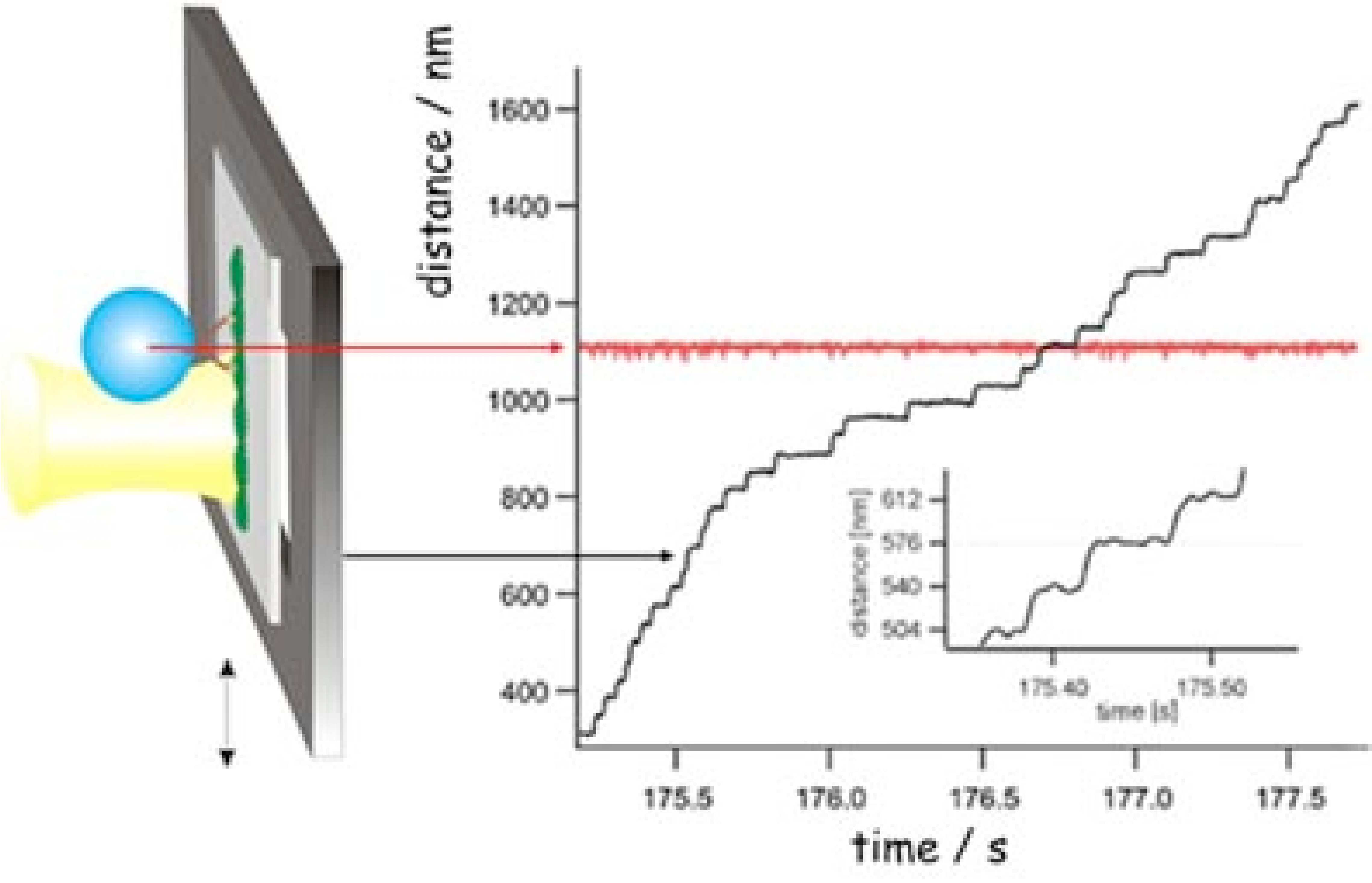
The Unreasonable Effectiveness of Equilibrium Theory for Interpreting Non-Equilibrium Experiments

A Thermodynamic Action Principle for Single Molecule Mechanics

R. Dean Astumian
University of Maine



distance / nm
1600
1400
1200
1000
800
600
400
175.5
176.0
176.5
177.0
177.5
time / s
distance [nm]
612
576
540
504
175.40
175.50
time [s]

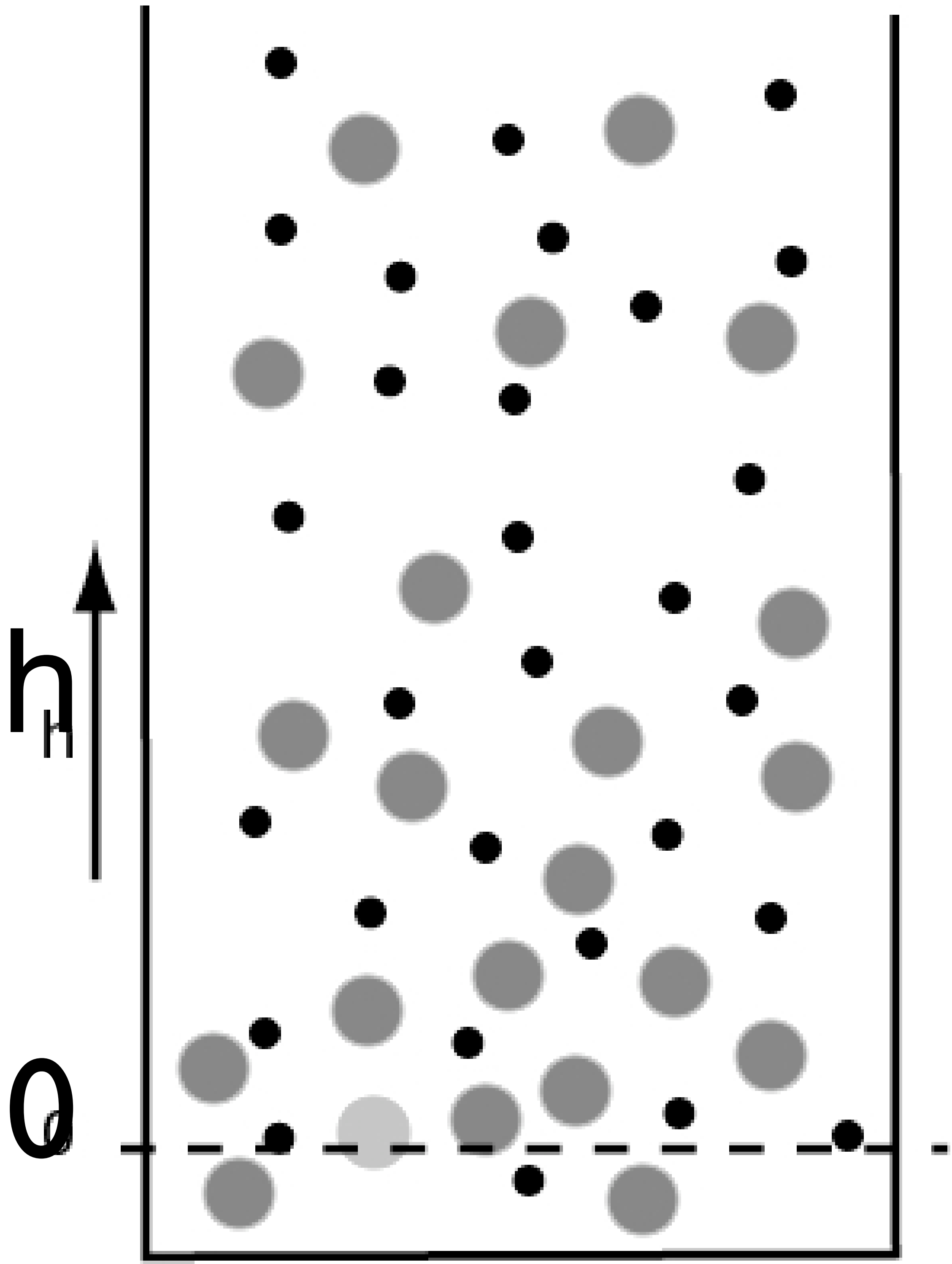
Take home messages: Proteins swim in molasses and walk in a hurricane

