SOME THEORETICAL AND METHODOLOGICAL ISSUES IN THE SIMULATION OF THE STOCHASTIC ACTIVITY OF A NEURONAL MODEL

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ABSTRACT - Membrane noises, intrinsic or extrinsic, are conspicuous and widespread entities that have an important role in neuronal information processing. Studies to elucidate the effects of noise on nerve cells can be done with relative ease using mathematical models. Nevertheless, even simple models are shown to require very complicated mathematics which are valid for very limited conditions. Computer simulations are more adequate for these cases but they require a convenient numerical integration methodology to avoid erroneous or paradoxical results. It is shown in this work that for a fourth order Runge-Kutta a reasonable choice is to divide the noise sequence variance by the step size and to choose the intermediate input value required at each step equal to the present value. Thereafter, the methods used to simulate three different colored Gaussian noises are presented. An approximately 1/f noise was obtained as the output of an IIR filter excited by white noise. The IIR filter was designed using the least squares inverse method. Lorentzian noise was generated by an exact recursive relation. The third type of noise was obtained by passing white noise through a resonant low-pass filter. The prototype continuous-time filter was obtained from the literature and the corresponding IIR digital approximation was designed by the impulse response invariance method.

INTRODUCTION

Nerve cells are always subjected to random influences arising from a multitude of sources. One source is the cell membrane itself (De Felice, 1981) and another are the synaptic inputs. When the latter occur in large numbers, their net effect at the neuron's trigger zone is a noise-like fluctuation in membrane current and potential.

Many authors have approached the problem by studying analytically the behavior of simple neuronal models subjected to noise (Sugiyama at al, 1970; Holden, 1976; Tuckwell and Richter, 1978; Ricciardi and Sacerdote, 1979). A commonly used model is the leaky integrator (parallel RC) with fixed threshold subjected to white Gaussian noise current input. Even with these restrictive conditions the mathematics are rather involved and the obtainable results are of limited scope. A further step taken by some authors is to include the effects of the passive spread of membrane potential variations along the dendrites down to the trigger zone (Wan and Tuckwell, 1979; Tuckwell and Walsh, 1983). Expectedly, the mathematics get even more complicated and again only restricted conditions are included in the analysis. Therefore, computer

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simulations seem to be more recommended if a broader analysis is desired and that is the approach taken in an ongoing research in this laboratory. The present paper addresses some theoretical and methodological issues related to the implementation of a simulation program.

THEORETICAL APPROACH TO THE MATHEMATICAL MODEL. NUMERICAL INTEGRATION

The cell membrane at any point along a neuron in the resting state may be reasonably well modeled by a parallel association of a resistance R and a capacitance C . The input is membrane current and the output is membrane voltage. When the membrane voltage reaches a threshold value V_{th} the model's capacitor is instantaneously discharged and to this threshold crossing event is associated the generation of an action potential, or spike, for short. In spite of its simplicity, this model, often called the leaky integrator with threshold, has been shown to give good results, for example, in studies of neural phase-locking or in experiments where rather long action potential trains are analyzed to extract average quantifiers such as mean rates and other statistics (Knight, 1972; Kohn and Segundo, 1983).

Below threshold, the differential equation relating "membrane potential" x(t) to input current i(t) is:

$$C\,\frac{dx(t)}{dt} + \frac{x(t)}{R} = i(t) \quad ; \quad x(t_o) = x_o \ , \ x(t) < V_{th} \ ; \qquad (1)$$

where C and R are the model's capacitance and resistance, respectively . When threshold is reached $(x(t)=V_{th})$, the membrane voltage is reset instantaneously to x_o . Therefore the model is globally nonlinear.

When modeling the effect of a large number of dendritic synapses on the membrane potential at the trigger zone, the papers found in the literature use a Gaussian white noise input current. The Gaussian assumption is reasonable since the superposition of a large number of small, random , independent depolarizations and hyperpolarizations may reasonably be assumed to be normal in a first approximation. The whiteness assumption is not as reasonable and therefore other spectral shapes will be used in this work.

