Simulation of mechanical to neural transduction in the auditory receptor

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(Received 8 March 1985; accepted for publication 16 October 1985)

A probabilistic model is described for transmitter release from hair cells, auditory neuron EPSP's, and discharge patterns. The model assumes that the release fraction of the transmitter is a function of stimulus intensity. It further assumes that some of this transmitter substance is taken back into the cell while some is irretrievably lost from the cleft. These assumptions differ from other recent models which propose multiple release sites, fixed release fractions, and no transmitter reuptake. The model produces realistic mammalian rate intensity functions, interval and period histograms, incremental responses, and adaptation effects. It mimics successfully the adaptation of successive EPSP amplitudes of the afferent neuron of the goldfish sacculus and offers a reinterpretation of the implications of these studies for hair cell synaptic mechanism.

PACS numbers: 43.63.Bq

INTRODUCTION

A number of models of primary auditory fiber activity have been developed which generate a sequence of firings, in time, in response to a stimulating waveform (Siebert, 1965; Weiss, 1966; Nilsson, 1977; Schroeder and Hall, 1974; Oono and Sujaku, 1975; Eggermont, 1973; Geisler *et al.*, 1979; Ross, 1982; Schwid and Geisler, 1982; Smith and Brachman, 1982). Most of these models can be characterized by two stages: a function relating acoustic stimulation to the release of transmitter substance from hair cells into the synaptic cleft; and a characterization of the response of the auditory nerve fiber to the presence of this transmitter in the cleft. The input to this kind of model is an acoustic stimulus; the output is a pattern of "events" simulating spike activity (Fig. 1) in afferent fibers of the VIIIth nerve.

Regrettably, the simple and readily computable models of Schroeder and Hall (1974) and Oono and Sujaku (1975) have been obliged to give way to more complex and computationally time consuming procedures. In an effort to encompass an increasing range of physiological phenomena, the number of components in the model has been increased. Ross (1982) replaces the traditional single reservoir of the transmitter within the hair cell by a cascade of four such reservoirs. Schwid and Geisler (1982) replace the hair cell membrane of uniform permeability with a set of six release sites each with its own permeability function, its own reservoir, and its own priority of access to a central replenishment reservoir; Smith and Brachman (1982) used 512 such sites, each with its own reservoir.

The recent development of multiple release site models was stimulated by the need to account for observations of the response of auditory nerves to brief tone bursts. In physiological preparations, tone onset causes an immediate rise in firing rate followed by a steady fall to an adaptation level which depends on the amplitude of the stimulating tone (e.g., Smith and Zwislocki, 1975). The rate of fall from the

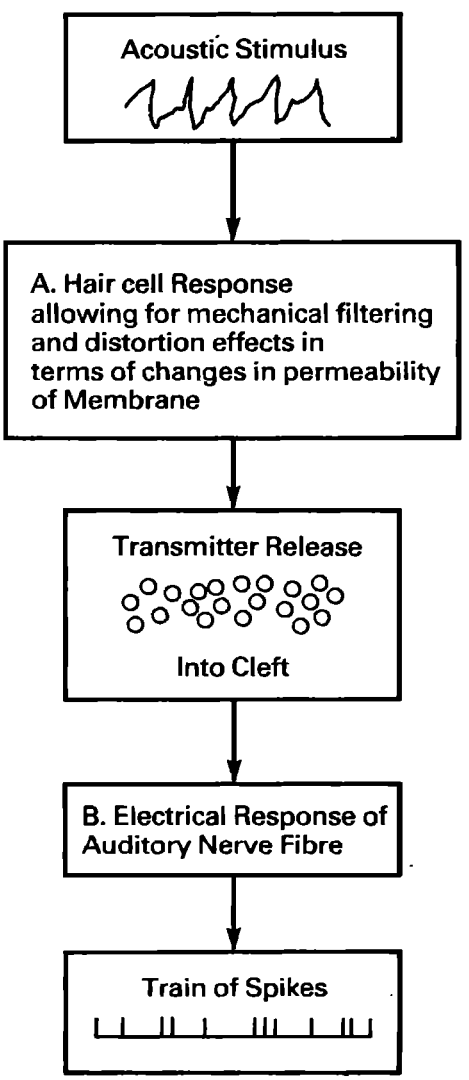

FIG. 1. Two-stage approach to modeling auditory nerve response to acoustic stimulation.

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onset rate down to the adaptation level is independent of the intensity of the tone or the background signal level.

Early models (Oono and Sujaku, 1975; Schroeder and Hall, 1974) have difficulty with this phenomenon. In their systems, a higher intensity tone burst leads to a more rapid depletion of transmitter level. The rate of fall is not independent of stimulation intensity in these models (Schwid and Geisler, 1982). This occurs because the release fraction (or the probability that a given transmitter quantum will be released) is determined directly by the stimulus intensity.

In these early models, the transmitter reservoir also becomes fully depleted in the presence of moderately intense stimulation. Continued firing is therefore dependent upon the steady manufacture of a new transmitter. This means that a step increase to an already suprathreshold stimulus cannot generate a new onset response because the firing rate has become entirely dependent upon the rate of transmitter manufacture, and not stimulus amplitude. Later models with their independent release sites and reservoirs were able to cope with both problems by keeping some transmitter in reserve for responding to increases in stimulation and by having a fixed release fraction unaffected by stimulus intensity. In these models, an intensity increase results in an increase in the *number* of sites which release the transmitter into the cleft and not an increase in the amount released by a given site.

These developments were encouraged by the results of Furukawa and Matsuura (1978) whose work on the goldfish appeared to imply that changes in stimulus intensity did not affect the probability of release of a transmitter quantum from the hair cell into the presynaptic cleft. Their conclusion was that the probability of release remained constant but the number of quanta *available for release* increased with stimulus intensity. This view is in accord with multiple reservoir hypotheses. If each reservoir is thought to have a different response threshold, the number of responding reservoirs will be directly related to stimulus intensity. If the probability of release of a quantum from an active reservoir is fixed, then the total number of quanta released will reflect the stimulus intensity.

It will be shown that Furukawa and Matsuura's conclusions do not necessarily follow from their observations and that the concept of multiple release sites with graded thresholds is unnecessary. First, a model will be presented to show that a much simpler formulation can generate acceptable behavior in the kinds of situations under discussion.

