PROTEIN PHYSICS

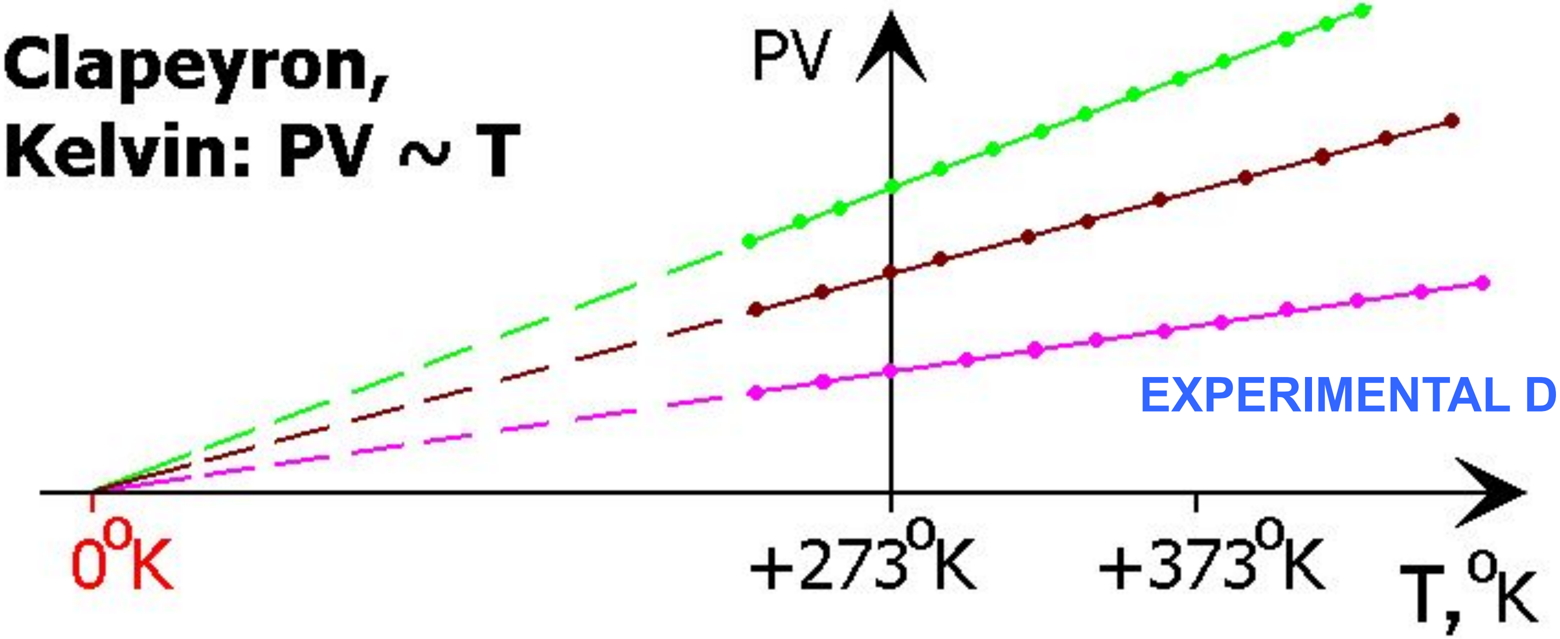
LECTURES 7-8

Basics of thermodynamics & kinetics

THERMODYNAMISC
&
STATISTICAL PHYSICS

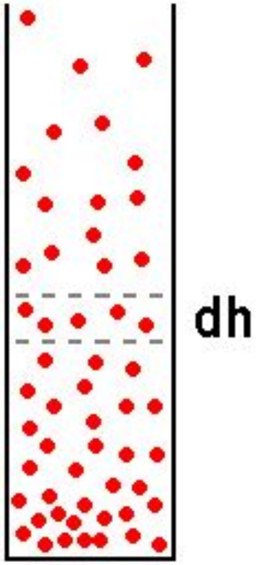
WHAT IS "TEMPERATURE"?

Clapeyron, Kelvin: PV ~ T



EXPERIMENTAL DEFINITION

$= t, ^\circ C + 273.15^\circ$



Gas laws:

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

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

Weight: $dP = mgn(-dh)$

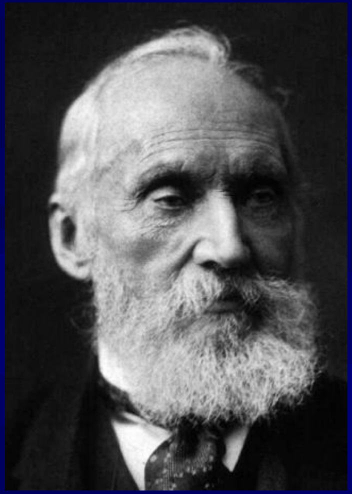
$\Rightarrow dP/dh = -n \cdot mg$

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

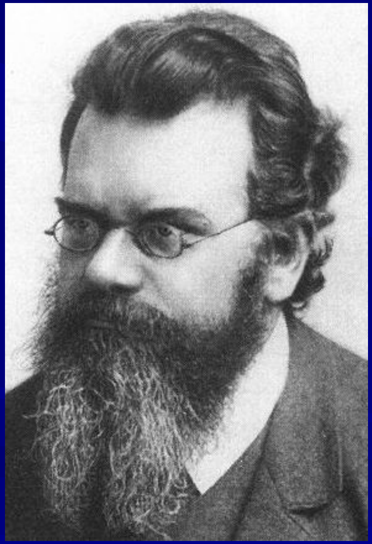
Boltzmann:

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

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

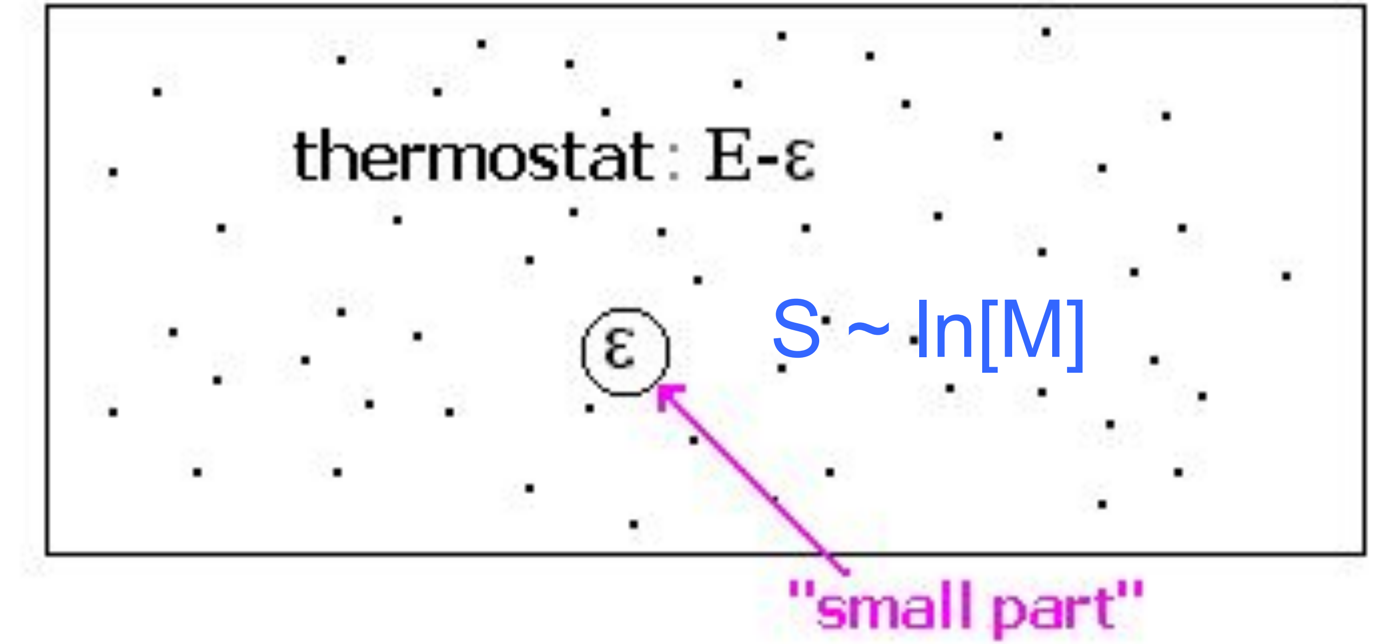


William **Thomson**, *1st Baron* **Kelvin** (1824 -1907)



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

WHAT IS “TEMPERATURE”?



