

PHYSICAL LIMITS TO SENSATION AND PERCEPTION

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PERSPECTIVES AND OVERVIEW

One of the most important conceptual developments in modern physics is the appreciation of fundamental limits to the reliability of even the most precise measurements. As these ideas were first explored in the early years of this century, several of the pioneers of the subject turned to a natural question: To what extent do our sensory systems, which are after all

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physical measuring devices, approach the limits to measurement imposed by the laws of physics?

The idea that the boundaries of perception are set by fundamental physical principles is very attractive. Tests of this hypothesis required several developments:

1. *Experimental methodology.* At the time that physical limits to perception were first proposed, quantitative description of perceptual performance was in its infancy. It was more than forty years before the concept of "sensory threshold" was clarified and translated into practical experiments.
2. *Theoretical complexity.* Our sense organs are complicated structures, and powerful theoretical methods are required to understand the physical limits to measurement in such systems.
3. *Biological significance.* Suppose we succeed in demonstrating that a particular sensory system reaches the relevant physical limits to its performance. What have we learned?

Substantial advances in each of these areas have been made in the last decade. Perhaps the most important has been the realization that a sensory system that reaches the physical limits to its performance is exceptional. Broad classes of plausible mechanisms simply cannot reach these limits, and in favorable cases very specific requirements are placed on the mechanisms of filtering, transduction, and amplification within the receptor cell.

The ideas that are relevant for understanding the physical limits to sensation and perception range from the quantum theory of measurement to the zoology of animals adapted to different sensory environments. Obviously it is impossible to do justice to this complete range of topics in a short review. What I do hope to communicate is how studies of the physical limits to sensory performance have changed our view of the sensory systems, both at the level of transduction mechanisms in receptor cells and at the level of the neural mechanisms responsible for processing sensory information.

FOUNDATIONS

Of major importance in this review is clarity in the use of phrases such as "sensory threshold," for behind fuzziness of language lurk serious conceptual problems. Here I review the theoretical background.

Signals and Noise, Detectability and Discriminability

It was once believed that each sensory system has a threshold below which stimuli generate no percept. Although variants of this idea continue to

appear, the notion of a fixed sensory threshold is wrong. The theory of signal detectability (89, 103) provides an alternative view, which has been systematically applied in a wide variety of psychophysical experiments (61). There is also significant physiological evidence against the classical threshold concept. In the inner ear, for example, receptor potentials are proportional to sound pressure (or pressure squared) for small-amplitude, pure-tone stimuli (42, 45, 60). The probability per unit time of auditory nerve firing is also modulated linearly or quadratically (71, 72, 90): An arbitrarily small stimulus generates a proportionately small but still non-zero response.

Limits to the detectability of small stimuli are set by noise. If we are trying to measure some stimulus x , we usually observe some variable y whose average value is (for example) proportional to x ($\langle y \rangle = gx$) but fluctuates as described by the probability distribution $P(y|x)$ for y given any particular x . These distributions are not abstract mathematical objects; x and y represent physical quantities, and hence $P(y|x)$ embodies assumptions about some underlying physical processes.

The typical sensory threshold experiment is to ask if we can distinguish between $x = 0$ (no signal) and some $x = x_0 \neq 0$; the two alternatives occur randomly with probabilities $P(x = 0)$ and $P(x = x_0)$. If we have just observed some particular y , the probability that the stimulus was $x = x_0$ is, by Bayes' theorem, $P(x = x_0|y) = P(y|x_0)P(x = x_0)/P(y)$, with $P(y) = P(y|x_0)P(x = x_0) + P(y|0)P(x = 0)$; the probability is similarly calculated for $P(x = 0|y)$. Optimal unbiased discrimination is based on maximum likelihood (61): If $\lambda(y) = \ln [P(x = x_0|y)/P(x = 0|y)] > 0$, we guess that y was generated by the signal $x = x_0$, while if $\lambda(y) < 0$ we guess that $x = 0$. The probability of correctly identifying the signal is then $P_c(x = x_0 \text{ vs } x = 0) = \int dy P(y|x_0)\Theta[\lambda(y)]$, where $\Theta[z]$ is the unit step function; $\Theta[z > 0] = 1$, $\Theta[z < 0] = 0$.

An example is independent additive Gaussian noise; $y = gx + \Delta$, where Δ is a random variable chosen from a Gaussian distribution whose statistics are independent of x , so that $P(y|x) = (2\pi\sigma^2)^{-1/2} \exp[-(y - gx)^2/2\sigma^2]$. If the stimuli $x = 0$ and $x = x_0$ are a priori equally likely, the maximum-likelihood decision rule is just that $x = x_0$ if $y > gx_0/2$. The probability of correctly identifying $x = x_0$ is $P_c(x = x_0 \text{ vs } x = 0) = (1/2)[1 + \Phi(gx_0/2\sigma)]$, with the error function $\Phi(z) = (2/\pi)^{1/2} \int_0^z d\zeta \exp(-\zeta^2/2)$. As the signal-to-noise ratio or "detectability," $d' = gx_0/\sigma$, approaches zero, $P_c \rightarrow \frac{1}{2}$, which corresponds to guessing randomly $x = 0$ or $x = x_0$. As $d' \rightarrow \infty$ we find $P_c \rightarrow 1$, so at large signal-to-noise ratios discrimination is perfect. Unit signal-to-noise ratio, $d' = 1$, corresponds to $P_c = 0.76$; this provides a convenient "threshold for reliable detection."

When x and y are functions of time (100) we write $y(t) =$

$\int dt' g(t, t')x(t') + \Delta(t)$. If $y(t)$ is a physical coordinate that responds to external signals $x(t)$, then the response must be causal; $y(t)$ cannot depend on $x(t')$ unless $t \geq t'$. It is also reasonable to assume that the response to a particular stimulus does not depend on the precise arrival time of that stimulus, so $g(t, t') = g(t - t')$ and $g(\tau < 0) = 0$. Similarly, the physical processes that generate the noise are not changing in time; any particular noise waveform $\Delta(t - t_0)$ occurs with equal probability for any time t_0 . The technical term for this property is "stationarity." For a finite time interval $-T/2 \leq t \leq T/2$ we can write $\Delta(t) = T^{-1/2} \sum_n \Delta_n \exp(-in\pi t/T)$. A stationary Gaussian noise source is characterized by $P(\{\Delta_n\}) = Z^{-1} \exp[-(1/2) \sum_n \Delta_n \Delta_{-n} / S_n]$; Z is a normalization constant. Other Gaussian distributions are possible, but they correspond to nonstationary noise. For large T the "variances" S_n are a continuous function of $\omega = n\pi/T$, $S_\Delta(\omega) = \int d\tau e^{+i\omega\tau} \langle \Delta(t)\Delta(t-\tau) \rangle$, termed the spectral density of the noise. The spectral density can also be defined by averaging the Fourier components² of $\Delta(t)$: $\tilde{\Delta}(\omega) = \int dt e^{+i\omega t} \Delta(t)$, $\langle \tilde{\Delta}(\omega)\tilde{\Delta}(\omega') \rangle = S_\Delta(\omega)2\pi\delta(\omega + \omega')$. Noise sources are often characterized by qualitative features of their spectra. Thus approximately constant $S(\omega)$ is termed white noise, $S(\omega) \sim 1/\omega$ is "1/f" noise, and so on.

