CompPhys09: New Developments in Computational Physics, Leipzig, Nov. 26, 2009

All-or-none protein-like folding of a homopolymer chain

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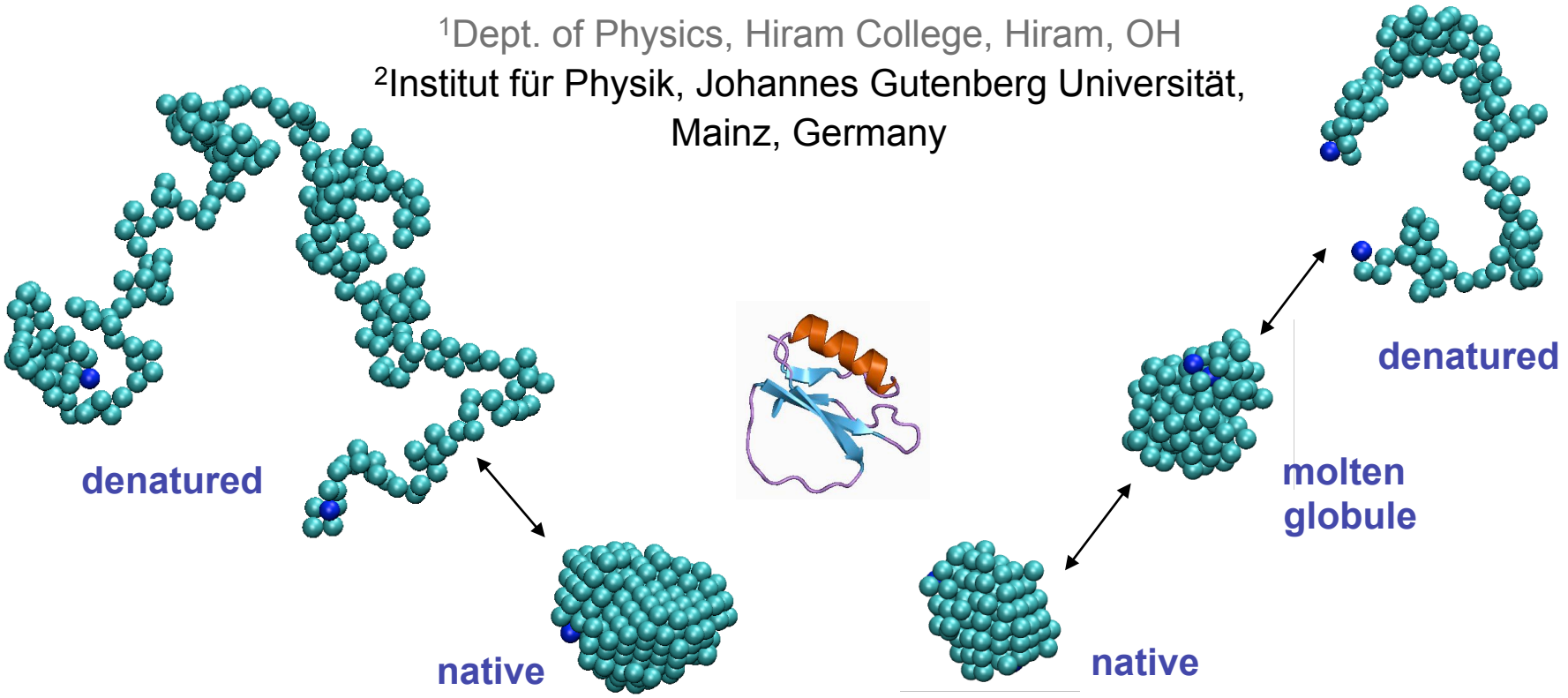
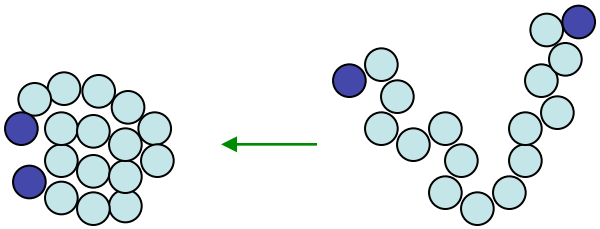


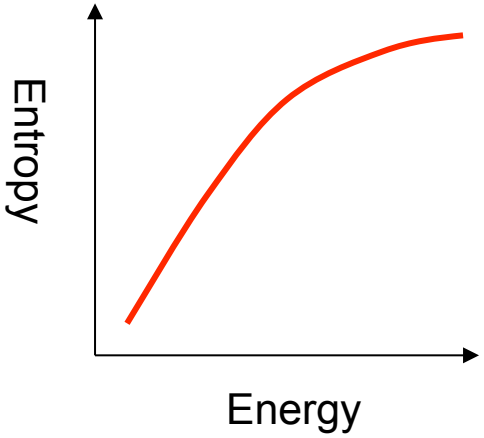
Can a simple homopolymer model capture some essentials of protein folding?

Single Chain Conformational Transitions

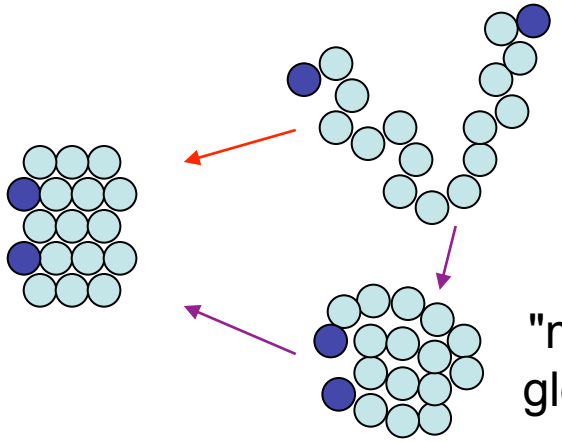
Homopolymer
Globule ⇔ Coil



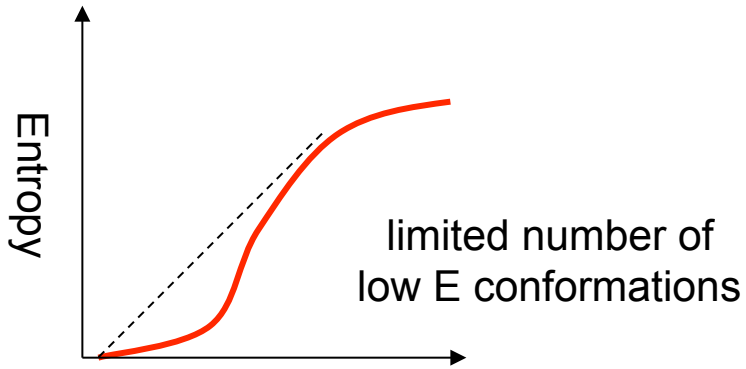
compact ← expanded
(both disordered)
continuous transition



Protein
Native ⇔ Denatured



order ← disorder
discontinuous transition



Finkelstein & Ptitsyn,
"Protein Physics" (2002)

Multiple Transitions in a Simple Chain Model

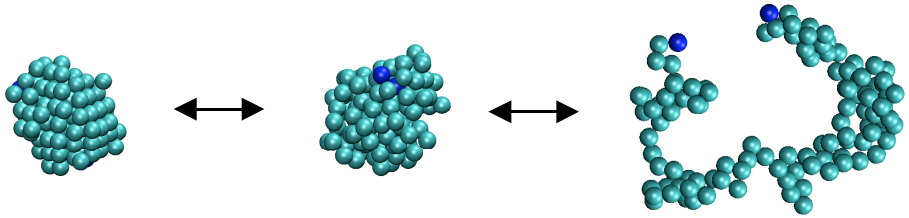
Zhou, Hall, and Karplus found a **"first-order" transition** in a model homopolymer

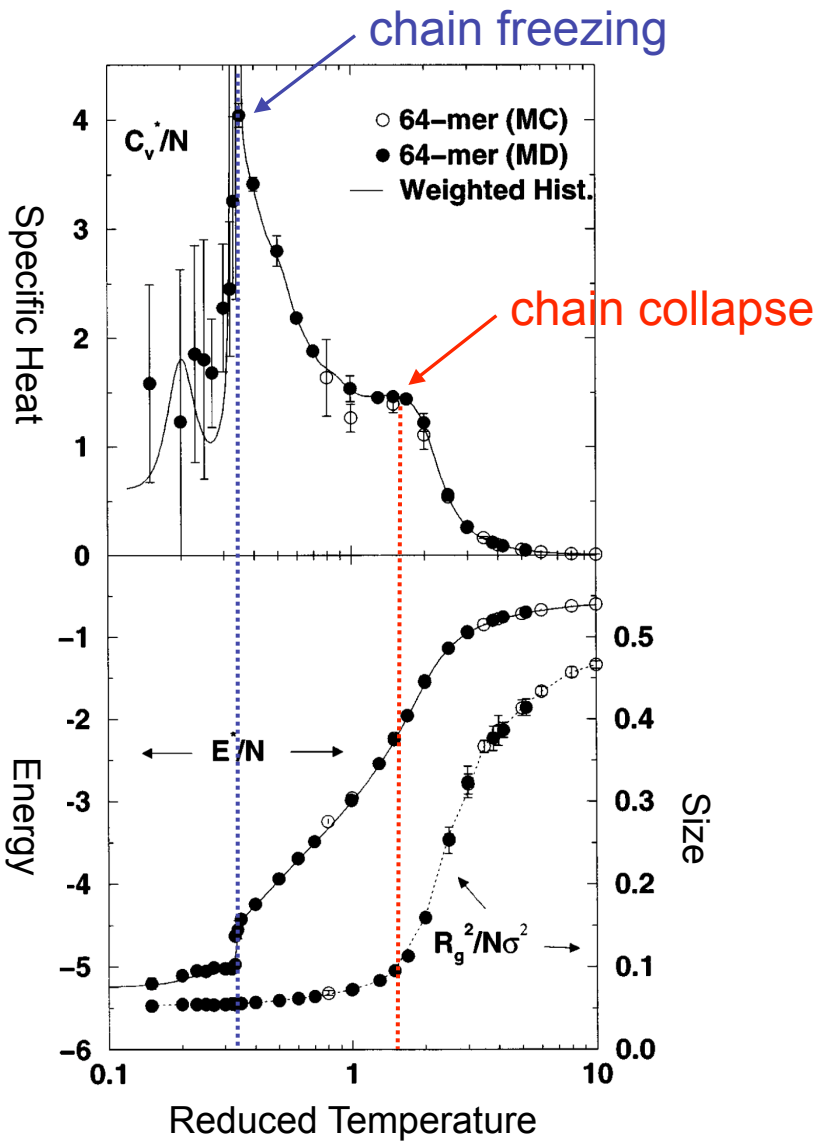
Model: Flexible Square-Well Chain
Length: N = 64
Well Diameter: λ = 1.5
MC and DMD simulations

