Chapter 4

A temporal model of two-tone suppression

Introduction

There has been a lot of effort to understand the mechanisms of two-tone suppression (2TS) in the last three decades, through both experimental studies (e.g., Sachs, 1969; Arthur et al., 1971) and modeling (e.g., Sachs and Abbas, 1976; Geisler, 1992). Recently, this nonlinear phenomenon has been linked to the active process in the cochlea (the cochlear amplifier, CA), which in turn has been attributed to the function of the outer hair cell (OHC) (Dallos, 1992). However, most of the experimental studies have concentrated on the rate aspects of 2TS (see Chapter 2 for a review), and so have modeling studies of the same time period. In fact, there has been only one clear attempt to model the temporal aspects of 2TS reported in the literature (Geisler, 1992). With our present still-imperfect understanding of the rate aspects of 2TS, the additional knowledge to be gained by exploring its temporal aspects becomes important in our continuing attempts to understand this phenomenon and the cochlear amplifier in general.

Recently, there have been efforts to understand the temporal aspects of 2TS through experimental studies at different levels in the auditory peripheral: the basilar membrane (BM)

level (Patuzzi et al., 1984b; Ruggero et al., 1992; Rhode and Cooper, 1993), the inner hair cell (IHC) level (Patuzzi and Sellick, 1984; Russell and Kössl, 1992), and the auditory nerve (AN) level (Sachs and Hubbard, 1981; Sellick, et al., 1982; Patuzzi et al., 1984a; Cai and Geisler, 1994; Chapters 2 and 3). These studies provided experimental data for the present modeling work.

Model formulation

This model represents a small longitudinal slice of the organ of Corti, involving three OHCs (represented by a single composite OHC), one inner hair cell (IHC) and the organ of Corti within which they are located. The basic configuration of the model is shown in Fig. IV-1A. The characteristic frequency (CF) tone is amplified by the cochlear amplifier, the gain of which is a function of the output of the OHC. The suppressor (SUP) tone, the frequency of which is much lower than CF, is not affected by the CA and thus not amplified. The suppressor tone and the amplified CF tone are summed up to yield the BM displacement. This displacement is applied to the OHC branch to control the gain of the CA, and to the IHC branch to produce the firings on the auditory nerve fibers. Thus, the suppression of the CF response at the BM level is produced by dynamically reducing the gain of CA.

The IHC branch

The first stage in the IHC branch is a highpass filter, representing the fact that, based on CM data and IHC recordings (Sellick and Russell, 1980; Nuttall et al., 1981), the IHC appears to be responding to BM velocity at low frequencies. The corner frequency of this "hydrodynamic" filter, which was estimated between 200 and 1000 Hz in different studies

(Russell and Sellick, 1983, 200-600 Hz; Patuzzi and Yates, 1987, 400-1000 Hz), is varied in the model, usually between 400-600 Hz. The next stage, the transfer characteristic (I/O curve) of the IHC, is represented by an asymmetric curve in Fig. IV-1A. This curve has the same basic form as used in Geisler (1992) (as shown in Fig. IV-2A) and was derived from the transfer characteristic of an IHC studied in the basal turn of the guinea pig cochlea (Russell et al., 1986). The last stage in the IHC branch is a first-order lowpass filter with a corner frequency of 1200 Hz, representing the basolateral membrane filter of the IHC (Dallos, 1984).

The feedback/gain control loop

The OHC transfer characteristic is represented in Fig. IV-1A as a symmetric (antisymmetric, to be exact) curve. The basic formula for the curve, the hyperbolic tangent (Fig. IV-2B), is the same as used in Geisler (1992), which was derived from Russell et al. (1986). This saturating I/O curve is the main nonlinearity in the model and is responsible for producing suppression at the BM stage. The second block in the OHC branch is a first-order lowpass filter representing the basolateral membrane filter of the OHC. It has the same 1200-Hz corner frequency as its counterpart in the IHC branch.

As in Geisler's (1992) original form, the model makes no assumption about the particular mechanisms with which the CA operates, since they are still subjects of debate at this time. Instead, it simply assumes that the gain of CA is related to the OHC output, an assumption which has many experimental underpinnings (e.g., Geisler et al., 1990). The basic control signal for the CA gain is the normalized OHC output y(t), drawn either before (point a, Fig. IV-1A) or after the lowpass membrane filter (point b, Fig. IV-1A). The difference between

Fig. IV-2 Transfer characteristics of hair cells used in the model. A. The IHC transfer characteristic, generated with an equation of the form exp(x) / (1 + exp(x)). It has the same basic form as that of Geisler (1992). The small circle indicates the "resting point". B. Hyperbolic tangent form of OHC transfer characteristic, generated by the tanh(x) function. The basic form is the same as that of Geisler (1992). Shown in the figure is the symmetrical form, but it can be adjusted to produce asymmetric characteristics. The small circle indicates the resting point for the symmetrical case. An asymmetrical form is produced by moving the resting pointing along the curve, for example, the arrow indicates the resting point for an asymmetry of 0.8. The number indicating the degree of asymmetry is arbitrarily scaled, but it is proportional to sound pressure measured in Pascals. C. Rectangular hyperbola form of OHC transfer characteristic. It is modeled from the transfer characteristic of an apical OHC (Fig. 10 of Dallos, 1986). It is asymmetric as shown and has Ph and Pd (cf., Eq. 5) of -0.3 and 1.9, respectively. The downward arrow indicates an equivalent sound pressure of 80 dB SPL.