Computation of the probability of correct discrimination between, for example, $x(t) = 0$ and $x(t) = x_0(t)$ is now straightforward. The result is of the same form as before, with an effective signal-to-noise ratio

$$(d')^2 = \int \frac{d\omega}{2\pi} \frac{1}{S_\Delta(\omega)} |\tilde{g}(\omega)\tilde{x}_0(\omega)|^2. \quad 1.$$

This result provides a rigorous basis for comparing sensory thresholds with physical models. If the model noise source is Gaussian, $d' = 1$ defines a signal level such that 76% correct signal identification is possible. If we have correctly identified the noise source it is impossible for a smaller signal to be detected with this reliability. Should smaller signals be reliably detected we have unambiguous evidence that our physical model is incorrect.

A second example of signal detection concepts is in modulated Poisson processes (100). These processes consist of discrete events, such as nerve impulses or photon arrivals at the retina, characterized by their arrival times t_μ , with the probability of an event occurring between t and $t + dt$ given by $r(t)dt$. Imagine now that we are forced to discriminate, in a time interval $0 < t < T$, between two signals that give rise to rate functions $r_+(t)$ and $r_-(t)$. In the limit that the "signal" $r_+(t) - r_-(t) = \delta r(t)$ is

² In the following, $\tilde{f}(\omega)$ always denotes the Fourier transform of a function $f(t)$, with the "+i" sign convention as shown here.

small, we can evaluate $P_c(+ \text{ vs } -)$ in closed form; the result is identical to that for a signal in Gaussian noise, with the detectability $(d')^2 = \int_0^T d\tau \delta r^2(\tau)/r(\tau)$.

Noise from Classical Statistical Mechanics

The basic principle of equilibrium statistical mechanics (85, 88) is that the probability of being in a configuration with energy E is proportional to $\exp(-E/k_B T)$, where T is the absolute temperature of the environment with which the system equilibrates and Boltzmann's constant k_B , is 1.36×10^{-23} J/K. Because this description is probabilistic almost any measurable quantity will fluctuate. These fluctuations act as a source of noise, which limits the reliability of any measurement.

For a mass m on a spring of stiffness κ the energy is $E = \frac{1}{2}mv^2 + \frac{1}{2}\kappa x^2$, where v is the velocity and x is the displacement of the object. Thus $P(x, v) = Z^{-1} \exp(-mv^2/2k_B T - \kappa x^2/2k_B T)$. We see that x and v are independent Gaussian random variables with zero mean and with variances $\langle(\delta v)^2\rangle = k_B T/m$ and $\langle(\delta x)^2\rangle = k_B T/\kappa$. The mean potential energy is $\frac{1}{2}\kappa\langle(\delta x)^2\rangle = \frac{1}{2}k_B T$, and the mean kinetic energy is also $\frac{1}{2}k_B T$. A system in thermal equilibrium is not a state of minimum energy, but fluctuates among many states; its mean energy is a measure of the temperature. This is the equipartition theorem, and the fluctuations that enforce this theorem are termed "thermal noise."

A second example concerns fluctuations in the energy itself. If the system has a set of states with energies E_s , the probability distribution of the energy is $P(E) = Z^{-1} \sum_s \delta(E - E_s) \exp(-E_s/k_B T)$. It can be readily verified that $\langle(\delta E)^2\rangle = k_B T^2(\partial\langle E\rangle/\partial T)$, where $\partial\langle E\rangle/\partial T$ is the specific heat C_v . It is convenient to think of the internal energy noise as equivalent to temperature fluctuations: $\langle(\delta T)^2\rangle = T^2 k_B/C_v$.

These results give the probability of finding any particular coordinate at one instant. If the receptor cell itself does not filter this coordinate or average it over time, then the equipartition noise level sets the limit to the detection of small signals. If the receptor cell does filter the incoming signal we need to know the temporal properties of the noise; these are determined by the fluctuation-dissipation theorem (FDT).

Consider again a mass-spring system, but now immersed in a fluid. Interaction with the fluid leads, in the simplest cases, to a drag force $F_{\text{drag}} = -\gamma(dx/dt)$. In addition, random collisions with the individual molecules of the fluid lead to a fluctuating or Langevin force δF . The Langevin equation of motion is then (85) $m(d^2x/dt^2) + \gamma(dx/dt) + \kappa x = F_{\text{ext}} + \delta F$, where F_{ext} is an external force. The properties of δF must be such that the total fluctuations $\langle(\delta x)^2\rangle$ agree with equipartition; dissipative processes remove energy from the system and the fluctuations generate a power flow

into the system to compensate and maintain equipartition. If the relaxation time for the energy is τ_E the power flow should thus be $\sim k_B T / \tau_E$. In a resonant system where the response bandwidth, Δf , is $\sim 1/\tau_E$ the “thermal noise power,” P_N , is $4k_B T \Delta f$ (99).

More generally, for a coordinate x that responds linearly to external forces $\tilde{x}(\omega) = \tilde{\alpha}(\omega)\tilde{F}(\omega)$, the response function $\tilde{\alpha}(\omega)$ is in general complex, and its imaginary part $\tilde{\alpha}''(\omega)$ is associated with dissipation. The FDT states that $x(t)$ exhibits Gaussian noise of spectral density (88) $S_x(\omega) = k_B T \omega^{-1} \tilde{\alpha}''(\omega)$. One can think of this noise as arising from a Langevin force with spectral density

$$S_F(\omega) = \frac{k_B T}{\omega} \frac{\tilde{\alpha}''(\omega)}{|\tilde{\alpha}(\omega)|^2} = \frac{k_B T}{\omega} \left[\frac{1}{\tilde{\alpha}(\omega)} \right]'' \quad 2.$$

In a chemical system, the coordinates are the concentrations of the various species, forces are the free-energy differences among the species (75), and response functions are determined by the kinetic equations. Application of the FDT to such models gives results that agree with statistical descriptions of molecules flickering among different chemical states (126), but such statistical pictures require assumptions about the behavior of individual molecules beyond those required to reproduce the macroscopic kinetics. The fluctuation-dissipation theorem guarantees that any microscopic mechanism that generates certain macroscopic behavior necessarily generates thermal noise of known characteristics.