When i(t) is white noise then rigorously (1) has no mathematical meaning because white noise is not mean square Riemann integrable. Despite the need for more refined approaches, such as Itô stochastic calculus (Jazwinsky, 1970) we shall use simpler mathematics. It can be shown (Jazwinsky, 1970) that x(t) is a continuous time continuous state space Markov process and therefore it is a diffusion process. The conditional or transition probability density $f(y,t|x_o,t_o)$, $t \geqslant t_o \in R$ can be computed from the forward Kolmogorov equation or Fokker-Planck equation (Cox and Miller, 1965):

$$\frac{\partial f(y,t|x_o,t_o)}{\partial t} = -\frac{\partial}{\partial y}\Big[\, a(y,t).f(y,t|x_o,t_o)\Big] + \frac{1}{2}\,\frac{\partial^2}{\partial y^2}\Big[\, b(y,t)f(y,t|x_o,t_o)\Big] \qquad (2)$$

where a(y,t) is the first infinitesimal moment and b(y,t) is the second infinitesimal mean, defined as

$$a(y,t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \left[E \left[x(t + \Delta t) - x(t) \mid x(t) = y \right] \right]$$

$$b(y,t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \left[E \left[(x(t + \Delta t) - x(t))^2 \mid x(t) = y \right] \right]$$

The diffusion process obtained from (1) when $i(t)$ is Gaussian white noise is the Ornstein-Uhlenbeck process and its infinitesimal moments are:

$$a(y,t) = \frac{\mu_I}{C} - \frac{1}{RC} y \tag{3}$$

$$b(y,t) = \frac{\sigma_I^2}{C^2} \tag{4}$$

where μ_I and σ_I^2 are the mean and constant power spectral density of the white Gaussian noise input current $i(t)$, respectively. Substituting (3) and (4) in (2) gives the partial differential equation that must be satisfied by the Ornstein-Uhlenbeck process:

$$\frac{\partial f(y,t \mid x_o t_o)}{\partial t} = - \frac{\mu_I}{C} \frac{\partial f(y,t \mid x_o,t_o)}{\partial y} + \frac{1}{RC} \frac{\partial \left[y.f(y,t \mid x_o,t_o) \right]}{\partial y} + \frac{1}{2} \frac{\sigma_I^2}{C^2} \frac{\partial^2 f(y,t \mid x_o,t_o)}{\partial y^2} \tag{5}$$

The initial condition for (5) at t_o is

$$f(x,t_o \mid x_o,t_o) = \delta(x - x_o)$$

where x_o is the initial state of the process. The boundary conditions for the neuronal model (1) are:

$$f(V_{th}, t \mid x_o,t_o) = 0 \qquad t > t_o$$

$$f(-\infty , t \mid x_o,t_o) = 0$$

where V_{th} is an absorbing regular boundary and $-\infty$ is a natural boundary (Karlin and Taylor, 1981). The inter-spike interval statistics are the same as the first passage time $T(V_{th},x_o)$ statistics because i the input process is white, and, ii after a spike is generated (i.e., the membrane potential $x(t)$ reached threshold and was reset to x_o) the system's history is lost. Many papers have dealt with the difficult problem of obtaining the probability density function of $T(V_{th}, x_o)$ either for special cases or using numerical approximations. A somewhat more manageable problem is the determination of the mean and variance of the first passage time (Ricciardi and Sacerdote, 1979). Therefore, from an analysis of the literature it seems that even for the case of white noise input it is unfeasible to obtain general expressions for the inter-spike interval probability density, the auto-intensity function, etc. For non-white inputs the analytical difficulties increase.

From the foregoing analysis it seems reasonable to say that for most of the questions concerning the stochastic behavior of (1) the recommended approach is numerical integration. Nevertheless, it cannot be overemphasized that numerical solutions can only give restricted information as they depend on the choice of particular parameters, while general conclusions are only possible through mathematics.

A numerical integration procedure replaces the stochastic differential equation (1) by a stochastic difference equation. The latter can readily be solved by a digital computer.

Equation (1) can be discretized in time in a straightforward manner by writing the solution $x(t_i + h)$ starting the system from $x(t_i)$, where h is the time discretization interval (or integration step). The resulting equation is

$$x(t_i+h) = e^{-h\omega_o} x(t_i) + \underbrace{\int_{t_i}^{t_i+h} \frac{1}{C} e^{-(t_i+h)\omega_o} e^{\lambda\omega_o} i(\lambda)\, d\lambda}_{n(t_i)} \qquad (6)$$

where $\omega_o \triangleq \frac{1}{RC}$

When $i(t)$ is a white Gaussian noise then $n(t_i)$ is a white Gaussian sequence with easily computable mean and variance. Therefore it is a simple matter to simulate this $n(t_i)$ in a digital computer. On the other hand, if $i(t)$ is colored Gaussian noise, $n(t_i)$ will be a colored Gaussian sequence with an autocovariance sequence which is very unpleasant to compute analytically. A numerical solution should give good aproximations to the autocovariance sequence of $n(t_i)$ if an expression is known for the autocovariance of $i(t)$. If the latter autocovariance is difficult to be obtained (for example if $i(t)$ is specified in the frequency domain in a complicated manner) then statistical estimation procedures could be used. In this work, however, a direct numerical solution to (1) was chosen instead of the other cumbersome approaches.