I. Viscous drag is so large that a protein is in mechanical equilibrium at every instant

II. Thermal noise is so large that nanoscale motions of a protein are best described as a random walk

Colloidal dispersion

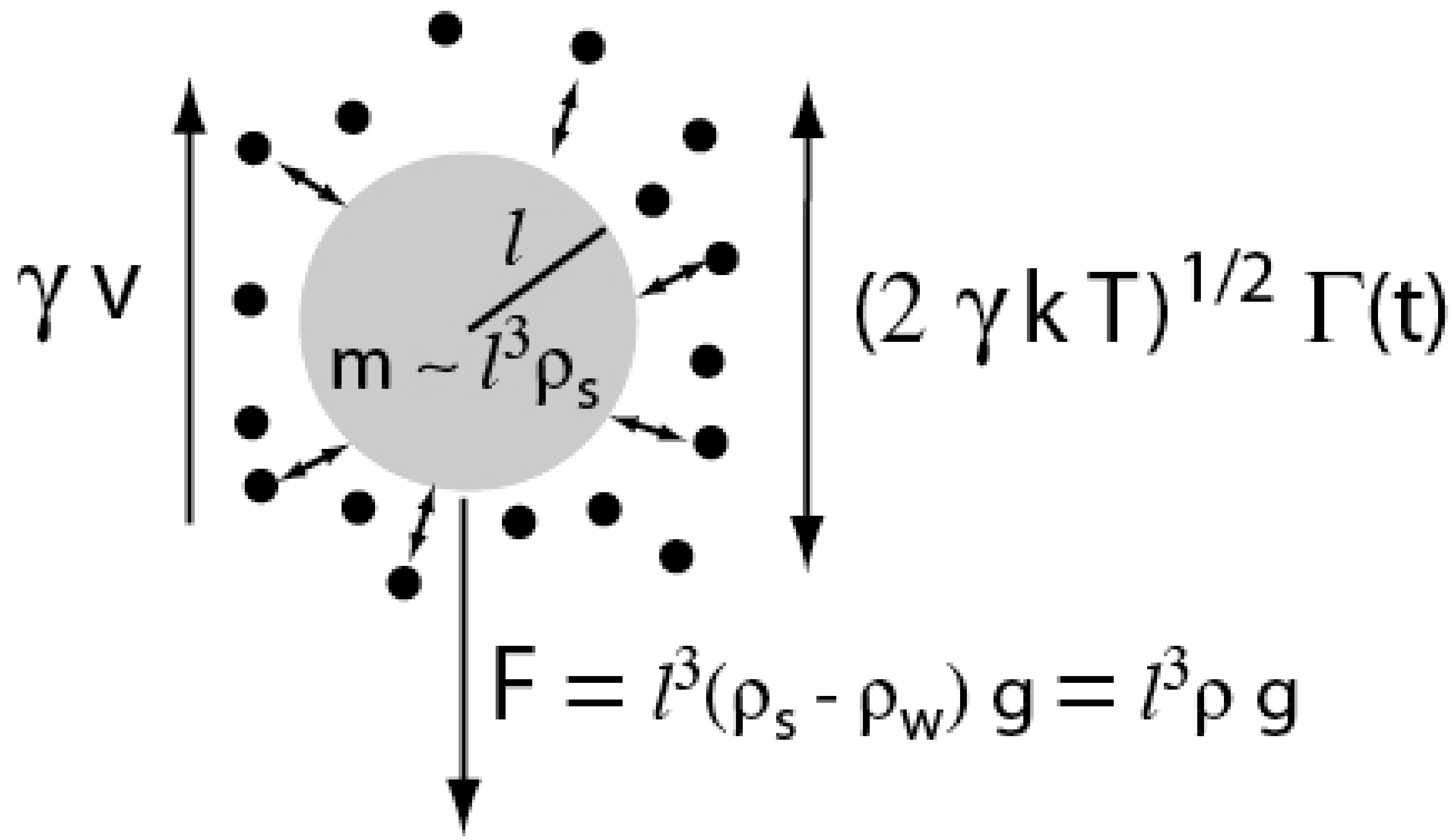
Barometric Distribution



$$m = 4\pi r^3(\rho_p - \rho_w)/3$$

$$\frac{c_{\mathrm{eq}}(h_{\mathrm{j}})}{c_{\mathrm{eq}}(h_{\mathrm{i}})} = \exp\left(\frac{-m\,g\,(h_{\mathrm{j}} - h_{\mathrm{i}})}{k_B T}\right)$$

Single particle “non-equilibrium” perspective



$$m\frac{dv}{dt} = F - \gamma v + \sqrt{2\gamma kT}\;\Gamma(t)$$

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$$m \sim l^3\rho \text{ and } \gamma \sim l\eta$$

$$l \sim 10^{-9}m,\ \eta \sim 10^{-3}kg/(ms),\ \text{and}\ \rho \sim 10^3 kg/m^3$$

$$F_{\text{char}} = \frac{\eta^2}{\rho} \sim 10^{-9}\text{kg m/s}^2 \qquad \frac{l\ v\rho}{\eta} \equiv \text{Re}$$

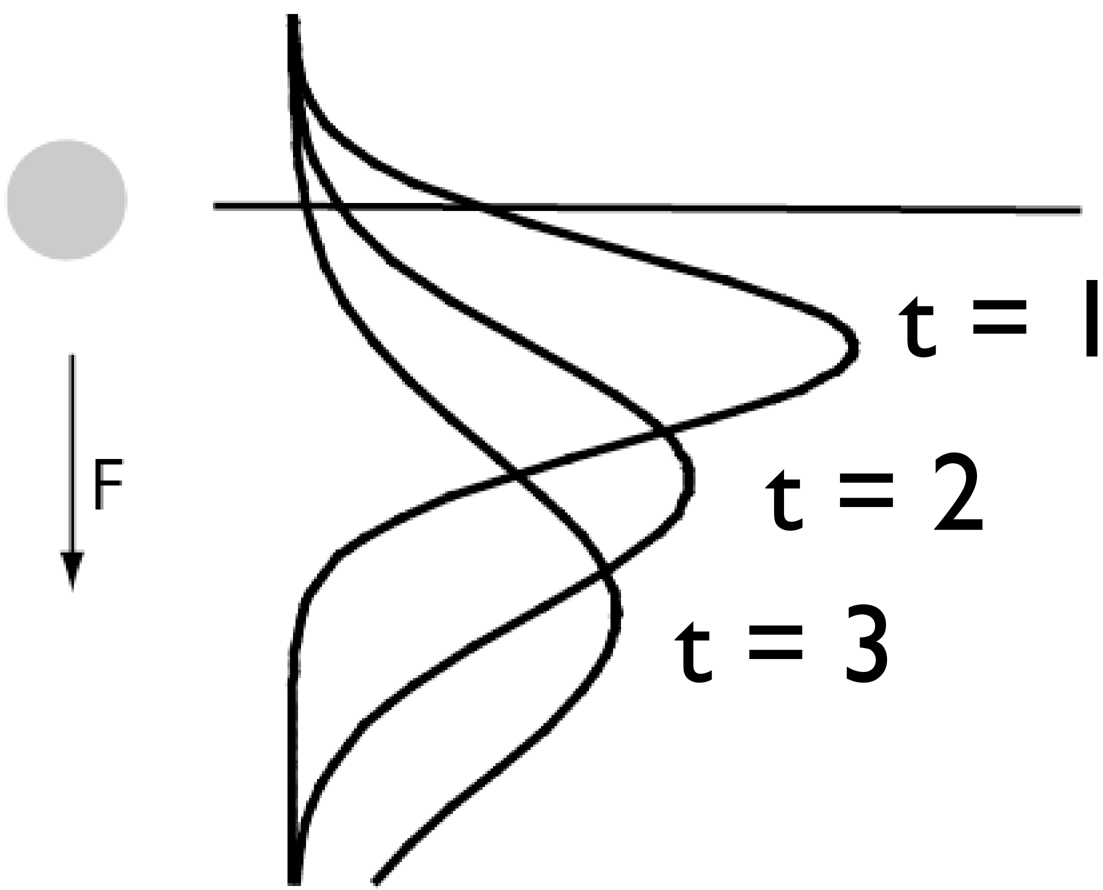
$$t_{\text{char}} = \frac{\rho\ l^2}{\eta} \propto \frac{m}{\gamma} \sim 10^{-12}\text{s} \qquad \frac{l^2\eta v}{kT} \equiv \text{Pe}$$

Overdamped Limit - Mechanical Equilibrium

$$\gamma \dot{h} = F + \sqrt{2\gamma k_B T}\,\xi(t)$$

$$\Downarrow$$

$$\frac{\partial P(h,t)}{\partial t} = D\frac{\partial^2 P(h,t)}{\partial h^2} + \frac{mg}{\gamma}\frac{\partial P(h,t)}{\partial h}$$



$$P(h_{\mathrm{j}}, t | h_{\mathrm{i}}, 0) \equiv P(h,t)$$

$$h = h_j - h_i$$

$$P(h,t) = \frac{\exp\left[\frac{-(h+(mg/\gamma)t)^2}{4Dt}\right]}{\sqrt{4\pi D t}}$$

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Experimental Demonstration of Violations of the Second Law of Thermodynamics for Small Systems and Short Time Scales

G. M. Wang,[1] E. M. Sevick,[1] Emil Mittag,[1] Debra J. Searles,[2] and Denis J. Evans[1]
[1]Research School of Chemistry, The Australian National University, Canberra ACT 0200, Australia
[2]School of Science, Griffith University, Brisbane QLD 4111, Australia

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Second Law of Thermodynamics Violated

nature scienceupdate

Second law broken

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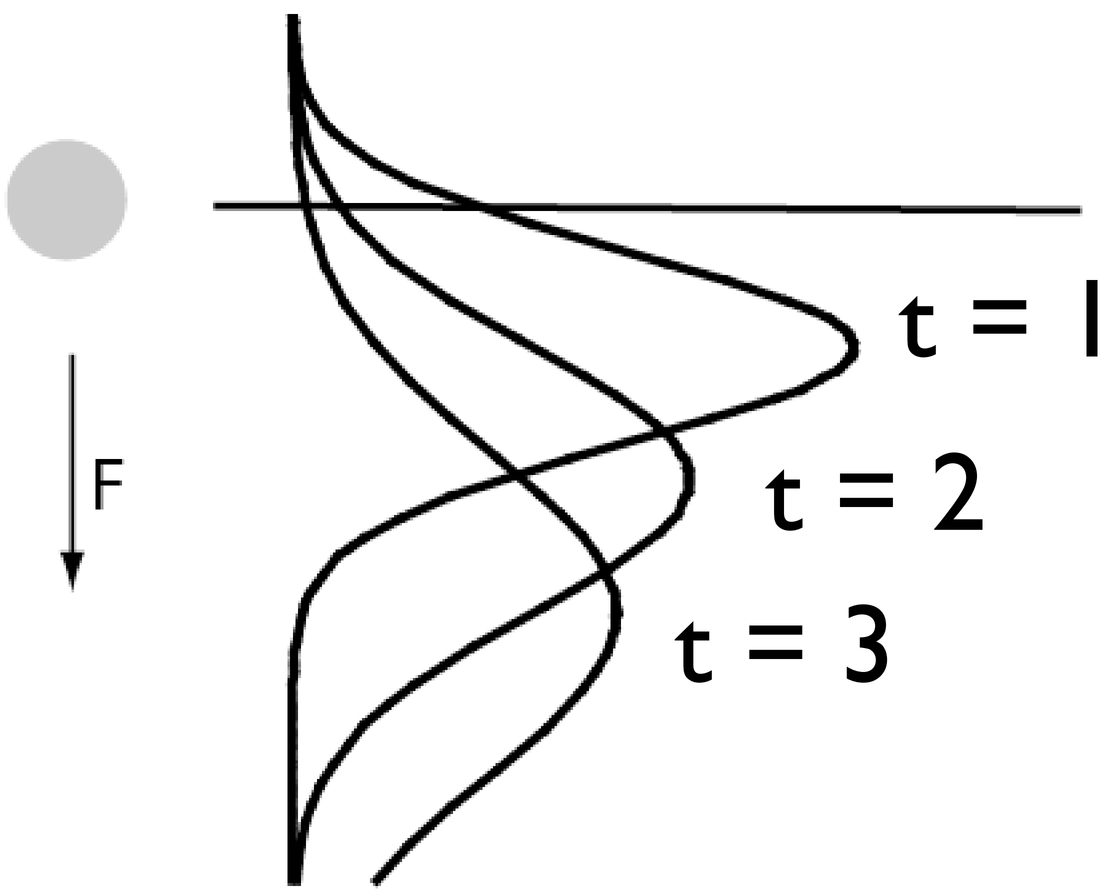
$$\Downarrow$$

$$\frac{\partial P(h,t)}{\partial t} = D \frac{\partial^2 P(h,t)}{\partial h^2} + \frac{mg}{\gamma} \frac{\partial P(h,t)}{\partial h}$$



$$P(h_{\mathrm{j}}, t | h_{\mathrm{i}}, 0) \equiv P(h,t)$$

$$h = h_j - h_i$$

$$P(h,t) = \frac{\exp\left[\frac{-(h+(mg/\gamma)t)^2}{4Dt}\right]}{\sqrt{4\pi D t}}$$

Gaussian probability distribution

$$P(h,t) = \frac{\exp\left[\frac{-(h+(mg/\gamma)t)^2}{4Dt}\right]}{\sqrt{4\pi Dt}}$$

