Neural Coding with Graded Membrane Potential Changes and Spikes

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Abstract. The neural encoding of sensory stimuli is usually investigated for spike responses, although many neurons are known to convey information by graded membrane potential changes. We compare by model simulations how well different dynamical stimuli can be discriminated on the basis of spiking or graded responses. Although a continuously varying membrane potential contains more information than binary spike trains, we find situations where different stimuli can be better discriminated on the basis of spike responses than on the basis of graded responses. Spikes can be superior to graded membrane potential fluctuations if spikes sharpen the temporal structure of neuronal responses by amplifying fast transients of the membrane potential. Such fast membrane potential changes can be induced deterministically by the stimulus or can be due to membrane potential noise that is influenced in its statistical properties by the stimulus. The graded response mode is superior for discrimination between stimuli on a fine time scale.

Keywords: neural code, graded membrane potential neurons, discriminability of stimuli, model, spike mechanism

1. Introduction

In many neurons the integration of hundreds or thousands of synaptic inputs leads to pronounced de- and hyperpolarizations of the membrane potential. Often these graded membrane potential fluctuations are transformed into spikes. Many studies addressed how stimuli are encoded by spike trains (reviews Rieke et al., 1997; Buračas and Albright, 1999). However, a large number of neurons do not generate spikes but transmit information by graded changes in their membrane potential and by continuous transmitter release (Fig. 1, reviews: Roberts and Bush, 1981; Morgans, 2000). Moreover, some neurons are known to transmit information with graded membrane potential fluctuations superimposed by active processes (reviews Marder and Calabrese, 1996; Warzecha and Egelhaaf, 2001). Strong graded membrane potential modulations were also found in intracellular recordings of spiking cortical neurons (e.g., Stern et al., 1997; Jagadeesh et al., 1992; Anderson et al., 2000), but it is unknown if they contribute to synaptic transmission. Local neurons that do not need to transfer information actively to pass a long distance could rely on their graded membrane potential changes for information transmission. Nevertheless, little is known about how encoding of stimuli with graded potentials compares to encoding with spikes.

Several studies that compared both response modes were done on interneurons in the visual system of the fly (Warzecha, 1994; de Ruyter van Steveninck and Laughlin, 1996; Haag and Borst, 1997, 1998; Laughlin et al., 1998; reviews: Egelhaaf and Warzecha, 1999; Warzecha and Egelhaaf, 2001). This system is well suited to compare the graded to the spiking mode of

