

FIRST PASSAGE TIMES IN BIOLOGY: APPROXIMATIONS

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INTRODUCTION:

The idea of a first passage time is easy to explain, but mathematically it is often very difficult to evaluate. Let  $X(t)$  be a random process in continuous time and let  $S(t)$  be a deterministic time function  $S(t)$  (an important special case is when  $S(t)$  is a constant). Given that  $X(t)$  has a value of  $x_0$  at time  $t_0$ , we want to know the time,  $t(S|x_0)$ , that  $X(t)$  FIRST crosses the boundary  $S(t)$ . Since this time varies from one sample path to the next,  $t(S|x_0)$  will be a random variable. Assuming  $x_0 < S(t_0)$ , then

$$t(S|x_0) = \inf\{t | X(t) \geq S(t) \text{ given } X(t_0) = x_0\}$$

The probability density function, p.d.f., of  $t(S|x_0)$  will be denoted by  $g(S, t|x_0)$ .

The first passage time is an example of a more general level crossing problem. An extensive bibliography of level crossing problems with emphasis on engineering applications can be found in Blake and Lindsey (1973) and Abrahams (1986). An introduction to the case where  $X(t)$  is a diffusion process (roughly, Markov with continuous sample paths) can be found in chapter 3 of Ricciardi (1977).

In this report, we primarily consider continuous time random processes with either a continuous state space or with first order discontinuities. In applications, these processes are often of the form of an autonomous stochastic differential equation (SDE), that is,

$$dx = a(x) dt + b(x) dW(t) \quad (1a)$$

or

$$dx = a(x) dt + b(x) dP(\lambda, t) \quad (1b)$$

where  $W(t)$  is a standard Wiener process (also called Brownian motion) and  $P(\lambda, t)$  is a homogeneous Poisson process with rate parameter  $\lambda$ . Intuitively, you can think of  $X(t)$  as the voltage trajectory in an RC circuit (with, in general, nonlinear elements) attached to a noisy current source.

The above scenario arises in many areas of biology: neurobiology (for reviews, see Holden, 1976; Yang and Chen, 1978; Tuckwell, 1987), population genetics (Maruyama, 1977, 1983), population biology and harvesting (e.g. Ryan and Hanson, 1985; Hanson and Tier, 1981), evolutionary biology (e.g., Lande, 1985; Kipnis and Newman, 1985), psychology (e.g., Ratcliff, 1980) and some other areas such as tumor growth (e.g., Smith and Tuckwell, 1973) and DNA sequence analysis.

Since this report concentrates on some heuristic approximation methods, a problem in neurobiology is used to illustrate the methods. The problem is the generation of action potentials in a nerve cell or neuron. A neuron is an animal cell with specialized electrical properties. When the voltage across the cell membrane at a particular spatial location, called the trigger zone, ex-

ceeds a voltage threshold, then a brief electrical pulse known as an action potential or spike ( $\approx 100$  mV and 1 msec in duration) is generated. The noisy input is due to inputs from other neurons at particular places on the neuron called synapses. If many inputs are present, central limit theory type arguments produce a diffusion approximation to the voltage process. On the other hand, when one or a few synapses dominate the behavior, a filtered Poisson model may be more appropriate.

We will illustrate some approximation methods for the first passage times through several neural models.  $X(t)$  will be the membrane voltage process referenced to the resting level, which is set to zero. The models are:

(I) the Ornstein-Uhlenbeck process (e.g., Sato, 1978; Ricciardi and Sarcedote, 1979)

$$dx = -x/\tau dt + \sigma dW(t) \quad (2)$$

with  $\tau$  and  $\sigma$  positive constants.

(II) Stein's model (Stein, 1967)

$$dx = -x/\tau dt + a_e dP(\lambda_e, t) - a_i dP(\lambda_i, t) \quad (3)$$

with  $\tau$ ,  $\lambda_e$ ,  $\lambda_i$ ,  $a_e$  and  $a_i$  all positive constants.