The new model differs in one important respect from all previous models of hair cell activity except, perhaps, Eggermont's (1973) analog system. It assumes that most of the transmitter substance ejected into the cleft is rapidly taken back into the hair cell (Fig. 2). While in the cleft, transmitter quanta have a chance to affect post synaptic processes but rapid metabolism and reuptake prevent catastrophic depletion of available transmitter within the hair cell. Some transmitter within the cleft is lost and this gives rise to a slow depletion which generates the adaptive decline. This loss from the cleft is eventually balanced by a relatively slow manufacture of transmitter within the cell and this balance gives rise to the steady-state condition of the adapted auditory nerve.

The reuptake principle is compatible with standard models of transactions at chemical synapses (McLennon, 1970). The new system is considerably simpler than recent proposals which assume a multiplicity of release sites, each with their own properties (Schwid and Geisler, 1982; Smith and Brachman, 1982). It will be shown that, despite its simplicity, the model is equally effective in generating many phenomena characteristic of auditory nerve activity. The first demonstration (model A) involves a special case of the more general model B. Model A illustrates the effects of a reuptake principle. Model B offers better adaptation properties.

I. MODEL A

The hair cell contains a quantity of the "free transmitter," $q(t)$, which leaks through a permeable membrane into the synaptic cleft. The permeability, $k(t)$, fluctuates as a function of the instantaneous amplitude of the acoustic stimulation, $s(t)$:

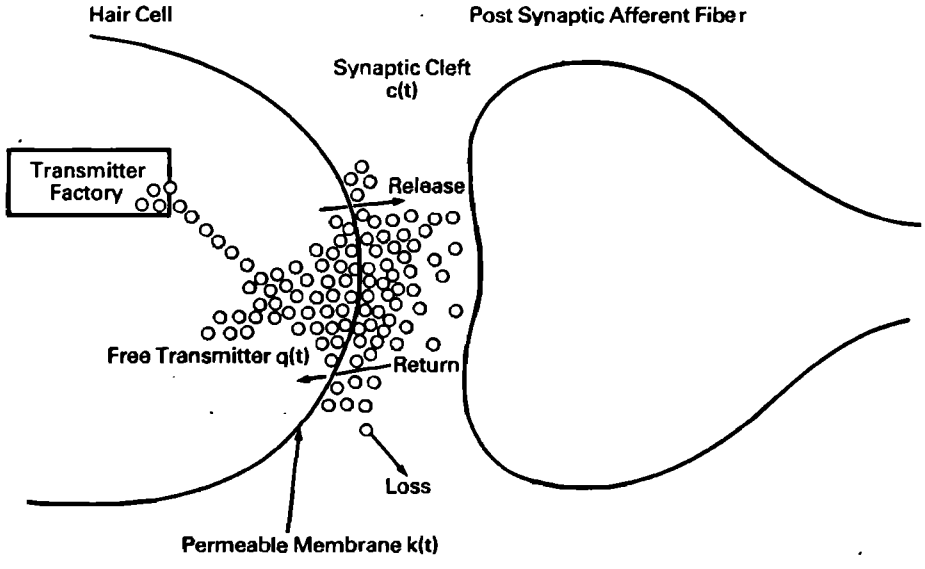


FIG. 2. Schematic representation of the key features of the model.

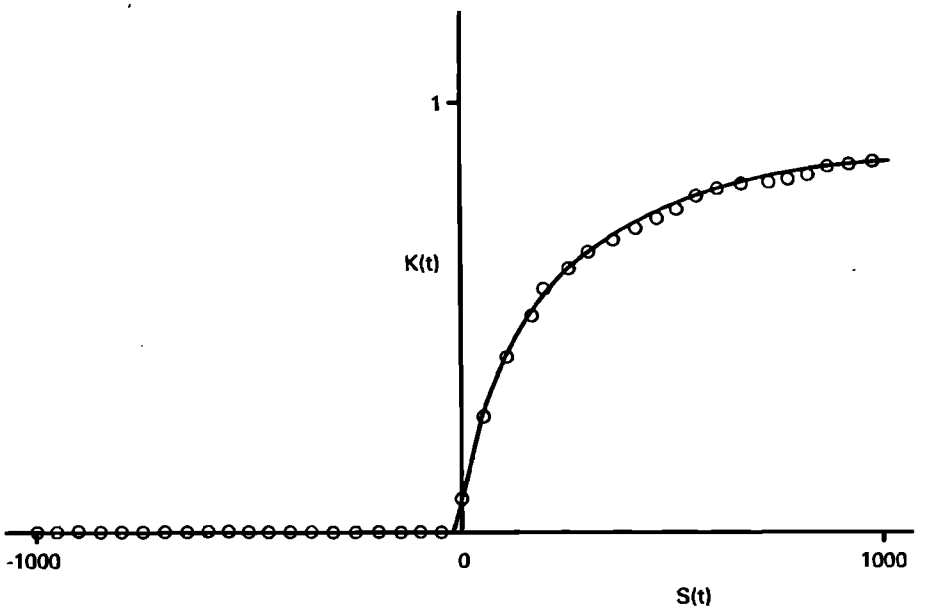


FIG. 3. Membrane permeability, $k(t)$, as a function of instantaneous amplitude, $s(t)$, given by expression (1).

$$k(t) = \frac{g[S(t)+A]}{S(t)+A+B}, \quad \text{for } s(t)+A>0$$
$$k(t) = 0, \quad \text{for } s(t)+A<0 \tag{1}$$

where A and B are positive constants, $B \gg A$.

Note that in the absence of any stimulation, when $s(t) = 0$, transmitter continues to leak at a rate $gA/(A+B)$ which gives rise to spontaneous activity in the nerve. Here $k(t)$ varies between 0 and g, and $-A$ defines the lowest instantaneous amplitude at which the membrane remains permeable; B specifies the rate at which $k(t)$ approaches its maximum value as a function of $s(t)$. The function (1) is illustrated in Fig. 3 and is a simple approximation of a function relating stimulation to internal cell voltage for the guinea pig (Russel and Sellick, 1978) and for the turtle (Crawford and Fettiplace, 1981). The function is negatively accelerated unlike that of Schroeder and Hall (1974) which is positively accelerated. The amount of the transmitter released into the cleft is $k(t)q(t)dt$. The assumption that internal cell voltage regulates membrane permeability is tentative but convenient.

