Statistical mechanics, the partition function, and first-order phase transitions

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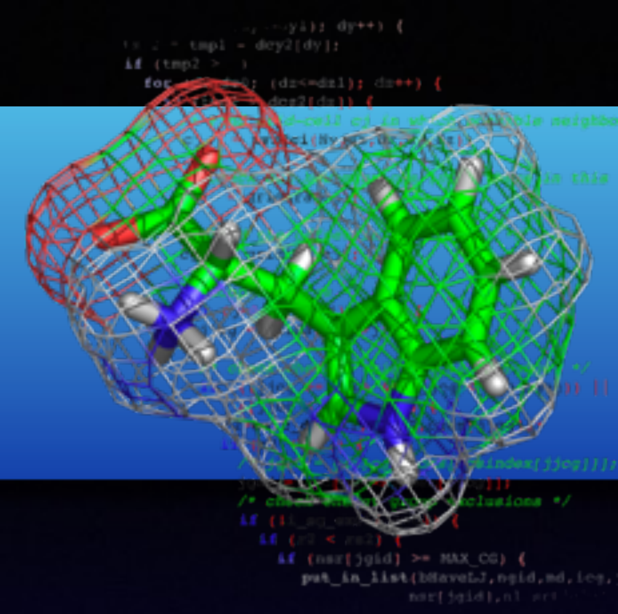
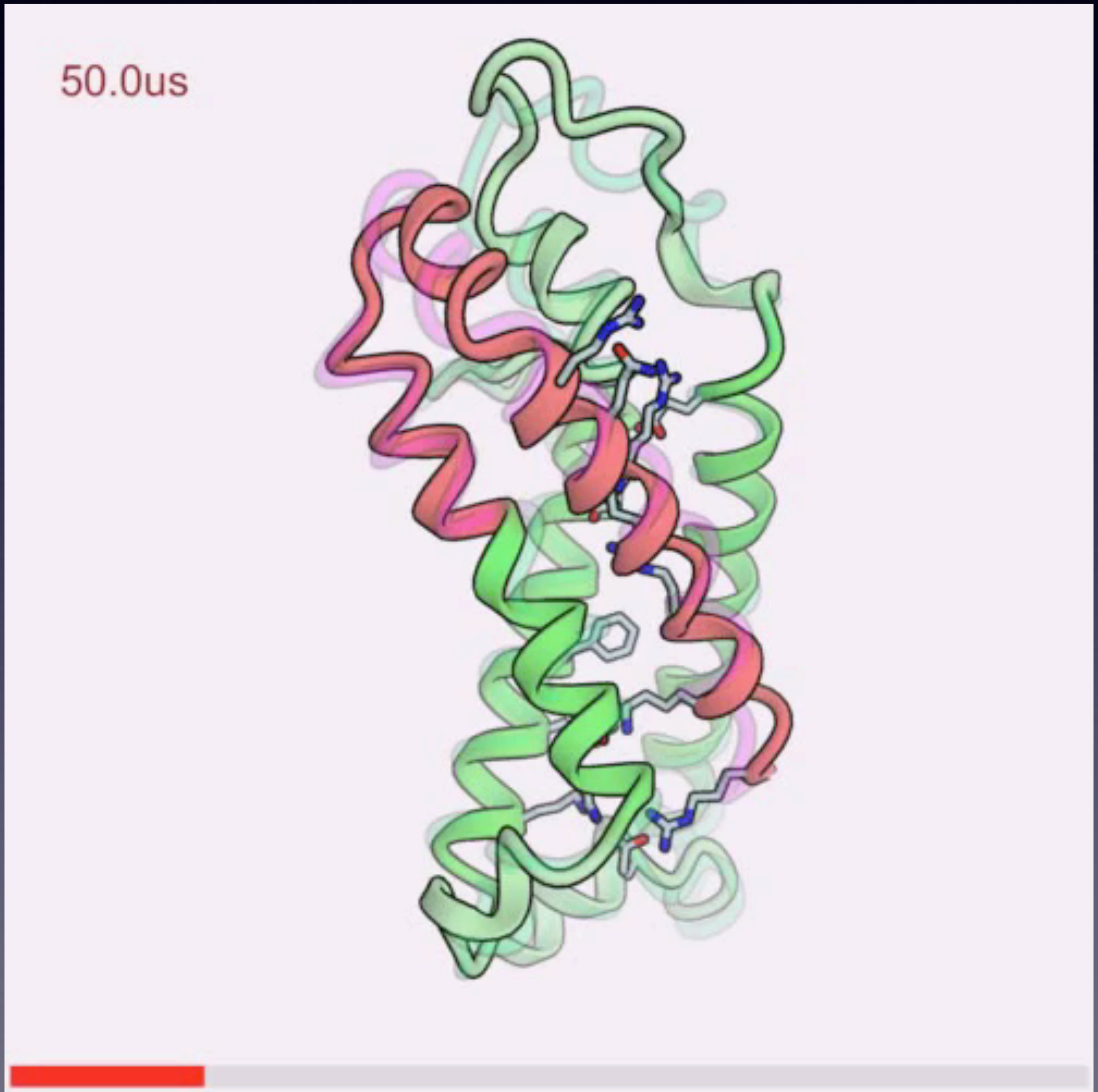
Recap



- Secondary structure & turns
  - Properties, simple stability concepts
  - Geometry/topology
- Amino acid properties, titration
- Natural selection of residues in proteins
- Free energy of hydrogen bond formation in proteins when in vacuo or aqueous solvent