PRL **77**, 2822 (1996)

Analogy with Bulk Fluid:
Solid ⇔ Liquid ⇔ Gas

Similar to Protein:
Native⇔Globule⇔Denatured



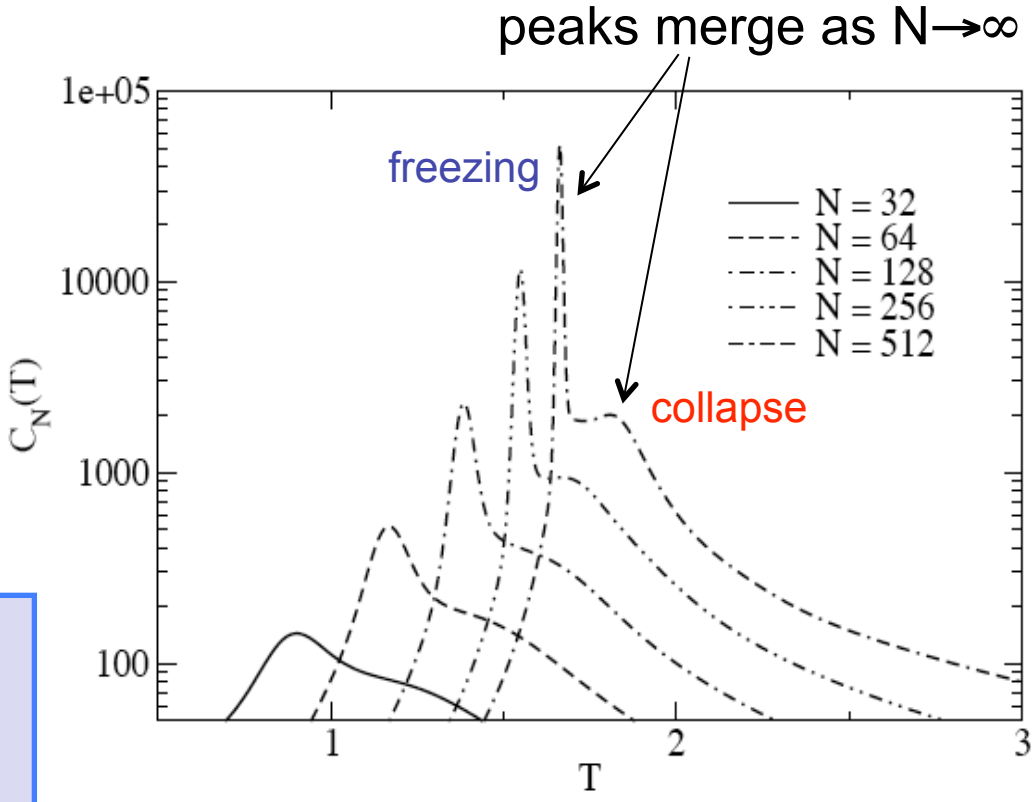


Protein-like "all-or-none" transition in a simple model?

Ten years later ... a new result:

Rampf, Paul, and Binder find evidence for a **"direct freezing"** transition in a simple model system.

Lattice Bond-Fluctuation Model
Chain Length: N = 32-512
Interaction Range: λ = 1.225
Wang-Landau Simulation Method



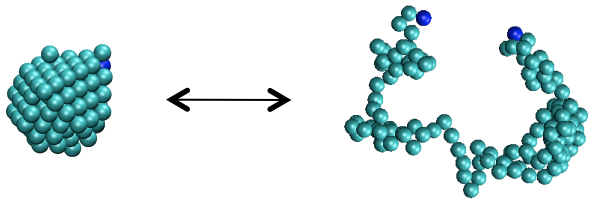
Europhys Lett. 70, 628 (2005); J. Polym. Sci. B 44, 2542 (2006);
PRE 75, 060801(R) (2007)

Analogous to simple liquid:

Solid ⇔ Gas

and single-step protein folding**?**:

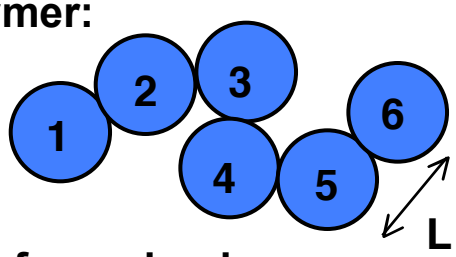
Native ⇔ Denatured



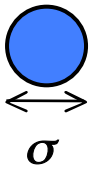
Question: can a finite-length homopolymer exhibit such an all-or-none transition?

SW Chain Model

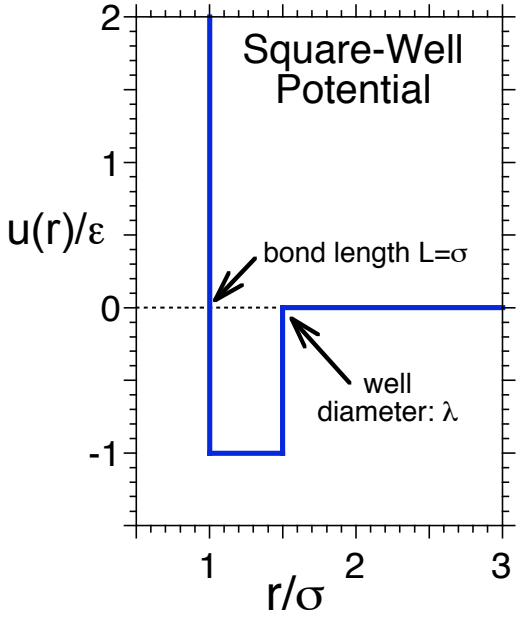
Polymer:



built from simple monomers:



monomer-monomer interaction



Model Parameters:

- ε = well depth (sets energy scale)
- σ = hard-sphere diameter
- L = fixed bond length (L = σ)
- **λ = interaction range/σ**
- $T^* = k_B T/\varepsilon$ = reduced temperature

Model has a discrete energy spectrum: $\mathbf{E_n = n\varepsilon}$

(**n** = number of monomer-monomer interactions)

Can study this model for a continuous range of λ

For SW *monomers*: liquid phase is unstable if λ ≤ 1.25

Question: Does the SW chain exhibit similar behavior?

Note: chain connectivity places an upper limit on entropy of "gas" phase

Density of States and Wang-Landau Sampling I

Density of States:

$g(E_n)$ = volume of configurational phase space for energy state E_n

Thermodynamics:

microcanonical entropy:
$S(E) = k_B \ln g(E)$

canonical partition function:
$Z(T) = \sum g(E) \exp(-E/k_B T)$

Wang-Landau algorithm* ... an iterative simulation method to compute **$g(E_n)$:**

Starting w/ **$g(E_n)=1$, $H(E_n)=0\ \forall\ n$, $f_0 = e$**

Generate sequence of chain conformations using acceptance criteria:

$$P_{acc}(a \to b) = \min\left(1, \frac{g(E_a)}{g(E_b)}\right)$$

Update DOS: **$g(E_n) \to f_m\, g(E_n)$**

Update visitation histogram: **$H(E_n) \to H(E_n)+1$**

When histogram ~flat ...
reduce modification factor: **$f_{m+1} = (f_m)^{1/2}$**
reset histogram to zero: **$H(E_n) = 0\ \forall\ n$**

iterate m levels

m=20 is standard

we need m>25

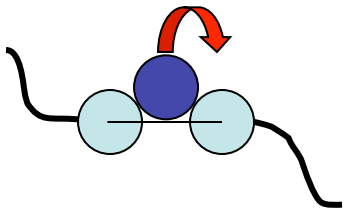
***Wang & Landau, PRL 86, 2050 (2001); PRE 64, 056101 (2001).**

Wang-Landau Sampling II

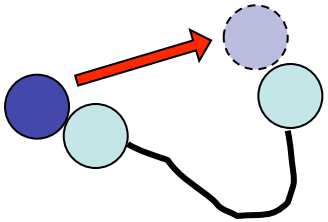
Success of the WL methods depends critically on underlying MC move set

These "standard" moves easily sample most of configuration space:

