

# Remote sensing the cochlea: Otoacoustics

Christopher Bergevin

Department of Physics & Astronomy  
York University  
Toronto, ON M3J1P3  
Canada

Sarah Verhulst

Dept. of Medical Physics and Acoustics  
Carl von Ossietzky University  
Germany

Pim van Dijk

Department of Otorhinolaryngology, Head & Neck Surgery  
University Medical Center, University of Groningen  
Netherlands

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# 1 Introduction

## 1.1 Motivations

An illustrative starting point is the remarkable functionality of the mammalian cochlea. As a biological detector of sound, the ear exhibits numerous characteristics that from a biomechanical point of view are, given limiting constraints (e.g., thermal noise, operating range of neural responses, fluid mechanics), impressive. Generalizing across the wide variety of mammalian species (see Vater and Kössl (2011)), these characteristics include (Hudspeth (1989); Dallos (1996)):

- Dynamic range spanning 12+ orders of magnitude of energy (e.g., Viemeister and Bacon (1988)) and a spectral range of  $\approx 6 - 12$  octaves (Heffner and Heffner, 2007)
- At threshold, the eardrum moves on the order of a picometer (pm) (Dalhoff et al., 2007) (for reference, the diameter of a hydrogen atom is 100 pm)
- At threshold, the basilar membrane (BM) moves on the order of 100 pm (Dallos, 1996; Robles and Ruggero, 2001), despite thermal noise agitating the hair cell bundles roughly to an order of magnitude more (Denk et al., 1989; Jaramillo and Wiesenfeld, 1998; Ricci et al., 2000). Dallos’ analogy (that ciliary displacement at threshold can be scaled up to a 5 cm movement of the top of a skyscraper, Dallos (1996)) is apt: sway due to wind can be 15–90 cm.
- Via the stria vascularis (one of the most vascularized tissues in the body), cochlear hair cells experience the highest resting trans-membrane potential [ $\approx 130-170$  mV, (Sewell, 1984; Offner et al., 1987) ] in the whole body
- Nonlinear nature that provides “compression”, allowing the ear’s large dynamic range to be encoded into the smaller input range of the central nervous system (see Oxenham and Bacon (2003); Bergevin et al. (2011a))
- The (healthy) ear not only detects sounds, but also generates and (coherently, stably) emits it as well (Kemp, 1978; Zurek, 1981; Lonsbury-Martin and Martin, 2008)

But despite these knowns, much remains unknown as to how the inner ear achieves this degree of functionality. This uncertainty is tied to the difficulty of direct cochlear physiology.

Why are intracochlear measurements hard? A simple answer is twofold. First, the cochlea is relatively inaccessible, being encased in one of the hardest bones of the body (petrous portion of the temporal bone). As such, many cochlear physiologists use mammalian species where the cochlea bulges out from the temporal bone, which improves accessibility, such as gerbil, chinchilla, or guinea pig. Second is its fragility. While von Békésy’s remarkable contributions (von Békésy, 1960) used excised postmortem tissue, it was not until much later that the knowledge of nonlinearity started to emerge by studying living ears (Johnstone and Boyle, 1967; Rhode, 1971) (note that the latter study used “nearly 150 animals”!), and further yet for the notion of an “active cochlea” to take hold (Allen and Neely, 1992; Manley et al., 2008). Similarly, it took a relatively long time before measurements compellingly demonstrated that basilar membrane (BM) and auditory nerve fiber (ANF) tuning were in fact similar, at least for 7–10 kHz in chinchilla (Rhode, 1978; Narayan et al., 1998), and the notion of the “second filter” deemphasized. Modern measures of intracochlear mechanics have further improved (e.g., Robles and Ruggero (2001); Ren (2002); Chen et al. (2011); Versteegh and van der Heijden (2013); Dong and Olson (2013); Lee et al. (2015)), although many key facets (e.g., relative motions/tuning within, and along, the organ of Corti) remain unresolved.

It is known that opening the bony wall of the cochlea (e.g., to allow for an optical path for laser doppler interferometry, LDV) one can potentially affect the mechanics under observation and thereby introduce a source of systematic error (Ulfendahl et al., 1991; Dong and Cooper, 2006). One way to circumnavigate this difficulty is to take a *remote sensing* approach. That is, observe the cochlea’s behavior in its normal healthy/native state without directly adversely affecting it. The term “remote sensing” appears to derive primarily from radar/sonar and satellite imaging, where the so-called “ground truth” (e.g., actually going

to a viewed location on Earth’s surface to verify identification from the orbital image) may or may not be known. One primary means to remotely sense the cochlea is by making use of the aforementioned fact that the ear emits sound, known as otoacoustic emissions (OAEs). As will be discussed, for the most part, only healthy ears emit and thereby provide a window into the normal function of the ear. Such has led to the remarkable development of OAEs for translational applications, which have revolutionized pediatric audiology (Probst et al., 1991; Janssen and Muller, 2008). In fact, spontaneous OAEs (SOAEs) are the most salient evidence presently known for the notion of an “active” ear, especially when coupled with the “rippling” audiometric thresholds (Zwicker and Schloth, 1984; Long and Tubis, 1988; Duifhuis, 2012). It is important to realize though that studying cochlear function via OAEs essentially represents an *inverse problem*, as motivated in previous theoretical studies of cochlear mechanics (de Boer, 1983, 1995; Zweig, 1991).

## 1.2 OAEs are an inverse problem

What is an inverse problem? A general definition (Ramm, 2005): “*Inverse problems are the problems that consist of finding an unknown property of an object, or a medium, from the observation of a response of this object, or medium, to a probing signal. Thus, the theory of inverse problems yields a theoretical basis for remote sensing and non-destructive evaluation.*” These types of problems arise across a broad array of fields (e.g., mathematics, geophysics, medical radiation, x-ray crystallography, acoustics). But to best illustrate the answer to the question in a current (otoacoustic) context, an analogy from Dr. Wei Dong is borrowed. Imagine a cocktail party going on in room, behind a closed door. Now imagine you are down at the other end of a long hallway from that room. You can only hear what sound leaks out from underneath the door and makes it down the hallway. Your job is to figure out who is at the party, what they are talking about, and what they are doing. Clearly, aside from being a difficult task, the problem is somewhat ill-posed (i.e., there are potentially numerous “correct” answers). This is why it is essential that studies of OAE generation are tempered by knowledge gained from both theoretical (Sec.3) and empirical studies (Secs.3.2.5, 3.6, 4). Note that many other “imaging” modalities commonly employed in auditory science and beyond (e.g., EEG, ABR, CAP, fMRI, ANF recording, MEG) also essentially face the same problem and constitute “remote sensing”, just in different flavors.

## 1.3 Themes to cover

To further set the stage for this chapter, here is a succinct summary of what is known: OAEs are acoustic responses, measured in the ear canal with a sensitive microphone (Kemp, 2008). They provide a non-invasive physiological measure of inner ear function, as they ultimately derive from the hair cells. In general, only healthy ears emit, while HI ones do not (or do so in a substantially reduced fashion). OAEs come in two basic types: spontaneous (arising in the absence of external sound, SOAEs) and evoked (in response to a stimulus, eOAEs). Most ears produce eOAEs (e.g., mammals, reptiles, birds, amphibians), even those of invertebrates (Mhatre, 2015), though SOAEs appear less prevalent. Importantly, OAEs are directly tied to auditory perception (Sec.2.2).

These facets, derived from a substantial body of high-quality research, presently serve to motivate further, deeper questions. Consider:

- How do hair cells work together (and with other accessory structures) to generate OAEs? How are such processes tied to forward auditory transduction?
- Aside from characterizing by stimulus-type (or lack thereof), are emission types better characterized by their prospective “generation mechanisms (e.g., Shera and Guinan (1999))”? Biophysically, what precisely is a “mechanism”? What determines the balance in strength between multiple mechanisms?
- Both similarities and differences exist when comparing OAEs across species, but what does such in fact actually tell us? Can such be related back to morphological aspects?



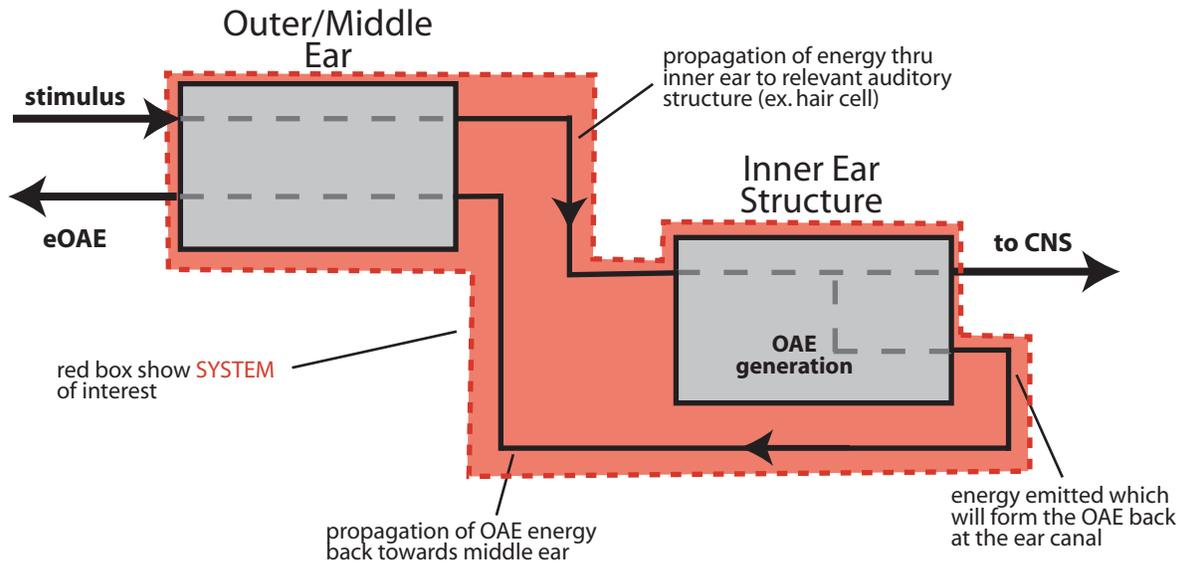
**Figure 1:** Artistic rendition of Dong’s otoacoustic inverse problem. [Illustration by Larissa McKetton].

- How does nonlinear emission growth link to the cochlear compression and subsequent perceptual consequences?

These questions, which ultimately do not (yet) have answers to, will be used as a lens to focus the content of this chapter. It is not intended to be exhaustive. In fact, there are numerous comprehensive reviews regarding OAE generation (e.g., Probst et al. (1991); Manley et al. (2008); Avan et al. (2013)). The goal is more limited in that the aim is to examine recent data and place such into a more unified context, with an emphasis on basic biophysical considerations.

