

PROTEIN PHYSICS

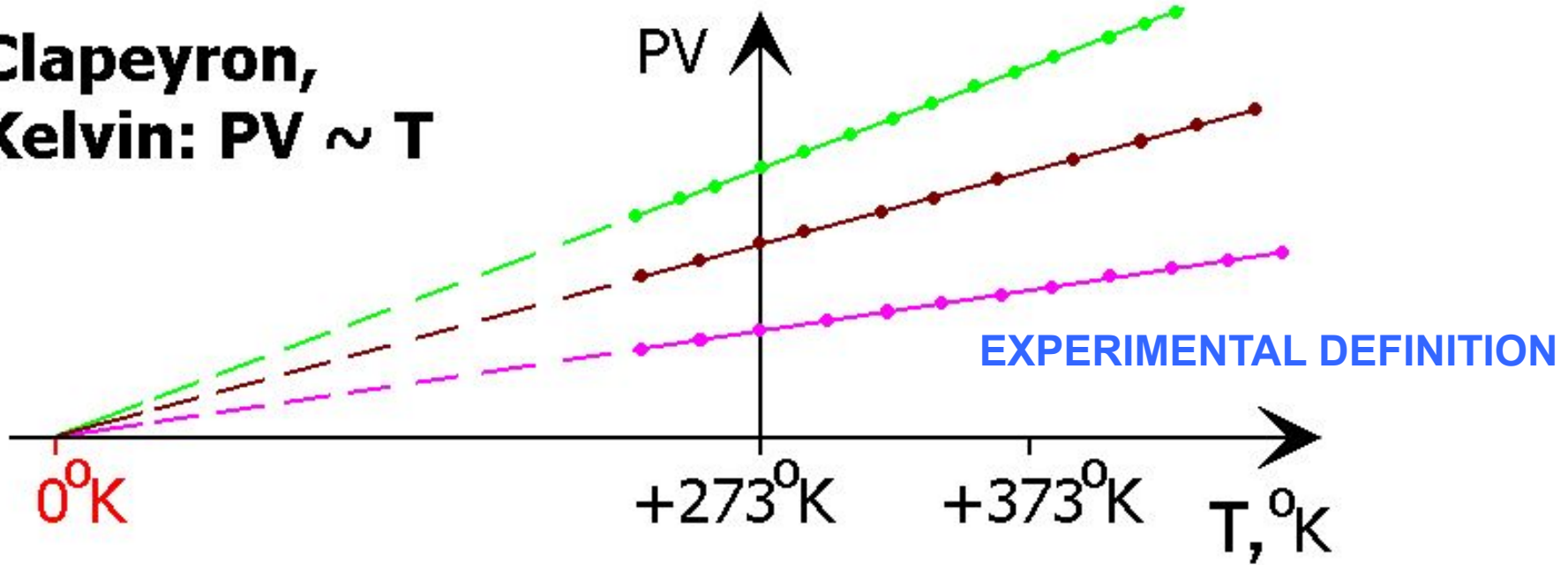
LECTURES 7-8

Basics of thermodynamics & kinetics

**THERMODYNAMISC
&
STATISTICAL PHYSICS**

WHAT IS "TEMPERATURE"?

Clapeyron,
Kelvin: $PV \sim T$



$$= t, ^\circ\text{C} + 273.15^\circ$$

Gas laws:

$$PV = NkT \Rightarrow P = nkT \quad (n \equiv N/V)$$

$$dP = dn \cdot kT \Rightarrow dP/dh = (dn/dh)kT$$

dh

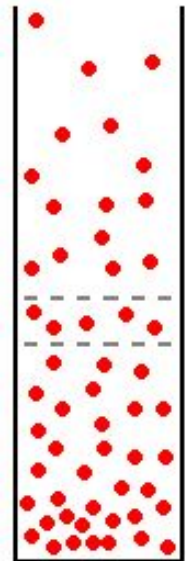
Weight: $dP = mgn(-dh)$

$$\Rightarrow dP/dh = -n \cdot mg$$

$$dn/dh = -n \cdot (mg/kT)$$

Boltzmann:

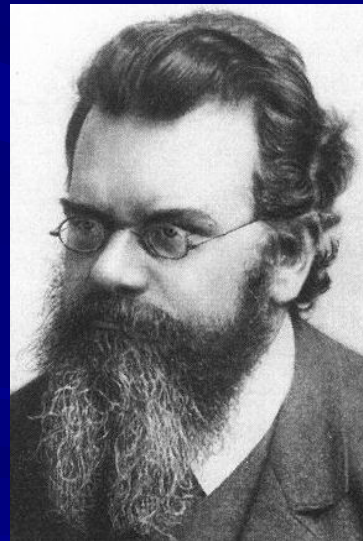
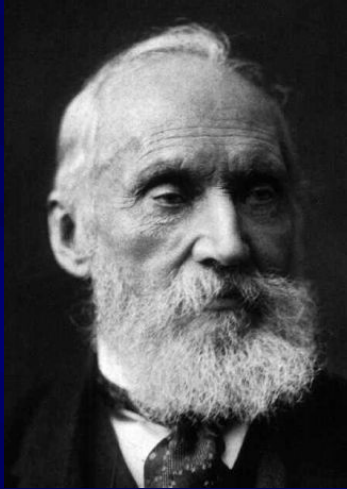
$$n \sim \exp(-mgh/kT) \sim \exp(-\epsilon/k_B T)$$



Benoît Paul Émile **Clapeyron** (1799 – 1864)

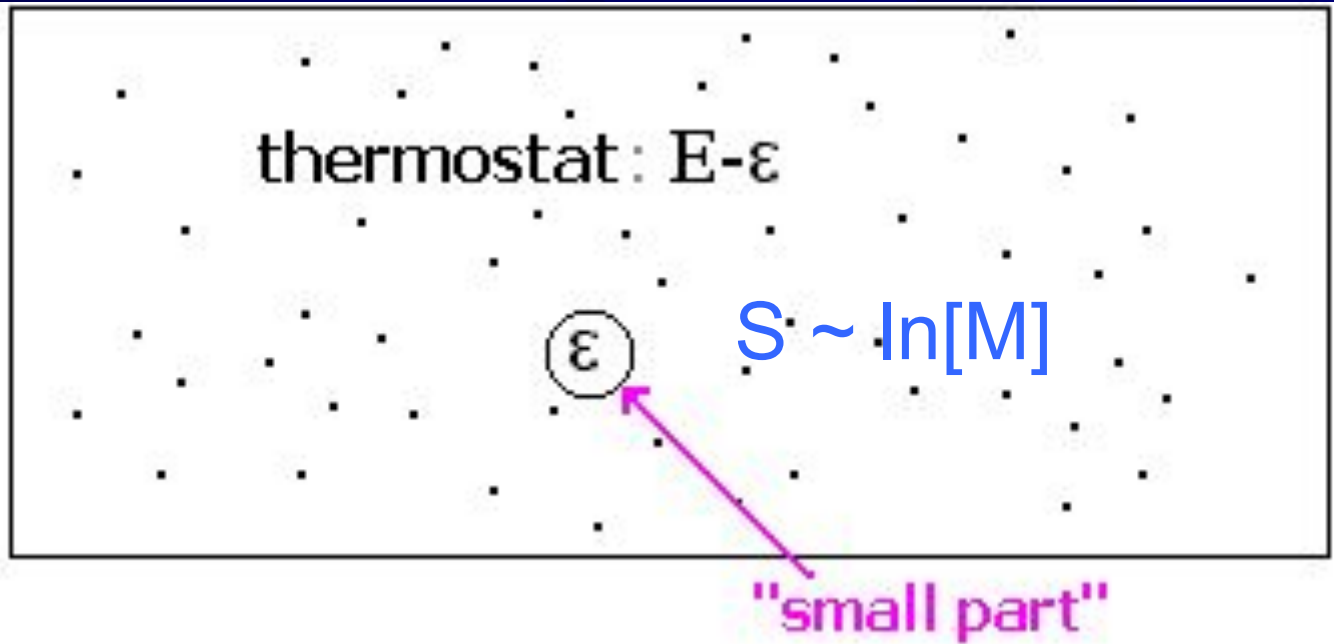


William Thomson, *1st Baron Kelvin* (1824 -1907)



Ludwig Eduard **Boltzmann** (1844 – 1906)

WHAT IS "TEMPERATURE"?



THEORY

Closed system:
energy
 $E = \text{const}$

CONSIDER: 1 state of "small part" with ε & all states of thermostat with $E-\varepsilon$. $M_{\text{all}}(E-\varepsilon) = 1 \cdot M_{\text{t}}(E-\varepsilon)$

$$k \cdot \ln[M_{\text{t}}(E-\varepsilon)] \equiv S_{\text{t}}(E-\varepsilon) \approx S_{\text{t}}(E) - \varepsilon \cdot (dS_{\text{t}}/dE)|_E$$

$$M_{\text{t}}(E-\varepsilon) \approx \exp[S_{\text{t}}(E)/k] \cdot \exp[-\varepsilon \cdot (dS_{\text{t}}/dE)|_E/k]$$

conclusions



COMPARE:

$$\text{Probability}_1(\varepsilon_1) = M_t(E-\varepsilon_1)/M(E) = \exp[-\varepsilon_1 \cdot (dS_t/dE)|_E/k] \quad (\text{GIBBS})$$

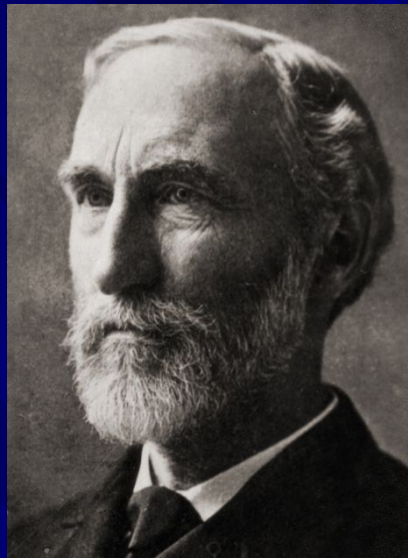
and

$$\text{Probability}_1(\varepsilon_1) = \exp(-\varepsilon_1/k_B T) \quad (\text{BOLTZMANN})$$

