Effect of outer hair cell piezoelectricity on high-frequency receptor potentials

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The low-pass voltage response of outer hair cells predicted by conventional equivalent circuit analysis would preclude the active force production at high frequencies. We have found that the band pass characteristics can be improved by introducing the piezoelectric properties of the cell wall. In contrast to the conventional analysis, the receptor potential does not tend to zero and at any frequency is greater than a limiting value. In addition, the phase shift between the transduction current and receptor potential tends to zero. The piezoelectric properties cause an additional, strain-dependent, displacement current in the cell wall. The wall strain is estimated on the basis of a model of the cell deformation in the organ of Corti. The limiting value of the receptor potential depends on the ratio of a parameter determined by the piezoelectric coefficients and the strain to the membrane capacitance. In short cells, we have found that for the low-frequency value of about 2–3 mV and the strain level of 0.1% the receptor potential can reach 0.4 mV throughout the whole frequency range. In long cells, we have found that the effect of the piezoelectric properties is much weaker. These results are consistent with major features of the cochlear amplifier. © 2003 Acoustical Society of America. [DOI: 10.1121/1.1526493]

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I. INTRODUCTION

An understanding of the frequency response and selectivity has always been a central problem of cochlear mechanics and hearing science (Zwislocki, 1953; Zweig \textit{et al.}, 1976). It is thought now that outer hair cell electromotility (Brownell \textit{et al.}, 1985, 2001)—changes in the cell length caused by changes in the cell membrane’s electric potential—is a key contributor to the sharp frequency selectivity and active amplification (cochlear amplifier) in the mammalian ear (Geisler, 1998; Dallos, 1996; Ruggero, 1992). Passive vibration of the basilar membrane and tectorial membrane in the cochlea is amplified by the active force and energy produced by the electromotile outer hair cells. Such amplification is observed under high-frequency stimulation in the basal turn of the cochlea where outer hair cells are short (Rhode, 1971; Cooper and Rhode, 1992). The active amplification disappears in the deeper areas of the cochlea where outer hair cells are long (Zinn \textit{et al.}, 2000; Hempt \textit{et al.}, 2000; Cooper and Rhode, 1995). Direct measurements of the active force produced by outer hair cells \textit{in vivo} under high-frequency conditions are unavailable at this time. The activation of isolated outer hair cells in the microchamber has shown the production of electromotile length changes and an active force at a constant level throughout the whole acoustic range of frequencies (Frank \textit{et al.}, 1999). Simulation of the high-frequency electromotile response of isolated outer hair cells has confirmed the production of significant length changes beyond 20 kHz (Tolomeo and Steele, 1998). These results indicate that if the outer hair cell is provided with sufficient changes in its membrane potential, the cell is capable of producing the active force necessary for the cochlear amplifier in a broad range of frequencies. The conventional view of the changes in the outer hair cell membrane potential (receptor potential) relates them to the transduction current coming to the cell as ionic channels open in response to an inclination of the stereocilia (Geisler, 1998; Pickles, 1988). This view leads to a paradox: the analysis of the basic circuit, including the stereocilia and the cell membrane with their electrical properties, shows a severe attenuation of the receptor potential at higher frequencies that would preclude the outer hair cells from producing the active force (Santos-Sacchi, 1988 and 1992; Housley and Ashmore, 1992). Mathematically, this attenuation is manifested in the receptor potential tending to zero with increasing frequencies (Housley and Ashmore, 1992). In addition, the phase shift (delay) between the trans-

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transduction current and receptor potential increases with frequency tending to the angle equal to ~90 degrees. An alternative view of the electric potential that drives outer hair cell electromotility under physiological conditions was developed by Dallos and Evans (1995) who assumed that outer hair cell motility is driven by the prescribed electric gradient between the cell core and the extracellular environment. The corresponding analysis showed a significant resulting potential of the cell membrane.

The major features of the outer cell mechanics and electromotility fit well the piezoelectric model because dimensional changes in the cell are observed in response to the application of an electric field (Brownell et al., 1985), and, conversely, an electric current is observed in response to the mechanical deformation of the cell (Gale and Ashmore, 1994). Although the outer hair cell is structurally far from piezoelectric crystals, the cell exhibits similar electromechanical coupling. The molecular mechanism of the piezoelectric-type behavior of the outer hair cell is related to motor protein Prestin (Zheng, 2000), voltage sensor (ions of chloride), and an interaction between the two (Oliver, 2001).

