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Diffusion Approximations to Channel Noise

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A birth and death process is considered in which $X_n(t)$ is the number of open channels in a patch of membrane containing n channels. The voltage response of such a patch to conductance fluctuations is obtained including moments and spectral density. Furthermore, a diffusion approximation, an Ornstein–Uhlenbeck process, is obtained based on a weak convergence result to represent the patch conductance. Results are also obtained for a second diffusion approximation, that having the same first two infinitesimal moments as the birth and death process.

1. Introduction

There have been many theoretical studies of continuous time Markov chain models for the reaction schemes of single ionic channels (e.g. Coulquhoun & Hawkes, 1977, 1981, 1982). The corresponding problem of parameter estimation has also been investigated (Horn & Lange, 1983). A recent study addressed the analysis of measurements from a patch containing several channels (Jackson, 1985). Prior to that Lam & Lampard (1979, 1981) had considered the opening and closing of a many channel system as a birth and death process.

We employ the birth and death process as a starting point for diffusion approximations. One diffusion approximation is based on a previous study of weak convergence of a sequence of birth and death processes to an Ornstein–Uhlenbeck process (McNeil & Schach, 1973). Another diffusion approximation is constructed which has the same first two infinitesimal moments as the birth and death process. The relation between these three processes in the steady state will be investigated. We will see that the diffusion approximations perform well and offer computational advantages when the number of channels is large.

2. The Birth and Death Process

In this section we outline the physical situation of interest and catalogue some results which were mostly given previously by Lam & Lampard (1979, 1981). We consider a patch of membrane containing n channels. It is assumed that each channel operates according to the classical mode of drug action

$$A + R \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} AR$$

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where A represents an unbound agonist molecule, R represents a receptor correrponding to a closed state and AR is the agonist-receptor complex corresponding to a open channel. We will subsequently consider more complicated reaction schemes.

The stochastic aspect of the opening and closing of each channel is as follows. A channel in the open state at time t has a chance $\alpha\Delta t + o(\Delta t)$ of becoming closed in $(t, t+\Delta t]$ and a channel which is closed at t has a chance $\beta\Delta t + o(\Delta t)$ of opening in $(t, t+\Delta t]$. Let $X_n(t)$ be the number of open channels at t. We define the transition probabilities

$$p_k(t) = \Pr\{X_n(t) = k \mid X_n(0) = n_0\} \tag{2.1}$$

omitting reference to the initial state. Assuming channels act independently we arrive at the following contingencies

$$\Pr\{X_n(t+\Delta t) = j \mid X_n(t) = k\} = \begin{cases} 1 - \Delta t(k\alpha + (n-k)\beta) + o(\Delta t), & j = k, \\ (n-k)\beta\Delta t + o(\Delta t), & j = k+1, \\ k\alpha\Delta t + o(\Delta t), & j = k-1. \end{cases} \tag{2.2}$$

These are found to imply

$$\frac{\mathrm{d}p_k}{\mathrm{d}t} = (n-k+1)\beta p_{k-1} - (k\alpha + (n-k)\beta)p_k + (k+1)\alpha p_{k+1} \tag{2.3}$$

which holds for $k = 0, 1, \ldots, n$ with the understanding that $p_{-1} = p_{n+1} = 0$ as there cannot be fewer than zero or more than n open channels. The probability generating function for p_k is defined as

$$\phi(v, t) = \sum_{k=0}^{n} v^k p_k(t) \tag{2.4}$$

and this is found to satisfy

$$\frac{\partial\phi}{\partial t} = \beta n(v-1)\phi + (\alpha + (\beta - \alpha)v - \beta v^2)\frac{\partial\phi}{\partial v}. \tag{2.5}$$

This equation can be solved with the initial condition

$$\phi(v, 0) = v^{n_0} \tag{2.6}$$

to yield

$$\begin{aligned} \phi(v, t) = \left(\frac{1}{\alpha+\beta}\right)^n &[\alpha + \beta v + \alpha(v-1)\,\mathrm{e}^{-(\alpha+\beta)t}]^{n_0} \\ &\times [\alpha + \beta v - \beta(v-1)\,\mathrm{e}^{-(\alpha+\beta)t}]^{n-n_0}. \end{aligned} \tag{2.7}$$

