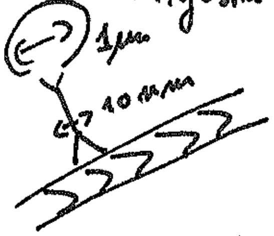
Chapter VI Molecular motors

I) Introduction

Molecular motors are protein capable of exerting a non-zero average work.

E.g. - kinesin & dynein transport vesicles along microtubules

- Myosin exert forces on actin filaments.

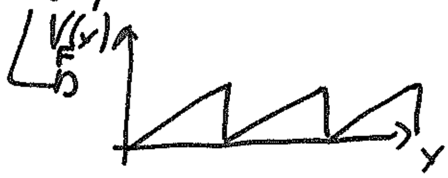


How is it possible? At this scale, temperature equilibrates in μs ⇒ isothermal motor.

① Spatial symmetry broken because fibres are polar.

If equilibrium $P \propto e^{-\beta V(x)}$

$J(x) = T\partial_x P + V' P = 0$ → no motion



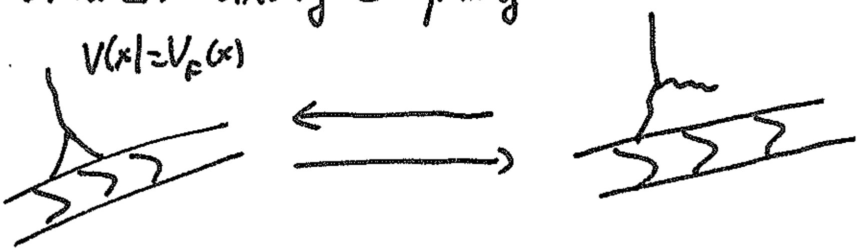
② Two-state model breaks detailed-balance

State 1: strong coupling

$V(x) = V_F(x)$

State 2: weak coupling

$V(x) \simeq 0$



In each state, the dynamics would relax to $e^{-\beta V(x)}$ and hence leads to vanishing current, but the transitions between the states prevent that. Q: how?

II Model and dynamics

Brownian dynamics in each state. Rates ω_1 and ω_2 at which the motor goes from $1 \to 2$ and from $2 \to 1$.

$P_i(x,t)$: the proba to find the system in i at time t.

$$P_1(x,t+dt) = \int dy\, P_1(y,t)\, P(1,x,t+dt|1,y,t) + \int dy\, P_2(y,t)\, P(1,x,t+dt|2,y,t)$$

states

At linear order in dt, only 1 state change is possible, with proba $\omega_i dt$ (n state-change occur with proba $\sim dt^n$)

① $P(1,x,t+dt|1,y,t) = $ (proba to stay in 1) $\times$ (proba to go from y to x in dt)

$$= (\underbrace{1-\omega_1(y)dt + O(dt^2)}_{\text{because } x-y \sim dt^\alpha})\ \underbrace{P_1(x,t+dt|y,t)}_{P_1(x,t|y,t)+dt\,\partial_t P(x,t|y,t)}$$

$$\simeq (1-dt\,H^1_{FP})\,\delta(x-y)$$

Fokker-Planck operator in state 1.

$$P(1,x,t+dt|1,y,t) \simeq (1-\omega_1(y)dt - dt H^1_{FP})\,\delta(x-y)$$

$$\int \text{——}\ P_1(y,t)\,dy \simeq (1-\omega_1(x)dt - H^1_{FP}\,dt)\,P_1(x,t)$$

② $P(1,x,t+dt|2,y,t) = $ (proba $2\to 1$) $\times$ (proba $y \to x$)

$$\simeq \omega_2(y)\,dt\,(1-dt\,H^i_{FP})\,\delta(x-y) \simeq \omega_2(y)\,dt\,\delta(x-y)$$

All in all

$$P_1(x,t+dt) = P_1(x,t) - dt\left(H^1_{FP}+\omega_1(x)\right)P_1 + \omega_2\,dt\,P_2(x,t)$$

$$\Rightarrow \quad \partial_t P_1(x,t) = -H^1_{FP}\,P_1(x,t) - \omega_1(x)\,P_1(x,t) + \omega_2(x)\,P_2(x,t)$$

$$\partial_t P_2(x,t) = -H^2_{FP}\,P_2(x,t) + \omega_1(x)\,P_1(x,t) - \omega_2(x)\,P_2(x,t)$$

rate of change of the proba to be in (i,x) at t

$\underbrace{-\nabla\cdot J_i}_{\text{dynamics in state } i}$

loss/gain due to hop from 1 to 2

gain/loss due to hops from 2 to 1.

