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# Chapter 1

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## Biophysical Principles of Sensory Transduction

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## Introduction: A Search for Underlying Principles

Among the properties that distinguish the animate from the inanimate are the capacities to reproduce, to move, and to respond to stimuli. Indeed, the study of such properties defines the field of biology. The last of these—the ability to respond—is predicated upon being able to detect a stimulus in the first place. Sensory transduction therefore plays an indispensable role in the lives of organisms. It is the mechanism by which external physical cues are transformed into internal biochemical or electrical signals that can be put to some further use. External cues carry all kinds of information about the environment; internal signals present a distilled version of that information. As such, information must be gathered, selected, registered, amplified, and encoded. This process can be simple, or it can be extraordinarily complex. In nature, schemes for signal transduction are every bit as varied as the creatures that use them. Consider, for a moment, the sheer number of cues to which biological organisms respond. It has long been obvious that sensory modalities go well beyond the classic five human senses of hearing, sight, taste, smell, and touch. Living things not only sense sound, light, chemicals, and pressure, but also position, heat, gravity, acceleration, electrical and magnetic fields, and even the passage of time. A glance at a list of some of the better-studied of these sensory systems (Table I) may lead to the impression that life has evolved to monitor just about everything. Can there be any unifying themes, any biophysical principles?

A physicist looking over Table I might point out that living things sense manifestations of just two of the four fundamental forces: the electromagnetic force and the gravitational force. The electromagnetic force has infinite range, and it dominates on the length scale at which life exists: from nanometers up to tens of meters. It holds molecules together, and is the basis for light, heat, sound, and all of chemistry. The gravitational force also has infinite range, and, although its effects are far weaker, it, too, affects living forms. But the remaining two forces, the strong force (or nuclear force) and the weak force (responsible, for example, for  $\beta$ -decay), appear to pass undetected through the biosphere. It is likely that, because the range of both the weak and strong forces is finite and short (small, even on the scale of an atom), large-scale consequences are wholly insignificant. Perhaps so. But who knows? Someone may yet find an example of a creature that detects nuclear processes or violates parity conservation.

Be that as it may, the foregoing discussion hardly constitutes a “biophysical principle” of sensory transduction. Knowing that sensory systems obey the laws of electromagnetism and gravity provides small comfort and little insight. Instead, to search for principles one needs to look carefully at individual senses, at their evolution, design, and function. Here, physics can play a role in helping to understand why sensory systems behave as they do.

Anyone who has spent time studying the senses cannot help but be struck by the astounding sensitivity of biological systems. Our own human senses are fairly dull compared with most other mammals, and yet we can hear a faint whisper, smell a whiff of perfume across a crowded room, find our way by dim moonlight, balance on our tiptoes, or determine the roughness (not to mention temperature) of a nearly smooth surface by merely running a fingertip across it. In purely engineering terms, these are impressive feats: the best man-made detection systems today are, in a great many instances, no better than the natural senses. Most are worse. What's more,

biological sensory systems are generally more compact, more robust, and more efficient. How are such levels of performance achieved? *May we speculate that biological sensory systems are, in some sense, optimal?*

It turns out that the question of “optimality” is ill posed. There are a number of reasons for this. First, and almost trivially, optimality supposes that a unique solution exists that maximizes the performance of a sensory system. In fact, there may well be multiple solutions to a sensory problem, any one of which achieves the desired level of perfection. The incredible natural variety of sensory systems reminds us that there are many ways to skin a cat. Second, there is no *a priori* reason to believe that

**TABLE I**  
A List of Some of the Better-Studied Sensory Modalities,  
in No Particular Order

vertebrate rod and cone vision	vertebrate taste transduction
chemotaxis in bacteria	animal map senses
vertebrate hearing	magnetotaxis in bacteria
echolocation in bats, birds	magnetoreception in invertebrates
taste reception	electroreception in fish
chemotaxis by eukaryotic cells	ultraviolet light detection
tactile responses of protozoans	insect chemical signaling
vertebrate olfaction	pH taxis in microorganisms
odorant detection insects	insect pheromone detection
yeast mating response	sense of elapsed time
circadian rhythms	insect rhabdomeric vision
osmotic responses of bacteria	stretch-inactivated receptors
salt taxis in bacteria	geotaxis in microorganisms
phototropism in plants	phototaxis in protozoa
phototaxis in bacteria	thermoreception in vertebrates
stretch-activated receptors	aquatic buoyancy regulation
vestibular senses	infrared sensing and imaging
insect tactile/vibration responses	polarized light detection
geotropism in plants	infrasound detection
proprioception	leukocyte chemotaxis/signaling
magnetoreception in vertebrates	sonar in marine mammals
gas partial pressure sensing	fluid or gas velocity detection
haltere-based orientation	fungal avoidance response
thermotaxis in microorganisms	osmoregulation in plants
crustacean rhabdomeric vision	nociception

optimality has been achieved. On the contrary, to do so would be tantamount to assuming that evolution had somehow run its course and produced a final product. It is arguably better to think of biological systems as “works in progress.” Third, and of fundamental importance, one cannot talk about optimization without first stipulating (1) the properties (functions) that are to be optimized, and (2) all the constraints (boundary conditions) for that optimization. This is where one rapidly gets into trouble with biological systems. It is simply not meaningful to say that performance is maximal unless a *context* is specified. Just what measure of performance is appropriate (signal amplitude? signal-to-noise ratio? speed? jitter? encoding fidelity?) and

what factors contribute to the “design criteria” (basic physics? environmental factors? size? metabolic cost? selective advantage?). As researchers on the outside looking in, we should view our task as being the identification of precisely these things: only then can questions of optimality be addressed meaningfully. To put it all in a more “biological” language:

*Evolution doesn't really seek to optimize. It seeks to iterate, to ramify, and to compromise. The solutions found by evolution are neither unique nor perfect.*

A corollary of this, therefore, is that:

*Sensory systems are not necessarily as good as they can be. They are just as good as they need to be.*

Unfortunately, we do not yet know enough about most sensory systems to speculate as to what kinds of information they really extract, or to what constraints they might be subject (i.e., just exactly how good they ought to be). In a number of felicitous cases, though, the response of a sensory system can be clearly identified, and its performance comes close to limits set by basic physics. That is, the performance of the sensory system does not appear to be compromised by, say, some cryptic need for a particular color, size, or sexual attractiveness. In such cases, it *does* make some sense to talk about optimization. Even for sensory systems whose performance falls well short of any physical limits, it is nevertheless a worthwhile exercise to try to understand what those limits are, if only to understand better the evolutionary context. Here, then, is the place for “biophysical principles.”

## A Unified Scheme for Sensory Systems

From an engineering standpoint, all sensory systems have features in common. Fig. 1 shows a block diagram depicting a conceptual framework for sensory systems. They all possess a *detection stage*, or primary transducer (symbolized by the upper gray box). In vertebrate vision, this would correspond to the photoreceptor molecule (opsin or rhodopsin); in bacterial chemotaxis, to a transmembrane receptor on the inner membrane that can bind either to attractants, or to attractants complexed with periplasmic binding proteins; in vertebrate hearing, to a set of mechanically gated channels in the hair cell’s stereociliary bundle. Most often, the detector is linked to accessory factors that serve to convey the signal to the detector (symbolized by the curved, antenna-like object attached to the detector). In vertebrate vision, this would correspond to the image-forming portion of the eye (lens, iris, retina, etc.); in bacterial chemotaxis, to the outer wall of the cell and to the periplasmic binding proteins; in vertebrate hearing, to the outer and middle ear, the basilar and tectorial membranes of the cochlea, and so on. The detection stage transduces the energy of the stimulus to some other form, usually chemical or electrical. As such, information becomes encoded (Encode I). The receptor now boosts this weak signal with an *amplification stage* (middle gray box), which involves a second filtering step (Encode II). Finally, the amplified signal is passed along to its destination by a *signaling stage* (lower gray box) that further serves to filter it (Encode III). In higher organisms, signaling outputs are usually afferent nerves. For single-celled organisms, signaling is internal (in bacterial chemotaxis, a diffusible signal molecule modulates the rotational direction of the flagellar motor).

The stages of detection, amplification, and signaling may be linked by various *feedback pathways*. Not all sensory systems have implemented the complete set of

pathways shown in Fig. 1, but most do have multiple levels of feedback. Feedback pathways mold the response characteristics of the cell. At the earliest stages, they serve to moderate the input signal itself (e.g., closing the pupil reduces light reaching the retina; tensing the muscles of the middle ear attenuates sounds). Feedback to the detection stage can be used to adjust the sensitivity of the detector (e.g., covalent methylation of a bacterial chemoreceptor changes its signaling characteristics). Feedback to the amplification stage provides what engineers call automatic gain control, or range adjustment (e.g., the adaptive shifts of the response of rod photoreceptors to changes in background illumination, or the adaptive shifts of the

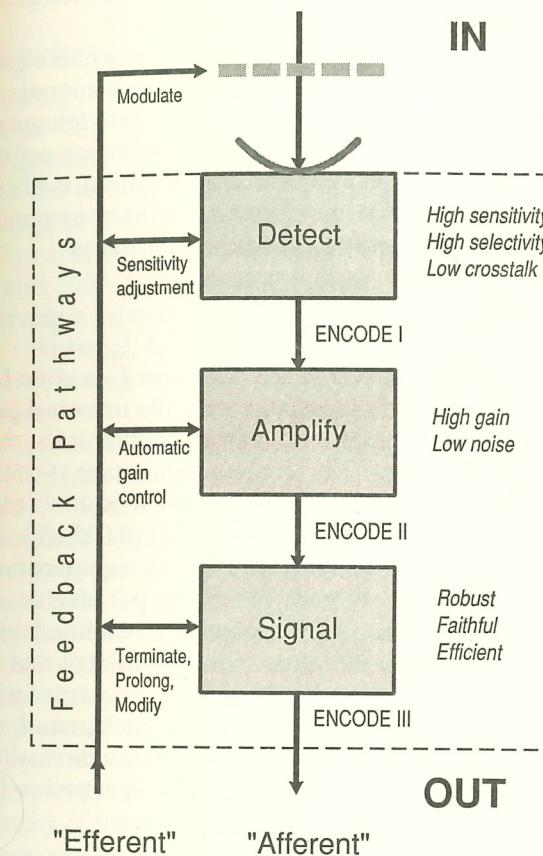


Figure 1. A universal scheme for sensory transduction.

response of inner hair cells to changes in the mean stereociliary bundle position). Feedback can also affect the bandpass characteristics of the amplifier, altering its frequency response. Feedback to the signaling stage can be used to vary the temporal characteristics of the response, prolonging it, terminating it prematurely, or otherwise modifying it (synaptic inhibition, potentiation, and habituation are examples of this). Feedback can even change the encoding scheme (say, by altering threshold spiking behavior or inducing oscillations). Finally, feedback pathways can be implemented both internally, inside the receptor itself (as in single-celled organisms), and externally, via efferent pathways from the nervous system.