the two points of feedback will be discussed at the end of this section. Assuming the maximum amplitude of OHC output is Ydmax in the depolarizing direction and Yhmax in the hyperpolarizing direction, then

$$y(t) = Yohc(t) / Ydmax, \qquad Yohc(t) >= 0,$$
$$y(t) = Yohc(t) / Yhmax, \qquad Yohc(t) < 0, \qquad (1)$$

where Yohc(t) is the OHC output. For a symmetric transfer function, such as is shown in Fig. IV-2B, Ydmax equals Yhmax. The basic control signal y(t) is then used to produce the raw gain in the following way,

$$Gr(t) = \max \{Gmax * (1 - |y(t)|), 1\}, \qquad (2)$$

where Gmax is the maximum gain of the CA (Gmax = 1000, or 60 dB). This process is graphically represented in Fig. IV-1B by a full wave rectifier and an invertor (notice that the fundamental frequency of the signal is doubled by the rectifier). The minimum CA gain allowed is unity (i.e., no CA). Thus, when the output of OHC is zero, the raw gain is maximum; when the OHC fully saturates at either end, the raw gain is minimum. The raw gain Gr(t) is then lowpass filtered by a "gain-smoothing" filter (Fig. IV-1B) to give the CA gain G(t). This gain-smoothing filter has a corner frequency between 100 and 1000 Hz depending on the stimulus parameters used. Although it is hypothetical, its use is justified since by intuition and by the properties of tuned circuits, the gain of the CA cannot change instantaneously. This filter by itself does not produce additional suppression, however, it has great influence over the temporal characteristic of the suppression pattern observed at the BM stage and thus that at the IHC/AN stage.

For the particular transfer function (hyperbolic tangent) assumed (Fig. IV-2B), the raw gain is expressed as

$$Gr(t) = \max \{Gmax * (1 - |\tanh(1.2\ p(t))|), 1\}, \qquad (3)$$

where p(t) is the equivalent BM displacement (input to the OHC and IHC) and

$$p(t) = G(t)\ A_{CF} * \sin(2\pi f_{CF} t) + A_{SUP} * \sin(2\pi f_{SUP} t), \qquad (4)$$

with A_{CF} and A_{SUP} being the magnitudes (in Pascals) of the CF and SUP tones respectively. In addition to using the hyperbolic tangent to model the OHC transfer function, we also tried other gain control signals, including one of Geisler's (1992) original form (i.e., 5th root of slope of hyperbolic tangent function), a Boltzman function similar to that used by Santos-Sacchi (1992), and the rectangular hyperbola (Russell and Sellick, 1983). These different variations only gave quantitative differences: one form might achieve better results in one aspect than others, while it might not be as good in other aspects. In particular, the rectangular hyperbola form is much more flexible in adjusting the shapes of the transfer functions. An example of such an OHC transfer function, which is asymmetric, is shown in Fig. IV-2C. It was derived from the transfer characteristic of an OHC from the third turn of guinea pig cochlea (Dallos, 1986). In this form, the OHC output is

$$Yohc(t) = Ydmax * p(t) / (Pd + p(t)), \qquad p(t) >= 0;$$
$$Yohc(t) = Yhmax * p(t) / (Ph + p(t)), \qquad p(t) < 0, \qquad (5)$$

where Pd and Ph are the equivalent BM displacements producing half saturating (half-

maximum) outputs in the depolarizing and hyperpolarizing directions, respectively. In this report, we have only included data obtained using the hyperbolic tangent and rectangular hyperbola functions.

As stated earlier, there are two possible points from which to draw the feedback signal in the model (Fig. IV-1). Using the location *before* the lowpass membrane filter (point a) is equivalent to using the OHC transduction current as the feedback signal (since the voltage is in phase with the transduction current before the lowpass filtering); while using the location *after* the lowpass filter (point b) uses the OHC membrane voltage as the feedback signal. The response-level curve at the BM stage with the CF tone as stimulus is shown in Fig. IV-3 for the current feedback location (point a). The curve is initially nearly linear, then compresses at higher intensities (with a slope of about 0.5) and returns to linear at even higher intensities. This sigmoidal characteristic is similar to what has been observed experimentally (Rhode, 1971; Johnstone et al., 1986). If the feedback is drawn after the lowpass filter, there is not much difference for lower CF cases, but for higher CF cases, since the high-frequency CF tone is strongly filtered, there is little or no feedback to the cochlear amplifier, thus the response-level curve is linear in the whole intensity range. For the figures shown in this paper, the feedback is drawn before the lowpass filter. With this particular setting, the OHC basolateral filter plays no role in the gain control mechanism.

Results

1. Two-tone responses

A low-CF example

Figure IV-4 shows some outputs (IHC receptor potentials) of the model, in which a rectangular-hyperbola type of OHC transfer function similar to Fig. IV-2C was used. The CF tone was 2000 Hz, presented at 30 dB, while the suppressor was a 100-Hz tone with intensities stepped between 80 and 95 dB SPL. To better visualize the responses, two complete cycles of response are plotted in each panel. At 80 dB, there is very little suppression, but the response amplitude is modulated by the suppressor tone. This result agrees with the experimental finding that, in AN-fiber discharge patterns, the synchronization threshold in the two-tone response is generally below the suppression threshold (Javel et al., 1983; Chapter 2). At 85 dB, there is a significant suppression at about 8 ms (downward arrow), which is leading the excitation phase due to the suppressor tone alone (left-pointing arrow) by about 2.5 ms, or 1/4 cycle of the suppressor tone. This phase relationship is also similar to actual AN data for these frequencies (Chapter 2). Another feature in the response is the asymmetry in the waveform (i.e., the response peaks are not symmetric and neither are the valleys), phenomena which are also observed in AN data (cf. Fig. II-3 of Chapter 2). Increasing the suppressor intensity by another 5 dB to 90 dB SPL produces a secondary suppression (arrow), which is about half a cycle away. At 95 dB, the response is basically due to the suppressor tone alone, although the CF component still can be seen near the major peak. The overall waveforms as well as some of the details in the responses shown in the figure are very similar to those of an AN fiber we studied experimentally (Chapter 2, Fig.

