Hopf Bifurcations and Hair Cells

M. Ospeck[1], V.M. Eguíluz[2], M.O. Margnasco[3]
[1]*Biophysics Section, Laboratory of Cellular Biology,*
National Institute on Deafness and Other Communication Disorders,
National Institutes of Health, Bethesda, Maryland 20892-0922 USA
[2]*Departamento de Física, Universidad de las Islas Baleares* and
Instituto Mediterráneo de Estudios Avanzados IMEDEA (CSIC-UIB)
E07071 Palma de Mallorca, Spain
[3]*The Rockefeller University, New York, New York 10021 USA*

January 9, 2002

Abstract

The Hopf bifurcation is the dynamical instability which occurs in a feedback amplifier as the positive feedback is increased to the point where the system starts to oscillate spontaneously. The howl heard in a public address system when the presenter moves so the microphone gets too close to the loudspeaker is an example of increased positive feedback leading to oscillatory behaviour through a Hopf bifurcation.

Hair cells are the sensory cells responsible for hearing and balance; they contain mechanosensitive transducer channels that convert mechanical vibration into an oscillation of their membrane potential. In many hair cells the membrane potential sinusoidally oscillates at small amplitude without input; their input-output transfer function has a large gain for small input and a reduced gain for larger inputs. These and other features are easily explained if hair cells are poised at a Hopf bifurcation.

An amplifier poised at the Hopf bifurcation will have a compressively-nonlinear transfer function and also infinitely sharp tuning for vanishingly small input. The cube-root shape of its transfer function provides for an extraordinarily large gain for a small input signal at the natural frequency and a reduced gain for larger inputs. Moreover, any biosensor for detecting periodic signals of any sort would enjoy these great advantages by employing this commonly occurring instability.

Key Words: *dynamic instability, hearing, biological amplifier*

The classic Helmholtz theory (1) posits that our hearing organ, the cochlea, is arranged like a harp or the backplane of a piano, with a number of highly tuned elements arrayed along a frequency scale, performing Fourier analysis of the incoming sound. This found strong support in Von Békésy's classic measurements (2) which demonstrated the mapping of sound frequencies to positions along the cochlea. Von Békésy observed the tuning to be quite shallow and found cochlear responses to behave linearly over the range of physiologically relevant sound intensities. His hypothesis was that a coarse mechanical tuning was to be followed by a "second filter," whose nature was surmised to be electrical. However, Von Békésy had performed his measurements on cadavers, whose dead cochleas lacked power sources or amplifiers that might have provided positive feedback.

Rhodes' pionnering work in Mössbauer velocimetry in live monkey cochleas (3),and, more recently, laser-interferometric velocimetry performed on live and reasonably intact cochleas has led to a very different picture (4; 5). There is, in fact, sharp mechanical tuning in a live cochlea, but it is *essentially nonlinear*, there being strong nonlinearities for amplitudes as small as the neural threshold. Only below neural threshold are linear responses recovered. Observation of the essential nonlinearity of the response at the level of cochlear mechanics contradicted von Békésy's finding. Also because it disappeared when the cochlea's ionic gradient was temporarily disturbed, it depended on a biological power supply(6).

Soon after having worked with Fred Hoyle on the Steady-State model of the universe, Thomas Gold began work on hearing, writing two papers in 1948 which came well ahead of their time (7; 8). In them he recognized that dissipation of the ear's internal vibrationis had to be large due to viscous damping by water, though the ear's performance strikingly appeared as if it was unaffected by such damping. A tuning fork "rings" maybe five thousand times when struck in air, though not much at all when struck in water. Gold resolved the contradiction by concluding that the ear must have a feedback amplifier that cancels the effect of viscous drag. He further went on to predict that the ear could sometimes have too much feedback gain and emit sound. At the time this was thought to be nonsensical and a strong point against his theories; much later, the discovery of spontaneous otoacoustic emissions would vindicate Gold's point of view (9). (There was in fact a case of a dog who's ears emitted a tone of about 50 dB SPL, i.e., having a conversational volume.) Recently these emissions have been found to be relaxation oscillations (10).

It is now known that the source of the ear's amplification are the hair cells; later on we'll discuss three distinct kinds of amplifiers known to exist inside different kinds of hair cells. Each amplifier can be poised close to a dynamical instability and ring spontaneously. Intuitively, when so poised, such a cell will respond with a very large gain to a small input signal at its natural frequency. In dynamical systems language, we would say that Gold's theory asserts that the elements of the hearing organ somehow poise themselves at a Hopf bifurcation, like a sound technician adjusting the volume of an amplifier to the loudest possible setting before feedback oscillation ensues (11). We shall show that at a Hopf bifurcation we generically expect essential nonlinearities, compression of dynamic range, sharp tuning for soft input, and broad tuning for loud input. In essence, many of the nonlinear aspects of hearing may stem from the Hopf bifurcation.

WHAT HAIR CELLS DO

In the clearly unbiased opinion of the authors, hair cells are probably among the prettiest cells; at the top of each there is an organelle shaped like an array of organ pipes called the hair bundle (Fig. 1A). The bundle is composed of stereocilia containing polymerized and cross-linked actin fibers which makes them into a stiff group of parallel cilia (12). Mechanosensitive channels lie at their tips and these are connected by fine *tip links* to the other cilia (13). Deflecting the bundle towards its tall end opens these channels and admits a positive current, mostly of K^+, into the cell. For a long time hair cells were thought to be sensitive transducers converting mechanical vibration into an electrical signal. Other sensory neurons are such transducers with their high sensitivity deriving from active processes at the cellular level. Unique though among sensory transducers, hair cells are in fact feedback amplifiers, charged with emitting as well as receiving, since they can exert forces back onto the structure that houses them.

