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# Analytical and Simulation Results for Stochastic Fitzhugh-Nagumo Neurons and Neural Networks

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**Abstract.** An analytical approach is presented for determining the response of a neuron or of the activity in a network of connected neurons, represented by systems of nonlinear ordinary stochastic differential equations—the Fitzhugh-Nagumo system with Gaussian white noise current. For a single neuron, five equations hold for the first- and second-order central moments of the voltage and recovery variables. From this system we obtain, under certain assumptions, five differential equations for the means, variances, and covariance of the two components. One may use these quantities to estimate the probability that a neuron is emitting an action potential at any given time. The differential equations are solved by numerical methods. We also perform simulations on the stochastic Fitzugh-Nagumo system and compare the results with those obtained from the differential equations for both sustained and intermittent deterministic current inputs with superimposed noise. For intermittent currents, which mimic synaptic input, the agreement between the analytical and simulation results for the moments is excellent. For sustained input, the analytical approximations perform well for small noise as there is excellent agreement for the moments. In addition, the probability that a neuron is spiking as obtained from the empirical distribution of the potential in the simulations gives a result almost identical to that obtained using the analytical approach. However, when there is sustained large-amplitude noise, the analytical method is only accurate for short time intervals. Using the simulation method, we study the distribution of the interspike interval directly from simulated sample paths. We confirm that noise extends the range of input currents over which (nonperiodic) spike trains may exist and investigate the dependence of such firing on the magnitude of the mean input current and the noise amplitude. For networks we find the differential equations for the means, variances, and covariances of the voltage and recovery variables and show how solving them leads to an expression for the probability that a given neuron, or given set of neurons, is firing at time $t$. Using such expressions one may implement dynamical rules for changing synaptic strengths directly without sampling. The present analytical method applies equally well to temporally nonhomogeneous input currents and is expected to be useful for computational studies of information processing in various nervous system centers.

**Keywords:** stochastic neuron model, Fitzhugh-Nagumo model, noise-induced activity, interspike intervals, stochastic neural network

## 1. Introduction

As pointed out by Mainen and Sejnowski (1995), information transmission in the central nervous system is often accomplished by the nonlinear transformation of continuously varying input currents to discrete trains of action potentials. However, this transformation is usually quintessentially noisy, which raises the issue of how signals, if they are stochastic, can be coded and decoded. Because electrophysiological studies via multiunit recording are limited to several neurons and PET studies reveal only gross features, mathematical modeling of the dynamics of neural activity is a useful adjunct to neurobiological experiments. Our aim in this article is to illustrate a new semianalytical approach for predicting the stochastic electrophysiological activity of neurons and neural networks.

There has been in the last several years, much interest in modeling and analysis of the stochastic aspects of neuronal spiking activity and the associated problems of coding. Softky and Koch (1993) have examined closely a range of models to compare their predicted variability in the interspike interval (ISI). Generally they concluded that traditional integrate and fire models underestimated the variability at high firing rates although simulations for a stochastic cable model (Tuckwell et al., 1984) had manifested large (>1) coefficients of variation for the interspike interval. Furthermore, it was once generally accepted that neurons often employ a frequency code to convey information. However, especially for mammalian cortical neurons, this simple *modus operandi* has been questioned. It has been postulated that the finer details of the timing within individual spike trains may themselves be important in transmitting and delivering information (Barlow, 1963; Strehler and Lestienne, 1986; Abeles and Gerstein, 1988; Hopfield, 1995; Parodi et al., 1996; Lestienne and Tuckwell, 1997), though this has been questioned by others (Shadlen and Newsome, 1995; Softky, 1996; see also Konig et al., 1996, for a comprehensive discussion). The actual variability of spike trains themselves has also been mentioned as a manifestation of the process of information transmission as it reflects the fact that the timing of spikes is important in this regard (Mainen and Sejnowski, 1995).

There are many levels at which one can address nervous system functioning. Recently there have appeared several articles in which the properties of both deterministic (for example, Schuster and Wagner, 1990; Hopfield and Herz, 1995) and stochastic (for example, Usher et al., 1993; Fukai and Shiino, 1995) networks of model neurons have been investigated. Original studies of neuronal networks were often based on the assumption that there are two possible states for each element of the network (McCullogh and Pitts, 1943; Hopfield, 1982). Models have become increasingly realistic (Maass, 1995) and included physiological details of neurons such as Hodgkin-Huxley (1952) elements and synaptic currents of various kinds (for example, Golomb et al., 1994). In addition to studies that employ phase analysis, simulation, or numerical integration of systems of ordinary differential equations, there have been a few direct analytical approaches to problems involving stochastic model neurons with synaptic input (Blanchard et al., 1993; Rodriguez, 1995).

Although there has been considerable progress with networks of model neurons, it is advantageous to have analytical methods for studying them as well as the properties of the elements of which they are composed. In this direction there have been advances with classical one-dimensional models (see, for example, Tuckwell, 1979, 1989; Lansky and Lanska, 1987), but these have mainly been of the linear (for subthreshold voltages) leaky integrate and fire type. There have been only a few *analytical* works concerning nonlinear models with noise, including the spatially distributed Fitzhugh-Nagumo system (Tuckwell, 1987, 1992) and the Hodgkin-Huxley system (Horikawa, 1991, 1992). However it is now possible to use software routines to implement studies of many compartmental model neurons with both linear and nonlinear dynamics (Bower, 1992; DeSchutter and Bower, 1994).

There are several nonlinear systems of differential equations that have been used to model neuronal electrophysiology. We employ here the Fitzhugh-Nagumo system that has been employed recently in a network model (Kruglyak and Bialek, 1993). Although this system does not have as firm an empirical basis as conductance-based models, it is relatively simple and more directly amenable to analysis. This property has been utilized in the case of the space-clamped Fitzhugh-Nagumo system with small additive Gaussian white noise by Kurrer and Schulten (1991). These authors used an expansion in terms of the noise parameter to linearize the Fokker-Planck equation, thus obtaining interesting insights into the diffusive effects along limit cycle solutions. They correctly conjectured that such effects would be important in sustaining synchronized activity in systems of coupled (neuronal) oscillators. In a subsequent investigation, Longtin (1993) considered a similar system but included a stimulus with sinusoidal intensity in addition to the noise. The interspike interval histograms were found to have the multimodal form similar to those of certain sensory neurons. It was also found that there was "spontaneous" noise-induced repetitive firing in the absence of the sensory stimulus.

## 2. Model Equations, Differential Equations for the Moments, and the Probability of a Spike

### 2.1. *Model Equations*

The space-clamped Fitzhugh-Nagumo system of two differential equations has been employed to provide insight into the more complex Hodgkin-Huxley system of four equations. It shares with the latter the properties of subthreshold responses and suprathreshold responses, including periodic solutions, representing action potentials or spikes in response to suitable stimuli.

We will study the following corresponding stochastic version of this model in which the components obey the following equations:

$$dX = [f(X) - Y + I]\,dt + \beta dW \qquad (1)$$

$$dY = b(X - \gamma Y)\,dt, \qquad (2)$$

where $X = X(t)$ is referred to as the voltage variable, $Y = Y(t)$ as the recovery variable, $W = \{W(t), t \geq 0\}$ is a standard (zero mean, variance $t$) Wiener process, $I = I(t)$ is a deterministic input current (stimulus), that may be constant or time-varying, and $b$ and $\gamma$ are positive constants. The function $f$ is a cubic

$$f(x) = kx(x - a)(1 - x), \qquad (3)$$

where $0 < a < 1$. Usually one takes $a < 1/2$ in order to obtain suitable suprathreshold responses.

The noise in Eq. (1) is additive and may represent channel noise. However it is usually taken as an approximation to superimposed randomly arriving excitatory and inhibitory postsynaptic potentials as in the linear subthreshold model, which leads to an Ornstein-Uhlenbeck process (Gluss, 1967; Capocelli and Ricciardi, 1971). Additive white Gaussian noise was also previously employed in the present context by Kurrer and Schulten (1991) and Longtin (1993).

The following notation will be employed for the first- and second-order moments: $E[X(t)] = \mu_1(t)$, $E[Y(t)] = \mu_2(t)$, *Var* $[X(t)] = V_1(t)$, $Var[Y(t)] = V_2(t)$, and $Cov[X(t), Y(t)] = K_{12}(t)$, where $E$ denotes expectation, *Var* denotes variance, and *Cov* denotes covariance. The method we shall employ has been presented for a general nonlinear stochastic system elsewhere (Rodriguez and Tuckwell, 1996). It is straightforward to obtain the following (integro-differential) equations for the means:

$$\frac{d\mu_1}{dt} = E[f(X) - Y + I(t)] \qquad (4)$$

$$\frac{d\mu_2}{dt} = bE[X - \gamma Y]. \qquad (5)$$

To obtain corresponding equations for the second-order moments we apply Ito's formula for change of variable (see, for example, Gihman and Skorohod, 1972) to obtain differentials for $(X - \mu_1)^2$, $(Y - \mu_2)^2$, and $(X - \mu_1)(Y - \mu_2)$. After taking expectations in the resulting formulas we obtain

$$\frac{dV_1}{dt} = 2E[(X - \mu_1)(f(X) - Y + I)] + \beta^2, \qquad (6)$$

$$\frac{dV_2}{dt} = 2bE[(X - \gamma Y)(Y - \mu_2)], \qquad (7)$$

and

$$\frac{dK_{12}}{dt} = E[b(X - \mu_1)(X - \gamma Y) + (Y - \mu_2)(f(X) - Y + I)]. \qquad (8)$$

### 2.2. *Differential Equations for the Moments*

Equations (4) to (8) cannot be solved as they stand, and we seek accurate approximations to their solutions by methods in Rodriguez and Tuckwell (1996) and outlined briefly in the Appendix A. We henceforth denote the approximate means by $m_1(t), m_2(t)$, the approximate variances by $S_1(t), S_2(t)$, and the approximate covariance by $C_{12}(t)$. This gives, after simplification, the following system of five coupled differential equations for the approximate first- and second-order central moments:

$$\frac{dm_1}{dt} = f(m_1) - m_2 + \frac{1}{2}f''(m_1)S_1 + I(t) \qquad (9)$$

$$\frac{dm_2}{dt} = b(m_1 - \gamma m_2) \qquad (10)$$

$$\frac{dS_1}{dt} = 2f'(m_1)S_1 - 2C_{12} + \beta^2 \qquad (11)$$

$$\frac{dS_2}{dt} = 2b(C_{12} - \gamma S_2) \qquad (12)$$

$$\frac{dC_{12}}{dt} = bS_1 - S_2 + C_{12}[f'(m_1) - \gamma b]. \qquad (13)$$

On utilizing (3), so that $f'(m_1) = k[2m_1(1+a) - a - 3m_1^2]$ and $f''(m_1) = k[2(1+a) - 6m_1]$, Eqs. (9) to (13) may be solved numerically.

### 2.3. The Probability of a Spike at Time t

On the assumption that $X(t)$ and $Y(t)$ are approximately jointly normally distributed, one has their joint distribution because their means, variances, and covariance are known. Assuming that there is a threshold for action potential generation in the voltage variable with value $\theta$, then the following expression (see Appendix B) gives an approximation $P_\theta(t)$ to the probability that at time $t$ the voltage variable $X(t)$ of the Fitzhugh-Nagumo neuron is above threshold level and emitting an action potential:

$$P_\theta(t) = 1 - \phi\left(\frac{\theta - m_1(t)}{\sqrt{S_1(t)}}\right), \qquad (14)$$

where $\phi(.)$ is the standard normal distribution function. This fact is used in Section 3.5. Note that even though $P_\theta(t)$ can be found from $m_1(t)$ and $S_1(t)$, determination of these two quantities requires the solution of all five of Eqs. (9) to (13).

## 3. Comparison of Analytical Results with Simulations

To obtain the first- and second-order moments of $X(t)$ and $Y(t)$ analytically we solved the five differential Eqs. (9) to (13), employing a fourth-order Runge-Kutta method with a step size of $\delta t = 0.01$, or $\delta t = 0.1$ if sufficient accuracy was obtained. Initial conditions were chosen such that the values of $X(0)$ and $Y(0)$ were known with certainty. Thus, $m_1(0)$ and $m_2(0)$ were given prescribed values and $S_1(0) = S_2(0) = C_{12}(0) = 0$. Random initial values were also employed, but their effect was predictably an increase in variability, and this can be always incorporated by integrating over an initial distribution.

We have considered various forms for the deterministic component $I(t)$ of the input current and various lengths of time for their application. Noteworthy is the fact that time-dependent currents (nonhomogeneous processes) present no problem for the present approach, which contrasts with the difficulties encountered with integrate and fire models. One of the main objectives is to ascertain under what conditions the analytical approach outlined above is in fact useful.

Thus we have additionally simulated the processes described by the evolution Eqs. (1) and (2) using a standard Euler method, which has proven convergence properties (Milstein, 1994). To apply this, with $X(k\delta t)$ and $Y(k\delta t)$ approximated by $X_k$ and $Y_k$ respectively, the simulation scheme consists of the recursive relations

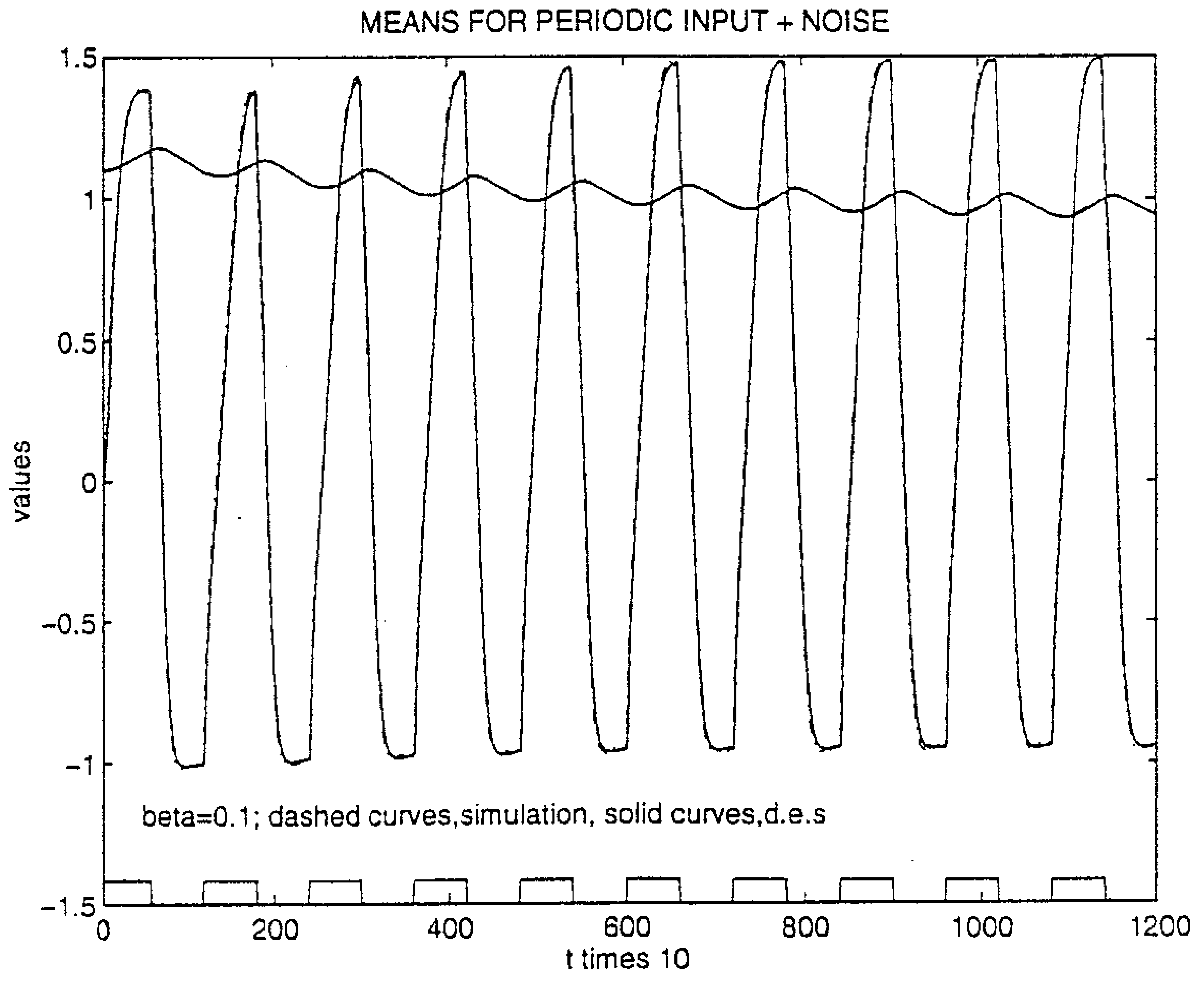
$$X_{k+1} = X_k + [f(X_k) - Y_k + I]\delta t + \beta\sqrt{\delta t}N_k$$
$$Y_{k+1} = Y_k + b[X_k - \gamma Y_k]\delta t,$$

where $k = 0, 1, 2, \ldots$ and $\{N_k\}$ is a sequence of independent and identically distributed standard normal random variables. The latter are obtained from computer library routines. All numerical work was done in double precision.

