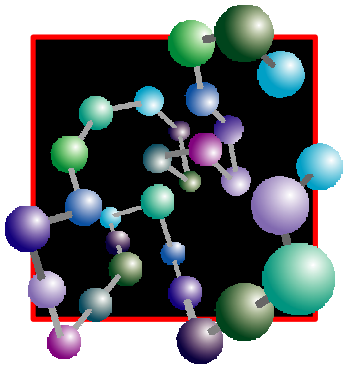
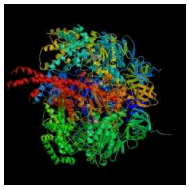
May 29, 2003
KITP – Santa Barbara

Crumpling, Jamming, and Percolation in a Toy Protein



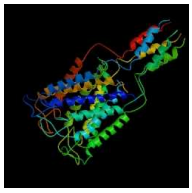
A. Borovinskii
R. Lua
A. Grosberg
(Minnesota)
J.Chuang, R.Du
(UCSF)
M.Rubinstein
(UNC)
NSF

MOTIVATION:



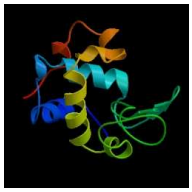
Motors:

Bovine Mitochondrial F1-Atpase



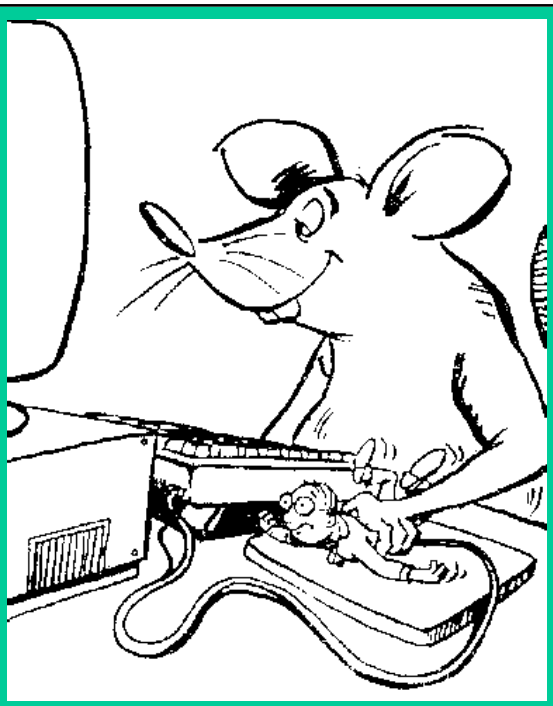
Ion channels:

Mechanosensitive Ion Channel

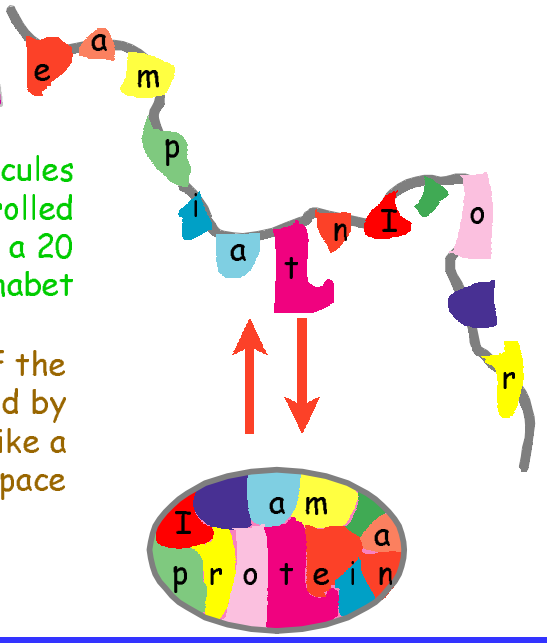


Enzymes:

Lysozyme



Famous Protein Folding Problem

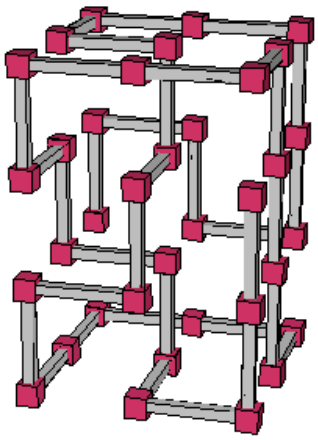


Proteins are chain molecules - genetically controlled messages written in a 20 letter alphabet