(III) Stein's model with a reversal potential (e.g., Tuckwell, 1979; Smith and Smith, 1984)

$$dx = -x/\tau dt + a_e (1-x/V_e) dP(\lambda_e, t) + a_i (1-x/V_i) dP(\lambda_i, t) \quad (4)$$

with the parameters as in model II and  $V_e > 0$  and  $V_i < 0$ .

(IV) a stochastic afterhyperpolarization model used to model the

firing of vestibular nerve fibers (Smith and Goldberg, 1986)

$$x(t) = (g_s V_s + g_k(t) V_k) / (1 + g_s + g_k(t)) \quad (5)$$

where  $V_s$  and  $V_k$  are positive (synaptic) and negative (potassium) equilibrium potentials respectively. The  $g$ 's are normalized membrane conductances with  $g_k(t)$  being a decaying exponential and  $g_s$  being a shot noise process produced by passing a Poisson impulse train through a causal, rectangular finite impulse response (FIR) filter. The leakage conductance has a value of 1.

Models I, II, III fit into the SDE framework of equation (1), while model IV is a timevarying, nonlinear transformation of a shot noise process. Model IV arises from a more complicated lumped circuit model of the trigger site with three parallel conductances: a leakage conductance, a synaptic conductance, and a potassium channel conductance. The voltage across the membrane satisfies a differential equation, which is approximated by equation (5) when the membrane time constant is short compared to the time constant of  $g_k(t)$  (see Smith and Goldberg, 1986 for details and biological justification for the approximation).

The approximation methods for first passage times will be classified according to whether or not the mean voltage,  $\mu(t)$ , of the process  $X(t)$  crosses the threshold  $S(t)$ . The term deterministic crossing will be used when the mean voltage crosses  $S(t)$  and nondeterministic crossing when the mean doesn't cross  $S(t)$ . For the deterministic crossing, we further distinguish two cases, long correlation time and short correlation time relative to the standard deviation of  $t(S|x_0)$ . For small fluctuations

about the mean voltage, the long correlation time case becomes a transformation of the voltage process at the time of deterministic crossing (Stein, 1967), while the short correlation case is approximated by a Wiener process with drift producing locally an inverse Gaussian distribution for the first passage time (Lerche, 1986). For nondeterministic crossings, the times of crossing become rare events as the threshold level becomes very large. In this case the first passage times have a limiting exponential distribution which is characteristic of a Poisson process. When  $S(t)$  is not a constant, the threshold can be subtracted from the mean voltage to give an "effective" mean voltage which can be thought of as a mean postspike recovery process. The problem now becomes when does the effective voltage process reach zero. The three approximation cases are now examined in more detail.

CASE 1: deterministic crossing, long correlation time

In this scenario the fluctuations in the first passage time (FPT) are basically small perturbations about the time,  $t^*$ , at which the mean voltage,  $\mu(t)$ , crosses  $S(t)$ . Our description is a simple generalization of the method used by Stein (1967, p 53) for model II. Let  $r(t) = S(t) - \mu(t)$  be the recovery process mentioned above,  $\sigma_t$  be the standard deviation of the first passage time distribution, and  $\sigma^*$  be our approximated standard deviation. The FPT p.d.f.  $g(S, t | x_0)$  can be approximated, at least locally, by a transformation of the marginal distribution of  $X(t)$  evaluated at  $t^*$  when: (1) the voltage distribution doesn't change its shape drastically near  $t^*$ , (2)  $\sigma_t$  is considerably

less than the correlation time of  $X(t)$  around  $t^*$ , (3)  $r(t)$  is invertible and sufficiently smooth. Let  $h$  be the inverse function of  $r(t)$ , that is  $h(r(t))=t$ . Then  $g(S,t|x_0)$  is approximately  $f(x)/|dh(x)/dx|$  evaluated at  $t^*$ , where  $f(x)$  is the marginal of  $X(t)$ . This is the usual Jacobian transformation of random variables. For example if  $f(x)$  is gaussian and  $r(t)$  is a decaying exponential, then  $g(S,t|x_0)$  is approximately lognormal.

