MOMENTS OF VOLTAGE TRAJECTORIES FOR STEIN'S MODEL

WITH SYNAPTIC REVERSAL POTENTIALS

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ABSTRACT

Expressions for the moments of the membrane potential in Stein's model with synaptic (excitatory and inhibitory) reversal potentials are presented. The mean and variance of the voltage trajectories are used to approximate the mean and standard deviation of the interspike intervals under certain conditions (Stein, 1967) that yield a small coefficient of variation. The limiting case of excitatory input only and negligible decay places a lower bound on the coefficient of variation of the interspike intervals.

Running Title: Moments of Voltage Trajectories

1. INTRODUCTION

A modification of Stein's model (1965) for stochastic neural activity with excitatory and inhibitory synaptic reversal potentials was developed by Tuckwell (1979). On the basis of simulation results, he suggested that a coefficient of variation of the interspike intervals greater than one was due to relatively strong inhibition. This proposition has recently been further examined by Wilbur and Rinzel (1983). They found it difficult to produce interval distributions with a coefficient of variation > 1 in the physiological range of the parameters. Smith (1979) used the model with excitation only as part of a study on the responses of vestibular nerve fibers to natural and electrical stimulation. A non-Gaussian diffusion process model, somewhat similar to that of Johannesma (1968), was recently derived by Kallianpur and Wolpert (1984) using a martingale limiting argument for a slightly generalized version of Tuckwell's model.

In this report, an expression for the moments of the unrestricted membrane voltage process is given (i.e., no threshold or absorbing barrier). Using the approximation method of Stein (1967, p. 53), the mean and standard deviation of the interspike intervals in this model may be approximated in the case of small "synaptic variability". In contrast to the work of Tuckwell and Wilbur and Rinzel above, our results examine the case of a small coefficient of variation. A limiting case with excitation only and a very long membrane time constant relative to the mean arrival time of inputs is also discussed.

2. THE MODEL

Following the notation of Tuckwell (1979) (with the exception that instead of his rate constant s, we use $1/\tau_m$) the membrane potential $V(t)$ satisfies the following stochastic differential equation whenever the voltage is below the threshold, $r(t)$, for firing

(1) $\qquad dV = -V/\tau_m \, dt + (V_E - V) \, a_E \, dP(f_E; t) + (V_I - V) \, a_I \, dP(f_I; t)$

where τ_m is the membrane time constant, $V_E(V_I)$ are the excitatory (inhibitory) reversal potentials, a_E and a_I are dimensionless positive constants, $P(f_E; t)$ and $P(f_I; t)$ are two independent homogeneous Poisson counting processes with intensities f_E and f_I respectively. The constants a_E and a_I scale the jump size of the Poisson processes, however the multiplicative reversal potential term results in nonlinear summation of postsynaptic potentials in the model. Let $b_E = a_E V_E$ and $b_I = a_I V_I$, then $b_E(b_I)$ represent the size of an epsp (ipsp) at rest, i.e. $V = 0$. For simplicity, we set the initial voltage $V(0) = 0$, i.e. the neuron resets to the resting level. After presenting a slight generalization of the model, we derive an expression for the moments of the process $V(t)$ in the case of no absorbing barriers, i.e., the voltage threshold, $r(t)$, is not present. Note that without the threshold, the process $V(t)$ is confined between the two inaccessible boundaries $V_E > 0$ and $V_I < 0$.

Denote the transition probability density function (p.d.f.) of $V(t)$ by $p(v,t,x,t_1)$ when the process is not restricted by an absorbing threshold, $r(t)$. This p.d.f. is clearly a mixed density, having a continuous and a discrete or impulsive part. The initial condition (the rest level here) contributes an impulse (Dirac delta function) at the origin. Until the first jump arrives from either Poisson process, each sample path remains at a value of zero. The mass of the impulse is simply the probability of no arrivals, i.e. $\exp(-(f_E + f_I)t)$.