The motor protein can be presented as fluctuating between two states with a probability depending on elementary electrical and mechanical energies (Dallos et al., 1993; Iwasa, 1994). The direct piezoeffect is associated with a perturbation of the electrical energy that enters the probability of the motor's fluctuation. The motor's fluctuation results in an effective mechanical response: cell's length and radius changes. The converse piezoeffect underlying the phenomena considered in the present paper is associated with a perturbation of the mechanical energy that also enters the probability of the motor's fluctuation. This fluctuation results in an effective electrical response and produces a displacement current.

Mountain and Hubbard (1994) discussed a piezoelectric model of the outer hair cell function and estimated a number of characteristics on the basis of electromechanical coupling in the cell. Steele et al. (1993) and Tolomeo and Steele (1995) have proposed linear piezoelectric constitutive relationships for the outer hair cell wall. These relationships are reciprocal in terms of the mechanical and electrical components. Dong et al. (2002) have confirmed the reciprocity by showing that the experimentally determined off-diagonal coefficients in linear piezoelectric relationships for the cell as a whole are close to each other. Spector (2001) has proposed a thermodynamically consistent mechanically linear and electrically nonlinear model of the cell wall. Spector (2000) has also analyzed the effect of the piezoelectric properties on the cell membrane potential under current-clamp conditions. Weitzel et al. (2002) have recently modeled the outer hair cell as a length-thickness extension piezoelectric resonator.

In the present paper, we have shown that much larger values of the receptor potential than those given by the conventional resistance–capacitance (RC) analysis can be predicted in the same traditional paradigm (stereocilia inclination–transduction current–receptor potential) if the piezoelectric properties of the cell wall are taken into account. These effective properties are attributed to the whole composite cell wall that includes the outermost lipid bilayer with motor-proteins, the intermediate cytoskeleton, and the innermost subsurface cisternae. In contrast to results of RC analysis, the receptor potential in our analysis does not tend to zero but is greater than a certain value throughout the whole frequency range. The limiting (asymptotic) value of the receptor potential depends on the ratio of a parameter that includes the piezoelectric coefficients of the wall and typical wall strain to cell capacitance. This ratio reaches 0.4 mV in short cells, and is small (probably, physiologically negligible) in long cells. This finding is consistent with the outer hair cells' performance in the cochlear amplifier. The major result of the paper means that the intrinsic properties of an individual outer hair cell contribute to the high-frequency receptor potential. This contribution along with those from electrical coupling among the cochlear elements is, probably, sufficient for the active force needed for the cochlear amplifier.

The major results of the present paper were announced in Spector et al. (2002).

II. MODEL

A. Equivalent circuit and equation in terms of the receptor potential

The equivalent electric circuit, including the stereocilia and the cell wall, is shown in Fig. 1. As in conventional RC analysis (Santos-Sacchi, 1992; Housley and Ashmore, 1992), the components of the circuit are characterized by their electrical properties (conductances and capacitances), and the sum of their electric potentials is equal to the prescribed value of the endocochlear potential with respect to the cell core $\Psi$. The new component of the circuit is the element responsible for an additional displacement current, a manifestation of the piezoelectric properties of the cell wall.

The linear version of the piezoelectric relationships in the cell wall has the form (Tolomeo and Steele, 1995; Spector, 2000)

$$N_s = C_{11}\varepsilon_x + C_{12}\varepsilon_y + e_s \Delta \Psi_e ,$$

![FIG. 1. Modified electric circuit, including the stereocilia and cell electrical properties, with an additional element $I_{pe}$ that represents a displacement current caused by the piezoelectric properties of the outer hair cell wall; $c$ refers to the cell and $s$ refers to the stereocilia; $G_c$ and $G_s$ are, respectively, the conductances of the cell and stereocilia, $C_c$ is cell membrane capacitance, and $\Psi$ is the endocochlear potential with respect to the outer hair cell core.](image-url)
\[ N_\theta = C_{12} \varepsilon_x + C_{22} \varepsilon_\theta + e_\theta \Delta \Psi_c. \]
\[ \frac{dD}{dS} = -e_x \varepsilon_x - e_\theta \varepsilon_\theta + c \Delta \Psi_c, \]

where \( N_\theta \) and \( N_\varepsilon \) are the longitudinal and circumferential components of the strain, \( \varepsilon_x \) and \( \varepsilon_\theta \) are the components of the strain, \( C_{12} \), \( C_{22} \), and \( C_{22} \) are the orthotropic elastic moduli, \( e_x \) and \( e_\theta \) are the components of the active force per unit membrane potential change, \( \Delta \Psi_c \) is the change in the membrane potential (receptor potential), \( D \) is electrical displacement, \( S \) is the surface area of the cell wall, and \( c \) is the specific capacitance of the cell.