Following Schroeder and Hall's (1974) practice, $s(t)$ is normalized such that $s^2(t) = 1$ corresponds to a sound level of approximately 30 dB *re*: 0.0002 dyn/cm^2.

The model assumes that the cell contains a manufacturing capability which slowly replenishes the store of the free transmitter at the rate $y[M - q(t)]$. This creates an upper limit of M units of the free transmitter within the cell. In the results to be reported, the transmitter was not quantized and M was set to one so that the replenishment rate was $y[1 - q(t)]$.

The synaptic cleft contains a fluctuating amount of transmitter substance, $c(t)$. An amount, $rc(t)dt$, is continuously returned to the hair cell and another amount, $lc(t)dt$, is continuously being lost.

We can now summarize these events. The cell transmitter level $q(t)$ is replenished through manufacture and return from the cleft but is depleted by loss into the cleft,

$$\frac{dq}{dt} = y[1 - q(t)] + rc(t) - k(t)q(t). \tag{2}$$

The cleft transmitter level $c(t)$ is depleted by irretrievable loss and return to the hair cell. It is replenished by release from the hair cell:

$$\frac{dc}{dt} = k(t)q(t) - lc(t) - rc(t). \tag{3}$$

While in the cleft, transmitter quanta have a finite probability of influencing the post-synaptic excitatory potential. The greater the level of the cleft transmitter, the higher the probability that a spike process will be triggered. This effect is approximated by the probabilistic function

$$\text{Prob (event)} = hc(t)dt, \tag{4}$$

where h is a constant of the model. A simple refractory period is imposed by denying any event which occurs within 0.001 s of a previous event.

Equations (1)–(4) and the refractory period constitute the whole model.

A. Computer simulations of model A

In the simulations to be reported, the transmitter was not quantized but values between 0 and 1 (i.e., $M = 1$) were assumed. The events were generated using a random number generator in conjunction with expression (4). Equations (1)–(4) were computed for each epoch. Epochs were 0.00005 s in length (dt). The results were found to be sensitive to epoch length if they were much longer than this value. The stimulating tone was a 1-kHz sinusoid, unless otherwise stated. The model parameters used were: $dt = 0.00005$, $gdt = 0.083$, $rdt = 0.625$, $ldt = 0.025$, $ydt = 0.00083$, $A = 5$, $B = 160$, and $hdt = 0.5$. These values were found by experimentation which aimed to produce an approximate spontaneous event rate of 50 s^{-1}, a maximum event rate of 150 s^{-1} at around 60 dB, and a time constant of event rate decay following stimulus onset of approximately 40 ms. The high value of rdt signifies that almost all of the transmitter released is returned to the hair cell within two-tenths of a millisecond. The relatively small values for the loss parameter (ldt) and the replenishment parameter (ydt) indicate

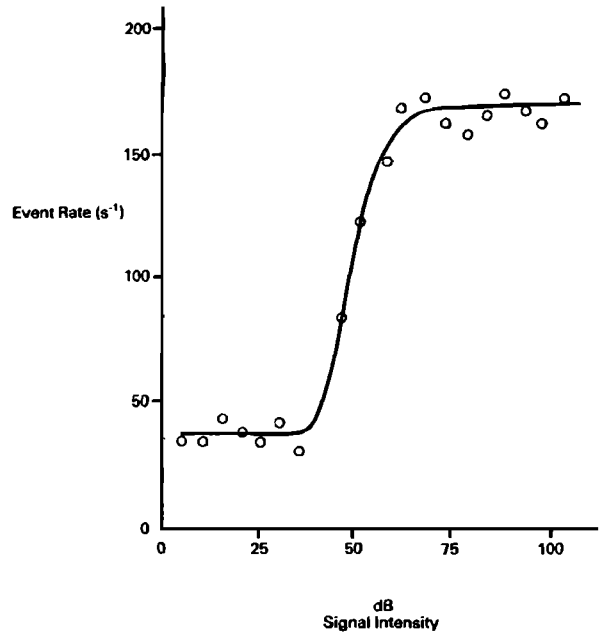


FIG. 4. Rate-intensity function using a single 2-s tone at each intensity level.

that they are less influential in the very short term but mediate slower processes such as adaptation and long-term recovery.

The hair cell being modeled is assumed to respond maximally at 1 kHz (best frequency). Mechanical frequency selective mechanisms and distortion effects are not simulated.

1. Rate-intensity function

Figure 4 presents the rate-intensity function for continuous tones of 2-s duration. The dynamic range of the function is approximately 25 dB. The spontaneous firing rate is 34 s^{-1} and saturation begins at 60 dB with a rate of approximately 170 s^{-1}.

2. Post-stimulus period histogram

Figure 5 gives period histograms for a 1-kHz sinusoid at various amplitudes sampled at a 20-kHz rate. The histogram develops the shape of a half-wave rectified version of the stimulus as intensity increases. At high intensity, the histogram shows a tendency to flatten at the peak. There is no sign of the left skewing at high intensities which troubled the Schroeder–Hall model.

3. Interspike interval histogram

Figure 6(a) shows how the distribution of intervals between successive events follows an approximate Poisson decay in the absence of any stimulation. Figure 6(b) shows an interspike interval (ISI) histogram for a 1-kHz tone at 70 dB. This result is in agreement with the expected pattern of intervals (Rose *et al.*, 1967).

4. Response to tone bursts

Special interest is attached to the response of the system to brief applications of a tone against a quiet background. In physiological preparations, tone onset causes an immediate rise in firing rate followed by a steady fall to an adaptation level. The rate of fall to the adaptation level is largely unaffected by the intensity of the tone or the preceding signal level. This feature has proved difficult to simulate in single reservoir models and was one of the justifications for introducing multiple site/reservoir systems in other recently published models.

Figure 7 shows the amount of the transmitter in the cleft during a session in which 6-dB increments are repeatedly given to a 1-kHz tone at intervals of 100 ms. Note that the cleft transmitter levels fluctuate from almost zero to the maximum shown within a single cycle of the stimulus sinusoid. We can use levels of synaptic cleft transmitter to represent the average firing rates because cleft transmitter levels are linearly, probabilistically related to event occurrences.