## 1.4 OAEs motivate biophysical research

Wrapping up this introduction, attention is drawn to a broader biophysical thread present here. Aside from elucidating the processes underlying peripheral auditory transduction, the study of OAE generation mechanisms provides broader avenues of exploration. As stated by a leading researcher in auditory science (Dallos, 1996): “Among vertebrates the biological processes that subserve frequency analysis vary a great deal. In other words, there is no such thing as **the cochlear mechanism**”. On one hand this is certainly true (i.e., searching for a universal description applicable broadly across biological systems is likely futile). But on the other, elucidating general biophysical principles can pay off handsomely, and the cochlea is a fertile ground for such. For example, consider the William Bialek’s discussion surrounding a definition of “biophysics” (Bialek, 2012). He raises the intriguing point of view that biophysics isn’t necessarily the application of physics to help tackle problems in life sciences (a reasonable perspective), but rather the converse. That is, biological systems, given their apparent complexity, can motivate new physics. Connecting this back to OAEs: As will be discussed, models of OAE generation stimulate novel directions of mathematical and physical theory, such as the dynamics of a network of nonlinear/active oscillators (e.g., Duke and Jülicher (2008); Vilfan and Duke (2008)) and the role that stochastics can play in emergent system behavior (e.g., Zweig and Shera (1995); Epp et al. (2010)).



**Figure 2:** Schematic providing an overview of how an OAE generation *mechanism* is defined. See text for discussion.)

## 2 Starting points

### 2.1 Terminology

It is important from the outset to define the terminology that will be used for the development of a theoretical framework and the interpretation of data. The entire region of interest is schematized in Fig. 2. Three key terms are highlighted. First, a **mechanism** is simply defined as a physical process. For example, a mechanism may be hair cell transduction or the propagation of energy through cochlear fluids or along the BM. Thus, a mechanism as defined here is not limited solely to the inner ear structure that generates the emission. Second, the **system** is what specifically forms the basis for an OAE. In the words of Hobbie and Roth (2007), “A system is that part of the universe that we choose to examine. The surroundings are the rest of the universe. The system may or may not be isolated from the surroundings.”. The OAE system includes all the processes involved in the transmission of sound into the inner ear, the generation of the OAE and the transmission of sound to the outer ear, and is comprised of multiple mechanisms. Contributing mechanisms to the system may, for example, include a nonlinear resonator, a delay-line, and a transformer (i.e. the middle ear). In Fig. 2, the system of interest is bounded by the red box. It also includes the forward path (from the stimulus location to the generation site), since any relevant transfer function (such as a delay) is going to affect the “input” to the generation site. For simplicity, efferent effects are ignored here. Third, OAE generation occurs at a **site** (or equivalently, a *source*; see Sec.3.1). A site is the physical location at which the emission originates. Multiple sites can contribute to the formation of an emission. In such an extended *region* of generation, the OAE is the integration across all the contributing sites (e.g., constructive/destructive interference can arise). When multiple sites exist, their associated emissions may or may not be produced by the same type of physical mechanism.

### 2.2 Connections to neurophysiological and psychophysical measures

Implicit in many studies of OAEs (e.g., Sec.4) is the assumption of a link between human psychophysics and human/animal physiology. This connection is crucially important, as it bridges an objective and non-invasive acoustic measure with perception, thereby cementing the use of OAEs as an important tool in

hearing science. Numerous studies have demonstrated these connections. Salient examples of connections include:

- SOAEs & audiometric thresholds – Zwicker and Schloth (1984); Long and Tubis (1988); McFadden and Mishra (1993); Lee and Long (2012); Dewey and Dhar (2014)
- SOAEs & ANF tuning – Taschenberger and Manley (1997); Manley (2001); Bergevin et al. (2015a)
- SOAEs & psychophysical tuning – Zwicker and Schloth (1984); Noreña et al. (2002); Epp et al. (2010); Hansen et al. (2014)
- SFOAEs & ANF tuning – Shera et al. (2002, 2010); Bergevin and Shera (2010); Joris et al. (2011); Bergevin et al. (2015a)
- SFOAEs & psychophysical tuning – Shera et al. (2002); Oxenham and Shera (2003); Charaziak et al. (2013)
- TEOAEs & psychophysical tuning – Neumann et al. (1997)
- DPOAEs & psychophysical masking – Johannesen and Lopez-Poveda (2008)
- DPOAEs & ANF tuning – Köppl and Manley (1993)
- eOAEs & evoked potentials – Neely et al. (1988); Purcell et al. (2003); Harte et al. (2009); Rasetshwane et al. (2012)

Furthermore, correlations have been demonstrated between various OAEs types, such as SOAEs and SFOAEs (e.g., Zwicker and Schloth (1984); Bergevin et al. (2012a); Dewey and Dhar (2014); Bergevin et al. (2015a)). Overall, these connections demonstrate that OAEs are not just merely “there”, but somehow tied to forward auditory transduction. Thereby, OAEs provide a means to characterize forward auditory transduction.

## 2.3 Hair cells as a foundation

Hair cells are a tractable starting point for elucidating OAE generation. The physiological evidence linking OAEs to hair cells is substantial. Work with non-mammalian hair cells in-vitro (e.g., Crawford and Fettiplace (1985); Martin and Hudspeth (1999)) have clearly demonstrated that hair cell bundles can act as an “active” (i.e., force-producing) nonlinear system, sometimes even as limit cycle oscillators (e.g., Ramunno-Johnson et al. (2009)). Extensive reviews along these lines are Fettiplace and Hackney (2006) and Martin (2008). In-vitro studies suggest similar behavior in mammalian hair cells (Kennedy et al., 2005). While the precise molecular mechanisms remain unclear, the protein *prestin* has clearly been implicated in normal hair cell function in mammals (Zheng et al., 2000; Liberman et al., 2002), though it is less clear for non-mammals (Köppl et al., 2004; Tang et al., 2013). While typically evoked acoustically, OAEs can also be via electrical stimulation (Xue et al., 1993; Ren and Nuttall, 1996; Manley et al., 2001; He and Ren, 2013), an observation that further allows connections to be made back to their cellular origins. Additionally, direct intracochlear measures, whether it be via BM motion (Robles and Ruggero, 2001), intracochlear pressure (e.g., Dong and Cooper (2006)), or more sophisticated modalities (e.g., Dong and Olson (2013); Lee et al. (2015)), provide a valuable degree of “ground truth” connecting OAEs and hair cells.

One additional important consideration is that eOAEs elicited using relatively high level stimuli ( $\simeq 50$  dB SPL or higher) need not stem from healthy/normal hair cell function. Even ears from dead animals (several hours postmortem) can show significant eOAE activity when using high levels, albeit usually reduced relative to in-vivo (van Dijk et al., 2003). Typically such activity disappears upon complete ossicular interruption (Bergevin, 2007) and presumably stems from residual passive nonlinear contributions from various structures to the input impedance of the inner ear (e.g., see Fig.4.20 in Patuzzi (1996)). For the most part, this mechanism is neglected for the rest of the chapter, so to chiefly focus on the notion that OAEs provide a means to study the “active ear”.

### 3 Models of OAE generation

Since their discovery in 1978, there has been a long and rich history regarding the theoretical modeling of OAEs. These efforts are useful because the models serve to help bridge cochlear mechanics and hair cells with OAEs, thereby cementing OAE use as a non-invasive probe as highlighted earlier. Models come in a wide variety of flavors, and just to name a few: electric circuits (e.g., Zwicker (1986a,b)), transmission lines (e.g., Zweig and Shera (1995); Talmadge et al. (1998); Sisto et al. (2007); Epp et al. (2010); Liu and Neely (2010); Verhulst et al. (2012); Meaud (2015)), standing wave cavities analogous to a laser (e.g., Shera (2003)), single active/nonlinear “limit cycle” oscillators (e.g., Wit (1986); Talmadge et al. (1991)), and systems of such coupled oscillators (e.g., Murphy et al. (1995b); Vilfan and Duke (2008); Wit et al. (2012); Fruth et al. (2014)). Note that the classifications made here are not necessarily mutually exclusive and certain types such as “state space” models (e.g., Ku et al. (2007, 2009)) could fit into multiple categorizations (e.g., transmission line models are essentially coupled oscillators). An interesting facet when looking across these (and other cochlear) models is the range of biomechanical assumptions made, such as the form of coupling of OHC-related forces and the role of irregularity (or “roughness”; see Sec.3.2.4).

Emissions are commonly classified by the stimulus used to evoke them, though arguments have been proposed that a better classification is via the underlying generation mechanism (Shera and Guinan, 1999). Nonetheless, an important distinction is present between two emission types: whether an evoking stimulus is present (eOAEs) or not (SOAEs). While eOAEs are readily measurable in most ears with the right equipment (see Sec.4.2), SOAEs are not. Some species exhibit more SOAE activity than others (see Bergevin et al. (2015a)). Similarly, within a given species, prevalence amongst individuals, sex, gender, and ethnicity can vary substantially (e.g., (Whitehead et al., 1993; Talmadge et al., 1993; Kuroda, 2007)). Even within an individual, there can be differences with age and the side of the head. It is not entirely clear why prevalence varies so much, though possible factors could be reverse propagation through the middle ear (Sec.3.4), the degree of roughness (Sec.3.2.4), and/or the coupling between hair cells (Sec.3.2.1).

Regardless, as stated earlier, SOAEs and their connection to the audiogram (Zwicker and Schloth, 1984; Long and Tubis, 1988) represent the most salient evidence for the notion of a cellular-based amplification mechanism at work in the ear (i.e., an “active ear”). Understanding SOAE generation may in fact ultimately be more tractable as there are fewer complicating factors (e.g., how the external stimulus may differentially drive/affect different mechanisms and/or sites). So while the bulk of otoacoustic research focuses on eOAEs (see Sec.4), SOAEs will be the initial focal point here. The narrative highlights two (broadly categorized) classifications: single source (Sec.3.1) and region models (Sec.3.2).

#### 3.1 Single source models

Early theoretical studies of SOAE generation considered the underlying mechanism to be a single source (Johannesma, 1980; Bialek and Wit, 1984; Wit, 1986; Talmadge et al., 1991; Murphy et al., 1995a; Neumann et al., 1997). That is, the complexities of the *system* were eschewed in favor of identifying to what extent the simplest model could reasonably describe the data. Subsequently, similar efforts were employed for eOAEs as well. The foundations of such models will be briefly provided, as well as examine what features of the data they are (and are not) capable of capturing.

##### 3.1.1 Oscillators as a basic fundamental element

Nearly all cochlear models have at their heart the notion of a driven oscillator. That is, a 2nd order system where energy is stored/shared/transferred between two reactive components (e.g., a mass and a spring). Morphologically, many features can play the role of oscillator (e.g., hair cell bundle in fluid, section of BM, tectorial membrane, or TM). Mathematically this can most simply be expressed via the second order ordinary differential equation (ODE):

$$m\ddot{x} + b\dot{x} + kx = F(t) \tag{1}$$

where  $x$  is the relevant physical displacement (e.g., deflection of BM or bundle),  $m$  is the effective mass (e.g., entrained fluid, TM),  $b$  the damping,  $k$  the stiffness (e.g., elasticity of the BM or bundle), and  $F$  an arbitrary non-autonomous driving force (e.g., external tone, thermal noise). The damping can arise in a number of different ways, such as viscous forces due to fluid coupling, or as recent results have indicated (Bormuth et al., 2014), frictional forces internal hair bundle linkage/channel dynamics. Note that this equation is sometimes expressed (e.g., Hudspeth (2008)) as a complex-valued first order ODE ( $z \in \mathbb{C}$ ):

$$\dot{z} = \alpha z + i\omega_o z + F(t) \quad (2)$$

where  $\alpha$  describes energy loss (i.e., damping) and  $\omega_o$  ( $\sim \sqrt{k/m}$ ) the oscillatory properties. Regardless of notation, several key aspects emerge from this description (i.e., resonance, tuning, phase). Note also that if  $b$ ,  $k$  and  $m$  are constant, then Eqn.1 is linear. If however they are allowed to vary as a function of  $x$ , the equation becomes nonlinear (thereby complicating analysis) and new behavior can arise (see Secs.3.1.2 and 3.2.3).

