Precision of Neural Timing: Effects of Convergence and Time-Windowing

MICHAEL C. REED
Department of Mathematics, Duke University, Durham, NC 27708, USA
reed@math.duke.edu

JACOB J. BLUM
Department of Cell Biology, Duke University Medical Center, Durham, NC 27710, USA

COLLEEN C. MITCHELL
Department of Mathematics, Duke University, Durham, NC 27708, USA

Action Editor: Alessandro Treves

Abstract. We study the improvement in timing accuracy in a neural system having n identical input neurons projecting to one target neuron. The n input neurons receive the same stimulus but fire at stochastic times selected from one of four specified probability densities, f, each with standard deviation 1.0 msec. The target cell fires if and when it receives m inputs within a time window of ϵ msec. Let $\sigma_{n,m,\epsilon}$ denote the standard deviation of the time of firing of the target neuron (i.e. the standard deviation of the target neuron's latency relative to the arrival time of the stimulus). Mathematical analysis shows that $\sigma_{n,m,\epsilon}$ is a very complicated function of n, m, and ϵ. Typically, $\sigma_{n,m,\epsilon}$ is a non-monotone function of m and ϵ and the improvement of timing accuracy is highly dependent of the shape of the probability density for the time of firing of the input neurons. For appropriate choices of m, ϵ, and f, the standard deviation $\sigma_{n,m,\epsilon}$ may be as low as $\frac{1}{n}$. Thus, depending on these variables, remarkable improvements in timing accuracy of such a stochastic system may occur.

A fundamental problem in neurobiology is to understand how the central nervous system (CNS) performs accurate calculations with components (i.e. neurons) whose properties vary in time, and from cell to cell, and which give variable responses under repeated trials. Local noise would compromise the information processing capabilities of successive levels of the CNS unless strong compensatory mechanisms were in place. Therefore, situations in which experimental evidence shows that information is sharpened as it progresses inward from the periphery to the CNS are particularly interesting for they may provide clues about such compensatory mechanisms.

A particularly striking example of increasing accuracy as one proceeds into the CNS from the periphery in the auditory system was discovered by Covey and Casseday (1991). Neurons in the auditory nerve (AN) synapse on cells in the cochlear nucleus (CN) and certain cells in the CN, notably octopus cells, send projections to cells in the columnar region of the ventral nucleus of the lateral lemniscus (VNLLc). Covey and Casseday discovered that in bats these VNLLc cells fire a single action potential in response to sound stimulation with a precise latency; the standard deviation of this latency under repeated trials is typically about 100 microseconds and in some cases as low as

30 microseconds. This is remarkable because in the AN of mammals typical standard deviations for latency under repeated trials in a single fiber are approximately 1 msec. Oertel and co-workers (Oertel, 1999; Oertel et al., 2000) have proposed that much of this improvement in accuracy is created by coincidence detection by octopus cells of incoming signals from converging AN fibers.

Timing and coincidence detection have long been studied in the auditory system. For example, coincidence detection appears to be a mechanism used by brainstem nuclei in mammals and birds to determine azimuthal sound location based on time or phase difference (Jeffress, 1948; Irvine, 1986; Colburn et al., 1990; Agmon-Snir et al., 1998) and bats show behavioral responses to exceptionally small binaural timing differences (Simmons et al., 1990; Pollak, 1993). In addition to the auditory system, timing and coincidence detection are important in a wide variety of other CNS systems. For example, it has been proposed that certain "binding" mechanisms in the visual system depend on timing and coincidence detection (Konig et al., 1996). Matell and Meck (2000) have suggested that the basal ganglia acts as a coincidence detector of cortical and thalamic inputs. Bilateral timing mechanisms are also involved in the improvement of coordination of motor systems in the cerebellum(Ivry, 1997). On these longer time scales the "signals" may be volleys of action potentials and the target may be a nucleus or subdivision thereof.

For many years, synchronous firing of groups of neurons has been proposed as the mechanism by which sensory patterns are represented in the cortex. One mechanism by which stable patterns of synchronous firing could be created is the synfire chain model introduced by Abeles (1991) and further developed by Aertsen, Diesmann, and others (see, for example: Riehle et al., 1997; Diesmann et al., 1999, 2001; Gewaltig et al., 2001). These investigators have shown that if the number of firing neurons is large enough and the initial standard deviation of firing times is small enough, then stable propagation is possible. We investigate here the improvement of the standard deviation of spike timing at a single target neuron which receives convergent input. Thus we are continuing the line of investigation in Marsalek et al. (1997). Detailed understanding of the improvement of the standard deviation for firing times at single neurons will be of value for understanding the properties of synfire chains using less restrictive hypotheses.
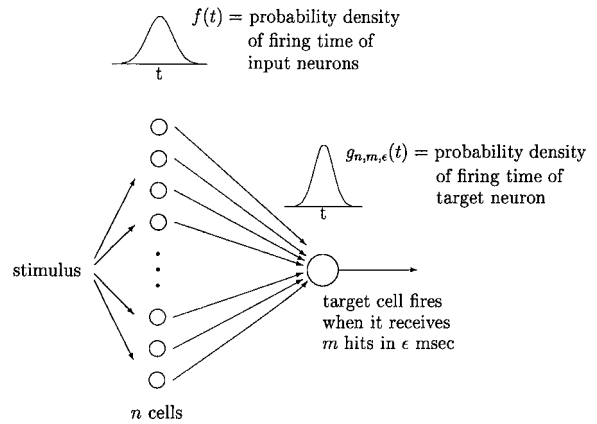

Figure 1. The connectional pattern. n input neurons, whose stochastic times of firing are selected from the probability density, f, project to a target cell. The probability density for the firing time of the target cell is $g_{n,m,\epsilon}(t)$.

We shall study the mathematical properties of coincidence detection in a highly simplified neural system. Consider the network shown in Fig. 1. There are n identical input neurons stimulated at the same time. Each responds by sending a single spike to the target neuron at a random time t with standard deviation s. The random times are drawn from one of four probability densities: uniform, normal, exponential, and hat. We assume that the target neuron fires one spike (if it fires at all) the first time it receives m spikes in the preceeding ϵ milliseconds. Let $\sigma_{n,m,\epsilon}$ denote the standard deviation of the time of firing of the target cell. If $\sigma_{n,m,\epsilon}$ is smaller than s, then the accuracy of the time of firing of the target cell has improved compared to the accuracy of its inputs. We want to investigate several specific questions. For example, does requiring more hits (i.e. increasing m) make firing more accurate? Does making the time window, ϵ, smaller increase accuracy? We report in this study the behavior of $\sigma_{n,m,\epsilon}$ as a function of n, m, and ϵ. As we will see below, some of the answers are surprising.

There are good physiological reasons for considering different initial probability densities. Though it is natural to assume a normal distribution, or a uniform distribution (for ease of computation), the latency distribution in auditory nerve fibers, for example, is close to exponential (Young et al., 1988; Yin, personal communication). Actual physiological probability densities are created by many different phenomena, for example, membrane variability, dendritic geometry, and synapse distribution (Softky, 1994; Agmon-Snir et al., 1998;

Segev and London, 2000), and will have many different forms depending on these physiological variables. As we shall see, the form of the initial probability density has a strong effect on the accuracy of the time of firing of the target cell.

