

Accuracy of Neuronal Interspike Times Calculated from a Diffusion Approximation

HENRY C. TUCKWELL† AND DAVIS K. COPE‡

*Department of Mathematics, University of British Columbia,
Vancouver, B.C., Canada, V6T 1W5*

(Received 10 April 1979)

The theory of neuronal firing in Stein's model is outlined as well as the corresponding theory for a diffusion approximation which has the same first two infinitesimal moments. The diffusion approximation is derived from the discontinuous model in the limit of large input frequencies and small postsynaptic potential amplitudes. A comparison of the calculated mean interspike intervals is made for various values of the threshold for firing and various input frequencies. The diffusion approximation can underestimate the interspike interval by up to 100% or severely overestimate it, depending on the input frequencies and the threshold. A general relation between the predictions of the two models is deduced.

1. Introduction

A fairly realistic model for the stochastic activity of some neurons is that of Stein (1965). The cell is assumed to have a trigger zone, which is a local patch at which the sodium conductance per unit area is high relative to the rest of the neuronal surface. This means that one can ascertain how close the cell is to firing if one knows how close the depolarization $V(t)$ at the trigger zone is to some threshold level θ . The existence of trigger zones is well established for some cells (Calvin, 1975). Stein's model contains the following simplifying assumptions concerning the random synaptic input. Excitatory current pulses arrive according to a Poisson process, $\pi(f_e, t)$, each event of which leads to an instantaneous increase in $V(t)$ by a_e , whereas inhibitory current pulses arrive at event times in a second Poisson process $\pi(f_i, t)$, which is independent of $\pi(f_e, t)$ and causes $V(t)$ to decrease by a_i . Between input events $V(t)$ decays to zero with a time constant τ . The neuron fires an impulse when $V(t)$ reaches θ whereupon, after a refractory period, $V(t)$ is reset to zero and subsequent inputs lead to another firing, etc. The model was generalized by Stein (1967) to handle a distribution of post-synaptic potential amplitudes and inclusion of reversal potentials has been taken into

† Present address: Department of Biomathematics, School of Medicine, University of California, Los Angeles, California 90024 U.S.A.

‡ Present address: Center for Naval Analyses, Alexandria, Virginia 22311 U.S.A.

account by other authors (Johannesma, 1968; Tuckwell, 1979). Various other models for neuronal activity with random input have been proposed and many are discussed in Holden's (1976) book.

The depolarization $V(t)$ in Stein's model is a continuous time, continuous state space Markov process whose sample paths have discontinuities of the first kind. The time between nerve impulses is the time of first passage to levels at or above θ and determining the moments of this random variable have proven difficult due to the fact that the equations involved are differential-difference equations of a type for which there are hardly any known methods of solution. For this reason, presumably, diffusion models, in which the discontinuities of $V(t)$ are smoothed out, have been considered as approximations to Stein's model, the first efforts in this direction being those of Gluss (1967), Johannesma (1968), and Roy & Smith (1969). The theory for diffusion processes is somewhat more tractable than for discontinuous processes as the corresponding equations are differential equations rather than differential-difference equations. A particular diffusion approximation and the discontinuous model have the same mean and variance for sub-threshold depolarizations. The question we consider here is how closely the two models predict the time between action potentials.

2. Theory

Stein's model can be cast as the stochastic differential equation for $V(t)$,

$$dV = -sV dt + a_e d\pi(f_e, t) - a_i d\pi(f_i, t), \quad V(0) = x < \theta, \quad (1)$$

where $s = 1/\tau$. The initial value of $V(t)$ is x . Let $T(x)$ be the first time at which the depolarization reaches or exceeds θ and let the n th moment of $T(x)$ be $M_n(x)$,

$$E[T(x)^n] = M_n(x). \quad (2)$$

Then from Tuckwell (1975) we have the recursion formulas

$$-sx \frac{dM_n}{dx} + f_e M_n(x + a_e) + f_i M_n(x - a_i) - (f_e + f_i) M_n(x) = -n M_{n-1}(x), \quad (3)$$

for $n = 1, 2, \dots$, with $M_0(x) = 1$. This system of equations is solved with the boundary condition $M_n(x) = 0$ for $x \geq \theta$ and with the constraint that $M_n(x)$ be continuous and bounded for $x \in (-\infty, \theta)$. The values of particular interest are $M_n(0)$. This system of equations has proven quite difficult to solve except in some simple cases. We have recently obtained solutions for $n = 1$, $a_e = a_i = 1$, for various values of θ , f_e and f_i (see Cope & Tuckwell, 1979, where a summary of previously obtained results is given). The method relies

on an asymptotic expansion for large negative x , continuation of this solution to near θ by means of an algebraic use of the differential-difference equation and then determination of relevant constants from the boundary condition.

