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Consequences of stochastic release of neurotransmitters for network computation in the central nervous system

(synaptic noise/quanta/postsynaptic inhibition/neural networks/computational "temperature")

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ABSTRACT **Neuronal membrane potentials vary continuously due largely to background synaptic noise produced by ongoing discharges in their presynaptic afferents and shaped by probabilistic factors of transmitter release. We investigated how the random activity of an identified population of interneurons with known release properties influences the performance of central cells. In stochastic models such as thermodynamic ones, the probabilistic input–output function of a formal neuron is sigmoid, having its maximal slope inversely related to a variable called "temperature." Our results indicate that, for a biological neuron, the probability that given excitatory input signals reach threshold is also sigmoid, allowing definition of a temperature that is proportional to the mean number of quanta comprising noise and can be modified by activity in the presynaptic network, a notion which could be included in neural models. By introducing uncertainty to the input–output relation of central neurons, synaptic noise could be a critical determinant of neuronal computational systems, allowing assemblies of cells to undergo continuous transitions between states.**

A major characteristic of the nervous system is its probabilistic nature, which introduces a large degree of uncertainty at the level of its connectivity and functions. This feature has hampered attempts to model higher brain functions, but it can also be taken as allowing a large degree of operational freedom—for example, in the context of a "selectionist" perspective (references in ref. 1). Among sources of randomness, the transmission of signals between neurons is an important one, and it has two origins. The first is structural: "synaptic connections" (2) encompass different numbers of active zones, or release sites. The second is functional: synaptic transmitter release is stochastic, so that postsynaptic potentials are made of a fluctuating number of basic units or quanta (3). In most structures, these two components of synaptic strength have not been assessed directly.

In mathematical neural networks (4) the introduction of stochastic input–output functions (5, 6) improved circuit performance, especially in "thermodynamic" models, where a formal parameter called "temperature" represents "noise" (7–10). This factor determines the range of uncertainty influencing whether a given excitatory input reaches the threshold for an all-or-none output. We asked if a similar function could be served in a real neuron by synaptic noise and if there is a mechanism for controlling the degree of this randomness.

Activation of the teleost Mauthner (M) cell requires overcoming a strong background inhibition (11, 12). In this neuron, a particular set of binomial parameters, n and p, describes adequately the release properties of a given individual presynaptic interneuron; they correspond to the number of release sites issued by this afferent fiber and to the chance that, after a spike, each of these sites undergoes exocytosis (13, 14). Synaptic noise is also quantal: "spontaneous" inhibitory postsynaptic potentials occur in discrete steps of the same size, q (15). It thus becomes a predictable sum of individual binomial release functions, each characterizing one presynaptic neuron, and reflecting its state of activity (16). This property was used to determine the ability of noise to prevent the M cell from being activated by various excitatory inputs.

MATERIAL AND METHODS

For a stimulation rate of 1 Hz, each of 42 previously investigated cells was characterized by one set of optimal parameters (2, 14) ranging from 0.17 to 0.74 and from 3 to 52 for p and n, respectively. Then, population histograms of quanta were computer-modeled by summing the individual binomial functions according to the relationship

$$P(x) = \frac{1}{N}\sum_{i=1}^{N}\binom{N_i}{x}p_i^{x}(1-p_i)^{N_i-x}, \qquad [1]$$

where $P(x)$ is the mean probability of quanta in the M cell, $N = 42$, N_i is the number of active zones of a given cell, and p_i is the cell's mean probability of release per site, q being treated as constant (15). In this equation, N inputs are independent and quanta add linearly, as shown by physiology. Such a population histogram is illustrated in Fig. 1*A*. However, there may be different rates of presynaptic activity. When afferent cells increase their firing rate, an exponential decrease in p solely accounts for the reduction of inhibitory potentials in the M cell (17). Thus all values of p_i were replaced by $p_i(f)$ in Eq. **1**. The resulting distributions, shown in Fig. 1 *B–D*, illustrate the effect of this scaling. They correspond to the range determined experimentally (15) when extracting quanta (Fig. 1*E*) from real synaptic noise: as f increases, the mean number of quanta (n_i) is shifted to the left.