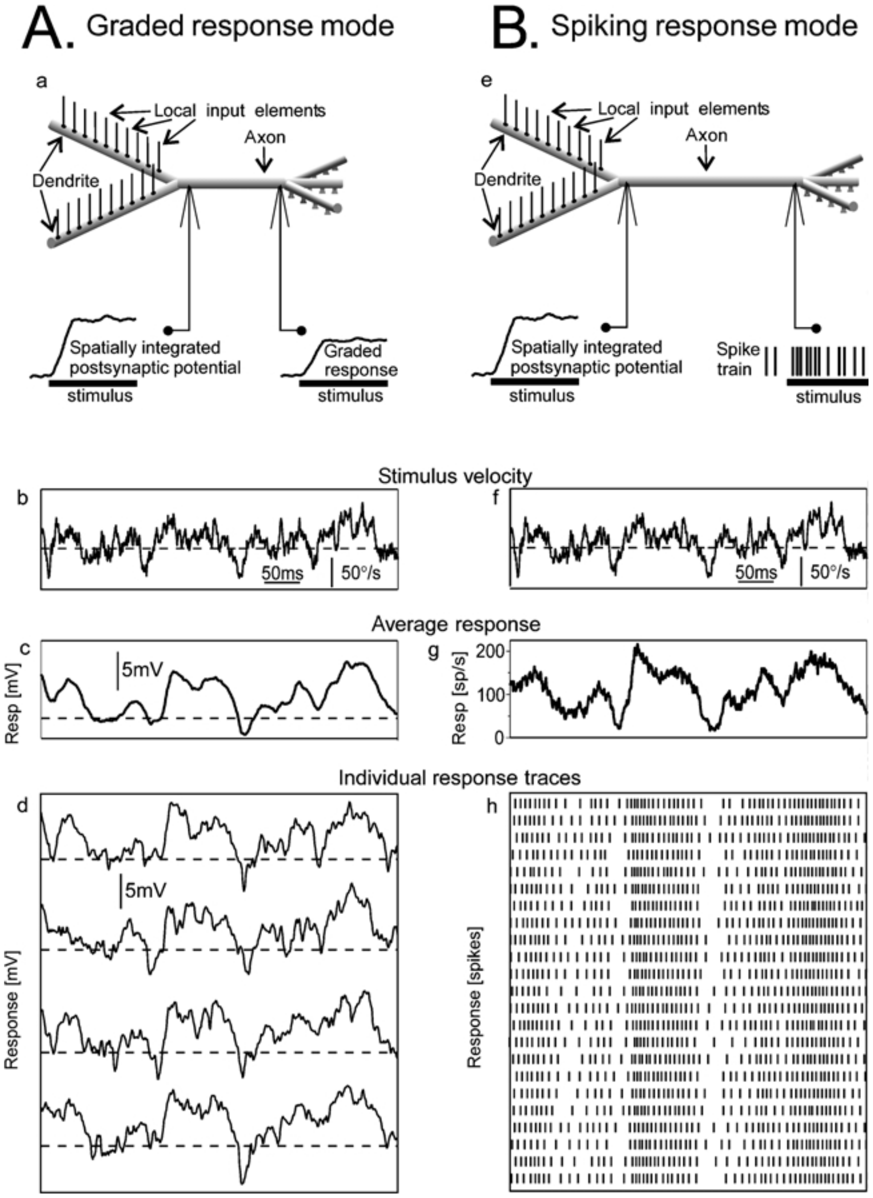

Figure 1. **Graded and spiking response mode: A:** (a) Sketch of a neuron that responds with graded membrane potential fluctuations even in its output region and (b)–(d) example for responses of a fly HS-cell responding with graded potentials to a dynamically changing motion stimulus. (b) Stimulus velocity, (c) average membrane potential, (d) examples of individual responses. **B:** (e) Sketch of a spiking neuron and (f)–(g) responses of the spiking H1-cell of the fly to the same motion stimulus as in A. (f) Stimulus velocity, (g) PSTH of spike response, (h) individual spike responses (each vertical line represents the occurrence of a spike). H1- and HS-cell have opposite preferred directions. To allow better comparison of the responses, the graded responses of the HS-cell are shown inverted. Depending on the motion stimulus the graded responses of the HS-cell sometimes are superimposed by active processes, but in this example only graded responses were recorded. For experimental methods, see Warzecha et al. (1998).

encoding stimuli because it contains neurons of either mode with similar synaptic input organization (Fig. 1 and Hausen, 1981, 1984; Egelhaaf and Warzecha, 1999). Information transmission by graded responses might be expected to be superior to that by spike responses because a continuous signal has potentially a greater capacity to transmit information than the binary signals of a spiking neuron. Nevertheless, most of the mentioned studies came to the conclusion that there is no marked difference between the information transmitted by both types of neurons. Only on a fine time-scale encoding of motion information by graded responses may be superior to the spike responses (Warzecha and Egelhaaf, 2001).

In the present study we analyzed by model simulations how well different stimuli can be discriminated on the basis of graded potential changes and spike trains, respectively and to what extend the discriminability depends on the time scale used for the analysis. The graded responses to stimuli were modeled as membrane potential fluctuations. Different stimuli elicited membrane potential fluctuations that differed with respect to their amplitude and dynamics. These membrane potential fluctuations were transformed into spike trains by a model of spike generation (Kretzberg et al., 2001). On this basis spike responses and graded responses could be compared directly. The model was fitted to reproduce experimental data from the spiking motion-sensitive H1-neuron in the fly visual system that was used in previous experimental studies for comparisons between both response modes (reviews: Egelhaaf and Warzecha, 1999; Warzecha and Egelhaaf, 2001). Although the model was adjusted to fit fly motion-sensitive neurons, the results of our simulations are not restricted to this cell type. Specifically, in this article we want to address the following questions:

- How do the amplitude and the dynamical properties of the membrane potential fluctuations influence the discriminability of different stimuli?
- How does the discriminability depend on membrane potential noise?
- On what time scale can different stimuli be discriminated best?
- Are there situations where stimuli can be better discriminated on the basis of spike responses than on the basis of graded membrane potential changes?

2. Methods

2.1. *Simulation of Responses to Different Stimuli*

The graded response to a stimulus was modeled as membrane potential fluctuations. To simulate spike responses to the same stimulus these fluctuations were transformed into spike trains. The responses to different stimuli were simulated by modifying properties of the membrane potential fluctuations. Each membrane potential trace consisted of two components.

The *deterministic component* is identical for each presentation of a given stimulus. It corresponds, for a given experimental situation, to the average membrane potential trace induced by many presentations of the same stimulus. In the present system analysis we do not take into account how the membrane potential fluctuations are caused by the stimuli. The deterministic component consisted of artificially generated fluctuations in one of four frequency bands (3.75–6.25 Hz, 15–25 Hz, 30–50 Hz, or 60–100 Hz) (see Fig. 2). These frequency bands were chosen to represent the dynamics of responses to stimuli in different sensory system that can differ considerably. For instance, in the auditory and the electrosensory system (Carr and Friedmann, 1999) responses are elicited in the high-frequency range, while in the visual motion pathway slow stimulus-induced fluctuations dominate (Haag and Borst, 1997; Warzecha et al., 1998). In our simulations the membrane potential fluctuated symmetrically around the resting level with a maximal amplitude of de- and hyperpolarizations of 10 mV. This range was found in intracellularly recorded responses of fly motion-sensitive cells (Fig. 1).

The *stochastic component* represents the membrane potential noise that differs for each membrane potential trace. The stochastic component was generated as Gaussian white noise that was filtered twice by a first-order low-pass filter with a time-constant of 1.6 ms. The noise was tuned to experimentally determined membrane potential noise of graded responding motion-sensitive neurons of the fly and had a standard deviation of 1.67 mV (Kretzberg et al., 2001).

To simulate the responses to different stimuli, the standard membrane potential traces for each frequency range (shown in Fig. 2) were compared to traces in which one of the following properties was modified:

- The deterministic membrane potential fluctuations were shifted by a constant offset. Experimentally, such a shift in the neuronal responses can be elicited—for example, in motion-sensitive neurons by superimposing a constant velocity motion to the stimulus.
- The amplitude of the deterministic membrane potential component was stretched by a constant factor. In experiments different response amplitudes are obtained with stimuli of different strength (e.g.,time-varying visual stimuli with different contrast).

