PERGAMON

International Journal of Solids and Structures 38 (2001) 2115–2129

INTERNATIONAL JOURNAL OF SOLIDS and STRUCTURES

www.elsevier.com/locate/ijsolstr

A nonlinear electroelastic model of the auditory outer hair cell

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Received 23 July 1999; in revised form 23 November 1999

Abstract

Mechanically linear and electrically nonlinear constitutive relations for the auditory outer hair cell membrane (wall) are proposed. These relationships are derived on the basis of dual thermodynamic potentials. The active forces and active strains generated by the cell, important characteristics of the cell's behavior under physiological conditions, are associated with the mixed (piezoelectric) terms in the dual thermodynamic potentials. By using experimental information from four independent experiments, where the cell is loaded mechanically or electrically, the free parameters of the model are estimated. In addition, the model is extended to a composite representation of the cell membrane. In that representation, the outer layer is considered active (electroelastic) and the inner layer is considered passive (purely elastic). The layers are connected by elastic springs. The graphs for the elastic energy stored in the passive layer versus the cell wall potential are presented.

Keywords: Cell membrane; Nonlinear model; Electroelastic shell; Cochlear mechanics

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1. Introduction

Constitutive relations are the basis for the understanding and modeling of the complex mechanics of the auditory outer hair cell, a receptor cell providing the amplification and frequency selectivity of the ear. The core of this cell's mechanics is electromechanical coupling occurring in the cell wall that results in the overall length changes of the cell (Brownell et al., 1985). Recent studies indicate that this coupling is primarily associated with the outermost component, the plasma membrane, of the composite wall (Kalinec et al., 1992; Holley, 1996). The cell length changes are nonlinear in terms of the applied electric field or the wall potential.

Iwasa and Chadwick (1992) have proposed constitutive relations of a linear isotropic elastic membrane for the outer hair cell wall, estimated the corresponding moduli, and discussed the active force generation. Ratnanather et al. (1996) and Spector et al. (1996a) have obtained alternative estimates of the isotropic moduli. To reflect bending of the cell that inevitably occurs under physiological and some experimental

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0020-7683/01/$ - see front matter
PII: S0020-7683(00)00156-6

conditions, Spector et al. (1996a,b, 1998a) have proposed a model of an elastic shell for the outer hair cell wall. One of the components of the cell wall, the cytoskeleton, is made of two protein networks with different elastic and geometric properties. The properties of the cytoskeleton cause overall anisotropy of the cell wall. To reflect this property of the cell wall, Steele et al. (1993) and Tolomeo and Steele (1995) have introduced a model of an orthotropic membrane and estimated the corresponding orthotropic moduli. Spector et al. (1998c) have considered a model of an orthotropic shell and estimated the in-plane and bending moduli. To reflect explicitly the composite structure of the cell wall, Spector et al. (1996b, 1998a) have proposed a model of a composite shell. Steele et al. (1993) and Tolomeo and Steele (1995) have proposed a model of a linear piezoelectric membrane and estimated the coefficients of the active force production per unit of the wall potential change. Some aspects of a nonlinear electroelastic model have previously been discussed by Spector (1999a,b).

In the present paper, we propose a full set of the constitutive relations for the outer hair cell wall, relationships that are linear mechanically and nonlinear electrically. We start with a 3-D thermodynamic potential for such a material and then reduce it to a 2-D version on the basis of assumptions typical for the shell theory. We also obtain a dual thermodynamic potential and show that the active forces and the active strains produced by the cell wall are described by the mixed (piezoelectric) terms in those potentials. We estimate the passive moduli of the cell wall on the basis of our interpretation of four independent experiments. They include the axial loading, osmotic challenge (pressure change), and micropipet aspiration experiments, where a mechanical load of different mode is applied to the cell and the microchamber experiment, where an electric field is applied to the cell. We obtain the whole curves for the active forces and active strains depending on the wall potential. Although the physiological range of the cell wall potential changes is quite narrow, we consider the analysis of the nonlinearity of the cell behavior important for the understanding of the mechanism of cell motility. It is also important for the interpretation of various experimental data where the cell wall potential is changed in a broad range. In addition to a single-layer shell, we consider a model where the composite nature of the cell wall is reflected explicitly. We propose a two-layer model with an active (electroelastic) outer layer and passive (elastic orthotropic) inner layer connected by deformable springs. We introduce a thermodynamic potential for such a composite and apply our model to an interpretation of the microchamber experiment (Dallos et al., 1993).

2. Constitutive relations

We start with a 3-D version of the thermodynamic potential (electric enthalpy) in terms of the 3-D strains and the electric field. Reflecting the mechanical linearity of the problem, this potential has to be quadratic in terms of the strains. We represent the terms that sometimes have the form of expansions with respect to the electric field (e.g., Tiersten, 1975, 1993) in the form of analytical coefficients in the quadratic form of the strains. Such representation is more convenient when these nonlinear functions are determined directly from the experiment (e.g., see Fung (1993) wherein mechanical nonlinearities are treated in a similar fashion). The thermodynamic potential takes the following form:

$$W(\varepsilon_{ij}, E) = \frac{1}{2}\sum_{ijkl} C_{ijkl}\varepsilon_{ij}\varepsilon_{kl} + \sum_{ij} F_{ij}(E)\varepsilon_{ij} + G(E), \quad i = 1,2,3, \;\; j = 1,2,3, \tag{1}$$

where C_{ijkl} are the elastic constants of the material, ε_{ij} are the strain components, E is a 1-D radially directed electric field (Fig. 1), and $F_{ij}(E)$ and $G(E)$ are prescribed functions of the electric field. Three terms on the right-hand side in Eq. (1) represent the mechanical, piezoelectric, and electric properties of the material, respectively.