One has:

$$(dS_t/dE)|_E = 1/T$$
$$k = k_B$$

$$\varepsilon \Rightarrow \varepsilon - k_B T, \quad M \Rightarrow M \times \exp(1) \equiv M \times 2.72$$



Josiah Willard **Gibbs**
(1839 –1903)



Joseph **Liouville**
(1809 - 1882)

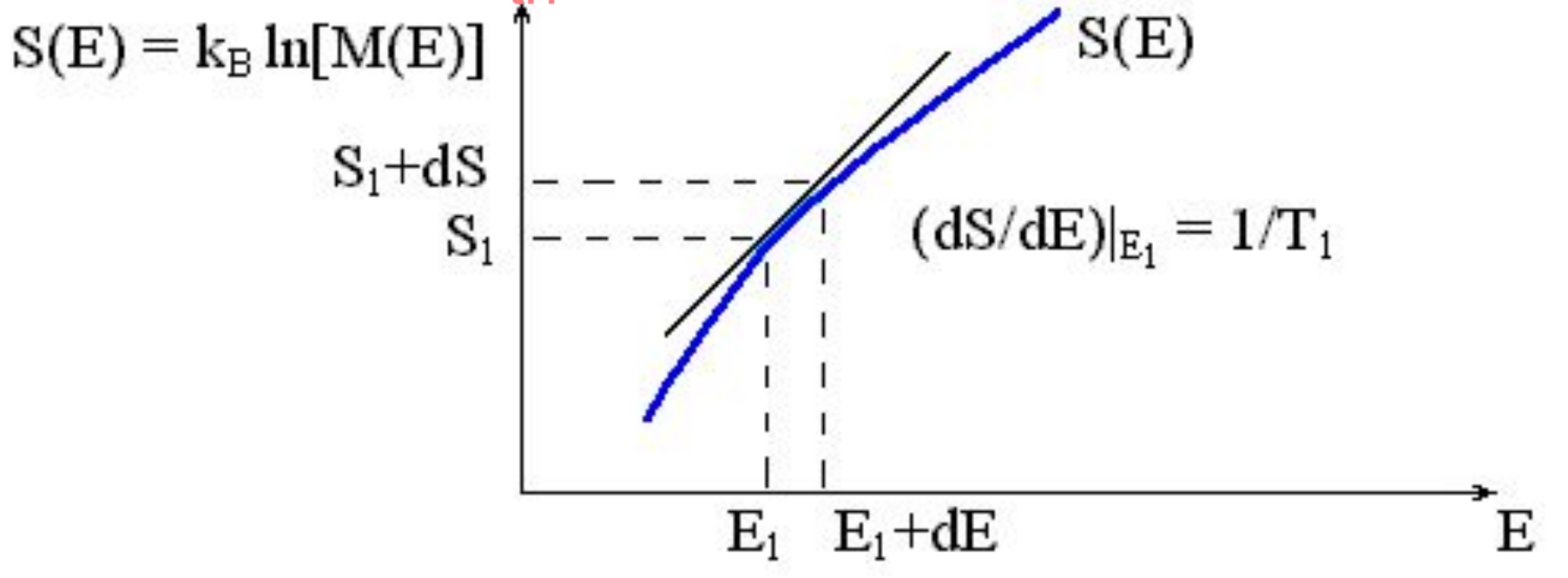


Яков Григорьевич **Синай**, 1935
Abel Prize 2014

“...связь между порядком и хаосом...”

$$1/r^3$$

$$(dS_{th}/dE) = 1/T$$



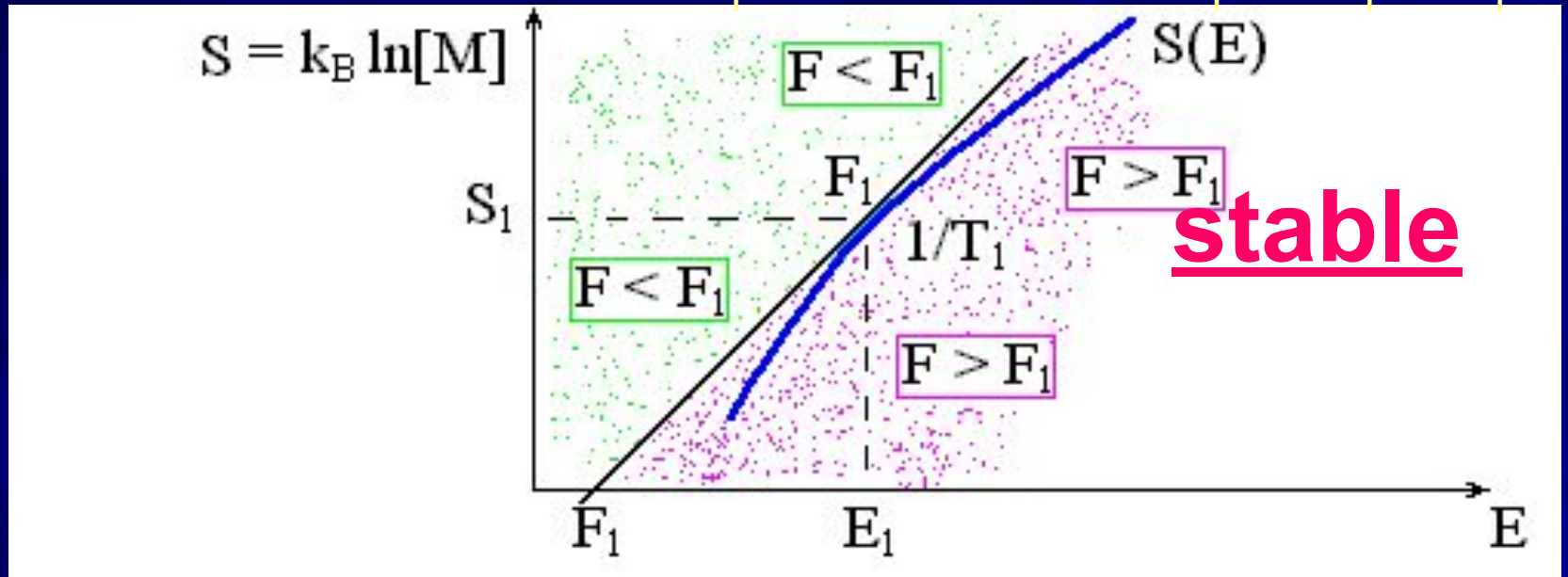
$$P_1(\varepsilon_1) \sim \exp(-\varepsilon_1/k_B T)$$

$$P_j(\varepsilon_j) = \exp(-\varepsilon_j/k_B T)/Z(T); \quad \sum_j P_j(\varepsilon_j) \equiv 1$$

$$Z(T) = \sum_i \exp(-\varepsilon_i/k_B T) \quad \text{partition function}$$

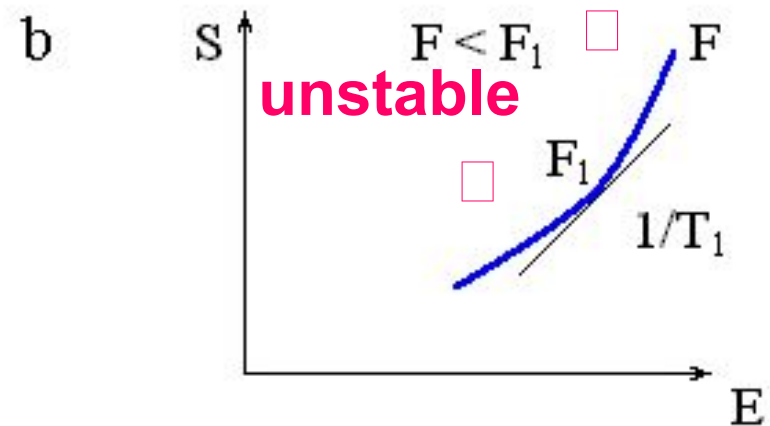
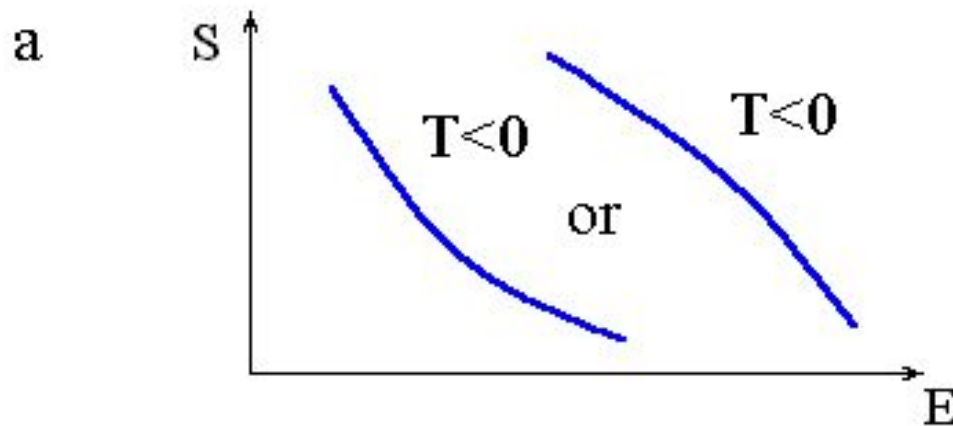
СТАТИСТИЧЕСКАЯ СУММА

Along tangent: $S - S(E_1) = (E - E_1)/T_1$
 i.e., $F = E - T_1 S = \text{const} (= F_1 = E_1 - T_1 S_1)$



Unstable (explodes, $v \rightarrow \text{inf.}$)

Unstable (falls)



Separation of potential and kinetic energies in classic (non-quantum) mechanics:

$$P(\varepsilon) \sim \exp(-\varepsilon/k_B T) \quad // \quad \text{Classic: } \varepsilon = \varepsilon_{\text{COORD}} + \varepsilon_{\text{KIN}}$$

$\varepsilon_{\text{KIN}} = mv^2/2$: does not depend on coordinates

Potential energy $\varepsilon_{\text{COORD}}$: depends *only* on coordinates

$$P(\varepsilon) \sim \exp(-\varepsilon_{\text{COORD}}/k_B T) \cdot \exp(-\varepsilon_{\text{KIN}}/k_B T)$$

$$Z(T) = Z_{\text{COORD}}(T) \cdot Z_{\text{KIN}}(T) \quad \Rightarrow \quad F(T) = F_{\text{COORD}}(T) + F_{\text{KIN}}(T)$$

