PROTEIN PHYSICS

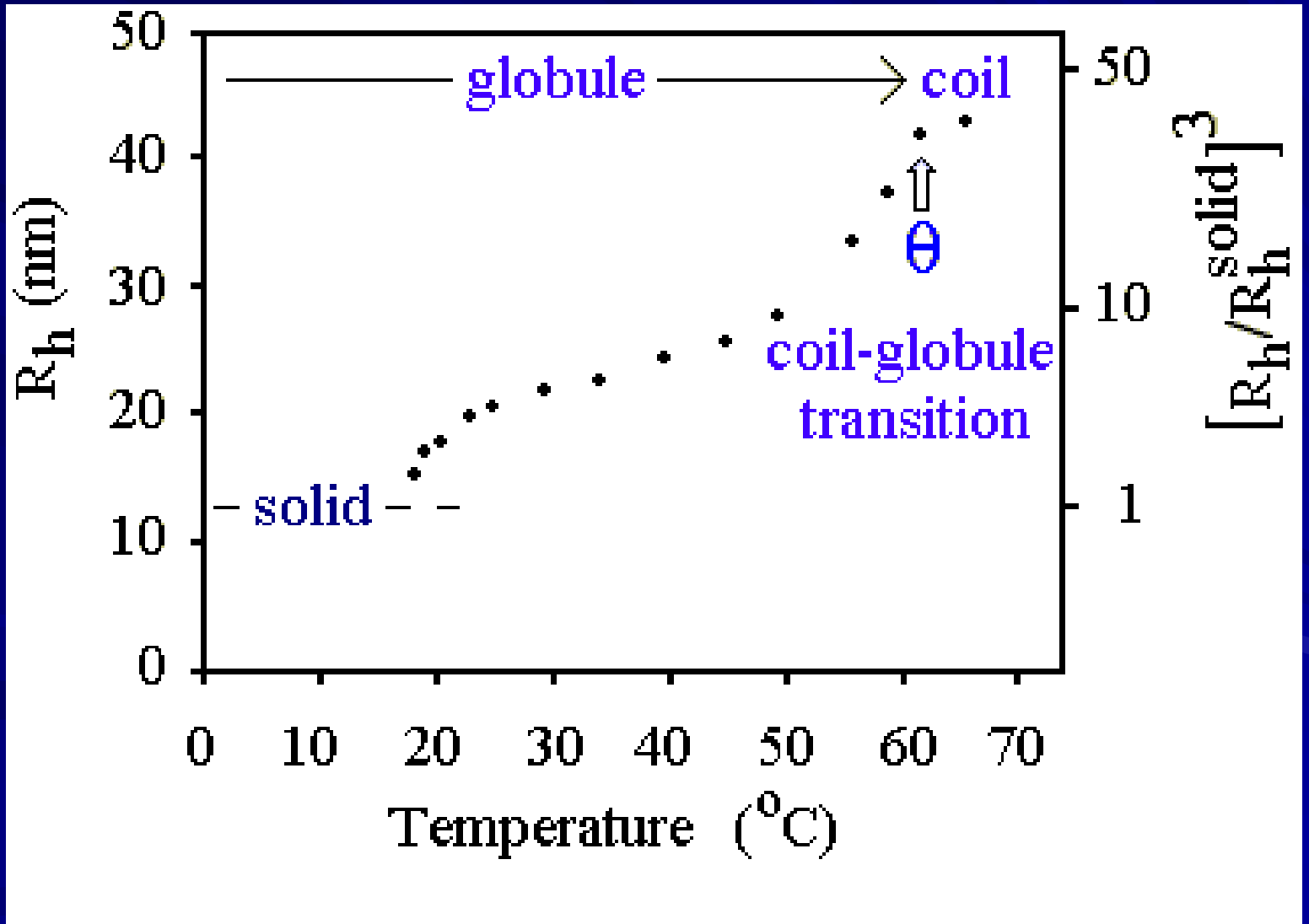
LECTURE 18

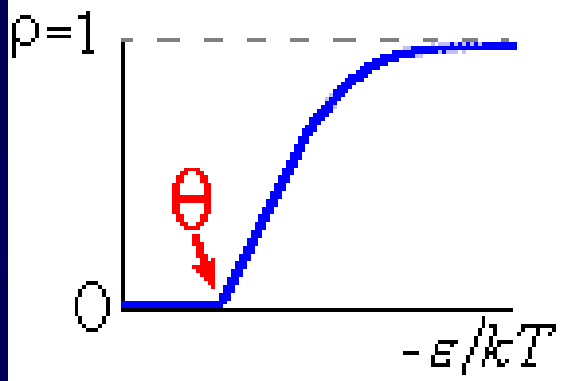
Protein Structures: Thermodynamic Aspects (2)

- Why protein denaturation is an “all-or-none” phase transition, unlike the globule-coil transition in “normal” polymers?

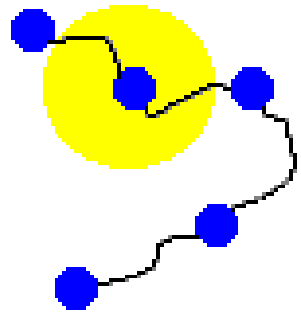
- “Energy gap” and “all-or-none” melting. “Protein-like” heteropolymers.

Globule-to-coil transition in “normal” synthetic polymers: It is *not* of the “all-or-none” type

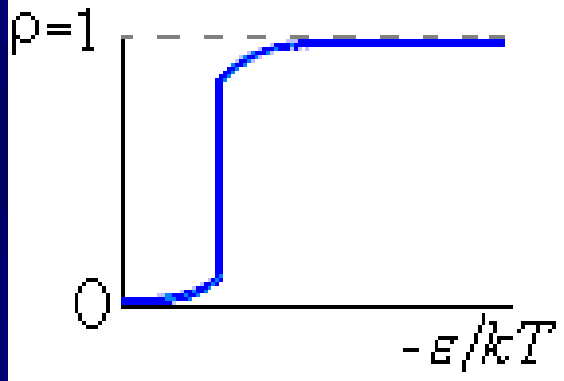




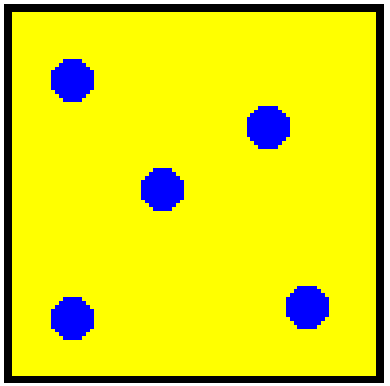
coil-globule transition in "normal" polymer: 2-nd order, at very low density of globule



chain-limited volume for a link



gas-liquid transition: 1-st order, at high density of liquid



PROBLEM: why does "all-or-none" (1-st order) phase transition does not exist in "normal" polymers, but exists in proteins?