$S \sim \ln[M]$

THEORY

Closed system: energy $E = const$

CONSIDER: 1 state of “small part” with ε & all states of thermostat with E-ε. $M_{all}(E-\varepsilon) = 1 \bullet M_t(E-\varepsilon)$

$$k \bullet \ln[M_t(E-\varepsilon)] \equiv S_t(E-\varepsilon) \cong S_t(E) - \varepsilon \bullet (dS_t/dE)|_E$$

$$M_t(E-\varepsilon) \cong \exp[S_t(E)/k] \bullet \exp[-\varepsilon \bullet (dS_t/dE)|_E/k]$$

conclusions

↓

COMPARE:

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

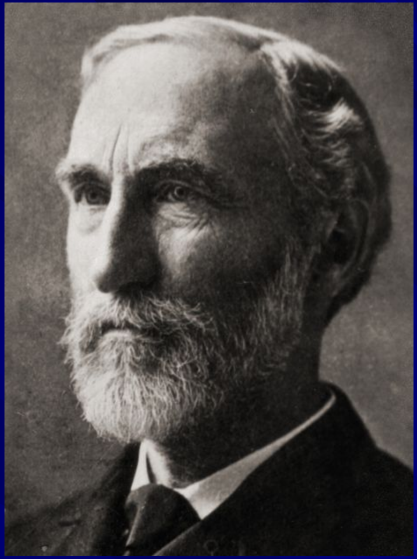
and

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

One has: $(dS_t/dE)|_E = 1/T$

$$k = k_B$$

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

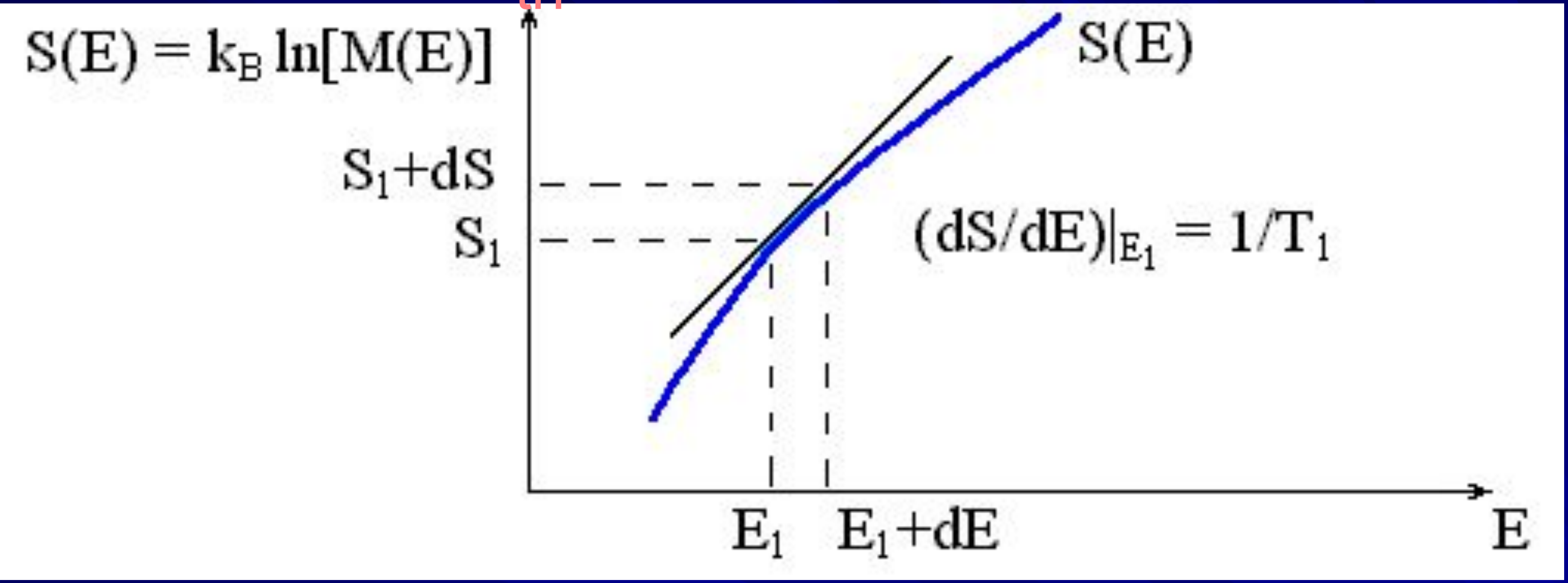


Josiah Willard **Gibbs**
(1839 –1903)

Joseph **Liouville**
(1809 - 1882)

Яков Григорьевич **Синай,** 1935
Abel Prize 2014
“…связь между порядком и хаосом…”
$1/r^3$

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



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

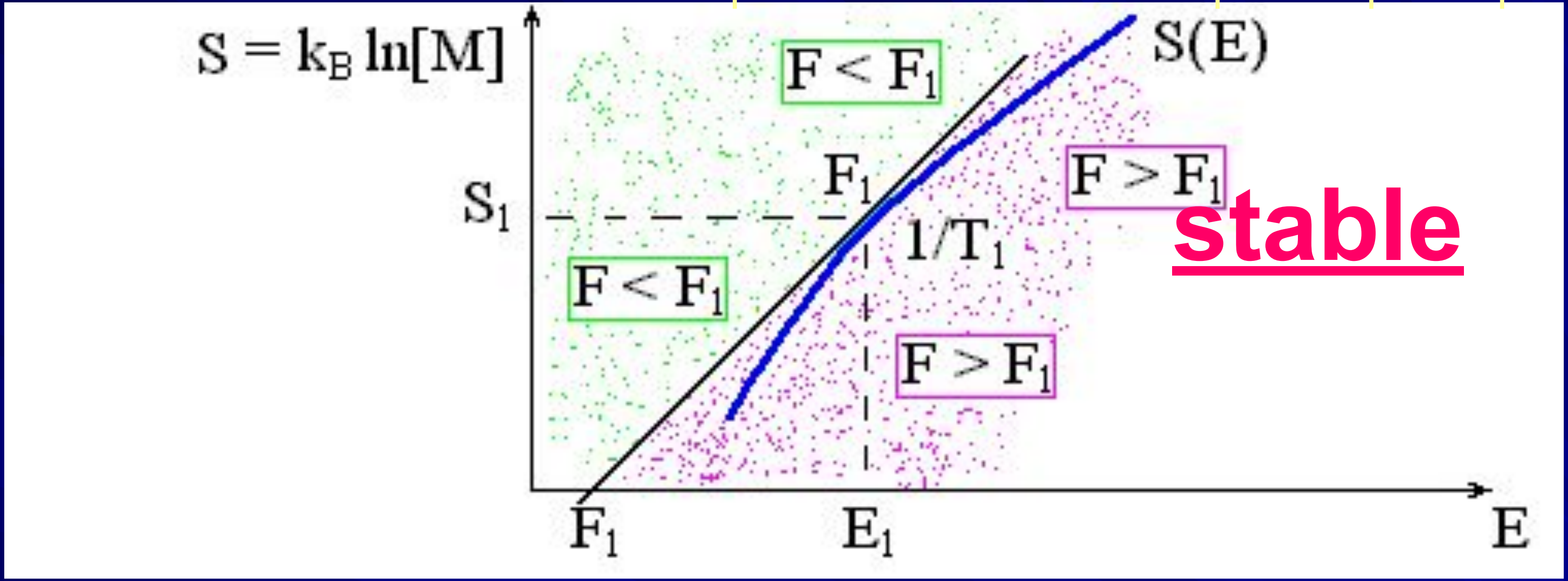
$P_j(\varepsilon_j) = \exp(-\varepsilon_j/k_B T)/Z(T);$ $\Sigma_j P_j(\varepsilon_j) \equiv 1$

$Z(T) = \Sigma_i \exp(-\varepsilon_i/k_B T)$ partition function

СТАТИСТИЧЕСКАЯ СУММА

Along tangent: $S - S(E_1) = (E - E_1)/T_1$

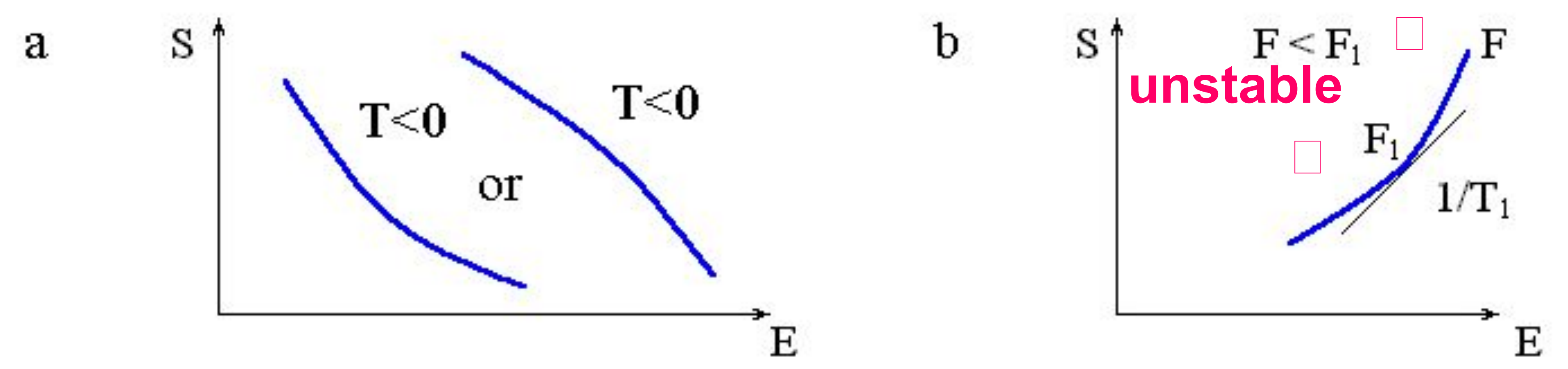
i.e., $F = E - T_1 S =$ *const* $(= F_1 = E_1 - T_1 S_1)$



stable

Unstable (explodes, v → inf.)

