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Elastic properties of organ of Corti tissues from point-stiffness measurement and inverse analysis

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ABSTRACT

We describe a method to use point-stiffness (PtSt) measurements, i.e., indentation measurements, to obtain elastic moduli of different organ of Corti (OC) tissues. A detailed finite element (FE) model of the OC is used to account for geometric effects in the indentation measurements. We also present a sensitivity analysis, performed within a Bayesian estimation framework, that can be used to improve experimental design. The sensitivity analysis shows that the basilar membrane (BM) PtSt is most sensitive to changes in the BM properties and to changes in the pillar cells (PC) properties. This result suggests that the BM and the PC dominate the macromechanics of the OC. The most likely values of the Young's modulus predicted for the middle turn for the BM arcuate, BM pectinate, and the PC are found to be 935 KPa (range 640–1360 KPa), 300 KPa (range 190–460 KPa), and 3 GPa (range 1–9 GPa), respectively.

1. Introduction

Our understanding of the micromechanics of the organ of Corti (OC) is impeded by our ignorance of the mechanical properties of its constituents. Measuring those properties directly is challenging due to both the small size scales involved and their inaccessibility.

One approach to circumvent this difficulty is to measure point-stiffness (PtSt) at accessible locations such as the basilar membrane (BM) or the reticular lamina (RL) in the presence of the supporting cells of the OC. The PtSt measurement technique can be traced back to the experimental work of Bekesy (1960), which was improved upon in Gummer et al. (1981) and Miller (1985) for their work on guinea pig to determine BM stiffness profiles as a function of the deflection depth. This technique was used more recently in Olson and Mountain (1991) and Naidu and Mountain (2001) to determine PtSt of gerbil's BM. Their results showed a good correspondence between in situ and excised cochlea PtSt measurements exists. This indicates that excised cochlear PtSt measurements reflect the micromechanical properties of an intact cochlea.

A PtSt measurement can be interpreted as an indentation test to measure elastic properties. Mechanical properties of biological tissues are commonly determined by indention methods. The method consists of using a force probe with specified tip geometry to create indentation in the tissue while measuring the displacement of the probe tip and the force exerted on the probe. The force–displacement data measured by indentation is related to the elastic properties of the tissue. Calibrating the force–displacement slope to extract Young's modulus (E) requires a reference mathematical solution. In most situations, the calibration constant is derived from the solution representing indentation of a homogeneous, linear elastic, isotropic, semi-infinite medium. In more complicated situations detailed finite element (FE) models can be used to calibrate force–displacement measurements that account for non-idealized geometries (Samani et al., 2001) and/or non-ideal material behavior (Zhang et al., 2008), or both (Cristofolini et al., 2010).

In the work described here, we use a geometrically detailed 3D FE solution of a piecewise homogeneous model of the gerbil cochlea. Our FE model represents several components with different elastic properties. Hence our model is complicated by the fact that we have several tissue types, each with its own set of material constants, interacting within the indentation region. Each indentation measurement, therefore, depends upon the (possibly distinct) elastic properties of several different tissues. In our "calibration," therefore, we must account for all these different tissue types, and must use several distinct indentation measurements simultaneously to relate the PtSt measurements to the

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tissue elastic moduli. This task is akin to solving an elastic inverse problem (cf. Samani et al., 2001), and we approach it in a Bayesian framework (Tarantola, 2005; Stuart, 2010). In the Bayesian framework, a posterior belief is updated based on prior beliefs and new evidence. In the current context, prior knowledge of the distributions of the moduli is used to obtain updated distributions based on new PtSt data.

2. Methods

The experimental measurements of the OC's PtSt performed in Naidu and Mountain (1998a) were simulated here using a 3D linear elastic isotropic FE model to determine the elastic properties of each individual structural component within the OC. The geometry of the model was based on direct measurements of anatomical features within the OC. The middle turn section of the gerbil cochlea around the 4 kHz place was modeled.

2.1. Representing the cochlear section geometry

In the present middle turn model the geometry is very detailed. It includes most of the known details of the OC and the interstitial space that are usually ignored in cochlear models. Fig. 1 shows the dominant cochlear components in the cross section, all of which are represented in the FE model. In Fig. 2, a 3D view of the model shows the complete cluster of the structural components. More precisely, $N=11$ components are modeled as described in Figs. 1 and 2.