Globule-to-coil transition
in “normal” synthetic polymers
is not of an “all-or-none” type.

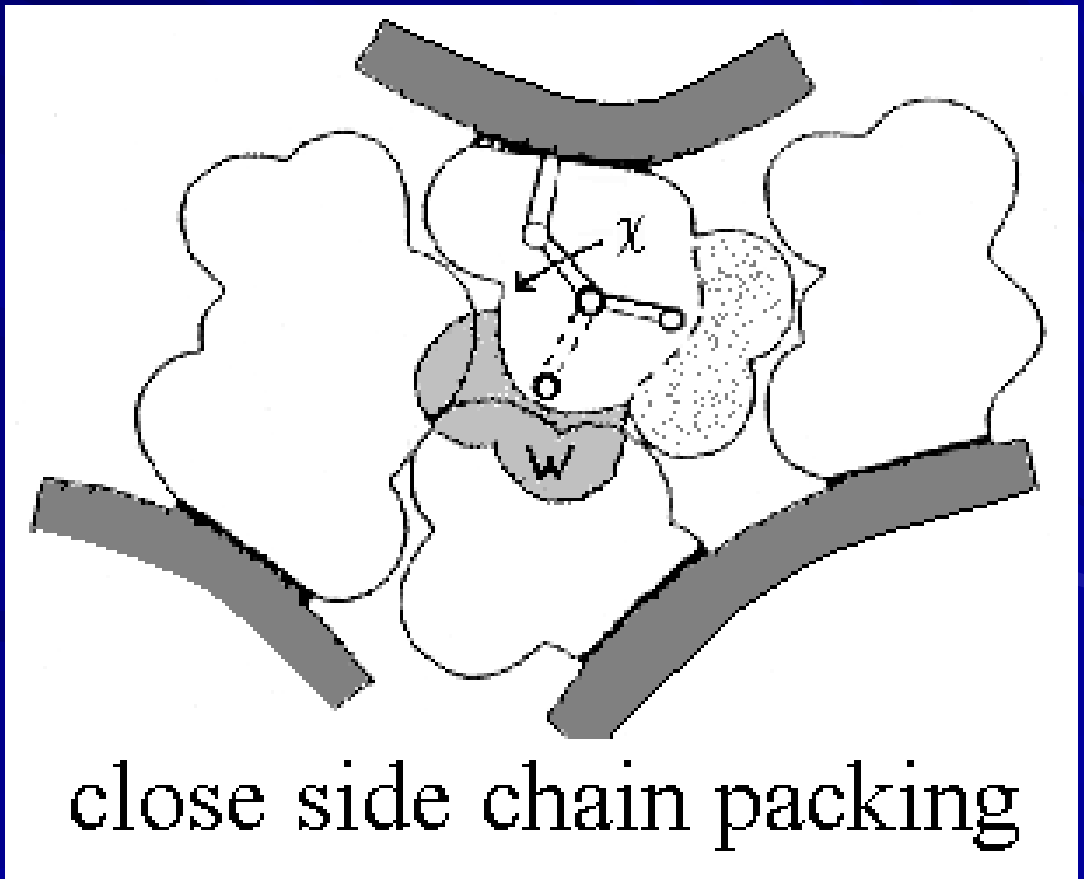
Besides,
globule-to-coil transition in polymers
resembles evaporation rather than
melting or sublimation, while
protein denaturation
resembles melting or sublimation of a crystal
rather than evaporation of a liquid.

Why?
Special construction of protein chain.

Why protein denaturation is an “all-or-none” phase transition?

