Effect of voltage-dependent membrane properties on active force generation in cochlear outer hair cell

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A computational model is proposed to analyze the active force production in an individual outer hair cell (OHC) under high-frequency conditions. The model takes into account important biophysical properties of the cell as well as constraints imposed by the surrounding environment. The biophysical properties include the elastic, piezoelectric, and viscous characteristics of the cell wall. The effect of the environment is associated with the stiffness of the constraint and the drag forces acting on the cell due to the interaction with the external and internal viscous fluids. The study concentrated on a combined effect of the transmembrane potential, frequency, and stiffness of the constraints. The effect of the voltage-dependent stiffness of the cell was particularly investigated and it was found to be twofold. First, it results in higher sensitivity and nonlinearity of the OHC active force production in the physiological range. Second, it determines smaller active forces in the hyperpolarization range. The resonant properties of the active force as functions of voltage and the constraint stiffness were also analyzed. The obtained results can be important for a better understanding of the OHC active force production and the contribution of cell electromotility to the cochlear amplification, sensitivity, and nonlinearity. © 2005 Acoustical Society of America. [DOI: 10.1121/1.2118387]

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I. INTRODUCTION

Outer hair cells (OHCs) are critically important for active hearing in mammals. These cells have a unique form of motility, named electromotility, responding to changes in the cell’s transmembrane potential (Brownell et al., 1985, 2001). The major features of electromotility are the cell’s length changes, nonlinear capacitance, and active force production. All three features remain effective within a broad frequency range (Frank et al., 1999; Gale and Ashmore, 1997a). The voltage dependence of the OHC characteristics has been known since the original discovery of electromotility when it was demonstrated that depolarized cells shorten and hyperpolarized cells elongate (Brownell et al., 1985). After that, the voltage dependence of length’s changes and that of nonlinear capacitance was studied extensively (Santos-Sacchi and Dilger, 1998; Santos-Sacchi, 1989; Iwasa, 1994; Santos-Sacchi and Navarette, 2002; Gale and Ashmore, 1994, 1997b). The important parameters of the voltage-dependent characteristics of OHC include the position and magnitude of the maximal value, the level of nonlinearity, slopes, etc. Moreover, these characteristics have been measured under hyper- and hypo-osmotic conditions as well as under the action of various agents known to affect hearing (Shehata et al., 1991; Hallworth, 1995, 1997; Lue et al., 2001; Ulfendahl, 1997). The voltage dependence of the active force was studied under low- and moderate-frequency conditions (Adachi and Iwasa, 1997; Iwasa and Adachi, 1997; Spector et al., 1999; He and Dallos, 2000).

To explain the voltage dependence of the major features of OHC electromotility, a model of molecular motors in the cell’s lateral wall has been proposed (Dallos et al., 1991; Iwasa, 1994, 2001). In this theory, the voltage dependence of the cell’s length changes, nonlinear capacitance, and active force was associated with the effect of the applied electric field on the probability of the motor being in different conformational states. Recently, the membrane protein, prestin, necessary for hearing and closely associated with outer hair cell electromotility, has been discovered (Zheng et al., 2000; Oliver et al., 2001; Liberman et al., 2002). The native electromotility of human embryonic kidney cells is enhanced when they are transfected with prestin and acquire a greatly enhanced voltage-dependent capacitance showing an association between the voltage dependence of OHC electromotility and the properties of the membrane protein prestin. The information on the voltage-dependent properties of OHC electromotility, on the other hand, can be used to characterize the properties of the motor mechanism and to extract its parameters.