Noise from Quantum Mechanics

Even at $T = 0$, in the absence of thermal noise, most coordinates remain random variables. This noise arises from quantum mechanics and can be qualitatively understood in terms of Heisenberg’s uncertainty principle, which constrains the reliability of simultaneous measurements of complementary variables, such as position and momentum. Repeated measurements of these quantities will show that they fluctuate with standard deviation δx and δp ; the uncertainty principle states that $\delta p \delta x \gtrsim \hbar/2$, with Planck’s constant $\hbar = 1.054 \times 10^{-34}$ J-s. If we measure the coordinate $x(t)$ as a function of time we can calculate the velocity and hence the momentum, so unless such measurements have a noise level proportional to \hbar the uncertainty principle will be violated. The “quantum noise” that enforces the uncertainty principle provides an independent limit to the reliability of measurements.

The spectral density of noise in a quantum system can be calculated by imagining a sequence of measurements of $x(t)$ at times t_i (54, 111, 132), or

by considering that the measurement of $x(t)$ constrains the possible paths (51a) that the system could have taken during the observation time (38, 95). The two methods give identical results whenever they can be compared meaningfully. For example, in a linear system with response function $\tilde{\alpha}(\omega)$ in equilibrium at temperature T , the spectral density of coordinate fluctuations is

$$S_x(\omega) = \frac{\hbar}{2} \tilde{\alpha}''(\omega) \coth(\hbar\omega/2k_B T) + \frac{\hbar}{2} |\tilde{\alpha}(\omega)|. \quad 3.$$

The first term in Equation 3 is the quantum version of the fluctuation-dissipation theorem. If the thermal energy $k_B T$ is much larger than the quantum energy $\hbar\omega$, we recover the classical result. This simple energetic comparison is the same one that governs the significance of quantum effects in thermodynamics (88). The second term in Equation 3 is a dynamical contribution to the noise, which cannot be understood from equilibrium thermodynamics; it expresses purely quantum phenomena such as “spreading of the wave packet” (51a). As a result, quantum effects can be important even if the quantum energy $\hbar\omega$ is $\sim k_B T \tilde{\alpha}''(\omega)/|\tilde{\alpha}(\omega)|$, which is much smaller than the thermal energy if the dissipation or damping, $\sim \tilde{\alpha}''(\omega)$, is small (32). This happens in very sharply tuned mechanical and electrical resonators.

There are many situations in which sharp tuning is desirable but the natural mechanical or electrical parameters of the system do not allow it. Under these conditions we can modify the passive dynamics using active feedback: We measure some coordinate, amplify and filter the signal, and apply a force back to the system in proportion to this signal. If we start with a system whose response function is $\tilde{\alpha}(\omega)$ and apply a feedback force $\tilde{F}_{\text{feedback}}(\omega) = \tilde{\gamma}(\omega)\tilde{x}(\omega)$, then $\tilde{\alpha}(\omega) \rightarrow \tilde{\alpha}_{\text{eff}}(\omega) = [\tilde{\alpha}^{-1}(\omega) - \tilde{\gamma}(\omega)]^{-1}$. In this way we can synthesize resonances at frequencies where there are no resonances in the passive system or sharpen the frequency selectivity of an existing resonance. We expect that as the response bandwidth of the active system is narrowed quantum noise becomes more significant.

The dominant noise source in a very narrow-band active feedback system is the amplifier. Viewed quantum mechanically, an amplifier is a device that effects a transformation from a set of coordinates at its input to a corresponding set at the output. Any such transformation that arises through the time evolution of a physical system must be unitary; it must preserve the overall conservation of probability as well as the formal structure of complementary variables on which the uncertainty principle is based. This requirement results in a quantum limit to the noise level of linear amplifiers (37). A feedback system is more complicated than an

isolated amplifier because the output of the amplifier is connected back to the input, but the physics is the same (19). In our example with $\tilde{F}_{\text{feedback}}(\omega) = \tilde{\gamma}(\omega)\tilde{x}(\omega)$, the amplifier contributes an effective force noise with spectral density $S_F^{\text{eff}}(\omega) \sim \frac{1}{2}\hbar|\tilde{\gamma}(\omega)|^2|\tilde{\alpha}_{\text{eff}}(\omega)|$. As the bandwidth decreases, $\tilde{\alpha}_{\text{eff}}(\omega)$ becomes more sharply peaked and the noise force increases for frequencies near resonance.

A different quantum noise is usually associated with optical phenomena. The energy of a system has contributions both from coordinates (potential energy) and from their conjugate momenta (kinetic energy). A classical force couples only to the coordinate. Thus we expect that such a force cannot, by the uncertainty principle, deposit a definite energy in the oscillator. Since the oscillator energy is in discrete quanta (photons in the electromagnetic case) of magnitude $\hbar\omega$, a classical force must produce a superposition of states with different numbers of quanta. In this case the probability of finding a given number of quanta obeys the Poisson distribution, although other distributions are possible (56). This randomness of signals, e.g. photon arrivals at a detector, means that measurements of energy or light intensity are subject to an irreducible quantum noise.

CASE STUDIES: SIMPLE SENSORY TASKS

In this section I examine the simplest tasks that confront the sensory systems: detection of small signals and discrimination of small changes in a constant background. I emphasize not only the extent of agreement between theoretical limits and observed performance, but also the more general lessons about function and mechanism that can be learned from this comparison.

Photon Counting in Vision

In 1909 Lorentz suggested that the eye could count single photons.³ In the 1940s de Vries (50) and Rose (105) noted that the random arrival of photons at the retina also sets a limit to the reliability of intensity discrimination. Their prediction that the threshold for reliable discrimination varies as $\delta I \sim I^{1/2}$ has been confirmed over a range of I in both behavioral and physiological experiments (5).

