have judiciously placed a hole in the cantilever to enhance, by pure mechanical means, the 16th harmonic of the vibration, coming in at a whopping 598 kHz (*6*). It is now also possible to make cantilevers with fundamental resonance frequencies of 1 GHz (*7*). All this points to a near future where mechanical devices enter the frequency realm of microprocessors.

The ultimate dream for those of us working with scanning probes is to be able to determine the chemical composition of an arbitrary surface down to single atoms, including their chemical bonding, and to measure the electronic structure with sensitivity to spin. Hembacher *et al*. have moved us a step closer to this dream by providing information about the bonding symmetry. Because tunneling is already included in their setup, it is just a matter of time to add tunneling spectroscopy (*8*), with spin sensitivity (*9*) as needed.

Pythagoras and his followers were mesmerized by the connection between geometry and music. They developed the "music of the spheres," a fanciful scheme for creating musical scales based on geometric ratios obtained with spherical geometries, a concept that also appealed to Kepler as he studied the motion of the planets around the Sun. We are now playing music on the atomic "spheres," and we are not even scratching the surface.

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PHYSIOLOGY

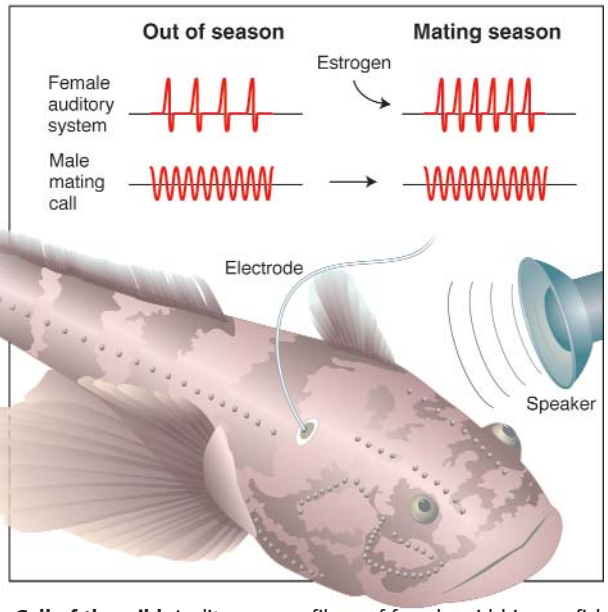
Heeding the Hormonal Call

Harold Zakon

An enduring question in evolutionary biology is: How optimized are organisms for their environment? This question is perhaps best addressed in the field of sensory biology. It is straightforward to specify both sensory stimuli—such as species-specific communication signals, signals from predator or prey, or noise—and the transmission properties of the environment. Furthermore, it is easy to measure the ability of an animal's sensory system to pick up these signals. Some sensory receptors are sharply tuned to particularly potent signals, whereas others are broadly sensitive to the total array of signals encountered. Of particular interest are examples of apparent mismatches between communication signals and the sensitivity of the receptors receiving them. Could it be that an appropriate well-matched signal has not yet been found? Are the sensory receptors optimally tuned to a different signal that belongs to the evolutionary past? Is the mismatch exploited during, for example, the selection of a mate? Or, is the mismatch a reflection of the dynamic nature of matching between communication signals and sensory systems—that is, does the matching between sender and receiver change depending on the stage of the life cycle or environmental conditions? The answer is provided by Sisneros and colleagues (*1*) on page 404 of this issue, who chose as their subject the plainfin midshipman (*Porichthys notatus*), a nocturnal fish that inhabits Pacific coastal waters. These investigators resolve the apparent mismatch between a vocal mating signal emitted by the male fish and the sensitivity of the female's auditory system by demonstrating that steroid reproductive hormones increase the sensitivity of the female's auditory system to the male's courtship calls.

Adaptive shifts in the sensitivity of sensory systems to life cycle stages or hormone levels are well established. Such shifts have been observed in the electrosensory (*2*–*4*), visual (*5*), and olfactory (*6*) systems of vertebrates. For example, the electroreceptors of weakly electric fish are tuned to the frequencies of their own electrical discharges to enable optimal electrolocation of prey. During the reproductive season, sex hormones alter the frequency of electric discharges so that the discharges emitted by males and females become more dissimilar. However, there is also a parallel shift in electroreceptor tuning to ensure that a match is maintained between the frequency spectrum of each animal's signal and its own receptors, thus ensuring that electrolocation is not compromised. Similarly, during the mating season, androgens shift the frequency sensitivity of electroreceptors of the male Atlantic stingray to optimally match the electrical signatures of female rays buried in the sand. One could argue that electroreceptors—which are evolutionarily and developmentally related to the hair cells of the vertebrate inner ear and the lateral line organs of fish—are highly specialized organs and so hormone-dependent changes in their sensitivity are not likely to be a general feature of other hair-cell systems.

In the new work, Sisneros *et al*. show that the auditory afferent fibers of the inner ear of female midshipman fish are more responsive (that is, better phase-locked) to particular components of the male's courtship call during the mating season than out of season (see the figure). The authors mimicked this change in auditory responsiveness by administering estrogen or testosterone to out-of-season females. They propose that estrogen acts directly on the auditory receptors themselves. In support



Call of the wild. Auditory nerve fibers of female midshipman fish are more responsive (that is, the action potentials are better phase-locked) to male mating vocalizations during the breeding season than out of season. Treating out-of-season females with estrogen makes their auditory nerve fibers respond robustly to male courtship calls (*1*). This finding explains an apparent misalignment between the sensitivity of the female's auditory system and male mating vocalizations. In this species, auditory sensitivity varies seasonally with the level of estrogen in the female.

