Rutgers 642:613 - Fall 2003

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Sec 3.5 - Probabilistic Channel Modeling

http://www.math.rutgers.edu/~sontag/613.html

Probabilities & Chemical Rate Equations

e.g.: two-state channel; suppose:

- can have only two states: “open” or “closed”
- probability of opening in time interval of length h, if was closed at start of interval, is $f(h)$
- probability of closing in time interval of length h, if was open at start of interval, is $g(h)$
- probability of two or more events happening is $o(h)$
- f, g differentiable at 0, $f(0) = g(0) = 0$

let $p(t)$ = prob channel open at time t,
so $1 - p(t)$ = prob channel closed at time t,

hence prob that open at time $t + h$ is (disjoint events):

(prob(was closed & opened) + prob(was open & didn’t close)
+ prob(several open/close events happened)

$$p(t+h) \;=\; (1-p(t))\,f(h) \;+\; p(t)\,(1-g(h)) \;+\; o(h)$$

so, writing $f(h) = \lambda h + o(h)$ and $g(h) = \mu h + o(h)$,

$$\begin{aligned} p(t+h) &= (1-p(t))\lambda h + p(t)(1-\mu h) + o(h) \\ \Rightarrow \frac{p(t+h)-p(t)}{h} &= \lambda(1-p(t)) - \mu p(t) \\ \Rightarrow & \quad \dot{p} = \lambda(1-p) - \mu p \end{aligned}$$

now, if we have N such channels, all evolving independently, then the number of open channels is $x(t) = Np(t)$, so, with $\alpha = \mu/N$ and $\beta = \lambda/N$:

$$\dot{x} = \beta(N-x) - \alpha x$$

which is consistent with

$$C \underset{\beta}{\overset{\alpha}{\rightleftarrows}} O$$

and $C(t) + O(t) \equiv N$

(similar considerations for all "monomolecular reactions")

Justification of powers like "n^4"

suppose each channel has two subunits each of which may be open or closed (channel open when both units open)

$$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} S_2$$

$$\begin{aligned}\dot{x}_0 &= \beta(1 - x_0 - x_2) - 2\alpha x_0 \\ \dot{x}_2 &= \alpha(1 - x_0 - x_2) - 2\beta x_2\end{aligned}$$

where S_i = prob that in state when i subunits open
or equivalently as above, proportion of channels with such

if behavior of subunits would be independendent at time t, then could look at probability that a subunit is open:

$$\dot{n} \;=\; \alpha(1 - n) - \beta n$$

and say that $x_2 = n^2$ and $x_0 = (1 - n)^2$
(probability that both subunits closed)

but not necessarily indep (initial conditions may be wrong)
– e.g. started with all channels closed or all open;
in fact, want to allow α, β to change, as in voltage-gated channels (probabilities time-varying: depend on voltage)
– not looking at steady-state behavior

however, this is true: if $\dot{n} = \alpha(1-n) - \beta n$ then

$$x_0(t) = (1-n(t))^2 \,, \;\; x_2(t) = n(t)^2$$

is a solution of the system of equations (for special initial conditions that satisfy $\sqrt{(}x_0) + \sqrt{(}x_2) = 1$), and, moreover, it is globally asymptotically stable:

write

$$y_0 := x_0 - (1-n)^2 \,, \;\; y_2 := x_2 - n^2$$

(for any solution – given any initial condition) then:

$$\begin{aligned} \dot{y}_0 &= -2\alpha y_0 - \beta(y_0 + y_2) \\ \dot{y}_2 &= -\alpha(y_0 + y_2) - 2\beta y_2 \end{aligned}$$

eigens are $-(\alpha+\beta)$ and $-2(\alpha+\beta)$,
so exponential stability as long as α, β constant
but want to consider time-varying α, β (voltage-gated)

so argue like this (different from book - book is wrong):

consider "Lyapunov function" $V(y_0, y_2) := y_0^2 + y_2^2$

$$(d/dt)V(y_0(t), y_1(t)) \;\leq\; -\delta V(y_0(t), y_1(t))$$

provided that $\min\{\alpha(t), \beta(t)\} = \delta > 0$
(use $x^2 + xy + y^2 \geq 0$), so