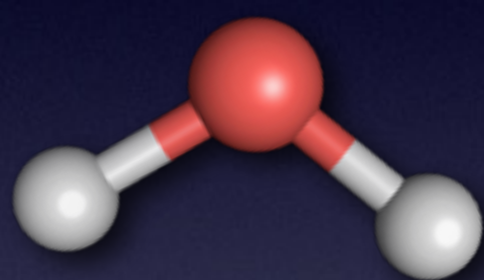
titratable amino acids

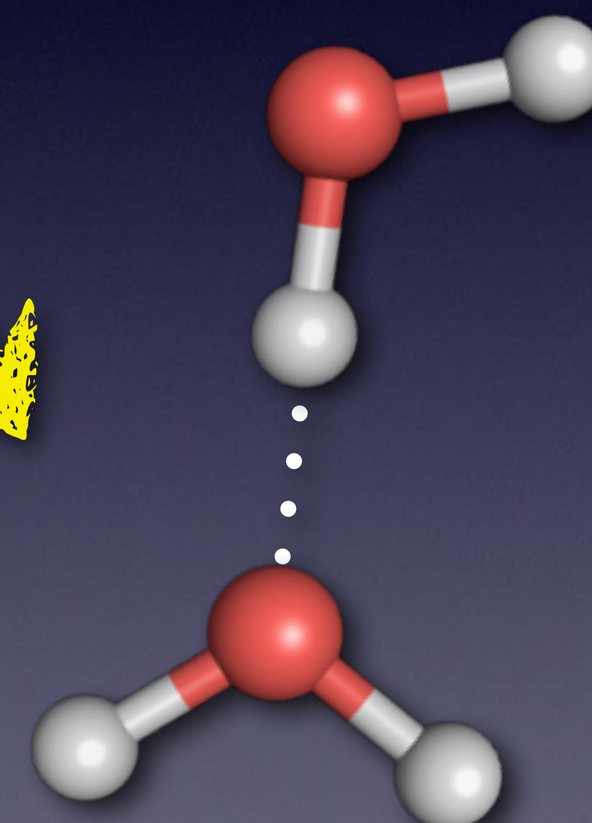


$F = E - TS$

$F = E - T(k \ln V)$ i.e. number of accessible states

probability $\propto \exp(-F/kT)$

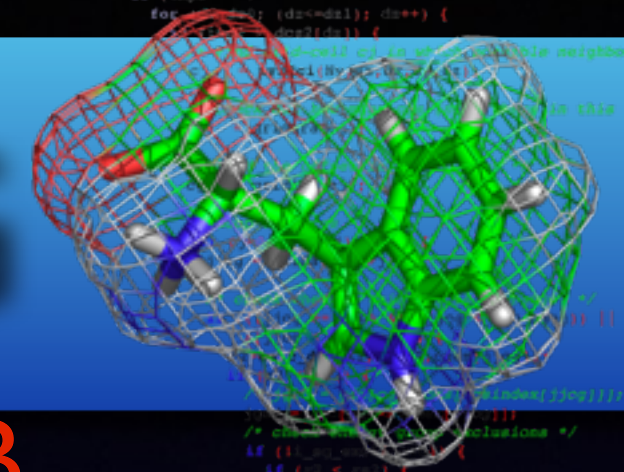


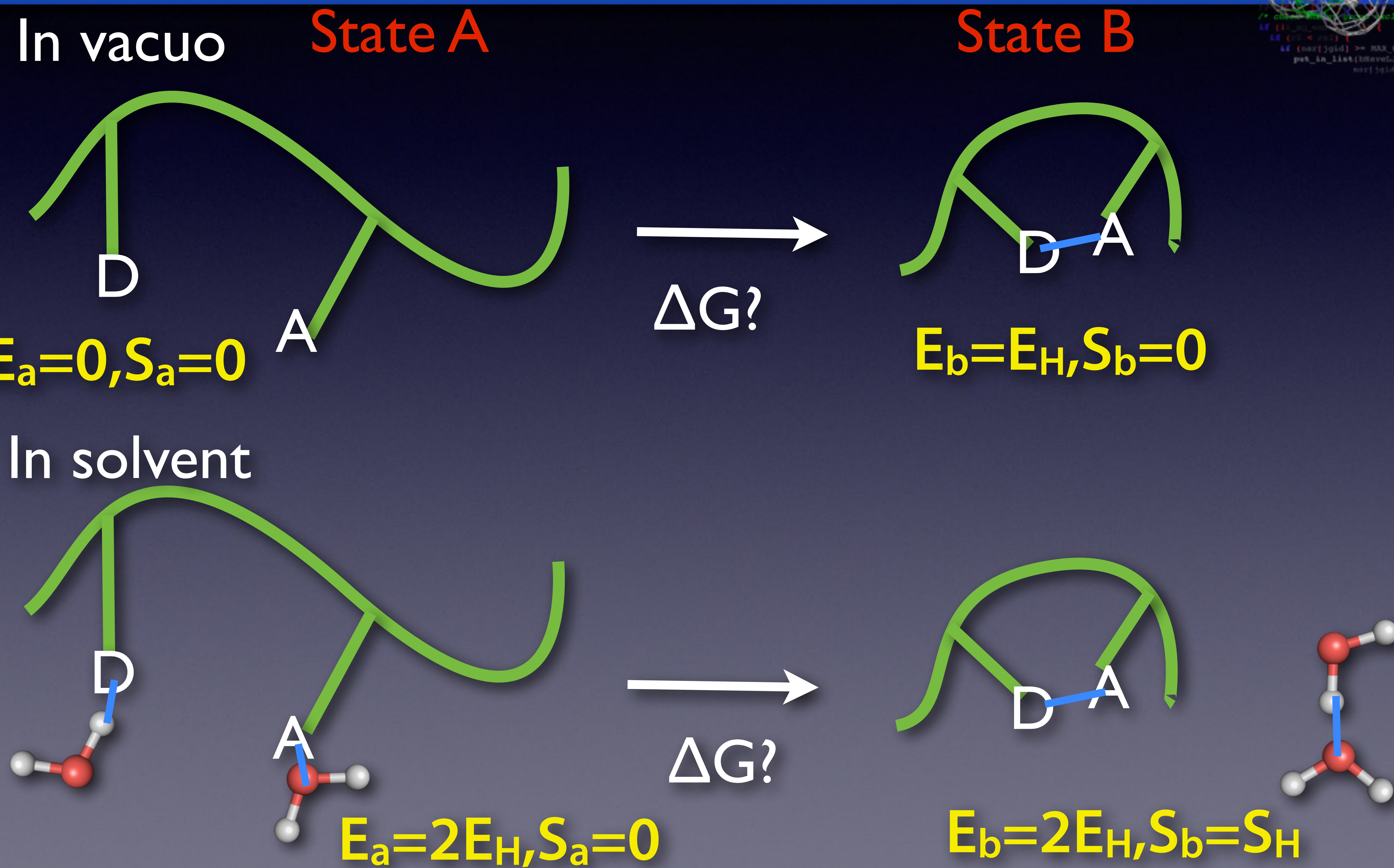


$E_H < 0$: Enthalpy of a hydrogen bond

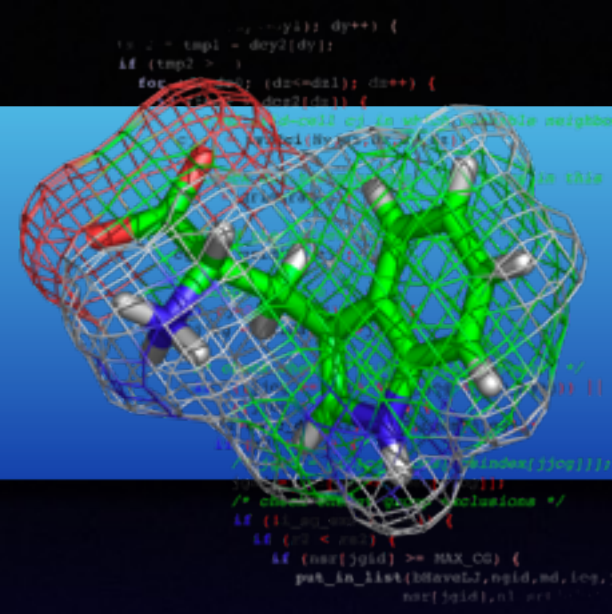
$S_{water} > 0$: Entropy of freely rotating body or complex (1 or 2 waters!)

Recap: H-bond ΔG



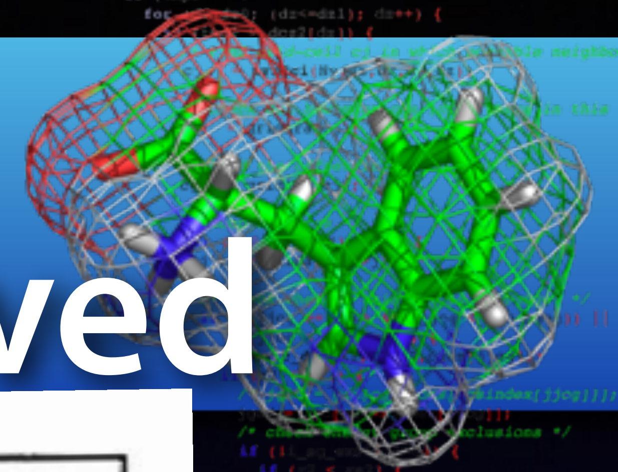


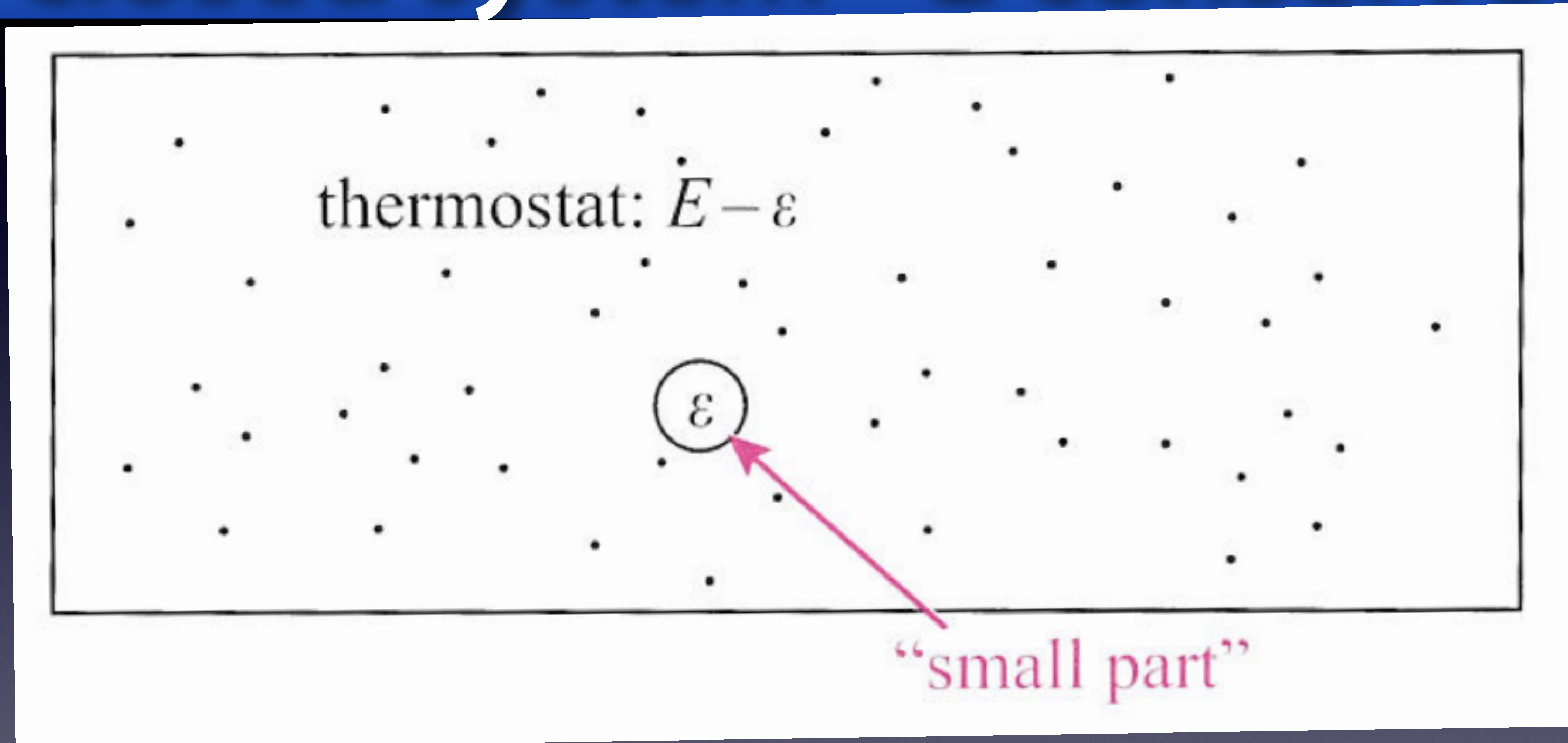
Today



- Statistical mechanics
- The partition function
- Free energy & stable states
- Gradual changes & phase transitions
- Activation barriers & transition kinetics

Fluctuations in a closed system - E conserved



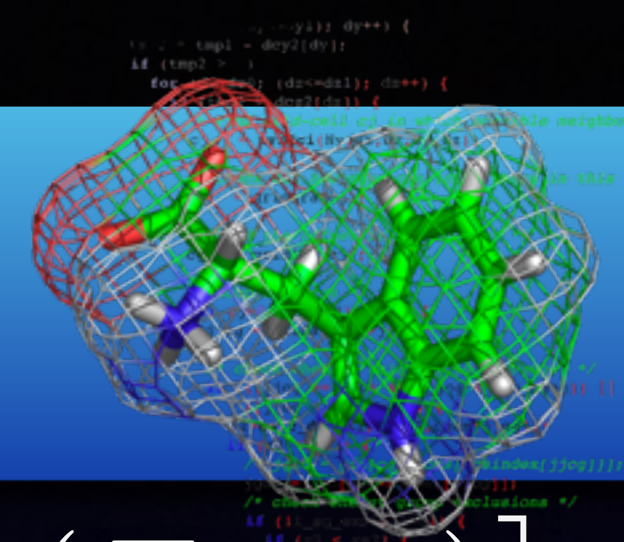


Consider all microstates of this system with energy E

thermostat microstates M_{therm} with the energy (E-ε)

Define: $S = k * \ln M_{therm}$

Entropy



$$S_{\text{therm}}(E-\epsilon) = \kappa \ln \left[M_{\text{therm}}(E-\epsilon) \right]$$

Now do series expansion; only 1st order matters - why?

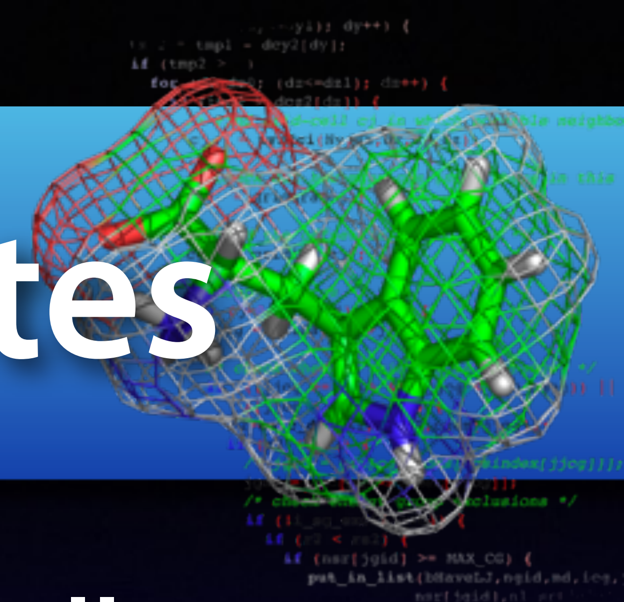
$$S_{\text{therm}}(E-\epsilon) = S_{\text{therm}}(E) - \epsilon \left(\frac{dS_{\text{therm}}}{dE} \right) \Bigg|_{E}$$

Solve for M

$$M(E-\epsilon) = \exp \left[\frac{S_{\text{therm}}(E-\epsilon)}{\kappa} \right]$$

$$= \exp \left[\frac{S_{\text{therm}}(E)}{\kappa} \right] \times \exp \left\{ -\epsilon \left[\frac{(dS_{\text{therm}}/dE)|_E}{\kappa} \right] \right\}$$