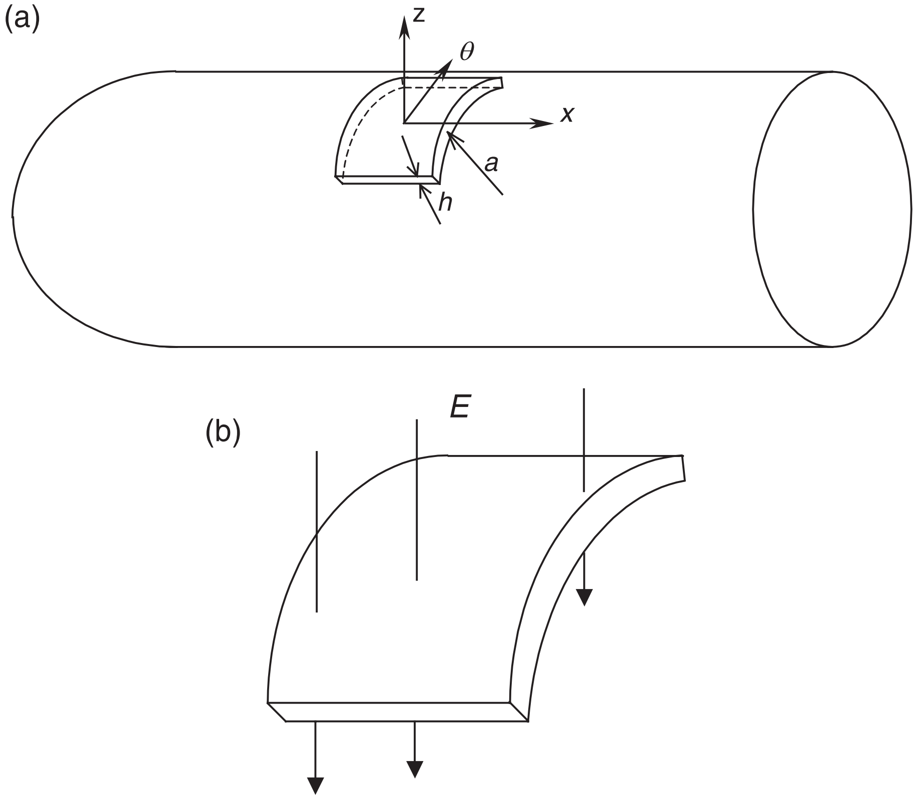

Fig. 1. Auditory outer hair cell: (a) Schematic sketch and geometric parameters (average radius a and the wall thickness h) and (b) an element of the cell wall under the action of a radially directed electric field E.

The stresses σ_{ij} and electric displacement D_{e} are determined by the following equations:

$$\sigma_{ij} = \frac{\partial W}{\partial \varepsilon_{ij}}, \quad D_{\mathrm{e}} = -\frac{\partial W}{\partial E}. \tag{2}$$

Making assumptions of the Kirchhoff shell theory (e.g., Novozhilov, 1959), we reduce potential W to its 2-D version. By using a cylindrical coordinate system x, θ, z (Fig. 1), we assume

$$\sigma_{33} = \sigma_{zz} = 0, \tag{3a}$$

$$\varepsilon_{13} = \varepsilon_{23} = \varepsilon_{xz} = \varepsilon_{\theta z} = 0, \tag{3b}$$

$$\varepsilon_{11} = \varepsilon_{xx}(z) = \varepsilon_x + z\chi_x, \tag{3c}$$

$$\varepsilon_{22} = \varepsilon_{\theta\theta}(z) = \varepsilon_\theta + z\left(\chi_\theta - \frac{\varepsilon_\theta}{a}\right), \tag{3d}$$

$$\varepsilon_{12} = \varepsilon_{x\theta}(z) = \varepsilon_{xz} + z\left(\tau - \frac{\varepsilon_{xz}}{a}\right), \tag{3e}$$

where ε_x, ε_θ, and $\varepsilon_{x\theta}$ are the strain components for the middle surface, and χ_x, χ_θ, and τ are the components of the curvature change and the twist of the middle surface. In terms of the wall electric potential ψ and electric field E, we assume

$$\psi(x,\theta,z) = \psi_0(x,\theta) + z\psi_1(x,\theta), \tag{4a}$$

$$E(x,\theta,z) = \frac{\partial\psi}{\partial z} = E_0(x,\theta). \tag{4b}$$

We substitute the z representations of the strains and electric field into Eq. (1). By neglecting the effects of the electric field on bending, we obtain the following expression for the reduced thermodynamic potential:

$$w(\bar{\varepsilon},\bar{\chi},E) = \int_{-h/2}^{h/2} W(\varepsilon_{ij},E)\left(1+\frac{z}{a}\right)\mathrm{d}z = \frac{1}{2}\bar{\varepsilon}\cdot[C]\bar{\varepsilon} + \frac{1}{2}\bar{\chi}\cdot[D]\bar{\chi} + \bar{f}(E)\cdot\bar{\varepsilon} + g(E), \tag{5}$$

where we introduce 3-D vectors $\bar{\varepsilon}(\varepsilon_x,\varepsilon_\theta,\varepsilon_{x\theta})$ and $\bar{\chi}(\chi_1,\chi_2,\tau)$ to represent the in-plane strains and the curvature (twist) changes, respectively. Also, $[C]$ and $[D]$ are the matrices of the in plane and bending moduli, respectively, and h is the thickness of the wall. The components of the reduced thermodynamic potential satisfy the following relationships:

$$\bar{f}(E) = (f_x(E), f_\theta(E), f_{x\theta}(E)) = h(F_{11}(E), F_{22}(E), F_{33}(E)), \tag{6a}$$

$$g(E) = hG(E), \tag{6b}$$

$$[D] = \frac{h^2}{12}[C]. \tag{6c}$$

The cell wall is not isotropic because one of its components (the cytoskeleton) comprises two protein networks with different elastic and geometric properties (Holley, 1996). We assume the wall to be orthotropic with $x\theta$-orthotropy axes. Potential (5) must be invariant with respect to reflections about two planes of the symmetry. We do not express the thermodynamic potential in terms of the invariants of orthotropy, instead we check directly the invariance of representation (5). The invariance of the first two terms in Eq. (2) is guaranteed by the orthotropic structure of matrix $[C]$. To provide the invariance for the rest of the potential in Eq. (5), we require

$$f_{x\theta} = 0. \tag{7}$$

On the basis of the introduced thermodynamic potential, we derive a full set of the constitutive relations

$$N_x = \frac{\partial w}{\partial \varepsilon_x} = C_{11}\varepsilon_x + C_{12}\varepsilon_\theta + f_x(E), \tag{8}$$

$$N_\theta = \frac{\partial w}{\partial \varepsilon_\theta} = C_{12}\varepsilon_x + C_{22}\varepsilon_\theta + f_\theta(E), \tag{9}$$