The balance of the currents in the circuit (Fig. 1) can be written as

\[ G_c \Delta \Psi_c + \frac{dD}{dt} = G_s \Delta \Psi_s, \]

where \( G_c \) and \( G_s \) are, respectively, the membrane and stereocilia conductances, and \( \Delta \Psi_s \) is the potential change associated with the stereocilia. Conductance \( G_c \) is a nonlinear function of the inclination of the stereocilia (Kros, 1996). We consider small inclinations of the stereocilia and use a linear approximation for \( G_c \). We assume that the cell is deformed by two vibrating complexes where one is associated with the basilar membrane and the Deiter’s cell and the other is associated with the reticular lamina and tectorial membrane (more detailed analysis of the cell deformation is given below). We also assume that the stereocilia are firmly attached to the tectorial membrane. These assumptions result in the equations

\[ \varepsilon_x = \varepsilon_x^0 \sin \omega t, \quad \varepsilon_\theta = \varepsilon_\theta^0 \sin \omega t, \quad G_s = G_s^0 + G_s^1 \sin \omega t. \]

Considering \( \varepsilon_x \) and \( \varepsilon_\theta \) in Eq. (3) as effective (uniform) strains, taking into account that the sum of \( \Delta \Psi_s \) and \( \Delta \Psi_c \) is equal to \( \Psi \), and substituting Eqs. (3) and (5) into Eq. (4) we obtain

\[ C_c \frac{d\Delta \Psi_c}{dt} + (G + G_s^0 \sin \omega t) \Delta \Psi_c \]
\[ = G_s^1 \psi \sin \omega t - \beta \omega \cos \omega t, \]

where \( C_c \) is whole-cell capacitance and

\[ G = G_c + G_s^0, \]
\[ \beta = -S (\varepsilon_x^0 e_x + \varepsilon_\theta^0 e_\theta). \]

In Eq. (6), the terms resulting in the constant component of the membrane potential are omitted.

**B. Model of the cell deformation in the organ of Corti**

In our model of the deformation of an outer hair cell in the organ of Corti, the cell is deformed by two planes moving with respect to each other [Fig. 2(a)]. The lower plane represents the basilar membrane and Deiter’s cell complex, and the upper plane represents the reticular lamina and tectorial membrane complex. The anatomy of the organ of Corti is such that outer hair cells are inclined in two directions (Geisler, 1998): along the cochlea toward the base [Fig. 2(b)] and across the cochlea toward the inner hair cell [Fig. 2(c)]. Thus, angle \( \alpha \) of the cell’s inclination with respect to the two planes in our model is a combination of two angles observed in the organ of Corti. To find the strain in the cell, we represent the cell by a hollow beam with an incompressible core inside. The deformation of the beam results from the relative displacement of its ends. This displacement is equal to the relative displacement \( \Delta \) of the upper and lower planes. Therefore, the cell (beam) is deformed by two components of the relative displacement of its ends: one is along the beam axes (\( \Delta \cos \alpha \)) and the other is normal to the beam axes (\( \Delta \sin \alpha \)). The first component causes a uniform axial strain of the cell accompanied by a circumferential strain that is two times smaller in magnitude and has the opposite sign. Such circumferential strain preserves the volume inside the cylindrical beam. The second, normal to the cell axes, component of the relative displacement causes bending of the beam. We now obtain the bending-related component of the axial strain in the beam. Since the upper end of the cell is embedded in the reticular lamina, we assume the fixed-end boundary condition for the upper end of the beam. The boundary condition for the lower end of the beam is determined by the mechanics of contact between the basal end of the outer hair cell and the supporting Deiter’s cell. Experimental information on this interaction is unavailable at this time. For that reason, we will estimate the cell deformation in two extreme cases of the contact between the outer hair and Deiter’s cell: no-slip contact (the fixed-end condition) and no-friction contact (the hinge-type condition). In both cases, the corresponding axial strain is skew-symmetric with respect to the beam axes, and it does not change the internal volume. Therefore the bending mode is not accompanied by an additional circumferential strain.

