

The Langevin Equation

$$\frac{dx}{dt} = v$$

$$m \frac{dv}{dt} = -\zeta v + \frac{\partial \phi}{\partial x} + f_B(t)$$

← 'Brownian force'

↑ viscous drag force

← force of external potential

↑ inertia
 ↓ small

$$\zeta \frac{dx}{dt} = -\frac{\partial \phi(x,t)}{\partial x} + f_B(t)$$

Numerical solution of Langevin Eq.

We want to generate sample trajectories according to Langevin Eq.

$$\int_t^{t+\Delta t} dt'$$

$$x(t+\Delta t) = x(t) - \frac{1}{\zeta} \int_t^{t+\Delta t} \frac{\partial \phi(x,t')}{\partial x} dt' + \frac{1}{\zeta} \int_t^{t+\Delta t} f_B(t') dt'$$

$$\approx x(t) - \frac{1}{\zeta} \frac{\partial \phi(x,t)}{\partial x} \Delta t + \frac{1}{\zeta} \int_t^{t+\Delta t} f_B(t') dt'$$

We need statistical properties of f_B . As it includes effect of many protein-water interactions, central limit theorem applies as $f_B(t)$ is normally distributed

$$\langle f_B(t) \rangle = 0 \text{ to avoid drift}$$

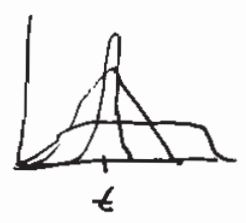
$$\langle f_B(t) f_B(s) \rangle = 2k_B T \zeta \delta(t-s)$$

When $\phi=0$ we shall recover ^{compare with} diffusion motion
 $\text{Var}[x(t)] = \langle x(t)^2 \rangle = 2Dt$, and

$$D = \frac{k_B T}{\zeta} \text{ [Einstein Relation]}$$

$$\delta(t-s) = \lim_{\sigma \rightarrow 0} \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{(t-s)^2}{2\sigma^2}\right]$$

Gaussian white noise



if $\mu=0$; $x(0)=0$

$$x(t) = \frac{1}{\gamma} \int_0^t f_B(t') dt'$$

$$\langle x(t) \rangle = \left\langle \frac{1}{\gamma} \int_0^t f_B(t') dt' \right\rangle = \frac{1}{\gamma} \int_0^t \langle f_B(t') \rangle dt' = 0$$

$$\begin{aligned} \text{cov}[x(t), x(s)] &= \frac{1}{\gamma^2} \left\langle \left(\int_0^t f_B(t') dt' \right) \left(\int_0^s f_B(t'') dt'' \right) \right\rangle \\ &= \int_0^t \int_0^s \langle f_B(t') f_B(t'') \rangle dt' dt'' = \\ &= \int_0^t \int_0^s 2D \delta(t'-t'') dt' dt'' = 2Ds \end{aligned}$$

Consistent with

$$\text{Var}[x(t)] = \langle x(t)^2 \rangle = 2Dt$$

Weiner process

So, $f_B(t)$ is normally distributed.