The "meaning" of the message is understood by folding the molecule like a jigsaw puzzle in 3D space

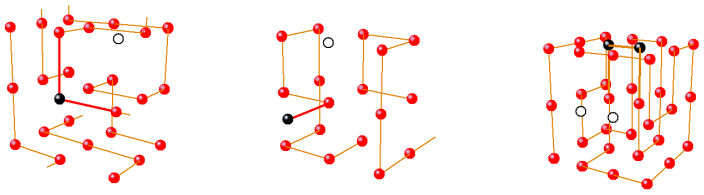
Sequence should be found to fold into a desirable structure.

Consider a spherical cow:



One particular conformation, as an example

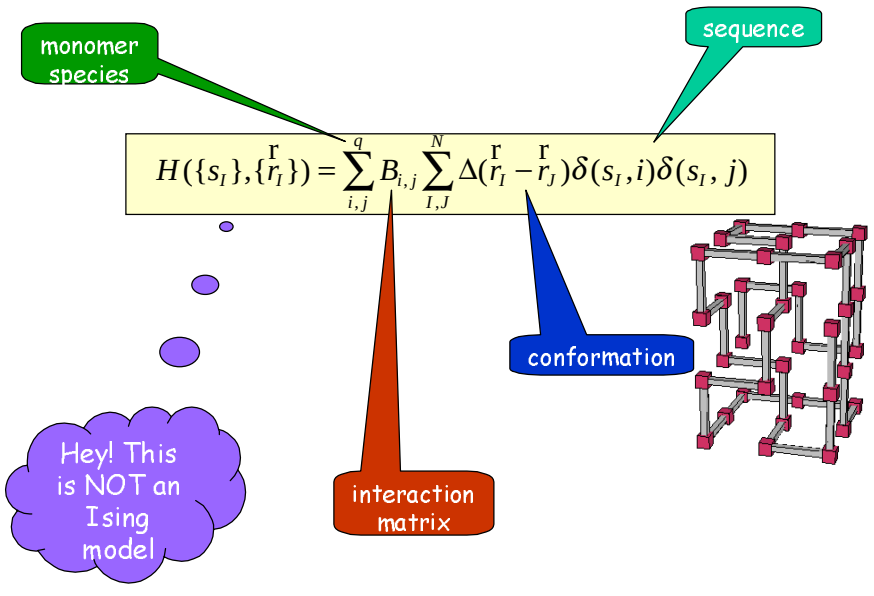
How does lattice polymer move?



Corner flip End flip Crankshaft

If no other restrictions are imposed, these moves guarantee ergodicity - every conformation can be obtained from every other conformation

Hamiltonian:



A dictionary:

Monomer	Atom
Number along the chain (including chemical name)	Position in space (including all details)
Coordinates in space	Orientation of spin
Homopolymer	Ordered system
Sequence design	Education (e.g., neural net)

Differences

Infinite range of interactions

Natural — Artificial

Dynamics

Navigation of conf space — Flips of individual spins

Imagine that you are able to produce MANY microscopically identical copies of a spin glass, and have to choose a "good" one ...

Protein Folding and Protein Evolution

- Levinthal's paradox: how can lowest energy state be identified given that majority of states cannot be even visited?
- "Good" sequences have to be selected.
- Selection of sequences is the job of evolution.
- "Evolution paradox": how could "good sequences" be selected from an exponentially large number of possibilities?

Self-assembly:

- Equilibrium vs. dynamics

Although native states are believed equilibrium, dynamics of folding is an issue

- Anfinsen experiment

10^{-3} sec to 1 sec

- Folding is an All-or-None process

(counterpart of I order phase transition)

A few simple REM style estimates:

Energy: the sum of ~N terms out of ~N^2 - independence;
Probability for the given structure to have energy some E below the average:

$$P(E): \exp\left[-E^2/2N\delta B^2\right]$$

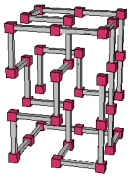
Number of states : $\exp[sN]$

Typical lowest energy state $E: -N\sqrt{s}\delta B$

The next lowest state is only ~δB above -
Don't eat pickles, no mutation stability, no all-or-none... bad!!

