

Can Fish and Cell Phones Teach Us about Our Health?

Michael A. Lee,[†] Carlos M. Duarte,[‡] Víctor M. Eguíluz,[§] Daniel A. Heller,^{||} Robert Langer,[†] Mark G. Meekan,[⊥] Hadley D. Sikes,[†] Mani Srivastava,[#] Michael S. Strano,^{*,†} and Rory P. Wilson[¶]

[†]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

[‡]King Abdullah University of Science and Technology, Red Sea Research Center, Thuwal 23955-6900, Saudi Arabia

[§]Instituto de Física Interdisciplinar y Sistemas Complejos IFISC (CSIC-UIB), E07122, Palma de Mallorca, Spain

^{||}Memorial Sloan Kettering Cancer Center, New York, New York 10065, United States

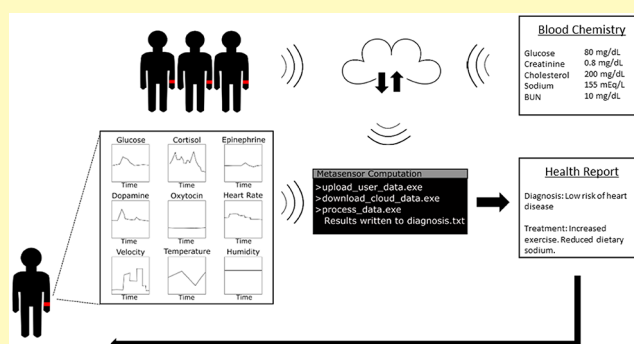
[⊥]Australian Institute of Marine Science, Indian Ocean Marine Research Centre, Crawley, Western Australia 6009, Australia

[#]Electrical Engineering Department, University of California, Los Angeles, California 90095, United States

[¶]Department of Biosciences, College of Science, Swansea University, Swansea, Wales, SA2 8PP, United Kingdom

ABSTRACT: Biologging is a scientific endeavor that studies the environment and animals within it by outfitting the latter with sensors of their dynamics as they roam freely in their natural habitats. As wearable technologies advance for the monitoring of human health, it may be instructive to reflect on the successes and failures of biologging in field biology over the past few decades. Several lessons may be of value. Physiological sensors can “encode” for a wider number of states than the one explicitly targeted, although the limits of this are debatable. The combination of orthogonal sensors turns out to be critical to delivering a high value data set. Sensor fusion and engineering for longevity are also important for success. This Perspective highlights successful strategies for biologging that hold promise for human health monitoring.

KEYWORDS: sensor, biologging, Internet of Things, data, medicine, diagnostics, machine learning



The Internet of Things (IoT) is widely discussed as the technological future and presented as inevitable. The idea is that with the maturation of the Internet and its consolidation over human communications, the next phase, that some would argue is well underway, is to connect the entire physical world to the Internet. The things that we encounter, we are promised, will be smarter, Internet connected, and primed to better anticipate and serve human needs. However, few appear to appreciate the myriad of potential ways this interconnected physical world could manifest itself, particularly in the area of the Internet-enabled human–machine interface. This interface is critical to human health and has begun to emerge in the form of fitness trackers and cell phone apps collecting users’ heart rate and activity levels. These technologies provide only a glimpse into what is possible. Imagine a world where you could present your personal physician with a year’s worth of not only your real time heart rate and activity levels but also dynamic glucose and insulin concentrations, cortisol, dopamine, serum fibrinogen, and a large panel of biomarkers of human health. As scientists, we do not yet know the predictive power of such data, or its potential to revolutionize medicine. However, we, the authors, offer that there may be insights from our collective work as teams of field biologists and engineers on these questions. We collectively have decades of experience with

what is called *biologging*, with an emphasis on marine animals, in which animals are tagged with sensors and studied as they roam freely in their natural habitats.¹ Among our authors, we also have pioneers of medical diagnostics and therapies to provide an overlapping human health perspective. Our experiences range from biochemical sensors for biomarkers;^{2,3} to sensors tagged directly on animals to discover new ecological insights ranging from feeding to migration;^{4,5} biochemical markers to characterize ocean health;⁶ and novel algorithms to elucidate systems from genetic all the way to socioeconomic.⁷ Through several examples of previous studies, we argue that biologging offers tremendous insight into the use of wearable sensors to study organismal behavior and into the use of analogous technologies for human health applications. With emerging advances in chemosensors, wearable sensors, and machine learning algorithms, we further emphasize that this intellectual exchange between biologging and biomedical sensor fields would maximize the impact of these innovations. It is our hope that the reader finds some of our collective