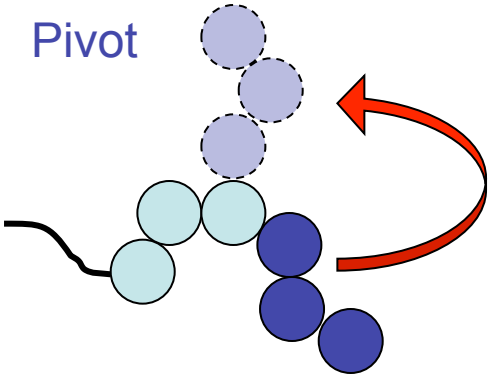
Single bead crankshaft



Reptation

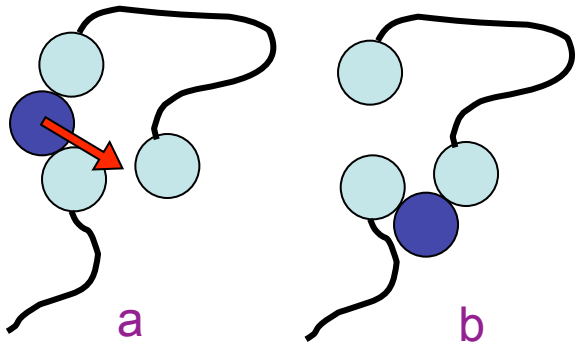


Pivot



... However, we need **this move** to access the lowest energy regions of phase space:

End-bridging



This move requires weight factors in the acceptance criteria:

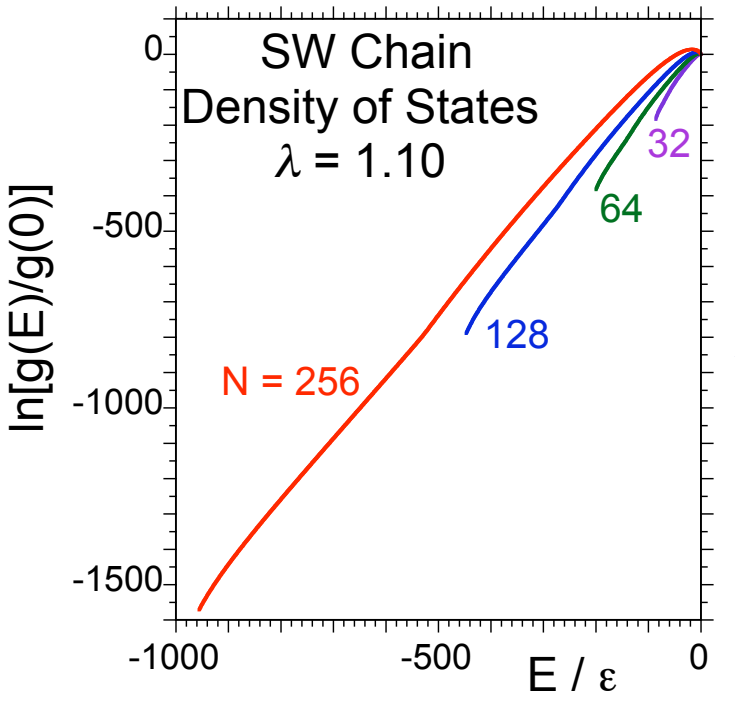
$w_a = n_a J_a$

# of bridgable sites in state a

Jacobian factor for state a

Escobedo & de Pablo, JCP **102**, 2636 (1995)

Single Chain DOS and Canonical Analysis



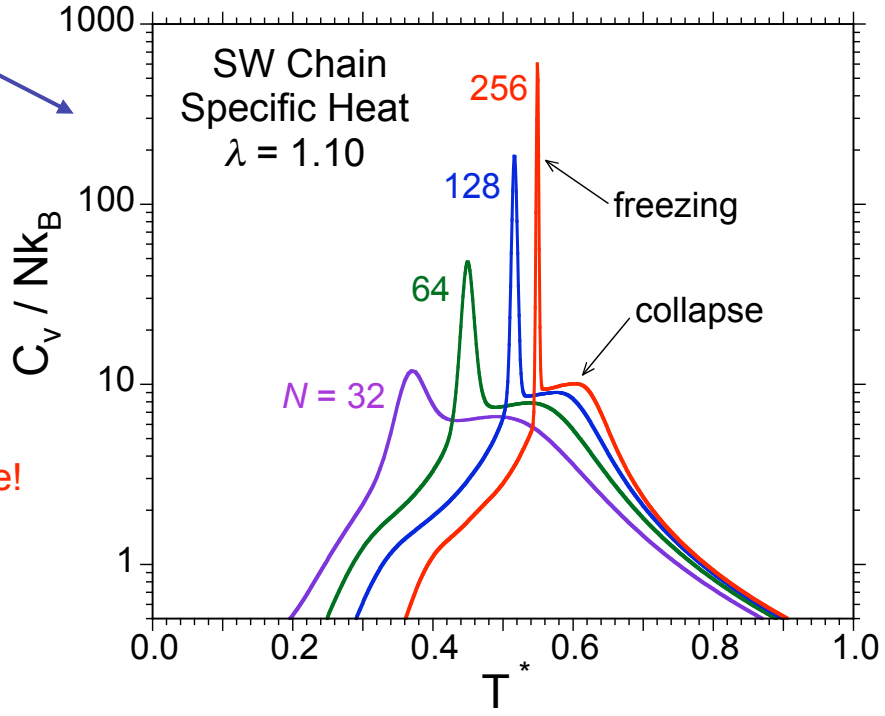
Canonical Analysis

Partition Function: $Z = \sum g(E)\, e^{-E/kT}$

Probability: $P(E,T) = g(E)\, e^{-E/kT} / Z$

Average Energy: $\langle E(T) \rangle = \sum EP(E,T)$

Specific Heat: $C(T) = d\langle E(T) \rangle / dT$

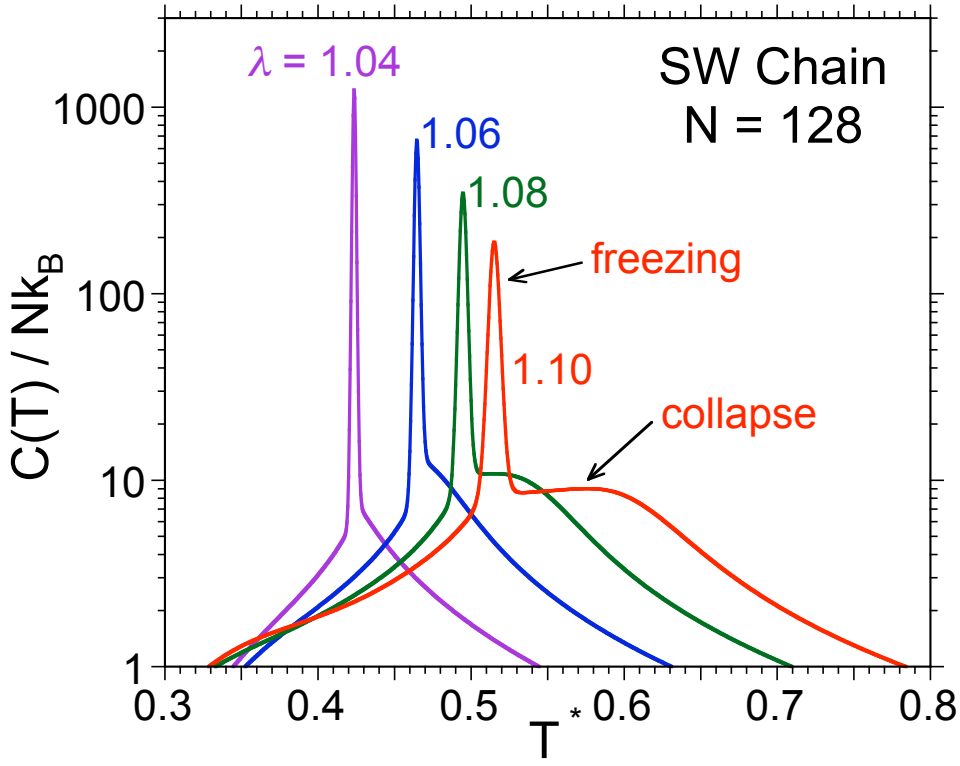


For N = 256: g(E) spans ~700 orders of magnitude!

Taylor, Paul, & Binder,
PRE **79**, 050801(R) (2009)

Phase Behavior for Finite Length Chain?

In the "canonical analysis", collapse and freezing specific heat peaks merge for small λ ...