Take the mammalian ear as an example (Fig. 1B). Sound waves from the eardrum

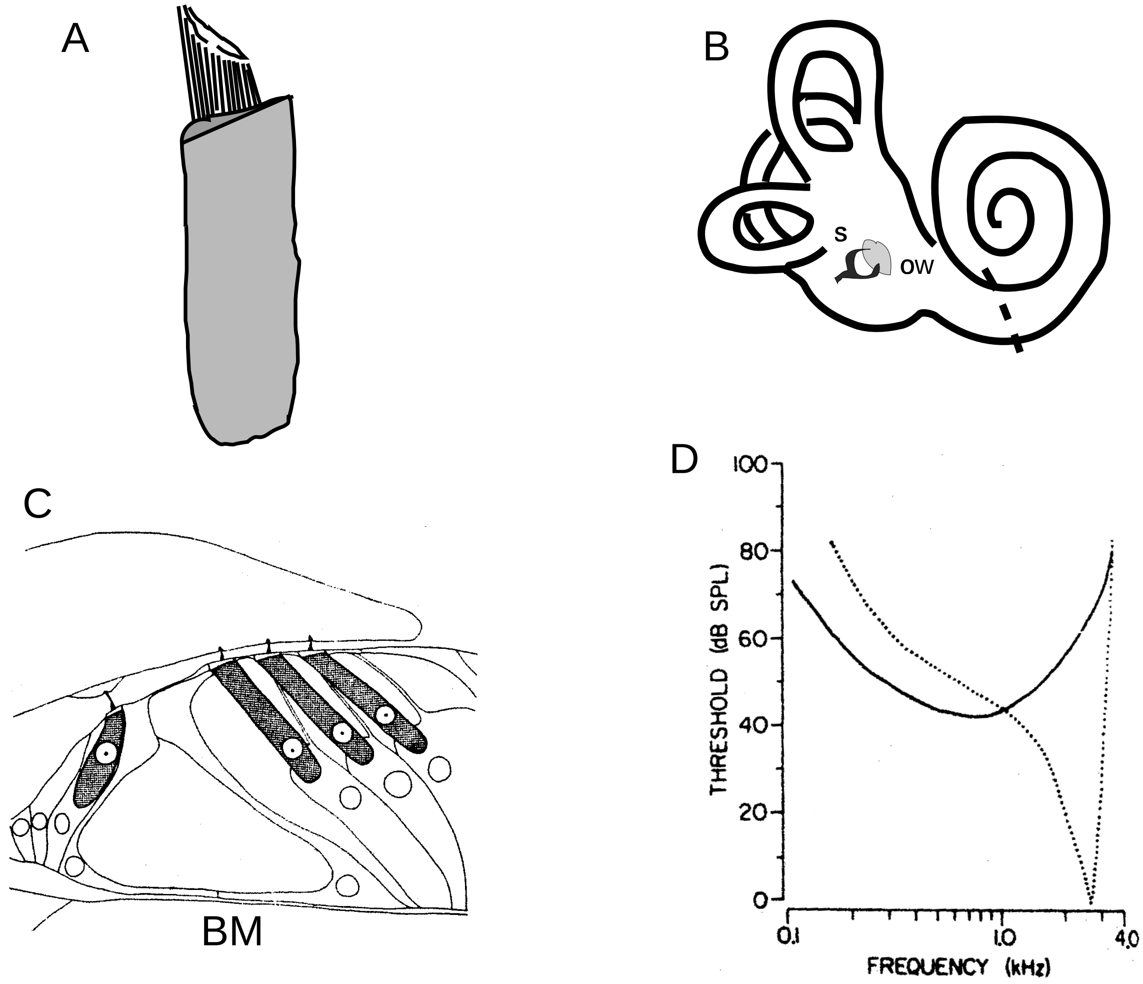

Figure 1: A: Hair cell with a stiff hair bundle of stereocilia at its top. Fine tip links between the individual stereocilia gate mechanosensitive channels when the bundle is deflected towards its tall end. B: Snail-shaped mammalian cochlea. Sound enters via the stirrup bone *s* coupled to the oval window *ow* at its high-frequency end. Dashed line is through a cross-section at the high-frequency end. C: Four hair cells in such a cochlear cross-section. Three outer hair cells at right amplify wave energy travelling into the figure and along the cochlea's basilar membrane BM. A single inner hair cell at left transforms the mechanical oscillation of its hair bundle into a nerve impulse going to the brain. D: A cochlear tuning curve (dotted line) shows high sensitivity and sharp frequency selectivity, both of which are lost when the outer hair cells are damaged (solid line) (C and D Courtesy of Liberman) (14). Note that 0 dB SPL amounts to a mechanical displacement on the order of 1 nm.

drive a membrane on the cochlea called the oval window, sound entering at the cochlea's high-frequency end. At each cross-section of the snail-shaped cochlea four hair cells are tuned to approximately the same frequency (Fig. 1C). These cross-sections are arranged in an order so that the high frequency waves are the first to be "picked off". Note that the cochlea is an unusual "backwards" wave guide, first picking off, or cutting off the propagation of high, rather than low, frequency waves along its basilar membrane. The reason for this is simple: it's as if each cochlear cross-section contained a band-pass filter actively sucking up wave energy at a particular frequency.

In a cochlear cross-section there are two distinct kinds of hair cells. A single flask-shaped *inner hair cell* picks off wave energy and transforms the mechanical oscillation of its hair bundle into a voltage oscillation and then via calcium into a nerve impulse propagating to the brain via an afferent (inward) fibre of the 8th nerve. Each cross-section also contains three rows of cylindrically-shaped *outer hair cells* whose job is to amplify the basilar membrane's wave energy at a specific frequency. Outer hair cells are mostly innervated by efferent (outward) nerve fibres so that they don't appear to be sending signals to the brain. Rather in the mammalian cochlea we seem to have a division of labor where inner hair cells suck up wave energy and send signals to the brain, while the outer hair cells amplify the energy in the wave. Indeed if one's outer hair cells are lost then one could still hear, although sensitivity and frequency selectivity would pretty much disappear (Fig. 1D) (14).

Figure 1D shows a so-called *tuning curve* . Here it plots the stimulus intensity input into the ear drum at a given frequency in order to obtain the minimal amount of firing of a nerve fibre at "its" threshold of hearing. Below this threshold noise would drive the firing of the fibre. If instead we "inverted" this tuning curve—plotting the output for a constant amplitude input as we swept the frequency—there would appear a resonance peak.

Resonance peaks are judged in terms of their quality Q, which is the number of radians until the wave's energy decays by e^{-1} —giving the "ringiness" of the resonance. Another way to get the Q is to divide the natural frequency of the resonance by its full width at half maximum power (Fig. 2). "Ringy" resonance peaks can be due to a passive oscillator like a tuning fork in air, but in the aqueous environment of

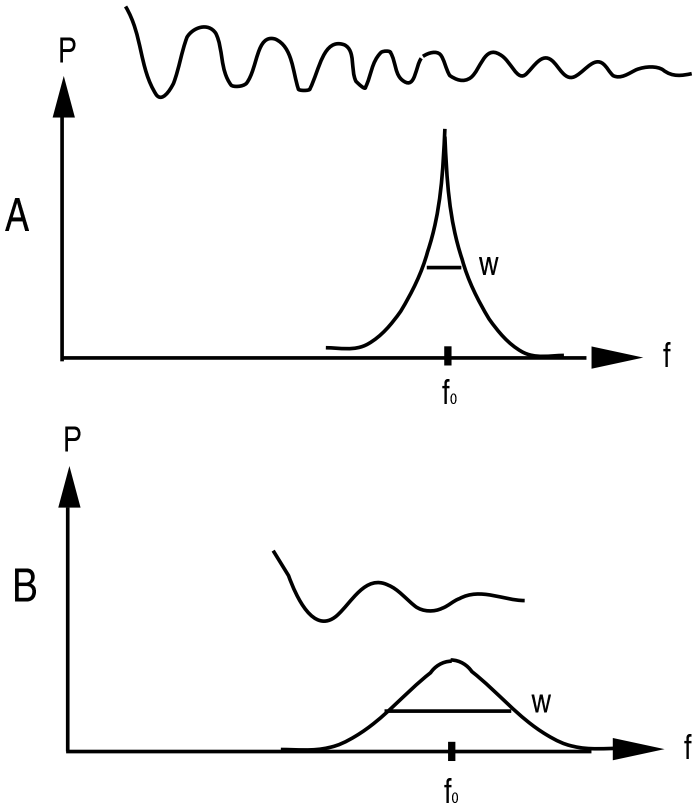

Figure 2: A: Power versus frequency plot for a moderately high-Q filter peak. w is the peak's full width at half maximum power. Here $Q = \frac{f_0}{w} \approx 10$ meaning that after exciting the oscillator with an impulse its energy will drop by e^{-1} after about 10 radians, or 2.4 cycles of oscillation. B: A lower-Q resonance is less "ringy" and has less sharp frequency selectivity.

the cochlea the oscillator must be active and have an energy source. Such a high-Q amplifier with a pointy peak is desirable because it provides a large gain only for one specific frequency—it combines sensitivity with selectivity. The mammalian cochlea appears to be a filter bank made up of a long line of high-Q active filters. At the heart of these high-Q filters are the hair cells, outers doing the amplifying work and inners as the pickups sending nerve impulses to the brain in separate frequency "channels".