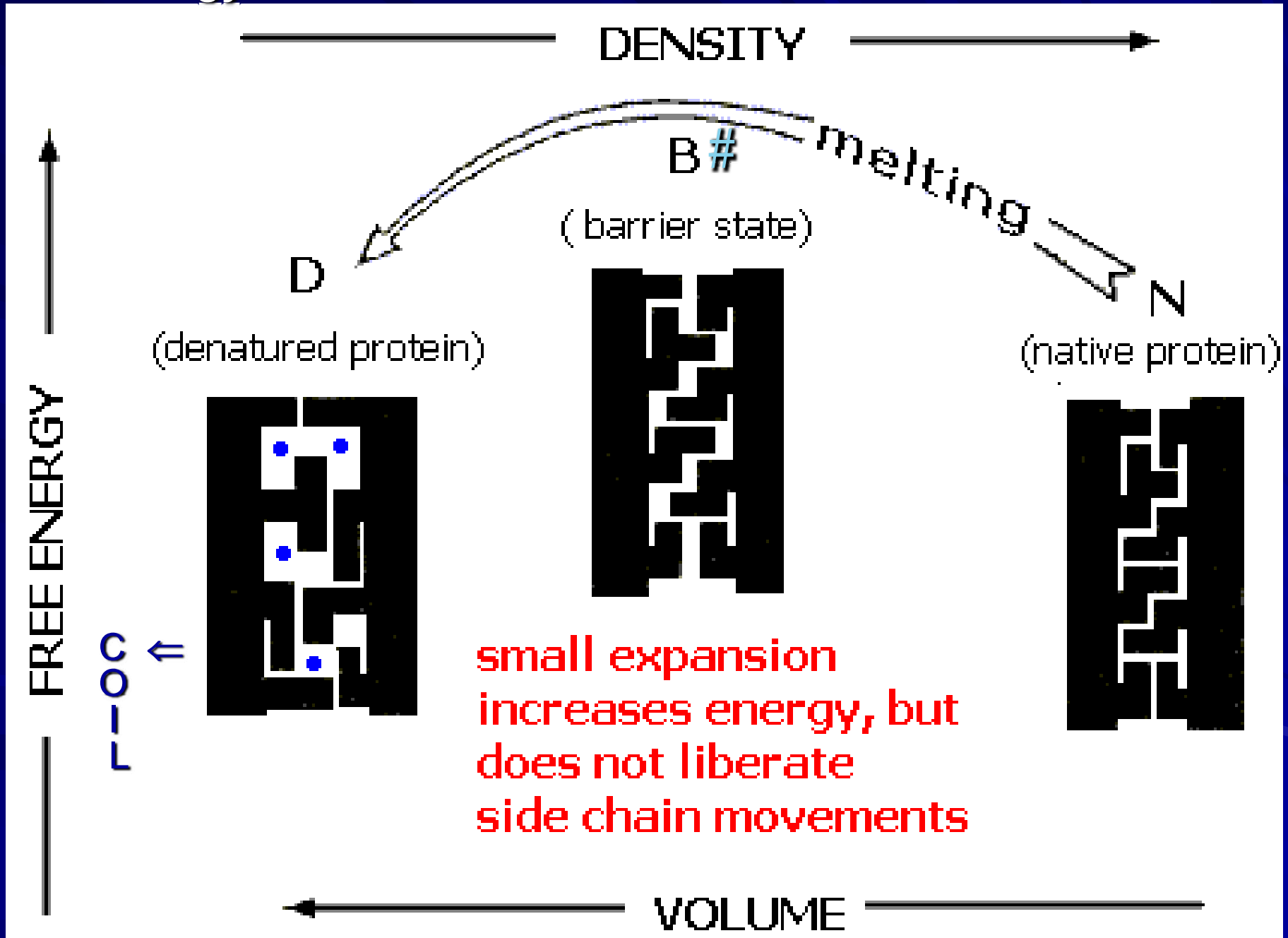
Peculiarities of protein structure:

- Unique fold;
- Close packing;
- Flexible side chains at rigid backbone
- Side chains rotamers



