Solvent-entropy driven searching for protein modeling examined and tested in simplified models

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Current structure prediction methods

Ab initio: too computationally expensive, poor accuracy at large scales

More successful methods: Based on alignments and energetics

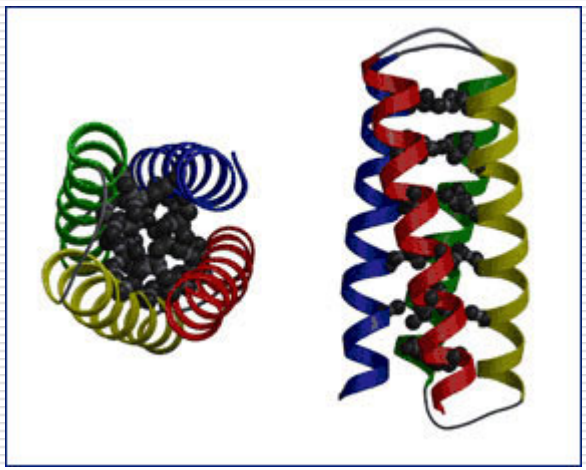
Alignments: not really understanding why, but recognizing patterns

Problems:
- degeneracy in sequences → structure mapping
- trouble with low complexity sequences (e.g. yeast)
- not "complete"
- not fully automated

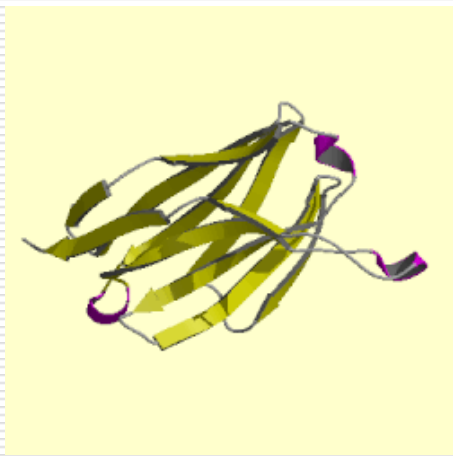
Current structure prediction methods

Energetics: based on conformational energy analysis of the protein

Problems: computationally expensive
require parameterization
cannot predict or discriminate among structures



or



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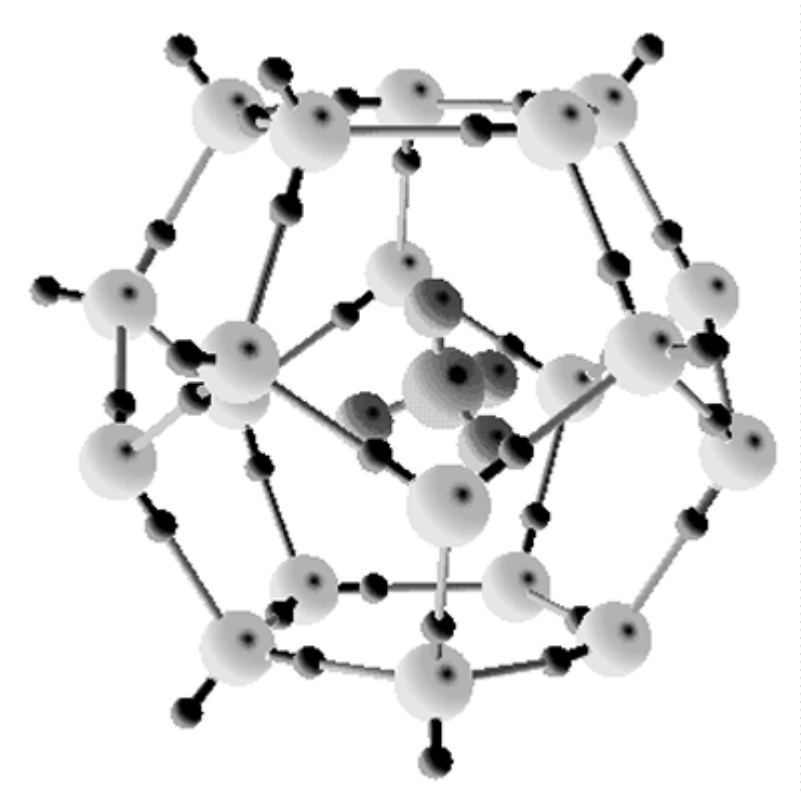
…Novotny 1984, 1988

