Modeling the Active Process of the Cochlea: Phase Relations, Amplification, and Spontaneous Oscillation

V. S. Markin and A. J. Hudspeth
Howard Hughes Medical Institute and Center for Basic Neuroscience Research, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9117 USA

ABSTRACT The high sensitivity and sharp frequency selectivity of acoustical signal transduction in the cochlea suggest that an active process pumps energy into the basilar membrane's oscillations. This function is generally attributed to outer hair cells, but its exact mechanism remains uncertain. Several classical models of amplification represent the load upon the basilar membrane as a single mass. Such models encounter a fundamental difficulty, however: the phase difference between basilar-membrane movement and the force generated by outer hair cells inhibits, rather than amplifies, the modeled basilar-membrane oscillations. For this reason, modelers must introduce artificially either negative impedance or an appropriate phase shift, neither of which is justified by physical analysis of the system. We consider here a physical model based upon the recent demonstration that the basilar membrane and reticular lamina can move independently, albeit with elastic coupling through outer hair cells. The mechanical model comprises two resonant masses, representing the basilar membrane and the reticular lamina, coupled through an intermediate spring, the outer hair cells. The spring's set point changes in response to displacement of the reticular lamina, which causes deflection of the hair bundles, variation of outer hair cell length and, hence, force production. Depending upon the frequency of the acoustical input, the basilar membrane and reticular lamina can oscillate either in phase or in counterphase. In the latter instance, the force produced by hair cells leads basilar-membrane oscillation, energy is pumped into basilar-membrane movement, and an external input can be strongly amplified. The model is also capable of producing spontaneous oscillation. In agreement with experimental observations, the model describes mechanical relaxation of the basilar membrane after electrical stimulation causes outer hair cells to change their length.

INTRODUCTION

Our ability to distinguish sounds of different frequencies depends principally upon the basilar membrane in the snail-shaped cochlea, or auditory receptor organ. In the human ear, the basilar membrane is a spiraling, 33-mm-long elastic strip, held taut by bony insertions along both edges. The membrane is surmounted by the organ of Corti, an epithelial ridge that includes the 16,000 hair cells that are the cochlea's sensory receptors (Fig. 1 *A*). The basilar membrane decreases in width from approximately 500 μm at its apical end to about 100 μm at its basal extreme. This variation, together with systematic changes in the basilar membrane's tension and mass loading, disposes the membrane to vibrate maximally at different positions in response to sounds of various frequencies. Low frequency tones excite the apical region of the basilar membrane, and high frequency sounds the basal portion. Between the extreme frequencies of human audibility, about 20 Hz and 20 kHz, frequencies are represented along the membrane monotonically and roughly logarithmically. As first disclosed by stroboscopic measurements (reviewed in von Békésy, 1960), the basilar membrane is a mechanical spectral analyzer that decomposes auditory inputs before detection of their pure-tone constituents.

In the search for understanding of cochlear function, the basilar membrane's action has been subjected to considerable mathematical analysis and computer modeling (de Boer, 1990; Lighthill, 1991; Zweig, 1991). In simple models, each radial element along the basilar membrane is represented as a viscously damped, elastic structure loaded by a cellular mass (Fig. 1 *B*). As techniques for the measurement of cochlear vibration have improved during the past two decades (Sellick et al., 1982; Cooper and Rhode, 1992; Ruggero et al., 1992), however, it has become increasingly apparent that the basilar membrane is far too sensitive, and its frequency tuning much too sharp, for such simple models to suffice.

Substantial improvements in a model's ability to represent the membrane's sensitivity and tuning can be brought about by including another degree of freedom. For example, the gelatinous tectorial membrane that overlies the organ of Corti has been postulated to vibrate as a second, independently tuned resonator (Zwislocki and Kletsky, 1979; Allen, 1980). Theoretical results accord still better with experimental data if the basilar membrane is postulated to exhibit negative damping, that is, if the dissipative effects of viscous drag are countered by an active supply of mechanical energy (Neely and Kim, 1983, 1986). There is evidence that such an active process exists: when electrically stimulated, outer hair cells exhibit length changes (Brownell et al., 1985; Ashmore, 1987; Dallos et al., 1991; Iwasa and Chad-

Received for publication 9 December 1994 and in final form 28 February 1995.

Address reprint requests to Dr. A. J. Hudspeth, Howard Hughes Med. Inst., Univ. of Texas Southwestern Med Ctr., 5323 Harry Hines Blvd., Dallas, TX 75235-9117. Tel.: 214-648-3664; Fax: 214-648-6324.

0006-3495/95/07/138/10 $2.00

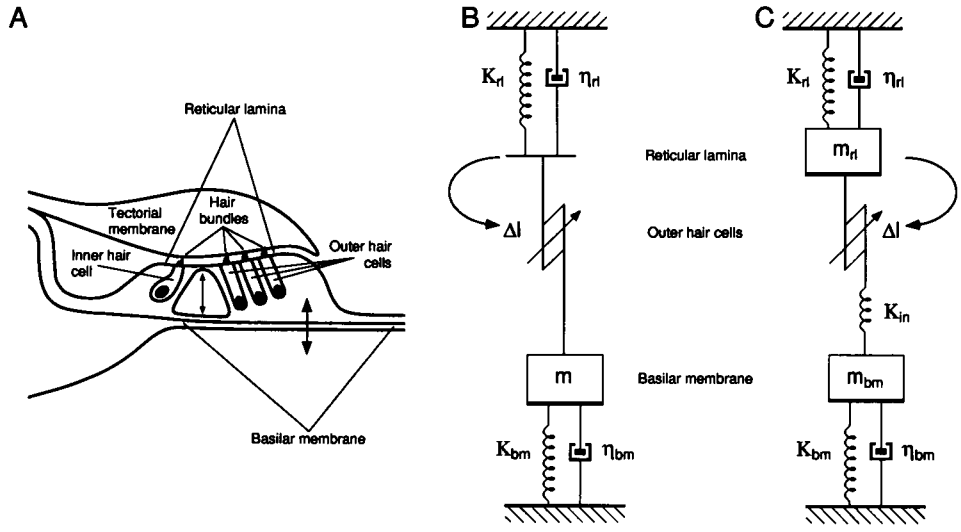

FIGURE 1 Anatomical and mechanical representations of a unitary increment of the cochlea. (*A*) A schematic section across the cochlea shows the elastic basilar membrane surmounted by the epithelial cells that comprise the organ of Corti. This organ includes four rows of hair cells, three of outer hair cells and one of inner hair cells. The mechanically sensitive hair bundles of these receptor cells extend from the upper epithelial surface, or reticular lamina, to contact the gelatinous tectorial membrane. The large double-headed arrow indicates the direction of oscillation of the basilar membrane; the small double-headed arrow depicts the motion between the reticular lamina and basilar membrane. (*B*) Mechanical representation of the single-mass model. (*C*) Mechanical representation of the two-mass model. In each instance, mass is denoted by m, hydrodynamic drag by η, and stiffness by K; the subscripts *bm* and *rl* refer to the basilar membrane and reticular lamina, respectively. When electrically stimulated, outer hair cells undergo a length change Δl. It is possible to suggest tentative relations between the anatomical structures in *A* and the mechanical elements in *C*. Mass m_{bm} represents the basilar membrane and lower portion of the epithelium in the organ of Corti; mass m_{rl} includes the reticular lamina and tectorial membrane. The spring K_{bm} reflects the stiffness of the basilar membrane, whereas the spring K_{rl} embodies the stiffness of the tectorial membrane's pivot and that of the hair bundles. The spring K_{in} represents principally the stiffness of the outer hair cells. The dashpots, η_{bm} and η_{rl}, reflect viscous drag acting on the respective moving parts of the cochlea.