$$S = N_{\theta x} = N_{x\theta} - \frac{M_{\theta x}}{a} = \frac{\partial w}{2\partial \varepsilon_{x\theta}} = 2C_{33}\varepsilon_{x\theta}, \tag{10}$$

$$M_x = \frac{\partial w}{\partial \chi_x} = D_{11}\chi_x + D_{22}\chi_\theta, \tag{11}$$

$$M_\theta = \frac{\partial w}{\partial \chi_\theta} = D_{12}\chi_x + D_{22}\chi_\theta, \tag{12}$$

$$H = \frac{1}{2}(M_{x\theta} + M_{\theta x}) = \frac{\partial w}{2\partial \tau} = 2D_\tau\tau, \tag{13}$$

$$d = \int_{-h/2}^{h/2} D_{\mathrm{e}}\left(1+\frac{z}{a}\right)\mathrm{d}z = -\frac{\partial w}{\partial E} = -f'_x(E)\varepsilon_x - f'_\theta(E)\varepsilon_\theta - G'(E). \tag{14}$$

Here C_{11}, C_{22}, and C_{12} characterize, respectively, the in-plane stiffness in the longitudinal direction, the circumferential direction, and the mixed mode of the stiffness, C_{33} is shear modulus, D_{11}, D_{22}, and D_{12} characterize the bending stiffness in the longitudinal direction, the circumferential direction, and the mixed mode of the bending stiffness, and D_τ is twist modulus. Also, N_x, N_θ, $N_{x\theta}$, and $N_{\theta x}$ are the components of the resultant force and M_x, M_θ, $M_{x\theta}$, and $M_{\theta x}$ are the components of the bending and twisting moment.

3. Dual thermodynamic potentials: active forces and active strains generated by the membrane

We introduce the thermodynamic potential dual to $w(\overline{\varepsilon},\overline{\chi},E)$ in terms of $\overline{N}\cdot\overline{\varepsilon}+\overline{M}\cdot\overline{\chi}$ duality (Ekeland and Temam, 1976; Bisegna and Luciano, 1996) with $\overline{N}$ and $\overline{M}$ representing the 3-D vectors (N_x, N_θ, S) and (M_x, M_θ, H). By applying generalized Legendre transformation to $w(\overline{\varepsilon},\overline{\chi},E)$, we obtain the dual potential expressed by the equation

$$w(\overline{N},\overline{M},E) = \sup_{\overline{\varepsilon},\overline{\chi}}[\overline{N}\cdot\overline{\varepsilon}+\overline{M}\cdot\overline{\chi}-w(\overline{\varepsilon},\overline{\chi},E)]. \tag{15}$$

Since there are no constraints imposed on $\overline{\varepsilon}$ and $\overline{\chi}$, we can invert Eqs. (8)–(13), express $\overline{\varepsilon}=\overline{\varepsilon}(\overline{N},E)$ and $\overline{\chi}=\chi(\overline{M},E)$, and substitute them into Eq. (5). As a result, we derive the following expression for the dual thermodynamic potential:

$$w(\overline{N},\overline{M},E) = \tfrac{1}{2}\overline{N}\cdot[C]^{-1}\overline{N}+\tfrac{1}{2}\overline{M}\cdot[D]^{-1}\overline{M}-\overline{N}\cdot[C]^{-1}\overline{f}(E)+G(E)-\tfrac{1}{2}\overline{f}(E)\cdot[C]^{-1}\overline{f}(E). \tag{16}$$

The strains are determined by the following equations:

$$\varepsilon_x = \frac{\partial w}{\partial N_x} = A_{11}N_x + A_{12}N_\theta - A_{11}f_x - A_{12}f_\theta, \tag{17a}$$

$$\varepsilon_\theta = \frac{\partial w}{\partial N_\theta} = A_{12}N_x + A_{22}N_\theta - A_{12}f_x - A_{22}f_\theta, \tag{17b}$$

$$\varepsilon_{x\theta} = \frac{\partial w}{2\partial S} = A_{33}S, \tag{17c}$$

where A_{ij} are the components of the compliance matrix $[C]^{-1}$.

To characterize the active properties of the cell membrane, we define the active forces $\overline{F}^{\mathrm{a}}$ as resultants corresponding to the no-strain conditions. We also define the active strains $\overline{\varepsilon}^{\mathrm{a}}$ as strains corresponding to the no-resultant conditions. Based on these definitions we obtain (Eqs. (8), (9), and (17a), (17b))

$$\overline{F}^{\mathrm{a}} = \overline{N}(\overline{\varepsilon}=0) = \overline{f}(E), \tag{18a}$$

$$\overline{\varepsilon}^{\mathrm{a}} = \overline{\varepsilon}(\overline{N}=0) = -[C]^{-1}\overline{f}(E). \tag{18b}$$

It means that the active forces are determined by the mixed term in the thermodynamic potential $w(\overline{N},\overline{M},E)$ (Eq. (5)), and the active strains are determined by the mixed term in the dual potential $w(\overline{N},\overline{M},E)$ (Eq. (16)). By further analyzing the strains (Eqs. (17a)–(17c)), we can represent them as

$$\overline{\varepsilon} = \overline{\varepsilon}^{\mathrm{p}}(\overline{N}) + \overline{\varepsilon}^{\mathrm{a}}, \tag{19}$$

and define the component

$$\overline{\varepsilon}^{\mathrm{p}}(\overline{N}) = [\overline{C}]^{-1}\overline{N}, \tag{20}$$

as the passive strains that characterize the mechanical (elastic) component of the wall deformational response.

4. Parameter identification

4.1. Estimation of the passive moduli

In the constitutive relations (8)–(14), the purely electrical term $G'(E)$ entering the last equation is completely uncoupled from the rest of the equations. This term relates the applied electric field to the corresponding charge change. The experimental data allow the direct determination of the functions $G'(E)$ or $G''(E)$ within a broad range of the electric field change. For our analysis of the passive moduli below, we use the value G'' calculated at the reference point and taken from the data of Dallos et al. (1993).