Observation of microstates

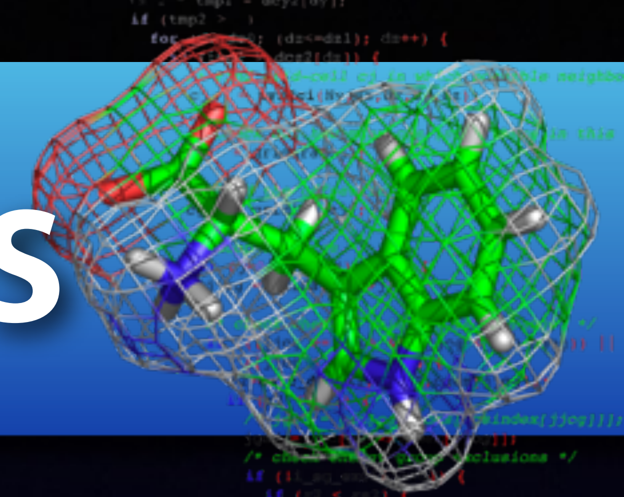


- The probability of observing the small part in this state is proportional to the number of microstates corresponding to it

$$p \propto M(E-\epsilon) \propto \exp\left\{-\epsilon\left[(dS/dE)|_E/\kappa\right]\right\}$$

$$(dS/dE)|_E = \frac{1}{T} \qquad\qquad \kappa = k$$

Energy increases

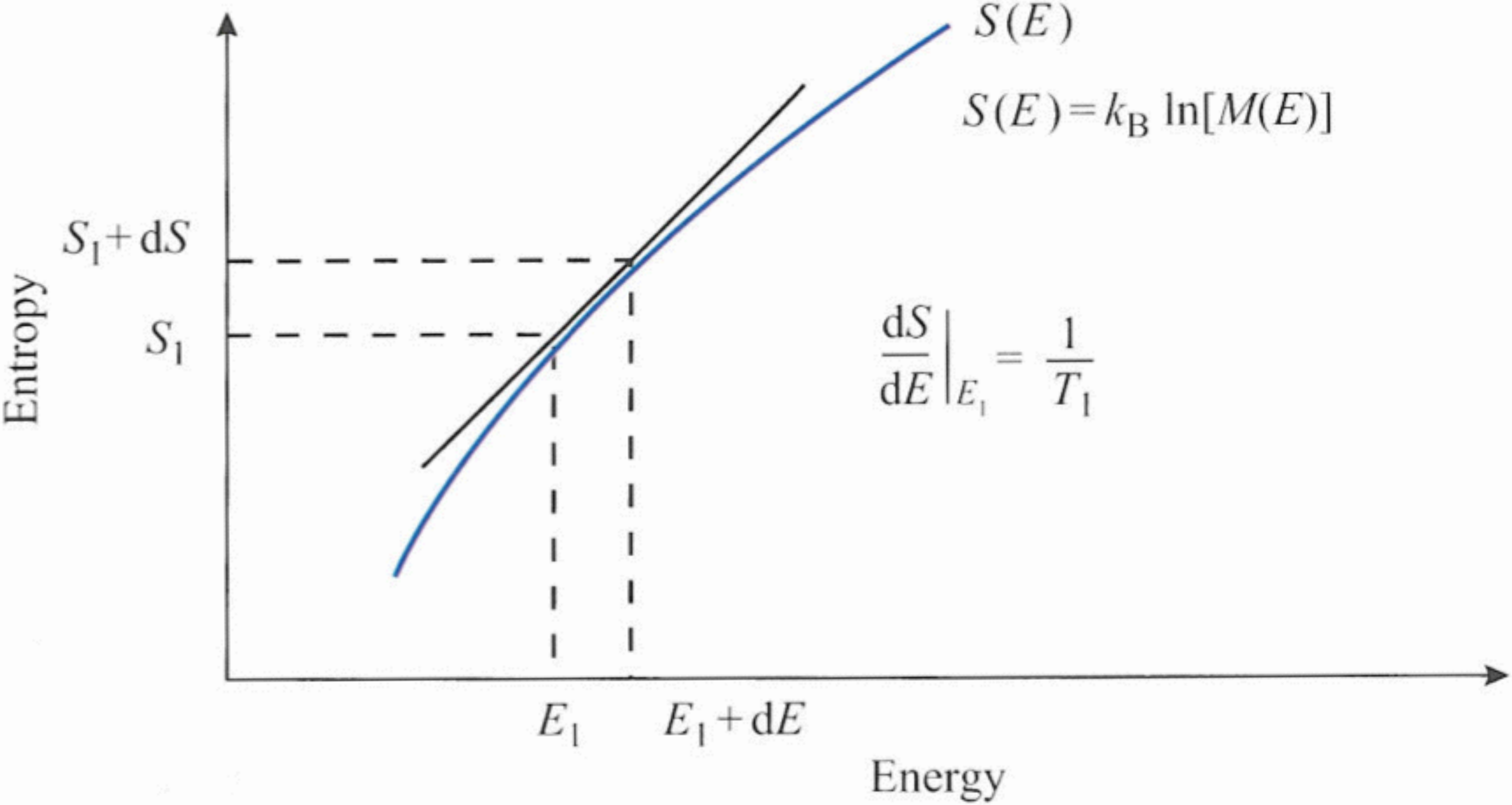


What happens when energy increases by kT?

$$\ln\left[M(E+k_BT)\right] = S(E+k_BT)/k_B =$$

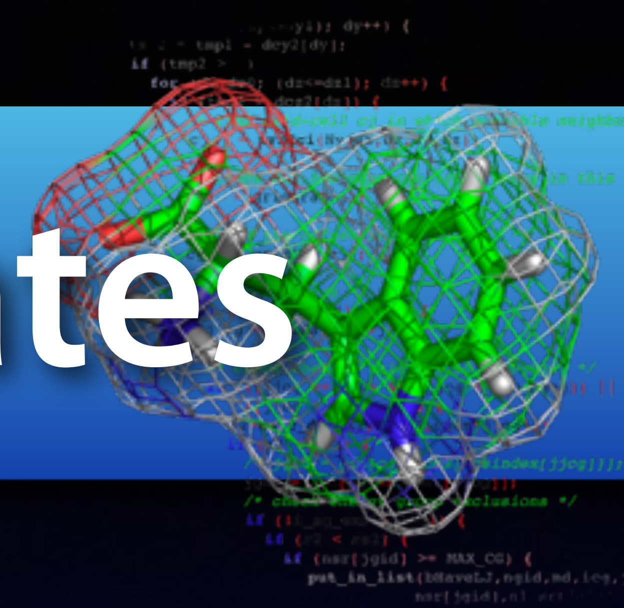
$$= \left[S(E)+k_B(1/T)\right]/k_B = ln\left[M(E)\right]+1$$

e (2.72) times more microstates,
regardless of system properties and size!



$S(E)$
$S(E) = k_B \ln[M(E)]$
$S_1 + dS$
S_1
Entropy
$\left.\frac{dS}{dE}\right|_{E_1} = \frac{1}{T_1}$
E_1
$E_1 + dE$
Energy

Probabilities of states



probability of being in a state i

$$w_i(T) = \frac{\exp\left(-\epsilon_i / k_B T\right)}{Z(T)}$$

Normalization factor

$$Z(T) = \sum_i \exp\left(-\epsilon_i / k_B T\right)$$

'The partition function'

$$E(T) = \sum_i w_i \epsilon_i$$

$$S(T) = \sum_i w_i S_i$$

How do we calculate S_i?

System distribution over states

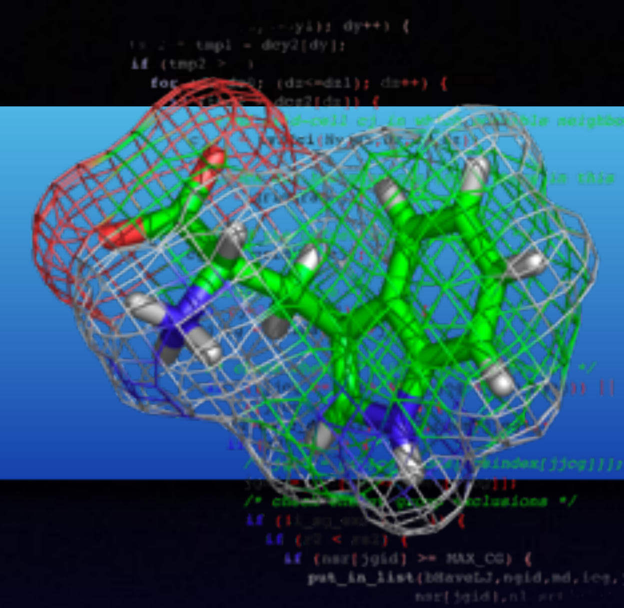
Consider N systems - how can we distribute them?

w_1	w_2	w_3	w_j
1	2	3	j

$$n_i = w_i N \qquad \sum_i w_i N = N$$

Question: how many ways can these systems be distributed over the j states?

Permutations



$$\frac{N!}{n_1!n_2!...n_j!} =$$

Stirling: $n! \approx (n/e)^n$

$$= (N/n_1)^{n_1}...(N/n_j)^{n_j} = (1/w_1)^{Nw_1}...(1/w_j)^{Nw_j}$$

$$= \left[1/(w_1^{w_1}...w_j^{w_j})\right]^N$$

for N systems

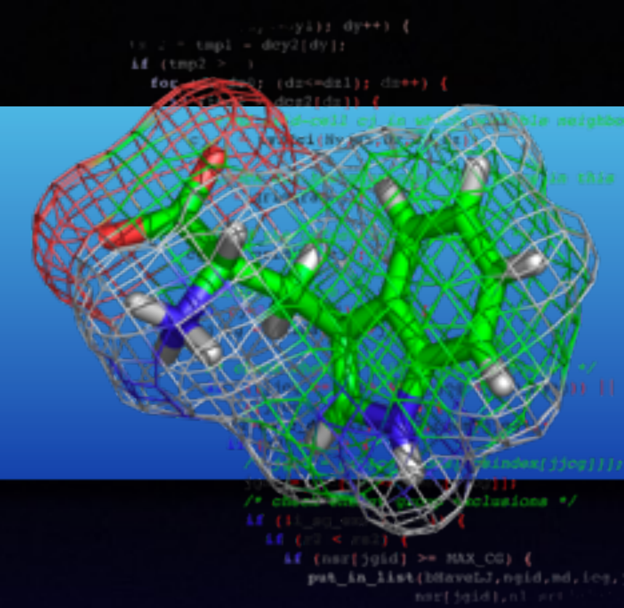
$$= 1/(w_1^{w_1}...w_j^{w_j})$$

for 1 system

...and the entropy becomes:

$$S = k_B \ln M = k_B \sum_i w_i \ln(1/w_i)$$

Free energy



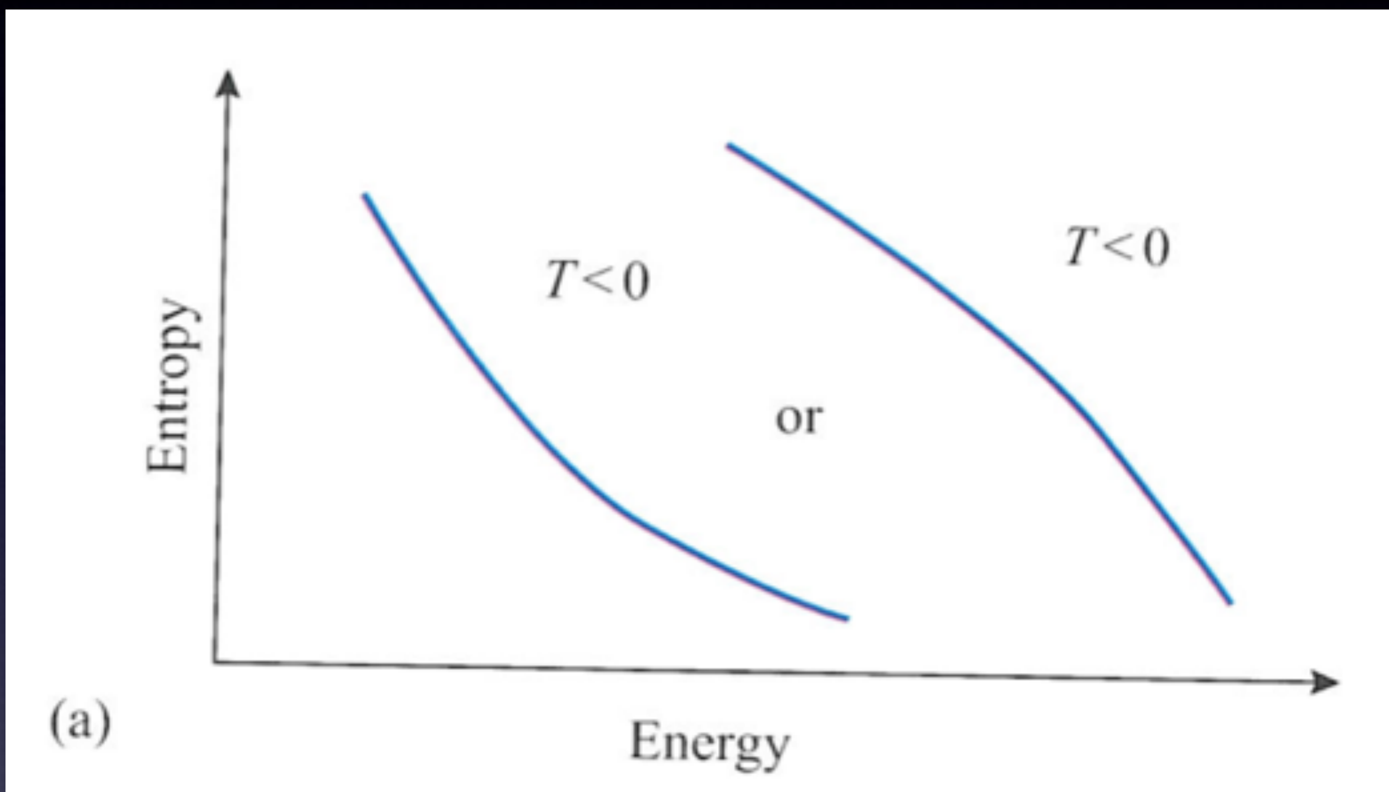
$$E(T) = \sum_i w_i \epsilon_i$$

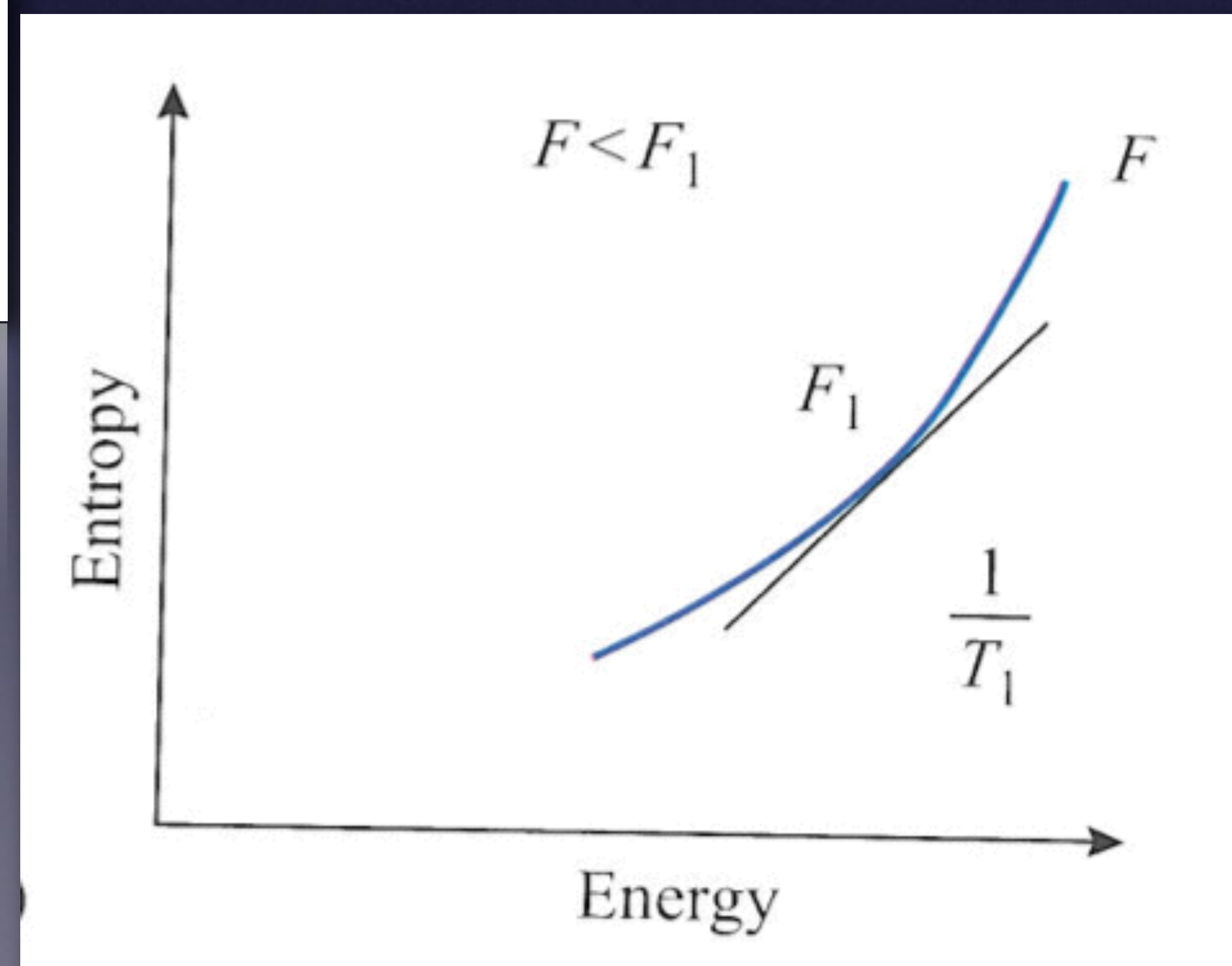
$$S = k_B \ln M = k_B \sum_i w_i \ln(1/w_i)$$

F = E - TS

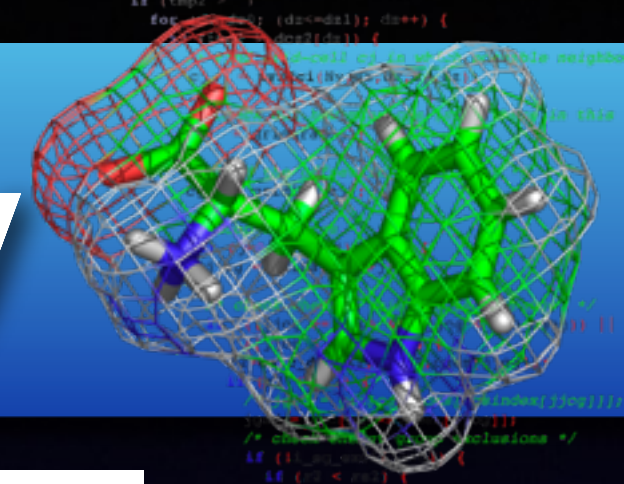
F = -kBT ln [Z(T)]

