A Homotopy Method for Predicting Low Energy Conformations of Polypeptides

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Problem

- Given:
  - Protein model
    - Potential energy function (force field)
    - Properties of constituent particles
- Goal:
  - Predict native (lowest energy) conformation
    - Energy minimization method
    - Comparative modeling method
      - Use **template** (known structure) to predict **target** structure

Proteins Model

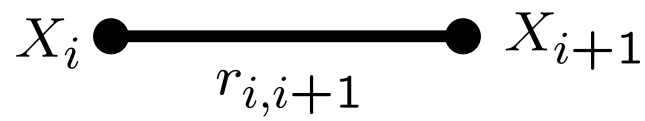
- Backbone model
  - Single chain of particles with residue attributes
- Properties of particles
  - Hydrophobic, Hydrophilic, Neutral
  - Diverse hydrophobic-hydrophobic interactions

[Veitshans, Klimov, and Thirumalai. *Protein Folding Kinetics*, 1996.]

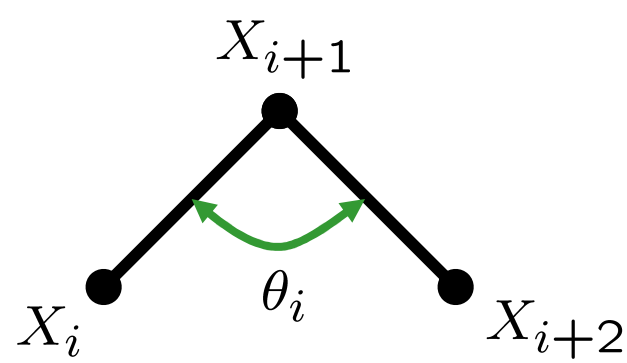
Potential Energy Function

$$E(X) = E_{bl}(X) + E_{ba}(X) + E_{dih}(X) + E_{non}(X)$$

$$E_{bl}(X) = \sum_{i=1}^{n-1} \frac{k_r}{2} \left(r_{i,i+1} - \bar{r}\right)^2$$



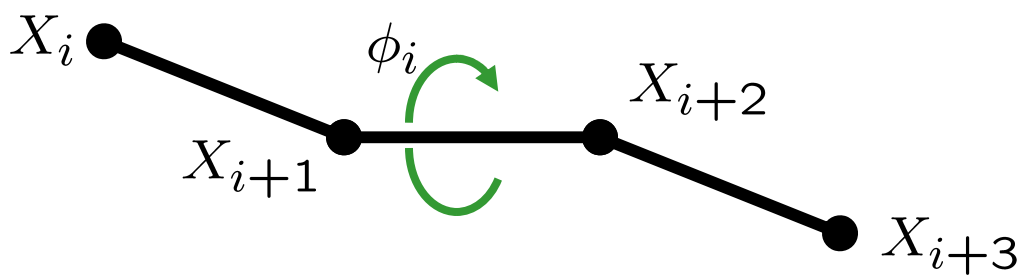
$$E_{ba}(X) = \sum_{i=1}^{n-2} \frac{k_\theta}{2} \left(\theta_i - \bar{\theta}\right)^2$$