Fig. IV-4 Inner hair cell voltage in a low-CF simulation. The 2000-Hz CF tone was presented at 30 dB. The suppressor was a 100-Hz tone and its intensity was varied as indicated in the figure. Rectangular hyperbola form of OHC transfer function (Fig. IV-2C) was used to generate the results (Pd = 1.8, Ph = -0.3). The corner frequency of the gain-smoothing filter was set to be 200 Hz and a 500-Hz IHC highpass filter was used. At a suppressor intensity of 85 dB, the model produced a suppression phase (downward arrow) which is leading the phase of excitation to the suppressor tone alone (left-pointing arrow) by about 1/4 cycle. At 90 dB, there is also a secondary suppression (arrow) which is about half a cycle away from the major one. At all intensities, the maximum two-tone response level is higher than the CF-alone response level (dashed lines). See text for details.

II-3). Our final observation about this figure is that although suppression is produced by adding the suppressor tone, the peaks of the two-tone responses are higher than the CF-alone response level (denoted by the dashed lines in the figure). This is similar to two-tone responses observed in the IHCs (Russell and Kössl, 1992 in the base; Cheatham and Dallos, 1992a in the apex) and in AN fibers with high spontaneous rates (SRs >= 20/s), but differs from that observed in lower-SR (< 20/s) AN fibers, for which the peaks of the two-tone responses are usually lower than the CF-alone response level (Chapter 3).

Asymmetry of OHC transfer function

In two-tone suppression experiments, two phases of suppression are often observed to occur during one cycle of the suppressor tone. Such results can be readily obtained in the model using a more or less symmetrical OHC transfer function. But two phases of suppressions are not a universal feature in the two-tone responses of auditory nerve fibers: while fibers with higher CFs tend to show two-suppressions in one cycle of the suppressor tone, those with lower CFs tend not to (Chapter 2). Even for the higher CF fibers, the two phases of suppression do not usually appear at the same suppressor intensity. In particular, we have shown (Fig. II-17 of Chapter 2) that fibers with similar CFs from the same experiment showed different suppression characteristics: some showed only one phase of suppression, while others showed two phases of suppression. Among the later, the phase of the major suppression was variable. This rather complex pattern can be modeled by adjusting the degree and direction of asymmetry of the OHC transfer function (Fig. IV-5). For easy adjustment of the OHC asymmetry, a hyperbolic tangent OHC transfer function (Fig. IV-2B) was used to produce these results. To facilitate comparison with the corresponding experimental data, this figure is arranged the same way as Fig. II-17 of Chapter 2 and only

Fig. IV-5 Inner hair cell voltage demonstrates effects of OHC asymmetry on the phases of suppression (CF tone: 2000 Hz, 30 dB; suppressor: 100 Hz). A hyperbolic tangent OHC transfer function was used to produce these results. The number in each plot indicates the asymmetry of OHC transfer function (cf., Fig. IV-2B). The directions of OHC asymmetry are shown graphically in the right column. To facilitate comparison with the corresponding experimental data, this figure is arranged a similar way as Fig. II-17 in Chapter 2; only one cycle of the responses was shown.

one cycle of the responses was shown. In the third row, for which a symmetrical OHC function was used, the two phases of suppression which appear at 85 dB (arrows) are about equal in depth and are separated by half a cycle. Changing the degree and direction of OHC asymmetry produced a continuous spectrum of change in the suppression pattern. When the OHC asymmetry is changed in the depolarizing direction (row two), the suppression in the first half cycle became shallower, although the phase did not change. A further increase of the asymmetry in this direction almost eliminated the minor suppression (top row). Change of the OHC asymmetry in the other direction reduced (row four) or eliminated (bottom row) the lagging phase of suppression. It should be noted that the different types of OHC transfer characteristics we used have been observed experimentally (Russell et al., 1986; Dallos, 1986), although the hyperpolarizing ones are not very common (Cody and Russell, 1987; also can be inferred from the responses shown in Fig. 1 of Russell and Kössl, 1992). This successful simulation of the AN data demonstrates the leading role of the model's OHC transfer function in producing different suppression patterns. It also suggests that OHCs from similar BM regions can have quite different characteristics.

Effect of gain smoothing filter

In the gain control loop, there is a lowpass filter to "smooth" the raw gain (Fig. IV-1B). Figure IV-6 shows the effect of this stage on the gain of CA when suppressors of different frequencies are used. The corner frequency of the gain-smoothing filter was fixed at 200 Hz. The CF tone, which was 2000 Hz, was presented at 30 dB, and the suppressor tone was presented at two intensities: 80 and 95 dB. Suppressor frequencies of 100 Hz (upper panel) and 200 Hz (lower panel) were used. Two cycles of gain are plotted in each case. For 80-dB stimulation, it can be seen that the minimum gain goes lower in the 100 Hz case than in

the 200 Hz case. The effect is more dramatic when the suppressor is presented at 95 dB: in the 100 Hz case, the gain can basically go back to the unsuppressed value (a peak near 10 ms, with a height around 350, arrow in upper panel); while in the 200 case, the gain is greatly reduced at all phases, with maximum gain around 150 (arrow in lower panel). Such peaks in the gain functions correspond to the zero-crossing moments in the input to the OHC. At those moments, the output of the OHC stage is minimal and thus the raw gain is maximal. This pattern in the gain function (i.e., higher zero-crossing peaks when a lower-frequency suppressor was used) is similar to what was observed experimentally in the discharge patterns of some lower-SR AN fibers (Chapter 2). In the example shown in Fig. II-25 of Chapter 2, the *same* fiber showed complete suppression with a 100-Hz suppressor, but with a 50-Hz suppressor, small responses remained at two phases which presumably correspond to the zero-crossing moments in the input to the OHC.