The really pretty part about the whole business is that the amplifiers inside the cochlea figured out an easy way to give an enormous gain to weak signals and at the same time to turn off gain when the input signal got large. They did this by poising on a Hopf bifurcation.

WHAT A HOPF BIFURCATION IS

AN INTRODUCTION TO DYNAMICAL SYSTEMS

At the turn of the 19th century, Henri Poincaré founded, pretty much in the same stroke, both topology and the qualitative theory of dynamical systems, two mathematical disciplines that have been closely interwoven ever since. Topology studies mathematical objects, like surfaces, by abstracting away every smooth deformation possible and keeping only that which cannot be done smoothly. In this way the details of the shape of a surface vanish, so that a soccer and a rugby ball are topologically identical; only relevant to topology is the way things are assembled together, since these cannot be changed smoothly. The surface of a doughnut cannot be smoothly changed into a sphere.

Similarly, when studying dynamical systems, it is observed that the qualitative behaviour of a system changes abruptly as a function of external parameters. Pushing furniture on a rug results in no motion at all for small forces, and an abrupt jump at a particular force; blowing on a sax results in a hiss for small blowing pressures, and a note appears abruptly as one increases air flow. Such abrupt transitions are called *bifurcations.* Just like the topology of surfaces cannot be changed smoothly, so that surfaces can be classified into discrete numbers, bifurcations can be classified into distinct classes.

So the theory of dynamical systems provides tools that can help us to understand complex dynamics from this very general perspective. In particular the concept of bifurcation is very useful because any system close to the same bifurcation is described by the same set of equations, called *normal forms.* Just like a sphere is, topologically, a model for all balls, soccer or rugby, normal forms provide models of transitions and instabilities that occur as some *control parameter* is varied, and any system making the transition can be "deformed smoothly" onto the normal form.

Before describing further what a bifurcation is it is convenient to introduce the concept of *phase space.* Phase space allows for easy representation of the evolution of the state variables of a system. One simple example is given by a pendulum with friction. In its phase space its angular position is plotted on the x-axis and the derivative of the angular position is plotted on the y-axis. If you push the pendulum off the vertical it will start swinging until it eventually stops—its phase space trajectory will be an inward spiral to the origin, i.e. towards zero displacement and zero velocity.

In general, the state of a system depends on the control parameters. Everybody has experienced the following situation when cooking. If you have a pot full of water and start heating it slowly, you will see that initially the water stays quiet without apparent movement, up to the moment when it starts moving violently. This is a bifurcation: qualitative changes in the dynamics of a dynamical system as a control parameter, in this case temperature, is varied. The parameter values at which they occur are called bifurcation points. One of the most common bifurcations observed is the so-called *Hopf bifurcation* (15). Below this bifurcation point, small disturbances decay to equilibrium after ringing for a while. If the decay becomes slower until it finally changes to growth at a critical value of the control parameter then the equilibrium state will lose its stability. In many cases the resulting motion, above the bifurcation point, is a small-amplitude, *limit-cycle* oscillation about the former fixed point. A simple set of differential equations describing this bifurcation is given by

$$\dot{r} = \mu r - r^3 \tag{1}$$

$$\dot{\theta} = \omega_0 \tag{2}$$

where r is the radial position, θ is the angular position, and μ is the control parameter. Sometimes a term that takes into account the dependence of frequency versus amplitude can be added (usually of the form $-br^2$). For $\mu < 0$ the system's fixed point *attractor* is given by $r_f = 0$ and its phase-space trajectories are inward spirals towards this attractor. However, for $\mu > 0$ the fixed point is unstable and small perturbations around the position $r = 0$ let the system escape from it. After leaving the neighborhood of $r = 0$ what does the system do? A close inspection of the equations indicates that $r_{lc}^2 = \mu$ is a new solution for $\mu > 0$. This solution corresponds to an oscillatory behavior with amplitude r_{lc}, and angular velocity ω_0.

When changing the control parameter from $\mu < 0$ to $\mu > 0$ the state of the system can be described by Figure 3. Initially the system will be at rest. As soon as the control parameter exceeds the transition point $\mu_H = 0$, the fixed point solution is no longer stable and a small amount of noise will make the system depart from it and wrap onto a limit-cycle attractor whose amplitude grows as the square root of the difference between the control parameter and its threshold value. This is the signature of a Hopf bifurcation (15).

More technically, a Hopf bifurcation can be described in terms of eigenvalues of the linearization about the fixed point solution. Writing Equations 1 and 2 in Cartesian coordinates

$$\dot{x} = \mu x - \omega_0 y - (x^2 + y^2)x \tag{3}$$

$$\dot{y} = \omega_0 x + \mu y - (x^2 + y^2)y \tag{4}$$

the Jacobian of the linearization around the fixed point $r_f = 0$ has eigenvalues $\lambda = \mu \pm i\omega_0$. The real part of the eigenvalues indicates the stability of the fixed point under consideration: If it's negative perturbations die out and the fixed point is stable, whereas if it's positive perturbations will grow. The eigenvalues cross the imaginary axis as μ increases from negative to positive values. In a Hopf bifurcation a pair of complex conjugate eigenvalues change their real part from negative to positive, while their imaginary part gives the angular frequency.

It is also important to consider the temporal response of the system. How fast does the system adapt to the asymptotic state, or attractor, after a perturbation. It's easy to see that μ sets the characteristic time scale so that amplitude relaxes to equilibrium as $e^{\mu t}$. Thus, far from the bifurcation the decay is very fast. However as we approach the bifurcation μ becomes small and the relaxation slows down.

FORCING

In the following we study the response of a system close to a Hopf bifurcation subjected to a periodic forcing. A generic equation describing a forced Hopf bifurcation

