

# **PROTEIN PHYSICS**

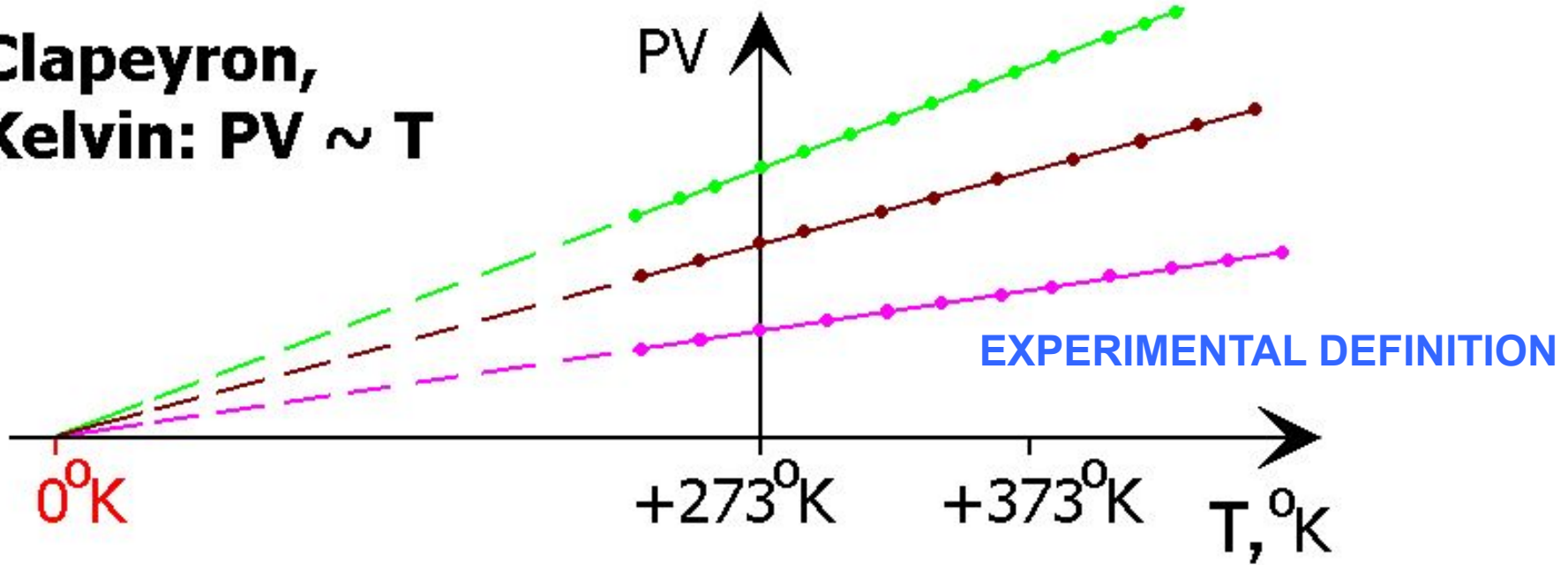
## **LECTURES 7-8**

**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

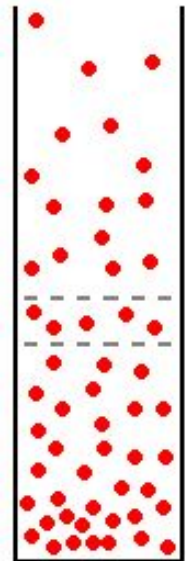
Weight:  $dP = mgn(-dh)$

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

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

**Boltzmann:**

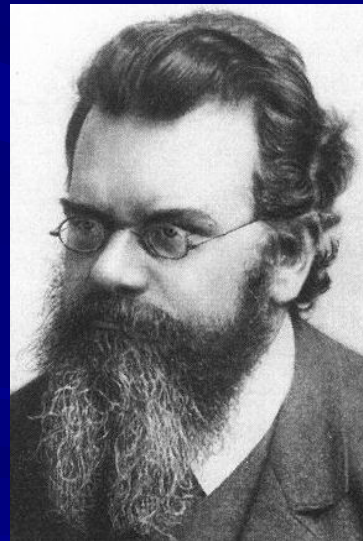
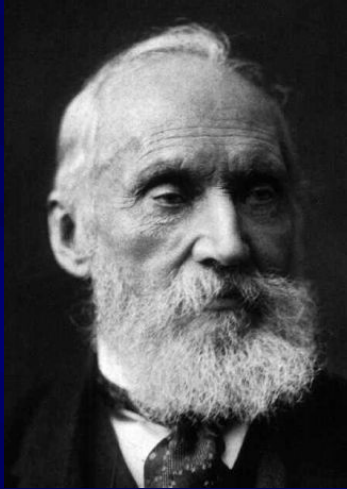
$$n \sim \exp(-mgh/kT) \sim \exp(-\epsilon/k_B T)$$



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

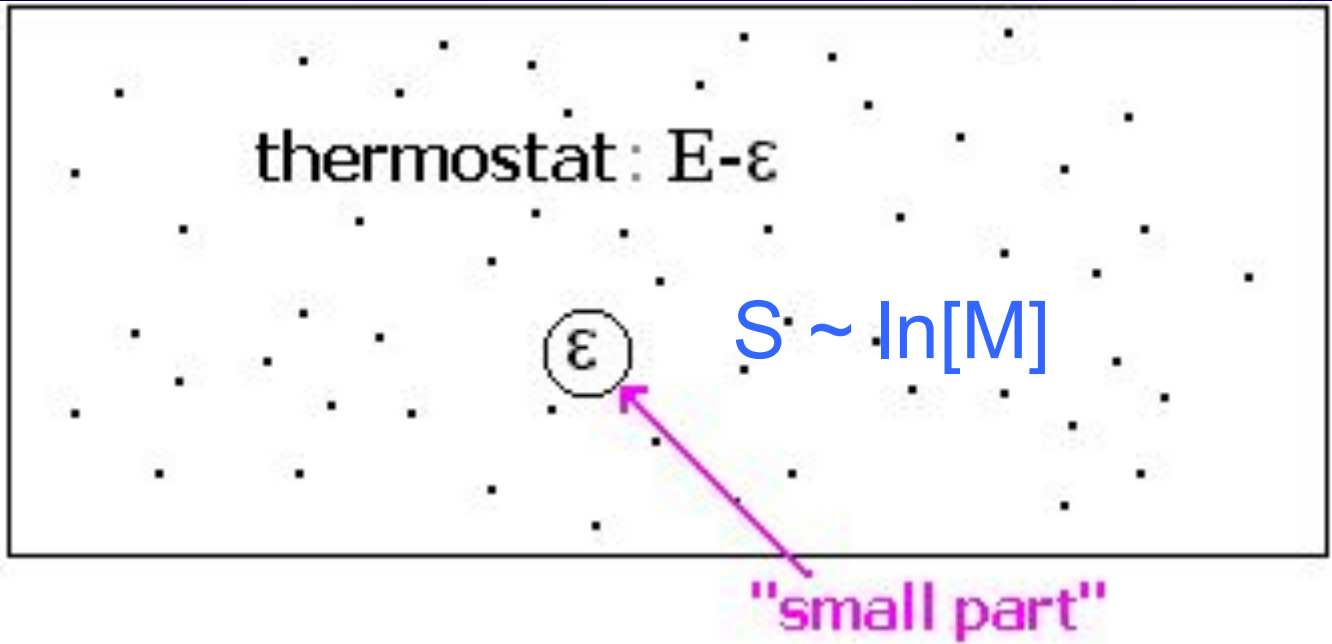


William Thomson, *1st Baron Kelvin* (1824 -1907)



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

# WHAT IS "TEMPERATURE"?



## THEORY

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

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

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

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

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

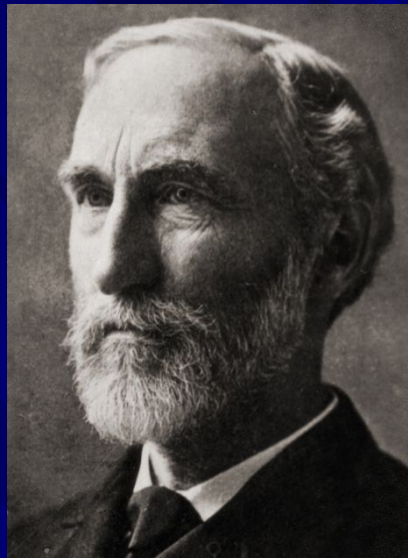
$$\text{Probability}_1(\varepsilon_1) = \exp(-\varepsilon_1/k_B T) \quad (\text{BOLTZMANN})$$

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)