Questions remain open as to the relative ratio of forces (Freeman and Weiss, 1988; Duifhuis, 2012) (e.g., are viscous forces so dominant that inertial forces play a negligible role?). As such, some models make drastically different assumptions about the underlying basis of the resonator (e.g., Hudspeth (2008); there inertial forces are ignored and their effective role is replaced by gating channel forces). Furthermore, some model classes consider the oscillator to be higher order (e.g., O Maoileidigh et al. (2012)), a point returned to in Sec.3.1.2. Nonetheless, the basic idea is clear: a resonant element serves as a starting point. Readers looking for more general/comprehensive references are pointed towards: French (1971), Andronov et al. (1966), Stoker (1950), and Hagedorn (1988).

### 3.1.2 Limit cycle oscillators

Now in order for the oscillator to yield something akin to an SOAE, it must be both “active” (i.e., energy-producing) and nonlinear (to ensure stability). One commonly employed formulation is the van der Pol system (Johannesma, 1980):

$$m\ddot{x} - \mu(1 - x^2)\dot{x} + kx = F(t) \quad (3)$$

where  $\mu$  is sometimes referred to as the “control parameter”. In a nutshell, for small displacements the damping is negative (this is the active part), while for larger displacements it becomes positive (thereby stabilizing the motion). Equivalently, feedback is introduced (which affects stability), insinuating that that SOAEs arise from unstable auditory filters. When using complex notion, this equation is commonly expressed in a simplified form (“normal form”) that captures qualitatively similar dynamics:

$$\dot{z} = -\mu z + i\omega_o z + z|z|^2 + F(t) \quad (4)$$

Regardless, these equations refer to what is commonly called a *limit cycle oscillator*. This also provides a natural place to make mention of a concept commonly discussed, that of a *Hopf bifurcation* (e.g., Hudspeth (2008)). Namely, there is a point where changes in the control parameter have a significant qualitative effect upon the system’s dynamics (see Bergevin et al. (2011a)).

Note that while mathematically making an oscillator active is trivial (i.e., just flip the sign of a parameter), physically it is an entirely different matter. Consider for example the notion of a *phase oscillator*, which is commonly studied in mathematics. There, a (self-sustained) oscillation is implicitly assumed and the equation of motion simply only describes the dynamics of the phase ( $\theta$ ):

$$\dot{\theta} = f(\theta, t) \quad (5)$$

A simple example being  $\dot{\theta} = \omega$  (a constant), whose dynamics are equivalent to a steady-state simple harmonic oscillator. More pressing here is the question as to what physiological process serves as the energy source in the (2nd order) van der Pol model? Presumably some molecular-level metabolic process. Some models have attempted to address this a bit more directly by succinctly including gating channel forces, though such

requires a higher order oscillator. For example:

$$m\ddot{x} + \gamma\dot{x} + kx - g(x, f) = F(t) \tag{6}$$

$$\tau\dot{f} = bx - f \tag{7}$$

where  $f$  is the force applied to the bundle through “adaptation” and  $g$  is the associated gating force (O Maoileidigh et al., 2012). Additionally, for “negative damping” to work, the oscillator must be 3rd order or higher (Binder et al., 2011). Looking ahead, it is noted that the question of (non)linearity becomes more complicated in models comprised of more than just one source, as discussed in Sec.3.2.3.

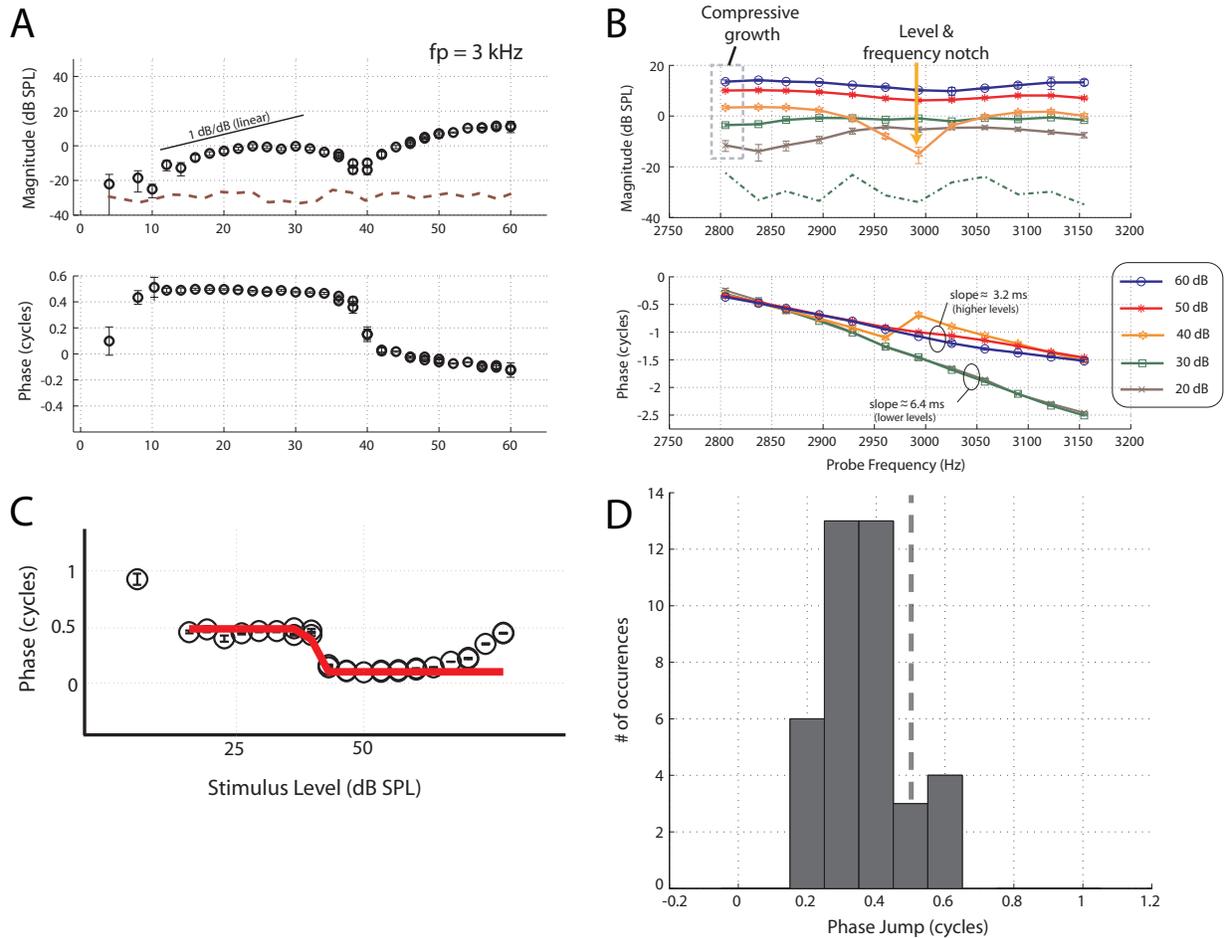
### 3.1.3 What single source models do and do not do

To first order, a large range of SOAE-related features are well-captured by a single van der Pol oscillator. The bi-modal nature of the amplitude distributions can readily be reproduced (Bialek and Wit, 1984; Talmadge et al., 1991), as can be the “relaxation dynamics” when SOAEs are exposed to external tones (Murphy et al., 1995a). But despite these successes, OAE data indicate that the underlying generation mechanisms are more complex. For example, a single van der Pol is capable of generating energy predominantly at a single frequency, not an idiosyncratic array of them as is commonly observed in SOAEs (see Fig.7). Furthermore, detailed analysis of SOAE peak dynamics indicates there are interactions between different SOAE peaks (van Dijk and Wit, 1990). To expand upon this point, it is illustrative to also consider single source models in the context of eOAEs.

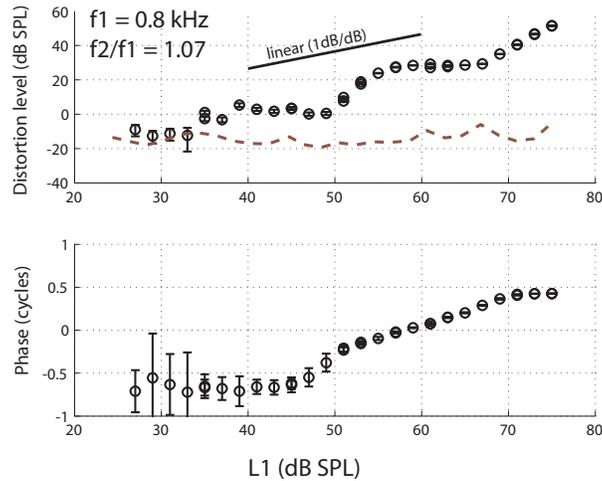
Given the cochlea’s relatively nonlinear nature, it is important to have a deep understanding of how the level of the evoking stimuli affects eOAEs. These characterizations can be referred to as “level-growth functions” or “input-output functions” (I/O). In addition to the compressive (i.e., nonlinear) nature of the BM velocity as first shown in the early 1970s (Rhode, 1971), it is well-known that I/Os for ANFs (Kiang et al., 1986), BM responses (Robles and Ruggero, 2001), and OAEs (Brown, 1987; Schairer et al., 2003; Bergevin, 2007) can be nonlinear and sometimes non-monotonic. That is, there are regions where higher level stimuli produce smaller magnitude responses than lower levels (Fig.3A). If there is a limited region of non-monotonic behavior, it is commonly referred to as a “notch”. Typically, the response phase demonstrates a shift along with the notch in the magnitude. It is stressed here that non-monotonic behavior is typically highly idiosyncratic, to an individual ear as well as for a given frequency or level. Shift your stimulus frequency(s) 100 Hz and an eOAE I/O shape could qualitatively change drastically, introducing a confounding reality from a clinical perspective. Furthermore, in reports where I/Os are shown averaged across individuals (e.g., Schairer et al. (2003); Johnson et al. (2006)), non-monotonic features tend to get averaged out.

A relatively straight-forward explanation of non-monotonicities was proposed as simply arising from a single nonlinearity (Engebretson and Eldredge, 1968; Weiss and Leong, 1985; Lukashkin and Russell, 1998). This basic idea was then extended to explain DPOAE growth (Lukashkin et al., 2002), propounding the notion that DPOAEs observable in the ear canal arise predominantly from what they call “*a single source, namely a nonlinear amplifier with saturating I/O characteristic*”. It is important to critically examine this notion, as there are wide implications for interpreting a broad range of eOAE behavior in terms of the underlying cochlear physiology such as the inferred “operating point” of the transducer (e.g., Bian et al. (2002); Liberman et al. (2004)).