close side chain packing

Free energy barrier # between Native and Denatured states



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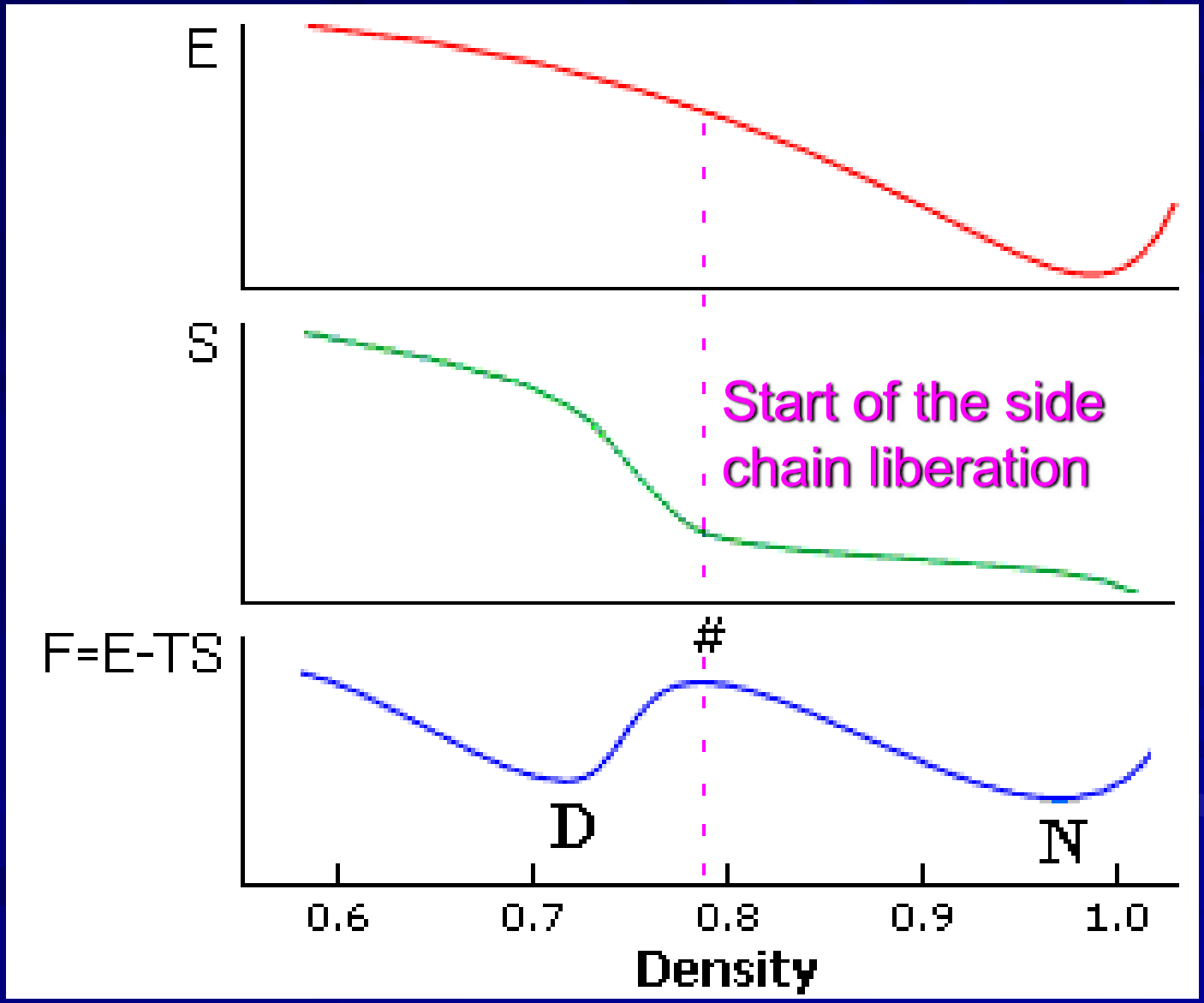
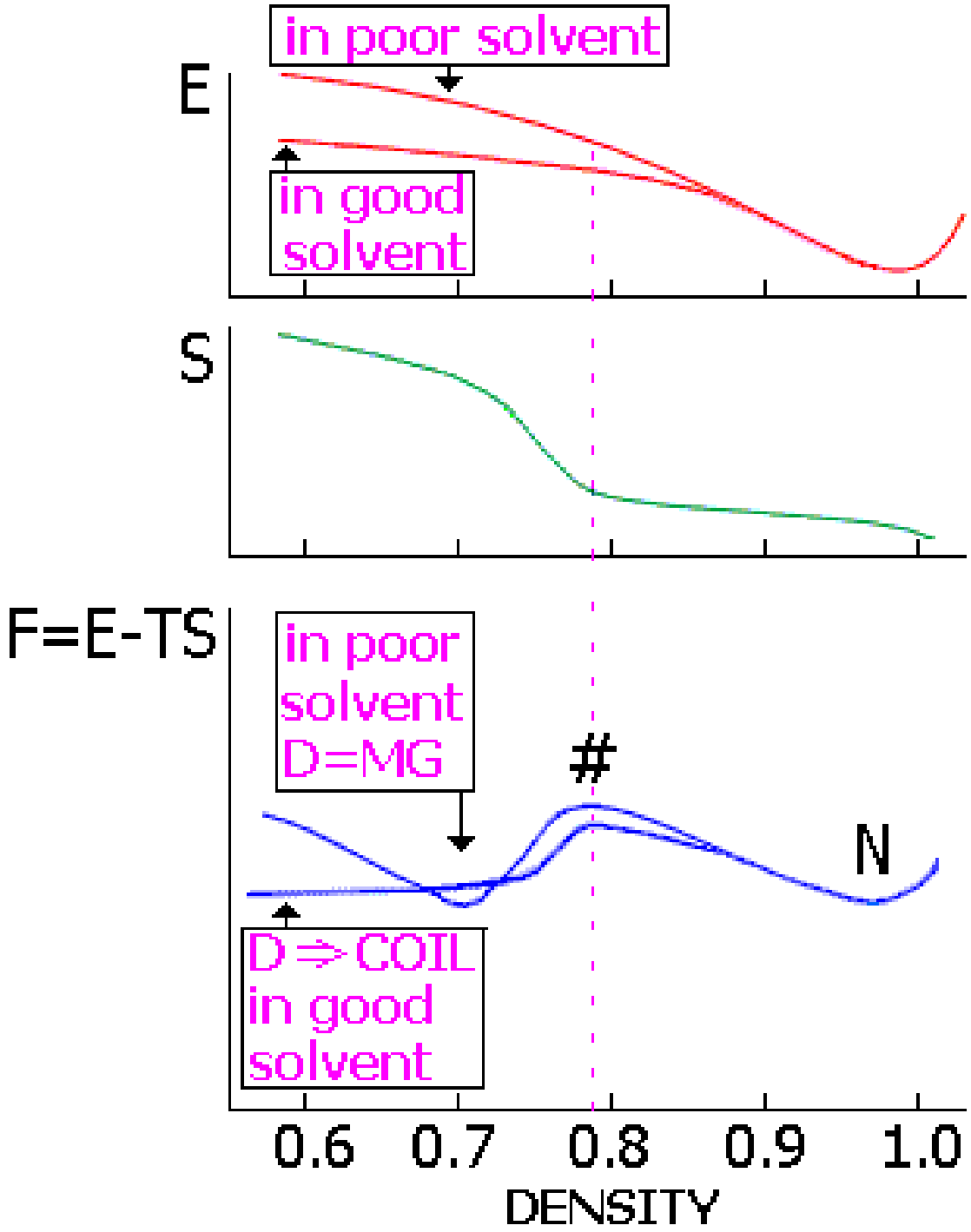




Transitions

Native → Globule

Native → Coil

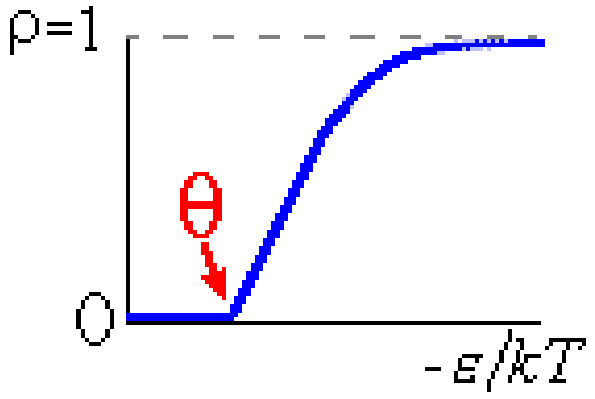
have to overcome the barrier # :