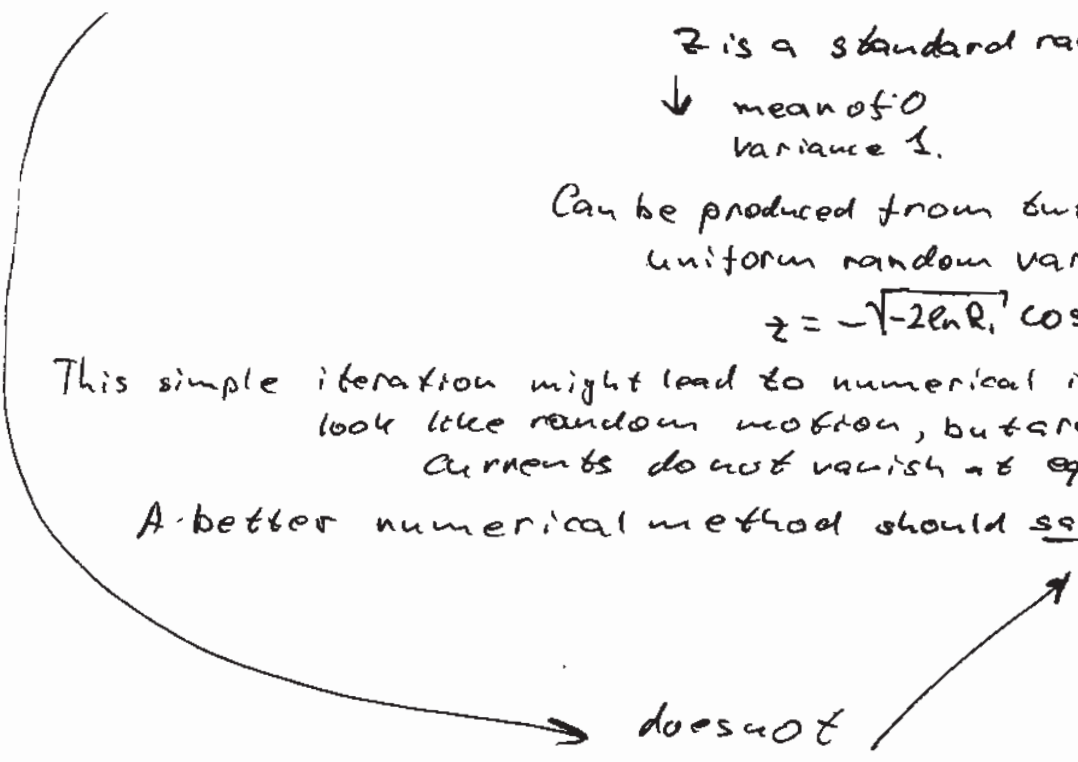
$$x(t+\Delta t) \approx x(t) - \frac{1}{\gamma} \frac{\partial \Phi}{\partial x} \Delta t + \sqrt{2D\Delta t} \cdot z, \text{ where}$$

z is a standard random variable
↓ mean of 0
variance 1.

Can be produced from two independent uniform random variables R_1, R_2 as
 $z = -\sqrt{-2\ln R_1} \cos(2\pi R_2)$

This simple iteration might lead to numerical instabilities that look like random motion, but are not, as the currents do not vanish at equilibrium.

A better numerical method should satisfy detailed balance



does not

The Smoluchowski model

Stochastic motion: trajectories look random.

Difficult to distinguish stochastic fluctuations from deterministic motion.

Average "drift" velocity \bar{v} makes sense to look at.

Imaging a large collection of ^{independent} particles moving together.

Concentration at x and t : $c(x, t)$

particles will diffuse and drift

Flux of particles passing through unit area, J [# / area / time]

Diffusion:

$$J_x = -D \frac{\partial c}{\partial x}, \quad F = -\frac{\partial \psi}{\partial x} \rightarrow \text{drift velocity } v = \frac{F}{\zeta}$$

Fick's law

$$J_x = -D \frac{\partial c}{\partial x} + v \cdot c$$

$$\text{Drift velocity } \rightarrow \frac{F}{\zeta} \cdot c = -\frac{D}{k_B T} \frac{\partial \psi}{\partial x} \cdot c$$

$$J_x = \underbrace{-D \frac{\partial c}{\partial x}}_{\text{Diffusion flux}} - \underbrace{\left(\frac{D}{k_B T} \frac{\partial \psi}{\partial x} \right) \cdot c}_{\text{Drift flux}} = -D \left(\frac{\partial c}{\partial x} + \frac{\partial (\psi / k_B T)}{\partial x} \cdot c \right)$$

$$= -\frac{1}{\zeta} \left(k_B T \frac{\partial c}{\partial x} + c \frac{\partial \psi}{\partial x} \right)$$

$$\text{At equilibrium, } J = 0: \frac{k_B T}{c_{eq}} \frac{\partial c_{eq}}{\partial x} + \frac{\partial \psi}{\partial x} = 0$$

$$\text{Integration over } x \Rightarrow c_{eq} = c_0 e^{-\psi / k_B T} \quad \leftarrow \text{Boltzmann distribution}$$

The number of particles is constant, $c(x, t)$ must obey a conservation law:

$$\frac{\partial}{\partial t} (c \cdot \Delta x) = \text{Net Flux into } \Delta x = J_x(\text{in}) - J_x(\text{out}) = J_x(x) - J_x(x+\Delta x)$$

$$\frac{\partial c}{\partial t} = -\frac{\partial J_x}{\partial x} \quad [\text{conservation of particles}]$$