To evaluate the effectiveness of the inhibitory noise vis-à-vis excitatory signals the latter were set at various values corresponding to n_eq_e (n_e and q_e, number and size of excitatory quanta), all above threshold for firing a spike in the absence of inhibition. For simplicity, $n_e = 0$ at threshold. Inhibitory noise reduces the probability of output whenever n_iq_i exceeds n_eq_e, and if we assume that $q_i = q_e$, the probability of output is

$$P(1) = 1 - p_O\cdot\int_{n_e}^{\infty} p(x_i)dx_i, \qquad [2]$$

where x_i is the probability density function of inhibitory quanta. Their probability of occurrence, p_O, was set at 0.5,

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Abbreviation: M cell, Mauthner cell.

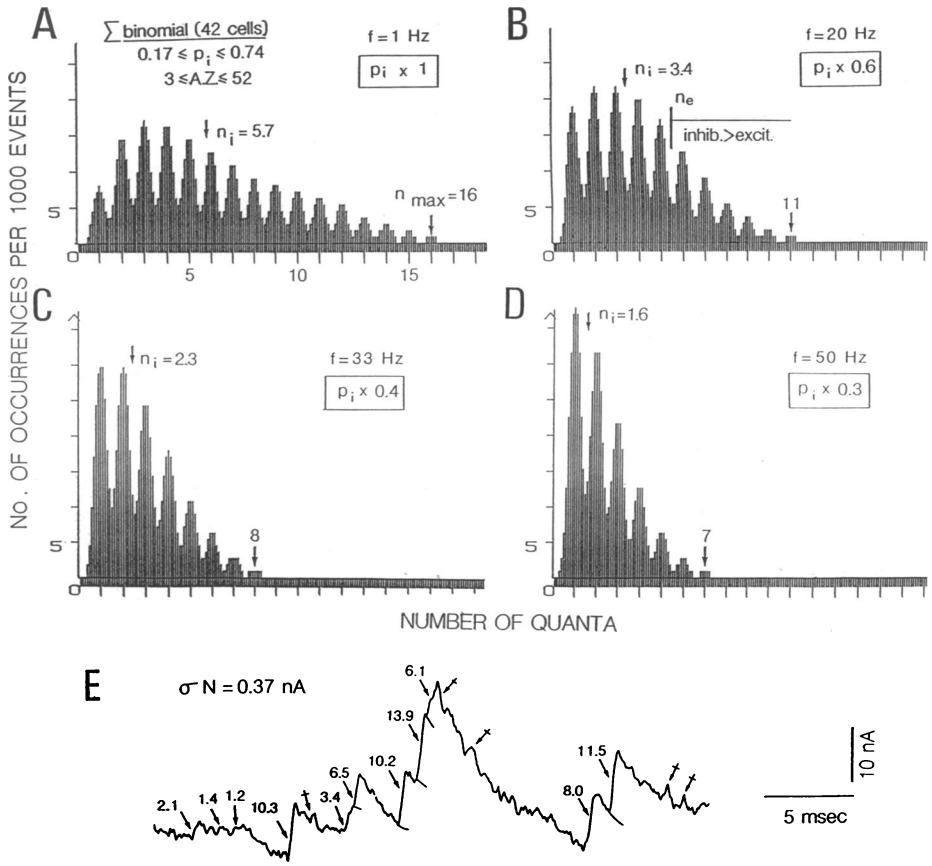

FIG. 1. Distribution of quanta issued by a population of inhibitory interneurons as a function of firing rate. (*A–D*) Computer-determined histograms of 1000 predicted responses obtained by adding binomial curves of 42 cells [each of which represents the best fit of the probability density function of fluctuating inhibitory postsynaptic potentials (IPSPs) recorded in the M cell after stimulation of this interneuron]. A.Z. is the number of active zones established on the M cell by each interneuron. p_i was weighted, as indicated in the boxes in the figure, for stimulus rates increased from 1 Hz (*A*) to 20 Hz (*B*), 33 Hz (*C*), and 50 Hz (*D*). Note that the mean number of inhibitory quanta (n_i) is progressively shifted to the left. These predicted population histograms were used to determine the probability that the number of inhibitory quanta (horizontal bar in *B*) was greater than a given number of excitatory quanta (n_e). The Gaussian variability around each peak ($\sigma = 0.24q$) is mainly due to instrumental noise. (*E*) Sample trace of synaptic noise obtained in conditions in which excitatory inputs were silent (single-electrode voltage-clamp record; inhibitory currents are outward because the M cell was loaded with Cl^-). Individual inhibitory components produced by activities in presynaptic interneurons are indicated by arrows, and their amplitudes are expressed in quanta (crossed arrows indicate possible responses rejected because of uncertainties about their baseline or shape index). The histogram of individual currents recorded during this experiment was similar to that shown in *D*, and the activity in presynaptic neurons was greater than 50 Hz.

since it was postulated that excitatory and inhibitory quanta had equal chances to occur.

