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Tertiary Structure Prediction of Proteins with disulfide bridges

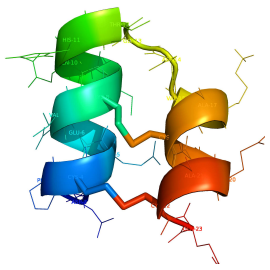
Ivan Kondov[1], *Abhinav Verma*[1,2] *and Wolfgang Wenzel*[2]
Institute for Scientific Computing[1], Institute for Nanotechnology[2], Forschungszentrum Karlsruhe, Germany

Guiding questions

- How does the amino acid sequence of a protein translate into three dimensional structure? Can we predict the 3D structure?
- How can we predict the native structure (within experimental resolution) of proteins containing disulfide bridges?

Example: 1WQE

NDPCEEVCIQHTGDVKACEEACQ



PFF01

A free-energy force field for helical proteins

The native three-dimensional structure of a protein is assumed to occupy the global free energy minimum. We employ stochastic optimization methods to perform the search for the global minimum of the free-energy. The free-energy within the forcefield PFF01 of the state $[\vec{r}]$ is partitioned into four contributions [**?**]:

$$G([\vec{r}]) = \sum_{ij} V_{ij}\left[\left(\frac{R_{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{R_{ij}}{r_{ij}}\right)^{6}\right] + \sum_{ij}\frac{q_i q_j}{\varepsilon_{g_i g_j} r_{ij}} + \sum_i \sigma_i \cdot A_i + \sum_{\text{Hbonds}} V_{hb}$$

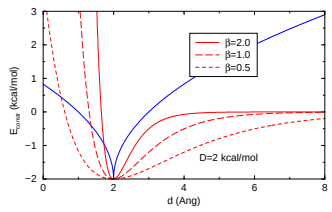
- Lennard-Jones-6-12 Potential (V_{ij} and R_{ij} mean potential depth and equilibrium distance for the Lennard-Jones-Potential, r_{ij} stands for the spatial distance between two atoms)
- electrostatic interaction (q_i and q_j are the partial charges of two atoms, $\varepsilon_{g_i g_j}$ the group-specific dielectric constants, depending on the amino-acid-type of the atom i and j belong to)
- implicit solvent interaction by minimal accessible surface area (σ_i gives the free-energy per area unit, A_i is the accessible surface area of atom i)
- Hydrogen bonding (dipole-dipole interaction is described by electrostatics; this term gives additional contribution by short-range backbone-backbone hydrogen bonding)

Constraining potential

Protein force fields still do not contain terms pertaining to disulfide bridges. We propose following potentials:

- "Cusp" potential: $E_{\text{constr}} = D\sqrt{|d - d_{S-S}|}$
- Morse potential: $E_{\text{constr}} = D((1 - e^{-\beta(d-d_{S-S})})^2 - 1)$

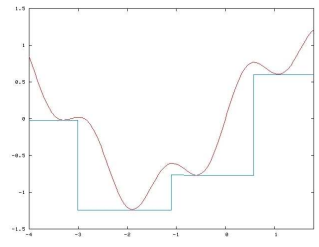
$d_{S-S} = 2\ \text{Å}$ —equilibrium length of the S-S bridge
d — distance between relevant sulfur atoms
D — S-S bonding energy



Which potential is better? How to find the parameter values?

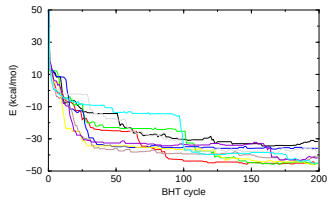
Basin hopping technique (BHT)

One of the simplest ideas to effectively eliminate high energy transition states of a free-energy surface is the basin hopping method (BHT), also known as Monte-Carlo with minimization [**?**].



An illustration of BHT, red (original energy) cyan (simplified energy)

