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# Sound-induced motility of outer hair cells explained by stochastic resonance in nanometric sensors in the lateral wall

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ABSTRACT

The mechanism of mammalian hearing has intrigued scientists for decades. It is widely assumed that the process of hearing begins when sound reaches the inner ear and causes the basilar membrane (BM) to vibrate. These vibrations are then detected and consequently amplified by the outer hair cells (OHCs). We question this sequence of events and the inauguration of sound-induced motility, i.e. transformation of sound pressure wave into directional vibrations. Based on the morphology of the mammalian cochlea, we suggest that motility of the OHCs could be due to the synchronized action of hundreds of thousands of nanometric acoustic sensors-actuators in the OHC's lateral wall. We propose that stochastic resonance in these nanometric units can account for all of the major features of mammalian hearing: a wide dynamic range; sharp frequency selectivity; generation of spontaneous otoacoustic emissions; and the ability to process relatively high frequencies. The proposed model might inspire the design of hypersensitive sensors and actuators, which potentially could be incorporated into new types of hearing aids.


## 1. Introduction

Sound is an alternating wave of high and low air pressure. Mammalian auditory systems have great sensitivity, and can capture, process, and respond to sounds over a wide range of spectral frequencies and intensities. The dynamic range of normal hearing in humans extends over 120 dB from the detection of very soft sounds to the tolerance limit for loud sounds; the span of the audible frequencies in humans is 20 Hz to 20 kHz. In contrast, other mammals, such as bats and dolphins, can hear sounds with an ultrasonic frequency (greater than 20 kHz) [1], whereas whales and elephants can hear sounds with an infrasonic or subsonic frequency (lower than 20 Hz) [1].

The cochlea is the auditory receptor in mammals and is a pressure transducer which converts physical vibrations into an electrical signal. Signal transduction is mostly realized by the inner hair cells (IHCs) in the cochlea. Signal amplification also occurs in the cochlea before transduction to an electric signal by IHCs. This amplification is attributed to the *cochlear amplifier*, whose main component comprises the outer hair cells (OHCs), which actively increase the amplitude of vibration of incoming sounds, even when the pressure fluctuation is only a few nano-atmospheres. The cochlear amplifier exhibits level-dependent compressive nonlinearity, i.e. amplification and sharpness of tuning decline as sound pressure levels (SPL) increase [2].

OHCs are specialized cells for mechanical amplification and are unique to mammals. They are long cylindrical cells whose length changes in response to an electrical stimulus: they shorten upon membrane depolarization and lengthen upon membrane hyperpolarization. The somatic motility or electromotility of OHCs has been attributed to prestin, a transmembrane motor protein and a member of the SLC26/SulP anion transporter family [3] which is abundant in the plasma membrane (PM) of the lateral wall (LW) of each OHC [4]. Prestin's configuration alters when membrane potential changes. Specifically, cell shortening occurs upon depolarization because the prestin's membrane area decreases and the cell lengthening occurs upon hyperpolarization because prestin's membrane area increases. Hence, prestin has been proposed as a piezoelectric transducer and its motor function is similar to that of

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an area motor [5].

How is sound-induced vibration inside the cochlea transduced into an electrical signal? When sound reaches the cochlea, the vibrations produce broadly-tuned displacement waves that travel along the basilar membrane (BM) and cause deflection of the hair bundles (HBs) of the IHCs and OHCs. As a result, the HB transduction channel opens and the hair cell's membrane depolarizes. Somatic motility ensues in order to amplify the vibrations, a chemical neurotransmitter is released, and action potentials are generated in the auditory nerve fibers. This sequence of events has three major shortcomings. First, the BM might not be involved in hearing when SPLs are low. Estimations of the BM's passive vibrations before amplification are on a sub-molecular scale at low SPLs (in the order of 1 pm at the hearing threshold of humans [6]). Hence, it seems implausible that the vibrations of a thermal noise in a passive element, such as the BM, could have a detectable impact on OHCs [6,7]. Furthermore, there are several clinical conditions, such as otosclerosis and round window atresia, in which the traveling wave is absent and hearing at low SPLs still occurs [8,9]. Second, the PM of the LW of an OHC could be a low-pass filter. If so, the response of the PM to an ion current would be attenuated at frequencies that are higher than the corner frequency, which has been reported to be less than 1 kHz in isolated OHCs [4,10]. It seems unlikely that amplification in mammals, which occurs at higher frequencies, would rely on somatic motility that is dependent on cycle-by-cycle changes in membrane potential [11]. Third, it is still unclear how electromotility, which is not inherently frequency-tuned [10], heightens frequency selectivity [12].