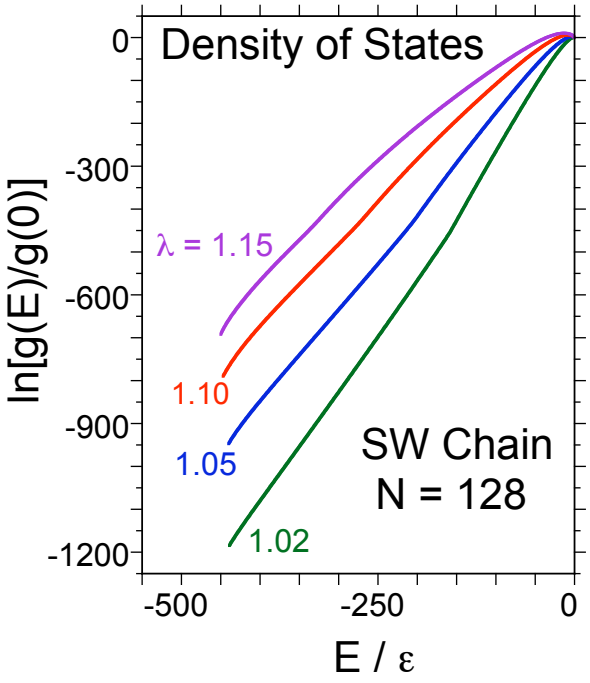


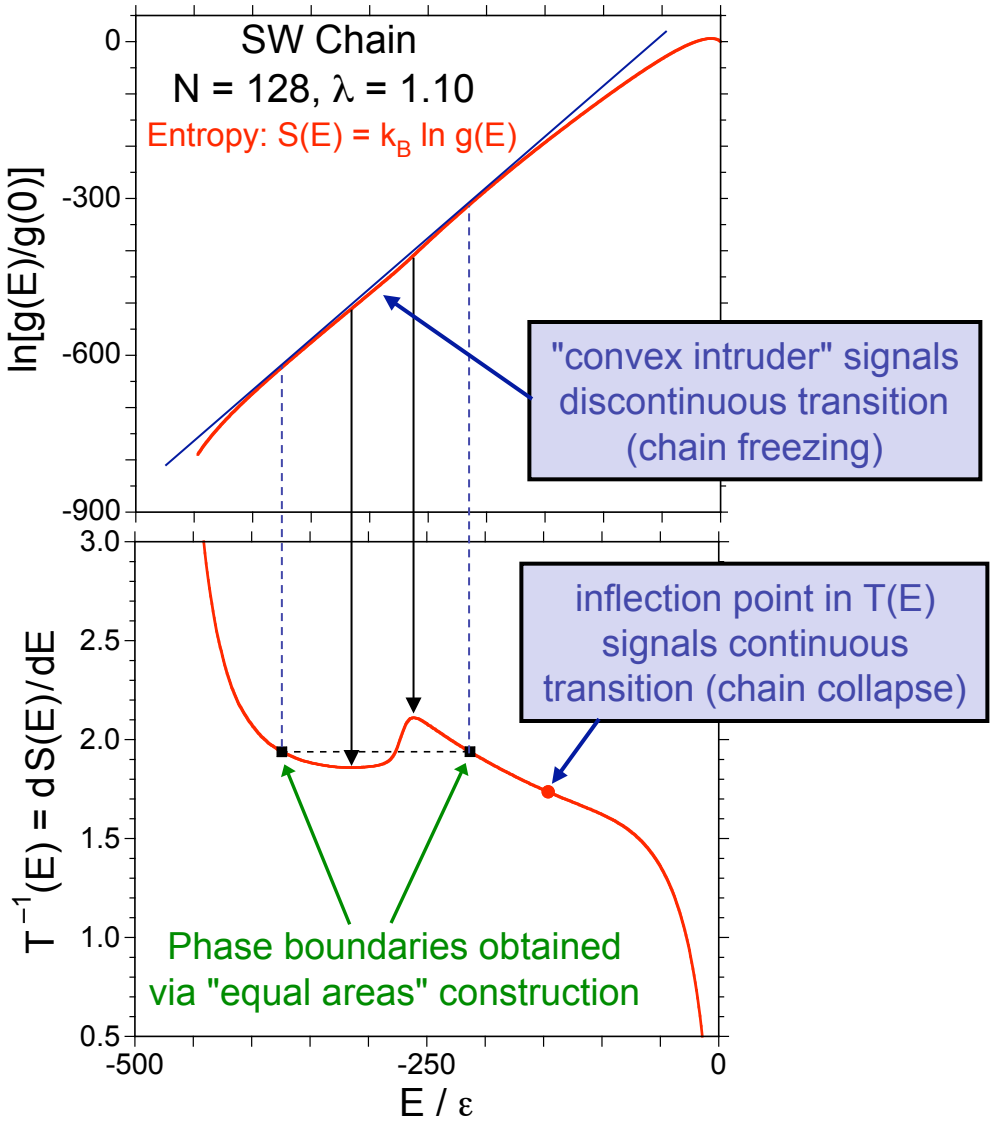
... a "microcanonical analysis" can be used to distinguish these transitions

Microcanonical Analysis I

Phase transitions in a finite system determined from **curvature** of the microcaonical entropy:

$S(E) = k_B \ln g(E)$





Gross, "Microcanonical Thermodynamics" (2001)

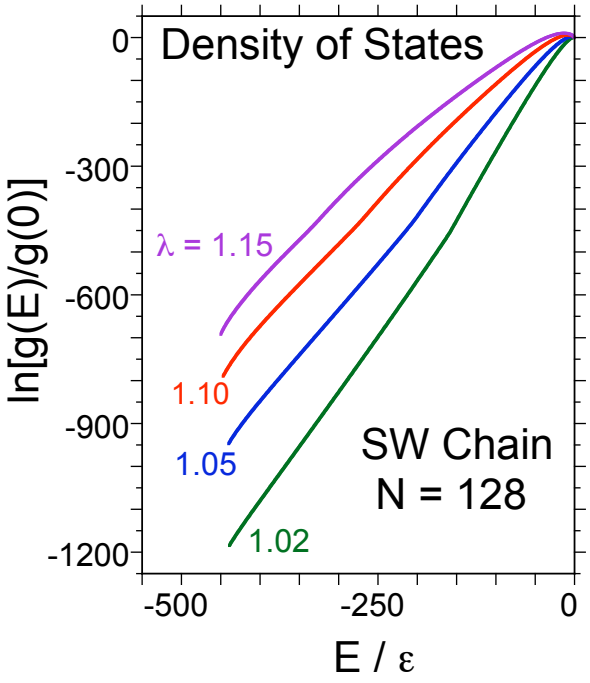
Junghans, Bachmann, & Janke, PRL **97**, 218103 (2006)

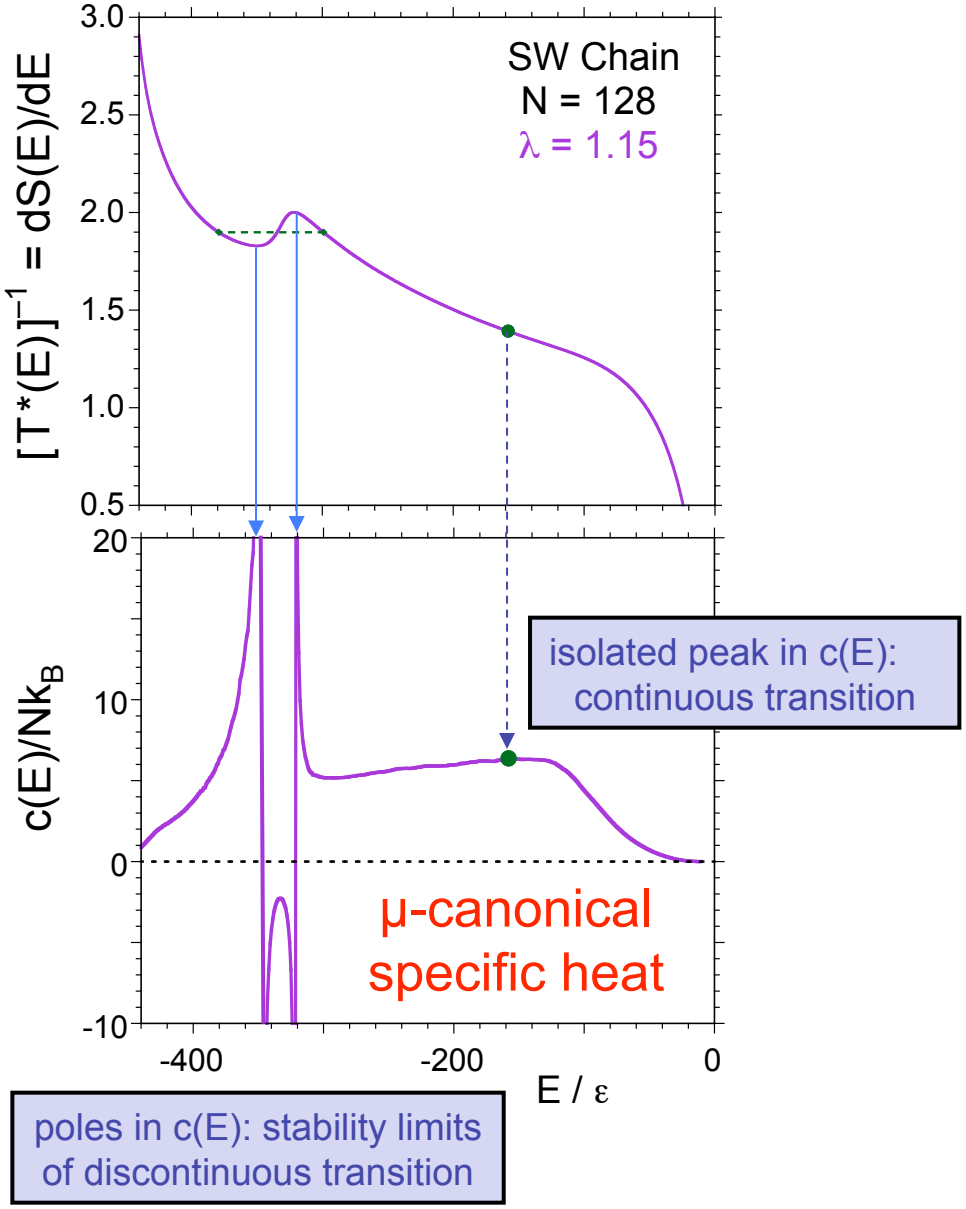
Taylor, Paul, & Binder, PRE **79**, 050801(R) (2009)

Microcanonical Analysis II

Phase transitions in a finite system determined from **curvature** of the microcaonical entropy:

$S(E) = k_B \ln g(E)$





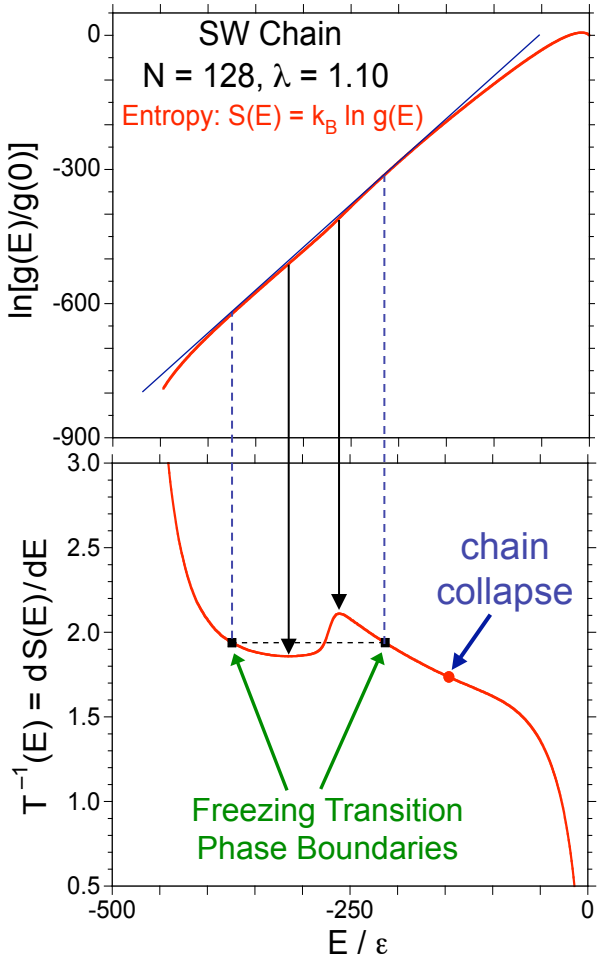
Gross, "Microcanonical Thermodynamics" (2001)

Junghans, Bachmann, & Janke, PRL **97**, 218103 (2006)

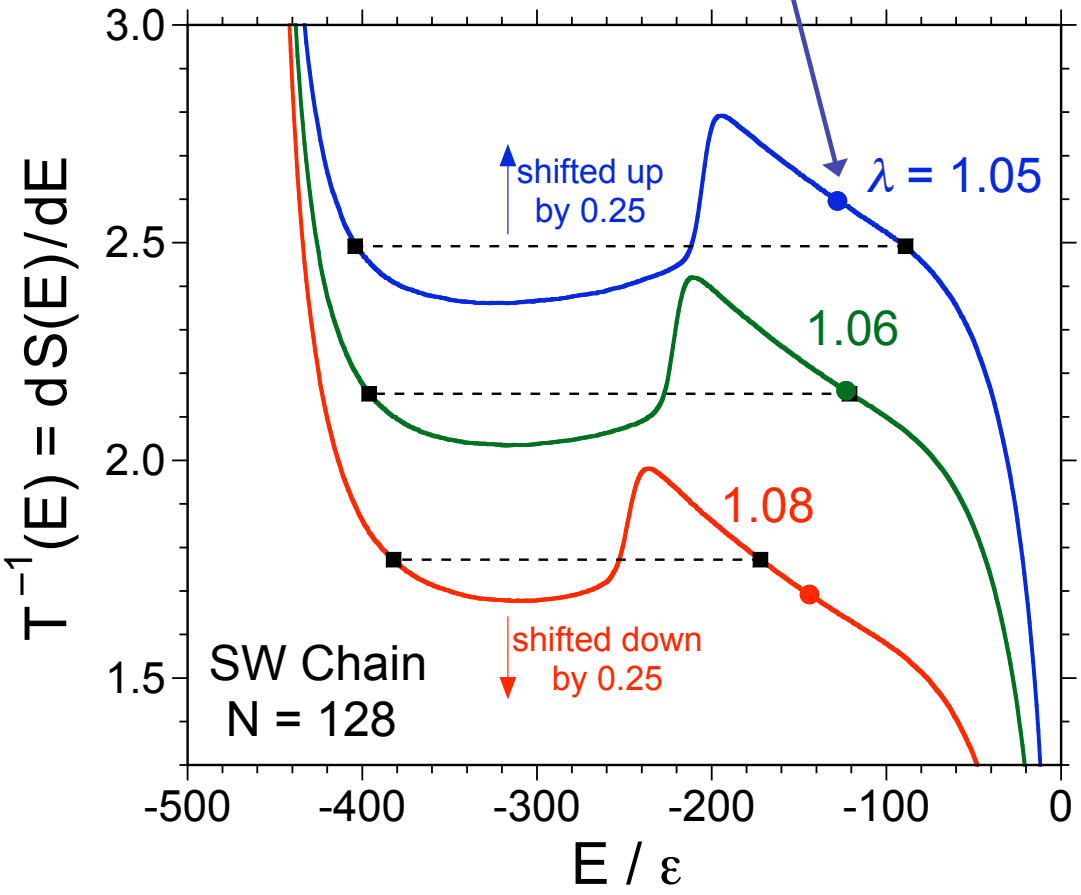
Taylor, Paul, & Binder, JCP **131**, 114907 (2009)

Microcanonical Analysis III

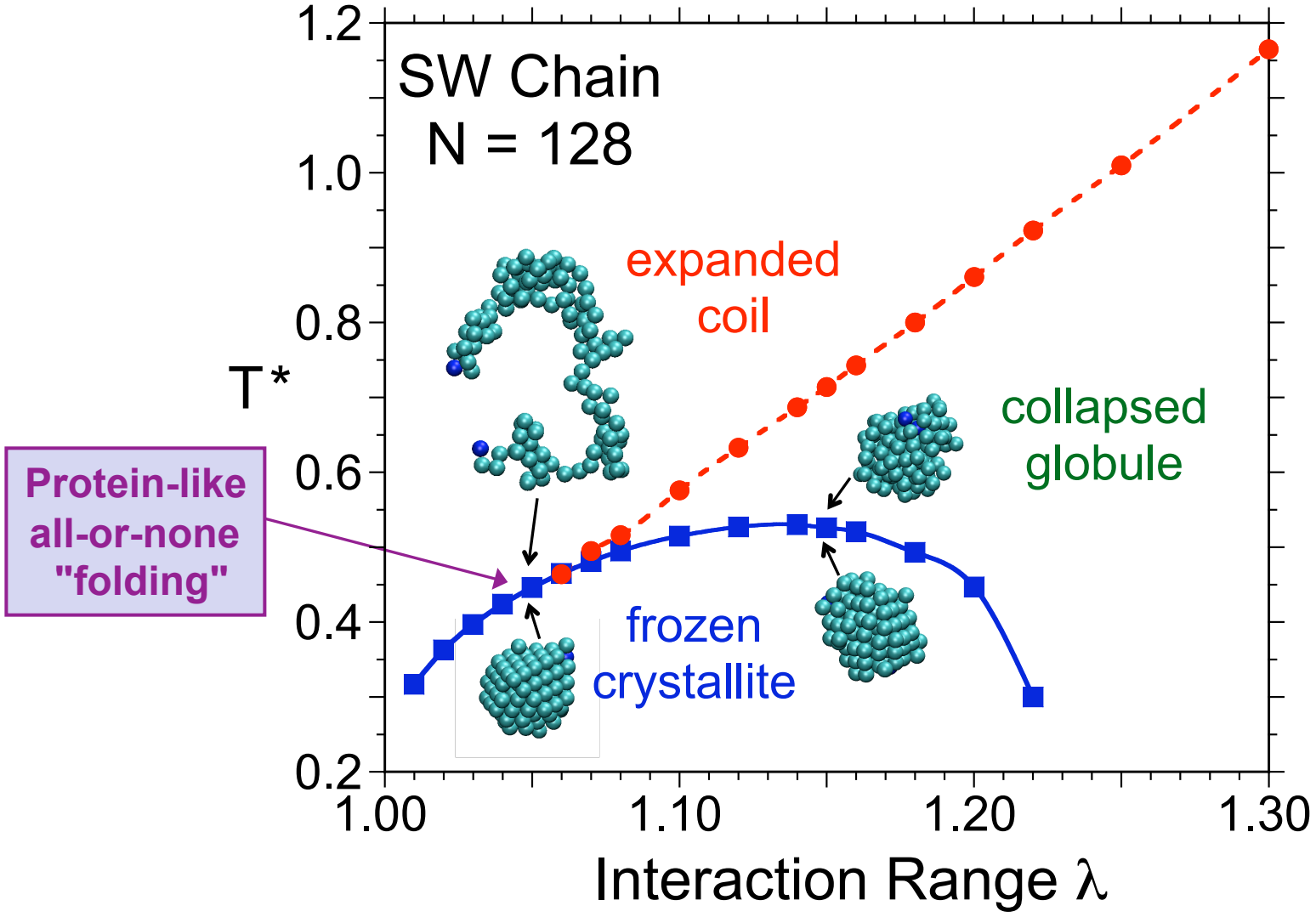
Phase transitions in a finite system determined from **curvature** of S(E)



Collapse transition is preempted by freezing for short-range interaction!

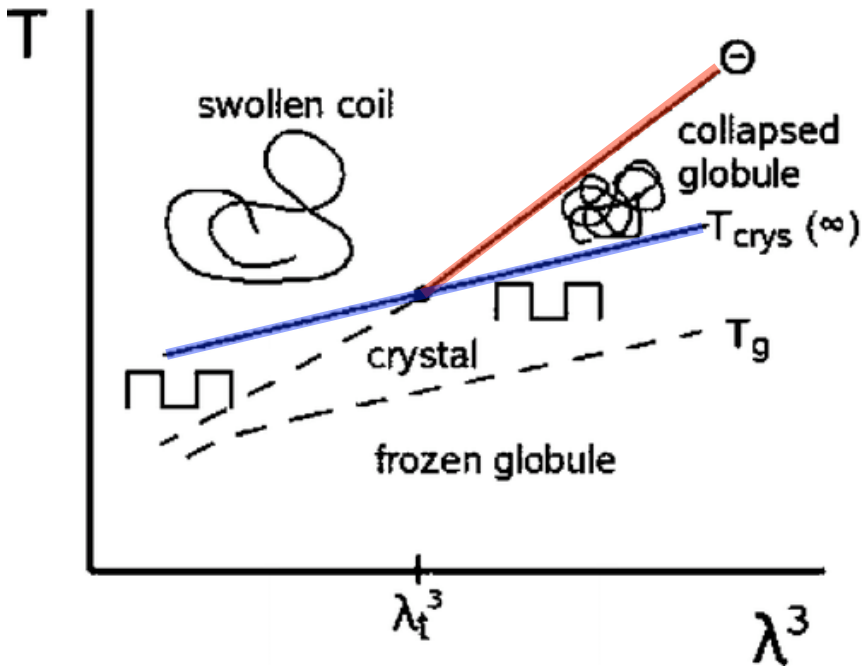


Single Chain Phase Diagram: T-λ Version



Taylor, Paul, & Binder, J. Chem. Phys. **131**, 114907 (2009)