Potential Energy Function

$$E(X) = E_{bl}(X) + E_{ba}(X) + \boxed{E_{dih}(X)} + \boxed{E_{non}(X)}$$

$$E_{dih}(X) = \sum_{i=1}^{n-3} [A_i(1 + \cos\phi_i) + B_i(1 + \cos 3\phi_i)]$$



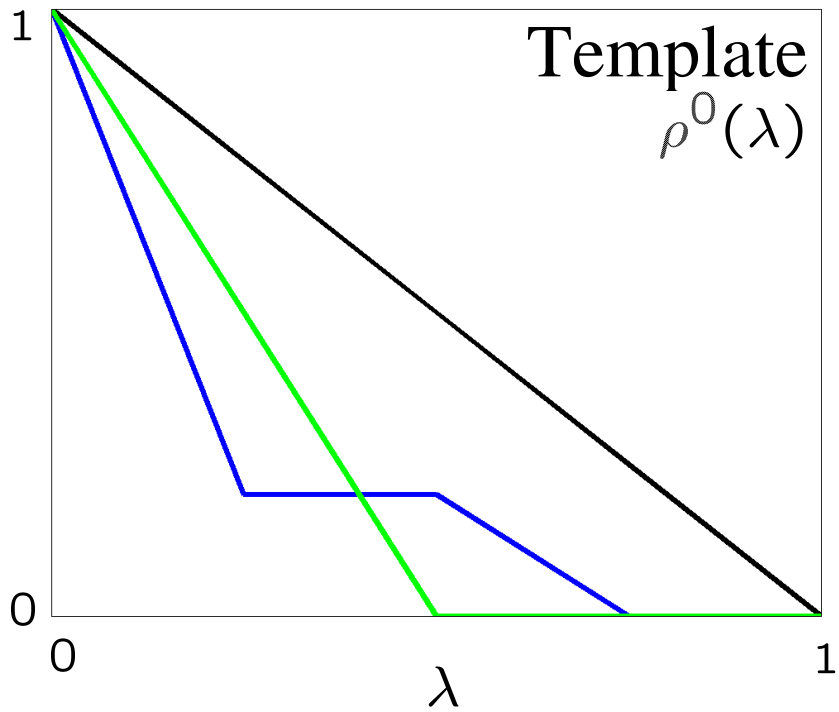
$$E_{non}(X) = \sum_{i=1}^{n-3} \sum_{j=i+3}^{n} \gamma_{ij} \left\{ \alpha_{ij} \left(\frac{\bar{r}}{r_{ij}} \right)^{12} - \beta_{ij} \left(\frac{\bar{r}}{r_{ij}} \right)^{6} \right\}$$

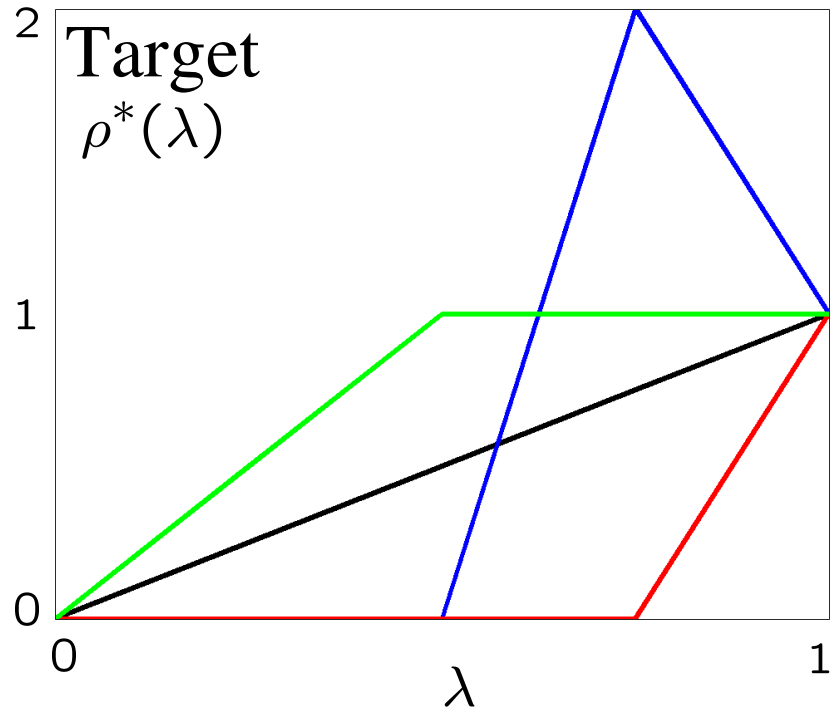
Homotopy Function

- Energy Functions:
  - Template: $E^0(X)$
  - Target: $E^*(X)$
- Homotopy Function:
  - $H(X(\lambda), \lambda)$
  - $H(X(0), 0) = \nabla E^0(X)$
    $H(X(1), 1) = \nabla E^*(X)$
  - $H(X(\lambda), \lambda) = \rho^0(\lambda) \nabla E^0(X) + \rho^*(\lambda) \nabla E^*(X)$

Homotopy Function

Different $\rho(\lambda)$ for individual energy terms





$\rho(\lambda) = 1 - \lambda$ $\rho^0_{dih}(\lambda)$ $\rho^0_{non}(\lambda)$

$\rho(\lambda) = \lambda$ $\rho^*_{dih-lf}(\lambda)$ $\rho^*_{non}(\lambda)$ $\rho^*_{dih-hf}(\lambda)$