Direct mechanical stimulation of OHCs by a sound wave is another possible mechanism of amplification [8,13–15]. It has been reported that cycle-by-cycle frequency-tuned motility occurs following acoustic stimulation of the PM of the LW of isolated OHCs [16,17]. Since direct acoustic stimulation is not limited by the PM's corner frequency, the somatic motility of OHCs may underlie the high-frequency hearing of mammals. This notion is supported by the unique harmonizing of cochlear morphology and function in mammals. The central bodies of the OHCs are surrounded by the large fluid-filled spaces of Nuel inside the organ of Corti (Fig. 1*A* and *B*), and this anatomical feature enables OHCs to sense pressure waves in the cochlear fluids. In addition, OHCs function as pressure vessels [18] because their cytoskeleton is reinforced by the subsurface cisternae (SSC) and the cortical lattice (CL), and this reinforcement can support a pressure difference across their LW. Moreover, sensitive hearing is coupled to the anatomical arrangement between the PM of the LW of each OHC and the spaces of Nuel, and this coupling is more evident at the base of the cochlea, where higher frequencies are coded [19,20] (see Fig. 1*B* vs. Fig. 1*C* and *D*).

In this report, we present a novel mechanism for sound-induced motility of OHCs and describe a new model for the initial sequence of events in the cochlea. Using simulations of the proposed model, we found that this model provides a comprehensive explanation for all of the main features of cochlear amplification in mammals, namely hypersensitivity at low SPLs, even when masked by thermal noise, high-frequency amplification, sharp tuning, compressive nonlinearity, and the generation of spontaneous otoacoustic emissions (SOAE).

Previous models of cochlear amplification in mammals describe amplification as an arbitrary motion that is initiated by a given driving force. Our model differs from these previous models in that amplification occurs when the sound or pressure wave is initially transformed to a tuned and amplified motion. How are pressure waves transformed into motion? Let us assume the pressure wave acts like a driving force over a given piston area and induces vibrations in a harmonic oscillator that comprises a piston (a mass) and a spring (an elastic element). When the sound wave reaches the piston, a pressure difference forms and the piston starts oscillating. The acoustic energy of pressure oscillations is thereby transformed into kinetic energy by the mass' vibrations (and potential energy of the spring). According to this approach, the force that drives the oscillator into motion is the acoustic pressure difference across the piston. However, this description has two major shortcomings when we discuss small micrometric systems, such as the inner ear and low SPL. First, no significant pressure drop is expected where the sound wavelength is at least three orders of magnitude greater than the size of a micrometer-sized object. Second, even when the pressure drop is maximal (although most unlikely to occur) a pressure difference of $10^{-4}$ Pa over a typical area of $10^4$ $\mu m^2$ ($10^{-8}$ $m^2$) will result by a tiny force, order of piconewton ($10^{-12}$ N), which will displace the piston by couple of angstroms. Since a new mechanism of pressure-motion transduction should be sought, we shifted our attention to the LW of the OHC which houses a unique unstable structure of molecular motors with piezoelectric properties and is capable of transforming low SPL into vibrations.

## 2. Model

### 2.1. The basic units in the PM of the LW of an OHC

The PM of the LW of OHCs comprises many identical nanometric-sized units, that were previously proposed as the functional units of the OHC [21,22]. Here, we claim that the function of these units is to sense acoustic waves. These sensors, which we will name nanometric acoustic motile sensors (NAMSs), are square sections of the PM, which are densely covered with prestin molecules and supported by four pillars of unknown composition. The pillars connect the PM to the underlying CL, a spectrin-actin network which covers the outermost SSC (Fig. 2*A*) [4]. The NAMSs become organized and densely packed in cochlear locations where high-frequency sounds are coded (Fig. 2*B–F*). The PM of the LW of OHCs appears rippled in transmission electron micrographs [23,24]. The appearance of these ripples in the PM of OHCs is unique, and it has been proposed that each ripple is a membrane reservoir or an excess membrane area [25,26]. In contrast, the PM of Deiters' cells, which anchor the OHCs and are also surrounded by the large fluid-filled spaces of Nuel, appears smooth in transmission electron micrographs (Fig. 2*G*). The basic premise of our model is that these excess membrane areas of the PM confer bistability to each NAMS: each NAMS has two stable curved states and a flat or straight NAMS is unstable.

### 2.2. Prestin activation in each state of the NAMS

Substantial experimental evidence exists that membrane curvature influences the functionality and conformation of prestin and other anion transporters [4,15,27,30–38]. Results of investigations on the fast motor kinetics of prestin suggest that the binding of intracellular chloride triggers prestin-based electromotility of an OHC [39,40]. Assuming prestin's voltage sensor on a NAMS is located on the internal aspect of the OHC's membrane [41], this sensor, perhaps a chloride binding site [38], would be revealed to the cytosol when a NAMS becomes concave, and concealed when a NAMS becomes convex with respect to an OHS′ radial axis [38]. Flexoelectricity is the term used to describe the coupling between polarization and strain gradients of a dielectric [42]. Since the PM is a dielectric, the NAMS can become electrically polarized when it bends [42], and if chloride binds to prestin, electromotility can be triggered [38]. Accordingly, we posit that depolarization of the OHC's membrane occurs when a NAMS becomes concave and