To estimate the parameters of our model, we use a set of four experiments. Under the conditions of three of them (Fig. 2a–c), the cell is under purely mechanical loading, and different modes of the strain are measured. Under the condition of the fourth experiment (Fig. 2d), the cell is mechanically unloaded and is under the action of an applied electrical field. Under conditions of the three mechanical experiments, the wall potential can vary, but there is no charge flux into or out of the cell wall.

In the first experiment (Fig. 2a), one of the cell ends is fixed in space, and an axial force F_{a} is applied to the other end through a glass fiber (e.g., Holley and Ashmore, 1988). The resultant axial displacement u is measured.

In the second experiment (Fig. 2b), the concentration of the liquid solution outside the cell is changed (osmotic challenge), thereby changing the pressure difference Δp between the liquid core of the cell and the

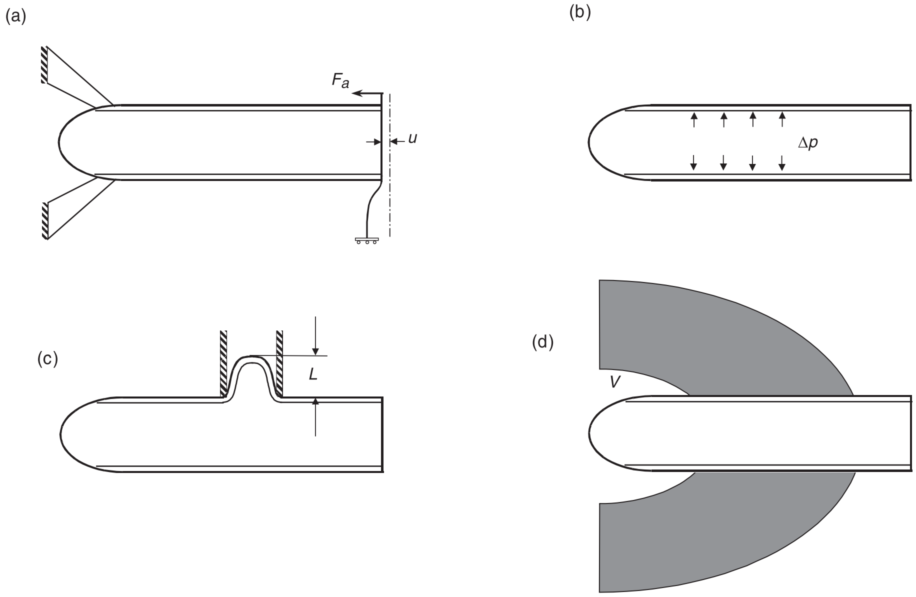

Fig. 2. Sketches of four experiments used for the determination of the parameters of the model: (a) Axial loading experiment, (b) osmotic challenge (pressure change) experiment, (c) micropipet aspiration experiment, and (d) microchamber experiment.

solution outside (Ratnanather et al., 1996). These pressure changes lead to the corresponding changes of the radius and length of the cell. The changes in the cell dimensions are measured, but pressure changes are not controlled in this experiment.

In the last mechanical experiment (Fig. 2c), aspiration pressure is applied to the cell via a cylindrical micropipet, a portion of the cell is aspirated inside the pipet, and its height L can be measured (Sit et al., 1997; Spector et al., 1996a, 1998b).

Under the conditions of the fourth experiment (Fig. 2d), a part of the cell is included in a microchamber with an electrolyte that has a prescribed potential V with respect to the environment outside the cell (Dallos et al., 1993). For two parts of the cell, these conditions result in potential changes that are approximately inversely proportional to the electrical resistances of those parts. Because of the cell motility under the action of the wall potential changes, each part exhibits the length and radius changes depending on the potential of the contents of the microchamber.

For the first two experiments, we assume a uniform membrane-type state and the current-clamp condition for the cell wall. Therefore, the constitutive relations reduce to Eqs. (8) and (9), supplemented by Eq. (14) with $d = 0$. We simplify this system by neglecting the nonlinearity of the functions $f_x(E)$, $f_\theta(E)$, and $G(E)$ within the range of the potential variation that resulted from mechanical loading of the cell. By linearizing functions f_x, f_θ, G' around the point of the reference potential and by denoting

$$e_x = \frac{\mathrm{d}f_x}{\mathrm{d}E}(E_r), \qquad e_\theta = \frac{\mathrm{d}f_\theta}{\mathrm{d}E}(E_r), \tag{21}$$

we obtain Eq. (14) in the form

$$e_x\varepsilon_x + e_\theta\varepsilon_\theta + e(E - E_r) = 0, \tag{22}$$

where $E - E_r$ is the electric field variation with respect to the reference point E_r, and $e = G''(E_r)$. Substituting $E - E_r$ from Eq. (22) into Eqs. (8) and (9), we obtain these equations in a modified form

$$N_x = C^*_{11}\varepsilon_x + C^*_{12}\varepsilon_\theta, \tag{23}$$

$$N_\theta = C^*_{12}\varepsilon_x + C^*_{22}\varepsilon_\theta, \tag{24}$$

where

$$C^*_{11} = C_{11} - \frac{e_x^2}{e}, \tag{25a}$$

$$C^*_{12} = C_{12} - \frac{e_x e_\theta}{e}, \tag{25b}$$

$$C^*_{22} = C_{22} - \frac{e_\theta^2}{e}. \tag{25c}$$

We apply these relationships first to an interpretation of the axial loading experiment. By doing a standard analysis of a long cylindrical membrane with edge caps and using the volume preservation condition that resulted in $\varepsilon_\theta = -0.5\varepsilon_x$ (e.g., Spector et al., 1998a), we obtain the equation

$$C^*_{11} - C^*_{12} + 0.25C^*_{22} = \gamma_a, \tag{26}$$

where $\gamma_a = F_\mathrm{a}l/\pi ua$, l is one-half of the cell length, a is the cell radius, F_a is the applied axial force, and u is the measured axial displacement (Fig. 2a).