Canonical Design of Sequences:

Given a "target" conformation



we anneal the sequence at some "temperature" T_{prep}

Peculiar Ising model

subject to "design" Hamiltonian

$$H^{des}(\{s_I\},\{\vec{r}_I\}) = \sum_{i,j}^{q} B_{i,j} \sum_{I,J}^{N} \Delta(\vec{r}_I - \vec{r}_J)\delta(s_I,i)\delta(s_I,j)$$

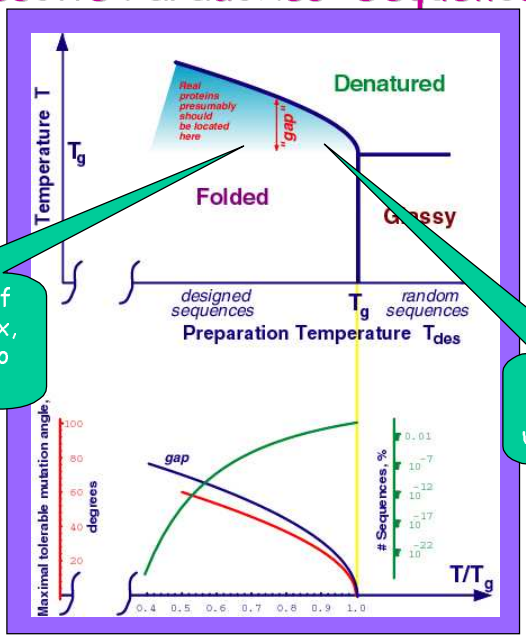
monomer species

interaction matrix

conformation

sequence

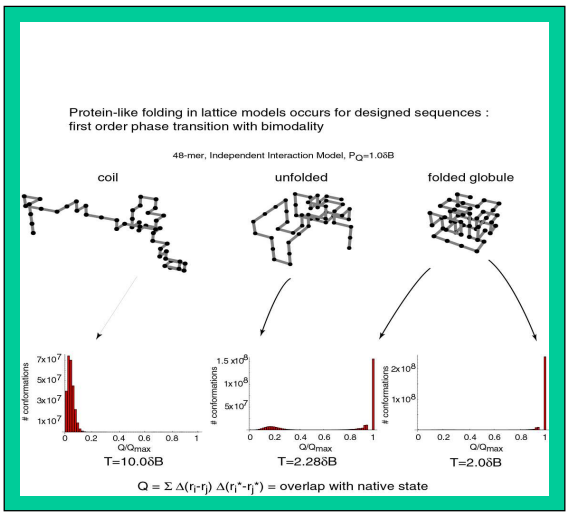
How to Resolve Paradoxes: Sequence design



Better solvers of Levinthal paradox, more difficult to select

Easier to select, but worse folders

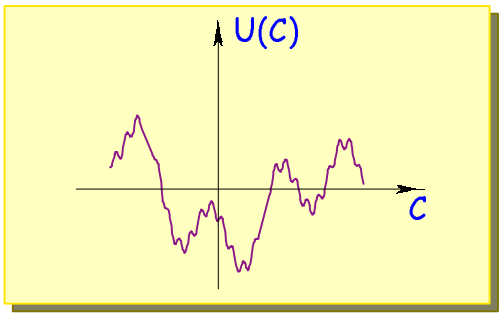
"Proteins" with selected sequences fold into the native conformation:

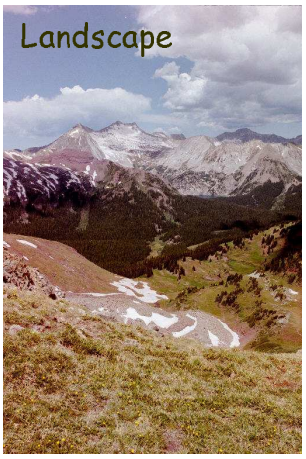


E.I. Shakhnovich, PRL, **72**, 3907, 1994

V. S. Pande, A. Yu. Grosberg, T. Tanaka, J. Chem. Phys. **101**, 8246, 1994

For every conformation C, there is energy U(C)...