In engineering design, there are desiderata (“specifications”) at each stage. Ideally, the primary detector should have high sensitivity and high selectivity. It should respond only to the designated stimulus (low crosstalk). As in an electronic instrument, the first stages of amplification should produce high gain, yet introduce little or no additional noise into the system. The signaling stage needs to encode the desired information with great fidelity, and it should be robust and efficient. The feedback pathways, properly implemented, can be used to increase the dynamic range, improve temporal response, raise noise rejection by the system, augment accuracy, and more. They should prevent the system from overloading, overdamping, or oscillating out of control. The scheme of Fig. 1 is, in some sense, universal: it applies as well to the design of a hand-held video camcorder as to the biological senses.

What, then, sets specific limits on design? Many factors come into play here and no simple answers exist. Ultimately, however, there is one ineluctable consideration. Organisms are composed mostly of water, and live at more or less constant temperatures, somewhere inside the narrow interval between the freezing and boiling points of water (0–100°C). Biochemistry is therefore, to an excellent approximation, isothermal. Because living creatures are nearly in thermal equilibrium with their surroundings, they must contend with being bathed in a background of thermal energy.

## The Importance of $kT$

The thermal energy,  $E_{\text{therm}}$ , associated with an absolute temperature,  $T$ , is given by  $kT$ , where  $k$  is Boltzmann’s constant. Boltzmann’s constant equals the universal gas constant,  $R$ , per molecule, i.e.,  $k = R/N_A$ , where  $N_A$  is Avogadro’s number: it has the value  $k = 1.38 \times 10^{-23} \text{ J/K}^{-1}$ , or  $1.38 \times 10^{-16} \text{ erg/K}^{-1}$ . Room temperature,  $\sim 25^\circ\text{C}$  ( $\sim 300\text{K}$ ), corresponds to a thermal energy  $E_{\text{therm}} \approx 4 \times 10^{-21} \text{ J} = 4 \times 10^{-14} \text{ erg}$ . Physicists tend to think of this energy as  $\sim 1/40$ th of an electron volt (0.025 eV). In chemists’ units, that comes to  $\sim 0.58 \text{ kcal/mol}$ . Classically, by the equipartition theorem, all bodies in thermal equilibrium have  $\frac{1}{2}kT$  of energy per degree of freedom. A biological sensor carries at least this much energy as a baseline level. Additional energy deposited by a sensory signal therefore falls on a system that is already energized by thermal noise. Whether or not the signal can be detected will depend on how much energy it carries compared with the thermal background, as well as how much time the detector has to make the measurement. For a discussion of these considerations, the reader is encouraged to consult the excellent review by Bialek (1987), from which portions of the following discussion were drawn.

## Vision Limits

Thermal energy need not be the limiting factor, however. Consider the case of vision, where quantum mechanical effects come into play. The energy in a photon, the quantum of light, is given by the Einstein relation  $E = hv = hc/\lambda$ , where  $v$  and  $c$  are the frequency and speed of light, respectively, and  $h$  is Planck’s constant. Planck’s constant has the value  $h = 6.62 \times 10^{-34} \text{ J}\cdot\text{s}$ , or  $6.62 \times 10^{-27} \text{ erg}\cdot\text{s}$ . For a single photon of blue-green light ( $\lambda = 500 \text{ nm}$ ), the energy comes to  $E \approx 57 \text{ kcal/mol}$ . That’s  $\sim 100$  times thermal energy! So vision is quantum limited, not thermally limited. Given the huge signal-to-noise ratio, there is no physical reason why biological photodetectors

could not count single photons, and there is ample evidence that they do just that. The classic psychophysical experiment of Selig Hecht, Simon Shlaer, and Maurice Pirenne (1942) demonstrated that humans could perceive a handful of quanta (six to eight) entering the dark-adapted eye. Given the improbability that all of these hit a single photoreceptor cell, it was argued that one photon produced the sensation of a dim flash. Years later, in an experimental tour de force, Denis Baylor and colleagues demonstrated single-photon responses in individual rod photoreceptor cells (Baylor et al., 1979, 1980). It is now clear that both vertebrate and invertebrate vision (c.f. Fuortes and Yeandle, 1964) can function right down to the photon-counting or “shot noise” limit.

## Hearing Limits

Hearing is an altogether different situation. The quantum of sound is the phonon, whose energy is also given by the Einstein relation above. Again, the proper comparison is between  $hv$  and  $kT$ , with  $v$  now representing the frequency of sound. For the sonic frequency range,  $v = 10\text{--}100,000 \text{ Hz}$ , this corresponds to a phonon energy of just  $7 \times 10^{-26}\text{--}7 \times 10^{-23} \text{ erg}$ . That implies  $kT/hv = 6 \times 10^8\text{--}6 \times 10^{11}$ : thermal energy exceeds quantum energy by some 10 orders of magnitude (Denk and Webb, 1989a)! There is little chance that single phonons can be detected. Vertebrate hearing is astoundingly sensitive, but it is classically limited, not quantum limited.