$$V(t) \leq e^{-\delta t} V(0) \to 0 \text{ as } t \to +\infty$$

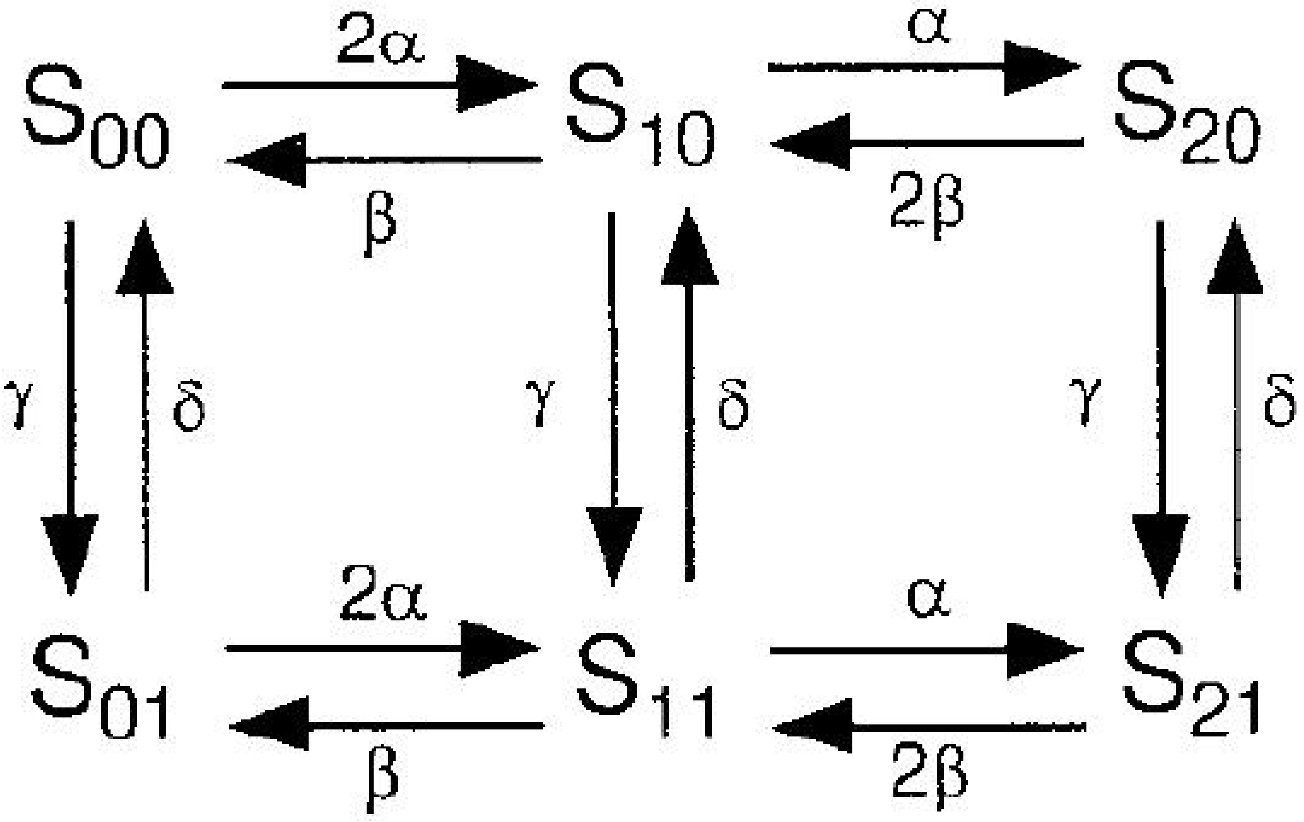
and hence $y_0, y_2 \to 0$,
i.e. $x_0 \approx (1-n)^2$ and $x_2 \approx n^2$ for all large t

conclude: probability of channel open (i.e. $x_2(t)$)
is $\approx$ the square of the solution for n (linear eqn)

more generally:

e.g. “sodium channel” with 2 m subunits and one h subunit (or even 3 m’s; two just for simplicity)

get formula: m^2h, $\dot{m} = \alpha(1-m) - \beta m$, $\dot{h} = \gamma(1-h) - \delta h$