The main phenomenon of electromotility, similar to the converse piezoelectric effect, is associated with a mechanical

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response to the application of an electric field (Brownell et al., 1985). The reciprocal phenomenon, the transfer of a charge across a part of the membrane in response to a mechanical perturbation of the membrane, which is similar to the direct piezoelectric effect, has also been demonstrated (Gale and Ashmore, 1997b; Zhao and Santos-Sacchi, 1999; Dong et al., 2002). This level of coupling was successfully described by linear and nonlinear piezoelectric-type relationships (Mountain and Hubbard, 1994; Tolomeo and Steele, 1998; Spector, 2000, 2001). However, it is likely that the electromechanical coupling in the outer hair cell lateral wall has additional modes. It has recently been shown that the stiffness of the cell as a whole, which was earlier considered as a purely passive characteristic, is also voltage-dependent (He and Dallos, 1999). This effect has been demonstrated for both low and moderate (up to 2 kHz) frequencies (He and Dallos, 2000). He et al. (2003) showed that the replacement of intracellular chloride required for the motor mechanism abolishes the voltage dependence of the cell stiffness (as well as the cellular electromotile response). In a possible explanation of the voltage dependence of the cellular stiffness, it has been proposed that the motor protein has an intrinsic finite stiffness that contributes to the stiffness of the whole cell (He and Dallos, 2000; Deo and Grosh, 2004). According to this model, the motor-related stiffness is different depending on what conformational state the motor takes.

Other voltage-dependent modes of electromechanical coupling in the cell wall can also be important for the outer hair cell performance under various conditions. Oghalai et al. (2000) have found that the lateral diffusion in the outer hair cell plasma membrane is voltage-dependent following a voltage profile similar to that of the voltage-dependent displacement. The piezoelectricity of the cell wall can enhance high-frequency receptor potential in the cell (Spector et al., 2003). Also, the strain-rate sensitivity of the cell wall that could be related to its viscoelastic properties can result in an increase in the cell’s receptor potential in the moderate-frequency range (Spector et al., 2005).

The OHC provides a positive feedback amplifying vibration of the basilar and tectorial membranes (Geisler, 1998; Dallos, 1996). This amplification (“cochlear amplifier”) is based on the active force and active energy produced by the cell and pumped into the vibrating basilar and tectorial membranes. Somatic motility is a key contributor to the OHC-related active characteristics. The voltage sensitivity of the active force in the physiological range of the cell’s transmembrane potential is important for the feedback provided by the OHC. In addition to the active amplification, hair cells are critical to the cochlear nonlinearities (Patuzzi, 1996). Voltage dependence and sensitivity of the OHC active force contribute to the nonlinearities of the cochlea as a whole. This contribution becomes more significant if a combination of two intrinsic OHC-related nonlinearities, length change versus voltage and stiffness versus voltage, are taken into account.

In the present paper, we extend our computational model (Liao et al., 2005) and apply it to the analysis of the active force production in a constrained OHC under high-frequency conditions. Here, we study the voltage dependence of the active force and concentrate on a combined effect of three factors, the transmembrane potential, frequency, and stiffness of the constraint. In terms of voltage dependence, we assume that the potential driving the cell’s electromotile response is significantly smaller than the resting (equilibrium) potential. This is a reasonable approximation of both physiological and experimental conditions where the cell is studied under high-frequency conditions. We start with general electrically nonlinear relationships and, on the basis of our assumption, linearize them about the point of the resting potential. In our model, the driving potential is a relatively small harmonic function with constant amplitude. In this approach, we mainly deal with the active force per unit transmembrane voltage. The resting potential enters our model in two ways. First, our model includes the coefficients that express the cell’s length and radius changes estimated under special conditions of no constraints and low frequencies; these coefficients are voltage-dependent. Second, the local elastic moduli of the cell wall depend on the whole cell stiffness, and the latter also depends on voltage. The frequency effect is mainly related to the viscous losses inside the cell wall and the wall interaction with the fluids inside and outside the cell. In our model, the stiffness of the constraints is associated with two springs attached to the ends of the cell (Fig. 1). These springs represent the effects of both the basilar and tectorial membrane complex in vivo and the attached AFM lever or glass fiber measuring the active force generation in vitro. We estimated the OHC active force within broad ranges of resting potential, frequency, and the stiffness of the constraint. We found that the effect of the constraint on the voltage dependence of the active force is significant. At any value of voltage, the active force decreases with frequency if the stiffness of the constraint is relatively low. It becomes reversed, and the active force increases with frequency if the stiffness of the constraint is high. Our model also shows that the effect of the voltage-dependent cell stiffness is important. We found that this effect results in a shift of the point of the highest voltage sensitivity of the active force toward the physiological value of the cell’s membrane potential. The obtained results can be important for a better understanding of the cochlear amplifier and nonlinearities associated with OHCs.