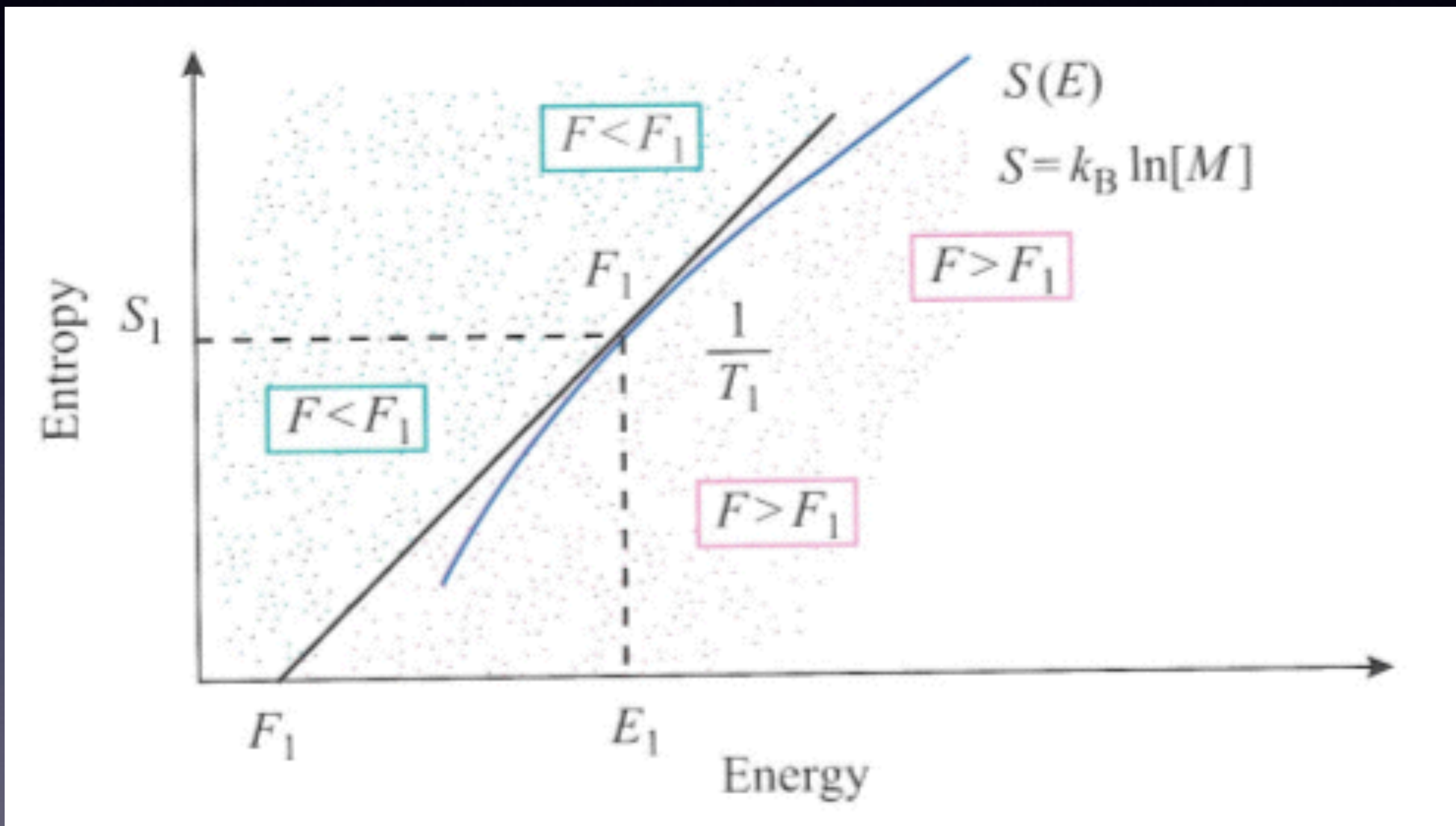
System instability



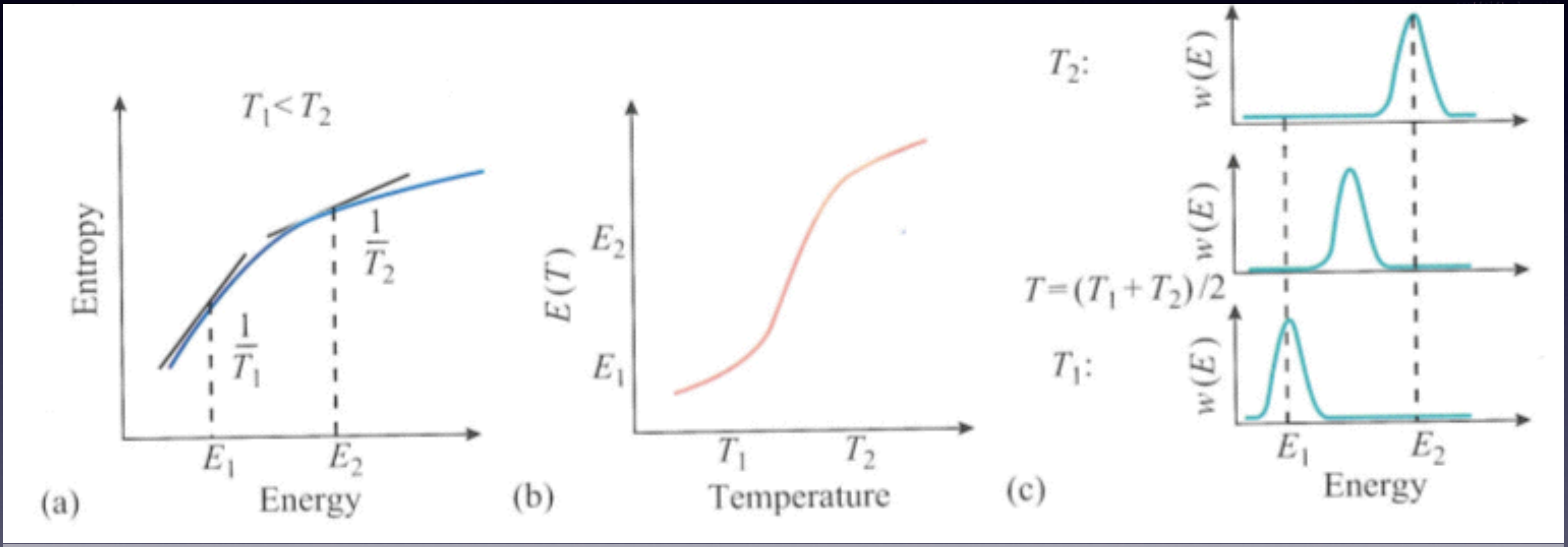


System stability



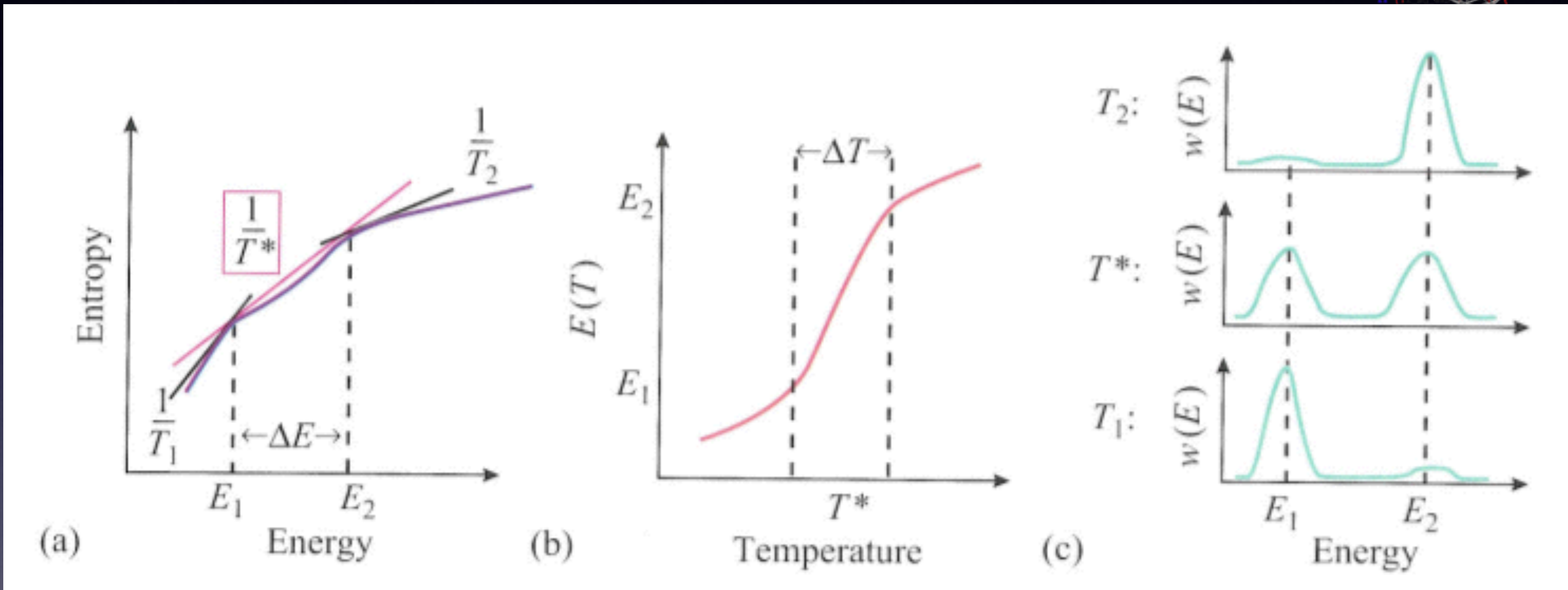


Gradual changes



What does this correspond to? Examples?

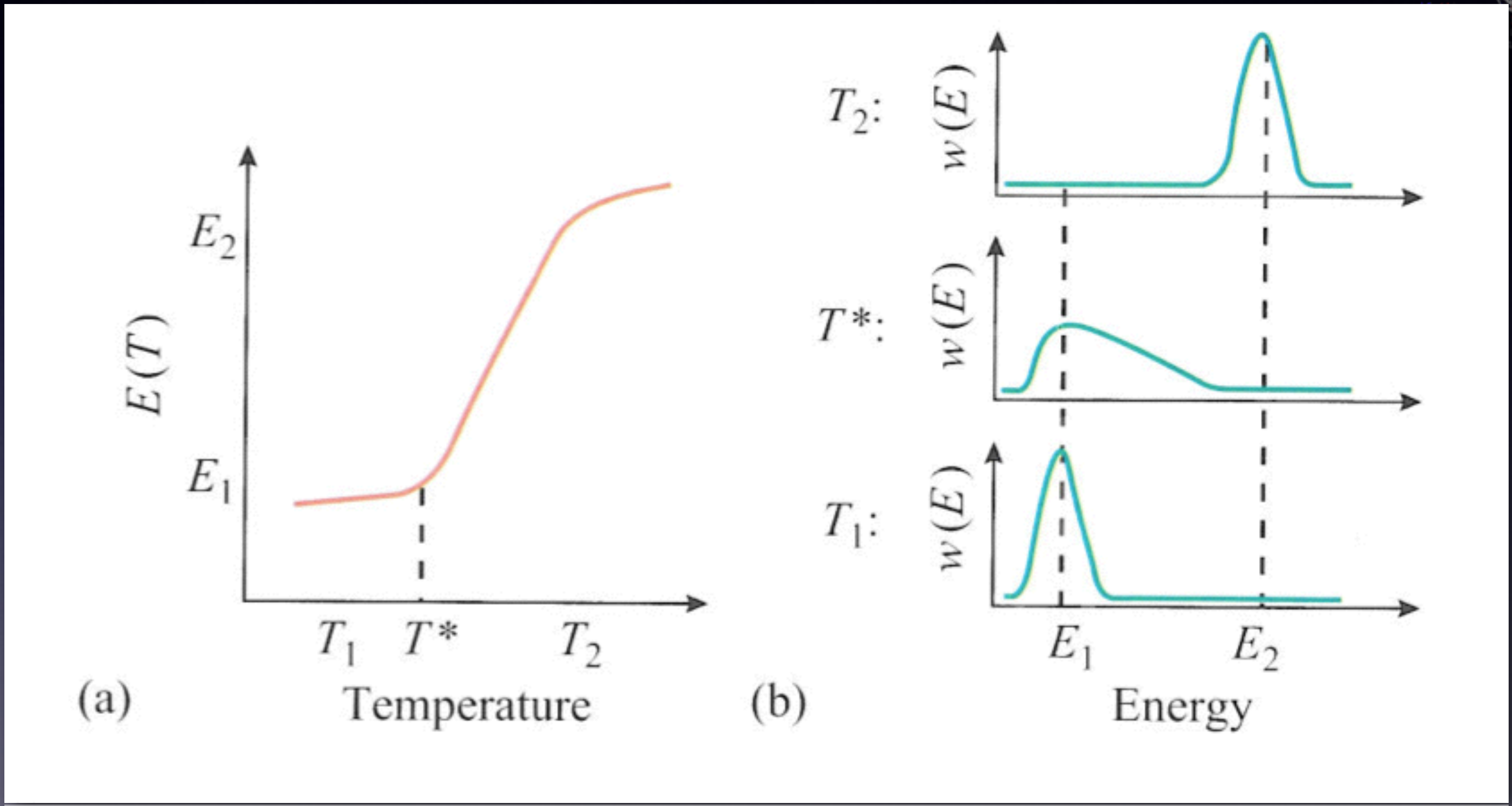
Abrupt changes



dT = 4kT^2 / E2-E1

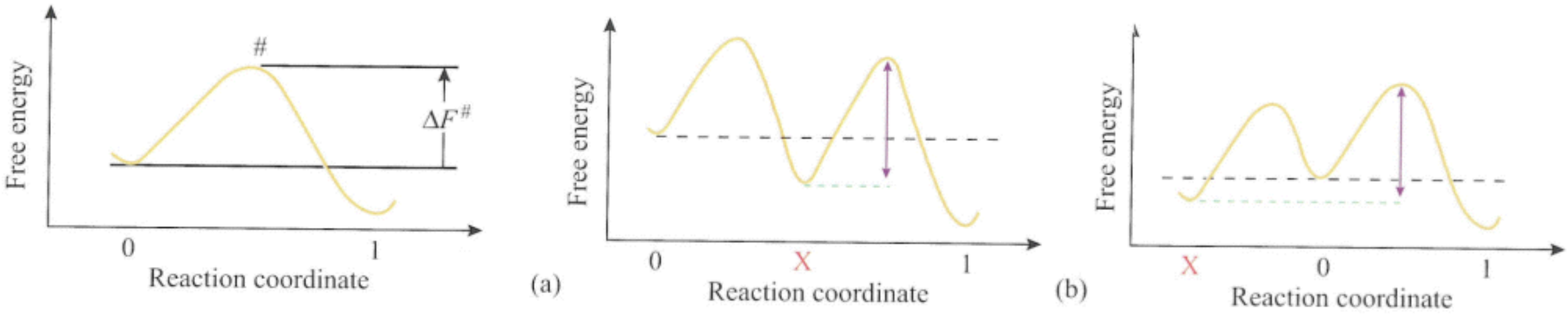
A first-order phase transition!