For an interpretation of the experiment with pressure change, we use the experimentally obtained ratio $\varepsilon_x/\varepsilon_\theta \approx -0.7$ (Ratnanather et al., 1996) and treat the cell wall as a long cylindrical membrane under the action of uniform pressure. If we express the unknown pressure in terms of the strains and take account of the above-mentioned experimental relationship for the strains, we come to the following equation in terms of the passive moduli:

$$1.4C_{11}^* + C_{22}^* - 2.7C_{12}^* = 0. \tag{27}$$

The experiment with micropipet aspiration is accompanied by conditions where the bending effects are substantial. Therefore, in this case, we have to consider the full systems (8)–(14). By again assuming the current-clamp condition, we replace C_{11}, C_{12}, C_{22} in Eqs. (8)–(14) with C_{11}^*, C_{12}^*, C_{22}^* from Eqs. (25a)–(25c). We use a modification of the solution of Spector et al. (1998b) related to the replacement of the C-constants in Eqs. (8) and (9). The relationship between the measured height of the aspirated tongue L and the unknown passive moduli of the wall takes the form,

$$L = \frac{\sqrt{2}ap_0R_\mathrm{i}}{\pi\varepsilon^{0.75}C_{22}^{0.75}}\left[\frac{C_{22}^*}{C_{11}^*C_{22}^* - (C_{12}^*)^2}\right]^{0.25}\frac{\alpha}{\alpha^2-1}[\alpha f(\alpha_i,\mu) - f(\alpha_0,\mu)], \tag{28}$$

which is a modification of Eq. (59) in Spector et al. (1998b). In Eq. (28), we have

$$f(A,\mu) = 0.5A - (0.5+\mu^2) + 0.2A^3, \tag{29}$$

$$\mu = \left[\frac{C_{22}^*C_{22}^*}{C_{11}^*C_{22}^* - (C_{12}^*)^2}\right]^{0.25}\varepsilon^{0.25}, \tag{30}$$

$$\alpha = \frac{R_\mathrm{o}}{R_\mathrm{i}}, \quad \alpha_i = \frac{R_\mathrm{i}}{a}, \quad \alpha_0 = \frac{R_\mathrm{o}}{a}, \quad \varepsilon = \frac{h^2}{12a^2}, \tag{31}$$

where p_0 is aspiration pressure, R_i and R_o are the inner and outer radii of the pipet.

Eqs. (26)–(28) are formulated in terms of three unknown elastic moduli, but they include the coefficients e_x and e_θ as well. The interpretation of the last experiment (Fig. 2d) results in expressions of the coefficients e_x and e_θ in terms of the passive elastic moduli. In this experiment, the cell is mechanically unloaded ($N_x = N_\theta = 0$) and is under the action of an electric field E. If $\varepsilon_x(E)$ and $\varepsilon_\theta(E)$ are the components of the strain caused by cell motility in response to the electric field, then Eqs. (8) and (9) can be written in the form

$$C_{11}\frac{\mathrm{d}\varepsilon_x}{\mathrm{d}E} + C_{12}\frac{\mathrm{d}\varepsilon_\theta}{\mathrm{d}E} + e_x = 0, \tag{32}$$

$$C_{12}\frac{\mathrm{d}\varepsilon_x}{\mathrm{d}E} + C_{22}\frac{\mathrm{d}\varepsilon_\theta}{\mathrm{d}E} + e_\theta = 0. \tag{33}$$

We use the data of Dallos et al. (1993) and calculate the derivatives at the point of the reference potential. Eqs. (25a–25c)–(28), (32), and (33) allow us to estimate the passive moduli along with the coefficients e_x and e_θ.

4.2. Estimation of the parameters of the active behavior

We now determine the whole functions $f_x(E)$ and $f_\theta(E)$ that are responsible for the electromechanical coupling in the cell wall. These functions can be found under conditions of purely electrical loading and are expressed by the following equations:

$$f_x(E) = -C_{11}\varepsilon_x(E) - C_{12}\varepsilon_\theta(E), \tag{34}$$

$$f_\theta(E) = -C_{12}\varepsilon_x(E) - C_{22}\varepsilon_\theta(E). \tag{35}$$

The microchamber experiment discussed above provides such conditions for the cell, and the corresponding active strains $\varepsilon_x(E)$ and $\varepsilon_\theta(E)$, considered in a broad range of the applied electric field, can be used for an approximation of the functions $f_x(E)$ and $f_\theta(E)$. Experimentally observed curves $\varepsilon_x(E)$ and $\varepsilon_\theta(E)$ have Boltzmann-type (sigmoidal-type) behavior (Dallos et al., 1993). On the basis of Eqs. (34) and (35), we approximate f_x and f_θ by the same type (Boltzmann-type) functions in the following form:

$$f_x(E) = a_x \frac{\exp[b_x(E - E_x^0)] - 1}{\exp[b_x(E - E_x^0)] + 1} - c_x, \tag{36}$$

$$f_\theta(E) = a_\theta \frac{\exp[b_x(E - E^0)] - 1}{\exp[b_x(E - E^0)] + 1} - c_\theta. \tag{37}$$

The free parameters in Eqs. (36) and (37), a_x, a_θ, b_x, b_θ, c_x, c_θ, E_x^0 and E_θ^0 are determined on the basis of the data of the microchamber experiment.

4.3. Results and their discussion

We collect our estimates in Table 1. In the first three lines, the passive in-plane moduli are presented. The last two lines give the values of the slopes of the functions f_x and f_θ that are important for the characterization of the physiological effect of outer hair cells on the hearing process. Experimental information is normally presented in terms of the transwall potential $\Delta\Psi$ (the difference between the potentials on the inner and outer surfaces of the cell wall). We represent our results in terms of the same characteristic. On the basis of Eq. (4b), we obtain

$$\Delta\Psi = Eh. \tag{38}$$

The solution of systems (25)–(28), (32), and (33) results in the C-moduli and *e*-coefficients that correspond to the same reference transwall potential $\Delta\Psi$ (electric field E). This potential established in isolated cells that undergo purely mechanical loading is about -30 mV. Under physiological conditions, the cell is more greatly polarized, and its potential is about -70 mV. The coefficient e_x and e_θ characterize the production by the cell wall of the active force per unit of the wall potential change that is a key parameter of the cell's effectiveness in the amplification and frequency selectivity of the ear. The values of these coefficients that correspond to physiological conditions (physiological level of the wall potential) are of primary interest. This is especially important for the coefficient e_x that determines the cell's action on the neighboring vibrating components of the cochlea. Because of this, we recalculate the values e_x and e_θ for $\Delta\Psi = -70$ mV by using the original estimates at $\Delta\Psi = -30$ mV and distributions (36) and (37).