RESULTS

Stochastic Transfer of Information in a Real Neuron: Determination of a Physical Correlate of Temperature. A simple situation is when the excitatory input occurs in synchrony with a specific inhibitory event as schematized in Fig. 2*A*: monosynaptic excitatory afferents (11) also inhibit the M cell via interneurons. Thus, a given excitatory signal was successively paired with the activation of each characterized inhibitory cell. The probability of output of the M cell, $P(1)$, at different firing frequencies of the network is then defined by a family of curves (Fig. 2*C*, solid lines) resembling those obtained for various values of the theoretical temperature T (Fig. 2*B*), where

$$P(1) = 1/(1 + e^{-\Delta E/T}). \quad [3]$$

In confirmation, best fits of the curves, using this equation (broken lines) and replacing ΔE, the variation of the computational energy (7), by n_e, allowed definition of a temperature that progressively increases the effectiveness of inhibitory noise as this parameter increases. The relationship between the mean number of inhibitory quanta, n_i, and the computed temperature is linear, according to $T = kn_i$, where $k = 0.64$.

Thus temperature and n_i have essentially similar roles and the logistic functions pertaining to formal (Fig. 2*B*) and more "real" (Fig. 2*C*) neurons would be equivalent, with the resulting form

$$P(1) = 1/(1 + e^{-n_e/kn_i}). \quad [4]$$

Introduction of the Time Dimensions: Conditions for an Effective Inhibitory Noise. In most physiological states, (*i*) the number of active interneurons can vary and (*ii*) the afferent signal is asynchronous with the inhibitory inputs and occurs even during noise-free periods, particularly at moderate firing rates. This time dimension was added to the model by expressing the fraction of time occupied by inhibitory noise as the product $Nf\tau$; these parameters stand, respectively, for the number of cells activated, their firing rate (in Hz), and the relative duration of quanta, taken here as equal steps of 6 msec [the mean life-time of Cl^- channels opened by quanta in the M cell (18)]. Two extreme states of the network, low and high frequencies of presynaptic firing, were compared. At 1 Hz or less, noise does not alter the coefficient of