Homotopy Method

- Goal
  - Equilibrium curve: $H(X(\lambda), \lambda) = 0$
  - Follow curve from $\lambda = 0$ to $\lambda = 1$
- Iteration

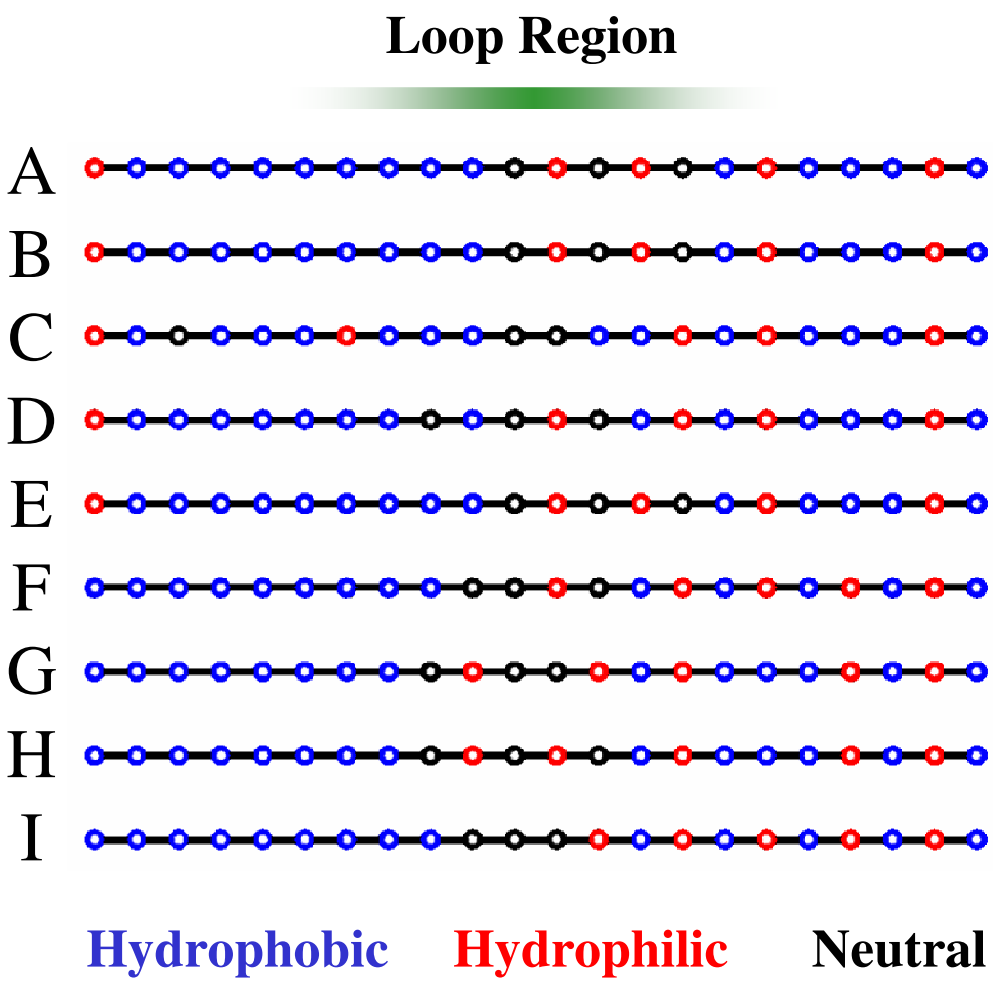
```
while (λ <= 1)
   solve H(X, λ) = 0 for X iteratively,
      using old X as starting value
   λ = λ + Δλ
end
```