### 3.1. Periodic Input with Noise

We first consider the application of an input current in the form of a regular rectangular wave. The period of $I(t)$ was set at 60 time units with equal durations of on and off phases. The amplitude was set at $I_{\max} = 1.5$ during on phases. Remaining parameters were set as follows: $a = 0.1, b = 0.15, \gamma = 0.2, k = 0.5$. Initial values are, with probability 1, $X(0) = 0, Y(0) = 1.1$. The noise parameter has the intermediate value $\beta = 0.1$. The computed results for the means, $E(X(t))$ and $E(Y(t))$ are shown in Fig. 1A, where dashed lines represent results from simulation, and solid lines are the solutions $m_1(t)$ and $m_2(t)$ in the system of five differential Eqs. (11) to (15). 100 trials were used in these simulations—that is, 100 sample paths were generated and the moments obtained from them.

At the bottom of Fig. 1A is the form (scaled) of the input current. It can be seen that the results for the two methods are almost indistinguishable. Figure 1B shows the variance of the voltage variable, $X(t)$, obtained by simulation and calculated as $S_1(t)$. Again, the agreement between the two methods is excellent and indicates that the analytic method is very accurate in this instance, especially considering that the computed quantity is between about 0.005 and 0.03 and that there is sampling error in the simulation results. Figure 1C shows the values of the variance of the recovery variable $Y(t)$ and the covariance of the two components as a function of time, obtained from simulation, along with the corresponding calculated quantities, $S_2(t)$ and $C_{12}(t)$. The agreement for the variance of $Y(t)$ is very good as the magnitude of this quantity is



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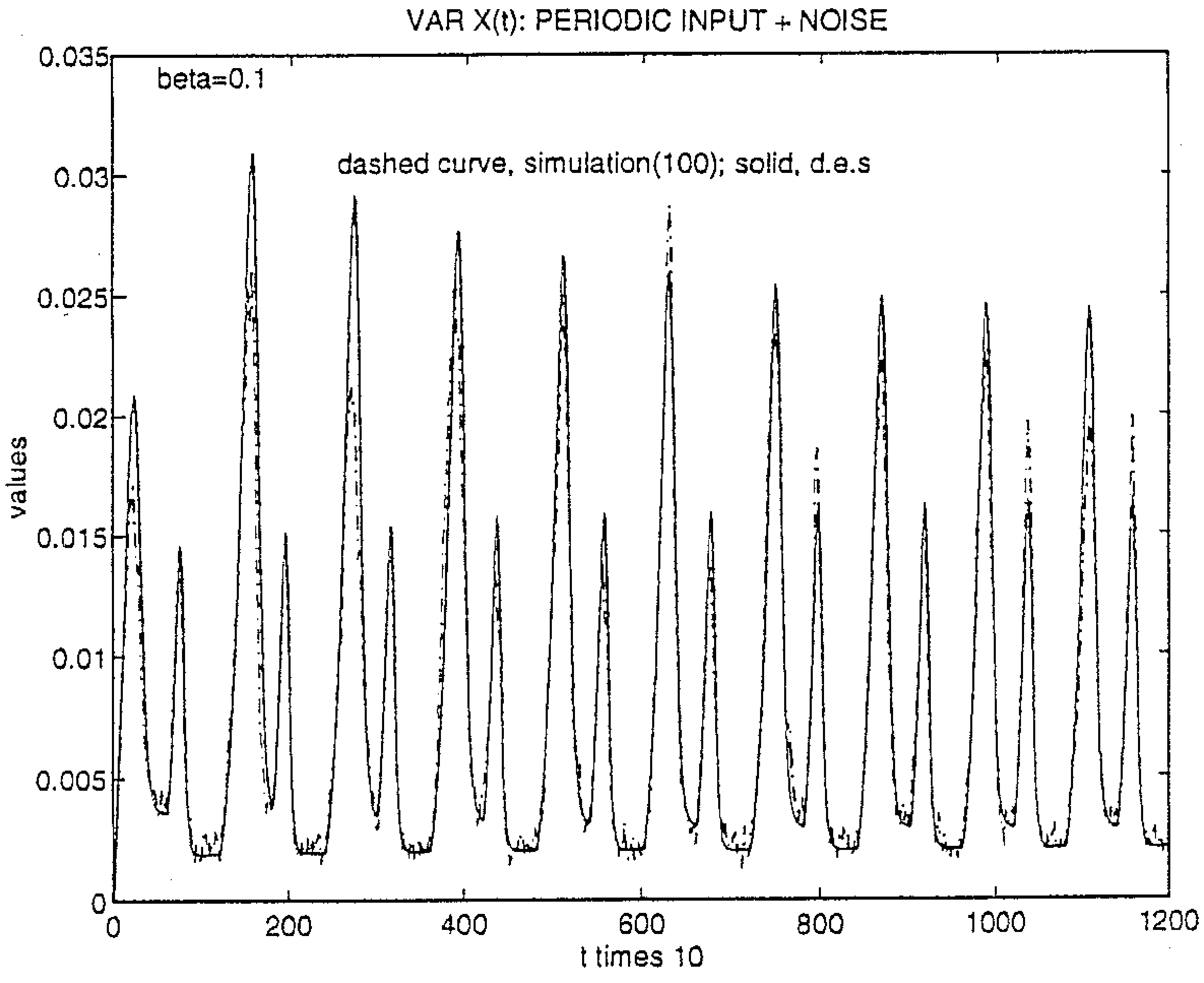

B

*Figure 1.* Showing the moments of the voltage and recovery variables for a regular rectangular current wave plus noise. $\beta = 0.1$. A. Means of $X(t)$ and $Y(t)$ for the current whose mean time-course is shown at the bottom of the figure. The magnitude of the on-phases of current is $I = 1.5$. The means obtained by simulation and by solving the differential equations for the moments are practically indistinguishable. B. Variance of the voltage component calculated by the two different methods. C. The variance of the recovery variable as a function of time and the covariance of the two components as calculated by the two different methods.

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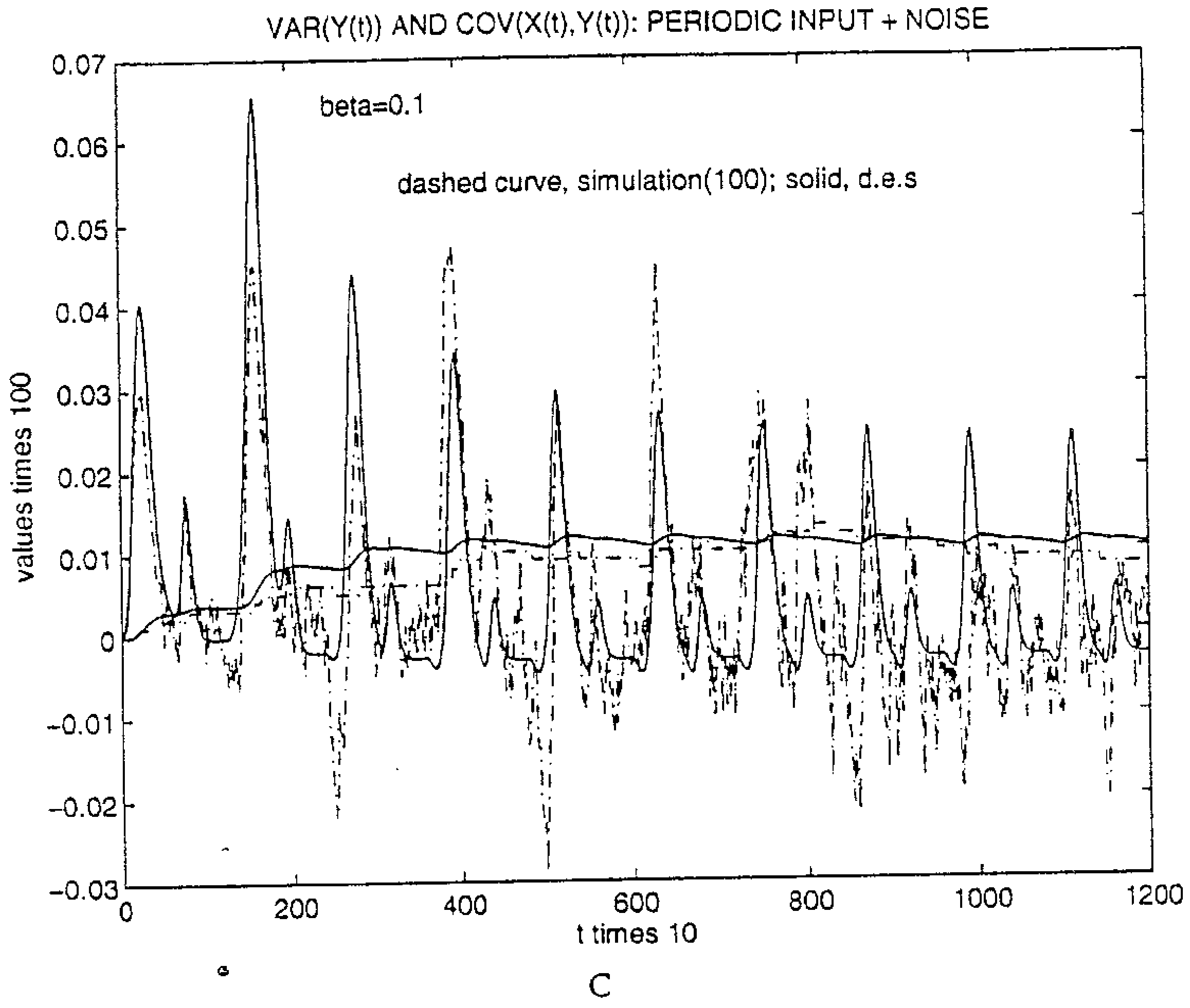


*Figure 1.* (*Continued*).

of order 0.0001. There is less agreement for the covariance obtained by the two methods. Although most of the positive peaks are in good agreement, there is less agreement when the covariance values from simulation attain their minima. When the noise parameter $\beta$ was increased to 0.25, the agreement was also excellent for the means, the variances, and to a lesser extent the covariance. Thus, with nonsustained deterministic input currents, the analytical method works very well over a wide range of noise amplitudes.

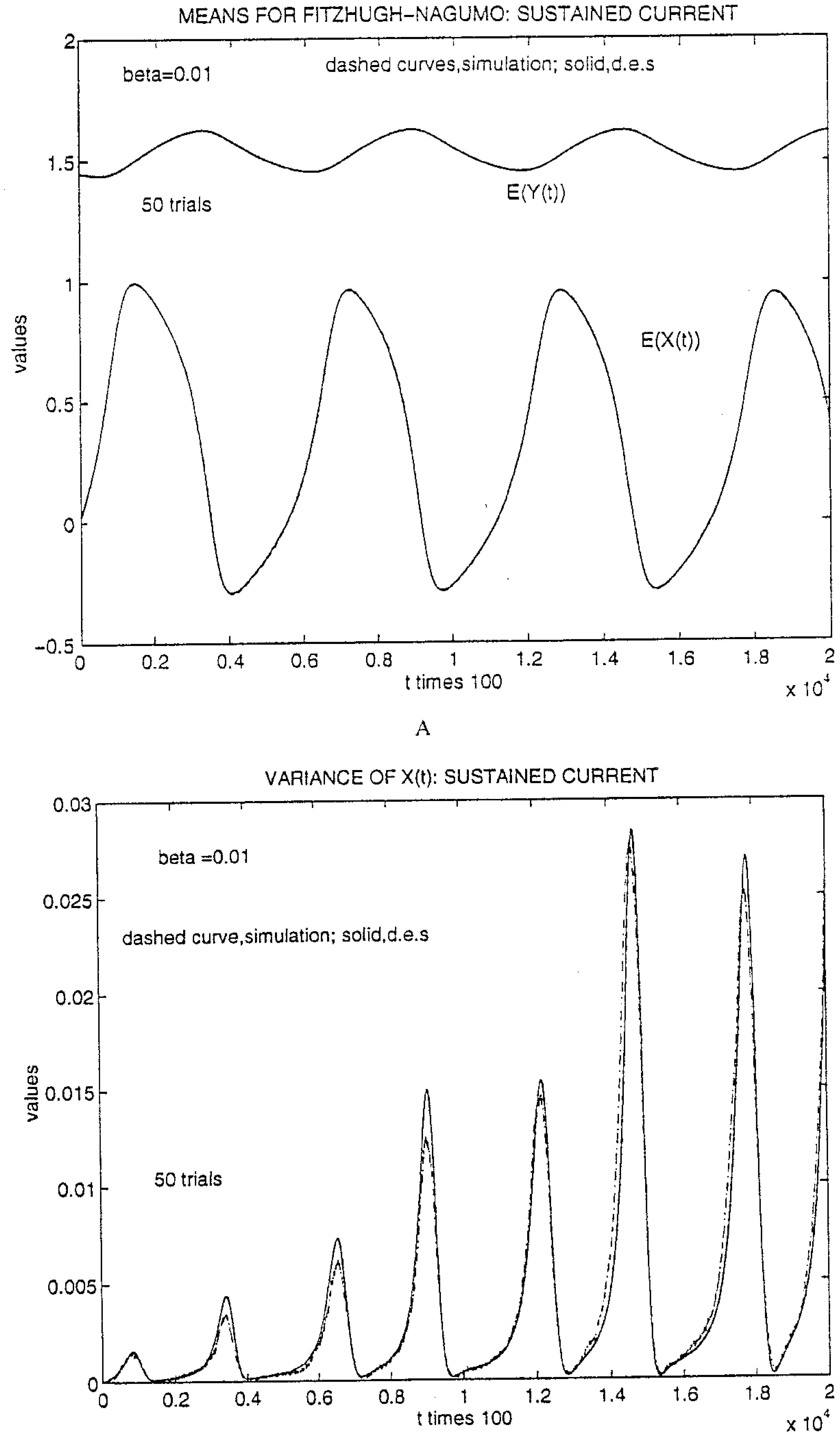
### 3.2. *Constant Mean Current with Small Noise Short-Term Applications*

***3.2.1. Results for the Moments with $\beta = 0.01$.*** We also investigated the usefulness of the analytical method for a sustained mean current of constant amplitude accompanied by white noise. In certain ranges of the amplitude of a constant current without noise it is known that repetitive pulse solutions may be obtained which mimic action potentials (Troy, 1976; Rinzel and Keener, 1983). In Fig. 2 we show results for a constant mean current $I = 1.5$, $t \geq 0$, with noise parameter set at the small value of $\beta = 0.01$. The initial values were set at $X(0) = 0.0$ and $Y(0) = 1.45$. The remaining parameter values are as in Section 3.1, except that for both the simulations and the numerical solution of the differential equations $\delta t = 0.01$, and for the simulations 50 trials were used.