The adaptation level at each successive increment does not fall below that of the preceding adaptation level even though transmitter levels in the cell are falling throughout the session. In this respect, the model's performance is an improvement over that of Oono and Sujaku's (1975) model as investigated by Schwid and Geisler (1982).

When tones lasting 0.25 s are switched on against a background of silence, we can measure the onset rate (the

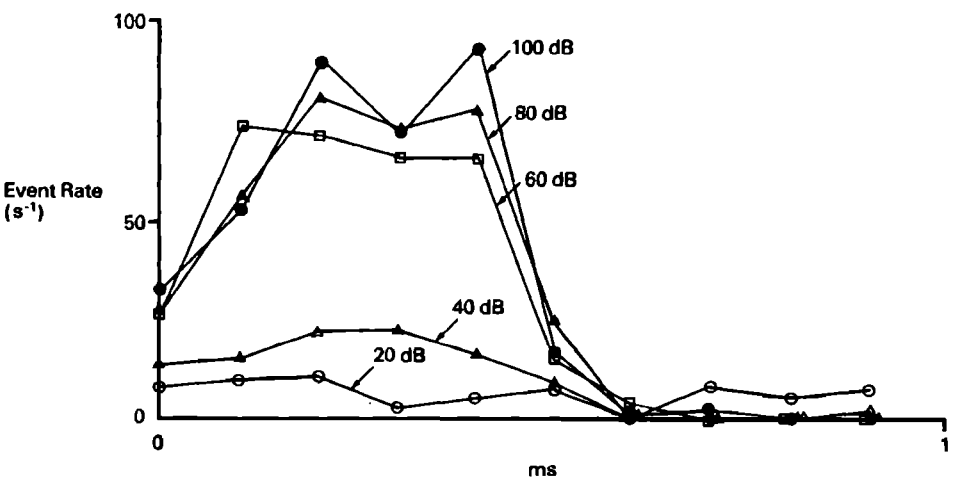


FIG. 5. Period histograms for 1-kHz sinusoids presented for 2 s each: 0.1-ms binwidth.

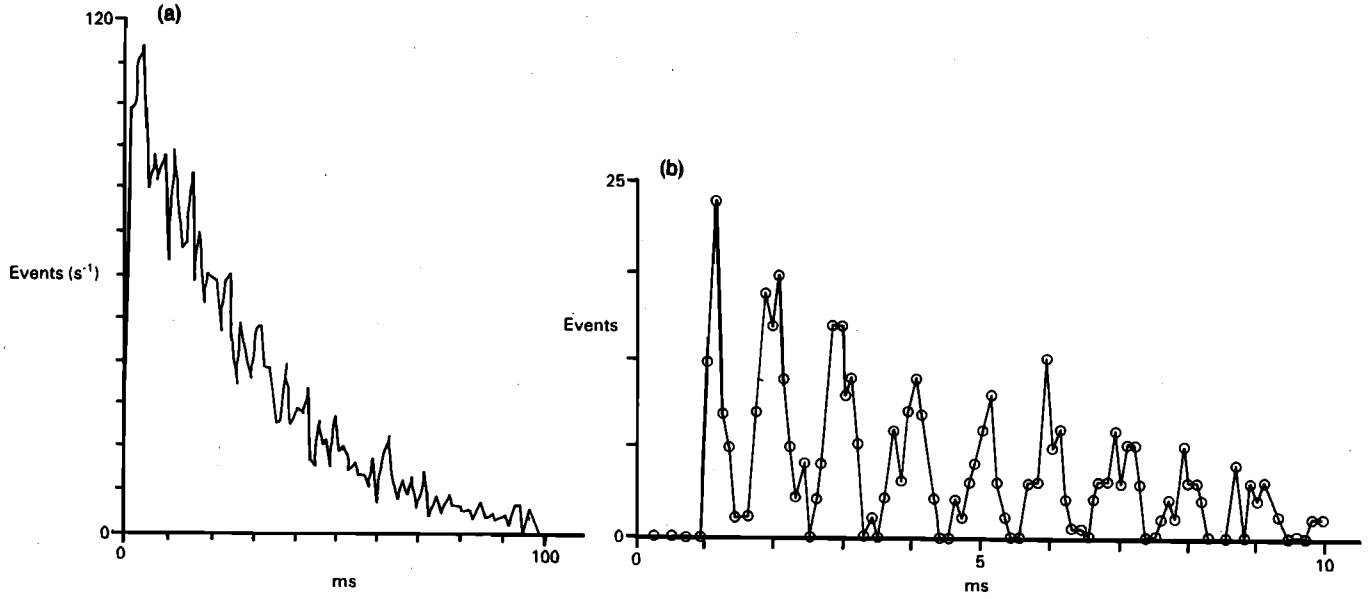


FIG. 6. Interspike interval histogram for (a) silence for 100 s (spontaneous event rate 33.2 events s^{-1}) and (b) 70-dB, 1-kHz sinusoid for 2 s (event rate 186.5 s^{-1}).

initial peak value), the steady-state rate (adaptation level), and the rate of decay between the two. Figure 8 shows the synaptic cleft contents resulting from a series of such pulses. Note that during the silent periods the cleft contents do not vary much except for a slow drift upwards. These results agree with physiological data whether based on post-synaptic potentials (Furukawa and Matsuura, 1978) or auditory nerve fiber firing rate (Smith and Brachman, 1982). The decay time constants do decline as the intensity increases but the effect is not great (38 ms at 45 dB and 23 ms at 100 dB). While such a decline is not reported in one laboratory (Westerman and Smith, 1984), it has been found in another (Yates *et al.*, 1985).

II. MODEL B

Model A illustrated how the introduction of a reuptake process permits us to dispense with the principle of multiple release sites and reinstate the principle of stimulus intensity control of the release fraction. The new model produced adaptation phenomena in addition to other standard features of auditory nerve activity.

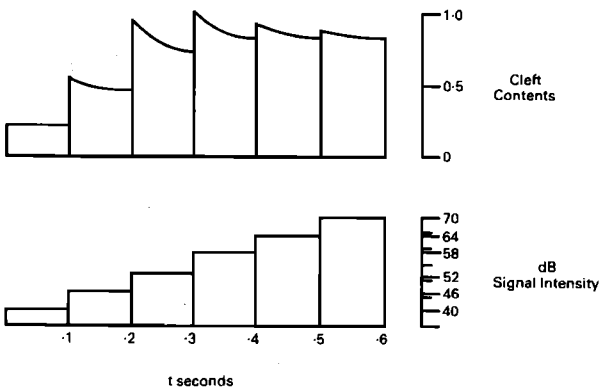


FIG. 7. Effect of 6-dB increments of a 1-kHz sinusoid on synaptic cleft contents $c(t)$. Each step lasts 0.1 s.