wick, 1992; Santos-Sacchi, 1992) that might perform work on the basilar membrane. Consistent with the presence of a force-producing process in the cochlea, ears have been found to emit sounds (for review, see Probst, 1990) upon transient stimulation (Kemp, 1978) and even spontaneously (Zurek, 1981).

Contemporary models of basilar-membrane motion have assimilated the cochlea's active process, as manifested by movements of outer hair cells. The pioneering work of Neely and Kim (1983, 1986) incorporated active motion of outer hair cells into a two-resonator model, but did not specify the exact contribution of outer hair cells to movements of the basilar membrane relative to the reticular lamina. A more recent attempt to understand the contribution of an active process was provided by Geisler (1991, 1993), who subjected a single-resonator model to detailed analysis. This model encounters a fundamental difficulty, however: the phase difference between movement of the basilar membrane and the force generated by outer hair cells provides inhibition, rather than amplification, of oscillations. The model produces realistic outputs only upon the introduction of a phase shift or temporal delay (Zweig, 1990, 1991), for which a physical analysis of the system as yet provides no justification.

The present communication, which builds upon the recent observation that the basilar membrane and reticular lamina can move independently (Mammano and Ashmore, 1993), demonstrates that a two-mass model with mechanically active hair cells can exhibit realistic sensitivity and sharp tuning without the necessity of invoking arbitrary mechanical elements.

DEFICIENCY OF THE SINGLE-MASS MODEL

Classical models of amplification in the cochlea are based on the assumption that upward displacement of the reticular lamina brings about a relative motion of the tectorial membrane away from the cochlea's bony core, or modiolus. This movement, in turn, causes positive displacement of hair bundles, opening of transduction channels, depolarization of hair cells, and shortening of outer hair cells (Fig. 1 *A*). Outer hair cells generate force at the expense of electrochemical gradients across their plasma membranes and could supply, in principle, additional energy to the oscillation. This single-mass model (Fig. 1 *B*) seems at first glance to be capable of effecting amplification: as the basilar membrane and reticular lamina move upward, the shortening of outer hair cells appears to add momentum to their motion. Should not oscillations therefore be amplified?

Detailed analysis shows that amplification does not occur under these circumstances. If a mass under the influence of a force F moves at a velocity u, then the power exerted on this mass is

$$P = Fu\,. \tag{1}$$

If this product is positive, the force supplies additional energy to the movement; if negative, energy is drained and

the movement is inhibited. If the system executes a periodic motion, the power varies with time; the effect on amplification must therefore be determined by evaluating the mean value of the power, $\langle P \rangle$. If both parameters, F and u, vary as sinusoidal functions of the same angular frequency, ω, then the conclusion will depend on the phase difference of their oscillations. The most favorable condition for pumping of movement is that in which the phase difference is zero, which implies that force is applied in the same direction as the mass is moving. Although changing with time, the power is then always positive (or zero).

If the phase difference is not zero, the average power can still be positive if the phase difference does not exceed the angle $\pi/2$ in either direction. If the phase difference is exactly equal to $\pm\pi/2$, the average power is zero. This is the case, for example, for a mass oscillating on a spring without any additional elements (Fig. 1 *B*). If an oscillation of amplitude a occurs at angular frequency ω, so that the mass's displacement from its resting position, X, is

$$X = a \sin(\omega t), \tag{2}$$

then

$$u = a\omega \cos(\omega t) = a\omega \sin(\omega t + \pi/2) \tag{3}$$

and

$$F = -KX = -aK \sin(\omega t) = aK \sin(\omega t + \pi), \tag{4}$$

in which K is the spring's stiffness. The phase relations among these three parameters are such that the velocity leads the displacement by a phase angle $\pi/2$, and the force leads the displacement by an angle π; the phase angle between force and velocity, therefore, is $\pi/2$. This result illustrates why the oscillation of a mass on a spring does not grow in amplitude. If the phase angle between force and velocity were to exceed $\pi/2$ in either direction, the average power would be negative and the force would drain energy from the oscillation.

The addition of outer hair cells to the model changes the situation. Although the displacement and velocity of the reticular lamina and the force in the spring are still given by Eqs. 2–4, we must now compare the variation of the force with the movement of the basilar membrane, which differs from the motion of the reticular lamina because of shortening of the outer hair cells. When the reticular lamina reaches its uppermost point of displacement, the transduction current is at its maximum; each outer hair cell, therefore, is being depolarized, so it continues to shorten and the basilar membrane to move upward. The motion of the basilar membrane, therefore, lags behind that of the reticular lamina by an angle between 0 and $\pi/2$. The angle between the force in the spring and the displacement of the basilar membrane, accordingly, exceeds $\pi/2$, so the periodic shortening of the outer hair cells inhibits oscillation of the basilar membrane rather than fosters it. This version of the single-mass model, accordingly, cannot provide amplification of basilar-membrane motion.

It is interesting to note that amplification could be achieved in a single-mass model if the hair bundles were oriented in the opposite direction or if the outer hair cells' voltage response were reversed. Either arrangement would provide an appropriate phase difference between force and displacement, such that energy would be pumped into the oscillations. For some reason, nature ignored these opportunities.

THE TWO-MASS MODEL

If the contraction of outer hair cells is to be a source of amplification in the cochlea, there must be an additional process that radically alters the phase relationships among the motions of the basilar membrane, the reticular lamina, and the outer hair cells. After introducing an explicit representation of the force produced by outer hair cells, we shall discuss such a process in the following sections.