From this an explicit expression for the probability distribution of the number of open channels at t may be found

$$\begin{aligned} p_k(t) = {} & \frac{(\alpha T + \beta)^{n_0}(\beta - \alpha T)^{n-n_0}}{(\alpha+\beta)^n} \\ & \times \sum_{j=0}^{n} \binom{n_0}{k-j}\binom{n-n_0}{j}\left(\frac{\alpha - \alpha T}{\beta + \alpha T}\right)^{n_0-k+j}\left(\frac{\alpha + \beta T}{\beta - \beta T}\right)^{n-n_0-j} \end{aligned} \tag{2.8}$$

where T is given by

$$T = \mathrm{e}^{-(\alpha+\beta)t} \tag{2.9}$$

The expected number of open channels at t when there are initially n_0 of them is

$$E(X_n(t)) = \frac{\beta n}{(\alpha+\beta)}(1-\mathrm{e}^{-(\alpha+\beta)t}) + n_0\,\mathrm{e}^{-(\alpha+\beta)t} \tag{2.10}$$

and the variance is

$$\begin{aligned}\mathrm{Var}\,(X_n(t)) = {} & \frac{\alpha\beta n}{(\alpha+\beta)^2} + \left(\frac{\alpha-\beta}{\alpha+\beta}\right)\left(n_0 - \frac{\beta n}{\alpha+\beta}\right)\mathrm{e}^{-(\alpha+\beta)t} \\ & + \left(\frac{n_0(\beta-\alpha)}{(\alpha+\beta)} - \frac{\beta^2 n}{(\alpha+\beta)^2}\right)\mathrm{e}^{-2(\alpha+\beta)t}.\end{aligned} \tag{2.11}$$

3. Covariance From Single Channel Results

We will subsequently need the covariance of the fluctuating conductance of a patch containing many channels. This can be conveniently obtained from results for a single channel. If $X(t)$ represents the state of a single channel, taking the value 1 when it is open and 0 when it is closed, then it follows from the theory of continuous time Markov chains (see for example Cox & Miller, 1965)

$$\begin{aligned}\mathrm{Cov}\,(X(s), X(t)) = {} & \left(\frac{\beta}{\alpha+\beta} + \left\{p_1(0) - \frac{\beta}{\alpha+\beta}\right\}\mathrm{e}^{-(\alpha+\beta)s}\right) \\ & \times\left(\frac{\alpha}{\alpha+\beta}\mathrm{e}^{-(\alpha+\beta)(t-s)} - \left\{p_1(0) - \frac{\beta}{\alpha+\beta}\right\}\mathrm{e}^{-(\alpha+\beta)t}\right)\end{aligned} \tag{3.1}$$

where $p_1(0)$ is the probability that the channel is open at $t=0$. In the case of n such channels which act independently as in the birth and death process of the previous section we obtain

$$\mathrm{Cov}\,(X_n(s), X_n(t)) = c_1\,\mathrm{e}^{-(\alpha+\beta)(t-s)} + c_2\,\mathrm{e}^{-(\alpha+\beta)t} - c_3\,\mathrm{e}^{-(\alpha+\beta)(s+t)} \tag{3.2}$$

where the following constants have been defined

$$c_1 = \frac{\alpha\beta n}{(\alpha+\beta)^2} \tag{3.3}$$

$$c_2 = \frac{\alpha-\beta}{\alpha+\beta}\sum_{j=1}^{n}\left\{p_{1,j}(0) - \frac{\beta}{\alpha+\beta}\right\} \tag{3.4}$$

$$c_3 = \sum_{j=1}^{h}\left\{p_{1,j}(0) - \frac{\beta}{\alpha+\beta}\right\}^2, \tag{3.5}$$

and where $p_{1,j}(0)$ is the probability that the jth channel is initially open.