Effect of IHC stage

One advantage of a model is that it is easy to isolate and study a particular part in an integrated structure, which might otherwise be difficult and sometimes impossible to do experimentally. In this section, we disabled the feedback loop by fixing the gain of the cochlear amplifier, leaving only the IHC branch at work. The results are shown in Fig. IV-7. In the top panel, the inputs to the IHC (response at the BM level) are shown for CF-alone and when the CF tone is added to the low-frequency suppressor (100 Hz). It can be seen that the maximum level reached in the two-tone case is much bigger than that in the CF alone case. The outputs of the IHC are shown in the middle panel. As compared to the CF-alone response, the two-tone response is suppressed at some phases, and increased in some other phases. But the increase is smaller than the decrease, so the average ("net") effect of the

Fig. IV-7 Inner hair cell voltages showing suppression produced by the IHC stage alone. The CA gain was fixed so that there was no suppression produced at the BM stage. The corner frequency of the IHC highpass filter was 472 Hz. The 2000-Hz CF tone was presented at 30 dB and the 100-Hz suppressor tone was presented at 100 dB. A. Input signals to the IHC stage. The CF-alone case is represented by the dotted line. B. IHC voltages. In the two-tone case (CF + SUP, solid line), there was suppression at some phases and enhancement at other phases, but the suppression was more than enhancement, so the net effect is suppression. C. The SUP component in the IHC output (two-tone case) was attenuated by a first-order highpass filter (1500 Hz) to emphasize the suppression of the CF component produced by the IHC stage. Notice that the CF component was also slightly attenuated by this filter.

suppressor tone on the IHC response is suppressive (cf. Geisler, 1992). The suppression of the CF component in the IHC response is seen more clearly in the bottom panel, where the low frequency suppressor component in the IHC response is filtered out by a highpass filter. The suppression of the CF component is obvious at the phase corresponding to the negative peak of the suppressor tone. Another observation concerns the relative phases of suppression and of excitation due to the suppressor tone alone. It can be seen from the middle panel that the envelope of the two-tone response is synchronized to the suppressor tone and that the phase difference between suppression and excitation is exactly half a cycle.

Suppression in high-CF cases

When the frequency of the CF tone is high, the CF component at the IHC output is attenuated by the membrane filter. Thus a slightly different suppression pattern is observed at the IHC stage although the response pattern at the BM stage is similar to those in lower-CF cases. In Fig. IV-8, we show an example with a high-CF tone (10 kHz) and a higher-frequency suppressor (1000 Hz). With such a high-CF tone, the CF component at the IHC output is heavily attenuated by the basolateral membrane filter (Fig. IV-8C). At suppressor intensities of 70 and 75 dB, there is basically no suppression at the BM stage (Fig. IV-8B), which can be seen more clearly in the CA gain (Fig. IV-8A), yet at the IHC stage the response is phasic (Fig. IV-8C), with a minimum near 0.8 ms (downward arrows) and a peak about half a cycle away at near 1.3 ms (left-pointing arrows). The AC response due to the CF tone is also suppressed, with a minimum slightly earlier than the minimum point in the "DC" response. This suppression of the CF component is obviously due to the same rectifier-based suppression at the IHC stage as shown in Fig. IV-7. At 80 and 85 dB, there are clear suppressions of the CF component at the BM stage near 0.9 ms (arrows), which are

Fig. IV-8 A high-CF example. The CF tone was 10 kHz in this case, and it was presented at 30 dB. The suppressor was a 1000-Hz tone. The suppressor intensities are indicated in the figure. Rectangular hyperbola form of OHC transfer function was used to produce the results (Pd = 1.8, Ph = -0.1). The corner frequency of the gain-smoothing filter was set at 1000 Hz. A. The CA gain functions when the suppressor tone was presented at 70 and 80 dB respectively. B. The responses at the BM stage. Arrows indicate suppressions of the CF component. C. The responses at the IHC stage. The left-pointing arrows indicate the phases of excitation due to the suppressor tone alone, and the downward arrows indicate the minimums in the IHC potentials. See text for details.

very close to the minima in the IHC outputs. At the same intensities, the basic patterns in the IHC output do not change very much except that there is more suppression of the CF component. At all intensities, the response pattern at the IHC stage is heavily influenced by and synchronized to the suppressor tone.

To further investigate the role of the IHC in the high-CF, higher-frequency suppressor case, we repeated the same procedure as in Fig. IV-7 (i.e., disabled the feedback loop by fixing the CA gain), using a 10-kHz CF tone and a 1000-Hz suppressor. The results are shown in Fig. IV-9. The top panel shows the input to the IHC stage (Fig. IV-9A). The middle panel (Fig. IV-9B) shows the responses of the model to the suppressor-tone alone and to the two-tones. It is clear that the minimum in the two-tone response is at about 0.75 ms (downward arrow), which leads the minimum in SUP-alone response (dashed line) at about 0.85 ms (upward arrow) slightly. By removing the suppressor component in the two-tone response through "band-stop" filtering, it can be seen that the CF component in the two-tone response was phasically suppressed, with a minimum at about 0.65 ms (arrow in Fig. IV-9C). This minimum leads the minimum in the unfiltered two-tone responses (downward arrow in Fig. IV-9B). Also, the maximum response level in the two-tone case is actually lower than that in the SUP-alone case, suggesting the CF tone is suppressing the response to the suppressor tone. This suppression of the suppressor tone response by the CF tone is due to the saturating nature of the IHC transfer characteristic.