In many cases we may only be interested in the first few moments of the FPT. The function  $h$  is now expanded in a Taylor series about  $r(t^*)$ . The approximations for the mean and variance are given below with  $y = r(t^*)$  and  $\mu_n$  is the  $n$ th central moment of  $X(t^*)$ .

$$E(t) \cong t^* + h''(y) \mu_2/2 + h'''(y) \mu_3/6 + \dots \quad (6)$$

$$\text{Var}(t) \cong (h' \mu_2)^2 + h' h'' \mu_3 - (h'' \mu_2/2 + h''' \mu_3/6)^2 + \dots \quad (7)$$

where prime denotes differentiation with respect to voltage. Recall that the first derivative of an inverse function can be expressed as the reciprocal of the derivative of the original function, so that

$$h' = 1 / (dr(t)/dt) = 1 / (dS(t)/dt - d\mu(t)/dt) \quad (8)$$

which is simply the derivative of the recovery process at  $t^*$ .

Stein's original approximation method was the first term of equations (6) and (7) and can be illustrated graphically as in Figure 1. Note that increasing  $h'$  decreases the approximate mean interval, so Stein required for condition (3) that  $r(t)$  be nearly linear in the neighborhood of  $t^*$ .

While we might expect such a procedure to work for diffusion processes, Figure 2 (model II, excitatory inputs only) and Table 1 (model III, excitatory inputs only) show that this approximation method also works for Poisson driven systems. In figure 2, the coefficient of variation,  $cv$ , (standard deviation divided by the mean) of the FPT is plotted against the  $cv$  of the voltage process for the case where the mean voltage trajectory is fixed by keeping the product  $a_e \lambda_e$  fixed at a constant value of 8 mV/msec. The solid line is that predicted from the above equations and has a slope of 0.92 and is a good approximation over this range. The correlation time of the process is in the worst case more than twice the resultant  $\sigma_t$ .

A similar procedure is followed in Table 1 for model III with the mean voltage being held constant in the same manner. Two different mean voltages were used (A,B) and (C,D) with the value of  $a_e$  differing by a factor of 16 within each pair. Further details can be found in Smith and Smith, 1984.

What happens if the three conditions above are not met, in particular what if the correlation time is quite short compared to  $\sigma_t$ . This brings us to our next method.

CASE 2: deterministic crossing, short correlation time.

Figure 1 is still the framework we are considering, but now we want the correlation time to be quite short and for the variance of  $X(t)$  to be increasing linearly locally around  $t^*$ . Then  $X(t)$  will be approximated as a Wiener process with a linear drift. The linear drift is simply the slope of the recovery process at  $t^*$  and the slope of the variance of the membrane



potential gives the intensity or scale parameter of the Wiener process. Said another way, around  $t^*$ , we have

$$X(t) \cong a t + b W(t) \quad (9)$$

where  $W(t)$  is a standard Wiener process. The first passage time to a constant threshold for a Wiener process with linear drift has an analytic solution which gives the well known inverse gaussian distribution for  $g(S, t | x_0)$ . Generalizations of this idea and a rigorous development of the so-called tangent method can be found in the recent monograph by Lerche (1986). Parameter estimation in the context of neural models for this situation has been examined by Lansky (1983).

What clues can we get from an empirical first passage time distribution that this situation might apply? The inverse gaussian distribution is skewed to the right and the skew increases with increasing cv, in particular the skew is three times the cv when skew is measured as the square root of Pearson's beta, i.e.

$$\text{skew} = E((t - E(t))^3) / (\sigma_t)^3.$$

In figure 3, this relationship between skew and cv is shown for a simulation series in model IV with a constant threshold. Each point represents 2000 simulated intervals and different points starting with the leftmost correspond to an decreasing set of values of the rate parameter that drives the shot noise process. All other parameters were fixed except one which controlled the serial correlation between interspike intervals. The two values of this parameter are denoted by x and boxes, and don't have a large effect on the plot (see Smith and Chen, 1986 for more

details). Two other two parameter distributions that are positively skewed are shown for comparison, the gamma (GA) and lognormal (LN). For the middle range of values of  $cv$ , which correspond to deterministic crossings and short correlation times, the simulated values bounce around the inverse gaussian curve (IG). For larger values of  $cv$ , we no longer have deterministic crossings, which brings us to our final approximation method.