A scaling law allows one to relate the values of $\sigma_{n,m,\epsilon}$ for different values of s. Suppose that $f(t)$ is a probability density with standard deviation s. Then $f_s(t) \equiv sf(st)$ is also a probability density and its standard deviation is 1. If we make explicit the dependence of the standard deviation of the time of firing of the target cell on the incoming density by writing $\sigma_{n,m,\epsilon,f}$, then a relatively straightforward calculation (see Mitchell, 2003) shows that,

$$\sigma_{n,m,\epsilon,f} = s\sigma_{n,m,\frac{\epsilon}{s},f_s} \tag{1}$$

Thus, the standard deviation of the output for a density f with $s \neq 1$ can be computed in terms of the standard deviation of the output for a scaled density with $s = 1$ by scaling the size of the time window and using the above formula.

Obviously, the mathematical question briefly outlined above is highly simplified compared to the complexity of real neural systems. By using a time-window rule of firing we ignore the detailed biophysics of the post-synaptic membrane and we ignore the possibility of direct inhibitory inputs. Nevertheless, the probabilistic and combinatorial phenomena that we investigate in this paper are necessarily embedded in models in which the geometry of the dendritic tree and biophysics of membranes are taken into account. In such more realistic models, however, the non-linear dynamic behavior and large number of parameters would make the mathematical questions treated here difficult to understand. Therefore, in this paper we have concentrated solely on the probabilistic and combinatorial issues.

1. Methods

In this section we give a formal description of the mathematical question corresponding to the neurobiological situation pictured in Fig. 1. We assume that each of the n input neurons reacts independently to an input signal, e.g. sound stimulation, by firing a single action potential. The firing time, t_i, of the ith input neuron is found by selecting randomly and independently for each input neuron from a probability density f. We assume that the travel times along the axons of the input neurons are identical, so the action potentials arrive at

the target neuron (after a time delay d) at times $d + t_i$. The target cell is assumed to fire at the first time at which it receives m action potentials in the previous ϵ milliseconds. Note that the target cell may not fire at all.

Let T denote the random variable whose value is the firing time of the target neuron, given that it does fire. We define

$$g_{n,m,\epsilon}(t) \equiv \text{the probability density of } T$$

and note that $g_{n,m,\epsilon}(t)$ depends on n, m, ϵ, and f. If one repeated the above experiment many times and made a histogram of the firing times of the target cell, the histogram (divided by the number of firings of the target cell) would approximate this probability density $g_{n,m,\epsilon}(t)$.

If one knows $g_{n,m,\epsilon}(t)$, then one can compute its mean and standard deviation $\sigma_{n,m,\epsilon}$ by the standard formulas:

$$\mu_{n,m,\epsilon} = \int_{-\infty}^{\infty} t g_{n,m,\epsilon}(t)\, dt \tag{2}$$

$$\sigma_{n,m,\epsilon}^2 = \int_{-\infty}^{\infty} (t - \mu_{n,m,\epsilon})^2 g_{n,m,\epsilon}(t)\, dt. \tag{3}$$

The mathematical question is to determine how $\sigma_{n,m,\epsilon}$ depends on the parameters of the problem, n, m, ϵ, and the probability density, f.

Unfortunately, even in this highly simplified biological situation, one cannot compute explicit formulas for $\sigma_{n,m,\epsilon}$ in terms of n, m, ϵ, and f, except in special cases. Our goal is to illustrate the behavior of $\sigma_{n,m,\epsilon}$ for biologically reasonable choices of the parameters. In auditory nerve fibers the probability density for latency looks approximately like a smoothed out exponential density (Rhode and Smith, 1985; Young et al., 1988; C.T. Yin, personal communication), although there is a lot of variation between different fibers. Other systems may have very different latency distributions for the incoming fibers. Thus, we will focus on four different choices for f that cover a wide range of situations: the uniform distribution, the normal distribution, the exponential distribution and the hat distribution, all with standard deviation equal to 1.0 msec as shown in Fig. 2.

As indicated in the Introduction, if we can understand the behavior of $\sigma_{n,m,\epsilon}$ for one fixed standard deviation, s, in the incoming fibers, the scaling law (1) allows us to understand $\sigma_{n,m,\epsilon}$ for all s. We shall fix the standard deviation of the latency of the inputs to be $s = 1$ msec since the standard deviation under
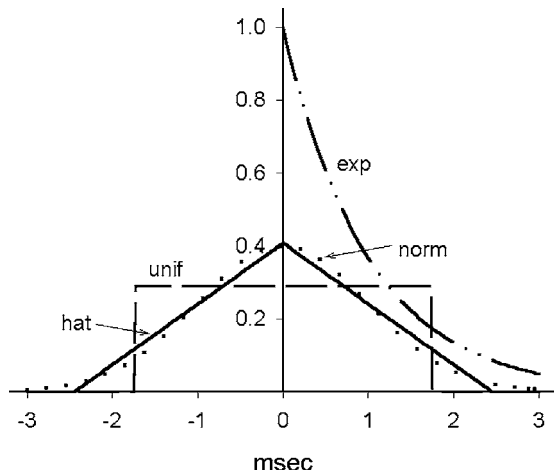
Figure 2. Four probability densities. Pictured in this figure are the probability density functions for the uniform (dashes), exponential (dashes and dots), normal (dots) and hat distributions (solid line). All distributions have standard deviation equal to 1.0 msec. For each density function, f, the probability that a random selection from that distribution lies between a and b msec equals $\int_a^b f(t)\,dt$.

Figure 3. Percentage of trials in which the target neuron fires. The solid curves show the percentage of successful firings of the target neuron as a function of ϵ when f is the exponential density for three different choices of m, the number of hits required to cause the target cell to fire. The dashed lines show the analogous curves when f is the normal density. In each case the number of incoming fibers, n, is 10.

repeated trials in auditory nerve fibers is of this magnitude (Rhode and Smith, 1985; Young et al., 1988; Heil and Irvine, 1997; C.T. Yin, personal communication). For the uniform distribution, the probability of the time of arrival is equal throughout an interval of length 3.46 msec (this is required so that the standard deviation is 1.0). The normal and hat distributions are symmetric with peaks at $t = 0$. The exponential distribution starts with its peak at $t = 0$ and decays exponentially. The standard deviation, $\sigma_{n,m,\epsilon}$, of the firing time of the target neuron does not depend on the mean of f and so, for pictoral simplicity, we have chosen the means of the uniform, normal and hat distribution to be 0 and the mean of the exponential to be 1. Since our main interest is the behavior of $\sigma_{n,m,\epsilon}$ as a function of the time window ϵ, and the number of hits required, m, we restrict ourselves to two choices for n, namely, $n = 4$ and $n = 10$.