... landscape theory

Current REM style theory…

Due mainly to J.Bryngelson & P. Wolynes (1987)
- phenomenology
and E. Shakhnovich & A. Gutin (1989)
- microscopic model

… is based on 1 step RSB:
Two states (conformations) are
either completely correlated (coincide!)
Or not correlated at all.

This is the statement about geometry of conformations

Space of conformations is…

Configuration space of a gas (or a liquid) is described by N position vectors of all atoms; it is 3N dimensional Euclidean space …

But "space" of configurations for a "polymer" of two "monomers" (one anchored) is a SPHERE

For N links, there are 2N degrees of freedom; not only 2N<3N, but the coordinates are angular - restricted

P.Dirac, around 1965:
Quantization on a curved manifold

Self-avoidance…

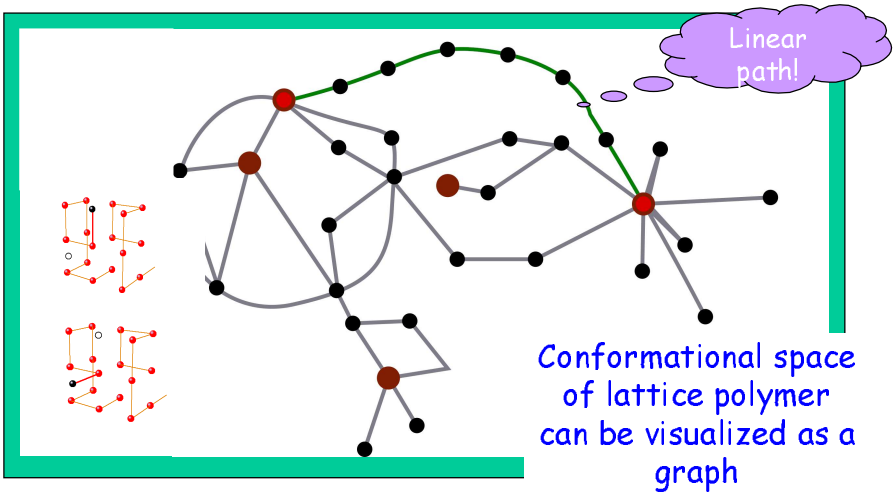
…removes some of the vertices from the "cube," actually - lion's share of them.

Chain compaction…

…makes self-avoidance constraints increasingly more severe, and strips the "cube" even further.

What remains?