Unstable (falls)



unstable

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

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

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

Potential energy ε_{COORD}: depends *only* on coordinates

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

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

==

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:

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

We may consider further only potential energy:

$E \Rightarrow E_{COORD}$

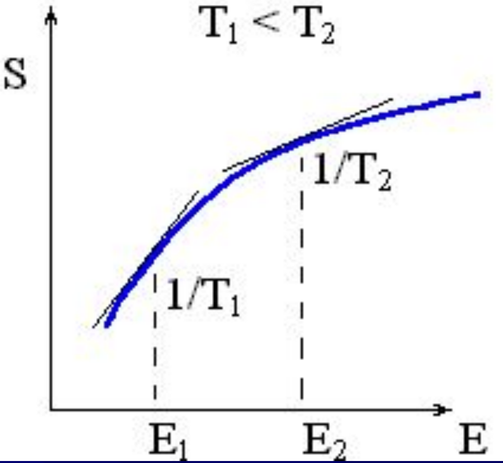
$M \Rightarrow M_{COORD}$

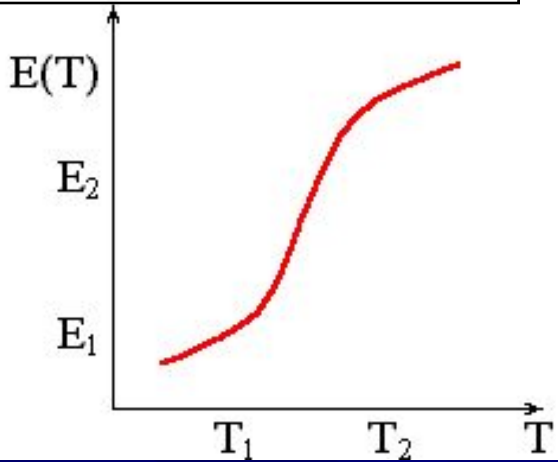
$S(E) \Rightarrow S_{COORD}(E_{COORD})$

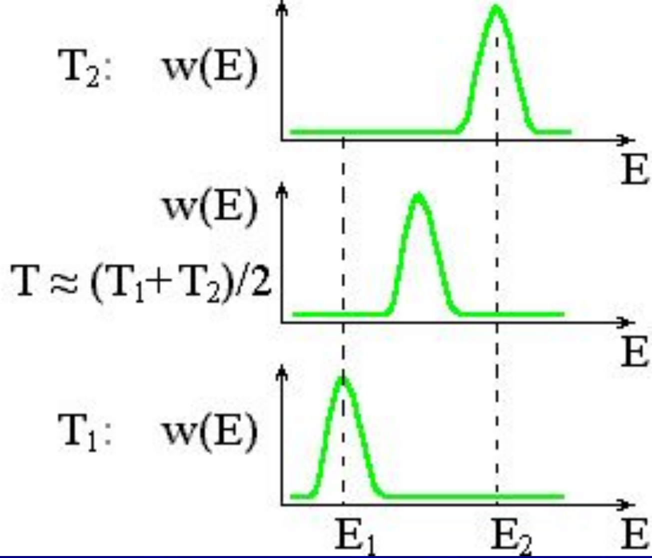
$F(E) \Rightarrow F_{COORD}$, **etc.**

TRANSITIONS:
THERMODYNAMICS

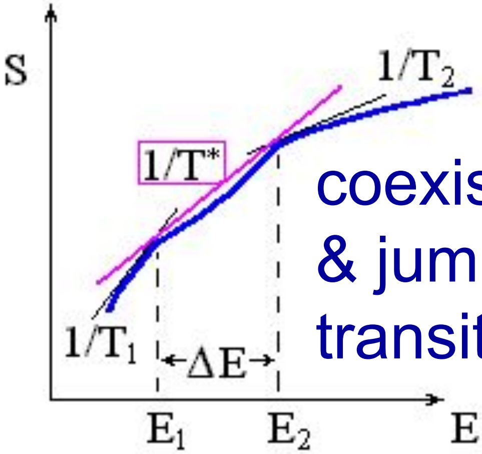
gradual transition



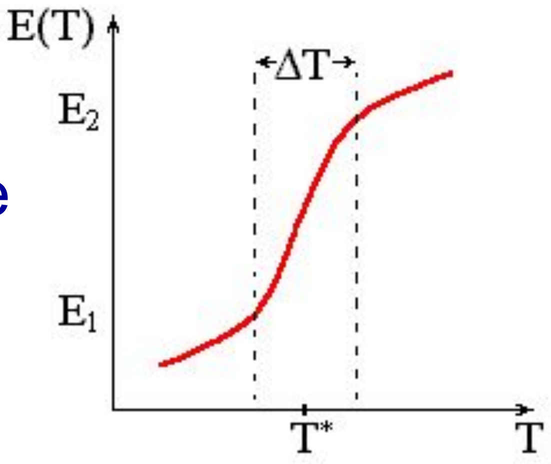


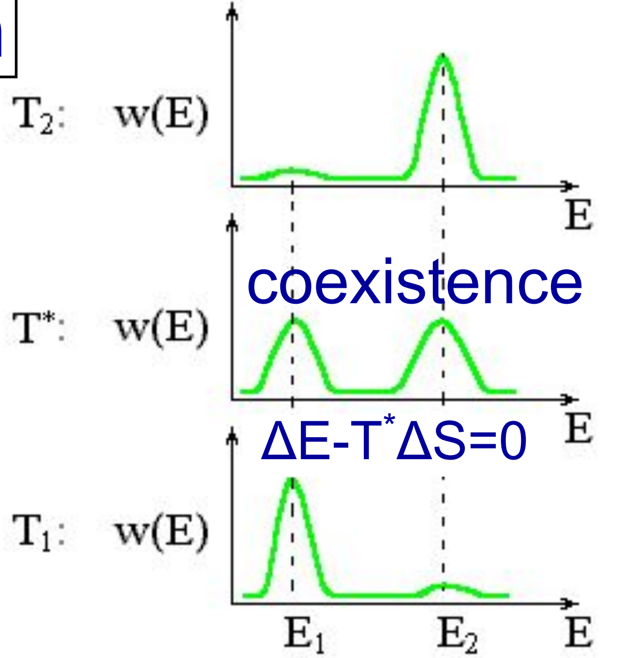


“all-or-none” (or 1st order) phase transition



coexistence
& jump-like
transition



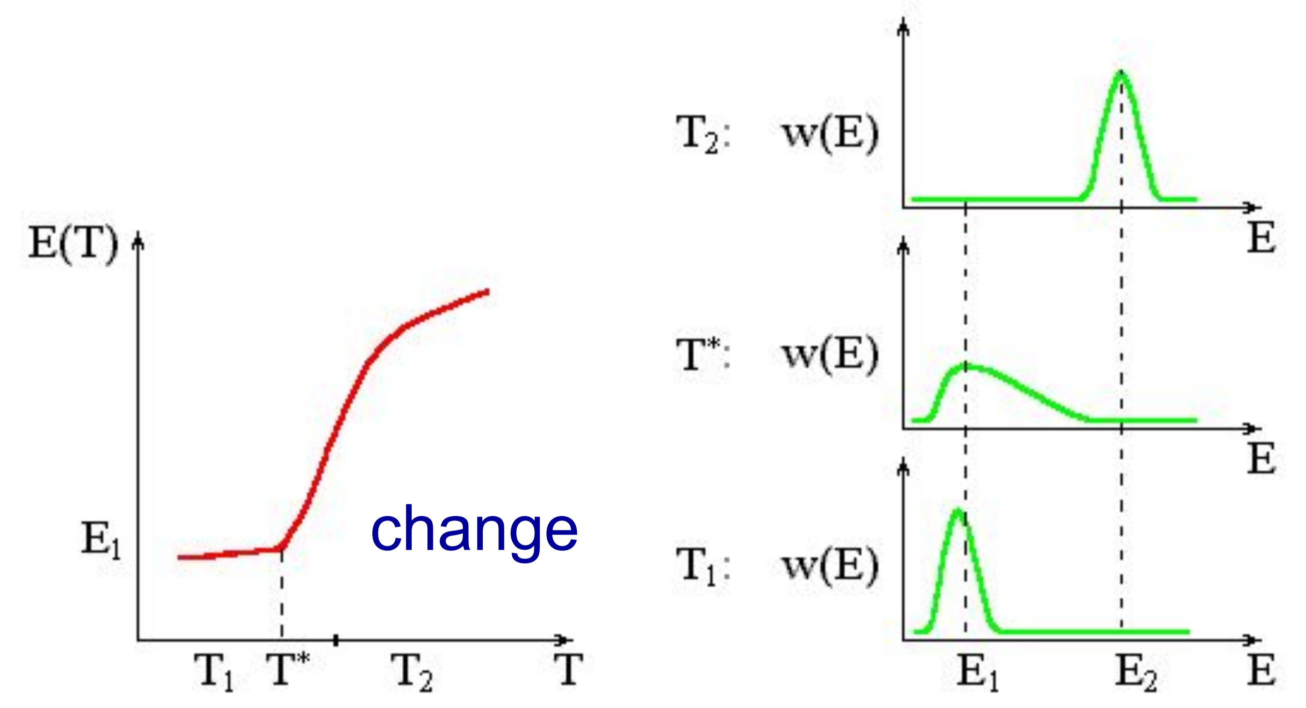


coexistence

$\Delta E - T^*\Delta S = 0$

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

Second order phase transition

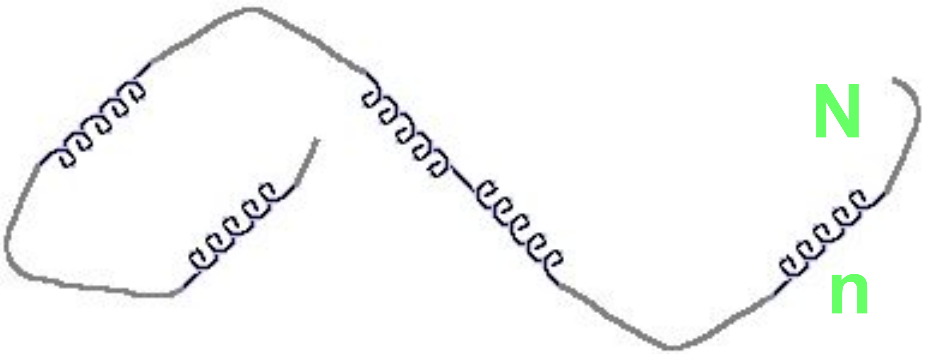


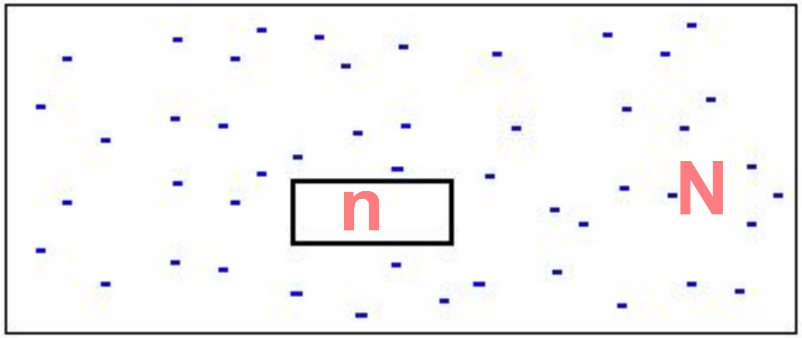
change

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

$\Delta F_{helix\_n} = \text{Const} + n \times f$

1D interface

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

3D interface

Mid-transition: $f = 0$

$\Delta S_{helix\_n} \sim \ln(N)$ ⟷ positions ⟷ $\Delta S_{ICE\_n} \sim \ln(N)$

