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):
\[
(\text{prob(\text{was closed} & \text{opened})} + \text{prob(\text{was open} & \text{didn’t close})} + \text{prob(\text{several open/close events happened})})
\]
\[
p(t + h) = (1 - p(t)) f(h) + p(t) (1 - g(h)) + o(h)
\]
so, writing \( f(h) = \lambda h + o(h) \) and \( g(h) = \mu h + o(h) \),

\[
p(t + h) = (1 - p(t)) \lambda h + p(t)(1 - \mu h) + o(h)
\]

\[
\Rightarrow \quad \frac{p(t + h) - p(t)}{h} = \lambda (1 - p(t)) - \mu p(t)
\]

\[
\Rightarrow \quad \dot{p} = \lambda (1 - p) - \mu p
\]

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

\[
C \xleftrightarrow{\alpha} O \xleftrightarrow{\beta} O
\]

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)

\[
\begin{align*}
S_0 & \xleftrightarrow{2\alpha} S_1 \xleftrightarrow{\alpha} S_2 \\
\beta & \quad 2\beta
\end{align*}
\]

\[
\begin{align*}
\dot{x}_0 &= \beta(1 - x_0 - x_2) - 2\alpha x_0 \\
\dot{x}_2 &= \alpha(1 - x_0 - x_2) - 2\beta x_2
\end{align*}
\]

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

if behavior of subunits would be independent 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 $\alpha, \beta$ 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

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

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

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

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

$$\dot{y}_0 = -2\alpha y_0 - \beta(y_0 + y_2)$$
$$\dot{y}_2 = -\alpha(y_0 + y_2) - 2\beta y_2$$
eigens are $-(\alpha + \beta)$ and $-2(\alpha + \beta)$, so exponential stability as long as $\alpha, \beta$ constant but want to consider time-varying $\alpha, \beta$ (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: $m^2 h$, $\dot{m} = \alpha (1 - m) - \beta m$, $\dot{h} = \gamma (1 - h) - \delta h$
An alternative model

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

\[ C \overset{\alpha}{\rightleftharpoons} O \overset{\gamma}{\rightarrow} I, \quad C \overset{\delta}{\rightarrow} I \]

concentrations satisfy:

\[ \dot{c} = -(\alpha + \delta)c + \beta g \]
\[ \dot{g} = \alpha c - (\beta + \gamma)g \]

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 $a, \lambda_1, \lambda_2$ 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.:

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

(same for others)

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

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

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

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

next look at histogram for $T = \text{latency of channel}$, i.e. time until first opening

what is this histogram in terms of parameters?

$$\text{Prob}(T > t) = \text{P(first transition } C \rightsquigarrow I) + \text{P(first transition } C \rightsquigarrow O \text{ but } T > t)$$
the first of these is $1 - A$, and the second is:
\[ \text{Prob(first transition } C \rightarrow O) \times \text{Prob}(T > t \mid \text{start in } C) \]
so \[ \text{Prob}(T > t) = 1 - A + A \ p_O(t), \]
where $p_O(t)$ is the probability that a closed channel will remain closed until time $t$ (or later)

\[ p_O = \text{exponential distribution} \ (\text{time to next arrival in queue, time to first failure, etc}), \]
as seen by following argument:

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

event “still in $C$ at time $t \mid \text{start in } C$” 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
\[ p_O(t) = (1 - Kh + o(h))^m \approx e^{-Kt} \ (\text{limit}) \]
conclude \[ \text{Prob(latency} > t) = 1 - A + Ae^{-(\alpha+\delta)t} \]
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 $\alpha$, and hence $\delta$ too

next, we determine $\beta, \gamma$ as follows:
recall, for probabilities of first transition out of state:

\[
C \xleftarrow{A} \overset{B}{\leftrightarrow} O \xrightarrow{1-B} I, \quad C \xrightarrow{1-A} I
\]

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

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