The impulsive part of the density can cause a problem in determining the backward and forward Kolmogorov equations for the process due to its lack of differentiability in the state variable v. Note that Stein's original model (1965) also has this problem. The theorems in say, Gihman and Shorohod (1972), for determining the backward (p. 293) and forward (p. 299) Kolmogorov

equations (BKE and FKE) are often used even though the formal conditions for their use are not met. This was done, for example, in Tuckwell's analysis of the model (1979). (Note the error in the FKE, equations (12), and the resultant equation for the mean depolarization, equation (14) were corrected in Tuckwell (1981), p. 167) with a kind acknowledgement to the first author). However, his subsequent analysis based on the BKE agrees well with simulations based on the stochastic differential equation over a range of parameter values. We expect, although have not yet shown, that treating the pdf as a generalized function and treating the solution as a so called weak solution would remove this problem.

A perhaps more realistic approach is to slightly generalize the model as follows. Add to the right hand side of equation (1), the term cdW(t), where c is a constant and W(t) is a standard Wiener process, i.e., zero mean and variance t,

(1a) $dV = -V/\tau_m \, dt + (V_E - V) \, a_E dP(f_E; t) + (V_I - V) \, a_I dP(f_I; t) + c \, dW(t)$

The portitions of the sample paths which previously gave rise to the impulsive part of the transition density now behave like sample paths of the Ornstein Uhlenbeck process until the first jump arrives. The impulsive density problem with the theorems on the Kolmogorov equations from Gihman and Shorohod is now removed.

Our result for the moments of the voltage trajectories can be rigorously obtained using the transition characteristic function from the strictly Poisson, i.e., c = 0, forcing function model (Snyder, 1975, p. 212) and agree with the expressions obtained from the generalized model in the limit as c → 0. Besides giving the analytic results some robustness, including a small amount of Gaussian noise in the model is probably also a more

realistic representation of the other small noise sources in the physical process. However, the process V(t) is now over the entire real line, again with natural boundaries, rather than on (V_I, V_E).

3. ANALYSIS OF THE MODEL

The backward Kolmogorov equation for the transition density corresponding to equation (1a) is

$$(2) \quad -\frac{\partial p}{\partial t_1} = -(f_E + f_I)p - x/\tau_m \frac{\partial p}{\partial x} + c^2/2 \frac{\partial^2 p}{\partial x^2} + f_E \, p(x + (V_E-x)a_E) + f_I \, p(x + (V_I-x)a_I)$$

with natural boundary conditions at $+/-\infty$, which agrees with Tuckwell's equation (11) with the addition of the diffusion term.

The forward Kolmogorov equation can be obtained from (2) via Gihman and Shorohod (1972, p. 299) using the inverse function method on the argument of the last two terms. The result is

$$(3) \quad \frac{\partial p}{\partial t} = -(f_E + f_I)p + \frac{\partial}{\partial v}(vp/\tau_m) + c^2/2 \frac{\partial^2 p}{\partial v^2} + f_E \, p((v-b_E)/(1-a_E)) \,/(1-a_E)$$

$$+ f_I \, p((v-b_I)/(1-a_I)) \,/(1-a_I)$$

again with natural boundary conditions. Recall that $b_E = a_E V_E$ and $b_I = a_I V_I$. The arguments of the last two terms correspond to Wilbur and Rinzel's r_e and r_i functions (their equation (1)).

Rather than integrate equation (3) for each moment of the voltage trajectory, the characteristic function method for generating moments will be used. The characteristic function $M_v(j\omega)$ associated with p.d.f. $p(v)$ is defined as

$$M_v(j\omega) = \int_{-\infty}^{\infty} p(x) \exp(j\omega x) \, dx$$

Using some elementary properties of Fourier transform pairs, the transformed version of equation (3) becomes

(4) $\dfrac{\partial M_v(j\omega)}{\partial t} = -(f_E + f_I) M_v(j\omega) - \omega/\tau_m \dfrac{\partial}{\partial \omega} M_v(j\omega) - c^2\omega^2/2\, M_v(j\omega)$

$\qquad + f_E e^{j\omega b_E} M_v(j\omega(1-a_E)) + f_I e^{j\omega b_I} M_v(j\omega(1-a_I))$

Assuming all moments exist and are finite, write $M_v(j\omega)$ as a power series in terms of the moments $\mu_n = E[v^n]$

$$M_v(j\omega) = \sum_{n=0}^{\infty} \mu_n (j\omega)^n/n!$$

substituting into (4) and equating powers of ω, the equation for μ_n, (after a little algebra and using the useful fact that multiplying polynomials means discrete convolution of coefficients) becomes