At the upper end of the beam, the displacement equal to \( \Delta \sin \alpha \) and the angle of inclination equal to zero are prescribed. At the lower end of the beam, the displacement equal to zero and either the angle of inclination or the bending moment equal to zero are prescribed. Equations (9) and
(10) below (e.g., Popov, 1990) give, respectively, the axial strain \( (\varepsilon_x^b) \) in the bent beam that correspond to the first and second boundary condition at the lower end,

\[
\varepsilon_x^b = -y \frac{12\Delta \sin \alpha (0.5L-x)}{L^3},
\]

\[
\varepsilon_y^b = -y \frac{3\Delta \sin \alpha (L-x)}{L^2},
\]

where \( L \) is the length of the cell (beam), and coordinates \( x \) and \( y \) specify the plane of bending of the cell (beam) with the \( x \)-axis directed along the cell. Thus, the total axial strain \( (\varepsilon_x) \) in the cell (beam) is given (depending on the boundary condition) by one of the following equations:

\[
\varepsilon_x = \frac{\Delta}{L} \left[ \cos \alpha - y \frac{12(0.5L-x)}{L^2} \sin \alpha \right],
\]

\[
\varepsilon_x = \frac{\Delta}{L} \left[ \cos \alpha - y \frac{3(L-x)}{L^2} \sin \alpha \right].
\]

In both cases, the circumferential component of the strain is given by the equation

\[
\varepsilon_\theta = -0.5 \frac{\Delta}{L} \cos \alpha.
\]

III. RESULTS

A. Analytical consideration

In terms of the receptor potential, Eq. (6) can be solved analytically by using separation of variables; the solution, however, is expressed in terms of complicated integrals. To implement this solution, an isolation of the limiting periodic solution and the following numerical integration are required. In the next sections, we use the direct numerical integration of Eq. (6). Here we treat analytically the case of short cells by neglecting the term \( G_c^1 \) sin \( \omega t \) compared to the term \( G \) in Eq. (6). For a 20-\( \mu \)m cell, the ratio \( G_c^1/G \) is about 0.02–0.05 (see Sec. III B). The harmonic solution of the simplified Eq. (6) takes the form

\[
\Delta \Psi_c = \frac{\sqrt{|f_1(\omega)|^2 + |f_2(\omega)|^2}}{f_3(\omega)},
\]

where

\[
f_1(\omega) = G_c^1 \Psi - \beta \omega^2 C_c,
\]

\[
f_2(\omega) = \omega (C_c G_c^1 \Psi + \beta G),
\]

and

\[
f_3(\omega) = \omega^2 C_c^2 + G^2.
\]

The phase shift between the transduction current and the resulting receptor potential is given by the equation

\[
\Theta = -\frac{180^\circ}{\pi} \arctan \frac{f_2(\omega)}{f_1(\omega)}.
\]

The asymptotic analysis of Eqs. (14)–(18) gives

\[
\Delta \Psi_c \sim \frac{\beta}{C_c} \text{ if } \omega \to \infty
\]

and

\[
\Theta \to 0 \text{ if } \omega \to \infty.
\]

If \( \beta = 0 \), Eq. (6) reduces to the equation describing the traditional RC circuit. In contrast to Eqs. (19) and (20), the traditional RC consideration results in the equations

\[
\Delta \Psi_c \to 0 \text{ if } \omega \to \infty
\]

and

\[
\Theta \to -90^\circ \text{ if } \omega \to \infty.
\]

B. Parameters used

We consider the effect of the piezoelectric properties on the receptor potential in long and short cells. We chose the lengths 20 and 60 \( \mu \)m, respectively, to represent these two types of outer hair cells. Housley and Ashmore (1992) measured the cell membrane capacitance and conductance and determined the dependence of these characteristics on the cell length. On the basis of those data, we use the values \( C_c = 20 \text{ pF} \) and \( G_c = 40 \text{ nS} \) for 20-\( \mu \)m cells and the values \( C_c = 36 \text{ pF} \) and \( G_c = 15 \text{ nS} \) for 60-\( \mu \)m cells. A similar value of long-cell (55.5 \( \mu \)m) capacitance was obtained by Kakehata and Santos-Sacchi (1995). For the endocochlear potential, we use the range \( \Psi = 120–150 \text{ mV} \) (Housley and Ashmore, 1992).