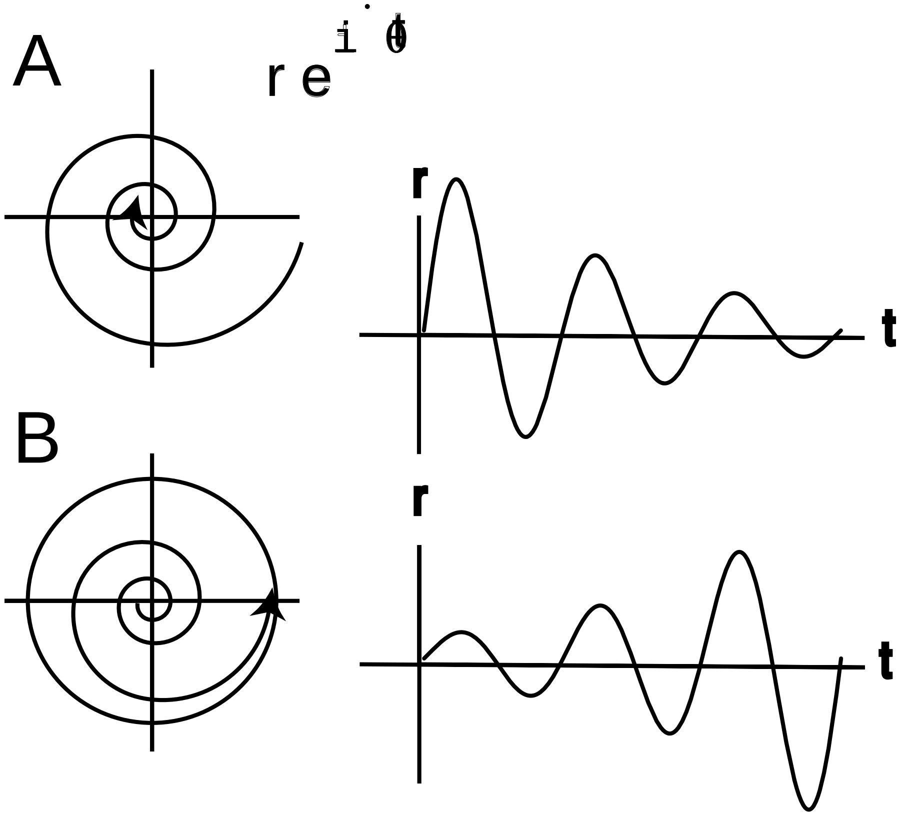

Figure 3: Canonical supercritical Hopf bifurcation for the system described by Equations 1 and 2. A: The dynamical system spirals in towards a fixed point attractor when the control parameter μ is less than zero. B: The system spirals away from the now-repelling fixed point and toward a stable limit-cycle attractor when μ is greater than zero. A Hopf bifurcation occurs when $\mu = 0$, and this is also where the system is most unstable to perturbation, and therefore the most sensitive.

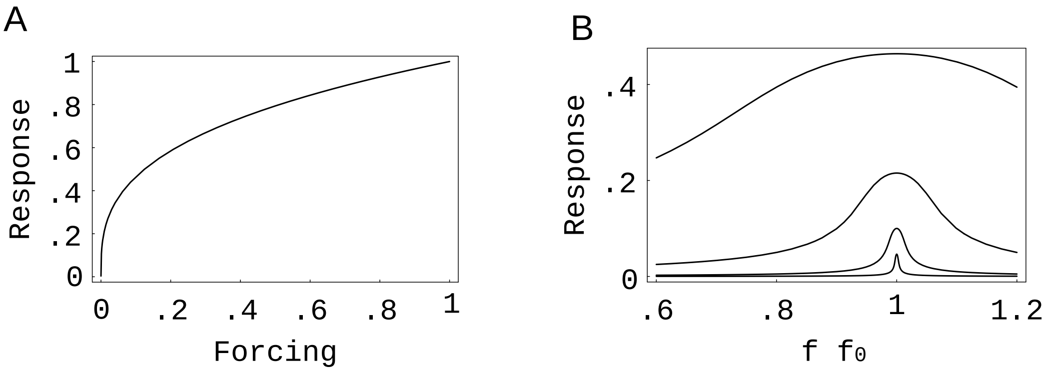

Figure 4: A: A cube-root shaped transfer function showing the response when forcing a system poised on a dynamical instability called a Hopf bifurcation at its natural frequency. Slope gain is infinite for vanishingly small input. B: The frequency response to different levels of forcing (F = .0001, .001, .01, .1) is shown going like Equation 6. The Hopf resonance becomes infinitely sharp for vanishingly small input at the point where the system begins to spontaneously oscillate (called the bifurcation).

can be written

$$\dot{z} = (\mu + i\omega_o)z - |z|^2 z + Fe^{i\omega t} \ , \tag{5}$$

where $z(t)$ is a complex variable of time, ω_0 is the natural frequency of oscillation, μ is the control parameter, F the amplitude of the external periodic forcing and ω its frequency (16). Please note that in order to recover Equations 1 and 2 we have to write $z = re^{i\theta}$. For the spontaneously oscillating system a variety of entrainment behaviors occur. Assuming a 1:1 locked solution, the frequency of the system is the same as that of the external forcing and we obtain at the bifurcation

$$F^2 = R^6 + (\omega - \omega_o)^2 R^2 \tag{6}$$

where $z = Re^{i\omega t + i\phi}$. Figure 4 shows that on resonance, no matter how small the forcing F might be, the response is nonlinear, $R = F^{1/3}$. It's worth noting that the differential amplification $\frac{dR}{dF}$ blows up like $F^{-2/3}$ at small forcing. Off resonance, for small F, the system's transfer function is linear $R \approx F/|\omega - \omega_o|$.

The width of the resonance depends on the amplitude of the forcing. Defining the half-width Γ of the resonance as the range in ω where response R falls by one-half, one obtains

$$\Gamma = \frac{3\sqrt{7}}{4} F^{2/3} \ . \tag{7}$$

The softest of forcings elicits a nonlinear response when the control parameter lies exactly at the bifurcation. What if the control parameter is not poised exactly at the bifurcation? Near the bifurcation there is a linear regime for soft sounds; how soft they need to be depends upon proximity to the bifurcation. At resonance in the sub-bifurcation regime, as $F \to 0$, $R \to -F/\mu$ and the amplification for infinitesimally small soft sounds is $-1/\mu$. Nonlinear compressibility starts to be observed when $F > (-\mu)^{2/3}$. Note that in the linear-regime amplification is proportional to the integration time $\frac{1}{\mu}$ given by the exponential in the absence of forcing.

COUPLED HOPF OSCILLATORS IN A WAVE GUIDE

Cochlear velocimetry data can be reproduced by an oscillator close to a Hopf bifurcation. Compression of the dynamic range, infinitely sharp tuning at zero input, and the generation of combination tones are naturally recovered by poising on this common instability (16; 17; 18) . This suggests that "inside the cochlea" there is a technician adjusting the control parameters of both hair cells and neurons in order for the cochlea to operate exactly at a Hopf bifurcation.

Even though this simple dynamical instability is capable of capturing essential features of hearing, there are still intriguing open questions. For example, although tuning curves obtained from an oscillator close to a Hopf bifurcation resemble those obtained empirically from the cochlea, they present some differences. Most evident is the universal asymmetry observed in the cochlear tuning curves: the slope for frequencies below the natural frequency is much less steep than for frequecies above it who present a very sharp slope (Figs. 1D and 5). This contrasts with Figure 4's depiction of the filter characteristics of a Hopf bifurcation, whose tuning curves are symmetric and more slowly increasing near the natural frequency. Although a more general form of Equation 2 can introduce some asymmetry in the response, it is very unlikely that this is the responsible for such a sharp increase. Is it possible to modify the dynamical system to account for this asymmetry?

We recall the main asymmetry of the cochlea: sound waves travel along the cochlea's basilar membrane from its high to low frequency regions (19). Hair cells located closer to the base of the cochlea have a high natural frequency, whereas those located in its appex have a low natural frequency. Consider an intermediate position: frequency components higher than the natural frequency of this particular filter have already been nonlinearly amplified by their corresponding outer hair cells and the resulting wave energies absorbed by resonant inner hair cells. However, lower frequency components are still unaltered at this position, so that the cochlear tuning curve's low frequency arm agrees well with that of a Hopf bifurcation. A bank of Hopf filters distributed along a wave guide in a way that cuts off high frequencies will likely be able to account for the shape of the cochlear tuning curve.

BIOPHYSICAL SYSTEMS UNDERLYING A HOPF BIFURCATION IN HAIR CELLS

We've just seen that poising on a Hopf bifurcation gives an amplifier an enormous small-signal gain. Consider a hair cell poised slightly above the bifurcation and spontaneously oscillating. Its control parameters have been adjusted for too much gain, i.e. the amplifier has too much positive feedback. Here we'll look at three different hair cell amplifiers and show in each case how increased positive feedback leads them to spontaneously oscillate. But first, we'll review a major invention called the negative-feedback amplifier ...