Model A is, however, lacking in at least two important respects. First, the rate of adaptation is perfectly uniform while short-term adaptation of auditory nerve fiber activity to abrupt signal onset has at least two components: one with a short time constant of 5 ms or less and another with a time constant of 30–50 ms. Second, model A is based on the unlikely assumption that the transmitter taken up from the cleft is immediately available for use as a free transmitter. Theories of the reuptake process usually require that the transmitter is broken down into inactive subcomponents in the cleft, where they are either lost by diffusion away from the cleft or taken up again into the cell to await reprocessing. This latter effect must be less than instantaneous.

A solution to the first problem has already been given by Ross (1982) and Smith and Brachman (1982), who used one or more reservoirs of transmitter between the original transmitter source and the regions of the free transmitter eligible for immediate release from the hair cell. Although

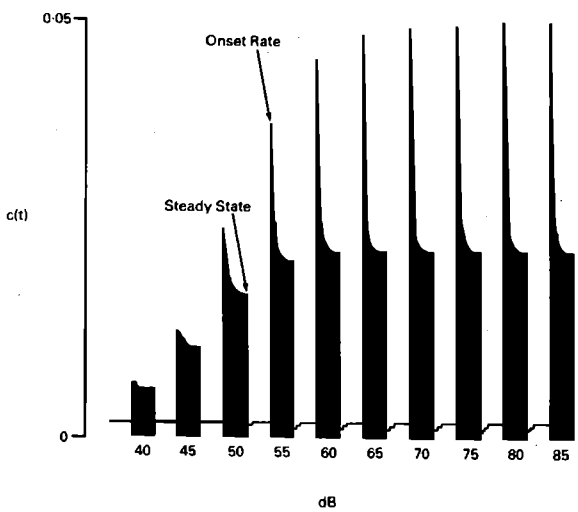
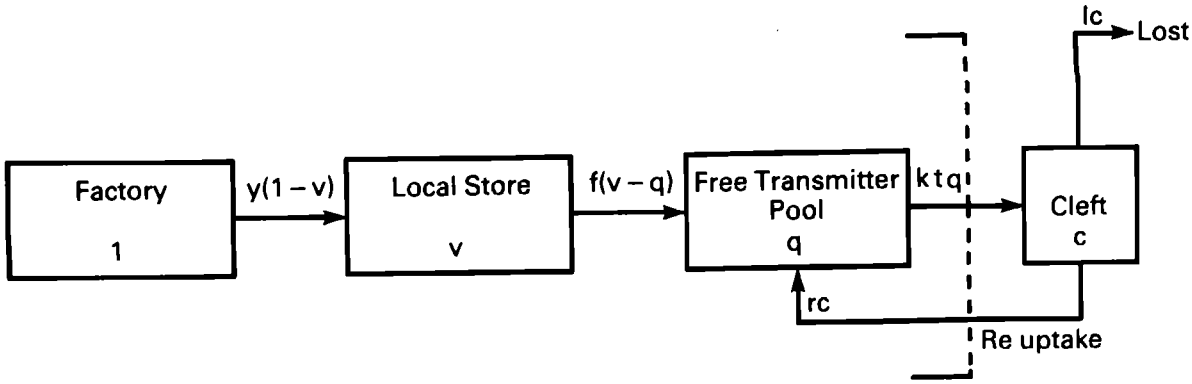


FIG. 8. Synaptic cleft contents, $c(t)$, in response to 1-kHz tone bursts lasting 0.25 s with intervening silence.



$$\frac{dv}{dt} = y(1 - v(t)) - f(v - q(t))$$

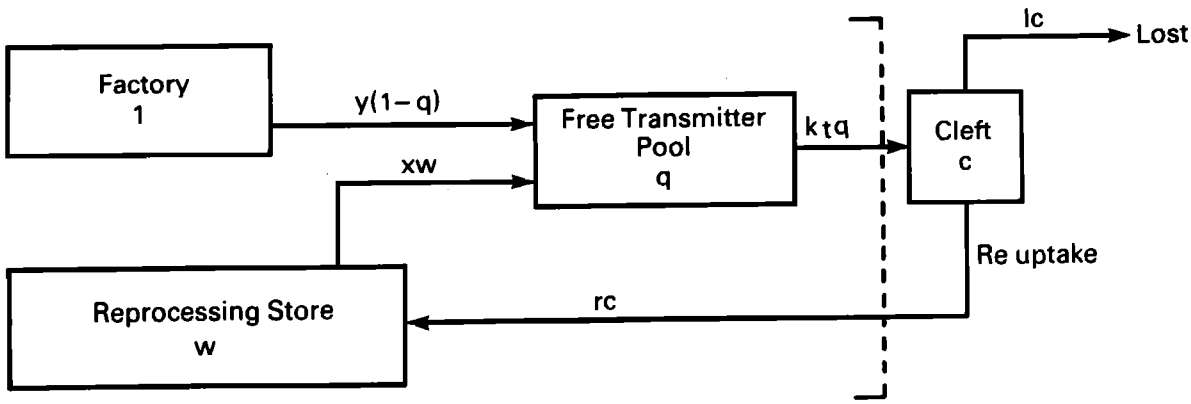
$$\frac{dq}{dt} = f(v - q(t)) - k(t)\,q(t) + rc(t)$$

$$\frac{dc}{dt} = k(t)\,q(t) - lc(t) - rc(t)$$

FIG. 9. Revision of original model incorporating a "local store" between the factory and the free transmitter pool.

neither solution can be translated directly into model A, the spirit of their mechanism is preserved in Fig. 9, which shows an amended version of model A with the associated differential equations. Computer simulation did indeed reveal a two-phase adaptation process but this amendment was abandoned in favor of another formulation which simultaneously addressed itself to the second problem of time delays involved in the reuptake of transmitter from the cleft.