The graphs in Figs. 3, 6, 7, and 8 were obtained by Monte Carlo simulations. For each simulation, n, m, ϵ, and the probability density, f, for the latency in the incoming fibers were specified. The experiment was repeated 10^5 to 10^7 times, as necessary, in order to obtain an accurate approximation to the probability density for the time of firing of the target cell, $g_{n,m,\epsilon}(t)$. Time was binned in units of 0.02 msec. From the probability density so obtained, the mean and standard deviation, $\sigma_{n,m,\epsilon}$, were obtained by machine computation by evaluating the appropriate integrals in Eqs. (2) and (3).
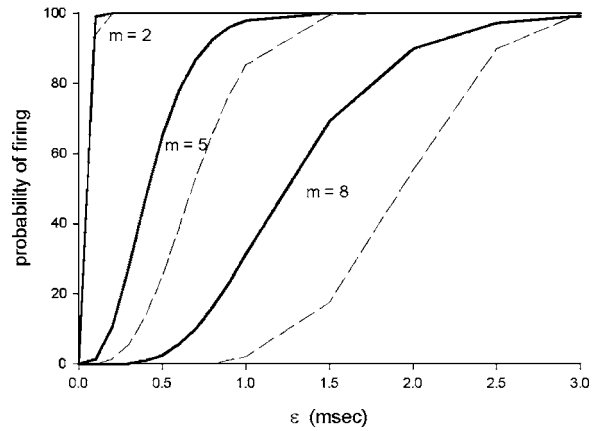
2. Results

We begin by examining the probability of firing of the target neuron as a function of m and ϵ. Then we investigate the behavior of $\sigma_{n,m,\epsilon}$ for two special cases, $\epsilon = 0$ (Section 2.1), and $\epsilon = \infty$ (Section 2.2). Finally we treat the general behavior of $\sigma_{n,m,\epsilon}$ as a function of ϵ (Section 2.3) and m (Section 2.4).

The curves in Fig. 3 show the probability of firing (percent successes) of the target neuron for different choices of f and m as a function of the size of the time window, ϵ.

When $m = 2$, i.e. only two hits are required, and $n = 10$, the target cell is essentially certain to fire when $\epsilon \geq 0.1$ msec. Of course, as ϵ gets extremely small the probability decreases to 0 as can be seen in the figure. However, if 5 hits are required the situation is much more interesting. For the exponential density, the probability of firing of the target falls from 97% to 10% as the time window ϵ decreases from 1 to 0.2 msec. If, however, f is the normal density, the probability of firing falls from 85% to 1% over the same ϵ range. If the number of hits required for a successful firing is increased to 8, then the differences between the two cases are even greater. For the normal density the probability of success of firing has fallen to 2% when ϵ is 1 msec while it remains at 31% for the exponential. Thus, if there are 10 incoming fibers, the behavior in the physiological range, approximately $\epsilon = 0.5$ msec

to $\epsilon = 1.0$ msec, is dramatically different in the three cases $m = 2, 5, 8$. If $m = 2$ the target cell is certain to fire, if $m = 8$ the target cell is highly unlikely to fire, and if $m = 5$ the probability of firing drops dramatically as the time window, ϵ, decreases through the physiological range. The hat and uniform densities give results similar to the normal (curves not shown). Thus we see that the probability of firing goes to zero as $\epsilon \to 0$, but that the rate depends strongly on m and the nature of the probability density, f, for the input neurons.

We now turn our attention to $\sigma_{n,m,\epsilon}$, the standard deviation of the latency of firing of the target neuron. From a physiological point of view, it does not make sense to make ϵ too small since, as shown above, the target cell will seldom fire. It also does not make sense physiologically to make the time window, ϵ, larger than a few milliseconds, since by that time the biophysical effect of the first hit on the membrane potential will have been "forgotten". Nevertheless, these two limiting cases, ϵ small (Section 2.1) and ϵ large (Section 2.2) are of interest because they are mathematically tractable and provide insight into the behavior of σ for large and small time windows.

2.1. The Case $\epsilon \to 0$

Under appropriate hypotheses on the properties of the probability density of the latency, $f(t)$, of the n independent incoming fibers, one can prove mathematically that

$$g_{n,m,\epsilon}(t) \to \frac{f(t)^m}{\int_{-\infty}^{\infty} f(t)^m \, dt} \qquad (4)$$

as $\epsilon \to 0$ (Mitchell, 2003). For example, this is true if f is piece-wise continuous, which is the case for our four choices for f. For convenience, we will denote the normalization $\int_{-\infty}^{\infty} f(t)^m \, dt$ by N. Thus, in this limit we have an explicit formula for the density $g_{n,m,0}(t)$ of T and we note that the density is independent of n. Intuitively, taking the mth power of a continuous density f and renormalizing will emphasize, that is, put more probability in, the region near the peak, and de-emphasize the regions away from the peak. This sharpening around the peak can be seen by comparing the renormalized densities for $m = 3$ in Fig. 4 with the densities for $m = 1$ shown in Fig. 2.

Thus, if the density f has a peak, we expect the standard deviation of $f(t)^m/N$ to be smaller than that of f and to decrease as m gets larger. Straightforward
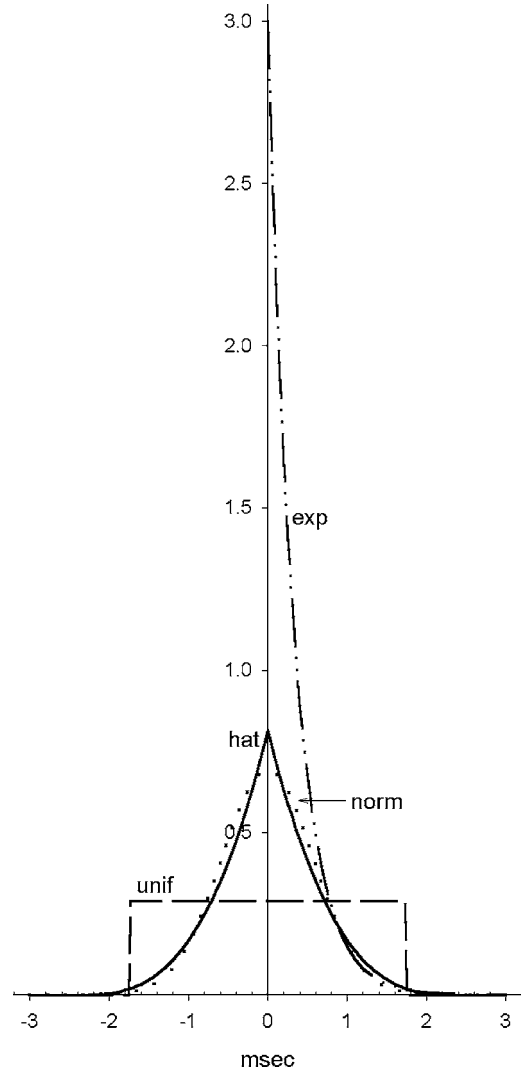

Figure 4. Third powers of the probability densities renormalized. The probability densities, $f(t)^m/N$, obtained by setting $m = 3$ and letting $\epsilon \to 0$ for the four choices of f are shown. For the exponential, hat, and normal densities, considerable sharpening can be seen compared to the probability densities in Fig. 2 where $m = 1$.