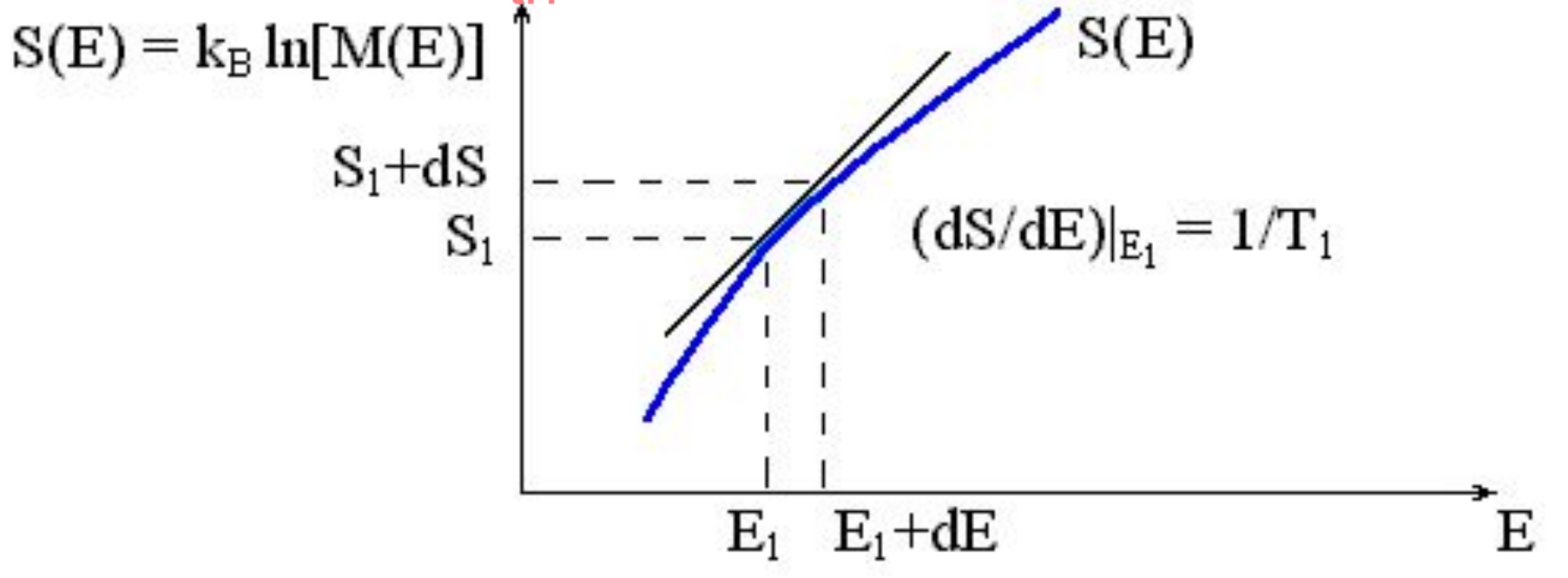


Яков Григорьевич **Синай**, 1935  
Abel Prize 2014

“...связь между порядком и хаосом...”

$$1/r^3$$

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



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

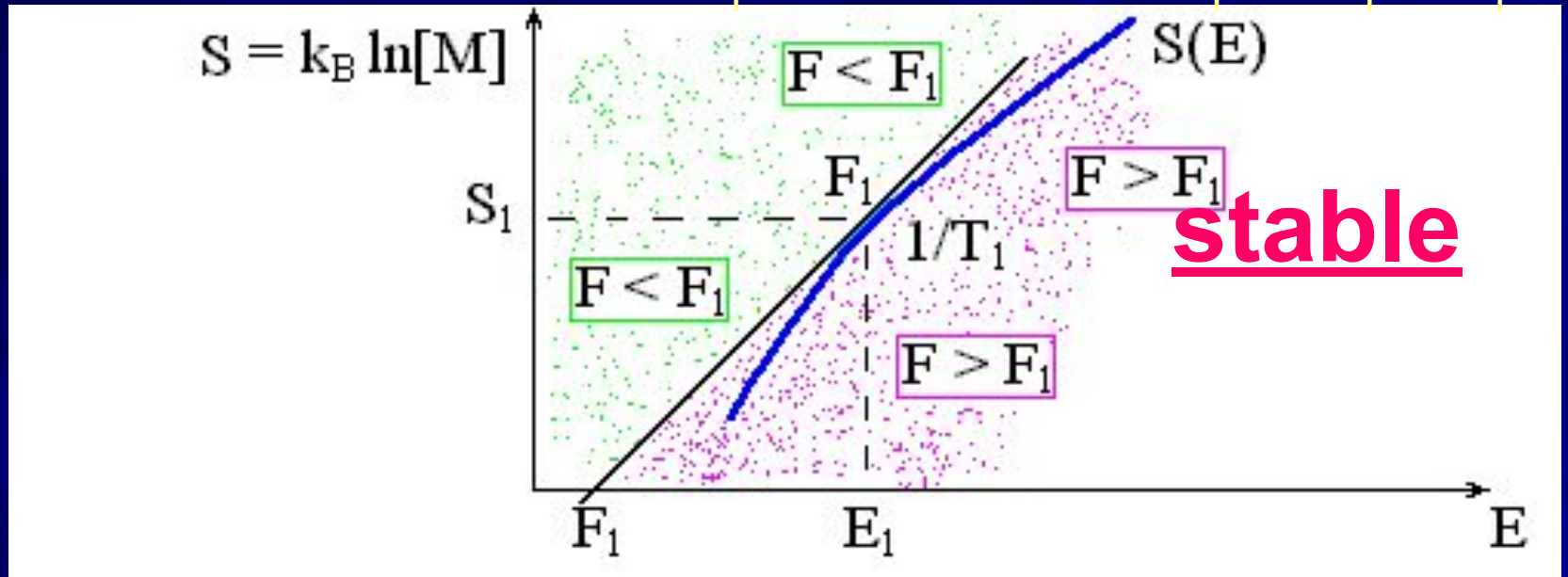
$$P_j(\varepsilon_j) = \exp(-\varepsilon_j/k_B T)/Z(T); \quad \sum_j P_j(\varepsilon_j) \equiv 1$$

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

СТАТИСТИЧЕСКАЯ СУММА

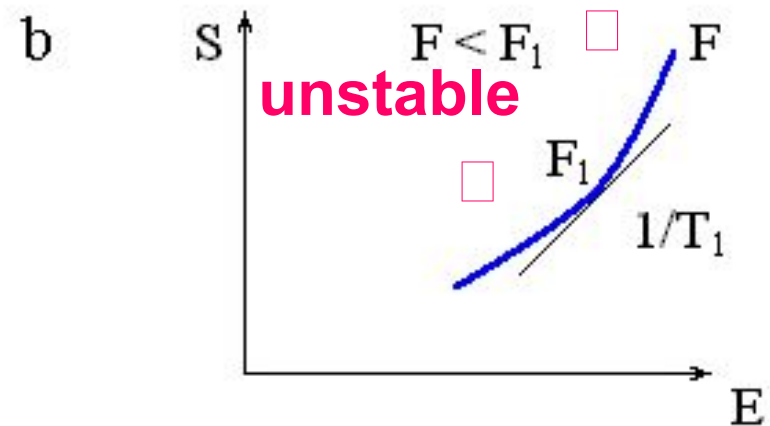
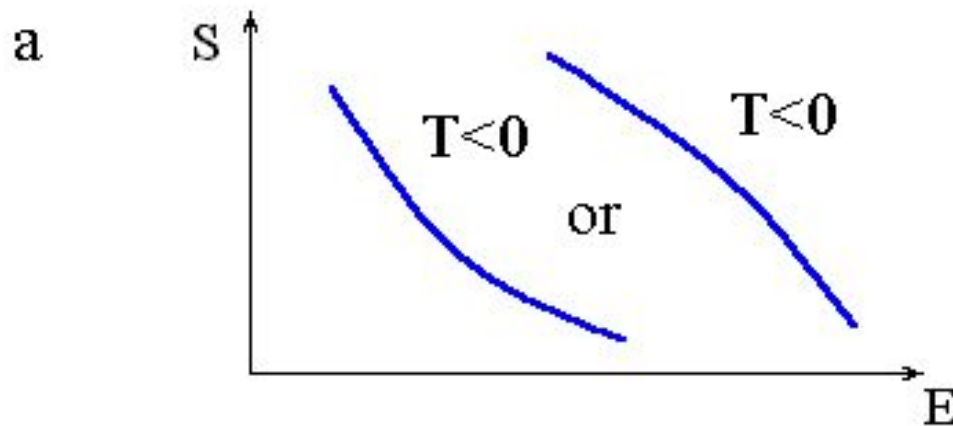


Along tangent:  $S - S(E_1) = (E - E_1)/T_1$   
 i.e.,  $F = E - T_1 S = \text{const} (= F_1 = E_1 - T_1 S_1)$