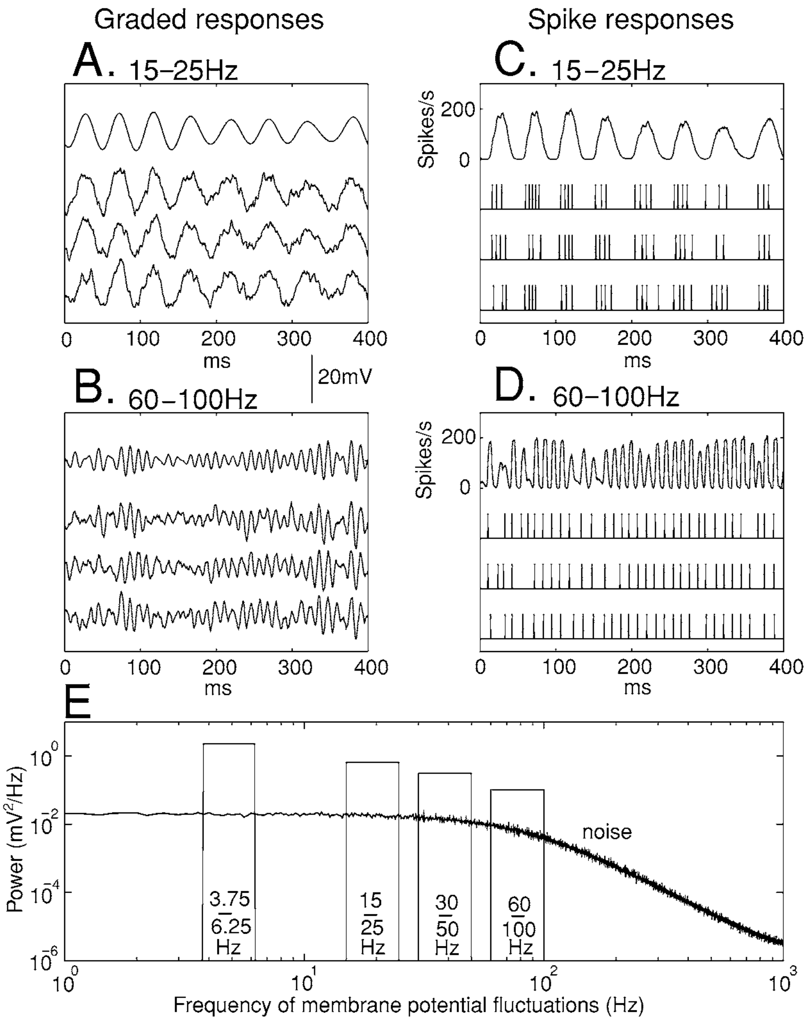

Figure 2. **Standard membrane potential traces and spike responses:** Membrane potential fluctuations in one of four different frequency ranges were used to represent responses to stimuli with different dynamics. **A, B:** Section of the deterministic membrane potential component (upper trace in each panel) and three examples of individual graded response traces consisting of a deterministic and a stochastic component are shown for the frequency ranges 15–25 Hz (A) and 60–100 Hz (B). Vertical calibration line between both panels denotes 20 mV. **C, D:** Corresponding PSTHs (spike responses averaged over 200 presentations and for illustration smoothed with a sliding time window of 10 ms in C and 5 ms in D) and individual spike responses. **E:** Power spectra of the stochastic membrane potential component (noise) and of the four deterministic membrane potential components that were used in the simulations.

- The dynamics of the deterministic membrane potential component was varied by stretching the time axis by a constant factor. This can be achieved in sensory systems by changing the time course of a dynamical stimulus.
- The amplitude of the stochastic component was stretched by a constant factor. This modification takes into account the finding that the statistical properties of membrane potential noise can depend on the stimulus (Cecchi et al., 2000; Warzecha et al., 2000).
- The time axis of the stochastic component was stretched by a constant factor. This modification takes into account that different stimuli may alter not only the noise amplitude but also its dynamics (Warzecha et al., 2000).

With the model of spike generation (see below and Kretzberg et al., 2001), spike trains were generated for the standard membrane potential traces as well as for the modified traces.

For each of the standard and the modified stimuli, 200 traces with statistically independent stochastic components were generated. The traces consisted of 13,500 data points with a bin width of 0.37 ms. Tests with larger amounts of data (longer or more traces) led to qualitatively similar results. All calculations were performed with Matlab 5.3.

2.2. *Model of Spike Generation*

To transform membrane potential fluctuations into spike trains, we used a time-dependent threshold model of spike generation (Kretzberg et al., 2001). The threshold $\theta(t_i)$ for spike generation was calculated for every time step t_i according to the equation

$$\theta(t_i) = \begin{cases} \infty & \text{if} \quad s \leq \gamma^{\text{ref}} \\ \theta_0 + \eta(s) + \rho(t_i) & \text{if} \quad s > \gamma^{\text{ref}} \end{cases}$$

with θ_0 as the constant basis threshold; $\eta(s)$ as the $\frac{\eta_0}{s-\gamma^{\text{ref}}}$ influence of the relative refractoriness; and $\rho(t_i)$ as the $-\frac{\rho_0}{T} \cdot \sum_{j=1}^{T} \frac{1}{j} \cdot (U(t_i) - U(t_{i-j}))$ influence of changes of the membrane potential $U(t)$ within last T data points. s denotes the time elapsed since the previous spike, and γ^{ref} the absolute refractory period. ρ_0 and η_0 are weight constants. A spike is generated if $U(t_i) > \theta(t_i)$.

The influence of membrane potential changes on the spike threshold was modeled explicitly to account for the experimental finding that steep depolarization ramps induced by current injection cause spiking at much lower depolarization levels than more gentle ramps (e.g., Johnston and Wu, 1995). The sensitivity of the threshold to the slope of membrane potential changes can be explained by the inactivation of a large fraction of voltage sensitive Na$^+$-channels during sustained depolarization (Azouz and Gray, 2000). In our model, $\rho(t)$ causes the threshold to decrease more as the membrane potential deplolarizes faster, making the generation of the next spike more probable.

