Poisson Processes in Biology

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1. Introduction

A simple Poisson process, $[N(t), t \geqslant 0]$, with parameter λ, is a random process with stationary independent increments such that if $0 < t_1 < t_2$, then

(1) $\quad Pr[N(t_2) - N(t_1) = k] = [\lambda(t_2-t_1)]^k \exp[-\lambda(t_2-t_1)]/k!$

$k = 0,1,2..$

As Khintchine [15] pointed out, it is more of a surprise than not that some naturally occurring processes look like simple Poisson processes. This extends into biology. An example arises at the junction between nerve and muscle called neuromuscular junction. Here little blips called miniature end plate potentials, representing changes in the electric potential difference across the muscle membrane, occur under certain conditions in accordance with the defining characteristics of a simple Poisson process [6,8]. The 'Poisson hypothesis' for these events has been looked at very closely with a battery of statistical tests [3,4]. Not surprisingly this has ultimately led to the refutation of the hypothesis. The subject is still of current interest in pharmacology because drugs may have a drastic effect on the sequence of times of occurrence of the miniature end plate potentials [20]. As yet the mechanisms involved in the events which culminate in the miniature end plate potentials have not been delineated, so it is a fertile area for modeling.

We will be concerned with the application of Poisson processes in models in neurobiology and population biology. Some of the work has appeared and some will appear in more detail in the near future. I am indebted to several people with whom the work has been joint or has benefited greatly from discussion - Davis K. Cope, Floyd B. Hanson, John B. Walsh and Frederic Y.M. Wan.

2. Modeling the activity of nerve cells

2.1. Biological Background

The fundamental unit of the nervous system is the nerve cell or neuron. Such cells have many different forms but the traditional paradigm is that a cell has the following important features. A branching structure called the dendritic tree, a cell body or soma which is often about spherical or pyramidal and an axon which starts somewhere around the cell body and extends possibly over large distances to often bifurcate and form junctions called synapses with 'target cells'.

Most neurons emit <u>action potentials</u> which usually tend to form at a region on the neuronal surface where there is a high density of sodium ion channels. This region is called a <u>trigger zone</u> and is often located just by the cell body. The occurrence of an action potential can be monitored by an extracellular or intracellular microelectrode and the times of occurrence recorded and stored in a computer.

Evidence for the variability of the time interval between action potentials even under 'steady' input conditions is now overwhelming. The first examples came from receptor cells called muscle spindles of frog [1,10]. Neurons in mammalian brain also exhibit various degrees of variability in their <u>interspike intervals</u>, the name often employed for the time between action potentials. Interest in this variability from an experimental point of view comes from classify-ing the pattern of activity in accordance with anatomical location [19] or with the behavioral state of the animal [2]. There is also the question of information transmission in the nervous system which seeks to explain how a sequence of spikes is read by target cells when the sequence is apparently random [18]. Here it is opportune to point out that variability of interspike times does not necessar-ily imply randomness in the mechanisms which produce the spikes. This can be seen by applying Scharstein's [23] novel graphical method of predicting a spike train from a given input current to a simple neuron model. The input may be completely regular (e.g. sinu-soidal) yet the output train can be highly irregular. The distinc-tion between this and the 'random spike train' can be found by computing serial correlation coefficients.

If the spike sequence from a neuron is random we address the question of how this randomness arises and attempt to elucidate the pattern of activity of cells with the aid of models for nerve cell activity. There are thought to be two main sources of randomness which contribute to the variability of the interspike interval. These are fluctuations in the properties of the spike generating mechanism and the random nature of the synaptic input. An example of a study of the former is that of Levine & Shefner [17]. Concern-ing the latter it should be noted that many neurons are covered with possibly thousands of synapses which are not all synchronized in their activity so that particularly for a 'spontaneously active' cell, the randomness of the synaptic input is a good candidate for producing variability in the spike train.

We will consider a few models of nerve cell activity with random input. The physiologist will realize how much reality is left out of these models, but unfortunately even the 'simple' models generate very difficult problems when we begin to ask for quantitative results. A review of the subject is contained in Holden's monograph [14].