Switching rates $\omega_i(x)$

Forget space and focus on $\underset{V_1(x)}{\text{State } 1} \underset{\omega_2(x)}{\overset{\omega_1(x)}{\rightleftarrows}} \underset{V_2(x)}{\text{State } 2}$

Dynamics $\partial_t P_1 = -\omega_1 P_1 + \omega_2 P_2$; $\partial_t P_2 = -\omega_2 P_2 + \omega_1 P_1$

Steady-state $\omega_1 P_1 = \omega_2 P_2$

① Thermally activated switch $\left.\begin{array}{l} \omega_1^{th}(x) = \omega(x) e^{\beta V_1(x)} \\ \omega_2^{th}(x) = \omega(x) e^{\beta V_2(x)} \end{array}\right\} \xrightarrow{\text{steady}}_{\text{state}} P_i(x) = \frac{1}{Z_i} e^{-\beta V_i(x)}$

② Chemically activated switch $(1), ATP \leftrightarrow (2), ADP + P$

$\cancel{\omega_1^{ch} = \gamma(x)\omega_1^{th}(x) e^{\beta(\mu_{ADP}-\mu_{ATP}^{EQ})}}$

$\omega_1^{ch} = \gamma(x)\,\omega_1^{th}(x)\, e^{\beta\Delta\mu_{ATP}}$; $\omega_2^{ch} = \gamma(x)\,\omega_1^{th}(x)\, e^{\beta \Delta\mu_{ADP} + \Delta\mu_P}$; $\Delta\mu_i = \mu_i - \mu_i^{eq.}$

$\mu_i = \mu_i^{sd} + \ln[i]$

Excess of ATP favors $1 \to 2$

——— ADP or P — $2 \to 1$

If $\Delta\mu_{ATP} \neq \Delta\mu_{ADP} + \Delta\mu_P$ then $\frac{\omega_1^{ch}}{\omega_2^{ch}} \neq \frac{\omega_1^{th}}{\omega_2^{th}} \Rightarrow$ competing steady-states

$\to$ out of equilibrium

③ In practice: both processes $\omega_i(x) = \omega_i^{th}(x) + \omega_i^{ch}(x)$

The Brownian dynamics in state (i) makes $P_i(x,t)$ relax to $e^{-\beta V_i(x)}$ with $J_i = 0$

$\to$ compatible with ω_i^{th} but not with ω_i^{ch} if one species is in excess

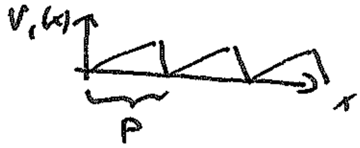
Comment: as time goes on, $[ATP] \to [ATP]^{eq}$ and the system relaxes to equilibrium

$\Rightarrow$ need to maintain $\Delta\mu_i \neq 0$ (food, breath, mitochondria, etc.)

Conclusion: $\Delta\mu_i \neq 0$ drives the system out of equilibrium $\Rightarrow$ is there a current?

III A simple example [Jülicher, Ajdari, Prost; RMP 69, 1269 (1997)]

$V_2 = 0$, ω_1 & ω_2 constant, $V_1(x)$ periodic with period p



Dynamics: $\partial_t P_1(x,t) = \frac{\partial}{\partial x}\left[T\frac{\partial}{\partial x} + V_1'(x)\right]P_1 - \omega_1 P_1(x) + \omega_2 P_2(x)$

$$\partial_t P_2(x,t) = \frac{\partial}{\partial x}\left[T\frac{\partial}{\partial x} \cancel{+V_2'}\right]P_2 + \omega_1 P_1(x) - \omega_2 P_2(x)$$

$P_{tot}(x) = P_1(x) + P_2(x)$

$$\partial_t P_{tot}(x) = T\partial_{xx}P_{tot} + \partial_x\left[V_1'(x)P_1(x)\right] = T\partial_{xx}P_{tot} + \partial_x\left[V_{eff}'(x)P_{tot}(x)\right]$$