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of this hypothesis, they provide molecular evidence that auditory epithelial cells of the female fish express estrogen receptors.

Although by no means contradicting theories of sensory exploitation and drive (*7*, *8*)—how male vocalizations have evolved as a result of detection and choice by females—the present study reminds us that sensory receptivity can be dynamic and context dependent. This should be taken into consideration when exploring cases of apparent mismatches between sensory signals and the receptors that respond to them. Furthermore, the new work extends the observations of hormone-dependent optimization of tuning from the fish electrosensory system to its evolutionary cousin, the auditory system. Indeed, there are scattered but intriguing reports that estrogen or testosterone may be crucial for the development and maintenance of the cochlea of the mammalian inner ear (*9*).

As a good study should, this one raises further questions. Why is the female midshipman's ear not tuned to the components of male vocalizations during the rest of the year? How are the ears of male fish tuned in and out of breeding season? The tuning of the auditory hair cells in nonmammalian vertebrates is largely based on the properties of their ion currents, less so on their mechanical properties. It is likely that steroid hormones act directly on the auditory receptors of the midshipman fish inner ear by modifying the ion currents responsible for electrical tuning and neurotransmitter release. The mammalian cochlea has dispensed with electrical tuning of its hair cells and has, instead, "invested" in a number of remarkable adaptations (both passive and active mechanical processes) for extending the high-frequency range of hearing. It is possible that the influence of steroid hormones on vertebrate auditory organs is an ancestral condition. The co-opting of hormones for regulating development of the mammalian cochlea rather than for hair-cell tuning may be a relatively recent evolutionary innovation. Stay tuned for further revelations!

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BIOCHEMISTRY

Completing the View of Transcriptional Regulation

Peter H. von Hippel

The *lac* repressor of *Escherichia coli* and its interactions with inducer and with specific and nonspecific DNA have long been the central model system for understanding transcriptional control. A molecular view of the system has come from the crystal structures of the *lac* repressor in its free form, bound to its specific operator DNA target site (RO), and bound to inducer (RI) (*1*). However, the picture lacked an important piece, namely *lac* repressor in complex with nonspecific DNA (RD). On page 386 in this issue, Kalodimos *et al*. (*2*) complete the picture by solving the structure of a dimer of the head-group DNA binding domains of *E. coli lac* repressor in complex with nonspecific DNA, a good representation of the RD complex (*3*). Comparing the structure and dynamics of this complex with a structure of the same domains bound to the specific *lac* operator site (representing the RO complex) provides a structural view of how these complexes might interconvert.

The first major effort to understand the control of gene expression grew out of the seminal genetic studies of Jacob, Monod, and co-workers on the *lac* operon. Their work established that (i) regulation of the three enzymes involved in lactose metabolism that are coded within the *lac* operon occurs at the level of gene expression rather than by activating enzyme precursors (*4*); and (ii) the inducer ligand acts on a repressor of transcription, rather than by activating an "inducer protein" (*5*). [A description of these early studies and their interpretations can be found in (*6*).]

The next step was taken by Gilbert and Muller-Hill, who isolated the *lac* repressor (*7*) and showed in vitro that it acts by binding to a specific DNA site located near the promoter of the *lac* operon (*8*). This established the notion of a binding complex of protein and DNA in which specific protein residues "recognize" a particular sequence of base pairs on the same principles as the residues in the active site of an enzyme recognize its substrate. Furthermore, the natural inducer of the *lac* repressor was shown to be a small-molecule intermediate in the lactose reaction pathway that binds specifically to *lac* repressor to give a complex that has lower affinity for the operator DNA target site.

Specific interactions between the hydrogen bond donors and acceptors of the protein binding site and those of the base pairs in the grooves of the DNA double helix provide the molecular basis of binding specificity and target recognition for DNA binding proteins such as *lac* repressor (see the figure). Thus, specific binding occurs in the grooves of double-stranded DNA (dsDNA). However, this binding is supported and stabilized by electrostatic interactions between the negatively charged phosphates of the sugar-phosphate backbones of the dsDNA and the basic amino acid residues that surround the binding site of the protein, and these interactions are largely independent of base pair sequence (see the figure).

This nonspecific binding of regulatory proteins to dsDNA can complicate efforts to establish binding specificity, but it is more than just an experimental nuisance. In fact, in the *lac* repressor regulatory system (and in many others), nonspecific DNA binding plays at least three central mechanistic roles.

First, RD complexes play an important role in the overall thermodynamics of the regulatory process (*9*). Binding of repressor to nonspecific DNA sites decreases the amount of R that is free in solution and thus is directly available to support the RO binding equilibrium. On a per-site basis RD binding is ~10^8-fold weaker than RO binding at physiological salt concentrations. However, the RD binding interaction is functionally nontrivial because the genome of *E. coli* contains ~10^7 base pairs, and thus ~10^7 overlapping nonspecific DNA binding sites that can potentially compete with operator for repressor binding. In addition, unlike RO binding, RD binding is not weakened by RI complex formation (*9*). Consequently, the successful removal of the *lac* repressor from its operator target site by inducer binding, both in vitro and in vivo, is critically dependent on the binding of both R and RI to nonspecific DNA (*9*, *10*).

In subsequent work, Record and his coworkers showed that nonspecific binding of

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