

Predicting the conformational preferences of proteins using a physics-based free energy method

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Preparation of input models for chameleon sequences

We prepared computer generated models in both α and β conformations for all five chameleon sequences mentioned in the main text. The crystallographic structure of GA95 and GB95 sequences have α and β fold respectively. To prepare the α and β fold for the GA95 sequence, we start with the crystallographic conformation of the native GA95 and GB95 sequences. We then remove the sidechains at three mutated positions in both folds and call the program SCWRL4¹ to generate the side chain conformations of the mutated residues and their neighbors. Followed by this step, we perform extensive molecular dynamics minimizations to remove any possible bad contact. This procedure was used to generate all α and β conformations for the five sequences that were used in the free energy calculation.

[Figure 1 about here.]

[Figure 2 about here.]

[Figure 3 about here.]

[Figure 4 about here.]

[Figure 5 about here.]

What can we say about low resolution models from CASP experiments?

In the main text, we discussed how well confinement method predicted preferences when the structures are not very far from the native. But the question remains how far from native can we go and still see that the method produces correct result. In this section we explored this question with models from the extracellular domain of the jumping translocation breakpoint protein (pdb id: 2KJX). Most of the groups could only generate low resolution models for this CASP9 target (id: T0531). In our comparison, we chose five models by the MUFOOLD-MD group, which was the best performing group for this target even though their best model had a GDT_TS value of only 44. The results presented in Figure S6 show: 1.) native is correctly identified as expected and 2.) Surprisingly there is a high level of correlation between the GDT ranking and the free energy ranking for model 1 and model 3, the other three structures with GDT_TS score less than 35 are ordered incorrectly. It is worth to note that models 2 and 3 have the same GDT and very different free energies, meaning that the actual ordering could change a lot². It is encouraging that at least the method can pick out the best model even though it is got a low GDT score: 44.

[Figure 6 about here.]

[Figure 7 about here.]

References

- [1] Krivov, G.G.; Shapovalov, M.V.; Dunbrack, RL Jr. Improved prediction of protein side-chain conformations with SCWRL4. *Proteins.* (2009) 77, 778-795.
- [2] Perez, A.; Yang, Z.; Bahar, I.; Dill, K.A.; MacCallum, J.L.; FlexE: Using Elastic Network Models to Compare Models of Protein Structure. *J. Chem. Theory Comput.*, 2012, 8, 3985-3991.