### CASE 3: nondeterministic crossings, large threshold

Intuitively what happens in this case is that the asymptotic value of the mean of the process is below the threshold, and the threshold, when measured in units of the standard deviation of the steady state voltage process, is far away from the steady state mean voltage. Crossings of the process will be rare and roughly a Poisson process. The time between arrivals for a Poisson process is exponentially distributed, so the first passage time will have an exponential distribution with the rate parameter being the reciprocal of the mean first passage time. This idea has been around for quite a while, with Newell showing the result for some diffusion processes in 1962, and Keilson giving a weak convergence result in 1966. Recently for several types of diffusion processes, Ricciardi and colleagues (1985, 1986) have established this result and asymptotic series for the rate parameter of the exponential distribution. Sato and Ricciardi (1983, 1984, 1986) have asymptotic results for non-constant boundaries.

Using the Ornstein Uhlenbeck process (model 1) and a constant threshold as an example, we will present a flavor of the

type of asymptotic results available and note other approaches for obtaining them. The results are more general in that the behavior of other models (III and IV) are seen to be well approximated by the OU process in the limit of large thresholds. The scenario for the last two figures is as follows: The mean first passage time for the OU process is tabulated and for thresholds more than  $3 \sigma_v$  away are well approximated by the first time of the asymptotic expansion when the process starts from 0. Models III and IV are not stationary processes, so we add a dead time equal to the time at which the mean and variance of  $X(t)$  reaches 95% of its steady state level, time is measured in units of the steady state process's correlation time, and voltages are normalized by the steady state standard deviation. We can now compare these processes to the normalized OU process. Only the mean FPT is considered since it is the only parameter needed to characterize the limiting exponential distribution. In figure 4, the shot noise model is seen to be well approximated by the OU process if the scaling and dead time are included. In figure 5, the neural model III is normalized to the standardized OU process and again produces good agreement as the threshold is increased. Note that neither of these processes have continuous sample paths nor gaussian marginal distributions. What is similar is the correlation structure for small time differences. Model III is similar to the OU process in that its linear drift term dominates at large threshold values.

Since the OU process is a diffusion process the method of Seigert outlined in Ricciardi (1977 chapter 3) can be used. The

starting value will be taken to be 0. The stationary distribution is normal with zero mean and a variance of  $\sigma^2 \tau / 2$ , c.f. equation (2), so we normalize the voltages (including the threshold) by dividing by  $\sigma \sqrt{\tau / 2}$ . The stationary distribution is now gaussian with zero mean and unit variance. From Keilson and Ross (1975), the leading term in the asymptotic series as  $S \rightarrow \infty$  for the mean FPT is

$$E(t(S|0)) \sim \sqrt{2\pi}^{-1} (1/S^*) \exp(-(S^*)^2/2) \quad (10)$$

where  $S^*$  is the normalized threshold. The rest of the asymptotic series in (10) can be obtained by multiplying the right hand side by the generalized hypergeometric function  ${}_2F_0(1, 1/(S^* \sqrt{2}), 1/(2S^{*2}))$ . The leading term agrees with the actual result within 10% for  $S^* > 3$ .

The leading term can be obtained in another way, using the method of stochastic perturbation of dynamic systems (Williams, 1982; Freidlin and Wentzell, 1984). Consider the stochastic differential equation

$$dx = b(x) dt + \sqrt{\varepsilon} \sigma(x) dW(t) \quad (11)$$

and consider what happens as  $\varepsilon \rightarrow 0$ . For the OU process,  $\sigma(x) = \sqrt{\varepsilon} \sigma$  and  $b(x) = -x/\tau$ . The exit time out of a domain  $D$ , which in our case is  $(-\infty, S)$ , is shown using generating function and boundary layer theory to be exponential and an expression for the rate parameter is given (Williams, 1982, p151). When we substitute for the parameters of the OU process, the leading term in the asymptotic series (10) is obtained. Since letting  $\varepsilon$  go to zero, means the normalized threshold goes to infinity. However