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

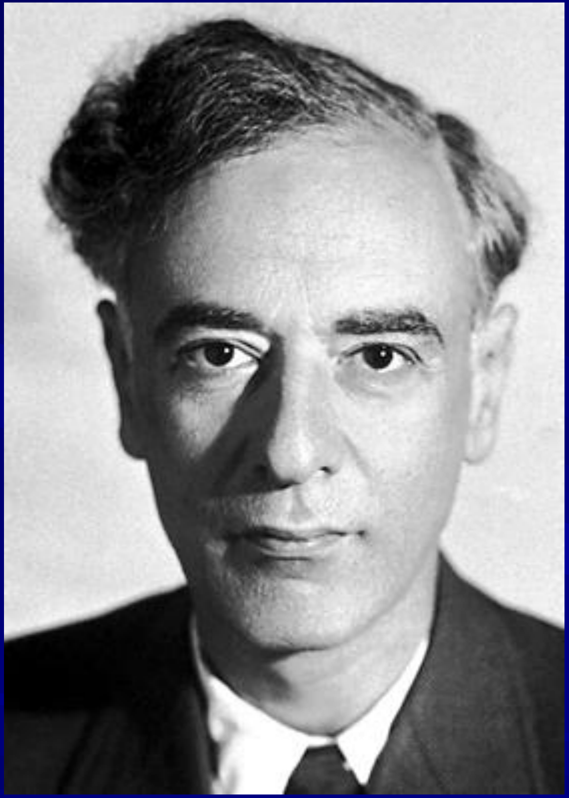
$\text{Const} \ll \ln(N)$

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

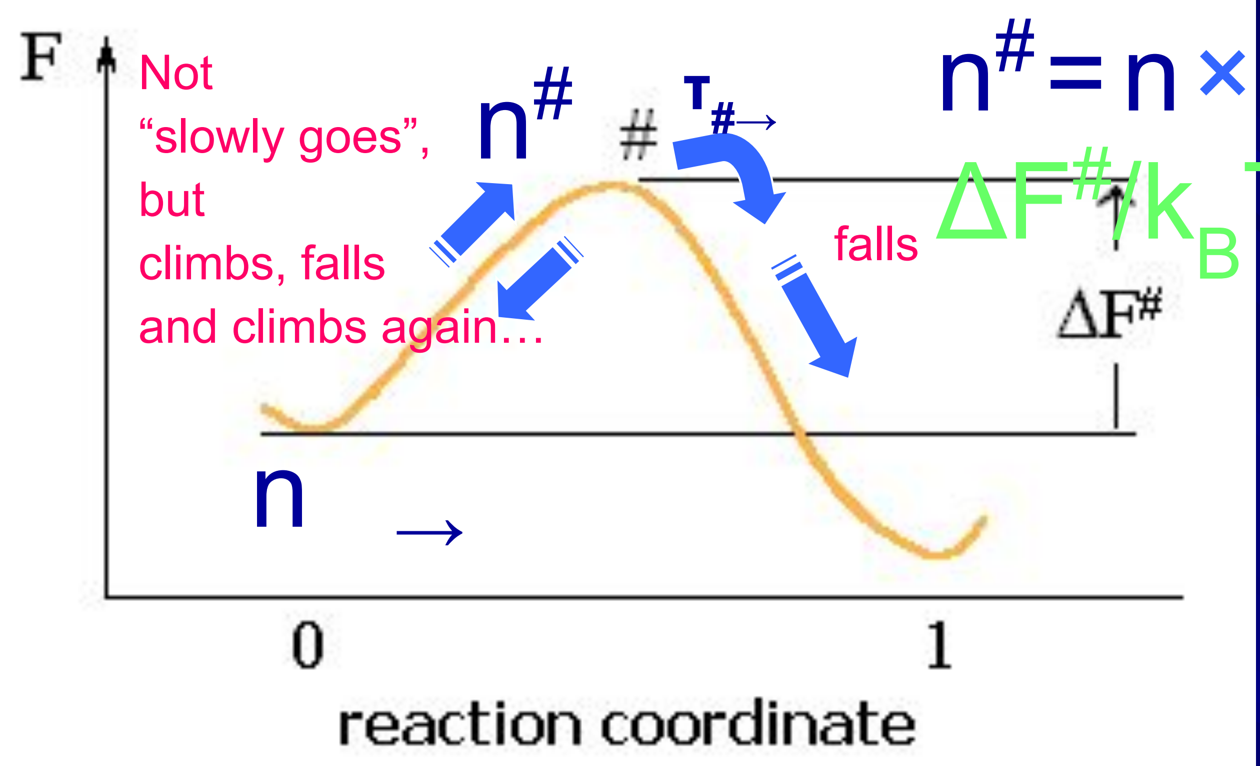
phases mix

phases do not mix

Лев Давидович **Ландау**
(1908 - 1968)
Нобелевская Премия 1962



TRANSITIONS:
KINETICS



Not
“slowly goes”,
but
climbs, falls
and climbs again…

$n^{\#}$

$\tau_{\#\to}$

falls

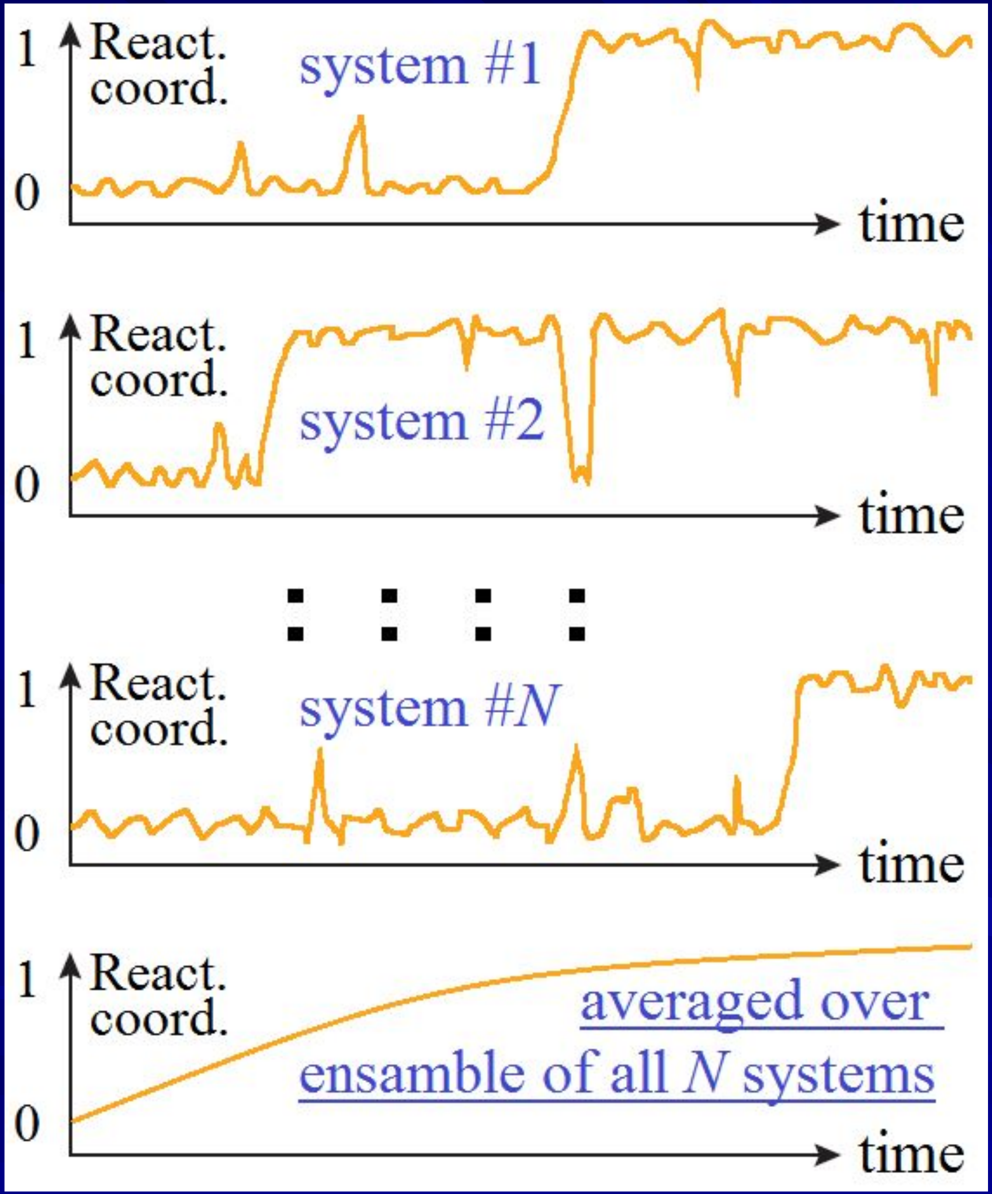
n →

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

TRANSITION TIME:

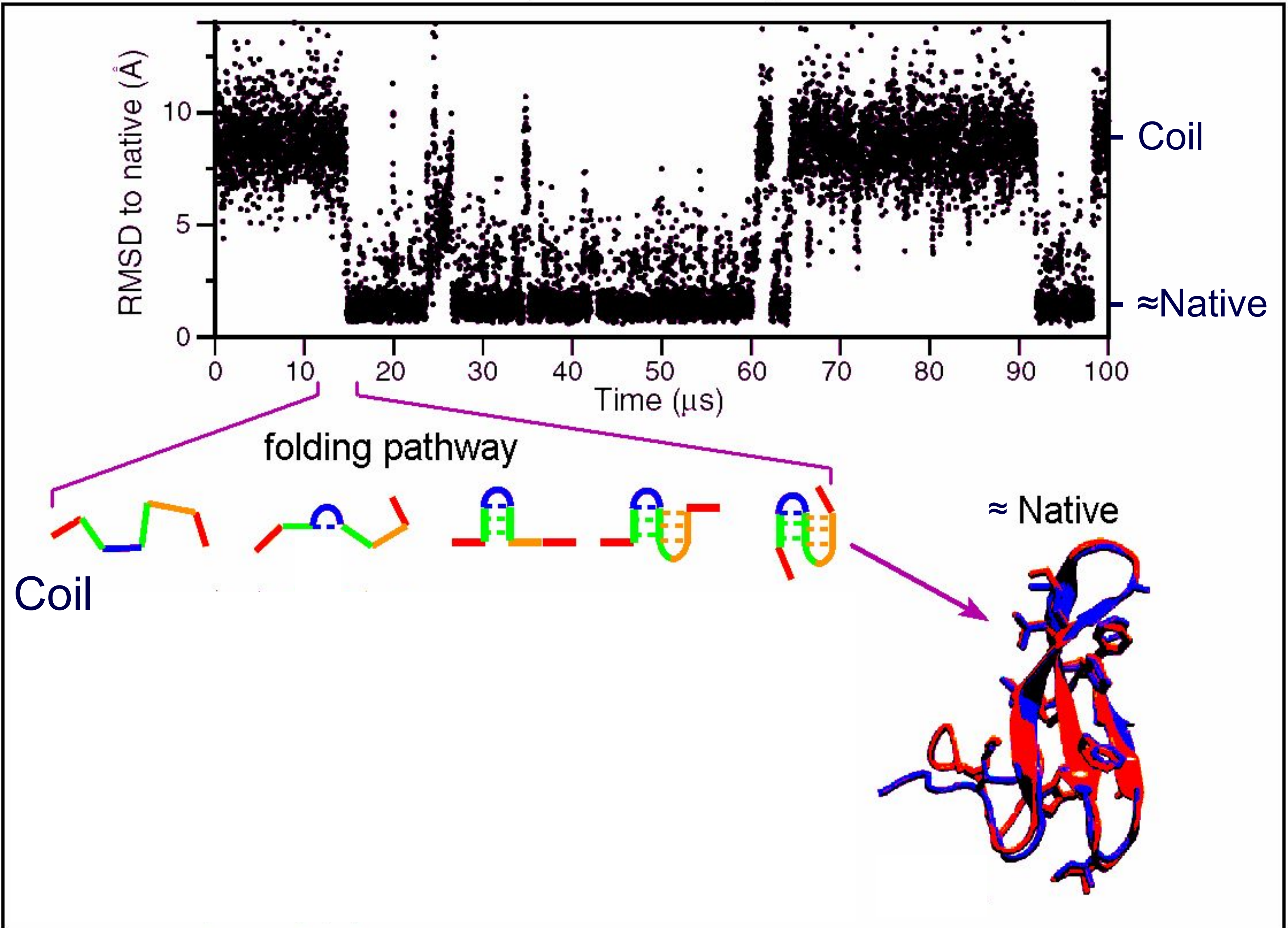
$$\mathbf{t}_{0\to1} = \mathbf{t}_{0\to\#1\to} \approx$$

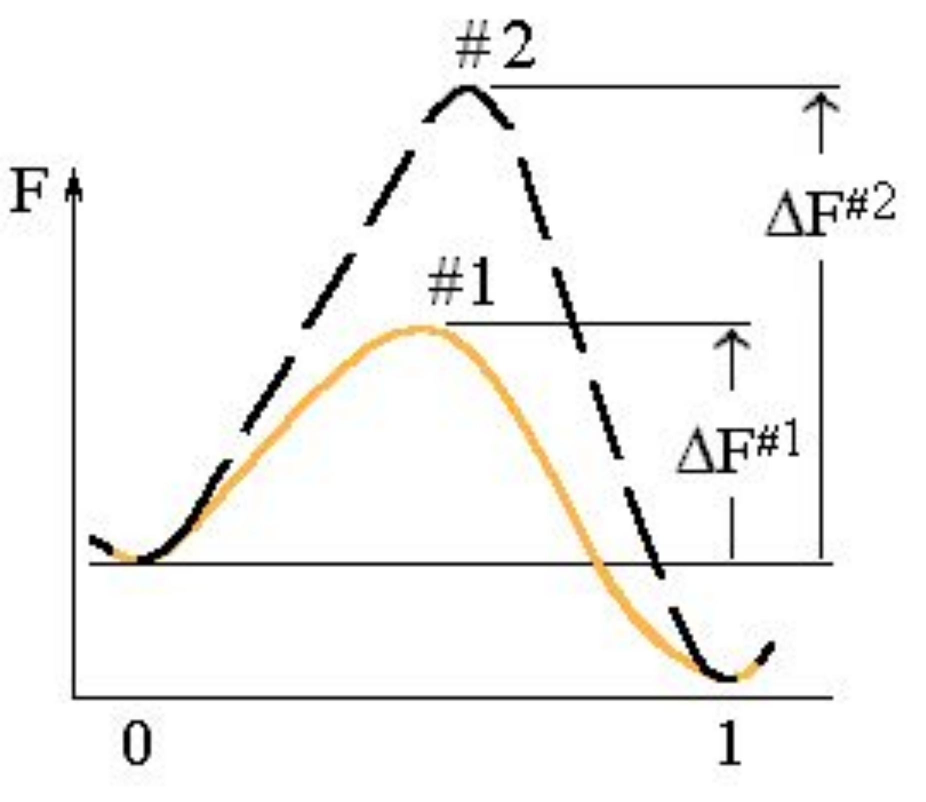
$$\approx \tau_{\#\to} (n/n^{\#}) = \tau_{\#\to} \times \exp(+\Delta F^{\#}/k_B T)$$


