Modeling Ensembles of Transmembrane β-barrel Proteins

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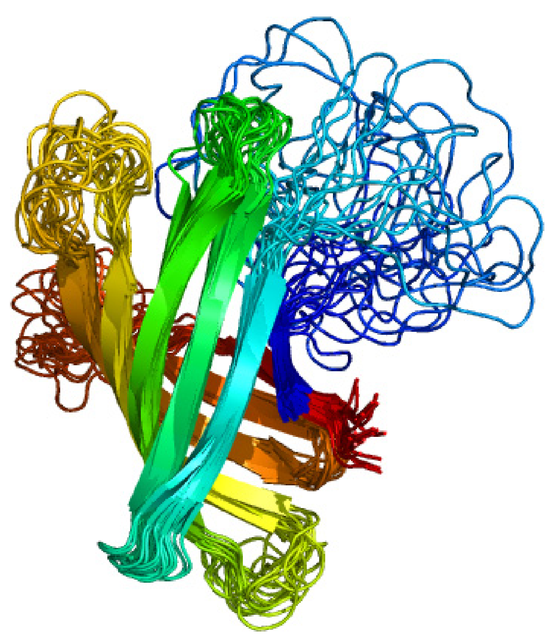
Motivations

Transmembrane β-barrel (TMB) proteins are embedded in the outer membrane of Gram-negative bacteria, mitochondria and chloroplasts. These proteins display a wide variety of functions and are relevant to various aspects of cell metabolism. In particular, outer-membrane proteins (omps) are used in active ion transport, passive nutrient intake, membrane anchors, membrane-bound enzymes, and defense against membrane-attack proteins.

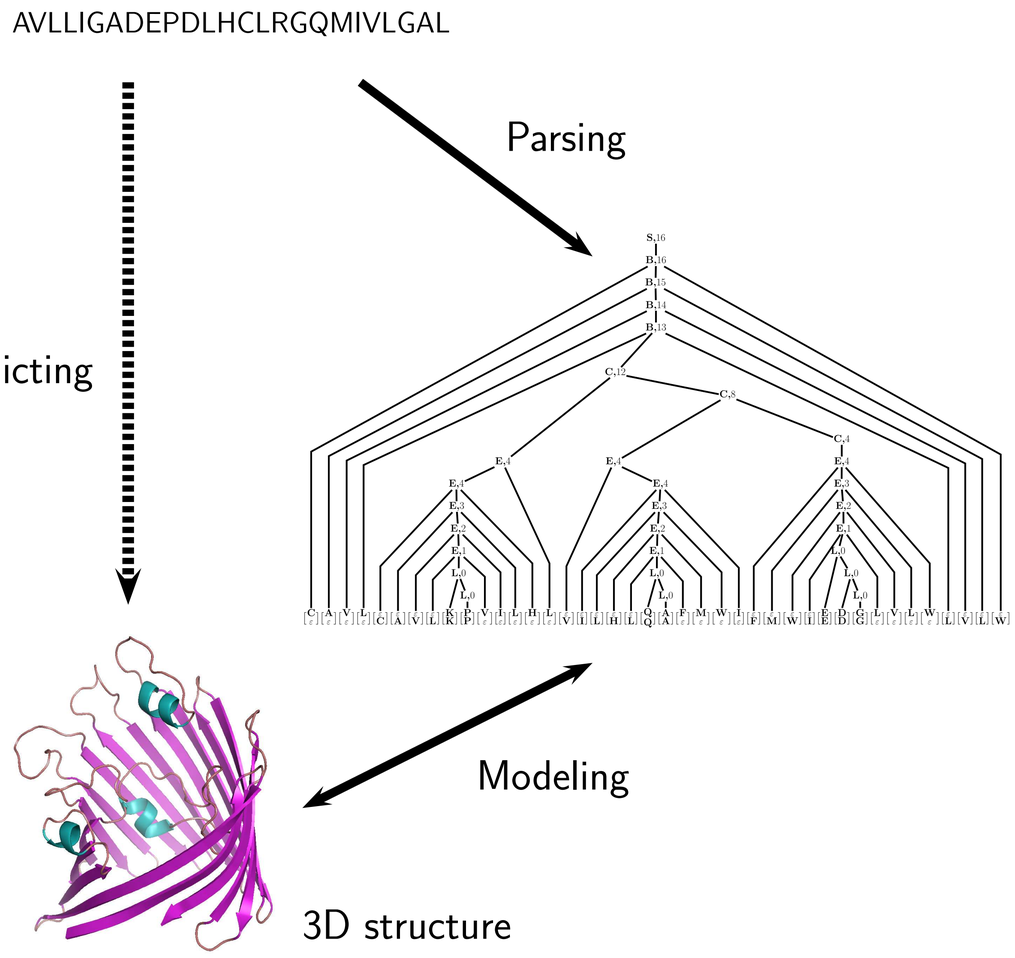
Current TMB structure prediction programs output only an optimal or near-optimal solutions and hence cannot reflect all folds that can be potentially adopted by a polypeptide. Inspired by previous work on RNA secondary structure [1], and expanding upon our previous transFold model [2], we move beyond the classical single structure prediction methods and introduce the first family of algorithms for investigating the set of all conformations present in the low energy ensemble by using the Boltzmann partition function.