One can see from Fig. 2A that the means of $X(t)$ and $Y(t)$ predicted by the two methods are again almost exactly the same. Figure 2B shows that there is similar agreement for the variance of $X(t)$. The agreement for the variance of $Y(t)$, as shown in Fig. 2C, is also very good; that for the covariance is not as close, but given the very small magnitudes involved and the sampling error in the simulation results, it is satisfactory. Note that the absolute value of the covariance grows here for small increasing $t$ because the initial condition was noise free yet the noise was "switched on" at $t = 0$.

***3.2.2. The Approximate Distribution of $X(t)$.*** The simulation method enables one to investigate the distribution of $X(t)$ for various parameter values and for different times. Although of interest in itself, this also enables us to check the validity of the assumptions made concerning the distribution of $X(t)$ in deriving the differential equations for the moments.

Figure 3 shows histograms of values of $X(t)$ from the simulations, with 1000 trials, with parameters as given in the previous subsection. The empirical distributions at time $t = 60$ seem to satisfy the assumptions, and the same is true for $t = 80$. However, for larger times, the



A

B

*Figure 2.* The same quantities in Figs. 1A to 1C except that now the current is uninterrupted and $\beta = 0.01$. The deterministic component of the current is such that there is repetitive firing without noise. A. The means of the two components calculated by the two different methods. The two sets of results can hardly be distinguished. B. The variance of $X(t)$ determined by the simulation method (dashed curve) and the analytical method (solid curve). C. The variance of $Y(t)$ (the always positive quantity) and the covariance of the two components.

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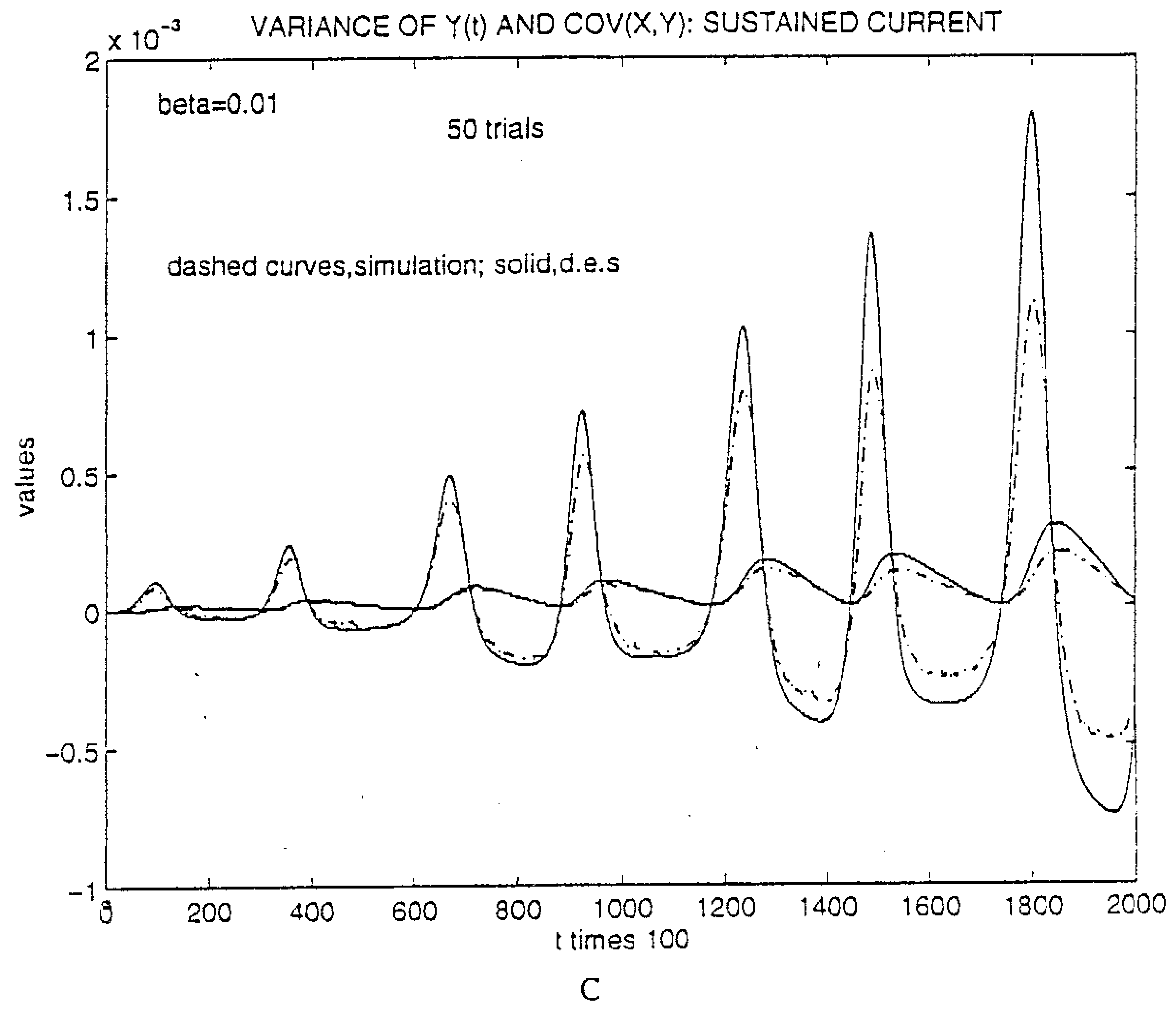


*Figure 2.* (*Continued*).

distribution seems to be somewhat skewed to smaller values of $X(t)$ violating the assumptions of the analytic approach. Nevertheless, the assumptions concerning the distribution are fairly well satisfied for most values of $t$ considered here.

***3.2.3. Results for $\beta = 0.05$.*** The results for the means are shown in Fig. 4A when the noise parameter is increased to 0.05. The variance of the voltage variable is shown in Fig. 4B. Initial values are $X(0) = 0$ and $Y(0) = 1.1$, the remaining parameters being the same as in the previous two sections. However, the close agreement between the simulation results and the analytical method of finding the moments occurs only for small times, where in fact it is very close. This will be elaborated on in Section 3.3.

Because it seemed that a key factor in the validity of the analytic approach might be the magnitude of the coefficients of variation of the component random processes, we computed this quantity as a function of time for the present case. We include a study of the coefficient of variation because it is often a useful indication of the relative magnitide or importance of random fluctuations in relation to mean values (Softky and Koch, 1993). It is seen in Fig. 4C that

$$CV_{X(t)} = \frac{\sqrt{Var X(t)}}{E(X(t))}$$

is small except where the variance of $X(t)$ is large and that this growth in its value occurs in a region where the analytical approximations for the moments agree very closely with the values obtained by simulation. It is concluded that $CV \ll 1$ is neither a necessary or sufficient condition for the accurate prediction of the moments by the method of solving the differential Eqs. (9) to (13).

### *3.3. Constant Current with Small Noise: Intermediate-Time Intervals*

When $\beta$ is increased, the method of obtaining the moments from the differential equations may not succeed for sustained applications of the applied current. This is seen for $\beta = 0.05$ in Fig. 5, where the means of $X(t)$ and $Y(t)$ are shown determined both by simulation and by solution of the differential equations. Simulation predicts that the means oscillate with decreasing amplitude. Figure 5B shows clearly how the moment equations yield solutions that become unstable after only a few, at most, periods. With $I$ and $\beta$ as parameters, it will be of interest to later consider such behaviors of the solutions of (9) to (13) using classical analysis of eigenvalues associated with equilibrium points of the nonlinear system.

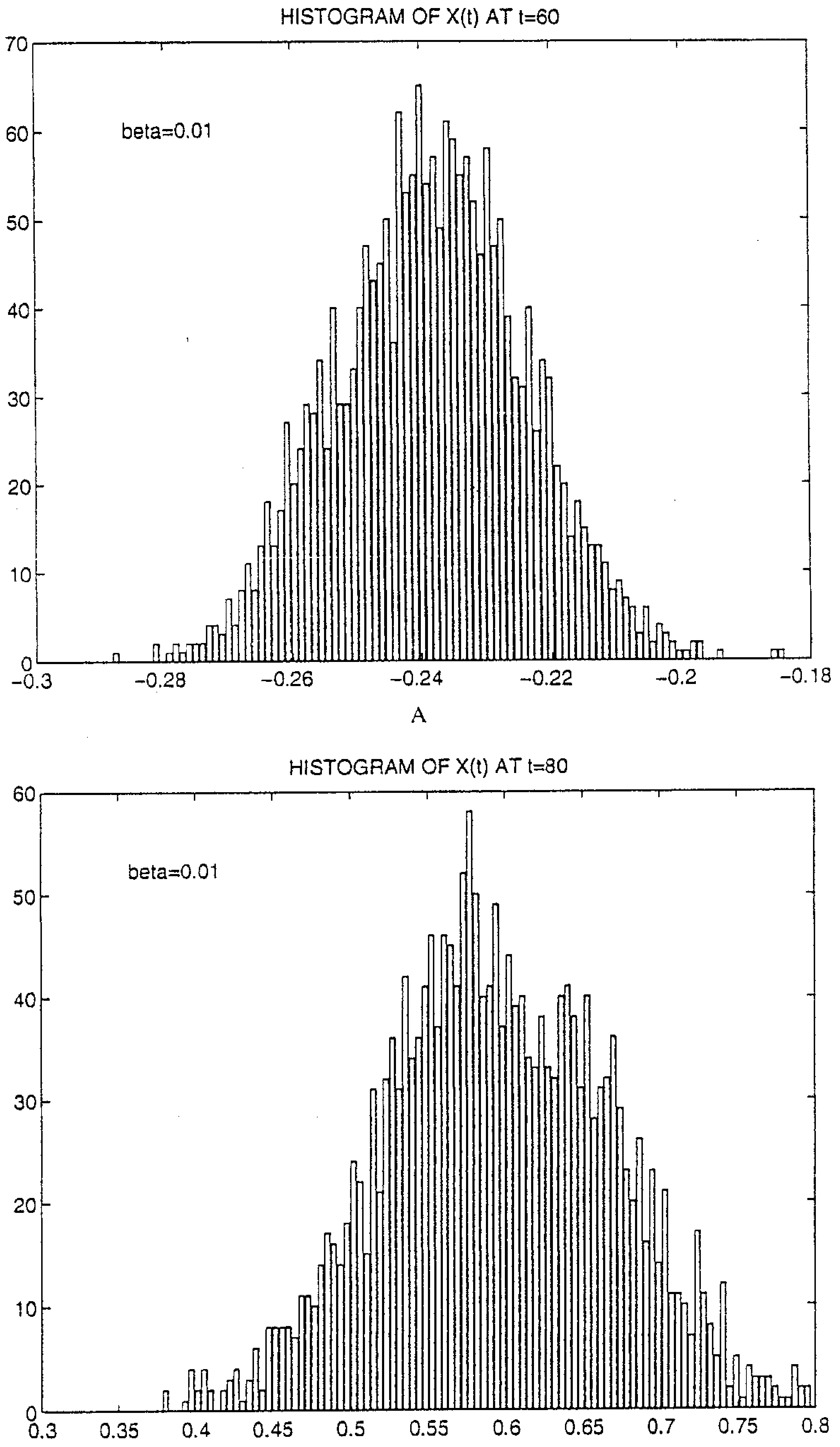
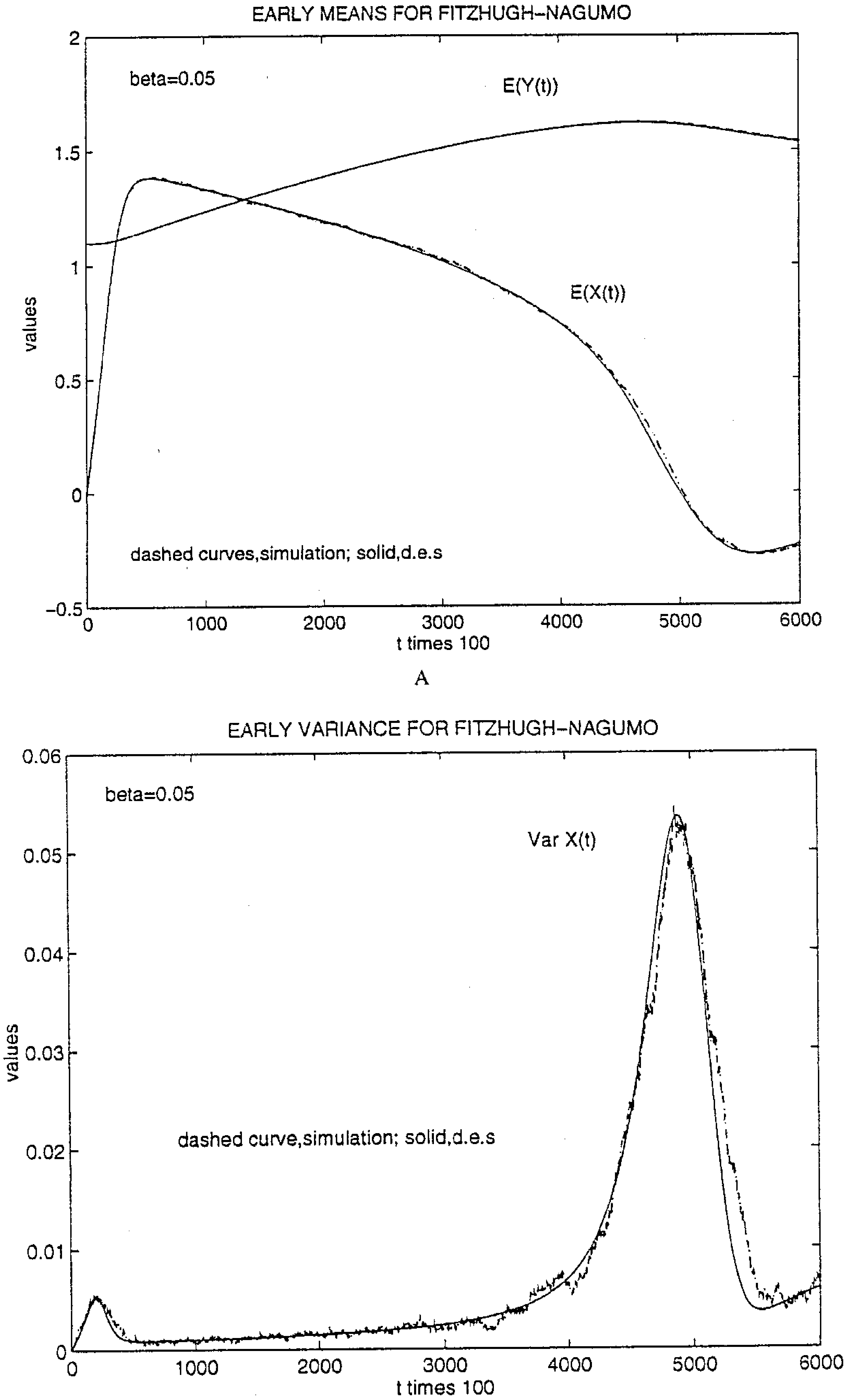


*Figure 3.* Estimates of the distribution of $X(t)$ for various $t$ from the simulation results. Times shown are $t = 60$ (A) and $t = 80$ (B). The distributions are almost symmetric at these small times.