A diffusion approximation for $V(t)$ can be obtained by considering a diffusion process $V^*(t)$ whose first two infinitesimal moments are the same as those of $V(t)$ (by definition the higher infinitesimal moments are zero for a diffusion process). For (1) we have a transition probability density $p(v, t|v_0, t_0)$, defined through

$$p(v, t|v_0, t_0) dv = \text{Prob} [V(t) \in (v, v + dv) | V(t_0) = v_0], \tag{4}$$

which satisfies the forward Kolmogorov equation,

$$\frac{\partial p}{\partial t} = s \frac{\partial}{\partial v} (vp) + f_e p(v - a_e) + f_i p(v + a_i) - (f_e + f_i)p. \tag{5}$$

If we expand $p(v - a_e)$ and $p(v + a_i)$ with Taylor series we obtain

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial v} [(-sv + f_e a_e - f_i a_i)p] + \sum_{n=2}^{\infty} \frac{f_i a_i^n + (-1)^n f_e a_e^n}{n!} \frac{\partial^n p}{\partial v^n} \tag{6}$$

which must be equivalent to the so-called kinetic equation (Stratonovich, 1963)

$$\frac{\partial p}{\partial t} = \sum_{n=1}^{\infty} \frac{(-1)^n}{n!} \frac{\partial^n}{\partial v^n} [K_n(v)p], \tag{7}$$

where $K_n(v)$ is the n th infinitesimal moment,

$$K_n(v) = \lim_{\Delta t \rightarrow 0} \frac{E\{[V(t + \Delta t) - V(t)]^n | V(t) = v\}}{\Delta t}. \tag{8}$$

Accordingly we must have

$$K_1(v) = -sv + f_e a_e - f_i a_i, \tag{9}$$

$$K_n(v) = f_e a_e^n + (-1)^n f_i a_i^n, \quad n = 2, 3, \dots \tag{10}$$

The diffusion approximation, $V^*(t)$, with the same first two infinitesimal moments as $V(t)$ will thus be described by the stochastic differential equation

$$dV^* = (-sV^* + f_e a_e - f_i a_i) dt + (f_e a_e^2 + f_i a_i^2)^{1/2} dW, \tag{11}$$

where $W(t)$ is a standard (zero mean, variance t) Wiener process, and its

transition density $p^*(v, t|v_0, t_0)$ will satisfy the forward Kolmogorov equation

$$\frac{\partial p^*}{\partial t} = \frac{\partial}{\partial v} [(sv - f_e a_e + f_i a_i) p^*] + \frac{f_e a_e^2 + f_i a_i^2}{2} \frac{\partial^2 p^*}{\partial v^2}. \quad (12)$$

This is recognizable as the Kolmogorov (Fokker-Planck) equation of the Ornstein-Uhlenbeck process, first studied by Uhlenbeck & Ornstein (1930).

Though we have written down the approximation (11) it should be shown that a diffusion approximation to the original process does in fact exist when the rates f_e and f_i of the Poisson processes tend to infinity and the amplitudes a_e and a_i tend to zero. The simplest procedure is to let

$$f_e = f_i = nf, \quad a_e = a_i = a/n^{1/2}, \quad (13)$$

whereupon, from (9) and (10),

$$K_1(v) = -sv, \quad (14)$$

$$\lim_{n \rightarrow \infty} K_2(v) = 2fa^2, \quad (15)$$

$$\lim_{n \rightarrow \infty} K_m(v) = 0, \quad m = 3, 4, \dots \quad (16)$$

One thus obtains the Ornstein-Uhlenbeck process

$$dV^* = -sV^* dt + a(2f)^{1/2} dW \quad (17)$$

for which some first passage results were first obtained by Wang & Uhlenbeck (1945) and more recently tables of first passage densities and moments have appeared (Keilson & Ross, 1975). Approximate formulas for these moments have been developed by Thomas (1975).