Elementary volume: $\Delta(mv)\Delta x \cong \hbar \Rightarrow (\Delta x)^3 \cong (\hbar/|mv|)^3$
 $= (\hbar^2/[mk_B T])^{3/2}$

$\Delta(mv) \cong m|v|$, and $|mv| \cong (mk_B T)^{1/2}$

IN THERMAL EQUILIBRIUM:

$$T_{\text{COORD}} = T_{\text{KIN}} = T_{\text{outer}}$$

**We may consider further
only potential energy:**

$$E \Rightarrow E_{\text{COORD}}$$

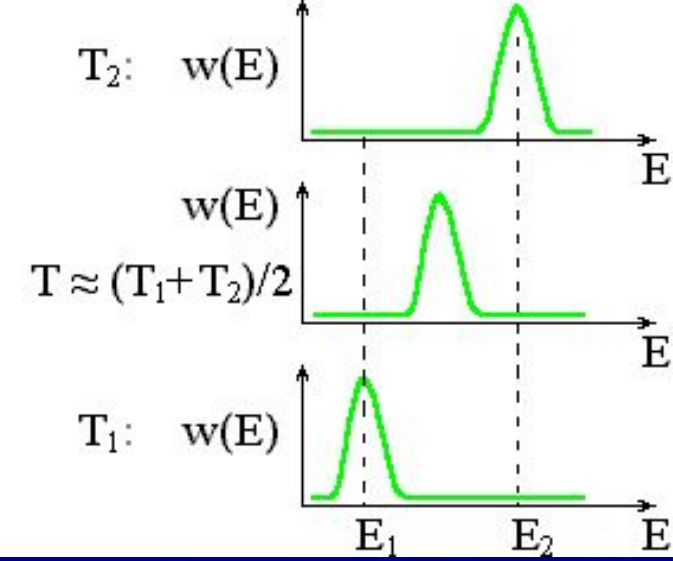
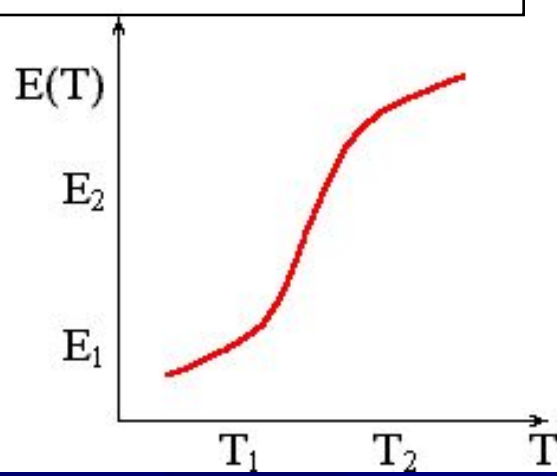
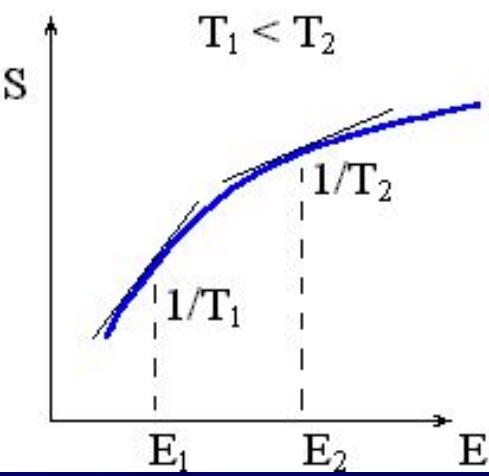
$$M \Rightarrow M_{\text{COORD}}$$

$$S(E) \Rightarrow S_{\text{COORD}}(E_{\text{COORD}})$$

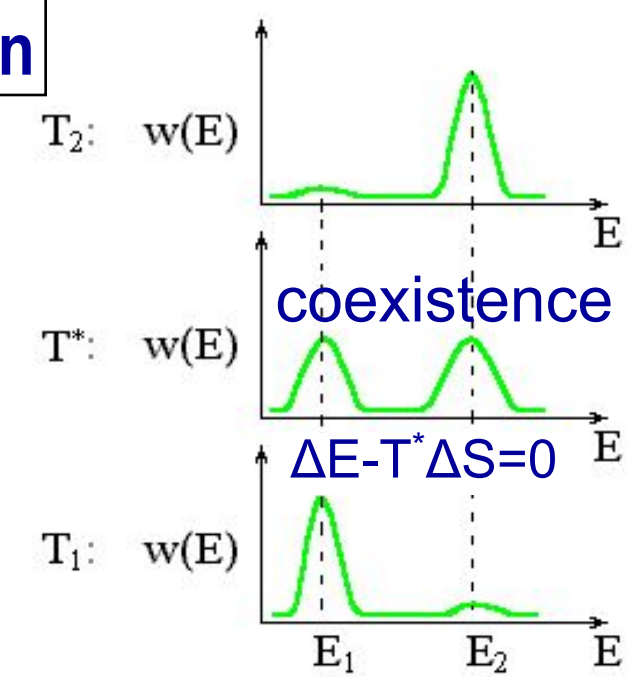
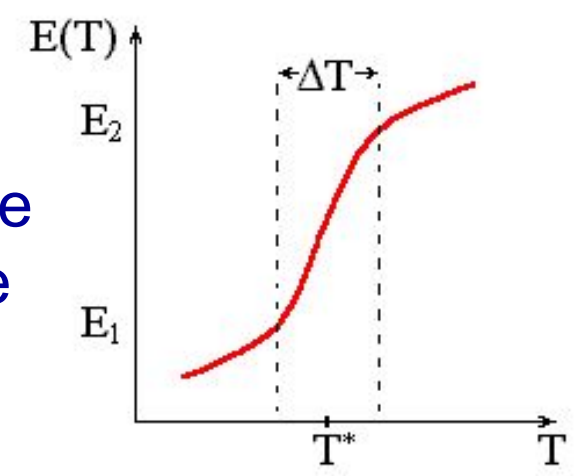
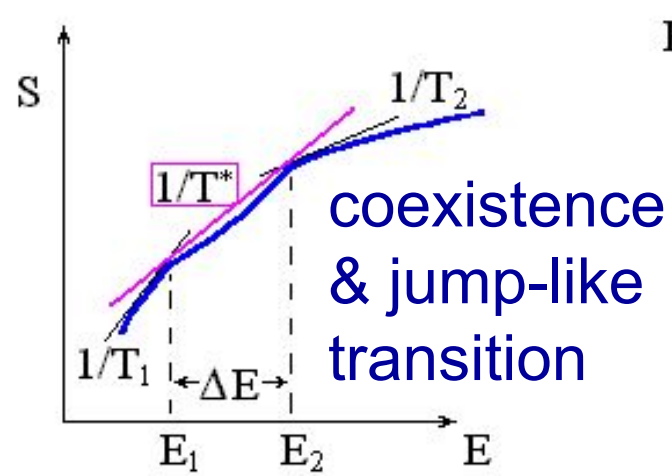
$$F(E) \Rightarrow F_{\text{COORD}}, \text{ etc.}$$

TRANSITIONS: THERMODYNAMICS

gradual transition

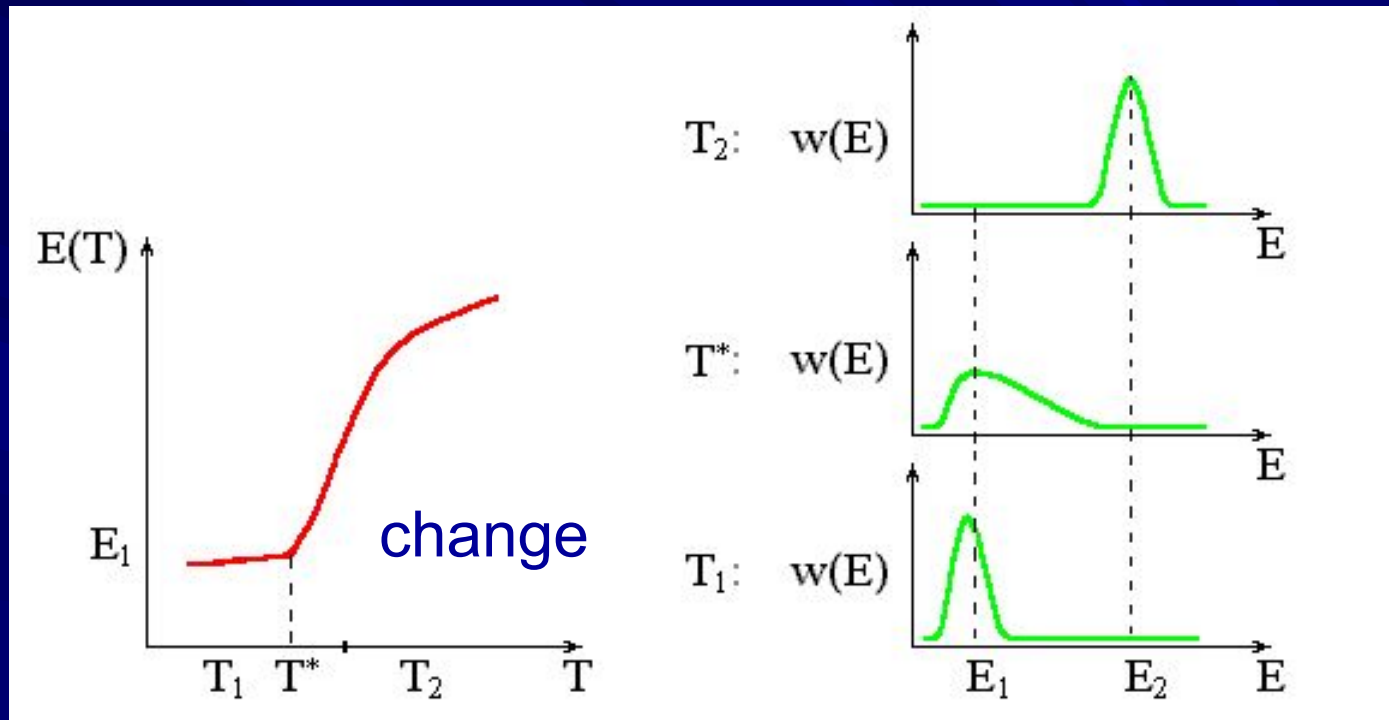


“all-or-none” (or 1st order) phase transition



Transition: $|\Delta F_1| = |-\Delta S \times \Delta T| \sim kT^* \implies (\Delta E/kT^*)(\Delta T/T^*) \sim 1$