NEGATIVE-FEEDBACK VERSUS POSITIVE-FEEDBACK AMPLIFIERS

In order to appreciate how hair cells do it we study the opposite—Harold Black's invention of the negative-feedback amplifier. In 1928 Black tried to patent the idea of negative-feedback and met with the skepticism usually reserved for perpetual motion machines (20). His idea was to start with a nonlinear amplifier that had a very large gain and then use negative feedback in order to throw away most of the gain and get

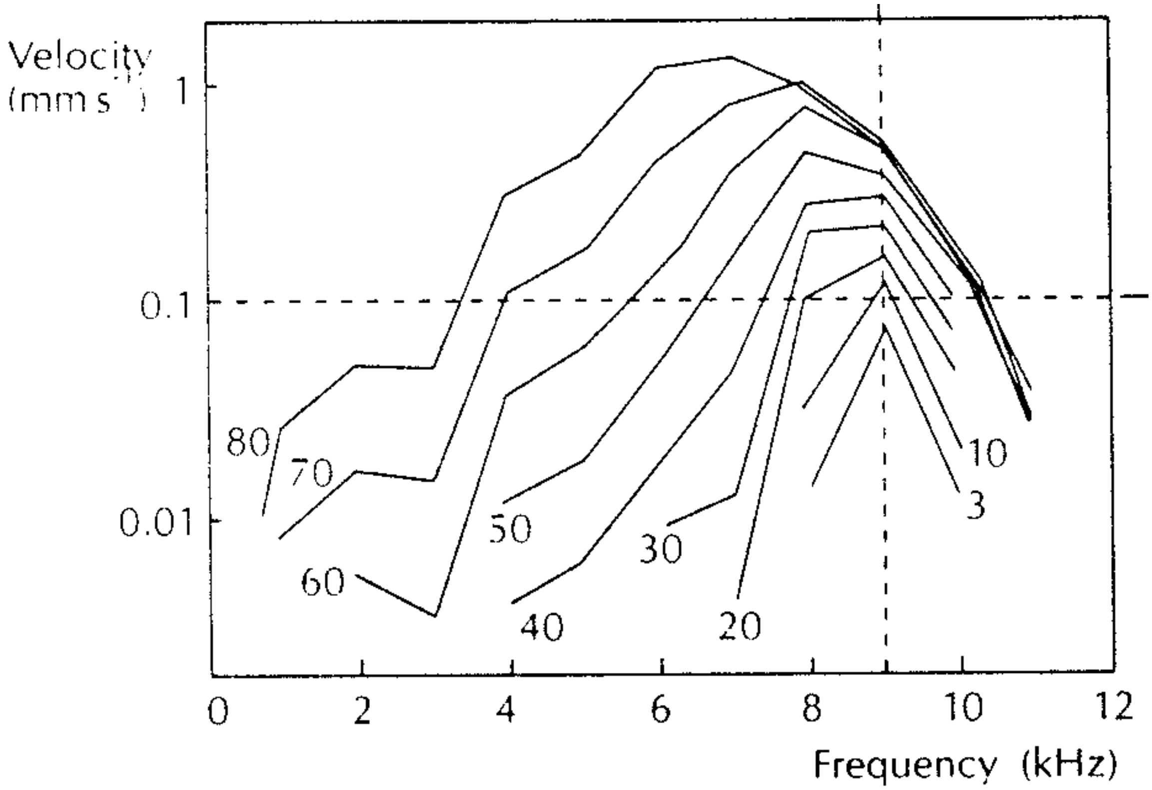

Figure 5: Laser velocimetric data from a living chinchillas cochlea displaying the root-mean-square velocity of one point on the basilar membrane as a function of driving frequency. Each curve represents a different level of stimulation, labeled in decibels sound-pressure level. The characteristic frequency at the position of measurement is 9 kHz. Notice that at 4 kHz, the curves from 40 to 80 dB span two decades (40 dB), whereas at 9 kHz the curves from 3 to 80 dB span just under one decade (20 dB). Note that the response at 9 kHz saturates beyond 60 dB. At 4 kHz, the response rises an average of 1 dB per decibel (linear behavior), whereas at 9 kHz the response rises only 0.3 dB per decibel (output going like input$^{\frac{1}{3}}$). Note furthermore the dramatic increase in bandwidth as the intensity increases (Courtesy of Ruggero) (4).

rid of all of the nonlinearities (Fig. 6). Since arbitrary electric signals are made up of many different frequency components Black's amplifier would amplify any electric signal without distortion—it was a great invention.

Contrast this with a positive feedback amplifier—start with Figure 6's schematic of Black's amplifier, but with an AMP that delivers a lot less gain, say between 1 and 2 instead of between 1000 and 2000. Next do just the opposite of Black and change the sign of the feedback connection from - to + while increasing FB strength to .5.

$$GAIN = \frac{AMP}{1 - AMP \cdot FB} \tag{8}$$

will now blow up for small inputs near frequency f_0. All of the nonlinearities in gain versus frequency and input amplitude will become exaggerated. By increasing $+FB$ by just the right amount we get a high-Q filter with a transfer function that decreases gain for larger input signals.

FROG SACCULAR HAIR CELL AMPLIFIER

Hair cells of the frog's vestibular organ, the sacculus, employ an amplifier based on *negative hair bundle stiffness* (21). When a transduction channel under tension pops open it provides a so-called gating force which immediately decreases the hair bundle's spring constant, since it acts in the same direction as the tension. This effect is known as *gating compliance* (22). Gating force can in fact be larger than the bundle spring's restoring force, hence negative hair bundle stiffness. By tapping an energy source, in this case a calcium gradient between the inside and outside of the bundle, gating compliance can be used to make a mechanical amplifier (Fig. 7A) (23). In this case transduction channels opened by tip link tension T, allow Ca^{++} to bind to receptors near the inside of the channel, closing it. With a time delay internal buffer sweeps up the Ca^{++} so that tension then reopens the channel. Perhaps the clearest evidence that such an amplifier exists is that under a light microscope one can easily observe spontaneous 10 Hz oscillations of the frog's vestibular hair bundles (24; 25).

To see the presence of positive feedback, displacement clamp a bundle that wants to oscillate. Hold it in a position so as to close its transduction channels and then let it go. A typical saccular hair bundle has 50 transduction channels each attached