Model B is illustrated in Fig. 10. The innovation here is that, following reuptake, the transmitter is subject to repro-



$$\frac{dq}{dt} = y(1 - q(t)) + xw(t) - k(t)\,q(t)$$

$$\frac{dc}{dt} = k(t)\,q(t) - lc(t) - rc(t)$$

$$\frac{dw}{dt} = rc(t) - xw(t)$$

FIG. 10. Model B, a revision of model A incorporating a reprocessing store for the transmitter substance taken up from the cleft.

Parameters

dt = 0·00005s	ydt = 0·001	rdt = 0·625	A = −8
gdt = 0·083	ldt = 0·025	xdt = 0·050	B = 320

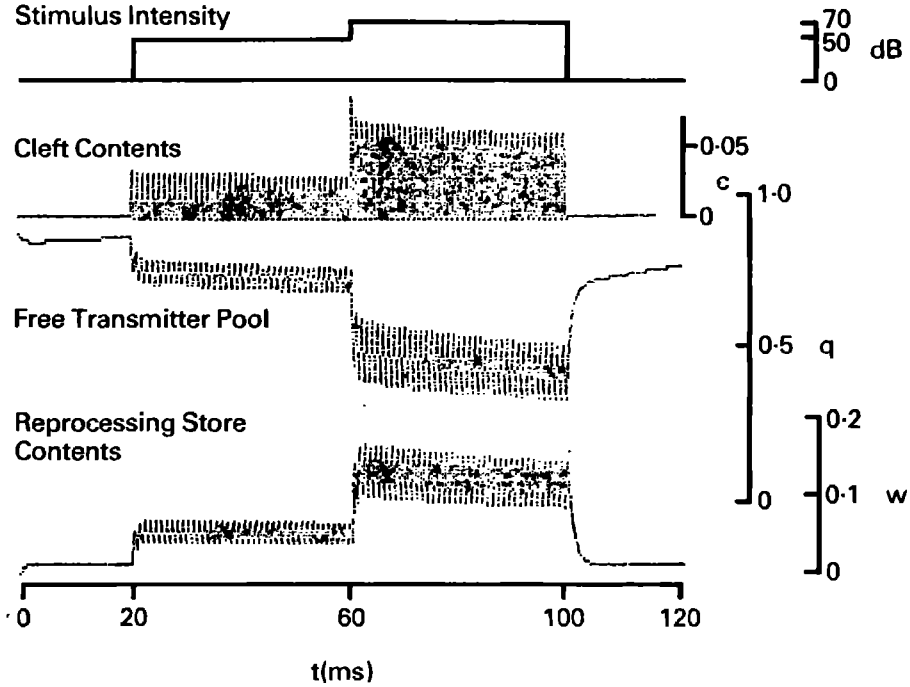


FIG. 11. Response of model B to a pedestal tone of 50 dB followed after 40 ms by an intensity increment of 20 dB.

cessing delays and, as a result, forms a reprocessing store which feeds the pool of the free transmitter eligible for immediate use. Following an abrupt stimulus onset, the free transmitter pool starts on a course of rapid depletion which is arrested by the arrival of reinforcements through the reprocessing loop. From this point, the free transmitter pool declines more slowly. This latter decline results from losses from the cleft. Eventually, these losses are balanced by a slowly increasing flow from the transmitter factory until an equilibrium is achieved and the system becomes fully adapted.

A. Computer simulation of model B

The response of the system to a pedestal tone of 50 dB followed immediately by an increment of 20 dB is illustrated in Fig. 11. The stimulus is a 1-kHz sinusoid and the pulses last 40 ms each (not enough to achieve complete adaptation). The rapid adaptation effect is best seen immediately after the increment onset. This is followed by a slower adaptation having a time constant of 42 ms.[1] Auditory nerve firing rate is assumed to be a linear function of cleft contents (c) after allowing for refractory effects. The scale of the diagram does not permit observation of the recovery of firing rate after the offset of the incremental tone. However, this can be observed in the recovery of q, the free transmitter pool, because during periods of silence the cleft contents are approximately a constant fraction $[A/(A+B)]$ of the free transmitter pool.

A more detailed exploration of the model using the pedestal plus increment technique of Smith and Zwislocki (1975) is shown in Figs. 12–14. Each successive pedestal was 6 dB higher (series A) or lower (series B) and the increment was + 6 dB (series A) or − 6 dB (series B). The silence period, pedestal, and increment duration were each 0.2 s allowing almost complete adaptation during each period. The key measures were pedestal onset rate, pedestal adaptation level, increment onset rate, and pedestal adaptation level. The *steady-state incremental response* was the difference between the increment onset rate and the immediately preceding pedestal adaptation level. The *onset incremental response* was the difference between a pedestal onset rate and the onset rate for the succeeding pedestal onset rate. Rates were based on a 1-ms window either immediately after the event or following 190 ms of adaptation.

Figure 13 shows the pedestal onset rates and adaptation steady-state levels across the range 30–90 dB. The steady-state function saturates earlier than the onset rate function, a result which is in agreement with Smith and Zwislocki's (1975) account. Figure 14 shows the event rate increment (series) and decrement (series B) for the steady-state incremental response and onset incremental response as a function of pedestal intensity. The two functions are parallel for stimulus increments (series A) but the adapted response is less marked than the unadapted response in series B. This result agrees with Smith and Brachman's (1982) account of their empirical studies of auditory nerve fiber activity in the Mongolian gerbil.

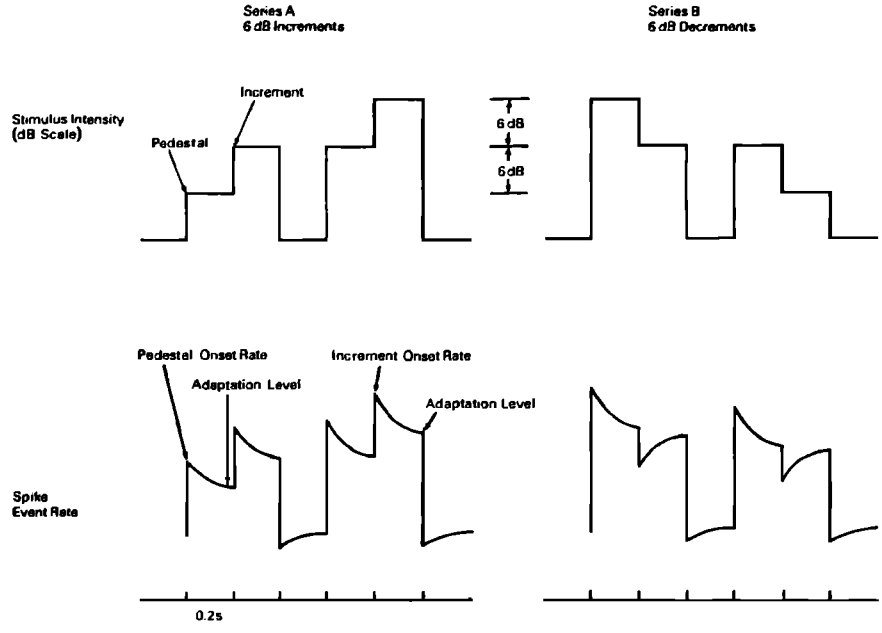


FIG. 12. Schematic representation of the pedestal plus increment technique of Smith and Zwislocki (1974) used to generate the results given in Figs. 13 and 14.