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probability of finding a single particle at $x(t)$:
 normalize the concentration by dividing over
 total population.

$$p(x,t) \equiv c(x,t) / \left(\int_0^L c(x,t) dx \right)$$

Smoluchowski Eq.:

$$\frac{\partial p}{\partial t} = D \left[\underbrace{\frac{\partial}{\partial x} \left(p \frac{\partial (\varphi/k_B T)}{\partial x} \right)}_{\text{drift}} + \underbrace{\frac{\partial^2 p}{\partial x^2}}_{\text{diffusion}} \right]$$

compare with:

$$\zeta \frac{dx}{dt} = - \frac{\partial \varphi(x,t)}{\partial x} + \eta(t) \quad [\text{Langevin}]$$

nondimensionalize: $0 \leq x \leq L \rightarrow$ domain size
 $x \rightarrow \frac{x}{L}$

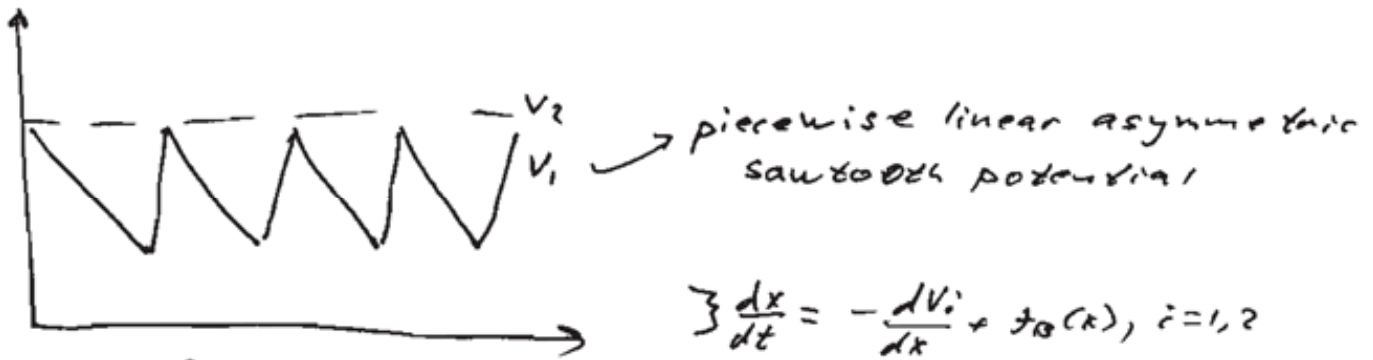
$$\tau = \frac{L^2}{D} \quad \text{timescale}$$

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} \left(p \frac{\partial \varphi}{\partial x} \right) + \frac{\partial^2 p}{\partial x^2} \quad \varphi \text{ is in } k_B T \text{ units.}$$

Boundary conditions

$p(x=0,t)$, $p(x=L,t)$, $p(x,t=0)$, where p is defined
 on $[0,L]$.

Flashing Ratchets



Switching of the potential is governed by chemical reaction.

$$\left\{ \frac{dx}{dt} = -\frac{dV_i}{dx} + f_0(x), i=1,2 \right.$$

Maximum mean velocity for smooth asymmetric potential $\delta U \sim k_B T$ is when $kn \sim D/L^2 \Rightarrow \langle v \rangle \sim \frac{Lk}{4}$

In general case, average velocity can be computed numerically:

$$\frac{\partial P_i}{\partial t} = D \frac{\partial}{\partial x} \left[\frac{\partial P_i}{\partial x} + \frac{\partial V_i / \partial x}{k_B T} P_i \right] + k(-P_i + P_j), i=1,2, j \neq i$$