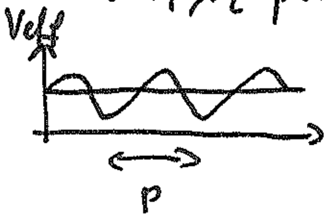
where $V_{eff}'(x) = \lambda(x)V_1'(x)$, with $\lambda(x) = \dfrac{P_1(x)}{P_{tot}(x)}$

Brownian dynamics in an effective potential $V_{eff}(x) = V_{eff}(0) + \int_0^x du\, \lambda(u)V_1'(u)$

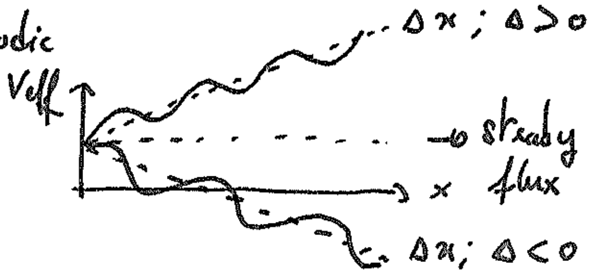
let $\Delta = \int_0^p dx\, \lambda(x)V_1'(x)$

V_1, V_2 periodic $\Rightarrow P_1, P_2$ periodic $\Rightarrow \lambda(x)$ periodic

If $\Delta = 0$



If $\Delta \neq 0$



What is the condition for $\Delta = 0$?

→ If $V_1(x) = V_1(-x) \Rightarrow P_1, P_2$ even $\Rightarrow \lambda(x) = \lambda(-x)$
$\Rightarrow V_1'(x)$ odd
$\Big\}$ $\lambda(x)V_1'(x)$ odd $\Rightarrow \Delta = 0$

→ Otherwise, $\Delta \neq 0$ generically $\Rightarrow$ current.

Comment: $\partial_t P_1 = T\partial_{xx}P_1 + \partial_x(V_1'P_1)$ satisfies DB with respect to $P \propto e^{-\beta V_1}$

$\partial_t P_2 = T\partial_{xx}P_2$ ——— $P \propto$ Constant

$\partial_t P_i = -\omega_i P_i + \omega_j P_j$ ——— $\dfrac{P_i}{P_j} = \dfrac{\omega_j}{\omega_i}$

All together → the competition between the $\neq$ steady-state drives the system out of equilibrium.

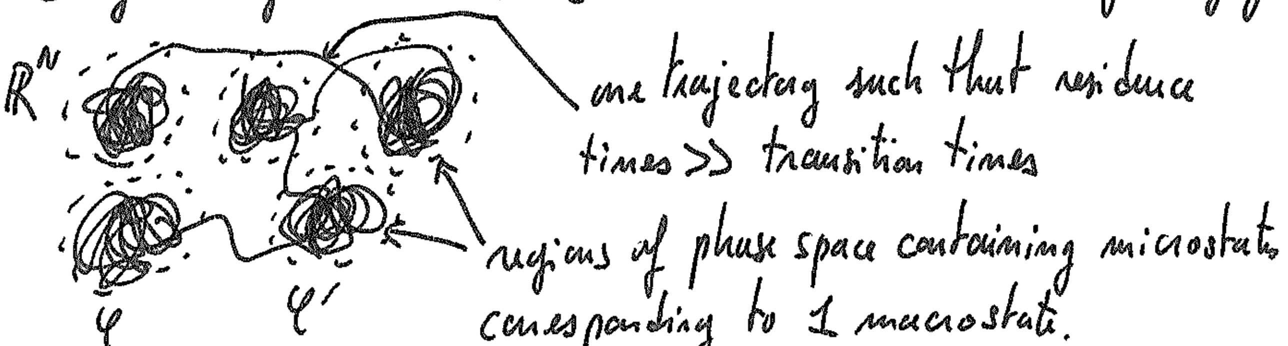
IV Collective behaviours of molecular motors

1 motor = 1 ratchet

N motors = N coupled ratchets $\Rightarrow$ horribly complicated...

Idea: coarse-graining the many microstates describing one motor bound to a given site into one macrostate.
All the trajectories leading to the next site then yield one transition rate.