The model parameters have been adjusted to fit experimental data of the spiking motion-sensitive H1-neuron in the visual system of the fly (Kretzberg et al., 2001). With this model properties of experimental data as the time course, spike count variance and correlated activity of two neurons can be reproduced (Warzecha et al., 2000; Kretzberg et al., 2001). All results shown in this article were obtained with parameter values $\theta_0 = 1$ mV, $\gamma^{\text{ref}} = 2$ ms, $\eta_0 = 20$ ms $\cdot$ mV, $\rho_0 = 3.75$, $T = 3$ (corresponding to approximately 1 ms). The entire analysis was also done with the other four parameter sets specified in Kretzberg et al. (2001). These parameter sets cover a broad range of different parameter values ($\theta_0 : 0 - 3$ mV, $\gamma^{\text{ref}} : 0 - 2$ ms, $\eta_0 : 20 - 40$ ms $\cdot$ mV, $\rho_0 : 0 - 9$, $T : 0 - 12$) representing cells that are influenced to a different amount by absolute and relative refractory period and by the slope of the membrane potential.

2.3. *Data Analysis*

We analyzed how well an ideal observer can discriminate two different stimuli S_1 and S_2 on the basis of spike trains or membrane potential traces elicited by these stimuli. This analysis was done by using a time window τ for the discrimination task. τ was varied to cover a range of different time scales that are potentially important for the encoding of the stimuli. For each of the four frequency ranges and of the five modifications of the membrane potential properties (see Section 2.1), 200 responses to the standard stimulus were compared with 200 responses to a modified stimulus. For each of the stimulus pairs all 400 traces had statistically independent stochastic components. With the model of spike generation all membrane potential traces were transformed into spike trains. The discriminability between the standard and the modified responses was analyzed in the same way for both response modes. This analysis consisted of four steps:

1. *Filtering of the response traces* All responses traces T_i were filtered with a sliding rectangular time window of size τ that was moved in steps of 1 ms. The filtered traces T_i^τ were calculated by determining for each instance of time either the mean spike count or the mean membrane potential within the time window τ. These calculations were performed for 11 values for τ between 1 ms and 5 s duration. The larger τ, the more the traces are smoothed, eliminating their fine temporal structure. How much the deterministic and the stochastic fluctuations of the membrane potential are averaged out depends on their spectral distributions relative to the length of the time window.
2. *Distances between filtered response traces* For all possible pairs of time-dependent response traces T_i^τ and T_j^τ their similarity was assessed by calculating their distance D^τ. T_i and T_j can be elicited by either of the two stimuli S_1 and S_2. The distance between

the filtered traces T_i^τ and T_j^τ was calculated according to the equation

$$D^\tau(T_i, T_j) = \sqrt{\frac{1}{N_T} \sum_{k=1}^{N_T} \left(T_{i_k}^\tau - T_{j_k}^\tau\right)^2}$$

N_T denotes the number of data points contained in each filtered response trace. A similar measure for distances between temporally filtered spike trains was used in van Rossum (2001).

3. *Clustering into estimated response classes* All traces elicited by the stimulus S_1 (or S_2) form together the *actual response class* C_1 (or C_2). For every trace $T_i \in C_2$ the mean distances d^τ to the traces of both response classes C_1 and C_2 were calculated according to the equations

$$d^\tau(T_i, C_1) = \frac{1}{N_{C_1}} \sum_{T_j \in C_1} D^\tau(T_i, T_j)$$
$$d^\tau(T_i, C_2) = \frac{1}{N_{C_2} - 1} \sum_{T_j \in C_2} D^\tau(T_i, T_j)$$

   (and for elements of C_1 accordingly). N_{C_1} and N_{C_2} denote the number of traces in the actual response classes C_1 and C_2, respectively. If $d^\tau(T_i, C_1) < d^\tau(T_i, C_2)$, T_i was assigned to the *estimated response class* R_1, otherwise to R_2. With this procedure each of the $N_{C_1} + N_{C_2}$ traces was assigned to either R_1 or R_2 (see also Victor and Purpura, 1996).
4. *Percentage correct* It was calculated how many of the traces are assigned correctly to the estimated response class that corresponds to their actual response class. This number relative to the total number of responses is the percentage of correct decisions.

3. Results

We analyze how well an ideal observer can discriminate between stimuli on the basis of either graded or spiking neuronal responses. The observer looks through a time window of length τ that is slid along two response traces of the same response mode. The responses are integrated within the time window, and therefore all time structure on a finer time scale than the integration window is lost. The task for the observer is to decide on this basis whether or not both responses are elicited by the same stimulus. We investigate in four ranges of membrane potential dynamics how well the original neuronal responses can be discriminated from traces that were manipulated in five different ways (see Section 2 and Fig. 2). The comparison is made on the basis of the graded responses and after they are transformed into spikes.

3.1. Mean Activities for Different Stimuli

The crudest way to discriminate between stimuli is to assess the mean responses averaged over the entire stimulus presentation. Because the membrane potential was chosen to fluctuate symmetrically around a given resting level, changing the amplitude or the time axis of the deterministic or the stochastic membrane potential component does not influence the mean potential. The only way to change the average membrane potential is to add a constant offset.