← symmetric flux

0 ————— L ; periodic boundary conditions
 $P(0, x) = P(L, x)$

normalization

$$\int_0^L [P_1(x, t=0) + P_2(x, t=0)] dx = 1$$

When P reaches a steady state, the net current is:

$$J = -D \left[\frac{\partial (P_1 + P_2)}{\partial x} + \frac{\partial V_1 / \partial x}{k_B T} P_2 \right] \quad J = J_1 + J_2$$

average velocity $\langle v \rangle = LJ$

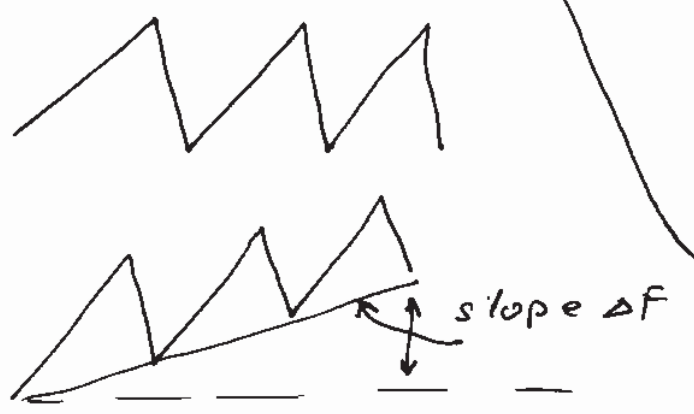
Energy is consumed by chemical reaction.

Can apply a load \rightarrow this is a molecular motor.
 (but not realized in biology)

~~Sep 2010~~

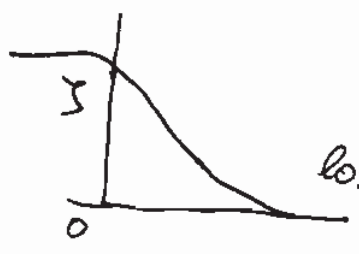
Other Ratchets!

Fluctuating force



$$\frac{\partial}{\partial x} U(x,t) = \frac{\partial}{\partial x} U(x) + \Delta F(t)$$

↑
Markovian
kinetics

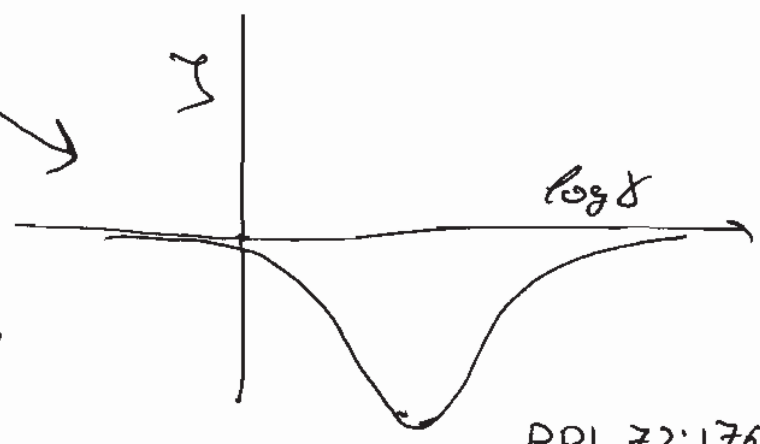


log δ → flipping
rate



⊗ Fluctuating barrier

$$\frac{\partial}{\partial x} U(x,t) = \frac{\partial}{\partial x} [U(x) + \alpha U(x,t)]$$



J → 0, δ → ∞

at ~~δ=0~~, Different signs
at

PRL 72:1766

Can be realized in Practice

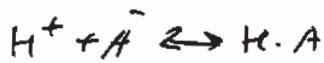
Science 276:917

Chemical reactions

Two common energy sources:

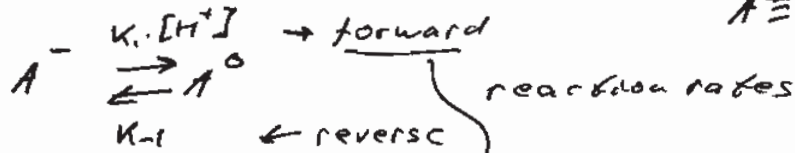
ATP hydrolysis and transmembrane proton-motive force.