(5) $\quad \dfrac{\partial}{\partial t} \mu_n + \mu_n/\tau_n = c^2 n(n-1)/2\ \mu_{n-2} + \sum_{k=1}^{n} \binom{n}{k} \alpha_{n-k}\mu_{n-k}$

where $n = 1, 2, \ldots$, $\mu_n = 0$ for $n < 0$ and $\mu_0 = 1$,

and $1/\tau_n = n/\tau_m + f_E (1 - (1 - a_E)^n) + f_I (1 - (1 - a_I)^n)$

and $\alpha_k = f_E b_E (1 - a_E)^k + f_I b_I (1 - a_I)^k$.

This is our main result. The left hand side is a first order linear differential operator and the forcing function on the right hand side is in terms of known functions, namely lower order moments. Alternatively, equation (5) can be written in matrix form as a system of first order equations with a vector of constants as the forcing function. Earlier we assumed existence and finiteness of the moments. This is easily checked by using induction on equation (5).

As mentioned earlier equation (5) could have been obtained for the case of $c = 0$ by beginning with equation (1) and using the transition characteristic function. The expression for the mean is independent of c in any case and is given by (c.f. eqn. 19 of Tuckwell, 1981).

(6) $\quad \mu_1(t) = \theta_1 (1 - \exp(-t/\tau_1))$

where

$$\theta_1 = (f_E b_E + f_I b_I)\tau_1, \text{ and } \tau_1 \text{ is as given above.}$$

Note that τ_1 is always less than τ_m i.e., the mean voltage reaches its asymptotic value faster than in the model without the reversal potential, but the asymptotic value θ_1, is less than in Stein's original model.

The expression for the variance is a little more complicated, namely

$$(7) \quad \sigma_v^2(t) = (\gamma + \varepsilon\theta_1)\tau_2(1-e^{-t/\tau_2}) - \theta_1\varepsilon(e^{-t/\tau_1}-e^{-t/\tau_2})/(1/\tau_2-1/\tau_1)$$

$$-\theta_1^2(1-e^{-t/\tau_1})^2$$

where $\gamma = c^2 + f_E b_E^2 + f_I b_I^2$ and $\varepsilon = 2(f_E b_E(1-a_E) + f_I b_I(1-a_I))$.

Higher order moments along with nonzero initial conditions on the moments can be obtained in straightforward manner using equation (5). As a check on our results, consider the limit as $V_E \to \infty$ and $V_I \to \infty$, then a_E and $a_I \to 0$ and $\tau_n \to \tau_m/n$ and $\alpha_k \to f_E b_E^k + f_I b_I^k$. Thus the equations for the moments agree with those of Stein's original model without a reversal potential in the appropriate limit with c = 0. In particular, the variance goes to $\gamma \tau_m/2$ (1 - exp($-2t/\tau_m$)).

4. APPROXIMATE INTERSPIKE INTERVAL MOMENTS

Only a few analytical results are available for the first passage time associated with equation (1). Tuckwell (1979) calculated the mean first passage time for a special case: a constant threshold, no inhibition and a small ratio of threshold to epsp size. Since we are interested in the case of a small coefficient of variation (cv), we will use Stein's approximation method for the mean and standard deviation of the interspike intervals (Stein, 1967 , p. 53). Regular firing patterns, or small cv's, occur in a number of neurons. For example, the peripheral vestibular nerve can have both very

regular (cv = .02) and irregular (cv = 1) firing patterns in the same animal (Goldberg, Smith and Fernández, 1984).

The approximate mean interval, $\hat{t}$, will be taken as the time when the mean voltage, $\mu_1(t)$, crosses the threshold $r(t)$. $\hat{t}$ will be finite if $\theta_1 > \inf r(t)$. Setting $\mu_1(t) = r(t)$ in equation (6), we obtain

(8) $\qquad \hat{t} = -\tau_1 \log (1 - r(\hat{t})/\theta_1)$

If $r(t)$ is a constant, say $\theta < V_E$, or $A + B \exp(-t/\tau_1)$, one can solve (8) for $\hat{t}$ analytically. Otherwise a zeros of functions routine can be used for numerical evaluation.