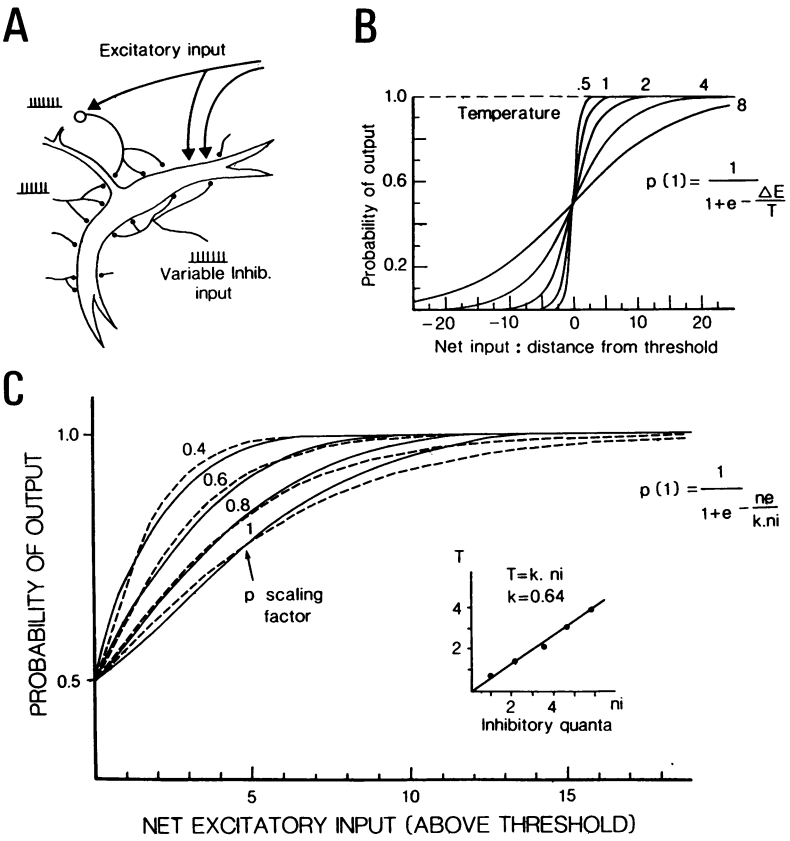

FIG. 2. Equivalence between the average number of inhibitory quanta and "temperature" of thermodynamic models. (*A*) Diagram of afferent connections of the M cell. Trains of spikes illustrate random activities which generate synaptic noise. (*B*) Probability of attaining threshold of output (ordinate) for different values ΔE of excitatory inputs (abscissa) in a Gibbs–Boltzmann model. The different logistic curves obtained by using the included equation indicate that, for a given value of input, uncertainty to reach threshold increases for progressively larger values of a parameter T called temperature (modified from ref. 4). (*C*) Effect of inhibitory noise on transmission of excitatory signals. Solid lines, computer-determined probability to reach threshold (ordinate) as a function of the net number of excitatory quanta in the signal (abscissa). Each curve was calculated by using the population distributions of Fig. 1. Broken lines, best fits obtained by assuming logistic functions as in *B*, which yielded values of 1.4, 2.2, 3.0, and 3.9, respectively, for the parameter T. (*Inset*) Linear relationship between temperature (ordinate) and the mean number of inhibitory quanta (abscissa). This relationship allows computation of the probability to reach threshold by replacing energy and temperature in the equation of *B* with the average number of excitatory (n_e) and inhibitory (n_i) quanta, respectively.

transmission unless a large population of interneurons (at least 150 cells) generates a continuous bombardment in the target M cell. In contrast, at 50 Hz, four to six interneurons are sufficient to affect the output.

Noise recorded in central cells is even more complex, as responses often overlap (Fig. 1*E*). The distribution, *Pk*, of quanta in multiple events is then equated with the convolution product of as many histograms $P(x)$ as the number (k) of simultaneously active presynaptic cells. Fig. 3*A*, obtained in this manner, indicates that overlap increases temperature, because the population histogram shifts to the right. In fact, about 33% of "real" noise is closely spaced responses at high frequencies (15), a case represented in Fig. 3*B*, which shows that this ratio can be simulated with as few as four interneurons. In other words, with this approach, one can infer how many cells are necessary to produce a particular input–output function, given knowledge of input firing rates.

Predictive Aspects of a Model Incorporating Stochastic Aspects of Release. To sum up, the distribution P of quanta results from the combination of (*i*) a convolution product, *Pk*, for the amplitude of multiple responses, where k is the number of coactive cells, and (*ii*) the probability that k cells fire in unison, computed by using a Poisson law $P_N(k) = e^{-\mu}\cdot\mu^k/k!$ (where μ is $Nf\tau$). Therefore,

$$P(x) = \sum_{k=1}^{N} P_N(k)\cdot Pk(x). \qquad [5]$$

The mean of this product, $n_i(Nf\tau)$, is more easily derived and is instrumental for predicting how the state of the presynaptic network shapes noise. It allows definition of a more accurate temperature term, T_a, which is the product of T_s (i.e., synchronous, standing for the effect of individual inhibitory events arriving at the time of the excitatory input) and $Nf\tau$. The ratio T_a/T_s increases as the number of active cells becomes larger, and this relation becomes steeper as their firing rate increases (Fig. 3*C*).

The net value of T_a, which corresponds to a synaptic noise close to that recorded in the M cell, combines (Fig. 3*D*) two opposing effects as f increases (as seen above), that is (*i*) the reduction of n_i and (*ii*) the increase of multiple responses with f (see Fig. 3*C*), an association leading to

$$T_a = Cfn_i(f), \qquad [6]$$

where the parameter $C = kN\tau$ depends upon the number of active cells. T_a increases with f but tends to saturate as the firing rate reaches high values, a phenomenon related to intrinsic release properties.