Convergence characteristics



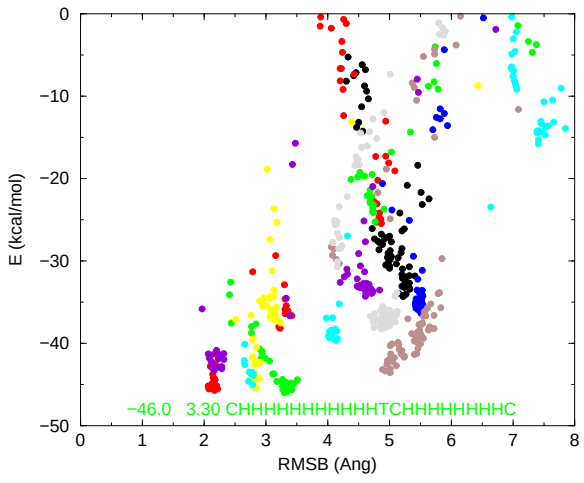
Best runs and simulation statistics

E	rmsb	secondary structure	constraint	initial conf	D	β
-51.0	1.93	CHHHHHHHHHHTCCHHHHHHHHC	morse	preopt	2	0.5
-49.1	2.03	CHHHHHHHHHHTCCHHHHHHHHC	morse	preopt	2	2.0
-48.7	1.98	CHHHHHHHHHHTCCHHHHHHHHC	morse	extended	2	0.5
-48.3	2.18	CHHHHHHHHHHHTCHHHHHHHHC	morse	preopt	2	1.0
-47.2	1.94	CHHHHHHHHHHTCCHHHHHHHHC	cusp	preopt	2	
-47.1	2.02	CHHHHHHHHHHTCCHHHHHHHHC	morse	extended	2	2.0
-55.8	1.95	CHHHHHHHHHHTCCHHHHHHHHC	morse	preopt	5	0.5
-52.7	2.09	CHHHHHHHHHHHTCHHHHHHHHC	morse	preopt	5	1.0
-52.1	1.94	CHHHHHHHHHHTCCHHHHHHHHC	morse	extended	5	1.0
-48.6	2.20	CHHHHHHHHHHHSCHHHHHHHHC	morse	preopt	5	2.0
-48.5	2.47	CHHHHHHHHHHCSCHHHHHHHHC	morse	extended	5	2.0
-47.3	1.80	CHHHHHHHHHHTCCHHHHHHHHC	cusp	preopt	5	
-39.2	2.62	CHHHHHHHHSSSSSHHHHHHHHC	cusp	extended	5	
-62.0	2.54	CHHHHHHHHHSCSCHHHHHHHHC	morse	extended	10	0.5
-62.0	2.07	CHHHHHHHHHHHSCHHHHHHHHC	morse	preopt	10	0.5
-60.2	1.93	CHHHHHHHHHHTCCHHHHHHHHC	morse	preopt	10	1.0
-54.3	2.96	CHHHHHHHHHTSCHHHHHHHHC	morse	extended	10	1.0
-54.1	2.21	CHHHHHHHHHHHSCHHHHHHHHC	morse	preopt	10	2.0
-48.6	2.05	CHHHHHHHHHHHSCHHHHHHHHC	cusp	preopt	10	

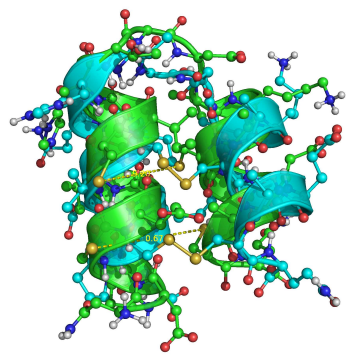
Percentage of successful runs (RMSB < 3Å)

	Cusp potential	Morse potential
preopt	53	54
extended	7	21
total	30	38

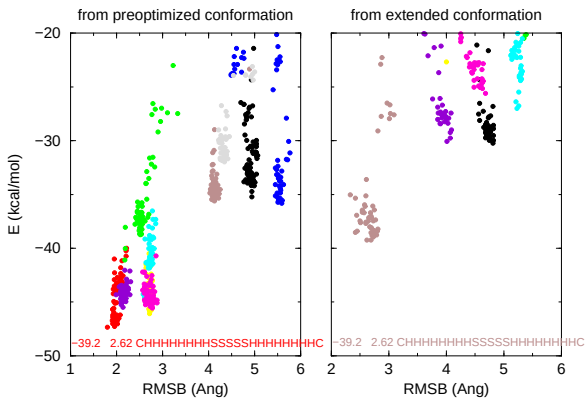
No constraining potential



An overlay of predicted (green) and experimental (blue) structures



"Cusp" potential, D=5 kcal/mol



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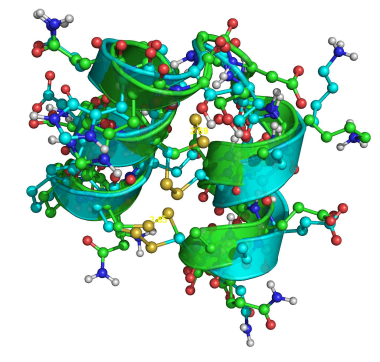
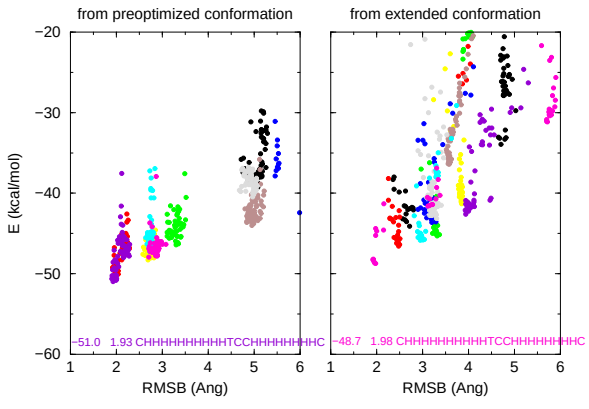


Morse potential, D=2 kcal/mol, $\beta = 0.5\ Å^{-1}$



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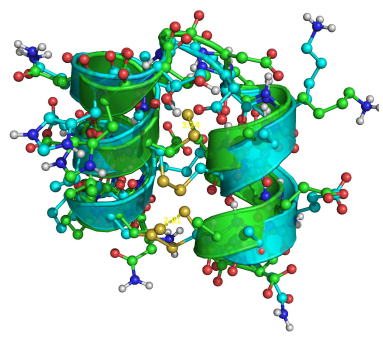

Conclusions and outlook

- Including constraining potentials improves
  - overall resolution (better RMSBs, below 2 Å)
  - the spacial alignment of SG atoms
  - disulfide bond lengths
- the Morse potential shows slight advantage in performance over the cusp potential
- optimizations from the extended conformation are not so successful with the cusp potential as with the Morse potential
- thorough performance evaluation necessary
- validation of the model with other helical proteins

References

1. T. Herges and W. Wenzel, Development of an all-atom forcefield for tertiary structure prediction of helical proteins, Biophysical Journal (2004).
2. A. Verma, A. Schug, K. H. Lee, and W. Wenzel, J. Chem. Phys. **124**, 044515 (2006).

Email: wenzel@int.fzk.de, ivan.kondov@iwr.fzk.de, verma@int.fzk.de
WWW: http://www.fzk.de/biostruct/