For excitation only and a constant threshold, θ, $\hat{t}$ tends to overestimate the mean interval obtained from simulations. However, $\hat{t}$ may be greater or smaller than the corresponding estimate, t^*, from the model without a reversal potential. The expression for t^* is

(9) $\qquad t^* = -\tau_m \log (1 - \theta/(f_E b_E + f_I b_I) \tau_m)$

For a given θ, τ_m, b_E, f_E, b_I, f_I, if $t^* > t_c$, then $t^* < \hat{t}$ and if $t^* < t_c$, then $t^* > \hat{t}$ where t_c is the time at which the mean voltage trajectories for the two models cross.

The approximate standard deviation, $\hat{\sigma}$, of the interspike intervals is given (via a geometric argument, Stein, 1967, equation 1.40) as

(10) $\qquad \hat{\sigma} = \sigma_V(t)/ |d/dt(\mu_1(t) - r(t))|$ at $t = \hat{t}$,

where $\sigma_V(t)$ is determined by equation (7) and $r(t)$ is assumed to be constant or monotonically decreasing around $\hat{t}$. Stein's conditions for the approximation to hold are: (1) the voltage distribution doesn't change its shape drastically near $\hat{t}$, (2) the resultant $\hat{\sigma}$ is considerably less than the time constant of the model, (3) $r(t)$ is nearly linear within a few standard deviations of $\hat{t}$. These conditions were stated for the model without a reversal potential but appear to be useful for the present model as well in that the approximations agree with

simulations. The appropriate conditions above are not satisifed for the examples given in Tuckwell, and Wilbur and Rinzel, who were primarily concerned with parameters that gave a large coefficient of variation. Two sets of simulation results are given below for monotonically decreasing thresholds. It is difficult to achieve regular firing patterns in this model with a constant threshold and epsps in the physiological range. The reason for this will be examined in the next section.

Table 1 compares the approximate method (denoted by *) to simulation results (N = 1000 in A, B, D and 200 in C) with excitation only in four cases. V_E = 70 mV and τ_m = 5 msec for all cases. The threshold r(t) = 10 + 1/(exp(t/TS) - 1) in mVolts (Geisler and Goldberg, 1966) with TS = 200 msec. For cases A and C, b_E = .125 mV, and for cases B and D, b_E = 2 mV. The value of f_E for the four cases are 160, 10, 80 and 5 arrivals/msec. The product $f_E b_E$, is 20 for A and B and 10 for C and D. Since τ_1 and θ_1 depend only on $f_E b_E$, they will be fixed for A and B and for C and D. The agreement with the approximation method is reasonably good, case D shows that as the standard deviation increases, the discrepancy increases as expected.

[TABLE 1 GOES ABOUT HERE]

In Figure 1, simulation results (N = 1000 for all points) are compared to the approximation method for a different threshold, namely r(t) = 10 + 100 exp (-t/TS) mV with TS = 10 msec. b_E is fixed at 2mV and V_E and τ_m are at the same values as above. The release rate f_E takes values of 5.75, 6.25, 6.75, 7.25, 7.75, 8.25, 10, 15, 20 and 25 arrivals/msec. In Figure A, we see that the estimated mean intervals tend to be slightly longer than the simulated ones. The approximated standard deviations in Figure B also tend to be longer than the simulated ones. The seventh point being an exception due to a few long intervals in the simulation. Figures A and B

are combined in Figure C as a plot of the cv vs mean interval. The deviation between the approximations (x) and the simulations ($\blacklozenge$) increases with increasing mean interval as expected. Other simulation examples to test the approximation method can be found in Smith (1979). Note that these points represent reasonably regular firing rates at moderate arrival rates. This will not be possible for a constant threshold unless the epsp size is drastically reduced.

[FIGURE 1 GOES ABOUT HERE]