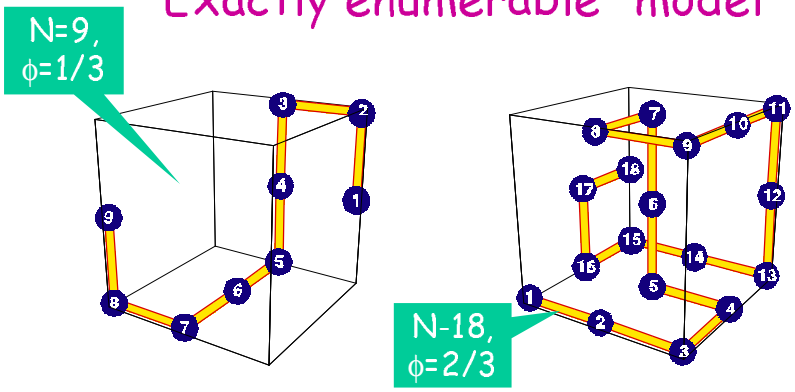
Conformational space of lattice polymer



Conformational space of lattice polymer can be visualized as a graph

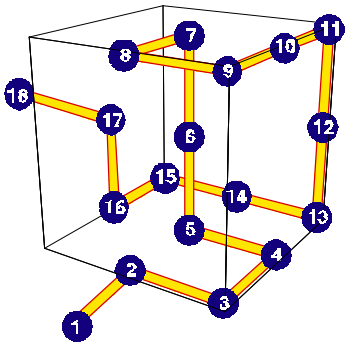
NO SUCH ISSUE IN SPIN GLASSES…

"Exactly enumerable" model

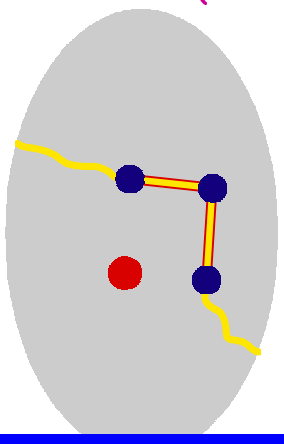


Instead of changing volume, we change chain length within a given confinement…

Another version of the model:
restricted R_g



Consider an almost dense polymer (on a cubic lattice):



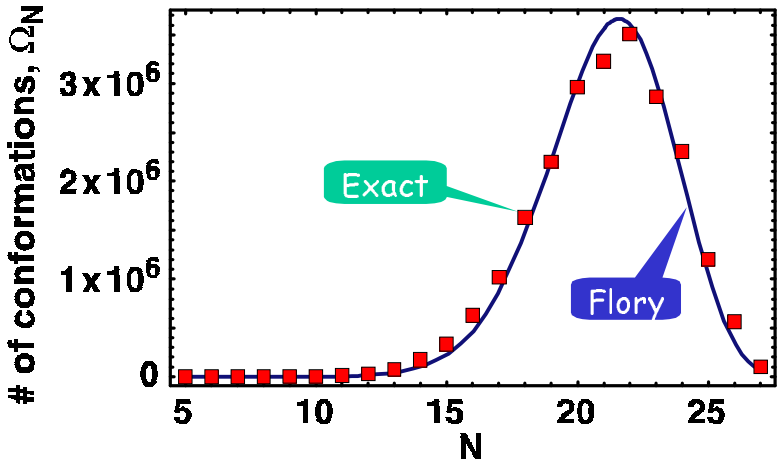
Imagine a very dense polymer, it is so dense that you don't see anything inside, just a mess …

But now there is a vacancy…

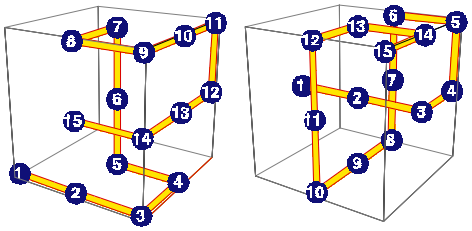
Can it move? It can ONLY if the chain is properly positioned nearby

Apart from exponentially improbable conformations, vacancy can move by a finite distance … connecting finite number of conformations

Exact enumeration of confined conformations:

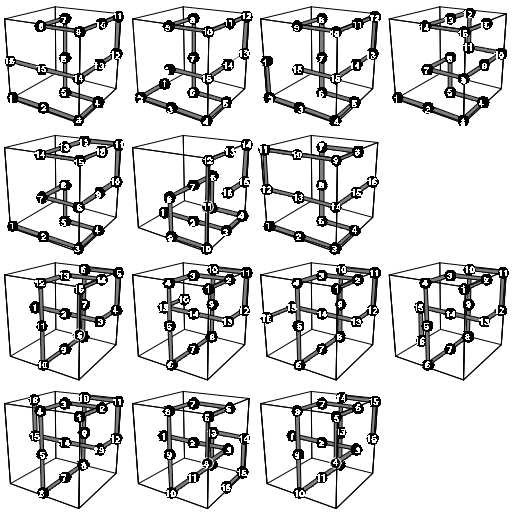


At N=15, two conformations violate ergodicity:



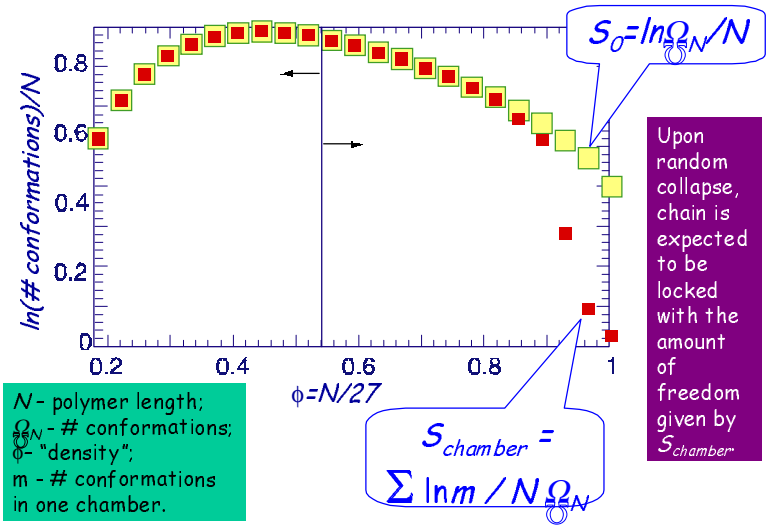
At N≤14, conformation space is ergodic: every conformation can be transformed into every other conformation. At N=15, ergodicity is broken by two conformations which cannot move.

"Locked Conformations," 16-mers:



Neither of these 14 conformations can move even a single step as long as it is confined in the 27 cube.

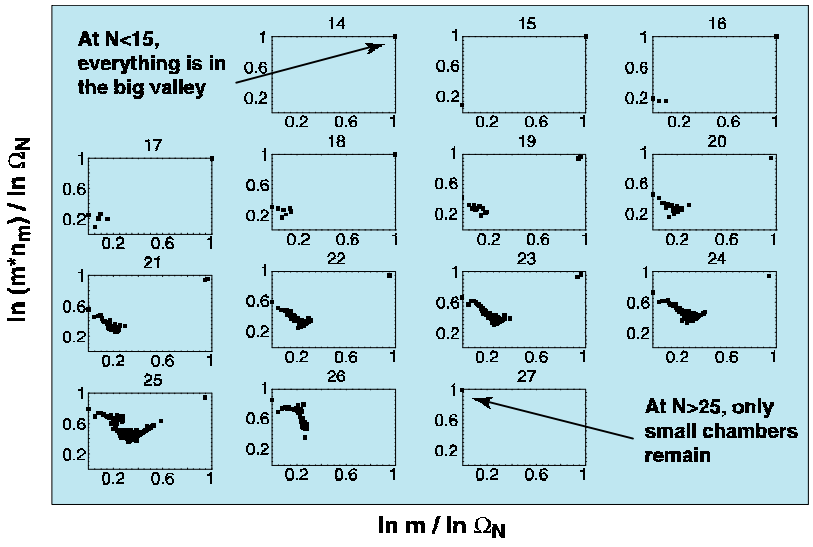
Entropy: quenched vs. annealed average



N - polymer length;
Ω_N - # conformations;
ϕ - "density";
m - # conformations in one chamber.

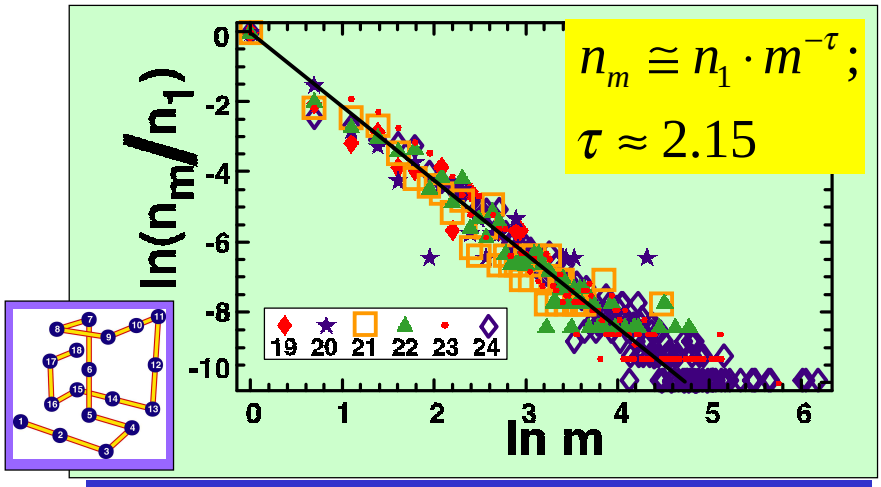
Upon random collapse, chain is expected to be locked with the amount of freedom given by $S_{chamber}$.