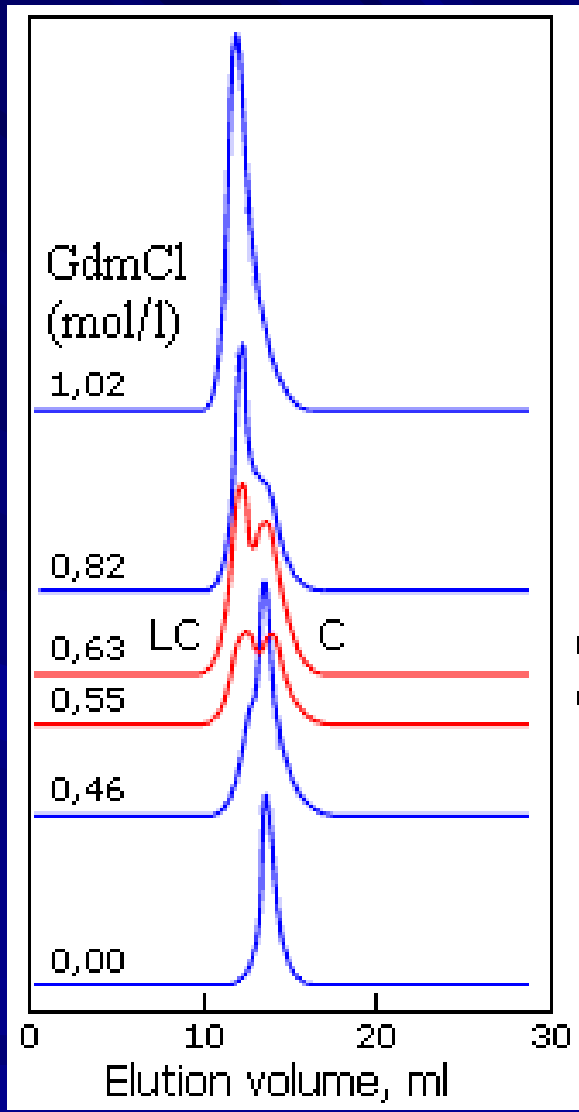
therefore,

"all-or-none"

Unfolding of MG

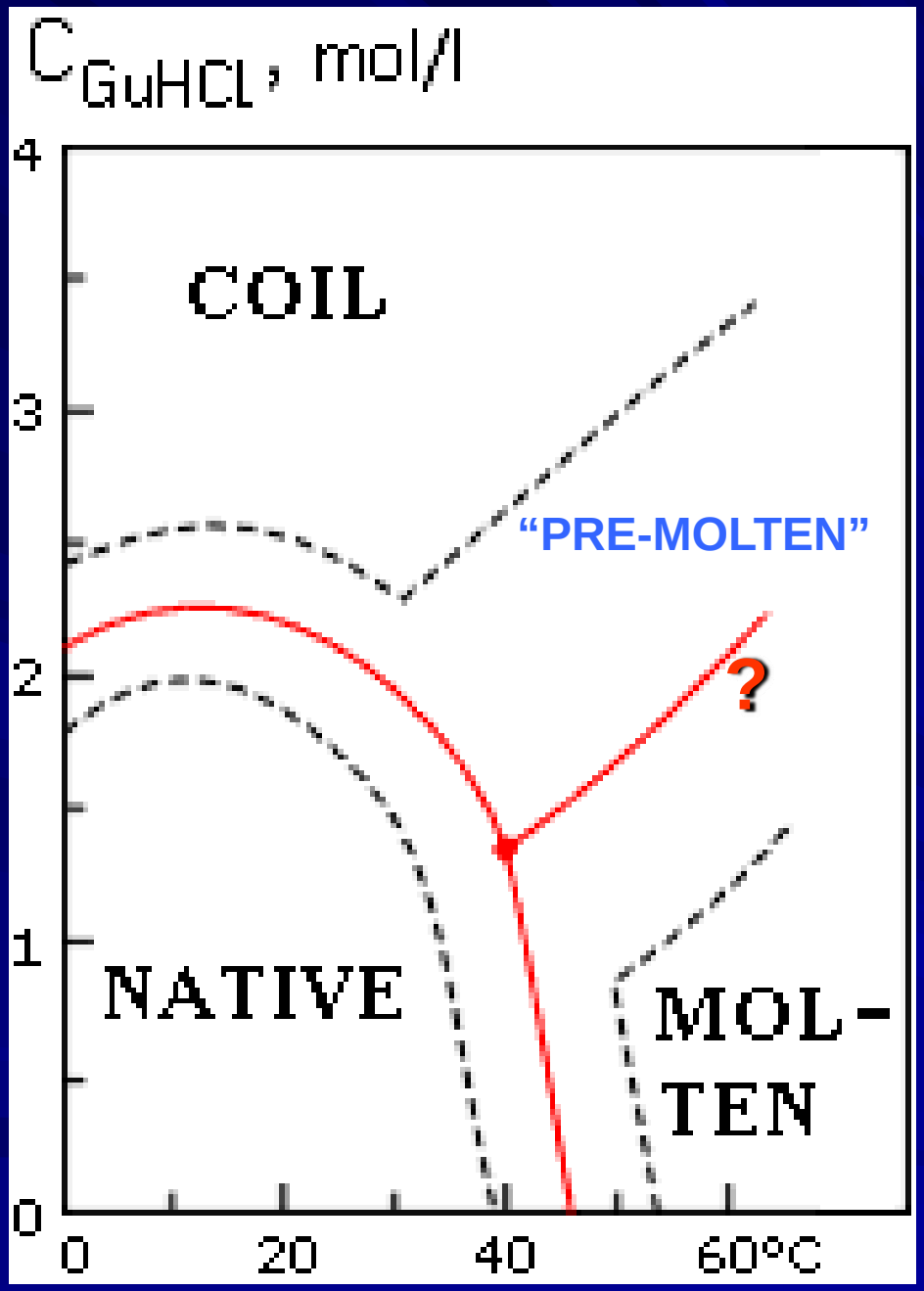
Coil - MG transition is gradual in many proteins





