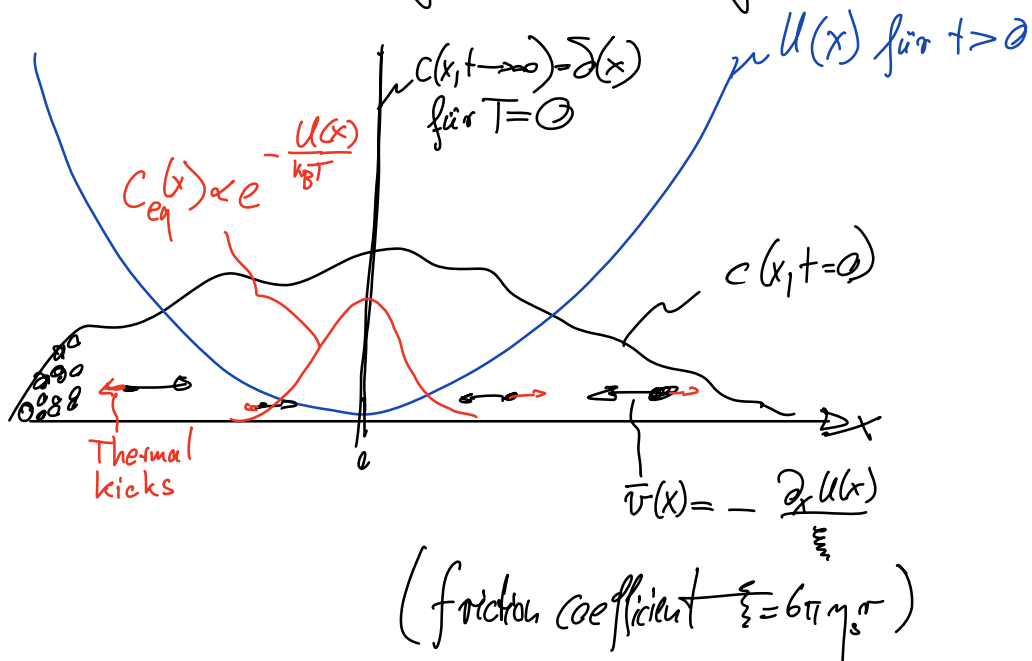


Brownian Motion as a Free Energy minimizing process

Consider a suspension of a large nr of ^{non-interacting} "ideal" beads:



$c(x,t) =$ Particle density @ x, t .

Goal: Construct a phenomenological model

for the dynamics $c(x,t) \rightarrow c_{eq}(t) \sim e^{-\frac{U(x)}{k_B T}}$,

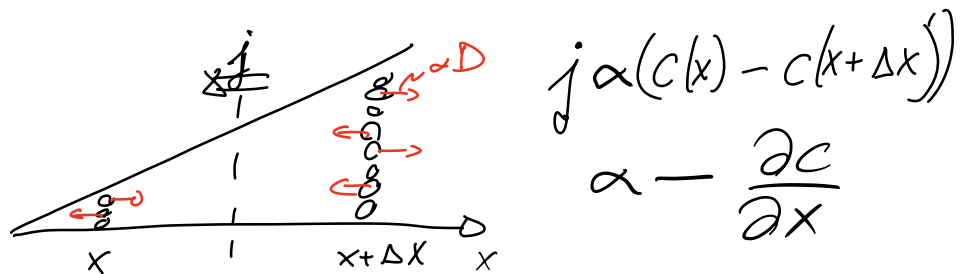
We will see: This Brownian Dynamics continuously lowers the Free Energy.

Dynamics: $\frac{dc(x,t)}{dt} = - \frac{\partial j(x,t)}{\partial x}$ continuity equation
 (represents particle number conservation)

The probability current $j(x,t)$ (=nr of particles passing through x per unit time)
 results from

i) deterministic motion $j_{det} = c \cdot \bar{v} = - \frac{c}{\xi} \partial_x U$

ii) random motion $j_{stoch} = -D \frac{\partial c}{\partial x}$ Fick's law



i)+ii) $\Rightarrow j = c \cdot v_{fl}$ with
 $v_{fl} = - \xi^{-1} \partial_x (U + D \xi \ln(c)) = - \xi^{-1} \partial_x \mu$
 $\equiv \mu(x)$

local chemical potential
 of non-interacting particles.

$$\Rightarrow \frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left(c \frac{\partial \mu}{\partial x} \right) = \frac{\partial}{\partial x} \frac{1}{\xi} \left(D \xi \frac{\partial c}{\partial x} + c \frac{\partial U}{\partial x} \right) \quad (1)$$

with $\mu(x) = k_B T \ln(c) + U$
(see below)

Smoluchowski Equation
(also called Fokker-Planck
or Generalized Diffusion Eq.)