Take the ratio:

$$\frac{P(h,t)}{P(-h,t)} = \exp\left(\frac{-mgh}{\gamma D}\right)$$

Time has disappeared! Use the relation

$$D = k_B T/\gamma$$

and we recover the "equilibrium" barometric distribution

Second Law:

$$< mgh > < 0$$

Probability densities are normalized

$$\int_{-\infty}^{+\infty} P(h,t)dh = \int_{-\infty}^{+\infty} P(-h,t)dh = 1$$

Now we have an equality:

$$\langle \exp\left(\frac{mgh}{k_B T}\right) \rangle = \int_{-\infty}^{+\infty} exp\left(\frac{mgh}{k_B T}\right) P(h)dh = 1$$

G.N. Bochkov and Yu. E. Kuzovlev, Physica 106A, 443-479 (1981),

$$P[Q(\tau); X(\tau)] \exp\left\{-\beta \int_{-\infty}^{\infty} X(\tau)\dot{Q}(\tau)\, d\tau\right\}$$
$$= P[\epsilon Q(-\tau); \epsilon X(-\tau)]$$

This FDT form is obvious enough from the physical point of view. From (2.11) one can see that the ratio of the probability of some macroscopic trajectory of a system to the probability of the time reversal trajectory is equal to exp(/3E). Therefore those trajectories relatively are more probable, for which E > 0

$$\langle \exp(-\beta E)\rangle = 1 \qquad\qquad \langle \exp(-\Delta S)\rangle = 1$$

Let us summarize briefly the results of the first part of the paper. The main result, which the developed fluctuation-dissipation theory is based upon, are time symmetry relations for the probability functional of arbitrary macro-variables (the generalized FDT). The generalized FDT is established both for the system perturbated dynamically from nonequilibrium state and for the system developed from nonequilibrium state thermally. Both variants of the theorem are direct consequence of microscopic motion reversibility but lead straight to irreversibility of macroscopic evolution.

G.N. Bochkov and Yu. E. Kuzovlev, Physica 106A, 443-479 (1981),

Microscopic Reversibility and Detailed Balance

$$c_{\mathrm{eq}}(h_i)P(h_j,t|\cdots|h_i,0) = c_{\mathrm{eq}}(h_j)P^{\dagger}(h_i,t|\cdots|h_j,0)$$

$$\frac{P(h_j,t|\cdots|h_i,0)}{P^{\dagger}(h_i,t|\cdots|h_j,0)} = e^{-mgh/k_BT}$$

The importance of being Gaussian

$$P(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(x-\mu)^2/2\sigma^2}$$

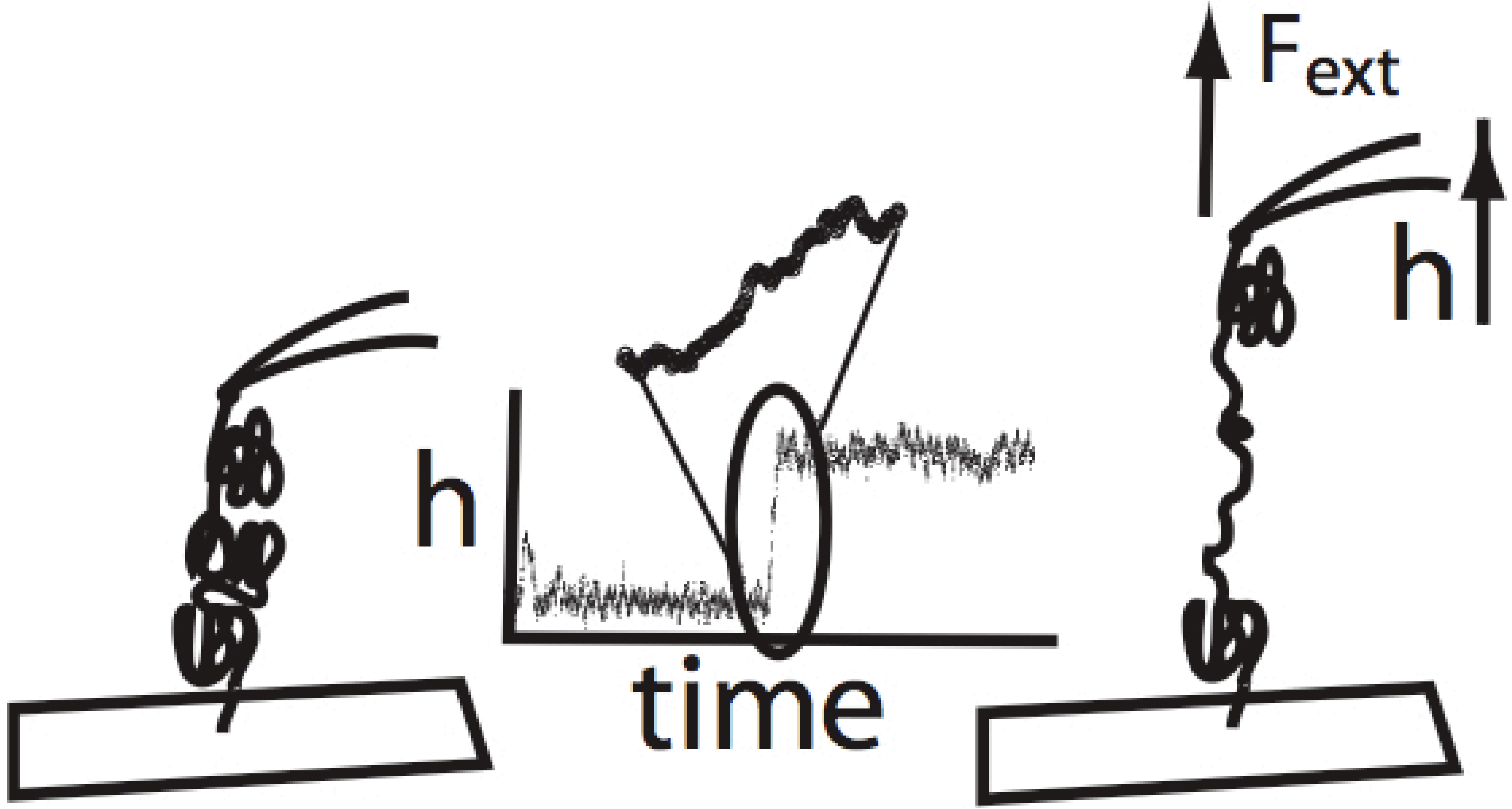
$$\frac{P(-x)}{P(x)} = e^{-2\mu x/\sigma^2}$$

$$\langle e^{-2\mu x/\sigma^2} \rangle = \int_{-\infty}^{+\infty} \frac{P(-x)}{P(x)} P(x) dx = 1$$

Onsager-Machlup Thermodynamic Action

$$R\dot{\alpha} = X + \epsilon$$

- "Near Equilibrium"
- "Linear Regime"
- Gaussian behavior



$$\gamma\dot{h} = F + \sqrt{2\gamma k_B T}\xi(t)$$

$$F = g(t)F_{\text{ext}} - U'(h)$$

External work

$$w_{\mathrm{ext}}[h(t)] = \int_0^t ds\ \left[g(s)F_{\mathrm{ext}} \times \dot{h}\right]$$

Work stored (lost) in the system

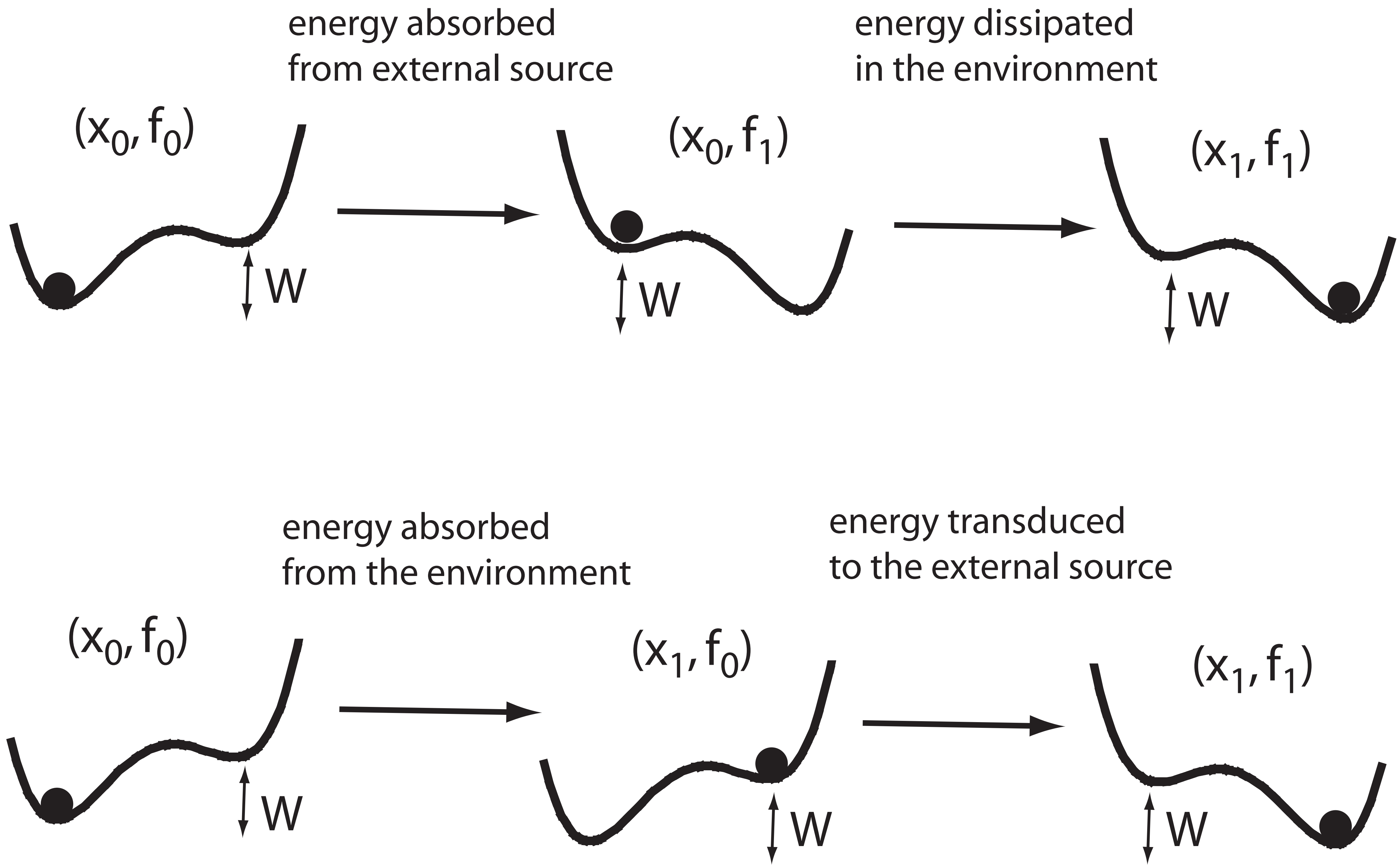
$$\Delta U = \int_0^t ds\ \left[U'(h) \times \dot{h}\right] = U(h(t)) - U(h(0))$$