Electromechanical (reverse) transduction

For small displacements of the reticular lamina, X_{rl}, the receptor current in a hair cell can be considered proportional to the displacement, $i = \beta X_{rl}$. The equation for the change in membrane potential, ΔV_m, therefore, can be presented as follows:

$$C_m \frac{d\Delta V_m}{dt} = \beta X_{rl} - \frac{\Delta V_m}{R_m}. \tag{5}$$

Here C_m is the membrane capacitance and R_m is the resting membrane resistance. If the reticular lamina undergoes mechanical oscillations of amplitude A_{rl} at angular frequency ω,

$$X_{rl} = A_{rl} e^{i\omega t}, \tag{6}$$

then the membrane potential oscillates at the same frequency,

$$\Delta V_m = \frac{\beta R_m A_{rl}}{\sqrt{1 + (\omega R_m C_m)^2}} e^{i(\omega t + \phi_m)}, \tag{7}$$

but is out of phase with the reticular lamina by an angle ϕ_m:

$$\phi_m = -\tan^{-1}(\omega R_m C_m) = -\tan^{-1}(\omega \tau_m). \tag{8}$$

Here the membrane time constant is defined by $\tau_m \equiv R_m C_m$. The membrane potential lags the mechanical oscillation of the reticular lamina by a retardation angle not exceeding a quarter of a period:

$$-\pi/2 < \phi_m < 0. \tag{9}$$

If the approximate values of an outer hair cell's electrical parameters are $R_m \approx 50$ MΩ and $C_m \approx 30$ pF (Housley and Ashmore, 1992), the membrane time constant is $\tau_m \approx 1.5$ ms and the electrical corner (roll-off) frequency is $f_c = 1/(2\pi R_m C_m) \approx 100$ Hz.

Now let us consider how this electrical signal can be transformed into mechanical movement. We shall assume that the cochlea's active process emerges from voltage-induced length changes in the outer hair cells (Fig. 2). Such a cell shortens when its membrane is depolarized from the resting potential and lengthens in response to hyperpolarization (Brownell et al., 1985; Ashmore, 1987; Dallos et al., 1991; Iwasa and Chadwick, 1992; Santos-Sacchi, 1992). In the linear range, the change of the outer-hair-cell length, Δl, is directly proportional to ΔV_m.

For fast mechanical relaxation in outer hair cells, the change in their length obeys a relation similar to Eq. 5; for the sake of simplicity, we have chosen the expression

$$\frac{d\Delta l}{dt} = \frac{-1}{\tau_m}(\Delta l + \xi X_{rl}) . \tag{10}$$

The parameter ξ is the transfer ratio relating the change in outer hair cell length to displacement of the reticular lamina; thus, it may be considered the active gain of the system. The sign in this equation is selected so that positive displacement causes a negative change in cellular length. If the reticular lamina undergoes harmonic oscillation according to Eq. 6, then the change in the outer-hair-cell length is

$$\Delta l = \frac{-\xi A_{RL}}{\sqrt{1 + (\omega\tau_m)^2}} e^{i(\omega t + \phi_m)} . \tag{11}$$

The phase angle, ϕ_m, is determined by the membrane's charging process (Eq. 8). Equation 11 reveals that the length of the outer hair cells oscillates with the same frequency as the reticular lamina, and that shortening of outer hair cells lags behind oscillation of the reticular lamina by less than a quarter of a period. The exact phase delay is determined by electromechanical processes in the outer hair cells. If necessary, an additional equation can be introduced to add delay in the variation of the outer hair cell length; we shall address this issue later.

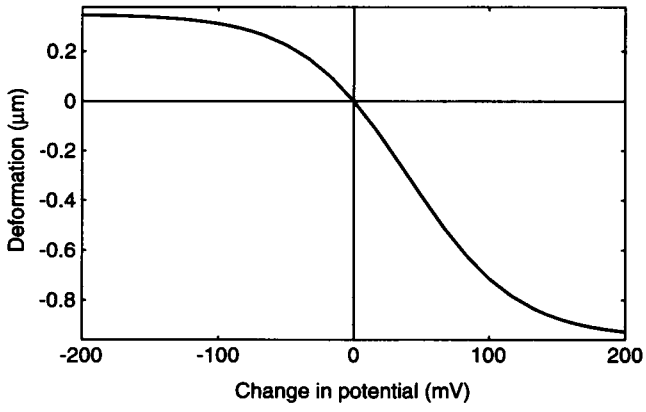

FIGURE 2 Length of outer hair cells as a function of the change in membrane potential from the resting level. The experimentally determined relation (Evans et al., 1991; Santos-Sacchi, 1992) was approximated by a Boltzmann function,

$$\Delta l = 1.3 \cdot \left\{ \frac{1}{1 + \exp[(V - 40)/40]} - 0.731 \right\},$$

in which Δl is given in mm and V in mV.

General equations

Recent interferometric measurements suggest that the basilar membrane and the reticular lamina are not rigidly connected but can move relative to one another (Khanna et al., 1989; Mammano and Ashmore, 1993). This result implies the existence of a second mass, which may be incorporated into a more complex model (Fig. 1 *C*). We have included here two dashpots that reflect the dissipation of energy due to the movements of the basilar membrane and reticular lamina in a viscous medium. The active element in this model, the outer hair cell, is explicitly included between the basilar membrane and reticular lamina; hair cell movement is posited to cause a relative movement between these two elastic structures. This arrangement contrasts with that in an earlier model (Neely and Kim, 1983) but accords with recent experimental observations (Mammano and Ashmore, 1993).

To reduce the number of parameters in the model, we suppose that the acoustical pressure difference within the cochlea, P_d, acts only on the basilar membrane, whereas the reticular lamina and tectorial membrane are moved by elastic coupling to the basilar membrane. These simplifications help us elucidate the mechanism of energy flow into the cochlea.

The mechanical displacements in the two-mass model presented in Fig. 1 *C* are governed by the following set of equations:

$$m_{bm}\frac{d^2X_{bm}}{dt^2} + \eta_{bm}\frac{dX_{bm}}{dt} + K_{bm}X_{bm} - K_{in}(X_{rl} - X_{bm} - \Delta l) = P_d ; \tag{12}$$

$$m_{rl}\frac{d^2X_{rl}}{dt^2} + \eta_{rl}\frac{dX_{rl}}{dt} + K_{rl}X_{rl} + K_{in}(X_{rl} - X_{bm} - \Delta l) = 0 . \tag{13}$$

Here masses are represented by m, drag coefficients by η, and stiffnesses by K; subscripts denote parameters relating to the basilar membrane (*bm*) or reticular lamina (*rl*). Upon substitution of the characteristic parameters,

$$\omega_{bm} = \sqrt{\frac{K_{bm}}{m_{bm}}}, \quad \omega_{rl} = \sqrt{\frac{K_{rl}}{m_{rl}}}, \quad \omega_{in} = \sqrt{\frac{K_{in}}{m_{rl}}}, \quad \zeta_{bm} = \frac{\eta_{bm}}{m_{bm}}, \quad \zeta_{rl} = \frac{\eta_{rl}}{m_{rl}}, \tag{14}$$

the system of equations may be rewritten as

$$\frac{d^2X_{bm}}{dt^2} + \zeta_{bm}\frac{dX_{bm}}{dt} + \omega_{bm}^2 X_{bm} - \omega_{in}^2(X_{rl} - X_{bm} - \Delta l)\left(\frac{m_{rl}}{m_{bm}}\right) = \frac{P_d}{m_{bm}} ; \tag{15}$$

$$\frac{d^2X_{rl}}{dt^2} + \zeta_{rl}\frac{dX_{rl}}{dt} + \omega_{rl}^2 X_{rl} + \omega_{in}^2(X_{rl} - X_{bm} - \Delta l) = 0\,; \quad (16)$$

$$\frac{d\Delta l}{dt} + \frac{1}{\tau_m}(\Delta l + \xi X_{rl}) = 0\,. \quad (17)$$

Equation 17, which describes length changes by outer hair cells, is included to render the set complete.