Due to its reasonably good behavior for solving deterministic problems, a fourth-order Runge-Kutta algorithm was chosen. However, wrong or paradoxical results are obtained if the algorithm is used without care. One instance happens when the step size is decreased resulting in a decrease in the output's variance. In the limit for $h \to 0$ the output would have zero variance which is absurd. A similar phenomenon occurs when (1) is discretized by assuming in (6) that $i(t)$ is constant between sampling times (Jazwinski, 1970). In this latter case it can be shown that it is sufficient to divide the noise variance by the step size h (plus some minor details) to obtain a perfect discrete-time representation. If a similar proof is tried for the fourth order Runge-Kutta the mathematics gets unwieldy and hence the adequacy of dividing the input noise variance was confirmed empirically by running many simulations. Another decision that this integration method required was that related to the input value $i(t_i + h/2)$ needed at an intermediate computation step. Three choices were tested empirically: i $i(t_i + h/2) = i(t_i)$; ii $i(t_i + h/2) = 0.5\,[i(t_i) + i(t_i + 1)]$; iii generate a new noise sample for $i(t_i + h/2)$. The first choice gave good results, while the second and third were not as good (M.B. Joaquim, 1986). Several tests were run comparing the Runge-Kutta algorithm, using Gaussian white noise input with variance σ^2/h and choice i above, with the exact discrete-time version of (1) obtained from (6). The overall differences in their outputs were small.

A good value for the step size was found to be 0.05 and it will be the only step size used from now on. However, a careful comparison of the outputs shows differences in their microstructure. Simulation runs (an example is given below) showed that these microstructure discrepancies cause only small errors in the inter-spike interval statistics. As these are the final descriptors of interest, the fourth order Runge-Kutta integration method with noise variance σ^2/h and with $i(t_i + h/2) = i(t_i)$ was considered to be adequate for the purposes presented before. An example run showing inter-spike interval statistics will be described in what follows to illustrate the adequacy of the adopted methodology. The model described by (1) was simulated with R=C=1 , $x_o = 0$, $V_{th} = 1$, i(t) white Gaussian noise with mean 0.5 and autocovariance $E[(i(t) - 0.5)(i(t + \tau) - 0.5)] = \delta(\tau)$. The simulations were run until 1000 spikes (or "action potentials") were obtained from (1). The exact integration method with a step size of 0.05 generated a spike-train whose inter-spike interval had an average 2.4822 and a variance 6.18257. The Runge-Kutta with the same step size 0.05 and with the white Gaussian sequence having a variance of 1/0.05 generated a train that had an average interval 2.5768 and a variance 6.55713 . The latter two values are in excess of the former by 3.8% and 6%, respectively. Fig. 1 shows inter-spike interval histograms from the trains generated by the two methods: exact (Fig. 1a) and Runge-Kutta (Fig. 1b). The overall behavior is the same exponential-like figure. There are small localized differences that have no statistical significance. The good numerical performance of the integration methodology for the case of white noise input is expected to apply also for the case of colored noise.

GENERATION OF NOISE SEQUENCES WITH 1/f POWER SPECTRUM

Excitable cells in nature have different types of membrane noise spectra (De Felice, 1981). One type is the 1/f and the noise is called 1/f noise or flicker noise. Obviously real-life spectra cannot be 1/f for all f as this function diverges for $f \to 0$. So the 1/f power spectral density should be taken as an approximation to the real spectrum, the latter attaining a finite peak value as $f \to 0$. A simple method is sought that can generate a sequence of samples with an approximately 1/f power spectral density. The computer generates sequences of samples that have an approximately flat spectrum. If one is able to find a simple digital filter that changes the flat spectrum to something approximately 1/f then the goal has been achieved. An IIR realization was chosen because it is faster than an FIR. Therefore the problem is to design an IIR digital filter, with few coefficients, that has an approximately $1/\sqrt{f}$ amplitude response (absolute value of the frequency response). It should be clear that the bilinear transformation design method is not feasible in this case because: i there is no straightforward analog filter prototype with a rational transfer function, and, ii the method's frequency warping is tolerable only for amplitude responses that have flat regions.