1
React. coord.
system #1
0
time
1
React. coord.
system #2
0
time
1
React. coord.
system #N
0
time
1
React. coord.
averaged over ensamble of all N systems
0
time

FiP35 protein: simulation of folding

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



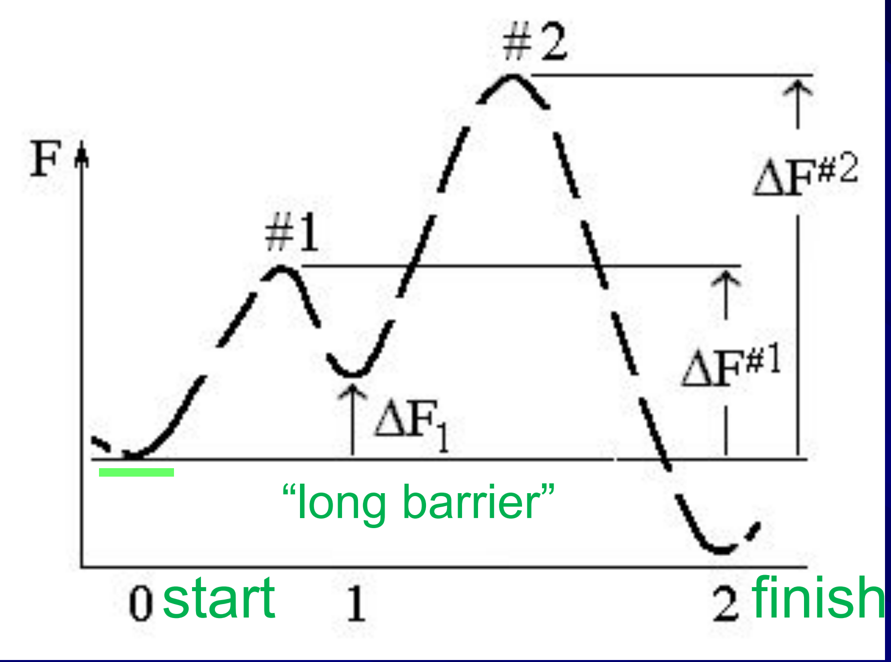


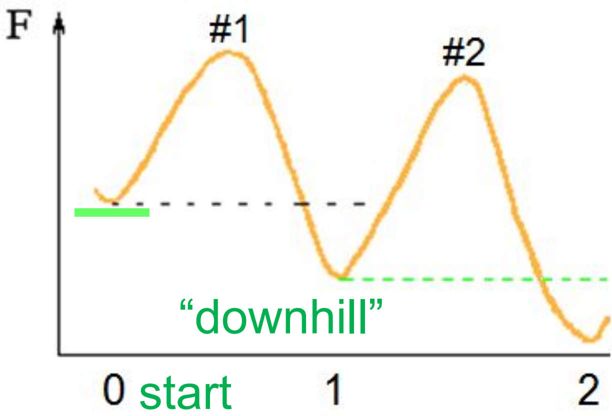
PARALLEL REACTIONS:

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

RATE = **1/ TIME**

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



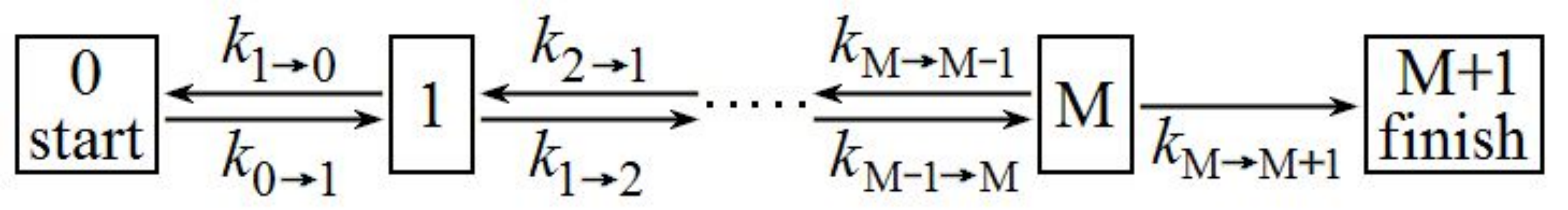


$$t_{0\to\ldots\to} \approx t_{0\to\#1\to1} + t_{1\to\#2\to2} + \ldots$$

CONSECUTIVE REACTIONS:

TRANSITION TIME ≅ SUM OF TIMES

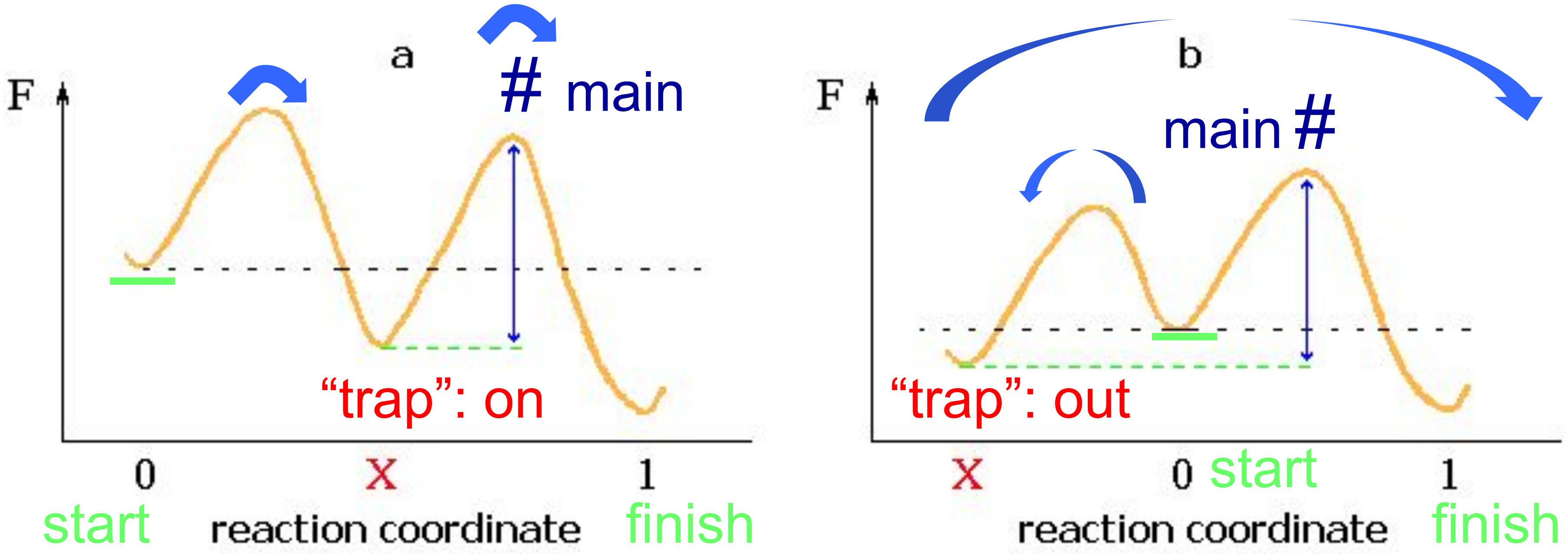
(or: ≈ the highest time)



"long barrier": $t_{0\to\ldots\to\text{finish}} \approx t_{0\to\#1\to\text{ finish}} + t_{0\to\#2\to\text{ finish}} + \ldots$

steady-state approximation

$$\text{TIME} \approx \tau_{\#\to}\times\exp(+\Delta F_1^{\#}/k_BT) + \tau_{\#\to}\times\exp(+\Delta F_2^{\#}/k_BT) + \ldots$$



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

TRANSITION <u>TIME</u> ≅ SUM OF <u>TIMES</u>

(or: ≈the longest time)

DIFFUSION: KINETICS

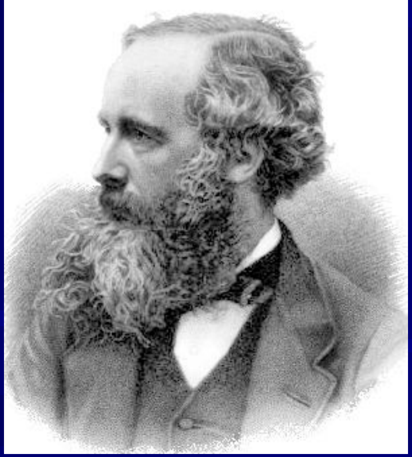
Mean kinetic energy of a particle: $\langle mv^2/2 \rangle \sim k_B T$

$$\langle \varepsilon \rangle = \Sigma_j P_j(\varepsilon_j) \cdot \varepsilon_j \qquad v^2 = (v_X{}^2)+(v_Y{}^2)+(v_Z{}^2)$$