Although firm numbers are hard to arrive at, basilar membrane displacements at the hearing threshold are believed to be in the range of atomic, or even subatomic, dimensions:  $\sim 0.1\text{--}1 \text{ \AA}$  (von Békésy, 1960; Sellick et al., 1983; Crawford and Fettiplace, 1985). This motion is even less than thermal excursions of the hair bundle itself. If the motion of the hair bundle were free and undamped, by equipartition  $\frac{1}{2}kT = \frac{1}{2}\kappa\langle x^2 \rangle$ , where  $\kappa$  is the bundle stiffness ( $\kappa \approx 10^{-3} \text{ N/m}$ ; Crawford and Fettiplace, 1985; Howard and Hudspeth, 1988) and the right-hand term is the spring energy of the bundle. This gives a root-mean-square thermal displacement  $\langle x^2 \rangle^{1/2} \approx 2 \times 10^{-9} \text{ m} = 2 \text{ nm}$ , which exceeds 1 Å. The resolution of this apparent paradox is that the broad-band thermal limit can be beaten by narrowing the temporal bandwidth of the detection system. The thermal (input) noise power,  $P$ , is given by the Nyquist theorem,  $P = 4kT\Delta v$ , and is “white” (i.e., flat for essentially all frequencies of interest). But the power spectrum of a damped resonator is not:  $P_{\text{res}} = kT/(\kappa^2 + 4\pi^2\nu^2\gamma^2)$ , where  $\gamma$  is the viscous drag, or damping (estimated at  $\gamma \approx 10^{-8} \text{ N}\cdot\text{s/m}$ ; Bialek, 1987). Putting in numbers, the root power spectral density of a hair bundle is about  $\sqrt{P_{\text{res}}} \approx 6 \times 10^{-12} \text{ m}/\sqrt{\text{Hz}}$ . By confining measurements to a fraction of the total bandwidth, say,  $\Delta v \leq 100 \text{ Hz}$ , one obtains  $\sqrt{P_{\text{res}}}\Delta v \leq 1 \text{ \AA}$ . So a hair cell might reliably measure ångströms, over a limited range, by careful tuning of its resonance. However, there is a catch! Simply narrowing the bandwidth with a passive resonant system doesn’t work at all, since it *pushes all the available noise power into the peak of the resonance*. (This is a consequence of the fluctuation-dissipation theorem, which relates the thermal noise spectrum to the imaginary [or damping] part of the response function; Landau and Lifshitz, 1977.) The resonant system must be active in order to take advantage of this bandwidth-narrowing mechanism. This is a powerful argument for the existence of active mechanical processes operating at the level of the hair bundle. Unless the numbers are wrong, the only alternative way that a hair cell might “beat” the thermal limit is by

functioning in some hard-to-fathom, macroscopically coherent, quantum-mechanical sense (Bialek, 1987), a prospect that most of us find quite unappealing—at least for now.

The astounding sensitivity of hearing is evident from recent experiments of Denk and Webb (1989a, b) showing that hair cells faithfully transduce Brownian (thermal) noise at their inputs. These experiments were made possible by the development of optical instrumentation that registers exceedingly small displacements (Denk and Webb, 1990). The coherence function (cross-spectral density) comparing the measured thermal displacements of the hair bundle to the voltage noise across the cell's membrane was as high as 0.75 (with 1.0 representing perfect correlation), corresponding to a “noise figure” of 1.25 dB. Impressive indeed.

## Chemoreception Limits

Olfaction, taste, and chemotaxis collectively represent the “chemical senses.” Most chemical sensing is mediated by the binding of compounds to cognate receptor proteins located on sensory cell surfaces. This binding event initiates a transmembrane signaling pathway through these receptors. (It should be pointed out that certain tastes, e.g., salty and sour, do not appear to use a direct receptor-binding mechanism, but instead work via ion channels. These remarks do not apply to them.) Specific transmembrane chemoreceptor proteins have been identified in both eukaryotes and prokaryotes, and they bind their substrates with an enormous range of dissociation constants, from  $K_D = 10^{-2}$ – $10^{-11}$  M, with  $10^{-3}$ – $10^{-6}$  M being typical for the bacterial receptors. Once again, let's compare the “quantal” binding energy with thermal energy. Writing  $K_D \approx \exp(-\Delta E/kT)$  for the weakest of these, we get  $\Delta E \sim 2.5$  kcal/mol, or  $\sim 4kT$  (strictly speaking, we have equated  $\Delta E = \Delta G^\circ$ , where  $\Delta G^\circ$  is the standard free-energy change, measured when all concentrations equal 1 M). Binding energies might be expected to range from  $\sim 2 kT$  to  $\sim 14 kT$ . Direct measurements of binding affinity suggest that values of  $\sim 1$  kcal/mol or more are typical. Since  $\Delta E > \Delta E_{\text{therm}}$ , chemical binding can be used, in principle, to count individual molecules: “shot noise-limited” performance is possible for chemoreception.

High binding energy can obviously be used to confer selectivity upon the receptor, but there is a trade-off. The higher the binding energy (i.e., the smaller the value of  $K_D$ ), the longer the dwell time on the receptor. This is because the dissociation constant  $K_D$  is the ratio of the kinetic off-rate to the kinetic on-rate for chemical binding ( $K_D = k_{\text{off}}/k_{\text{on}}$ ). The on-rate cannot be arbitrarily high, since it will ultimately be limited by diffusional encounters between the chemical and its receptor, to a value near  $3 \times 10^8 \text{ s}^{-1} \text{ M}^{-1}$  (Fersht, 1977). Hence  $k_{\text{off}} = k_{\text{on}}K_D$ . For a  $K_D$  of  $10^{-6}$  M, that comes to an off-rate of  $300 \text{ s}^{-1}$ , corresponding to a characteristic dwell time of milliseconds. But with a dissociation constant of  $10^{-11}$  M, the off-rate plummets to just  $3 \times 10^{-3} \text{ s}^{-1}$ , or a dwell time over five minutes! Meaningful comparisons cannot be made on a time scale shorter than the dwell time.