In contrast, after the membrane potential fluctuations are transformed into spike trains, the resulting mean spike count strongly depends on the membrane potential properties (Fig. 3). The mean spike count rises approximately linearly with increasing amplitude of the membrane potential fluctuations for all frequency ranges (Fig. 3A). This is due to the fact that the rectification nonlinearity of spike generation leads to more spikes during the depolarization phases that are increased in amplitude and ignores the amplitude of hyperpolarization phases.

Compressing the time scale of the deterministic membrane potential component (Fig. 3B) leads to faster fluctuations, but the amplitude of de- and hyperpolarizations stays constant. This manipulation does not much influence the mean spike responses in the low-frequency ranges. In contrast, in the high-frequency range the mean spike count rises with the frequency of the membrane potential fluctuations. This dependence is due to the fact that spikes tend to time-lock very reliably to fast membrane potential fluctuations (Kretzberg et al., 2001). This time-locking is also the reason why for all conditions (Fig. 3) the resulting spike count is higher for high-frequency membrane potential fluctuations (60–100 Hz) than for low-frequency fluctuations (e.g., 5.75–6.25 Hz).

When a constant offset is added to the membrane potential, the resulting spike count increases approximately linearly with the offset (Fig. 3C). This result was expected because the spike count of the model depends linearly on the membrane potential for a wide

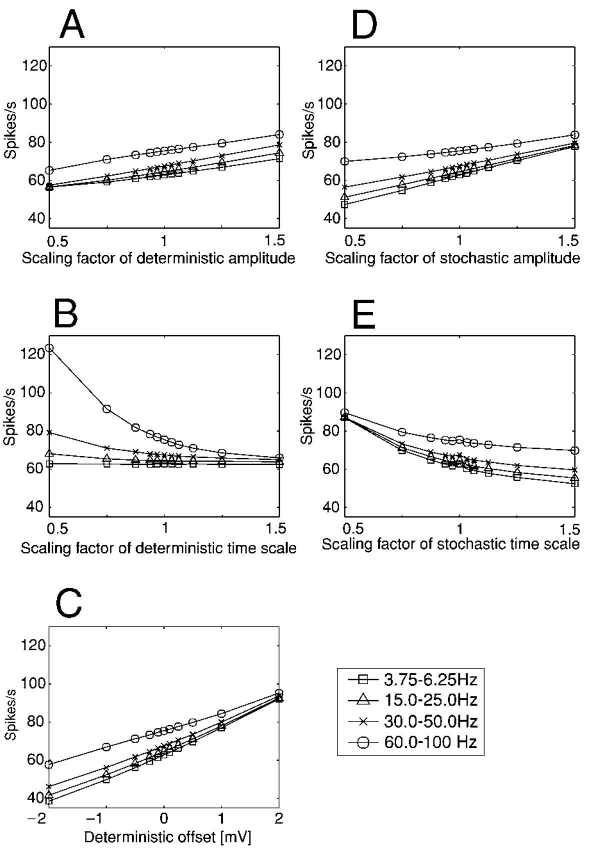

Figure 3. **Mean spike responses to different stimuli:** Mean spike counts were calculated for membrane potential fluctuations with deterministic components in four different frequency ranges (see inset). **A, B:** Spike counts were averaged over the whole response traces (5 s) and are plotted as a function of the factor by which either the amplitude or the time axis is modified. The amplitude (A) or the time axis (B) of the deterministic membrane potential component was increased and decreased in logarithmic steps between $1/32$ and $1/2$. **C:** A constant offset between -2 mV and 2 mV was added to the deterministic membrane potential. **D,E:** The stochastic membrane potential component was changed by increasing or decreasing either the amplitude (D) or the time axis (E) in the same logarithmic steps as in A, B. The deterministic component was left unaltered. In B, E abscissa values <1 correspond to a compression of the time axis and consequently to faster dynamics of the deterministic (B) or stochastic (E) membrane potential changes.

range of membrane potentials (Warzecha et al., 2000). The same dependency has been found for the motion-sensitive H1-neuron in the fly.

Increasing the standard deviation of the stochastic component leads to more spikes (Fig. 3D) in a similar way as amplitude increments of the deterministic membrane potential component.

Faster dynamics of the stochastic membrane potential component increases the spike count as well (Fig. 3E). This effect is most pronounced for changes of the stochastic fluctuations that are superimposed on a slowly fluctuating deterministic component (Fig. 3E). In contrast, when the dynamics of the deterministic membrane potential component is changed, the spike count increases most for very fast fluctuations (compare Fig. 3B).

3.2. *Discriminability of Different Stimuli*

How well can small differences between two stimuli be detected by an ideal observer on the basis of either the membrane potential traces or the resulting spike responses? In Fig. 4A–D the discriminability is calculated for two stimuli that cause the amplitude of the deterministic membrane potential fluctuations to differ by a factor of $1/8$. For all four dynamic ranges the graded responses to both stimuli can be perfectly discriminated when differences on a fine time scale are taken into account. This is because the standard deviation of the stochastic fluctuations is smaller than the average difference between the deterministic membrane potential components. Therefore, the mean distance between two traces within one actual response class is smaller than the distance between traces elicited by different stimuli. For coarser time scales the discrimination performance decreases because averaging smoothes out not only the membrane potential noise but also the deterministic component that fluctuates in the simulations presented here symmetrically around the resting level. For perfect discrimination the time window must be the shorter the faster the deterministic membrane potential fluctuations are. In contrast, to discriminate between spike responses the time window must not be too short to allow discrimination on the basis of noisy response traces (Fig. 4A–D). The rectification nonlinearity of spike generation provides a reliable discrimination between responses to different stimuli only if the responses are averaged over more than one depolarization phase. Thus, for short time windows the graded response mode is superior to the spiking mode. For long time windows ($>\approx$ 100 ms) the spike responses can be discriminated better than the graded responses, if the latter fluctuate symmetrically around a given membrane potential value that is independent of the stimulus.