Received: May 23, 2019

Accepted: August 30, 2019

Published: October 2, 2019

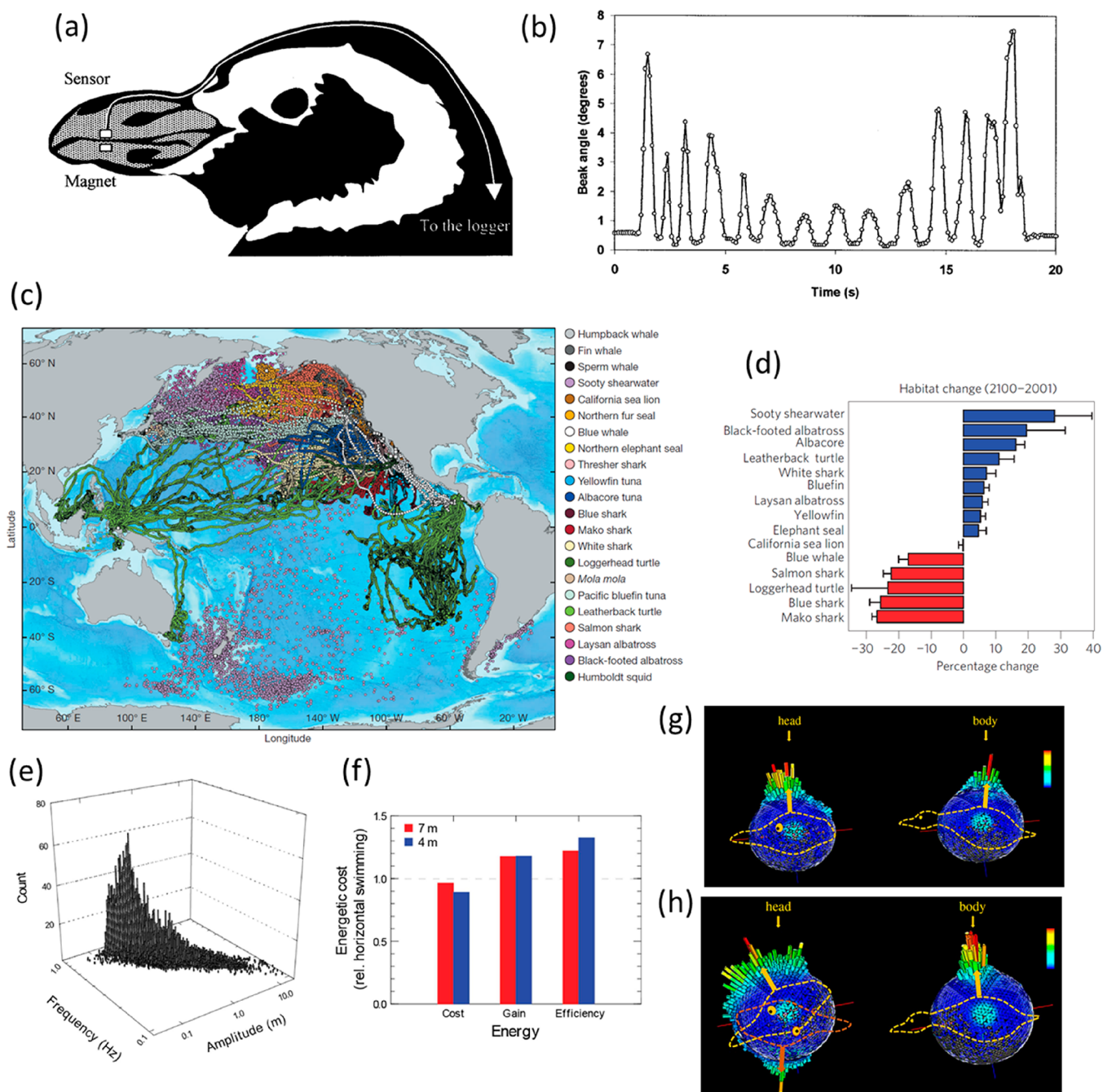


Figure 1. Biologging and its lessons for human health monitoring. (a) A Hall sensor and magnet were placed on the jaws of penguins and other animals to detect mouth movements. Reprinted in part with permission from Wilson, R.; Steinfurth, A.; Ropert-Coudert, Y.; Kato, A.; Kurita, M. Lip-reading in remote subjects: an attempt to quantify and separate ingestion, breathing and vocalisation in free-living animals using penguins as a model. *Mar. Biol.* **2002**, *140* (1), 17–27. DOI: 10.1007/s002270100659. Copyright 2002 Springer Nature.⁹ (b) The jaw sensor detected individual components of breathing and eating during movements, allowing new insights into the animals' diets and their mode of feeding. Reprinted in part with permission from Wilson, R.; Steinfurth, A.; Ropert-Coudert, Y.; Kato, A.; Kurita, M. Lip-reading in remote subjects: an attempt to quantify and separate ingestion, breathing and vocalisation in free-living animals using penguins as a model. *Mar. Biol.* **2002**, *140* (1), 17–27. DOI: 10.1007/s002270100659. Copyright 2002 Springer Nature.⁹ (c) The Tagging of Pacific Pelagics program (TOPP) collected location data from 23 species of animals in the Pacific Ocean over 9 years, yielding a huge data set that provided insight into migratory patterns and species habitat hubs. Reprinted in part with permission from Block, B. A.; Jonsen, I. D.; Jorgensen, S. J.; Winship, A. J.; Shaffer, S. A.; Bograd, S. J.; Hazen, E. L.; Foley, D. G.; Breed, G. A.; Harrison, A. L.; et al. Tracking apex marine predator movements in a dynamic ocean. *Nature* **2011**, *475* (7354), 86–90. DOI: 10.1038/nature10082. Copyright 2011 Springer Nature.