We have shown in Fig. IV-7 that with IHC suppression the two-tone response is synchronized to the suppressor tone, thus the minima in the both single-tone and two-tone responses appear at the same time. How to account for the difference in minima in Fig. IV-9? This small difference is in fact due to the basolateral membrane filter of the IHC. The

Fig. IV-9 Another example of suppression produced at the IHC stage. The 10-kHz CF tone was presented at 30 dB and the 1000-Hz suppressor tone was presented at 85 dB. Other settings were the same as for Fig. IV-7. A. Input signal (BM displacement) to the IHC stage. B. IHC potentials. The dotted line represents the SUP-alone response. In the two-tone case (CF + SUP), the suppressor component dominated the response, but the suppression of the CF component can still be seen. C. The SUP component in the IHC output (two-tone case) was "removed" through "band-stop" filtering (25-5000 Hz, 6 dB/Oct on both sides) to emphasize the suppression of the CF component produced by the IHC stage. The "band-stop" filtering was realized by adding the lowpass (25 Hz) and highpass (5000 Hz) filtered two-tone responses.

suppression pattern in the IHC response is carried by the "amplitude-modulated" like signal (cf. Fig. IV-9C), which is high-frequency in nature (with center frequency at CF). For a 10-kHz CF tone, it is well above the corner frequency of the IHC basolateral membrane filter (~1200 Hz) and it is subject to a phase delay of about 90 degrees. This phase delay corresponds to only about 0.025 ms in time delay. Thus there is basically no change in the position of the minimum in the CF component of the two-tone response after the membrane filter. The phase delay on the 1000-Hz suppressor tone, however, corresponds to a relatively large time delay (a 90-degrees phase delay corresponds to a 0.25-ms time delay), producing a difference between the points of minima in the CF component of the two-tone response and SUP-alone response. The minimum point in the full two-tone response is thus between the two and leads the minimum point in the SUP-alone response slightly. Such relationships (i.e., the minimum in a two-tone response leads that in the SUP-alone response) have been observed experimentally for high-CF and higher-frequency suppressors (Fig. II-28 of Chapter 2).

2. Tone-pip responses

Cheatham and Dallos (1994) studied the effect of low-frequency (LF) biasing tone (20 Hz) on the response of hair cells to tone-pips (also Dallos and Cheatham, 1992). They found that, depending on the phase of the LF tone at which the tone-pips were placed, the responses to the tone-pips were affected differently. Such experiments were simulated with the present model. A 50-Hz tone serves as the low-frequency biasing tone, and the tone-pip (CF tone, 5 kHz) is placed at the positive, negative or zero-crossing phases of the LF tone. The positive and negative phases of the LF tone provide the tone-pip biases towards the depolarizing or hyperpolarizing directions of the OHC transfer curve, respectively, which

correspond theoretically to the maximum displacements towards scala vestibuli (SV) or scala tympani (ST) of BM motion, while the zero-crossing of the LF tone corresponds to maximum BM velocity. The simulated OHC responses are shown in Figs. IV-10 and IV-11. Figure IV-10 is arranged in a similar way as Fig. 1 of Cheatham and Dallos (1994). The top panel shows the response to the tone-pip alone. The response is highly asymmetric in the positive (depolarizing) direction. In the middle panel, the response to the tone-pip when it occurs at the low-frequency phase corresponding to maximum BM displacements towards ST and SV respectively are shown. Each tone-pip response is directed towards the unbiased position. The same responses with the low-frequency component removed are shown in the bottom panel. When the BM is biased towards ST, the response to the tone-pip is further "displaced" towards the positive direction as compared to the case without biasing. When the BM is biased towards SV, the response to the tone-pip is also asymmetric, but towards the negative direction. These response characteristics are very similar to the responses obtained from the organ of Corti (Cheatham and Dallos, 1994, Figs. 1 and 2) and in individual OHCs (Fig. 13 of Dallos and Cheatham, 1992; Fig. 10 of Cheatham and Dallos, 1994). When the tone-pip is placed near the point of maximum velocity, however, the effects, as shown in Fig. IV-11, are minimal, as was also observed by Cheatham and Dallos (1994, Fig. 3).

Since the LF biasing tone is mostly filtered out by the highpass filter in the model (cf. Fig. IV-1A), we expect that its effect on the IHC response is minimal. The responses of the simulated IHC to the tone-pip alone and with 50-Hz biasing are shown in Fig. IV-12. In order to compare with the comparable experimental data of Cheatham and Dallos (1994, their Fig. 11), the responses to the 50-Hz tone alone were subtracted. With the tone-pip alone, the response is highly polarized to the positive direction. When the tone-pip was

Fig. IV-10 The model's OHC responses to 5000-Hz tone-pips and a 50-Hz biasing tone. The tone-pips and the biasing tone were presented at 40 and 75 dB, respectively. Hyperbolic tangent form of OHC transfer function (with an asymmetry of -0.3) was used to generate the outputs. The asymmetry is not required to simulate the basic pattern as observed by Cheatham and Dallos (1994). The top panel shows the response to a tone-pip alone. In the middle panel, the responses to tone-pips and the biasing tone are shown when the tone-pips were placed at the moments when the BM was biased with maximum displacement towards scala tympani (ST) and scala vestibuli (SV) respectively. The bottom panel shows the same responses as in the middle panel but with the responses to the biasing tone subtracted.

placed at different phases of the biasing tone, the basic responses are similar to the case of tone-pip alone, except that when there is a biasing tone it takes longer time to reach the maximum response level. These characteristics are similar to those in the comparable IHC data of Cheatham and Dallos (1994).