Generalization of the Model to Excitatory Noise. Excitation, in addition to being synchronized as modeled here, can contribute to noise. Since release at excitatory inputs is also probabilistic and quantal (see ref. 19), the complete shape of the input–output function of the M cell is most likely similar to that of Fig. 2*B*. We assumed quantal excitatory conductances equalled inhibitory ones. If they were smaller (see ref. 20), the constant k would be larger and replaced in Eq. 4 by $K = kq_i/q_e$. Also, the two halves of the probability curves would be asymmetric (it can be noted that n_eq_e replaces ΔE, which thus also finds a physical location at the junctional level). Finally, the probability of output of a real neuron can be generalized as

$$P(1) = 1/(1 + e^{-n_e/K\bar{n}}), \qquad [7]$$

with $\bar{n}$ being the mean number of excitatory or inhibitory quanta if one of them dominates. When they overlap, the computation of temperature remains essentially the same, but K is multiplied by a factor α depending upon the ratio of excitatory and inhibitory events at any time (for example, $\alpha = \sqrt{2}$ when their distributions are similar). In general, excitatory noise tends to boost weak signals and thus might be the major determinant of the left side of the logistic curve: biological "temperature" would have two components, orig-

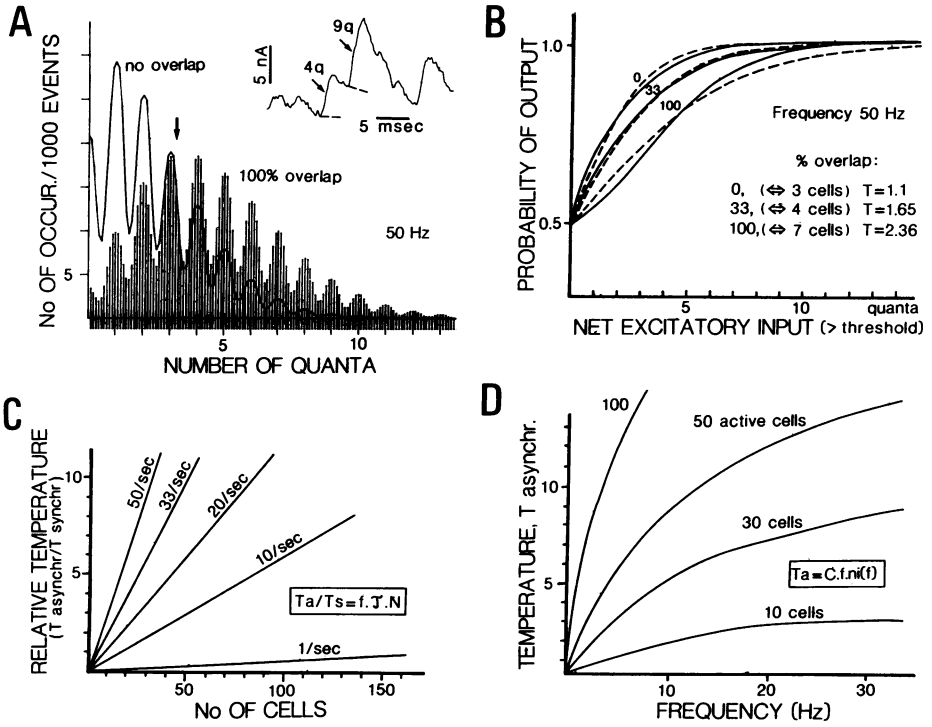

FIG. 3. Variation of temperature when activity increases in the inhibitory network. (*A* and *B*) Effect of the overlap of two responses. (*A*) Comparison of the distributions of quanta when synaptic noise includes only simple (solid curve representing the envelope of Fig. 1*D*) and double (histogram) responses (firing rate: 50 Hz). The distribution of double responses was computed by the convolution product $P_2(a + b = k) = \Sigma_{t=1}^{k} P_1(a = k - t) \cdot P_1(b = t)$. (*Inset*) Sample recording showing two components (arrows) including four and nine quanta, riding on top of each other. (*B*) Probability of reaching threshold obtained by using the distribution of *A*, as a function of the excitatory input, for the indicated proportions of doublets (solid lines), and best fits with logistic curves (broken lines), illustrating the associated increase of temperature. Symbol ⇔ stands for equivalent to. (*C* and *D*) Increase of temperature by multiple overlaps of responses. (*C*) Variations of the number of activated interneurons *N* (abscissa) for different frequencies (*f*) of discharge in the inhibitory network versus relative temperature (ordinate) defined as the ratio between asynchronous (T_a) and synchronous (T_s) temperatures (see text). (*D*) Relation between asynchronous temperature (ordinate) and frequency of presynaptic firing (abscissa) for various pools of interneurons. Note that the asynchronous temperature can be computed as shown in the figure (box), using a parameter $C = kN\tau$ which depends upon the number of active cells (symbols defined in text).

inating at separate classes of synapses, a refinement allowing more flexibility than in present theories.