In Fig. 13, the onset rate adapts less quickly than the steady-state rate but the effect is not very clear because the permeability function is saturating very soon after the steady-state rate. To illustrate that these two processes are separable in the model, the demonstration described in the previous paragraph was repeated using different parameters. The value of B was increased from 320 to 5000 and (to keep the dynamic range in approximately the same place) *ldt* was changed to 0.25 and *ydt* to 0.05. The results of this simulation are given in Fig. 15.

III. DISCUSSION

Despite its simplicity, the model is successful in producing a wide range of phenomena normally associated with afferent auditory nerve fiber activity. The output from the system is a stream of events precisely located in time and suitable for input into a second stage such as a model of activity in brain stem units.

The multiple release site models of Schwid and Geisler (1982) and Smith and Brachman (1982) were both justified by their success in modeling adaptation phenomena.

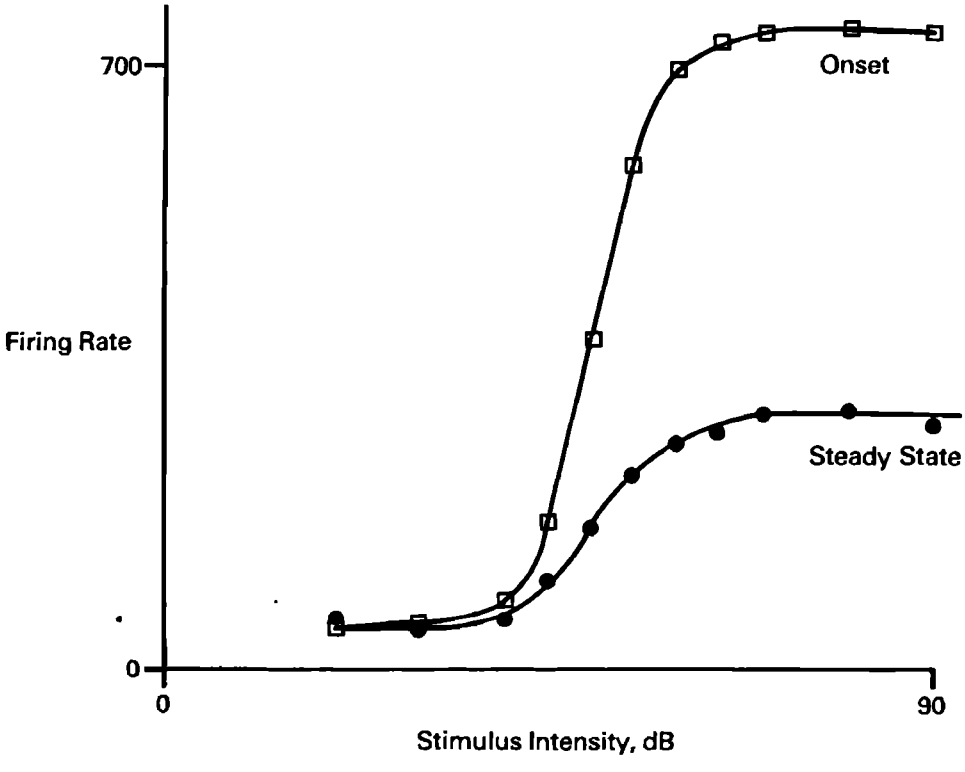


FIG. 13. Pedestal onset rates (squares) and adaptation steady-state rates (filled circles) for model B. See Fig. 12 and text for explanation.

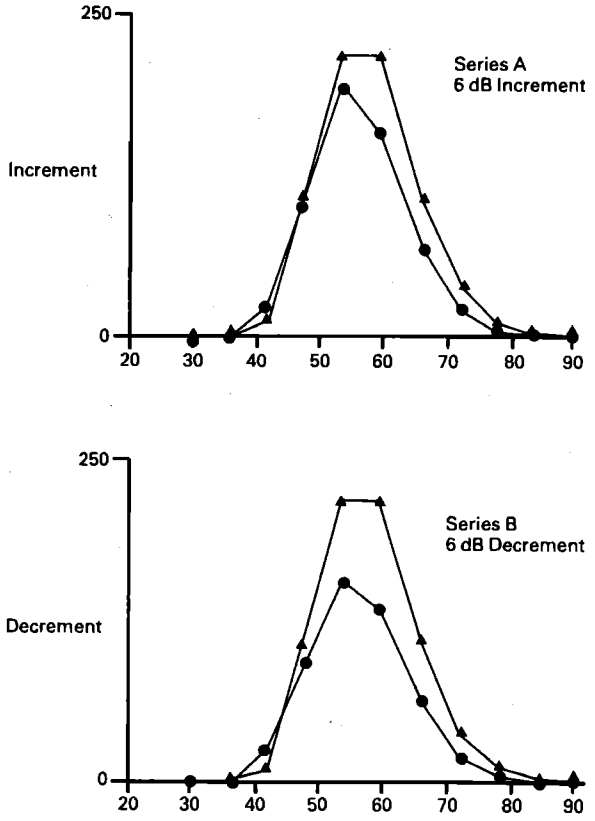


FIG. 14. Steady-state incremental response (filled circles) and onset incremental response (filled triangles) as a function of stimulus intensity using pedestal plus increment stimuli. See Fig. 13 and text for explanation. Series A, 6-dB increments. Series B, 6-dB decrements.