3. Suppression of the responses to a low-frequency tone by a CF tone at the OHC stage

Cheatham and Dallos (1994) also studied the effect of the CF tone on the LF tone in the OHC/organ-of-Corti responses, in which the LF response was suppressed by the CF-tone. Our model also produced similar results. In Figs. IV-13 and IV-14, some examples of model outputs at the OHC stage are shown. The intensity of the CF tone was usually fixed at a certain level (e.g., 40 dB in Fig. IV-13A) while that of the LF tone was varied. The thin lines are the responses to the LF tone alone while the thick lines are the two-tone responses (with the CF component attenuated through lowpass filtering at 1500 Hz). Similar to Fig. 4 of Cheatham and Dallos (1994), there is obvious suppression of the LF component in the model output (Fig. IV-13A). There is an inverse relationship between suppression and the intensity of the LF tone. This suppression of the LF responses is due to the same mechanism that reduced the CF component in the OHC output (i.e., saturation of OHC transduction current). At a LF intensity of 90 dB, the model output shows “asymmetric” behavior in the positive half cycle: there is more suppression in the rising limb (arrow), which was not present in the experimental data (Fig. IV-4A of Cheatham and Dallos, 1994). This difference between our model output and the experimental data suggests a faster onset of suppression of the cochlear amplifier (see Discussion).

The suppression of the LF responses by the CF tone is a strong function of the CF intensity.

When the intensity of the CF tone was increased to 45 dB (Fig. IV-13B), more suppression is achieved at each of the respective LF intensities, which is expected. However, when the intensity of the CF tone was decreased to 35 dB, as shown in Fig. IV-14, the situation became slightly more complex. From a LF intensity of 85 dB to 80 dB, the amount of suppression of the LF component on the positive side increased, but further decreasing the LF intensity results in less suppression of the LF response on the positive side. Such behavior is due to the fact that the combined input of the LF tone and the CF tone is not large enough to drive the OHC to saturation at this direction. These figures show that the suppression of the LF responses by the CF tone is also a function of the LF intensity.

Discussion

1. Summary of results

This phenomenological model, although an over-simplification, does a very good job in simulating some of the 2TS results.

a. The model produced temporal suppression patterns which are very close in general characteristic to those observed in AN fibers, with the phase of suppression leading the phase of excitation due to the suppressor tone by about a quarter of a cycle for a lower frequency suppressor and about half a cycle for a higher frequency suppressor (Chapter 2).

b. By changing the direction and degree of the asymmetry of the OHC transfer function, the model can simulate different suppression patterns displayed by AN fibers, such as varying

phases of the major suppression and the occurrence and degree of the minor suppression (Fig. II-17 of Chapter 2), and the fewer secondary suppressions in lower-CF fibers.

c. While the temporal pattern of the model response is similar to what was observed experimentally in AN fibers, the *amplitude* pattern agrees with those observed in IHC and high-SR fibers but *differs* from those in lower-SR fibers (Chapter 3). The significance of this difference will be discussed in part 5 of this section.

d. By using only the IHC stage, the model produced suppression that is similar to some of those observed experimentally.

e. With no additional changes whatsoever, the model also simulated successfully the tone-pip data and the suppression of the LF component by the CF tone reported by Cheatham and Dallos (1994).

All of these successful simulations suggest that the basic assumption in our model (saturation of OHC current produces suppression) can account for a wide variety of two-tone phenomenon.

2. The gain-smoothing filter

Contained in the model's CA is a lowpass filter to "smooth" the gain so that it does not change instantaneously. This smoothing corresponds to the transient time of a highly tuned circuit (Hayt and Kemmerly, 1986). For a fixed corner frequency, the effect on the suppression pattern produced by suppressors with different frequencies is slightly different

(Fig. IV-6). If the SUP frequency is lower than the corner frequency, there is no suppression at the SUP phases corresponding to the zero-crossing points in the input waveform, even at high intensities, because at those moments there is no output at the OHC stage and so the raw CA gain equals the maximum gain. In this case, the filter is "fast enough" to follow the changes in the raw gain (Fig. IV-6, 100 Hz case), and a highly phasic suppression pattern occurs. However, if the suppressor frequency is equal to or higher than the corner frequency of the gain-smoothing filter, the filter output cannot change fast enough to follow fully the changes in the raw gain. In this case, a less phasic and a more nearly tonic reduction of the CA gain results (Fig. IV-6, 200 Hz case). This "tonic" suppression, combined with some unknown mechanisms that produce the main tonic suppressions seen in low-SR fibers (see Chapter 3, also part 5 of this section), provides the basis for complete suppression in those fibers (Chapter 2). The fact that in the *same* low-SR fiber, complete suppression was produced by a 100-Hz suppressor but not a 50-Hz suppressor (Fig. II-25 of Chapter 2) supports the role of this gain-smoothing filter in producing complete suppression in some fibers, although this role is secondary as compared to the mechanisms that produce the main tonic suppression in low-SR fibers. The same data also suggest that the corner frequency of the filter is more likely dependent upon the CF region the fiber originates in than a function of the suppressor frequency.

Since phase-specific suppression has been observed at both BM (Rhode and Cooper, 1993) and neural (Sachs and Hubbard, 1981; our Chapter 2) levels for suppressors of at least 1000 Hz in the basal region of the cochlea and sometimes 4000 Hz in some AN fibers (Chapter 2), the corner frequency of the gain-smoothing filter must be quite high in the high-CF region. On the other hand, complete suppression can be achieved in some AN fibers even with a 100-Hz suppressor, suggesting that the corner frequency of this filter can be quite low. In our

model, the corner frequency is set to be around 200 Hz (Fig. IV-4) for low-CF and lower-frequency suppressor cases, and a larger value is used to get phase specific suppression in high-CF and higher suppressor frequency cases (e.g., 1000 Hz used for a CF of 10 kHz in Fig. IV-8), and both achieved realistic results. In the 1000-Hz BM example of Rhode and Cooper (1993, Fig. 9), they noticed that the suppression is delayed by 0.1 ms delay (or 36 degrees) relative to maximum displacement of BM towards either scala, which could be easily accounted for by a filter corner frequency of slightly higher than 2000 Hz (with a 2000 Hz lowpass filter, the delay would be 45 degrees, or 0.125 ms).