Simplest model: binding of H^+ to negatively charged amino acid



Amino acid exists in two states: A^- (charged)

$A^0 \equiv A.H$ (neutral)



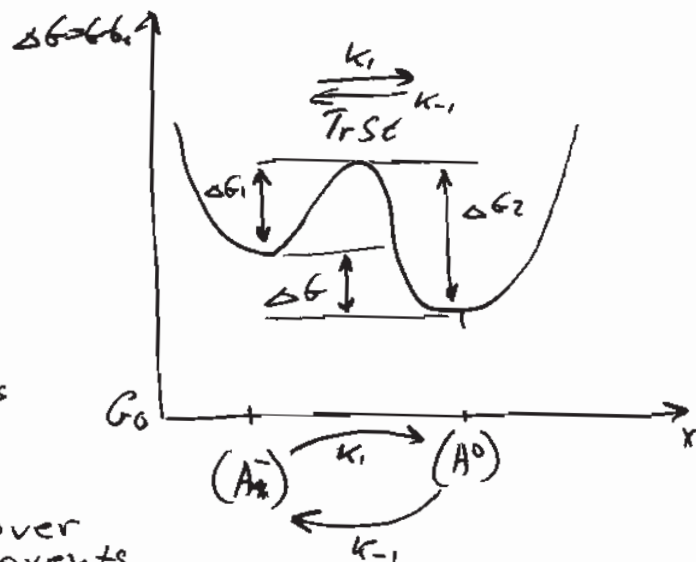
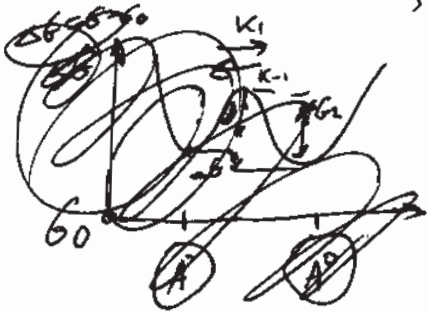
depends on ion concentration

$k_1 [H^+] \equiv k_1^*$ (pseudo-first order rate constant)

Reaction is usually a fast process and results in ~~the~~ redistribution of the electrons.

Reaction coordinate \rightarrow fundamental concept of modeling chemical reactions. 1D path through high-dimension state space system moves from reactants to products.

For our reaction, $\gamma(A)$ can be a distance between (H^+) and (A^-)



For fixed $[H^+]$

forward reaction proceeds with a rate $k_1^* [A^-]$

Average over many events.

For example, a proton diffuses to amino acid inside a protein - electrostatics is

As $[H^+]$ increases, more "tries" happen.

$A^- \leftarrow A^0$ kinetic energy must overcome electrostatic attraction
 only when completely escapes to the left well
 it counts as k_{-1}

The net flux:

$$J_z = k_1[A^-] - k_{-1}[A^0]$$

Eventually, $J_z = 0$
 $K_{eq} = \frac{[A^0_{eq}]}{[A^-_{eq}]} = \frac{k_1}{k_{-1}}$
 K_{eq} - equilibrium constant

$K_{eq} = \exp(\Delta G/k_B T)$
 specifies how far the reaction goes, but not the rate of the reaction.

$$\Delta G = \Delta H - T\Delta S$$

electrostatic attraction between (A^-) and (H^+)
 $T\Delta S$ "hidden coordinates", influence how (H^+) diffuses in and escapes.

The rate of jumping from right to left is

$$k_{-1} = v \cdot \exp(-\Delta G_2/k_B T) =$$

$$= v \cdot \underbrace{\exp(\Delta S/k_B)}_{\text{entropic term accounts for geometric and "hidden" effects}} \cdot \underbrace{\exp(-\Delta H/k_B T)}_{\text{enthalpic term is a free energy payoff for a successful jump}} \cdot \underbrace{\exp(-\Delta F_L/k_B T)}_{\text{If reaction involves mechanical stepping by the load force } F_L \text{ penalty for performing work against the load.}}_{\text{Power stroke}}$$

attempt frequency factor
 Diffusion controlled reaction $\sim D/L^2$

ΔG_2 determines the reaction rate
bimol $\sim \exp(\Delta G_0/k_B T) \rightarrow$ Arrhenius factor

All "hidden" factors are incorporated in the rate, so

9)

$$\frac{d[A^{\circ}]}{dt} = -\frac{d[A^{-}]}{dt} = \text{net flow over the energy barrier} =$$

$$= J_{\uparrow} = k_1^*[A^{-}] - k_{-1}[A^{\circ}]$$

if P_{-} and P_{\circ} are the probabilities to have (A^{-}) or (A°) state,

$$\frac{d\vec{P}}{dt} = \vec{J}_{\uparrow} = \vec{K} \vec{P}, \text{ where } \vec{P} = \begin{pmatrix} P_{-} \\ P_{\circ} \end{pmatrix}; \vec{K} = \begin{pmatrix} k_1^* - k_{-1} \\ -k_1^* \quad k_1 \end{pmatrix}$$

In general, $J_{\uparrow} = k(P) \cdot P$
 ↓ matrix of transition rates, which can contain reactant concentrations.