Let us define a stationary version of X_n which we denote by $\hat{X}_n$ and to which X_n tends as $t\to\infty$. This is also the process X_n which results when each channel has initially its stationary probability. For the stationary version we have, from (2.10) and (2.11), a mean

$$E(\hat{X}_n(t)) = \frac{\beta n}{\alpha+\beta} \tag{3.6}$$

a variance

$$\operatorname{Var}(\hat{X}_n(t)) = \frac{\alpha\beta n}{(\alpha+\beta)^2} \tag{3.7}$$

a covariance

$$\operatorname{Cov}(\hat{X}_n(s), \hat{X}_n(t)) = c_1\, e^{-(\alpha+\beta)(t-s)} \tag{3.8}$$

and a temporally invariant probability distribution which is binomial

$$\Pr(\hat{X}_n(t) = k) = \binom{n}{k}\left(\frac{\beta}{\alpha+\beta}\right)^k \left(\frac{\alpha}{\alpha+\beta}\right)^{n-k}, \qquad k = 0, 1, \ldots, n. \tag{3.9}$$

We now suppose that a channel, when open, has a conductance of constant magnitude $\bar{g}$, although it probably varies from channel to channel. The whole patch conductance is assumed to be given by

$$g(t) = \bar{g} X_n(t), \tag{3.10}$$

and the corresponding stationary conductance is

$$g(t) = \bar{g}\hat{X}_n(t).$$

4. Diffusion Approximations

When the number of channels is large the trajectories of the process $X_n(t)$ are relatively smooth and it is natural to turn to a continuous approximation. There are two courses of action available in this direction and we shall examine both of them and compare the resulting diffusions with the original birth and death process via their stationary distributions.

THE WEAK CONVERGENCE-BASED DIFFUSION

The first diffusion approximation we consider is based on the following result which follows from a more general theorem of McNeil & Schach (1973).

THEOREM

If $\{X_n(t)\}$ is a sequence of birth and death processes as defined above, then

$$\frac{X_n(t) - \dfrac{\beta n}{\alpha+\beta}}{\sqrt{n}} \xrightarrow{w} U(t) \tag{4.1}$$

where $\xrightarrow{w}$ means weak convergence and $\{U(t)\}$ is an Ornstein-Uhlenbeck process with stochastic differential equation

$$dU = -(\alpha+\beta)U\,dt + \sqrt{\frac{2\alpha\beta}{\alpha+\beta}}\,dW \tag{4.2}$$

where $\{W(t)\}$ is a standard Wiener process.

We note that the mean and variance of $U(t)$ are given by

$$E(U(t)) = u_0\,e^{-(\alpha+\beta)t} \tag{4.3}$$

$$\mathrm{Var}\,(U(t)) = \frac{\alpha\beta}{(\alpha+\beta)^2}(1-e^{-2(\alpha+\beta)t}) \tag{4.4}$$

where $\Pr\{U(0)=u_0\}=1$. For an account of weak convergence see for example Billingsley (1968) or Kurtz (1981).

To obtain what we call the weak convergence based diffusion approximation $\{Y_n(t)\}$ we simply rearrange the expression in the convergence result and put

$$Y_n(t) = \frac{\beta n}{\alpha+\beta} + \sqrt{n}\,U(t). \tag{4.5}$$

The Ornstein-Uhlenbeck process is much studied. It has $\pm\infty$ as natural boundaries and is Gaussian. At time t we therefore have that $Y_n(t)$ is a normal random variable with mean

$$E(Y_n(t)) = \frac{\beta n}{\alpha+\beta} + \left(Y_n(0) - \frac{\beta n}{\alpha+\beta}\right)e^{-(\alpha+\beta)t} \tag{4.6}$$

and variance

$$\mathrm{Var}\,(Y_n(t)) = \frac{\alpha\beta n}{(\alpha+\beta)^2}(1-e^{-2(\alpha+\beta)t}). \tag{4.7}$$

Just as with the birth and death process we may define a stationary version $\hat{Y}_n$ which Y_n approaches at $t\to\infty$. It is clear that $\hat{Y}_n(t)$ is a normal random variable with mean and variance which are the same as those of $\hat{X}_n(t)$. Hence its density is

$$\tilde{p}_{\hat{Y}_n}(y) = \frac{\alpha+\beta}{\sqrt{2\pi\alpha\beta n}}\exp\left\{-\frac{\left(y-\frac{\beta n}{\alpha+\beta}\right)^2(\alpha+\beta)^2}{2\alpha\beta n}\right\}. \tag{4.8}$$

The covariance of $\hat{Y}_n(s)$ and $\hat{Y}_n(t)$ is also given by (3.8).