calculations show that:

$$\sigma_{n,m,0} = \begin{cases} 1 & \text{if } f = \text{uniform} \\[2mm] \dfrac{1}{m} & \text{if } f = \text{exponential} \\[2mm] \dfrac{1}{\sqrt{m}} & \text{if } f = \text{normal} \\[2mm] \sqrt{\dfrac{12}{(m+2)(m+3)}} & \text{if } f = \text{hat} \end{cases}$$
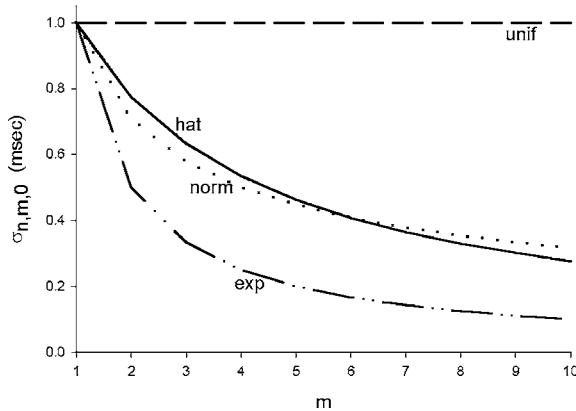
Figure 5. The behavior of $\sigma_{n,m,\epsilon}$ when $\epsilon = 0$. The graphs of $\sigma_{n,m,0}$ as a function of m are shown for the uniform, exponential, normal, and hat densities.

To understand these formulas, consider the case where f is the uniform distribution and imagine a very small time window. The target cell fires at the time T when there are for the first time m hits in the previous ϵ msecs. The probability of achieving a firing gets smaller as ϵ gets smaller. However, the location of the firing time (if it does fire) will be approximately uniform over the same interval. Therefore, the standard deviation of T should be approximately 1. So, if f is the uniform distribution, there is no improvement in the standard deviation. The other distributions have peaks and, as m gets larger, more and more of the probability is centered near the maxima, and therefore $\sigma_{n,m,0}$ decreases as m increases. This is illustrated in Fig. 5 where $\sigma_{n,m,0}$ is graphed for each density as a function of m. Note that $\sigma_{n,m,0}$ decays like $\frac{1}{m}$ for the hat and the exponential distributions, while $\sigma_{n,m,0}$ decays like $\frac{1}{\sqrt{m}}$ for the normal. This occurs because the hat and exponential have sharp peaks rather than a smooth peak like the normal distribution.

2.2. The Case $\epsilon \to \infty$

As ϵ gets larger and larger the time window restriction has less and less effect. Thus, in the limit when $\epsilon \to \infty$, the target neuron will fire when the mth action potential arrives (this is equivalent to the simplest integrate and fire model considered by Marsalek et al. (1997)). The mth largest of n selections from a density f is called an order statistic and this random variable has probability

density:

$$g_{n,m,\infty}(t) = \frac{n!}{(m-1)!(n-m)!} \\ \times F(t)^{m-1}(1 - F(t))^{n-m} f(t) \quad (5)$$

where $F(t)$ is the cumulative distribution function of $f(t)$, that is $F(t) = \int_{-\infty}^{t} f(s)\,ds$ (see, for example, Arnold et al., 1993; Balakrishnan and Rao, 1998a, 1998b). Since one has an explicit formula for the density of T one can compute, either by hand or by machine, the standard deviation $\sigma_{n,m,\infty}$ of T.

To illustrate the behavior of order statistics, we choose $n = 10$, i.e., there are 10 input fibers. Figure 6 shows graphs of the standard deviation, $\sigma_{10,m,\infty}$, of the firing time of the target cell as a function of m.

Consider first the case where the latencies of the incoming fibers are selected from a uniform distribution. If $m = 1$, i.e. the target cell fires at first hit, then $\sigma_{10,1,\infty} = 0.287$ msec. Note that this is much lower than the standard deviation of latency in the incoming fibers which is 1.0 msec. This increased precision in time of firing of the target cell arises because the first of 10 hits selected from the uniform distribution is highly likely to occur near the left edge (i.e., near -1.7 msec). Similarly, the 10th hit is highly likely to occur near the right edge (i.e., near $+1.7$ msec) and because of the symmetry of the uniform distribution will have the same standard deviation as for the first hit. For $m = 4, 5, 6$ or 7 the standard deviation $\sigma_{10,m,\infty}$ is considerably higher because there is more variation in the time of arrival of the mth hit in these cases. Note,
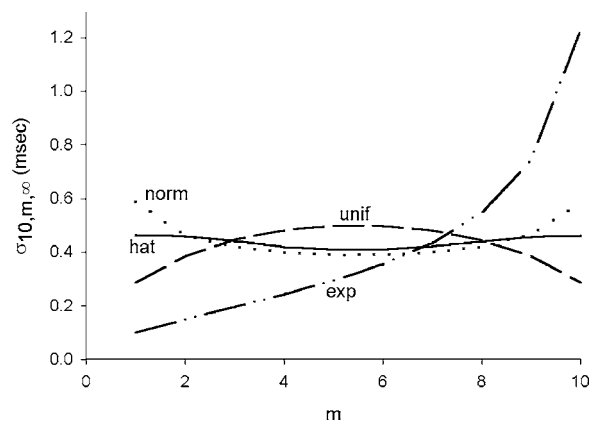

Figure 6. Order statistics. The graphs of $\sigma_{10,m,\infty}$ as a function of m for the four indicated probability densities.

however, that even in these cases the precision of the time of firing has been improved by at least a factor of two.

For the exponential distribution, firing on the first hit is extremely precise, $\sigma_{10,1,\infty} = 0.1$ msec, because the first hit is very likely to occur in the narrow peaked region of the exponential distribution shown in Fig. 2. By contrast, the 10th hit is likely to occur out in the tail of the exponential distribution and its time of occurence will have a great variability. If fact, $\sigma_{10,10,\infty} = 1.22$ msec, even greater than the variability of the incoming signal times. This illustrates that for a non-symmetric distribution like the exponential, the number of hits required to fire the target cell may make a large difference in the improvement or degradation of the precision of timing.

For the hat distribution, firing on the first hit is less precise than for the uniform because the first hit is likely to occur in the furthest left region along the t axis with area $\frac{1}{n}$ under the density curve and this region is wider for the hat than for the uniform. On the other hand, the middle hits have smaller standard deviations for the hat distribution because of its peak. When f is the normal distribution, the results are quite similar to the those for the hat distribution, except that the standard deviation goes up significantly for 1st hit and 10th hit because those hits are very likely to occur in the early or late tails of the normal distribution. Notice that the number of hits required for firing, m, does not matter very much for the normal and hat distributions, and that in both cases the precision of timing is increased by a factor of approximately two.

We have seen that if a cell fires when it receives it's mth hit out of 10, the improvement in the precision of firing depends on m. The amount of improvement and the variability of $\sigma_{10,m,\infty}$ are highly dependent on the nature of f, the probability density for the latency of the input neurons.

Note that if $m = 1$, then we are always in the case of order statistics no matter what the size of the time window since the target cell fires at first hit. That is,

$$\sigma_{n,1,\epsilon} = \sigma_{n,1,\infty} \qquad (6)$$

for all ϵ and all n whatever the form of the incoming latency density f.