II. MODEL

Figure 1 presents the main features of our model. Panels (a) and (b) demonstrate applications of our model of the constrained cell to physiological and experimental conditions, and panel (c) shows how the constraints are treated in the model. Finally, panel (d) presents an element of the cell wall with the external tractions and internal resultants. In our model, the cell wall is considered as viscoelastic and piezoelectric material described by the following equations:

\[
\begin{bmatrix}
N_x \\
N_\theta
\end{bmatrix} =
\begin{bmatrix}
C_{11} & C_{12} \\
C_{12} & C_{22}
\end{bmatrix}
\begin{bmatrix}
\varepsilon_x \\
\varepsilon_\theta
\end{bmatrix}
+ 2 \eta
\begin{bmatrix}
s_x \\
s_\theta
\end{bmatrix}
+ \begin{bmatrix}
f_x' \\
f_\theta'
\end{bmatrix},
\]

where \(N_x\) and \(N_\theta\) are the components of the stress resultant (i.e., the product of the stress and cell wall thickness) generated in the cell wall; the subscripts \(x\) and \(\theta\) indicate the axial
and circumferential directions, respectively; \( C_{ij} \) are the orthotropic elastic moduli of the cell wall; \( \varepsilon_s \) and \( \varepsilon_\theta \) are two components of the total (observable) strain, \( \eta \) is the cell wall viscosity; \( s_r \) and \( s_\theta \) are the components of the deviatoric part of the strain rate (e.g., Evans and Skalak, 1980); and \( f_s^a \) and \( f_\theta^a \) are the longitudinal and circumferential components of the active force corresponding to low-frequency conditions. The latter forces are associated with the converse piezoelectric effect in the cell wall.

By relating the components of the strain rate \( (s_r, s_\theta) \) to the components of the velocity (time derivative of the wall displacement), we obtain the constitutive relations in their final form (Tolomeo, 1995; Ratnamather et al., 1996; Tolomeo and Steele, 1998; Spector et al., 1998, 1999; Spector and Jean, 2003; Liao et al., 2005):

\[
\begin{bmatrix}
N_r \\
N_\theta
\end{bmatrix} = \begin{bmatrix}
C_{11} & C_{12} \\
C_{12} & C_{22}
\end{bmatrix} \begin{bmatrix}
\frac{\partial u_r}{\partial x} \\
\frac{u_r}{r_c}
\end{bmatrix} \begin{bmatrix}
\frac{\partial u_x}{\partial x} \\
\frac{\partial u_x}{\partial \theta} \\
\frac{\partial u_r}{\partial \theta} \\
\frac{\partial u_r}{\partial \theta}
\end{bmatrix} + \begin{bmatrix}
\eta - \eta \\
- \eta - \eta \\
\frac{f_s^a}{r_c} \\
f_\theta^a
\end{bmatrix},
\]

where \( r \) denotes the radial (normal to the cell wall) direction, \( r_c \) is the cell radius, and \( u_r \) and \( u_\theta \) are two components of the wall displacement.

The functions \( f_s^a \) and \( f_\theta^a \) are given by the equations (e.g., Spector et al., 1999):

\[
f_s^a = -(C_{12} e_s^a + C_{12} e_\theta^a),
\]

\[
f_\theta^a = -(C_{22} e_s^a + C_{22} e_\theta^a),
\]

where \( e_s^a \) and \( e_\theta^a \) are the components of the active strain determined in the microchamber experiment under low-frequency conditions (Dallos et al., 1993).