A

B

*Figure 4.* The means of the two components (shown in A) by the two methods and the variance of the first component (shown in B). Here the value of $\beta$ is increased to 0.05. Agreement is good between the results of the two methods for the relatively small time interval shown. C. The changes in the magnitude of the coefficient of variation of the first component throughout the time interval when the variance of $X(t)$ is large. The numerical method is accurate despite the large coefficient of variation of $X(t)$.

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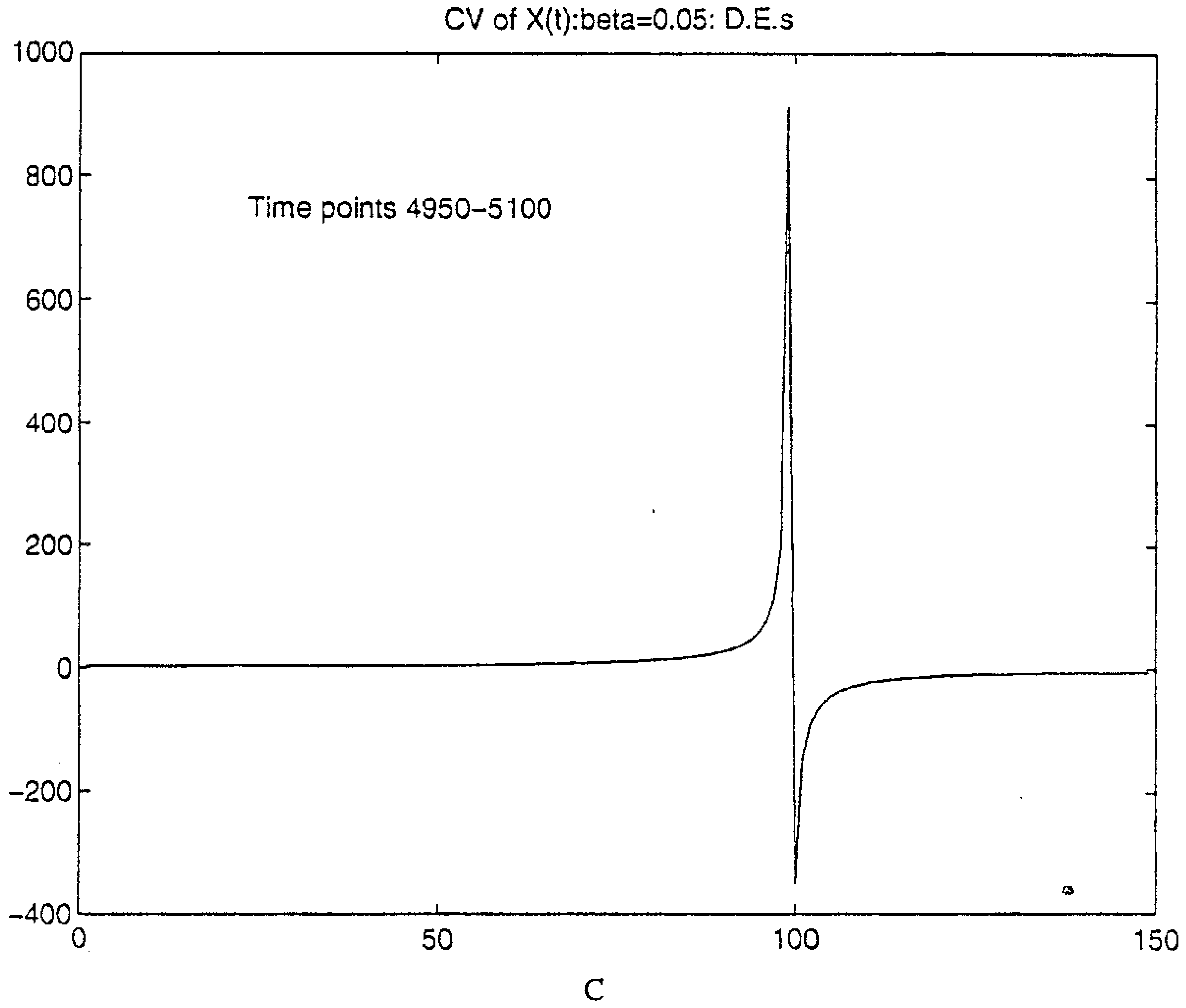
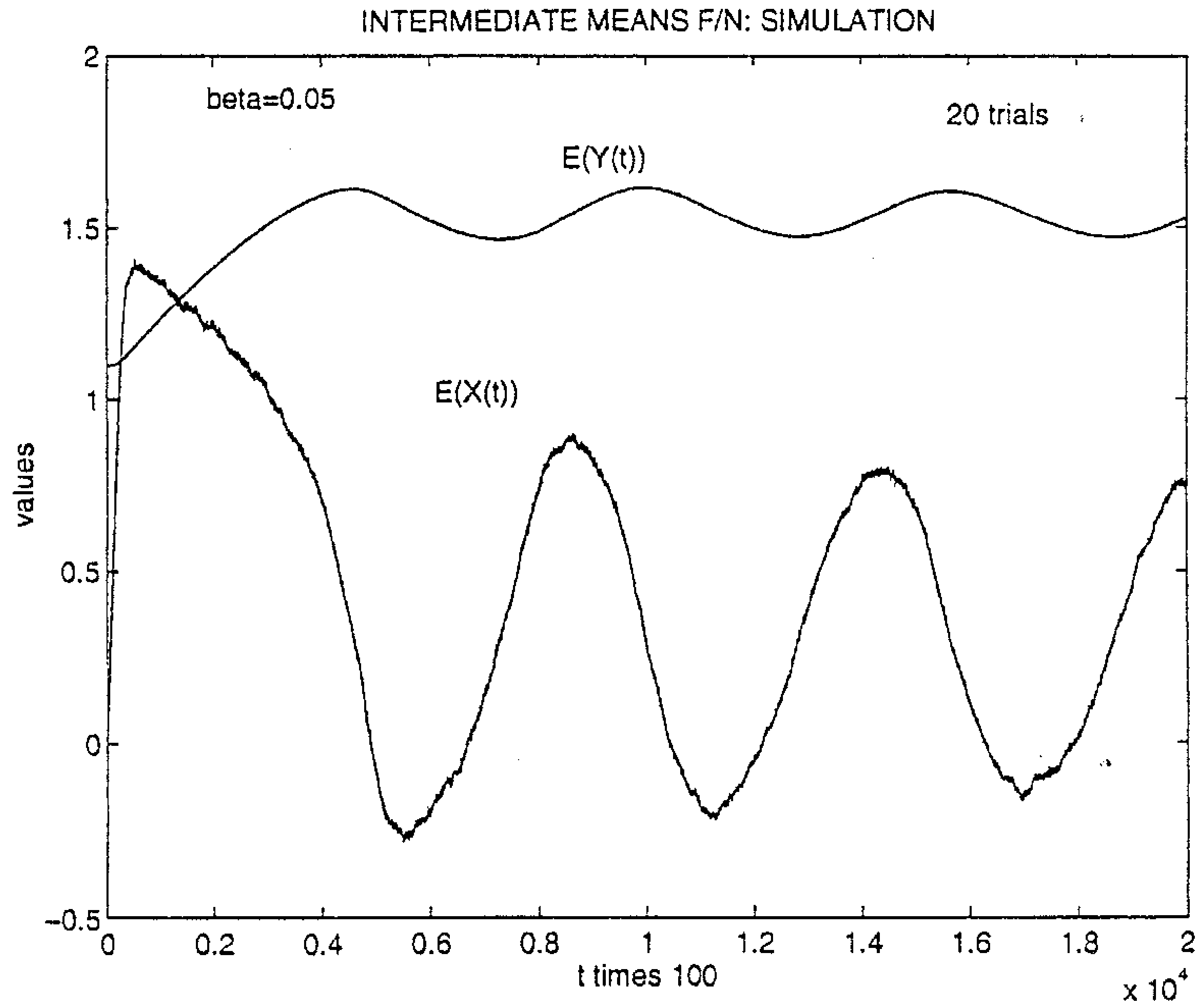


C

*Figure 4.* (*Continued*).



A

*Figure 5.* A. The simulation method of determining the means continues to work when the current is sustained. B. The solutions of the moment equations may break down for a continued application of noisy current. (*Continued on next page.*)

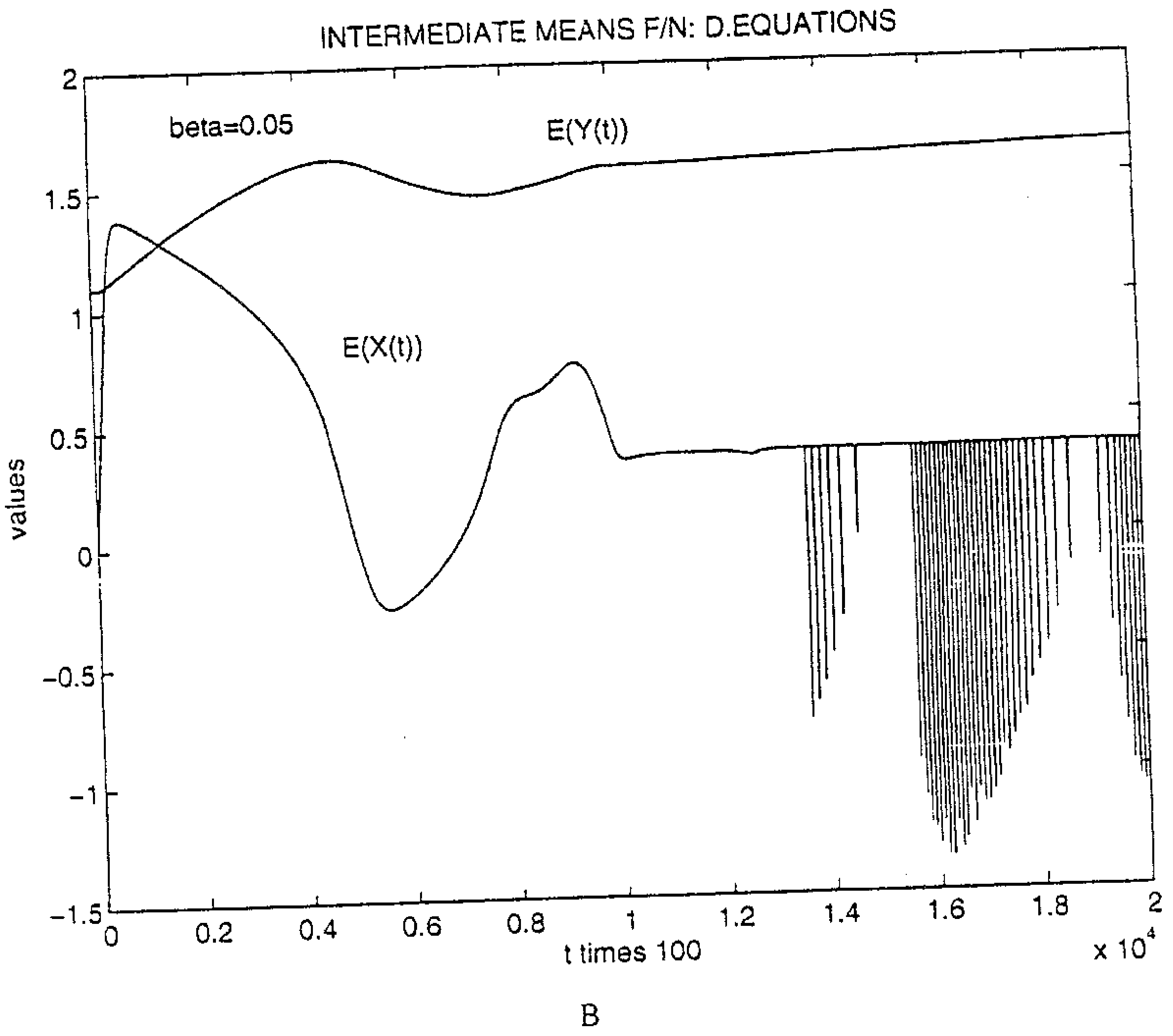


*Figure 5.* (*Continued*).

### 3.4. *The Probability that the Neuron is Spiking*

As indicated in Section 2, the assumption that the voltage variable $X(t)$ and the revovery variable $Y(t)$ are approximately jointly Gaussian enables one to estimate the probability that a neuron is firing if the first- and second-order moments are known. This estimate is given by Eq. (14). The value of $\theta$ is not as well defined for the Fitzhugh-Nagumo system as it is in the Hodgkin-Huxley system, but based on several observations of spike trains one can ascribe a reasonable value to the threshold variable $\theta$. If $X(t) > \theta$ holds, then it may be stated with a fair degree of certainty that a spike is in the process of being emitted; the time of emission of a spike can be taken as that at which $X(t)$, the voltage variable, crosses $\theta$ with a positive derivative.

We give an example of the estimation, by analytical methods, of the probability $P_\theta(t)$ that at time $t$ the neuron is in fact spiking. Here the parameter values are $a = 0.1, b = 0.015, \gamma = 0.2, k = 0.5, \beta = 0.01, \theta = 0.6$, and $I = 1.5$, and we have used the initial values be $X(0) = 0, Y(0) = 1$.