Finally, we note that formula (1) becomes particularly simple in the limit $\epsilon \to \infty$:

$$\sigma_{n,m,\infty,f} = s\,\sigma_{n,m,\infty,f_s}.$$

If we denote $\sigma_{n,m,\infty,f}$ by σ_{out} and s by σ_{in} then we have:

$$\sigma_{out} = \sigma_{in}\,\sigma_{n,m,\infty,f_s}. \qquad (7)$$

Thus, in this limit where $\epsilon \to \infty$, σ_{out} is proportional to σ_{in}. In the general case, the size of the time window is involved; see formula (1).

2.3. Time-Window Behavior

We now consider the effect of the size of the time window, ϵ, on the standard deviation of the time of firing, T, of the target cell, which of course depends on n, and m. The dependence on m is considered in the next section. Here, we make four different choices for (n, m) to show the different kinds of dependence of $\sigma_{n,m,\epsilon}$ on ϵ.

Figure 7A shows the behavior of $\sigma_{n,m,\epsilon}$ as a function of ϵ for the case $m = 2$, $n = 4$, i.e. there are 4 inputs and 2 hits within ϵ msec are required to fire the target cell. Particularly striking is that when the incoming latency density, f, is normal, hat, or exponential, the $\sigma_{4,2,\epsilon}$ curves are non-monotone with peaks near $\epsilon = 0.5$ msec. In fact, all four curves (including the one for f uniform) are monotone decreasing for $\epsilon > 0.5$ msec, which means that increasing the size of the time-window *improves* the time accuracy of firing of the target cell. This seems counter-intuitive, but there is a good reason for this behavior. For a moderate-sized time window ($\epsilon = 0.5$ msec in this case), the successful hit might be the second, third, or the fourth hit and thus the time distribution of hits will be fairly spread out and therefore have a fairly large standard deviation. As ϵ is increased, the successful hit (i.e. the one that fires the cell) is more and more likely to be the second hit, and therefore the probability density for the time of firing will be more narrow. We note that when f is the uniform distribution the curve is always monotone decreasing, so increasing the time window always improves the accuracy of firing of the target cell.

When ϵ gets large, we expect $\sigma_{n,m,\epsilon}$ to approach the value given by order statistics. For the exponential and normal distributions (with standard deviation $= 1.0$ msec), the standard deviation of the second order statistics for $n = 4$ are 0.417 msec and 0.600 msec, respectively, i.e. an appreciable improvement in the accuracy of the time of firing. As one can see in Fig. 7A, the curves for $\sigma_{4,2,\epsilon}$ approach these values as ϵ gets large.

As ϵ decreases below 0.5 msec, $\sigma_{4,2,\epsilon}$ decreases somewhat when f is the hat, normal, or exponential
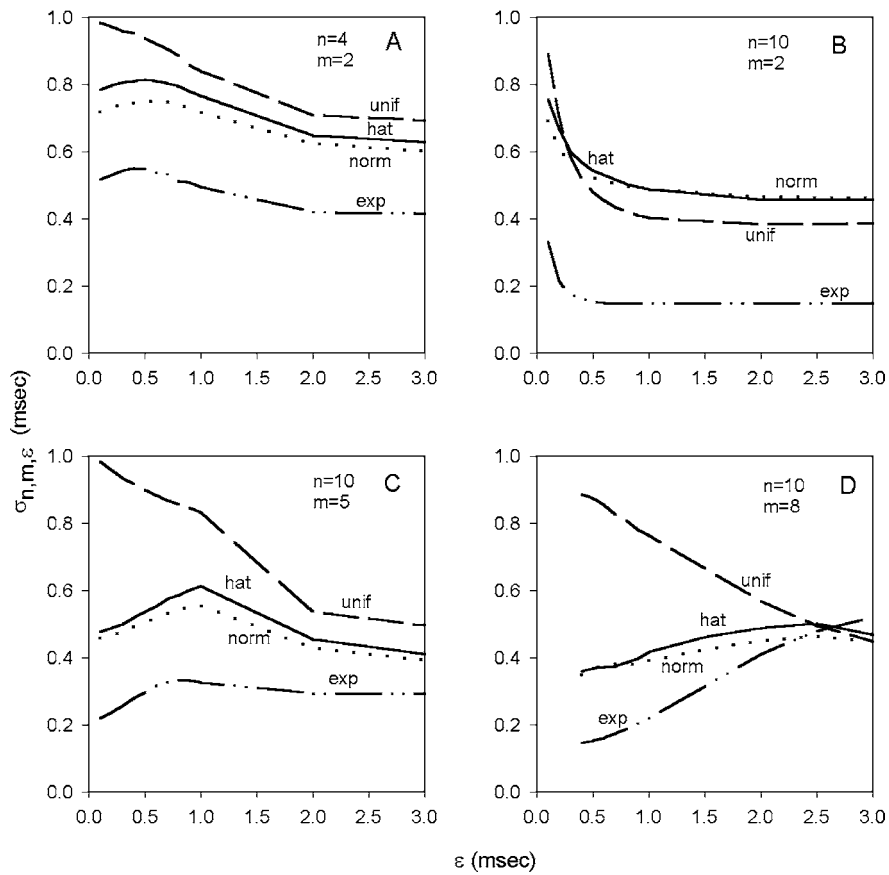
Figure 7. Behavior of $\sigma_{n,m,\epsilon}$ as a function of ϵ. Panels A, B, C, and D show graphs of the functions $\sigma_{4,2,\epsilon}$, $\sigma_{10,2,\epsilon}$, $\sigma_{10,5,\epsilon}$, $\sigma_{10,8,\epsilon}$, respectively.

distribution. Thus in this range, and for these choices of f, making the time window smaller improves the accuracy of time of firing of the target cell. As $\epsilon \to 0$ the curves approach the limiting values, $\sigma_{4,2,0}$, discussed in Section 2.1, namely 1.0, 0.5, 0.707, and 0.775 msec, when f is uniform, exponential, normal, or hat, respectively.

The nature of the distribution of latency in the incoming fibers (i.e. f) has a large effect on how much the accuracy of timing is improved. In this case, where we require 2 out of 4 hits in an ϵ time window, exponential is always better than normal which is better than hat, which is better than uniform, and the exponential gives an appreciably larger improvement than any of the others for all ϵ. It is remarkable that, except when f is uniform, the size of the time window has relatively little effect on the improvement of timing accuracy.

Suppose the number of incoming fibers is increased from 4 to 10, but we still require 2 hits within an ϵ time window to fire the target cell. In this case (Fig. 7B),

each of the $\sigma_{10,2,\epsilon}$ curves is monotone decreasing in ϵ, so increasing the size of the time window always improves accuracy. Most of the improvement occurs in the range 0 to 0.5 msec. Again, the case when f is exponential gives a much larger improvement in the standard deviation than for the other choices of f. Note that the improvement of timing is clearly better when there are 10 incoming fibers than when there are 4 for $\epsilon \geq 0.2$ msec.