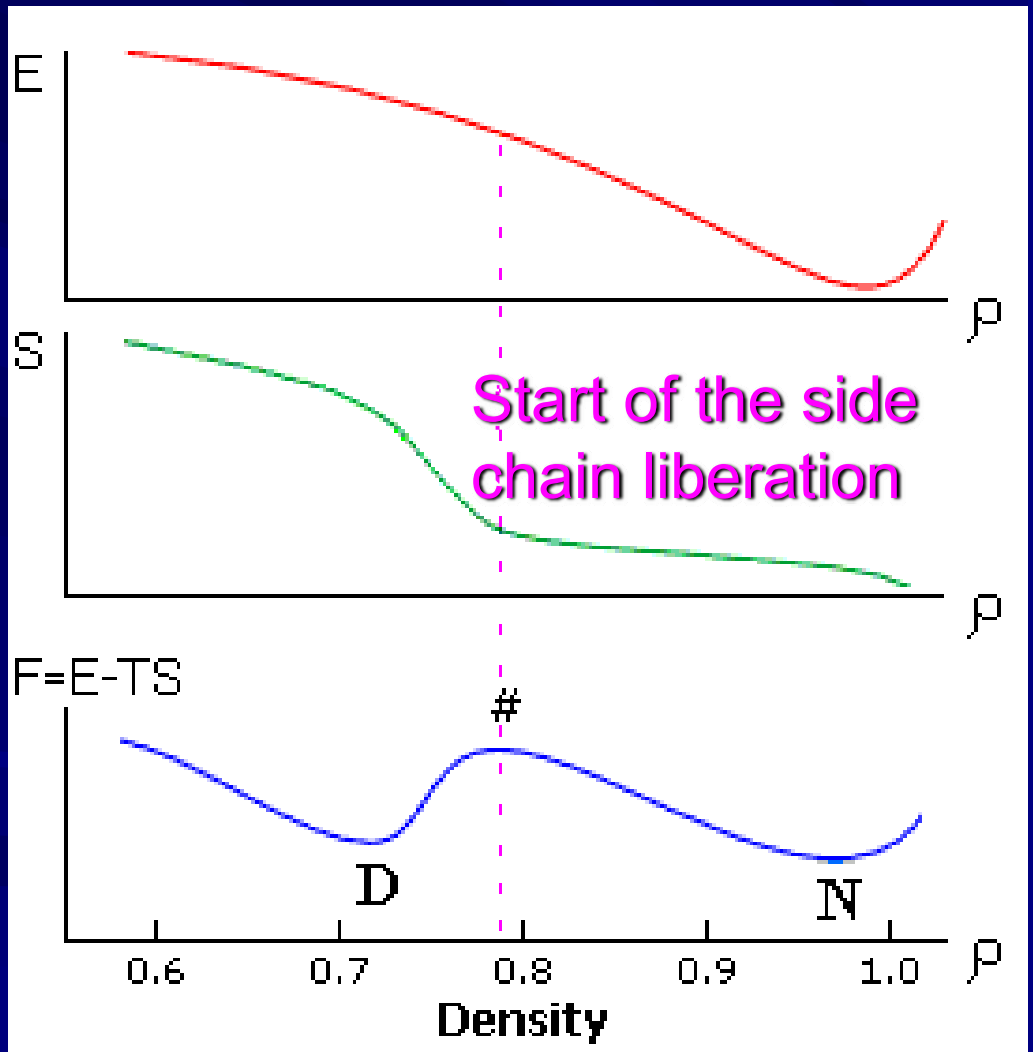
Coil - MG transition is "all-or-none" in some proteins

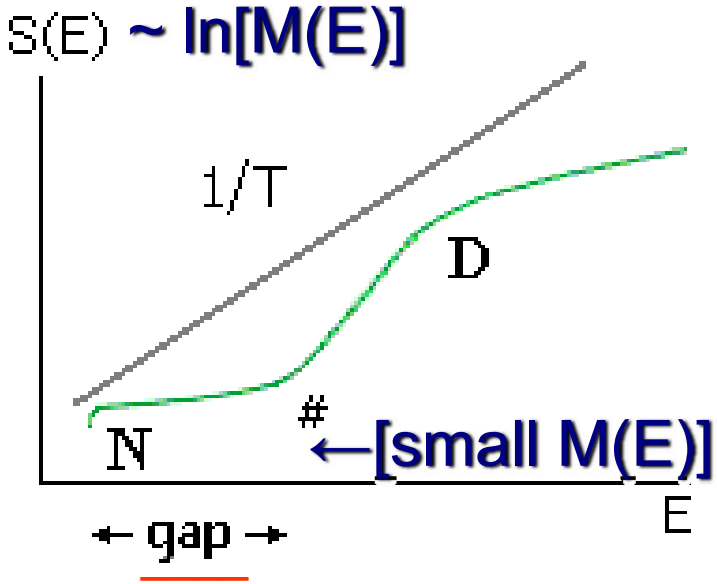
(Uversky, … Ptitsyn, 1992)



(Tanford, 1968)

"All-or-none" melting: a result of the "energy gap"





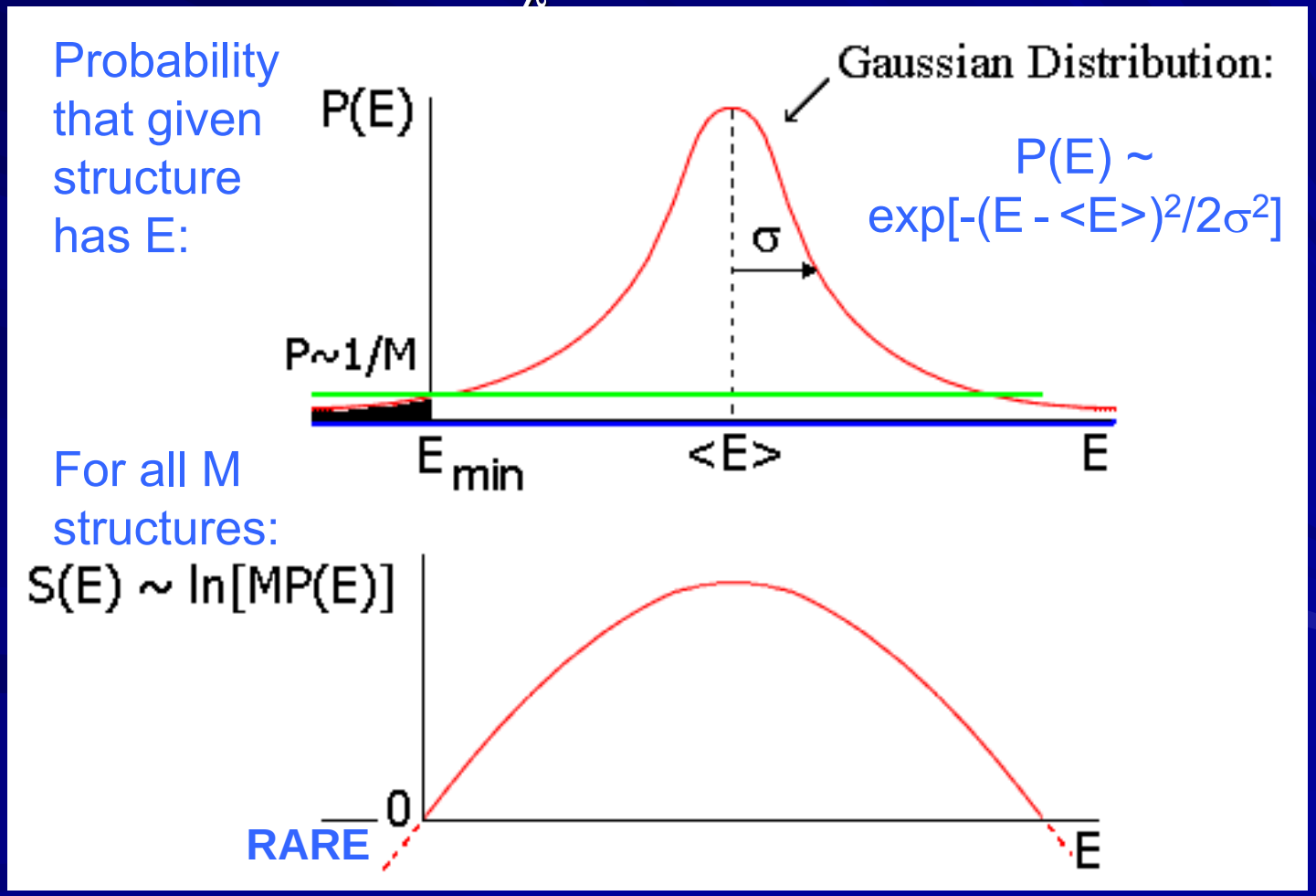
IS THE GAP "NATURAL"?