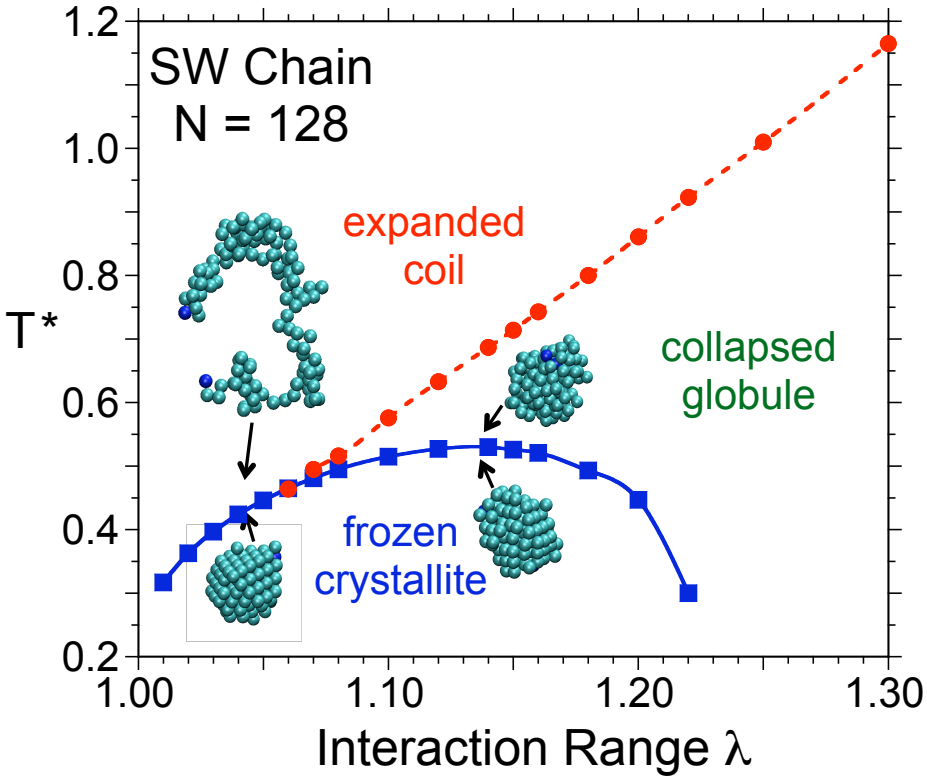
Prediction:



range of interaction

Binder and Paul
Macromolecules **41**, 4537 (2008)

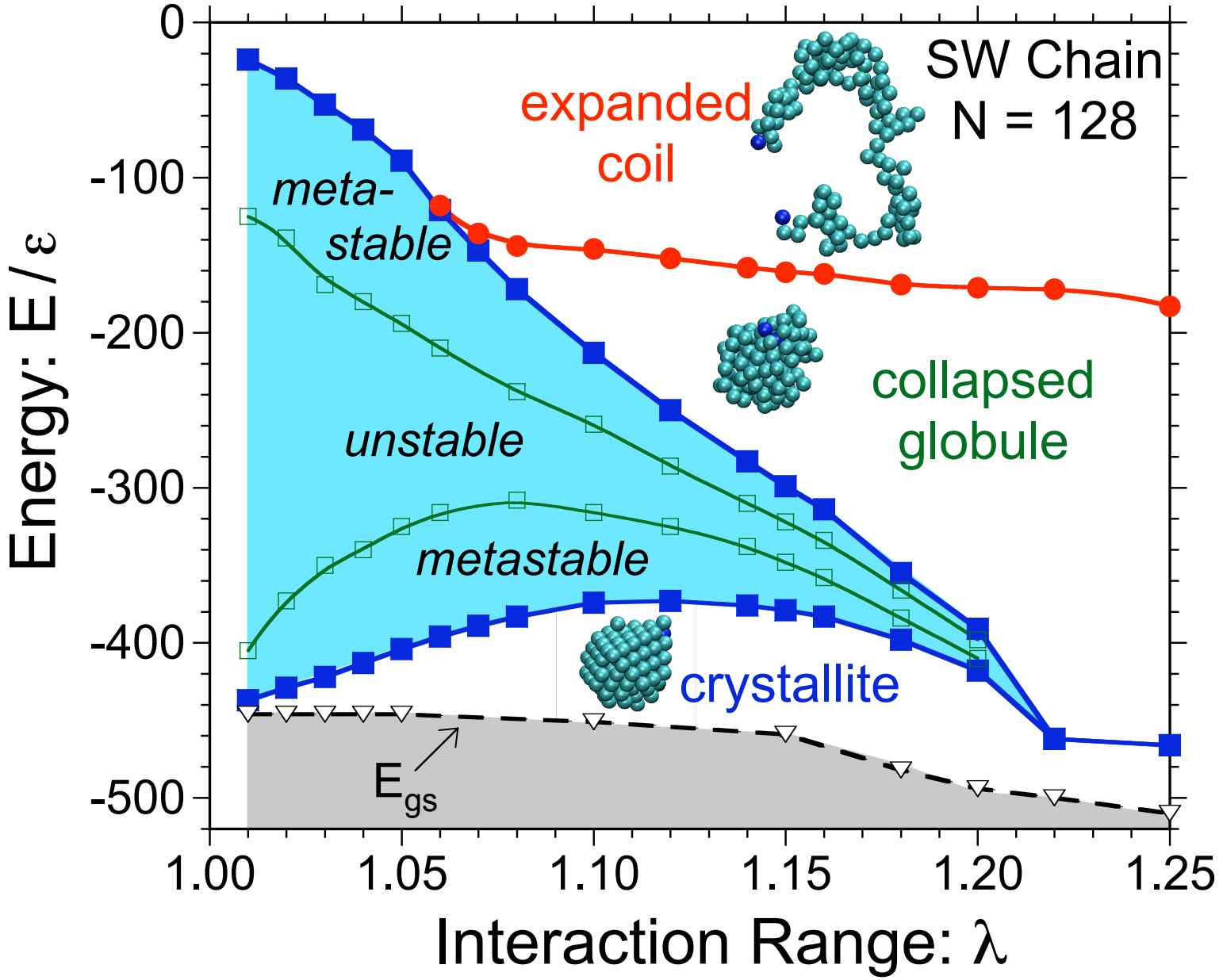
Calculation:



triple point moves to
λ = 1.15 in N → ∞ limit

Taylor, Paul, & Binder
J. Chem. Phys. **131**, 114907 (2009)

Single Chain Phase Diagram: E-λ Version



Protein Thermodynamics: Free Energy Landscape

All-or-none folding of a N = 128 SW Chain with λ = 1.05

Defining a physical **folding temperature** sets the model energy scale

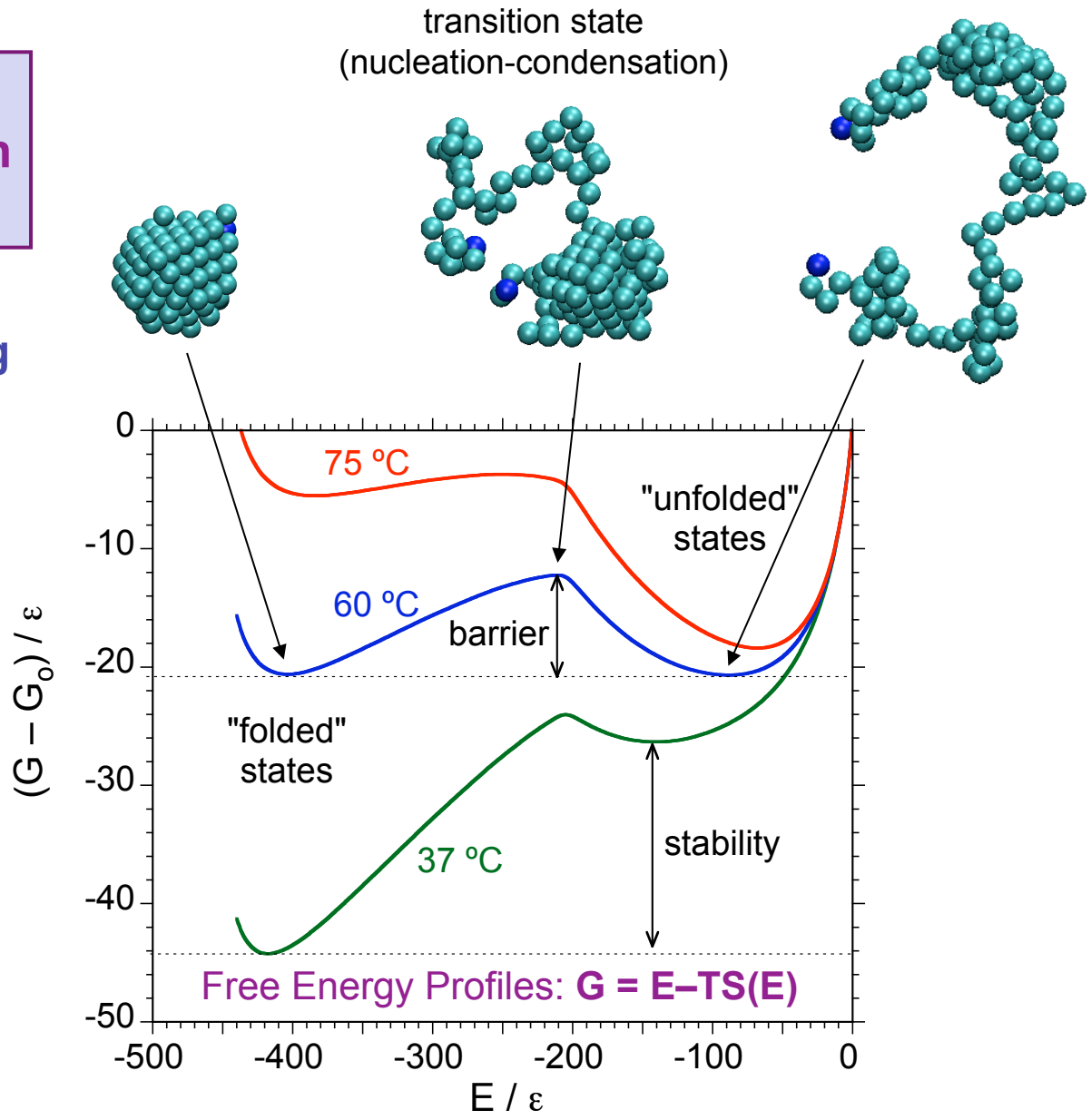
Here we take

T_{fold} = 333 K (60 ºC)