The need for shot noise-limited performance (and speed) becomes apparent when considering the problem of bacterial chemotaxis. Bacteria such as *Escherichia coli* are quite tiny, only about 1  $\mu\text{m}$  or so in length. They can respond to amino acids, sugars, and other small compounds in their environment that reach the cell's surface by diffusion. *E. coli* swim at speeds of  $\sim 30 \mu\text{m/s}$  in random walks of runs lasting  $\sim 1$  s,

punctuated by tumbles lasting  $\sim 0.1$  s. When gradients of an attractant are encountered, runs with a favorable component up the gradient are lengthened. The result is a random walk with a sensory-imposed drift that carries the cell up the gradient (Berg and Brown, 1972; for a review, see Macnab, 1987). Consider a small volume of bacterial medium containing attractant, 1  $\mu\text{m}$  on a side, i.e., about the size of a bacterium. If the cell could somehow count all the molecules in this volume, it would count around 600,000 molecules if the compound were present at 1 mM, 600 molecules if the compound were present at 1  $\mu\text{M}$ , and 60 molecules if the compound were present at  $10^{-7}$  M. Counting molecules is statistically analogous to counting colored marbles drawn from an urn: the sampling error is proportional to the square root of the number counted. For these concentrations, those errors are  $\sim 800$ , 25, and 8 molecules, respectively. At the low end of concentration, the relative error is already  $> 10\%$  (8 in 60). Behaviorally, bacteria are known to respond to compounds at threshold concentrations below  $\sim 10^{-7}$  M. Leukocytes can detect  $\sim 10^{-11}$  M, and the silk moth *Bombyx mori* can detect the pheromone *bombykol* at  $\sim 10^{-12}$  M (for reviews, see Schiffmann, 1982; Kaissling, 1983; Payne et al., 1986; Macnab, 1987). How can this be accomplished?

The physical limits of chemoreception were explored in a landmark paper by Berg and Purcell (1977) which is distinguished not only for its depth, but also for its physical insight and mathematical elegance. Students of sensory transduction should consider reading this paper, and the more accessible monograph by Berg (1983), *de rigueur*. There isn't space here to recapitulate their findings, but the following back-of-the-envelope calculation, adapted from Berg and Purcell (1977), computes one estimate of the error that cells make in detecting chemicals.

Assume that the cell is a “perfect receptor,” i.e., it can count all the molecules reaching it. As we saw above, the fractional error expected for a single count of the  $n$  molecules in a small volume,  $V$ , will be given by

$$\frac{\delta C}{C} = \frac{\delta n}{n} = \frac{1}{\sqrt{n}} = \frac{1}{\sqrt{CV}}$$

where  $C$  is the concentration (in molecules per unit volume). This “raw measurement” may be improved by making  $N$  statistically independent counts in a time,  $T$ . To do so, the cell must wait a time,  $\tau$ , between counts, so that the molecules that have already been counted in its environment will have a chance to diffuse away and be replaced with a new, statistically independent, set. This takes a time  $\tau \approx a^2/6D \approx V^{2/3}/6D$ , where  $a$  is the dimension of the cell and  $D$  is the diffusion constant of the molecule (recall that for diffusive processes,  $x^2 \sim 6Dt$ ). Since  $N = T/\tau$ ,  $N = 6DT/V^{2/3}$ . This improves the raw measurement by a factor of  $1/\sqrt{N}$ , and the error becomes:

$$\frac{\delta C}{C} = \left(1 \Big| \sqrt{\frac{6DT}{V^{2/3}}} \right) \left(\frac{1}{\sqrt{CV}}\right) = \frac{1}{\sqrt{6DTCV^{1/3}}} = \frac{1}{\sqrt{6DTca}}$$

The fractional error falls as the inverse square root of the time as well as the concentration. A bacterial cell has a fraction of a second to count molecules during a typical run. For a typical amino acid ( $D \approx 10^{-5} \text{ cm}^2/\text{s}$ ), a fractional error of 1% is possible in 1 s for a concentration of  $C \approx 2 \times 10^{12} \text{ molecules/cm}^3 = 3 \text{ nM}$ .

But what about thermal noise? It turns out that the thermal fluctuations in concentration sensed by the cell are nothing more than counting errors in disguise. The

probability that a thermal fluctuation in energy,  $\Delta E_C$ , occurs is proportional to the Boltzmann factor  $P(\Delta E_C) \propto \exp(-\Delta E_C/kT)$ . The expression for this energy, derived in the Appendix, is  $\Delta E_C = (kT/2n)\delta n^2$ , where  $n$  is the mean number of molecules and  $\delta n$  is the fluctuation about that mean value.  $\Delta E_C$  depends linearly on the temperature,  $T$ . Inserting this expression into the Boltzmann factor gives  $P(\Delta E_C) \propto \exp(-\delta n^2/2n)$ . Notice that the dependence on temperature has dropped out entirely, resulting in a symmetric, Gaussian distribution with mean  $n$  and standard deviation  $\sqrt{n}$ . Put into words, “thermal fluctuations” in concentration are temperature independent (!) and have precisely the statistical properties one expects to get when counting a sample of  $n$  molecules.

Do bacteria, in fact, achieve shot noise-limited behavior? Yes. A change in the average occupancy of just one of the thousand or so aspartate chemoreceptors on a cell of *E. coli* during a run interval alters its probability of tumbling significantly (Block et al., 1983; Segall et al., 1986). It is likely that the other chemical senses also approach this level of performance.