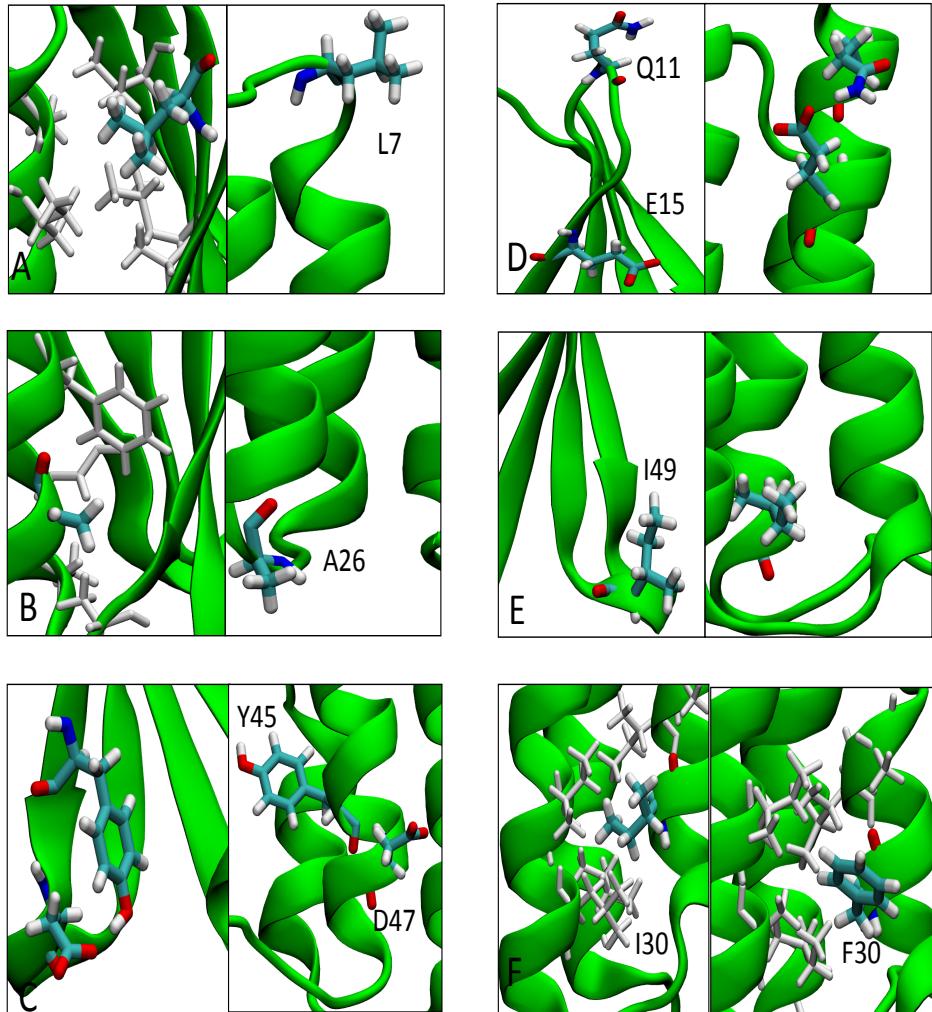


Figure S1: Per residue free energy calculations indicate significant differences of side chain orientation of key amino acid residues. These amino acid residues displace the free energy equilibrium to either β or α conformation. All figures in the left are in β conformation, whereas the right ones are in α conformation except in Figure (F) where both are in α conformation. Sidechains of hydrophobic residues L7 in (A) and A26 in (B) are oriented towards the protein interior in β conformation. In such conformation they have hydrophobic interactions with other hydrophobic residues colored in white. In α conformation these residues are exposed to the protein surface. (C) Y45 forms H-bond with D47 with GB95 sequence and β conformation. (D) Q11 and E15 forms a salt bridge in β conformation which is absent in the α conformation. (E) Hydrophobic I49 is exposed to the protein surface in β conformation, whereas in α conformation it is inside protein hydrophobic core. (F) Sidechain of I30 is inside the protein hydrophobic core as it has a smaller sidechain with GA95 sequence and α conformation. In contrast, Phe-30 with larger sidechain is exposed to the protein surface with GB95 sequence and β conformation.

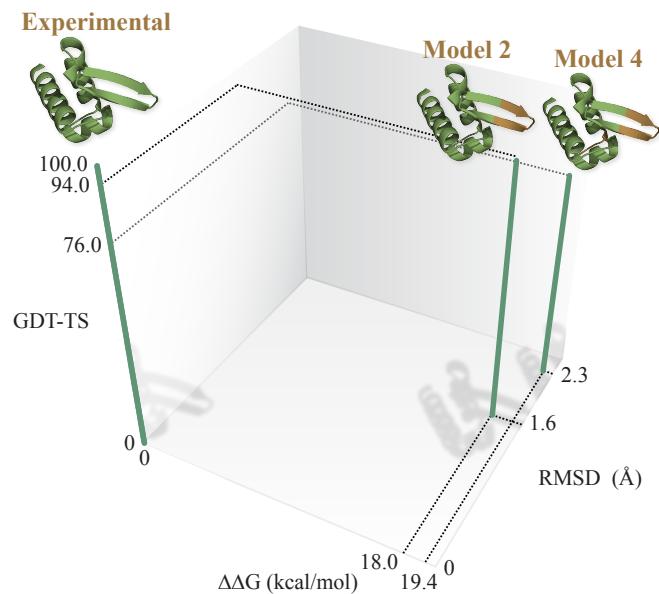


Figure S2: Native structure and two models (from group “Splicer”) for target T0560.