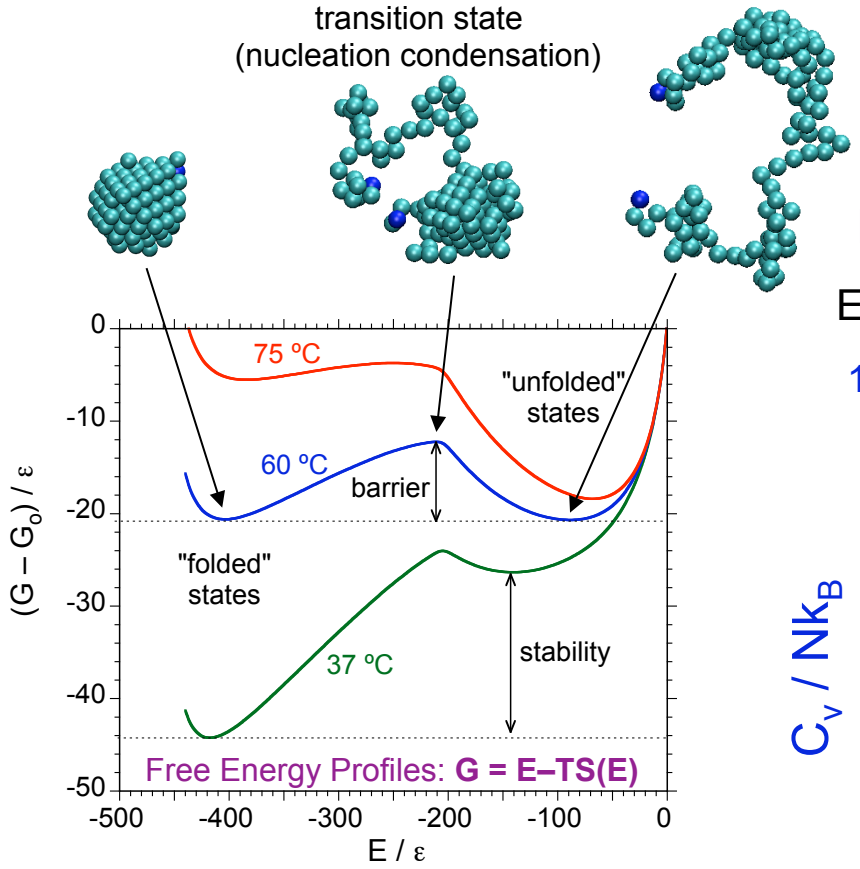
⇒ ε = 1.5 kcal/mol

Taylor, Paul, & Binder, PRE **79**, 050801(R) (2009)

See Chan and Kaya: Proteins **40**, 543 & 637 (2000); **52**, 510 (2003).



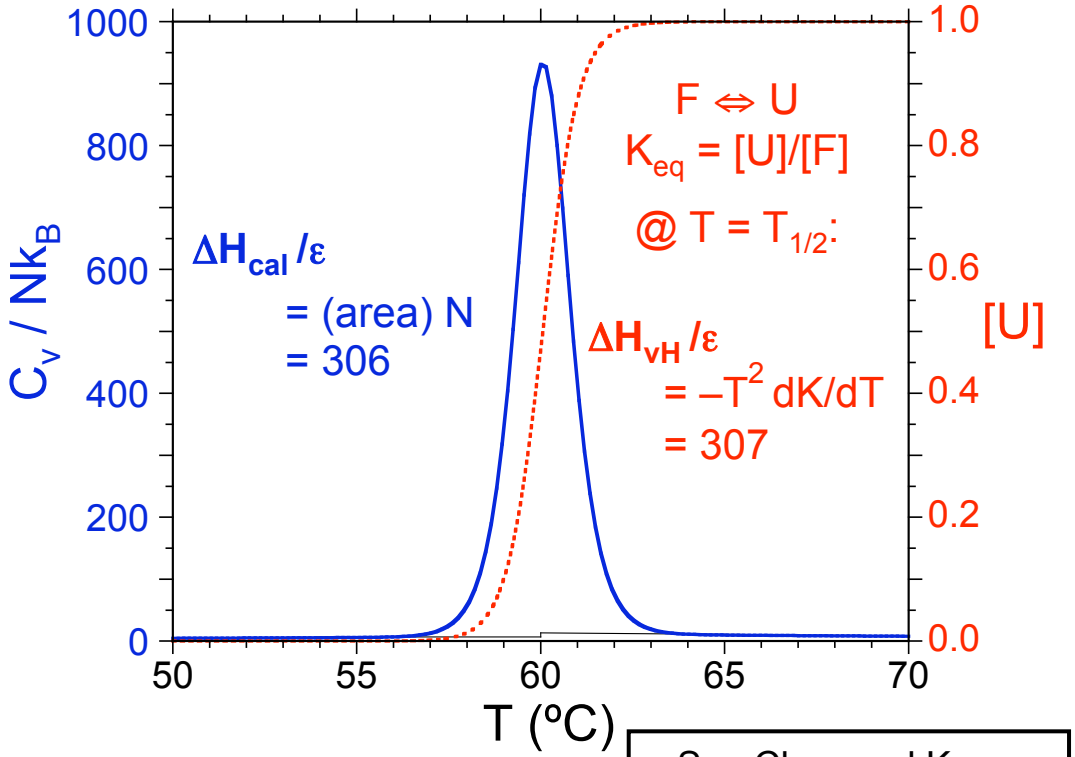
Protein Thermodynamics: Calorimetry



Transition enthalpy gives "distance" between folded/unfolded states.

Experimental test for "two-state" folding:

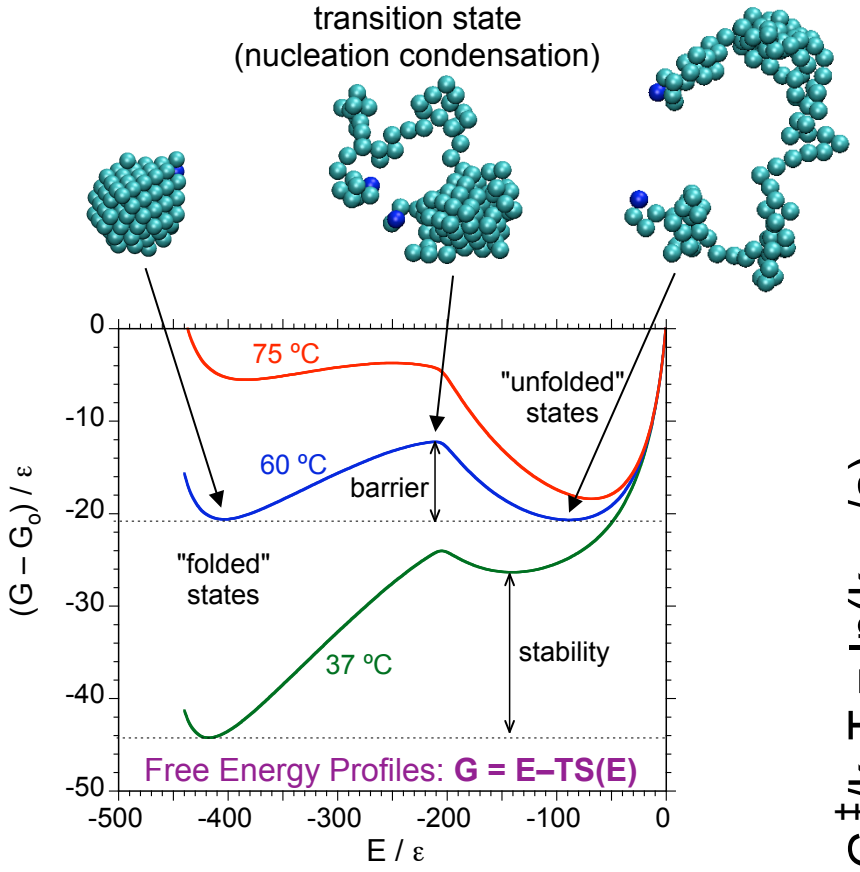
Equality of **calorimetric** and **van't Hoff*** enthalpies



*experimentally this is determined from the height of C_v

See Chan and Kaya: Proteins **40**, 543 & 637 (2000); **52**, 510 (2003).