the results from stochastic perturbation theory apply to a wider class of problems provided we scale the threshold appropriately. The restrictions on  $b(x)$  and  $\sigma(x)$  are continuity and smoothness (e.g. Lipschitz) and that  $x = 0$  be the only attractor of the deterministic (no noise here) system. The problem can also be viewed as a particle in a potential well. Kipnis and Newman(1985) have extended the exit time results to bi- and multi stable potential wells, and Day (1987) has extended earlier results to include nonsmooth quasipotentials. This is just a sampling of recent work in these active area.

Finally we mention a third way to obtain the leading term in equation (10) which using the Poisson nature of the rare crossings, namely extreme value theory of statistics. Using quite different arguments than the two above methods Leadbetter et al. (1983,p 236) obtain the leading term in (10) as the rate parameter for Poisson process of so-called " $\varepsilon$ " upcrossings for the OU process.

#### DISCUSSION:

We have illustrated, in terms of four relatively simple neural models, the three ranges of behavior of first passage times where heuristic approximation methods can be useful. While the approximation methods are no substitute for careful mathematical analysis and for simulations of models too complicated to be fully analyzed mathematically, they can be used as a guide for preliminary work and in ascertaining the robustness of the model's structure. Even with current computers, simulations of some first passage time problems require a prohibitive amount of

cpu time. The preliminary use of approximations here is almost mandatory.

The plot of skew vs coefficient of variation was seen to be a diagnostic for locating regions of inverse Gaussian and of exponential behavior of the p.d.f. of the interspike intervals. This plot, with standard errors included, can also be used as a guide to how long of a data record is needed to distinguish among different models.

For the asymptotic behaviour of the first passage time in the nondeterministic crossing case, it was noted that the rate parameter of the limiting exponential distribution has been obtained in three ways for the Ornstein Uhlenbeck process. This interplay between the three approaches (asymptotic series in Seigert's approach, perturbation of dynamic systems via Wentzell-Freidlin method, and Poisson nature of upcrossings from extreme value theory) is richer and more extensive than presented here (Smith and Sato, in preparation). Further study of the relation between recent results in extreme value theory and in exit times for one dimensional diffusion processes, along the lines of Newell's work (1962), seems warranted.

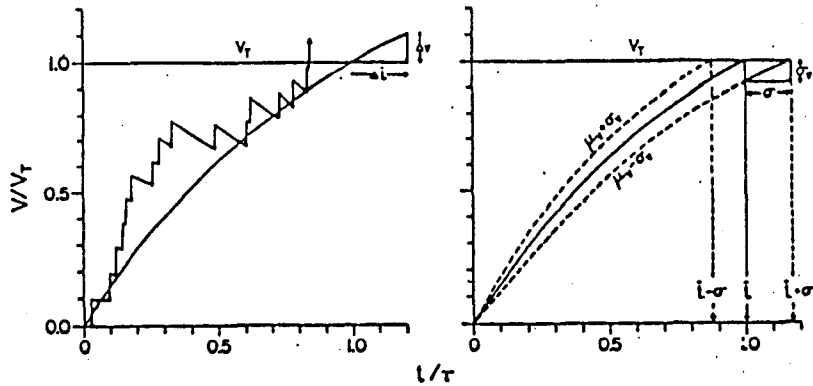
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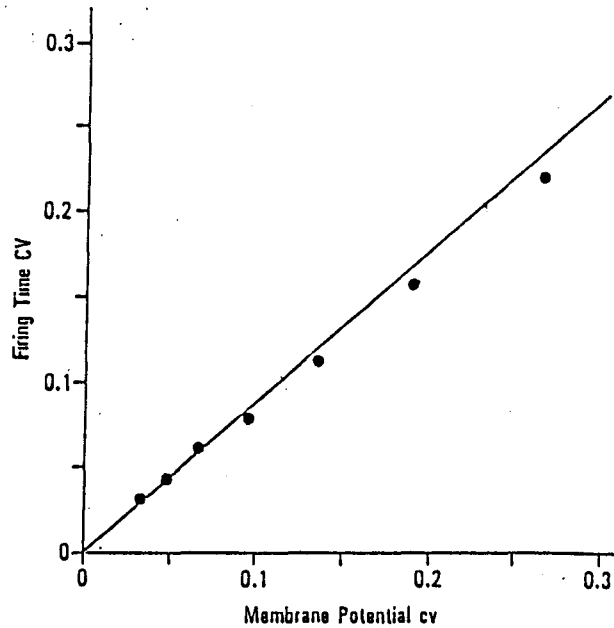
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**Figure 1.** Schematic illustration of deterministic crossing case. Left panel shows a sample path and the mean  $\mu(t)$  of the process. The voltage is normalized by the value of the constant threshold  $V_T$  and time is normalized by the time of deterministic crossing,  $\tau$ . Right panel shows three trajectories. The middle one is the mean voltage and the other two are the mean  $\pm$  a standard deviation. The projection of the times of intersection of the three curves are indicated by vertical lines. The tangent approximation to the standard deviation of the crossing time,  $\sigma$ , is given by  $\sigma_v$  divided by the slope,  $d\mu/dt$ , evaluated at the time of deterministic crossing.