The least squares inverse design (Oppenheim and Schafer, 1975) was judged to be a good method for the problem at hand. The first thing that is needed in this technnique is the desired impulse response $h_d(n)$. The desired $\sqrt{1/f}$ amplitude response of the continuous time system follows from a transfer function $1/\sqrt{s}$. The impulse response associated with this transfer function is (by inverse Laplace transformation) proportional to $1/\sqrt{t}$. The discrete-time version was computed by sampling $1/\sqrt{t}$ at every 0.0005 s , which is small enough to cause negligible aliasing in the frequency range from 0 to 1000 Hz. To keep the filter simple, a pure auto-regressive filter was chosen with only 5 poles. A short computer program calculated the autocorrelation sequence of the truncated (to 1000 samples) impulse response sequence. Next, a standard Gauss-elimination program was used to find the filter coefficients as the solution of a set of linear equations. The computed coefficients of the filter's transfer function $H(z) = 1/(1-a_1z^{-1}-a_2z^{-2}-a_3z^{-3} - -a_4z^{-4} - a_5z^{-5})$ were: $a_1 = 0.36976$, $a_2 = 0.15362$, $a_3 = 0.10217$, $a_4 = 0.08492$, $a_5 = 0.09452$. The resulting filter's amplitude response and the theoretical characteristics are shown in Fig. 2. The error is below 2.5 dB in the frequency range from $f_s/384$ up to $(3/8)f_s$ where f_s is the sampling rate. If desired, this error could be reduced by choosing an ARMA filter or a higher order AR filter, but the approximation obtained by the 5 pole AR filter was deemed adequate for the purposes of the simulation problem.

All the noises used in the simulations were normally distributed. They were generated using the method of Box and Muller (1958) applied on the uniformly distributed white sequence available from the computer. The digital filtering of a white Gaussian sequence produces another Gaussian sequence but with a different power spectral density.

GENERATION OF LORENTZIAN NOISE

This type of noise, generated spontaneously by the cell's membrane or due to multiple synaptic bombardment, has a low-pass power-spectrum proportional to $1/(\omega^2 + \alpha^2)$. The power spectral density of an Ornstein-Uhlenbeck process has such a description and this fact is used in this work for the generation of such a noise sequence.

Due to space limitations, we shall only sketch the derivation of the difference equation that generates "Ornstein-Uhlenbeck sequences".

An Ornstein-Uhlenbeck process is generated by (1) with $V_{th} = +\infty$ and white Gaussian noise input. It can be shown that its mean is

$$E\left[x(t)\right] = x_o e^{-t\omega_o} + \frac{\mu_i}{C\omega_o}(1 - e^{-\omega_o t}) \tag{7}$$

where $\mu_i = E\left[i(t)\right]$

and its autocovariance function is

$$ACV_{xx}(t,t+\tau) = \frac{\sigma^2}{2\omega_o C^2} e^{-\tau\omega_o}(1 - e^{-2\omega_o t}) \quad ; \quad \tau > 0 \tag{8}$$

The discrete time system that will generate Ornstein-Uhlenbeck sequences $\{w(n)\}$ has the general description

$$w(n+1) = a\, w(n) + b\, u(n) + g\mu_i \quad ; \; w(0) = x_o \tag{9}$$

where: $u(n)$ is a white Gaussian sequence with zero mean and variance σ^2

μ_i is a constant input equal to $E\left[i(t)\right]$

a, b and g are to be determined.

The determination of a, b and g is based on the fact that both the continuous time and the discrete time Ornstein-Uhlenbeck processes are Gaussian and therefore fully described by their mean and autocovariance. Writing out the general solution of (9) it can be shown that

$$E\left[w(k)\right] = a^k x_o + g\mu_i \frac{a^{k-1}-1}{a-1} \quad (10)$$

and

$$ACV_{ww}(k,k+m) = \frac{b^2\sigma^2}{1-e^{-2h\omega_o}} \; e^{-mh\omega_o}(1 - e^{-2kh\omega_o}) \; ; \quad k > 0 \quad (11)$$

The time instant t corresponds to the discrete-time kh and τ to mh. Comparing (7) with (10) and (11) the following relations are obtained:

$$a = e^{-h\omega_o} \quad (12)$$

$$g = \frac{1 - e^{-h\omega_o}}{C\omega_o} \quad (13)$$

$$b = \frac{\sqrt{1 - e^{-2h\omega_o}}}{C\sqrt{2\omega_o}} \quad (14)$$

Expressions (13) and (14) are not in a final form, because every new cut-off frequency ω_o that is chosen will result in a different asymptotic constant value for $\overset{o}{w}(n)$.