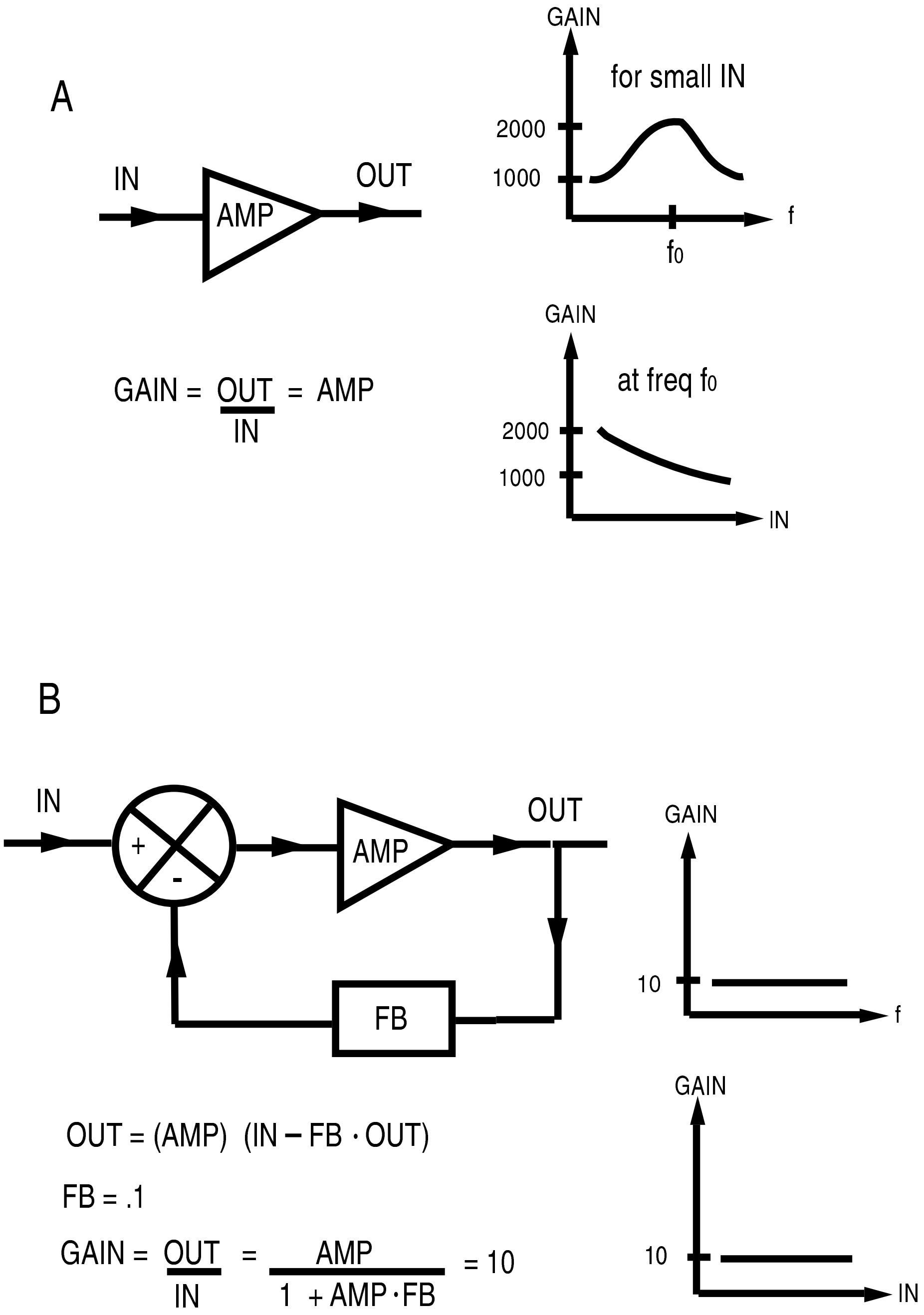

Figure 6: A: A very high-gain amplifier having nonlinearities in its gain versus frequency and gain versus input amplitude. B: By configuring such a nonlinear amplifier with a negative feedback connection Black was able to eliminate the nonlinearities.

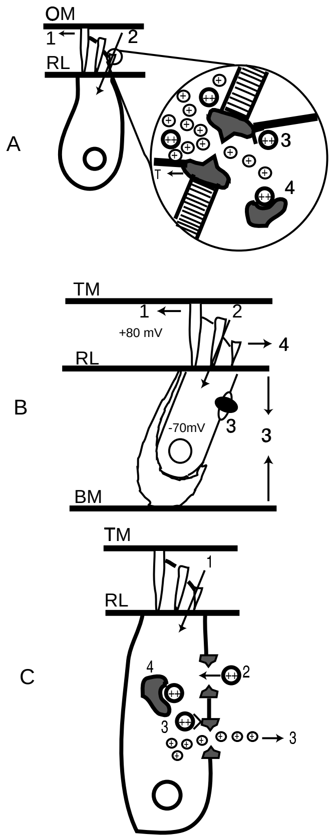

Figure 7: Various hair cell amplifiers are based on dynamical instabilities which lead to a limit-cycle oscillation. A: A frog vestibular hair bundle oscillates without input. The bundle deflects towards its tall end, increasing tension T and popping open transduction channels (1) which admits a current of K^+ along with some Ca^{++} into the cell (2). Ca^{++} then binds to an internal site and closes the channel (3). Then Ca^{++} unbinds while internal buffer sweeps it up (4) so that the channel once again pops open. B: The mammalian cochlea contains outer hair cells arranged in feedback loops which can be poised above Hopf bifurcations so as to spontaneously oscillate. When the bundle deflects towards its tall end (1) it opens transduction channels so that the resulting current depolarizes the cell (2). When this happens piezoelectric proteins in the cell wall contract (3), compressing the cell, and deflecting the bundle (4) so as to close transduction channels and hyperpolarize the cell. Hyperpolarization causes the piezoelectric proteins to expand, elongating the cell, deflecting the bundle back towards its tall end and restarting the cycle. C: In the hearing organ of the frog the membrane potential of its hair cells oscillates without input. Steady bundle current through partly open transduction channels depolarizes the cell (1), activating voltage-gated Ca^{++} channels which further depolarizes the cell (2). This Ca^{++} turns on Ca^{++}-gated K^+ channels with a time delay (3), hyperpolarizing the cell. Meanwhile bundle current continues into the cell so that as (4) buffer sweeps up the Ca^{++} and the K^+ channels close, membrane potential once again depolarizes, restarting the cycle.

to a tip link spring, and all of these springs are thought to be in parallel (22). Each channel with its tip link is an individual oscillator—when you let go of the bundle tension will begin to increase over all the links so that a group of channels will gate. During their gating, tension must redistribute over the remaining closed channels so that the tension per channel increases. Each cycle this positive feedback effect will induce other channels to synchronize their gating. Soon the entire bundle will be engaged in a large limit-cycle oscillation where most of the channels are opening and closing in synchrony.

MAMMALIAN OUTER HAIR CELL AMPLIFIER

Inside the mammalian cochlea there are electromechanical feedback loops which can use the *somatic electromotility* of the outer hair cell to provide a force opposing drag (26). Assuming that outer hair cell force is able to cancel all of the drag force at a given basilar membrane position and frequency, then such a region could ring indefinitely in a small limit-cycle.

Let's go once through such a limit-cycle. First imagine that the bundle deflects towards its tall end, opening transduction channels so that the resulting current depolarizes the cell. When this happens piezoelectric proteins in the cell wall contract(27), compressing the cell, and deflecting the bundle so as to close transduction channels and hyperpolarize the cell (Fig. 7B). Hyperpolarization causes the piezoelectric proteins to expand, elongating the cell, deflecting the bundle towards its tall end and restarting the cycle.

You'd be able to see the presence of positive feedback if you could voltage-clamp an outer hair cell in vivo and then let it go. Voltage noise, say hyperpolarizing, would cause a small elongation, deflecting the bundle so as to open transduction channels. If the bundle is sensitive enough then the resulting depolarization will be larger than the original hyperpolarizing noise. Here it is again, positive feedback directing a build up to a limit-cycle.

The clearest evidence for such an amplifier is the great sensitivity of the outer hair cell's bundle (28), the large force produced by electromotility of its cell body (29), the speed of this electromotile response (30) and finally the existence of spontaneous otoacoustic emissions where the mammalian ear produces sound in a quiet environment (9). Note that while the outer hair cell is part of an electromechanical feedback loop which can make use of *somatic electromotility* to poise at a Hopf bifurcation, that its amplifier could in fact be based either partially or totally on *negative hair bundle stiffness* (23). At this writing the issue remains unresolved.