Equilibrium ($t \rightarrow \infty$):

$$\frac{\partial c}{\partial t} = - \partial_x j \rightarrow 0 \quad \text{für } t \rightarrow \infty$$

$$\Rightarrow j = \text{const.} \stackrel{!}{=} 0 \quad (\text{wegen } j(x \rightarrow \pm \infty) = 0)$$

$$= - \frac{c}{\xi} \partial_x \mu \Rightarrow \mu = U + D \xi \ln(c) = \text{const.}$$

$$\Rightarrow c_{eq} \propto \exp\left(-\frac{U(x)}{D \xi}\right) \stackrel{!}{=} \exp\left(-\frac{U(x)}{k_B T}\right)$$

(since it has to be the Boltzmann distribution)

$$\Rightarrow D = \frac{k_B T}{\xi}$$

Stokes-Einstein Relation

velocity fluctuations

dissipation

$$\langle \Delta X^2(t) \rangle = 2 D t$$

Friction coefficient of a ball of radius R : $\xi = 6\pi\eta R$. Typical proteins have $R \approx 2\text{nm}$
 $\Rightarrow D_{\text{protein}} \approx 100 \frac{\mu\text{m}^2}{\text{s}}$
 c.f. bacteria, $D_{\text{bac}} \approx 0.5 \frac{\mu\text{m}^2}{\text{s}}$

Note on eq. (1):

$$j \propto \frac{\partial \mu(x)}{\partial x},$$

where $\mu(x) \equiv U(x) + k_B T \ln(c)$.
This is our good old **chemical potential!**

Thus $j = 0$ if $\mu = \text{const.}$

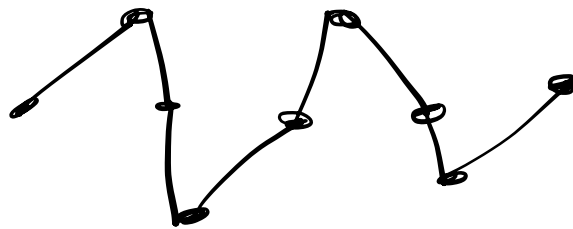
= correct condition
for **thermodynamic
equilibrium.**

This suggests a generalization: Smoluchowski equation.

$$\partial_t \Psi(\{x_i\}) = - \partial_i J_i$$

$$J_i = - \Psi \sum_j H_{ij} F_j \quad F_j = - \partial_j (U + k_B T \ln(\Psi))$$

The Smoluchowski equation is a versatile tool to describe the dynamics of interacting degrees of freedom:



freely jointed chain

= model of a flexible polymer.

Free Energy Minimization:

Proposition: The functional

$$F[C] = \int dx c(x,t) \cdot \mu(x)$$

is monotonously decreasing

time-dependent

free energy:

$$= \langle U \rangle - TS$$

$$S = -k_B \langle \log C \rangle.$$

$$\frac{dF}{dt} = \int dx \left[\mu \frac{\partial c}{\partial t} + c \frac{\partial \mu}{\partial t} \right]$$

(1), partielle tot

$$\stackrel{\geq 0}{=} - \int dx c \underbrace{\left(\frac{\partial \mu}{\partial x} \right)^2}_{\geq 0} + \underbrace{k_B T \int dx \frac{\partial c}{\partial t}}_0 + \underbrace{\text{boundary terms}}_{=0}$$

because: $p \rightarrow 0$ for $x \rightarrow \infty$

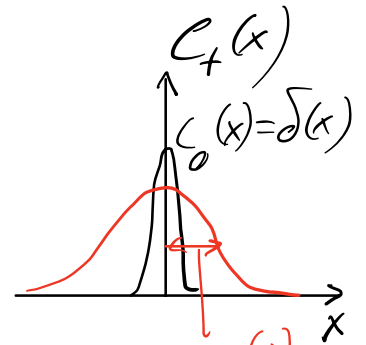
< 0 unless $\mu = \text{const} \Rightarrow C = C_{\text{eq}}$.