In our model, the local moduli \( C_{ij} \) are voltage-dependent because they are functions of the whole cell stiffness, and the cell stiffness depends on the cell’s membrane potential. The dependence of moduli \( C_{ij} \) on the cell’s stiffness is described by the following equations (Spector et al., 1999):

\[
C_{11} = 0.25 C_{22} + 2.08 \gamma,
\]

\[
C_{12} = 0.5 C_{22} + 1.08 \gamma,
\]

\[
C_{22} = 0.2 + 0.8 \times 10^{-3}/\gamma,
\]

where both \( C_{ij} \) and the whole cell stiffness \( \gamma \) are in the units of N/m. The voltage dependence of cell stiffness \( \gamma(V_c) \) can be approximated as (He and Dallos, 2000)

\[
\gamma = 10^{-3} \frac{k_1}{1 + e^{(-k_2 V_c + k_3)}} + k_6,
\]

where \( \gamma \) is in the unit of N/m; \( V_c \) is the command voltage (mV); \( k_1 = 8.2, k_2 = -0.0005, k_3 = -0.46, k_4 = -0.0133, k_5 = 0.4, k_6 = 2.38 \). We adjusted parameter \( k_6 \) to make the moduli \( C_{ij} \) estimated at the reference point (in vitro normal resting potential) consistent with our previous data (Spector et al., 1999; Liao et al., 2005).
The proposed model can be applied to the analysis of the OHC high-frequency performance both in the microchamber experiment and under physiological conditions. In the former case, the cell’s transmembrane potential is the sum of the cell’s resting potential and a sinusoidal driving potential. The driving potential is determined by the AC component of command voltage generated in the microchamber. In the latter (physiological) case, the transmembrane potential of the cell is the sum of the cell’s resting potential and the receptor potential. Normally, the receptor potential is a few millivolts, much smaller than the resting potential of about −70 mV. In the analysis of the high-frequency microchamber experiment, Frank et al. (1999) did not report explicitly the amplitude of the driving potential; instead they presented their results in a normalized form. Our interpretation of the Frank et al. (1999) results is that their driving potential was small compared to the resting (equilibrium) potential. Otherwise, the corresponding amplitudes would have been reported since the cellular characteristics involved in the experiment are voltage-dependent.

Thus, in our analysis below, we linearize the original nonlinear Eq. (2) about the point of the resting potential assuming that the driving (receptor) potential is much smaller. Also, to simplify the discussion, we will refer to the two potentials involved in the analysis as the resting and driving potentials. In the physiological case, these two potentials should be interpreted as the resting and receptor potentials, respectively. As a result of the introduced linearization, Eq. (2) takes the following form

\[ \begin{bmatrix} N_x \\ N_\theta \end{bmatrix} = \begin{bmatrix} C_{11}(V_0) & C_{12}(V_0) \\ C_{12}(V_0) & C_{22}(V_0) \end{bmatrix} \begin{bmatrix} \frac{\partial u_x}{\partial x} \\ \frac{u_x}{r_c} \end{bmatrix} + \begin{bmatrix} \eta - \eta \\ -\eta - \eta \end{bmatrix} \begin{bmatrix} \frac{\partial^2 u_x}{\partial x^2} + \frac{\partial u_x}{\partial x} \\ \frac{\partial^2 u_x}{\partial r_c^2} + \frac{u_x}{r_c} \end{bmatrix} + V \begin{bmatrix} \frac{\partial^2 u_x}{\partial V^2}(V_0) \\ \frac{\partial^2 u_x}{\partial V^2}(V_0) + \frac{\partial u_x}{\partial V}(V_0) \end{bmatrix}, \]

where \( V_0 \) is the resting potential and \( V \) is the driving potential. According to Eq. (3), we have