2.2 Stein's model

In this model which was introduced by Stein [24], the spatial extent of the cell is ignored. Some justification for this comes from the existence of trigger zones which are usually quite small. Based on neurophysiological investigations with intracellular electrodes the electrical activity of some cells can be approximated as that of a resistor and capacitor in parallel. This leads to exponential decay of the depolarization in the absence of inputs. The model actually

dates back to 1907 when it was used by Lapicque [16]. The input currents to this model cell are approximated by delta functions and their arrival times made to coincide with the times of occurrence of events in simple Poisson processes.

Let $X(t)$ be the depolarization at time t with initial value $X(0) = x$. Excitation increases $X(t)$ by a_1 units and has mean rate λ_1; inhibition arrives independently, decreasing $X(t)$ by a_2 and has mean rate λ_2. Taking account of the exponential decay we can write a stochastic differential equation for $X(t)$:

$$(2) \quad dX(t) = -X(t)dt + a_1 dN_1(t) - a_2 dN_2(t), \quad X(0) = x, \quad X(t) < \theta,$$

where $N_1(t)$ and $N_2(t)$ are Poisson processes with parameters λ_1 and λ_2. Here time is measured in units of the membrane time constant. The equation is valid only for $X(t)$ less than the threshold for firing of action potentials which is assumed in the first instance to be constant. Let $T_\theta(x)$ be the random variable

$$(3) \quad T_\theta(x) = \inf\{t \mid X(t) \geqslant \theta \mid X(0) = x < \theta\}.$$

We identify this as the random time between action potentials, save for the addition of an assumed fixed absolute refractory period. $T_\theta(x)$ is a <u>first passage time</u> for $X(t)$ to level θ. The determination of the distribution function of $T_\theta(x)$ requires solution of a partial differential difference equation, whereas finding the moments of $T_\theta(x)$ requires solution of the recursion system of ordinary differential difference equations. With $M_n(x)$ the n-th moment, these are

$$(4) \quad -x\frac{dM_n}{dx} + \lambda_1 M_n(x + a_1) + \lambda_2 M_n(x - a_2) - (\lambda_1 + \lambda_2)M_n(x) = -nM_{n-1}(x),$$

$n = 0,1,2,\ldots$, $x < \theta$., as can be found by applying theorems on first exit times for Markov processes [28]. Equations such as this have been investigated hardly at all, especially on account of the occurrence of both forward and backward differences. The boundary condition at θ is that $M_n(x) = 0$, $x \geqslant \theta$, $n = 1,2,\ldots$ but with $\lambda_2 \neq 0$ the condition at $x = -\infty$ is difficult to prescribe.

2.2.1 An exact calculation

When $\lambda_2 = 0$ (no inhibition) we can sometimes solve (4) for small θ and small n exactly. A simple illustrative example will suffice. For convenience set $\lambda_1 = a_1 = 1$ and consider the equation for the first moment:

$$(5) \quad -x\frac{dM_1}{dx} + M_1(x + 1) - M_1(x) = -1, \quad x < 2.$$

We can restrict the domain of M_1 to $[x_1, 2)$ where $x_1 < 0$. $X(t)$ can only exit from $[x_1, 2)$ at the right hand end point. It is sufficient for our problem to take $x_1 = 0$ because we are primarily interested in an initial condition at resting level, $x = 0$. On $[1,2)$ put $M_1(x) = F_1(x)$ and on $[0,1)$ put $M_1(x) = F_2(x)$. Then F_1 satisfies the simple ordinary differential equation

$$(6) \quad \frac{dF_1}{dx} + \frac{F_1}{x} = \frac{1}{x},$$

with solution $F_1(x) = x^{-1}[x + c_1]$, with c_1 a constant of integration. This is used on $[0,1)$:

(7) $\quad \dfrac{dF_2}{dx} + \dfrac{F_2}{x} = \dfrac{2}{x} + \dfrac{c_1}{x(x+1)}$.