Notes:

- Dynamics is time irreversible
due to coarse-graining
(see next lecture)

Basic solution of the diffusion eq. u.:

$$u=0 \Rightarrow \frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2} \quad (1)$$



Assume point-like initial conditions: $c(x,0) = \delta(x)$

$\sigma(t)$,
standard
deviation.

Fourier transform of eq. u (1):

$$c(x,t) = \int_{-\infty}^{\infty} \frac{dq}{2\pi} e^{-iqx} c(q,t)$$

$$\wedge (1) \Rightarrow \frac{\partial c(q,t)}{\partial t} = -Dq^2 c(q,t),$$

Now, this is an ordinary differential eq. u
(in contrast to the partial diff. eq. u. (1).)

The solution is

$$c(q,t) = c(q,0) e^{-Dq^2 t}$$

$c(q,0)$ follows from Fourier transforming (2):

$$c(q,0) = \int_{-\infty}^{\infty} dx e^{iqx} c(x,0)$$
$$= \int_{-\infty}^{\infty} dx e^{iqx} \delta(x) = 1$$

$$\Rightarrow c(q,t) = e^{-Dq^2 t}$$

Fourier back transform:

$$c(x,t) = \int_{-\infty}^{\infty} \frac{dq}{2\pi} c(q,t) e^{-iqx} =$$

$$= \int_{-\infty}^{\infty} \frac{dq}{2\pi} e^{-Dq^2 t - iqx}$$

$$= \int \frac{dq}{2\pi} e^{-\underbrace{\left(\sqrt{Dt}q - \frac{ix}{2\sqrt{Dt}}\right)^2}_{\equiv Q} - \frac{x^2}{4Dt}}$$

$$= e^{-\frac{x^2}{4Dt}} \frac{1}{2\pi\sqrt{Dt}} \underbrace{\int_{-\infty}^{\infty} dQ e^{-Q^2}}_{\sqrt{\pi}}$$

$$\Rightarrow c(x,t) = \frac{e^{-\frac{x^2}{4Dt}}}{\sqrt{4\pi Dt}} = \frac{e^{-\frac{x^2}{2\sigma_t^2}}}{\sqrt{2\pi\sigma_t^2}} \quad (3)$$

$$\text{with } \sigma_t^2 \equiv \langle (x(t) - x(0))^2 \rangle = 2Dt$$

N.B.:

This is a Green's function solution.
The solution to any initial condition
can be found by convolution with (3).

N.B.:

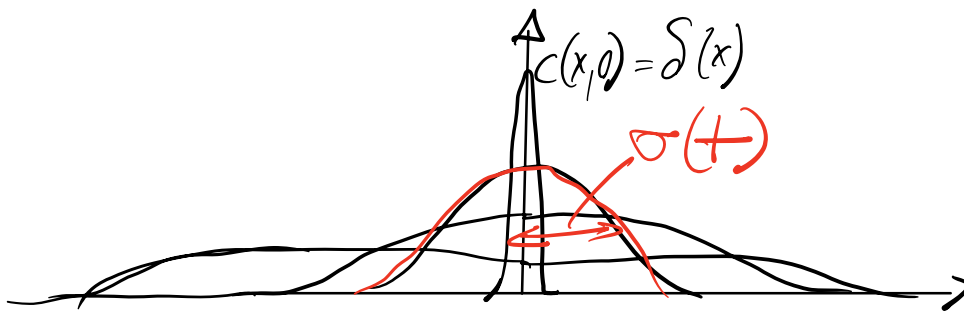
In our examples (so far), all particles
are non-interacting.

$$\Rightarrow c(x,t) = N \cdot p(x,t)$$

with $p(x,t)$ being the probability
of a single particle to be at x,t .

Applications of the Diffusion eqy

Recap: • $D = \text{const}$ || no external force.

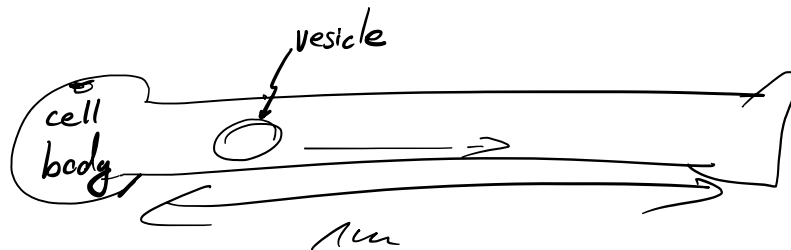


$$c(x,t) = \frac{e^{-\frac{x^2}{4Dt}}}{\sqrt{4\pi Dt}} = \frac{e^{-\frac{x^2}{2\sigma_t^2}}}{\sqrt{2\pi\sigma_t^2}}$$