In producing the model results, we used OHC transduction current as the feedback signal. This signal is transformed and lowpass filtered by the gain-smoothing filter. Thus, the CA gain lags the current signal by up to 90 degrees at high frequencies (smaller phase lag at lower frequencies) and is approximately in phase with the OHC voltage. This agrees with the findings that the OHC voltage drives the cochlear amplifier (e.g., Dallos, et al., 1991), and that the current is leading the OHC motility (which is in phase with membrane voltage) by about 90 degrees (except at very low frequencies) (Santos-Sacchi, 1992).

An interesting and important question concerns the physical basis of the gain-smoothing filter. An obvious candidate is the basolateral membrane filter of the OHC. Both the gain-smoothing filter and the OHC membrane filter are lowpass in nature, and the time constants needed by the gain-smoothing filter is similar in range to that of the OHC membrane filter. Housley and Ashmore (1992) have shown that in isolated guinea-pig OHCs, the time constants at room temperature varied from 3 to 0.2 ms from the apex to the base of the cochlea. These numbers correspond to roughly 50 to 800 Hz in filter corner frequencies, which is about the range assumed in the model. But there is one difficulty, which concerns

the way the filter works. It is assumed that in the model that the OHC transduction current has first to be rectified (cf. eq. 2) before it is fed to the gain-smoothing filter. In the case of the membrane filter, apparently no such rectification is allowed.

If the physical basis for the gain-smoothing filter is indeed the membrane filter, there must be a frequency limit for phase-specific suppression which is mainly determined by the time constant of the filter. The data from guinea pig gave a shortest time constant of 0.2 ms for basal OHCs (Housley and Ashmore, 1992), which corresponds to a corner frequency of about 800 Hz. Based on this corner frequency and some other factors, an upper limit for phase-specific suppression on the BM of guinea pig can be predicted.

3. Role of IHC in 2TS

An important result from this model is the demonstration of the ability of the simulated IHC to produce suppression by itself, through its saturating transfer function. A role of IHC in producing suppression has been suggested before (e.g., Javel et al., 1983), but there has been no direct experimental demonstration of it. The modeling work presented here presents one possible scenario. In the model's response, the two-tone response is highly synchronized to the suppressor tone. Regardless of the fiber CF and the frequency of the suppressor tone, the phase of suppression produced at the model's IHC stage always leads the phase of excitation due to the suppressor tone alone by about half a cycle (Fig. IV-7). For the high-CF, higher-frequency suppressor case, the minimum in the two-tone response may slightly lead the minimum in the SUP-alone response (Fig. IV-9), due to the small phase lag of the suppressor response produced by the IHC basolateral membrane filter. Similar phase relationships are observed in some of our experimental data (Chapter 2, Figs. II-28 to II-30), suggesting that

the suppressions in those cases might be due, at least in part, to the IHC stage. For the IHC stage to produce suppression, the input to the IHC prior to transduction process must be relatively large so that it reaches saturating range of the transfer function in one or the other direction. Thus, IHC suppression is probably more important for higher frequency suppressors (above the corner frequency of the highpass filter in Fig. IV-1A) than for lower frequency suppressors, since for lower frequency suppressors, the suppressor component is heavily attenuated by the highpass filter before being fed to the IHC transduction process. In fact, in the example with a higher frequency suppressor (Fig. IV-8), the IHC stage produced suppression at an intensity even lower than that at which suppression was produced at the BM stage.

With a high-frequency CF tone, in the cases that the suppressor frequency is low or the suppressor frequency is high but the intensity is low, the role of IHCs is probably more important in modulating the response due to the CF tone than in producing suppression. Since the high-frequency CF component of the IHC receptor potential is attenuated by the basolateral membrane filter, leaving mostly the DC component, a small suppressor component is enough to modulate the DC response due to the CF tone, although it may not be large enough to produce additional suppression. The fact that in the high-CF AN data the phase lead (phase of suppression leading the phase of excitation of SUP alone) is close to half a cycle (Chapter 2) supports the above idea.

4. Suppression of the LF component

The suppression of the LF suppressor component in the OHC responses by the CF tone (Figs. IV-13 and IV-14) is in fact due to the same mechanism that caused suppression of the

CF component, i.e., the saturating of OHC transduction current. The dependence of this phenomenon upon the intensities of both the CF tone and the LF suppressor suggests a rather complex mutual interaction between the CF tone and the LF suppressor at the OHC/BM stage, rather than a simple suppression of the CF tone by the LF suppressor tone.

Although the model outputs fit the experimental data of Cheatham and Dallos (1994) qualitatively, there are some quantitative differences, namely, there was more suppression of the LF component in the rising limb than in the falling limb (Fig. IV-13). The difference, however, can be eliminated if we assume that the reduction of the CA gain is faster than its recovery (the recovery process is basically determined by the present setting of the gain-smoothing filter). In that case, the fast onset of suppression would quickly reduce the CF tone in its input so that it is not strong enough to suppress the LF tone, thus the suppression of the CF tone on the rising limb would be reduced or disappear.

In the current model, the LF suppressor tone is not affected by the cochlear amplifier. Any suppression of the LF component which occurs in the OHC stage would not affect the LF input to the IHC stage in any way. Therefore, the suppression of the LF tone which is seen at the IHC/AN stage (e.g., Figs. II-19 and II-20 of Chapter 2; Figs. 4 and 7 of Sachs and Hubbard, 1981) must be produced at the IHC stage by the saturating characteristic of the IHC I/O function (cf. Fig. IV-9B).

5. Mechanism of 2TS

Based on our experimental data (Chapters 2 and 3) and the modeling work presented in this report, we can summarize our vision of 2TS mechanism as follows.