Following the standard analysis of a dynamic system, one can find the normal modes of oscillations of this model. These modes are determined by the eigenvalues of the system, that is, by the solutions of the equation

$$\begin{vmatrix} -\omega^2 + i\omega\zeta_{bm} + \omega_{bm}^2 + \omega_{in}^2\dfrac{m_{rl}}{(m_{bm})} & -\omega_{in}^2\left(\dfrac{m_{rl}}{m_{bm}}\right) & \omega_{in}^2\left(\dfrac{m_{rl}}{m_{bm}}\right) \\ -\omega_{in}^2 & -\omega^2 + i\omega\zeta_{rl} + \omega_{rl}^2 + \omega_{in}^2 & -\omega_{in}^2 \\ 0 & \dfrac{\xi}{\tau_m} & i\omega + \dfrac{1}{\tau_m} \end{vmatrix} = 0\,. \quad (18)$$

If the system is symmetrical, as defined by the relations

$$m_{rl} = m_{bm}\,, \quad \omega_{rl} = \omega_{bm}\,, \quad \zeta_{rl} = \zeta_{bm}\,, \quad (19)$$

then the equation for the eigenvalues simplifies to

$$(-\omega^2 + i\omega\zeta_{bm} + \omega_{bm}^2) \quad (20)$$

$$\times\left[(-\omega^2 + i\omega\zeta_{bm} + \omega_{bm}^2 + 2\omega_{in}^2)\left(i\omega + \frac{1}{\tau_m}\right) + \frac{\xi\omega_{in}^2}{\tau_m}\right] = 0\,.$$

The driving-point (or input) impedance of the basilar membrane, $Z = F/u = P_d/(dX_{bm}/dt)$, may be derived from the equations above. To avoid excessively cumbersome expressions, we present only the result for a symmetrical system:

$$Z = \frac{m_{bm}}{i\omega}(-\omega^2 + i\omega\zeta_{bm} + \omega_{bm}^2) \quad (21)$$

$$\times\left\{1 + \frac{\omega_{in}^2}{\left[-\omega^2 + i\omega\zeta_{bm} + \omega_{bm}^2 + \omega_{in}^2 + \dfrac{\xi\omega_{in}^2(1 - \xi\omega\tau_m)}{1 + \omega^2\tau_m}\right]}\right\}.$$

APPLICATION OF THE TWO-MASS MODEL

Passive system

If the outer hair cells do not change their length, $\xi = 0$, the system is passive, and mechanical oscillations do not depend on electrical processes. For the sake of simplicity, let us consider the symmetrical case described by Eq. 20. The eigenvalues of this system are

$$\omega_1 = \sqrt{\omega_{bm}^2 - \frac{1}{4}\zeta_{bm}^2} + \frac{i}{2}\zeta_{bm}\,; \quad (22)$$

$$\omega_2 = \sqrt{\omega_{bm}^2 + 2\omega_{in}^2 - \frac{1}{4}\zeta_{bm}^2} + \frac{i}{2}\zeta_{bm}\,; \quad (23)$$

$$\omega_3 = \frac{i}{\tau_m}\,. \quad (24)$$

The third eigenvalue describes electrical relaxation in the outer hair cell, which in the passive system is uncoupled from mechanical oscillations.

The first two eigenvalues are complex frequencies of two normal modes of mechanical oscillations. In each normal mode, the basilar membrane and reticular lamina oscillate at a single frequency specified by the real part of the relevant eigenvalue; the imaginary part indicates the rate of attenuation of the oscillation amplitude. Because the imaginary parts of the eigenvalues are positive, these relations specify damped oscillations. The first normal mode is given by the equations

$$X_{bm} = A_{bm}e^{i(\omega_1 t + \phi_{bm})} \quad \text{and} \quad X_{rl} = A_{rl}e^{i(\omega_1 t + \phi_{rl})}\,, \quad (25)$$

in which A_{bm} and A_{rl} represent the movement amplitudes of the basilar membrane and the reticular lamina, respectively. The oscillations, therefore, occur in phase and with the same amplitude. In the second, faster mode,

$$X_{bm} = A_{bm}e^{i(\omega_2 t + \phi'_{bm})} \quad \text{and} \quad X_{rl} = A_{rl}e^{i(\omega_2 t + \phi'_{rl})}\,. \quad (26)$$

the oscillations occur with the same amplitudes but in counterphase. The general solution is a combination of these normal modes.

If an external sound pressure $P_d = A_P \exp(i\omega t)$ is applied to the basilar membrane, then in the steady state the basilar membrane and reticular lamina move at the same frequency, ω, but with different amplitudes that depend on the relation between the frequency of the external force and that of the normal modes. These amplitudes can be found either by solution of Eqs. 15–17 or from the driving-point impedance, Eq. 21. For example, the amplitude of basilar-membrane movement is

$$A_{bm} = \frac{A_p}{\omega|Z|}\,. \quad (27)$$

The system displays two resonances with similar amplitudes (Fig. 3).

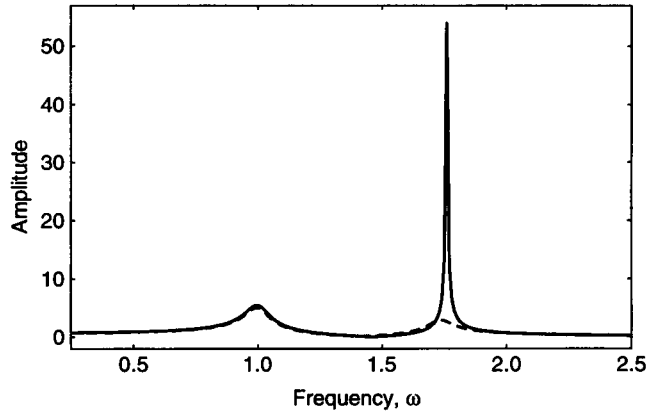

FIGURE 3 Amplitude of forced membrane oscillations as a function of frequency for a unitary external force. (----) Passive response; (——) active response. The curves were calculated with the normalized parameter values $\xi = 0$ (passive response) or $\xi = 0.3899$ (active response), $\zeta = 0.1$, $\tau_m = 1$, $\omega_{in} = 1$, $\omega_{bm} = 1$.