Changes of the time axis of the deterministic membrane potential component can be discriminated well for time scales between several tens and hundreds of milliseconds. This is true even if the time axis is

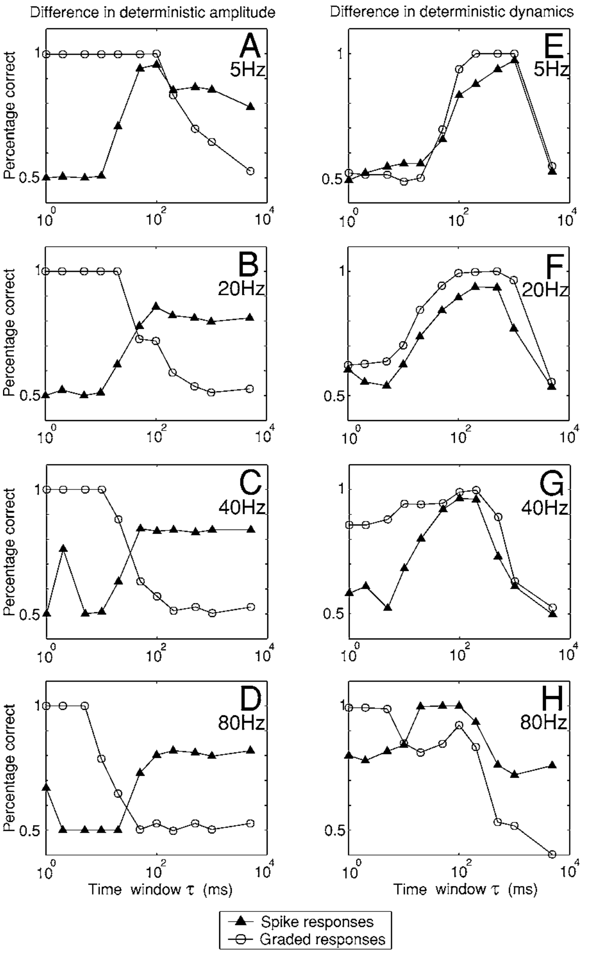

Figure 4. **Discriminability of two stimuli that alter the deterministic membrane potential components.** The discriminability between two stimuli was calculated as the percentage of correct decisions. Pairs of graded or spiking responses were compared on the basis of time windows τ between 1 ms and 1 s as well as for the mean of the whole response traces (5 s). Different stimuli were assumed to alter either the amplitude (**A–D:** amplitude increased by 1/8) or the dynamics (**E–H:** time axis dilated by 1/32) of the deterministic membrane potential component. The statistical properties of the stochastic membrane potential component were the same for all traces. A value of 1 (0.5) denotes 100% (50%) correct discrimination. Frequency ranges of membrane potential fluctuations are as specified in Fig. 2 (e.g., 5 Hz denotes the range from 3.75 to 6.25 Hz).

modified only by a factor of 1/32 (Fig. 4E–H). The range of time windows that enable an optimal discrimination is similar for both response modes. If the time window used for smoothing is too short, the stochastic component of the individual traces predominates the effects of changing the deterministic membrane potential dynamics. By averaging over a too long time interval, essentially the mean activity is measured. The mean activity does not change markedly by stretching the time axis unless very fast fluctuations are used (Figs. 3B, 4E–H). The time scale for optimal discrimination depends on the dynamics of the membrane potential. The faster the membrane potential fluctuates, the finer is the time scale for optimal discrimination. Only spike responses elicited by very fast fluctuations can be discriminated well for almost the whole range of time scales. In this case, the phase-locking of spikes to the deterministic membrane potential fluctuations causes the spike count to increase when the time axis is compressed. Thus, stimuli that induce different membrane potential dynamics in the high-frequency range can be discriminated better on the basis of spike trains than on the basis of graded responses, unless a very fine time scale is used for the comparison. For slower fluctuations the discriminability is better on the basis of graded responses.

The discriminability of stimuli increases with their dissimilarity. In contrast to changing the time axis of the deterministic membrane potential component by 1/32, amplitude changes by a factor of 1/8 are necessary for a good performance of discrimination on the basis of spike responses (Fig. 4). Hence, our measure of discriminability between responses to different stimuli is more sensitive to changes in dynamics than to changes in amplitude of the deterministic response component.

On the basis of graded responses a constant offset of the deterministic response component can be discriminated perfectly on all time scales (not shown). This is true even for differences that are much smaller than the standard deviation of the stochastic membrane potential component. On the basis of spike responses, long time windows are needed to discriminate between the stimuli that induced a small offset in the responses (not shown).

Figure 5 shows how well an ideal observer can discriminate between responses to two stimuli that elicit the same deterministic membrane potential fluctuations but that induce stochastic fluctuations with different statistical properties. For all frequency ranges and all investigated time scales, it is impossible to discriminate between these stimuli on the basis of graded responses. As long as the stochastic fluctuations are symmetrical around the deterministic membrane potential, the differences are always averaged out. In contrast, the spike count rises when the stochastic fluctuations are either increased in amplitude (Fig. 3D) or made faster (Fig. 3E). These spike-count differences can be