5. LIMITING CASE: EXCITATION ONLY AND NEGLIGIBLE DECAY

Here we examine the case of no inhibition and $\tau_m \to \infty$, often called the perfect integrator model. It is intended to model situations where $1/f_E \ll \tau_m$. Equation (1) becomes

$$(11) \qquad dV = b_E (1 - V/V_E) \, dP(f_E; t).$$

One way to write the solution to (11) is (again assuming sero initial conditions)

$$(12) \qquad V(t) = V_E (1 - (1 - a_E)^k)$$

where k is the number of jumps of $P(f_E; t)$ up to time t. Said another way, (12) is a monotonic nonlinear transformation of a Poisson counting process. The first passage times to reach a constant threshold θ will be distributed as an Erlang probability density with parameters f_E and n with n given by

$$(13) \qquad n = \begin{cases} GI(\log (1 - \theta/V_E)/\log (1 - b_E/V_E)) & b_E < \theta, \\ 1 & b_E \geq \theta \end{cases}$$

where GI( ) denotes greatest integer. n is simply the number of jumps to reach the threshold. The mean, standard deviation and cv of the interspike intervals are n/f_E, n/f_E^2, and $1/\sqrt{n}$. Note that the cv does not depend on f_E.

Comparing this limiting case to our original model with excitation only, it is fairly clear that the mean, standard deviation and cv are all less than the corresponding quantities from equation (1). Another comparison of interest

is to the model without the reversal potential. For $0 < b_E < \theta$ and typical physiological values for θ and V_E, n may be approximated by

$$\hat{n} = (V_E \log (1 - \theta/V_E))/b_E.$$

For the model without the reversal potnetial in the limiting case, $n^* = \theta/b_E$. For $V_E = 70$ mV and $\theta = 10$ mV, the two values are quite similar, namely $10/b_E$ and $10.79/b_E$ respectively.

The problem with the constant threshold is that very small values of b_E are required to obtain very regular units since the cv goes as $\sqrt{b_E}$. For the above values of V_E and θ, the limit for $b_E = 2$ mV is .408. This limit is approached in simulations of equation (1) but rather slowly, for example with $\tau_m = 5$ msec and $f_E = 2.45$/msec the cv = .487 and the firing rate is 337 sp/sec. For a lower limit on the cv of .048 a b_E of .025 mV is required. The problem with very small values for b_E is two fold. First the limiting dependence of cv goes as the square root of b_E, which requires very small values and secondly, if a small value of b_E is used the firing rate falls off precipitously when the asymptotic mean voltage, θ_1, fails to reach the threshold at small values of f_E.

The solution to the problem is to also have a monotonically decreasing threshold rather than a constant one. The cv's in Figure 1 are all < 0.1 but have an epsp size of 2 mV. If the limiting case cv is calculated for a threshold of 54.6 mV (the value that the mean voltage crosses the threshold for $f_E = 25$ in Figure 1) a value of .1374 is obtained. The simulated value of the cv is .0466. The reason the simulation beats the limit is that the slope of the threshold at the crossing time is 4.47 mV/msec which gives a modified lower limit (dividing by the slope) of .0307.

6. DISCUSSION

Incorporation of the synaptic reversal potentials into the original Stein model (1965) is somewhat more realistic in that it allows for nonlinear summation of epsp's and ipsp's. However, representing the recovery process

by a timevarying threshold is somewhat artificial in that it is separated from the equation for the dynamics of the membrane voltage. One way to combine the recovery process with the neuronal excitation is through a timevarying potassium conductance which gives rise to an afterhyperpolarization as in Kernell's motoneuron model (1968). A stochastic version of this model was used to study the wide range of regularity of firing in the vestibular nerve under natural and electrical stimulation (Smith and Goldberg, in preparation).

Analytic results for the first passage time problem in simple neuron models are difficult to obtain. The approximation method of Stein is similar to treating the voltage process as being perfectly correlated around the time of crossing. Then approximation methods for functions of random variables can be used (Papoulis, 1965). Other approaches have been used for diffusion approximations to neural models. The method of Kostyukov (1978) appears somewhat general and promising. However it requires an explicit expression for the transition p.d.f., which prohibits its use in most Poisson driven models. The characteristic function of the transition p.d.f. can be found for Stein's original model (Saaty, 1967, p. 408), but does not appear to have a closed form for its inverse Fourier transform. More work is clearly needed on approximation methods for the moments of firing times.