System with amplification

If outer hair cells actively participate in the transduction process by changing their lengths, they do not influence the first normal mode of oscillation, which maintains the frequency given by Eq. 22. The frequency of the second normal mode can be found analytically for the case in which the variation in outer hair cell length is so small that $\xi \ll 1$; in that instance,

$$\omega_2 = \omega_0 + \frac{\xi\omega_{in}^2\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)}{2\omega_0\left[\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)^2 + \omega_0^2\tau_m^2\right]} + \frac{i}{2}\left[\zeta_{bm} - \frac{\xi\tau_m\omega_{in}^2}{\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)^2 + \omega_0^2\tau_m^2}\right]. \quad (28)$$

Here ω_0 is the frequency of this mode in the absence of the active process;

$$\omega_0 = \sqrt{\omega_{bm}^2 + 2\omega_{in}^2 - \frac{1}{4}\zeta_{bm}^2}\,. \quad (29)$$

As follows from Eq. 26, free oscillation of the basilar membrane in this mode can be presented as

$$X_{bm} = A_{bm}e^{-\mathrm{Im}(\omega_2)t}\sin[\mathrm{Re}(\omega_2)t]\,, \quad (30)$$

with an appropriate phase shift. The frequency of oscillations in that mode is

$$\mathrm{Re}(\omega_2) = \omega_0 + \frac{\xi\omega_{in}^2\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)}{2\omega_0\left[\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)^2 + \omega_0^2\tau_m^2\right]}. \quad (31)$$

The active process, therefore, changes the frequency of oscillation, which may either decrease or increase depending upon the membrane time constant, τ_m, and the drag coefficient, ζ_{bm}. If either parameter's value is very small, the active process always increases the frequency of oscillation. Otherwise, if $\tau_m\zeta_{bm} > 2$, the active process decreases the frequency.

Another important effect of the active process concerns the damping characteristics that are determined by the imaginary part of the eigenvalue in Eq. 28,

$$\mathrm{Im}(\omega_2) = \frac{1}{2}\left[\zeta_{bm} - \frac{\xi\tau_m\omega_{in}^2}{\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right)^2 + \omega_0^2\tau_m^2}\right]. \quad (32)$$

If $\mathrm{Im}(\omega_2) > 0$, this normal mode is damped. This case arises in the absence of active movement of outer hair cells, whereupon the active gain ξ=0.

If the active gain $\xi > 0$, the imaginary part of ω_2 decreases and attenuation becomes less pronounced. Dissipation of energy in the system is offset partially by the active motion of the outer hair cells and, hence, the two-mass model can provide amplification. Fig. 4 presents the rate of attenuation of free oscillation as a function of the active gain, ξ. Attenuation decreases linearly with increasing ξ, reaches zero at the critical value,

$$\xi_{so} \equiv \frac{\zeta_{bm}[1 - \tau_m\zeta_{bm} + \tau_m^2(\omega_{bm}^2 + 2\omega_{in}^2)]}{\tau_m\omega_{in}^2}, \quad (33)$$

and thereafter becomes negative. This is a very important property of the model: the active gain characterizes the intensity of the active process and the amount of additional energy that can be delivered to the oscillation. For some value of the active gain, at which the amount of energy supplied by outer hair cells becomes great enough, attenuation disappears and the system begins to oscillate spontaneously; the parameter ξ_{so} represents the smallest value of the active gain that provides spontaneous oscillation. When it first appears, that is, for $\xi = \xi_{so}$, this oscillation has the frequency

$$\omega_{so} = \omega_0 + \frac{\zeta_{bm}}{2\omega_0\tau_m}\left(1 - \frac{1}{2}\tau_m\zeta_{bm}\right). \quad (34)$$

Depending upon the membrane time constant and drag coefficient, this frequency can be either higher or lower than the frequency without amplification.

The ability of the system to generate spontaneous oscillation depends upon the values of several parameters; in the simplified, symmetrical case of Eq. 19, these parameters are ζ_{bm}, τ_m, ω_{bm}, and ω_{in}. The most obvious dependence of the critical value of the active gain, ξ_{so}, is on the drag coeffi-

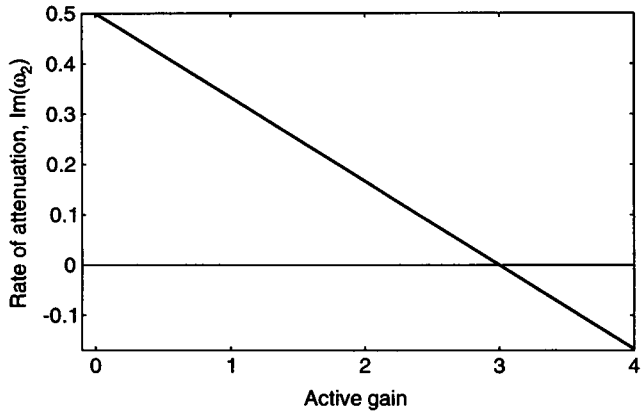

FIGURE 4 Rate of attenuation of free basilar-membrane oscillation as a function of the active gain, ξ. The curve was calculated with the normalized parameter values $\zeta = 1$, $\tau_m = 1$, $\omega_{in} = 1$, $\omega_{bm} = 1$.

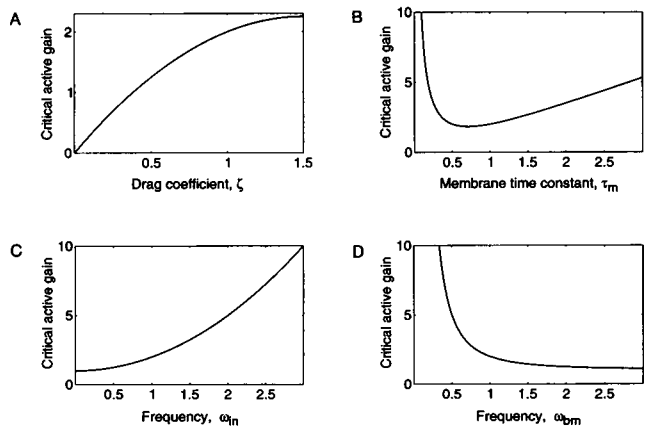

FIGURE 5 Dependence of the critical active gain, ξ_{SOAE}, on normalized parameters of the system. (*A*) Drag coefficient, ζ. (*B*) Membrane time constant, τ_m. (*C*) Characteristic frequency, ω_{in}. (*D*) Characteristic frequency, ω_{bm}. The normalized parameter values that do not explicitly appear on the plots were $\zeta = 1$, $\tau_m = 1$, $\omega_{in} = 1$, $\omega_{bm} = 1$.

cient, ζ_{bm}. If this coefficient is zero, the system requires no help from outer hair cells to maintain oscillation: in the absence of energy dissipation, the system can oscillate indefinitely by itself. The greater the drag coefficient, the larger the active gain must be for oscillation to occur. This may be illustrated by a state diagram (Fig. 5 *A*), in which the part of the plot above the curve corresponds to spontaneous oscillation; the region below the curve represents damped oscillation.