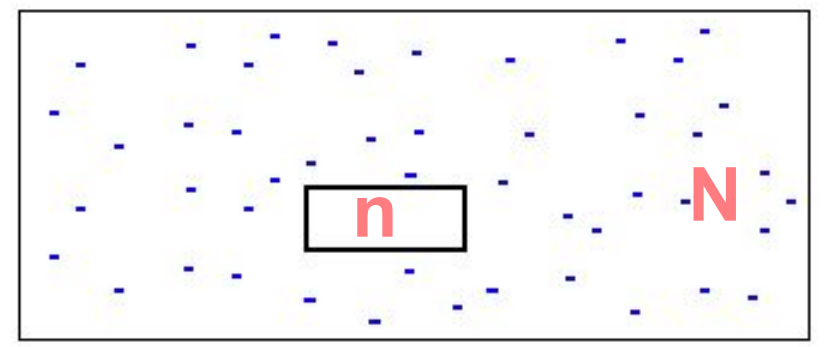
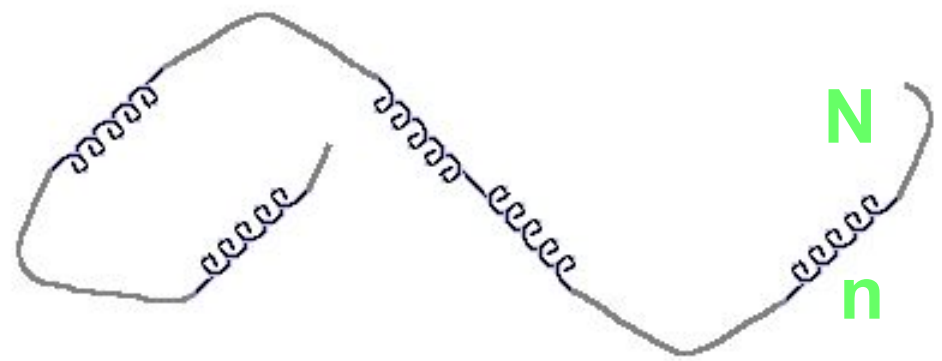
Second order phase transition



Recently observed in proteins;
rare case

**LANDAU: Helix-coil transition:
NOT 1-s order phase transition**

**Melting:
1-s order phase transition**



Helix & coil: 1D objects

Ice & water: 3D

objects
 $\Delta F_{\text{helix}_n} = \text{Const} + n \times f$
 1D interface

$\Delta F_{\text{ICE}_n} = C \times n^{2/3} + n \times f$
 3D interface

Mid-transition: $f = 0$

$\Delta S_{\text{helix}_n} \sim \ln(N)$

$\Delta S_{\text{ICE}_n} \sim \ln(N)$

N : very large; $n \sim \alpha N$, $\alpha \ll 1$ (e.g., $\alpha \sim 0.001$)