Solvent ordering by hydrophobic molecules

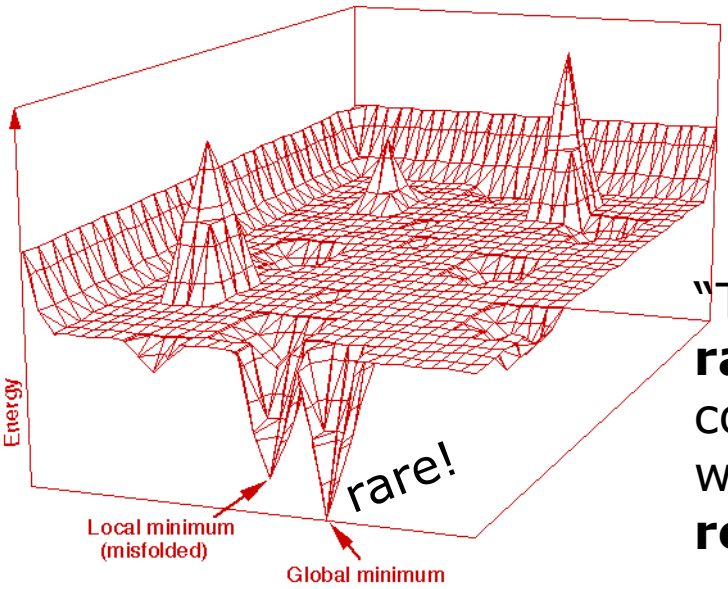


Solvent entropy maximization!

Protein structure is the one that maximizes solvent entropy

Driving force: solvent entropy maximization
Accommodating forces: polypeptide sterics, electrostatics, etc.

Not calculating solvent entropy exactly, but **representing** it.



"The global minimum no longer appears as **one rare state** among a large number of alternative conformations, but as the protein conformation with the **highest number of microstate representations of the solvent**."

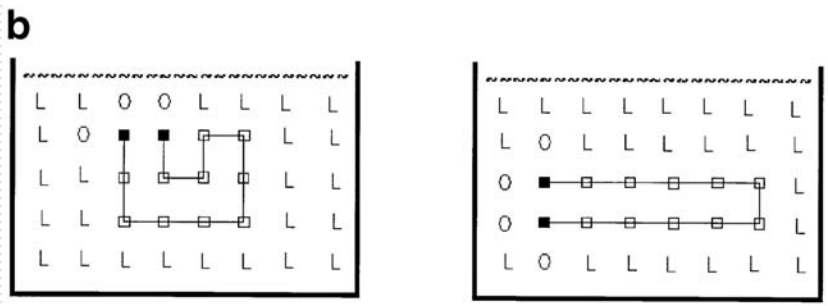
Experimental Objective

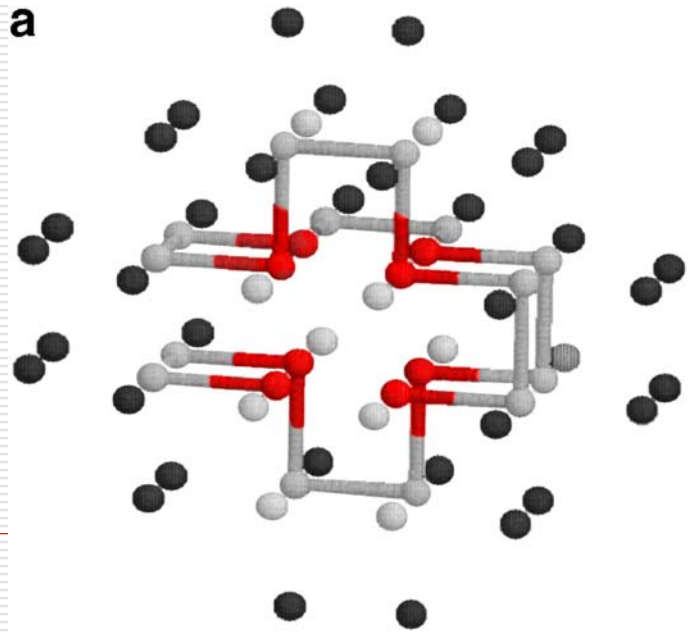
Compare the performance of different algorithms under simple and demanding conditions.