Langevin dynamics in $\mathbb{R}^N \Rightarrow$ Markov chain on a set of configurations.



$$\int_{\varphi} dx_i \int_{\varphi'} dx_j \; P(x_i, t+dt \,|\, x_j, t) \equiv \underbrace{W(\varphi' \to \varphi)}_{\text{transition rate}} dt$$

Comment: in practice the projection from $\mathbb{R}^N$ to $\{\varphi\}$ is very difficult.

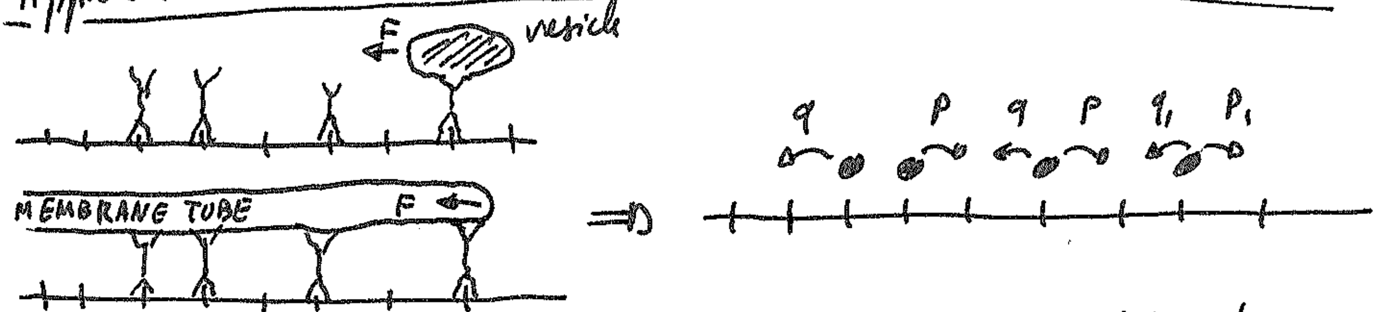
Model: Set of configurations $\{\varphi\}$ and transition rates between them.

$$P(\varphi, t+dt) = P(\varphi, t) \times (\text{proba to stay in } \varphi \text{ in } [t, t+dt]) + \sum_{\varphi' \neq \varphi} P(\varphi', t) \times (\text{proba to go from } \varphi' \text{ to } \varphi)$$

$$= P(\varphi, t) \times \Big(1 - \sum_{\varphi' \neq \varphi} W(\varphi \to \varphi') dt\Big) + \sum_{\varphi' \neq \varphi} P(\varphi', t)\, W(\varphi' \to \varphi) dt + O(dt^2)$$

Master equation: $\boxed{\partial_t P(\varphi) = \sum_{\varphi' \neq \varphi} W(\varphi' \to \varphi) P(\varphi', t) - \sum_{\varphi' \neq \varphi} W(\varphi \to \varphi') P(\varphi)}$

Application to molecular motors: the asymmetric simple exclusion process (ASEP)

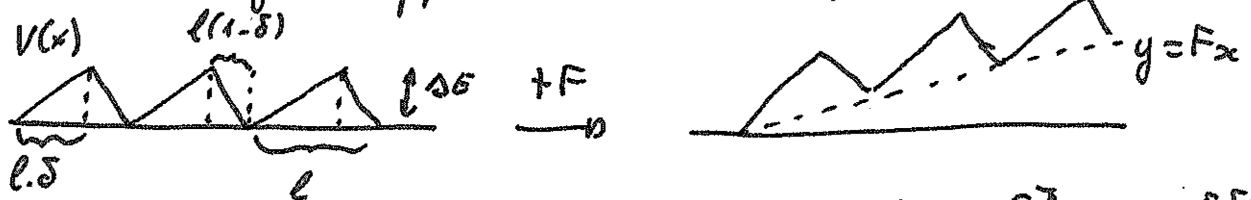


[MacDonald, Gibbs, Dipkin, Biopolymers 6, 1-25, 1968] to model ribosomes along DNA.

Particles hop at constant rates onto free sites.

How to model the force applied to the first motor?