In Fig. 3, we show the graphs $f_x(\Delta\Psi)$ and $f_\theta(\Delta\Psi)$ that characterize the cell's active behavior. The reference point coincides with the physiological resting potential -70 mV.

The nonlinearity of the functions f_x and f_θ is much more pronounced if the cell is hyperpolarized with respect to the physiological resting potential, and the graphs are very asymmetric with respect to this point. The longitudinal component of the active force f_x is about two times smaller than the circumferential one

Table 1
Passive elastic moduli and the coefficients of the active force production of the outer hair cell wall[a]

C_{11} (N/m)	0.16
C_{12} (N/m)	0.31
C_{22} (N/m)	0.62
e_x (N/mV)	4.8×10^{-3}
e_θ (N/mV)	9×10^{-3}

[a] The coefficients are calculated at the point of the physiological potential equal -70 mV.

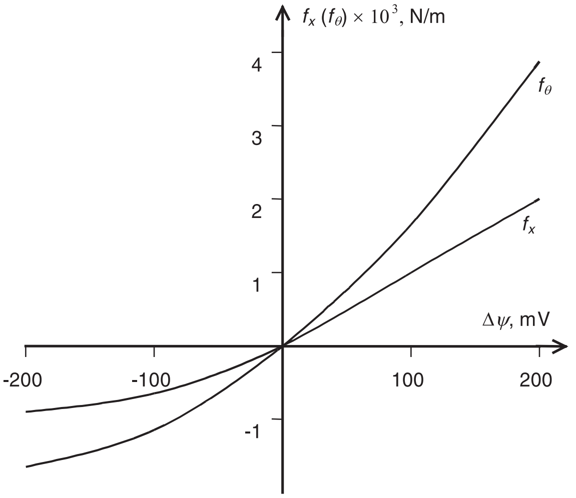

Fig. 3. Longitudinal f_x and circumferential f_θ components of the active force generated by the cell wall in response to changes of the cell transwall potential.

f_θ throughout the whole range of the potential $\Delta\Psi$. The data of Table 1 show strong anisotropy of the mechanical properties with the ratio of the diagonal C-moduli close to four. The ratio of the active force f_θ to f_x or the coefficient e_θ to e_x characterizes anisotropy of the active properties of the cell wall. Such anisotropy also takes place but it is not so high as for the mechanical properties.

5. Analysis of the composite structure of the cell wall

5.1. Constitutive relations for the composite wall

To reflect the major structural components of the composite outer hair cell wall, we represent the wall as two layers with deformable connections between them. The outer layer (plasma membrane) is considered as an isotropic nonlinear electroelastic shell; the inner layer (a combination of the cytoskeleton and the subsurface cisternae) is considered as an orthotropic linear elastic shell, and the connections (radial pillars) are represented by distributed elastic springs (Fig. 4). The discussed model corresponds to the hypothesis of an active plasma membrane (Kalinec et al., 1992) with the transmission of the active strains and forces generated within it to the passive cytoskeleton and subsurface cisternae.

We start with a thermodynamic potential that includes terms related to the active and passive layers and to the deformable connections between them. This potential takes the following form:

$$\begin{aligned}\omega = {} & \tfrac{1}{2}\bar{\varepsilon}^1\cdot[C^1]\bar{\varepsilon}^1 + \tfrac{1}{2}\bar{\chi}^1\cdot[D]\bar{\chi}^1 + \bar{f}(E)\cdot\bar{\varepsilon}^1 + G(E) + \tfrac{1}{2}\bar{\varepsilon}^2\cdot[C^2]\bar{\varepsilon}^2 + \tfrac{1}{2}\bar{\chi}^2\cdot[D^2]\bar{\chi}^2 \\ & + \tfrac{1}{2}k_n(w^1-w^2)^2 + \tfrac{1}{2}k_x(u_x^1-u_x^2)^2 + \tfrac{1}{2}k_\theta(u_\theta^1-u_\theta^2)^2,\end{aligned} \tag{39}$$

where $\bar{\varepsilon}^1$ and $\bar{\chi}^1$ represent, respectively, the in-plane strains and the curvature changes and twist for the second layer. Also, $[C^1]$ and $[D^1]$ are the matrices of the orthotropic in plane and bending moduli of the first layer, $[C^2]$ and $[D^2]$ are the matrices of the isotropic in plane and bending moduli of the second layer, u_x^1, u_θ^1 and w^1 are the components of the displacement of the active layer, u_x^2, u_θ^2, and w^2 are the components of the

