W10 - Molecular dynamics as a Markov process

Physical models of living systems, Nelson chp 8

"stochastic simulations,
applications to biomolecular networks", Gonze

"Modeling of stochastically gating of ion channels" G.D. Smith

- Ion channel
- RNA production/regulation
  (birth/death master equation)

"How molecules change with time"

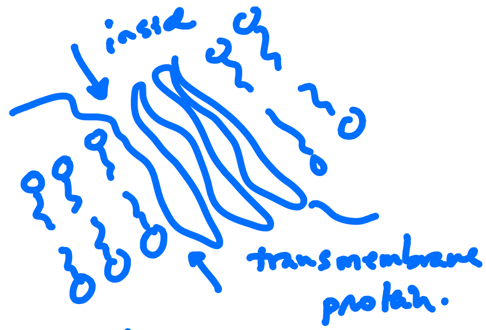
"How molecule concentrations change with time"

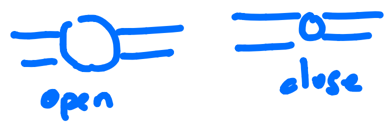
Stochastic gating of a single Ion channel

gated channels:

Can be gated by:

- Ions: Ca^{2+}, Na^{2+}, K^{+}
- Voltage
- light (channelrodopsin)





Measure the dynamics of a single Ion channel

using a Markov process with 2 states

$$O\ (\text{open}) \underset{k_O}{\overset{k_C}{\rightleftharpoons}} C\ (\text{closed})$$

k_C, k_O are reaction constants of the process, that of course, we are going to interpret as probabilities.

① a discrete time Markov process

$$P(C, t \to O, t+\Delta t) = k_O \cdot \Delta t$$

$\Delta t \to 0$

$$P(O, t \to C, t+\Delta t) = k_C \cdot \Delta t$$

② a continuous time Markov process

$$P(O \mid t), \quad P(C \mid t)$$

Discrete-time Markov process

S_i = state of ion at time $i \cdot \Delta t$

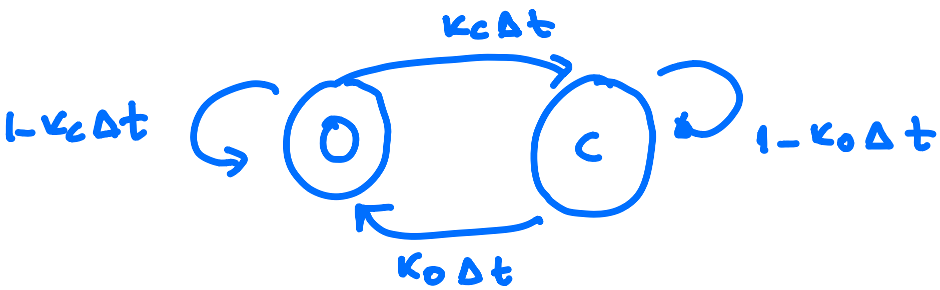
$$S_0 \xrightarrow{t(S_0 \to S_1)} S_1 \to \dots \quad S_i \xrightarrow{t(S_i \to S_{i+1})} S_{i+1} \to \dots$$

$$t(C \to O) = P(O, t+\Delta t \mid C, t) = k_o \cdot \Delta t$$

$$t(O \to C) = P(C, t+\Delta t \mid O, t) = k_c \cdot \Delta t$$

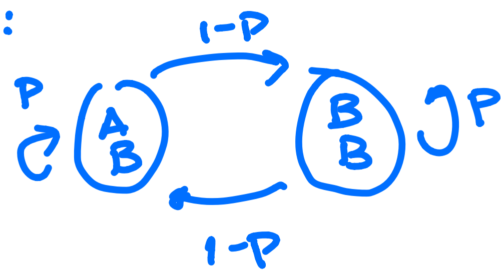
$$t(C \to C) = P(C, t+\Delta t \mid C, t) = 1 - k_o \Delta t$$

$$t(O \to O) = P(O, t+\Delta t \mid O, t) = 1 - k_c \cdot \Delta t$$



compared to:

W06/W07



The HMM probabilities are dependent on $\underline{\underline{\Delta t}}$

$$P(S_i = O \mid S_{i-1} = O) = 1 - \Delta t \cdot k_c$$

$$P(AB \mid AB) = P$$

The transition probability matrix

$P(O|t)$ =: prob that at t, channel is O

$P(C|t)$ =: " " " , channel is C

$$P(O|t) + P(C|t) = 1$$

Master eqs:

$$P(O|t+\Delta t) = (1-k_C \Delta t)\, P(O|t)$$
$$k_O \cdot \Delta t \; P(C|t)$$

$$P(C|t+\Delta t) = (1-k_O \Delta t)\, P(C|t)$$
$$k_C \Delta t \; P(O|t)$$

Matricial representation

$$\begin{bmatrix} P(O|t+\Delta t) \\ P(C|t+\Delta t) \end{bmatrix} = \begin{bmatrix} 1-k_C \Delta t & k_O \Delta t \\ k_C \Delta t & 1-k_O \Delta t \end{bmatrix} \begin{bmatrix} P(O|t) \\ P(C|t) \end{bmatrix}$$

$$T_{\Delta t} = \begin{bmatrix} 1-k_c\Delta t & k_o\Delta t \\ k_c\Delta t & 1-k_o\Delta t \end{bmatrix}$$

$$\underbrace{\begin{bmatrix} P(o|t+\Delta t) \\ P(c|t+\Delta t) \end{bmatrix}}_{\vec{P}(t+\Delta t)} = T_{\Delta t} \underbrace{\begin{bmatrix} P(o|t) \\ P(c|t) \end{bmatrix}}_{\vec{P}(t)}$$

$$\vec{P}(t+\Delta t) = T\,\vec{P}(t)$$

Then for $t+2\Delta t$

$$\vec{P}(t+2\Delta t) = T\,\bar{P}(t+\Delta t)$$
$$= T^2\bar{P}(t)$$

in general $$\boxed{\vec{P}(t+n\Delta t) = T^n\,\bar{P}(t)}$$

The Chapman-Kolmogorov equation.

[A general result for any continuous-time Markov process]

The deterministic solution

$\Delta t \to 0$

$$P(C|t+\Delta t) = k_c \Delta t \; P(O|t) + (1 - k_o \Delta t) \, P(C|t)$$

$$P(O|t+\Delta t) = k_o \Delta t \; P(C|t) + (1 - k_c \Delta t) \, P(O|t)$$

$$P(C|t+\Delta t) - P(C|t) = k_c \Delta t \, P(O|t) - k_o \Delta t \, P(C|t)$$

$$P(O|t+\Delta t) - P(O|t) = k_o \Delta t \, P(C|t) - k_c \Delta t \, P(O|t)$$

$$\frac{P(C|t+\Delta t) - P(C|t)}{\Delta t} = k_c - (k_c + k_o) \, P(C|t)$$

$$\frac{P(O|t+\Delta t) - P(O|t)}{\Delta t} = k_o - (k_c + k_o) \, P(O|t)$$

at $\Delta t \to 0$

$$\left\{ \begin{aligned} \frac{dP(C|t)}{dt} &= k_C - (k_C + k_O)\, P(C|t) \\ \frac{dP(O|t)}{dt} &= k_O - (k_C + k_O)\, P(O|t) \end{aligned} \right\}$$

differential eqs.

can be solved:

$$P(C|t) = \frac{k_C}{k_O + k_C} + \left(P(C|0) - \frac{k_C}{k_C + k_O} \right) e^{-(k_C + k_O)t}$$

$$P(O|t) = \frac{k_O}{k_O + k_C} + \left(P(O|0) - \frac{k_O}{k_C + k_O} \right) e^{-(k_C + k_O)t}$$

$P(C|0) = 1$

$k_O > k_C$

This is a general result

for $P(t+\Delta t) = T\,P(t)$

$$\frac{P(t+\Delta t) - P(t)}{\Delta t} = \frac{T - I}{\Delta t} P(t)$$

Introduce $Q = \frac{T - I}{\Delta t} = \begin{bmatrix} -k_c & k_o \\ k_c & -k_o \end{bmatrix}$

Q = rate matrix = changes per unit time.

$$\frac{d\bar{P}}{dt} = Q\,\bar{P}(t)$$

general solution

$$\bar{P}(t) = e^{tQ}\,\bar{P}(t)$$

Note $e^{tQ} \neq \begin{bmatrix} e^{-tk_c} & e^{tk_o} \\ e^{tk_c} & e^{-tk_o} \end{bmatrix}$

$$e^{tQ} = I + tQ + \frac{t^2}{2!}Q^2 + \frac{t^3}{3!}Q^3 + \cdots$$

Expectations over many channels

$$S = \begin{cases} 1 & \text{if channel open} \\ 0 & \text{if channel close} \end{cases}$$