The distribution of chamber sizes is bimodal:



m -chamber size; n_m - # of chambers of the size m.

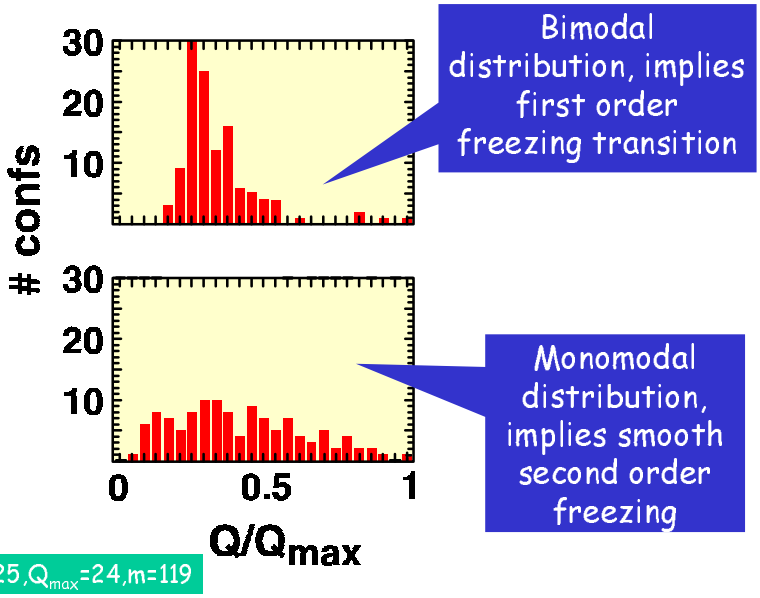
For a compact polymer, conformational space is a fractal foam



m -chamber size; n_m - # of chambers of the size m.

R. Du, A.Yu. Grosberg, T. Tanaka, M. Rubinstein, PRL **84**, 2417, 2000.

Internal structure of chambers:

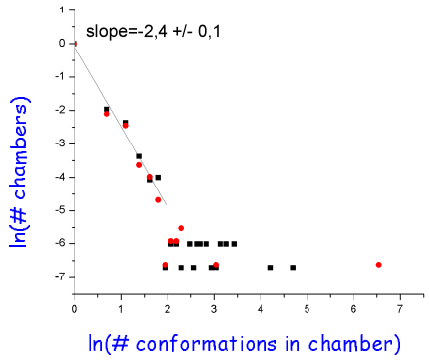


Bimodal distribution, implies first order freezing transition

Monomodal distribution, implies smooth second order freezing

N=25, Q_{max}=24, m=119

Chamber distribution for the open model:

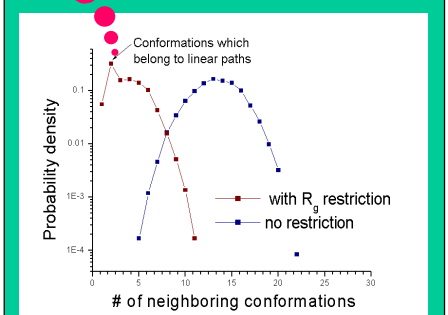


Overall, the properties are pretty close for both open and closed models.

$R_g^{compact}$=1.2583; R_g<1.304; R_g<1.305

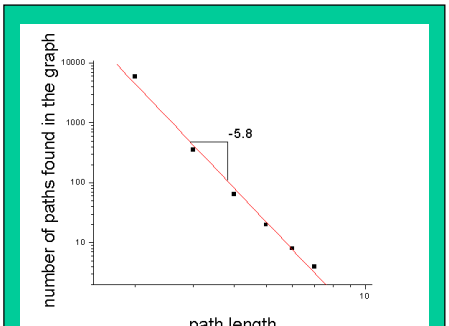
There are surprisingly many linear paths …

Wow… what's that?



Distribution of connectivities suggests small-world network …

A. Scala, L. A. N. Amaral, & M. Barthélémy, Europhys. Lett. 55, 594, 2001.



Distribution of non-branching paths on the graph

Thank you!