A different change...



A second-order phase transition!

Free energy barriers

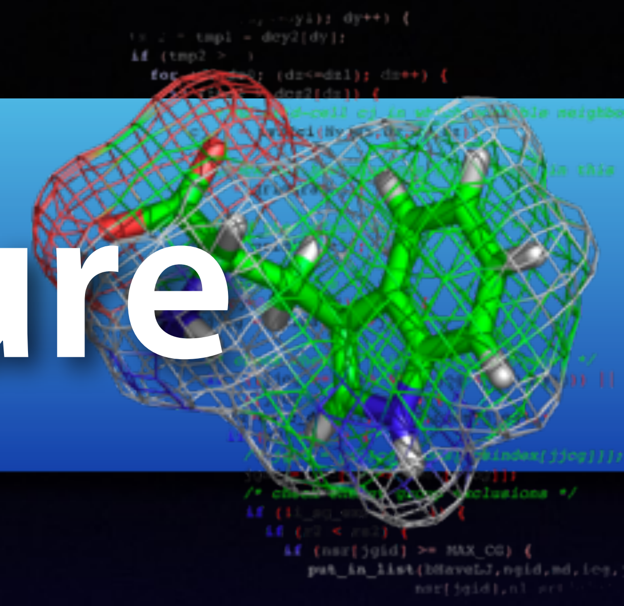


$n^{\#} \approx n \exp(-\Delta F^{\#}/k_B T)$ $\tau(n/n^{\#}) \approx \tau \exp(\Delta F^{\#}/k_B T)$

$$t_{0\rightarrow 1} \approx \tau \exp\left(+\Delta F^{\#}/k_B T\right)$$

Transition rate: $k_{0\rightarrow 1} = 1/t_{0\rightarrow 1}$

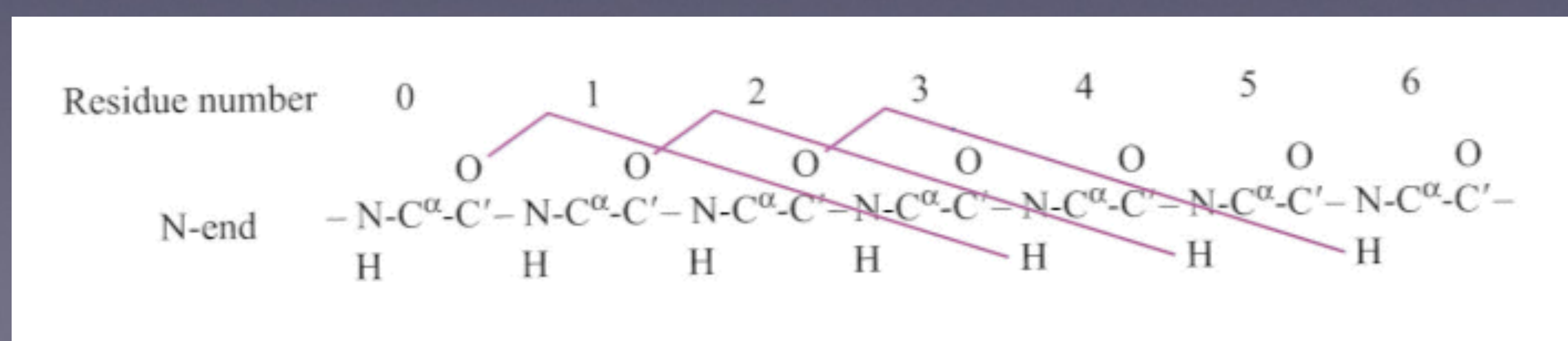
Secondary structure



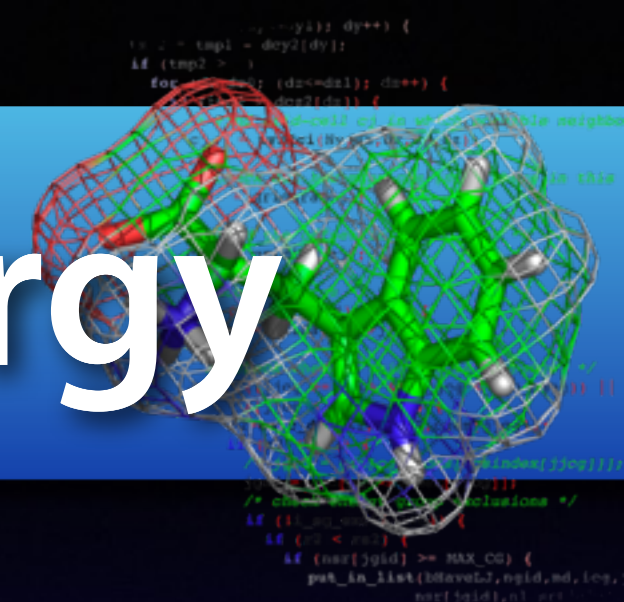
- Alpha helix formation
- Equilibrium between helix & coil
- Beta sheet formation
- Properties of the “random” coil,
  or the denatured state - what is it?

Alpha helix formation

- Hydrogen bonds: i to i+4
  - 0-4, 1-5, 2-6
- First hydrogen bond "locks" residues 1,2,3 in place
- Second stabilizes 2,3,4 (etc.)
- N residues stabilized by N-2 hydrogen bonds!



Alpha helix free energy



- Free energy of helix vs. "coil" states:

number of residues

H-bond free energy

Entropy loss of fixating one residue in helix

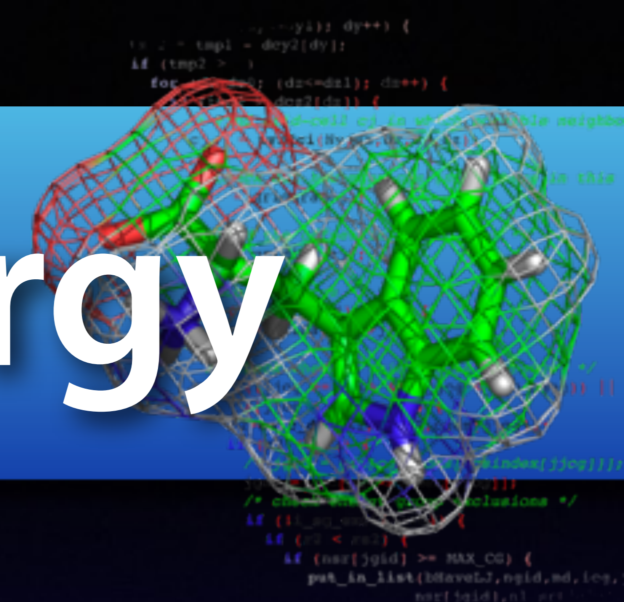
$$
\begin{aligned}
\Delta F_\alpha = F_\alpha - F_{\text{coil}} &= (n-2) f_{\text{H-bond}} - nTS_\alpha \\
&= -2 f_{\text{H-bond}} + n\left(f_{\text{H-bond}} - TS_\alpha\right)
\end{aligned}
$$

Helix initiation cost

Helix elongation cost

$$\Delta F_\alpha = f_{\text{INIT}} + n f_{\text{EL}}$$

Alpha helix free energy



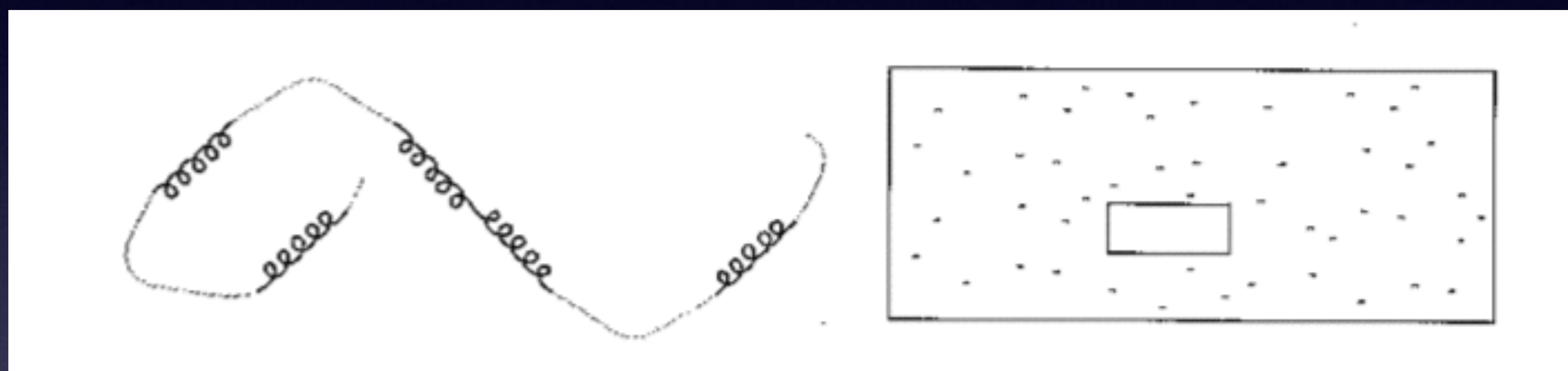
$$
\begin{aligned}
\exp\left(-\Delta F_\alpha / k_B T\right) &= \exp\left(-f_{\text{INIT}}/k_B T\right)\exp\left(-n f_{\text{EL}}/k_B T\right) \\
&= \exp\left(-f_{\text{INIT}}/k_B T\right)\left[\exp\left(-f_{\text{EL}}/k_B T\right)\right]^n \\
&= \sigma s^n
\end{aligned}
$$

$$
\begin{aligned}
s &= \exp\left(-f_{\text{EL}}/k_B T\right) \\
\sigma &= \exp\left(-f_{\text{INIT}}/k_B T\right)
\end{aligned}
$$

$$
\sigma = \exp\left(-f_{\text{INIT}}/k_B T\right) = \exp\left(+2 f_{\text{H}}/k_B T\right) << 1
$$

Equilibrium constant for helix of length n

How does a helix form?