The more general process where the net mean input is not zero can also be derived by taking limits in a different fashion. To see this, set

$$f_i = f_e + k_i, \quad a_i = a_e + m_i, \quad (18)$$

where now a_e and m_i go to zero and f_e and k_i go to infinity as n becomes infinite according to

$$f_e = nf, \quad a_e = a/n^{1/2}, \quad m_i = \mu/n, \quad k_i = kn^{1/2}. \quad (19)$$

We now have

$$\lim_{n \rightarrow \infty} K_1(v) = -sv - f\mu - ka, \quad (20)$$

$$\lim_{n \rightarrow \infty} K_2(v) = 2fa^2 \quad (21)$$

$$\lim_{n \rightarrow \infty} K_m(v) = 0, \quad m = 3, 4, \dots \quad (22)$$

so that the more general diffusion approximation

$$dV^* = (-sV^* + \alpha) dt + \beta dW \tag{23}$$

is obtained, where $\alpha = -(f\mu + ka)$ and $\beta = a(2f)^{1/2}$. Note that α is negative, but positive α can also be obtained if we set $f_e = f_i + k_e$, $a_e = a_i + m_e$, and let $f_i = nf$, $a_i = a/n^{1/2}$, $m_e = \mu/n$, $k_e = kn^{1/2}$ and again take the limits as $n \rightarrow \infty$.

Considering the diffusion process $V^*(t)$ defined through the stochastic equation (11), and defining the random variable $T^*(x)$ as the time at which $V^*(t)$ first leaves the interval $(-\theta_1, \theta)$ where $x = V^*(0) \in (-\theta_1, \theta)$ and $\theta_1 < 0$, we have, from Darling & Siebert (1953) that the n th moment of $T^*(x)$,

$$M_n^*(x) = E[T^*(x)^n], \tag{24}$$

satisfies the recursion system of differential equations

$$\frac{1}{2}(f_e a_e^2 + f_i a_i^2) \frac{d^2 M_n^*}{dx^2} + (f_e a_e - f_i a_i - sx) \frac{dM_n^*}{dx} = -nM_{n-1}^*(x), \tag{25}$$

for $n = 1, 2, 3, \dots$, with $M_0(x) = 1$ and boundary conditions $M_n^*(-\theta_1) = M_n^*(\theta) = 0$. Thus, as pointed out by Yang & Chen (1978), one can obtain the moments of the interspike interval without knowledge of its probability density. The Laplace transform of the density has been obtained by various authors (Roy & Smith (1969) express it in terms of confluent hypergeometric functions of the second kind, Capocelli & Ricciardi (1971) express it in terms of parabolic cylinder functions), and the problem of constructing the density of $T^*(x)$ from its moments has recently been considered by Sato (1978).

The equation for $M_1^*(x)$ can be integrated to give a solution as a double integral (see for example, Thomas, 1975). The quantity of interest here is $M_1^*(0)$ which, when we let $\theta_1 \rightarrow \infty$, is the expected time at which the threshold θ for firing is reached when the neuron is initially in the resting state. This quantity can be expressed in the following way after Roy & Smith (1969):

$$M_1^*(0) = \frac{\tau}{2} \left\{ \sum_{k=0}^{\infty} \frac{2^{k+1}(X^{2k+2} - Y^{2k+2})}{(k+1)(2k+1)!!} + 2\pi^{1/2} [Y\Phi(\frac{1}{2}, \frac{3}{2}; Y^2) - X\Phi(\frac{1}{2}, \frac{3}{2}; X^2)] \right\}, \tag{26}$$

where

$$X = \tau^{1/2}(f_e a_e - f_i a_i - \theta/\tau)/(f_e a_e^2 + f_i a_i^2)^{1/2}, \tag{27}$$

$$Y = \tau^{1/2}(f_e a_e - f_i a_i)/(f_e a_e^2 + f_i a_i^2)^{1/2}, \tag{28}$$

and $\Phi(a, b; x)$ is the confluent hypergeometric function of the first kind [see

Abramowitz & Stegun (1964), for example]:

$$\Phi(a, b; x) = 1 + \frac{ax}{b} + \frac{a(a+1)}{b(b+1)} \frac{x^2}{2!} + \dots \quad (29)$$

It has been found that the computation of $M_1^*(0)$ from the series (26) is quite efficient for "physiologically reasonable" values (between about 2τ and 200τ for many mammalian central nervous system neurons).