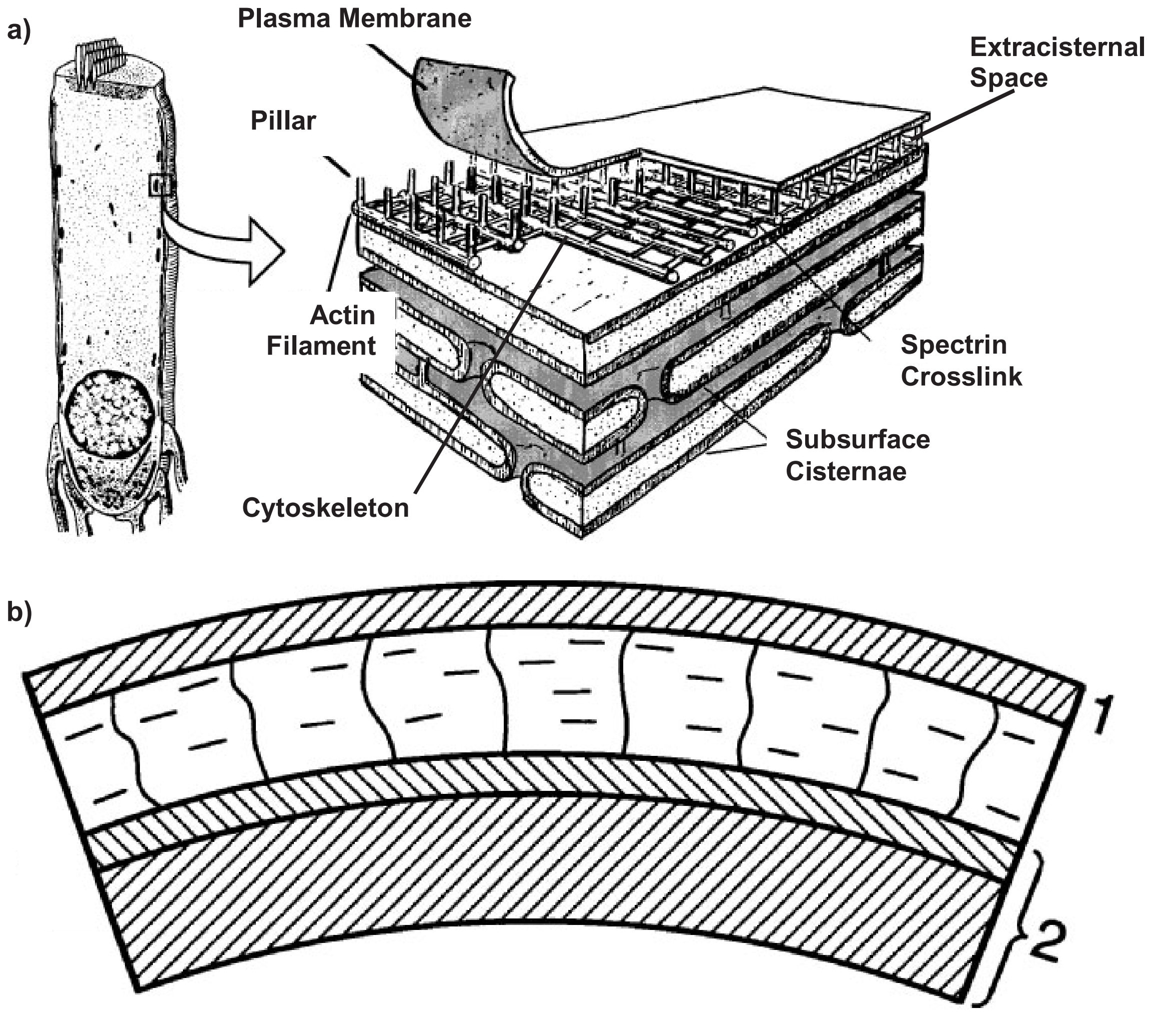

Fig. 4. Outer hair cell composite wall: (a) General view of the cell and the major components of the cell wall, and (b) model representation in the form of two layers connected by elastic springs.

displacement of the passive layer, k_x, k_θ, and k_n are the stiffness coefficients for the connections, and functions $\overline{f}(E)$ and $G(E)$ represent piezoelectric and purely electric properties of the active layer. The first four terms in ω represent the thermodynamic potential of the active layer. We differentiate this part of the potential with respect to $\overline{\varepsilon}^1$, $\overline{\chi}^1$, and E, and, similar to the analysis of the single-layer wall, derive the constitutive equations for the active layer. The next two terms represent the mechanical energy of the passive layer that can be used to derive the constitutive relations within that layer. The last three terms in Eq. (39), represent the mechanical energy of the deformed connections between the two layers. By varying the displacements of the two layers, we can derive the equilibrium equations for the composite wall. In a simpler, axisymmetric case these equations take the form

$$\frac{\partial N_x^1}{\partial x} + k_x(u_x^1 - u_x^2) = 0, \tag{40}$$

$$\frac{\partial N_x^2}{\partial x} - k_x(u_x^1 - u_x^2) = 0, \tag{41}$$

$$\frac{\partial^2 M_x^1}{\partial x^2} + \frac{N_\theta^1}{a} + k_n \frac{(w^1 - w^2)}{a} = p^1, \tag{42}$$

$$\frac{\partial^2 M_x^2}{\partial x^2} + \frac{N_\theta^2}{a} - k_n \frac{(w^1 - w^2)}{a} = p^2, \tag{43}$$

where N_x^1, N_θ^1, M_x^1, and M_θ^1 are the components of the resultant force and bending moment in the first (active) layer and N_x^2, N_θ^2, M_x^2, and M_θ^2 are the components of the resultant force and bending moment in the second (passive) layer. Here, we neglect shear effects of the fluids inside and outside the cell as well as within the extracisternal (Fig. 4) space. The effect of these fluids enters the equilibrium equations through pressure gradients p^1 and p^2 across the active and passive layers, respectively.

5.2. Application to the microchamber experiment

As an application of the proposed model, we consider the problem of electrical stimulation of the cell under the conditions of the microchamber experiment (Fig. 2d). We assume the uniformity and axisymmetry of the stresses and strains along the cell. We consider the pillars and elastic connections between two layers (Fig. 4) much stiffer than other components of the wall, and this assumption results in the following equations:

$$\varepsilon_x^1 = \varepsilon_x^2 = \varepsilon_x^{\mathrm{a}}, \tag{44a}$$

$$\varepsilon_\theta^1 = \varepsilon_\theta^2 = \varepsilon_\theta^{\mathrm{a}}. \tag{44b}$$

We also neglect additional pressure generated inside the cell as a result of the active strains, an assumption analyzed by Dallos et al. (1993) and Tolomeo and Steele (1995). Since no additional pressure under the conditions under consideration is created, there are no changes in the overall (i.e., for the whole wall) resultant forces. It is important to note that nonzero resultants in each layer are present. They have the same absolute values and opposite sign to make the overall resultants equal to zero.

We can obtain elastic energy accumulated within the passive layer as a result of the electrical excitation of the active layer. This energy is determined by the following expression:

$$U_2 = 0.5[C_{11}^2(\varepsilon_x^{\mathrm{a}})^2 + 2C_{12}^2\varepsilon_x^{\mathrm{a}}\varepsilon_\theta^{\mathrm{a}} + C_{22}^2(\varepsilon_\theta^{\mathrm{a}})^2]. \tag{45}$$

We next find the active strains and elastic energy generated by the cell wall as functions of the transwall potential. This potential is determined by the command voltage applied through the microchamber. The active strains can be estimated directly from the data of the microchamber experiment (Dallos et al., 1993). It should be emphasized that the active strains found here on the basis of a particular experiment are the universal characteristics of the outer hair cell's plasma membrane. They determine the response of the plasma membrane to the electric potential challenge under conditions of unchanged membrane forces (stresses). The dependence of the active strains on the transwall potential is illustrated in Fig. 5. The two components have opposite signs, and the absolute value of the circumferential component is about 3.5 times smaller than that of the longitudinal one. The saturation is clear for the direction of the cell hyperpolarization. It is less observable for the cell depolarization direction.