At about the same time that de Vries carried out the above work, Hecht et al (65) and van der Velden (125) independently mounted one of the classic experiments of modern biophysics. Suppose that effective absorp-

³ For a discussion of the history see Bouman (31). I am grateful to Professor Bouman for clarifying Lorentz' role in the development of these ideas. Of further historical interest is Bohr's (30) discussion of possible quantum limits to other senses.

tion of k or more photons by the retina constitutes "seeing." If a flash of light delivers on average N photons, then as noted above there are conditions under which the number of photons actually absorbed by the retina will be a random variable chosen from a Poisson distribution whose mean is QN , with Q the quantum efficiency. The probability of the observer seeing is then

$$P_s = e^{-QN} \sum_{l=k}^{\infty} \frac{(QN)^l}{l!}. \quad 4.$$

The curve P_s vs $\log N$ has a shape that is diagnostic of k and independent of Q .

Hecht et al and van der Velden measured the frequency of seeing and compared it with the predictions of Equation 4. Hecht et al found excellent fits to their data for $k = 5-7$ photons; van der Velden found $k = 2$ photons. Since the few photons in question are distributed over several hundred receptor cells, the probability that any one cell captures two photons is miniscule. Absorption of a single photon must thus produce a significant signal in one receptor, and each such signal must contribute to vision.

Teich et al (122, 123) performed frequency-of-seeing experiments with two different light sources, one with Poisson statistics and one for which the photo-count distribution is broader than Poisson. They observed decreased reliability of perception with the latter light source, as expected if the variability of human responses is indeed set by the random absorption of photons.

Sakitt (110) asked subjects to score visual stimuli on a scale from zero to six based on perceived intensity. The mean rating varied linearly with the mean number of photons arriving at the cornea. If the rating is equal to the number of photo-counts at the retina then the probability of a rating greater than or equal to k should follow Equation 4; in Sakitt's experiment there are five independent curves that must all be fit by the same value of Q . Agreement with the Poisson model is excellent. Apparently humans can quite literally count single photons.

Single-photon responses from photoreceptor cells were first reported in intracellular voltage records from *Limulus* (55). Voltage recordings from single vertebrate rod cells do not reveal obvious quantal responses because the rods are electrically coupled (39), but the photocurrent can be directly recorded by sucking the outer segment of the rod into a pipette (8). In response to one photon, a rod cell from the toad, *Bufo marinus*, produces a current pulse (9) that can often be fit by $I(t) = I_0(t/\tau)^3 \exp(-t/\tau)$, with $I_0 \sim 1.2$ pA and $\tau \sim 0.7-1.4$ s. The current noise consists of two components (10). The first is Gaussian noise with spectral density

$S_f(\omega) = S_f(0)/[1 + (\omega\tau)^2]^{-2}$; $S_f(0) \sim 0.1 \text{ pA}^2 \text{ Hz}^{-1}$. The detectability of a single photon, from Equation 1, is

$$(d')^2 = \int \frac{d\omega}{2\pi} \frac{1}{S_f(\omega)} \left| \int_0^\infty dt I(t) e^{i\omega t} \right|^2 = \frac{I_{0\tau}^2}{2S_f(0)} \sim 30\text{--}75.$$

The probability of confusing a single photon with the Gaussian noise background is thus less than 1%. The second noise arises from spontaneous current pulses occurring at a rate $r = 0.021 \text{ s}^{-1}$ (20°C), which are indistinguishable from the single-photon response. The level of this noise is very close to psychophysical estimates (4) of the “dark noise” level in vision (10, 11).

The retinal chromophore of the visual pigment rhodopsin undergoes *cis/trans* isomerization in response to photon absorption (27). The observed dark noise places a bound on the rate of spontaneous isomerization; with 2×10^9 rhodopsin molecules in the pipette, the rate per molecule is 10^{-11} s^{-1} , or once every 3000 years (10, 11). If the rate for retinal in solution, $4 \times 10^{-8} \text{ s}^{-1}$ at 20°C (68), applied to the actual visual pigment, photon counting would be impossible. In contrast, the photoisomerization rate is $> 3 \times 10^{11} \text{ s}^{-1}$ (27), and the initial event must be even faster to account for the low quantum yield of fluorescence (51); on these time scales the molecule is not at a definite temperature (18). The photoisomerization rate of free retinal is 10^9 s^{-1} (70). Note that fluorescence quenching is functionally important; without it a photon absorbed at one point would be re-emitted and possibly counted in a neighboring rod cell, so that both sensitivity and spatial resolution would be sacrificed.

Since the activation energies for spontaneous isomerization of free retinal and rhodopsin are similar (10, 11, 68), the suppression of dark noise is not simply an energetic effect but is dynamical, as are the special features of ultrafast reactions (18). Thus to understand how the rod cell counts single photons, we require a clear physical picture of how protein dynamics can influence reaction rates (20, 59).

Threshold Signals in the Inner Ear

The classic experiments of von Békésy (127) and Autrum (2, 3) suggested that hearing organs can respond to displacements of atomic and subatomic dimension. Widely divergent claims have been made regarding the relation of these displacements to the expected physical noise level (3, 50a–c, 52, 62, 91). Schweitzer and I re-examined this issue and reported preliminary conclusions beginning in 1980 (16–18, 22–24, 114). New experiments allow improved estimates of the threshold signals, and parameters that we had

to guess in our original noise calculations have now been measured. We have thus substantially improved our account of the noise problem (W. Bialek & A. Schweitzer, in preparation); here I outline the issues.

In the simplest model of hearing the hair cell makes instantaneous, or broad-band, measurements on the position of its stereocilia (69). Broad-band measurements of the hair-cell voltage will then exhibit noise equivalent to at least the equipartition noise of the ciliary bundle, $\langle(\delta x)^2\rangle = k_B T/\kappa$. In no inner-ear organ has the bundle stiffness been found to exceed $\kappa \sim 10^{-3} \text{ N m}^{-1}$ (44, 53, 67, 119). Thus $\delta x_{\text{RMS}} > 2 \times 10^{-9} \text{ m}$.

In the turtle (1, 42) the sensitivity of hair-cell voltage to sinusoidal sound pressure at the eardrum is $\sim 10^3 \text{ mV Pa}^{-1}$, the broad-band noise level is 1–5 mV, and the displacement of the basilar membrane (on which the hair cells sit) per unit pressure is $\sim 85 \text{ nm Pa}^{-1}$ (43). These data determine an equivalent broad-band displacement noise of $8.5\text{--}43 \times 10^{-11} \text{ m}$.