ELECTRICALLY RESONANT HAIR CELL AMPLIFIER IN THE FROG EAR

The membrane potential of hair cells in the frog's hearing organ, the amphibian papilla is unstable. It spontaneously oscillates in the 100 Hz range. This is an extreme form of the phenomenon called *electrical resonance* (31; 32; 33; 34; 35)in which about a thousand Ca^{++} -gated, large conductance potassium channels are colocated in synaptic zones along with several thousand Ca^{++} channels (36). Without stimulation steady current through partly open transduction channels depolarizes the cell, activating Ca^{++} channels which further depolarizes the cell (Fig. 7C). This Ca^{++} turns on Ca^{++}-gated K^{+} channels with a time delay, hyperpolarizing the cell. Meanwhile transduction channel current continues into the cell so that as the K^{+} channels begin to close, membrane potential once again starts to climb. In fact membrane potential executes a limit-cycle oscillation (37). This spontaneous, sinusoidal potential oscillation is the clearest evidence of a Hopf bifurcation in the frog ear.

If you voltage-clamp a frog ear hair cell at its average membrane potential and then let it go then once again you'd be able to see the positive feedback build up a limit-cycle oscillation. Again say noise makes a small hyperpolarization. If the bundle sources enough positive current into the cell and the K^{+} channels are sufficiently voltage-sensitive (via Ca^{++}) then the tiny hyperpolarization will turn off the K^{+} channels enough so that bundle current will make a depolarizing rebound larger than the original hyperpolarization.

CUBE-ROOT SHAPE OF THE TRANSFER FUNCTION

So it would appear that nature employs at least three distinct kinds of amplifiers in its hair cells, each with their control parameters adjusted so as to increase positive feedback and access a Hopf bifurcation. One biophysical theme common to all three amplifiers is that in the AMP inside their feedback loop is a channel whose open probability oscillates. All of these channel's open according to sigmoid-shaped Boltzmann probability distributions. So we have a Boltzmann function converting displacement or voltage into a channel open probability—in the outer hair cell x is the amplitude of vibration of the basilar membrane and P_0 is the open probability of the transduction channel, in the frog ear x is membrane potential and P_0 is the open probability of the calcium channel. Say the system mechanically oscillates infinitesimally with a peak-to-peak size x while poising on a Hopf bifurcation at the midpoint of the Boltzmann, where it's steepest (Fig. 8). The oscillating part of the open probability will go like $\delta P_0 = \frac{dP_0}{dx}\, x$. The active force generated will be proportional to δP_0 which is in turn proportional to $\frac{a}{4}\, x$. This feeds back to cancel out the infinitesimal oscillation's drag force so as to poise the system and allow it to ring indefinitely. However, when we force the system the resulting larger oscillations will have their gain reduced by $\frac{dP_0}{dx}$ second order term—for them not all of the drag gets cancelled. External forcing will have to make up for this deficit which goes like $\frac{a^3\, x^2}{16}\, x$. This is the physical reason why all of these systems have their output going like the cube-root of their input.

APPLICATIONS TO OTHER BIOSYSTEMS

Simply because they're easy to make and they provide high performance one could guess that inside any biological sensor in the business of periodic signal detection there would be a filter based on a Hopf bifurcation.

One good candidate for such a Hopf filter would be the ampullary cell in the electroreceptor of the paddlefish. The paddlefish is a bottom feeder in murky waters. He uses his electrosensitive ampullary cells to detect the electrical activity associated with the swimming motions of water fleas (38). Electroreceptors are thought to be derivatives of hair cells that have lost their mechanical sensitivity. These cells may nonetheless retain the hair cell's strategy of electrical resonance for frequency tuning, such as seen in the frog ear. Ampullary cells are sensitive to electric fields as weak as 2 mV$\cdot m^{-1}$. The neurons innervating them show noisy electrical oscillations at rest; during stimulation these oscillations are synchronized by external electric fields. Ampullary cells thus behave like noisy phase-locked loops (38) and would appear to

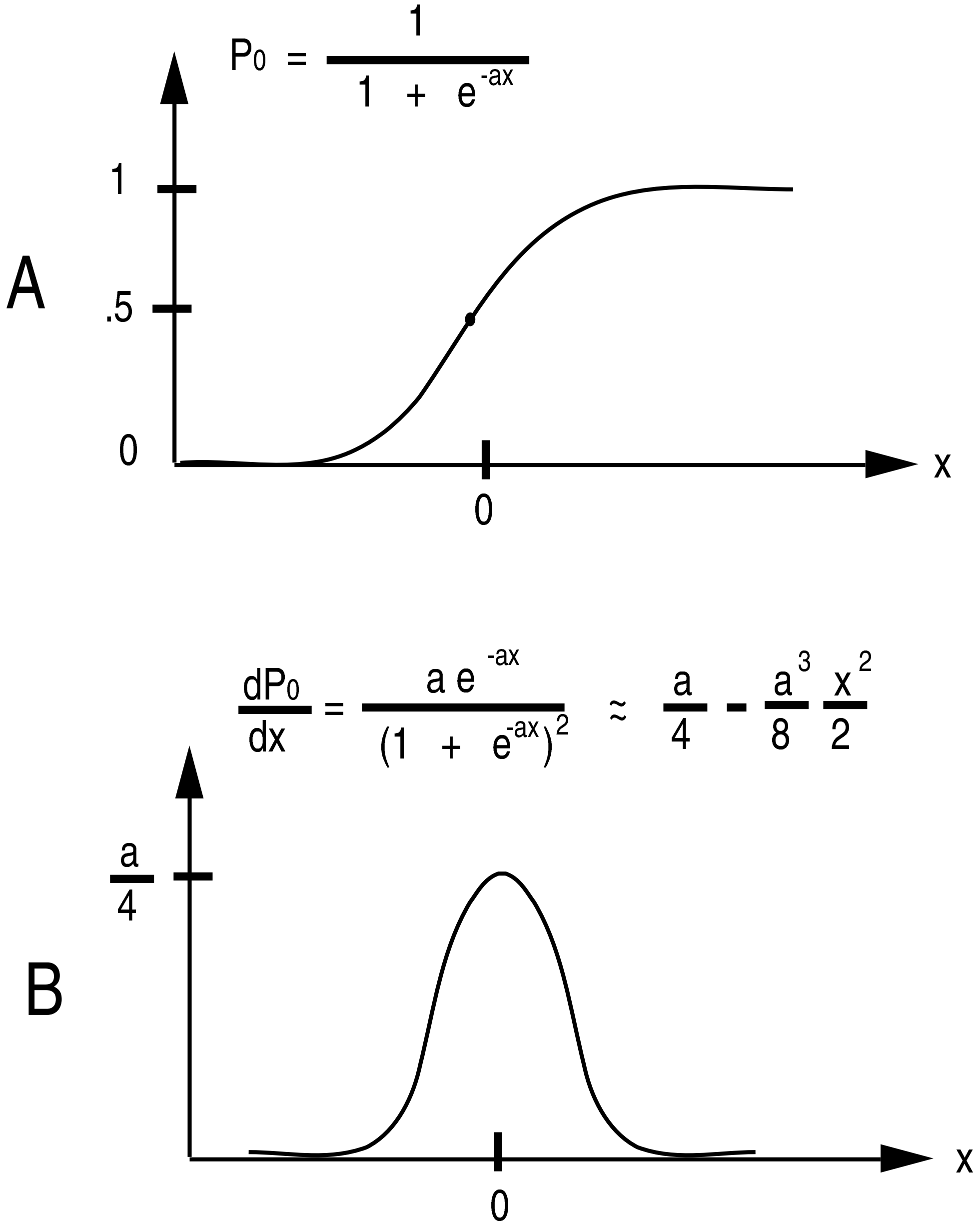

Figure 8: It is the saturating nonlinearity in the Boltzmann function which accounts for the cube-root shape of the compressive nonlinearity in each of the hair cell amplifiers. A: A sigmoid-shaped Boltzmann function describing the open probability of a channel versus an independent variable such as membrane potential or mechanical displacement. B: First derivative of the Boltzmann function with respect to the independent variable. Expansion of the derivative at $P_0 = .5$ reveals a constant first term and a negative second order term. The negative second order term is responsible for the Hopf bifurcation's compressive nonlinearity (see text).

be an excellent candidate for a Hopf bifurcation.

