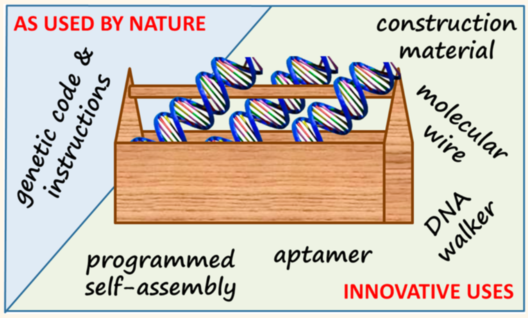
Nature Inspires Sensors To Do More with Less

Shawn P. Mulvaney* and Paul E. Sheehan

Chemistry Division, U.S. Naval Research Laboratory, Washington, DC 20375, United States

ABSTRACT The world is filled with widely varying chemical, physical, and biological stimuli. Over millennia, organisms have refined their senses to cope with these diverse stimuli, becoming virtuosos in differentiating closely related antigens, handling extremes in concentration, resetting the spent sensing mechanisms, and processing the multiple data streams being generated. Nature successfully deals with both repeating and new stimuli, demonstrating great adaptability when confronted with the latter. Interestingly, nature accomplishes these feats using a fairly simple toolbox. The sensors community continues to draw inspiration from nature's example: just look at the antibodies used as biosensor capture agents or the neural networks that process multivariate data streams. Indeed, many successful sensors have been built by simply mimicking natural systems. However, some of the most exciting breakthroughs occur when the community moves beyond mimicking nature and learns to use nature's tools in innovative ways.



Electronic noses (EN) and electronic tongues (ET) are arrays of sensors that detect a wide range of compounds potentially present in gas or liquid samples. Fundamental to both ENs and ETs is the attempt to identify a specific target, often at trace levels, from a complex matrix by mimicking aspects of the human sensory system. In 1982, Persaud and Dodd first suggested the basic design principle of ENs: summing the responses from an array of semispecific sensors yields a "fingerprint" of the sample.[1] The individual components of the sample could then be positively identified by pattern recognition algorithms. This is essentially the same process used by our brain to distinguish the smells of garlic, cinnamon, or cumin in an entree. Similarly, ETs have developed pattern recognition for liquid samples with the distinction of electronic tongue being applied to sensor arrays that focus on the main classes of taste—salty, sweet, sour, bitter, and umami. This concept has been highly successful, and to date, ENs and ETs have been designed from potentiometric, voltammetric, mass-sensitive, and optical sensors. Each year, more aspects of the natural system have been incorporated, as have been described in several excellent reviews.[2−6]

In this issue of *ACS Nano*, Song and coworkers describe an ET for the detection of sucrose, fructose, aspartame, and saccharin. Intriguingly, they used the taste bud's natural sweet receptors, heterodimeric G-protein-coupled receptors (GPCRs).[7] The GPCRs, as well as calcium ion channels, were first incorporated into nanovesicles that were then attached to carbon nanotube field effect transistors (FETs). The arrangement in the vesicles means that the capture of a sweet tastant opens the Ca^{2+} channel and the flux of ions into the nanovesicle changes the gate property of the FET, thus converting the chemical signal into an electronic one (Figure 1). The ET showed excellent specificity for natural and artificial sweeteners and no response to the structurally similar, but tasteless, sugars cellobiose and D-glucuronic acid. By utilizing the human taste bud's most relevant proteins for recognition of sweet tastants, the authors built a sensor that could even perform in complex matrices such as tea and coffee. This work complements the authors' previously published work on bitter taste receptor sensors[8,9] and that of Liu *et al.*, who developed an impedance-based ET with ion channels spanning lipid bilayers.[10]

The fundamental design of Song *et al.*'s sensor takes mimicry one step further in adapting nature's tools to address challenges with transduction and compatibility

* Address correspondence to shawn.mulvaney@nrl.navy.mil.