More interesting is the dependence of ξ_{so} on the electrical characteristic time, τ_m (Fig. 5 *B*). If the electrical charging process is very fast, ξ_{so} becomes infinite; spontaneous oscillation is then impossible. To achieve the necessary phase shift between the movement of different parts of the system, the system requires the delay provided by the charging process and subsequent shortening of the outer hair cells. With an increase in the value of τ_m, the critical active gain ξ_{so} initially decreases but subsequently rises again. The optimal value of τ_m, at which spontaneous oscillation can occur with the minimal contribution from outer hair cells, is

$$\tau_m^{opt} = \frac{1}{\sqrt{\omega_{bm}^2 + 2\omega_{in}^2}}. \quad (35)$$

If drag force does not influence significantly the oscillation frequency of the system, this value is close to the inverse angular frequency of the second mode of oscillation given by Eq. 29. In that case, the optimal membrane time constant is equal to a fraction of the oscillation period, T:

$$\tau_m^{opt} = \frac{T}{2\pi}. \quad (36)$$

The value of ξ_{so} also depends upon the frequencies ω_{in} and ω_{bm}. When ω_{in} decreases, ξ_{so} increases without limit (Fig. 5 *C*). The reason for this behavior is that the energy produced by outer hair cells is transmitted to the system through a spring of stiffness K_{in}; as this spring becomes less stiff (ω_{in} decreases), it becomes less effective at transferring energy. The opposite holds true for the dependence of ξ_{so} on ω_{bm} (Fig. 5 *D*).

Summarizing these observations, one can say that the presence of spontaneous oscillations in the system depends on the given set of parameter values. The total parameter space is divided into two parts, in which the system either displays spontaneous oscillation or produces damped oscillations. At the border between these two regions, which is actually a surface in the multidimensional parameter space, the system undergoes steady-state oscillation at a constant amplitude: the dissipation of energy in viscous processes is exactly compensated by the active work of outer hair cells. If the system dwells close to the border, then a slight variation of any parameter's value can cause the appearance or disappearance of spontaneous oscillation.

If an external periodic force were applied to the active system, then in the steady state both masses would move at the same frequency. The oscillation amplitude would remain practically the same as in the passive system except in the very narrow region around the second normal mode, where it would increase enormously (Fig. 3). The model thus demonstrates a high frequency selectivity. In this particular calculation, we used an arbitrary set of parameter values that, however, was subcritical; the system did not display spontaneous oscillations. If in the application of external force the set of parameter values slightly changed, however, then amplification could become even greater.

The curve relating amplitude and frequency (Fig. 3) can be transformed into a tuning curve. Fig. 6 *A* provides the predicted isoresponse curve for the case in which an external force is applied directly to the basilar membrane. This intermediate result, which could be termed a local tuning curve, differs from the conventional tuning curve in which stimulation is accomplished by a traveling wave upon the basilar membrane. To illustrate the interaction of local tuning with the traveling wave, we combined our model's results with a relation describing the amplitude of a travel-

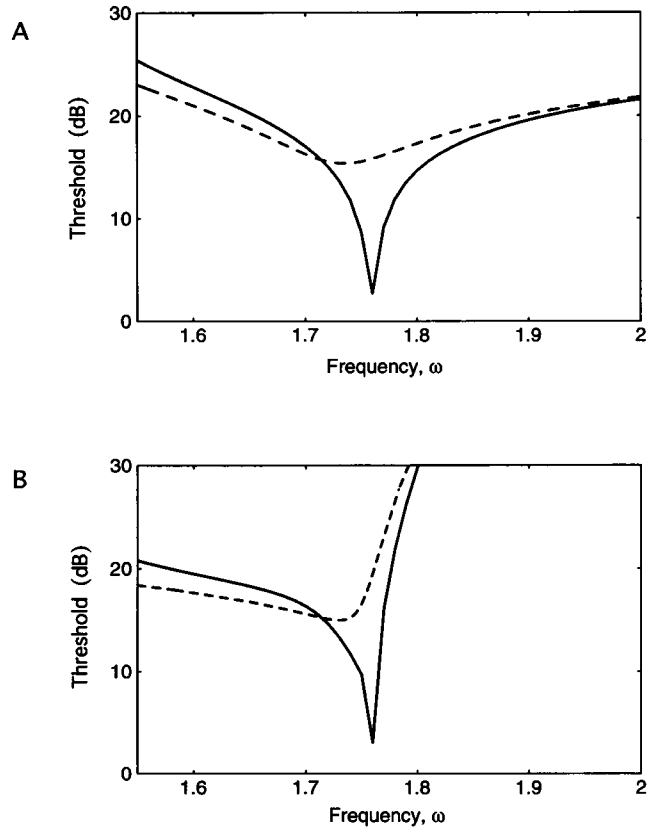

FIGURE 6 Tuning curves calculated for a passive response (----) and an active response (——), drawn from the data of Fig. 3. The threshold is presented with respect to a basilar-membrane displacement of 100 units in the parameter system used in Fig. 3. The curves in *A* reflect only the local tuning properties of the basilar membrane, whereas those in *B* include the traveling wave as well.

ing wave in a passive cochlea as a function of frequency (Zweig et al., 1976). By comparing forced oscillation in passive and active systems, we determined a local amplification coefficient and calculated the amplitude of the traveling wave with amplification. Finally, we converted this amplitude into a conventional tuning curve (Fig. 6 *B*), which closely resembles those obtained in numerous experiments (for review, see Patuzzi and Robertson, 1988). Among the striking differences in tuning with and without active gain, two points are especially noteworthy. First, the best frequencies in the passive and active systems differ, the active system being shifted to a slightly higher frequency. Second, the response threshold for low frequency stimulation is higher in the active system than in the passive one.

Response to voltage-step stimulation

In the experiments of Mammano and Ashmore (1993), an electrical stimulus across the organ of Corti changed the membrane potential of outer hair cells and produced basilar-membrane step displacements. The reticular lamina moved in the opposite direction with an excursion 5- to 10-fold that of the basilar membrane. Both displacements were accompanied by damped oscillations.

The behavior of the experimental system is governed by Eqs. 15 and 16 with appropriate initial conditions. We suppose that, during application of an external electrical stimulus, the length of the outer hair cells changes stepwise by some value, Δl. When the electrical stimulus ceases, Δl becomes equal to zero. The initial positions of the basilar membrane and the reticular lamina at the moment of application of external stimulus are arbitrary,

$$X_{bm} = X_1 \quad \text{and} \quad X_{rl} = X_2 \quad \text{at} \quad t = 0\,, \tag{37}$$

but the velocities are specified as zero,

$$\frac{dX_{bm}}{dt} = 0 \quad \text{and} \quad \frac{dX_{rl}}{dt} = 0 \quad \text{at} \quad t = 0\,. \tag{38}$$

Assuming that the masses of the basilar membrane and reticular lamina are roughly equal (Mammano and Ashmore, 1993), we may estimate the parameter values for this system by curve fitting. The time course of the calculated oscillations is presented in Fig. 7; the results closely approximate the experimental observations (Mammano and Ashmore, 1993). In the simulation, the equilibrium displacement of the reticular lamina is 21 nm and that of the basilar membrane is 2.7 nm; both numbers exactly coincide with the experimental observations. The numerical agreement between the predictions of the two-mass model and the experimental data is by no means surprising in view of the number of parameters included in the model. The only unique relation between these parameters that may be extracted from the experimental data is that between the stiffnesses K_{bm} and K_{rl} (Mammano and Ashmore, 1993); selection of the other parameter values is rather flexible. These values could be better constrained through further experimentation, for example, with sinusoidal stimuli.