This can be more easily seen by looking at the expression of the asymptotic value in (7):

$$\lim_{t\to\infty} E\left[x(t)\right] = \frac{\mu_i}{C\omega_o}$$

This value should not vary when the cut off frequency is changed. Therefore one should keep R=1 constant and vary C in order to get the desired cutt-off frequency. The following expressions result:

$$C = \frac{1}{\omega_o} \quad (15)$$

$$g = 1 - e^{-h\omega_o} \quad (16)$$

$$b = \frac{\sqrt{1 - e^{-2h\omega_o}}\,\sqrt{\omega_o}}{\sqrt{2}} \quad (17)$$

Therefore equations (9), (12), (16) and (17) programed in a digital computer will generate exact samples from a continuous-time Ornstein-Uhlenbeck process. This same results might have been obtained by starting from equation (6) .

GENERATION OF NOISE FILTERED BY A QUASI-ACTIVE MEMBRANE

The classical passive dendritic tree model has a low-pass type transfer function with a flat passband. The transfer function is taken between a current injected at any point along the tree and the resulting trigger zone current. This transfer function is reasonably well approximated, within an appropriate frequency band, by a first order low-pass filter. However, this passive dendritic behavior is not a general finding in neurophysiology. The phenomenon of resonance is well documented in the biophysical literature and in this case the membrane may be said to be in a quasi-active state. Koch (1984) linearized the Hodgkin-Huxley equations and then found the frequency response of an infinite length cable. The overall shape of the amplitude response was low-pass, exhibiting a resonance at about 70Hz. His Fig. 6 is reproduced here in Fig. 3a and used in this work as a paradigm transfer function to be implemented in the computer simulations. The high frequency asymptote increases with ω (derived theoretically). Between 400 and 800 Hz it is about - 8 dB/octave. The measured Q (quality factor) of the resonance peak is about 1. As the resonance peak amplitude of a second order low-pass system with Q=1 is much smaller than that seen in Fig. 3a, a low-frequency zero has to be added. The resulting two-pole-one-zero approximation has an impulse response that shoots up instantaneously at t=0 and then decays, which is quite different from Koch's findings (Fig. 3d). A first order transfer function is then subtracted from the two-pole-one-zero transfer function, resulting in very good time and frequency domain fittings to Koch's results (see Figs. 3b and 3c). The final transfer function is:

$$H(s) = \frac{1282.11224s + 247082.82}{s^2 + 453s + 205209} - \frac{1200}{s+5000} \tag{18}$$

For frequencies between 400 and 800 Hz the asymptote is -6 dB/octave. For higher frequencies (less than 12 KHz) it is - 12 dB/octave.

The next step was to implement a discrete time approximation to (18). Again an IIR digital filter was chosen due to its faster operation. The bilinear transformation method is not recommended as it will cause deformations in the amplitude response. The impulse response invariance design method was considered to be adequate because its only distortions arise from aliasing. If the discretization interval is sufficiently small, aliasing can be neglected.

The first term in the right of equation (18) has the general expression:

$$H_1(s) = a \frac{s+b}{s^2 + cs + d}$$

with

$a = 1282.11224$
$b = 192.71544$
$c = 453$
$d = 205209$

and has a partial fraction expression

$$H_1(s) = a \left[\frac{g}{s-p} + \frac{g^*}{s-p^*} \right]$$

where

$$p = \frac{-c + j\sqrt{4d - c^2}}{2}, \quad p^* = \frac{-c - j\sqrt{4d - c^2}}{2} \tag{19}$$

$$g = \frac{1}{2} + j\left(\frac{(c/2) - b}{\sqrt{4d - c^2}}\right) \tag{20}$$

The corresponding H(z) using the impulse response invariance design is (Oppenheim and Schafer, 1975)

$$H_1(z) = a\left[\frac{g}{1 - e^{pT}z^{-1}} + \frac{g^*}{1 - e^{p^*T}z^{-1}}\right] \quad (21)$$

where T is the time discretization interval or sampling period.