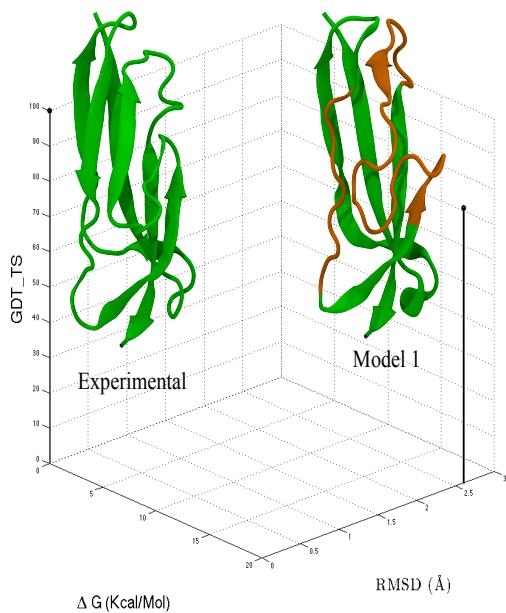


Figure S3: Native and best computer generated model structure of CASP Target T0569.

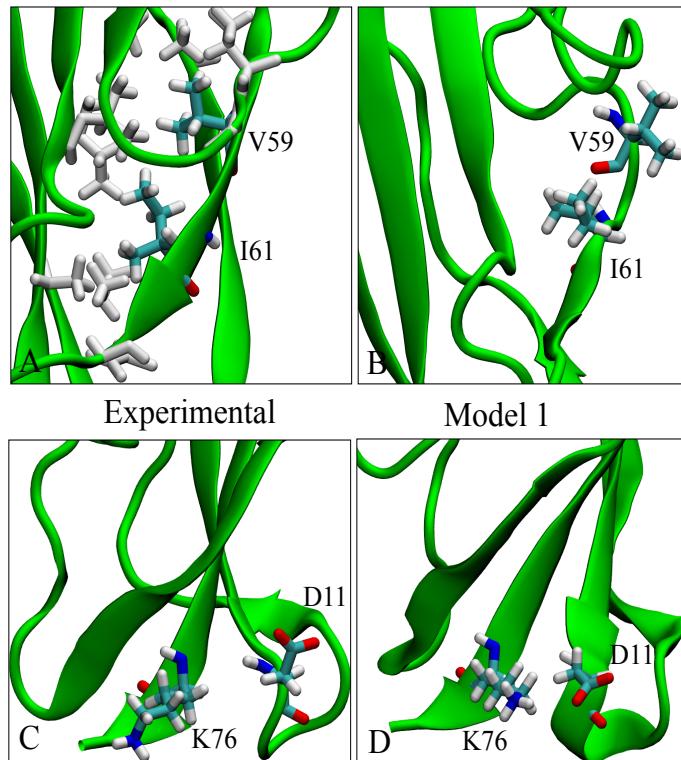


Figure S4: Key differences between the experimental structure and the computer generated models as indicated by the per residue free energy calculation. The side chains of hydrophobic residues, V59 and I61 are oriented towards the protein hydrophobic core in (A) , in (B) they are exposed to the surface. The beta sheet containing these residues is disordered in the generated model due to a salt bridge between K76 and D11 in (D) the computer generated structure, which is absent in the (C) native structure.