DISCUSSION

We have demonstrated that a widely studied form of single-mass model of local oscillations in the cochlea cannot

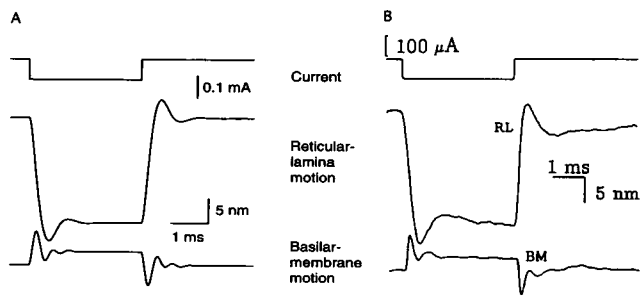

FIGURE 7 Calculated motions of the excised basilar membrane and reticular lamina in response to an impulse of electrical current. The theoretical responses (*A*) closely reproduce the experimental results (*B*) (Mammano and Ashmore, 1993). The responses were calculated with the following parameter values; Δl = 47 nm, ζ_{bm} = 6500 s^{-1}, ζ_{rl} = 6500 s^{-1}, ω_{in} = 5000 rad·s^{-1}, ω_{bm} = 14000 rad·s^{-1}, ω_{rl} = 5000 rad·s^{-1}, $m_{bm} = m_{rl}$, P_d = 0.

provide amplification of acoustical signals because of an inappropriate phase relation between basilar-membrane displacement and change in outer hair cell length. In fact, active contraction of outer hair cells in this model effects inhibition rather than amplification of oscillations.

The alternative to this common formulation, a two-mass model, can overcome the difficulty. For the sake of clarity, we have considered here a symmetrical system for which the normal modes represent oscillations of the basilar membrane and the reticular lamina either in phase (first mode) or in counterphase (second mode). For a symmetrical system, the oscillation amplitudes in both instances are equal. The first mode resembles oscillation in a single-mass model, in the sense that the basilar membrane and reticular lamina move in the same direction. This mode accordingly cannot provide amplification. The second mode describes movement of the basilar membrane and the reticular lamina in opposite directions, so that downward displacement of the basilar membrane evokes a contraction of the outer hair cells with an appropriate delay. This relation is exactly the property needed to boost the basilar membrane's movement.

The second normal mode can cause amplification, whose extent depends on the intensity of the outer hair cell movement. The active gain, ξ, describes the relation between reticular-lamina displacement and the change of equilibrium distance between the basilar membrane and reticular lamina. If the active gain is small, then the model exhibits damped oscillations in the absence of external forces. With an increase of the active gain beyond its critical value, ξ_{so}, attenuation disappears and the system oscillates spontaneously. If the present model is correct, this transition may manifest itself by the appearance of spontaneous otoacoustical emissions (SOAE; Zurek, 1981; for review, see Probst, 1990). Such emissions, which are thought to arise from the reflection of traveling waves at mechanical inhomogeneities in the cochlea (Fukazawa, 1992; Shera and Zweig, 1993; Talmadge and Tubis, 1993), require that stored energy be converted into mechanical oscillations; the mechanism considered in this paper may effect this transformation.

If a periodic external force is applied to the basilar membrane, it causes forced oscillations in the system with several interesting properties. Although there is no amplification of the first normal mode of oscillation, frequencies around the second normal mode are strongly amplified. The model exhibits high selectivity in that the range of frequencies amplified is very narrow; if application of a periodic external force causes a transition from a subcritical to a supercritical state, tuning (as manifested in spontaneous oscillations) becomes still sharper. The characteristic frequencies of the passive and active systems are different, that in the active system being shifted to a slightly higher value. Finally, at a frequency below the characteristic frequency, the threshold in the active system exceeds that in the passive one.

In response to an electrical step stimulus, the reticular lamina moved severalfold as much as the basilar membrane (Mammano and Ashmore, 1993). A similar phenomenon was observed in the acoustical response of the excised cochlea (Khanna et al., 1989): vigorous movement of the reticular lamina contrasted with moderate basilar-membrane motion. Because the gating of transduction channels in hair cells depends upon movement of the reticular lamina, this disparity in the motions of various parts of the cochlear partition may serve to create additional gain in mechano-electrical transduction.

Nonlinear effects

The analysis in this paper was carried out for the simplest possible linearized system, a standard approach in the modeling of active processes in the cochlea. Some deficiencies of the linear approach, however, are worth noting.

We found the conditions under which spontaneous otoacoustical emission can be generated by the active two-mass system: emission occurs in a supercritical system when the active gain, ξ, exceeds a critical value, ξ_{so}. Linear analysis suggests that spontaneous oscillation reaches an infinite amplitude, however, which is obviously unrealistic. When oscillation of the basilar membrane becomes large, the active movement of outer hair cells saturates (Fig. 2) and ceases to contribute additional energy to the movement. To find the amplitude of spontaneous oscillation, we must take into account the following. As follows from Eq. 17, in spontaneous oscillation

$$\left(i\omega + \frac{1}{\tau_m}\right)\Delta l = \frac{\xi}{\tau_m} X_{bm}\,. \tag{39}$$

If the active gain is near the critical value, ξ_{so}, and if Δl cannot exceed a saturating value Δl_{sat}, then the oscillation amplitude is approximately

$$|X_{bm}| \approx \frac{\Delta l_{sat}}{\xi_{so}} \sqrt{1 + \omega_0^2 \tau_m^2}\,. \tag{40}$$

With the membrane time constant, τ_m, near the optimal value given by Eq. 35, the estimate for the amplitude of spontaneous oscillation is simply

$$|X_{bm}| \approx \frac{\Delta l_{sat}}{\xi_{so}}\,. \tag{41}$$

Because of saturation in the active movement of outer hair cells, amplification in the cochlea is nonlinear: large signals are amplified less than small ones. This result represents the effect of a compressive nonlinearity.

Alternative mechanisms of amplification

Mammano and Ashmore (1993) noted an interesting possible deformation of the basilar membrane: under the influence of outer hair cell contraction, one portion of the basilar membrane (the *pars tecta*) might move in one direction, whereas the other part (the *pars pectinata*) would move in

the opposite direction with a smaller amplitude. Differential motion of two parts of the basilar membrane was also assumed in an earlier model (Kolston, 1988; Kolston et al., 1989), but the authors came to a different conclusion about the relative amplitudes of the two movements. Because the edges of the basilar membrane are affixed to bony ridges, such a deformation should generate additional tension in the membrane. In the model of Fig. 2, this would manifest itself as an increase in the stiffness K_{bm}. This effect could also be used for the amplification of oscillations; the mechanism of amplification is quite complicated, however, and we shall not analyze it here.