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:**

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

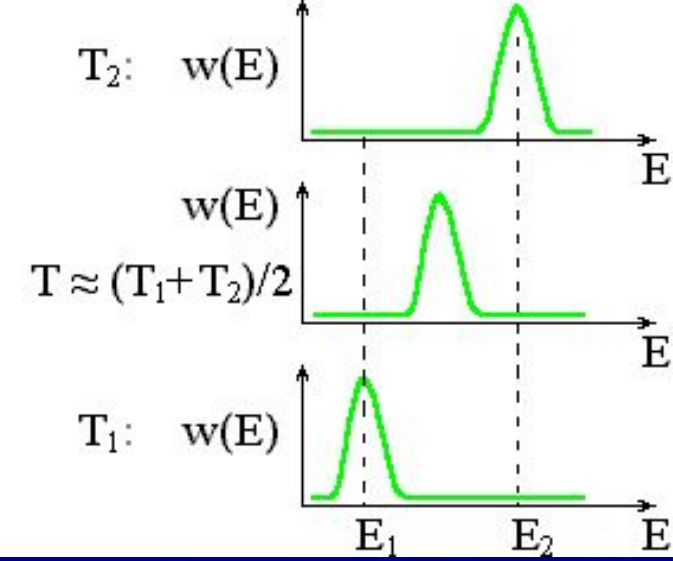
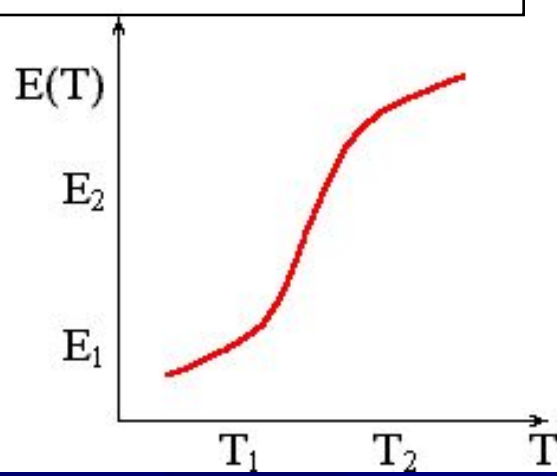
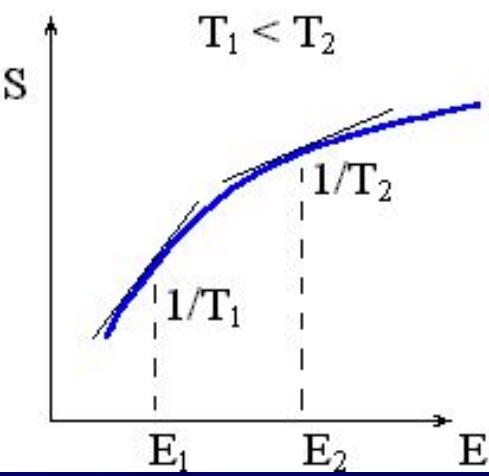
$$M \Rightarrow M_{\text{COORD}}$$

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

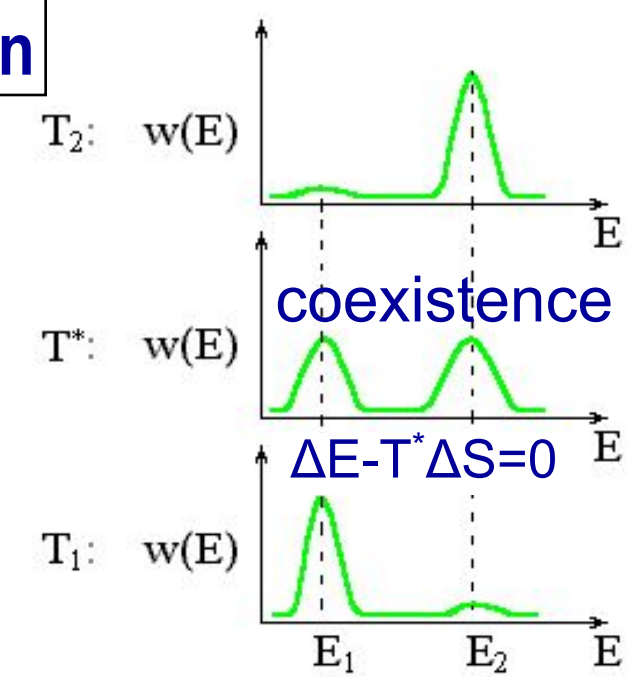
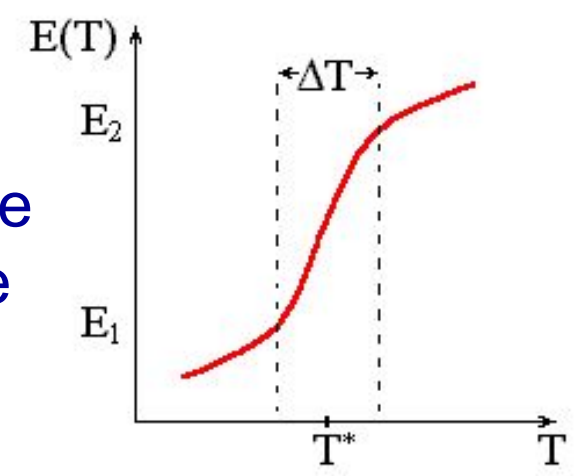
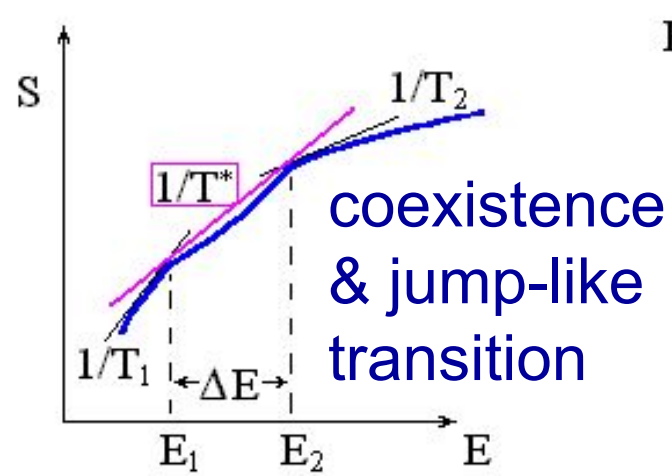
$$F(E) \Rightarrow F_{\text{COORD}}, \text{ etc.}$$