The random process $V(t)$ described by equation (1) and the diffusion approximation described by equation (11) have, in the absence of any barriers, the same mean,

$$E[(Vt)] = E[V^*(t)] = (f_e a_e - f_i a_i)[1 - \exp(-st)]/s, \quad (30)$$

where we have assumed $V(0) = V^*(0) = 0$, and same variance,

$$\text{Var}[V(t)] = \text{Var}[V^*(t)] = (f_e a_e^2 + f_i a_i^2)[1 - \exp(-2st)]/2s. \quad (31)$$

This being the case, one might expect the times at which $V(t)$ and $V^*(t)$ reach θ for the first time to about the same. A precise comparison is not possible because $V(t)$ may jump above θ to cause a level crossing whereas $V^*(t)$ must, since the sample paths of diffusion processes are continuous, hit θ precisely to give a neuron firing. It is nevertheless of interest to compare the random variables $T(0)$ and $T^*(0)$ and we will do this by comparing their mean values. It must be pointed out that the comparisons are not made in order to show that the mean interspike time calculated from the diffusion model is sometimes a bad approximation to that for the discontinuous process. The philosophy is rather to find out when the diffusion approximation is a good one for this purpose and when it performs best. Since the diffusion approximation is derived rigorously in the limiting cases of large input frequencies and small postsynaptic potential amplitudes, we expect to find the best agreement for $M_1(0)$ and $M_1^*(0)$ in such limiting cases. We will find however that the diffusion approximation often performs reasonably well away from these limiting regions.

3. Results and Discussion

The expected times between impulses in the two models were calculated for various θ , f_e , and f_i with a_e and a_i fixed at unity. In particular, values were obtained in the "physiological range" for $\theta = 3, 4, 6, 8$, and 10 . The values of $M_1(0)$ were obtained as previously described (Cope & Tuckwell, 1979) and the values of $M_1^*(0)$ were calculated from the Roy & Smith formula (26). The unit for the calculated quantities is the membrane time constant τ and the input frequencies f_e and f_i will be given in units of τ^{-1} . The comparison

between $M_1(0)$ and $M_1^*(0)$ is made by determining, at each set of values of f_e , f_i and θ , the % error of the diffusion calculation

$$E = \frac{\text{Diffusion} - \text{Exact}}{\text{Exact}} (100\%) = \{[M_1^*(0)/M_1(0)] - 1\}(100\%). \quad (32)$$

In Table 1 we show some of the calculated values of $M_1(0)$ and $M_1^*(0)$ for $\theta = 4$, $f_i = 2, 6$, and for $\theta = 8$, $f_i = 2, 10$, at various frequencies of excitation.

TABLE 1
A comparison of mean interspike intervals for the discontinuous model

θ	f_i	f_e	$M_1(0)$	$M_1^*(0)$
4	2	2	55.1	56.7
		3	10.4	9.39
		4	4.21	3.69
		5	2.40	2.10
4	6	3	324	195
		4	52.3	38.5
		5	15.7	12.5
		6	6.82	5.69
		7	3.77	3.21
		8	2.43	2.09
8	2	4	167	327
		5	33.0	40.6
		6	11.7	11.9
		7	5.92	5.60
		8	3.71	3.43
		9	2.64	2.42
		10	2.03	1.86
		11	1.60	1.42
8	10	8	261	218
		9	81.7	70.4
		10	32.8	28.8
		11	16.0	14.2

In Figs 1 and 2 the values of E are plotted against f_e for various f_i for $\theta = 4$ and $\theta = 8$. For each θ , values of E seem to approach a limiting negative value as f_e becomes large. There appear to be two kinds of curve: one which approaches the limiting value from above, through positive values of E ; the other approaches the limiting value from below. The former class has a band of frequencies of excitation where the diffusion model overestimates the expected time to reach θ . As θ increases, the number of frequencies of inhibition where such a band exists increases. For $\theta = 3$, the curve for $f_i = 0$