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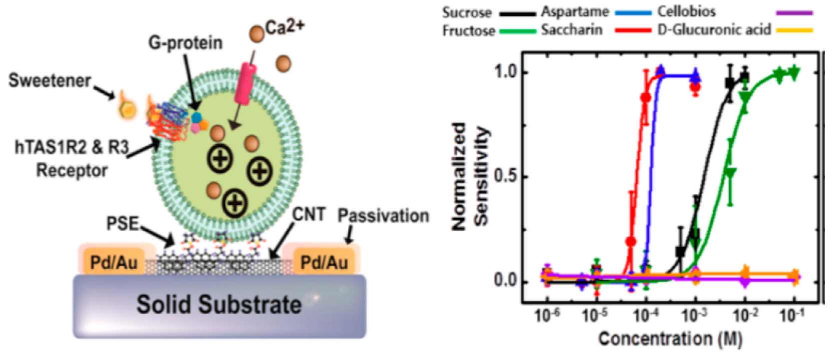

Figure 1. Electronic tongue: nanovesicles with sweet taste receptors attached to a carbon nanotube field effect transistor. The electronic tongue specifically detects sweet tastants and shows no response to tasteless sugars. Reprinted from ref 7. Copyright 2014 American Chemical Society.

with complex matrices. After growing the GPCRs in HEK-293 kidney cell lines, the cell walls were weakened and nanovesicles were separated from the main cell with lipid bilayers still intact. These nanovesicles contain not only the membrane-bound GPCR proteins but also the Ca^{2+} ion channels. When a sweetener is captured by the GPCR receptor, the Ca^{2+} channel is opened and the nanotube FET transduces the transport of ions into the nanovesicle. In reality, the authors have built an indirect sensor that transduces Ca^{2+} ions, but the cascading nature of the design makes it respond directly to the capture of sweet tastants. This clever design leverages nature's own proteins and machinery to improve sensor performance. First, the sensor gains the differential response of the GPRCs toward only the sweet tastants. Second, the lipid bilayer serves as an excellent antifouling layer, protecting the carbon nanotube FET surface from direct contact with complex media. Third, the lipid bilayer localizes the measurable Ca^{2+} ions in a compartment near the sensor's gate. Here again, the authors were inspired by one of nature's design principles. Compartmentalization is used extensively in cells to run their many parallel processes successfully in subdiffusion length proximity.

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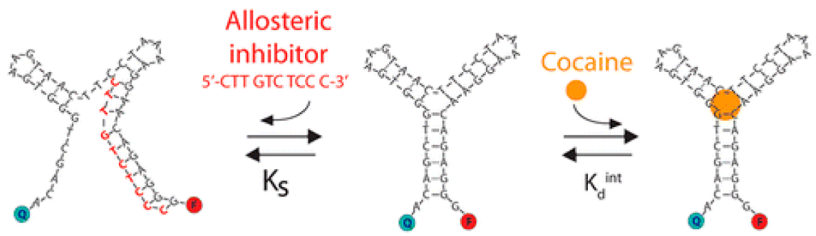
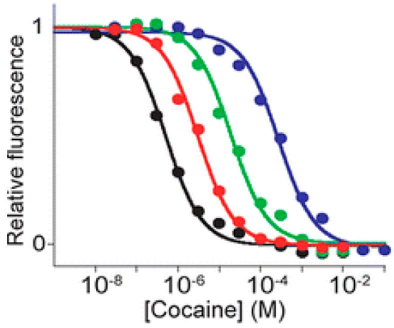
OUTLOOK AND FUTURE CHALLENGES

Plant, animal, and human sensory systems have long taught the scientific community how to build better sensors. Nature's lessons can be seen in all aspects of the sensor literature—antibodies, enzymes, hydrophilic and hydrophobic films, neural networks, and photoconversion to name but a few. Antibodies in biosensors are a particularly clear example.[11−13] First, the immune system was understood to be an antigen recognition system. Then, researchers copied those receptors for biosensing by using the antibodies themselves to provide sensitivity and specificity. When the advantageous properties of polyclonal, monoclonal, Fab fragments, and single domain camelid antibodies were understood, researchers then leveraged their unique characteristics to gain even greater sensor functionality. The point of learning, though, is eventually to surpass the teacher. So, researchers are now showing that artificial antibodies and antibody-like recognition systems are viable alternative receptors.[12,13]

The goal of surpassing the teacher is critical to the field since not all qualities of natural elements enhance sensor performance. This is seen in the work by Song *et al.*, who use nature's receptors for sweet tastants to great effect but go to great lengths to use nanovesicles instead of the kidney cells in which the GPCRs were grown.[7] Providing conditions where the kidney cells could function properly would have severely limited the operational space of the final sensor since the kidney cells would have to be maintained in a highly controlled environment to remain viable. Similarly, the use of individual enzymes or proteins in a sensor would require conditions that maintain their three-dimensional structure and biological function. Temperature, pH, salinity, and toxicity will always need to be considered when using any natural, and some abiotic, components in a sensor design.