### Thermoreception Limits

What about thermal signals themselves? Most animals sense temperature, and many strains of bacteria are thermotactic. Insects, such as cockroaches and other beetles, are exceedingly sensitive to minute temperature gradients. Snakes of the viper family are equipped with specialized pit organs that permit crude infrared imaging, and vampire bats are also have specialized detectors, located in their snouts, for the infrared (these are used to locate subcutaneous blood vessels in their prey). Let's see how well such organisms can do. The record holder in the insect world is probably the eyeless cave beetle, *Speophyes lucidulus* (Loftus and Corbière-Tichané, 1981; Corbière-Tichané and Loftus, 1983), whose antennal sensillum shows both hot and cold sensitivity, with a threshold for firing near  $3 \times 10^{-3} \text{ }^\circ\text{C}/\text{s} = 3 \text{ mdeg C/s}$ . Cave beetles live in large, dark caves, where the air is still and the ambient temperature and humidity fluctuate by only tiny amounts over long periods, and where good thermal detection clearly has a selective advantage. The California cockroach, *Periplaneta americana*, does just a bit less well:  $\sim 20 \text{ mdeg C/s}$  (Loftus, 1969). Presumably, environmental fluctuations in open air (convection, breezes, etc.) produce thermal drifts that make the need for better detection superfluous. The pit organ of the rattlesnake, or of the golden eyelash viper, *Bothrops schlegeli*, has a receptive field of  $\sim 60^\circ$ , yet the animal strikes to within  $5^\circ$  of its target. It can sense thermal gradients estimated at  $1\text{--}10 \text{ mdeg C/s}$  (Waterman, 1989). Bialek (1987) has derived an expression for the noise level in a thermoreceptor, considered as a blackbody radiator in thermal equilibrium with its environment. He found that the cave beetle, in particular, performs close to the physical limit. It is notable that this same physical limit can be derived by considering the beetle as a counter for infrared photons. Such photons have longer wavelengths (lower energies) than visible photons, and long averaging times are needed; this accounts for the slowness of thermal sensing.

Imae and colleagues (Maeda et al., 1976; Maeda and Imae, 1979; Imae, 1985) have studied thermotaxis in the bacteria *E. coli* and *S. typhimurium*, and found that temperature sensing is mediated by the same transmembrane receptors that are used to sense chemical changes. Bacteria are both cold and warm sensitive, and will move in thermal gradients to find the preferred temperature ( $\sim 37^\circ\text{C}$  for enteric bacteria).

The most abundant bacterial chemoreceptor, the serine transducer Tsr, also functions as the main heat sensor. In fact (and in consequence), addition of serine acts as a competitive inhibitor of increased temperature. *Tsr*<sup>-</sup> cells lose all responses to serine and much of their thermosensing ability. The less abundant chemoreceptor proteins, Tar, Trg, and Tap, also mediate thermotaxis, but are somewhat less temperature sensitive. Tsr, Tar, and Trg play additional roles as warm receptors; Tap (the dipeptide receptor) does double duty as a cold receptor (Nara et al., 1991). The threshold limit for bacterial thermotaxis is impressively low, and has been estimated at  $20 \text{ mdeg C/s}$  (Imae, 1985). The true value, in fact, may be even lower.

One way to improve signal-to-noise in a thermal detection system is to cool the detector so that it is no longer in thermal equilibrium with the surroundings. This is routinely done, for example, in man-made infrared sensors and cameras, which have Peltier refrigerators or liquid nitrogen reservoirs. Since thermal noise is proportional to the absolute (and not the relative) temperature, significant cooling is required. However, I am unaware of any example of true biological refrigeration, and in any case temperatures much below freezing are inconsistent with life! However, it has been observed that infrared detectors in the nose of the vampire bat are well insulated from body heat by a fatty pad at the base of the snout, and operate at temperatures several degrees below normal. The pit organs of vipers have a thin, gas-filled, insulating layer interposed between the sensory epithelium and the rest of the organ (Waterman, 1989). It may be that every bit helps.

### Electroreception Limits

Many aquatic organisms respond to electric fields, especially electric fish, sharks, skates, and rays (Kalmijn, 1982; Heiligenberg, 1984; Bullock and Heiligenberg, 1986). This is hardly surprising, since oceans are filled with electrical signals containing useful information. Freshwater fish live immersed in a weakly conducting medium, and saltwater fish live in a rather better conductor. The weakly electric fish navigate, communicate, and locate using electrical signals. Electrical responses have also been observed in insects, pigeons, and other terrestrial organisms. Electrostatic fields near the earth's surface generate field gradients  $\sim 1 \text{ V/cm}$  in air, while electrical storms can produce fields in excess of  $10 \text{ V/cm}$ . Even isolated chicken or bovine fibroblasts have been found to react to weak oscillatory electrical fields. What sets the limits for electroreception?

Most cells respond to oscillating (AC) electrical fields in the range  $10^{-2}\text{--}10^{-4} \text{ V/cm}$ . But sharks, in particular, respond to fields as low as  $10^{-9} \text{ V/cm}$  (Kalmijn, 1982)! The speeds of electrical oscillations vary widely: electric fish produce sharply pulsed fields with repetition rates from 5 to 3,000 Hz, with 200–400 Hz being typical. This falls into roughly the same range of frequencies as human hearing. Electrical impulses generated by the firing of nerves in swimming creatures also tend to fall in the audio range. So, following the same logic as with hearing, the energy of the quantum associated with these fields,  $h\nu$ , will be about ten orders of magnitude less than thermal energy  $kT$ : electroreception is dominated by thermal, not quantum, effects.