\[ f_x^\prime = \frac{\partial f_x^\prime}{\partial V} = -\left[ \frac{\partial C_{11}(V_0)}{\partial V} e_x^\prime(V_0) + C_{11}(V_0) \frac{\partial e_x^\prime(V_0)}{\partial V} \right. \]

\[ + \left. \frac{\partial C_{12}(V_0)}{\partial V} e_y^\prime(V_0) + C_{12}(V_0) \frac{\partial e_y^\prime(V_0)}{\partial V} \right] V, \]

\[ f_\theta^\prime = \frac{\partial f_\theta^\prime}{\partial V} = -\left[ \frac{\partial C_{12}(V_0)}{\partial V} e_x^\prime(V_0) + C_{12}(V_0) \frac{\partial e_x^\prime(V_0)}{\partial V} \right. \]

\[ + \left. \frac{\partial C_{22}(V_0)}{\partial V} e_y^\prime(V_0) + C_{22}(V_0) \frac{\partial e_y^\prime(V_0)}{\partial V} \right] V, \]

where the voltage derivatives of the local moduli are derived by using the chain rule applied to Eqs. (4) and (5).

The stress and displacement in Eq. (1) can be expressed in terms of Fourier series in the cell wall domain and fluid domain. Then, the Fourier series are substituted into the governing equations for the corresponding domain, and the boundary conditions are taken into account. Finally, the cell end displacement \( u_{\text{end}} \) can be calculated. The force acting on the constraint is obtained as

\[ F_{\text{end}} = k_{\text{const}} u_{\text{end}}, \]

where \( k_{\text{const}} \) is the stiffness of the cell constraint, represented by a spring attached at the cell’s end. The force calculated by this equation is equal to the active force generated by the cell as a result of its electrical stimulation. Other details of the model can be found in the Appendix.

### III. RESULTS

The presentation of the results in Figs. 2–5 is organized as follows. To emphasize the effect of the voltage-dependent stiffness, each parameter of the cell is presented for fixed \( C_{ij} \) (stiffness of the cell is fixed and voltage-independent) and for variable \( C_{ij} \) (voltage-dependent stiffness is taken into account). Besides that, Figs. 3–5 are meant to show the active force per unit transmembrane potential as a function of three parameters, resting potential, frequency, and the stiffness of the constraint. In order to do that, each of the Figs. 3–5 corresponds to one of the values of the constraint stiffness, and it is presented in a three-panel format. The panels (a) in Figs. 3–5 demonstrate 3-D surfaces of the force as a function of frequency and resting potential. In each figure, the panels (b) and (c) present 2-D cross sections of the 3-D surface shown in the panel (a), and these cross sections correspond
to fixed frequency and fixed resting potential, respectively. Also, the panels (b) present the results for three, low (1 kHz), high (20 kHz), and very high (100 kHz) frequencies, and the panels (c) show the data for two values of the resting potential, one for −50 mV and the other for 10 mV.

In Fig. 2, we show two coefficients $e_x = \partial^2 f / \partial V^2$ and $e_\theta = \partial^2 f / \partial V \partial \theta$ given by Eq. (7) that express the active force production per unit transmembrane potential under low-frequency conditions. Figure 3 presents the active force per unit transmembrane potential as a function of frequency and resting potential for the stiffness of the constraint of 0.05 N/m. Such stiffness is close to that of the tectorial membrane (Zwislocki and Cefaratti, 1989), and it is also close to the lower limit of the stiffness of the reticular lamina overlying the OHCs (Scherer and Gummer, 2004). The data in Fig. 4 are presented for the value of the stiffness of the constraint 0.2 N/m, which is close to the upper limit of that of the reticular lamina. Finally, Fig. 5 shows the results
for the stiffness of the constraint (1.25 N/m) close to the stiffness of the basilar membrane in the cochlear basal turn (Gummer et al., 1981).