# **TRANSITIONS: THERMODYNAMICS**

# gradual transition

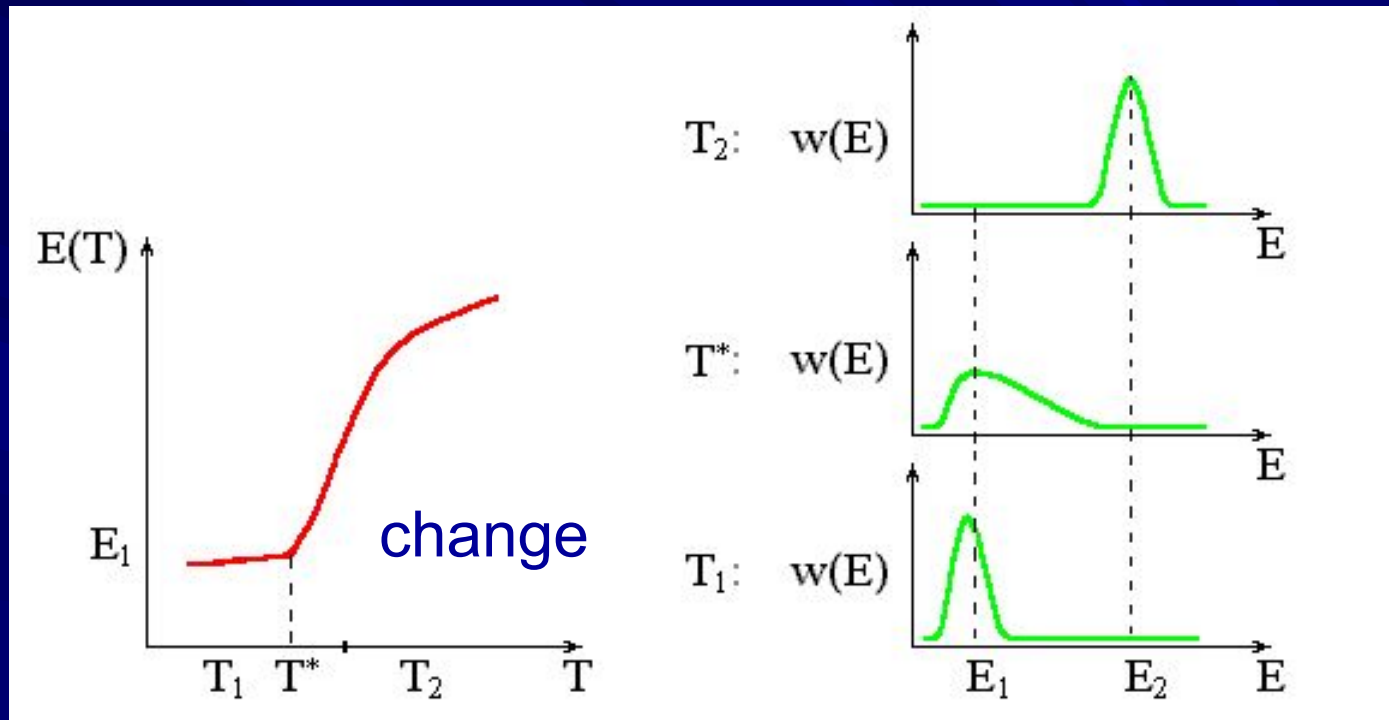


# “all-or-none” (or 1st order) phase transition



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

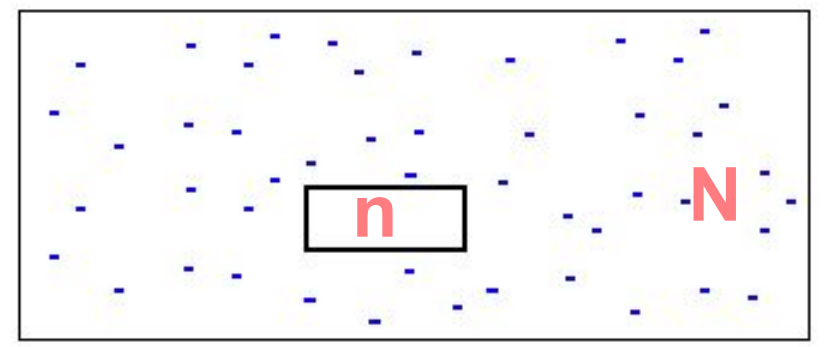
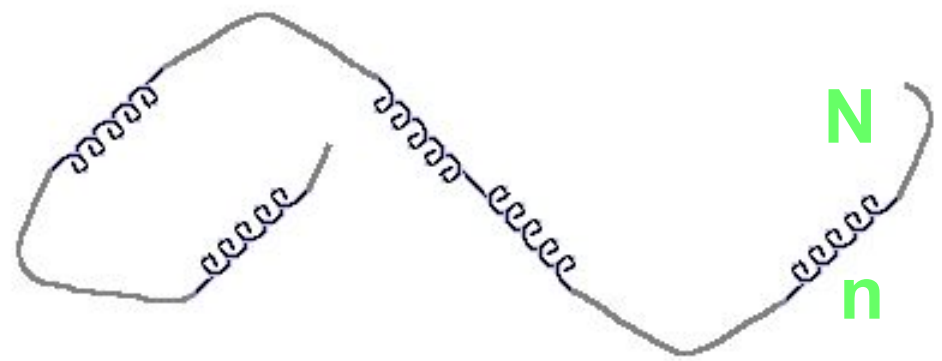
## Second order phase transition



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.,  $\alpha \sim 0.001$ )