Ratchet



Energy barrier ΔE: forward $p \propto e^{-\beta\Delta E} \Rightarrow p_1 \propto e^{-\beta[\Delta E + F.\delta\ell]} = p e^{-\beta F\delta\ell}$

backward $q \propto e^{-\beta\Delta E} \Rightarrow q_1 \propto e^{-\beta[\Delta E - F(1-\delta)\ell]} = q e^{+(1-\delta)\beta F\ell}$

Too many letters $\Rightarrow$ units such that $\beta F\ell = f$.

IV.1 Isolated motor and stall force

On average, p_1 jumps to the right per unit of time
q_1 ——— left ——— } average speed $v^{(1)} = p_1 - q_1$

Simple proof: $i(t)$ position of the motor at time t.

$\langle i(t)\rangle = \sum_j j\, P(i(t)=j) \Rightarrow \partial_t \langle i(t)\rangle = \sum_j j\, \partial_t P(i(t)=j)$ ← very cumbersome, we simply write $P(j)$

Master eq° $\partial_t P(\mathcal{C}) = \sum_{\mathcal{C}'} W(\mathcal{C}'\to\mathcal{C}) P(\mathcal{C}') - W(\mathcal{C}\to\mathcal{C}') P(\mathcal{C})$

Here $\mathcal{C} \leftrightarrow j$

Identify all pairs $\mathcal{C}, \mathcal{C}'$ such that $W(\mathcal{C}\to\mathcal{C}') \neq 0$ or $W(\mathcal{C}'\to\mathcal{C}) \neq 0$

$\mathcal{C} \leftrightarrow j$, $\mathcal{C}' \leftrightarrow j \pm 1$.

$$\partial_t P(j,t) = W(j-1\to j) P(j-1) + W(j+1\to j) P(j+1) - [W(j\to j-1) + W(j\to j+1)] P(j)$$
$$= p_1 P(j-1) + q_1 P(j+1) - (p_1+q_1) P(j)$$

$$\partial_t \langle j\rangle = \sum_j j p_1 P(j-1) + j q_1 P(j+1) - j(p_1+q_1) P(j)$$

$$= \sum_k (k+1) p_1 P(k) + \sum_k (k-1) q_1 P(k) - \sum_k k (p_1+q_1) P(k)$$

$$= (p_1 - q_1) \sum_k P(k) = (p_1 - q_1) \Rightarrow \langle j(t)\rangle - \langle j(0)\rangle = (p_1 - q_1) t$$

$$\Rightarrow v_1^n = p_1 - q_1$$

Stall force F such that $v_1^n(F) = 0 \iff p_1 = q_1 \iff p e^{-\delta f} = q e^{(1-\delta) f}$

$$\iff \boxed{f = \ln \frac{p}{q}}$$

Comment: f does not depend on δ since only the work along a full period matters.

IV.2) Two motors

We allow for short-range interactions between motors

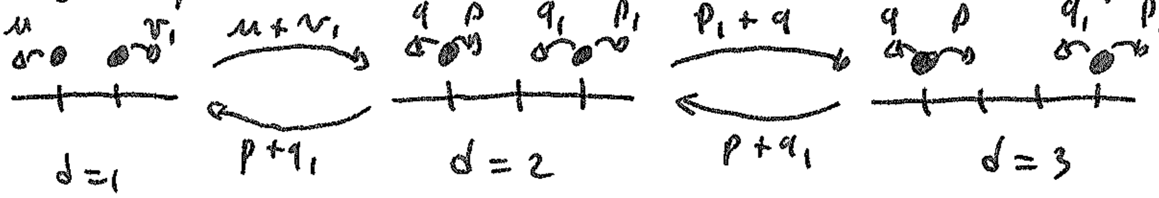
$v_1 = v e^{-\delta f}$

$v_1 > p_1$ & $u > q \Rightarrow$ repulsive interactions

$v_1 < p_1$ & $u < q \Rightarrow$ attractive ——

IV.2.1) Average distance between two motors

$P_d(k)$: proba that the distance between the motors is equal to k.



$$\partial_t P_d(1) = (p+q_1) P_d(2) - (u+v_1) P_d(1) \qquad (1)$$

$$\partial_t P_d(2) = (u+v_1) P_d(1) - (p+q_1) P_d(2) \qquad (2)$$
$$- (p_1+q) P_d(2) + (p+q_1) P_d(3)$$