James Clerk

Maxwell :

(1831 –1879)



$$\langle mv^2/2 \rangle =$$

$$\frac{\int_0^\infty\int_0^\infty\int_0^\infty \exp[-(mv^2/2)/k_BT]\cdot(mv^2/2)\cdot dv_X dv_Y dv_Z}{\int_0^\infty\int_0^\infty\int_0^\infty \exp[-(mv^2/2)/k_BT]\cdot dv_X dv_Y dv_Z} =$$

$$\frac{k_BT\cdot\int_0^\infty\int_0^\infty\int_0^\infty \exp[-(mv^2/2k_BT]\cdot(mv^2/2k_BT)\cdot dv_X dv_Y dv_Z}{\int_0^\infty\int_0^\infty\int_0^\infty \exp[-(mv^2/2k_BT]\cdot dv_X dv_Y dv_Z} =$$

$$\frac{k_BT\cdot\int_0^\infty\int_0^\infty\int_0^\infty \exp[-r^2]\cdot r^2\cdot dr_1 dr_2 dr_3}{\int_0^\infty\int_0^\infty\int_0^\infty \exp[-r^2]\cdot dr_1 dr_2 dr_3} = \frac{3}{2}k_BT$$

in 3D

Friction stops a molecule within picoseconds:

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

D – diameter;
$m \sim D^3 \cdot 1\,g/cm^3$ – mass;
η – viscosity

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

Sir George Gabriel **Stokes**
(1819-1903)

Albert **Einstein**
(1879-1995)

DIFFUSION:

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

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

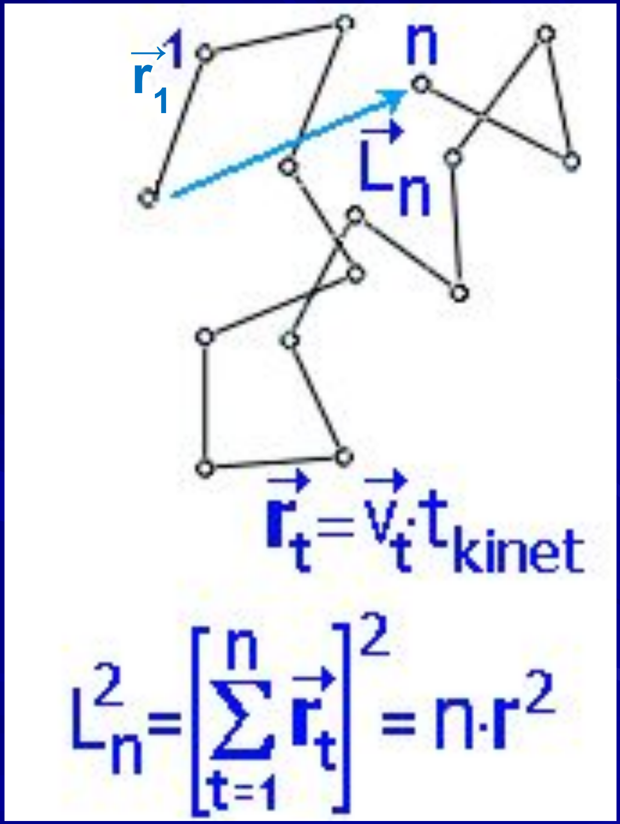
Friction stops a molecule within picoseconds:

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

DIFFUSION:

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

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



CHARACTERISTIC DIFFUSION TIME: nanoseconds

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

$t_{difft} \approx t_{kinet} \cdot (D/L_{kinet})^2 = D^2/\mathit{D}_{diff}$

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

The End

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

$$Z(T) = \boldsymbol{\Sigma}_j \exp(-\varepsilon_j/k_B T)$$

$$\boldsymbol{\Sigma}_j P_j(\varepsilon_j) = 1$$

$$E(T) = <\varepsilon> = \boldsymbol{\Sigma}_j \varepsilon_j \cdot P_j(\varepsilon_j)$$

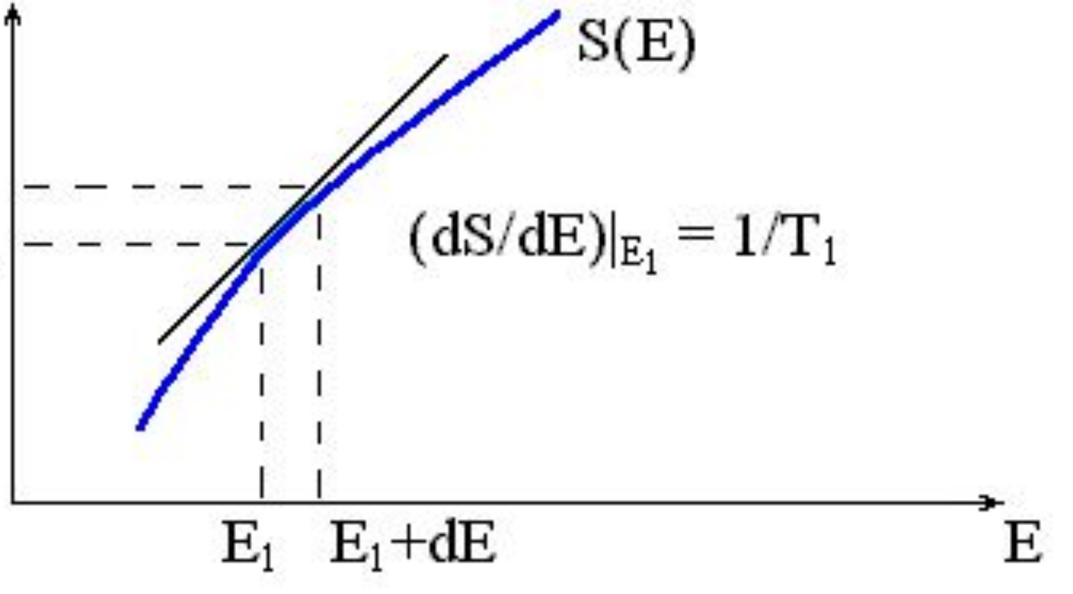
if all $\varepsilon_j = \varepsilon$: #STATES = 1/P, i.e.: $S(T) = k_B \cdot \mathbf{\ln(1/P)}$

$$S(T) = k_B <\ln(\#\text{STATES})> = k_B \cdot \boldsymbol{\Sigma}_j \ln[1/P_j(\varepsilon_j)] \cdot P_j(\varepsilon_j)$$

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

STATISTICAL MECHANICS

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



STATISTICAL MECHANICS

"Small part": $P_j(\varepsilon_j, T_{th}) \sim \exp(-\varepsilon_j/k_B T_{th})$;

$$E(T_{th}) = \Sigma_j\, \varepsilon_j \square P_j(\varepsilon_j, T_{th})$$

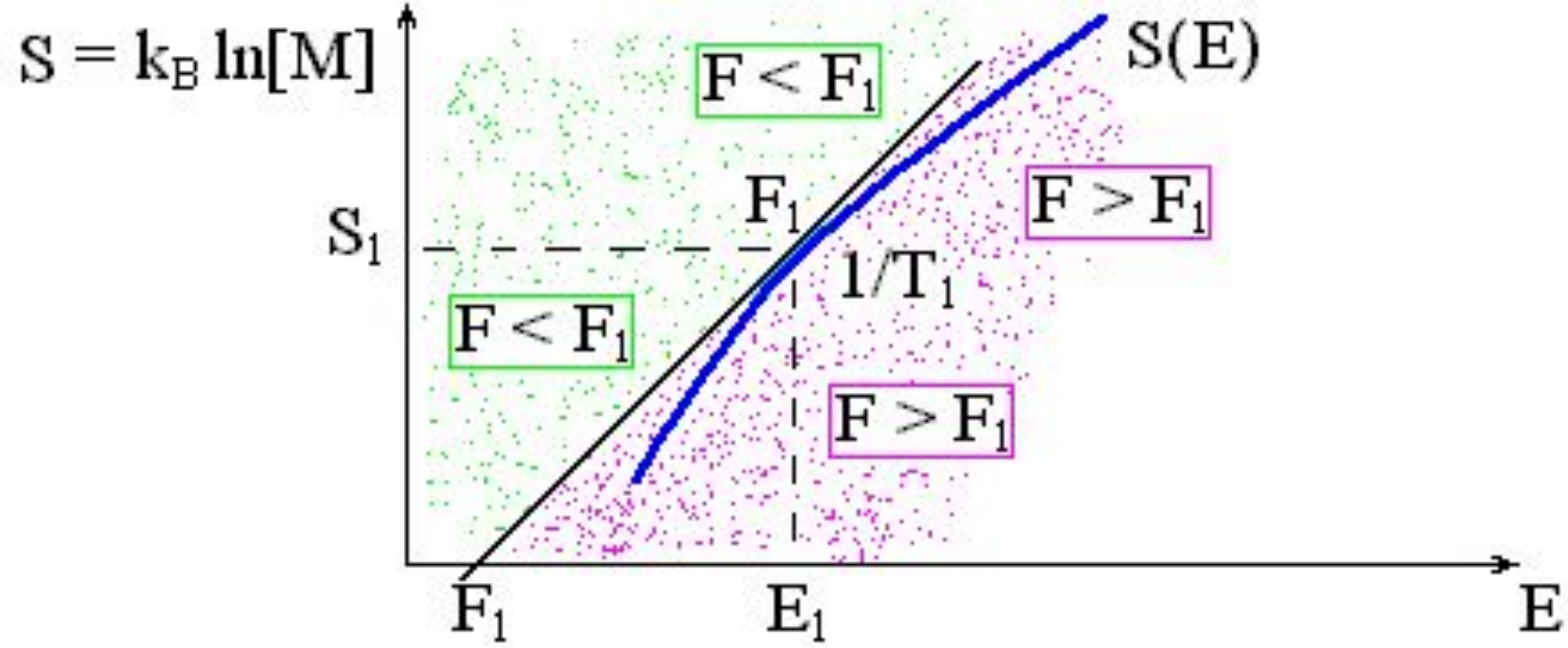
$$S(T_{th}) = k_B \square \Sigma_j \ln[1/P_j(\varepsilon_j, T_{th})] \square P_j(\varepsilon_j, T_{th})$$