This is solved to give

(8) $\quad F_2(x) = x^{-1}[2x + c_1 \ell n(x+1) + c_2]$,

with c_2 a second constant of integration. The values of c_1 and c_2 are found by imposing the conditions that $M_1(x)$ is continuous and bounded on $[0,2)$. This leads to the solution

(9) $\quad M_1(x) = \begin{cases} 1 + [1/(1 - \ell n 2)]x, & x \in [1,2), \\ \\ 2 + [1/(1 - \ell n 2)][\ell n(x+1)]/x, & x \in [0,1). \end{cases}$

This solution has a discontinuity at $x = 2$ where it jumps from a positive value to zero (see Figure 2 of [27]). Exact calculation is possible for other parameter values and for the second moment as long as the threshold θ is small (less than three). These calculations do reveal some interesting facts concerning the coefficient of variation of the interspike interval. Physiologists use coefficient of variation as a measure of the noisiness of the transmitted signal, as it is in fact the inverse of the 'signal to noise ratio'. It had been thought that the coefficient of variation was a monotonically increasing function of the mean interval but calculations reveal that in some parameter ranges the dependence is not monotonic but includes maxima and minima for a given threshold. However, it seems that the predicted structure may not be observed experimentally because it is based on a model which is not realistic enough and other sources of randomness would drown out the structure. Full details are in [32].

2.2.2 Numerical methods

For large θ and when there is inhibition we have solved the differential difference equation (4) for small n by two methods [5, 32]. In the first approach, devised by Wolfgang Richter, the differential difference equation is written as a coupled linear system of ordinary differential equations which was solved using Runge-Kutta techniques. It was possible to ascertain the dependence of the moments of the interspike time on θ and also on the input rate of excitation. An attempt was made by the method of moments to predict the three parameters of the model (the threshold to excitatory postsynaptic potential amplitude ratio, the time constant of the cell membrane circuit and the rate of arrival of excitatory inputs) for two cells of the cat cochlear nucleus. Though the predicted values are all reasonable, they cannot be taken seriously because of the great oversimplifications of the model and the assumptions made in its implementation.

When there is inhibition we have employed a different technique [5]. This relied on an asymptotic form for the solution for large negative x which contained an additive unknown constant. The solution is thus extended to positive values of x and the boundary condition at θ was employed to find the previously unknown constant. This method seemed to work although no boundary condition was employed at large negative x. The integration of such equations could benefit from theoretical investigations, with particular emphasis on the development of numerical methods.

2.2.3 Diffusion approximation

A diffusion approximation, $X^*(t)$, may be constructed for $X(t)$ given by equation (2), such that the first and second infinitesimal moments of the two processes are the same. This leads to

$$(10) \quad dX^*(t) = (-X^*(t) + \alpha)dt + \sigma dW(t),$$

where $\alpha = \lambda_1 a_1 - \lambda_2 a_2$, $\sigma = (\lambda_1 a_1^2 + \lambda_2 a_2^2)^{1/2}$ and $W(t)$ is a standard Wiener process. The sequence of approximating processes whose infinitesimal moments converge to those of $X^*(t)$ is the Ornstein-Uhlenbeck process which has mainly appeared in connection with modeling the phenomenon of Brownian motion. By computing solutions of the differential difference equation (4) and comparing them with solutions of the corresponding equation for $X^*(t)$:

$$(11) \quad \frac{\sigma^2}{2} \frac{d^2 M_n}{dx^2} + (\alpha - x) \frac{dM_n}{dx} = -nM_{n-1}(x), \quad n = 1, 2, \ldots,$$

[22] it is possible to see how the diffusion approximation fairs in estimating the threshold crossing time. This had been done for $n = 1$ and a general scheme for the error deduced. [31]. It is pointed out that overshoot of threshold can occur for the discontinuous process $X(t)$ but not the diffusion, $X^*(t)$.