While appealing from a reductionist point-of-view, the simplicity of the “single source” model appears to be its greatest weakness. At least two main lines of evidence argue against the applicability of this model. First, many aspects of non-monotonic features are not consistent with key predictions of the model (Bergevin, 2007), such as linear growth at lower level (even for cubic DPOAEs), the size of the phase jump (not necessarily 1/2 cycle), phase varying smoothly with level (i.e., not just a jump), extended portions of highly compressed growth, and the frequency-dependent nature of I/Os (Fig.3). These aspects are even more apparent in non-mammalian OAEs (Fig.4), whose ears are relatively “simpler” (see Sec.3.6) and thereby the single source notion might be more readily expected to apply (e.g., less additional degrees of freedom). Second, it is well known that DPOAE source “unmixing” (e.g., Mauermann et al. (1999); Kalluri and Shera (2001)) demonstrates that roughly two generation components with differing latencies exist, and that these



**Figure 3:** Example of eOAE dependence upon stimulus level (Bergevin, 2007) ( $L_p = L_s + 15 \text{ dB}$ ,  $f_p = f_s + 40 \text{ Hz}$ ). **A.** Representative SFOAE I/O for a human subject. Presentation of levels was randomized and some repeat measurements at certain levels were made. Dashed line indicates the noise floor. Some phase values were shifted vertically by one cycle. The particular curve shown here is representative, but there can be significant variation in the qualitative shape across individuals (for a fixed set of parameters) and stimulus frequencies (in a given individual). **B.** SFOAE frequency dependence measured at different stimulus intensities in a single human subject. A notch, both with respect to frequency and level, is apparent around 3 kHz and 40 dB SPL. Furthermore, there is a transition in the phase gradients, depending upon whether the stimulus level is below (larger gradient) or above (smaller gradient) 40 dB SPL. **C.** Example of SFOAE phase dependence on probe level. Also shown via the thick, solid curve is an estimation of the phase jump via nonlinear regression (hyperbolic tangent function), when a notch in the magnitude or jump in the phase was visually apparent. **D.** Size of SFOAE phase jump about a notch, compiled together from multiple stimulus frequencies and species. The peak of the distribution indicates that the phase jumps tend to be smaller than 1/2 cycle (red dashed line), typically 0.3-0.4 cycles.



**Figure 4:** Example of a DPOAE ( $2f_2 - f_1$ ) I/O from an individual leopard gecko ear. Primary levels were equal ( $L_1 = L_2$ ) and the levels were randomized (several of which were repeated). Error bars indicate the s.e.m. across the 35 waveforms collected for a given measurement (Bergevin, 2007).

can constructively/destructively interfere to yield a measured DPOAE at the ear canal (typically referred to as “fine structure”) and that such can be differentially affected (Mauermann and Kollmeier, 2004; Jeung and Long, 2007; Rao and Long, 2011). In fact, there are numerous reports (e.g., Goodman et al. (2003); Shera (2003); Jedrzejczak et al. (2004); Siegel et al. (2005); Goodman et al. (2009); Charaziak and Siegel (2015)) and reviews (e.g., Shaffer et al. (2003); Shera and Abdala (2012)) indicating that both SOAEs and eOAEs are generated over multiple spatially-distributed areas.

## 3.2 Region models: Working together – OAEs as an emergent property

So while single source models have provided a valuable starting point, the *next generation* of models takes a more global approach that considers the ear as a system of parts (i.e., multiple sources that can interact). Or put another way, to quote Roger Sessions (often attributed to Einstein): “Everything should be as simple as it can be but not simpler!” It appears plausible that elements of the single source model(s) are at work, but it is ultimately now more fruitful to consider the OAEs as a summed response that represents the interaction of multiple generation sources. That is, the complexity of OAEs (e.g. I/Os) is an *emergent* property due to the distributed nature of the cochlea. As discussed further in Sec.3.3), the most widely accepted theory posits two distinct generation mechanisms (Kemp, 1986; Shera and Guinan, 1999), each of which can manifest as an array of different sources spread out throughout the cochlea. Thus the discussion is shifted towards *region* models (see Sec.2.1).

### 3.2.1 Basic considerations for coupled oscillators

In addition to weaknesses of single source models noted earlier, recent evidence compellingly points towards the importance of coupling between hair cells. Consider for example that mice very rarely exhibit SOAEs. But when the normal boundary conditions coupling hair cells together was changed via a mutation in the TM structure (effectively making it less stiff by preventing formation of the striated-sheet matrix), SOAEs could readily be observed in them Cheatham et al. (2014).

When one has a simple 1-D collection of linear coupled oscillators (arrayed along dimension  $\xi$ ), a *normal mode* formulation is commonly employed (French, 1971). The basic idea is that there are vibration patterns

where all elements oscillate at the same frequency. All possible “modes” then form a basis space, from which any possible motion is a superposition. So while motion can appear complex, the decomposition into simpler components makes the problem analytically tractable. A common example is the nodal patterns that can be observed on a circular membrane (e.g., drum head). It is instructive to note that in the limit of many oscillators, one can proceed from a discrete to continuous formulation (i.e.,  $\sum \Delta\xi \rightarrow \int d\xi$ ).

When dealing with active oscillators, things become more complicated. As an example, consider just two ( $x_1$  and  $x_2$ ), such as the “twin-engine” model (Aranyosi, 2006), which was proposed in the context of explaining “glides” (i.e., frequency variations in the BM impulse response). The equations of motion are given by

$$m_c \ddot{x}_2 + k_c x_2 = m_1 \ddot{x}_1 + [b_1 - g_1(x_1)] \dot{x}_1 + k_1 x_1 + F(t) \quad (8)$$

$$b_c \dot{x}_1 = m_2 \ddot{x}_2 + [b_2 - g_2(x_2)] \dot{x}_2 + k_2 x_2 \quad (9)$$

where the subscript  $c$  denotes the coupling terms and  $g$  is “a nonlinear velocity-dependent term in each resonator, defined as the derivative of a Boltzmann function”. In this case, not only can the oscillators trade energy back and forth, but since they can also inject it, stability can arise through a form of *feedback* (e.g., Dallos and Corey (1991); Zweig (1991)).

Connecting back to Sec.3.1.2, as a general note, attention is drawn to the common approach employed in many studies of coupled active systems of using “phase oscillators” (Pikovsky et al., 2001). Here, magnitudes are assumed constant and the dynamics given simply as

$$\dot{\theta}_n = F(\theta_m, \dot{\theta}_m, t) \quad (10)$$

where  $\theta_n$  is the (unwrapped) phase of the  $n$ th oscillator and whose phase velocity may depend upon itself or the other oscillators coupled to it (denoted by  $m$ ). A striking example where these models have been successful are the fireflies lining the tidal rivers in Malaysia as highlighted by David Attenborough in the BBC show *The Trials of Life* (see also Strogatz and Stewart (1993)). Whether such models might be useful for studying SOAE generation remains unclear, it is assumed that the reduction in dimensionality may be problematic (i.e., magnitude does matter) and that the minimal order of the underlying elements needed to describe the inner ear is two. Whether this is definitively true remains to be proven.

In the context of SOAE modeling, different approaches have been taken, such as standing waves via coherent reflection (Shera, 2003), transmission lines (Choi et al., 2008; Epp et al., 2010), and “coupled oscillators” (Murphy et al., 1995b; Vilfan and Duke, 2008; Wit et al., 2012). Ultimately, these formulations are all in fact “coupled oscillator” models, just with different assumptions about the “coupling”. Coupling typically falls into two different categories: “global” arising hydrodynamically (e.g., Zweig (1976); Nobili et al. (1998); Epp et al. (2010)), and nearest-neighbor only (e.g., Vilfan and Duke (2008)) via resistive and/or reactive elements (e.g., overlying TM). Connecting back to Sec.3.2.3, while a single active oscillator may require nonlinearity for stability, an active system may not (e.g., Zweig (1991)). Or conversely, SOAE models don’t necessarily require limit cycle oscillators per se, as a self-sustained oscillation can arise as a systems level response (e.g., Shera (2003)). Regardless, two common threads arise between all classes of model: randomness and waves.

### 3.2.2 The role of waves

In his seminal paper first reporting the existence of OAEs (Kemp, 1978), Kemp started off by stating “*Cochlea wave propagation characteristics...*”, subsequently following up with a 1986 paper entitled “Otoacoustic emissions, travelling waves and cochlear mechanisms” (Kemp, 1986). It thus may not be surprising that, much of the current understanding OAE generation revolves around a wave-based framework (which implicitly is a region model type). Even in Shakespearean terms (“by any other name”), the moniker *cochlear reflectance* has been proposed for a “normalized” measure of eOAEs (Rasetshwane and Neely, 2012). However, numerous observations systematically comparing OAE between humans and non-mammals, many of whom lack a direct analog to BM traveling waves, have shown revealing similarities and differences when examined through a wave-based mechanism lens (e.g., Bergevin et al. (2008, 2015a)). Such motivates the

question: What role precisely should “waves” play in understanding OAE generation/propagation? While this topic appears to be well-trodden ground (e.g., Nobili et al. (2003); Shera et al. (2004); Duke and Jülicher (2008)), it can be argued that this is not merely an issue of semantics.

To address the original question posed, what precisely is meant by “wave” needs to be clarified in the context of OAE generation. The concept of a wave lies at the foundation of physics and many other branches of sciences including mathematics (and cochlear mechanics). As such, the interested reader is pointed towards more authoritative (but reasonably introductory) texts describing waves in more detail (e.g., Elmore and Heald (1969); Georgi (1993)). For the sake of discussion here and simplicity, it is noted that a wave is described by a function  $f(x, t)$  (over spatial dimension  $x$ ) that satisfies the partial differential equation (PDE)

$$\frac{\partial^2 f}{\partial x^2} = \frac{1}{c^2} \frac{\partial^2 f}{\partial t^2} \quad (11)$$

where  $c$  is a constant. From a mechanical point of view, this PDE essentially amounts to the combination of two fundamental laws. For example, within the context of deriving a 1-D transmission-line model of the cochlea (Zweig et al., 1976; Zweig, 1976), the wave equation manifests from Newton’s 2nd law (regarding BM displacement) and conservation of mass (regarding longitudinal fluid motion). A general solution to this equation has the form  $f(x \pm ct)$  (d’Alembert’s solution), such that time and space are scaled relative to one another. In many instances (but not all), solutions have a periodic nature [e.g.,  $f(x, t) = F \cos(x \pm ct)$ , or more generally  $f(x, t) = F_+ e^{i(x \pm ct)} + F_- e^{i(-x \pm ct)}$  to allow for forward and reverse traveling waves].

Why is a wave as defined as such here? A key idea is that if one considers the various dynamically relevant structures of the cochlea (e.g., hair cells, BM, TM) as oscillators, then the presence of a wave indicates some relative *phase difference* between them. Two consequences immediately arise. First, a main consideration here is *timing* and what that means for the interactions and collective dynamics of the various players. Thus, as originally motivated by Shera and Guinan (2008), a more useful working definition for “wave” is not what is/is not propagating along the BM per se, but instead the relative timing difference between different constituent parts of the cochlea. Such will be important to bridge the gap they identified when they proposed that OAE properties “... are determined not by subcellular biophysics but by macromechanical (and emergent) properties of the cochlea ... many features of OAEs ... are perhaps best understood in this way” (Shera and Guinan, 2008). The field is arguably now well-poised to bridge the micro– (e.g., molecular motors, individual hair cells) and macro–scopic (e.g., the cochlea as a whole, system of coupled hair cells) descriptions, much in a similar way as to the role statistical mechanics plays in thermodynamics and biophysics. Second, the presence (in a one dimensional sense) of both a forward and backward traveling wave allows for the notion of SOAEs to arise via some sort of standing wave mechanism (e.g., Shera (2003)).