THE STANDARD DIFFUSION APPROXIMATION

When a diffusion process is so constructed by simply ascribing to it the infinitesimal mean and variance of the original process, we call such an approximation the standard diffusion approximation. It has the advantage of being easy to derive without appealing to any convergence results. From the transition probabilities of the birth and death process given by (2.2) we find

$$E(X_n(t+\Delta t)-X_n(t)\,|\,X_n(t)=z)=(\beta n-(\alpha+\beta)z)\Delta t+o(\Delta t) \tag{4.9}$$

$$\operatorname{Var}(X_n(t+\Delta t)-X_n(t)\,|\,X_n(t)=z)=(\beta n+(\alpha-\beta)z)\Delta t+o(\Delta t). \tag{4.10}$$

It follows that the infinitesimal mean and variance of the standard diffusion approximation, which we denote by $\{Z_n(t)\}$ are $\beta n-(\alpha+\beta)z$ and $\beta n+(\alpha-\beta)z$ respectively. Put in another notation, the stochastic differential equation of this process is

$$\mathrm{d}Z_n=(\beta n-(\alpha+\beta)Z_n)\,\mathrm{d}t+\sqrt{\beta n+(\alpha-\beta)Z_n}\,\mathrm{d}W. \tag{4.11}$$

This process is more difficult to analyze than the previous diffusion. If its transition density is $p(z,t\,|\,z_0)$ then this will obey a forward Kolmogorov equation

$$\frac{\partial p}{\partial t}=-\frac{\partial}{\partial z}([\beta n-(\alpha+\beta)z]p)+\frac{1}{2}\frac{\partial^2}{\partial z^2}([\beta n+(\alpha-\beta)z]p). \tag{4.12}$$

The range of $Z_n(t)$ is arbitrary. One choice is that of the original birth and death process, $[0, n]$. One could then arbitarily decide what boundary conditions to apply at 0 and n. However, there is an alternative procedure which turns out to be very advantageous. This is as follows.

One notices that the infinitesimal mean vanishes at

$$z_{1,n}=\frac{\beta n}{\alpha+\beta}$$

and the infinitesimal variance vanishes at

$$z_{2,n}=-\frac{\beta n}{\alpha+\beta}.$$

On investigating the nature of these points as boundary points for the process $Z_n(t)$ (see for example Breiman, 1968) one finds that $z_{1,n}$ is regular and $z_{2,n}$ is entrance. That this is the case is actually clear on physical grounds by examining the magnitudes of the drift and the diffusion terms at these points. A convenient choice for the range of Z_n is thus $(z_{2,n},\infty)$. It will be seen that with this choice of possible values, Z_n actually spends very little time outside the interval $[0, n]$.

Let the stationary density for Z_n be $\tilde{p}(z)$. Then, from (4.12) $\tilde{p}$ must satisfy the ordinary differential equation

$$\frac{1}{2}\frac{\mathrm{d}^2}{\mathrm{d}z^2}([\beta n+(\alpha-\beta)z]\tilde{p})-\frac{\mathrm{d}}{\mathrm{d}z}([\beta n-(\alpha+\beta)z]\tilde{p})=0, \qquad z_{2,n}<z<\infty. \tag{4.13}$$