The model: MC on a lattice

HP polypeptide model: H = ***h***ydrophobic [dark]
P = hydro***p***hilic [light]

OL solvent model: O = ***o***rdered [light]
L = ***l***ess ordered [dark]
N_i = #of L blocks





The model: MC on a lattice

2D model: 5 chains; lengths = 12
18
24
33
48

3D model: 4 chains; lengths = 12
14
22
28

Comparing Entropy & Energy: 3 ways to evaluate

A = energy
B = entropy
C = entropy and energy

Simulation Flowchart

- Start from random conformation
- From C_1 with solvent entropy N_1 and energy E_1, a single random change yields C_2. Reject and regenerate if C_2 clashes.
- C_2 evaluated by algorithms A, B, or C for acceptance.
- Continue until $C_{100,000}$
- Repeat 100 times

Move set and scoring

Move set: a single bead random move (non clashing)

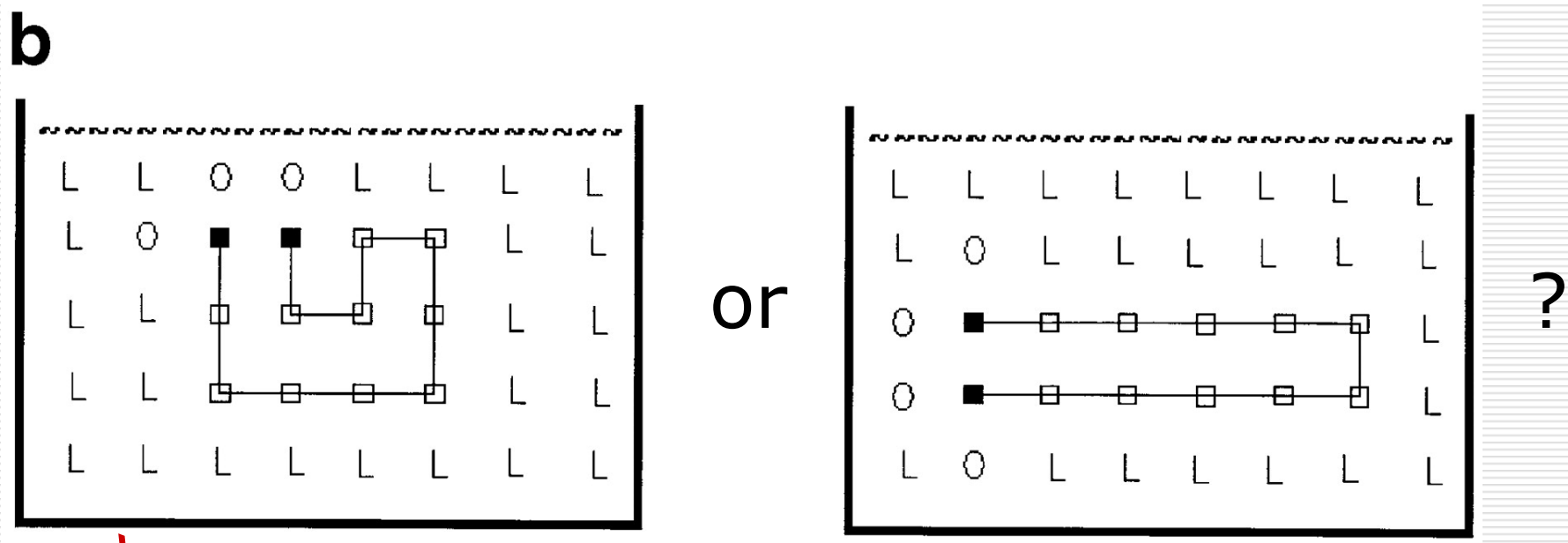
Successive conformations = C_1, C_2, etc

Solvent entropy function, $S_O = 1$ if O
$S_L = 1/f$ if L

$f < 1$ = "entropy weight"

Polypeptide energy function, ΔE = **-1** for direct contact between two non-consecutive hydrophobic beads (i.e. hydrogen bonds)

Entropy vs. Energy



You're a winner!