Random Energy Model (**REM**)

$M \sim 2^N$ structures of N various particles

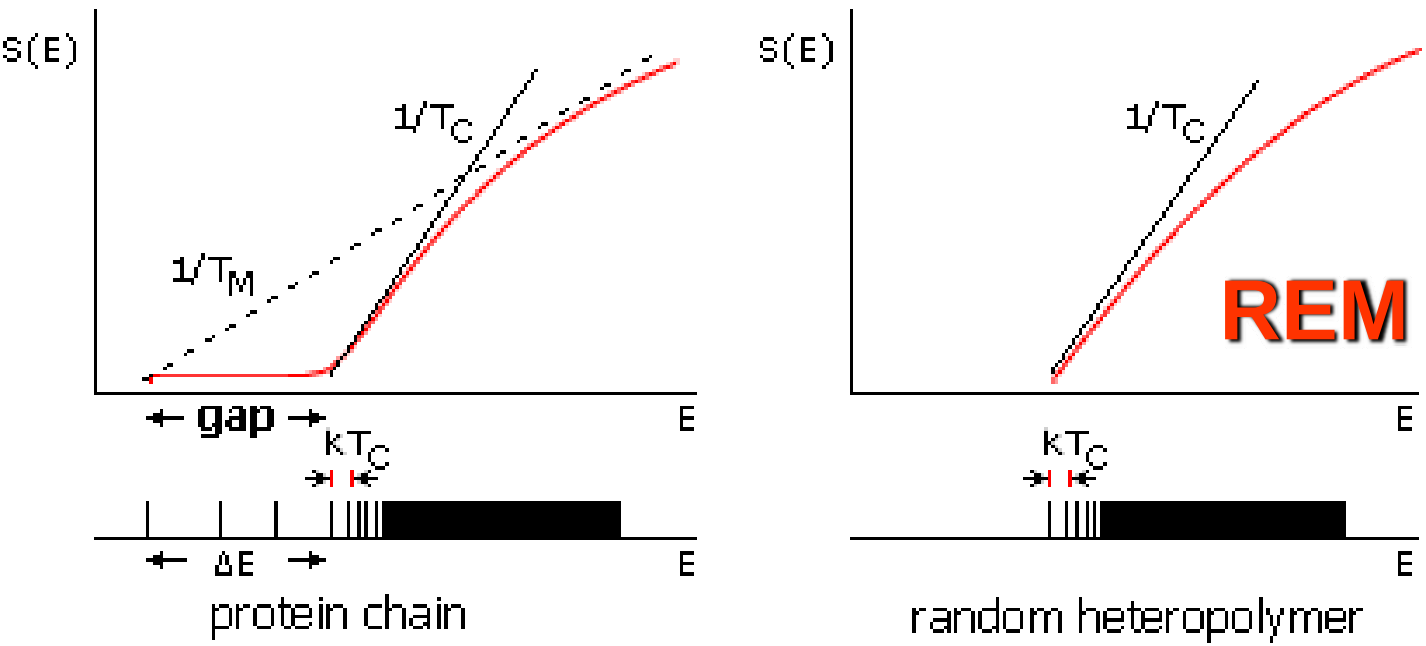
interactions in "**i**": ~ N

Energy of "structure **i**": $E_i = \sum_\lambda \varepsilon_\lambda^{(i)}$ $\Rightarrow$ **Statistics:** $\langle E \rangle$, σ



"Energy gap" and "all-or-none" melting.

"Protein-like" heteropolymers.



|←GAP→| : necessary for "all-or-none" melting

temperature T_M: protein melting

temperature T_C: chain vitrifying

Fraction of "protein-like" random heteropolymers:

REM: $\mathrm{FRACTION}(\Delta E) \sim \exp(-\Delta E/kT_C)$

REM
(random energy model)

ENERGY SPECTRA

GAP WIDTH ΔE

The gap has some (small) chance to be be of a significant width

WHY DO PROTEINS USUALLY HAVE ONLY 1 NATIVE FOLD?

REM:

1 NATIVE FOLD: WONDER, $\sim \exp(-\Delta E/kT_C)$;

2 NATIVE FOLDS: WONDER SQUARED…

(but: serpins)

GAP WIDTH ΔE: MAIN PROBLEM OF EXPERIMENTAL PROTEIN PHYSICS

PHYSICAL ESTIMATE: ???