$\vdots$

$$\partial_t P_d(m) = (p_1+q) P_d(m-1) - (p+q_1) P_d(m) \qquad (m)$$
$$- (p_1+q) P_d(m) + (q_1+p) P_d(m+1)$$

 Steady-state $\partial_t P_d(i)=0\,;\ \forall i$

$$(1) \Rightarrow P_d(2) = \frac{\mu+v_1}{p+q_1} P_d(1) \equiv r_1 P_d(1)\,;\quad r_1 = \frac{\mu+v_1}{p+q_1}$$

$$(1+2) \Rightarrow P_d(3) = \frac{p_1+q}{p+q_1} P_d(2) \equiv r\, P_d(2) = r r_1 P_d(1)\,;\quad r = \frac{p_1+q}{p+q_1}$$

$$(1+\dots+n) \Rightarrow P_d(n+1) = r P_d(n) = \dots = r^{n-1} r_1 P_d(1) \Rightarrow P_d(n\geq 2) = r^{n-2} r_1 P_d(1)$$

Normalisation: $$\sum_{k=1}^{\infty} P_d(k) = 1 = P_d(1) + r_1 P_d(1) + \dots = P_d(1)\left[1 + r_1 \sum_{k=0}^{\infty} r^k\right] = P_d(1)\left(1+\frac{r_1}{1-r}\right)$$

$$\Rightarrow \boxed{P_d(1) = \frac{1-r}{1-r+r_1}\,;\quad P_d(k\geq 2) = \frac{r_1(1-r)}{1-r+r_1} r^{k-2}}$$

Comment: $p_1 < p$ & $q_1 > q \Rightarrow r = \frac{p_1+q}{p+q_1} < 1$; otherwise, no stationary state.

Comment: $P_d(k)$ decreases as $r^k \propto e^{k \underbrace{\ln r}_{<0}} \Rightarrow \langle k \rangle$ finite, of order $\frac{1}{|\ln r|}$
The mean distance between the motors is finite $\Rightarrow$ they go at the same speed.

IV.2.2) Mean speed of the first motor

$$\langle v \rangle = v_{isolated} \cdot p(isolated) + v_1 P_d(1) = (p_1-q_1)\left[1-P_d(1)\right] + v_1 P_d(1)$$

$$= \frac{(p_1-q_1)(\mu+v_1)}{p+q_1-p_1-q+\mu+v_1} + \frac{v_1(p+q_1-p_1-q)}{p+q_1-p_1-q+\mu+v_1}$$

$$= \frac{\mu(p_1-q_1) + v_1(p-q)}{p+q_1-p_1-q+\mu+v_1} \equiv V^{2M}$$

Stall force: $V^{2M} = 0 = \mu e^{-\delta f}(p-qe^{f}) + v e^{-\delta f}(p-q)$

$$\Leftrightarrow \mu q e^{f} = \mu p + vp - vq$$

$$f_s^{2M} = \ln\left[\frac{vp}{\mu q} + \frac{p}{q} - \frac{v}{\mu}\right] = \ln\left[\frac{p}{q} + \frac{v}{\mu}\overbrace{\left(\frac{p}{q}-1\right)}^{>0}\right] > f_s^{1M}$$

The force to stop two motors is always larger because the 2nd motors prevents the first one from stepping backward.

Comment: $f_s^{2M} = 2 f_s^{1M} \Leftrightarrow \ln\left(\frac{p}{q} + \frac{v}{\mu}\frac{p}{q} - \frac{v}{\mu}\right) = \ln\frac{p^2}{q^2}$

$$\Leftrightarrow \frac{v}{\mu}\left(1 - \frac{p}{q}\right) = \frac{p}{q}\left(1 - \frac{p}{q}\right) \Leftrightarrow \frac{p}{q} = \frac{v}{\mu}$$

If interactions derive from (free) energy $\left.\begin{array}{l} v = p e^{-\beta\Delta E} \\ \mu = q e^{-\beta\Delta E}\end{array}\right\} \frac{p}{q} = \frac{v}{\mu}$

Then one needs twice the force to stop two motors.