Dissipated work

$$w_{\mathrm{dis}}[h(t)] = w_{\mathrm{ext}}[h(t)] - \Delta U$$

Time dependent potential function

$$F(x,t) \;=\; U'(x) + f(t)$$



$$\gamma \dot{h} = F + \sqrt{2\gamma k_B T}\xi(t)$$

For discretized time

$$P(\xi_k) \propto e^{-\xi_k^2 \Delta t/2}$$

Probability for any sequence of "Brownian" kicks

$$P\left[(\xi_n, t|\ldots|\xi_0, 0)\right] \propto \prod_{k=0}^{\mathrm{n}} e^{-\xi_k^2 \Delta t/2} = e^{\sum_{k=0}^{n} -\xi_k^2 \Delta t/2}$$

In the continuum limit

$$P\left[\xi(t)\right] \propto e^{-\int_0^t ds\, \xi^2(s)/2}$$

Rearrange the langevin equation

$$\xi(t) = \left(\dot{h} - F/\gamma\right)/\sqrt{2D}$$

To write

$$P\left[\xi(t)\right] \propto e^{-S/D}$$

Where

$$\frac{S}{D} = \frac{1}{4D}\int_0^t ds\,\left[\dot{h} - F/\gamma\right]^2$$

$$= \frac{\Delta U - w_{\mathrm{ext}}[\xi(t)]}{2\gamma D} + \frac{1}{4D}\int_0^t ds\,\left(\dot{h}^2 + F^2/\gamma^2\right)$$

The ratio of probabilities for forward and reverse paths

$$\frac{P[\xi(t)]}{P[\xi^\dagger(t)]} = e^{(w_{\text{ext}}[\xi(t)]-\Delta U)/k_B T}$$

The work probability density function (not gaussian) is

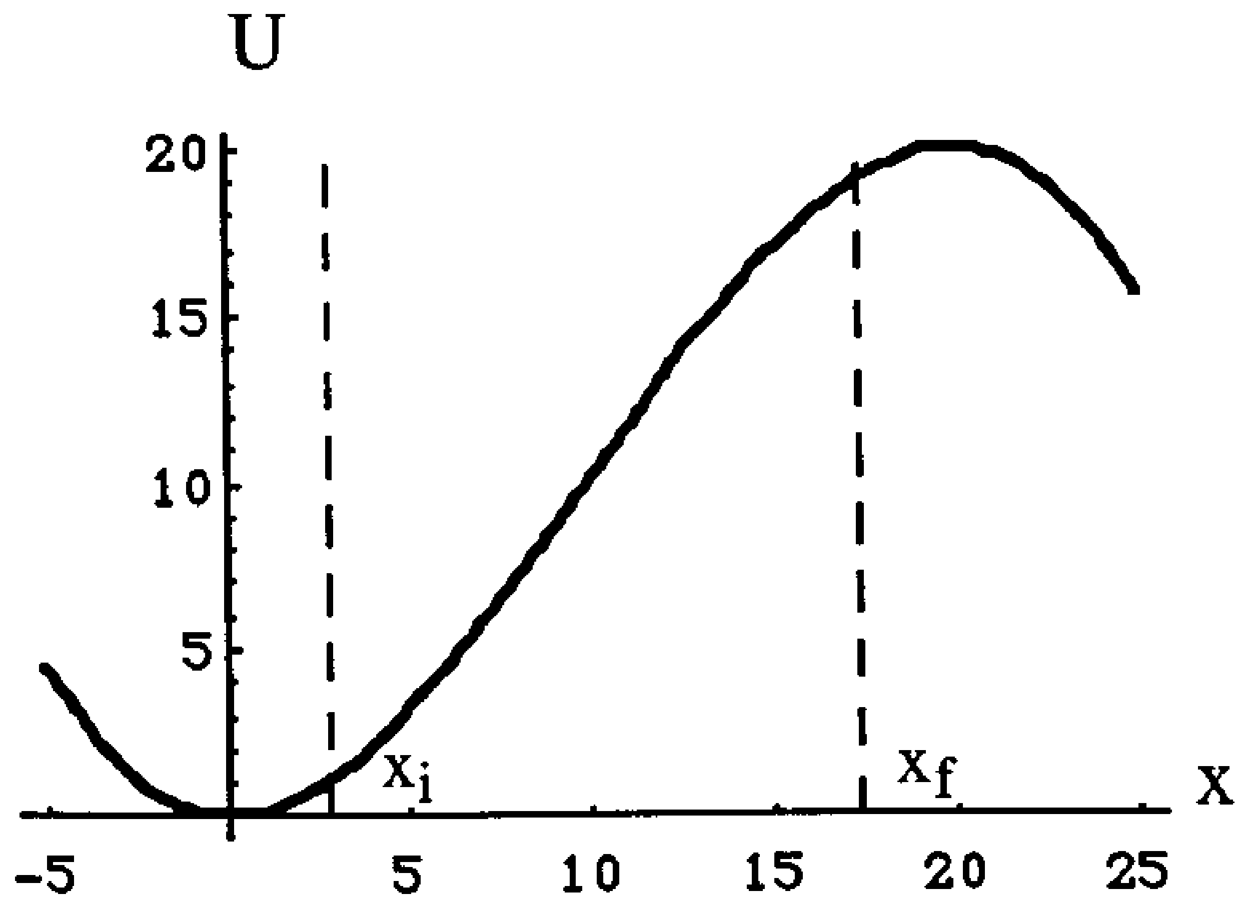
$$P(W_{\text{dis}}) = \int_{\xi(t)} d\xi'(t)\ \delta(W_{\text{dis}} - w_{\text{dis}}[\xi'(t)])\ P[\xi'(t)]$$

with the ratio

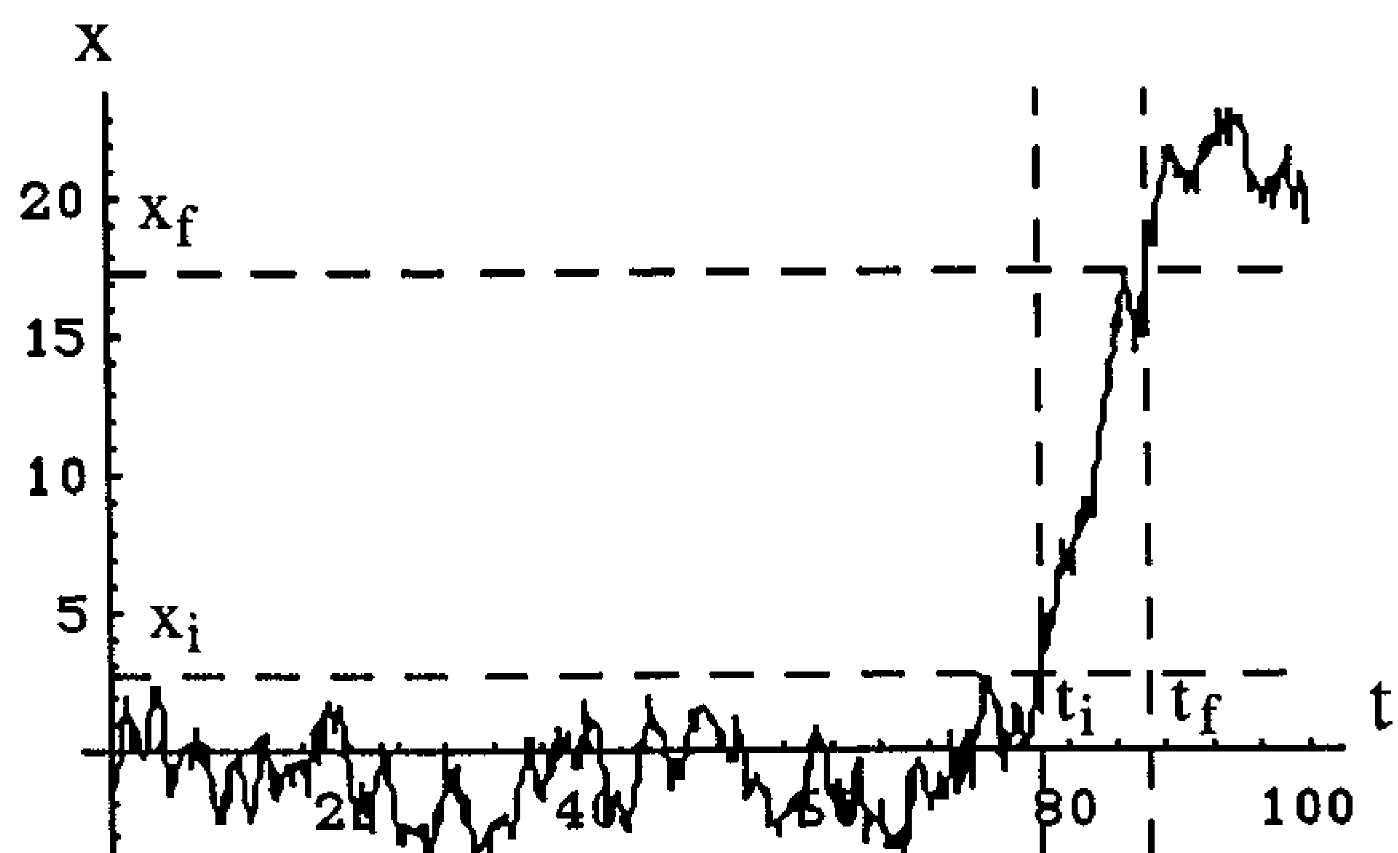
$$\frac{P(W_{\text{dis}})}{P(-W_{\text{dis}})} = e^{W_{\text{dis}}/k_B T}$$