As (21) has complex parameters its digital computer implementation requires operations with complex numbers which slows down the computing speed. Equation (21) is therefore changed to have only real parameters:

$$H_1(z) = a\left[\frac{g - (g\,e^{p^*T} + g^*\,e^{pT})z^{-1} + g^*}{1-(e^{pT}+ e^{p^*T})z^{-1} + e^{(p+p^*)T}z^{-2}}\right] \quad (22)$$

Substituting equations (19) and (20) into (22) and redefining the parameters one obtains the following expression that is in a form suitable for numerical computations:

$$H_1(z) = a\left[\frac{1-z^{-1}q_1\left[q_3 + q_4\sin(q_2)\right]}{1-z^{-1}2q_1q_3 + z^{-2}q_5}\right] \quad (23)$$

with

$$q_o = \sqrt{4d-c^2}$$

$$q_1 = e^{-\frac{c}{2}T}$$

$$q_2 = \frac{q_o}{2}T$$

$$q_3 = \cos(q_2)$$

$$q_4 = \frac{c - 2b}{q_o}$$

$$q_5 = e^{-cT}$$

The complete transfer function is obtained by adding the term corresponding to the second term in the right side of (18):

$$H(z) = H_1(z) - \alpha/(1-z^{-1}\beta) \quad (24)$$

where $\alpha = 1200$

$\beta = e^{-5000T}$

The realization consists of a parallel association of a second order and a first order system.

A comment is needed on the choice of T. The continous-time transfer function (18) has a resonance at about 70Hz. The sampling interval T for the impulse response invariant design should be small enough to make the aliasing small. On the other hand, the simulated continuous time system has normalized time and frequency variables. The sampling interval for this normalized system (1) is 0.05, as already pointed out before. If the resonance peak in the normalized frequency scale is f_{res} then the sampling interval is

$$T = \frac{0.05}{70}\,f_{res}$$

As an example, take a neurophysiologically relevant value

$f_{res} = 0.32$, so $T = 2.2857 \times 10^{-4}$. In other words, the sampling rate for converting (18) into (24) is 4375Hz which is clearly high enough to minimize aliasing effects. Besides the value $f_{res} = 0.32$, other two values, 0.08 and 0.16 , will be used in the simulations. For these, the sampling rate is even higher, therefore causing no aliasing distortions.

SIMULATION OUTPUTS

In the simulation system that was developed, the simplest output of a simulation of (1) shows the membrane voltage as a function of time and the associated spikes that occur every time the threshold is crossed (see Fig. 1). This output is useful to give a feeling of the rate and pattern of spike generation.

Most of the interesting information is obtained from the spike train itself and hence statistical analyses are applied to the associated point processes (Moore et al, 1966). The following statistics are provided by the simulation system: mean interval, interval standard deviation, interval histogram (see Fig. 2), autocorrelation histogram, scatter plot of the (i+j)th interval × (i)th interval ($j \in Z^+$).

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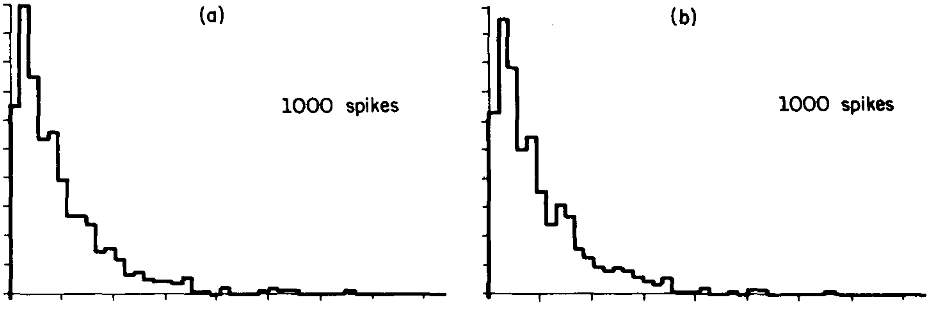

Fig. 1 - Inter-spike interval histograms for exact (a) and Runge-Kutta numerical method (b).