**Figure 2.** Illustration of Stein's approximation method for model II. The abscissa is the cv of the membrane potential process and the ordinate is the cv of the firing times. The 7 points are from simulations (1000 interspike intervals each) of model II with excitatory inputs only. The membrane time constant is 5 msec. The mean voltage trajectory is the same for all seven cases since the product  $\lambda a_e = 8$  mV/msec for each case, with  $a_e$  taking on values of 4, 2, 1, 0.5, 0.25, 0.125 and 0.0625 mV. The solid line is that predicted from the approximation method and has a slope of 0.92. The threshold function is  $S(t) = 10 + 100 \exp(- t/200)$  mV and time is in msec.

TABLE

Case	Mean Interval (msec)	Standard Deviation (msec)	Firing Rate (sp/sec)	cv
A	6.65	.143	150.4	.0215
A*	6.66	.142	150.3	.0214
B	6.63	.628	150.7	.0947
B*	6.66	.572	150.3	.0860
C	10.62	.397	94.2	.0374
C*	10.59	.418	94.4	.0394
D	10.26	1.577	97.5	.1538
D*	10.59	1.675	94.4	.1582

\* (approx.)

TABLE 1: Illustration of Stein's approximation method for Model III.

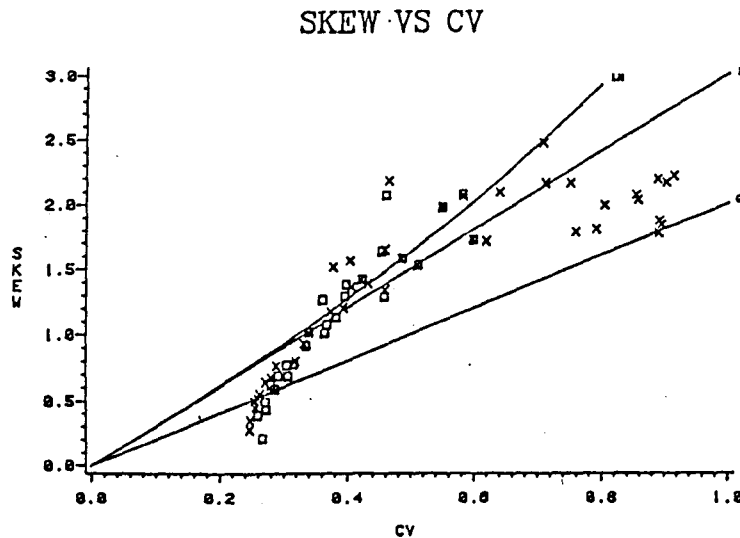


Figure 3: The relation between skew and cv for simulations of model IV. Skew is measured as Pearson's square root of beta1. Each symbol represents 2000 simulated intervals. Different points correspond to different values of the Poisson release rate that drives the shot noise process. The higher rates produce smaller cv values. The three reference curves are the corresponding relations for the following two parameter distributions: lognormal (LN), inverse gaussian (IG), and gamma (GA). Note that an exponential distribution has a cv of 1 and a skew of 2.