and finally

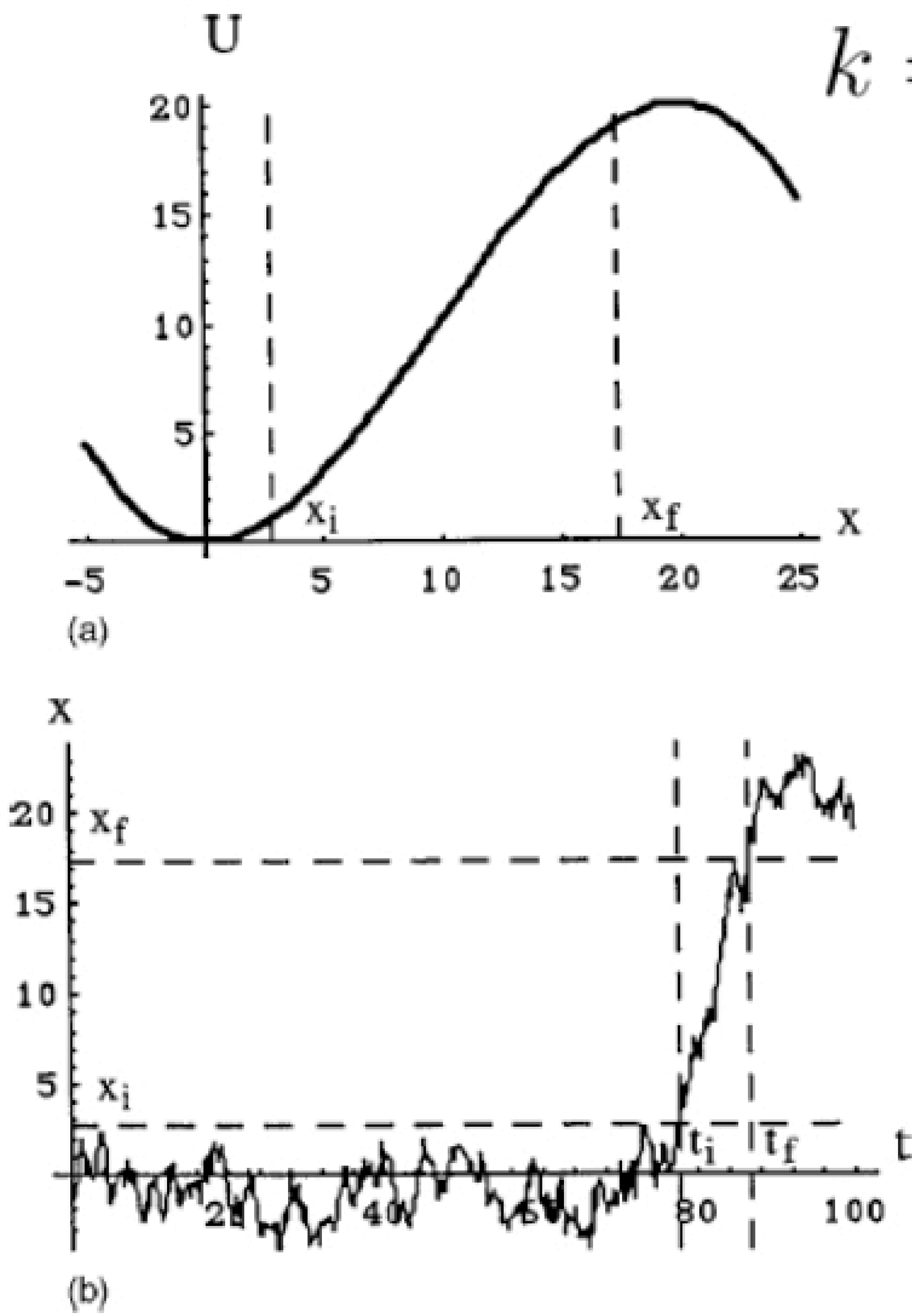
$$\langle e^{-W_{\text{dis}}/k_B T}\rangle = \int_{-\infty}^{\infty} dW_{\text{dis}} e^{-W_{\text{dis}}/k_B T} P(W_{\text{dis}}) \quad = 1$$



(a)



(b)



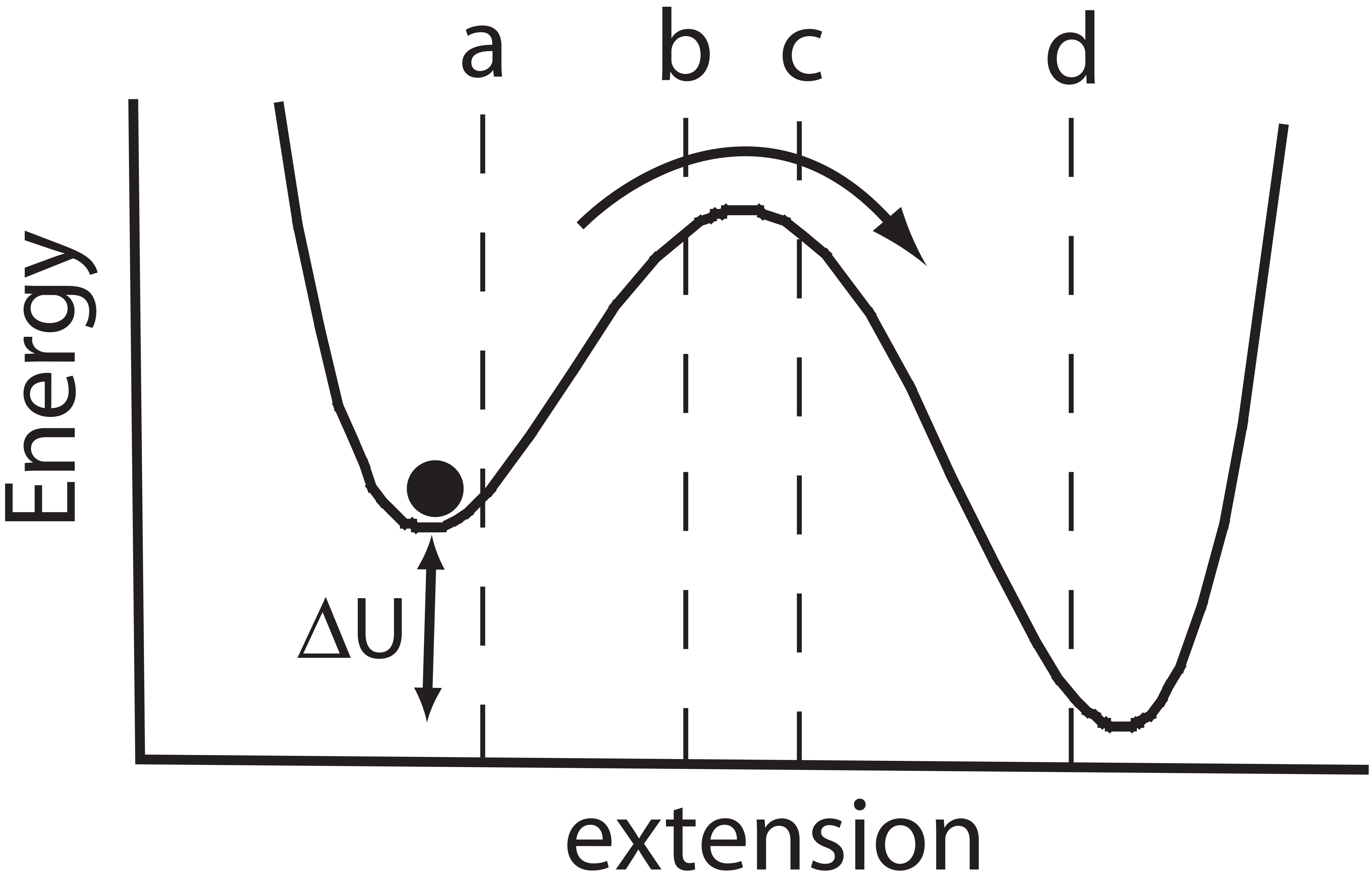
$$k = A \exp\left(-E^{\ddagger}/k_B T\right)$$