- Assumptions:
- ① Reaction is instantaneous
 - ② transition out of a state depends only on the state itself, not history.

Mechanochemical Model

Potential $\Phi(x,t)$ includes internal and external forces:

$$\Phi(x,t) = \Phi_I(x,t) + \Phi_L(x,t)$$

Internally generated forces External load forces.

will depend on the chemical state of the system!
 ↓
Typically F_L is a constant force
 $\Phi_L = F_L \cdot x; \frac{\partial \Phi}{\partial x} = -F_L$
 ↑
 act opposite to the motor progress

Each chemical state ~~is~~ is characterized by its own probability distribution $P_k(x,t)$,
 k ranges over all the chemical states
 x -coordinate, t → time.

Each chemical state will have a separate potential $\Phi_k(x,t)$.

Smoluchowski equation for each chemical state!
 Must be solved simultaneously.

For the neutralization reaction:

$$\frac{\partial}{\partial t} \begin{pmatrix} P_1 \\ P_2 \end{pmatrix} = \text{Net flow in space} + \text{Net flow along reaction coordinate}$$

$$= - \overbrace{\begin{pmatrix} \left(\frac{\partial}{\partial x_1} \right) J_{x_1} \\ \left(\frac{\partial}{\partial x_2} \right) J_{x_2} \end{pmatrix}}^0 + \overbrace{\begin{pmatrix} J_{\xi} \\ J_{\xi_2} \end{pmatrix}}^0$$

$$= -D \left\{ \begin{array}{l} -\frac{\partial}{\partial x_1} \left[P_1 \frac{\partial (P_1/k_B T)}{\partial x_1} + \frac{\partial P_1}{\partial x_1} \right] \\ -\frac{\partial}{\partial x_2} \left[P_2 \frac{\partial (P_2/k_B T)}{\partial x_2} + \frac{\partial P_2}{\partial x_2} \right] \end{array} \right\} + \begin{pmatrix} \kappa_{-1} P_2 - \kappa_{1*} P_1 \\ \kappa_{*} P_1 - \kappa_{-1} P_2 \end{pmatrix}$$

$P_i(x_i, t)$, $i=1,2$ keep track of the motion along the spatial and reaction coordinates; $J_{\xi_1} = -J_{\xi_2}$ flux ~~at~~ along the reaction coordinate

Potential energy surface of a molecular motor

Potential of mean force:

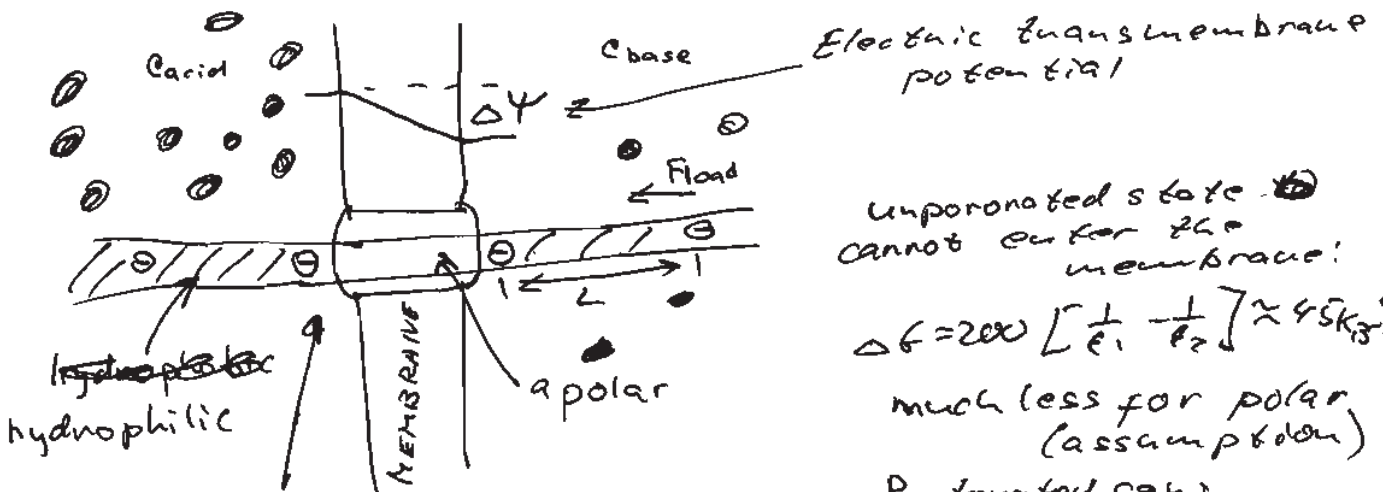
- ① interactions within the motor, and between the motor and its track
- ② Interaction between the motor and fuel molecules
- ③ interaction of all the above with solvent.