Methods

Structure modeling

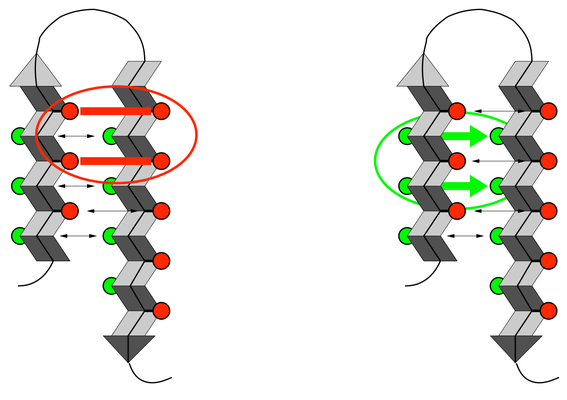
We use the grammatical framework introduced with transFold [2].



Instead of computing the minimum folding energy, we use the model to compute the Boltzmann partition function.

Novel energy model

Inspired by the RNA nearest neighbor energy model, we design an energy model using statistical potentials for stacking pairs of residues in TM β-strands.

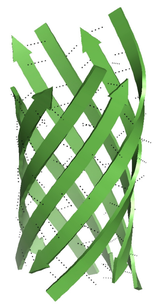


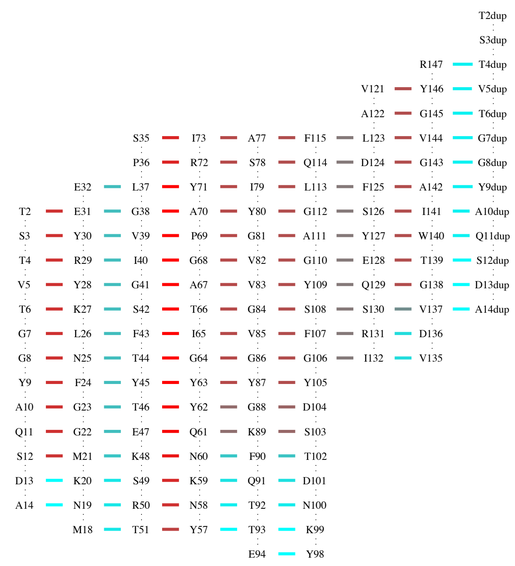
These potentials are computed from a non-redundant dataset of globular β-sheets.

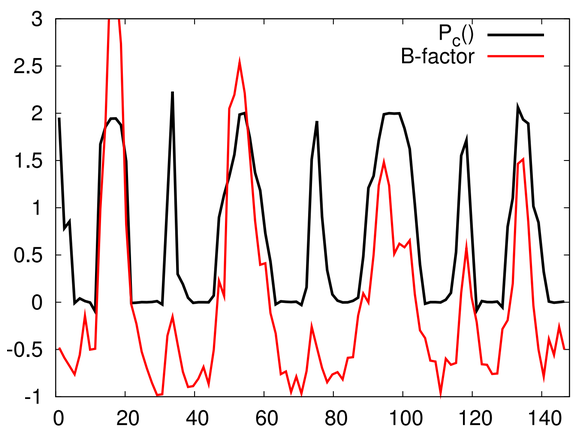
Results

The inter-strand residue contact probabilities are merged into a *stochastic contact map*.

Mapping the Boltzmann contact probabilities onto the hydrogen bonds experimentally observed, allows to evaluate critical regions.







The contact probability profile (i.e. the probability of a residue to interact with any other residue) correlates with the experimental B-values.

References

[1] J.S. McCaskill. The equilibrium partition function and base pair binding probabilities for RNA secondary structure. *Biopolymers*, 1990.

[2] J. Waldispühl, B. Berger, P. Clote and J.-M. Steyaert. Predicting Transmembrane β-barrels and Inter-strand Residue Interactions from Sequence. *Proteins: Structure, Function and Bioinformatics*, 2006.

[3] J. Waldispühl, C.W. O'Donnell, S. Devadas, P. Clote, B. Berger. Modeling Ensembles of Transmembrane β-barrel Proteins. *submitted*.

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