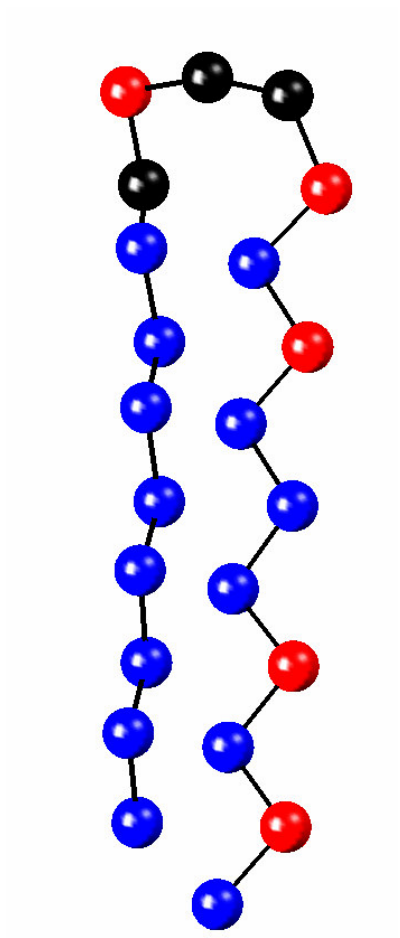
Experiments

- 9 Chains with known structure
  - 22 particles
- Methods
  - Homotopy method
  - Newton's method with trust region (TR) [sfminbx]
- Measure of success
  - Structural overlap function: $0 \leq \chi \leq 1$
  - Percentage of interparticle distances off by more than 20% of the average bond length ($\bar{r}$)

[Veitshans, Klimov, and Thirumalai. *Protein Folding Kinetics*, 1996.]

Experiments

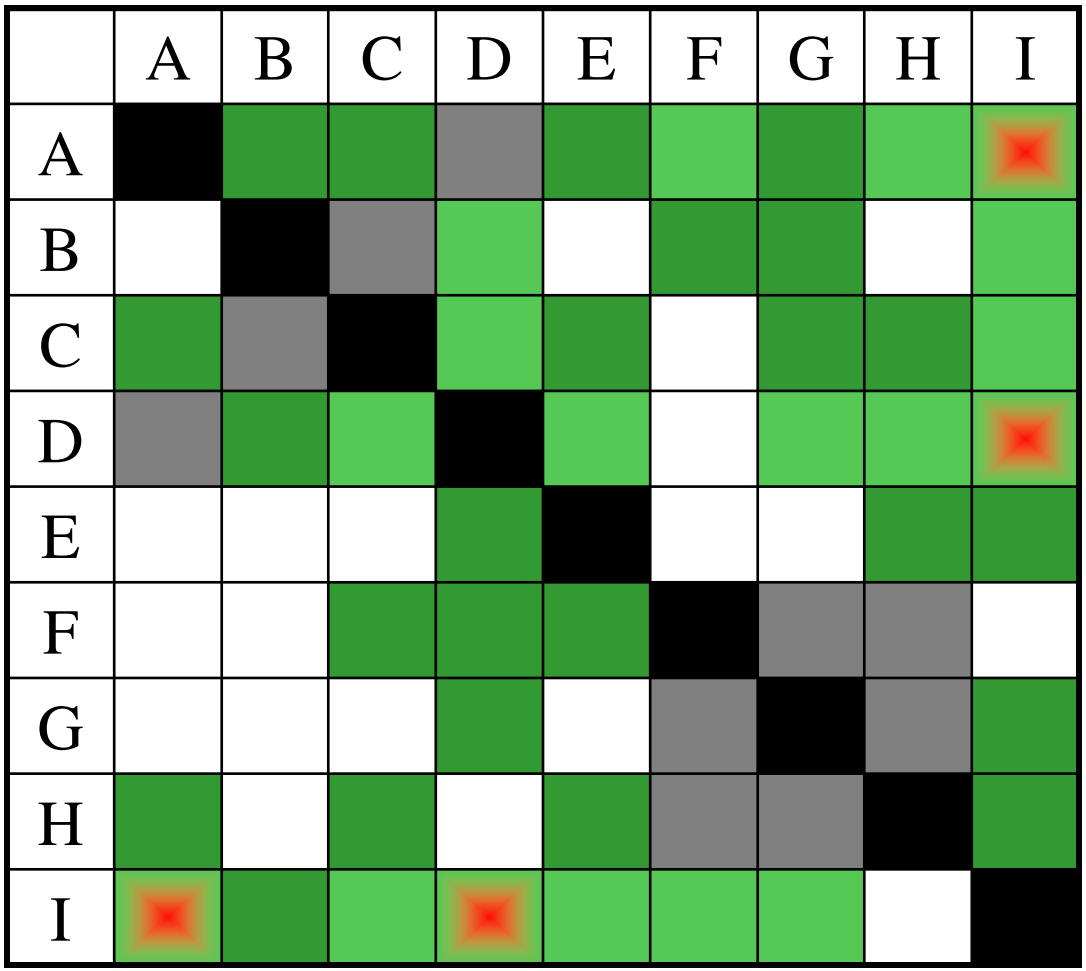




Results

Target

Template



Template=Target
10/72

Newton w/TR
4/62 (6%)