In the guinea pig (45, 107) inner hair cells produce median responses of 0.2 mV to pure-tone sound pressures at the behavioral threshold; the most sensitive cells produce 1.6 mV. Noise levels appear to be less than 1 mV. In Mössbauer studies of the guinea pig basilar membrane (116) the threshold for observing the “compound action potential” corresponded to a displacement of $\sim 3.5 \times 10^{-10} \text{ m}$, but this threshold is typically (46) 10–20 dB above the behavioral threshold for reliable detection. In interferometric studies of the cat cochlea (78–82), displacements of at most 10^{-10} m were observed at 23–25 dB SPL (dB re 20 μPa), while the mean behavioral threshold at these frequencies is -5 dB SPL at the eardrum (94). These data suggest that displacements smaller than 10^{-10} m are reliably detected. Further evidence for the detection of subångström signals is provided by the vibratory receptors of the frog *Leptodactylus albilabris* (92).

The signals that can be reliably detected in broad-band recordings from single hair cells are at least 25 dB smaller than our estimates of the broad-band ciliary displacement noise. This suggests that the hair cell in fact filters the mechanical signal. Other possible solutions, such as amplification of basilar membrane motion, suffer from independent noise problems (17, 18).

If ciliary mechanics are dominated by stiffness and damping, the spectral density of displacement noise from the FDT is $S_x = k_B T \gamma [\kappa^2 + (\gamma\omega)^2]^{-1}$. From attempts to displace ciliary bundles with fluid streams (53), an upper bound on the drag coefficient has been determined (24): $\gamma < 10^{-8} \text{ N-s m}^{-1}$ in the 1 kHz region. This value is not far above estimates from hydrodynamic models (33). With $\gamma = 10^{-8} \text{ N-s m}^{-1}$ and $\kappa = 10^{-3} \text{ N m}^{-1}$, $S_x = (6 \times 10^{-12})^2 \text{ m}^2 \text{ Hz}^{-1}$. Reliable detection of displacements smaller than $\delta x \sim 1 \text{ \AA}$ requires a bandwidth $\Delta f < 100 \text{ Hz}$, in agreement with

direct measures of auditory tuning (91). The threshold power, $4k_B T \Delta f$, is $\sim 1.6 \times 10^{-18}$ W, in agreement with experiment (83).

If the bundle were passively resonant (129) forces would be filtered but the total (equipartition) displacement noise would just be compressed into a narrow band around the resonance, not reduced. Electrical filtering with conventional membrane channels (126) is necessarily noisy, and is unlikely to overcome thermal noise without additional amplification (18). These are not arguments against the existence of such mechanisms, but rather indications that they are not sufficient to solve the noise problem.

One mechanism by which the hair cell can solve the thermal noise problem is active feedback. As noted above, application of a feedback force proportional to an amplified and phase-shifted version of the displacement allows substantial bandwidth narrowing and hence thermal noise reduction (97). Gold (57) suggested in 1948 that active mechanisms might operate in the inner ear, although he focused on basilar membrane rather than stereocilium mechanics. A biological example of active mechanical filtering is provided by the asynchronous insect flight muscles (133).

Gold noted the most dramatic property of active filters: If they became unstable under pathological conditions the ear would emit sound. Consistent observation of spontaneous and evoked acoustic emissions from the ear began in 1978 (76, 77, 91, 135), and the active filter hypothesis was revived (47, 48, 77). Narrow-band acoustic emissions can, however, be explained even if active elements are not present in the mechanics of the inner ear (J. B. Allen, unpublished; 91).

Analysis of instabilities of active filters in the presence of noise (18, 23, 25) reveals qualitative statistical properties that cannot be reproduced by passive, stable systems. If $x = 0$ is a stable point, the probability distribution of x has a local maximum at $x = 0$; the system tends to spend as much time as possible at the stable point. The opposite is true for an unstable system; the system tries to diverge from $x = 0$, and the distribution has a local minimum at this point. The probability distribution for ear-canal sound pressure in frequency bands surrounding an emission from the human ear (25, 134; W. Bialek & H. P. Wit, in preparation) shows a clear local minimum of the distribution at zero sound pressure. Other statistical properties agree quantitatively with predictions from simple active filter models.

A second approach to testing the active filter scenario is to search for violations of the fluctuation-dissipation or equipartition theorems (16, 18). These theorems apply to a system in equilibrium with its environment, while an active filter is held away from equilibrium by the feedback forces from the amplifier. Direct measurements on ciliary bundles from the turtle basilar papilla have demonstrated that equipartition is indeed violated.

(44). This is strong evidence that the picture derived from the noise analysis of active filtering at the level of the stereocilia is qualitatively correct.

Limits beyond those imposed by thermal noise are imposed by quantum mechanics. Calculation of these limits requires more care⁴ (W. Bialek & A. Schweitzer, in preparation), but to understand why quantum noise can be relevant a less thorough approach is acceptable.

If feedback is applied to generate a resonance at frequency ω in a bundle dominated by stiffness and damping, then from the results quoted above the quantum force noise added by the amplifier is $\delta F_{\text{RMS}} \sim (\hbar\omega\kappa/2)^{1/2} \sim 10^{-17}$ N at $\omega \sim 10^3$ Hz. If the ciliary bundle stands freely in the fluid, this force noise is equivalent to a fluid displacement noise of $\delta x_{\text{fl}} \sim \delta F/\gamma\omega \sim 10^{-12}$ m, which is only about one order of magnitude smaller than smallest signals for which we have evidence of reliable detection.

At very high frequencies the hair cell responds to a low-pass filtered version of x^2 , the square of ciliary displacement. Such measurements are qualitatively different from measurements of x itself and are subject to different limits. To see this, note that the force conjugate to x^2 is actually half the stiffness (κ), since $\frac{1}{2}\kappa x^2$ is the potential energy. At temperature T the mean-square displacement is just $k_B T/\kappa$, so the response of x^2 to changes in κ is described by $\alpha \sim k_B T/\kappa^2$. From Equation 3, the effective quantum noise level, δx_{eff} , is $\sim (k_B T\hbar/\kappa^2\tau)^{1/4}$ in an integration time τ , or once again $\delta x \sim 10^{-12}$ m for $\tau \sim 100$ ms (41).

If we could say with certainty that the ear makes a quantum-limited measurement we could conclude with equal certainty that the processes of transduction, amplification, and filtering that make this measurement possible could not be described in conventional chemical terms (18, 24).

Molecule Counting in Chemoreception

Many biological processes are chemoreceptive in character. The true chemical senses, from chemotaxis in bacteria to smell and taste in primates, are obvious examples, but the immune and hormonal systems face the same problems of molecular recognition. Here we are interested in those systems for which the most quantitative data are available at small signal levels.