with $\sigma_t^2 \equiv \langle (x(t) - x(0))^2 \rangle = 2Dt$

Let's put in numbers:

i) Nerve Cell



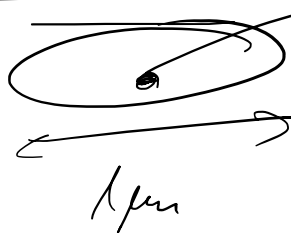
Is diffusion fast enough to transport vesicles?

$$D = 95 \mu\text{m}^2/\text{s} = \frac{kT}{6\pi\eta R}$$

$$\frac{\langle x^2 \rangle}{2D} = t = 12 \text{ days!}$$

⇒ Nerve cells need active transport!

ii) E. coli:



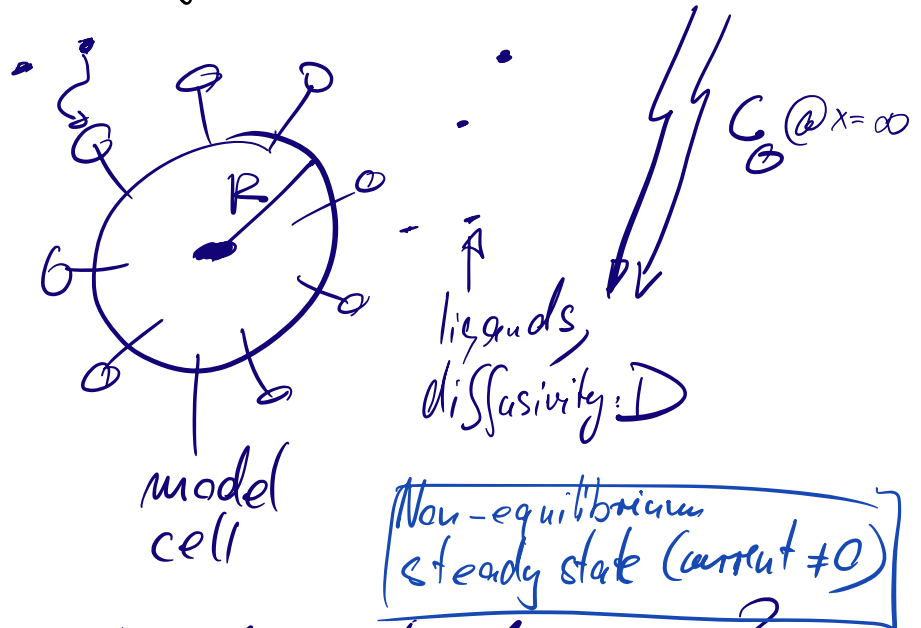
RNAP; $R = 2,5 \mu\text{m}$

$$D \approx 100 \mu\text{m}^2/\text{s}$$

$$t = \frac{R^2}{2D} \approx 2 \text{ ms}$$

⇒ diffusion is fast enough!

Application: Diffusion sets fundamental limits to Rates of biological and chemical reactions.



How many ligands captured per sec?

Use diffusion eqn. to model free ligands: radial dist. from origin.

$$\frac{\partial c}{\partial t} = D \nabla^2 c = D (\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2})$$

$$0 = D \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \frac{\partial c}{\partial r}) ; c = c(r, t)$$

$$\text{ss.} : 0 = \frac{\partial c}{\partial t} \Rightarrow \frac{\partial c}{\partial r} = \frac{\text{const.}}{r^2} \text{ for } r > R$$

$$c(r) = \frac{-A}{r} + B = -\frac{A}{r} + c_0 \Rightarrow c(\infty) = c_0$$

i) Perfect absorber limit: $c_s(R) = 0$.

$$\Rightarrow c_s(r) = c_0 \left(1 - \frac{R}{r}\right).$$

particle current $j(R) = |\vec{j}(\vec{R})| = D \partial_r c(r,t) = \frac{D c_0 R}{R^2}$

$1D: \partial_t c = -\partial_x j(x,t)$	$3D: \partial_t c = -\vec{\nabla} \cdot \vec{j}(\vec{r},t)$
$j(x,t) = -D \partial_x c(x,t)$	$\vec{j}(\vec{r},t) = -D \vec{\nabla} c(\vec{r},t)$

of particles per time per area.