The results are shown in Fig. 6 for the probability $P_\theta(t)$ that the neuron is spiking as a function of time, determined from the formula (14) (solid line) with the solutions of the differential equations for the moments and directly from simulation results (dashed line). For the simulations the estimate of $P_\theta$ is the fraction of all trials with $X(t) > \theta$. The agreement between the two sets of results is good. It can be seen that the discrepancy increases somewhat as a function of time since the noise was switched on, as the initial conditions were chosen to be deterministic (same starting point for $X, Y$ in the simulations, and initial variances and covariance zero for the differential equation method). Agreement is expected to be better when the input current is sporadic as is more likely with the arrival of postsynaptic potentials at various locations on the somadendritic surface. This is because, as we have seen in Section 3, the analytical method of determining the moments from the differential Eqs. (9) to (13) performs best when the current is less sustained when its mean value is high. Constant sustained currents are not expected in the usual operation of most CNS neurons.

## 4. Simulation Results for Sustained Application of Noise

It is known that repetitive activity of some nerve cells may persist for very long times. The prime examples

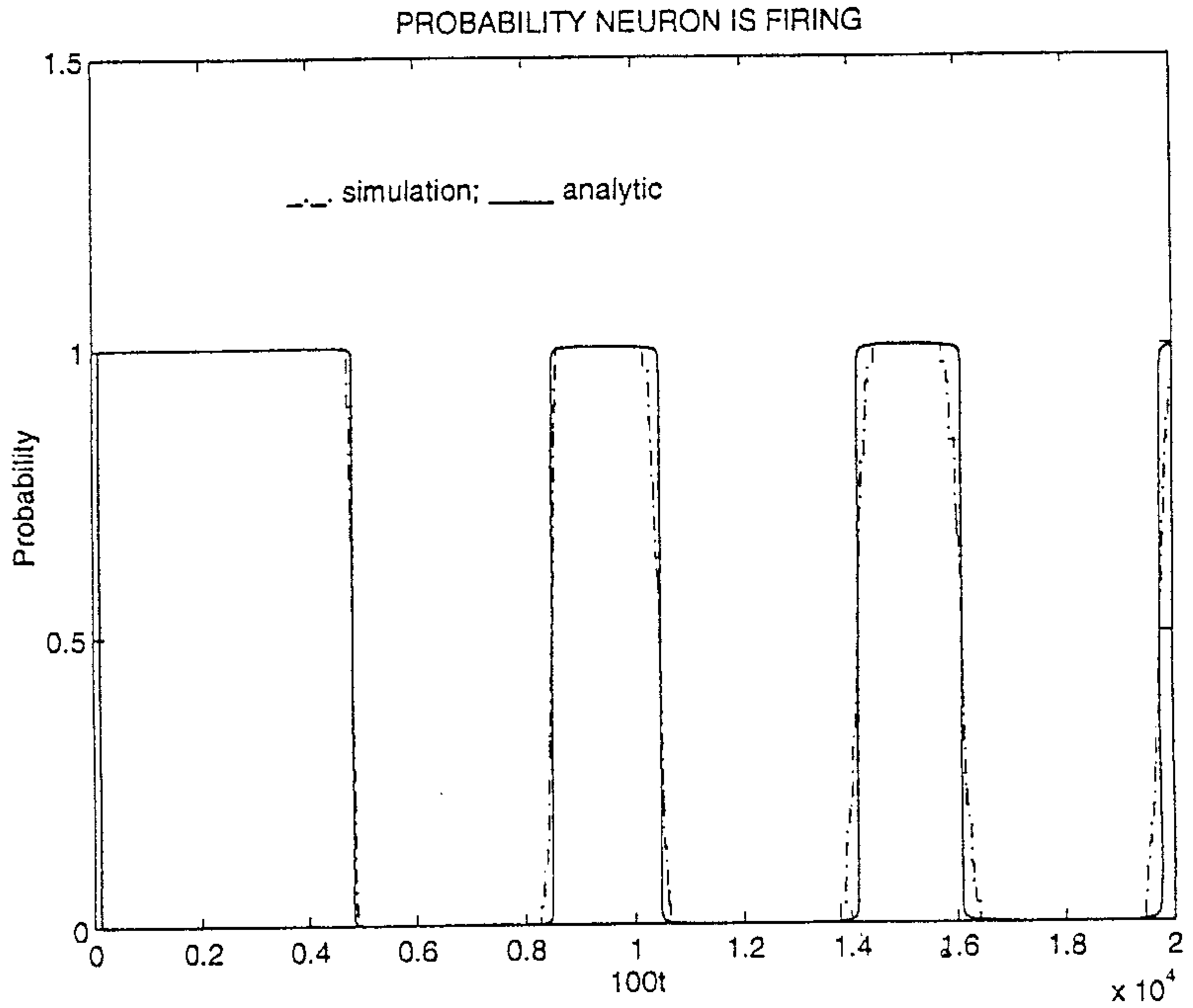


*Figure 6.* Probability that the neuron is emitting an action potential at time $t$. Solid curve is the value obtained from Eq. (14) using the mean and variance of $X(t)$ determined from the differential equations. The broken curve is the value estimated from simulations (30 trials).

are pacemaker cells (for example, Junge and Moore, 1966), but there are mammalian CNS cells that also have the capability of persistently emitting an almost periodic train of spikes in response to constant injected current (Granit, 1970; Calvin and Schwindt, 1972; Calvin and Sypert, 1976). On the other hand, there are the classic *in vitro* experiments in which white noise was injected directly into a neuron's soma and spike activity was observed (Bryant and Segundo, 1976) or in which a space-clamped preparation (squid axon) was driven by white noise (Guttman et al., 1974). In the latter experiment cross-correlation of input signal and membrane voltage were determined, and a linearized analysis was performed. More recently, Mainen and Sejnowski (1995) have injected steady and fluctuating currents into cortical cells and examined the subsequent spike trains. With a constant current the train was of increasing irregularity as the stimulus duration increased. However, the noisy input seemed to evoke, for the same input current trajectory, an accurately reproducible spike sequence as Bryant and Segundo (1976) had found earlier for *aplysia* neurons. In the last three mentioned experiments, Gaussian white noise was injected directly into a nerve cell so that the model employed in the present article is of the kind that would apply to these preparations but especially to the experiment of Guttman et al. Mainen and Sejnowski (1995) had noticed from intracellular records from neocortical cells *in vitro* that the rapid fluctuations in membrane potential due to arriving excitatory and inhibitory postsynaptic potentials could be expected to be approximated by a Gaussian white noise input current and hence performed their current clamp experiments using white-noise generated input. Using their approach it is possible to also expect to gain insight into *in vivo* neuronal activity in the presence of noisy input currents. In addition to these possibilities for a comparison of theory and experiment with noisy nonlinear neuronal models, there are several experiments where white-noise current has been used with the objective of determining Wiener kernels (e.g., Naka et al., 1985). In this article, however, attention is focused on the Fitzhugh-Nagumo system. In a subsequent paper (Rodriguez and Tuckwell, 1997) we will report findings using the present methods for the more complex Hodgkin-Huxley equations, for which the system (9) to (13) is replaced by one of 14 differential equations. We expect these methods, by comparing experimental trajectories and statistical properties with the computed ones for the model, to be useful in obtaining estimates of biophysical constants.

However, in our premier application of this approach we wish mainly to investigate the validity of the analytical approximation method.

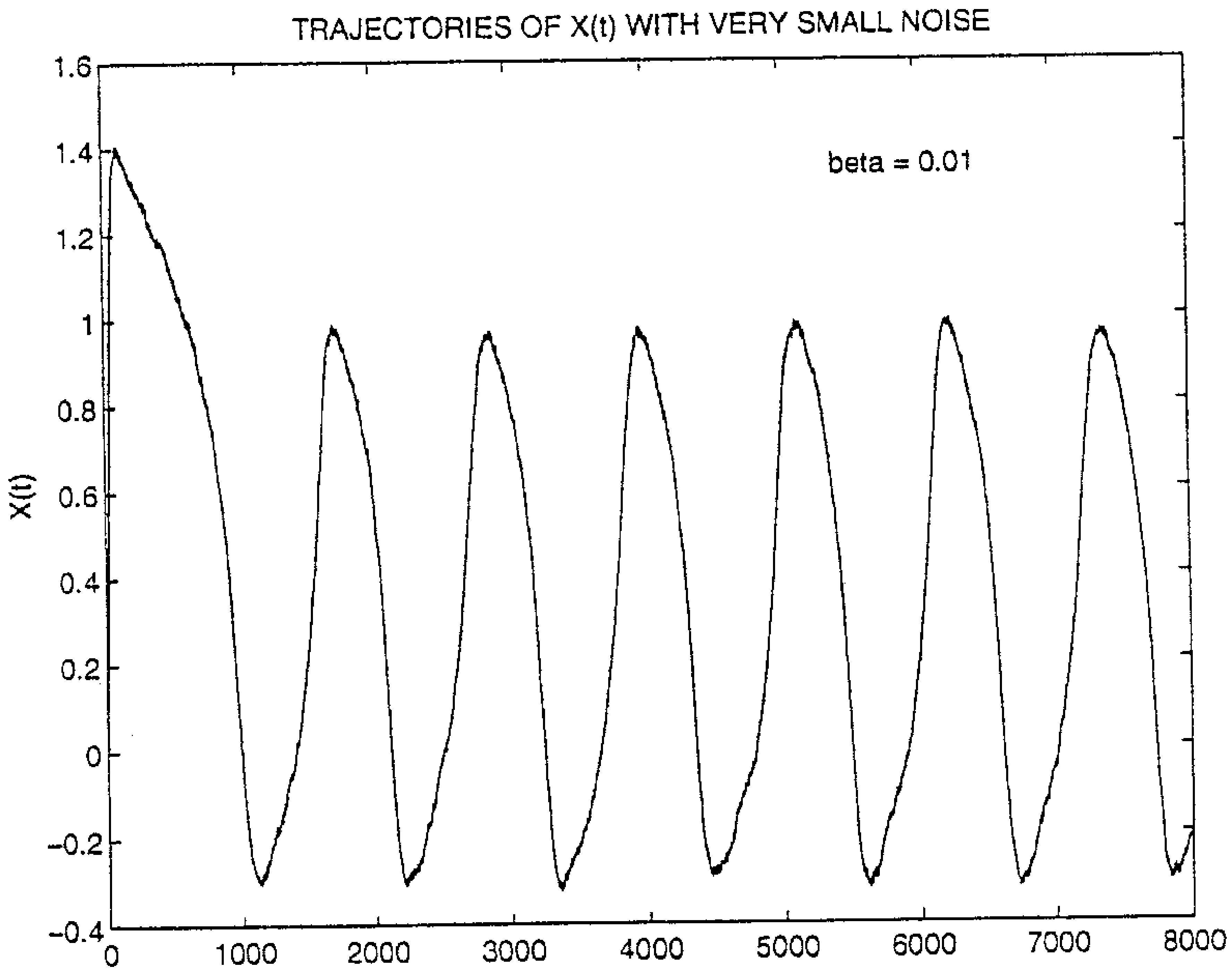
Some neurons that fire repetitively exhibit very little variability in their interspike intervals, and it is natural to ask how great an input noise a cell may tolerate and still emit a regular train. To address this question fully a more complete model is required than a Fitzhugh-Nagumo model, but we have made some investigations of this matter with this model as it is a guide for studies on more complex models and has the advantage of having only a few parameters as observed by Kurrer and Schulten (1991) and Longtin (1993).

### *4.1. Trajectories with Noise*

There have been deterministic analyses of the response of a Fitzhugh-Nagumo neuron and related models under space-clamp conditions, that have elucidated the conditions for repetitive activity (Troy, 1976; Rinzel and Keener, 1983). Although there are stability theorems that one may apply to nonlinear stochastic systems (Gihman and Skorohod, 1972), these usually concern only stochastic boundedness under the influence of small disturbances and do not concern the properties of the trajectories that relate to repetitive pulselike solutions.

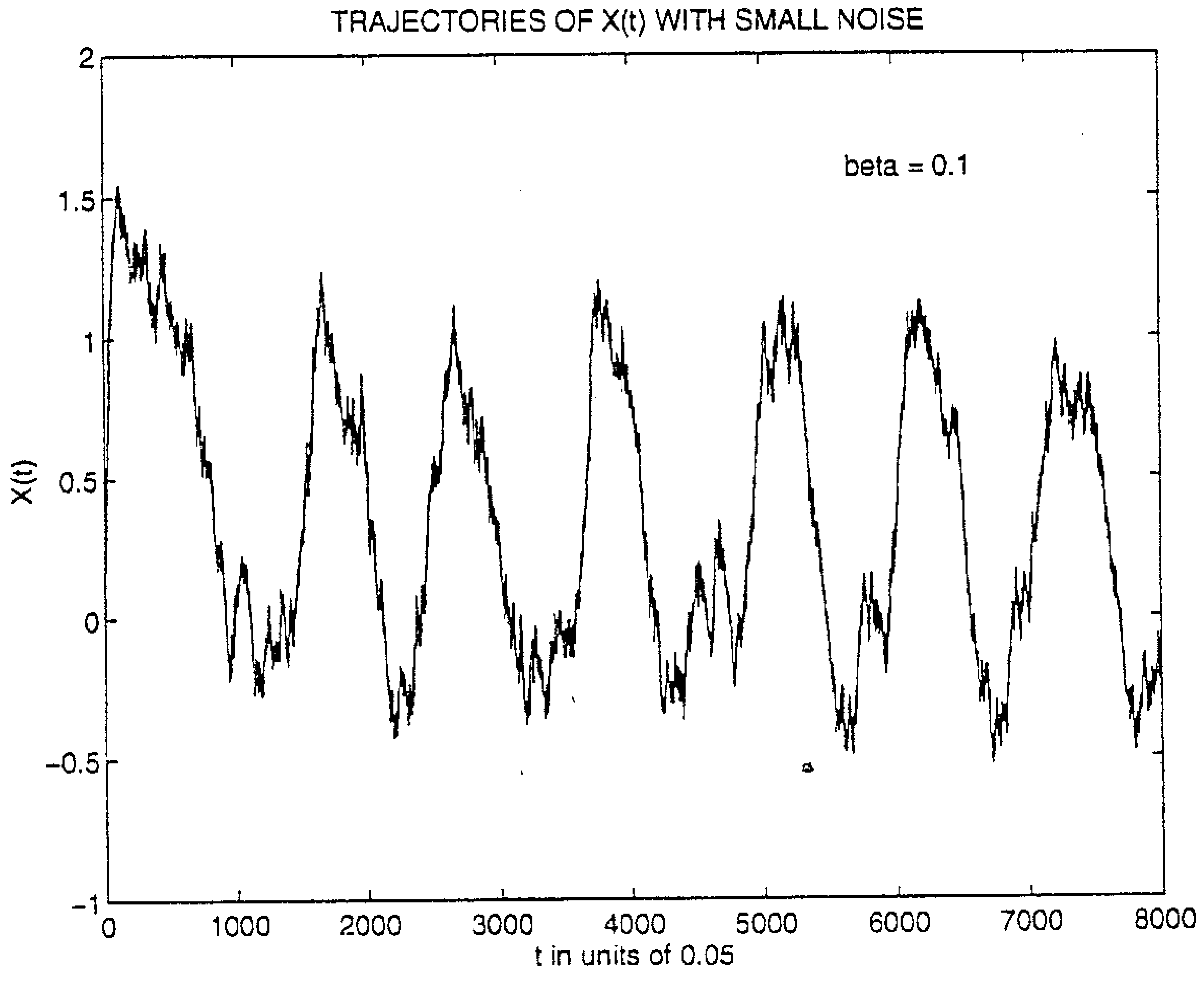
It is of more immediate interest to examine the nature of the trajectories of the voltage and recovery variables when there is a sustained current of constant amplitude for various magnitudes of the noise amplitude. Space limitations prevent an exhaustive study as all parameters vary over wide ranges so we have chosen a representative set of values for $a, b, \gamma, k$, and $I$. The values of the first three of these parameters were as above; the value of the mean current was $I = 1.5$, which resulted in sustained periodic activity in the absence of noise. Figure 7A shows a trajectory; from computer simulation, for the voltage variable $X(t)$ when there is very little noise with $\beta = 0.01$. This differs very little from the deterministic trajectory and one can easily distinguish regular pulselike solutions. Indeed, the mean for these parameter values was given in Fig. 2A and is for short times approximately periodic.