To see the effect of keeping the ratio of required hits, m, to total fibers, n, constant, but increasing both, we examine the case $m = 5$ and $n = 10$; see Fig. 7C. Note that as in Fig. 7A, the curves are non-monotone, but the peaks have moved from $\epsilon \approx 0.5$ msec to $\epsilon \approx 1.0$ msec. Also, as in Fig. 7A, the accuracy of time of firing of the target cell is always best if f is exponential, next best for hat, next best for normal, and worst for uniform. For all choices of f and time windows ϵ, $m = 5$ and $n = 10$, gives more accurate time of firing for the target cell than the case when $m = 2$ and $n = 4$.

Thus increasing the number of incoming fibers and the number of hits required in constant ratio improves accuracy.

We now leave the number of incoming fibers at 10, but increase the number of hits required to fire the target cell to $m = 8$; see Panel D. For f exponential, the time of firing of the target cell is very accurate when ϵ is small ($\sigma_{10,5,0} = \frac{1}{5}$ msec and $\sigma_{10,8,0} = \frac{1}{8}$ msec). As ϵ increases there is a large monotonic increase in $\sigma_{10,8,\epsilon}$. And, for ϵ large, 8 hits required gives much less accuracy than when 5 hits are required (compare with Panel C). The reason is that when ϵ is large $\sigma_{10,8,\epsilon}$ is approximately given by order statistics and the standard deviation of the 8th hit will be larger than the standard deviation of the 5th hit because it is likely to occur out in the tail of the exponential. Note that when f is either hat or normal, the size of the time window doesn't make much difference, and that all four choices for f give similar results at large values of ϵ.

2.4.   Dependence on m, the Number of Hits Required

In this section we investigate the dependence of $\sigma_{n,m,\epsilon}$ on m, for different choices of the time window, ϵ. The number of fibers is fixed at $n = 10$.

Figure 8A shows the graphs of $\sigma_{10,m,0.2}$ as a function of m when $\epsilon = 0.2$ msec for our four choices of the incoming latency density, f. A priori, one might think that increasing m would increase the accuracy of the time of firing of the target cell. On the contrary, it is particularly striking that all four curves are non-monotone and increase as m is increased from 1 to 2 to 3. The change is particularly dramatic when f is the exponential or the uniform distribution. In the case of the exponential, $\sigma_{10,m,0.2}$ is 0.1 msec when $m = 1$, i.e. the accuracy of the time of firing has increased by an order of magnitude. This occurs because the smallest selection out of 10 random selections from the exponential density is highly likely to occur very early where the
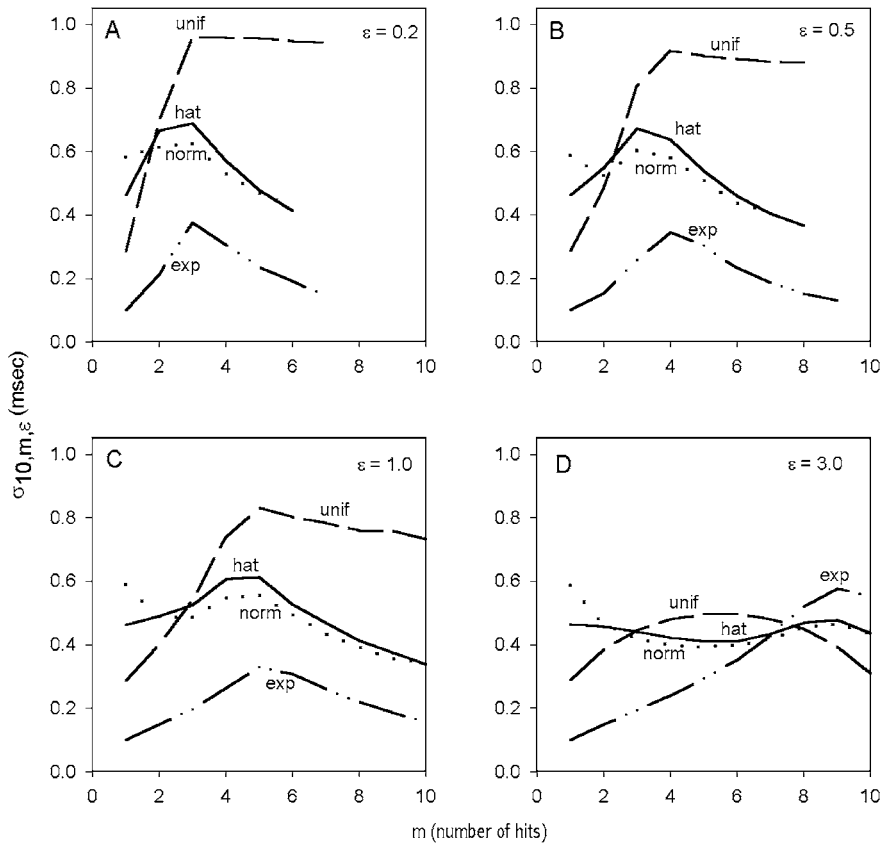

Figure 8.   Behavior of $\sigma_{n,m,\epsilon}$ as a function of m. Panels A through D show the graphs of $\sigma_{10,m,\epsilon}$ as a function of m for the choices $\epsilon = 0.2$, $\epsilon = 0.5$, $\epsilon = 1.0$, $\epsilon = 3.0$ msec, respectively. In each panel, the graphs show $\sigma_{10,m,\epsilon}$ for the four choices of incoming density $f(t)$, uniform, exponential, hat, and normal.

exponential is peaked. If m is increased the likely time of the mth hit in the 0.2 msec window will be later and thus will occur on a somewhat flatter part of the exponential density. This is why $\sigma_{10,m,0.2}$ increases to 0.37 when $m = 3$. However, when m increases still further, $\sigma_{10,m,0.2}$ decreases because if *many* hits are required to be almost coincident in order for the target cell to fire, they will likely occur earlier (i.e. nearer the peak) in the exponential. The reason the coincidence is likely to occur earlier is that for a given size of the time window there is more probability, p, for each hit to occur within the time window if it occurs earlier. The probability of m hits in the time window will involve the mth power of p and will be very small if p is very small and m is large. Note that even in the "worst" case, $m = 3$, there is an almost 3-fold increase in accuracy of time of firing compared to the standard deviation $\sigma = 1$ msec of f.

In the case when f is the uniform density, $\sigma_{10,m,0.2}$ is 0.28 msec when $m = 1$ and increases to 0.96 msec when $m = 3$. If only one hit is required, then we are in the case of order statistics for the uniform distribution and (by formula (3)) $\sigma_{10,1,0.2} = \sigma_{10,1,\infty} = 0.28$ msec (as shown in Fig. 6). If two hits are required, there is only a small chance that the earliest two will be within 0.2 msec, i.e. that the target cell fires at second hit. If there are two hits within 0.2 msec, it may be the 5th and 6th or 9th and 10th, so the time of occurence of such a pair will likely be spread out over the interval of the uniform distribution. Thus we would expect that $\sigma_{10,m,0.2}$ will increase dramatically as m goes from 1 to 2, and it does. For m large we expect the time of coincidence to be almost uniformly distributed on the interval and therefore the standard deviation should be almost 1 msec, as seen in Fig. 8A for $m \geq 3$.