Move acceptance algorithms

Three implementations:

A = energy:

accept C_2 if rnd < $e^{-\Delta E/T}$

Boltzmann style!

B = entropy:

accept C_2 if rnd < $K*f^{(N1-N2)} = e^{(T\Delta S/T)}$

C = entropy and energy:

accept C_2 if rnd < $K*f^{(N1-N2)}e^{-\Delta E/T}$

K = constant

Results

How many times per 100 runs did the algorithm find the native structure?

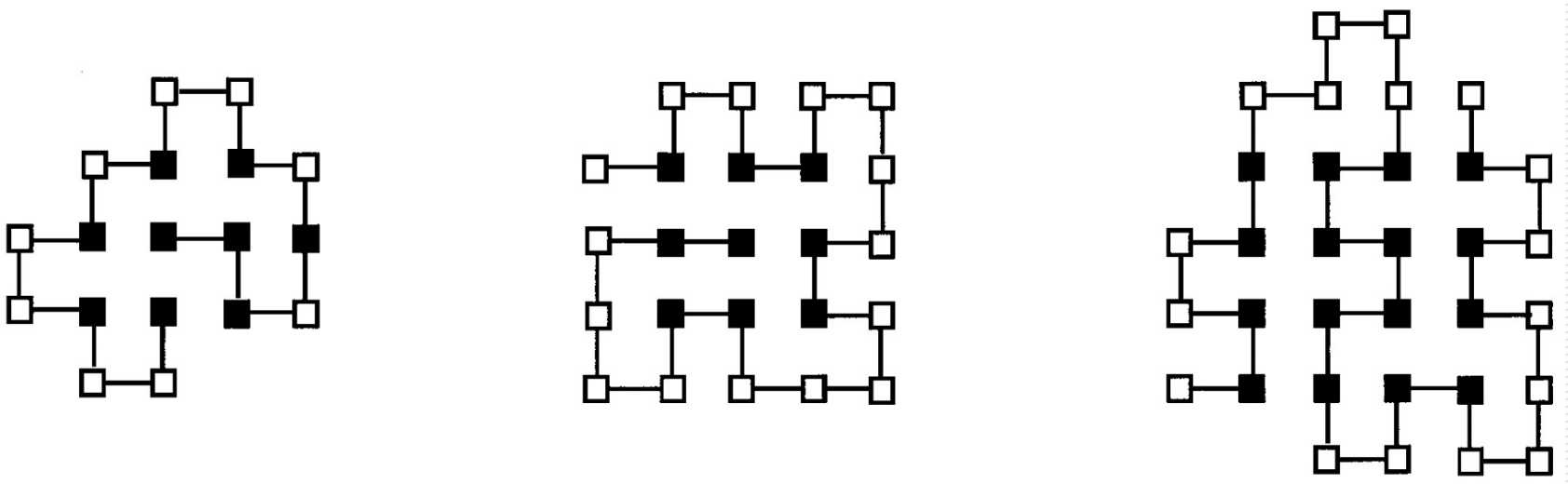
Algorithm C: best performance

Algorithm B: better performance

Algorithm A: OK performance

Computation speed was better with entropy

2D Native Fold Images

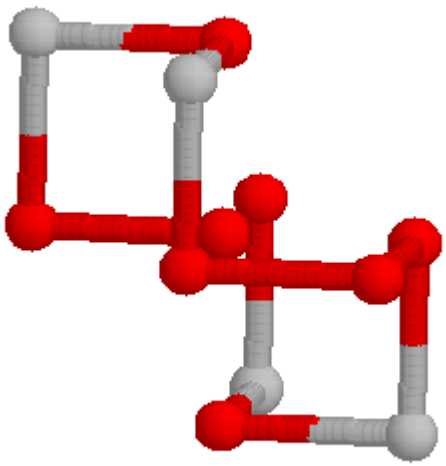


18mer

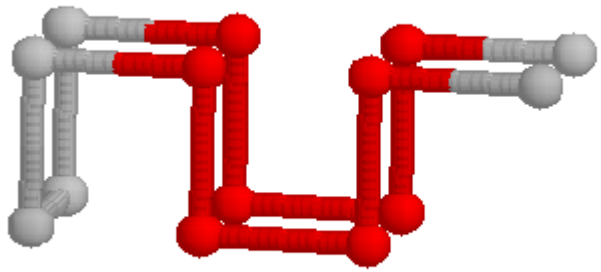
24mer

33mer

3D Native Fold Images

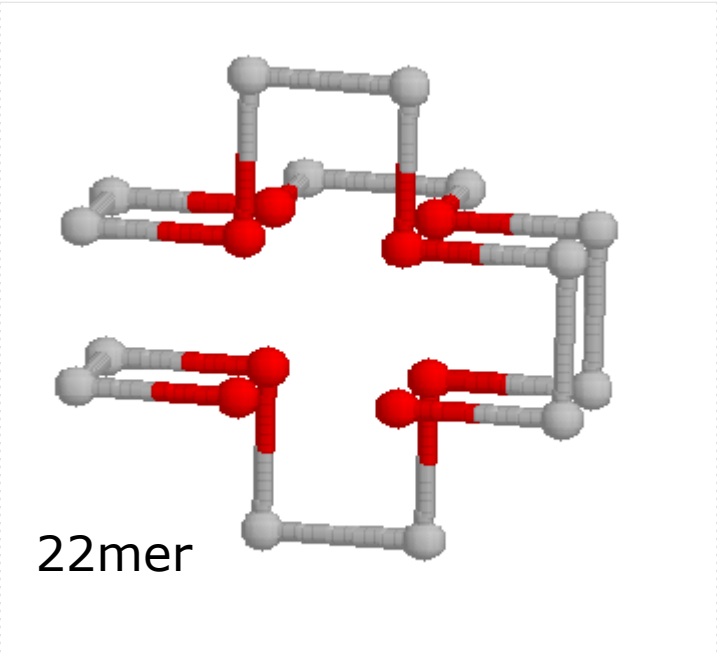


12mer