In Fig. 7B is shown a trajectory when the noise parameter is increased to $\beta = 0.1$. This was the same value of $\beta$ used in Section 3.1 for an intermittent current. The sample paths are erratic, but pulselike regular solutions are distinguishable. However, when the noise parameter is increased to $\beta = 0.5$, as in Fig. 7C, where the phase plane is shown, the paths are very erratic. Here it is difficult to recognize well defined spikes as the solutions are so *noise-dominated.*

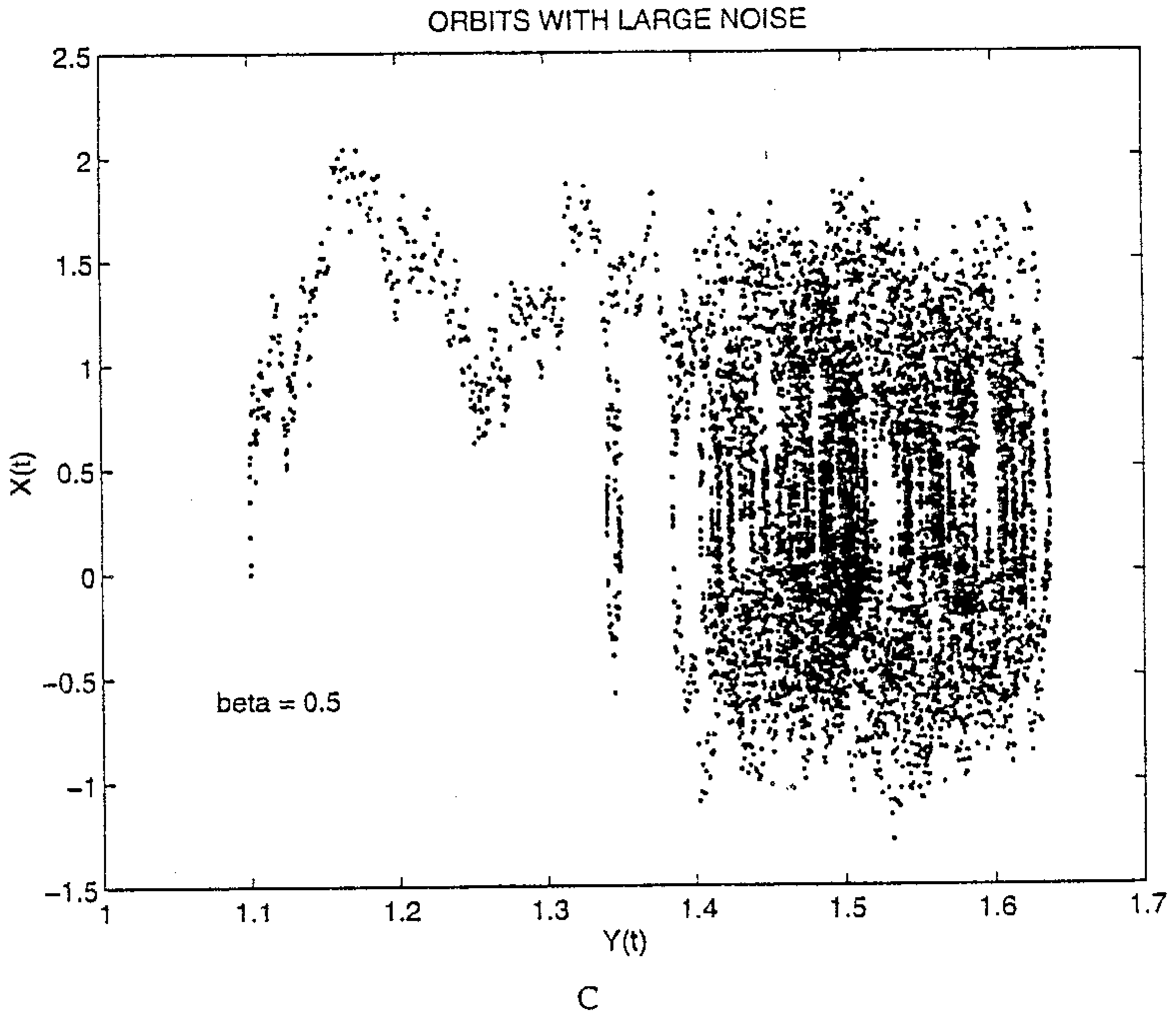


A

*Figure 7.* Showing trajectories for various magnitudes of the noise parameter. A. $X(t)$ for $\beta = 0.01$. B. Trajectory of $X(t)$ for $\beta = 0.1$. C. Trajectory in the phase plane (X, Y) when the noise parameter is $\beta = 0.5$. *(Continued on next page.)*



B



C

*Figure 7.* (*Continued*).

### 4.2. Interspike Intervals

*4.2.1. **Types of Distributions.*** If $\beta$ is not so large that spikes are practically unidentifiable, one may obtain samples of interspike intervals from computer-generated sample paths. This was done for the previous set of parameter values ($a = 0.1$, $b = 0.015$, $\gamma = 0.2$, $k = 0.5$) for various values of $\beta$ and $I$. Histograms of interspike intervals, based on 1000 observations, are shown in Figs. 8A and 8B, for $\beta = 0.01$ and $\beta = 0.035$ respectively. An observation consists of a threshold crossing with positive derivative in the voltage variable, which for such small values of the parameter $\beta$ were invariably followed by fully developed spikes. The mean and standard deviation of the interspike interval are shown on the Figures.

These distributions seem to be approximately Gaussian and resemble closely the form of those for pacemaker cells (Junge and Moore, 1966). The coefficients of variation are small as would be expected when the noise is small and the interspike interval is close to the period of the oscillations in the absence of noise.

*4.2.2. **Temporal Homogeneity.*** We examined the distribution of the first interspike interval in a train and compared it with the distribution of the twentieth such interval. For small values of $\beta$ where periodic behavior was clearly discernible, the mean and variance of the interspike interval were not significantly different. Thus, even though the *mean* of $X(t)$, or the amplitude of its oscillations may decrease, there is little change in the interval of time between "spikes".

*4.2.3. **Effect of Increasing $\beta$ at Fixed I.*** For very large values of $\beta$ the difficulty in recognizing true spikes means that a histogram of interspike intervals may become difficult to realize. The model is not as robust in the presence of noise as the more complex Hodgkin-Huxley model, in the sense that in the latter spikes are more genuinely "all or none" events. Nevertheless, we have developed automatic methods for spike identification and hence the determination of interspike intervals using a threshold criterion—that the voltage variable had to cross a chosen value ($\theta$) with positive $dX/dt$. The chosen value for $\theta = 0.6$ for the set of parameters given above was relatively high in order to eliminate non spikelike responses (as can be seen later in Fig. 9A). In Fig. 8C we show plots of frequency of spikes against the noise parameter $\beta$ for $I = 0.5$, 1.0, 1.5, and 2.0. Here frequency is defined

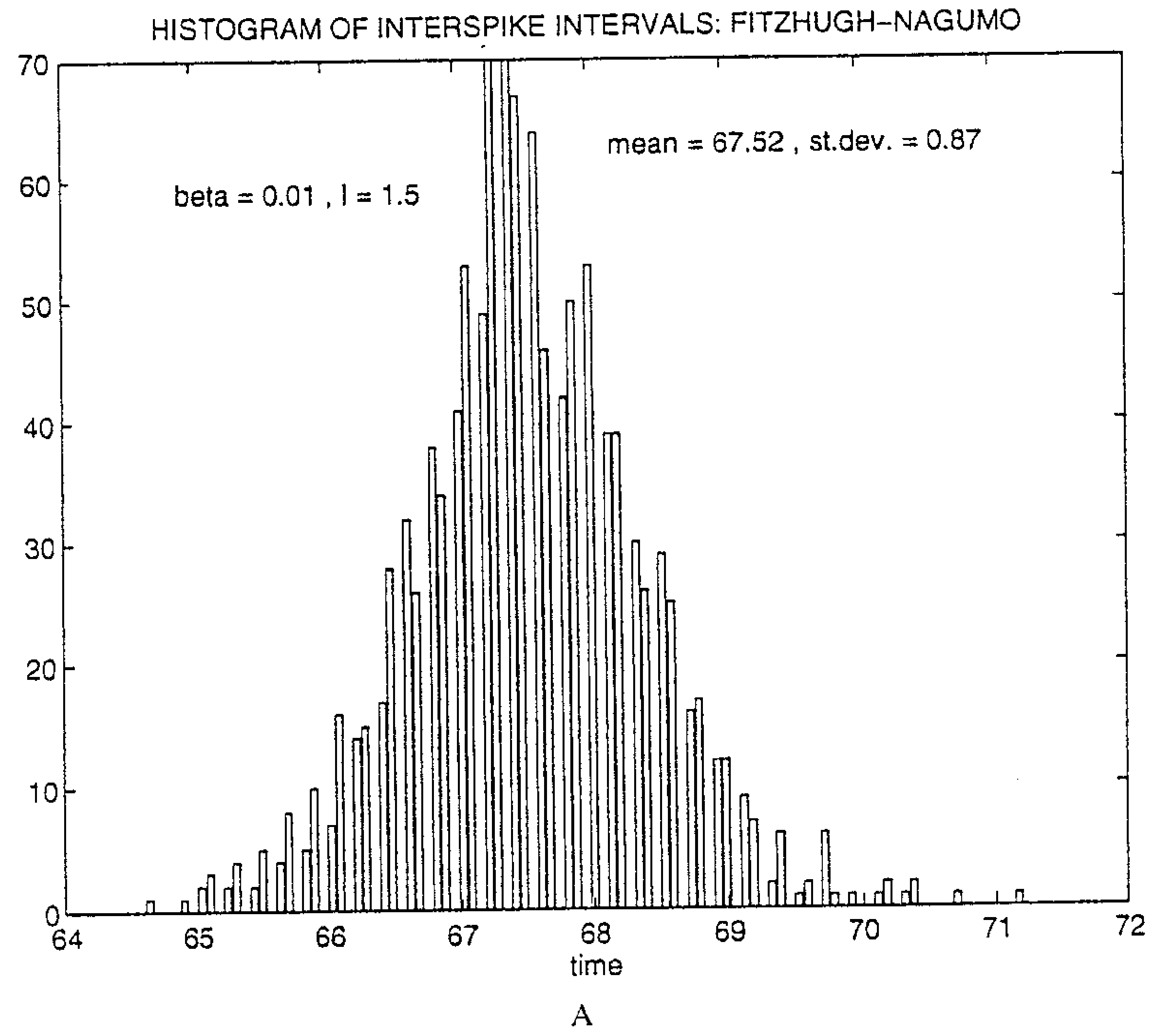


*Figure 8.* A and B. Histograms of interspike intervals for the noisy Fitzhugh-Nagumo model for $I = 1.5$ when (A) $\beta = 0.01$ and (B) $\beta = 0.035$. In both of these cases, trains of spikes would occur in the absence of noise. C. The changes in mean frequency of action potentials for various values of the steady current ($I$) as indicated in the upper right corner key, as the noise parameter increases. There were 1000 threshold crossing for each pair of parameter values $I$, $\beta$.

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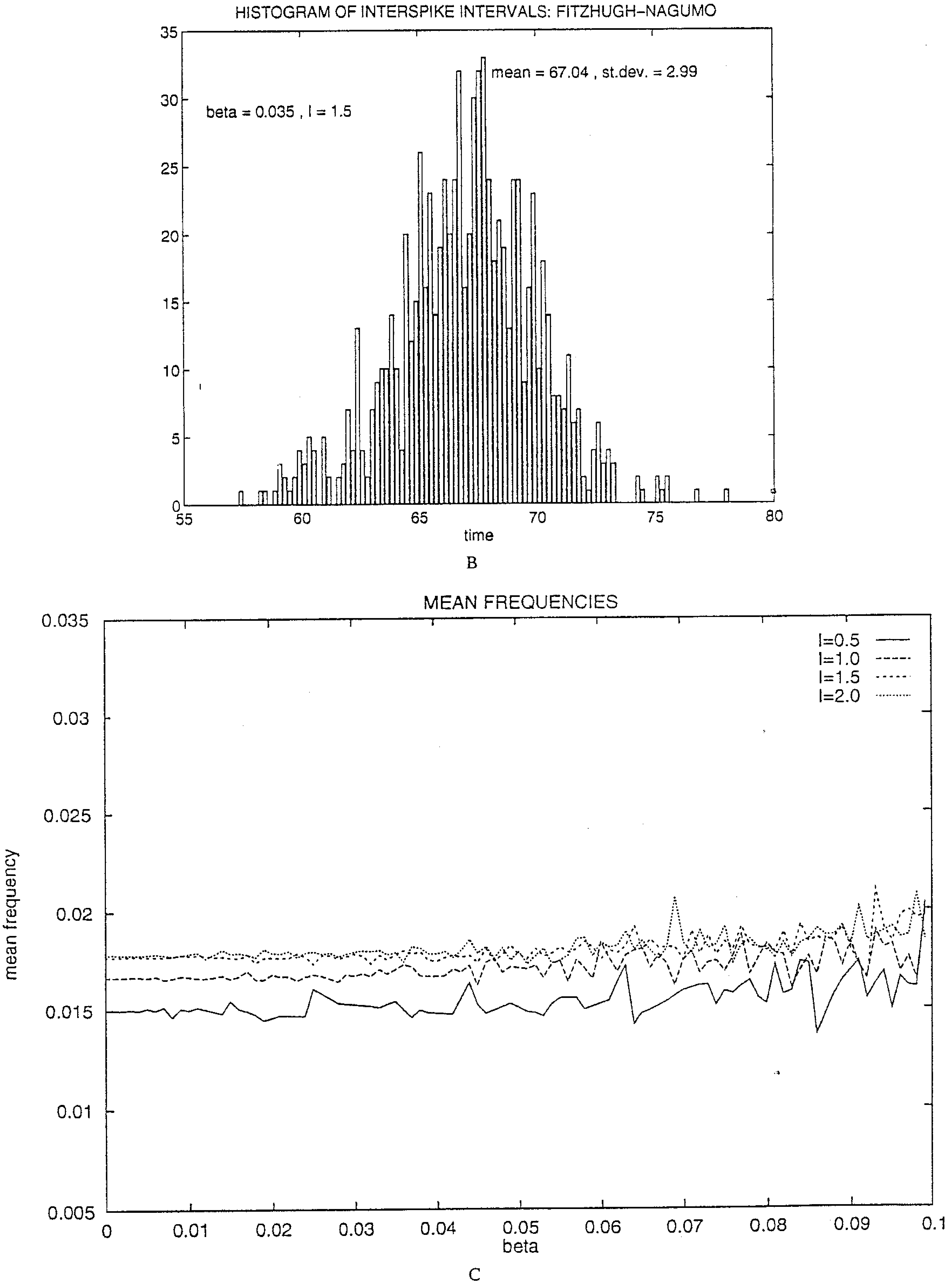

*Figure 8.* (*Continued*).