- First, consider ice in water

$$n \propto V \propto r^3$$

$$A \propto r^2 \propto n^{2/3}$$ Surface tension costly!

- S = k ln(N)

How does a helix form?

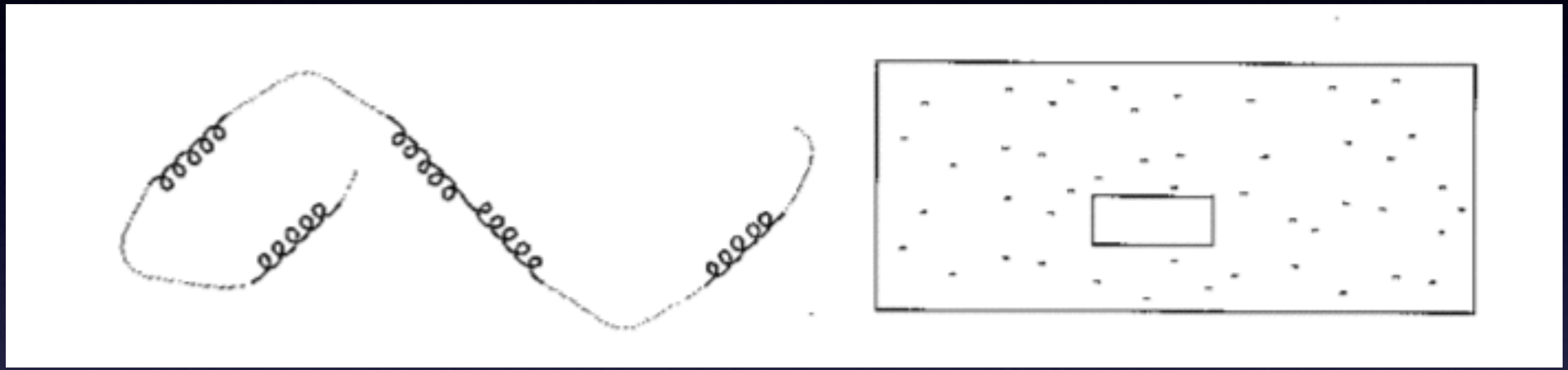
- Landau: Phases cannot co-exist in 3D
- First order phase transitions means either state can be stable, but not the mixture
- Think ice/water - either freezing or melting

$n \propto V \propto r^3$

$A \propto r^2 \propto n^{2/3}$ Surface tension costly!

- But a helix-coil transition in a chain is 1D!
- Interface helix/coil does not depend on n

How does a helix form?



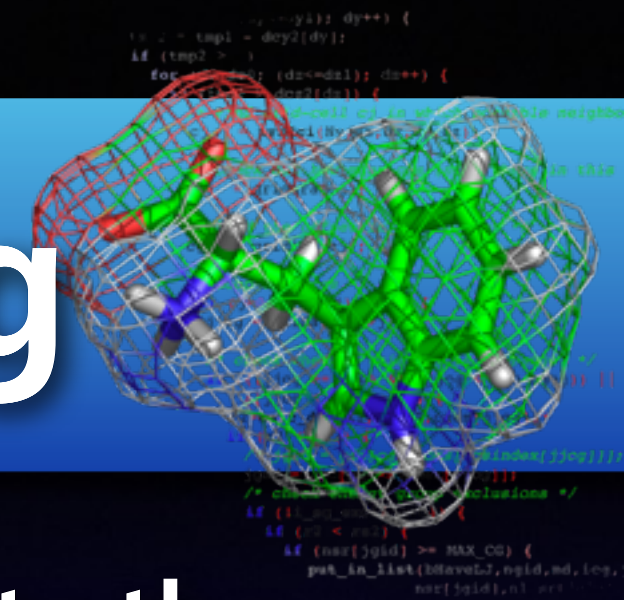
ice/water: n molecules in ice, N in water

energy cost * n^2/3 & entropy: k ln N

helix/coil: n residues in helix out of N in total

f_{INIT} - kT ln (N-n) i.e. opposite to water/ice!

Helix/coil mixing



- Or: What helix length corresponds to the transition mid-point? $f_{\mathrm{EL}} = f_{\mathrm{H}} - TS_\alpha = 0$
- Assuming helix can start/end anywhere, there are N^2/2 positions

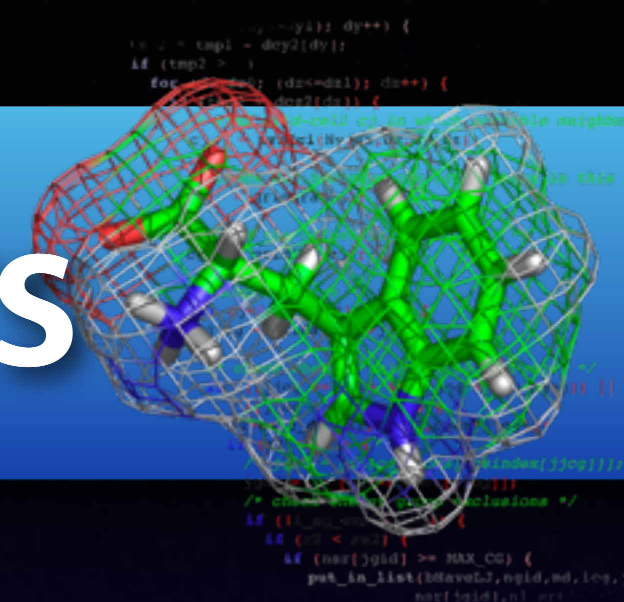
$$S = k \ln V \approx k \ln N^2 = 2k \ln N$$

$$\Delta F_{\mathrm{helix}} \approx f_{\mathrm{INIT}} - 2kT \ln N$$

- At transition midpoint we have ΔF=0 & N=n_0

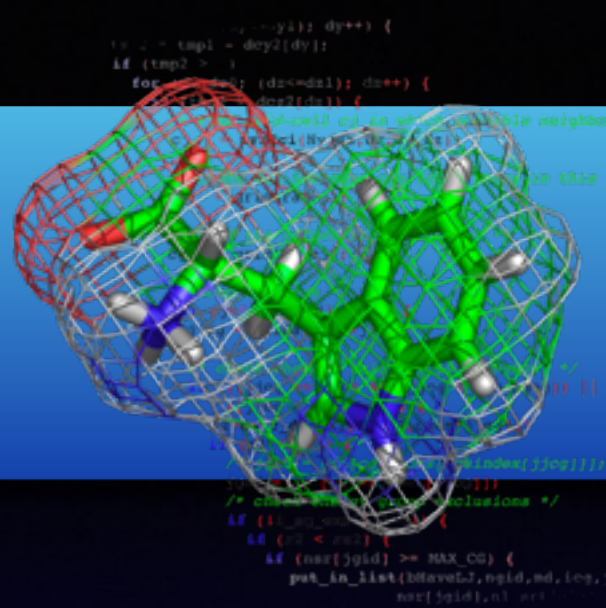
$$n_0 = \exp\left(f_{\mathrm{INIT}}/2kT\right) = 1/\sqrt{\sigma}$$

Helix parameters

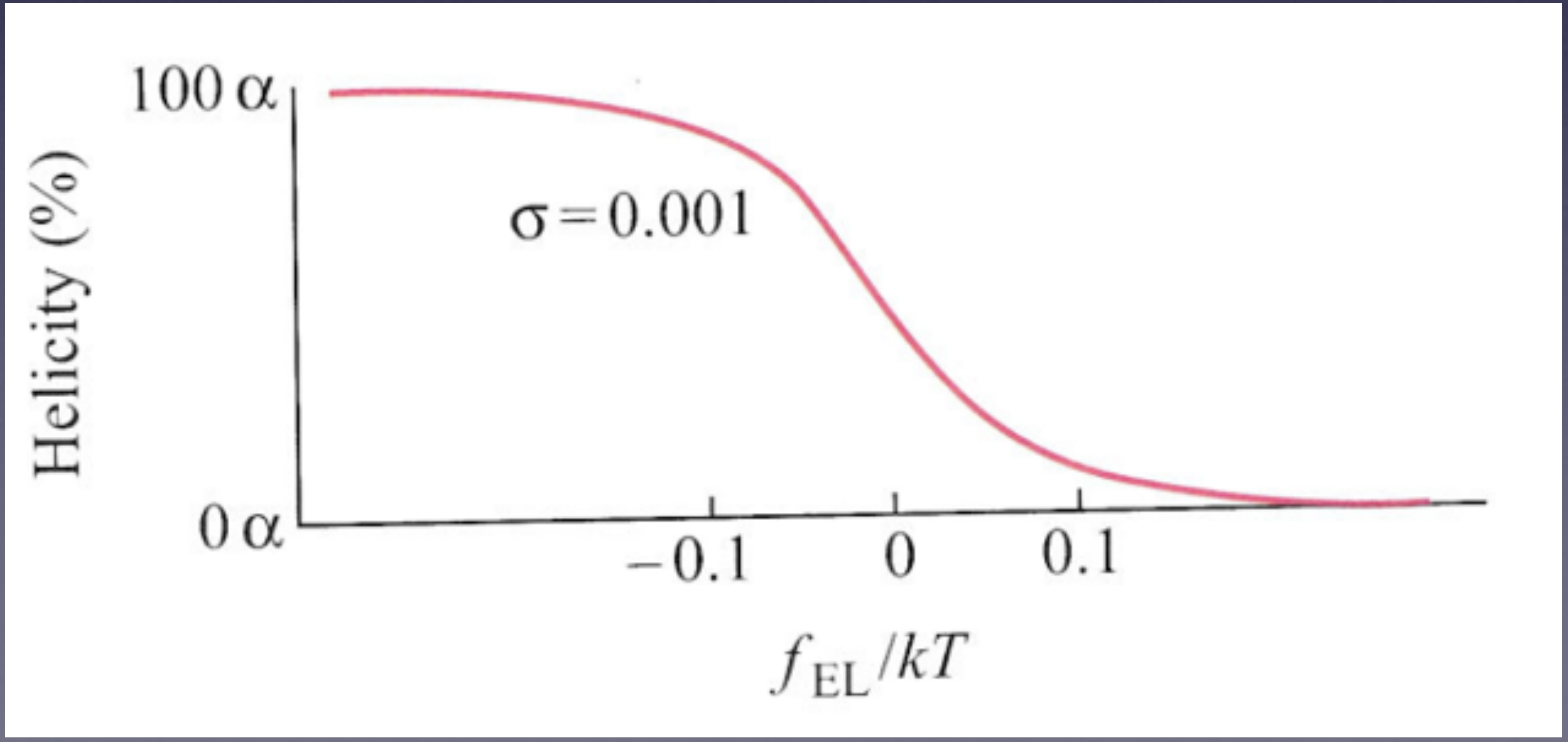


- We can measure n_0 from CD-spectra
- Calculate σ from last equation
- Typical values for common amino acids:
  $n_0 \approx 30 \quad f_{INIT} \approx 4$ kcal/mol $\quad \sigma \approx 0.001$
- $f_H = -f_{INIT}/2 = -2$ kcal/mol
- $TS_\alpha = f_H - f_{EL} \approx -2$ kcal/mol
  (Conformational entropy loss of helix res.)