### 3.2.3 Linearity: To be or not to be?

At face value, the commonly measured DPOAE  $2f_1 - f_2$  obviously stem from some form of nonlinearity. But in many regards, SFOAEs and CEOAEs are commonly assumed to arise from a linear reflection-based mechanism (Zweig and Shera, 1995), with strong empirical support (e.g., Kalluri and Shera (2007b)). The distinction becomes more readily apparent in the widely-accepted “taxonomy” for OAEs (Shera and Guinan, 1999): of the two highlighted generation mechanisms, one is inherently linear and the other nonlinear. Thereby, conceptually, the question arises as to what extent OAE models should be linear or not. Or as Ku et al. (2009) succinctly put it: “*It is somewhat surprising that linear analysis can account for so many features of the cochlea when it is inherently nonlinear*”.

Numerous model classes explicitly assume some form of nonlinearity (e.g., Talmadge et al. (2000); Vilfan and Duke (2008); Epp et al. (2010); Liu and Neely (2010); Verhulst et al. (2012); Duifhuis (2012)), while others take linear (e.g., Zweig (2015)) or quasi-linear (e.g., Talmadge and Tubis (1993); Zweig and Shera (1995); Shera (2003); Bergevin and Shera (2010)) approaches. Quasi-linear means the fundamental equations are linear, but some form of implicit/ad hoc assumption is made that mimics a nonlinearity (e.g., roughness does or does not matter between two different stimulus level conditions, “addition of appropriate stabilizing nonlinearities”). It should be noted that eOAE models can be stable while being both linear and active (e.g., energy input in one location can be dissipated at another location or via other time-dependent forces,

Zweig (1991)), although SOAE modeling efforts thus far have implicitly assumed some form of nonlinearity to avoid instability (e.g., Talmadge and Tubis (1993); Ku et al. (2009))).

To summarize, it is unclear if there is a *correct* answer to the question posed by this section’s title. Anecdotally, George Zweig recently stated (upon one of the current authors arguing to him that models ultimately need to be nonlinear since the system they are describing obviously are) “You go to learn to walk before you learn to fly.” Or as he wrote (Zweig, 2015), “The nonlinear response of the cochlea is of great interest. But what linear equation should be made nonlinear?” Similar to the last section, the next section initially focus upon SOAEs before moving to eOAEs in Sec.3.3.

### 3.2.4 Stochastics: Role of noise & roughness

In a broad class of biophysical problems, the notion of some form of a stochastic element crucially at play has become increasingly accepted (Bialek, 2012) and the cochlea is no exception. Randomness can be considered as arising in two different context: dynamic and static.

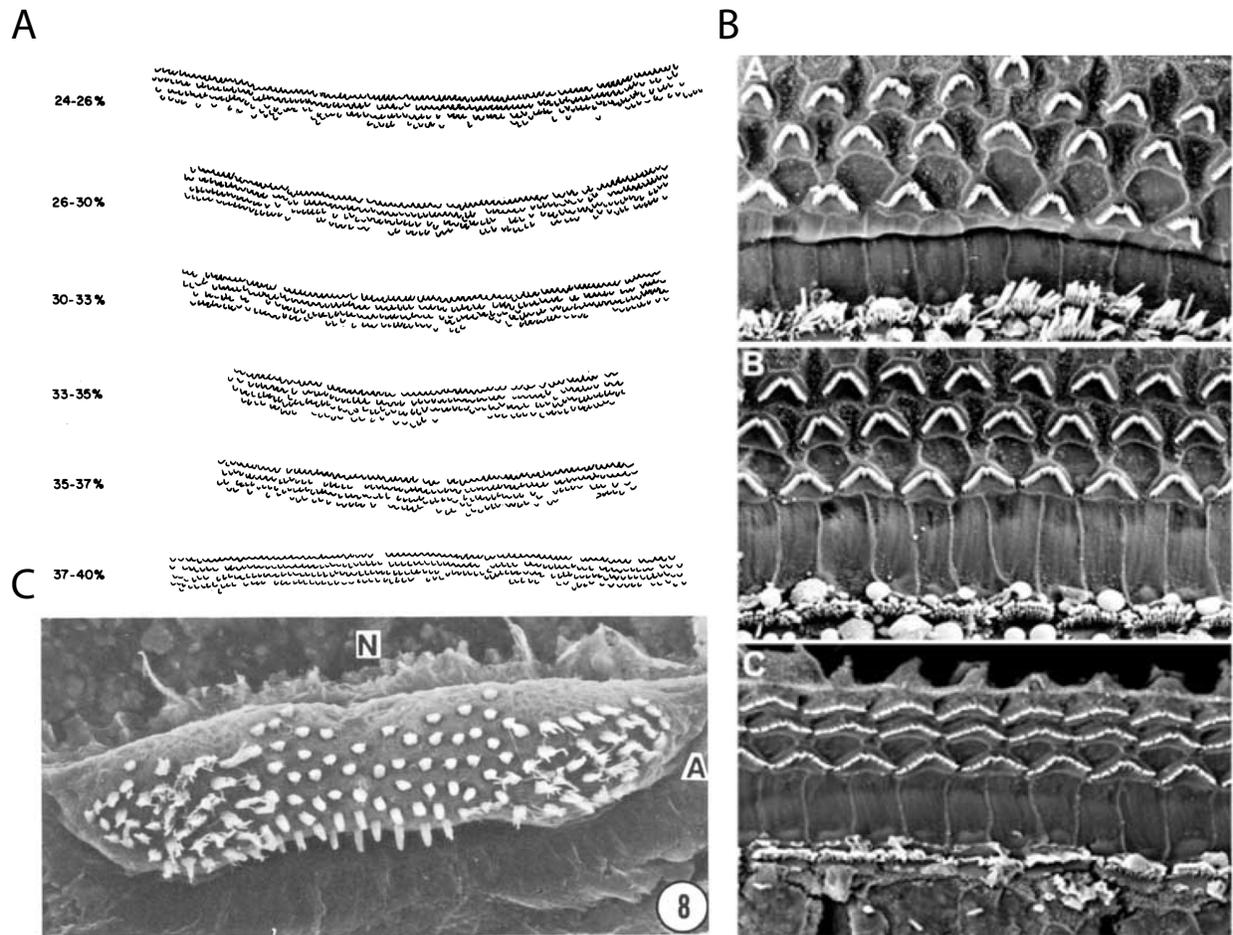
With regard to *dynamic* randomness, thermal noise is chiefly being referred to here. It is worth noting that study of hair cell bundle responses to noise have been revealing, such as the violation of the fluctuation-dissipation theorem (Duke and Jülicher, 2008; Dinis et al., 2012). Internal cochlear noise also affects responses close to threshold (van Dijk and Long, 2015). For OAE modeling, three basic considerations are important. First is the stochastic forces an individual bundle experiences. Recent work with bullfrog vestibular cells (Kozlov et al., 2012) has suggested thermal forces cause fractional Brownian motion (i.e., temporal fractal-like correlations exist, indicative of “stochastic processes with memory”). Second is similarly related, but deals with the nature of the object subjected to the noise. Depending upon the underlying potential energy configurations available, effects such as *stochastic resonance* may be at play and require consideration (Jaramillo and Wiesenfeld, 1998). Lastly is the question of how thermal forces are distributed across the oscillators. For example, how independent are the stochastic driving forces between two adjacent oscillators?

The notion of *static* randomness, commonly referred to as irregularity or “roughness”, is widely believed to play a crucial biomechanical role in OAE generation (Manley, 1983; Zweig and Shera, 1995; Mauermann et al., 1999; Epp et al., 2010). Especially when viewed through the lens that hair cells work together and OAEs are essentially an emergent phenomena from such (Shera and Guinan, 2008). Specifically, the basic idea is that given a fixed arrangement of hair cells that is unique to a given ear (Fig.5) somewhat akin to a fingerprint, this roughness affects the interactions between hair cells. For example within the context of a standing wave model for SOAE generation (Shera, 2003), SOAEs occur when the appropriate reflecting boundary condition is setup, depending upon the underlying roughness. As stated by Ku et al. (2008), “only frequencies with a traveling wave that undergoes an integer round-trip phase change between the middle ear boundary and the inhomogeneity will become unstable”. In fact, many classes of current OAE models implicitly build in some static aspect of irregularity (e.g., (Shera, 2003; Vilfan and Duke, 2008; Ku et al., 2008; Gelfand et al., 2010; Bergevin and Shera, 2010; Epp et al., 2010; Fruth et al., 2014)). How to best measure and subsequently quantify roughness is presently unclear. For example, hair cell arrangement may not be the only/chief consideration in anatomical roughness that plays a significant role. Noisiness in BM stiffness, hair cell power output, or longitudinal TM coupling could factor in. Previous studies have been stimulating (e.g., Martin et al. (1988); Lonsbury-Martin et al. (1988)), but further physiological work is desirable along these lines.

### 3.2.5 Comparing macroscopic models to SOAE data

In many cases, linear formulations of region models can be handled analytically (e.g., Zweig and Shera (1995)), but nonlinear formulations are typically only tractable numerically. By shifting away from relatively simple single-source frameworks, region models furthermore have enough degrees of freedom to produce just about any type of (desired) behavior. So the issue arises as to how to most meaningfully compare back to empirical data.

Consider for example basic question: What precisely constitutes an SOAE peak? Clearly not all “peaks” are created equal (simply look at Fig.7). Using peaks as a benchmark (e.g., *Is a peak present or not?*),



**Figure 5:** Irregularity (“roughness”) in the arrangement of hair cells. **A.** Non-human primate (Lonsbury-Martin et al., 1988). **B.** Mouse (Spiden et al., 2008). **C.** Collared lizard (Miller, 1981). All figures (NOT YET) used with permission.

some pre-existing region models (e.g., Vilfan and Duke (2008); Wit and van Dijk (2012); Fruth et al. (2014)) capture qualitative and quantitative aspects of the data. But they also fail to capture other (key) properties, such as peak width. Thus focusing primarily on peaks may be misleading, especially if the dynamics (e.g., Bialek and Wit (1984); Burns et al. (1984); Long and Tubis (1988); Shera (2003); Bergevin and Salerno (2015)) are ignored. One could thus argue the necessity of characterizing SOAE activity beyond focusing on “peaks”. For example, aspects such as “baseline” SOAE activity readily apparent in non-mammals (e.g., Manley et al. (1996)), temperature-dependence (e.g., van Dijk et al. (1989)), and SOAE interactions with external stimuli (e.g., Long and Tubis (1988); Manley et al. (1996); Bergevin et al. (2015a)) are surely revealing something crucial.

One area where progress can be made is to determine more effective ways to analyze OAE data. For example, a wide range of methodologies exist in an area broadly known as “nonlinear time series analysis” (e.g., Kantz and Schreiber (2004)) that may allow salient properties of SOAEs or SFOAEs to be more meaningfully extracted from recorded data, given inherent trade-offs between temporal and frequency resolution. Such improvements in analysis methods will provide more meaningful connections between theory and experiment. Consider that indications of chaotic behavior have also been reported (e.g., Keefe et al. (1990)), but whose implications remain unclear/unexplored.