$$A \approx (10^5 - 10^7)s^{-1}$$

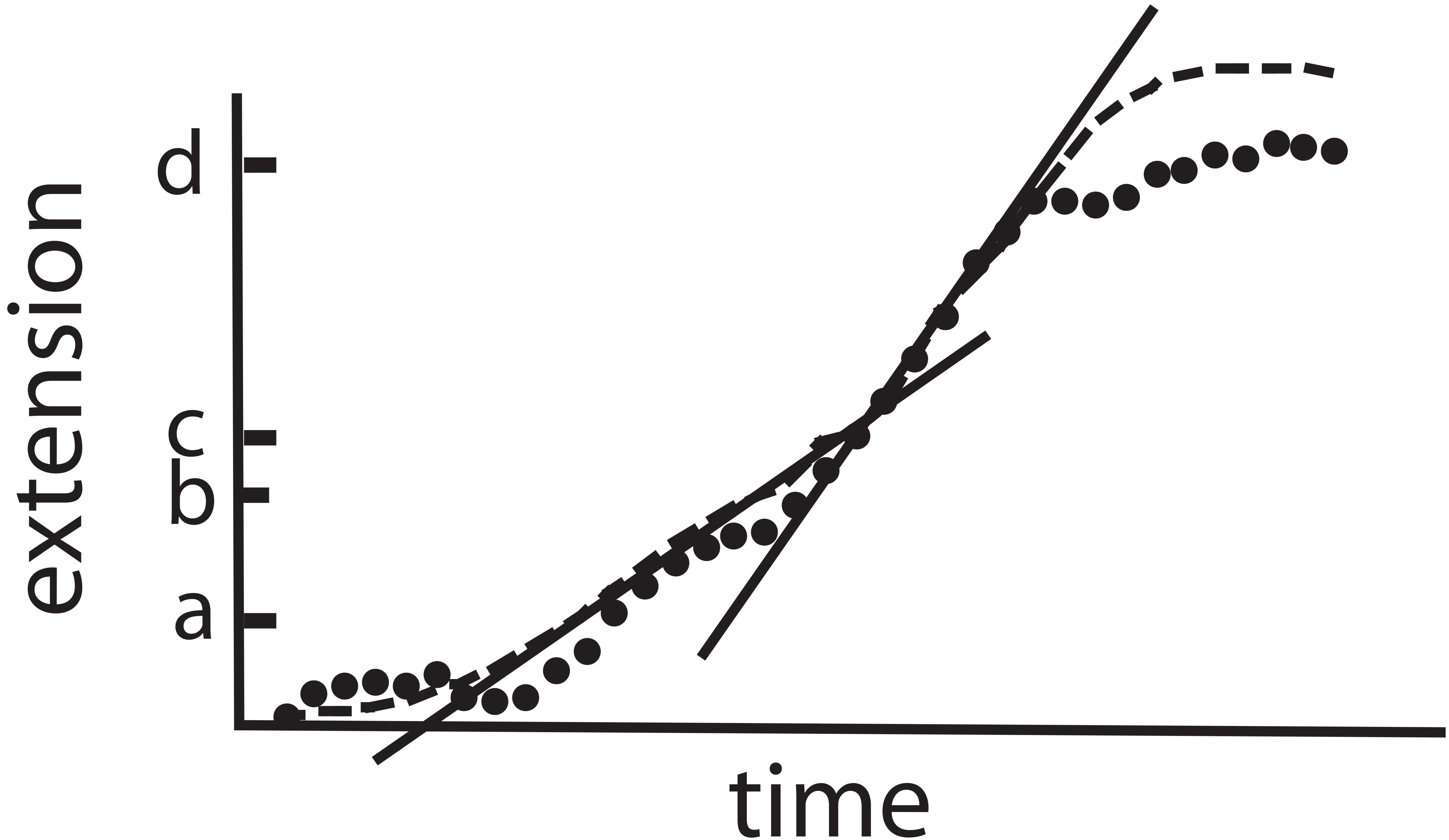
$$E^{\ddagger} \approx (5 - 10)k_B T$$

$$k \approx (5 - 50000)s^{-1}$$

$$1/\tau_{int} \approx (10^5 - 10^7)s^{-1}$$

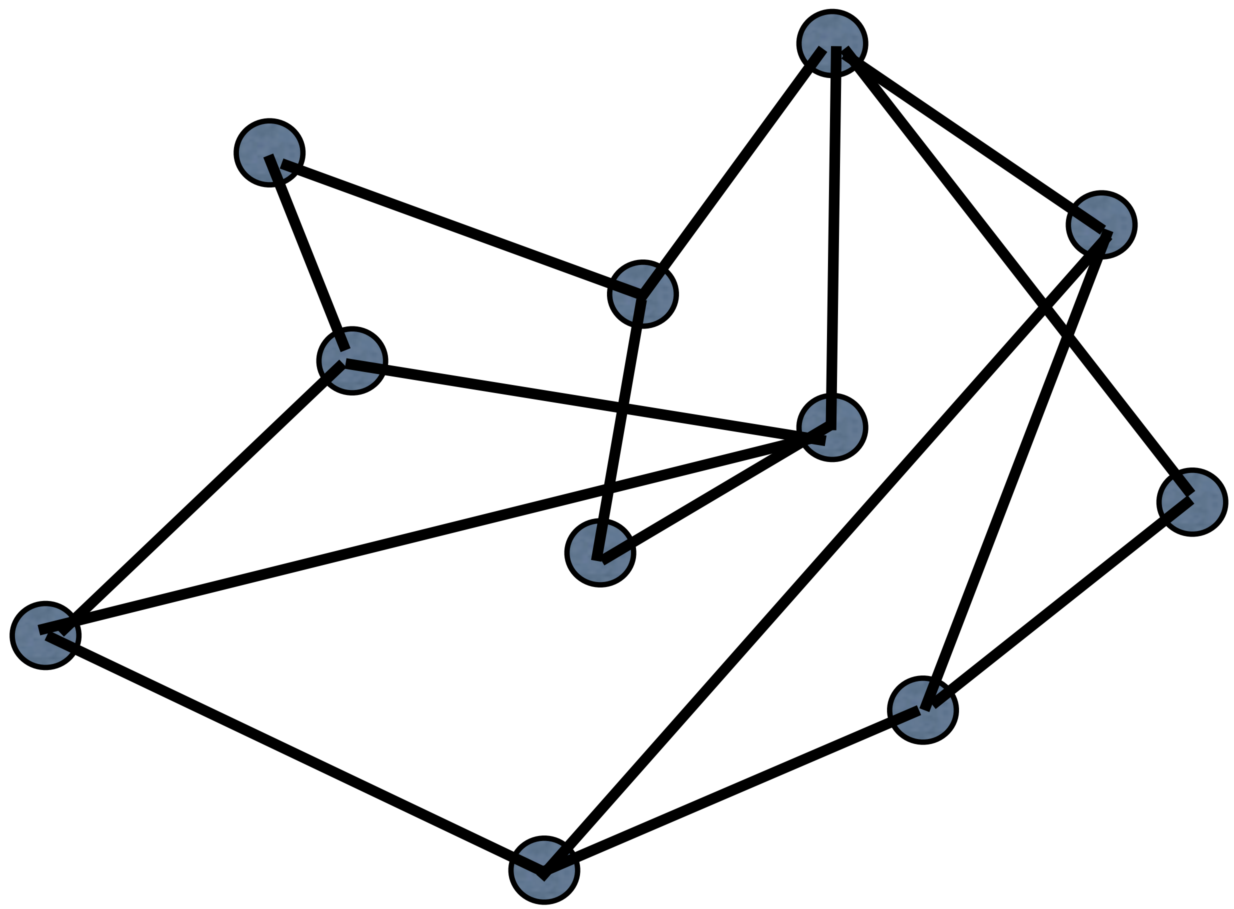


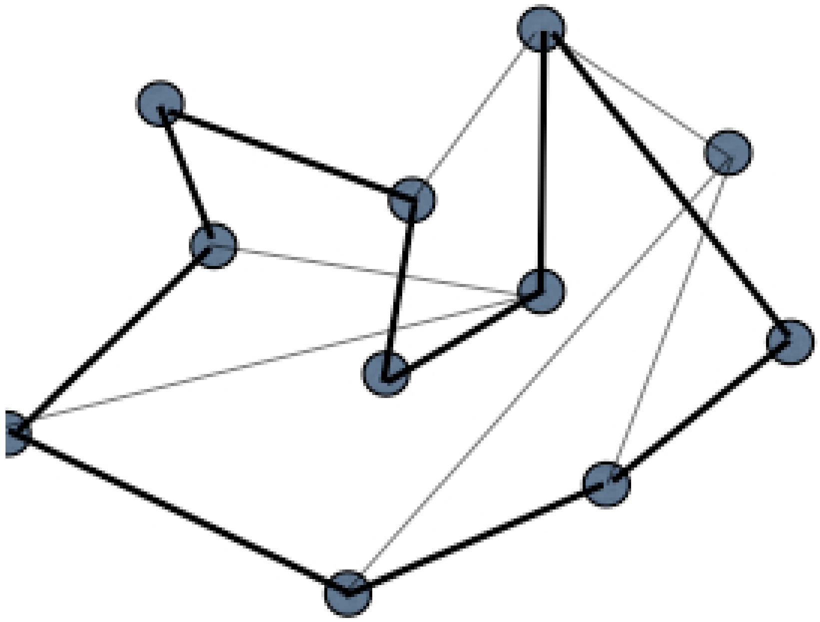
a
b
c
d
Energy
ΔU
extension



extension
d
c
b
a
time

Enzyme Cycle Kinetics





effective rate constants

$$k_+ \quad k_-$$

with ratio

$$\frac{k_+}{k_-} = \exp(\beta \Delta G)$$

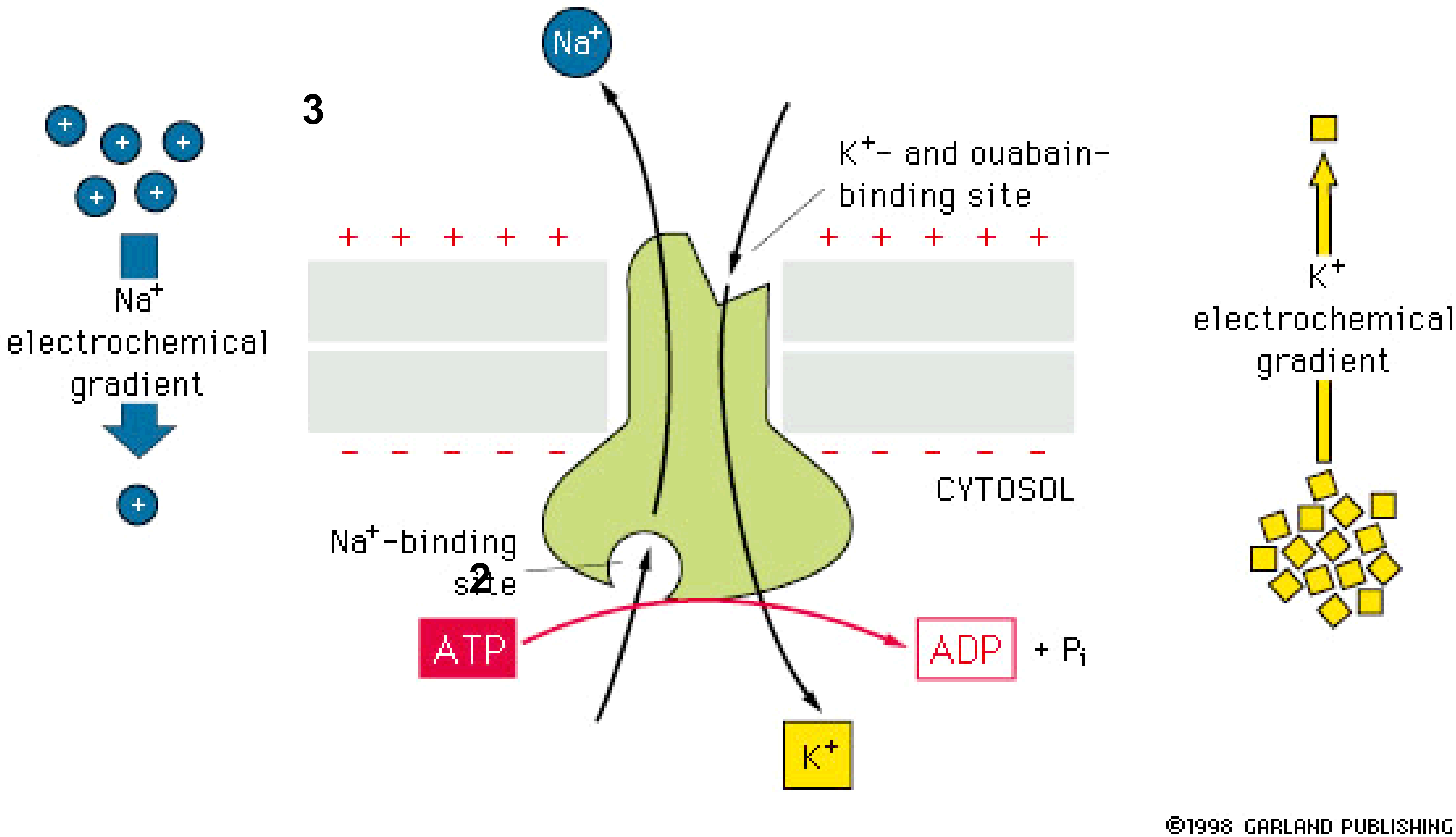
$$\frac{\partial P(n,t)}{\partial t} = \frac{1}{2}(k_+ + k_-)\frac{\partial^2 P(n,t)}{\partial n^2} + (k_+ - k_-)\frac{\partial P(n,t)}{\partial n}$$

$$P(n) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(n-\mu)^2/2\sigma^2} \quad \frac{P(n)}{P(-n)} = e^{2n\tanh(\Delta G/(2k_B T)}$$