The community's *modus operandi* remains to match the correct sensor to the application, guided by the trade-offs in performance and operation that influence selection of natural elements, abiotic alternatives, and hybrids of the two. The progression from simply copying nature to devising systems that surpass and extend their best qualities has resulted in a diverse and highly capable toolbox. Yet, major advances and new research directions tend to be realized when the community mimics nature's adaptability. For instance, a major innovation for the sensors community was realizing that biomolecules could be





Inhibitor	Sequence	K_d (μM)
no inhibitor	-	0.5
Inhib_10	5'-CTT GTC TCC C-3'	2.9
Inhib_12	5'-TCC TTG TCT CCC-3'	19
Inhib_14	5'-TTT CCT TGT CTC CC-3'	235

Figure 2. Aptamer sensor for the detection of cocaine. The binding affinity of the aptamer was altered by competition with short oligonucleotide strands operating as allosteric effectors. The binding affinity was altered over 3 orders of magnitude. Reprinted from ref 20. Copyright 2012 American Chemical Society.

precise construction tools. In 1996, the Mirkin group demonstrated the programmed assembly of metal nanoparticles using oligonucleotide strands.[14] The well understood complementarity of the nucleotide bases, along with the relative stability of oligonucleotide strands, yielded a seemingly endless number of unique attachment sequences. Much research has grown from this work,[15] including the concept of programmed self-assembly of sensor arrays. Several groups have exploited this method to create protein arrays with superior performance compared to the same arrays made with classical protein immobilization strategies.[16−18] Furthermore, DNA-based programmed self-assembly enables the community to mimic another of nature's skills, the ability to reset its sensing elements; proteins tethered through DNA can be dislodged through melting or chemical dehybridization and a fresh protein array self-assembled atop the sensor substrate. A further example of biomaterials used for construction is virus particles. The cowpea mosaic virus has been shown to assemble into highly ordered, low-defect crystals with a geometry that is difficult to create with other materials.[19] These virus crystals make an excellent scaffold that supports derivatization, thereby enabling the patterning of metamaterials.

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Perhaps one of the clearest examples of copying and then improving on nature is Porchetta and co-workers' aptamer-based sensor work.[20] A great challenge for the sensors community is that almost all biosensors have a fixed dynamic range. Typically, the S-shaped binding curves span no more than 2 orders of magnitude in concentration, but natural systems have evolved to handle broader concentration profiles either by using multiple recognition elements, through binding-site mutation, or *via* allosteric effectors. Allosteric effectors are antigens that bind to a secondary site on the protein receptor and, in so doing, alter the target affinity of the primary epitope. Recapitulating these effects in a biosensor would require an enormous effort in molecular biology. Instead, Porchetta *et al.* used a simple series of DNA strands to perform all of the tasks. First, a DNA aptamer replaced the antibody capture molecule. Second, 10mer, 12mer, and 14mer oligonucleotide strands that are complementary to the aptamer were used as allosteric effectors. The results were a sensor for cocaine detection with 3 orders of magnitude dynamic range and much finer gradations in detection than could be achieved with protein mutagenesis (Figure 2). Allosteric-like control of the binding affinity provided the authors precise control of the sensor sensitivity over a 50000-fold linear range, a result well beyond the natural system's performance.

The field of sensing remains very young compared to nature's millennia of experience. More importantly, nature's proven adaptability to new stimuli continues to enrich the knowledgebase from which scientists gain inspiration. Steady progress will continue to be made by scientists mining that knowledgebase while refining and developing sensing tools. However, the potential for leaps forward and new research directions exist if the community adapts its thinking. Can we as scientists learn to multitask with our toolbox? Can certain tools perform two completely different jobs? Song *et al.* used their lipid bilayer in both a traditional manner, to maintain protein function, and in an innovative manner, to enhance signal-to-noise. Both aspects were crucial to the system's ability to perform. This and the other examples presented in this Perspective demonstrate how nature can inspire the sensors community to do more with less.

Conflict of Interest: The authors declare no competing financial interest.

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