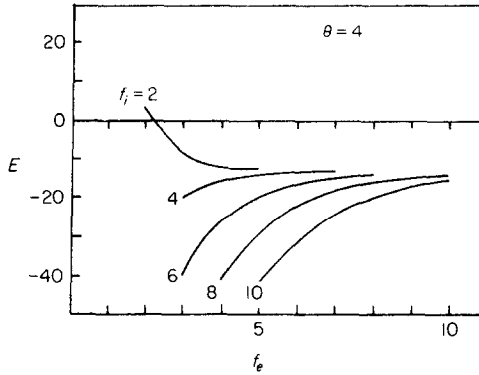


FIG. 1. Values of the percentage error E , when $\theta = 4$, of the mean interspike time calculated from the diffusion model relative to the results of the discontinuous model as a function of excitatory input frequency, f_e , for various values of the inhibitory frequency f_i .

approached the limit from above, whereas the curves for $f_i = 2, 4, 6, 8, 10$ were never positive. For $\theta = 4$, $f_i = 0, 2$ gave some positive values of E ; $\theta = 8$, $f_i = 0, 2, 4, 6$ (values for $f_i = 4, 6$ are not shown in Fig. 2 because of overcrowding), and for $\theta = 10$, $f_i = 0, 2, 4, 6, 8, 10$ all gave some positive values of E .

The asymptotic behavior for large f_e can be explained by considering the limit of very large frequencies of excitation at fixed θ and f_i . Since the decay becomes negligible in the limit, the value of $M_1^*(0)$ must approach the value

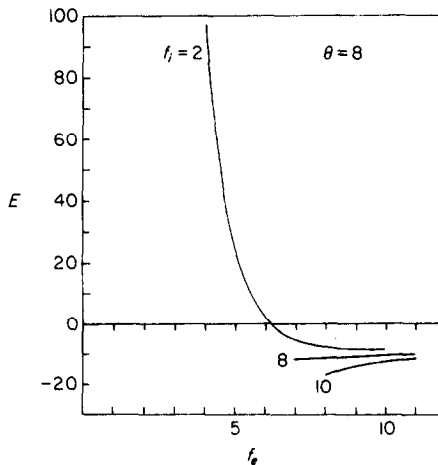


FIG. 2. As in Fig. 1 with $\theta = 8$.

for a Wiener process with drift $f_e t$. Hence, for $\theta = n$,

$$M_1^*(0) \underset{f_e \rightarrow \infty}{\sim} n/f_e. \tag{33}$$

For the discontinuous process one must, for all finite f_e , wait for at least $(n + 1)$ events in $\pi(f_e, t)$ before $V(t)$ reaches $\theta = n$, so that

$$M_1(0) \underset{f_e \rightarrow \infty}{\sim} (n + 1)/f_e. \tag{34}$$

Hence, for large f_e we have the limiting behavior for E :

$$E \underset{f_e \rightarrow \infty}{\sim} -100/(n + 1)\% = E_L. \tag{35}$$

The values of E at the largest f_e for each curve in Fig. 1 are between -15% and -12.5% and since $\theta = 4$ here, the limiting value is $E_L = -20\%$. In Fig. 2 the corresponding values of E are between -8.4% and -11.2% and since $\theta = 8$, the limiting value is $E_L = -11\%$. Thus the asymptotic values for extremely large f_e have not been reached on the figures.

Consider now the other extreme $f_e = 0$. With no excitatory inputs, $V(t)$ can never go above zero if $V(0) = 0$ and so $T(0) = \infty$ with probability 1 and hence $M_1(0) = \infty$. The diffusion process $V^*(t)$ on the other hand may diffuse above 0 and hit θ in a finite time. Hence $M_1^*(0) < \infty$. Thus we have

$$E \underset{f_e \rightarrow 0}{\sim} -100\%, \tag{36}$$

regardless of the value of f_i as long as $f_i \neq 0$. Therefore every curve in Figs 1 and 2 eventually approaches $E = -100\%$ as $f_e \rightarrow 0$, even the curves for $f_i = 2$.

Now consider a fixed intermediate value of f_e . First suppose f_i is much smaller than f_e . In the extreme case $f_i = 0$, $V(t)$ will reach θ quite quickly and the diffusion process will not be able to keep up with the jump process. In such a case we expect $M_1^*(0) > M_1(0)$, or a positive value of E . When f_i is much larger than f_e the discontinuous process spends most of its time below zero and the diffusion $V^*(t)$ tends to reach θ ahead of $V(t)$. This makes the value of E negative, corresponding to the class of curves that never visit positive values.