BIOLOGICAL ESTIMATE:

1 OF ~1 000 000 000 RANDOM SEQUENCES MAKES A "PROTEIN-LIKE" STRUCTURE (SOLID, WITH A SPECIFIC BINDING: PHAGE DISPLAY).

THIS IMPLIES THAT $\Delta E \sim 20\ kT_C$

($\Delta H_{melt} \sim 100\ kT_M >> \Delta E$):

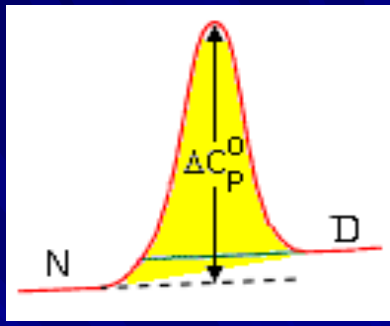
consistent with

NARROW GAP, i.e.,

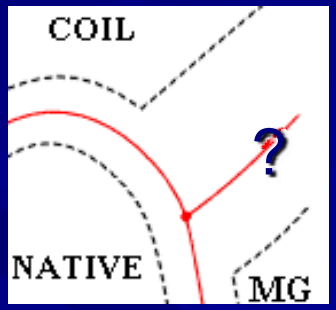
T_M IS ONLY A LITTLE HIGHER THAN T_C.

Protein Structures: Thermodynamics

- Protein denaturation: cooperative and, moreover, an “all-or-none” transition in small proteins and separate domains.



- Solid native state, unfolded coil & “molten globule”.



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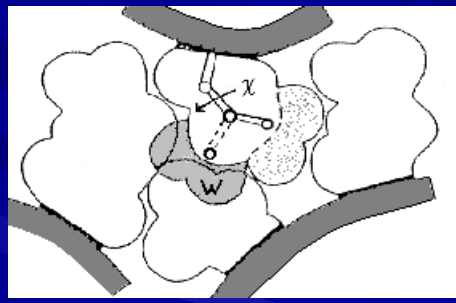

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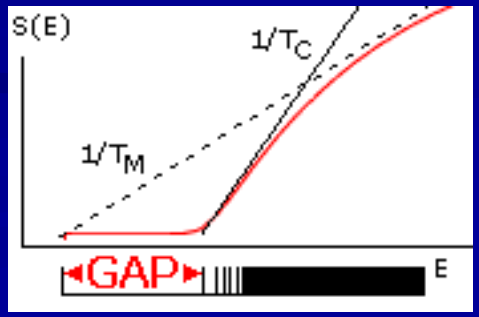
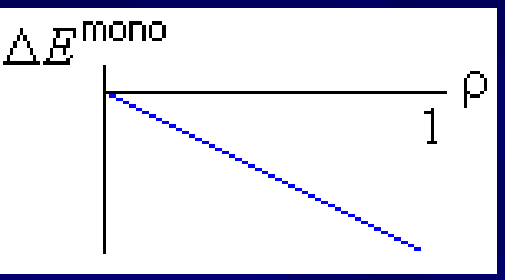
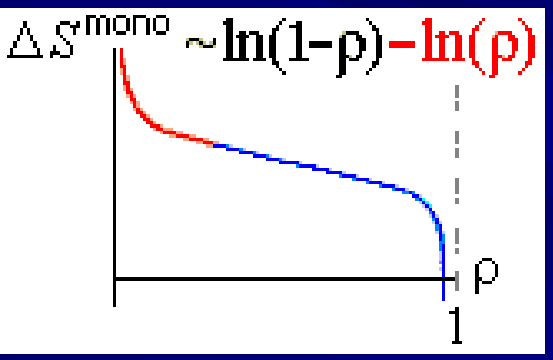
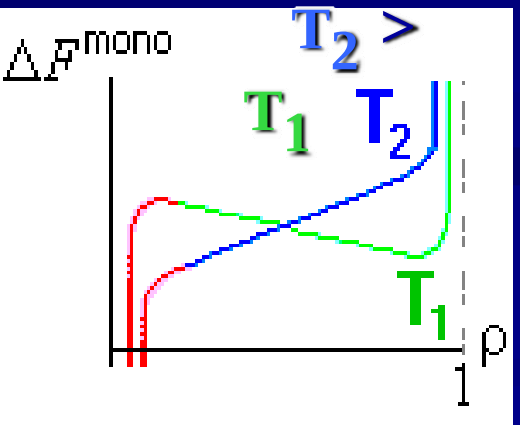


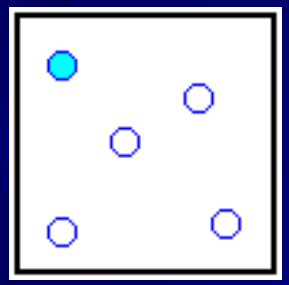
Comparing globule-to-coil transition in polymers to 1-st order phase transition like evaporation

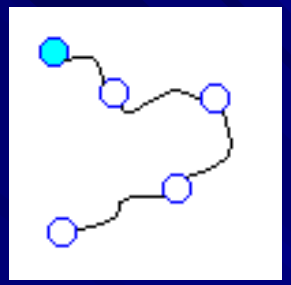
Separate monomers





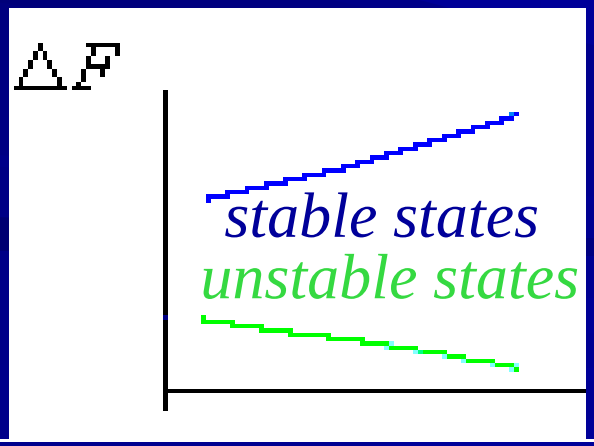






Per a particle:
$\Delta F = \Delta H - T\,\Delta S$
$= \mu$ ***(chemical potential)***

Transition: $\Delta F_1 = \Delta F_2$



Polymer chain