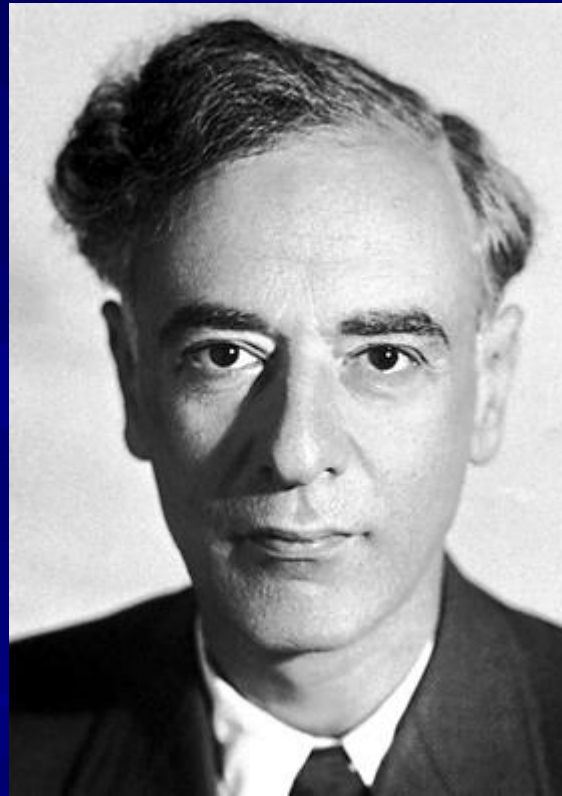
$\text{Const} \ll \ln(N)$

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

*phases mix*

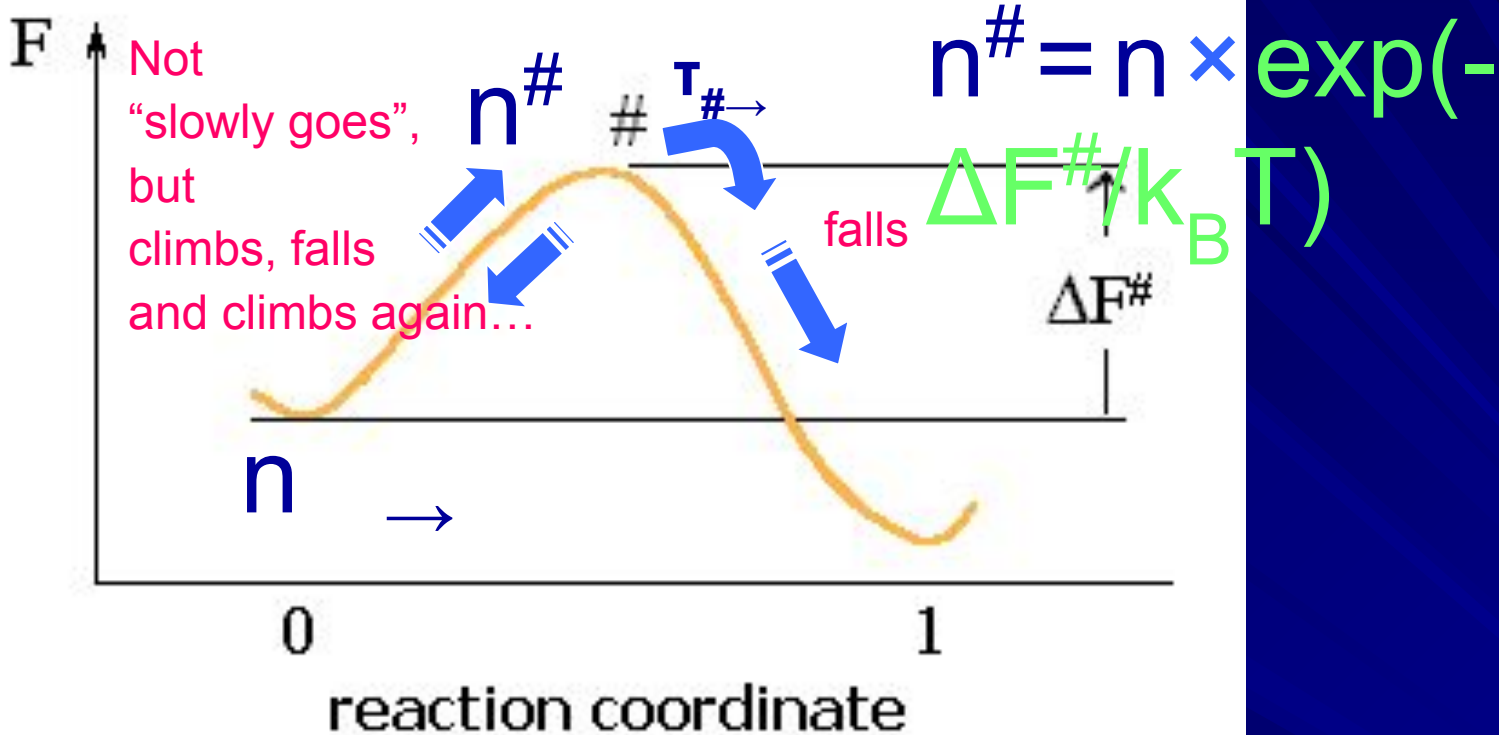
*phases do not mix*

Лев Давидович Ландау  
(1908 - 1968)  
Нобелевская Премия 1962



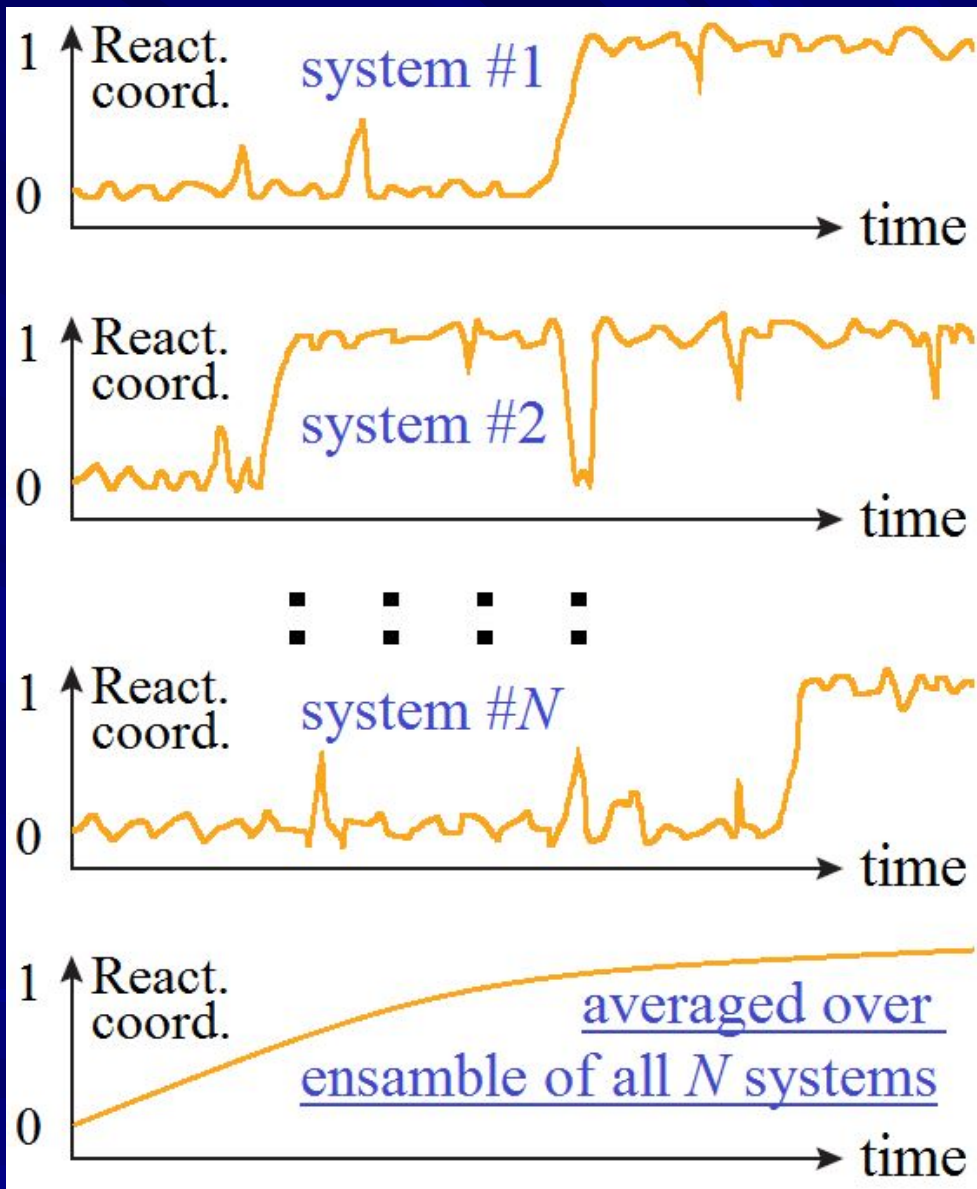


# **TRANSITIONS: KINETICS**



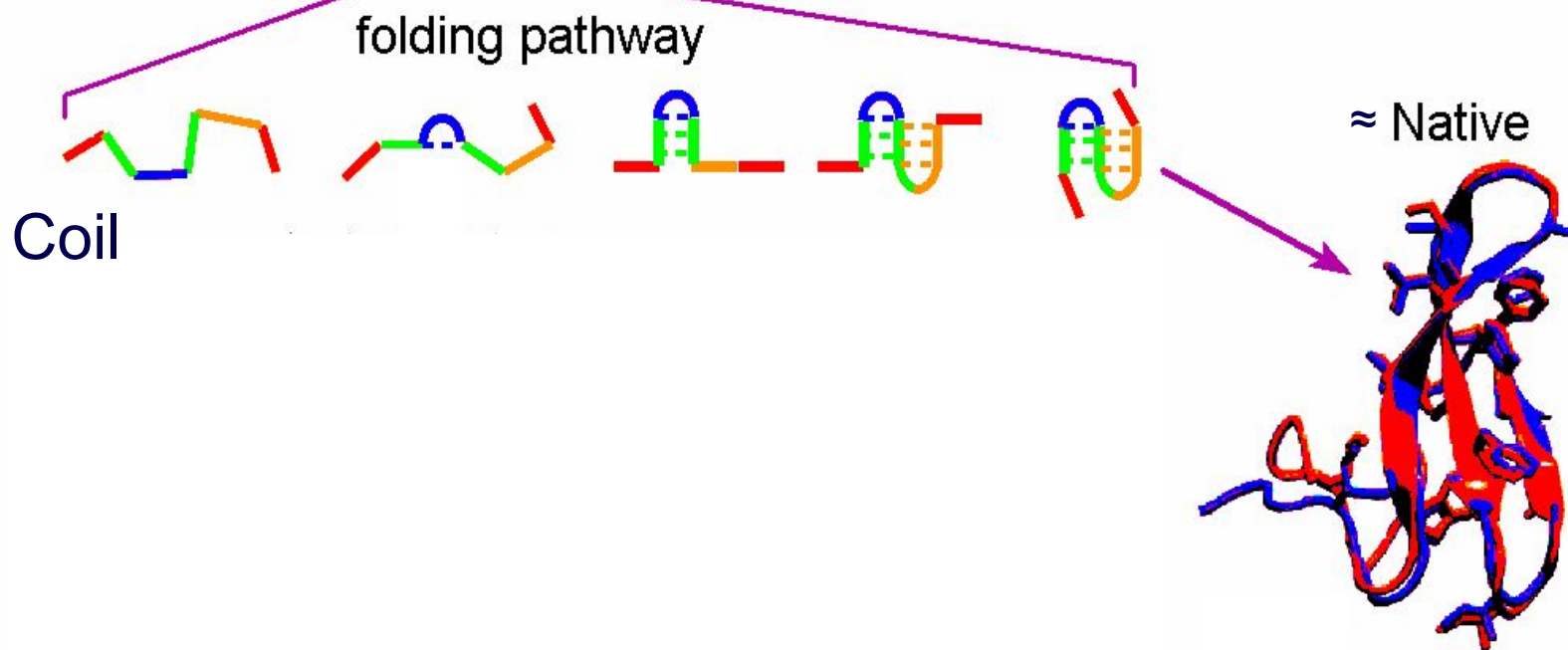
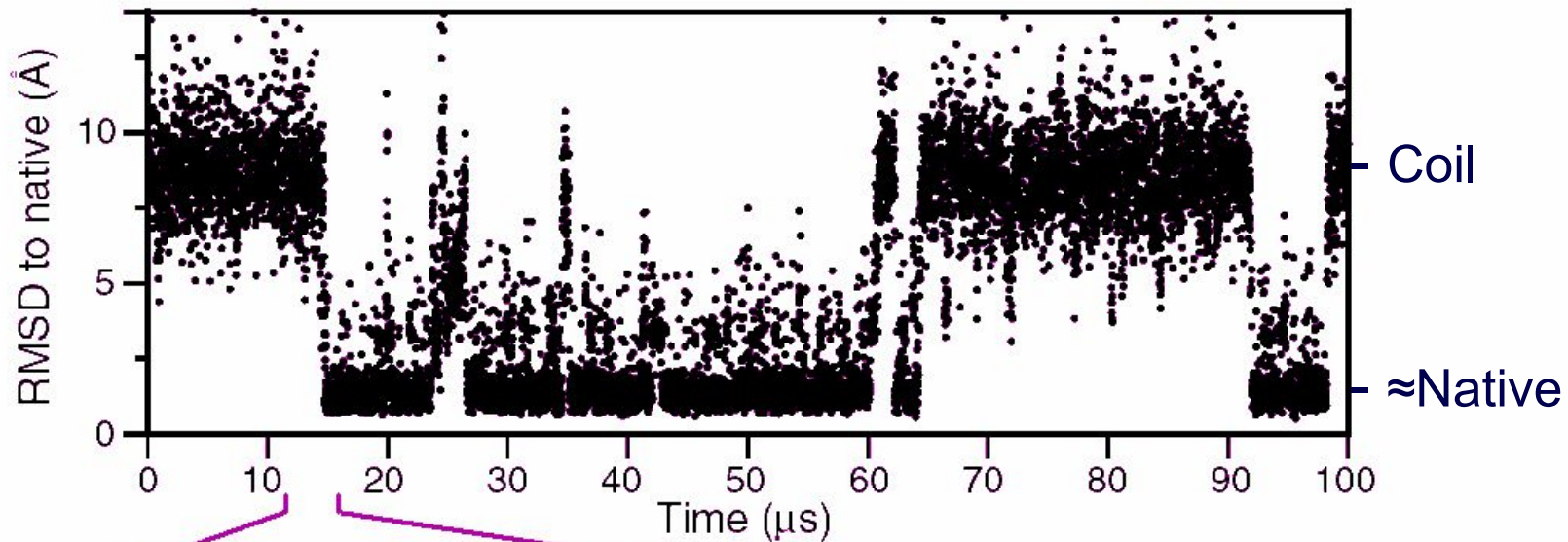
# TRANSITION TIME:

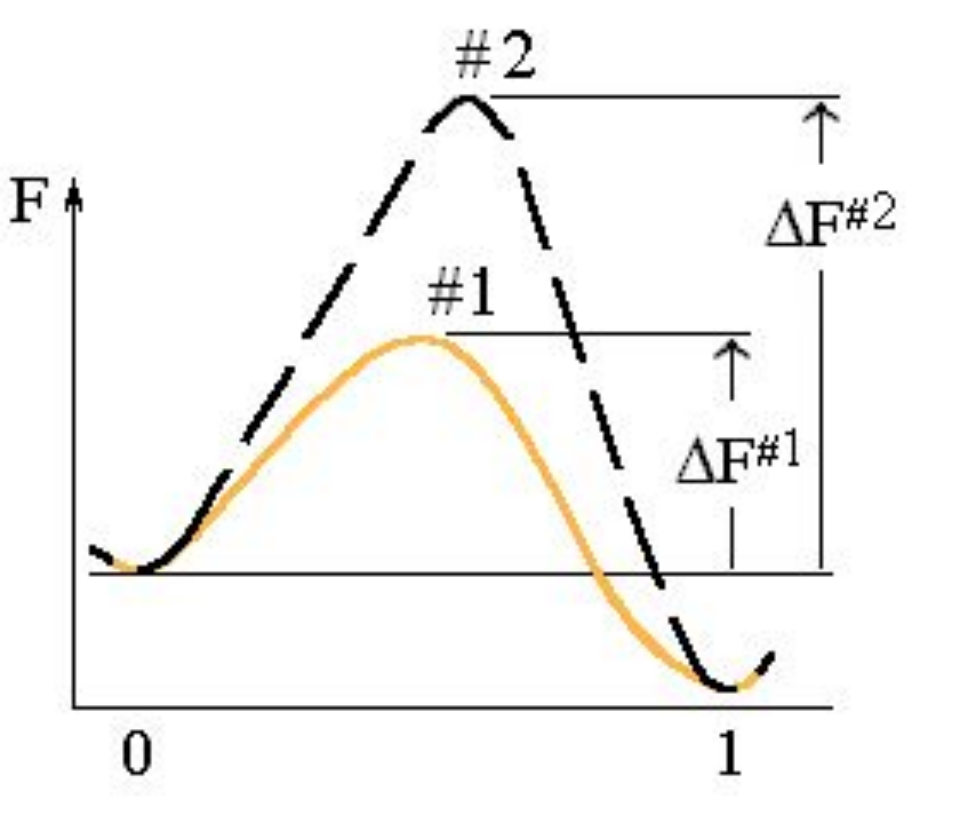
$$t_{0 \rightarrow 1} = t_{0 \rightarrow \# \rightarrow 1} \approx \tau_{\# \rightarrow} \left( \frac{n}{n^{\#}} \right) = \tau_{\# \rightarrow} \times \exp(+\Delta F^{\#}/k_B T)$$



# FIP35 protein: simulation of folding

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



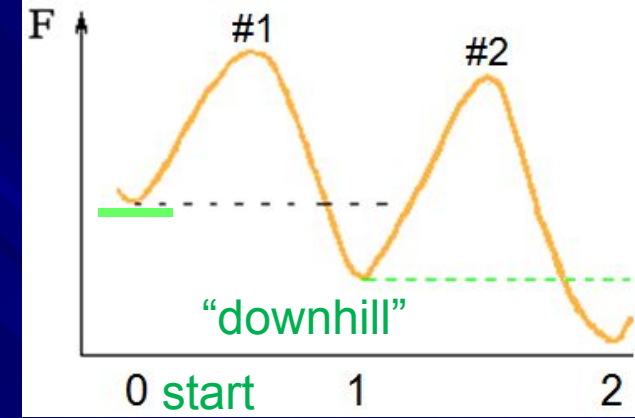
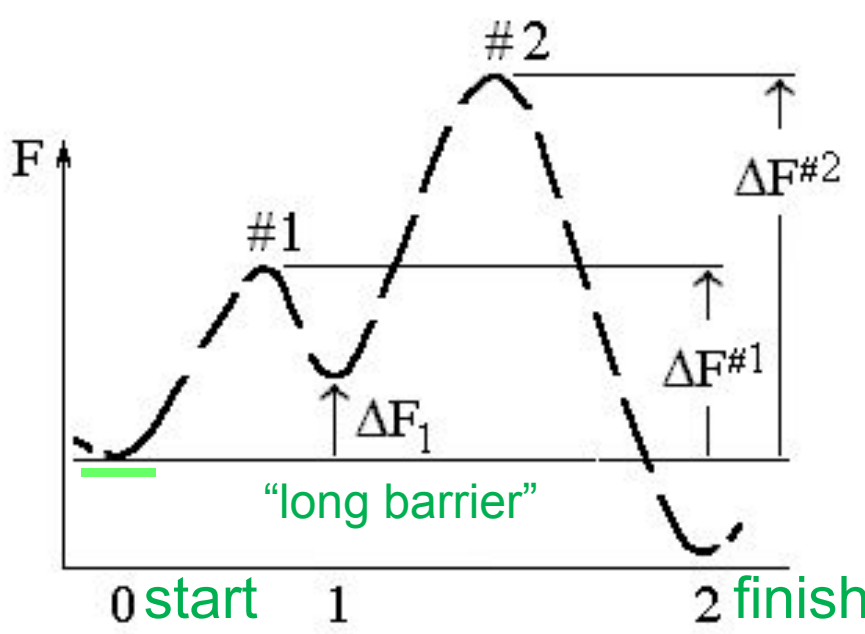