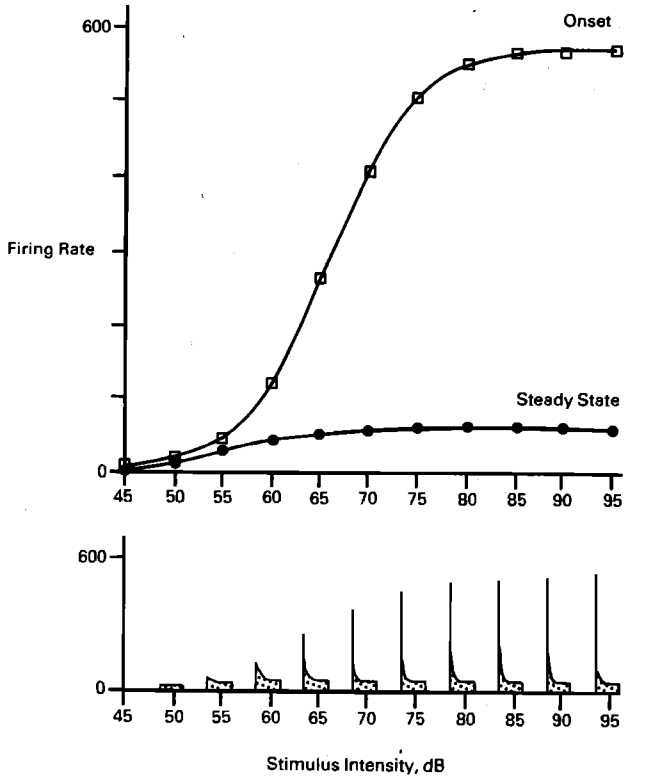


FIG. 15. Repeat simulation using the paradigm illustrated in Fig. 12, using the parameters given in Fig. 13 except for the following: $B = 5000$, $ltd = 0.25$, and $ydt = 0.05$.

Further justification was made in terms of Furukawa's work on EPSP's in the hair cell-afferent synapse in the goldfish sacculus (Furukawa *et al.*, 1978; Furukawa and Matsuura, 1978; Furukawa *et al.*, 1982). On the basis of their physiological studies, they concluded that the release fraction was a constant and was not influenced by stimulus intensity. They further concluded that the amount of transmitter available in the cell for release was not stable but fluctuated rapidly in accordance with stimulus intensity. This fluctuation was accounted for by the multiple release site hypothesis. Each site had its own transmitter quanta and its own release threshold. Once the stimulus exceeded the threshold for a given site, the transmitter quanta became eligible for release but each quantum then had a fixed probability of being released.

Since Furukawa's conclusions are directly opposed to the assumptions of the model presented here, the matter warrants further analysis. The argument hinges on whether the present model is also compatible with his physiological results, in which case Furukawa may have drawn the wrong conclusion about the mechanism.

The physiological data analyzed were the strengths of successive EPSP's (m) following an intensity increment or decrement. Using the binomial distribution, it was possible to express m in terms of two independent parameters n and p such that $m = np$. During experimental manipulation, it was found that p remained steady while n was responsive to stimulus intensity changes. It was then inferred that n referred to the population of transmitter quanta available for release at any given instant while p was the probability that an available quantum would be released from the cell into the cleft. If we further assume that every quantum entering the cleft contributes additively to the EPSP, it can be seen that the strength of the EPSP can be understood as the product of p and n.

The statistical analysis is not questioned but there is room for reinterpretation of the significance of the parameters p and n. This is possible if we assume that n represents the number of quanta in the cleft and p the probability that a given quantum will successfully traverse the cleft to influence the EPSP. This alternative interpretation is easier to defend in terms of current conceptions of synaptic activity. There is, of course, no reason to expect that stimulus intensity will influence the probability of traversing the cleft, once in it. As a consequence, we expect p to be invariant. There is every reason to expect the amount of transmitter in the cleft n to be linked to stimulus intensity. Therefore, the responsiveness of n to intensity changes and the lack of response of p are readily understood in conventional terms without recourse to the elaborate mechanism of multiple release sites each with their own threshold.

It follows that the model presented here is consistent with observations of Furukawa and his co-workers but provides an alternative interpretation of the significance of their results for an understanding of mechanism. Since model B is capable of demonstrating adaptive phenomena, it is prob-

ably as powerful as other recent models.

Model B has much in common with the recent models of Ross (1982) and Smith and Brachman (1982) in that the transmitter is compartmentalized into stores with only some of the transmitter available for immediate release. These stores are fueled from a "global store," "infinite reservoir," or "factory." The major difference concerns the principle of transmitter reuptake and reprocessing which is employed by neither Ross nor Smith and Brachman. Further, the present model avoids the use of multiple release sites which characterize the model of Smith and Brachman.

While it is tempting to regard the system as cascading reservoirs of the transmitter (cf. Ross), this would be misleading since the only concentration gradient used is that between the factory and the "free transmitter pool." Transfer into the cleft, reuptake, and outflow from the reprocessing store are all independent of concentration gradients. Future analysis may, however, show that these processes ought to be sensitive to concentration.

The simulations reported above did not quantize the transmitter substance, but this can be achieved by using integer arithmetic and setting the parameter M (maximum cell free transmitter) to a value much greater than one. When using very small time intervals, the movement of fractions of the transmitter quanta must be replaced by probabilities of movement of individual quanta but the net result is roughly the same. As a guide to the value of M, we might look again to Furukawa's results. If we assume that his "transmitter available for release" is, in fact, the "transmitter available in the cleft," we can tentatively use his figures to estimate our quantity $c(t)$. He gives a highest value of approximately 50 quanta, occurring immediately after a 90-dB tone onset. In the above study, $c(t)$ was rarely more than 5% of the maximum possible value of total system transmitter level, suggesting a useful starting value of 1000 for M. A quantized model using this value for M has been tested in exactly the same way as the unquantized model using the same parameters and gives results no different from those reported above.

ACKNOWLEDGMENTS

The author would like to thank Tony N. Pettitt and Brian C. J. Moore for helpful discussions during the preparation of this paper. The extension of model A to model B was stimulated by comments on the original manuscript by R.L. Smith and S. Ross.

[1]Recently, Yates *et al.* (1985) have confirmed the two-component nature of the adaptation effect but they disagree with Smith on the precise course of adaptation. The issue remains controversial.

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