### 3.3 Evoked emissions

The primary focus thus far has been upon SOAEs. Given that eOAEs deal with an external stimulus that “drives” the system and thereby injects energy, eOAEs are typically defined by the sounds used to evoke them (e.g., TEOAEs, SFOAEs, DPOAEs). Modeling efforts have primarily focused on several key considerations (see Shera and Guinan (2008)):

- notion of reflected energy and a coherence amongst scattering sites distributed along the BM
- distinction between “place-fixed” and “wave-fixed” mechanisms
- how energy propagates into and out of the inner ear (see also Sec.3.4)

One means by which these various notions have been described is the notion of an OAE “taxonomy” (Shera and Guinan, 1999), where emissions are classified not by the location of their generation nor the type of stimulus used to evoke them, but instead by their “generation mechanism. Within the framework proposed by Shera and Guinan, there are two primary mechanisms: coherent reflection (Zweig and Shera, 1995; Shera and Guinan, 2008) and nonlinear distortion.

As discussed in an earlier section (3.1.3), the notion of whether OAEs arise in localized spatial location or distributed over a broader region was examined. While the “single-source” model (Lukashkin et al., 2002) was argued against, the precise nature by which OAE generation is in fact “distributed” is unclear. For example, studies of SFOAE generation have argued both for (e.g., Zweig and Shera (1995); Shera and Guinan (2008)) and against (e.g., Siegel et al. (2005)) localized generation regions. Furthermore, most frameworks for characterizing DPOAE generation assume that there multiple generation sources in the cochlea, which can have different characteristics (Shera and Abdala, 2012).

#### 3.3.1 eOAE delays

One key consideration is the *delay* associated with eOAEs. That is, how long does it take for an emission to come back out relative to the stimulus being used to evoke it. This notion is somewhat akin to the delay of an echo. In some paradigms, OAEs are measured in steady-state and the delay is apparent in ripples in the probe level (as measured by the microphone in the canal) due to constructive and destructive interference (e.g., Zwicker and Schloth (1984); Manley et al. (1987); Shera and Guinan (1999); Bergevin et al. (2011c)). Another common method is via *phase-gradient* delays. That is, once the magnitude and phase of the emission have been properly extracted across frequency (and assuming the SNR is high enough and there is appropriate resolution), the slope of the unwrapped phase versus frequency (called the “phase-gradient

delay”) reveals the delay (French, 1971; Hartmann, 1998; Knight and Kemp, 2000; Bergevin, 2007; Shera et al., 2010). For linear systems, this would be equivalent to the group delay. Lastly, delays can be estimated directly in the time domain (Whitehead et al., 1996; Meenderink and Narins, 2006), which have been found to match up well to those estimates from the steady-state frequency domain.

Two additional comments related to OAE delays bear consideration. First, caution is required when correlating phase-gradient delays to actual time delays, as the generation mechanism(s) itself could confound such a relationship. For example,  $2f_1 - f_2$  DPOAE phase-gradients are small compared to those of  $2f_2 - f_1$  (Knight and Kemp, 2000; Bergevin et al., 2008). Does this mean that  $2f_1 - f_2$  comes out much faster (almost instantaneously) relative to  $2f_2 - f_1$ ? No, as time domain studies of delay have shown (e.g., Whitehead et al. (1996)). Instead this discrepancy is thought to arise due a difference in generation mechanisms (e.g., Shera and Guinan (1999, 2008)), which was discussed in Sec.3.3. Second, with this last point in mind, several studies have examined how SFOAE phase-gradient delays can be used as a proxy measure for cochlear tuning. A basic intuition for this can be provided by a freshman physics problem: a damped driven harmonic oscillator (Shera et al., 2010). When the oscillator has low damping, it is more sharply resonant (i.e., it has a stronger “preference” for frequencies close to its characteristic frequency) and sluggish (i.e., it takes a longer time to build up a steady-state response since the oscillator can store more energy, which the external drive can only put in on a cycle-by-cycle basis). This connection between delays and tuning leads us into the next section.

### 3.4 How do OAEs exit the inner ear?

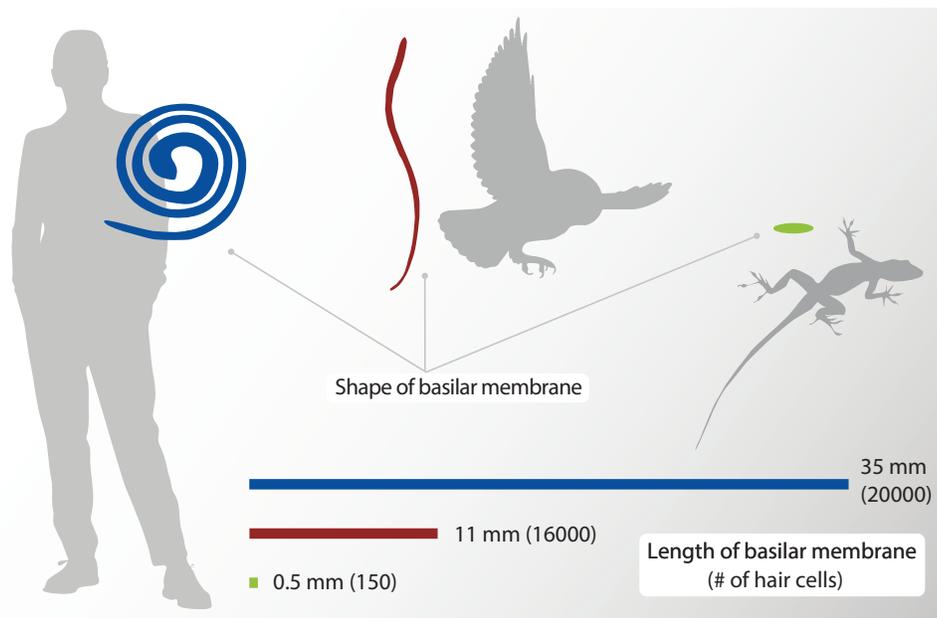
Related to Sec.3.2.2, the question regarding OAEs and waves is further highlighted by the debate how the emissions get back out of the cochlea. That is, whether OAEs propagate through the cochlea via “slow” (i.e., BM-based) or “fast” (i.e., fluid compression-based) waves (e.g., He et al. (2008); Dong and Olson (2008); Meenderink and van der Heijden (2010); He and Ren (2013)), or even as recently proposed via waves on Reissner’s membrane (RM) (Reichenbach et al., 2012). The plausibility of a RM pathway is still presently unclear, as little physiological data exists on the mechanical properties (e.g., Young’s modulus) of Reissner’s membrane (many modeling efforts consider the structure to be essentially acoustically “transparent” i.e., pressure within the scala media and scala vestibuli are in phase), nor how such waves would couple back to the stapes.

Another key consideration is that upon exiting the cochlea, OAE energy must essentially drive the middle and outer ear in “reverse”. Despite the passive gain (of upwards of 40 dB) going inwards, presumably the middle ear behaves in a reciprocal fashion (Shera and Zweig, 1993) and there is an attenuation in sound pressure going outwards. Several studies have examined this aspect, either using DPOAEs as an “intracochlear” source (Magnan et al., 1997; Dong and Olson, 2006), extracted temporal bones (Puria, 2003), or other methods (e.g., Keefe and Abdala (2007)). Detailed knowledge in this regard is crucial towards understanding the power produced by the ear in SOAE generation and attempts to relate such to individual hair cells (e.g., Manley and Gallo (1997)).

### 3.5 Pulling the pieces together

In summary, regardless of whether one is discussing SOAEs or eOAEs, a basic biomechanical picture of the ear emerges as a collection of coupled nonlinear oscillators. The precise form of the oscillators and their coupling are still open to debate (see Secs.3.2.2, 3.2.3, 3.2.4, and 3.3), but this basic theoretical framework has provided a strong foundation for current theories of OAE generation. It is noted that a recent study argued that wave-based and coupled oscillator models are not orthogonal notions (Bergevin et al., 2015a). But what common ground between model classes in fact exists remains unresolved. Consider for example: Can the standing wave-theory account for limit cycle entrainment behavior characteristics?

As motivated in Sec.1, study of OAE generation represents an intriguing *inverse problem* and provides an excellent foundation for studying a broad range of basic biophysical questions. For example, consider again the study of Thomas and Lindner (2014), which attempted to develop a meaningful definition of phase for a broad range of biologically-relevant problems (e.g., hair cells behaving as limit cycle oscillators). In a followup letter that appeared (Pikovsky, 2015), the author nicely states “The definition of the phase of



**Figure 6:** Related to Fig.7, a visual comparison of the shape and length of the basilar membrane. [graphic modified from original by Per Ruppel]

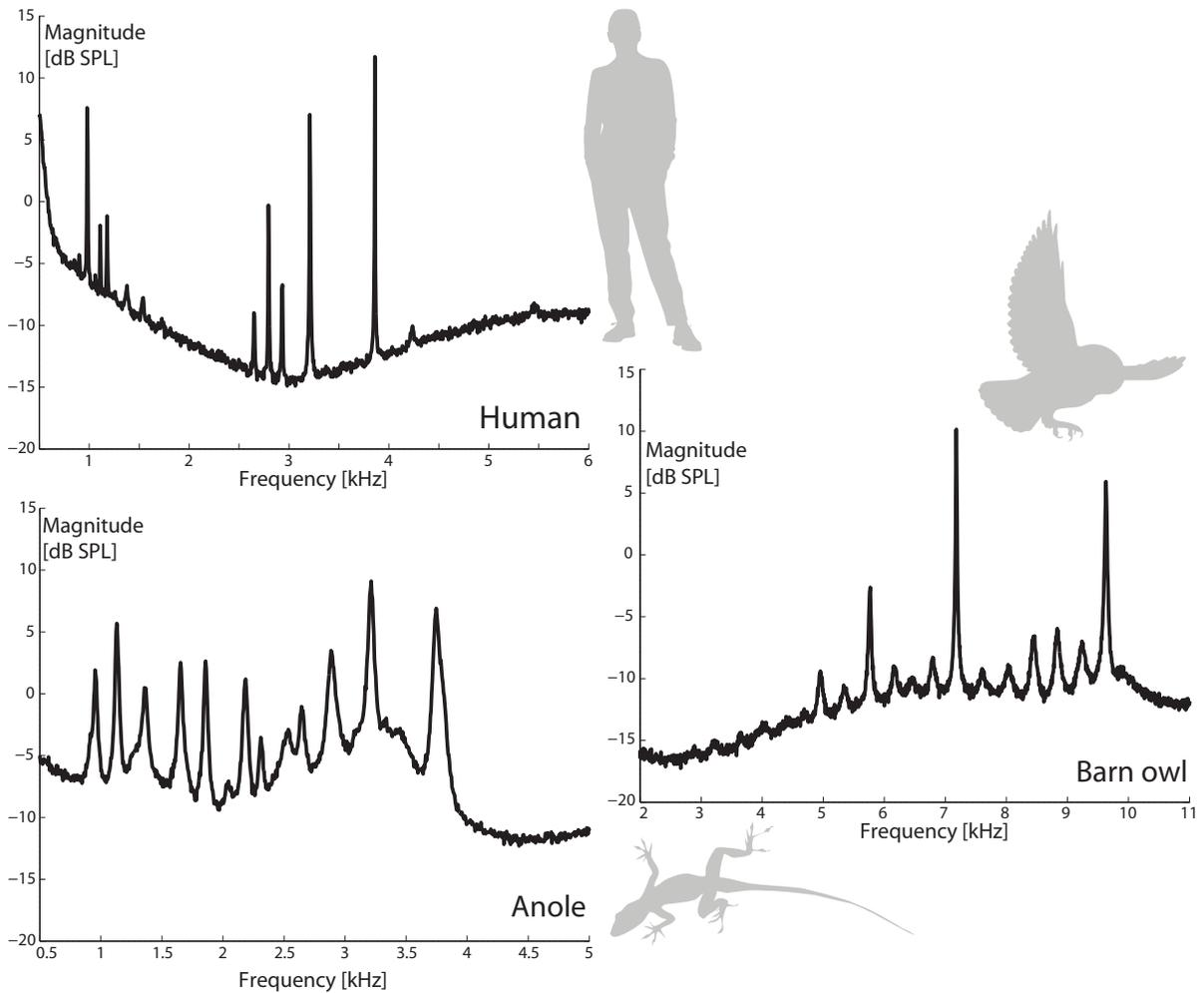
oscillations is straightforward for deterministic periodic processes but nontrivial for stochastic ones. ... The notion of the phase of periodic oscillators lies at the heart of characterization of oscillatory processes.”, which should nicely resonate (no pun intended) with any researcher studying the auditory system. The point being that OAEs (and models of such) provide an excellent “case study” (so to say) to explore these sorts of fundamental questions/concepts. Nonetheless, despite the many unresolved questions, a solid foundation for understanding OAE generation mechanisms is in place (e.g., Shera and Guinan (1999)). Looking ahead, one way to capitalize off such is next consider the universality of OAEs.