Like every other abstract representation of the cochlea, the two-mass model simplifies and idealizes anatomical reality. Although the elements of the model are lumped parameters representing several anatomical structures, we can hypothesize which structures are the main contributors to each parameter (see legend of Fig. 1 C). Although the analysis provided above is based upon a specific form of the two-mass model, the principles involved are equally applicable to other possible modes of oscillation in the cochlea. It remains possible, for example, that the active process resides in the hair bundles, rather than or in addition to the cell bodies of outer hair cells. The two masses relevant to the oscillation might then be the basilar membrane with the organ of Corti and the overlying tectorial membrane (Zwislocki and Kletsky, 1979). If hair bundles provide a positively directed force with a suitable phase delay after positive bundle stimulation, this arrangement would yield the full complement of responses described above.

We thank the members of our research group for critical comments on the manuscript.

This work was supported by National Institutes of Health grant DC00317. A.J.H. is an Investigator of the Howard Hughes Medical Institute.

REFERENCES

Allen, J. B. 1980. Cochlear micromechanics—a physical model of transduction. *J. Acoust. Soc. Am.* 68:1660–1670.

Ashmore, J. F. 1987. A fast motile response in guinea-pig outer hair cells: the cellular basis of the cochlear amplifier. *J. Physiol.* 388:323–347.

Brownell, W. E., C. R. Bader, D. Bertrand, and Y. de Ribaupierre. 1985. Evoked mechanical responses of isolated cochlear outer hair cells. *Science.* 227:194–196.

Cooper, N. P., and W. S. Rhode. 1992. Basilar membrane mechanics in the hook region of cat and guinea-pig cochleae: sharp tuning and nonlinearity in the absence of baseline position shifts. *Hearing Res.* 63: 163–190.

Dallos, P., B. N. Evans, and R. Hallworth. 1991. Nature of the motor element in electrokinetic shape changes of cochlear outer hair cells. *Nature.* 350:155–157.

de Boer, E. 1990. Can shape deformations of the organ of Corti influence the travelling wave in the cochlea? *Hearing Res.* 44:83–92.

Evans, B. N., R. Hallworth, and P. Dallos. 1991. Outer hair cell electromotility: the sensitivity and vulnerability of the DC component. *Hearing Res.* 52:288–304.

Fukazawa, T. 1992. Evoked otoacoustic emissions in a nonlinear model of the cohclea. *Hearing Res.* 59:17–24.

Geisler, C. D. 1991. A cochlear model using feedback from motile outer hair cells. *Hearing Res.* 54:105–117.

Geisler, C. D. 1993. A realizable cochlear model using feedback from motile outer hair cells. *Hearing Res.* 68:253–262.

Housley, G. D., and J. F. Ashmore. 1992. Ionic currents of outer hair cells isolated from the guinea-pig cochlea. *J. Physiol.* 448:73–98.

Iwasa, K. H., and R. S. Chadwick. 1992. Elasticity and active force generation of cochlear outer hair cells. *J. Acoust. Soc. Am.* 92: 3169–3173.

Kemp, D. T. 1978. Stimulated acoustic emissions from within the human auditory system. *J. Acoust. Soc. Am.* 64:1386–1391.

Khanna, S. M., Å. Flock, and M. Ulfendahl. 1989. Comparison of the tuning of outer hair cells and the basilar membrane in the isolated cochlea. *Acta Otolaryngol. Suppl.* 467:151–156.

Kolston, P. J. 1988. Sharp mechanical tuning in a cochlear model without negative damping. *J. Acoust. Soc. Am.* 83:1481–1487.

Kolston, P. J., M. A. Viergever, E. de Boer, R. J. Diependaal. 1989. Realistic mechanical tuning in a micromechanical cochlear model. *J. Acoust. Soc. Am.* 86:133–140.

Lighthill, J. 1991. Biomechanics of hearing sensitivity. *J. Vibrat. Acoustic.* 113:1–13.

Mammano, F., and J. F. Ashmore. 1993. Reverse transduction measured in the isolated cochlea by laser Michelson interferometry. *Nature.* 365: 838–841.

Neely, S. T., and D. O. Kim. 1983. An active cochlear model showing sharp tuning and high sensitivity. *Hearing Res.* 9:123–130.

Neely, S. T., and D. O. Kim. 1986. A model for active components in cochlear biomechanics. *J. Acoust. Soc. Am.* 79:1472–1490.

Patuzzi, R., and D. Robertson. 1988. Tuning in the mammalian cochlea. *Physiol. Rev.* 68:1009–1082.

Probst, R. 1990. Otoacoustic emissions: an overview. *In* New Aspects of Cochlear Mechanics and Inner Ear Pathophysiology, Adv. Oto-Rhino-Laryngol., Vol. 44. C. R. Pfaltz, editor. Karger, Basel. 1–91.

Ruggero, M. A., L. Robles, N. C. Rich, and A. Recio. 1992. Basilar membrane responses to two-tone and broadband stimuli. *Phil. Trans. R. Soc. Lond. B.* 336:307–315.

Santos-Sacchi, J. 1992. On the frequency limit and phase of outer hair cell motility: effects of the membrane filter. *J. Neurosci.* 12:1906–1916.

Sellick, P. M., R. Patuzzi, and B. M. Johnstone. 1982. Measurement of basilar membrane motion in the guinea pig using the Mössbauer technique. *J. Acoust. Soc. Am.* 72:131–141.

Shera, C. A., and G. Zweig. 1993. Noninvasive measurement of the cochlear traveling-wave ratio. *J. Acoust. Soc. Am.* 93:3333–3352.

Talmadge, C. L., and A. Tubis. 1993. On modeling the connection between spontaneous and evoked otoacoustic emissions. *In* Biophysics of Hair Cell Sensory Systems. H. Duifhuis, J. W. Horst, P. van Dijk, and S. M. van Netten, editors. World Scientific Publishing, Singapore. 25–31.

von Békésy, G. 1960. Experiments in Hearing. E. G. Wever, translator and editor. McGraw-Hill Book Company, New York. 401–534.

Zurek, P. M. 1981. Spontaneous narrow-band acoustic signals emitted by human ears. *J. Acoust. Soc. Am.* 69:514–523.

Zweig, G. 1990. The impedance of the organ of Corti. *In* The Mechanics and Biophysics of Hearing. Lecture Notes in Biomathematics, Vol. 87. P. Dallos, C. D. Geisler, J. W. Matthews, M. A. Ruggero, and C. R. Steele, editors. Springer-Verlag, Berlin. 362–369.

Zweig, G. 1991. Finding the impedance of the organ of Corti. *J. Acoust. Soc. Am.* 89:1229–1254.

Zweig, G., R. Lipes, and J. R. Pierce. 1976. The cochlear compromise. *J. Acoust. Soc. Am.* 59:975–982.

Zwislocki, J. J., and E. J. Kletsky. 1979. Tectorial membrane: a possible effect on frequency analysis in the cochlea. *Science.* 204:639–641.