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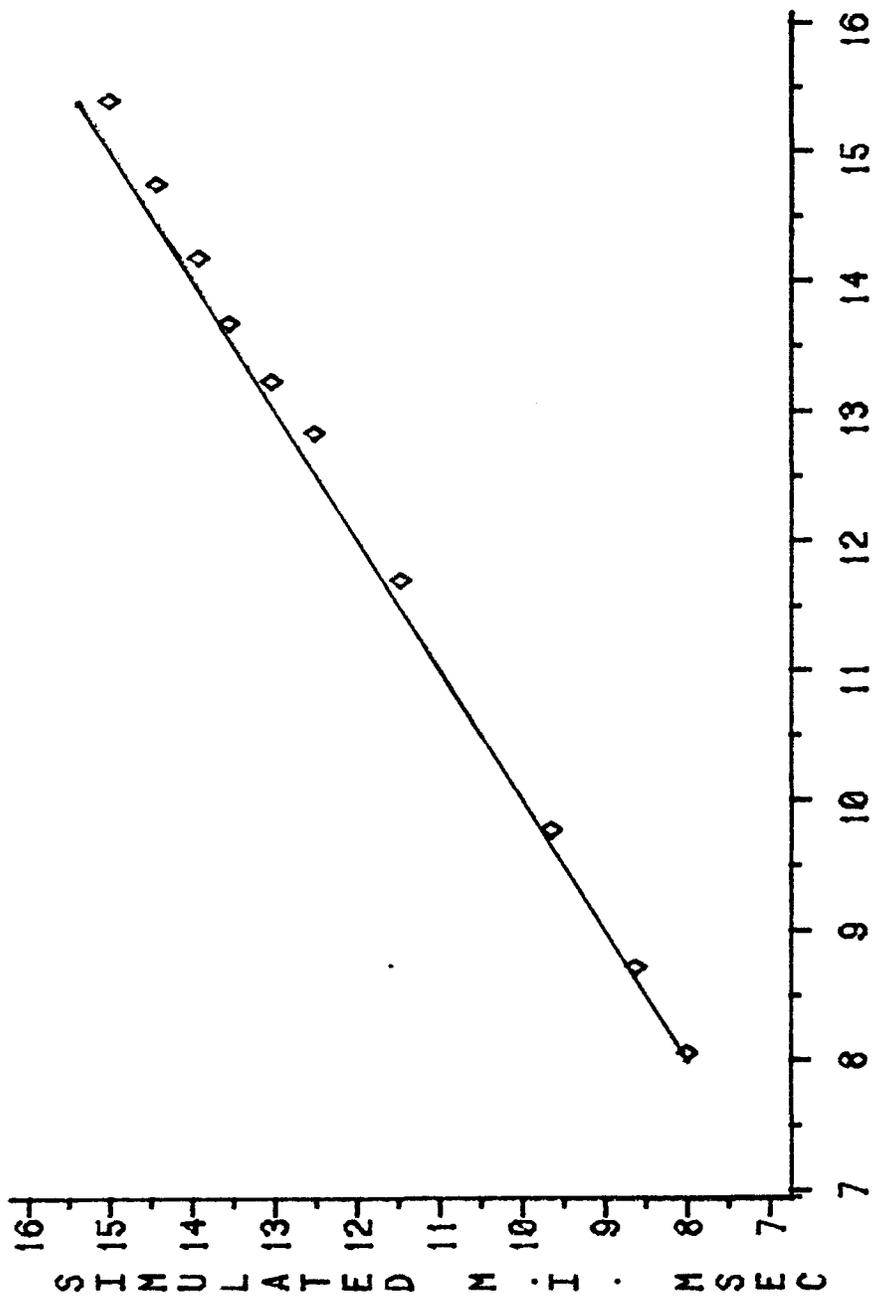
TABLE 1