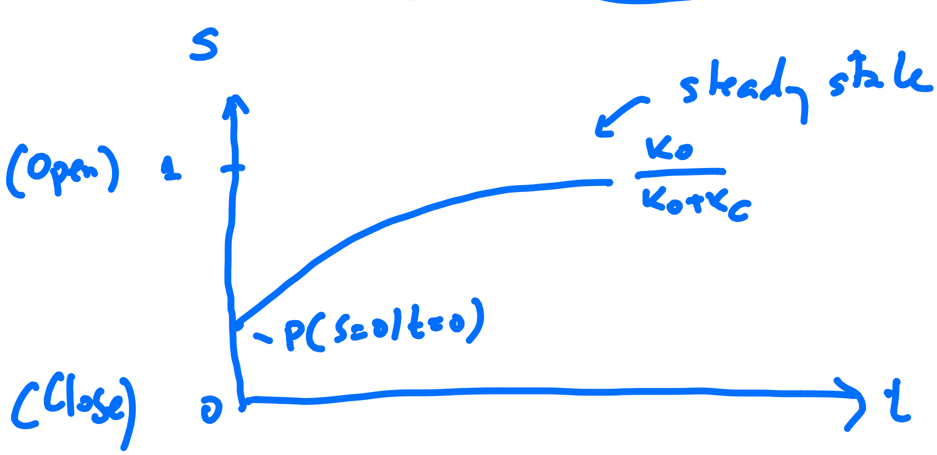
$$\langle S(t) \rangle = 1 \cdot P(S=0|t) + 0 \cdot P(S=c|t)$$

$$= P(S=0|t)$$

$$= \frac{k_o}{k_o+k_c} + \left(P(S=0|t=0) - \frac{k_o}{k_o+k_c} \right) e^{-(k_o+k_c)t}$$

steady state solution

$$\boxed{\langle S(t) \rangle \xrightarrow[t\to\infty]{} \frac{k_o}{k_o+k_c}}$$



$\underbrace{\text{Stochastic Simulation}}_{\Delta t}$: MC algorithm.

look at one channel as if $O \rightleftarrows C$

$$\begin{tikzcd} O \arrow[r, bend left, "k_c \Delta t"] & C \arrow[l, bend left, "k_o \Delta t"] \end{tikzcd}$$

+ if channel is at $S = O$
  - draw r in $U[0,1]$
  - if $r < k_c \Delta t \rightarrow S_{i+1} = C$
  - else stay O : $S_{i+1} = O$

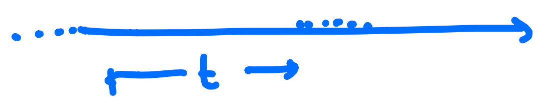
+ if channel is at $S = C$
  - draw r in $U[0,1]$
  - if $r < k_o \Delta t \rightarrow S_{i+1} = O$ (changes)
  - else stay C $S_{i+1} = C$

$\longrightarrow$ class code

compare
- $\rightarrow$ stochastic simulation for 1 channel
- $\rightarrow$ average deterministic solution

Dwell times

Dwell time $= \langle \tau \rangle =:$ expected time for a channel to remain open (O) before it changes to close (C)



A channel is open at t, probability that stays open at $t+\tau$

$$P(O\ t+\tau \mid O, t) = P(O, t+\tau \mid O, t+\tau-\Delta t)$$
$$P(O, t+\tau-\Delta t \mid O, t+\tau-2\Delta t)$$
$$\vdots$$
$$P(O, t+\Delta t \mid O, t)$$

if $\tau = m \cdot \Delta t$

$$= (1 - k_c \Delta t)^m = \left(1 - k_c \frac{\tau}{m}\right)^m$$

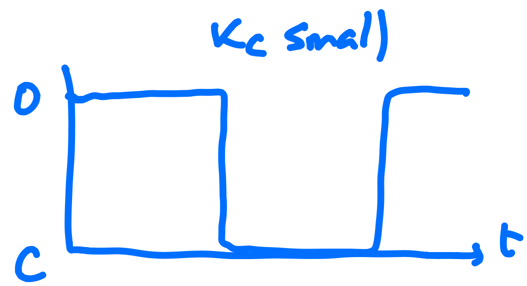
$$\lim_{m \to \infty} = e^{-k_c \tau}$$

Then the pdf of a dwell time τ requires to add the instantaneous probability of changing from $O \to C = \kappa_C$

then $$P_O(\tau) = \kappa_C e^{-\kappa_C \tau}$$

And the expected dwell time

$$\langle \tau \rangle_O = \frac{1}{\kappa_C}$$



similarly $$\langle \tau \rangle_C = \frac{1}{\kappa_O}$$