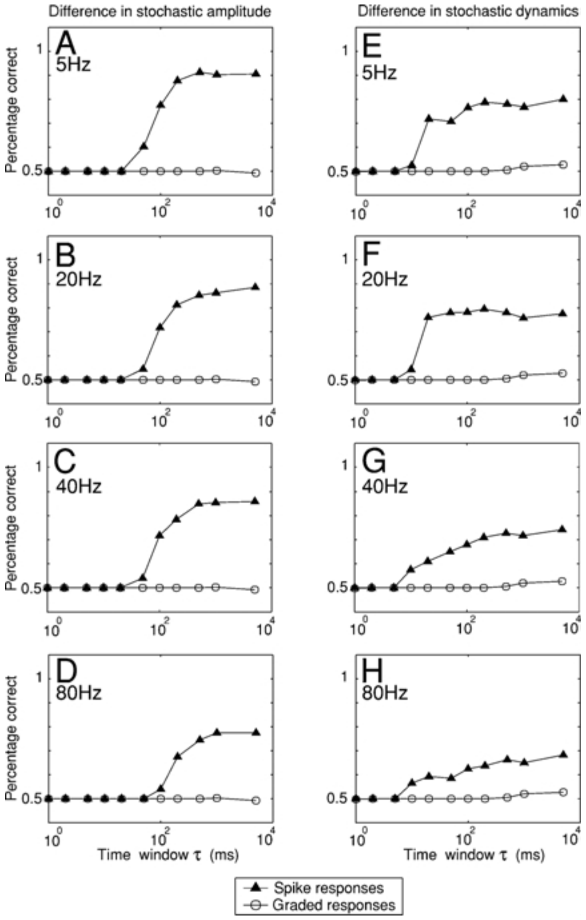

Figure 5. **Discriminability of two stimuli that alter the stochastic membrane potential component.** The discriminability between two stimuli was calculated in the same way as in Fig. 4. In contrast to Fig. 4 the deterministic membrane potential component was unaltered while the statistical properties of the stochastic component were varied. The noise traces were changed either in their amplitude (**A–D:** amplitude increased by 1/8) or in their dynamics (**E–H:** time axis dilated by 1/8).

detected in sufficiently long time windows. For all ranges of deterministic membrane potential dynamics the time window for integration has to be at least 100 ms to allow the ideal observer to detect a difference of factor 1/8 between the standard deviation of the stochastic components (Fig. 5A–D). When the time axis changes by a factor of 1/8, the difference can be detected even on the basis of time windows of 10 ms (Fig. 5E–H).

The exact values for the discriminability of stimuli on the basis of spike responses depend on the model parameters that are used for spike generation. The discrimination of stimuli that induce different deterministic fluctuations of the membrane potential is merely influenced quantitatively. Although very different parameter sets were used for the simulations (see Section 2), the resulting percentages of correct decision are very similar. To discriminate different noise statistics superimposed on the same deterministic component, the parameters that determine the influence of membrane potential changes on the threshold are important. When a set of model parameters is used that does not explicitly take into account the influence of membrane potential changes within the last time steps ($\rho_0 = 0$, $T = 0$) (see Section 2), differences in the stochastic membrane potential component are not so well detected. Especially the discriminability of differences in the dynamics of the stochastic component does not deviate much from chance level (not shown).

4. Discussion

Whether spiking or graded neuronal responses are more suitable to discriminate between different stimuli depends on the characteristics of the responses that are affected by the stimuli as well as on the time scale on which the responses are taken into account. On a fine time scale most stimuli that change the deterministic response component can be discriminated best on the basis of graded responses. Spike generation provides a mechanism of rectification and of amplification of fast changes in the neuronal response. Hence, in situations when response fluctuations in the high-frequency range have to be detected, spike responses can lead to a better discrimination between stimuli than graded responses.

These results are likely to depend on the specific measure of discriminability and the properties of the used membrane potential traces (see below). Moreover, we do not want to imply that the discrimination procedure we used reflects neuronal mechanisms. Nevertheless, even with our relatively simple measure we obtained results that might be inspiring for further analyzes of neural coding.

4.1. *Time Scales of Encoding*

A classical approach to investigate discriminability between responses to different stimuli is to use an ideal-observer paradigm. The observer is ideal not in the sense of knowing everything but in the sense of making a maximum likelihood decision on the basis of the available information. This kind of approach is frequently applied to spiking neurons (reviews: Gabbiani and Koch, 1998; Parker and Newsome, 1998; Buračas and Albright, 1999). Here, we apply it also to graded responses. We analyze the dependence of discriminability on the time scale used for the analysis. Instead of the response traces themselves we use distances between temporally filtered responses (compare van Rossum, 2001) for the assignment to one of the stimuli. Nevertheless, our results are comparable with results from previous studies. On the basis of spike responses analyzed in several systems and with different measures, discriminability was found to be optimal for time scales of some tens to some hundreds of milliseconds (Vogels and Orban, 1990; Geisler et al., 1991; Victor and Purpura, 1996, 1997; Mechler et al., 1998; MacLeod et al., 1998; Ratnam and Nelson, 2000; Machens et al., 2001; Warzecha and Egelhaaf, 2001). We also found this range to be optimal for discriminating spike responses to all stimuli used in this study (Figs. 4 and 5). Nevertheless, the optimal time scale for stimulus discrimination may be much finer for sensory systems where a high degree of temporal precision is important for the encoding task (Victor and Purpura, 1997). Moreover, the exact time scale for optimal stimulus discrimination depends on the stimulus parameter that is varied and the amount of variation (Victor and Purpura, 1996; Deco and Schürmann, 1998; see also Fig. 4).

