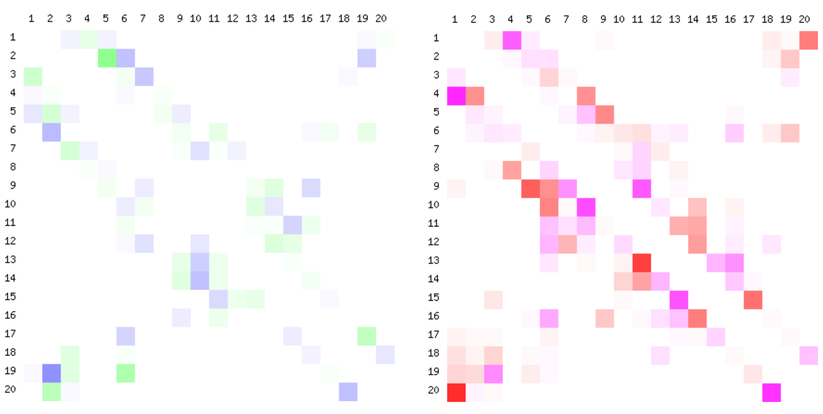
Principal component analysis



Residue-residue contacts

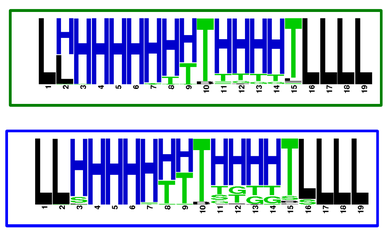


Tc5b 282K 300K
Tc5bD9E 282K 300K



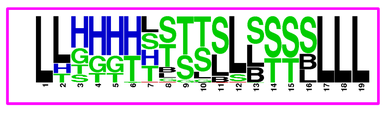
Secondary structure

Tc5b 282K



Tc5bD9E 282K

Tc5b 300K



Tc5bD9E 300K

Changes in close (≤ 7.5 Å) Cα-Cα contacts

Changes in closest residue-residue contacts

References

[1] Richter, B., Gsponer, J., Várnai, P., Salvatella, X. and Vendruscolo, M. (2007) The MUMO (minimal under-restraining minimal over-restraining) method for the determination of native state ensembles of proteins. J. Biomol. NMR 37, 117–135.
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[4] Ángyán, A.F., Szappanos, B, Perczel, A., Gáspári, Z. (2010) CoNSEnsX: an ensemble view of protein strucures and NMR-derived experimental data. BMC Struct. Biol. 10:39.

Acknowledgements

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