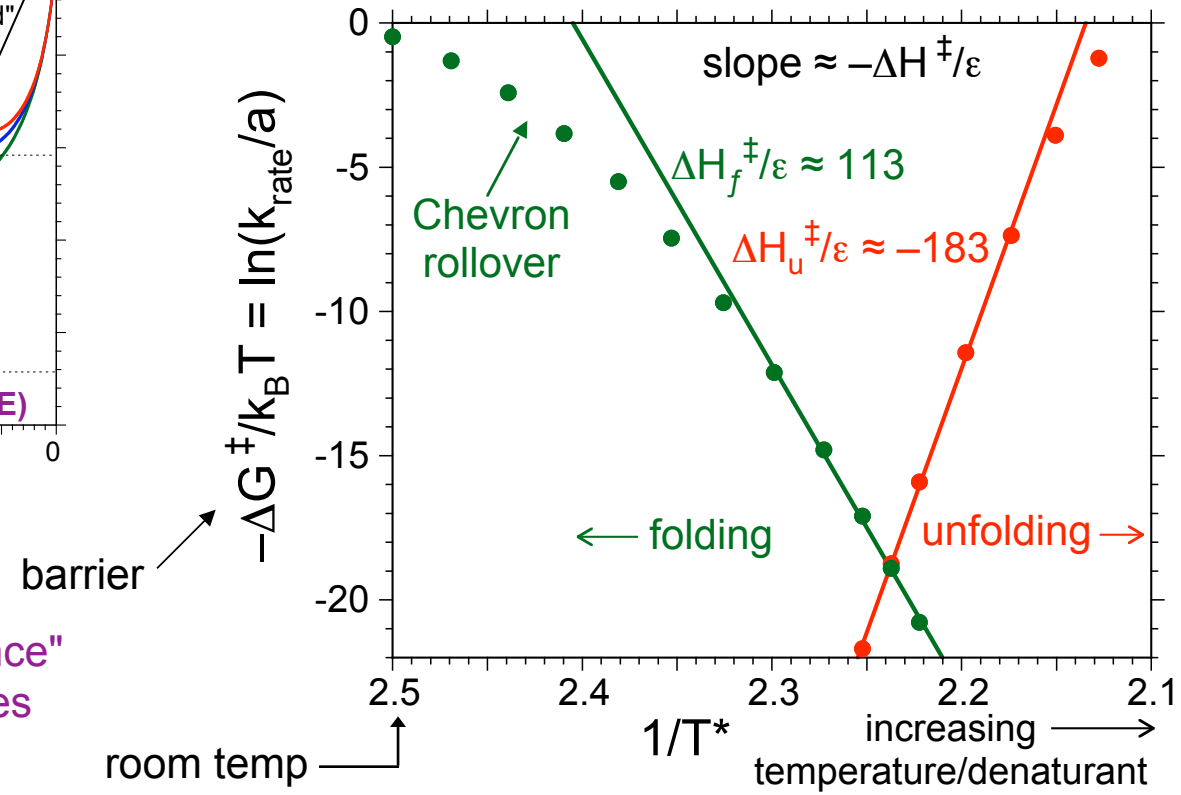
Protein Thermodynamics: Chevron Plot



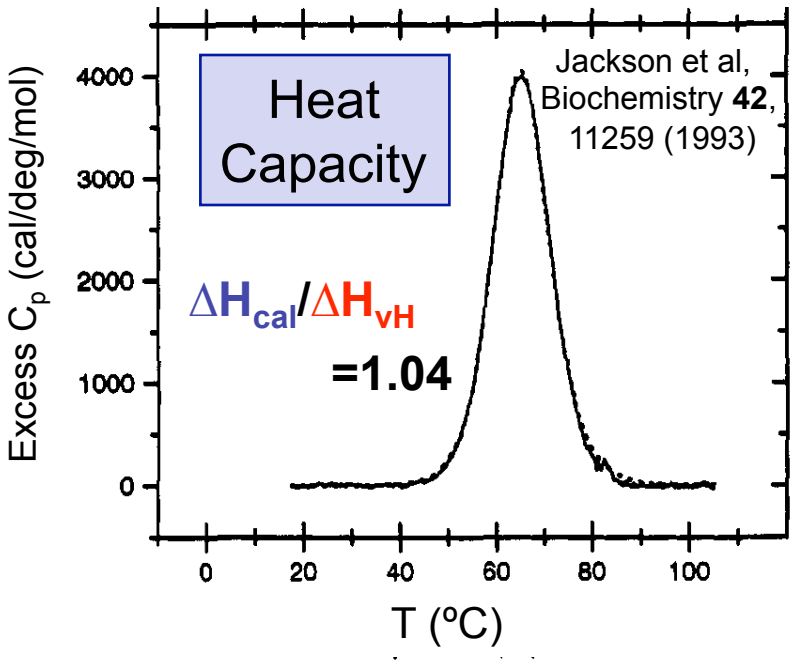
Chevron slopes give "distance" from folded/unfolded states to transition state.

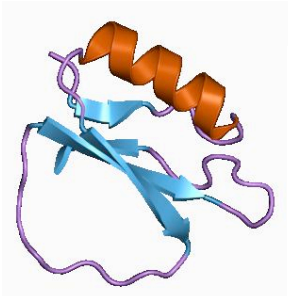
Experimental test for "two-state" folding:

Barrier height via kinetics ...
Anti-Arrhenius/Arrhenius behavior for folding/unfolding.

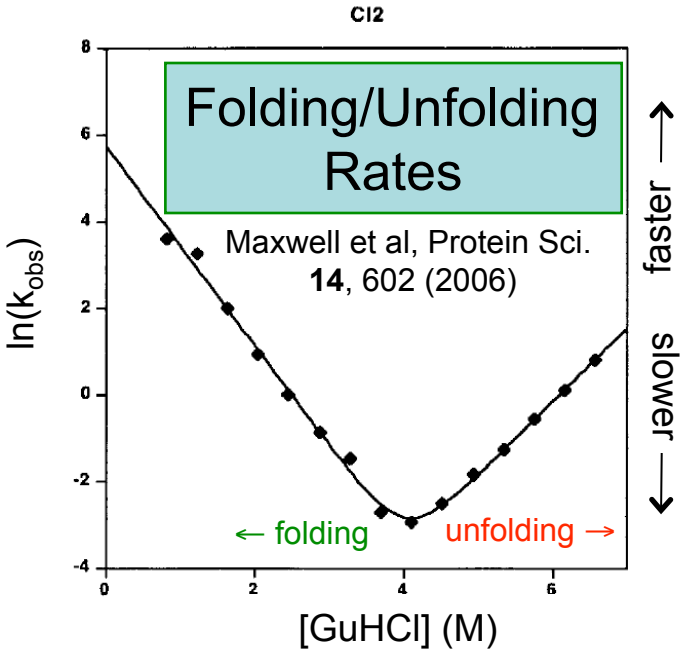


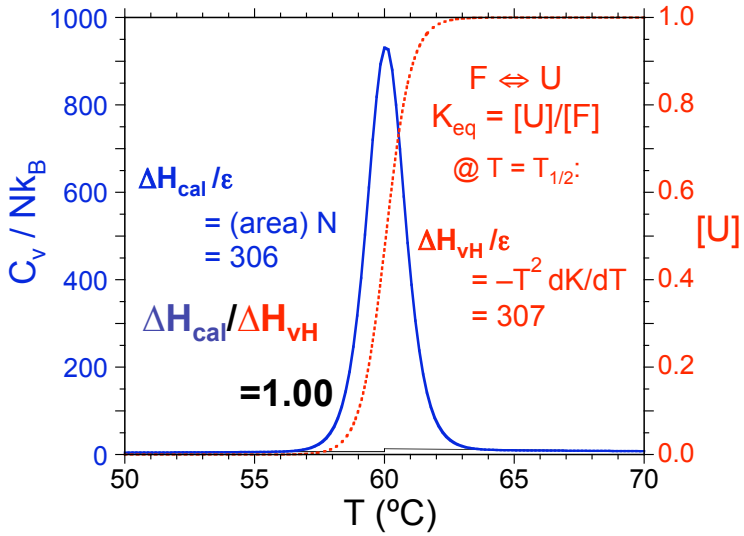
Experimental Data for Chymotrypsin Inhibitor 2 (CI2)

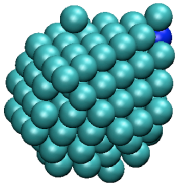




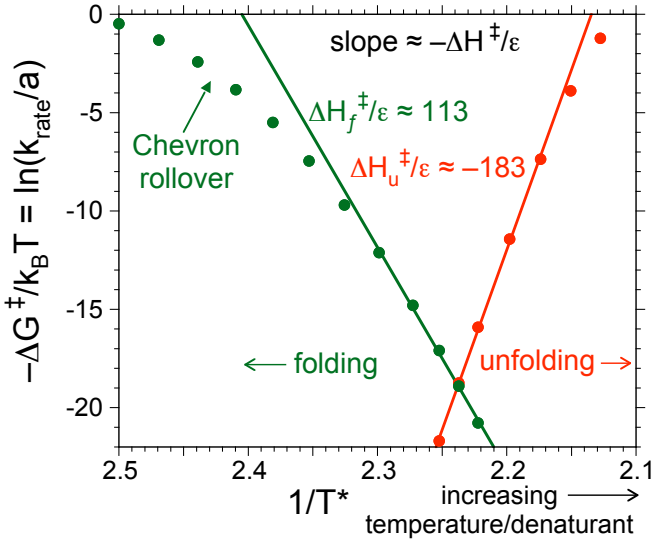
83 residue protein







128 bead SW chain



Summary and Outlook

Flexible SW Chain Model

Findings: Short range interaction results in "all-or-none" folding.

see: PRE **79**, 050801(R) (2009); JCP **131**, 114907 (2009)

Reproduces many key aspects of protein thermodynamics.

To do: Heteropolymer model (such as HP type).

[difficulty: bridging moves change sequence]

Explore free energy landscapes.

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Special thanks to the Binder group for their hospitality!

Happy "American" Thanksgiving