2.2.4 Computer simulation

With package programs available for random number generation, it is straightforward to carry out computer simulations for Stein's nerve cell model. An example of first passage time densities for $X(t)$ obtained through approximating histograms is given in [29]. One feature of such densities is the presence of an extremely large tail in the case of inhibitory inputs and experimentalists' hypotheses about the nature of the density [2] were possibly explained. An interesting observation was that only when there was significant inhibition could the coefficient of variation of the interspike interval take values greater than units [30]. This leads to the conjecture that if the coefficient of variation is greater than one, then the cell under observation must be receiving significant amounts of inhibitory input. More recently Frederic Wan [36] has shown using singular perturbation methods for solving (11) with σ small, that this conjecture is true for the diffusion model $X^*(t)$.

2.2.5 Generalization of Stein's model

Stein's model may be generalized to include an arbitrary distribution of jump amplitudes [25]. Here $X(t)$ satisfies the stochastic differential equation

$$(12) \quad dX(t) = -X(t)dt + \int_R uN(du,dt),$$

where $N(.,.)$ is a Poisson random measure [9] such that

$$(13) \quad \Pr[N(A,t) = k] = (t\lambda(A))^k \exp[-t\lambda(A)]/k!, \quad A \in B(R), \quad k=0,1,2,\ldots.$$

$\lambda(\cdot)$ being the rate measure. The moment equations (4) become

$$(14) \quad -x \frac{dM_n}{dx} + \int_R M_n(x + u)\lambda(du) - \Lambda M_n(x) = -nM_{n-1}(x),$$

where Λ is the total jump rate. Apart from the case already considered, the case where there is an exponential ditribution of excitatory inputs has also been studied [26], in which case (14) becomes

$$(15) \qquad \frac{-x\,dM_n}{dx} + \alpha \int_R M_n(x + u)e^{-\beta u}du - \frac{\alpha}{\beta} M_n(x) = -nM_{n-1}(x).$$

A further generalization of the model equation (2) is the inclusion of smooth noise along with the discontinuities so that the process is a diffusion with jumps occuring at time intervals which are exponentially distributed:

$$(16) \qquad dX(t) = -X(t)dt + a_1 dN_1(t) - a_2 dN_2(t) + \sigma dW(t),$$

which leads to the moment equations

$$(17) \qquad \frac{\sigma^2}{2} \frac{d^2 M_n}{dx^2} - x \frac{dM_n}{dx} + \lambda_1 M_n(x + a_1) + \lambda_2 M_n(x - a_2) - (\lambda_1 + \lambda_2)M_n(x)$$

$$= -nM_{n-1}(x), \qquad n = 1,2,\ldots$$

This equation should yield some interesting problems in singular perturbation methods and is of interest to see how small jitter may influence the firing time in the presence of random inputs of larger magnitudes.

2.3.   Modification of Stein's model

In Stein's model the amplitude of the postsynaptic potentials is independent of the value of the membrane potential at their time of occurrence. There is much physiological evidence that this is not true and that for excitation and inhibition there are reversal potentials [7] at which these amplitudes become zero. To include these reversal potentials is not difficult formally as we now have:

$$(18) \qquad dX(t) = -X(t)dt + (X_1 - X(t))a_1 dN_1(t) + (X_2 - X(t))a_2 dN_2(t), X(0)=x,$$

where X_1 and X_2 are the (constant) reversal potentials and a_1 and a_2 are further constants. The earlier form for the expectation of $X(t)$ [30] should read

$$(19) \qquad E[X(t)] = (k_2/k_1) + [x - (k_2/k_1)]\exp(-k_1 t),$$

where $k_1 = 1 + \lambda_1 a_1 + \lambda_2 a_2$, $k_2 = \lambda_1 a_1 X_1 + \lambda_2 a_2 X_2$. λ_1 and λ_2 being the rate parameters of the Poisson processes. I thank Charles Smith for pointing this out.

The first passage time moments now satisfy a slightly different set of differential difference equations which cannot be solved as a system of ordinary equations on intervals of constant size. Some analytic results were obtained for excitation only and it was found that for reasonable values of the reversal potentials, substantially different firing times occur [30].