The conductance of the stereocilia can be estimated on the basis of its nonlinear dependence on the stereocilia displacement (Kros, 1996) by using a linear approximation. An alternative way to estimate conductance of the stereocilia is via a range of the low-frequency receptor potential. By using Eqs. (14)–(17), the following equation in terms of conductance of the stereocilia can be obtained:

\[
\frac{G_s^1}{G_s^1 + G_c} = \frac{\Delta \Psi_c^0}{\Psi}.
\]

The parameter \( \Delta \Psi_c^0 = \Delta \Psi_c(\omega = 0) \) can be interpreted as a low-frequency receptor potential that has been measured by several groups. Dallos (1996) estimated the low-frequency receptor potential corresponding to a low-level acoustic signal, 40 dB, to be close to 5 mV. Mammano and Ashmore (1993) obtained comprehensive experimental data on mechanical and electrical parameters inside the organ of Corti. The low-frequency receptor potential estimated on the basis of the known value of the injected current was found to be about 2.5 mV. Taking into account these estimates of \( \Delta \Psi_c^0 \), the range of the endocochlear potential \( \Psi \), and the value of the conductance of the cell membrane \( G_c \), we estimate conductance of the stereocilia as 1–2 \( \mu \)S.

We now discuss the characteristics that enter the equation for parameter \( \beta [\text{Eq. (8)}] \). On the basis of measurements of the reticular lamina and the basilar membrane amplitudes
(Mammano and Ashmore, 1993), the corresponding relative displacement can be estimated to be close to 20 nm. We use this value as an estimate of the parameter $\Delta$ that characterizes the relative displacement of two planes and the strain in the outer hair cell in our model. At this time, experimental estimates of the outer hair cell’s deformation under high-frequency conditions are unavailable. However, it has been shown that for high frequencies, particularly in the area of the active amplification, displacements of the cochlear partition become much greater. Therefore, we could expect an increase in the strain of outer hair cells situated in a confined space between the partitions. There is also independent evidence that the active component of the strain does not decrease significantly up to high frequencies. Frank et al. (1999) have shown that the active force that can be considered approximately proportional to the active strain stays almost constant within a broad range of frequencies. Thus, our value of the strain obtained on the basis of Mammano and Ashmore’s (1993) measurements can be considered a conservative estimate.

Spector et al. (1999) and Spector (2001) obtained the piezoelectric coefficients $e_x$ and $e_y$ in the form of functions of the cell stiffness parameter. Differences in the stiffness of the cell were the major source of the variability (see data from several groups below) of the estimates of the active force per unit transmembrane potential. By having the dependence of the piezoelectric coefficients $e_x$ and $e_y$ on the cell stiffness, we were able to compare more accurately our estimates with those from other groups.

The stiffness parameter introduced by Spector et al. (1999) is inversely proportional to the length of the cell. We use the dependence of the piezoelectric coefficients on the cell stiffness parameter to estimate these coefficients for cells of different lengths. The coefficient $e_x$ does not change significantly between the length 20 and 60 $\mu$m. Thus we use the value $e_x = 5 \times 10^{-3}$ NV$^{-1}$ m$^{-1}$ in both cases. This value falls within a range of the data obtained by several groups. The estimates of the parameter $e_x$ made by Xue et al. (1993), Iwasa and Adachi (1997), Hallworth (1997), and Tolomeo and Steele (1998) are, respectively, $6.4 \times 10^{-3}$, $4 \times 10^{-3}$, $2 \times 10^{-3}$, and $1.6 \times 10^{-3}$ NV$^{-1}$ m$^{-1}$. The piezoelectric coefficients also enter the parameter $\beta$ via combination $e_x - 0.5e_y$ that appears as a result of the substitution of the circumferential strain [Eq. (13)] into parameter $\beta$. This combination changes very significantly between the lengths 20 and 60 $\mu$m. By using the data of Spector et al. (1999) we estimate the discussed combinations of the piezoelectric coefficients as $4 \times 10^{-3}$ and $0.3 \times 10^{-3}$ NV$^{-1}$ m$^{-1}$, respectively, in the cases of 20 and 60 $\mu$m lengths of the cell. The angle of the cell’s inclination $\alpha$ affects the strain in the cell membrane. As we mentioned before, this angle is a combination of two angles of inclination of the outer hair cell, along and across the cochlea. The first angle is about the same for short and long cells (Geisler, 1998). The second angle changes strongly along the cochlea decreasing toward short cells (Geisler, 1998). We use the values 25 and 45 degrees of angle $\alpha$, respectively, in our consideration of short and long cells.