$\text{Const} \ll \ln(N)$

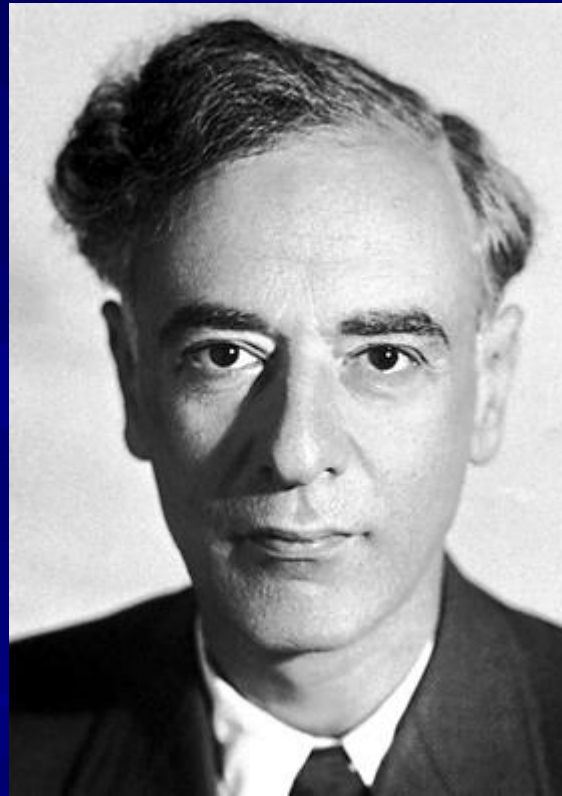
$\alpha^{2/3} \cdot N^{2/3} \gg \ln(N)$

phases mix

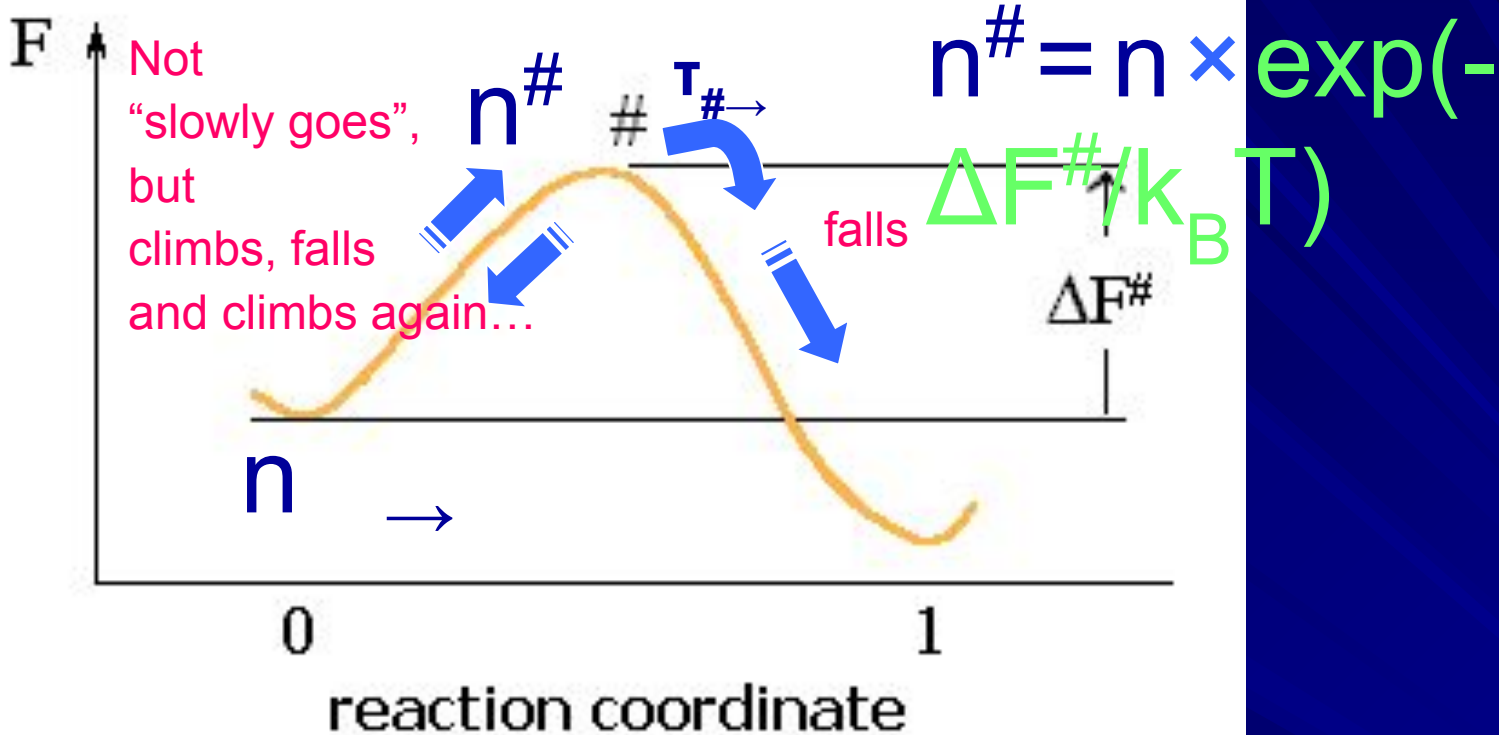
phases do not mix



Лев Давидович Ландау
(1908 - 1968)
Нобелевская Премия 1962

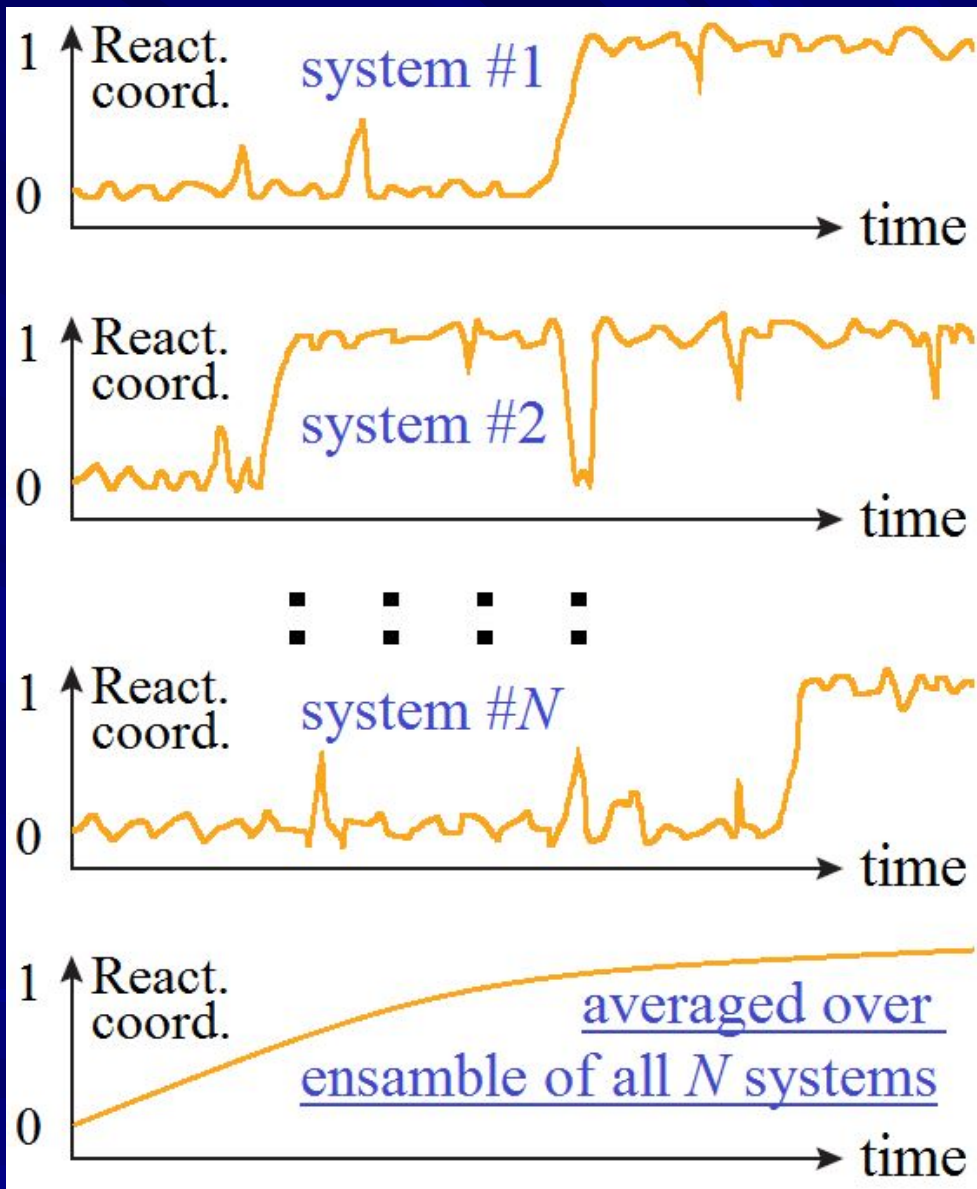


TRANSITIONS: KINETICS



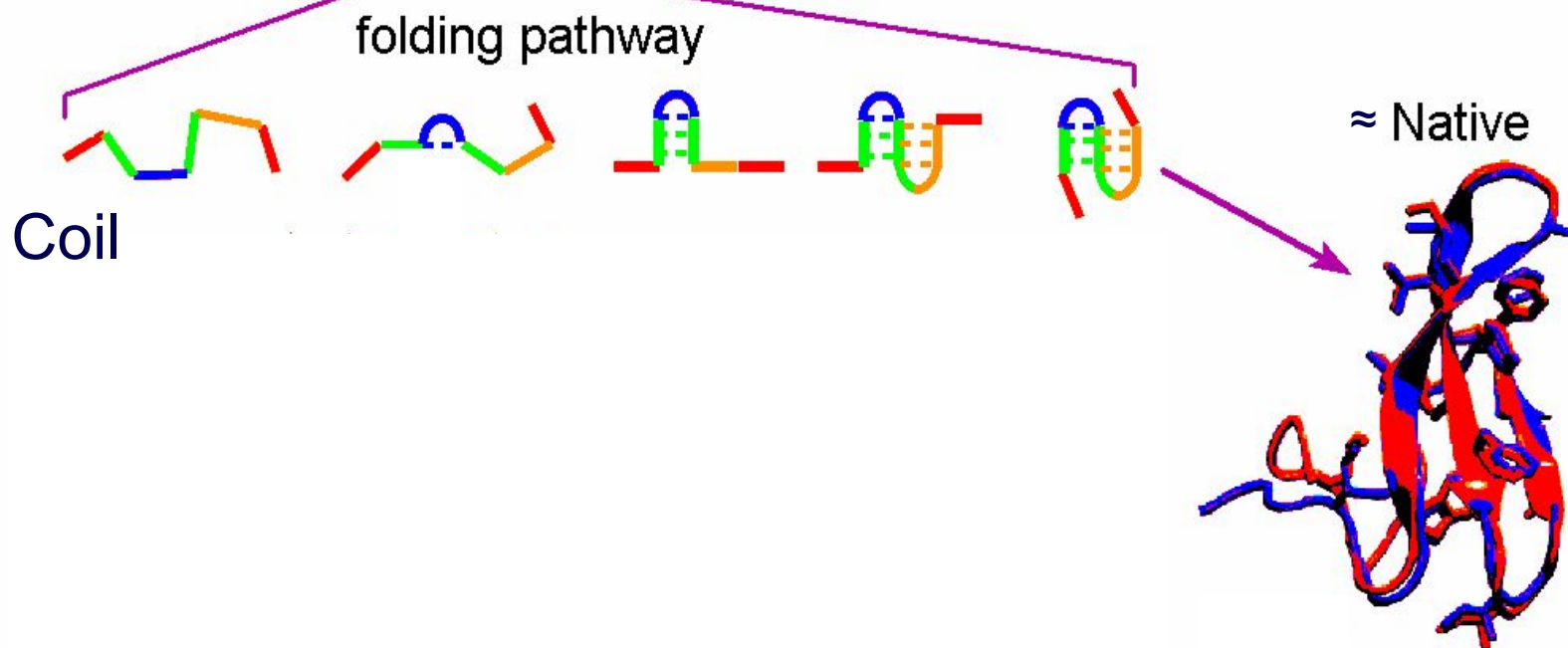
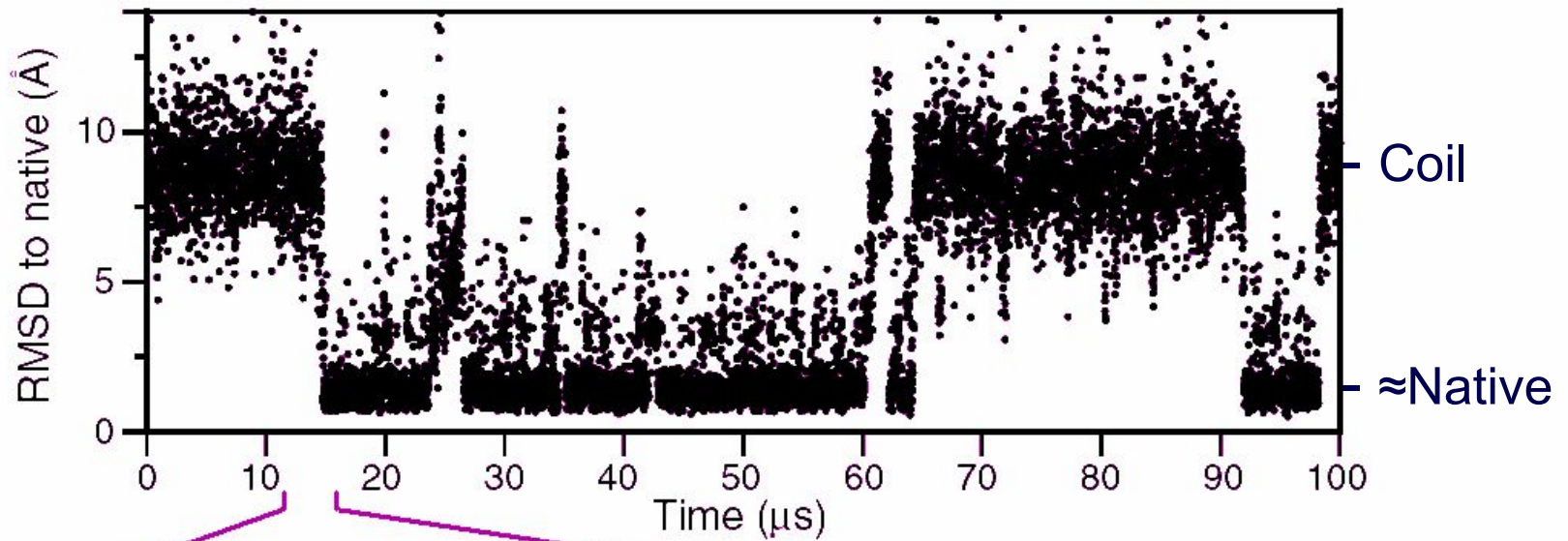
TRANSITION TIME:

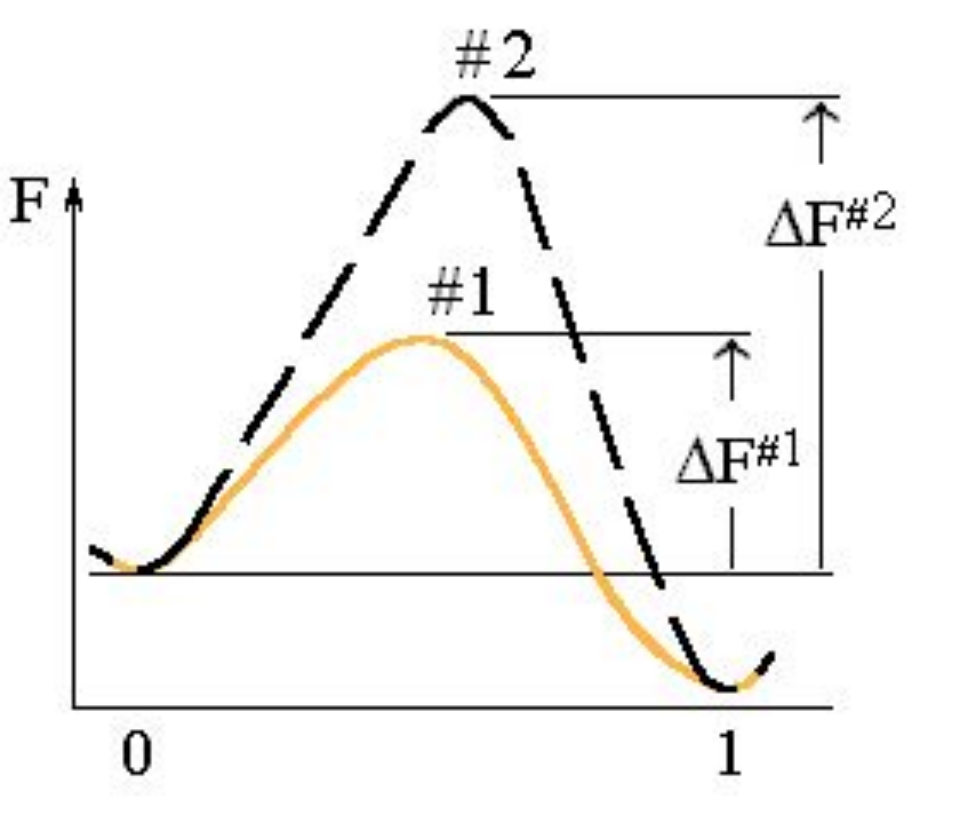
$$t_{0 \rightarrow 1} = t_{0 \rightarrow \# \rightarrow 1} \approx \tau_{\# \rightarrow} \left(\frac{n}{n^{\#}} \right) = \tau_{\# \rightarrow} \times \exp(+\Delta F^{\#}/k_B T)$$