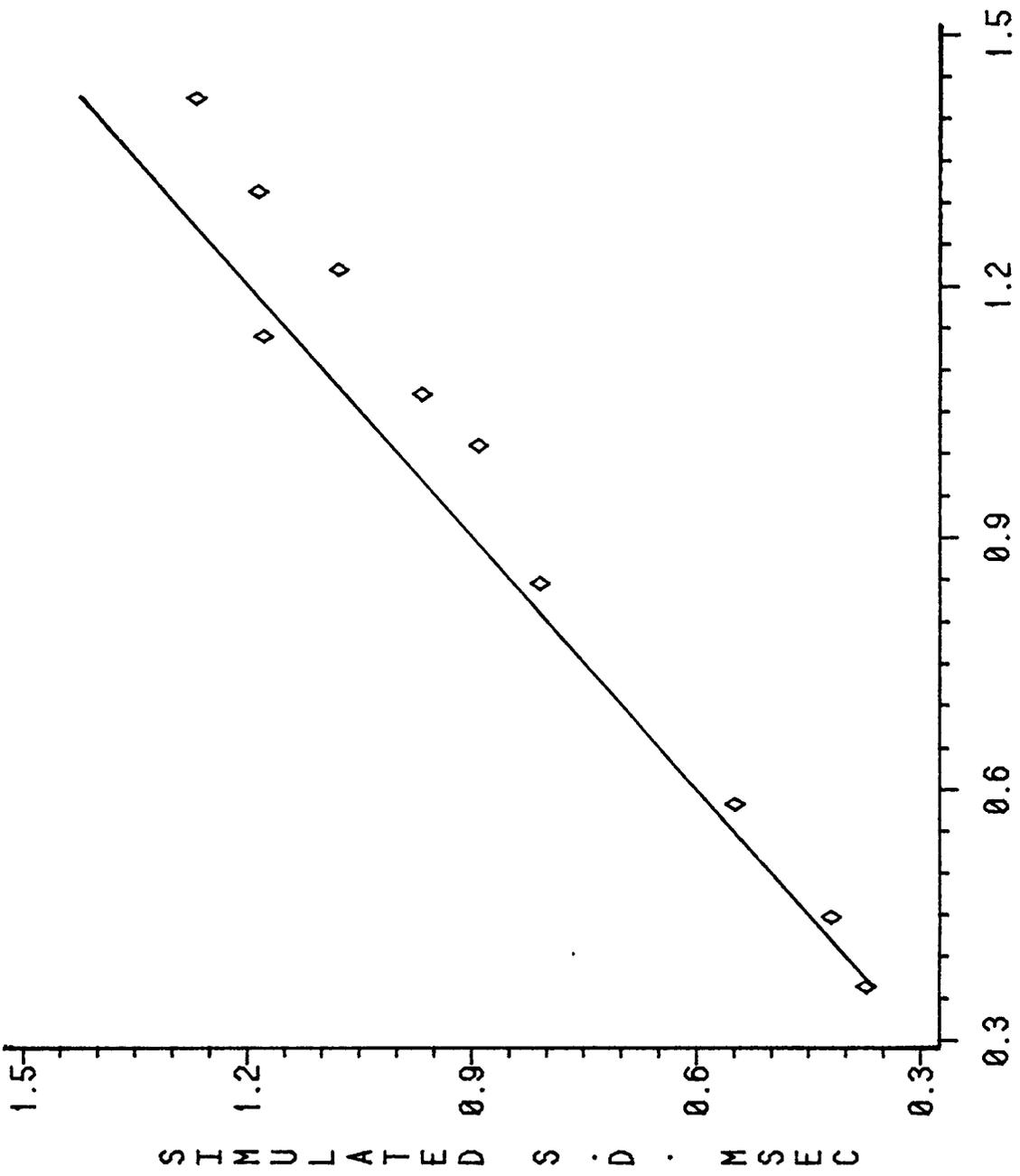| Case	Mean Interval (msec)	Standard Deviation (msec)	Firing Rate (sp/sec)	CV
A	6.6477	.14306	150.43	.02152
A*	6.6557	.14244	150.25	.02140
B	6.6339	.62322	150.74	.09470
B*	6.6557	.57245	150.25	.08601
C	10.6172	.39704	94.187	.03740
C*	10.5882	.41754	94.445	.03943
D	10.2554	1.57714	97.510	.15379
D*	10.5882	1.67509	94.445	.15820

FIGURE LEGEND

Figure 1. The mean and standard deviation of the interspike intervals from
simulations of equation (1) are compared with the approximation
method given by equations (8) and (10). See text for parameter values.
In (A), the simulated mean intervals are plotted against the ones
from the approximation method. In (B), there is a corresponding
plot for the standard deviations. In (C), the coefficient of variation
(cv) is plotted against the mean interval (MI). Simulation values are
denoted by ◊ and approximation method ones by *.

A

APPROX. M.I. (MSEC)

B

APPROX. S.D. (MSEC)

C

MEAN INTERVAL (MSEC)

COEF. OF VARIATION

0.10 0.09 0.08 0.07 0.06 0.05 0.04

7 8 9 10 11 12 13 14 15 16