***PARALLEL REACTIONS:***

**TRANSITION RATE =  
SUM OF RATES**  
(or: ≈the highest rate)

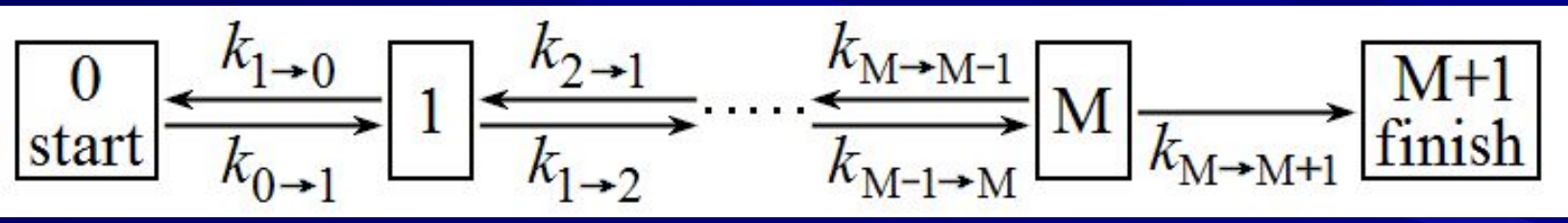
**RATE = 1/ TIME**

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



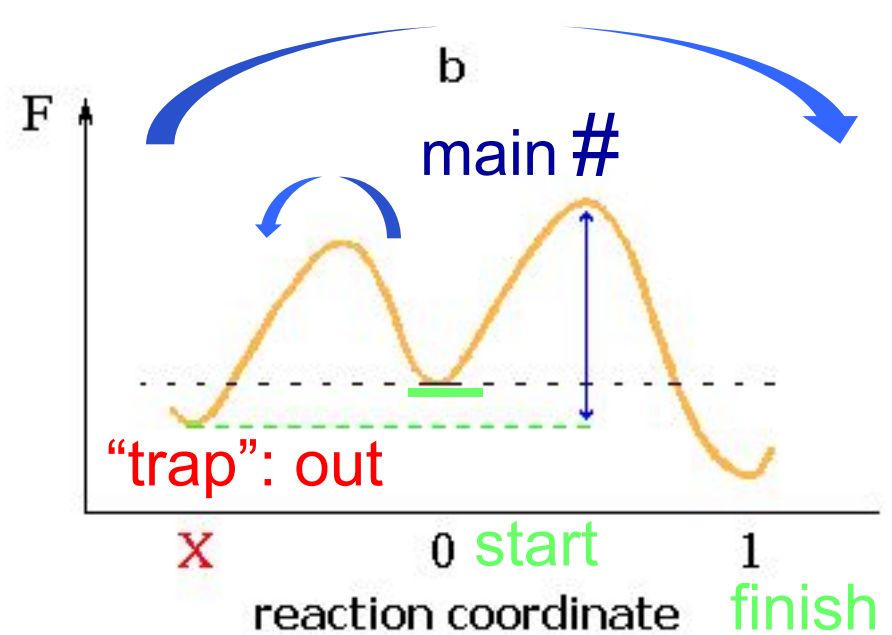
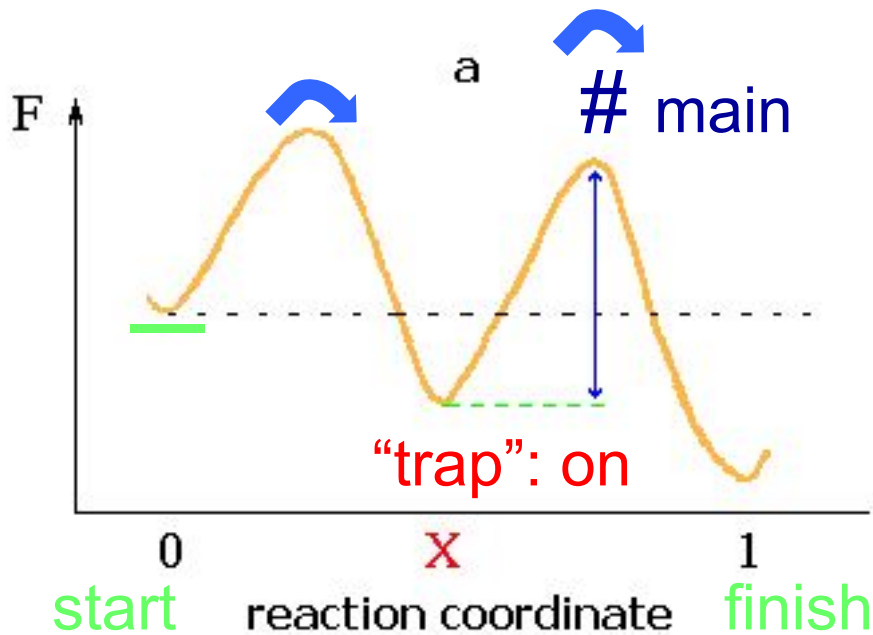
$$t_{0 \rightarrow \dots \rightarrow} \approx t_{0 \rightarrow \#1 \rightarrow 1} + t_{1 \rightarrow \#2 \rightarrow 2} + \dots$$

**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**



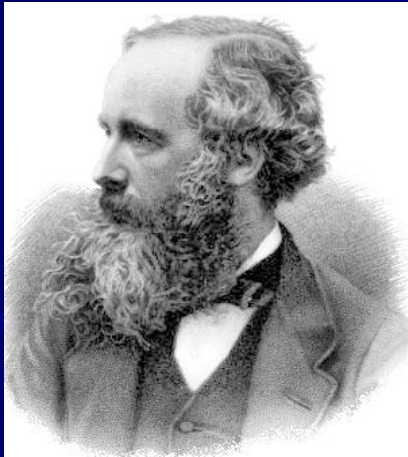
Mean kinetic energy of a particle:  $\langle mv^2/2 \rangle \sim k_B T$

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

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]

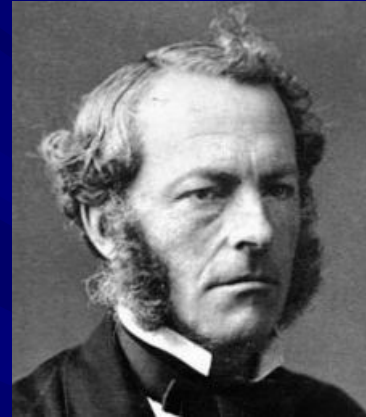
D – diameter;

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

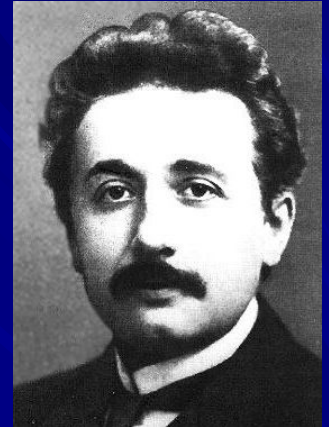
$\eta$  – viscosity

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

in water



Sir George Gabriel Stokes  
(1819-1903)



Albert Einstein  
(1879-1995)

## DIFFUSION:

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

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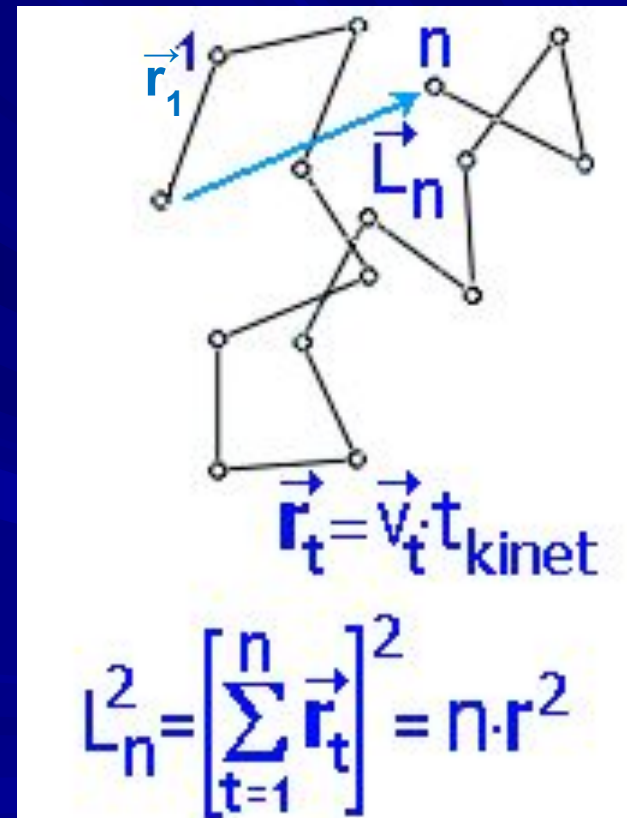
## CHARACTERISTIC DIFFUSION

### 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”:  $P_j(\epsilon_j) = \exp(-\epsilon_j/k_B T)/Z(T)$ ;

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

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

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

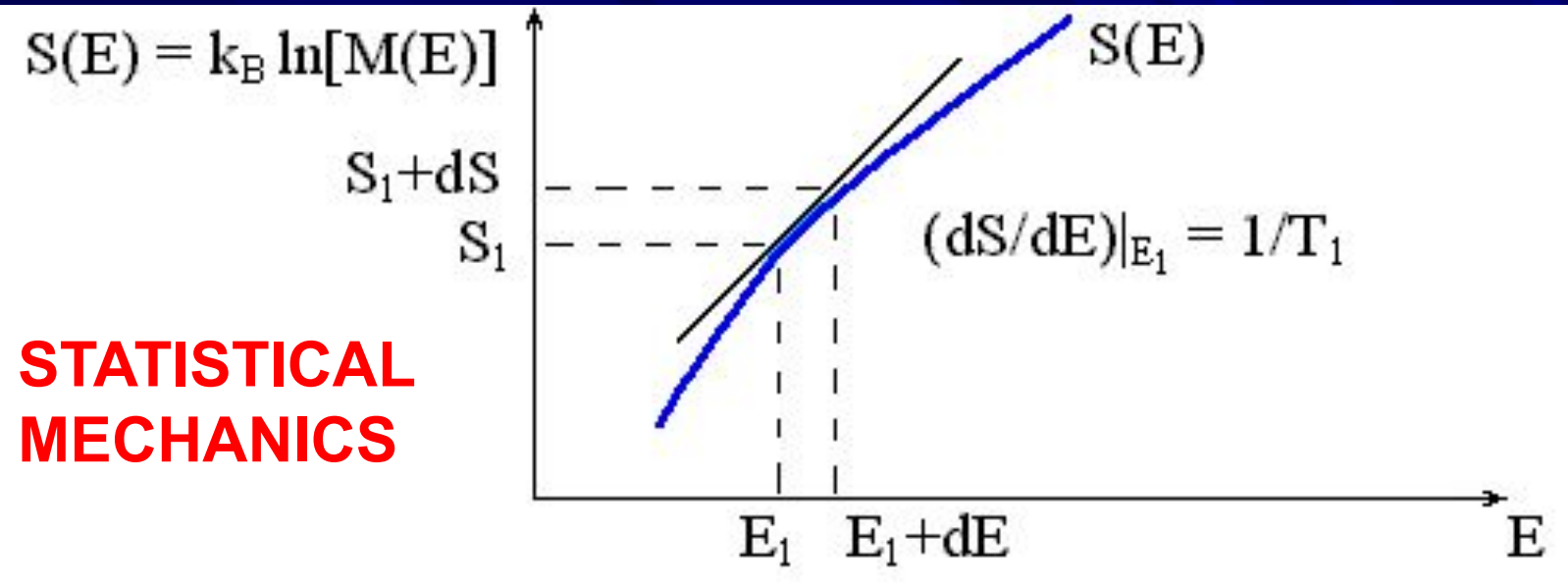
if all  $\epsilon_j = \epsilon$  : #STATES =  $1/P$ , i.e.:  $S(T) = k_B \cdot \ln(1/P)$