Homotopy
18/62 (29%)

Homotopy*
42/62 (68%)

Conclusions

- Homotopy method
  - More successful than standard minimizers
- Homotopy functions
  - Allows control of individual energy terms for describing a path from a template conformation to a target conformation
  - New functions needed to handle loop regions
- Future work
  - Proteins (AMBER,CHARMM)

Acknowledgements

- SIAM
  - Student Travel Award
- National Library of Medicine
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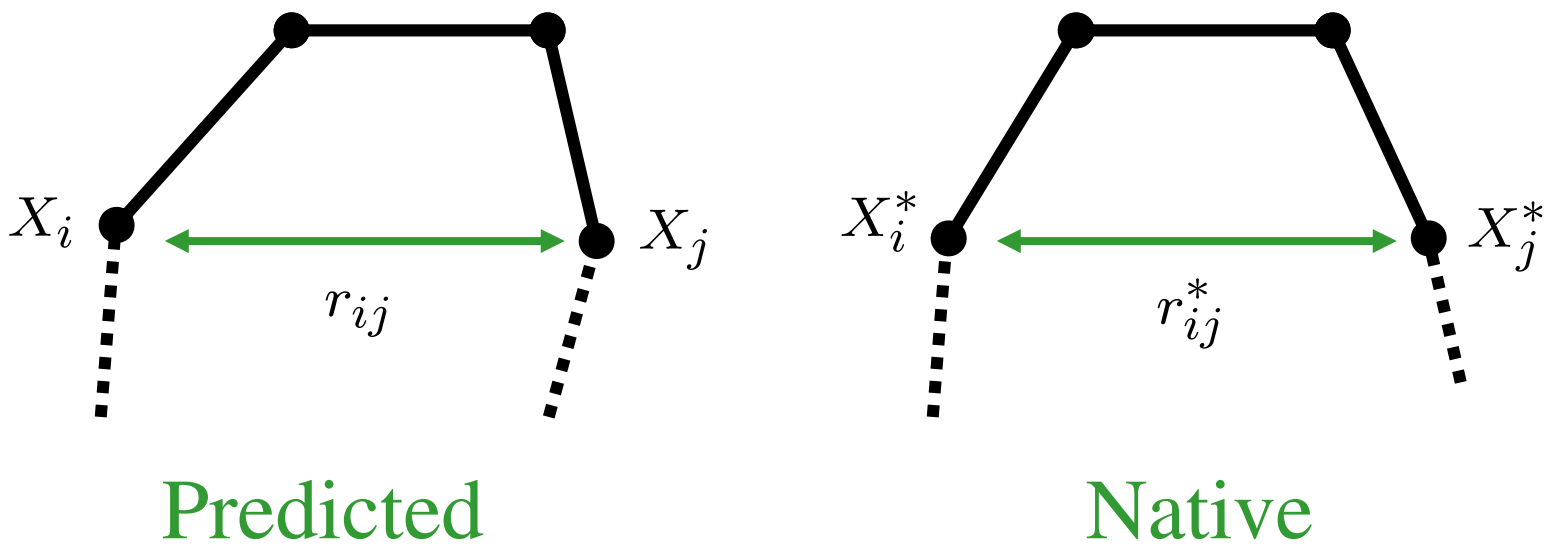
- Dev Thirumalai, Dmitri Klimov
  - Model, suggestions

Structural Overlap Function

$$\chi = 1 - \frac{2}{n^2 - 5n + 6} \sum_{i=1}^{n-3} \sum_{j=i+3}^{n} \Theta\left(0.2\bar{r} - \left|r_{ij} - r_{ij}^*\right|\right)$$



Sequence Homology (%)

Target

Template

	A	B	C	D	E	F	G	H	I
A	100								
B	77	100							
C	86	91	100						
D	91	86	77	100					
E	73	82	73	82	100				
F	68	68	59	77	86	100			
G	68	68	59	77	86	100	100		
H	68	68	59	77	86	100	100	100	
I	73	59	64	68	77	73	73	73	100

Max

100

Min

59