The FitzHugh-Nagumo simplified model of the Hodgkin-Huxley model of a nerve membrane contains two Hopf bifurcations (39). An integrate and fire neuron is a leaky integrator of synaptic currents having a voltage threshold where a fast sodium conductance instability makes the voltage runaway, and this leads to a stereotyped action potential response. A resonate and fire neuron, on the other hand, requires periodic synaptic input at the right frequency in order to make an action potential. Such a resonate and fire neuron if poised at a Hopf bifurcation would reveal itself with subthreshold voltage oscillations. Close to the bifurcation for small signals it would acquire the Hopf filter characteristics of enormous gain and infinitely sharp frequency selectivity (Fig. 4). Simple packet exchange or communications protocols between neurons in a network could be based upon poising them on Hopf bifurcations.

CONCLUSIONS

Hair cells poise on dynamical instabilities called a Hopf bifurcations so as to make high-Q filters that are both very sensitive and very frequency-selective. An added bonus is that filter gain is reduced for larger input signals.

We've reviewed the basic mathematics underlying a Hopf bifurcation in order to understand its simple filter characteristics. Also we've gone over two physical principles involved in making such an amplifier: Hopf amplifiers are based upon the use of positive feedback. Also hair cells must employ channels in their feedback loops which open according to Boltzmann functions and it is the shape of this function which is responsible for the cell's output going like the cube-root of its input. Finally we've gone over three distinct hair cell amplifiers, each of which can easily be poised on a Hopf bifurcation.

We expect Hopf bifurcations to be commonly used by biosensors for periodic signal detection.

References

[1] H. L. F. Helmholtz, *On the Sensations of Tone as a Physiological Basis for the Theory of Music* (Dover Publications, Inc., New York, 1954).

[2] G. von Békésy, *Experiments in Hearing* (McGraw-Hill Book Co., New York, 1960).

[3] W. S. Rhode. J. Acoust. Soc. Am. **49**, 1218 (1971).

[4] M. A. Ruggero, Curr. Opin. Neurobiol. **2**, 449 (1992).

[5] M.A. Ruggero et al, J. Acoust. Soc. Am. **101**, 2151 (1997).

[6] M. A. Ruggero and N. C. Rich, J. Neurosci. **11**, 1057 (1991).

[7] T. Gold and R. J. Pumphrey, Proc. Roy. Soc. Lond. B **135**, 462 (1948).

[8] T. Gold, Proc. Roy. Soc. Lond. B **135**, 492 (1948).

[9] D.T. Kemp, Arch. Oto.-Rhino.-Laryngol. **224**, 370 (1979).

[10] W.J. Murphy et al, J. Acoust. Soc. Am. **100**, 3979 (1996).

[11] This is the principle of a regenerative receiver which amplifies by adding just enough positive feedback that the receiver barely oscillates. The design was popular in the 1920s because it could be constructed with a single vacuum tube, but it was abandoned because it emits into the very bandwidth it receives. The superregenerative receiver is a self-quenching version; both were invented by Edwin Armstrong, who also invented broad-band FM.

[12] L. G. Tilney and J. C. Saunders, J. Cell Biol.,**96** 807 (1983).

[13] J. O. Pickles, S. D. Comis and M. P. Osborne. Hearing Res. **15** 103 (1984).

[14] M. C. Liberman and L. W. Dodds, Hear. Res. **16** 55 (1984).

[15] S. H. Strogatz, *Nonlinear dynamics and chaos*, (Perseus Books, Reading, MA, 1994).

[16] V. M. Eguíluz, M. Ospeck, Y. Choe, A. J. Hudspeth, and M. O. Magnasco. Phys. Rev. Lett. **84** 5232 (2000).

[17] S. Camalet, T. Duke, F. Julicher, and J. Prost. PNAS. **97** 3183 (2000).

[18] J.H.E. Cartwright, D.L. Gonzálewz, O. Piro, Phys. Rev. Lett. **50**, 870 (1993).

[19] M. O. Magnasco. in preparation.

[20] P. Horowitz and W. Hill, *The Art of Electronics. 2nd ed.* (Cambridge University Press, Cambridge, UK, 1989).

[21] P. Martin, A. D. Mehta and A. J. Hudspeth, PNAS. **97**, 12026 (2000).

[22] J. Howard and A. J. Hudspeth, Neuron **1** 189 (1988).

[23] Y. Choe, M. O. Magnasco, and A. J. Hudspeth, PNAS **95** 15321 (1998).

[24] P. Martin and A. J. Hudspeth. PNAS. **96**14306 (1999).

[25] A. J. Ricci, A. C. Crawford and R. Fettiplace, J. Neurosci **20** 7131 (2000).

[26] M. Ospeck, X. -x. Dong and K. H. Iwasa. submitted to Biophys. J.

[27] X. -x. Dong, M. Ospeck and K. H. Iwasa. Biophys. J. in press.

[28] I. J. Russel, G. P. Richardson and A. R. Cody, Nature **321** 517 (1986).

[29] K. H. Iwasa and M. Adachi, Biophys. J. **73** 546 (1997).

[30] G. Frank, W. Hemmert and A. W. Gummer, PNAS **96** 4420 (1999).

[31] A. C. Crawford and R. Fettiplace. J. Physiol. **306** 79 (1980).

[32] A. C. Crawford and R. Fettiplace. J. Physiol. **312** 377 (1981).

[33] R. S. Lewis and A. J. Hudspeth. Nature. **304** 538 (1983).

[34] A. J. Hudspeth and R. S. Lewis. 1988a. J. Physiol. **400** 237 (1988).

[35] A. J. Hudspeth and R. S. Lewis. 1988a. J. Physiol. **400** 275 (1988).

[36] W. M. Roberts, R. A. Jacobs and A. J. Hudspeth, J. Neurosci. **10** 3664 (1990).

[37] M. Ospeck,V. M. Eguíluz, and M. O. Magnasco, Biosphys. J. **80** 2597 (2001).

[38] A. Neiman, X. Pei, D. Russell, W. Wojtenek, L. Wilkens, F. Moss, H. A. Braun, M. T. Huber, and K. Voigt. 1999. Phys. Rev. Lett. **82** 660 (1999).

[39] R. FitzHugh. Mathematical models of excitation and propagation in nerve. In *Biological Engineering.* (H. P. Schwann, editor. McGraw-Hill, 1962).