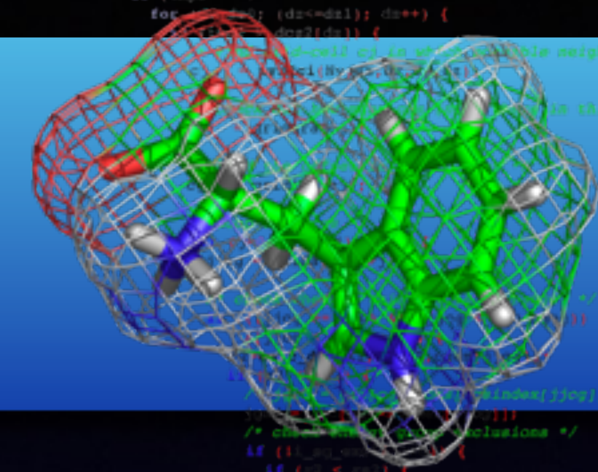
Helix stability



- Temperature dependence
- Elongation term dominant for large n_0
- $dF(alpha) = f_{INIT} + n_0 * f_{EL}$

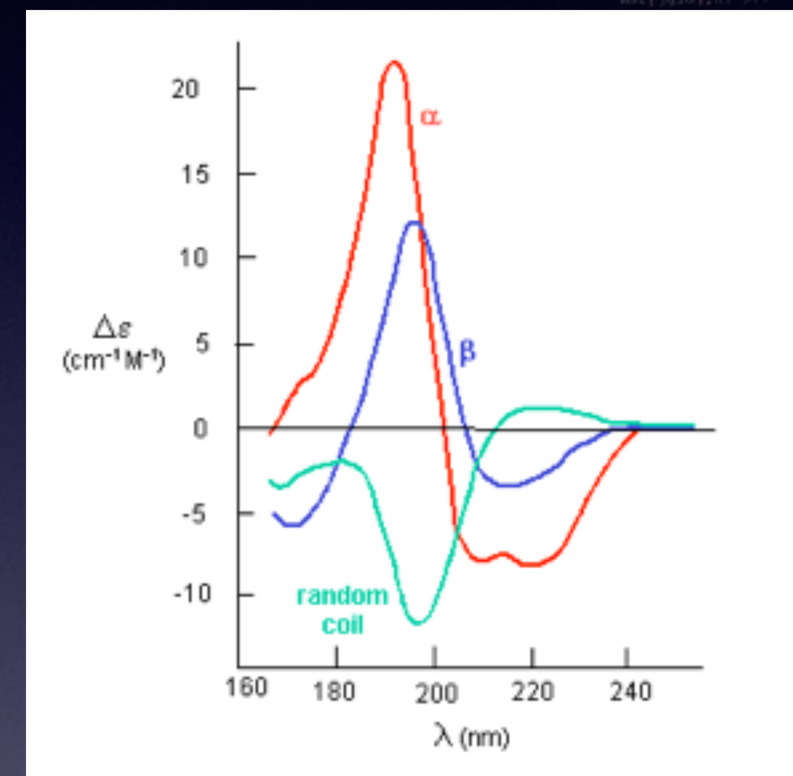


Highly cooperative, but NOT a formal phase transition! (width does not go to zero)



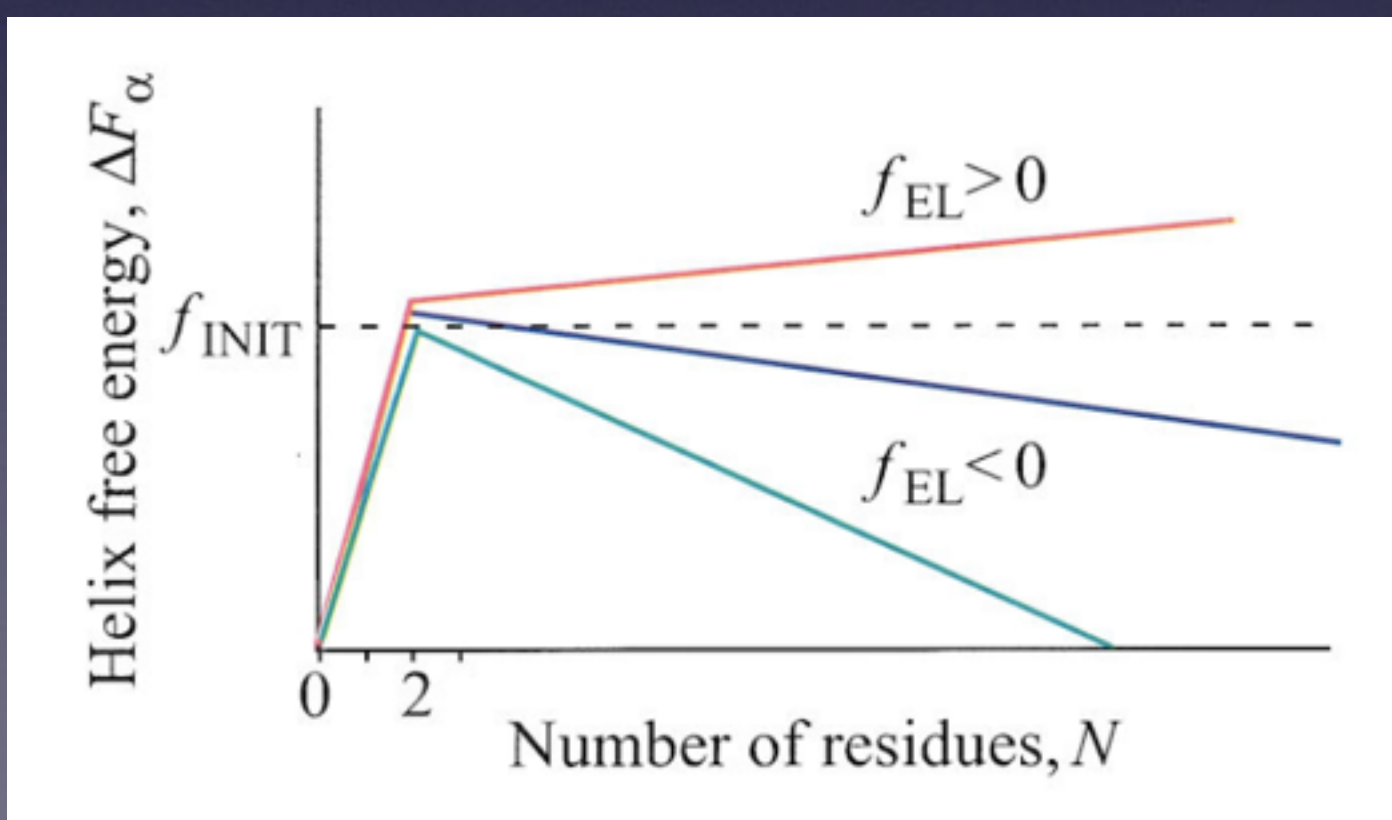
Helix studies

- CD spectra
- Determine s & σ
- Alanine: s≈2, f_{EL}≈-0.4kcal/mol
- Glycine: s≈0.2, f_{EL}≈+1kcal/mol
- Proline: s≈0.01-0.001 , f_{EL}≈+3-5kcal/mol
- Bioinformatics much more efficient for prediction, though!



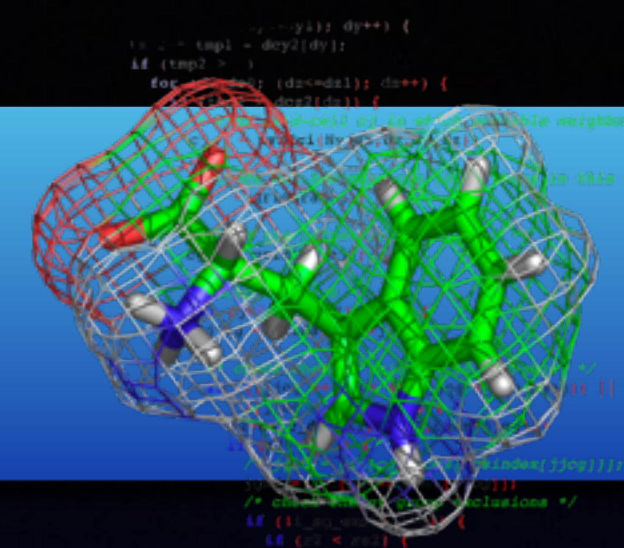
Rate of Formation

- Experimentally: Helices form in ~0.1µs! (20-30 residue segments)
- One residue < 5 ns...



What is the limiting step?

Formation...



- Rate of formation at position 1:

τ: 1-residue elongation

$$t_{\mathrm{INIT0}} = \tau \exp\left(f_{\mathrm{INIT}}/kT\right) = \tau/\sigma$$

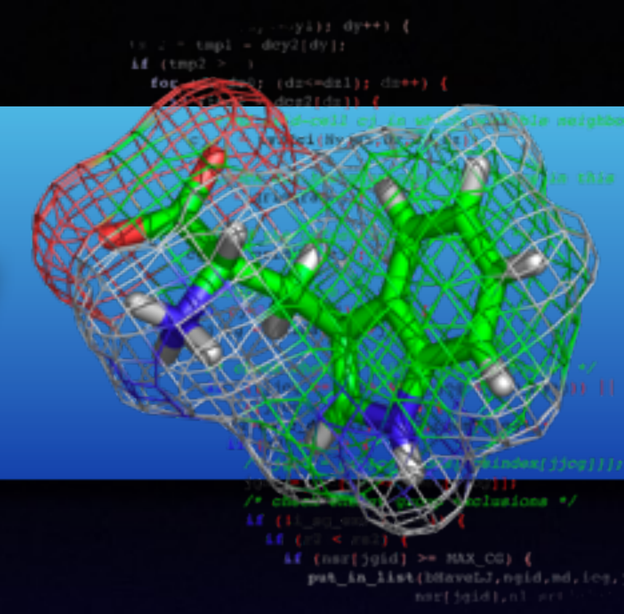
- Rate of formation anywhere (n0≈1/√σ):

$$t_{\mathrm{INIT}} = \tau/\sqrt{\sigma}$$

- Propagation to all residues: $tn_0 = \tau/\sqrt{\sigma}$

- Half time spent on initiation, half elongation!

Helix summary



- Very fast formation
- Both initiation & elongation matters
- Quantitative values derived from CD-spectra
- Low free energy barriers, ~1kcal/mol
- Characteristic lengths 20-30 residues