An alternative model

assume once depolarized, stays inactive
(for very long compared to this process)
three states: Closed, Open, Inactive

$$C \underset{\beta}{\overset{\alpha}{\rightleftarrows}} O \xrightarrow{\gamma} I\,, \quad C \xrightarrow{\delta} I$$

concentrations satisfy:

$$\begin{aligned} \dot{c} &= -(\alpha+\delta)c + \beta g \\ \dot{g} &= \alpha c - (\beta+\gamma)g \end{aligned}$$

where using "g" instead of "o" for clarity;
ignoring equation for I by conservation

how to measure kinetic constants from experimental data?

suppose data give $g(t)$ as a function of t
(measure current, proportional to number of open channels)

plan: (1) write soln of ODE system, (2) then match to data

trace $= -(\alpha+\delta+\beta+\gamma) < 0$, det $= (\alpha+\delta)(\beta+\gamma)-\alpha\beta > 0$
stable; generically assume roots different: $\lambda_2 < \lambda_1 < 0$
general solution for g is $g(t) = ae^{\lambda_1 t} + be^{\lambda_2 t}$
suppose start at $g(0) = 0$; then $a + b = 0$
conclude soln is $g(t) = a(e^{\lambda_1 t} - e^{\lambda_2 t})$

we may identify *three* numbers a, λ_1, λ_2 from function g, and these are functions of the four parameters $\alpha, \beta, \delta, \gamma$ (see book for formulas)

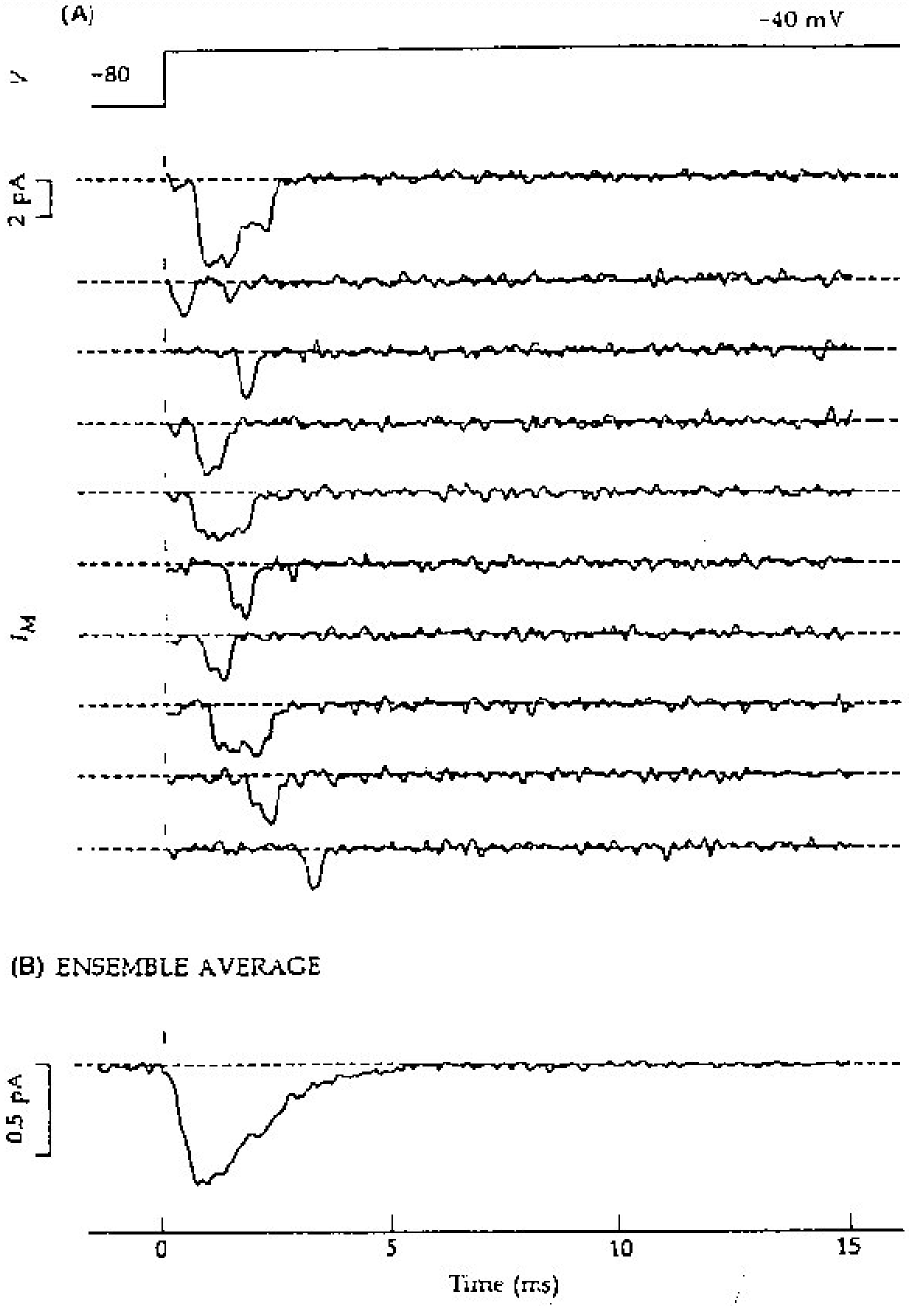
cannot solve for all four (see exercise 18 for example)