### 3.6 A “comparative” viewpoint

Since OAEs were first discovered in humans, researchers quickly realized that emissions arises in a wide variety of animals such frogs (Palmer and Wilson, 1982), lizards (Rosowski et al., 1984), and even invertebrates (Kössl and Boyan, 1998). Manley et al. (2008) provides a comprehensive review in this regard. Regardless of whether one’s interest is human cochlear mechanics or neuroethology, the general biophysical considerations laid out thus far combined with the observation that most ears produce OAEs provides an important opportunity. That is, the need for a field of study that compares and tests OAE generation models across species with different cochlear mechanical properties, thereby improving understanding of how emissions are generated and more directly link to the underlying cochlear mechanics. Another way to state this is to quote the preface to the 1993 Mechanics of Hearing proceedings (Duijhuys et al., 1993):

*“The discovery of otoacoustic emissions has played a catalytic role in the research on hair cells in general and the motility of hair cells in particular. To their originally understood role as passive transducer, we can now add their role as actuator, amplifier, range adjuster and stiffness controller. In other words, hair cells play a vital role in the mechanisms of hearing. The variability in hair cell shape and local environment, ranging from the mammalian cochlea via the basilar papilla of the bird to the lateral line organ of the fish helps us put the increasing knowledge in the right perspective.”*

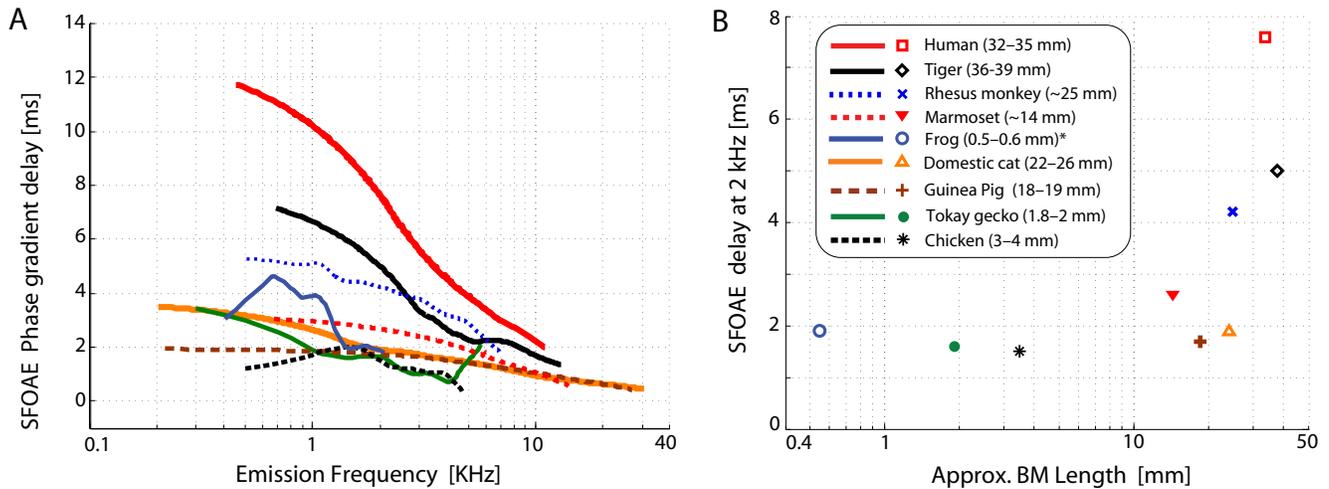
Most vertebrate ears share a common feature: stereovillar hair cells (see Sec.3.1.1). The number of such within a given ear, how they are coupled together (i.e., presence and structure of tectorial membrane), their molecular composition (e.g., density of prestin), their bundle properties (e.g., number and height of microvilli,



**Figure 7:** Comparison of SOAE activity from representative “robust” emitters from three different species (Bergevin et al., 2015a). While not included here, frogs are interesting in that they exhibit SOAEs (Palmer and Wilson, 1982; van Dijk et al., 1989) and (unlike the other species included here) their hair cells do not even sit atop a flexible BM, but rigid bone.

internal coupling), their ionic environment (e.g., effective endocochlear potential), and even the underlying substrate they are embedded in or sit atop (i.e., flexible BM, or rigid bone) can vary dramatically across taxonomic boundaries (Fig.6). Despite this, many striking similarities and differences in OAE properties emerge upon systematic comparison (e.g., Fig.7).

In terms of similarities, one recent study (Bergevin et al., 2008) indicated that the empirical basis for the wave-fixed versus place-fixed distinction (Shera and Guinan (1999); see also Sec.3.3) can be found in a wide class of ears, even those that presumably lack a BM traveling wave. A subsequent study (Bergevin et al., 2015a) examined predictions of the “standing wave” model (Shera, 2003) in non-mammalian ears and found good agreement, indicating shared properties at work in the underlying generation mechanisms. From an evolutionary point of view, whether such ultimately arose via a homology or analogy remains to be determined. In terms of differences, one distinction with respect to humans has drawn significant attention: SFOAE phase-gradient delays are relatively much longer in humans than any other species examined thus far (Fig.8). As alluded to in Sec.2.2, this difference in delay has been proposed to be indicative of relatively sharper cochlear tuning in humans (Shera et al., 2002). While initially controversial (e.g., Ruggero and Temchin (2005); Siegel et al. (2005)), subsequent investigations (Shera et al., 2010; Joris et al., 2011; Bergevin et al., 2012b) have provided further support and also account for morphological aspects such as BM length



**Figure 8:** A. Comparison of SFOAE phase-gradient delays and BM lengths for several different species (40 dB SPL probe level; same stimulus paradigm/parameters used for all). For the frog, the provided length corresponds only to the amphibian papilla. Data taken from the following: Shera and Guinan (2003); Bergevin et al. (2008, 2011b, 2012b); Joris et al. (2011). B. Mean delay at 2 kHz as a function of approximate BM length.

(e.g., Bergevin et al. (2011b, 2012b), Fig.8B). Current studies are attempting to look at tuning estimates derived from neural, otoacoustic, and psychophysical from a single species to further validate current interpretations on SFOAE delays (e.g., marmoset: Bergevin et al. (2011b), ferret: Sumner et al. (2014)). Another telling difference is that within lizards, species with continuous TM have relatively few/large SOAEs peaks while species without have many smaller peaks

In short, otoacoustics are a common property across much of the animal kingdom and there are many similarities (and differences) across groups (e.g., Bergevin (2011); Berezina-Greene and Guinan (2015)). Presumably these interrelationships, in the face of vast morphological differences, speaks to the existence of a key underlying biophysical principle(s) at work in all types of ears. At a minimum, it is clear that two distinct hair cell types, a flexible membrane, nor a tectorial membrane are a priori required for OAE generation. Such knowledge can in turn stimulate advancements in evolutionary theory about hearing (Manley, 2000). Less clear is how such aspects factor into the wave- versus place-fixed taxonomy describes earlier (e.g., Bergevin et al. (2008)). It should also be noted that SOAEs have been shown to exist in a mutant mouse model at relatively high frequencies (15–30 kHz), extending the known upper frequency range for SOAE generation mechanisms Cheatham et al. (2014). Returning to the theme posed in the introduction, another quote is provided here that can be used to summarize a comparative approach to OAEs (Bialek, 2012): *“The challenge is not to find the most important or ‘fundamental phenomenon, but rather to see through any one of many interesting and beautiful phenomena to the deep physics problems that are hiding underneath the often formidable complexity of these systems..”*

## 4 Putting OAEs to work

Having examined the mechanisms underlying generation and current models of such, this section shines light on practical aspects of OAEs and their (current/potential) use. Reader are also referred to more extensive reviews (Probst et al., 1991; Robinette and Glattke, 2007; Janssen and Muller, 2008; Lonsbury-Martin and Martin, 2008; Shera and Abdala, 2012). These studies (along with those highlighted in Secs.2.2, 3.6), which yield perspective into precisely how informative OAEs in fact are, provide salient empirical “ground truth” that helps inform and constrain theoretical models for cochlear mechanics.

## 4.1 Characterizing cochlear health: “Screening” in both scientific and clinical contexts

Given the connections highlighted in Sec.2.2, OAEs have been developed extensively as a means to probe peripheral auditory function in both scientific (e.g., *Is my genetically modified mouse deaf?*) and clinical settings (e.g., *Is this day-old baby deaf?*). For the most part, evoked OAEs are used as a proxy measure for hearing ability based upon their relative size: if the signal is above the noise floor (or some sort of pre-determined threshold), the ear is considered *normal* (or healthy). Generally, these screenings are quick and cost-effective, given their non-invasive and objective nature. However, they do require a relative absence of noise. Some salient examples include:

- Clinical hearing screening, especially in pediatric audiology – Kemp et al. (1990); Probst et al. (1991); Kennedy et al. (1991); Grewe et al. (1994); Abdala et al. (1996)
- Basic research hearing screening in humans – Dorn et al. (2001); Boege and Janssen (2002); Lopez-Poveda and Johannesen (2009)
- Basic research hearing screening in animals – Liberman et al. (2002); Cheatham et al. (2014)
- Use in veterinary diagnostics/care – McBrearty and Penderis (2011); McBrearty et al. (2012)

Note that caution is needed, as auditory neuropathies (i.e., pathologies in the neural pathway connecting the cochlea to the brain) can sometimes allow for “normal” OAEs despite hearing impairment being present (e.g., Berlin et al. (2003)). Additionally, issues stemming from middle ear dysfunction (e.g., otitis media) can affect OAEs and thereby misinform clinical diagnoses (Owens et al., 1992). In these cases, including other measurement modalities (e.g., ABR) is helpful.