FIP35 protein: simulation of folding

D.E. Shaw et al., Oct. 2010, *Science* **330**, 341





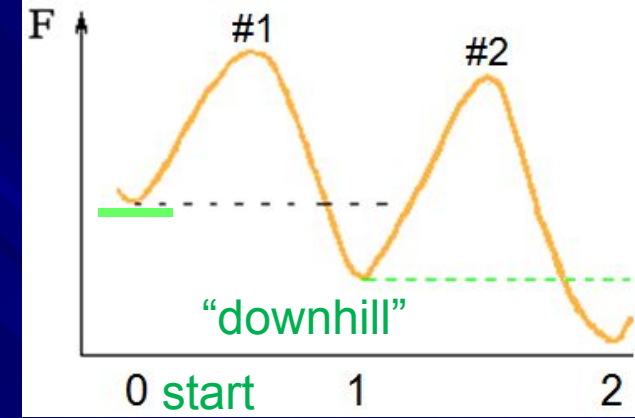
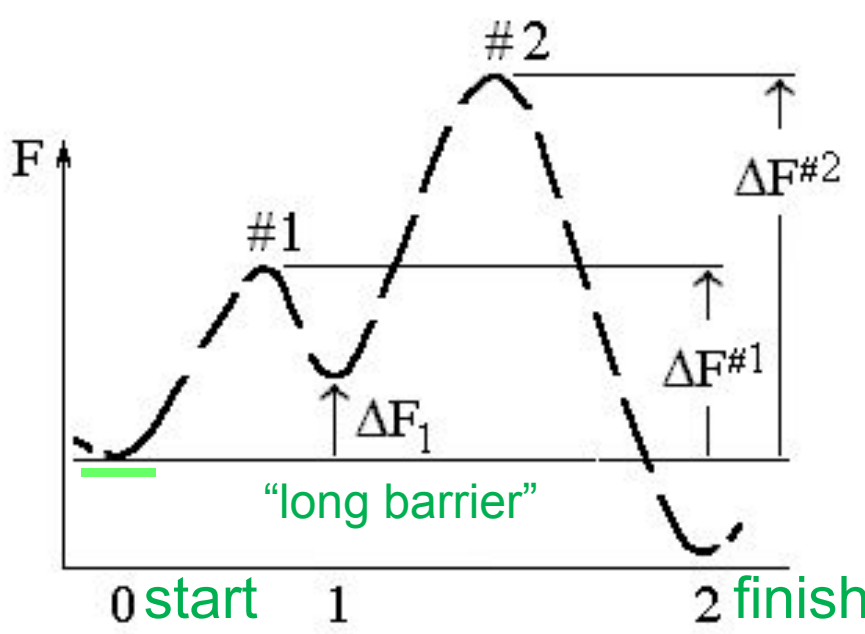
PARALLEL REACTIONS:

**TRANSITION RATE =
SUM OF RATES**

(or: ≈the highest rate)

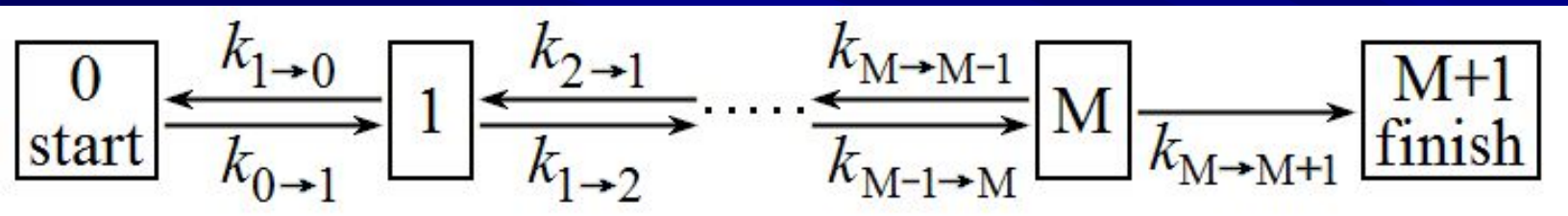
RATE = 1/ TIME

$$1/\text{TIME} = (1/\tau_{\# \rightarrow}) \times \exp(-\Delta F_1^{\#}/k_B T) + (1/\tau_{\# \rightarrow}) \times \exp(-\Delta F_2^{\#}/k_B T)$$



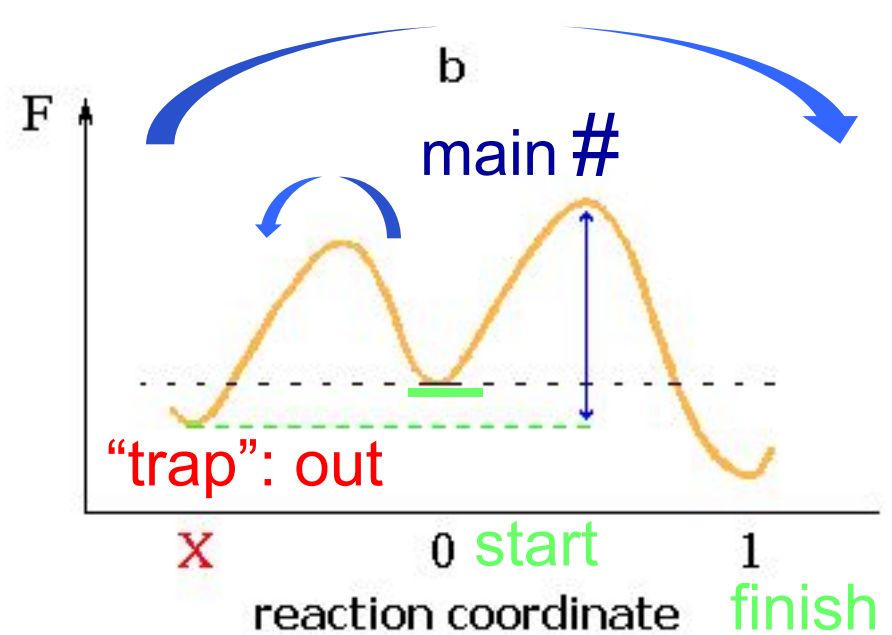
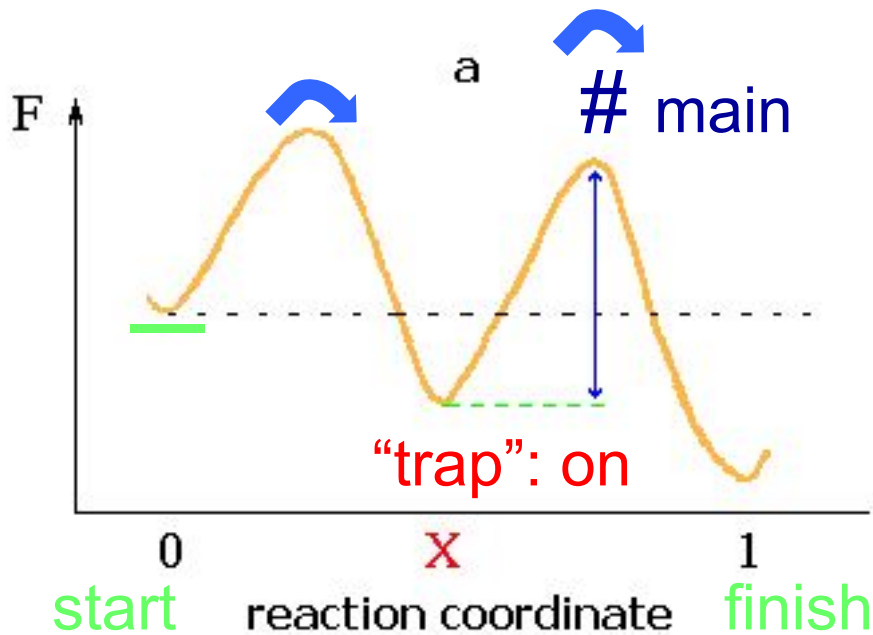
$$t_{0 \rightarrow \dots \rightarrow} \approx t_{0 \rightarrow \#1 \rightarrow 1} + t_{1 \rightarrow \#2 \rightarrow 2} + \dots$$

CONSECUTIVE REACTIONS:
TRANSITION TIME \approx SUM OF TIMES
 (or: \approx the highest time)



“long barrier”: $t_{0 \rightarrow \dots \rightarrow \text{finish}} \approx t_{0 \rightarrow \#1 \rightarrow \text{finish}} + t_{0 \rightarrow \#2 \rightarrow \text{finish}} + \dots$
 steady-state approximation

$$\text{TIME} \approx \tau_{\# \rightarrow} \times \exp(+\Delta F_1^{\#} / k_B T) + \tau_{\# \rightarrow} \times \exp(+\Delta F_2^{\#} / k_B T) + \dots$$