What is the magnitude of the receptor noise? The following argument is adapted from Weaver and Astumian (1990). By the Nyquist theorem,  $\langle \delta V^2 \rangle = 4RT\Delta\nu$ , where  $\delta V$  is the noise voltage fluctuation,  $R$  is the resistance of the medium,  $T$  is the

absolute temperature, and  $\Delta\nu$  is the frequency bandwidth of the receptor system. The bandwidth, in turn, will be limited by  $RC$  filtering in the cell. For a cell with a given membrane capacitance,  $C$ , the effective bandwidth becomes  $\Delta\nu = 1/4RC$ , so  $\langle\delta V^2\rangle = kT/C$  (Johnson noise). Modeling the cell as a sphere of radius  $r$ , we write  $C = 4\pi r^2\epsilon\epsilon_0/d$ , where  $d$  is the membrane thickness and  $\epsilon\epsilon_0$  is the product of the permittivity and the dielectric strength (S.I. units). Putting in reasonable values gives  $\langle V^2 \rangle^{1/2} \approx 3 \times 10^{-5}$  V, or 30  $\mu$ V. When an external field,  $E$ , is applied to the sphere, the transmembrane voltage changes by an amount  $\Delta V_{\text{mem}} \approx \frac{1}{2}Er$ . At the detection limit, this voltage will be comparable to the noise voltage. Setting  $\Delta V_{\text{mem}}$  equal to  $\langle\delta V^2\rangle^{1/2}$  gives

$$E_{\min} = \frac{2}{3r^2} \left( \frac{kTd}{4\pi\epsilon\epsilon_0} \right)^{1/2}$$

For  $r = 10$   $\mu$ m and  $d = 5$  nm,  $E_{\min} \approx 2 \times 10^{-2}$  V/cm. This “limit” is well above the observed threshold for most electroreceptors, and it’s seven orders of magnitude away from the shark’s performance!

One step toward resolution of this discrepancy is to make the cells long and narrow. This has the effect of causing a greater potential drop across the membrane in the longitudinal direction, and raises the effective limit to  $E_{\min} = 8 \times 10^{-4}$  V/cm for  $r = 25$   $\mu$ m and  $l = 150$   $\mu$ m,  $l$  being the cell’s length and  $r$  its cross-sectional radius (Weaver and Astumian, 1990). It is worth pointing out, in this context, that electroreceptive organs in fish contain highly elongated cells. But the limit is still too high. Suppose the electrical field were periodic, with frequency  $v$ . The cell could then average for a time,  $t$ , and collect input over  $N = vt$  cycles, improving its estimate by a factor  $1/\sqrt{N} = 1/\sqrt{vt}$ . The AC threshold for a spherical cell now becomes

$$E_{\min} = \frac{2}{3r^2} \left( \frac{kTd}{4\pi\epsilon\epsilon_0} \right)^{1/2} \frac{1}{\sqrt{vt}}$$

which, for  $v = 1$  kHz and  $t = 1,000$  s, gives a revised estimate of  $2 \times 10^{-5}$  V/cm (or  $8 \times 10^{-7}$  V/cm for an elongated cell). Finally, to bring about a further improvement in signal-to-noise, electroreceptor cells might implement a bandwidth-narrowing mechanism of the kind proposed for hearing. But, as discussed earlier, tuning cells to a narrow bandwidth does not improve noise immunity, unless some active mechanism underlies the tuning. Weaver and Astumian (1990) have proposed coupling the periodic electrical potential to a Michaelis-Menten type enzyme imbedded in the cell membrane as a way of achieving tuning, but it remains to be seen whether this is a workable scheme, and whether real electroreceptors employ any such mechanism.

## Magnetoreception Limits

Sharks, skates, and rays are so sensitive to electrical fields that they are able to sense the earth’s magnetic field through electromagnetic induction generated by their movements across magnetic flux lines. Their magnetoreceptive mechanism is indirect. On the other hand, birds, bees, butterflies, salmon, tuna fish (and probably a host of other organisms) are able to detect magnetic fields directly, probably by means of ferromagnetic or superparamagnetic detectors. The cellular basis of this form of magnetoreception remains a mystery, and magnetosensory organs (or cells) have yet to be identified. But here are some data worth pondering. The earth’s

magnetic field is about 0.5 Gauss at the surface (a note on units: 0.5 G = 50,000  $\gamma$  = 50  $\mu$ T; hence  $\gamma$ ’s equal nanotesla, nT). Its strength increases by some 3–5 $\gamma$  per kilometer from the equator to the geomagnetic pole. It varies periodically, the circadian variation being 10–100 $\gamma$  (it also reverses polarity chaotically every 10,000–100,000 years or so). Magnetic storms produce fluctuations of 10–3,000 $\gamma$ . Terrestrial magnetic anomalies (iron deposits and such) represent deviations of 30–30,000 $\gamma$ . To employ magnetic fields for serious navigation (i.e., determination of fractions of a kilometer), as pigeons and bees apparently do, a sensitivity of several  $\gamma$  would seem to be in order. In fact, behavioral thresholds have been measured at 5–20 $\gamma$  for pigeons and 1–10 $\gamma$  for honeybees (for reviews, see Martin and Lindauer, 1977; Kirschvink and Gould, 1981; Frankel, 1984; Gould, 1984; Kirschvink, 1989).