In Figs. 6 and 7, we plot the potential dependence of mechanical energy (45) accumulated in the passive layer. There are no reliable data on the C^1 and C^2 moduli that would allow us to plot the quantitative values

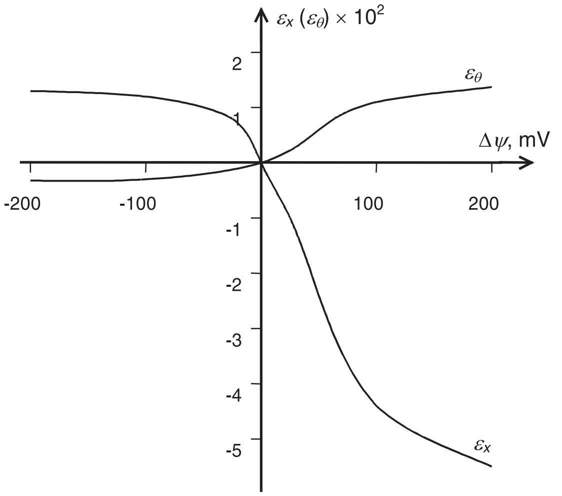

Fig. 5. Longitudinal ε_x and circumferential ε_θ components of the active strain generated by the cell wall in response to changes of the cell transwall potential.

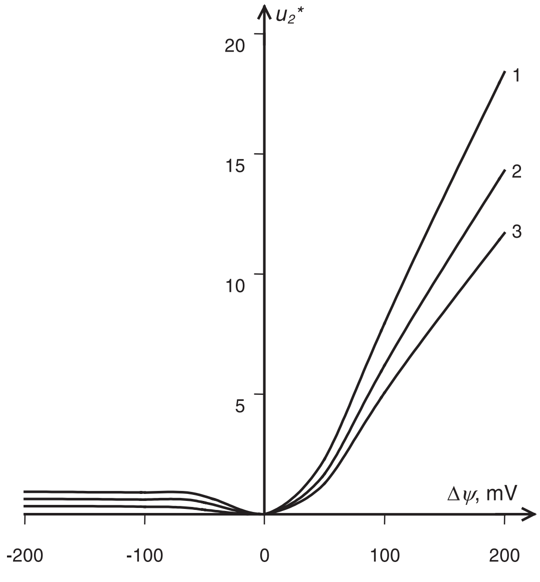

Fig. 6. Mechanical energy U_2^* stored in the passive layer for different ratios of its in-plane stiffness moduli versus the cell transwall potential ($C_{22}^2/C_{11}^2 = 3$ and 1, 2, 3 correspond, respectively, to $C_{12}^2/C_{11}^2 = 1$, 1.3, and 1.5).

of U_2. To show a qualitative dependence of mechanical energy stored on the membrane voltage, we use dimensionless functions given by the following equation:

$$U_2^* = \frac{U_2}{0.5C_{11}^2(\varepsilon_x^-)^2}. \tag{46}$$

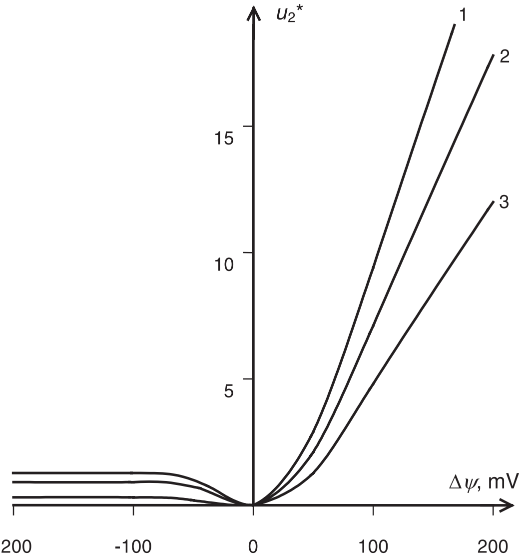

Fig. 7. Mechanical energy U_2^* stored in the passive layer for diffeternt ratios of its in-plane stiffness moduli versus the cell transwall potential ($C^1_{22}/C^2_{11} = 5$ and 1, 2, and 3 correspond, respectively, to $C^2_{12}/C^2_{11} = 1$, 1.4, and 1.8).

Here ε_x^- denotes the limiting value of the x component of the active strain corresponding to the extreme hyperpolarization of the wall (substituted from Dallos et al., 1993).

To specify elastic energy U_2^*, we make additional assumptions. The ratio C^2_{22}/C^2_{11} determines anisotropy of the passive layer. In this composite layer, the cytoskeleton is anisotropic and the subsurface cisternae can be considered isotropic. This means that anisotropy of the whole passive layer is lower than that for the cytoskeleton. The above ratio of two moduli for isolated cytoskeleton has been measured by Tolomeo et al., (1996). It was estimated to be close to 6. We use this estimate as an upper bound of the C^2_{22}/C^2_{11} ratio for the whole passive layer. The second ratio, C^2_{12}/C^2_{11}, entering the expression of elastic energy U_2^* has the following upper bound determined by the positiveness of U_2:

$$\frac{C^2_{12}}{C^2_{11}} < \sqrt{\frac{C^2_{22}}{C^2_{11}}}. \tag{47}$$

Based on those bounds, we choose ranges for the ratios of elastic moduli entering U_2^*. In Figs. 6 and 7, we present a set of graphs giving the voltage dependence of elastic energy U_2^* for several values of the ratios of elastic moduli. These values belong to the ranges discussed above. All graphs show similar behavior. For the chosen reference value −70 mV, hyperpolarization is accompanied by much greater mechanical energy than depolarization corresponding to the same magnitude of the potential change. Hyperpolarization results in the strong asymmetry with respect to the reference point of function U_2^*. Magnitude of mechanical energy saturates for extreme hyperpolarization of the membrane. This behavior is similar to that for the absolute values of the active forces and the active strain.

The developed constitutive relations for the outer hair cell are an effective tool for better understanding of this cell's properties and the role in the hearing process. They also help to understand various forms of electromechanical coupling and strain and energy exchange that occur in the composite wall of the cell. The proposed models can be used in simulation of abnormal cells affected by pathologies of the ear, side effects of some drugs, or aging.

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