From these arguments and the exact results of Figs 1 and 2, we conclude that, for a given θ , the family of curves for the various values of f_i are as sketched in Fig. 3. Each curve (except possibly the one for $f_i = 0$) must emanate from $E = -100$ when $f_e = 0$, corresponding to relation (36). Also, as $f_e \rightarrow \infty$, E must in accordance with relation (35) tend to the limiting value $-100/(n + 1)$ for $\theta = n$. Since the right hand limiting values on the curves for $\theta = 4$ and $\theta = 8$ shown in Figs 1 and 2 were greater than the corresponding values of E_L , we must suppose that at higher f_e the curves will reach a

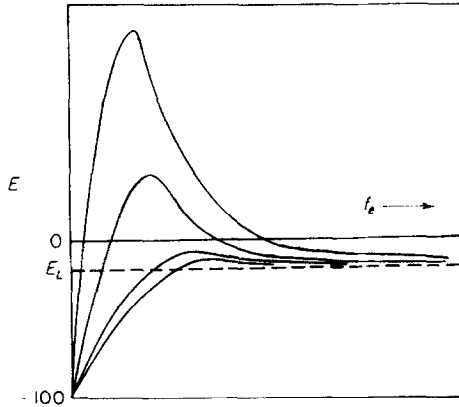


FIG. 3. General scheme of the error curves for various f_i .

maximum and then decrease to the values E_L . This leads to the idea that each member of the family of curves starts at $E = -100$, tends to increase and has a maximum which for smaller f_i actually occurs at positive values of E , whereas for larger f_i the maximum value of E is negative.

It can be seen that the diffusion model predicts, in the limit of large f_e and f_i , the mean interspike time given by the discontinuous model, rather well, especially when θ is large. Under certain conditions, however, the error may be of the order of up to 100% too small and under other conditions the diffusion prediction may be orders of magnitude too large for the mean interspike time. Hence theories of neuron firing as a function of inhibitory and excitatory frequency based on diffusion models must be regarded with due caution.

We thank John Walsh of the University of British Columbia for helpful discussion. Supported in part by National Research Council of Canada grants A4559 and A9259.

REFERENCES

- ABRAMOWITZ, M. & STEGUN, I. A. (1964). *Handbook of Mathematical Functions*, Washington, D.C.: National Bureau of Standards.
- CAPOCELLI, R. M. & RICCIARDI, L. M. (1971). *Kybernetik* **8**, 214.
- CALVIN, W. H. (1975). *Brain Res.* **84**, 1.
- COPE, D. K. & TUCKWELL, H. C. (1979). *J. theor. Biol.* **80**, 1.
- DARLING, D. A. & SIEGERT, A. J. F. (1953). *Ann. Math. Statist.* **24**, 624.
- GLUSS, B. (1967). *Bull. Math. Biophys.* **29**, 233.
- HOLDEN, A. V. (1976). *Models of the Stochastic Activity of Neurons*, New York, Heidelberg, Berlin: Springer-Verlag.

- JOHANNESMA, P. I. M. (1968). In *Neural Networks* (E. R. Caianello, ed.). New York: Springer-Verlag.
- KEILSON, J. & ROSS, H. F. (1975). *Sel. Tabl. math. Stat.* **3**, 233.
- ROY, B. K. & SMITH, D. R. (1969). *Bull. Math. Biophys.* **31**, 341.
- SATO, S. (1978). *Math. Biosci.* **39**, 53.
- STEIN, R. B. (1965). *Biophys. J.* **5**, 173.
- STEIN, R. B. (1967). *Biophys. J.* **7**, 37.
- STRATONOVICH, R. L. (1963). *Topics in the Theory of Random Noise*, vol. I. New York: Gordon & Breach.
- THOMAS, M. U. (1975). *J. Appl. Prob.* **12**, 600.
- TUCKWELL, H. C. (1975). *Biol. Cyb.* **18**, 225.
- TUCKWELL, H. C. (1979). *J. theor. Biol.* **77**, 65.
- UHLENBECK, G. E. & ORNSTEIN, L. S. (1930). *Phys. Rev.* **36**, 823.
- WANG, M. C. & UHLENBECK, G. E. (1945). *Rev. Mod. Phys.* **17**, 323.
- YANG, G. L. & CHEN, T. C. (1978). *Math. Biosci.* **38**, 1.