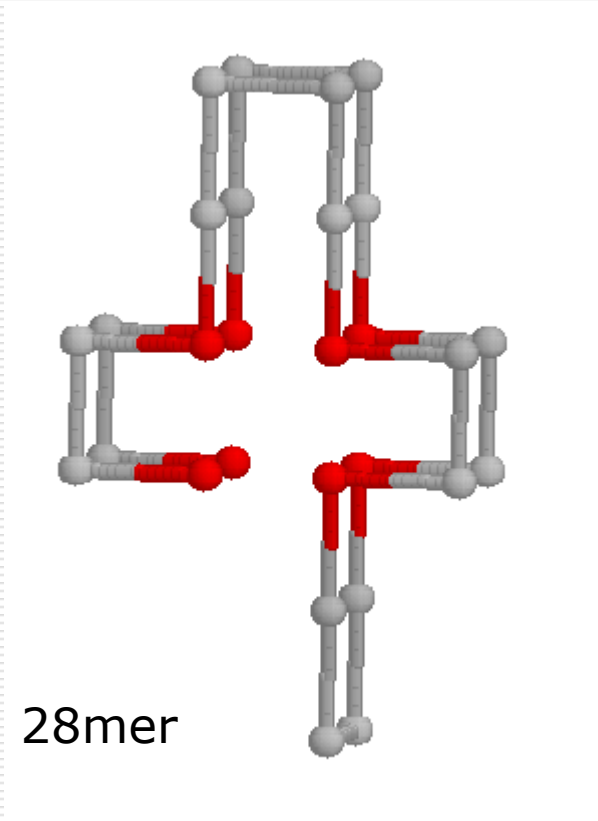


14mer

3D Native Fold Images

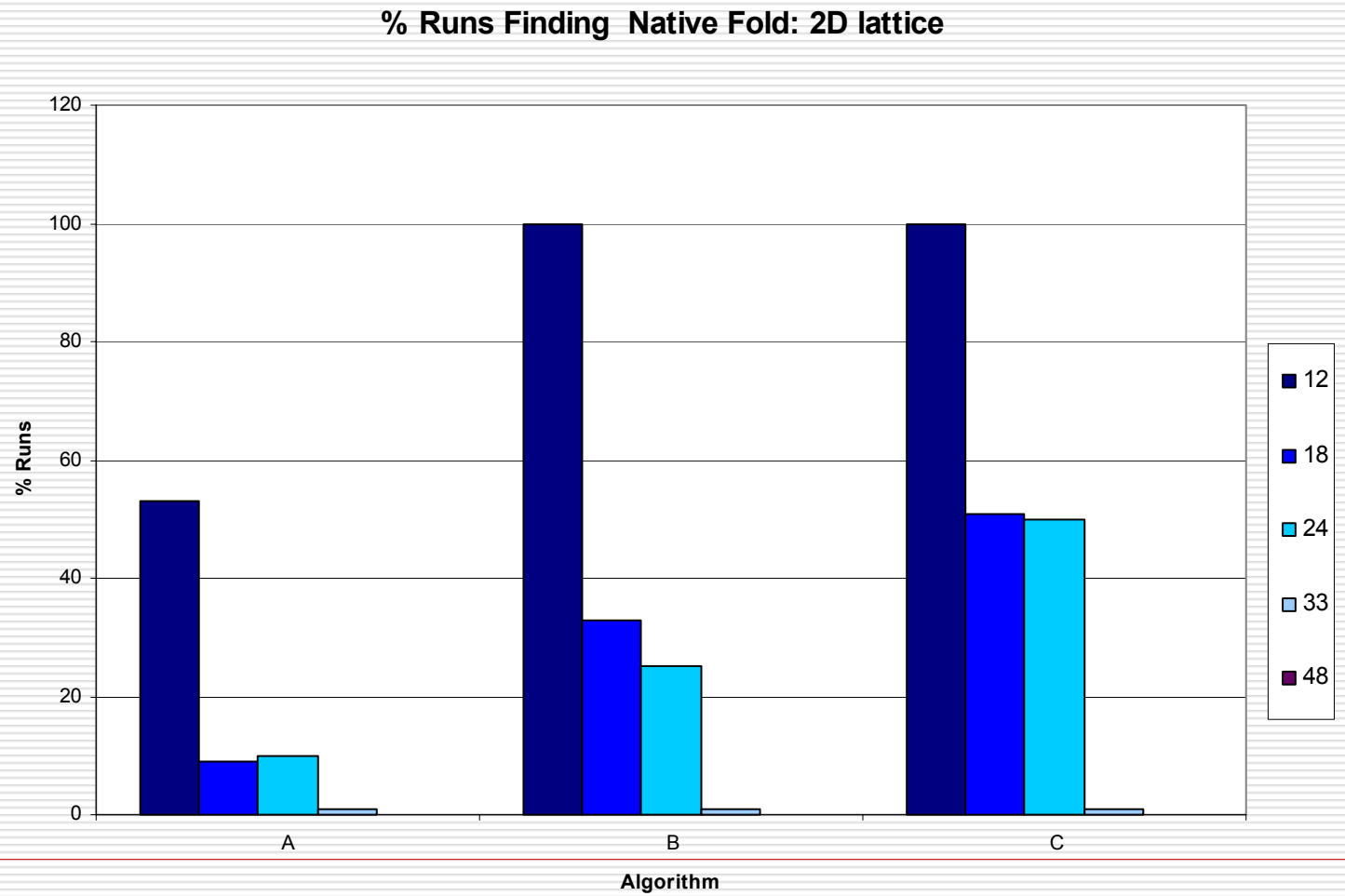


22mer

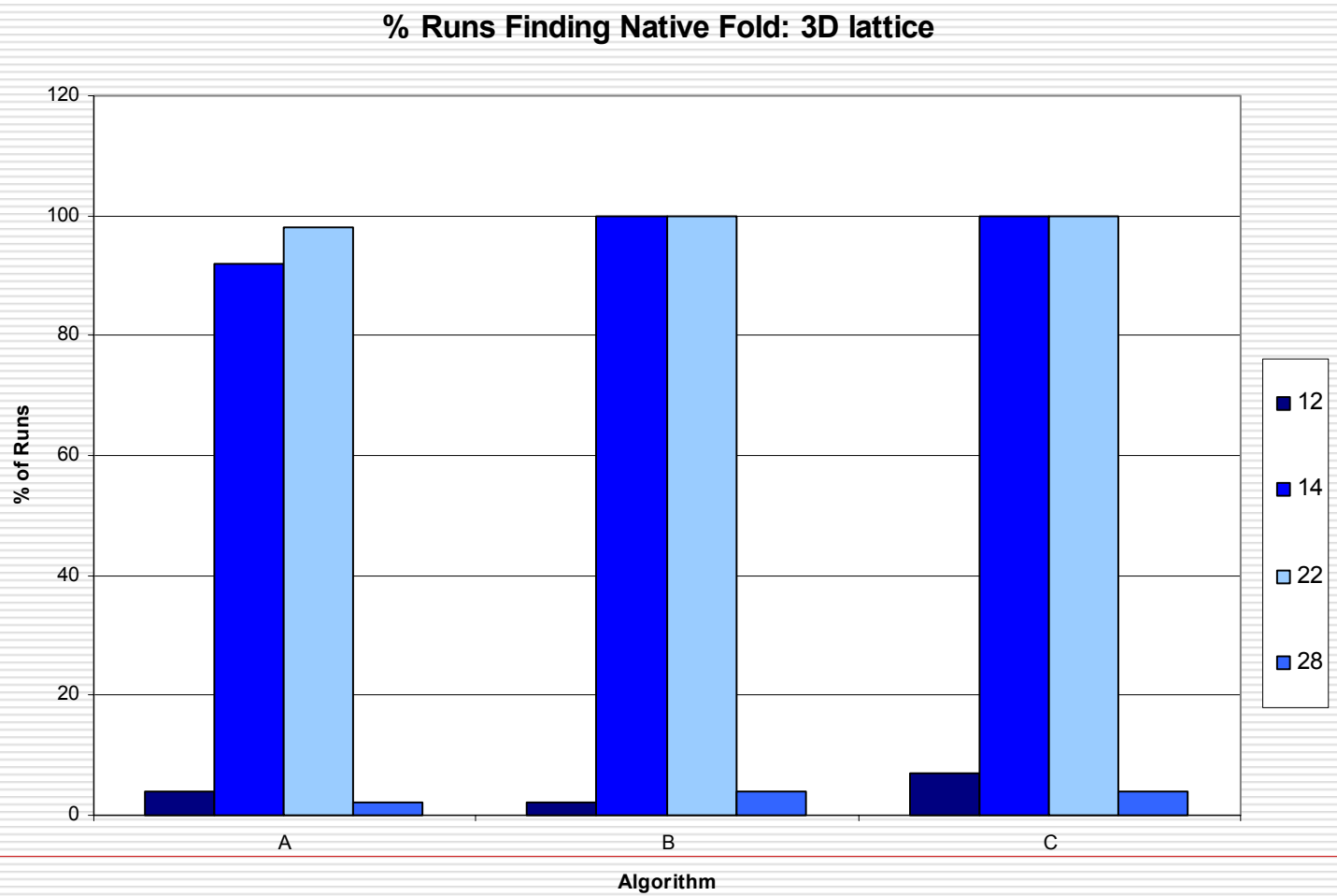


28mer

Results: 2D lattice



Results: 3D lattice



My Research

Summer
MD simulation of dynamics of myoglobin-CO complex with CHARMM and GB continuum solvation. Trajectory analysis by PCA.

Fall, Winter, Spring…and Summer again
More detailed solvent-entropy driven lattice models of protein structure and folding.

References

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- Lau, K.F. and Dill, K.A. (1989) *Macromolecules*, **22**, 3986-3997
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Thanks!

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I'm leaving you with my children