2.4   Varying Threshold

In the above models the threshold for action potential generation was assumed to be constant. This is an approximation for most cells as there is intrinsic refractoriness as well as threshold elevation

due to aftercurrents. These phenomena can be included in the above framework by making θ a function of time.

A method for handling time varying thresholds is available if the threshold satisfies a differential equation of first order. The following result for a general Markov process is obtained not by viewing first passage of a scalar process $X(t)$ to a time varying barrier $Y(t)$ but by considering the equivalent first exit problem in the phase plane for the vector valued process $(X(t), Y(t))$.

Theorem. Let $X(t)$ be a Markov process satisfying the stochastic differential equation

$$(20) \quad dX(t) = \alpha(X(t))dt + \beta(X(t))dW(t) + \int_R \gamma(X(t),u)N(du,dt), X(0) = x,$$

and let $Y(t)$ be the solution of the deterministic equation

$$(21) \quad dY(t)/dt = \delta(Y(t)), \quad Y(0) = y.$$

Let $T(x,y)$ be the time of first passage of $X(t)$ to $Y(t)$:

$$(22) \quad T(x,y) = \inf\{t | X(t) = Y(t) | X(0) = x, Y(0) = y\},$$

and set

$$(23) \quad M_n(x,y) = E[T^n(x,y)], \quad n = 1,2,\ldots$$

Then assuming $T(x,y)$ is finite with probability one, the moments satisfy the recursion system of partial-differential-integro equations,

$$(24) \quad \frac{1}{2} \beta^2(x) \frac{\partial^2 M_n(x,y)}{\partial x^2} + \alpha(x) \frac{\partial M_n}{\partial x} + \delta(y) \frac{\partial M_n}{\partial y}$$

$$+ \int_R M_n(x + \gamma(x,u))\lambda(du) - \Lambda M_n = -nM_{n-1},$$

with boundary conditions that $M_n(x,y) = 0$ for $x > y$, assuming $X(t)$ starts below $Y(t)$.

Proof. The proof is simple upon considering the vector valued process and applying standard results for first exit times. Further details can be found in [34] where some applications are presented.

2.5 Spatial Models

In deterministic modeling of nerve cells spatial effects have long known to be important. The same stimulus delivered close to the cell body will have a different effect when delivered on distal dendrites. The pioneering work in this area was Rall's [21]. We can consider instead of a point model such as Stein's, a spatial model of the kind used in deterministic modeling. Such models represent portions of the cell as cylinders with cable structures containing resistors and capacitors. These are still passive elements as no intrinsic threshold properties arise. With suitable units for time and distance, if we consider a nerve cylinder of length L with a Poisson input at $x = x_0 \in (0,L)$, we then find that the depolarization satisfies the <u>stochastic partial differential equation</u>

(25) $\quad \frac{\partial V}{\partial t} = -V + \frac{\partial^2 V}{\partial x^2} + \delta(x - x_0)a_1 \frac{dN_1}{dt}, \quad 0 < x < L, \quad t > 0,$

where $V(x,t)$ is the depolarization, a_1 is a constant, $\delta(.)$ is Dirac's delta function and $N_1(.)$ is a Poisson process with rate λ_1. We will assume for simplicity that the boundary conditions are

(26) $\quad V_x(0,t) = V_x(L,t) = 0,$

and the initial data is

(27) $\quad V(x,0) = 0,$

though the results extend to other cases. An eigenfunction expansion for $V(x,t)$,

(28) $\quad V(x,t) = \sum_{n=0}^{\infty} \phi_n(x)V_n(t),$

is possible, where

(29) $\quad \phi_n(x) = \begin{cases} (1/L)^{1/2}, & n = 0, \\ (2/L)^{1/2} \cos(n\pi x/L), & n = 1,2,\ldots, \end{cases}$

are the spatial eigenfunctions. The random processes $V_n(t)$ satisfy ordinary stochastic differential equations of the kind in Stein's point model:

(30) $\quad dV_n(t) = -\mu_n^2 V_n(t)\, dt + a_1\phi_n(x_0)dN_1(t),$

where the eigenvalues are,

(31) $\quad \mu_n^2 = 1 + n^2\pi^2/L^2, \quad n = 0,1,2,\ldots$

The moments of $V(x,t)$ are computable as infinite sums and their values in the steady state obtainable. Results are similar for the case of a white noise input for the first two moments and the covariance [33, 35]. First passage theory can be applied to truncated versions of the sum in (28) and lead to problems with vector-valued jump processes which have not been previously considered.