**IV. DISCUSSION**

We developed here a computational model to estimate the OHC’s active force, and our model explicitly incorporates a number of important factors associated with the biophysical properties of the cell and the environment around the cell. The biophysical factors include the orthotropic elastic moduli, piezoelectric parameters, and the viscosity of the cell wall. The effect of the environment is associated with the cell’s interaction with the surrounding fluids and with the constraints imposed on the cell. The proposed scheme can be applied to both physiological and experimental conditions, and it covers two types of constraints imposed on the outer
hair cell, the basilar and tectorial membrane complex and the
AFM lever or glass fiber attached to the cell. The cases con-
sidered in Figs. 3–5 correspond to the stiffness of the springs,
which are attached to the cell's ends, equal to that of the
basilar membrane, tectorial membrane, and reticular lamina.
Here the stiffness of two springs is the same, and to fully
represent the effect of the in vivo constraints, future versions
of the model will include the case of two springs with dif-
ferent properties.

The main focus of the present model is the voltage de-
pendence of the OHC active force and the combined effect of
the transmembrane potential, frequency, and constraint. The
voltage dependence of the active force is associated with
several voltage-dependent parameters that enter the constitu-
tive relations given by Eqs. (1) and (2). First, the components
of the active strain, $\varepsilon^a_x$ and $\varepsilon^a_r$, which express the relative
length and radius changes under special, no-resultant and
low-frequency conditions, vary with voltage (Dallos et al.,
2000).
Second, the local elastic moduli, $C_{ij}$, depend on the whole cell stiffness [Eq. (5)], which is voltage-dependent (He and Dallos, 1999, 2000; He et al., 2003). We have previously estimated (Spector et al., 1998; Spector and Jean, 2003) the local moduli $C_{ij}$ by using a combination of the data from three experiments, the osmotic challenge, axial loading, and micropipette aspiration. In those experiments, the membrane potential was not clamped and the data for different voltages were not collected. A comprehensive analysis of the voltage dependence of the local elastic moduli can be done if the three mentioned experiments are redone under the conditions of controlled voltage. However, the overall cell stiffness is a key parameter of the OHC physiology whose voltage dependence has been extensively studied in recent papers (He and Dallos, 1999, 2000; He et al., 2003; Deo and Grosh, 2004). Thus, we concentrate here on the voltage dependence of the local moduli associated with the voltage-dependent cell stiffness.

In Figs. 3–5, the active force changes significantly within the considered broad ranges of the resting potential, constraint stiffness, and frequency. However, the results corresponding to low-frequency range can be compared with estimates obtained earlier. The stiffness of the glass fibers attached to the cell in the low-frequency experiments of Hallworth (1995) and Iwasa and Adachi (1997) is much smaller than that in our modeling (Figs. 3–5). Iwasa and Adachi (1997) combined their experimental measurements with a model to estimate the isometric active force per unit transmembrane potential, and they obtained the value of about 100 pN/mV. The low frequency data in Fig. 5 corresponding to the highest value of the constraint stiffness (about 60 pN/mV) are probably close to the isometric force. Thus, these data are consistent with the corresponding results of Iwasa and Adachi (1997).

The shape of the two surfaces in Figs. 3–5 corresponding to three different values of the stiffness of the constraint is similar. The surfaces obtained for fixed values of the local moduli $C_{ij}$ (without the effect of the voltage-dependent stiffness) are bell shaped in each cross section corresponding to a certain frequency. In the general case, when the voltage dependence of the cell stiffness is taken into account, these cross sections have an inflection point in the depolarization range. The cross sections of the surfaces along the frequency axis are almost flat after that inflection point. The value and position of the peaks depend on the stiffness of constraint (see also more discussion below).