4.2. *Encoding of Stimuli with Different Dynamics*

Discriminability of stimuli depends critically on the temporal frequency content of the corresponding neuronal responses. It depends particularly on the relative contribution of deterministic and stochastic membrane potential component to the fast membrane potential fluctuations. In the case of visual interneurons in the fly, deterministic fluctuations in the range below 30 Hz are much more prominent than faster deterministic fluctuations (Haag and Borst, 1997; Warzecha et al., 1998). In contrast, neuronal responses in the auditory system and the electrosensory system time-lock to stimuli at much higher frequencies (Carr and Friedmann, 1999). It was found in many experimental and modeling studies that spikes couple very precisely to fast fluctuations of the membrane potential (e.g., Mainen and Sejnowski, 1995; Stevens and Zador, 1998; Warzecha et al., 1998). This amplification of transients by the spike-generation mechanism (see Haag and Borst, 1996; Cecchi et al., 2000; Kretzberg et al., 2001) is the reason that stimuli leading to fast membrane potential fluctuations with different dynamical properties can be discriminated better on the basis of spike responses than on the basis of graded responses unless a very fine time scale is used for the discrimination (Fig. 4H).

4.3. *Influence of Noise*

In many situations neuronal noise limits the discriminability of stimuli on the basis of neuronal responses. If there were no stochastic fluctuations of the membrane potential, the discrimination between responses to different stimuli inducing different deterministic responses would always be perfect. Nevertheless, in the inevitable presence of noise differences in the statistics of the stochastic membrane potential fluctuations could be helpful to discriminate between different stimuli, if they are fast enough to trigger spikes. It has been shown, for instance, for fly motion-sensitive neurons (Warzecha et al., 2000) and cat LGN cells (Cecchi et al., 2000) that the statistical properties of membrane potential noise can depend on stimulus parameters. In the present study it is assumed that the stochastic membrane potential component fluctuates symmetrically around the deterministic membrane potential and has more power in the high-frequency range than the deterministic component (Fig. 2), as was found in the visual pathway for motion detection (e.g., Laughlin, 1989; Haag and Borst, 1997; Warzecha et al., 1998). As a consequence, differences in the statistics of the membrane potential noise can be discriminated on the basis of spike responses but not of graded membrane potentials (Fig. 5), and the discriminability depends on the influence of membrane potential changes on the spike mechanism.

4.4. *Differences Between Response Modes*

As a consequence of the membrane time constant, the membrane potential cannot change arbitrarily fast. Nevertheless, within each instance of time the graded signal can have a whole range of different values, while the spike signal can be only spike or no spike. Therefore, graded membrane potential traces contain more information than binary spike signals. Accordingly, higher rates of information transmission were found for graded neuronal responses than for spiking ones (de Ruyter van Steveninck and Laughlin, 1996). To code for something that needs more than one bit, the spiking signal must be taken into account for a longer time than is needed to produce a single spike. As a consequence, it may be possible to code for the same stimulus within a shorter time interval by the graded response mode than with spikes. We find this expectation to be confirmed for the discrimination between membrane potential traces with different amplitudes (Fig. 4A–D) or constant offsets. Here the differences can be detected within short time windows much better on the basis of graded responses than on the basis of spikes. A similar result was obtained for the discriminability of stimuli for fly visual neurons (Warzecha and Egelhaaf, 2001). For longer integration times the discriminability of spike responses is at least similar or even better than the discriminability on the basis of graded responses (Fig. 4A–D, (Warzecha and Egelhaaf, 2001)). Although the graded signal contains more information for any instance of time, this information cannot be used when the signal is integrated over an extended period of time as long as the membrane potential fluctuates symmetrically around its resting level. Only when the symmetry is eliminated (for instance, when the stimulus induces an offset of the membrane potential or by spike generation), the signals can be discriminated on a coarse time scale. On the other hand, for different computational tasks it is advantageous for the cell responding in a graded way to be capable of producing de- and hyperpolarizations. For instance, motions sensitive fly neurons code for both directions of motion. Here the rectification process due to spiking allows only a coarse coding on nonpreferred direction motion (Haag and Borst, 1997).

Although spike generation does not take into account all of the information contained in the membrane potential, it amplifies fast membrane potential fluctuations. This allows the ideal observer used in our study to detect on the basis of spike trains differences in the fast dynamics of the membrane potential, no matter whether they are induced stochastically (Fig. 5) or deterministically by the stimulus (Fig. 4H). Perhaps this is the reason that fly HS-cells, for example, use a combined code where graded membrane potential fluctuations can be superimposed by active spike-like depolarizations (Hengstenberg, 1977; Haag and Borst, 1998). One could speculate that these cells combine the advantages of both response modes. Indeed, stimulus fluctuations could be reconstructed best on the basis of the full HS-signal rather than on the basis of its graded response component or its spike component alone (Haag and Borst, 1998). Moreover, the HS-cell can respond to faster temporal changes in their synaptic input than another cell in the fly visual system that responds exclusively with graded signals (Haag and Borst, 1996). Transient inputs are amplified in HS-cells by the active processes in a similar way as does our model (Fig. 4H and 5).

In conclusion, the transformation of graded postsynaptic potentials into spikes can help to detect fast changes. This finding could be relevant in sensory systems in which neuronal responses couple tightly to the stimulus and in presence of stimulus-dependent high-frequency noise. On the other hand, graded responses have the advantage that they potentially can transfer more information within short time intervals. The example of the fly's HS-cells show that it is possible to combine both response modes by superimposing graded membrane potential fluctuations with spike-like processes. Perhaps this mixed coding strategy is better suited for the encoding of dynamical stimuli than either graded potentials or spikes on their own. We would not be surprised if the improving techniques of intracellular recordings in cortical neurons would reveal that cortical neurons, at least local ones, also use graded membrane potential fluctuations, in addition to spikes, to convey information.

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