C. Numerical results

Below we present the data on the amplitude and phase shift of the outer hair cell’s membrane receptor potential for short (20 $\mu$m) and long (60 $\mu$m) cells. In the analytical solution above, we neglected the time-dependent term in front of $\Delta \Psi_c$ in Eq. (6). For longer cells, this term becomes more significant (the ratios $G_1/G$ are equal, respectively, to 0.05, 0.13, and 7.1 for cells of 20-, 60-, and 85-$\mu$m lengths) and here we use the direct integration of Eq. (6). For any initial conditions the transient part of the numerical solution was oscillatory with the amplitude changing with time. After a certain number of cycles (oscillations) the solutions stabilized and reached a limiting periodic solution. In the case of 20-$\mu$m cells, the numerical limiting periodic solution did not differ more than 6%–7% from the purely sinusoidal solution predicted by the analytical treatment above. In the case of longer cells (especially, 80-$\mu$m cells) the limiting periodic solutions looked like distorted sinusoidal functions asymmetric with respect to the time axis because of a dc shift. The numerical results presented below are based on the limiting periodic components of the solutions of Eq. (6). This equation was integrated by using software Mathematica, and in all cases the initial condition was $\Delta \Psi_c^0 = 0$. We discuss first the results for short, 20-$\mu$m cells. To demonstrate the effect of the piezoelectric properties more explicitly, we represent the frequency dependence in two ranges of frequency: from 1 to 4 kHz and from 10 to 40 kHz. We discussed above the parameters $G_1$ and $\Psi$ that determine the initial value of the receptor potential $\Delta \Psi_c$. To reflect the variation of these two parameters, we present two sets of curves corresponding to combinations of $G_1$ and $\Psi$ that result in the values $\Delta \Psi_c = 2.5$ mV and $\Delta \Psi_c = 5.6$ mV. Taking into account the ranges of the relative displacement of two planes in our model of the cell deformation, the strain in the cell wall, the angle of the cell’s inclination, and the piezoelectric coefficients, we present the curves for three values of the parameter $\beta$: $4 \times 10^{-15}$, $5 \times 10^{-15}$, and $7 \times 10^{-15}$ NmV$^{-1}$. For comparison, we also include the curves for $\beta = 0$, the case that corresponds to the conventional RC analysis.

Figures 3(a) and (b) show the variation of the amplitude of the receptor potential for the frequencies within ranges 1–4 and 10–40 kHz, respectively. Figure 3(c) shows the amplitudes of the receptor potential throughout the whole frequency range in the log/log scale. The initial value of the receptor potential is 2.5 mV in all three cases. Four curves in each figure correspond to the values of the parameter $\beta$ equal to 0, $4 \times 10^{-15}$, $5 \times 10^{-15}$, and $7 \times 10^{-15}$ NmV$^{-1}$. Figures 4(a) and (b) show similar sets of graphs in the case of $\Delta \Psi_c = 5.6$ mV. In Figs. 5(a) and (b), the phase shift between the receptor potential and the transduction current is plotted. The sets of curves in Figs. 5(a) and (b) correspond to the cases $\Delta \Psi_c = 2.5$ mV and $\Delta \Psi_c = 5.6$ mV, respectively.

We also present the results for longer, 60-$\mu$m, cells. Figures 6(a) and (b) show the variation of the receptor potential in the frequency range 10–40 kHz for the cases $\Delta \Psi_c = 2.5$ mV and $\Delta \Psi_c = 5.6$ mV, respectively. If we assume the same relative displacement of two planes and take into ac-
count the corresponding piezoelectric coefficients, then the values of the parameter $b$ used above in the case of short cells reduce, respectively, to $0.7 \times 10^{-15}$, $0.8 \times 10^{-15}$, and $1.1 \times 10^{-15}$ NmV$^{-1}$ in the case of long cells. In Figs. 6(a) and (b), the curves for this set of $b$ are presented. The curves that correspond to $b=0$ are also included.

**IV. DISCUSSION**

The main result of the present study is that the outer hair cells in the basal part of the cochlea are under the action of a much greater electromotility-driving receptor potential than it was previously thought on the basis of the RC-type analysis. This new estimate of the receptor potential is obtained by taking into account intrinsic piezoelectric properties of the cell under the traditional paradigm in which inclination of the stereocilia causes the transduction current and this current results in a receptor potential. The piezoelectric properties result in an additional displacement current that balances the severe attenuation of the high-frequency receptor potential caused by the capacitive properties of the cell wall.