Stuiver & de Vries (50d, 120) performed a frequency-of-smelling experiment on human subjects. While the results are not as clear as for vision, the evidence points to reliable detection of ~ 50 molecules. Similar experiments

⁴Our preliminary discussions were based in part on an incorrect estimate of the ciliary damping constant, as noted previously (24). Below I use the estimate derived from Reference 53, which I believe to be accurate.

have been done on the generation of nerve impulses in insect olfactory receptors (74).

Perhaps the most detailed studies of chemoreception at small signal levels have been studies of bacterial chemotaxis (14). Berg & Purcell (15) beautifully clarified the theory of noise in such measurements. I summarize their conclusions regarding the physical limits to chemotactic performance:

1. If an organism the size of a bacterium suddenly stops propelling itself, inertia will carry it only a few ångströms against the viscosity of the surrounding water.
2. The flux of molecules to the cell is controlled by the size of the cell and the relevant molecular diffusion constant. No energetically feasible amount of movement can improve on diffusive intake. Bacteria can swim to more favorable environments, but this requires that they be able to sense their environment.
3. The rate at which cell-surface receptors adsorb molecules from the surrounding fluid is also limited by diffusion, but the total rate is nearly maximal when only a small fraction of the cell surface is covered by receptors.
4. If a small cell swims relatively rapidly its attempts to measure concentration differences from front to back are subject to large artifacts and poor signal-to-noise ratios. To measure gradients the organism must, while swimming, compare concentrations at different times.
5. In comparing concentrations the bacterium must swim straight for a minimum length of time to guarantee that it takes an independent sample of the concentration. If the time interval is too long the comparison does not work because rotational Brownian motion will have randomized the cell trajectory.
6. Random fluctuations in concentration and in the occupancy of cell-surface receptors provide a significant source of noise in chemotaxis. This can be overcome only by temporal averaging.
7. As with the diffusive flux, the signal-to-noise ratio for chemoreception saturates rapidly as the number of receptors increases.
8. The chemotactic performance of *Escherichia coli* and *Salmonella typhimurium* approaches the limits imposed by chemical fluctuations. These cells must thus count each molecule that binds to their surface receptors.

A generalization of the Berg-Purcell arguments in which chemical fluctuations are treated as a form of thermal noise is in complete agreement with the points above (W. Bialek, unpublished). In particular, while more complex kinetic schemes for receptor-ligand interaction lead to changes in the noise level, the noise has a minimum level that is set only by the physics of diffusion. The use of thermal noise theory also allows us to explicitly

treat the correlations in occupancy of neighboring receptors and confirms the conclusion that as the number of receptors increases, the signal-to-noise ratio saturates rapidly.

The noise level defines the minimum integration time, τ , within which a desired concentration change can reliably be detected. Berg & Purcell (15) calculated τ for the concentration changes detected by bacteria under a variety of conditions and found $\tau \sim 0.1$ – 1.5 s. However, the cell becomes completely disoriented as a result of rotational Brownian motion in just a few seconds. The bacterium must thus integrate for $\sim \tau$ and “forget” on a time scale of ~ 2 – 10τ , thus behaving like a bandpass filter with center frequency of ~ 1 Hz. Direct measurements of the temporal response of bacterial motility to brief pulses of chemoattractants or repellents have quantitatively confirmed the predicted bandpass behavior (28).

Infrared and Thermal Senses

In dark caves or the desert night the infrared region of the electromagnetic spectrum may provide more information than the visible. Several species of snakes possess specialized pit organs that make use of this information. Here I discuss the performance of this sensory system as well as the remarkable antennal thermosensors of the cave beetle *Speophyes lucidulus*.

Two very different sensory mechanisms have been considered: a photochemical one as in ordinary vision, where the cell counts photons, and a bolometric one in which the cell detects the temperature rise that results from absorption of radiation. In the bolometric picture the cell's temperature, T , determines the mean rate at which the cell radiates power to the world through some relation $\bar{P}(T)$. In thermal equilibrium δT fluctuates, and we assume, following the Langevin approach (96), that these fluctuations arise from some fluctuating power δP with spectral density S_p chosen so that $\langle (\delta T)^2 \rangle = k_B T^2 / C_v$. Thus $S_p = k_B T^2 (\partial \bar{P} / \partial T)$.

If the cell is strongly absorbing (63), the minimum noise level is set by blackbody radiation, for which $\bar{P}(T)$ can be written as an integral over the Planck distribution,

$$\bar{P}(T) = 2Ac \int \frac{d^3\mathbf{k}}{(2\pi)^3} F(\mathbf{k}) \frac{\hbar\Omega_{\mathbf{k}}}{\exp(\Omega_{\mathbf{k}}/k_B T) - 1},$$

where A is the cell area, c is the speed of light, \mathbf{k} is the wave vector of the photon, and $\Omega_{\mathbf{k}} = c|\mathbf{k}|$. At $T = 300$ K, $S_p = 6 \times 10^{-28} [A/100 (\mu\text{m})^2] \text{ W}^2 \text{ Hz}^{-1}$; the threshold for reliable detection in a measurement bandwidth Δf is $\delta P = (2S_p \Delta f)^{1/2}$. On long time scales, δP produces temperature fluctuations, δT , of $\delta P (\partial \bar{P} / \partial T)^{-1}$ or $\sim 10^{-4} \text{ K} [(\Delta f / 1 \text{ Hz}) (100 (\mu\text{m})^2 / A)]^{1/2}$.

If we describe the cell as a photon counter, the random arrival of blackbody photons provides a microscopic basis for the Langevin δP (87). From the FDT we know that this approach must give the same results as the bolometric calculations.

Experiments on single neurons in crotalid snakes (36) and on the striking reaction of these animals (63) suggest thresholds for P of $\sim 4 \times 10^{-9}$ W. But these results do not establish the threshold for reliable detection; the snake probably strikes only at targets whose infrared emission approximates that typical of a warm-blooded creature, while the single-unit thresholds were based on subjective criteria. When the temperature of the receptor was varied (36), $\delta T = 0.025$ K produced ~ 50 s $^{-1}$ increases in firing rate; the spontaneous rate was $r_0 \sim 10$ s $^{-1}$. The firing is approximately a Poisson process, and the increase in firing rate is proportional to the temperature change, so these two results determine an equivalent temperature noise of $\delta T \sim 10^{-3}$ K $(\Delta f/\text{Hz})^{1/2}$.