As discussed in Section 2.2, first hit gives less accuracy for the time of firing of the target cell if f is the hat or normal distribution than if f is exponential or uniform. As m increases to 3, $\sigma_{10,m,0.2}$ increases somewhat for both the hat and normal, and then decreases for larger m. Notice that $\sigma_{10,m,0.2}$ changes much less as m goes from 1 to 10 for the hat and the normal than for the uniform or exponential distributions.

If the size of the time window increases to 0.5 msec, the shapes of the $\sigma_{10,m,0.5}$ versus m curves remain the same with the following exceptions (compare Fig. 8B to Fig. 8A). The peaks of the $\sigma_{10,m,0.5}$ curves for the exponential and uniform cases have shifted from $m = 3$ to $m = 4$. Secondly, the curve for the normal density *decreases* when m goes from 1 to 2 whereas it *increases*

when $\epsilon = 0.2$ msec. Note that in both cases the magnitude of the change in $\sigma_{10,m,0.5}$ is quite small.

If the size of the time window increases to 1.0 msec (Fig. 8C), the peaks of all four curves shift to $m = 5$. Note that the curve for the normal density retains its complex form and that the curve for the uniform density is significantly lower for large m.

If the time window is large (3.0 msec compared to the standard deviation of 1.0 msec for each of the choices for f), then the $\sigma_{10,m,3}$ curves should begin to look similar to the curves for order statistics. Indeed, comparing Fig. 8D to Fig. 6, we see that the curves are already quite similar. Notice that the curve for the uniform density in Fig. 8D is nearly symmetric and the peak is considerably lower than in Fig. 8C. And, for the exponential density, the $\sigma_{10,m,3}$ curve increases rapidly up to $m = 9$, where it reaches its peak.

3. Discussion

The standard deviation, $\sigma_{n,m,\epsilon}$, of the time of firing of the target neuron depends on the shape of the probability density, $f(t)$, for the time of firing of the input neurons, the number of hits required, m, the size of the time window, ϵ, and the number of incoming fibers, n. We shall discuss in this order the effects of these variables and the main unexpected findings of this study.

To what extent does the improvement in timing accuracy depend on the shape of the probability density, f, of the time of firing of the input neurons? We examined four different incoming densities, each with standard deviation 1.0 msec. As shown in Fig. 5 through 8, there are major differences in the degree of improvement in the accuracy of firing of the target cell depending on the shape of f. In most cases (i.e. for most values of the other parameters), the exponential distribution yields the largest improvement in standard deviation and the uniform distribution yields the smallest improvement. The improvement if f is exponential is substantial, with σ decreasing from 1.0 msec to as little as 0.1 or 0.2 msec in many cases. On the other hand, the improvement tends to be substantially less if f is uniform. Note, however, that if the time window is large (Figs. 6, 8D) and m is high, then the uniform may actually give more improvement in accuracy than the exponential. The hat and the normal densities are so similar that it is difficult to distinguish between their graphs (Fig. 2). Nevertheless, their differences (i.e. the hat density is pointed and the normal has non-zero probability out to infinity) have significant effects in some cases on the

improvement of accuracy. When $m = 1$ the hat always gives more accuracy than the normal no matter what the time window (Fig. 8) because first hit for the normal is more variable since the tail of the normal extends to $-\infty$.

Does accuracy improve if one requires more hits in a small time window? Not necessarily! Consider Fig. 8A which shows the graphs $\sigma_{10,m,0.2}$ as a function of the numbers of hits m for the four choices of f. In all cases the accuracy of firing of the target cell gets substantially worse as m increases from 1 to 2 to 3. The accuracy improves as m gets larger, except for the uniform distribution where the accuracy remains low (i.e. σ near 1 msec). Similar phenomena can be seen for other time windows in Fig. 8B–D. If $\epsilon = 1.0$ msec, the accuracy gets worse as m increases in the range $m = 1$ to $m = 5$. For a large time window, $\epsilon = 3.0$ msec, the accuracy gets worse over the entire range $m = 1$ to $m = 9$ if f is exponential.

Does accuracy improve if one requires the same number of hits but in a smaller time window? Not necessarily! In Fig. 7B ($n = 10, m = 2$), it can be seen that accuracy of the time of firing of the target neuron gets worse as ϵ gets smaller over the whole range of ϵ for all four choices of the density, f. For other choices of n and m the situation is more complicated: accuracy may improve or worsen as ϵ is decreased, depending on the range of ϵ considered, the values of n and m, and the choice of f.

As indicated in Sections 2.1 and 2.2 of the Results Section, the limiting cases $\sigma_{n,m,0}$ and $\sigma_{n,m,\infty}$ are easier to handle analytically than the intermediate cases $0 < \epsilon < \infty$. Since we expect $\sigma_{n,m,\epsilon}$ to be close $\sigma_{n,m,0}$ for ϵ small and close to $\sigma_{n,m,\infty}$ for ϵ large, perhaps only these two limiting cases need be considered. Unfortunately, the standard deviation under repeated trials (s) in auditory nerve fibers in approximately 1 msec and typical integration times (ϵ) for auditory brainstem cells are roughly 1 msec. So, the "time window" is about the same order of magnitude as the standard deviation in the incoming signals. Thus, there are good physiological reasons, at least in the auditory system, to consider the behavior of $\sigma_{n,m,\epsilon}$ over the whole range of ϵ.

For simplicity, we have only examined the case $n = 10$ in this paper (except for one graph, Fig. 7A). Nevertheless, it is clear that the dependence of $\sigma_{n,m,\epsilon}$ on n is important. Note the large difference between Fig. 7A and Fig. 7B when n is increased from 4 to 10. Note also the differences between Fig. 7A and Fig. 7C

which show that the behavior of $\sigma_{n,m,\epsilon}$ does not depend only on the ratio of m to n. In the simple case where f is exponential and the target cell fires at first hit ($m = 1$), then $\sigma_{n,1,\epsilon} = \frac{1}{n}$, a fact used by Young et al. (1988) to explain the improved accuracy of firing in cochlear nucleus bushy cells. The behavior of $\sigma_{n,m,\epsilon}$ as a function of n in more complicated situations will be the subject of future work.

Marsalek et al. (1997) examined the relationship between the standard deviation of the timing of synaptic inputs to a neuron and the standard deviation (which they term "jitter") of the timing of its spike output in several special cases. First they consider an integrate and fire (I&F) model where each incoming spike adds a fixed voltage to the target cell, which fires when a threshold voltage is reached. This is just the case of order statistics considered in Section 2.2 where m is the number of inputs required to achieve threshold (our m is their nth). They showed that if the input density is normal and $n = m$, then increasing n lowers σ. They also compute explicitly a formula for σ as a function of n and m in the case where the input density is uniform and derive formula (7) in that case. They then added leakage to the I&F model (making explicit calculations impossible) and their computer simulations, again assuming a normal initial density, showed for a physiologically reasonable time constant $\tau = 10$ msec that marked improvements in σ were possible. Leakage in their model is roughly equivalent to a finite time window, ϵ, in our model because as the leakage gets faster the input spikes must arrive within a shorter time period to fire the target cell for any given threshold. Thus, our results in Section 2.3 show how the standard error of the output depends in a complicated and interesting way on the size of ϵ (on the size of τ, intuitively). We also show the detailed behavior of $\sigma_{n,m,\epsilon}$ as a function of m (Section 2.4) and the dependence on the nature of input probability density.