We found a significant effect of the voltage-dependent stiffness on the active force production. First, this effect causes a shift of the range of the highest sensitivity of the force from the area of depolarization to that of hyperpolarization [Figs. 3(a), 4(a), 5(a), 3(b), 4(b), and 5(b)]. The highest sensitivity of the force generation corresponds to the maximum of the force per unit transmembrane potential. In Figs. 3(b), 4(b), and 5(b) the resting potential corresponding to the maximum of the force per unit transmembrane potential shifts from about 10 mV to about −40 mV. The in vitro normal resting potential (without electrical stimulation) in the isolated OHC in the microchamber is around −30 mV (Ashmore and Meech, 1986; He and Dallos, 2000). The in vivo OHC normal resting potential is around −70 mV. Thus, due to the effect of the voltage-dependent stiffness, the point of the highest sensitivity of the active force generation becomes quite close to the physiological range of the resting potential. As a result of such shift, the sensitivity of the active force estimated at the point of the physiological potential is higher. The case of 20 kHz in Figs. 3(b), 4(b), and 5(b) is probably the most important to the analysis of the cochlear amplifier. Comparing the curves that correspond to the voltage-dependent and constant $C_{ij}$, we can estimate the effect of the shift of the force per unit transmembrane potential on the magnitude of this force within the physiological range. In the case of the 20-kHz frequency and for all considered values of the stiffness of the constraint, we found that the effect of the voltage-dependent cell stiffness causes an increase in the value of the force per unit transmembrane potential of around 50% in the physiological range. Another aspect of the discussed shift is associated with an increase in the nonlinearity of the active force per unit transmembrane potential as a function of voltage in the physiological range. At the beginning of the hyperpolarization area near the physiological range of the potential, Figs. 3(b), 4(b), and 5(b), the force function enters a “linear” range of almost constant slope in the cases of constant stiffness of the cell. In contrast, the slopes change significantly if the voltage-dependent stiffness is taken into account. This is because the maximal value of the force is reached at a potential of about −40 mV, instead of the value of about 10 mV observed in the case of the voltage-independent cell stiffness. Thus, the voltage-dependent stiffness causes an increase in both the sensitivity and nonlinearity of the active force as a function of voltage, and it can have important implications for the mechanics of the cochlea as a whole. We also found an additional effect of the voltage-dependent stiffness: a decrease in the force per unit transmembrane potential in the depolarization area. The values of these forces are about two times smaller than those corresponding to the case of the constant (voltage-independent) cell stiffness. This result obtained in a broader range of the transmembrane potential can be important for the analysis of the properties of the motor mechanism.

Here, we consider a number of physiologically meaningful values of the stiffness of the constraint (see Sec. III). The main effect of that stiffness is on the corner frequency and the maximum (resonance) value of the active force. In the case of relatively low values of stiffness, such as 0.05 N/m, there is a minimal resonance, and the force begins to decrease after the corner frequency of about 10 kHz. For higher values of the stiffness (0.2 N/m), a resonance appears at around 20 kHz with the ratio of the maximal value to the plateau value of about 1.2. When the constraint stiffness is high (1.25 N/m), the resonance becomes quite significant with the peak point close to 100 kHz and the maximum-to-plateau values ratio of about 1.6. The frequency roll-off in all cases is associated with the viscous losses in the cell wall and the fluids.

Here it is assumed that the viscosity of the extracellular fluid is similar to that of water. We also chose $1 \times 10^{-7}$ Ns/m for the cell wall viscosity and 6
significant attention in recent papers. Weitzel et al. (2003) have analyzed a one-dimensional model of the cell with assigned inertial and piezoelectric properties, and the authors have found ultrasound resonances in the system's admittance. Grosh et al. (2004) have applied an electrical stimulation to the cochlea and observed high-frequency resonances in the movement of the cochlear partition. Scherer and Gummer (2004) found resonances in the electromechanical force measured at the top of the organ of Corti, and the observed resonant frequency is located within the acoustic range. In the present work, we discuss the resonant properties of the active force per unit transmembrane potential, the function described by the dynamical system of the Navier-Stokes equations for the fluids (discussed in Liao et al., 2005) and the equation of the cell's wall [Eq. (2)]. These resonant properties are determined by the mechanical parameters: the stiffness of the constraint, the mass of the fluids involved in vibration of the cell, the viscosity of the fluids and the cell’s wall as well as parameters of the piezoelectric nature (active strain and voltage-dependent stiffness).