$$\mu = (k_+ - k_-)t \qquad \sigma^2 = (k_+ + k_-)t$$

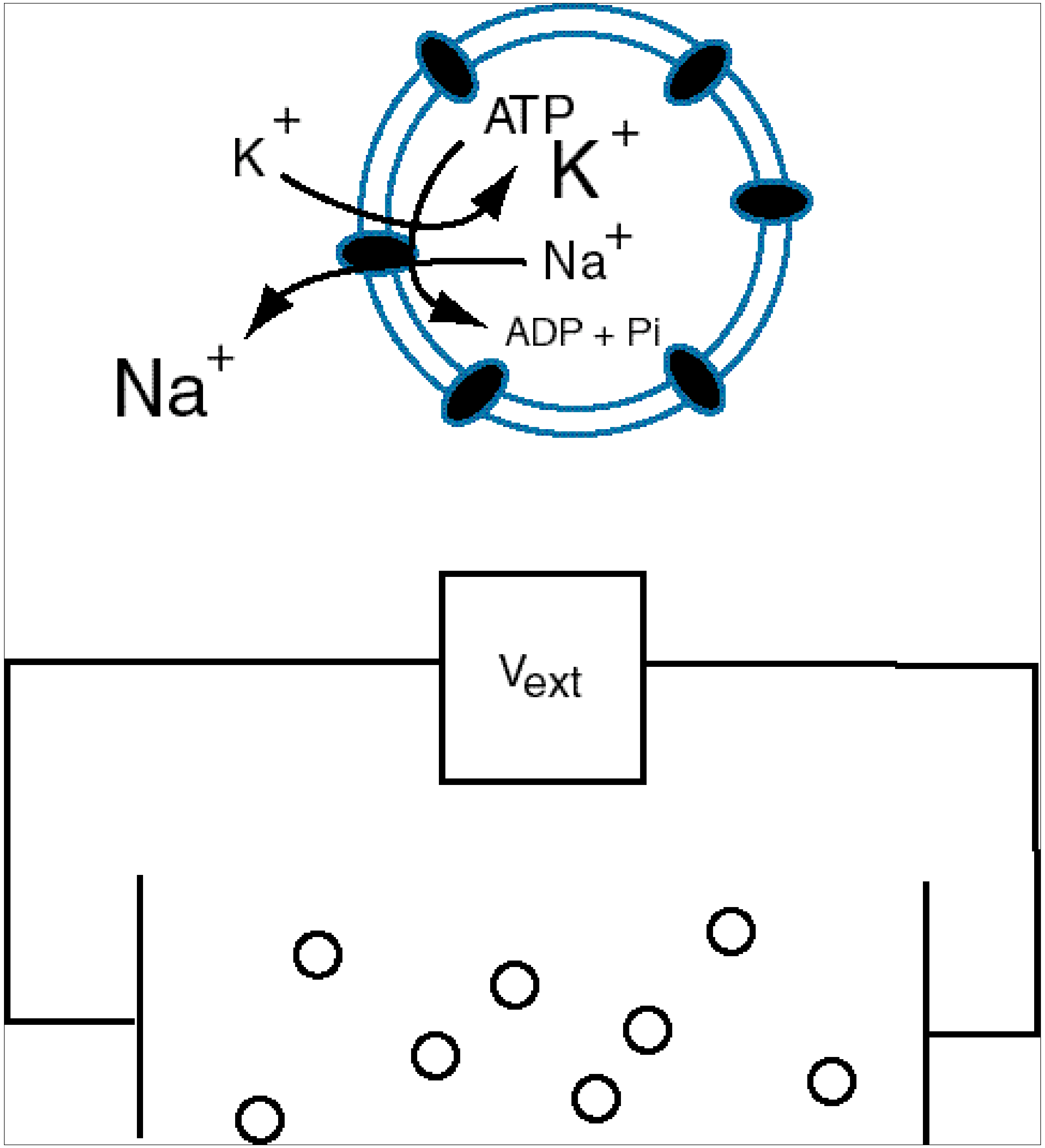
T.L. Hill, Biochemistry, 14: 2127-2137 (1975)

Na^+-K^+ transport ATPase

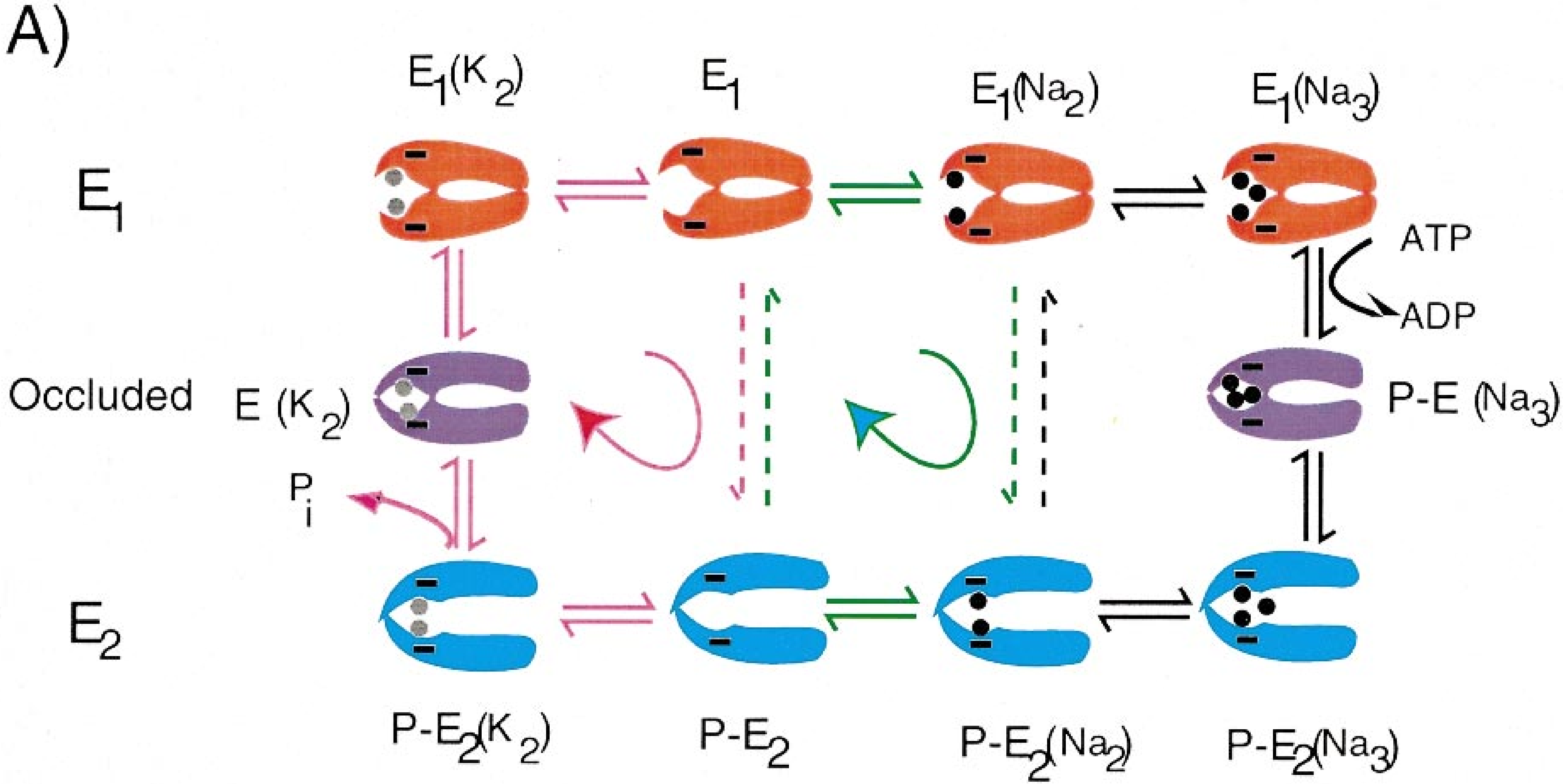


"Ion pumps do not function by a power stroke mechanism; instead, pump operation involves transitions between molecular states, each of which is very close to thermal equilibrium with respect to its internal degrees of freedom, even at very large overall driving force."

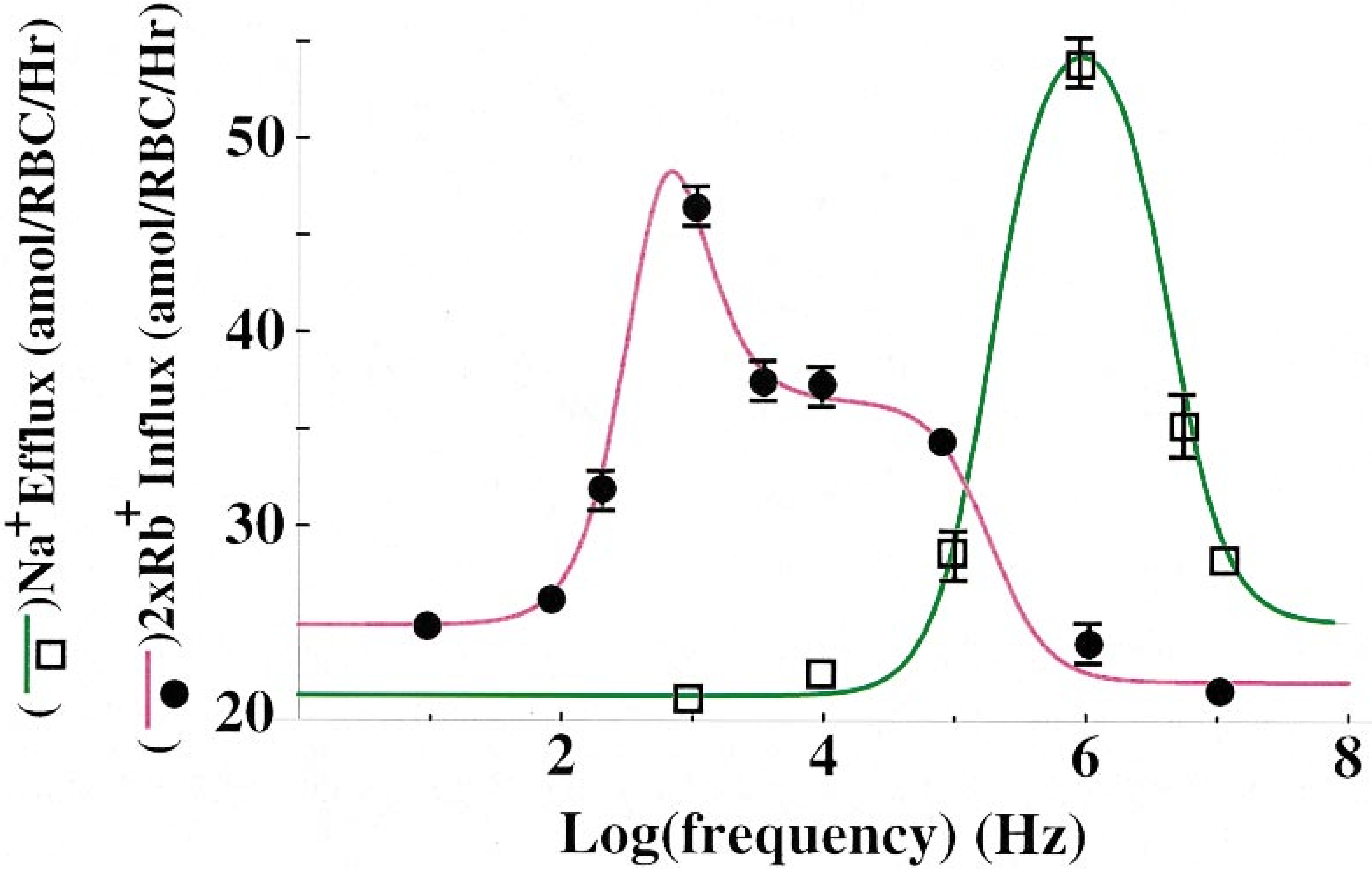
Peter Lauger, "Ion motive ATPases"