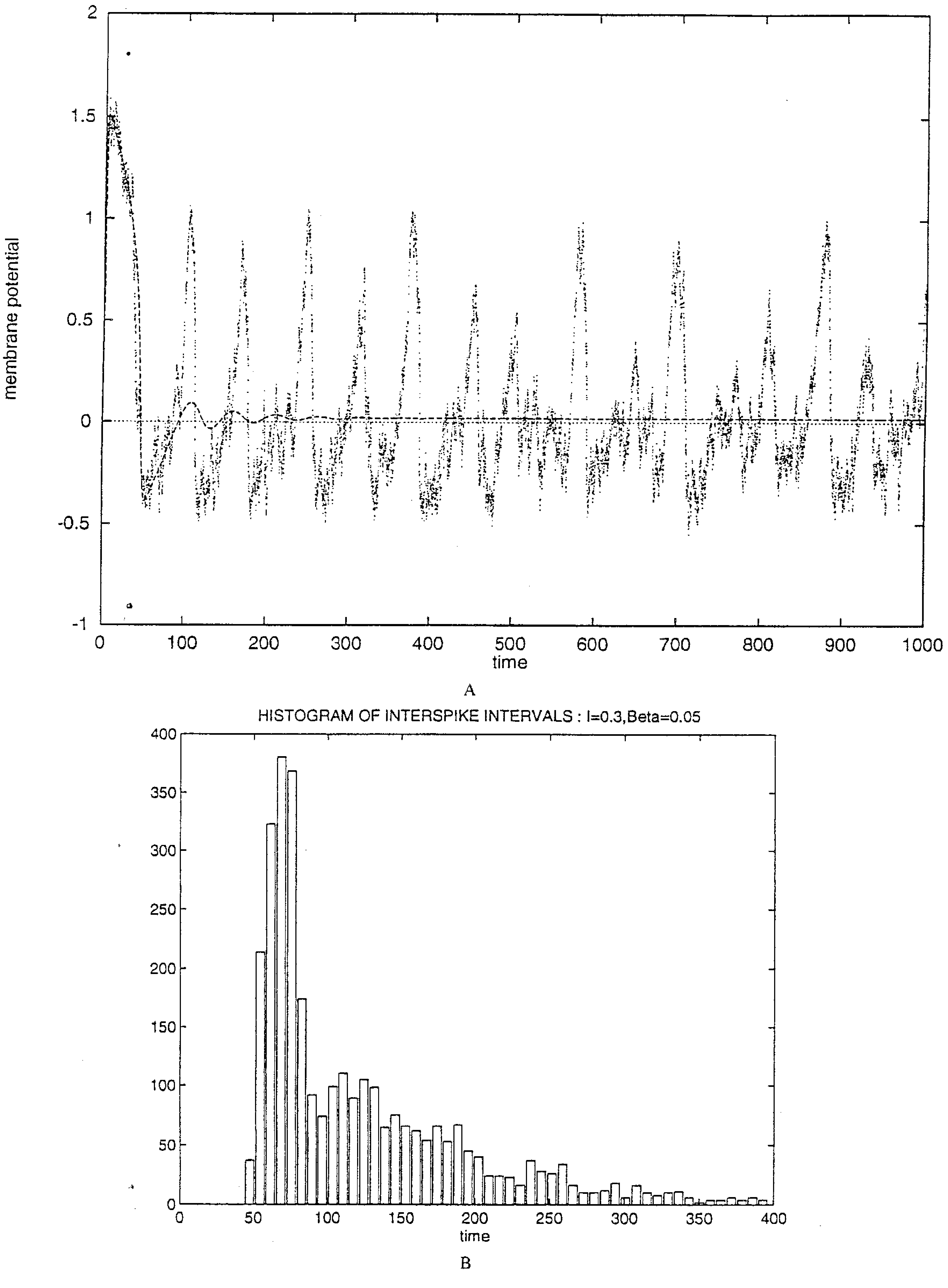

*Figure 9.* Spike trains induced by noise. A. Sample paths for $I = 0.1$, without noise (solid line) and with noise (dotted line). The trajectory without noise is a decaying oscillation with one spike at the beginning. In contrast, with noise there is a persistent spike train. B. Here is shown a histogram of interspike intervals for a spike train induced by noise—that is, in the absence of noise there was no spike train, the current being too small (without noise) to give repetitive activity. C. Frequency of action potentials versus current for various values of the noise parameter. Line: no noise. Small diamonds: $\beta = 0.01$. Crosses: $\beta = 0.05$. Squares: $\beta = 0.1$. Note that the frequency is nonzero even for very small or very large values of the mean current—where no spike trains exist without noise.

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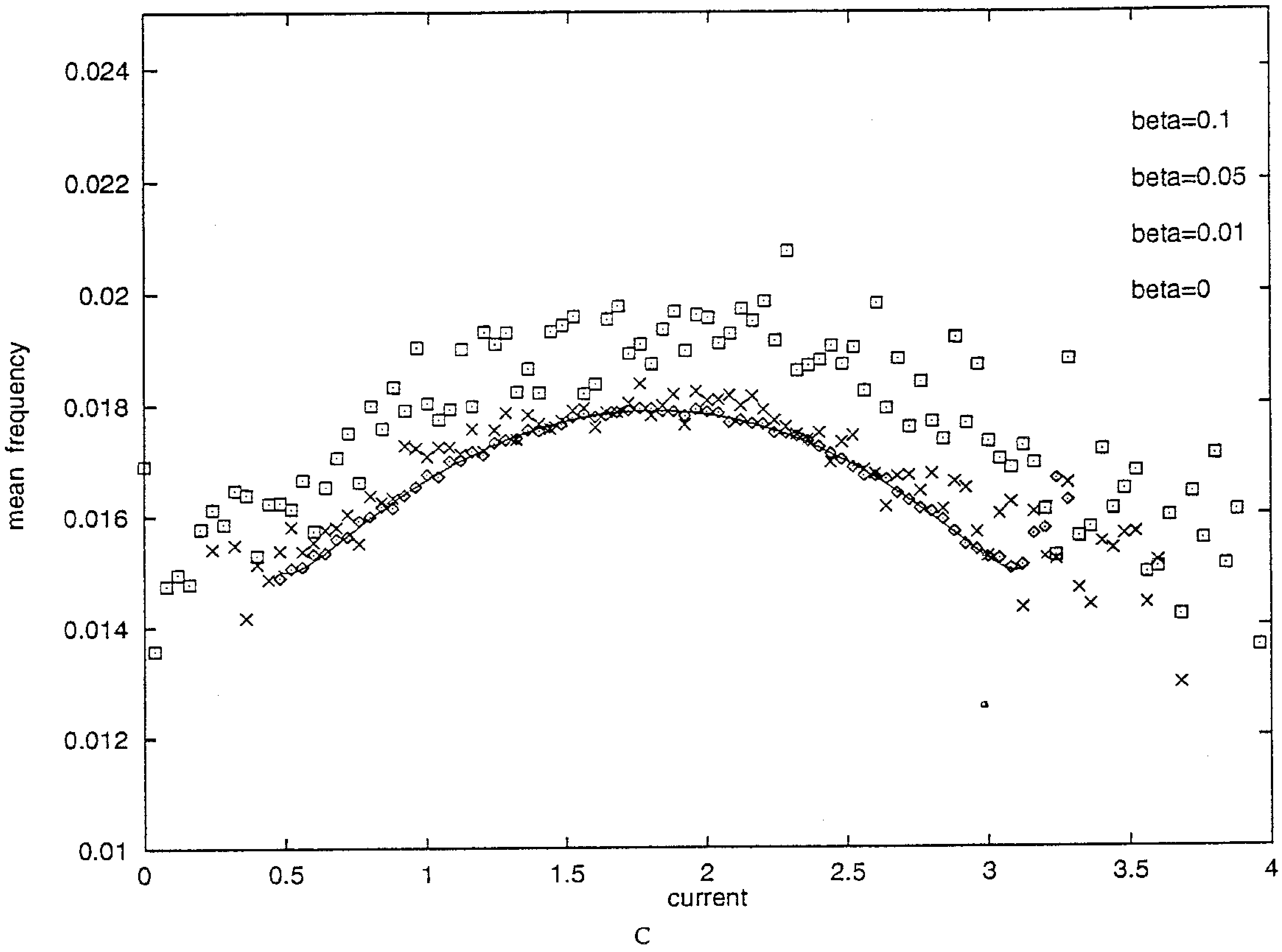

*Figure 9.* (*Continued*).

as the reciprocal of the mean interval and is obtained from 1000 threshold crossings of trajectories of $X(t)$.

It can be seen that in the range of noise parameters considered, there is a gentle increase in firing rate as the noise grows in amplitude. Furthermore, when $I$ is very small or very large (outside the Hopf bifurcation values, which are about $I = 0.3$ and $I = 3.3$), spike train formation does not commence until the noise parameter is large enough (see below).

*4.2.4. **Noise-Induced Spikes.*** When repetitive activity does not occur for a given value of the input current $I$, a spike train of a persistent nature can be induced if the noise is large enough (Longtin, 1993). This is shown graphically in Fig. 9A. Here the parameters are such that without noise a single spike is emitted, but this is followed by a decaying oscillation. This is because the current is $I = 0.1$, and this is less than the critical value of $I$ at the lower bifurcation point. On the other hand, introducing noise with $\beta = 0.1$ gives rise to a persistent, though not extremely regular, spike train.

In Fig. 9B is shown an interspike interval histogram for a small current where there is no spike train without noise, but a spike train persists in the presence of (zero mean) additive noise ($\beta = 0.1$). It can be seen, as expected, that this distribution is of high variability, the coefficient of variation of the interspike interval being 0.56.

*4.2.5. **Regions of Repetitive Activity.*** The existence of Hopf bifurcations at critical currents leading to repetitive activity in the Fitzhugh-Nagumo model is well known. We show a representative case in Fig. 9C. In addition we show the mean frequency of spikes in spike trains with noise and constant current. This supplements Fig. 8C. The extension in the ranges of $I$-values at which repetitive, though not periodic, spiking occurs as induced by noise can be clearly seen.

## 5. Extension of the Method to Neural Networks

We indicate briefly a direction for future research by considering a model neural network in which each of $n$ neurons is represented by two components, $X_j(t)$ and $Y_j(t)$, being for example voltage and recovery variables as in the Fitzhugh-Nagumo system. In general, this leads to a system of $2n$ coupled nonlinear stochastic differential equations of the form

$$dX_j = \left[ g(X_j, Y_j) + I_j(t) + \sum_{k=1}^{n} J_{jk}\theta(X_k) \right] dt + \beta_j dW_j, \quad (15)$$

$$dY_j = h(X_j, Y_j)\, dt. \quad (16)$$

Here $\{J_{jk}\}$ is a set of possibly variable synaptic strengths for coupling between neuron $k$ and neuron $j$, $\theta(.)$ is a threshold function, $I_j(t)$ is the applied current for neuron $j$, $W_j$, $j = 1, 2, \ldots, n$ are Wiener processes, and $\beta_j$ are the corresponding noise parameters that may be time-dependent. The extension of the analytical approach to such network models is described in Appendix C, where differential equations for the evolution of the approximate means and covariances are given.

With a knowledge of the first- and second-order moments, under the assumption that the network dynamical variables are jointly Gaussian distributed, which is expected to be approximately true for intermittent stimulation (see Section 3.1) and relatively small $\{\beta_j\}$, the complete probability distribution of the entire system of network variables can be obtained at any time point. (This is not an assumption that the whole network process is Gaussian.) This is because the covariance matrix and the means are sufficient to totally describe such a distribution. In particular, the joint probability that the voltage variables of various combinations of neurons are above threshold and therefore that this set is spiking is easily obtained.

In particular, let $P_k(t; \theta_k)$ be the probability that neuron $k$ is firing at time $t$ in the sense that its voltage is above its threshold value $\theta_k$. Then by the same reasoning as used to derive Eq. (14) in the case of a single neuron, we have the approximation

$$P_k(t; \theta_k) = 1 - \phi\left( \frac{m_k(t) - \theta_k}{\sqrt{S_k(t)}} \right). \quad (17)$$

Again, however, although it seems that this estimate only requires a knowledge of the two quantities $m_k(t)$ and $S_k(t)$, the whole system of $n(2n+3)$ equations for the first- and second-order moments must be solved in order to find them. Note that $P_k(t; \theta_k)$ is the probability that neuron $k$ is firing, regardless of the states of all the other neurons. Similarly one can obtain an expression for the probability $P_{i_1 i_2 \ldots i_m}(t)$, where $1 \leq m \leq n$, that the set $i_1, i_2, \ldots, i_m$ of neurons are firing.

It is important to be able to implement learning rules in which synaptic strengths may depend on the activities of the various cells in the network (see, for example, Levy and Desmond, 1985). Often Cajal-Hebb type rules are used, which lead to the strengthening of a synapse if there is positive correlation between pre- and postsynaptic activity. These rules are easy to apply if a sample of trajectories is available because one can then estimate the covariance of the frequencies of firing, $f_i(t)$, $f_k(t)$, of cells $i, k$, and the corresponding standard deviations $\sigma_{f_i}(t), \sigma_{f_k}(t)$. Then $\delta J_{ik}$ can be assumed to be proportional to $Cov[f_i, f_k]/\sigma_{f_i}\sigma_{f_k}\delta t$. However, the present approach does not yield the required statistical properties of the frequencies so that such rules are not readily or directly applicable. However, an alternative is to use, for example, a rule of the kind

$$\delta J_{ik} = \alpha_{ik}(P_i + P_k)^{\eta}[1 - 2\,|P_i - P_k|]\delta t, \quad (18)$$

with $\eta \geq 1$ and where $\alpha_{ik}$ is a constant characterizing the synapse. Such a rule can be implemented directly because $P_i$ and $P_k$ can be obtained as outlined above, for $i, k = 1, \ldots, n$. This gives a maximum value when $P_i = P_k = 1$ and a minimum in the event that either of $P_i$ or $P_k$ is unity and the other zero. It is possible also to implement rules in terms of the $P_{ik}(t)$ that is the joint probability that pre- and postsynaptic neurons are firing at time $t$, since $P_{ik}(t)$ can also be obtained, with the assumptions underlying the present approach, from the expression for a bivariate normal distribution.