Integrating twice gives a general solution

$$\tilde{p}(z)=k_1\left(\int_0^z \mathrm{e}^{Ax}(a+cx)^{-B}\,\mathrm{d}x\right)\mathrm{e}^{-Az}(a+cz)^{B-1}+k_2\,\mathrm{e}^{-Az}(a+cz)^{B-1} \tag{4.14}$$

where we have introduced the constants

$$a = \beta n$$

$$A = \frac{2(\alpha + \beta)}{(\alpha - \beta)}$$

$$B = \frac{4\alpha a}{(\alpha - \beta)^2}$$

$$c = \alpha - \beta.$$

Analysis reveals that in order that $\tilde{p}$ remain positive for all z in $(z_{2,n}, \infty)$ we must put $k_1 = 0$. The normalization requirement $\int \tilde{p}\, dz = 1$ then provides the values of k_2. There then results the following expression for the stationary density

$$\tilde{p}(z) = \frac{A^B C^{1-B} e^{-Aa/c}}{\Gamma(B)} e^{-Az}(a + cz)^{B-1}. \tag{4.15}$$

To underscore the fact that the choice of range for Z_n was a good one, it is noted that the mean and variance of the distribution with density (4.15) are precisely those of the stationary birth and death process $\hat{X}_n$.

We see therefore that we have three random processes, the original birth and death proces $\{X_n(t)\}$ and the two diffusion approximations $\{Y_n(t)\}$ and $\{Z_n(t)\}$ with corresponding stationary versions $\{\hat{X}_n(t)\}$, $\{\hat{Y}_n(t)\}$ and $\{\hat{Z}_n(t)\}$ all of which have the same mean and variance.

The stationary distributions of the three processes are given by (3.9), (4.8) and (4.15). In order to show how close these three distributions are we have calculated them for the following values of the parameters: $\alpha = 0{\cdot}2\ \text{msec}^{-1}$, $\beta = 0{\cdot}02\ \text{msec}^{-1}$, $n = 100$ and the results are shown in Fig. 1. The binomial distribution for $\hat{X}_{100}$ has a maximum at $\Pr(X_{100} = 9) = 0{\cdot}138$ and the densities of $\hat{Y}_{100}$ and $\hat{Z}_{100}$ were drawn

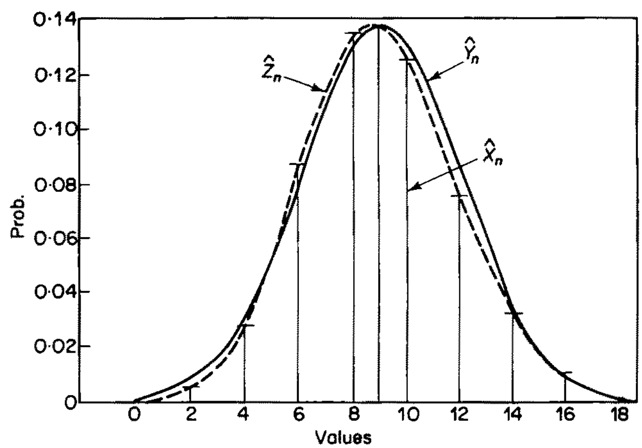

FIG. 1. A comparison of the binomial distribution for the stationary birth and death process $\hat{X}_n$ with the stationary densities of the diffusion approximations $\hat{Y}_n$ and $\hat{Z}_n$.

on such a scale that their maximum values are also 0·138. In all cases the maximum values are 9·09 and the standard deviations are 2·87. It can be seen that there is very close agreement amongst the three distributions, thus supporting the use of the diffusion approximations when the number of channels is large. However, n could probably still be much smaller and the agreement still be quite good.

5. Voltage Response to Conductance Fluctuations

We will investigate the response of a space-clamped patch of membrane to conductance fluctuations. To this end, we consider a circuit containing a current source I and the following elements in parallel: a membrane capacitance C_m, a membrane conductance $G_m > 0$, and a fluctuating conductance due to the opening and closing of channels, which we denote by g. The equilibrium potential associated with the ionic current through the channels is V_E and the voltage across the membrane is V. Thus we have the following differential equation

$$C_m \frac{\mathrm{d}V}{\mathrm{d}t} + G_m V = I + (V_E - V)g(t). \tag{5.1}$$

Now put

$$\frac{G_m}{C_m} = \gamma \tag{5.2}$$

$$\frac{V_E}{C_m} = V_e \tag{5.3}$$

and assume that the voltage fluctuations are small relative to V_E so that $V_E \gg V$. Then we may consider, in the absence of applied currents,

$$\frac{\mathrm{d}V}{\mathrm{d}t} + \gamma V = V_e g(t), \qquad V(0) = v_0. \tag{5.4}$$