Marsalek et al. (1997) also considered an explicit non-linear somatic membrane model with a large number of voltage dependent ion conductances. They found that for reasonable parameter ranges σ can be less than the input standard deviation and that the results were similar to their results for the I&F and the leaky I&F models. This supports our contention in the Introduction that the combinatorial and probabilistic calculations in this study reveal phenomena that will also occur in neural models with more biophysically realistic membrane properties. There is experimental evidence that hippocampal neurons use feed-forward

inhibition to create time-windowed firing rules (Pouille and Scanziani, 2001). Further studies are required to ascertain the quantitative differences between time-windowed models, leaky I&F models, and fully non-linear models, in the improvement of the accuracy of time of firing of the target cell.

In conclusion, we would like to make two points. First, the variation in latency under repeated trials that we use as input in this model arises in actuality from the geometry of synapse placement on dendrites of different shapes and sizes and variability in the underlying biophysical processes. Recent theoretical (Agmon-Snir et al., 1998; Segev and London, 2000; Cai et al., 2000) and experimental (Stuart et al., 1999; Oertel, 1999; Oertel et al., 2000) studies address the issue of coincidence detection as a function of dendrite structure, synaptic distributions, and channel properties. The effect on coincidence detection of other kinds of stochastic variability (e.g. variable placement of a synapse on a dendrite) arise in these contexts. Determining the way in which such variability affects function is a fundamental tool for understanding the relationship between structure and function in the nervous system.

Second, the complexity of the behavior that we have found (e.g. the non-monotone nature of many of the $\sigma_{n,m,\epsilon}$, curves) suggests that determining the relationship between structure and function in the nervous system may be very difficult. In our case, "function" means enhancing the accuracy of time of firing. "Structure" means the amount of convergence, n, and the firing rule (m and ϵ) at the target cell. Since the $\sigma_{n,m,\epsilon}$, curves are often non-monotone, there are many different possible evolutionary choices for improving the function of the system (i.e. the accuracy of the time of firing of the target cell). In some circumstances, one could get improvement either by increasing or by decreasing m. Similarly, one could get improvement either by increasing or by decreasing ϵ. This makes it difficult to understand the relationship between the structure on one hand and the function on the other hand, even for this simple system.

Acknowledgments

References

Abeles M (1991) Corticonics: Neural Circuits of the Cerebral Cortex. Cambridge University Press, Cambridge, UK.

Agmon-Snir H, Carr CE, Rinzel J (1998) The role of dendrites in auditory coincidence detection. Nature 393: 268–272.

Arnold B, Balakrishnan N, Nagaraja H (1993) A First Course in Order Statistics. John Wiley & Sons, New York.

Balakrishnan N, Rao C (1998a) Handbook of Statistics 16, Order Statistics: Theory and Methods. Elsevier Press, New York.

Balakrishnan N, Rao C (1998b) Handbook of Statistics 17, Order Statistics: Applications. Elsevier Press, New York.

Cai Y, McGee J, Walsh EJ (2000) Contributions of ion conductances to the onset responses of octopus cells in the ventral cochlear nucleus: Simulation result. J. Neurophysiol. 83: 301–314.

Colburn HS, Han Y, Culotta CP (1990) Coincidence model of MSO responses. Hear. Res. 49: 335–346.

Covey E, Casseday JH (1991) The monaural nuclei of the lateral lemniscus of an echolocating bat: Parallel pathways for analyzing temporal features of sound. J. Neurosci. 11: 3456–3470.

Covey E, Casseday JH (1995) The lower brainstem auditory pathways. In: A. Popper, R. Fay, eds., Hearing by Bats. Springer-Verlag, New York. pp. 235–295.

Diesmann M, Gewaltig M-O, Aertsen Ad (1999) Stable propagation of synchronous spiking in cortical neural networks. Nature 402: 529–533.

Diesmann M, Gewaltig M-O, Rotter S, Aertsen Ad (2001) State space analysis of synchronous spiking in cortical neural networks. Neurocomputing 38–40: 565–571.

Gewaltig M-O, Diesmann M, Aertsen Ad (2001) Cortical synfire-activity: Configuration space and survival probability. Neurocomputing 38–40: 621–626.

Heil P, Irvine DRF (1997) First-spike of auditory-nerve fibers and comparison with auditory cortex. J. Neurophysiol. 78: 2438–2454.

Irvine DRF (1986) The Auditory Brainstem. Springer-Verlag, New York.

Ivry R (1997) Cerebellar timing systems. Internat. Rev. Neurobiol. 41: 555–573.

Jeffress LA (1948) A place theory of sound localization. J. Comp. Psychol. 41: 35–39.

Klug A, Kahn A, Burger RM, Bauer EE, Hurley LM, Yang L, Grothe B, Halvorsen MB, Park TJ (2000) Latency as a function of intensity in auditory neurons: Influences of central processing. Hearing Res. 148: 107–123.

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

Marsalek P, Koch C, Maunsell J (1997) On the relationship between synaptic input and spike output jitter in individual neurons. PNAS 94: 735–740.

Matell MS, Meck WH (2000) Neurophysiological mechanisms of interval timing behavior. BioEssays 22: 94–103.

Mitchell C (2003) Mathematical properties of time windowing in neural systems. Duke University thesis.

Oertel D (1999) The role of timing in the brainstem nuclei of vertebrates. Annu. Rev. Physiol. 61: 497–519.

Oertel D, Bal R, Gardner S, Smith P, Joris P (2000) Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus. Proc. Natl. Acad. Sci. 97: 11773–11779.

Pollak GD (1993) Some comments on the proposed perception of phase and nanosecond time disparities by echolocating bats. J. Comp. Physiol. A 172: 523–531.

Pouille F, Scanziani M (2001) Enforcement of temporal fidelity by somatic feed-forward inhibition. Science 293: 1159–1163.

Rhode W, Smith P (1986) Encoding time and intensity in the ventral cochlear nucleus of the cat. J. Neurophysiol. 56: 261–286.

Riehle A, Grun S, Diesmann M, Gewaltig M-O, Aertsen Ad (1997) Spike synchronization and rate modulation differentially involved in motor cortical function. Science 278: 1950–1953.

Segev I, London M (2000) Untangling dendrites with quantitative models. Science 290: 744–750.

Simmons JA, Ferragamo M, Moss CF, Stevenson SB, Altes RA (1990) Discrimination of jittered sonar echoes by the echolocating bat, *Eptesicus fuscus*: The shape of target images in echolocation. J. Comp. Physiol. A 167: 589–616.

Softky W (1994) Sub-millesecond coincidence detection in active dendritic trees. Neuroscience 58: 13–41.

Stuart G, Spruston N, Hauser S (1999) Dendrites. Oxford Univ. Press.

Young E, Robert J-M, Shofner W (1988) Regularity and latency of units in ventral cochlear nucleus: Implications for unit classification and generation of response properties. J. Neurophysiol. 60: 1–28.