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

Along tangent: $S - S(E_1) = (E - E_1)/T_1$

i.e.,

$F = E - T_1 S = const \ \ (= F_1 = E_1 - T_1 S_1)$



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

$P(\varepsilon) \sim \exp(-\varepsilon/k_BT)$ Classic: $\varepsilon = \varepsilon_{COORD} + \varepsilon_{KIN}$

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

Potential energy ε_{COORD}: depends only on coordinates

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

$Z_{KIN}(T) = \Sigma_K \exp(-\varepsilon_K/k_BT)$: don’t depend on coord.

$Z_{COORD}(T) = \Sigma_C \exp(-\varepsilon_C/k_BT)$: depends on coord.

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

===

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

$P(\varepsilon_{\mathbf{KIN}}+\varepsilon_{\mathbf{COORD}}) \sim \exp(-\varepsilon_{\mathbf{COORD}}/k_{\mathbf{B}}T)\bullet\exp(-\varepsilon_{\mathrm{KIN}}/k_{\mathbf{B}}T)$

$P(\varepsilon_{\mathbf{COORD}}) = \exp(-\varepsilon_{\mathbf{COORD}}/k_{\mathbf{B}}T) / Z_{\mathbf{COORD}}(T)$

$Z_{\mathbf{COORD}}(T) = \boldsymbol{\Sigma}_{C}\exp(-\varepsilon_{C}/k_{B}T)$: depends **ONLY** on coordinates

$P(\varepsilon_{\mathbf{KIN}}) = \exp(-\varepsilon_{\mathbf{KIN}}/k_{\mathbf{B}}T) / Z_{\mathbf{KIN}}(T)$

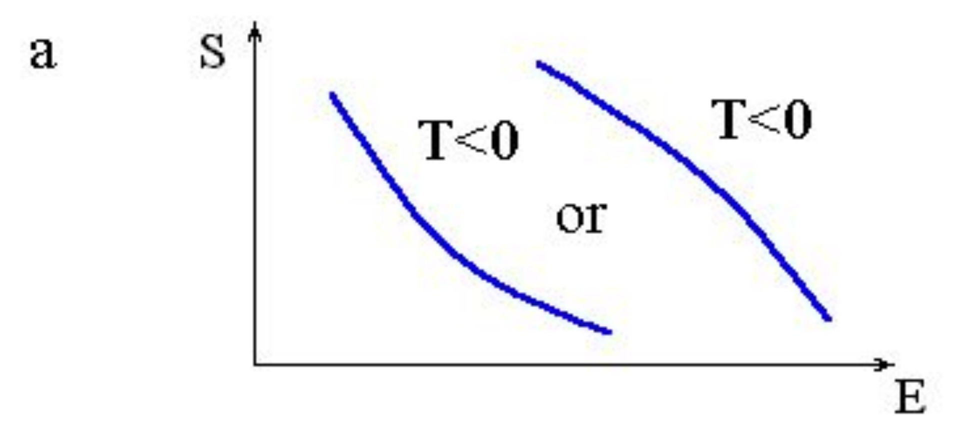
$Z_{\mathrm{KIN}}(T) = \boldsymbol{\Sigma}_{K} \exp(-\varepsilon_{K}/k_{B}T)$: don't depend on coord.

T<0: unstable (explodes)

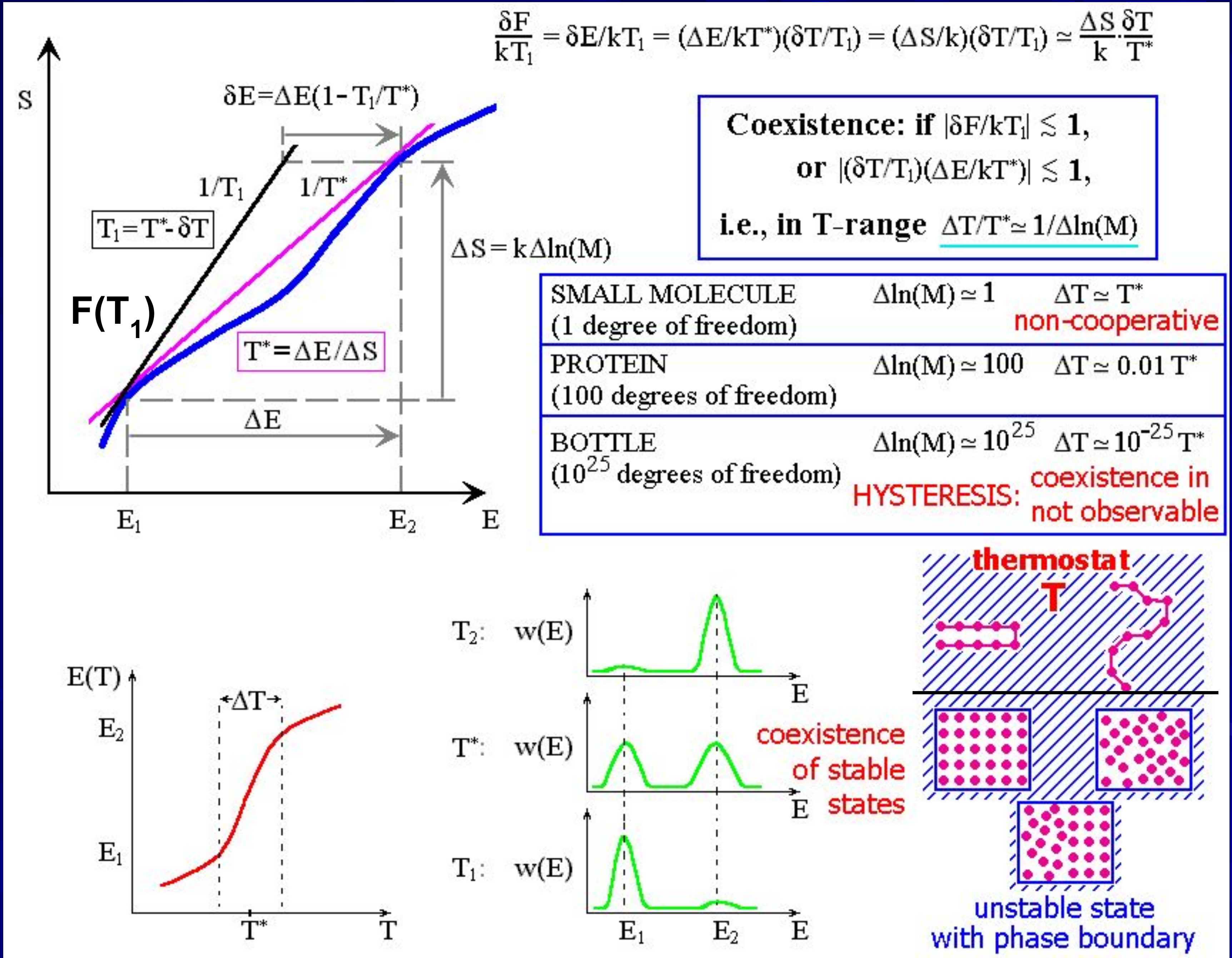
$<\varepsilon_{\mathrm{KIN}}> \Rightarrow \infty$ **at T<0**

due to

$P(\varepsilon_{\mathrm{KIN}}) \sim \exp(-\varepsilon_{\mathrm{KIN}}/k_{\mathbf{B}}T)$



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



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

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

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

coexistence of stable states

unstable state with phase boundary