3. Modeling the growth of populations

There are many examples of population growth where sudden decreases occur apparently due to random disasters [12]. We have attacked the problem of estimating the persistence time of a population which is beset by occasional disasters of fixed magnitude by considering the population size as satisfying the stochastic differential equation

(32) $\quad dX(t) = rX(t)[1 - X(t)/K]dt - \alpha dN(t), \quad X(0) = x \in (0,K),$

where K is a constant called carrying capacity, r is the intrinsic growth rate and α is the magnitude of the portion of the population removed by a disaster. In the absence of disasters the growth obeys the simple logistic law.

For the model described by (32) the extinction of the population is considered as the passage of $X(t)$ to 0 for the first time. Hence the problems in calculating extinction time are very similar to those in determining the firing time of the nerve cell model of

Stein. The moments $M_n(x)$ of the extinction time now satisfy the recursion system,

$$(33) \quad rx(1 - \frac{x}{K}) \frac{dM_n}{dx} + \lambda[M_n(x - \alpha) - M_n(x)] = -nM_{n-1}(x),$$

$n = 1,2,\ldots,$ with boundary condition $M_n(x) = 0$ for $x < 0$. The equations for $n = 1,2$ have been solved by numerical methods employing a singular decomposition [11]. Probably the most interesting feature of these results, apart from their quantitative values, is the appearance of plateaus in the extinction time moments as functions of x for small disaster rates relative to the growth rates. The implication is a safety zone for populations in low disaster rate environments where the expected survival time is not very sensitive to how close the population size is to carrying capacity. That is, no ecological advantage is obtained by maintaining a high level population size when disasters are relatively infrequent.

We have also made the disasters a function of population size. The simplest problem to consider is that when the amount of the population removed is proportional to the present magnitude of the population. The stochastic differential equation for this case is

$$(34) \quad dX(t) = rX(t)[1 - X(t)/K]dt - \alpha X(t)dN(t), \quad X(0) = x, \quad 0 < \Delta < x < K.$$

Here the population cannot, if $\alpha < 1$, ever be driven to level zero, so a small level population size must be chosen as the extinction level. The equations corresponding to (33) become

$$(35) \quad rx(1 - \frac{x}{K}) \frac{dMn}{dx} + \lambda[M_n((1 - \alpha)x) - M_n(x)] = -nM_{n-1}(x),$$

and constant steps cannot be employed in the integration procedure. Numerical results as well as some computer simulations which enable a comparison to be made of the models (32) and (34) are contained in a forthcoming article [12]. We are currently extending these results to incorporate a distribution of disaster amplitudes in both density-dependent and density independent situations [13].

There are two kinds of problems in this area that would profit from attention. The first is the inclusion in a model such as (34) the presence of smaller amplitude noise by means of a diffusion term:

$$(36) \quad dX(t) = rX(t)[1 - X(t)/K]dt - \alpha X(t)dN(t) + \sigma dW(t),$$

where σ is small. The effects of this extra term will be to make zero accessible to $X(t)$ and the appropriate moment equations will be

$$(37) \quad rx(1 - \frac{x}{K}) \frac{dMn}{dx} + \frac{\sigma^2}{2} \frac{d^2 Mn}{dx^2} + \lambda[M_n((1 - \alpha)x) - M_n(x)] = -nM_{n-1}(x).$$

Again, such equations should lead to some interesting applications of singular perturbation methods with boundary layers at $x = 0$ and $x = K$. A second problem worth looking at in this context is a vector valued version of the above discontinuous model equations so that extinction in coupled systems of, say, predator and prey may be considered via their first exit times. However, both of these as yet untackled problems will present some very difficult computational tasks.

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