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

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

**STATISTICAL MECHANICS**

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



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

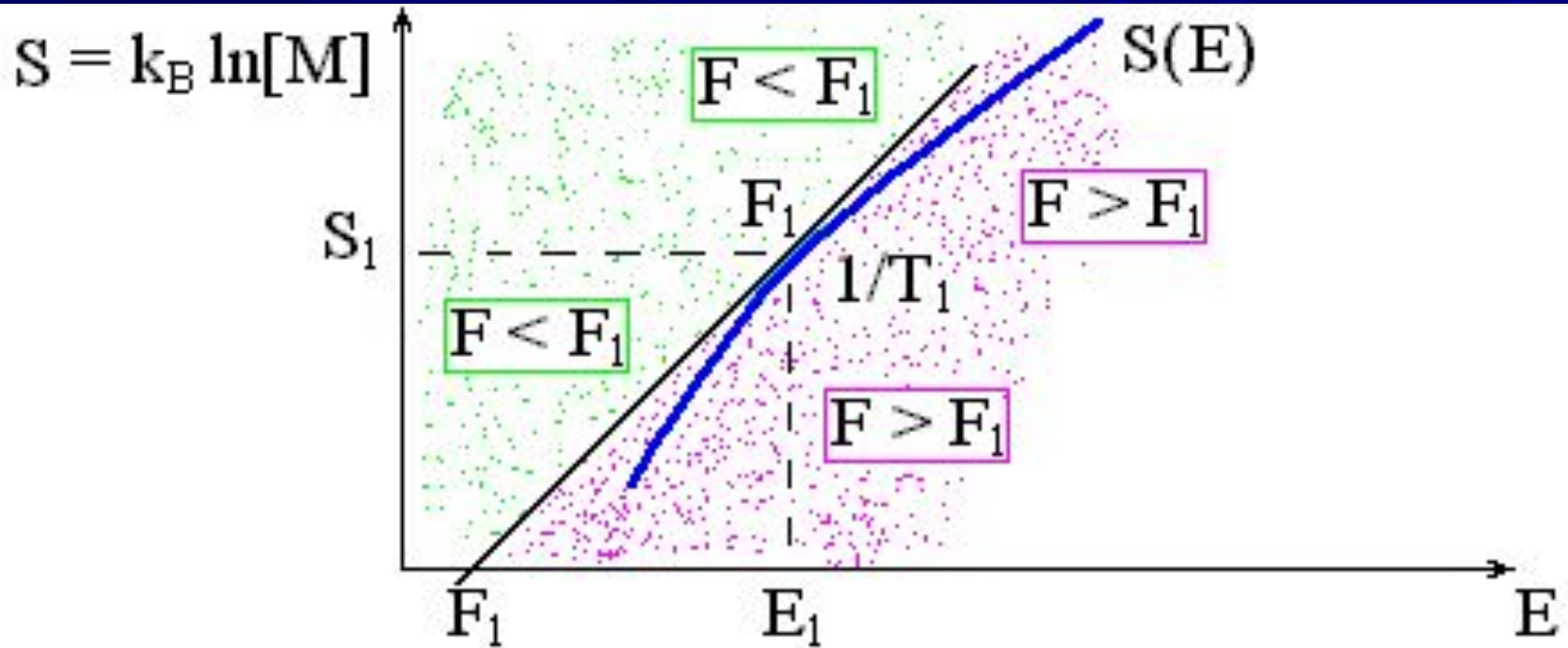
$$E(T_{th}) = \sum_j \epsilon_j \square P_j(\epsilon_j, T_{th})$$

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

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

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

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:  $\Delta(mv)\Delta x = \hbar \quad \Rightarrow \quad (\Delta x)^3$**



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

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

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

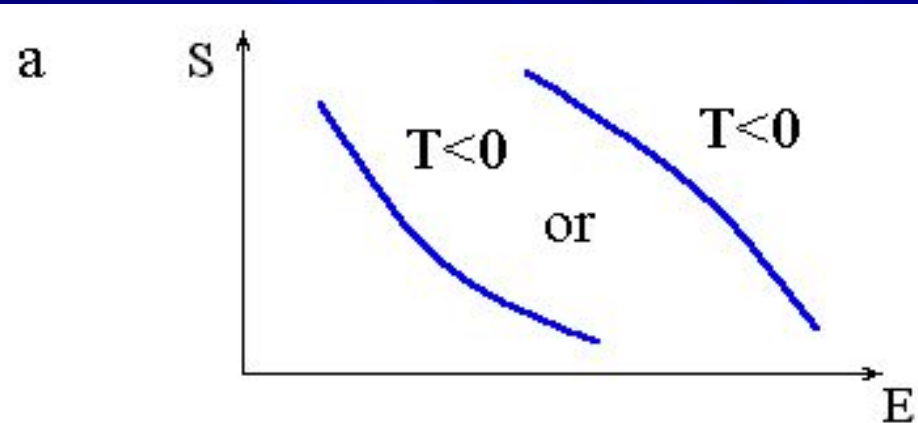
$$P(\varepsilon_{\text{KIN}}) = \exp(-\varepsilon_{\text{KIN}}/k_B T) / Z_{\text{KIN}}(T)$$

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

**T < 0: unstable (explodes)**

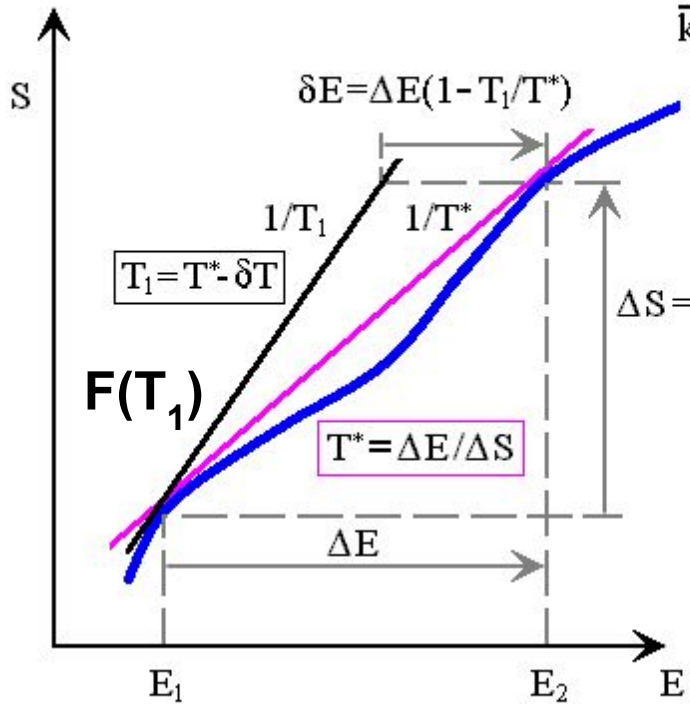
$\langle \varepsilon_{\text{KIN}} \rangle \Rightarrow \infty$  at  $T < 0$   
due to

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



# “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)	$\Delta \ln(M) \approx 1$	$\Delta T \approx T^*$ <b>non-cooperative</b>
PROTEIN (100 degrees of freedom)	$\Delta \ln(M) \approx 100$	$\Delta T \approx 0.01 T^*$
BOTTLE ( $10^{25}$ degrees of freedom)	$\Delta \ln(M) \approx 10^{25}$	$\Delta T \approx 10^{-25} T^*$ <b>HYSTERESIS: coexistence not observable</b>