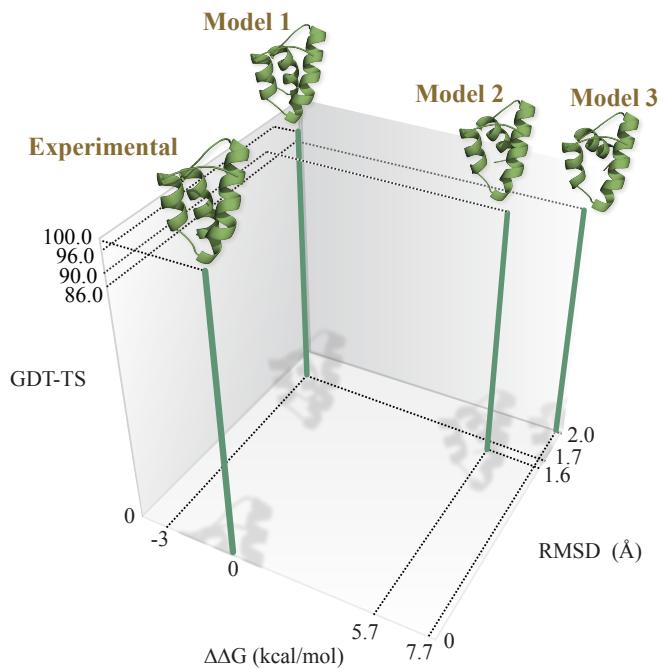


Figure S5: The free energy based ranking of the experimental and three predicted structures for an engineered protein (PDB ID: 2L09 and CASP code:T0538). Models 1,2 and 3 are from the group PconsR, Shell and FOLDIT respectively. In this case, one of the predicted structure was found to be more stable than the experimental structure.

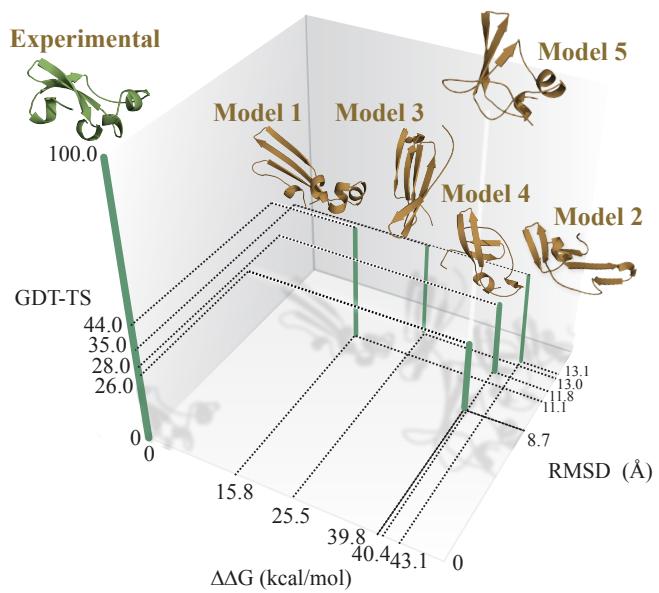


Figure S6: The native structure and 5 models of extracellular domain of the jumping translocation breakpoint protein (pdb id: 2KJX and the CASP code: T0531).

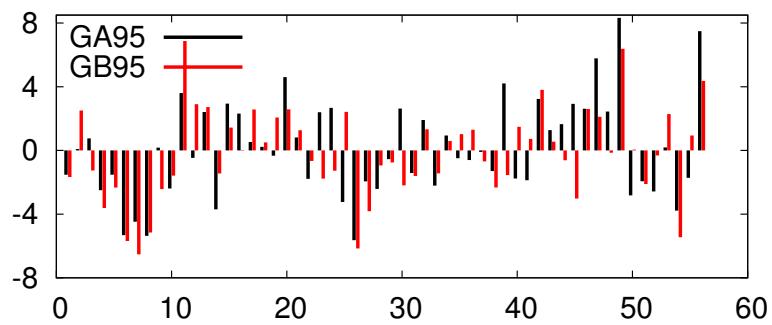


Figure S7: Per-residue difference free energies for the α and β conformations of the GA95 and GB95 sequences.