To compare magnetic orientational energy with thermal energy, one needs to know the strength of the magnetic interaction of the field with the sensor. In the absence of an identified sensor, this poses a problem! However, magnetotactic bacteria have been found that accumulate chains of single-domain particles of biological magnetite (“magnetosomes,” Blakemore, 1975), and become oriented during swimming by torques arising from interactions with the earth’s field. One might hazard a guess that putative eukaryotic magnetoreceptors will have comparable physical properties. Let us proceed accordingly. *A. magnetotacticum* has remnant magnetic moment around  $M = 10^{-12}$  e.m.u. The expression for orientational energy is  $\Delta E_{\text{mag}} = -\mathbf{M} \cdot \mathbf{B} = -MB \cos \theta$ , where  $B$  is the magnetic field strength and  $\theta$  is the angle between the field and the magnetic dipole. The mean orientation can be computed by weighting ( $\cos \theta$ ) by its Boltzmann probability,  $\exp(-E_{\text{mag}}/kT)$ , and averaging over all orientations. One obtains the Langevin function,  $\langle \cos \theta \rangle = \coth \alpha - 1/\alpha$ , where  $\alpha = MB/kT$ . Putting in the numbers for a bacterium gives  $\alpha \sim 16$  and  $\langle \cos \theta \rangle > 0.9$  when  $B = 0.5$  G (Frankel, 1984). Bacterial cells are therefore well oriented by the earth’s field. However, for  $B = 5\gamma$ ,  $\alpha$  drops to  $\sim 1.6 \times 10^{-3}$ . At this low field strength, the energy of orientation is less than 1/600th of the thermal energy. Just as for hearing and electroreception, such a minuscule energy raises questions about detector design. For now, there are no answers.

How does the magnetic field near the behavioral threshold ( $\sim 1\gamma$ ) compare with electromagnetic noise generated by nerves? After all, neurons in the brain are firing action potentials all the time, and these time-varying electric fields produce their own magnetic flux. As a starting point, we could use the law of Biot and Savart for the field produced at a radius,  $r$ , around a wire carrying current,  $I$ :  $B = \mu_0 I / 2\pi r$ , where  $\mu_0$  is the magnetic susceptibility of the vacuum (in S.I. units). Modeling a nerve fiber as a wire, we choose  $I \approx 10$  nA and  $r \approx 10$   $\mu$ m. This gives  $B = 0.2$  nT = 0.2 $\gamma$ . This background field strength is not very much smaller than the behavioral thresholds. Empirically, magnetoencephalographs, which use SQUID magnetometers to measure external electromagnetic fields produced by nervous activity in the brain, register magnetic signals ranging from picotesla up to nanotesla.

## Conclusions

The examples discussed here represent only some of the many sensory modalities. Certain senses, such as vision, appear to be quantum limited, at least in principle. Others, such as hearing, electroreception, and magnetoreception, are clearly not. Still others, like chemoreception and thermoreception, sit on the borderline. But if

there is an emergent theme, it is this. Where physical limits can be clearly established, examples can be found of organisms whose sensory performance approaches those physical limits rather closely. This is perhaps surprising, in view of the teleological arguments presented earlier, in the Introduction. However, the facts force us to conclude that Nature places a very high value on sensory perfection. So much so, in fact, that sensory systems have become highly evolved.

If this is indeed true, then one could turn the whole argument around and *adopt physical performance as a measure of optimality*, even though there may be no compelling evolutionary reason to do so. From this perspective, we assume that organisms have already done whatever it takes to achieve some measure of physical perfection, and then ask what design constraints will follow as consequences. Theoretical knowledge gained in this way can be used to guide further experimentation, for example, by searching for hitherto-unseen features or properties: the physics has predictive value.

Recently, Bialek and co-workers have applied optimization considerations to the information carried by spiking neurons in the movement-sensitive portion of the fly visual system (Bialek et al., 1991). By so doing, they have been able to “decode” signals carried by spike sequences, and thereby quantify the information conveyed. The measured information transfer rate turns out to be almost as high as the absolute bound (physical limit) set by the spike entropy: several bits of information per spike. So it seems that not just sensory transducers, but secondary neurons—perhaps even the entire nervous system—might be usefully explored using variational principles based on selected measures of optimization (optimal transduction, optimal encoding, optimal processing, etc.). Now, if we only had a better idea of exactly what those measures of optimization ought to be . . .

## Appendix: Thermal Fluctuations in Concentration

To calculate the work done in producing a local concentration change, we write:

$$\delta E = \delta G - \mu \delta n$$

where  $E$  is the work,  $G$  is the Gibbs' free energy,  $\mu$  is the chemical potential, and  $n$  is the number of molecules. Expanding  $G$  about equilibrium in a Taylor's series:

$$\delta G = \partial G|_0 + \frac{\partial G}{\partial n}|_0 \delta n + \frac{\partial^2 G}{\partial n^2}|_0 \delta n^2 + \dots$$

But  $\mu \equiv \partial G / \partial n$ , so upon substitution:

$$\delta G = \partial G|_0 + \mu|_0 \delta n + \frac{1}{2} \frac{\partial \mu}{\partial n}|_0 \delta n^2 + \dots$$

Since  $\partial G|_0 = 0$  at equilibrium (by definition), retaining terms up to second order, we get:

$$(\delta G - \mu \delta n) = \delta E = \frac{1}{2} \frac{\partial \mu}{\partial n}|_0 \delta n^2$$

The chemical potential of a species in an ideal (dilute) solution is given by

$$\mu = kT \ln C = kT \ln \left( \frac{n}{V} \right)$$

where  $C$  is its concentration and  $V$  is the volume. So  $\partial \mu / \partial n = (kT/n)$ ; substituting this expression into the work gives the energy associated with a thermal fluctuation:

$$\delta E = \frac{1}{2} \frac{kT}{n} \delta n^2$$

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