DISCUSSION

Our results indicate that stochastic synaptic noise determines the uncertainty of the input–output relation in the M cell, which is typical of central neurons (discussed in ref. 11), according to a function similar to that used in thermodynamic models (10). "Temperature" therefore finds a physical substrate solely represented, *in the right half of Fig. 2*B, by the mean number of inhibitory quanta building up noise, and it is enhanced when the number of active cells and/or their individual firing rates are increased. An extension of these laws to excitatory noise can be considered.

In formal networks, each input is weighted by deterministic coefficients which at most vary according to Hebbian rules (21), a restriction that does not reflect the full repertoire of synaptic plasticity. Along this line, simple binomial predictions imply that *p* is the same at all terminals of a given neuron. But the mean of the distributions of quanta composing noise would be the same if this were not the case (22) because the quantal content *np* of each cell would still correspond to the mean of the simple binomial which best fits the histogram of the evoked responses (19).

It has been recognized that noise, whatever its physical meaning, can improve the performance of neuronal networks (8, 23–27) and the concept of temperature has been applied to characterize this term in various neural models (23, 28, 29). This noise was related to fluctuations of membrane potential in real neurons in some studies (25, 30, 31), but considerations about its origin were only inferential. For instance, it has often been taken as Gaussian (27, 32), as an extreme case of Poisson distributions (33), or with large variances (25, 30, 31), partly due to observations at pharmacologically treated neuromuscular junctions. In real neurons, it is a composite of binomial functions and is under the control of the presynaptic network. Relevant synaptic factors are therefore (*i*) the average quantal content of the population (which in this series was 5.75 ± 3.38 at 1 Hz) and (*ii*) the probabilistic all-or-none mode of transmitter release, which guarantees a wide spectrum of inhibitory events.

During computations by formal models, temperature is modified *a priori* to control the uncertainty of output. It is remarkable that in the nervous system, this process can be guaranteed by the architecture of the presynaptic circuit (34), by its pattern of activation, and by intrinsic regulation of *p* producing a depression or a facilitation (19) of background noise. Also, the inhibitory network has physiological and structural constraints limiting its range of efficacy. For example, the M-cell inhibitory circuitry includes about 150 cells (11), which sets an upper limit for meaningful computations of the equations above. The distribution of inhibitory quanta would be Gaussian if a large population of cells were coactive, as postulated by the central limit theorem, a situation achieved only when the collateral network is synchronized during recurrent collateral inhibition (11, 12), which cuts off excitation with absolute certainty. It can be noted that even in extreme cases a sigmoid (or Fermi–Dirac) distribution is an excellent approximation of a cumulative

Gaussian (9). Yet the binomial aspect of release should be preferred, given its synaptic meaning.

Synaptic noise is often considered as a contaminant of biological signals, so that the notion that it may be of functional importance for the nervous system is often disregarded. As demonstrated by models (27, 35), it helps a network to associatively store and memorize even weak inputs which would otherwise be lost. More generally, stochasticity guarantees that the diversity of states accessible to a given assembly is explored, as postulated in a generalized theory of learning (1, 36, 37). This capacity raises the question of its status in the processing and learning of information by the nervous system.

Noise from various sources, including intrinsic oscillators, is always present in central cells. Several propositions can be advanced. First, since the number of quanta in it is proportional to structural factors, there must be limitations to its variability due to (*i*) the degree of innervation relating a presynaptic cell to its target, which is set during epigenesis (references cited in ref. 1) and may be controlled after maturation; one example may be an inverse relation between p and the number of active zones so that the product np varies within a well-defined domain (17) and (*ii*) the range of firing of the presynaptic network. Second, in a central neuron such as the M cell, which triggers a vital escape reaction (11), noise must vary discontinuously to adjust the criteria for selecting, at any time, stimuli which among many may be relevant for an appropriate response. Its fluctuations leave a certain degree of freedom to this choice. If an external input is strong, the resulting behavior is stereotyped—i.e., the cell fires a spike. If not, stochastic factors dominate and the discharge of the cell remains probabilistic, a behavior which also may be adaptive for survival.

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