curve5, gk0=0.5, tk=2.357, p=1, a=1.00, n=2000  
 TD=2.25TK IC=0.8

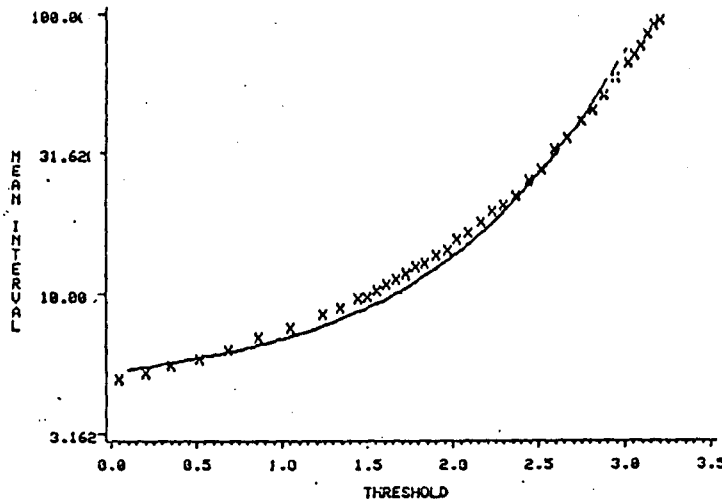


Figure 4: Asymptotic Ornstein Uhlenbeck approximation to model IV. Abscissa is normalized threshold and ordinate is mean interval. A dead time of 2.25 times the time constant is used and voltages are normalized by the standard deviation of the steady state voltage process. The solid curve is the relationship for the OU process and the x's are from simulations of model IV.

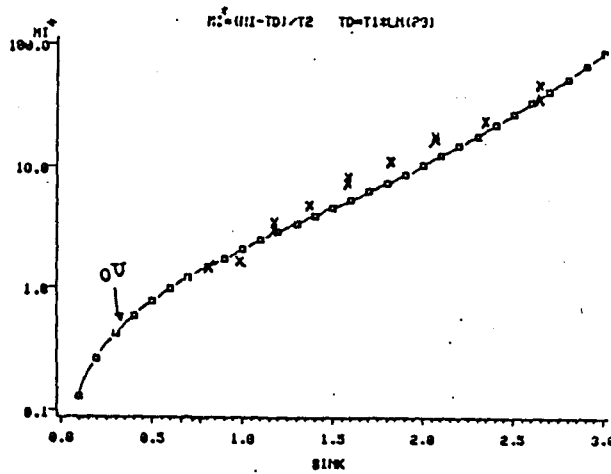


Figure 5: Asymptotic Ornstein Uhlenbeck approximation to model III. Abscissa and ordinate are as in figure 4. The dead time is the time for the mean voltage to reach 90% of its asymptotic level. The points represent simulations of model III and the solid line the OU process. The OU process curve in figures 4 and look different due to the order being the time scale of the OU process (fig.5) or of the simulated process (fig.4). Values below a threshold of zero represent deterministic crossings.

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<p>Three approximation methods are examined for the first passage time (FPT's) of continuous time stochastic processes. The methods are illustrated through four stochastic neural models for the generation of action potentials. The deterministic crossing, long correlation time case approximates the FPT distribution by a transformation of the marginal distribution at the time of deterministic crossing. The deterministic crossing, short correlation time case approximates the process locally by a Wiener process with drift, producing an inverse Gaussian distribution. The final case is the nondeterministic crossing, large threshold case which produces exponential FPT's in the limit. Three ways to produce this result for the Ornstein Uhlenbeck process are noted.</p>				
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