**TRANSITION TIME IS ESSENTIALLY
EQUAL FOR "TRAPS" AT AND OUT OF
PATHWAYS OF CONSECUTIVE REACTIONS:**

**TRANSITION TIME \cong SUM OF TIMES
(or: \approx the longest time)**

DIFFUSION: KINETICS

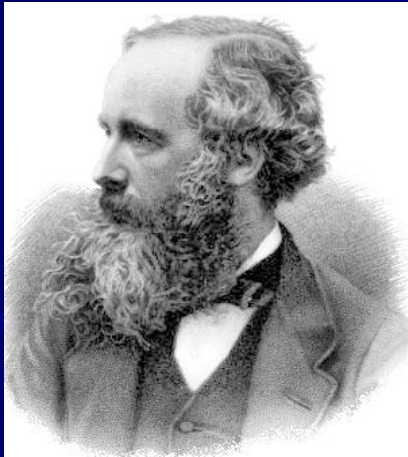
Mean kinetic energy of a particle: $\langle mv^2/2 \rangle \sim k_B T$

$$\langle \epsilon \rangle = \sum_j P_j(\epsilon_j) \cdot \epsilon_j \quad v^2 = (v_x^2) + (v_y^2) + (v_z^2)$$

James Clerk

Maxwell :

(1831 – 1879)



$$\begin{aligned} \langle mv^2/2 \rangle &= \frac{\int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-(mv^2/2)/k_B T] \cdot (mv^2/2) \cdot dv_x dv_y dv_z}{\int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-(mv^2/2)/k_B T] \cdot dv_x dv_y dv_z} \\ &= \frac{k_B T \cdot \int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-(mv^2/2k_B T)] \cdot (mv^2/2k_B T) \cdot dv_x dv_y dv_z}{\int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-(mv^2/2k_B T)] \cdot dv_x dv_y dv_z} \\ &= \frac{k_B T \cdot \int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-r^2] \cdot r^2 \cdot dr_1 dr_2 dr_3}{\int_0^{\infty} \int_0^{\infty} \int_0^{\infty} \exp[-r^2] \cdot dr_1 dr_2 dr_3} = \frac{3}{2} k_B T \quad \text{in 3D} \end{aligned}$$

Friction stops a molecule within picoseconds:

$$m(dv/dt) = -(3\pi D\eta)v \quad [\text{Stokes law}], \text{ or} \quad m(dv/dt) = -(k_B T/D_{\text{diff}})v$$

[Einstein-Stokes]

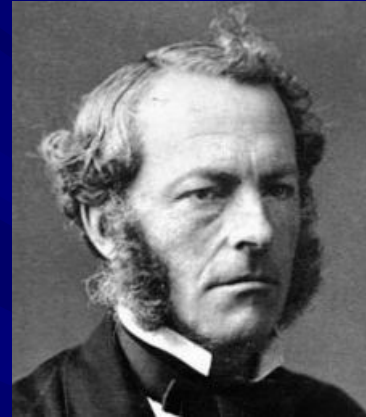
D – diameter;

$m \sim D^3 \cdot 1\text{g/cm}^3$ – mass;

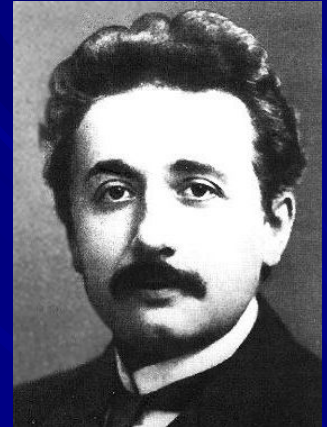
η – viscosity

$$t_{\text{kinet}} \approx 10^{-13} \text{ sec} \times (D/\text{nm})^2$$

in water



Sir George Gabriel Stokes
(1819-1903)



Albert Einstein
(1879-1995)

DIFFUSION:

During t_{kinet} the molecule moves by $L_{\text{kinet}} \sim v \cdot t_{\text{kinet}}$

Then it restores its kinetic energy $mv^2/2 \sim k_B T$ from thermal kicks of other molecules, and moves in another random side

CHARACTERISTIC DIFFUSION TIME: nanoseconds



Friction stops a molecule within picoseconds:

$$t_{\text{kinet}} \approx \boxed{10^{-13} \text{ sec} \times (D/\text{nm})^2} \quad \text{in water}$$

DIFFUSION:

During t_{kinet} the molecule moves by $L_{\text{kinet}} \sim v \cdot t_{\text{kinet}}$

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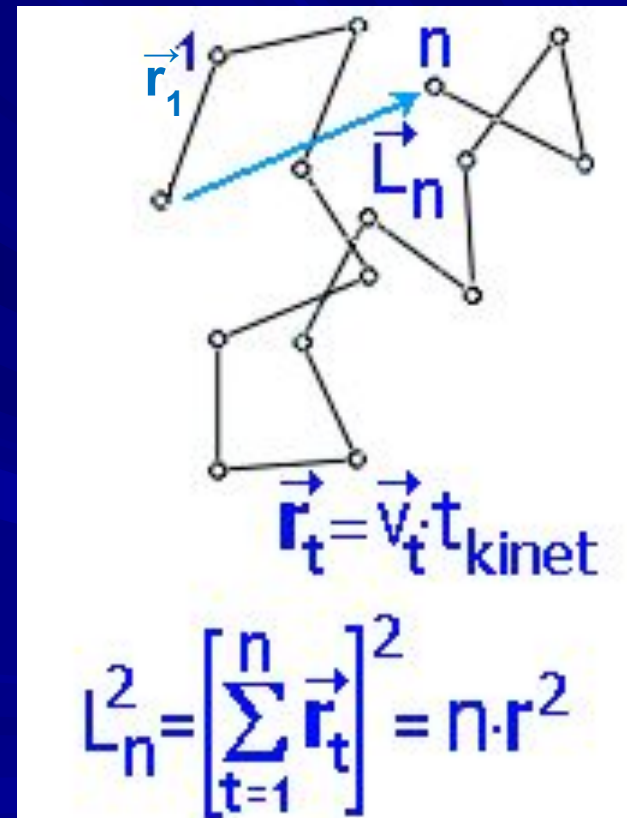
CHARACTERISTIC DIFFUSION

TIME: nanoseconds

The random walk allows the molecule to diffuse at distance D (\sim its diameter) within $\sim (D/L_{\text{kinet}})^2$ steps, i.e., within

$$t_{\text{diff}} \approx t_{\text{kinet}} \cdot (D/L_{\text{kinet}})^2 = D^2/D_{\text{diff}}$$

$$\approx \boxed{4 \cdot 10^{-10} \text{ sec} \times (D/\text{nm})^3} \quad \text{in water}$$



The End

For “small part”: $P_j(\epsilon_j) = \exp(-\epsilon_j/k_B T)/Z(T)$;

$$Z(T) = \sum_j \exp(-\epsilon_j/k_B T)$$

$$\sum_j P_j(\epsilon_j) = 1$$

$$E(T) = \langle \epsilon \rangle = \sum_j \epsilon_j \cdot P_j(\epsilon_j)$$

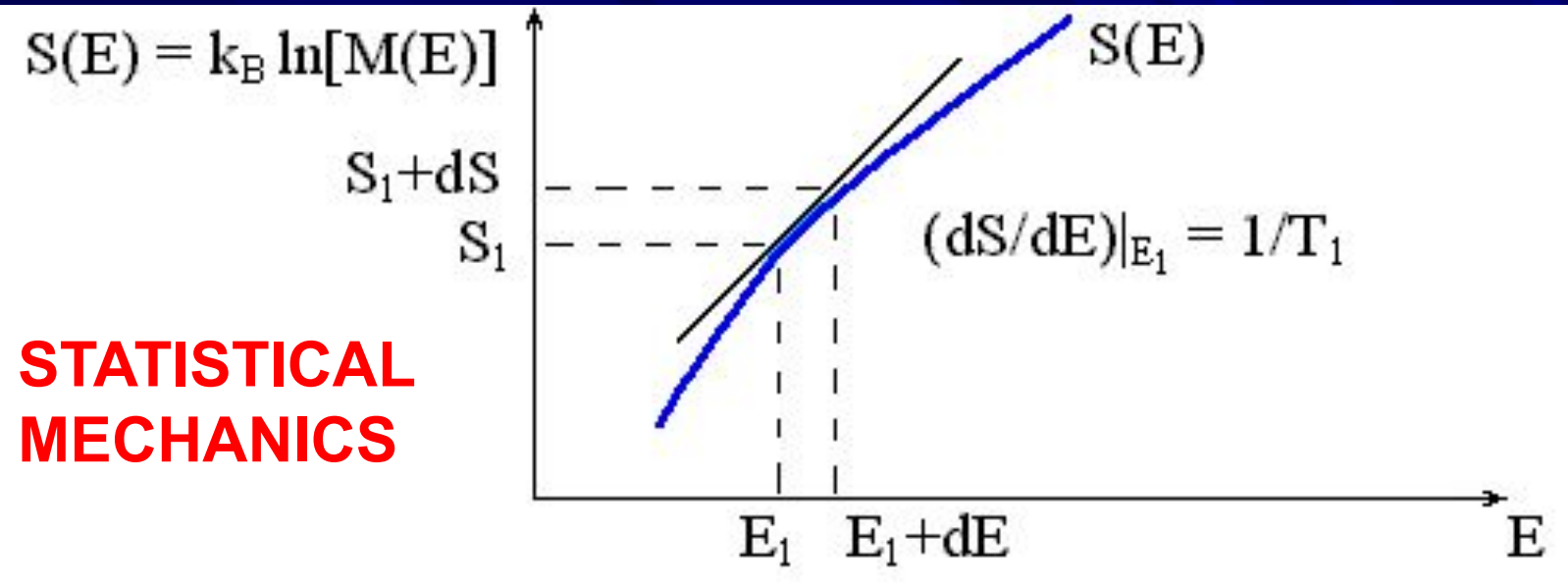
if all $\epsilon_j = \epsilon$: #STATES = $1/P$, i.e.: $S(T) = k_B \cdot \ln(1/P)$

$$S(T) = k_B \langle \ln(\text{\#STATES}) \rangle = k_B \cdot \sum_j \ln[1/P_j(\epsilon_j)] \cdot P_j(\epsilon_j)$$

$$F(T) = E(T) - TS(T) = -k_B T \cdot \ln[Z(T)]$$

STATISTICAL MECHANICS

Thermostat: $T_{th} = dE_{th} / dS_{th}$



“Small part”: $P_j(\epsilon_j, T_{th}) \sim \exp(-\epsilon_j / k_B T_{th})$;