The solution of this equation is

$$V(t) = v_0 \,\mathrm{e}^{-t} + V_e \,\mathrm{e}^{-\gamma t} \int_0^t \mathrm{e}^{\gamma t'} g(t')\,\mathrm{d}t' \tag{5.5}$$

and one may now determine the properties of the process $\{V(t)\}$.

Taking expectations gives

$$E(V(t)) = v_0 \,\mathrm{e}^{-\gamma t} + V_e \,\mathrm{e}^{-\gamma t} \int_0^t \mathrm{e}^{\gamma t'} E(g(t'))\,\mathrm{d}t'. \tag{5.6}$$

Employing the birth and death process $\{X_n(t)\}$ to represent $\{g(t)\}$ as in (3.10) and calling the corresponding voltage V_n,

$$E(V_n(t)) = v_0 \,\mathrm{e}^{-\gamma t} + \bar{g} V_e \left[\frac{\left(n_0 - \dfrac{\beta n}{\alpha + \beta} \right)}{\gamma - (\alpha + \beta)} \left\{ \mathrm{e}^{-(\alpha+\beta)t} - \mathrm{e}^{-\gamma t} \right\} + \frac{\beta n}{\gamma(\alpha + \beta)} \left\{ 1 - \mathrm{e}^{-\gamma t} \right\} \right] \tag{5.7}$$

It is clear that as $t \to \infty$, $E(V(t))$ approaches the steady state value

$$E(V_n(\infty)) = \frac{V_e \beta n \bar{g}}{\gamma(\alpha+\beta)}. \tag{5.8}$$

This quantity has an interesting physical interpretation, expecially when we write it in the following form

$$E(V_n(\infty)) = V_E \left(\frac{\beta}{\alpha+\beta}\right)\left(\frac{\bar{G}}{G_m}\right) \tag{5.9}$$

where

$$\bar{G} = \bar{g}n \tag{5.10}$$

is the total available conductance via ionic channels when they are all in the open state. Realizing that the mean time spent in the open state is $1/\alpha$ and that the mean time spent in the closed state is $1/\beta$, we see that (5.9) can be expressed as

Mean steady state membrane potential
= ionic equilibrium potential × fraction of mean time that channels are open
× ratio of total channel conductance to non-channel conductance. (5.11)

Invoking erogodicity we find that the mean measured membrane potential will be given by (5.9), or, in words (5.11). Thus, when there is fluctuating conductance due to channel opening and closing, the apparent *resting potential is shifted in the direction of* V_E *by an amount given by* (5.9). Since the expressions for $E(Y_n(t))$ and $E(Z_n(t))$ are identical to that for $E(X_n(t))$, the results (5.7), (5.9) and (5.11) apply when either of the diffusion approximations are employed.

6. Covariance, Variance and Spectral Density

There are two covariance calculations which we will perform for the voltage. One is for the process defined already as $\{V(t)\}$ in (5.5). The other is for the voltage process which results when one used the stationary version $\hat{g}(t)$ of the fluctuating conductance which is given by $\bar{g}$ times the stationary version $\hat{X}(t)$ of the birth and death process. In the latter case we define

$$V^*(t) = v_0^* \, e^{-\gamma t} + V_e \, e^{-\gamma t} \int_0^t e^{\gamma t'} \hat{g}(t') \, dt'. \tag{6.1}$$

Then using the standard formula for the covariance of the integral of a process (e.g. Parzen, 1962) we find

$$\operatorname{Cov}(V^*(t_1), V^*(t_1+\tau)) = V_e^2 \, e^{-\gamma(2t_1+\tau)} \int_0^{t_1} dt' \int_0^{t_1+\tau} dt'' \, e^{\gamma(t'+t'')} \operatorname{Cov}(\hat{g}(t'), \hat{g}(t'')). \tag{6.2}$$