Source of energy is chemistry, PMF surface MUST have at least one ~~at~~ reaction coordinate. other - mechanical variables.

Rate constants!

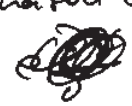
- 1) Some rate constants depend on the spatial location of the motor, external load.
- 2) Two intermediates can be connected by more than one pathway

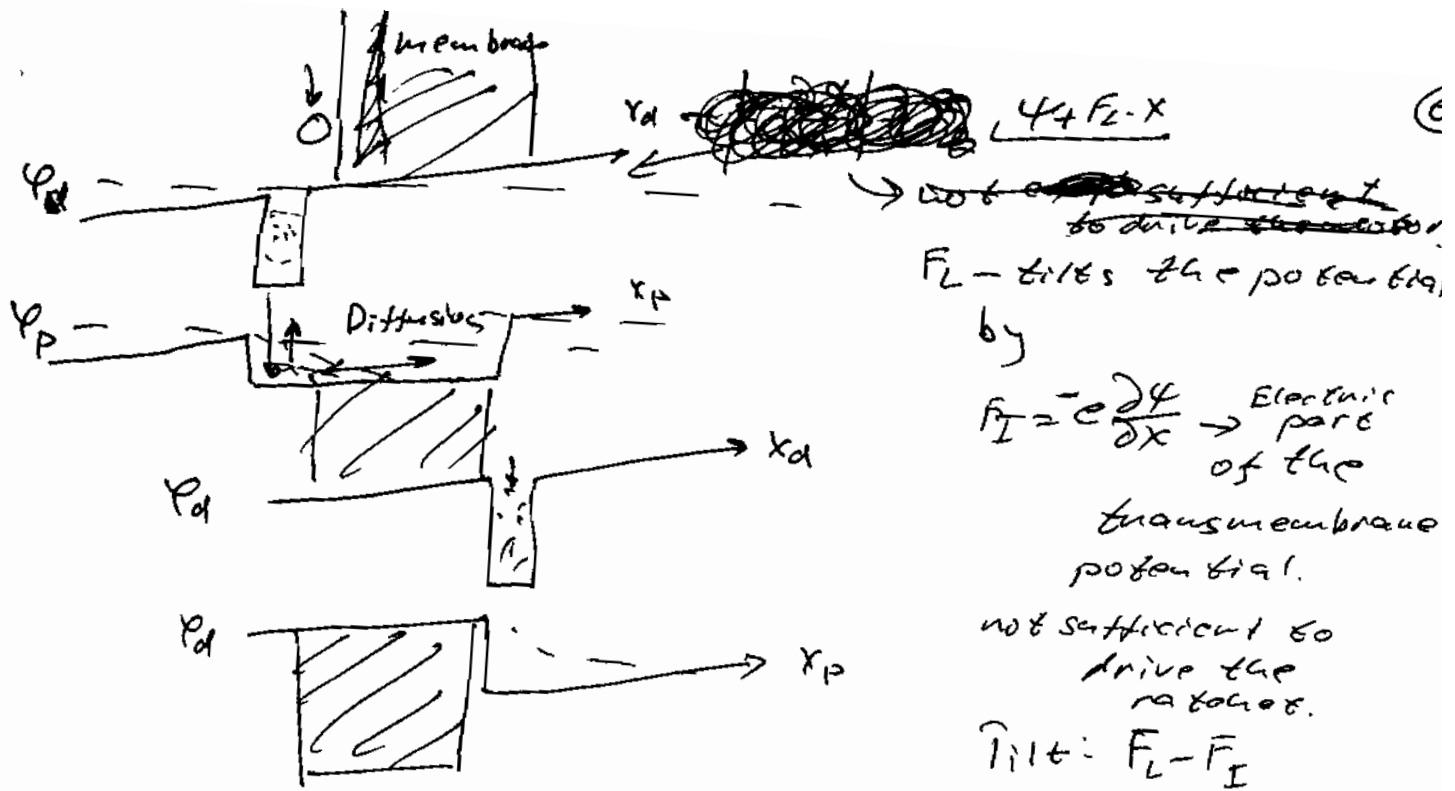
Simple Molecular Motor



unprotonated state ~~⊕~~
 cannot enter the membrane!
 $\Delta G = 200 \left[\frac{1}{\epsilon_1} - \frac{1}{\epsilon_2} \right] \approx 45 k_B T$
 much less for polar (assumption)
 Protonated can!

Enough to look just at one side.
 Deprot. \Rightarrow no motion
 Prot \Rightarrow motion





Limit of fast diffusion

$P_d(t)$ - probability ~~density~~ of the deprotonated state
 → [non-dimensional]

$P_p(x, t)$ [1/nm], $0 \leq x \leq L$ - distance between the protonation sites

$$\frac{dP_d}{dt} = \text{Net deprotonated spatial flux} + \text{Net reaction flux} = J_{x_d} + J_R \leftarrow \text{same (*)}$$

$$\frac{dP_p}{dt} = \text{Net protonated spatial flux} - \text{Net reaction flux} = J_{x_p} - J_R \leftarrow \text{same (*)}$$

$$J_{x_d} = 0 \text{ (cannot move deprotonated)}$$

$$J_{x_p} = D \frac{\partial}{\partial x} \left(\frac{\partial P_p}{\partial x} - \frac{F_I - F_L}{k_B T} P_p \right), \quad J_{x_p}(0) = J_{x_p}(L) = 0$$