The found values of the receptor potential in short cells are six to ten times greater (depending on the parameter $b$) than those obtained without consideration of the piezoelectric properties for frequencies above $30$ kHz [Figs. 3(b) and 4(b)]. Such potential coincides with the result of the RC analysis. The piezoelectric wall has a qualitatively new behavior under high-frequency conditions: the receptor potential is greater than a certain value throughout the whole frequency range. This value is equal to the ratio of the composite piezoelectric parameter $\beta$ [Eq. (8)] to the capacitance of the cell. The asymptotic value of the receptor potential is independent of its low-frequency value $\Delta \Psi_0$. Because of this property the ratios of the newly estimated receptor potential to that obtained from the RC analysis in the cases in Figs. 3(b) and 4(b) are close to each other.
Our analysis shows that high-frequency receptor potentials are determined by two displacement currents: capacitive and piezoelectric-type. The transduction current proportional to the endocochlear potential plays a smaller role in the establishment of the high-frequency receptor potential. However, the importance of the endocochlear potential becomes clear if we consider the machinery of electromotility as a whole. One argument for that is related to the balance of chloride ions. Oliver et al. (2001) have recently shown that the moving charges that trigger the motor’s response are chloride ions. The balance of these ions is maintained via chloride channels located along the lateral wall (Rybalchenko and Santos-Sacchi, 2002). The endocochlear potential provides a potential gradient necessary for transport of chloride ions. The balance of ions of potassium is also important. Although in our model parameter $\beta$ is mostly associated with chloride ions, the resulting changes in the endocochlear potential open voltage-gated potassium channels at the bottom of the cell (Housley and Ashmore, 1992; Mammano and Ashmore, 1996). The balance of potassium ions is provided by transduction channels located in the stereocilia bundle, and those channels are governed by the endocochlear potential. Thus, our model is consistent with the endocochlear potential being a necessary component of ionic balance (transport) and a contributor to the active force and energy produced by electromotile outer hair cells.

When the frequencies are low, the effect of the piezoelectric properties is small [Figs. 3(a) and 4(a)]. In the case of Fig. 4(a) ($\Delta\Psi_c^0 = 5.6 \text{ mV}$), the difference between the present analysis and the RC consideration is below 25% throughout the whole range of frequencies 1–4 kHz. In the case of Fig. 3(a) ($\Delta\Psi_c^0 = 2.5 \text{ mV}$), the difference is more visible and reaches 1.4–2 times depending on the value of $\beta$. Nevertheless, in both cases the effect of the piezoelectric properties on the receptor potential is much smaller than that in the case of high frequencies.

The frequency response in the proposed model still exhibits a roll-off, as in the RC analysis. The high-frequency asymptotic value of the receptor potential is 7–10 and 9–16 times smaller than its initial value in the cases $\Delta\Psi_c^0 = 2.5 \text{ mV}$ and $\Delta\Psi_c^0 = 5.6 \text{ mV}$, respectively. Because the piezoelectric properties do not produce a significant effect below several kilohertz, the corner frequencies in our model are close to those determined by the RC analysis both in short and long cells. However, the roll-off in our model of the outer hair cell membrane is much less severe than that pre-
dicted by the RC analysis: the estimated ratios of the high-frequency potential to its low-frequency value is about an order of magnitude greater than the result of the RC analysis.

According to the mathematical analysis of the problem presented above, the phase shift between the transduction current and receptor potential tends to zero when the frequency tends to infinity. Figures 5(a) and (b) show the phase shift in short cells within a realistic high frequency range, 20–40 kHz. This phase shift indicates a small lead of the receptor potential: the corresponding angle is between 6 and 10 degrees in the case of Fig. 5(a) and it is between 15 and 25 degrees in the case of Fig. 5(b). This differs completely from the case $\beta=0$ where the piezoelectric properties are disregarded and the phase shift is practically constant and equal to $-90$ degrees. The phase shift between the input transduction current and the output active force produced by outer hair cells is a characteristic of the effectiveness of the machinery of electromotility. This phase shift is an important parameter of models of the whole cochlea. For example, Chadwick (1996) and Geisler and Sang (1995) assume this phase shift (phase shift between the deflection of the stereocilia and the active force) to be equal to zero, but Fukuzawa (1997) uses the value $-90$ degrees referring to the effect of the cell’s membrane capacitance predicted by the RC analysis. The phase shift between the transduction current and the active force can be represented by the sum of two components. The first is the phase shift between the transduction current and the receptor potential, and the second is the phase shift between the receptor potential and the active force. Experimental information on either of these components under high-frequency in vivo conditions is unavailable at this time. Frank et al. (1999) have demonstrated in vitro that the second of these angles is small up to high frequencies [in Frank et al.’s (1999) notations, that angle is close to 180 degrees]. Thus, in combination with Frank et al.’s (1999) data, our result on the phase shift between the transduction current and the receptor potential supports the models of the cochlea with zero phase shifts between the deflection of the stereocilia and the produced active force.