Utilizing (3.8) and performing the required integration gives

$$\operatorname{Cov}(V_n^*(t_1), V_n^*(t_1+\tau)) = \frac{V_e^2 \bar{g}^2 \alpha\beta n}{(\alpha+\beta)^2(\gamma+\alpha+\beta)(\gamma-\alpha-\beta)}(e^{-\tau(\alpha+\beta)} - e^{-t_1(\gamma-\alpha-\beta)-\gamma\tau} - e^{-t_1(\gamma+\alpha+\beta)-\tau(\alpha+\beta)} + e^{-2\gamma t_1-\gamma\tau}),$$

where the subscript n on V_n^* as usual indicates the number of channels, Clearly as $t_1 \to \infty$ this becomes the covariance of a covariance stationary process

$$K_{\hat{V}_n}(\tau) = \frac{V_e^2 \bar{g}^2 \alpha\beta n}{(\alpha+\beta)^2(\gamma+\alpha+\beta)(\gamma-\alpha-\beta)} \mathrm{e}^{-\tau(\alpha+\beta)} \tag{6.4}$$

and the variance is

$$\operatorname{Var}(V_n^*(t)) = \frac{V_e^2 \bar{g}^2 \alpha\beta n}{(\alpha+\beta)^2(\gamma+\alpha+\beta)(\gamma-\alpha-\beta)} \times (1 - \mathrm{e}^{-t(\gamma-\alpha-\beta)} - \mathrm{e}^{-t(\gamma+\alpha+\beta)} + \mathrm{e}^{-2\gamma t}) \tag{6.5}$$

with asymptotic value

$$\operatorname{Var}(\hat{V}_n^*(t)) = \frac{V_e^2 \bar{g}^2 \alpha\beta n}{(\alpha+\beta)^2(\gamma+\alpha+\beta)(\gamma-\alpha-\beta)}. \tag{6.6}$$

When instead the original birth and death process is used for the conductance we obtain,

$$\operatorname{Cov}(V(t_1), V(t_1+\tau)) = V_e^2 \mathrm{e}^{-\gamma(2t_1+\tau)} \int_0^{t_1} \mathrm{d}t' \int_0^{t_1+\tau} \mathrm{d}t'' \, \mathrm{e}^{\gamma(t'+t'')} \operatorname{Cov}(g(t'), g(t'')) \tag{6.7}$$

and this results in

$$\begin{aligned}
&\operatorname{Cov}(V_n(t_1), V_n(t_1+\tau)) \\
&\quad = \operatorname{Cov}(V_n^*(t_1), V_n^*(t_1+\tau)) + V_e^2 \bar{g}^2 \Bigg(\frac{c_2}{\gamma(\gamma-\alpha-\beta)} \{\mathrm{e}^{-(\alpha+\beta)(t_1+\tau)} - \mathrm{e}^{-\gamma(t_1+\tau)} \\
&\quad - \mathrm{e}^{-\gamma(\gamma+\alpha+\beta)t_1 - (\alpha+\beta)\tau} - \mathrm{e}^{-2\gamma t_1 - \gamma\tau}\} \\
&\quad + \frac{c_3}{(\gamma-\alpha-\beta)^2} \{\mathrm{e}^{-(\alpha+\beta)(t_1+\tau)} - \mathrm{e}^{-(\gamma+\alpha+\beta)t_1 - \gamma\tau} \\
&\quad - \mathrm{e}^{-(\gamma+\alpha+\beta)t_1 - (\alpha+\beta)\tau} + \mathrm{e}^{-2\gamma t_1 - \gamma\tau}\} \Bigg).
\end{aligned} \tag{6.8}$$

It is apparent that as $t_1 \to \infty$

$$\operatorname{Cov}(V_n(t_1), V_n(t_1+\tau)) \to \operatorname{Cov}(V_n^*(t_1), V_n^*(t_1+\tau))$$

regardless of the initial probabilities $p_{1,j}(0)$ which occur in c_2 and c_3. Furthermore, if the initial probabilities are the stationary ones for each channel, the covariances of V_n and V_n^* are equal for all t_1 and all τ.