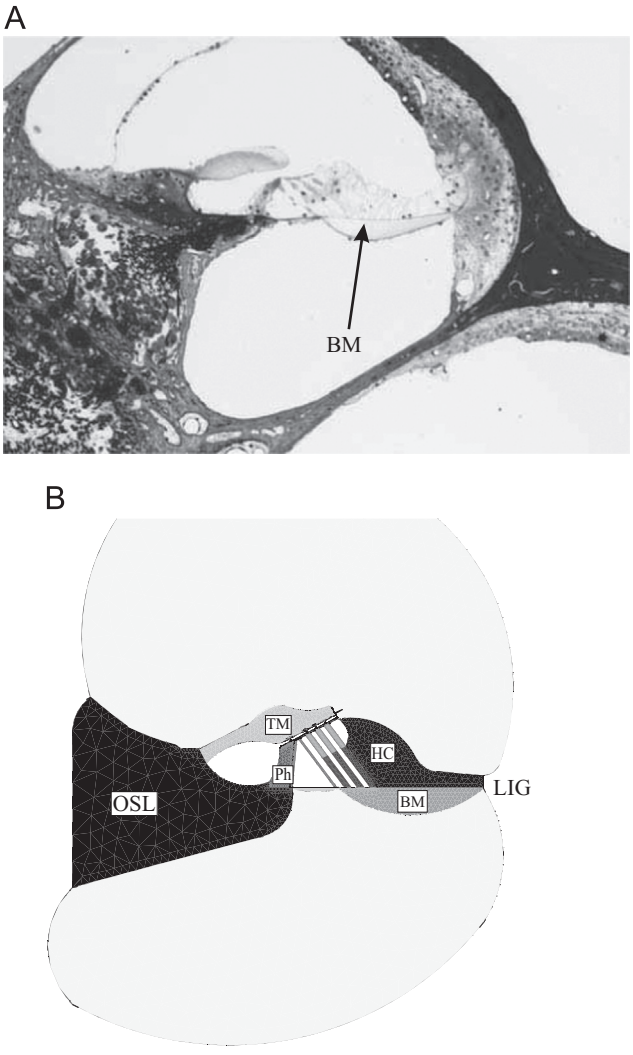

Fig. 1. The cochlea cross section is accurately represented in the FE model. (A) Histological section of the middle turn gerbil cochlear cross section enclosed in the temporal bone. The organ of Corti (OC) sits on the basilar membrane (BM) (*arrow*). The BM+OC complex is suspended between the spiral ligament (LIG) on the right and the osseous spiral lamina (OSL) on the left. The hammer like structure protruding from the OSL is the tectorial membrane (TM). Surrounding the suspended complex are the scalae fluids. (B) FE representation showing the parts of the cochlear cross section including the cochlear fluids.

All of the different tissues are represented as 3D isotropic elastic solids. In the cochlea, the basilar and tectorial membranes are fibrous with fibers arranged to give orthotropic properties. This fibrous feature is more pronounced in the basal part of the cochlear spiral, and diminishes in density as it progresses apically (Iurato, 1962). Naidu and Mountain (1998b) have studied the pattern of deflection of the BM and show that the BM is nearly isotropic in the apex. Hence, the BM may be treated as isotropic in the apical turns. To a first approximation, the BM is modeled as an isotropic elastic solid for the present middle turn model of the cochlea.

The dimensions for the middle turn of the gerbil cochlea are listed in Table 1 with the data source. Several dimensions are estimated from stacks of images described in Karavitaki and Mountain (2007). The resolution of the image measurement is estimated to be 230 nm/pixel. Some parameters were derived from geometric constraints and are listed at the bottom of Table 1. The short section comprises 5 OHC and 5 PC in each row.

The actual volumes of the various components of the OC were matched in the FE-model using combinations of Boolean operations on primitive body shapes represented within ADINA (Bathe, 1986).

2.2. Experimental conditions and modeling assumptions

A sketch of the PtSt measurements in Fig. 3 shows the locations where stiffnesses were measured. Experimental PtSt data are available at two and three radial locations, respectively, when the OC is surgically removed from the BM (see Fig. 3A) and when the OC lies on the BM (Fig. 3B). They correspond to PtSt measurement location 1, under the BMAZ, location 2, under the HC, i.e., under the BMPZ, and location 3, under the PC when the OC is present, as shown in Fig. 3B. A fourth location between locations 2 and 3, under the DC/OHC, is used to validate the OC model. The PtSt values are summarized in Table 2. Measurements on the isolated BM were obtained for the middle turn and used to provide initial estimates of the Es for the BM components.

Because of the small deflection and the low frequency (quasi-static) probe drive used in the experiment (Naidu and Mountain, 1998a), a linear and a quasi-static deflection of the drained OC can be used to simulate the stiffness experiment. A Poisson's ratio of 0.49 is chosen for the practically incompressible cellular component of the OC.

Because the probe deflection at a given point affects the surrounding region, the length of the model must be chosen to include this spread of the deformation. This non-locally reactive deflection is characterized by the space constant defined as the extent of the deformation from its center. The short section length of 45.0 μm is greater than the experimental space constant of 32.8 μm measured in Naidu and Mountain (2001). Symmetric boundary conditions are used, thus doubling the effective length of the model. Hence, there are about three space constants within the total length of the model. This assures that the section is longitudinally coupled, as it is in the experiment.

Here, the force probe is not physically modeled. It is represented as a pressure load over an area with dimension equal to the probe tip, which was 10 μm in diameter.

2.3. Estimating Es from PtSt measurements

2.3.1. Bayesian description

The FE model of the middle turn of the cochlea requires as input the E-values of each constituent. By identifying the E-values that most closely predict the measured data, we thus infer the properties of the individual components. In order to quantify both the modulus estimate and confidence in those estimates, we chose to formulate this inverse problem in a Bayesian context (Tarantola, 2005; Stuart, 2010).

To that end, we assume that the errors in the measured PtSt values are independent, identically normally distributed with a standard deviation of $\Delta\mathbf{k}=[\Delta k_1, \Delta k_2, \Delta k_3]$ for the three stiffness measurements. Then we may write the likelihood function for the observed stiffness values $\mathbf{k}=[k_1, k_2, k_3]$ ($M=3$) given the vector of individual moduli $\mathbf{E}=[E_1, E_2, \ldots, E_{11}]$:

$$P(\mathbf{k}|\mathbf{E}) \propto \exp\left(-\frac{1}{2}\sum_{i=1}^{M}\left(\frac{1}{\Delta k_i}\right)^2 (k_i^{target}-k_i(\mathbf{E}))^2\right). \quad (1)$$

Here, $k_i(\mathbf{E})$ is the function representing the predicted PtSt given the Es.

To build our prior expectations on the moduli, we choose the prior distribution of the moduli $P_0(\mathbf{E})$, to be log-normal, with prior standard deviation reflecting our confidence in their order of magnitude. Based on earlier measurements, we assume $\ln(E_j/E_j^0)=\mathcal{N}(0,(1/\log_{10}(e))^2)$, giving an uncertainty of one order of magnitude in the prior E-values. Here, E_j^0 are our initial guesses/prior E-values for each tissue component.