The results for long, 60-$\mu$m, cells are presented in Figs. 6(a) and (b). Qualitatively, the behavior of the receptor potential is similar to that in the case of short cells: the potential has a lower limit when frequencies increase. Because of the length dependence of the piezoelectric properties, the high-frequency values of the receptor potential are about six to seven times smaller than those for short cells under the conditions of the same relative displacements of two cochlear complexes. The high-frequency values of the receptor potential in long cells are about 0.05 mV and are, probably, physiologically insignificant. The main results presented in Figs. 3–5 are briefly summarized in Table I. The table indicates that the effect of the piezoelectric properties of the membrane is strong when short cells are under high-frequency stimulation. This effect is weak in short cells stimulated by a low-frequency signal as well as in long cells throughout the whole frequency range. This finding is consistent with observations of the cochlear amplifier in the basal and apical parts of the cochlea stimulated by high- and low-frequency signals.

We use the inhomogeneous axial strain (11) and (12) for an estimate of the constant receptor potential of the outer hair cell wall. The piezoelectric model of the present paper describes the electromechanical coupling in an element of the cell wall. Thus, a more accurate analysis of the 3-D distribution of the strain in the cell wall can be used for estimates of electrical gradients along and around the cell. This might be important for a better understanding of transport (diffusion) of ions involved in the mechanism of electromotility.

The model and findings of the present paper are supported by a number of experimental observations. First, the piezoelectric model reflects electromechanical coupling in the cell wall where active strains (dimensional changes) are generated in response to the application of an electric field and, conversely, an electric current is generated in response to the application of a strain (strain rate) to the cell. There is also a molecular-level interpretation of these properties that is based on the identified molecular motor and its voltage sensor. Second, the piezoelectric parameter $\beta$, the key characteristic that in our model determines the high-frequency receptor potentials, is a combination of the derivatives of the active force with respect to the receptor potential and the strain in the cell wall. Despite some differences in measurements of the active force production per unit transmembrane potential there is a reasonable range for this characteristic that we used in this study. Also, the strain level was estimated on the basis of the displacements of the basilar membrane and tectorial membrane measured in situ. Third, the electrical properties of the stereocilia and the cell wall entering the major circuit equation were experimentally determined for cells of different lengths.

The supporting experimental facts mentioned above do not provide a more direct test of the main prediction of the paper that the piezoelectric properties of the cell wall increase the receptor potential driving outer hair cell electromotility. Thus, it is important to suggest a doable experiment that could confirm our prediction. Such an experiment could be an analysis of the high-frequency performance of outer hair cells under different level of strain (He, 2002). The level of strain can be regulated by loading (unloading) the cell. The strain variation cause changes in the piezoelectric parameter $\beta$ that, in turn, changes the high-frequency receptor potential. The level of loading should leave the strain small enough to correspond to a low (moderate) level of the acoustic signal.

The model proposed in the paper shows that an individual outer hair cell is capable of producing a significant receptor potential through the traditionally viewed mechanism that includes inclination of the stereocilia, transduction current, and receptor potential. The piezoelectricity-related contribution of an individual outer hair cell, along with those

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<th>High frequencies</th>
<th>Low frequencies</th>
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<tr>
<td>Short cells</td>
<td>strong</td>
<td>weak</td>
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<tr>
<td>Long cells</td>
<td>weak</td>
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### Table I. The effect of the piezoelectric properties of the cell wall on outer hair cells in the cochlea for different frequency ranges of the acoustic signal
related to the cochlear electrical environment, could result in high-frequency receptor potentials sufficient for the production of the active force driving the cochlear amplifier.

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Spector et al.: Outer hair cell piezoelectric properties 461