More recent studies in the eyeless cave beetle *Speophyes lucidulus* confirm the reliable detection of millikelvin signals and illustrate the importance of sensory ecology in guiding biophysical experiments (40, 93). Corbière-Tichané & Loftus (40) measured thermal signals in the beetle's natural habitat, and sometimes found temperatures stable to ± 0.01 K over several minutes. With temperature drift of several millidegrees per second they were able to correlate the firing rate of the antennal thermoreceptors with both the temperature and its time derivative as $r(t) \sim r_0 + \alpha \delta T(t) + \beta \delta \dot{T}(t)$, with typical parameters $\alpha \sim 7$ s $^{-1}$ K $^{-1}$ and $\beta \sim 780$ K $^{-1}$; spontaneous firing rates, r_0 , were 5–10 s $^{-1}$. Again assuming that neural firing is a Poisson process, we find that in a 1-Hz band surrounding 2 Hz the equivalent temperature noise of these thermoreceptor neurons is $\sim 2 \times 10^{-4}$ K, which compares favorably with the theoretical limit.

Limits also arise from the transduction mechanism. Consider three possibilities:

1. Thermal expansion of some structure may be followed by mechanoreception. Typical thermal expansion coefficients in proteins are $\sim 10^{-4}$ K $^{-1}$ (104), so even if the relevant structure is as long as the sensory hair (93) it will expand by only $\sim 10^{-11}$ m in response to the threshold signal. This is in the same range as the displacement signals detected by the ear, so we have the same noise problems.
2. Temperature effects on a chemical reaction rate may be followed by chemoreception. Reaction rates typically vary as $R \sim A \exp(-E_a/k_B T)$, where E_a is the activation energy. For reliable detection of the rate change in a time τ we require $\delta R \gtrsim (R/\tau)^{1/2}$. Thus for $\tau \sim 1$ s and a fairly generous E_a of ~ 0.25 eV, $R \gtrsim 10^9$ s $^{-1}$ for $\delta T \sim 10^{-3}$ K. But if the

reaction in question releases a reasonable free energy (~ 0.5 eV), this reaction will dissipate a power comparable to the total metabolic power output of a cell. Even this is insufficient unless the cell counts every molecule.

3. Temperature effects on membrane conductance may be followed by electroreception. If the conductance is activated as above, $G \sim A \exp(-E_a/k_B T)$, and the driving force is ~ 100 mV, shot noise and thermal (Johnson) noise both require that the modulated current be ~ 100 pA to reliably detect $\delta T \sim 10^{-3}$ K. This is comparable to the maximum transduction current in many receptors.

These are not rigorous arguments. The point is that millidegree temperature changes can be detected by biologically plausible mechanisms, but only if these mechanisms reach their respective physical limits.

CASE STUDIES: SYNTHESIS OF HIGHER-ORDER PERCEPTS

The reliability of perception is determined in part by the efficiency and effective noise level of the computations performed by the central nervous system. In the past decade a few key experiments, guided by theoretical developments, have probed this computational noise level in interesting ways.

The Missing Fundamental

If we listen to a sound with components at harmonically related frequencies nf_0 , we assign to this sound a pitch f_0 even if the component $n = 1$ is not present. Seebeck (115) discovered this in the last century, but the issue languished until Schouten's (112) work nearly one century later. The rich variety of phenomena associated with the missing fundamental has been reviewed by de Boer (48a).

Synthesis of the missing fundamental is now viewed as pattern recognition in the spectral domain: Given a set of resolved spectral components at frequencies f_μ , the brain discerns pattern $f_\mu \approx n_\mu f_0$, where n_μ is a set of integers. But f_μ is represented in the nervous system by some noisy estimate x_μ . This noise can be seen in simple frequency discrimination experiments, in which stimuli at f and f' are reliably discriminable only if $|f - f'| \gtrsim \sigma_1(f)$, where $\sigma_1(f)$ is an effective Gaussian noise level; $\sigma_1(f \sim 1 \text{ kHz}) \sim 3$ Hz for sounds of moderate intensity. If the auditory nervous system registers the set of estimates $\{x_\mu\}$, the probability that this arose from a harmonic sequence with fundamental f_0 is roughly

$$P(\{n_\mu\}, f_0) \sim \frac{1}{Z} \exp \left\{ -\frac{1}{2} \sum_\mu \frac{(x_\mu - n_\mu f_0)^2}{\sigma_1^2(n_\mu, f_0)} \right\} = \frac{1}{Z} \exp[-E(\{n_\mu\}, f_0)].$$

For the best estimate of f_0 we should apply maximum likelihood, minimizing the energy $E(\{n_\mu\}, f_0)$ as a function of f_0 and the integers $\{n_\mu\}$.

Goldstein (58) made these ideas precise and noted that the relevant noise level $\sigma(f)$ is an effective noise level at the point where the energy minimization is performed. Thus the set of parameters $\sigma(f)$ must be fit to data on pitch matching, discrimination, and identification. In Goldstein's original estimates, derived largely from the musical interval recognition experiments of Houtsma & Goldstein (66), $\sigma(f)$ was three to ten times larger than $\sigma_1(f)$. This suggests that the added complexity of the pitch extraction computation is associated with a tremendous increase in the effective noise level, with the "temperature" $\sigma^2(f)$ increasing by as much as a factor of one hundred.

Beerends & Houtsma (12) have remeasured $\sigma(f)$ by testing recognition of the familiar notes do, re, mi, fa, so in harmonic tone complexes missing their fundamentals. These authors suggested that this experiment is much less contaminated by memory effects than the earlier study (66), which required recognition of the chromatic notes E^b , E, F, $F^\#$, G, etc. In the newer results $\sigma(f)$ is much closer to $\sigma_1(f)$, perhaps within a factor of two, which suggests that the nervous system can perform complex computations without much added noise. A similar conclusion is suggested by the observation (12) that $\sigma(f)$ determined in the identification of single pitches can be used to predict performance in the more complex tasks of separating the pitches in simultaneous harmonic complexes.

Recognizing Ensembles of Images

The frequency-of-seeing experiment indicated that variability of human responses is controlled by characteristics of the stimulus and not by the sensory nervous system. This idea can be adapted to complex perceptual tasks by asking observers to discriminate not between particular pairs of stimuli but rather between statistical ensembles of stimuli. This approach was first used by Julesz (73), who tried to identify some qualitative features of texture perception.

Random dot patterns can be generated according to many different statistical rules. Barlow & Reeves (6, 7) asked their subjects to discriminate between patterns in which the rule produced correlations between the positions of dots on opposite sides of a symmetry axis and patterns in which this correlation was absent. Since the correlation is never perfect, there is a finite value of d' that is the optimum discriminability for that pair of ensembles. To reach optimum performance the observer must (*a*)

not add significant noise to the image as it is processed, (b) make full use of a priori information about the statistical properties of the ensemble, and (c) reliably compute the relevant likelihood ratios.