## 6. Conclusions

Modeling neuronal behavior with stochastic Fitzhugh-Nagumo systems offers the advantage that it is simpler with far fewer parameters than more complex conductance based models such as Hodgkin-Huxley. In such a framework we have applied an analytical method for investigating neuronal activity in the presence of noise. The method consists of solving a system of associated nonlinear differential equations for the moments of the voltage and subsidiary variables. We have illustrated this using the first- and second-order moments for a Fitzhugh-Nagumo neuron with an input that has a time-varying steady component and an additional noisy component. Simulations may be readily performed for such systems, but the results by their very nature are a sample whereas an analytical framework can provide accurate and more general insights. We have found that the analytical method works very well when either the noise is small and there is a sustained deterministic component, or if the deterministic component is intermittent and the noise amplitude varies over a large range. The latter situation is appropriate for many neuronal systems in their natural modes of operation, and it is noted that there is no restriction to a temporally homogeneous input.

We have demonstrated that not only can one use the analytical approach to determine the moments of the neuronal dynamical variables, but also an analytical estimate can be made of the probability that a neuron is emitting a spike at any given time. We have also provided a framework for the application of the analytical method to networks where the probability of a given configuration of neuronal spike patterns can be readily determined and indicated an appropriate new learning rule which can be applied directly in the present approach. In simulation studies we have confirmed and elaborated on previous (Longtin, 1993) findings of extended ranges of spiking in the presence of noise and that interspike interval distributions have a Gaussian form for spike-inducing inputs with small relative variability and gammalike (including exponential) for those with greater variability as in the case of noise-induced spikes.

## Appendix A

In order to derive the differential equations for the moments we introduce the transition probability density function $p(x, y, t \mid x_0, y_0, 0)$ for the process $(X, Y)$ and we assume (Jazwinski, 1970) that $p(x, y, t \mid x_0, y_0, 0)$ is symmetric about the mean $(\mu_1, \mu_2)$ and that its mass is concentrated close to this point. Under these assumptions the odd central moments of order three and greater and even central moments of order greater than two may be neglected. These assumptions will be seen to be justified by virtue of their giving, for certain parameter values, estimates of the moments that agree well with those obtained by simulation and from examination of empirical distributions.

We use the following result to obtain the required differential equations. Let $G(X(t), Y(t), t)$ be a suitable function of $X(t)$ and $Y(t)$ and possibly the time, $t$. Its mean is defined as the double integral

$$E[G(X(t), Y(t), t)] = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} G(x, y, t)p(x, y, t)\,dx\,dy,$$

where we have omitted reference to the initial conditions. We now expand the transition density $p$ in a Taylor series about the mean and utilize the assumed properties of symmetry and tightness about the mean and the definitions of first- and second-order moments to obtain

$$\begin{aligned} E[G(X, Y, t)] = {} & G(\mu_1, \mu_2, t) + \tfrac{1}{2}G_{xx}(\mu_1, \mu_2, t)S_1 \\ & + \tfrac{1}{2}G_{yy}(\mu_1, \mu_2, t)S_2 \\ & + G_{xy}(\mu_1, \mu_2, t)C_{12} + \cdots, \end{aligned} \tag{A1}$$

where subscripts $x$ and $y$ denote partial differentiation with respect to the first and second arguments of $G$.

## Appendix B

We wish to estimate the probability $P_\theta(t)$ that the neuron is emitting an action potential at time $t$—that is, it is in the process of emitting a spike. This is to be distinguished from the probability distribution of the interspike interval. Assuming that $X(t)$ and $Y(t)$ are approximately jointly normally distributed, one has their joint distribution because their means, variances, and covariance are known. Then the probability that the voltage variable $X(t)$ is greater than some threshold value $\theta$ no matter what the value of the recovery variable is

$$P_\theta(t) = Pr\{X(t) > \theta, Y(t) \in (-\infty, \infty)\}.$$

Using the expression for the bivariate normal density this is given by the expression

$$\begin{aligned} P_\theta(t) = {} & \frac{1}{2\pi\sqrt{S_1S_2 - C_{12}^2}} \int_\theta^\infty \int_{-\infty}^\infty \exp\left[-\frac{1}{2\left(1 - \frac{C_{12}^2}{S_1S_2}\right)}\right. \\ & \times \left\{\frac{(x_1 - m_1)^2}{S_1} - \frac{2C_{12}(x_1 - m_1)(x_2 - m_2)}{S_1S_2}\right. \\ & \left.\left. + \frac{(x_2 - m_2)^2}{S_2}\right\}\right] dx_1\,dx_2. \end{aligned} \tag{A2}$$

However, since we are integrating over all values of the recovery variable, we obtain the marginal distribution of the voltage variable and this can be shown by direct, fairly long calculation to have an exact one-dimensional normal distribution (see also Wilks, 1962) with mean $m_1(t)$ and variance $S_1(t)$. Hence the quantity in (A2) is as given in Eq. (14) of the text.

## Appendix C

We consider a neural network model as described by Eqs. (15) and (16). On renaming the $2n$ variables as $U_j = X_j, U_{j+n} = Y_j, j = 1, \ldots, n$, the system may be written

$$dU_j = \left[ g(U_j, U_{j+n}) + I_j(t) + \sum_{k=1}^{n} J_{jk}\theta(U_k) \right] dt + \beta_j dW_j \qquad \text{(A3)}$$

$$dU_{j+n} = h(U_j, U_{j+n})\, dt, \qquad \text{(A4)}$$

where again $j = 1, 2, \ldots, n$. Then using the methods in our previous article (Rodriguez and Tuckwell, 1996) it follows that the following differential equations hold for the approximate means $m_j(t) = E[X_j(t)], j = 1, 2, \ldots, n$ of the voltage variables and $m_{j+n}(t) = E[Y_j(t)], j = 1, 2, \ldots, n$ of the recovery variables of the $n$ Fitzhugh-Nagumo neurons:

$$\frac{dm_j}{dt} = f(m_j) - m_{j+n} + I_j(t) + \sum_{k=1}^{n} J_{jk}\theta(m_k) + \sum_{k=1}^{n} J_{jk}\theta''(m_k)S_k, \qquad \text{(A5)}$$

and

$$\frac{dm_{j+n}}{dt} = b(m_j - \gamma m_{j+n}), \qquad \text{(A6)}$$

where $j = 1, 2, \ldots, n$, $S_k(t)$ is the variance of $X_k(t)$, and $\theta''$ is the second derivative of $\theta$.

We also have the differential equations satisfied by the second-order moments for each network neuronal variable. We define the covariance of $U_j(t)$ and $U_k(t)$ as $C_{jk}(t)$. Then we have, for $1 \leq j \leq i \leq n$,

$$\frac{dC_{ij}}{dt} = (f'(m_i) + f'(m_j))C_{ij} - C_{i+n,j} - C_{i,j+n} + \beta_i^2 + \beta_j^2. \qquad \text{(A7)}$$

When $n + 1 \leq i \leq 2n$, $1 \leq j \leq n$, we have

$$\frac{dC_{n+q,j}}{dt} = (f'(m_j) - b\gamma)C_{n+q,j} - C_{n+q,n+j} + bC_{qj} + \sum_{k=1}^{n} \theta'(m_k)J_{kk}C_{n+q,k}, \qquad \text{(A8)}$$

whereas when $n \leq j \leq i \leq 2n$, the covariances satisfy

$$\frac{dC_{n+q,n+r}}{dt} = b(C_{q,n+r} + C_{n+q,r}) - 2b\gamma C_{n+q,n+r}, \qquad \text{(A9)}$$

where $q$ and $r$ range from $1, \ldots, n$.

In particular, the following differential equations for the variances are obtained:

$$\frac{dS_i}{dt} = 2\left[f'(m_i)S_i - C_{i,i+n} + \beta_i^2\right], \quad i = 1, \ldots, n, \qquad \text{(A10)}$$

and

$$\frac{dS_{n+q}}{dt} = 2b[C_{q,n+q} - \gamma S_{n+q}], \quad q = 1, \ldots, n. \qquad \text{(A11)}$$

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## References

Abeles M, Gerstein GL (1988) Detecting spatiotemporal firing patterns among simultaneously recorded single neurons. *J. Neurophysiol.* 60:909–924.

Barlow HB (1963) The information capacity of nervous transmission. *Biol. Cybern.* 2:1.

Blanchard P, Combe P, Nencka H, Rodriguez R (1993) Stochastic dynamical effects of neuronal activity. *J. Math. Biol.* 31:189–198.

Bower JM (1992) Modelling the nervous system. *Trends in Neuroscience* 15:411–412.

Bryant HL, Segundo JP (1976) Spike initiation by transmembrane current: A white noise analysis. *J. Physiol.* 260:289–314.

Calvin WH, Schwindt P (1972) Steps in production of motoneuron spikes during rhythmic firing. *J. Neurophysiol.* 35:297–310.

Calvin WH, Sypert G (1976) Fast and slow pyramidal tract neurons: An intracellular analysis of their contrasting repetitive firing properties in the cat. *J. Neurophysiol.* 39:420–433.

Capocelli RM, Ricciardi LM (1971) Diffusion approximation and first passage time for a model neuron. *Kybernetik* 8:214–223.

DeSchutter E, Bower JM (1994) An active membrane model of the cerebellar Purkinje cell. I. Simulation of current clamps in slice. *J. Neurophysiol.* 71:375–400.

Fukai T, Shiino M (1995) Memory recall by quasi-fixed point attractors in oscillator neural networks. *Neural Comp.* 7:529–548.

Gihman II, Skorohod AV (1972) Stochastic Differential Equations. Springer-Verlag, Berlin.

Gluss B (1967) A model for neuron firing with exponential decay of potential resulting in diffusion equations for probability density. *Bull. Math. Biophys.* 29:233–243.

Golomb D, Wang X-J, Rinzel J (1994) Synchronization properties of spindle oscillations in a thalamic reticular nucleus model. *J. Neurophysiol.* 72:1109–1126.

Granit R (1970) The Basis of Motor Control. Academic, New York.

Guttman R, Feldman L, Lecar H (1974) Squid axon membrane response to white noise stimulation. *Biophys. J.* 14:941–955.

Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117:500–544.

Hopfield JJ (1982) Neural networks and physical systems with emergent collective computational capabilities. *Proc. Natl. Acad. Sci. USA* 79:2554–2558.

Hopfield JJ (1995) Pattern recognition computation using action potential timing for stimulus representation. *Nature* 376:33–36.

Hopfield JJ, Herz AVM (1995) Rapid local synchronization of action potentials: Toward computation with coupled integrate and fire neurons. *Proc. Natl. Acad. Sci. USA* 92:6655–6662.

Horikawa Y (1991) Noise effects on spike propagation in the stochastic Hodgkin-Huxley models. *Biol. Cybern.* 66:19–25.

Horikawa Y (1992) Spike propagation during the refractory period in the stochastic Hodgkin-Huxley model. *Biol. Cybern.* 67:253–258.

Jaswinski, A.H. (1970) Stochastic Processes and Filtering Theory. Academic, New York.

Junge D, Moore GP (1966) Interspike interval fluctuations in *Aplysia* pacemaker neurons. *Biophys. J.* 6:411–434.

Konig P, Engel AK, Singer W (1996) Integrator or coincidence detector? The role of the cortical neuron revisited. *Trends in Neurosciences* 19:130–137.

Kruglyak L, Bialek W (1993) Statistical mechanics for a network of spiking neurons. *Neural Comp.* 5:21–31.

Kurrer C, Schulten K (1991) Effect of noise and perturbations on limit cycle systems. *Physica D* 50:311–320.

Lansky P, Lanska V (1987) Diffusion approximation of the neuronal model with synaptic reversal potentials. *Biol. Cybern.* 56:19–26.

Lestienne R, Tuckwell HC (1997) The significance of precisely replicating patterns in mammalian CNS spike trains. *Neuroscience*, in press.

Levy WB, Desmond NL (1985) The rules of elemental synaptic plasticity. In: WB Levy, JA Anderson, S Lehmkuhle, eds. Synaptic Modification, Neuron Selectivity and Nervous System Organization. Lawrence Erlbaum, London, pp. 105–121.

Longtin A (1993) Stochastic resonance in neuron models. *J. Stat. Phys.* 70:309–327.

Maass W (1995) On the computational power of networks of spiking neurons. Advances in Neural Information Processing Systems. MIT Press, Cambridge, MA, vol. 7, pp. 183–190.

Mainen Z, Sejnowski TJ (1995) Reliability of spike timing in neocortical neurons. *Science* 268:1503–1506.

McCulloch WS, Pitts W (1943) A logical calculus of the ideas imminent in nervous activity. *Bull. Math. Biophys.* 7:89–93.

Milstein GN (1994) Numerical Integration of Stochastic Differential Equations. Kluwer, Dordrecht.

Naka K-I, Sakuranaga M, Ando Y-I (1985) White noise analysis as a tool in visual physiology. In: AR Liss, ed. Contemporary Sensory Neurobiology. New York, pp. 307–321.

Parodi O, Combe P, Ducom J-C (1996) Temporal coding in vision: coding by spike arrival times leads to oscillations in the case of moving targets. *Biol. Cybern.* 74:497–509.

Rinzel J, Keener JP (1983) Hopf bifurcation to repetitive activity in nerve. *SIAM J. Appl. Math.* 43:907–922.

Rodriguez R (1995) Coupled Hodgkin-Huxley neurons with stochastic synaptic inputs. In: Modern Group Theoretical Methods in Physics. Kluwer, Amsterdam, pp. 233–242.

Rodriguez R, Tuckwell HC (1996) Statistical properties of nonlinear dynamical models of single neurons and neural networks. *Phys. Rev. E* 54:5585–5590.

Rodriguez R, Tuckwell HC (1997) The response of a Hodgkin-Huxley model neuron to stochastic inputs (in preparation).

Schuster HG, Wagner P (1990) A model for neuronal oscillation in the visual cortex. *Biol. Cybern.* 64:77–82.

Shadlen MN, Newsome WT (1995) Noise, neural codes and cortical organization. *Curr. Opin. Neurobiol.* 4:569–579.

Softky WR (1996) Fine analog coding minimizes information transmission. *Neural Networks* 9:15–24.

Softky, WR, Koch C (1993) The highly irregular firing of cortical cells as inconsistent with temporal integration of random EPSP. *J. Neurosci.* 13:334–350.

Strehler BL, Lestienne R (1986) Evidence on precise time-coded symbols and memory of patterns in monkey cortical neuronal spike trains. *Proc. Natl. Acad. Sci. USA* 83:9812–9816.

Troy, WC (1976) Bifurcation phenomena in Fitzhugh's nerve conduction equations. *J. Math. Anal. Appl.* 54:678–690.

Tuckwell HC (1979) Synaptic transmission in a model for stochastic neural activity. *J. Theor. Biol.* 77:65–81.

Tuckwell, HC (1987) Statistical properties of perturbative nonlinear random diffusion from stochastic integral representations. *Phys. Lett. A* 122:117–120.

Tuckwell HC (1989) Stochastic Processes in the Neurosciences. SIAM, Philadelphia.

Tuckwell HC (1992) On the randomly perturbed reduced Fitzhugh-Nagumo equation. *Physica Scripta* 46:481–484.

Tuckwell HC, Wan FYM, Wong YS (1984) The interspike interval of a cable model neuron with white noise input. *Biol. Cybern.* 49:155–167.

Usher M, Schuster HG, Niebur E (1993) Dynamics of populations of integrate and fire neurons, partial synchronization and memory. *Neural Comp.* 5:570–586.

Wilks SS (1962) Mathematical Statistics. Wiley, New York.