so, how to identify *all* parameters?

(if we could observe C as well as O, then we'd be able to identify all parameters — e.g. take numerical derivatives and do a regression; but C not directly observable separately from inactivated channels)

information given by *g* is *average* only!

patch-clamp techniques allow *single*-channel recordings



interpret rates $\alpha, \ldots$ as probabilities of transitions in small intervals (independent events in disjoint intervals), e.g.:

Prob(open at time $t+h \mid$ open closed at time t) $= Ah + o(h)$

(same for others)

note: Prob(first transition from C is to O) $= A = \frac{\alpha}{\alpha+\delta}$

and Prob(first transition from O is to C) $= B = \frac{\beta}{\beta+\gamma}$

conditional (on there having been a transition) probabilities; wrong in book pp.110, l.2-5, where says $A =$ prob of transition $C \rightsquigarrow O$

first estimate $1 - A$ ($\therefore$ also A) by looking at experimental records: channel never activated over entire period

next look at histogram for $T =$ *latency* of channel, i.e. time until first opening

what is this histogram in terms of parameters?

Prob$(T > t) =$

P(first transition $C \rightsquigarrow I$) + P(first transition $C \rightsquigarrow O$ but $T > t$)

the first of these is $1 - A$, and the second is:
Prob(first transition $C \rightsquigarrow O$) $\times$ Prob($T > t \,|\,$start in C)
so Prob($T > t$) $= 1 - A + A\, p_O(t)$,
where $p_O(t)$ is the probability that a closed channel will remain closed until time t (or later)

$p_O =$ exponential distribution (time to next arrival in queue, time to first failure, etc), as seen by following argument:

split interval $[0, t]$ into a large number m of subintervals

event "still in C at time $t\,|$ start in C" means that on each interval of size $h = t/m$ we stayed in C, which happens with prob $1 - Kh + o(h)$, where $K = \alpha + \delta$

events in disjoint intervals are independent, so
$p_O(t) = (1 - Kh + o(h))^m \approx e^{-Kt}$ (limit)
conclude Prob(latency$> t$) $= 1 - A + Ae^{-(\alpha+\delta)t}$
so now fit and obtain $\alpha + \delta$ (and A if didn't have it from previous step) so since $A = \frac{\alpha}{\alpha+\delta}$, we have α, and hence δ too

next, we determine β, γ as follows:

recall, for probabilities of *first transition out of state*:

$$C \underset{B}{\overset{A}{\rightleftarrows}} O \xrightarrow{1-B} I\,, \quad C \xrightarrow{1-A} I$$

Prob that channel first goes to I: $1 - A$

Prob that channel first goes to O, then to I: $A(1-B)$

Prob that channel goes to O, C, I: $AB(1-A)$

in general: Prob opens exactly k times:

$$A^k B^{k-1}(1-B) + A^k B^k (1-A) \;=\; (AB)^k \left(\frac{1-AB}{B}\right)$$

so can estimate B from any of these, or better from entire plot of this probability distribution as estimated from data

finally, aguing just as for latency, distribution of *open times* is $e^{-(\beta+\gamma)t}$, so, since $B = \frac{\beta}{\beta+\gamma}$, obtain β and hence γ too

using these ideas, it was estimated that inactivation of Na channels is sometimes *faster* than inactivation ("overtured traditional ideas", see book for references)