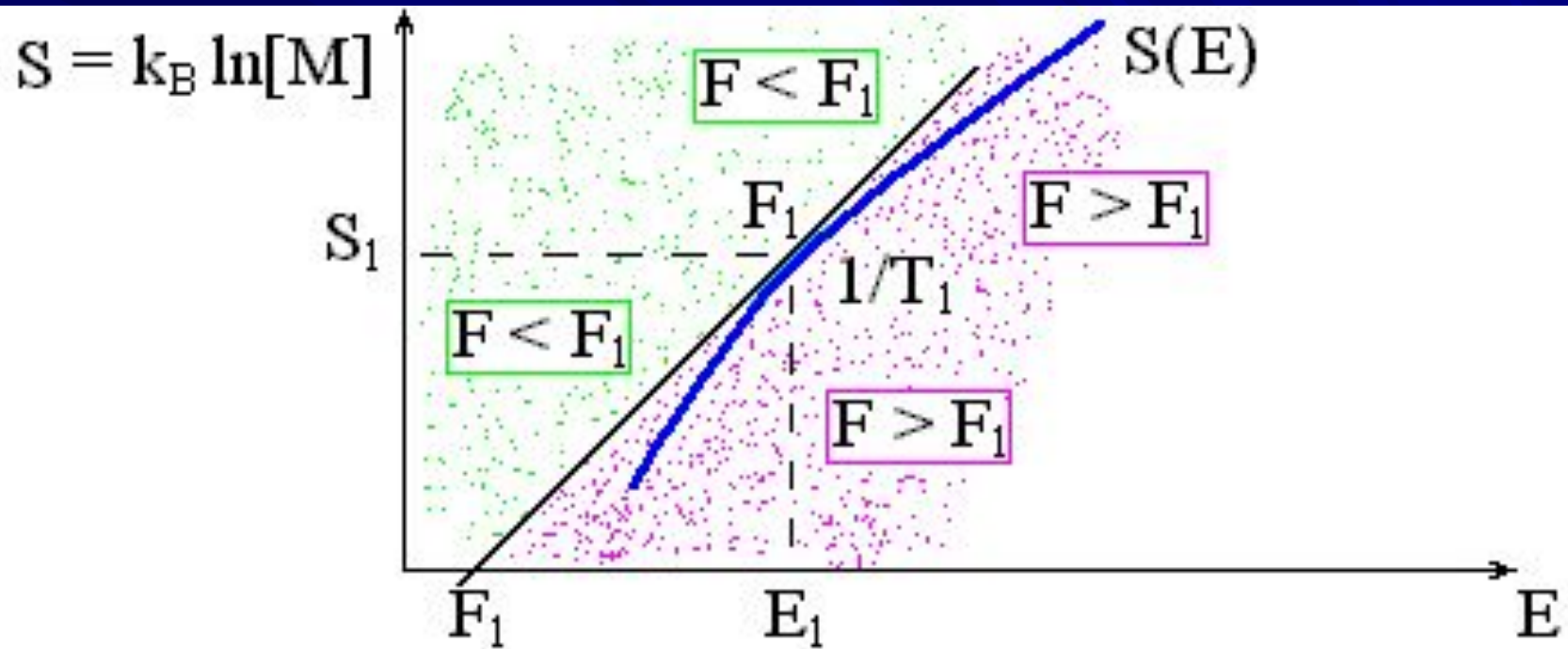
$$E(T_{th}) = \sum_j \epsilon_j \square P_j(\epsilon_j, T_{th})$$

$$S(T_{th}) = k_B \square \sum_j \ln[1/P_j(\epsilon_j, T_{th})]$$

$$\square P_j(\epsilon_j, T_{th})$$

$$T_{small\ part} = dE(T_{th}) / dS(T_{th}) = T_{th}$$

Along tangent: $S - S(E_1) = (E - E_1)/T_1$
 i.e.,
 $F = E - T_1 S = \text{const} (= F_1 = E_1 - T_1 S_1)$



Separation of potential energy in classic (non-quantum) mechanics:

$$P(\varepsilon) \sim \exp(-\varepsilon/k_B T) \quad \text{Classic: } \varepsilon = \varepsilon_{\text{COORD}} + \varepsilon_{\text{KIN}}$$

$\varepsilon_{\text{KIN}} = mv^2/2$: does not depend on coordinates

Potential energy $\varepsilon_{\text{COORD}}$: depends only on coordinates

$$P(\varepsilon) \sim \exp(-\varepsilon_{\text{COORD}}/k_B T) \cdot \exp(-\varepsilon_{\text{KIN}}/k_B T)$$

$Z_{\text{KIN}}(T) = \sum_K \exp(-\varepsilon_K/k_B T)$: don't depend on coord.

$Z_{\text{COORD}}(T) = \sum_C \exp(-\varepsilon_C/k_B T)$: depends on coord.

$$Z(T) = Z_{\text{COORD}}(T) \cdot Z_{\text{KIN}}(T) \quad \Rightarrow \quad F(T) = F_{\text{COORD}}(T) + F_{\text{KIN}}(T)$$

Elementary volume: $\Delta(mv)\Delta x = \hbar \Rightarrow (\Delta x)^3$

$$P(\varepsilon_{\text{KIN}} + \varepsilon_{\text{COORD}}) \sim \exp(-\varepsilon_{\text{COORD}}/k_B T) \cdot \exp(-\varepsilon_{\text{KIN}}/k_B T)$$

$$P(\varepsilon_{\text{COORD}}) = \exp(-\varepsilon_{\text{COORD}}/k_B T) / Z_{\text{COORD}}(T)$$

$$Z_{\text{COORD}}(T) = \sum_c \exp(-\varepsilon_c/k_B T): \quad \text{depends ONLY on coordinates}$$

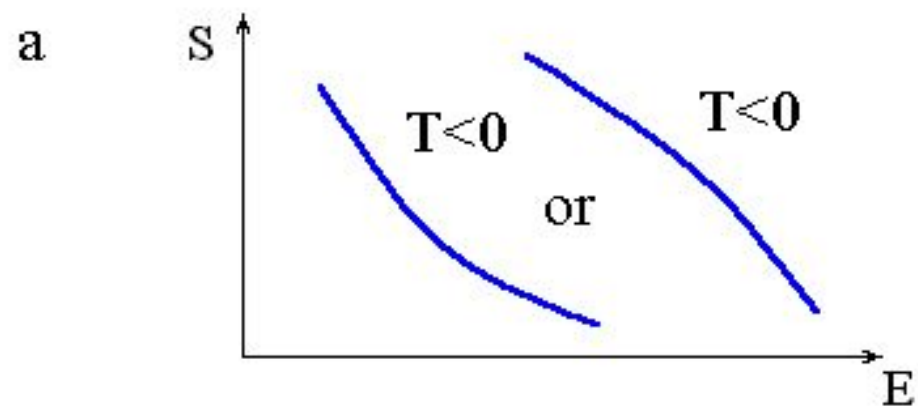
$$P(\varepsilon_{\text{KIN}}) = \exp(-\varepsilon_{\text{KIN}}/k_B T) / Z_{\text{KIN}}(T)$$

$$Z_{\text{KIN}}(T) = \sum_K \exp(-\varepsilon_K/k_B T): \text{ don't depend on coord.}$$

T < 0: unstable (explodes)

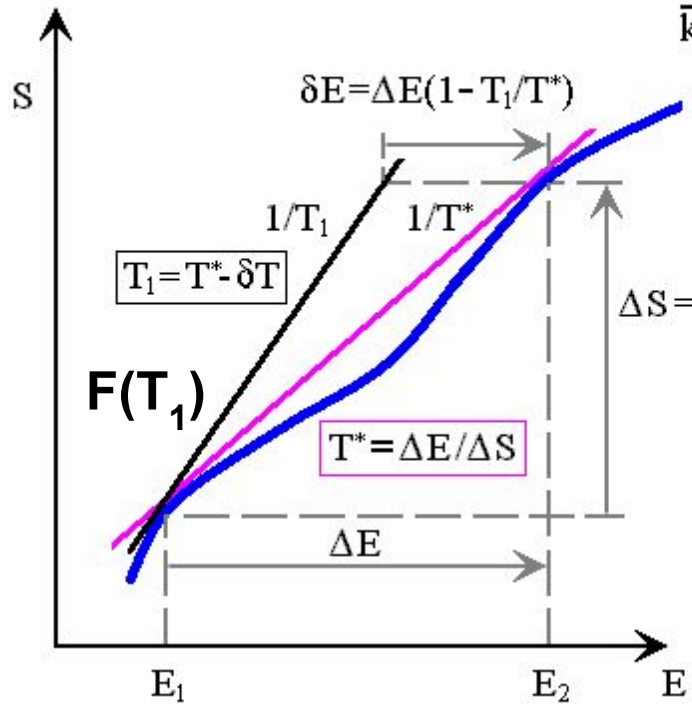
$\langle \varepsilon_{\text{KIN}} \rangle \Rightarrow \infty$ at $T < 0$
due to

$$P(\varepsilon_{\text{KIN}}) \sim \exp(-\varepsilon_{\text{KIN}}/k_B T)$$



“all-or-none” (or first order) phase transition

$$\frac{\delta F}{kT_1} = \delta E/kT_1 = (\Delta E/kT^*)(\delta T/T_1) = (\Delta S/k)(\delta T/T_1) \approx \frac{\Delta S}{k} \frac{\delta T}{T^*}$$



Coexistence: if $|\delta F/kT_1| \lesssim 1$,
 or $|(\delta T/T_1)(\Delta E/kT^*)| \lesssim 1$,
 i.e., in T-range $\Delta T/T^* \approx 1/\Delta \ln(M)$

| | | |
|---|---------------------------------|--|
| SMALL MOLECULE (1 degree of freedom) | $\Delta \ln(M) \approx 1$ | $\Delta T \approx T^*$ non-cooperative |
| PROTEIN (100 degrees of freedom) | $\Delta \ln(M) \approx 100$ | $\Delta T \approx 0.01 T^*$ |
| BOTTLE (10^{25} degrees of freedom) | $\Delta \ln(M) \approx 10^{25}$ | $\Delta T \approx 10^{-25} T^*$ HYSTERESIS: coexistence not observable |