If we wish to compute the spectral density of the voltage response when the covariance stationary form has been attained, it matters not whether we use V_n^* or V_n. Thus in either case the *spectral density* is the Fourier transform of (6.4)

$$f_{\hat{V}_n}(\omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \mathrm{e}^{-i\tau\omega} K_{\hat{V}_n}(\tau) \, \mathrm{d}\tau.$$

This gives the familiar Lorentzian,

$$f_{\hat{V}_n}(\omega) = \frac{V_e^2 \bar{g} \alpha\beta n}{\pi(\alpha+\beta)(\gamma+\alpha+\beta)(\gamma-\alpha-\beta)} \cdot \frac{1}{(\alpha+\beta)^2+\omega^2}.$$

Thus the spectral densities of (a) the single channel conductance (b) the conductance of a patch containing many channels (c) the voltage response of a patch containing a finite arbitrary number of channels all have the same form and the value of $\alpha+\beta \simeq \alpha$ may be obtained from any one of them.

Finally we make some remarks concerning the use of the weak convergence based diffusion approximation. Letting V_n be the voltage across an n-channel patch with conductance represented by the birth and death process, the previous weak convergence result may be restated as

$$\frac{1}{\sqrt{n}}\left(\frac{\mathrm{d}V_n/\mathrm{d}t+\gamma V_n}{V_e\bar{g}}-\frac{\beta n}{\alpha+\beta}\right) \xrightarrow{w} U(t).$$

The left-hand side is a sequence of processes—random elements with values in the metric space $D[0,\infty)$. Multiplying by $\mathrm{e}^{\gamma t}$ and integrating from 0 to t and making use of Corollary 1 of Theorem 5.1 of Billingsley (1968, p. 31), we have

$$\left[\frac{\mathrm{e}^{\gamma t}V_n(t)-V_n(0)}{V_e\bar{g}}-\frac{\beta n}{\gamma(\alpha+\beta)}(\mathrm{e}^{\gamma t}-1)\right]\Big/\sqrt{n} \xrightarrow{w} \int_0^t \mathrm{e}^{\gamma t'}V(t')\,\mathrm{d}t'.$$

Putting $V_n(0)=v_0$, a further rearrangement shows that $V_n(t)$ is approximately distributed, for large n, as

$$V_n(t) \overset{d}{\simeq} V_e\bar{g}\left(\sqrt{n}\,\mathrm{e}^{-\gamma t}\int_0^t \mathrm{e}^{\gamma t'}U(t')\,\mathrm{d}t'+v_0\,\mathrm{e}^{-\gamma t}+\frac{\beta n}{\gamma(\alpha+\beta)}(1-\mathrm{e}^{-\gamma t})\right).$$

Since $U(t)$ is Gaussian, we see that $V_n(t)$ is approximately normally distributed with known mean and variance. The mean is

$$E(V_n(t)) = V_e\bar{g}\left(\frac{u_0\sqrt{n}}{\gamma-\alpha-\beta}\{\mathrm{e}^{-(\alpha+\beta)t}-\mathrm{e}^{-\gamma t}\}+v_0\,\mathrm{e}^{-\gamma t}+\frac{\beta n}{\gamma(\alpha+\beta)}(1-\mathrm{e}^{-\gamma t})\right).$$

Thus as $t\to\infty$, $V_n(t)$ approaches a stationary version with mean

$$E(V_n(\infty))=\frac{\beta n V_e\bar{g}}{\gamma(\alpha+\beta)}$$

which agrees with (5.8). The exact distribution of $V_n(t)$ using the birth and death process is difficult to determine but the diffusion approximation enables an estimate of this distribution to be easily made as $V_n(t)$ is well approximated by a Gaussian random variable with known mean and variance. This is vividly reinforced by examining the voltage noise distribution in motoneurons as reported by Jack *et al.* (1981).

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