We proposed here a model to analyze the active force production in an individual OHC that takes into account important biophysical properties of the cell as well as constraints imposed on the cell by the surrounding environment. We concentrated on a combined effect of the resting potential, frequency, and stiffness of the constraint. We particularly investigated the effect of the voltage-dependent stiffness of the cell and found it twofold. First, it results in higher sensitivity and nonlinearity of the OHC active force production in the physiological range. Second, it determines smaller active force in the hyperpolarization range. We have also analyzed the resonant properties of the active force as a function of voltage and the constraint stiffness. The obtained results can be important for a better understanding of the mechanism of the active force associated with somatic motility of outer hair cell and its contribution to the cochlear amplifier.

**APPENDIX: MODEL EQUATIONS**

The stress generated in the cross section of the cell wall is balanced by the tractions on the cell wall surface due to the surrounding fluids. The viscous intracellular and extracellular fluids are governed by linearized Navier-Stokes equations. The cell wall is considered as viscoelastic and piezoelectric material.

The equilibrium equations for the cell wall are

\[ N_\sigma = \sigma \cdot \sigma_r, \]  
\[ N_x = -\int_a^e \sigma_x d\bar{x} + N_{\text{end}} + N_{\text{spring}}, \]

where \( \sigma_x \) and \( \sigma_r \) are two components of traction acting on the cell wall surface, and \( N_{\text{end}} \) and \( N_{\text{spring}} \) are the stress resultants generated at the cell end by the closed end and constraint, respectively. The constraint is treated as a spring, and therefore

\[ N_{\text{spring}} = -\frac{k_{\text{spring}}}{2\pi r_c} u_{\text{end}}, \]

where \( r_c \) is the cell radius. The closed end is treated as an oscillatory rigid plate and is subject to fluid resistance, which is transmitted and applied to the cell wall. This force is calculated by

\[ N_{\text{end}} = -\frac{k_{\text{end}}}{2\pi r_c} u_{\text{end}}, \]

where

\[ k_{\text{end}} = 16 \left[ \frac{i\lambda^2}{6} + (1.32e^{0.27\lambda}) \right] \mu r_c \omega e^{i\omega t}, \]

and \( \lambda = \rho r_c^2 / \mu \), \( \mu \) is fluid dynamic viscosity, \( \rho \) is fluid density, \( \omega \) is circle frequency, and \( i = \sqrt{-1} \) (Zhang and Stone, 1998). It should be mentioned that the method we use does not include the complete interaction of the fluid flow, the cell’s wall, and the cell’s closed ends, such as an additional radial stress in the cell wall as a consequence of the cell ends pushing back and forth the intracellular fluid. However, Tolomeo (1995) did consider the effect of the cell’s closed ends and, on the basis of his theoretical approach, found this effect insignificant. By using a simplified approach, our previous paper (Liao et al., 2005) compared the difference between the results for the closed-end and open-end conditions, and also found it to be insignificant.

Finally, the solution in terms of the Fourier coefficient of the cell wall displacement is obtained by this equation:

\[ u_{\text{cell}} = \left[ k_{\text{cell}} + k_{\text{fluid}} + k_{\text{end}} + k_{\text{spring}} \right]^{-1} \cdot (-\sigma_{\text{piez}}), \]

where \( u_{\text{cell}} \) and \( \sigma_{\text{piez}} \) are, respectively, the vectors of the Fourier coefficients of the cell wall displacement and the stress due to electrical stimulation of the cell. Also, \( k_{\text{cell}} \), \( k_{\text{fluid}} \), \( k_{\text{end}} \), and \( k_{\text{spring}} \) are the matrices that determine the stiffness associated with the cell wall, fluids, closed end, and constraint, respectively (Liao et al., 2005).