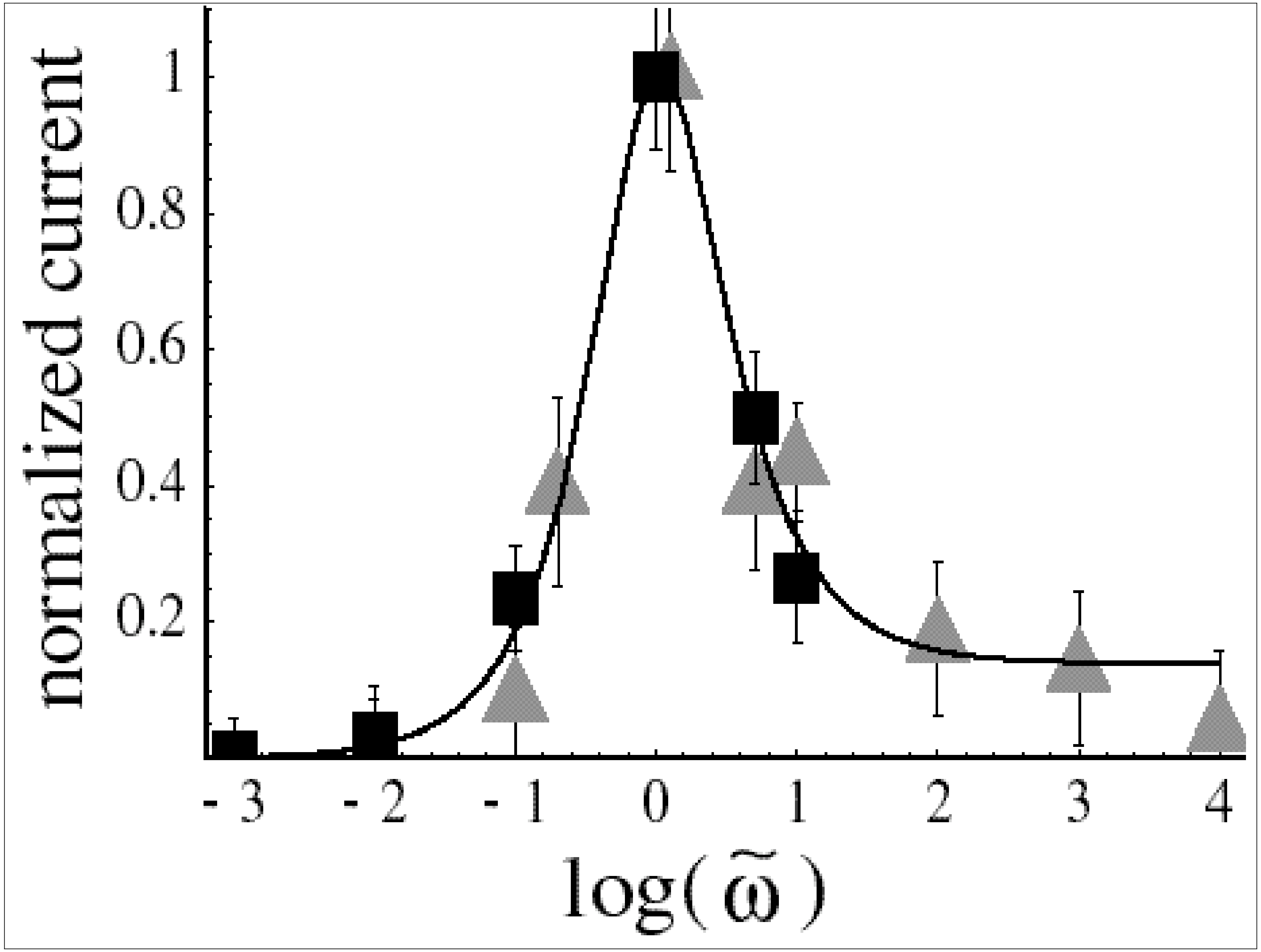
Serpersu and Tsong, (1984) JBC 259, 7155; Liu, Astumian, and Tsong, (1990) JBC 265, 7260


A)
$E_1(K_2)$
E_1
$E_1(Na_2)$
$E_1(Na_3)$
E_1
ATP
ADP
Occluded
$E\ (K_2)$
$P\text{-}E\ (Na_3)$
P_i
E_2
$P\text{-}E_2(K_2)$
$P\text{-}E_2$
$P\text{-}E_2(Na_2)$
$P\text{-}E_2(Na_3)$

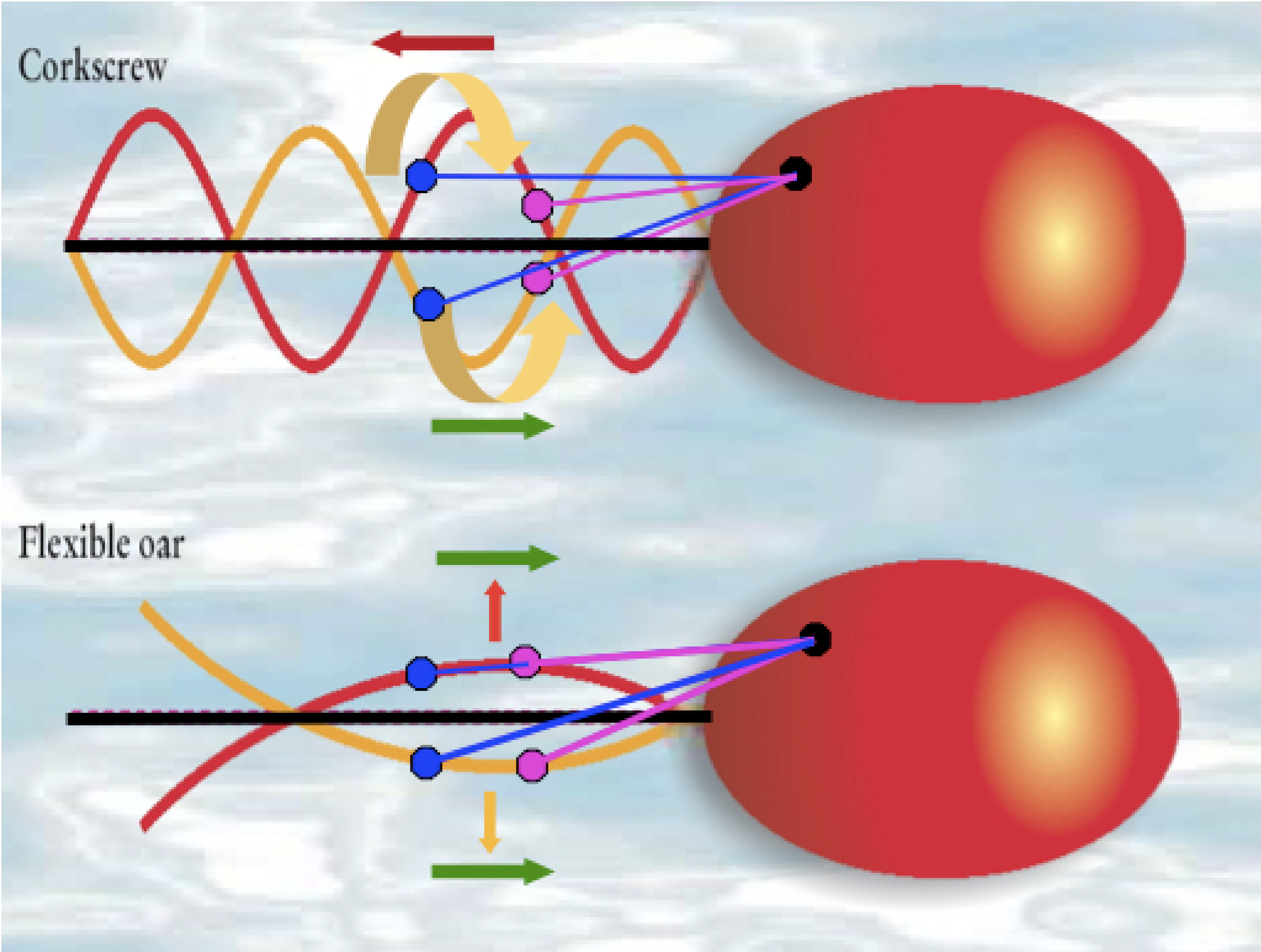
B)



Robertson B, Astumian RD (1991) Frequency dependence of catalyzed reactions in a weak oscillating field. J Chem Phys 94: 7414–7419

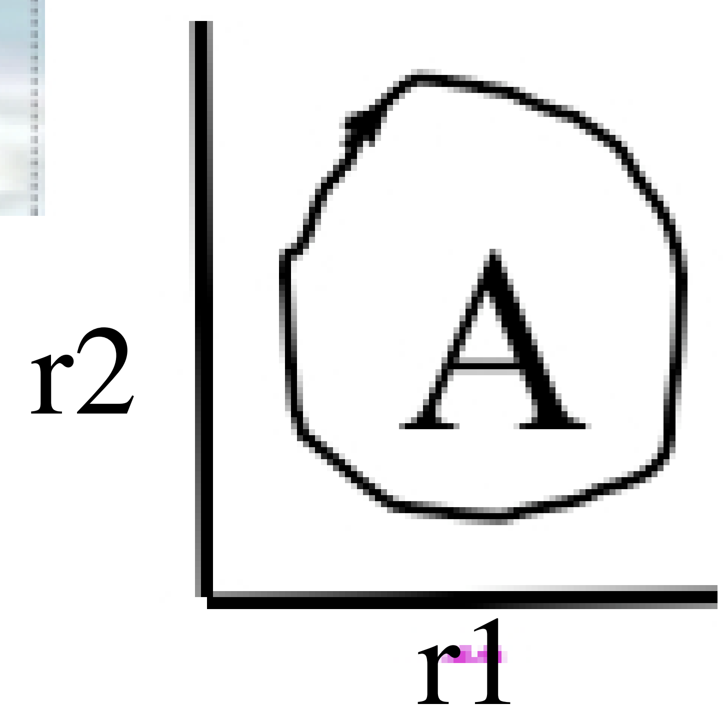


$$I_{\rm ad} \approx F_1 Q_{\rm eq,1} \frac{\tilde{\omega}}{1+\tilde{\omega}^2} \qquad I_{\rm nonad} \approx A \frac{r^2 \tilde{\omega}^2}{1+r^2\tilde{\omega}^2.}$$



adiabatic

non-adiabatic



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