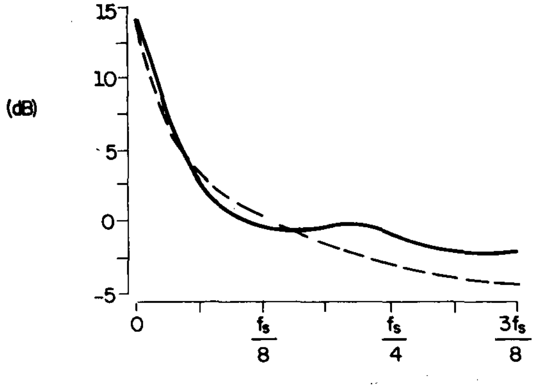

Fig. 2 - Amplitude response of IIR approximation (solid line) to theoretical $1/\sqrt{f}$ response (broken line).

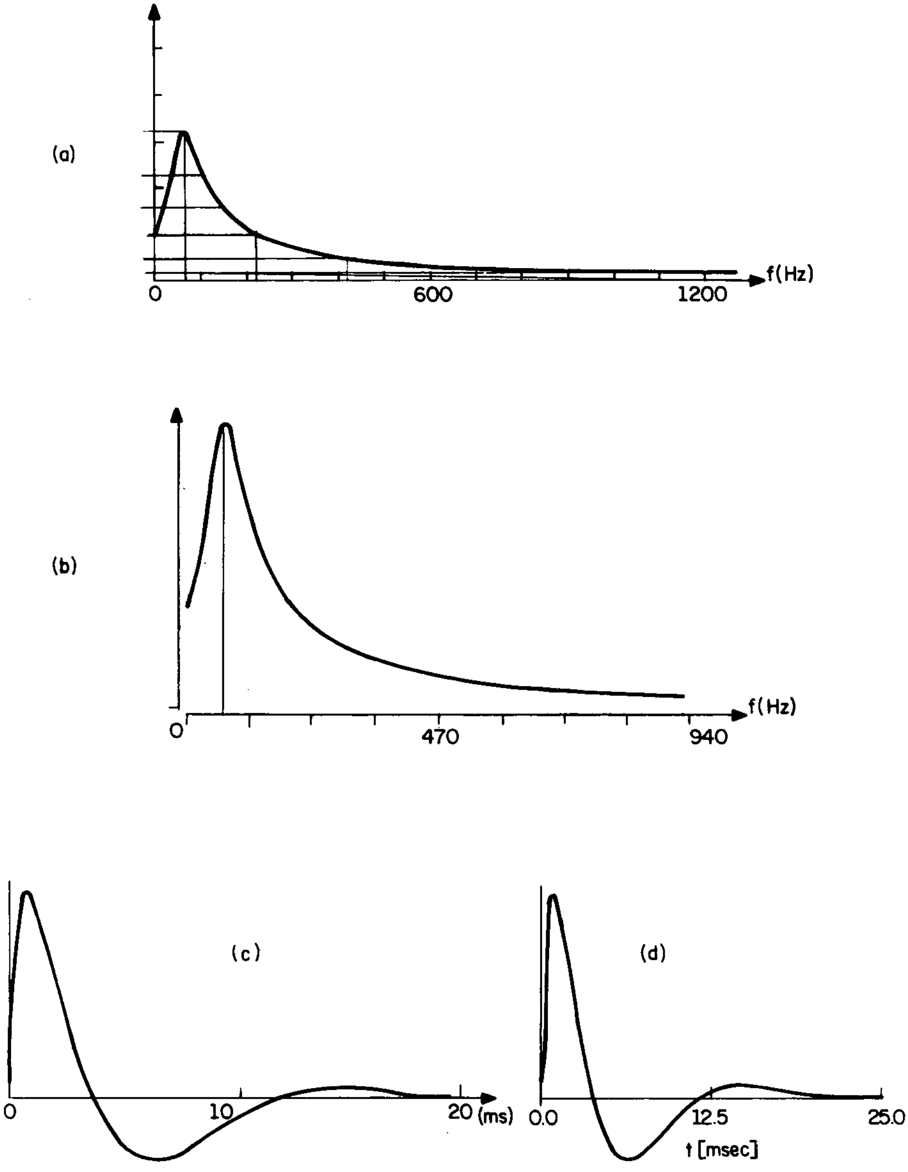

Fig. 3 - Amplitude response of Koch's (1984) cable transfer function (a) and of the third order linear approximation (b). Impulse response of the approximation (c) and the original impulse response (d) of Koch (1984).