total flux of captured particles

$$\Phi = j(R) \cdot 4\pi R^2 = \frac{4\pi D c_0 R}{\left[\frac{L^2}{s} \cdot \frac{1}{L} \cdot L = \frac{1}{s}\right]}$$

Universal bound on chemical reaction rates

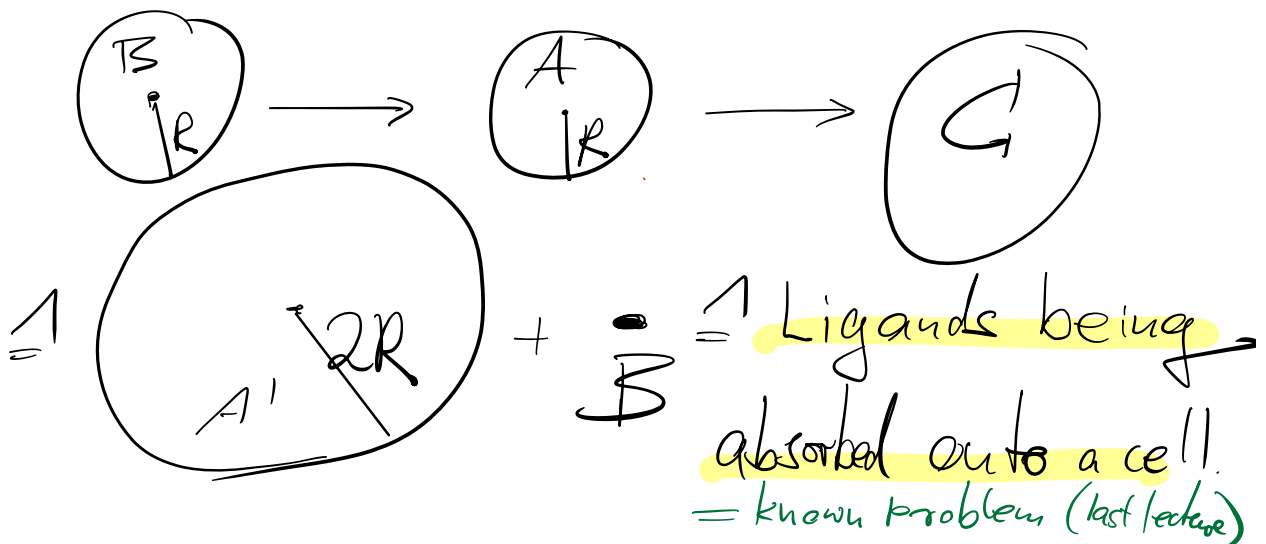
Key question

How fast is $A + B \xrightarrow{k} C$
if it is limited by A-B collision rates?

i.e. each A-B collision leads to one C.

$$\Rightarrow k = c_A \cdot \tilde{\kappa}_{A+B}, \text{ where}$$

where $\tilde{\kappa}_{A+B}$ is the rate at which
a focal A particle is hit by B particles.



Since $x_A - x_B$ diffuses w/ twice the diffusion constant, we have

$$\frac{\# \text{ collisions of B on focal A}}{\text{time}} = 4\pi (2D) (2R) c_B = \tilde{k}_{A+B}$$

$$\Rightarrow \frac{\partial c_c}{\partial t} = k_{\text{diff}} c_A \cdot c_B \quad (1)$$

where

$$k_{\text{diff}} = 16\pi D R = 16\pi R \frac{k_B T}{6\pi\eta R} = \frac{8k_B T}{3\eta}$$
$$\approx 7 \cdot 10^9 \frac{1}{\text{M.S}}$$

Notes:

- Most enzymes are 100-1000 times slower
 \Rightarrow they require more than 1 collisions to form a product.
- ... could be modeled by assuming a finite absorption rate.

- Relation to Michaelis-Menten kinetics :

$$\text{Rate of product formation} = k_{\max} [E] \frac{[S]}{K_M + [S]} \xrightarrow{[S] \rightarrow 0} \underbrace{\frac{k_{\max}}{K_M}}_{\text{enzyme efficiency}} [E][S]$$

compare w/ eq. (1) \Rightarrow

The enzyme "efficiency" is bounded by k_{diff}

$$\left[\frac{k_{\max}}{K_M} \right] = \frac{1}{\text{Concentration} \cdot \text{time}}$$