Suppression produced at the BM stage

There have been a lot of reports concerning 2TS produced at the BM stage and there is no doubt that suppression of the CF response component can be produced at the BM stage (see Introduction). However, it should keep in mind that at the BM level, both in the experimental data (e.g., Rhode and Cooper, 1993) and in our model (Fig. IV-8), there is no "tonic" suppression produced with a low-side suppressor: the total response actually increases when a suppressor tone is added to a CF input, although the CF component in the response is reduced. Thus in the following discussion about BM suppression, we only consider the suppression of the CF component ("synchrony suppression").

Assuming that the OHC transduction current is in phase with the BM displacement, the basic temporal suppression pattern, as assumed in the model, follows the transduction current and thus the BM displacement. Due to the gain-smoothing stages, there may be a delay of up to 90 degrees (1/4 cycle of the suppressor tone) between maximum suppression observed on BM and the maximum BM displacement, depending on the relationship between the suppressor frequency and the filter corner frequency. When the suppressor frequency is much lower than the filter corner frequency, there is little or no delay and thus the maximum suppression is basically in phase with the BM displacement. When they are equal, the maximum suppression lags BM displacement by ~60 degrees. When the suppressor frequency is much higher than the filter corner frequency, the maximum suppression lags BM displacement by as much as 90 degrees.

If there were no filtering, the response at the BM would reach the unsuppressed level at those moments corresponding to the zero-crossing points of the suppressor component in the input

to OHC. Due to the gain-smoothing filter, the BM response cannot reach the unsuppressed level at those moments, except for suppressors well below the filter corner frequency (Fig. IV-6).

Role of IHC in shaping the temporal response pattern and producing suppression

As discussed earlier in this section, the IHC stage is also capable of producing suppression by itself through the saturating characteristic of its transfer function, if the input prior to the transduction process is relatively high. For low-CF and lower-frequency suppressor cases, the amplitude of the suppressor tone is relatively low, due to the hydrodynamic highpass filter of IHC. In most cases, the BM/OHC stage must be producing suppression (of the CF response) at a lower intensity than that at which the IHC begins to produce suppression. Thus, the role of IHC in producing suppression is probably less important. The highpass filter, however, advances the phase of excitation due to the lower-frequency suppressor tone by up to 90 degrees (relative to BM displacement), thus in the IHC output the phase of suppression is leading the phase of excitation due to the suppressor tone alone by about 90 degrees (cf. Fig. IV-4), which is what was observed in the responses of AN fibers (Chapter 2).

For high-CF and higher-frequency suppressor cases, since the suppressor is not attenuated by the highpass filter, the suppressor may produce suppression even at a lower intensity than at which suppression of the CF response is produced at the BM stage (cf. Fig. IV-8). Since the high-frequency CF component in the IHC output (which carries the temporal information about suppression produced at the BM stage and/or IHC stage) is attenuated by the basolateral membrane filter, only the "DC" component (which carries the average rate

suppression produced at the BM stage and/or IHC stage) is preserved. Since the suppressor component is not attenuated by the membrane filter, it modulates the DC component so that the temporal information carried in the final IHC receptor potential is mainly about the suppressor tone. Thus it is not surprising that the phase of suppression at the AN level led the phase of excitation due to suppressor tone alone by nearly half a cycle when higher-frequency suppressors were used (Chapter 2).

One may notice that in Fig. IV-8 the major suppression produced at the BM stage is basically in phase with the suppression produced at the IHC stage. If at the BM stage a secondary suppression appears at higher intensities, it should be expected to be about half a cycle away from the major one and thus in phase with the phase of excitation due to the suppressor tone alone. This factor, together with the dominance of the suppressor tone in the AC response, explains why secondary suppressions were never seen in high-CF fibers using suppressors above 500 Hz (Chapter 2).

Post-IHC influence

It has been shown in our experimental data that both the phase of suppression and the rate threshold of suppression in AN fibers are independent of the fiber SR (Chapter 2). The SR-independence of the rate suppression threshold was also observed by Schmiedt (1982). These findings support the idea that the major temporal suppression phenomenon is produced at or before the IHC stage. However, the amplitude response pattern is dependent on fiber SR, with a relative-response index greater than unity (i.e., the maximum response level in the two-tone part exceeding the CF-alone response level) in high-SR fibers (which in turn is similar to those observed in IHCs, Russell and Kössl, 1992; Cheatham and Dallos, 1992) and

a relative-response index below unity in lower-SR fibers (Chapter 3). Although the model can simulate the results from IHCs and high-SR AN fibers, and it can account for the *phasic* behavior of the lower-SR AN fibers, it is unable to account for the *amplitude* behavior of those lower-SR fibers. Thus there must be some additional mechanism(s) after the IHC receptor potential and before the AN spike initiation that are responsible for the behavior we saw experimentally in the lower-SR fibers.

6. Limitations of the model

Although the model successfully demonstrated a lot of interesting 2TS and related phenomena, it has some limitations. For example, the model assumes that only the magnitude of the CF tone is affected by the cochlear amplifier, thus it could not predict the change in the phase of CF tone due to the suppressor tone (Deng and Geisler, 1985). It assumed frequency-independent OHC and IHC transfer functions, but this is probably not the case as shown by Dallos and Cheatham (1989) and suggested by our AN data (Chapter 1). Fortunately, this assumption would only change the characteristics of the model quantitatively. There is also an implied assumption in the model, i.e., adjacent OHCs or IHCs have similar properties. But this may not be the case, as can be seen from the OHC asymmetry example (phase of major suppression) in our experimental data (Chapter 2). Finally, the model requires the suppressor tone to be outside the active region, so that it can not be readily extended to the situation where the suppressor is close to CF.