Comment: the second motor always increase the stall force, but not always the speed $\Rightarrow$ possible to have $V^{2M} < V^{1M}$.

$$V^{2M} - V^{1M} = \frac{\mu(p_1 - q_1) + v_1(p-q)}{p - q + \mu + v_1 - (p_1 - q_1)} - \frac{(p_1 - q_1)[p - q + \mu + v_1 - (p_1 - q_1)]}{p - q + \mu + v_1 - (p_1 - q_1)} \equiv \frac{Num}{Den}$$

$$Den = p(1 - e^{-\delta f}) + q[e^{(1-\delta)f} - 1] + \mu + v_1 > 0$$

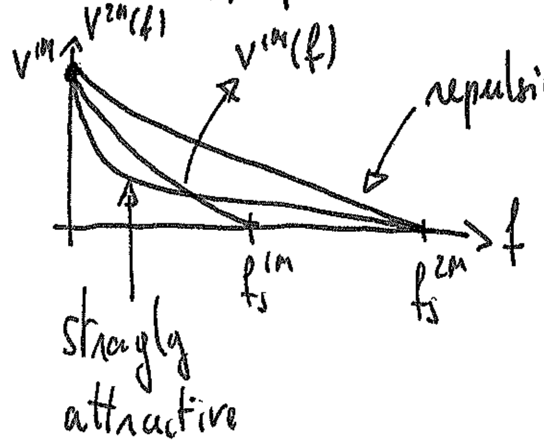
$$Num = v_1[p - q - p_1 + q_1] - (p_1 - q_1)[p - p_1 + q_1 - q] = (v_1 - p_1 + q_1)\underbrace{(p - p_1 + q_1 - q)}_{>0 \text{ if } f>0}$$

Comment: $f \to 0$, $V^{2M} = V^{1M}$, motors are unbound.

$f > 0$ if $v_1 > (p_1 - q_1)$ then $V^{2M} > V^{1M}$

$\Leftrightarrow v > p - q e^{f}$

If $v < p - q$ then $V^{2M} < V^{1M}$ as $f \to 0$; but $V^{2M} > V^{1M}$ if $f = f_s^{1M} = \ln\frac{p}{q}$



V Detailed balance for Markov chains

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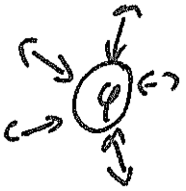
① At the rates level

$$\partial_t P(q) = \sum_{q' \neq q} W(q' \to q) P(q') - W(q \to q') P(q)$$

Steady-state: $\underbrace{\sum_{q' \neq q}}_{\text{Global balance in and out of } q} W(q' \to q) P_s(q') = \sum_{q' \neq q} W(q \to q') P_s(q)$



The sum of outward proba flux (r.h.s) is balanced by the sum of inward proba fluxs (l.h.s.)

Detailed-balance: $\boxed{\forall q, q' \quad W(q \to q') P(q) = W(q' \to q) P(q')}$

The fluxs are balanced along each link.

② At the trajectory level

Escape rate: $r(q) = \sum_{q' \neq q} W(q' \to q)$ is the total rate at which the systems hops out of configuration q.

Escape time: τ, the time at which the system first escape from q.

$\tau = N dt$, in the limit $dt \to 0$, $N \to \infty$, τ constant

Proba ($q \to q'$ during dt) $= W(q \to q') dt$

Proba(out of q ———) $= \sum_{q'} W(q \to q') dt$

Proba(stay in q ———) $= 1 - \sum_{q'} W(q \to q') dt$

$$P(\tau) dt = \underbrace{\left(1 - \sum_{q'} W(q \to q') dt\right)^{N-1}}_{\text{Stays in } q \text{ for } [0, (N-1)dt]} \times \underbrace{\sum_{q'} W(q \to q') dt}_{\text{exits in } [(N-1)dt, N dt]} \simeq (1 - r(q) dt)^{N-1} r(q) dt$$