\uparrow
 external potential

(7)

J_R = deprotonation at acidic reservoir
 + deprotonation at basic reservoirs
 - net protonation at both reservoirs

$$= k_a P_p(0) + k_a P_p(L) - \bar{k}_p P_d$$

Net protonation: $\bar{k}_p = k_a c^{acid} + k_a c^{base}$

Non-dimensionalize:

$$(x/L) \rightarrow x$$

$$(k_a t/L) \rightarrow t$$

$$\Lambda = D/k_a L \leftarrow \text{Ratio of reaction to diffusion time scales.}$$

Δ net work moving the motor distance L

$$W = \frac{(F_2 - F_1)L}{k_B T}$$

Equilibrium constant $\alpha = \bar{k}_p L / k_d$

$$F_I = e \Delta \psi / L \leftarrow \text{assumed to be constant.}$$

$$\frac{dP_d}{dt} = -\alpha P_d + P_p(0) + P_p(L)$$

$$\frac{dP_p}{dt} = \alpha P_d - P_p(0) - P_p(L) + \Lambda \frac{\partial}{\partial x} \left(\frac{\partial P_p}{\partial x} - w P_p \right)$$

Reaction limited: $\Lambda \gg 1$

~~Steady state distribution $P(x)$:~~

~~$$\frac{d}{dx} (w P) = 0$$~~

~~$$P(x) = \frac{w}{c^{acid}} e^{-wx} + \frac{w}{c^{base}} e^{-w(L-x)}$$~~

$$\langle U \rangle(F_2) = \frac{k_p k_a L w (c^{acid} e^{-w} - c^{base})}{(e^w - 1) k_p L (c^{acid} + c^{base}) + k_d w (e^w + 1)}$$

$$F_2 = F_1 + \frac{k_B T}{L} \ln \left[\frac{c^{acid}}{c^{base}} \right] \Rightarrow F_2 \cdot L = e \Delta \psi - 2.3 k_B T \Delta pH$$