Under certain conditions the performance of human observers in the Barlow-Reeves experiments corresponded to a value of $(d')^2$ within a factor of two of the theoretical optimum. As the observer synthesizes the Gestalt percept of symmetry he or she makes use of essentially all the information in the image; the reliability of the percept is limited by the statistical properties of the image and not by the computational limitations of the nervous system. Generalizations of this conclusion may be explored using ensembles that require the observer to perform ever more complex computations to make full use of the available information (26).

Hyperacuity and Visual Movement Detection

Human observers reliably distinguish between a single line and a pair of lines with equal total brightness at line separations of $\sim 1'$ of arc. In spatial interval detection, where two parallel lines are separated by angle θ or $\theta + \delta\theta$, one finds discrimination is reliable at $\delta\theta \lesssim 6''$ of arc, which is the angle subtended by two inches viewed from one mile, or one tenth of the spacing between receptors on the retina (130). Similar results are obtained for vernier acuity or for the detection of movement across the visual field. This remarkable performance is termed hyperacuity (131).

Until recently there were no data indicating hyperacuity in the response of single neurons. In 1984 de Ruyter et al (49b) reported preliminary results on the reliability of coding in a single wide-field movement-sensitive neuron [H1 (64)] in the blowfly visual system. Movement steps trigger several spikes, and by presenting each stimulus $\sim 10^4$ times we accumulated good estimates of the probability distributions $P(\{t_\mu\}|\theta_0)$ for spike arrival times t_μ conditioned on the step size θ_0 . From these distributions we were able to compute the probabilities for correct discrimination of θ_0 vs θ_1 using the maximum likelihood formalism reviewed above. Discrimination based on just two or three spikes following a step was sufficient to allow detection of $\delta\theta = |\theta_0 - \theta_1|$ with $\sim 80\%$ reliability for $\delta\theta$ of approximately one tenth the spacing between receptor cells on the retina (21, 49a).

In the monkey striate cortex the probability of spike generation in response to gratings is a very steep function of grating position (102); these data suggest that a simple spike/no spike decision rule allows reliable discrimination between gratings whose positions differ by roughly one fifth of a receptor spacing. Similar conclusions have been reached about vernier acuity tasks in cat cortical neurons (121), while somewhat less quantitative evidence suggests performance in the hyperacuity range for cat retinal ganglion cells (117).

Robust intracellular recordings can also be taken from the photoreceptor cells of the fly. Such recordings have indicated that the cell voltage responds linearly to the contrast pattern $C(\phi, t)$, with independent Gaussian additive noise:

$$V_n(t) = \int d\tau T(\tau) \int d\phi M(\phi - \phi_n) C(\phi, t - \tau) + \delta V_n(t).$$

The n th receptor cell is located at position ϕ_n and T and M are temporal and spatial transfer functions, respectively. For simplicity I indicate only one angular coordinate; δV_n is characterized by the spectral density $S_V(\omega)$. All of these quantities have been directly measured (49a), and within this model the limit to discrimination between different trajectories, $\theta(t)$, can be calculated for a given pattern. The optimal $(d')^2$ for step-size discrimination is within a factor of two of the observed neural discrimination performance during the behaviorally relevant (86) 40 ms after the step (49a). Apparently a few spikes carry essentially all of the information about movement that is available at the retina; the fly's visual system performs an optimal and essentially noiseless processing of the photoreceptor voltages.

OUTLOOK

In his classic book *What is Life?*, Schrödinger (113) drew attention to the remarkable precision achieved by the cellular mechanisms responsible for transmission of genetic information. Schrödinger introduced the "naive classical physicist" who, not knowing quantum mechanics, does not appreciate that one can construct tremendously stable structures on the molecular scale. In the absence of such "micro-stability," this scientist can understand the stability of the genome only in macroscopic, statistical terms, as a collective property of large numbers of molecules. While this appears to be a reasonable point of view, it turns out to be wrong; genetic information is stored in single molecules.

It has conventionally been assumed that the nervous system's ability to perform reliable computations is similarly a macroscopic phenomenon, the result of averaging over the erratic behavior of many individual neural elements.⁵ Against this view, Delbrück (49) suggested that the sensory systems may yet reveal a precision and subtlety of mechanism far beyond that appreciated from molecular genetics. Bullock (34, 35) has cautioned

⁵This view is often traced to von Neumann, but from the text of his Silliman Lectures (128) I think the attribution may be inaccurate.

that evidence for imprecision and unreliability in the nervous system may equally well reflect our ignorance of how information is encoded.

The case studies reviewed above provide examples of single receptor cells that perform their appointed tasks with a precision and reliability that approaches the limits imposed by the laws of physics. This fact alone allows the prediction of qualitatively significant cellular mechanisms, such as active filtering in the inner ear and the integration and adaption processes of chemotaxis, which are in fact observed. In at least one instance—vision—we can approach the problem of sensory performance at the molecular level, where once again single molecules are apparently responsible for the reliability and precision of biological function. This example also brings us up against fundamental issues regarding the dynamics of biological macromolecules. We have seen systems in which complex neural processing of sensory information can occur with essentially no addition of noise, where the nervous system succeeds in extracting nearly all of the available information about particular features of the stimulus, and where the results of this optimal information processing are encoded in just a few spikes from one neuron.

The evidence for optimal performance of the sensory systems is still scattered. It is thus impossible to know whether this precisionist view of sensory systems is more generally applicable. It is easy to formulate criteria for optimality that are not met in these systems, but deeper analysis may reveal that these criteria themselves are flawed; a nice example is the issue of diffraction-limited optics in the compound eye (118). In the next few years the approach to optimality should be tested more quantitatively in several systems where the data are already suggestive.

A more important question is whether the notion of physically limited performance will continue to be a fruitful source of ideas about function and mechanism. In this respect the most exciting, if speculative, possibility is that these concepts can be applied to a wider variety of “almost sensory” phenomena. Are the exquisite spatio-temporal patterns of coordinated ciliary beating (84, 101) limited in their stability and precision by the Brownian noise forces acting on the cilia? Is the precise control of polymer length and cross-linking observed in stereocilia (124) and flagella (106) limited by chemical fluctuations during assembly? Are there fundamental physical limits to the precision of molecular and cellular recognition events? Having planted myself firmly on terra incognita, it is perhaps best to close.

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