$$\simeq e^{-(N-1) dt\, r(q)} r(q) dt \sim r(q) dt\, e^{-\tau r(q)}$$

$$\boxed{P(\tau) = r(q) e^{-\tau r(q)}}$$

Comment: $P(\tau > t) = \int_t^\infty d\tau\, P(\tau) = e^{-t r(q)}$

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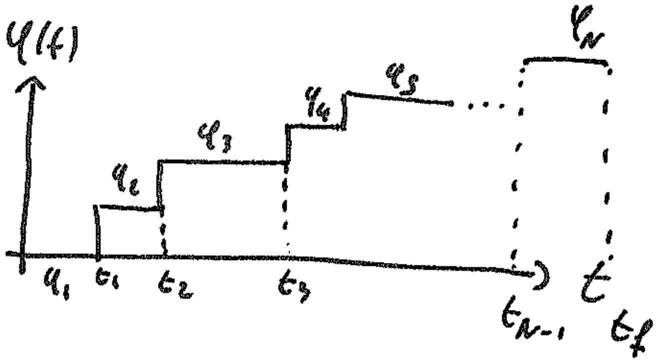
When the jumps occurs, the probability to go from q to q' is

$$\frac{W(q\to q')}{\sum_{q''} W(q\to q'')} = \frac{W(q\to q')}{r(q)}$$



probability of a trajectory:
Start from q_1 in steady-state
$\to q_N$ at t_f.

$$P(\{q\}) = P_{ss}(q_1)\, r(q_1)\, e^{-r(q_1)t_1} \frac{W(q_1\to q_2)}{r(q_1)} \cdot r(q_2)\, e^{-r(q_2)(t_2-t_1)} \frac{W(q_2\to q_3)}{r(q_2)} \cdots \frac{W(q_{N-1}\to q_N)}{r(q_{N-1})}$$
$$\times\, e^{-(t_f-t_{N-1})r(q_N)}$$

If there is detailed balance, $P_{ss}(q_i)\,W(q_i\to q_{i+1}) = P_{ss}(q_{i+1})\,W(q_{i+1}\to q_i)$

$$P(\{q\}) = e^{-r(q_1)t_1}\left(\frac{W(q_2\to q_1)}{r(q_2)}\, r(q_2)\, e^{-(t_2-t_1)r(q_2)}\right)\times\left(\frac{W(q_3\to q_2)}{r(q_3)}\, r(q_3)\, e^{-(t_3-t_2)r(q_3)}\right)$$
$$\times \cdots \frac{W(q_N\to q_{N-1})}{r(q_N)} \cdot r(q_N)\, e^{-r(q_N)(t_f-t_{N-1})}\, P_{ss}(q_N)$$

$$= P(\{q(t_f-t)\})$$

Forward & backward trajectories have the same probability.

Summing over all intermediate steps $P_{ss}(q_1)\cdot P(q_N, t_f \mid q_1, 0) = P_{ss}(q_N)\, P(q_1, t_f \mid q_N, 0)$

③ At the transition matrix level

Vector $|P\rangle$ of dimension $\#\{q\}$; the i^{th} component $P_i = P(q_i, t) = P_q(t)$

$$\partial_t P(q,t) = \sum_{q'\neq q} W(q'\to q)\, P(q',t) - \Big(\sum_{q'\neq q} W(q\to q')\Big) P(q) \Leftrightarrow \partial_t P_q = \sum_{q'} M_{qq'}\, P_{q'}$$

$$M_{q,q'\neq q} = W(q'\to q)\;;\; M_{qq} = -\sum_{q'\neq q} W(q\to q') \qquad \Leftrightarrow \partial_t |P\rangle = M\,|P\rangle$$

like a Fokker-Planck equation!
in finite dimension

Detailed balance

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$\forall\, q \neq q' \quad P(q) W(q \to q') = P(q') W(q' \to q)$

$\Leftrightarrow \quad M_{q'q} P_q = M_{qq'} P_{q'}$

$\Leftrightarrow \quad M^{+}_{qq'} = P_q^{-1} M_{qq'} P_{q'}$

$\Leftrightarrow \quad \boxed{M^{+} = \mathcal{P}^{-1} M \mathcal{P}}$; where $\mathcal{P} = \mathrm{diag}(P_q)$

But also $\quad P_q^{-1/2} M_{qq'} P_{q'}^{1/2} = P_{q'}^{-1/2} M_{q'q} P_q^{1/2} =$

If $D = \mathrm{diag}(P_q^{1/2})$ $\quad \tilde{M} = D^{-1} M D$ is such that $(\tilde{M})^{+}_{qq'} = \tilde{M}_{qq'}$

$\tilde{M}$ is hermitian $\Rightarrow$ orthogonal eigenbasis (unlike M)

$\Rightarrow$ real spectrum (like M)