An intriguing avenue of exploration is how eOAEs can be used to assess auditory function in HI-individuals. Basic comparisons between normal hearing and HI are well established (e.g., Gorga et al. (1993); Prieve et al. (1993)) and have served to provide a useful benchmark for clinical applications. But recent studies have begun to examine further aspects, such as changes associated with frequency selectivity (e.g., Gruhlke et al. (2012); Charaziak et al. (2015)), which may help with understanding difficulties associated with speech recognition in noisy environments. Another interesting avenue is pathologies “post-cochlea”, such as acoustic neuromas (Telischi et al., 1995).

Expanding upon this previous point, further studies for “translational” applications other than clinical audiological screening or OHC health include (along with references):

- Monitoring intra-cranial pressure (ICP) – de Kleine et al. (2000); Voss et al. (2006)
- Cochlear blood flow – Telischi et al. (1998); Mom et al. (1999)
- Effects of ototoxic drug exposure – Probst et al. (1993); Stavroulaki:1999 et al. (1999); Lonsbury-Martin and Martin (2001); Reavis et al. (2011)
- Efferent-related effects – Francis and Guinan (2010); Garinis et al. (2011); Boothalingam et al. (2015)
- Attention-related effects – Walsh (2012)
- SFOAEs as a measure of tuning – Shera et al. (2002); Oxenham and Shera (2003); Shera et al. (2010); Joris et al. (2011)
- DPOAEs as a measure of tuning – Abdala (1998); Lonsbury-Martin and Martin (2008)
- Basis of absolute pitch – Bergevin et al. (2015b)
- Biometric applications – (Liu and Hatzinakos, 2014)
- Assessing (forward and reverse) middle ear function – (Dalhoff et al., 2011)

- Understanding OAE differences across human groups, such as ethnic and sex disparities (Whitehead et al., 1993; McFadden and Pasanen, 1998).

One difficult obstacle in several of these potential applications is establishing an appropriate baseline (e.g., Reavis et al. (2015)). For example, what are reasonable fluctuations in OAE properties an audiologist could expect, and thereby meaningfully detect a change (e.g., due to ototoxic exposure) of significance. Another important consideration was examined by Eustaquio-Martin and Lopez-Poveda (2011), who argue that given the nonlinearity of the ear, one must be careful distinguishing between *iso-response* and *iso-input* measures. Such could affect optimal strategies for clinical OAE measurement paradigms.

## 4.2 Practical measurement aspects

### 4.2.1 How does one measure OAEs?

At the most basic level, the ingredients are: a quiet room (ideally a sound-isolation chamber), a “probe” that contains an earphone (i.e., speaker) or two and a sensitive microphone and fits into the ear canal, and a computer interface that can handle the signal processing aspects. Descriptions providing an overview of OAE measurement basics abound (e.g., Keefe (1998); Bergevin (2007); Kemp (2008); Shera and Abdala (2012)). Since basic data acquisition equipment has become so relatively cheap, it is conceivable that OAEs might become more commonly measured (e.g., via the smartphone in your pocket). One major limiting constraint though is noise. Since OAE responses are small, unless you are measuring an eOAE with a high-level stimulus, it is likely that noise will mask any emission. Obvious sources are background noise that arises acoustically (e.g., the sound of the air-handling system in the room) or electrically (e.g., AC line noise), “internal” noise (e.g., electronics of the microphone, physiological noise of the subject such as coughing or clenching teeth, and artifacts (e.g., electrical cross-talk in the probe, nonlinearities of the speaker). Typically, a significant fraction of time is put into identifying and reducing noise sources, though “artifact rejection” algorithms can help substantially here (e.g., Shera and Guinan (1999)).

Another key consideration is calibration. That is, one wants to know precisely the sound pressure levels they present/measure. A key first step is to calibrate your microphone via a known sound source (e.g., a pistonphone) and ensure the frequency response is known. Many manufacturers strive to make microphones have a “flat frequency response” (i.e., varies no more than a few decibels across the relevant frequency range), which helps significantly with set up. Typically, earphones are calibrated in situ when coupled to a given ear. This can be done rapidly using a noise stimulus. Ideally one gives consideration to account for is standing wave interference in the ear canal (e.g., Siegel (1994)). Basically, the OAE probe is measuring pressure closer to the entrance of the canal rather than at the TyM. Because of the potential for standing waves (especially about 4 kHz in adults, given the relevant distances), careful consideration is needed. Several strategies have been reported to deal with this effect (e.g., Siegel (1994); Scheperle et al. (2008); ?).

### 4.2.2 Stimulus types

The first measures of OAEs reported were evoked by a click (Kemp, 1978), where the resulting emission appeared as an “echo”. Subsequently, various sorts of stimuli were used that included a single tone, two tones, and tone bursts (or none at all!) (Zwicker and Schloth, 1984). Since then, a wider variety of stimulus types have been explored, including: noise (Maat et al., 2000), chirps (e.g., (Neumann et al., 1994; Keefe, 1998), multi-tone complexes (“zwuis”) (Meenderink and van der Heijden, 2011), and swept tones (we will return to this in a moment). As noted earlier, eOAEs do not a priori require an acoustic stimulus and can be evoked electrically (Xue et al., 1993; Ren and Nuttall, 1996; He and Ren, 2013).

As discussed in Sec.3.2.3, given the nonlinear nature of the cochlea, one key consideration is whether narrow- and wide-band stimuli yield similar responses. While further study is needed, at least at lower levels there appears a “near equivalence” between the two (Kalluri and Shera, 2007b), suggestive of a degree of linearity. For narrowband stimuli (e.g., tones), presentation is usually stepped across frequency in discrete steps. As has become apparent through studies of DPOAE fine structure and SFOAE phase-gradient delays

(see Sec.3.3.1), having sufficient frequency resolution is important. One relatively recent development is the use quasi-narrowband stimuli, such as swept-tones and chirps (Long et al., 2008; Bennett and Ozdamar, 2010; Kalluri and Shera, 2013; Chen et al., 2013), which have the advantage of providing a relatively rapid measure across a broad frequency range yet maintain a suitable SNR (over, say, a click).

### 4.2.3 Extracting eOAEs

Since eOAEs tend to be small, at face value, it is a challenge to separate the emission from the stimulus being used to evoke it. Especially when one factors in the acoustics of the coupling space and (inevitable) nonlinearities of the sound source. Numerous strategies have been successfully developed (e.g., Guinan (1990); Wit et al. (1994); Tognola et al. (1998); Shera and Guinan (1999); Jędrzejczak et al. (2004); Kalluri and Shera (2007a); Vetesník et al. (2009); Keefe (2012)). Note that while OAEs are predominantly measured acoustically in the canal, several studies have examined other means of detection: vibration patterns (via LDV) on the tympanic membrane (e.g., Dalhoff et al. (2007); Turcanu et al. (2009); Dalhoff et al. (2011)), intracochlear fluid pressure (e.g., Avan et al. (1998); Dong and Cooper (2006)), and intracochlear BM vibration (via LDV) (e.g., Nuttall et al. (2004); Shera and Cooper (2013)). As motivated in the introduction, these observations form an important component of “ground truth” for OAE studies. Note that Sec.3.3.1 provides an overview of how to determine delays associated with eOAEs.

## 5 Looking ahead: What is next in terms of ‘remote sensing’ of the cochlea?

This chapter began by highlighting several functional aspects of the cochlea, which subsequently served to motivate several salient questions as to how such is ultimately achieved. The bulk of the narrative then developed some basic biophysical considerations and highlighted a fraction of the research literature that has attempted to address these questions, to varying degrees of success. This chapter ends on a note looking further ahead, by drawing attention to several open areas of otoacoustic-related research:

- What sort of collective dynamics might emerge from the “system” (given the nonlinear nature of the underlying hair cells)? Put another way, how is the cochlea as a whole different/more than the sum of its parts? Presumably statistical mechanics will play an important role in this regard, bridging micro- and macro-*s*copic model formulations.
- Can OAEs be used to clarify the role that viscous forces of the inner ear fluids play? While a single hair bundle is presumably subject to a low Reynold’s number environment, perhaps their collective behavior can cause a net decrease in the relevant frictional forces (in a fashion similar to motile bacteria, e.g., Lopez et al. (2015)).
- While many aspects of cochlear function are linear-ish, the overall behavior is very nonlinear (e.g., compression is a fundamental means of operation!). Thus as motivated by Ku et al. (2008): How does the cochlea behave in such a relatively linear fashion when it is so inherently nonlinear in terms of its basic building blocks?
- The existence of SOAEs suggest that the cochlea is close to an instability (though see also Zweig (2003)), but obviously show the system is ultimately stable. However, many classes of (active) cochlear models have difficulty producing SOAE patterns with stability comparable to what is seen physiologically. Why? Put another way, what aspects of cochlear function allow it to be quasi-stable?
- What is the biophysical basis for the general frequency stability of SOAEs, even after exposure to moderate sounds? Or frequency-dependent changes with temperature?
- Using OAEs as a means to quantitatively estimate power associated with hair cell output. At least one previous study has examined this notion (Manley and Gallo, 1997), but the problem is a difficult

one as the effective “collective” response is unknown, as is the effective impedance the generators “see looking back out”.

- Potential biometric uses of OAEs
- Elucidating level dependence of eOAE phase-gradient delays (e.g., at low stimulus levels, do they become level-independent?) and the implications for linearity and tuning
- Idiosyncrasy of SOAEs: Why don’t all ears emit SOAEs, despite common sensitivity thresholds? Why do some species exhibit robust SOAE activity than others? What is this telling us about the notion of “irregularity”? How might we best quantify cochlear roughness and correlate such to OAEs? How level-dependent is the role of irregularity and what does such tell us?
- Reconciling how a vast array of morphologies (including invertebrate ears) give rise to OAEs, let alone ones with similar properties. How do various morphological (e.g., BM length, number of hair cells) and functional aspects (e.g., number of octaves spanned in audiogram, tuning) interrelated?
- Are there optimal strategies for combining otoacoustics with advancements in intra-cochlear imaging (e.g., optical coherence tomography)?
- Aside from producing knock-out/in animal models, how might the power of molecular biology be combined with otoacoustic measures? For example, motivated by the *photoinactivation* used by Fisher et al. (2012), could one conceivably develop an “OAE-activation” framework for intracochlear (fluorescent?) imaging?
- Are further improvements in microphone technology possible (e.g., further reduction in the noise floor)?
- Can OAEs be used not only to objectively estimate an individual’s sensitivity, but also their selectivity? How might OAEs be more effectively used in HI-individuals in this regard?
- A recent study has argued for a “staircase”-like structure to the individual ears tonotopic map, such that extended spatial regions effectively share the same characteristic frequency (Shera, 2015). In what ways might such be related/connected to the argument that “frequency clusters” in (nearest-neighbor) coupled oscillator models underly SOAE generation (Vilfan and Duke, 2008; Wit and van Dijk, 2012)?
- “Suppression tuning curves” for SOAEs have been demonstrated to match remarkably well to ANF responses in lizards (e.g., Koppl and Manley (1994)). Detailed study of such remains to be done for mammals. Could SOAE suppression (or in turn, entrainment) provide a useful measure of cochlear tuning in humans?

We end here by quoting the final sentence in Kemp’s landmark 1978 paper (Kemp, 1978): *“If proven it [i.e., the hypothesis that OAEs are generated by normal cochlear function] would provide a new insight into the microscopic behavior of the cochlear transduction mechanism which is not adequately understood.”* Kemp was certainly correct (although his discovery yielded much more than just “a new insight”), despite the fact that we ultimately still have a long way to go.....

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