¹² (d) TOPP data combined with environmental data point to large shifts in animal habitats due to global warming. Reprinted in part with permission from Hazen, E. L.; Jorgensen, S.; Rykaczewski, R. R.; Bograd, S. J.; Foley, D. G.; Jonsen, I. D.; Shaffer, S. A.; Dunne, J. P.; Costa, D. P.; Crowder, L. B.; et al. Predicted habitat shifts of Pacific top predators in a changing climate. *Nat. Clim. Chang.* **2013**, *3* (3), 234–238. DOI: 10.1038/nclimate1686. Copyright 2013 Springer Nature.¹⁴ (e) A sensor suite, consisting of video cameras, accelerometers, speed sensors, and magnetometers, tagged on whale sharks elucidated the animal's swimming patterns, including frequency and amplitude of fin beats. Reprinted in part with permission from Meekan, M. G.; Fuiman, L. A.; Davis, R.; Berger, Y.; Thums, M. Swimming strategy and body plan of the world's largest fish: implications for foraging efficiency and thermoregulation. *Front. Mar. Sci.* **2015**, *2*

Figure 1. continued

(September), 1–8. DOI: 10.3389/fmars.2015.00064. Copyright 2015 Meekan.⁵ (f) The whale shark's swimming patterns point to a strategy to maximize the energy efficiency of swimming, feeding, and thermoregulation. Reprinted in part with permission from Meekan, M. G.; Fuiman, L. A.; Davis, R.; Berger, Y.; Thums, M. Swimming strategy and body plan of the world's largest fish: implications for foraging efficiency and thermoregulation. *Front. Mar. Sci.* **2015**, *2* (September), 1–8. DOI: 10.3389/fmars.2015.00064. Copyright 2015 Meekan.⁵ (g,h) Accelerometers placed on the head and body of Magellanic penguins (top) and Imperial cormorant (bottom) elucidated the connection between each animal's neck physiology and its feeding behaviors. The peaks on the sphere illustrate the frequency at which the dorsal surface of the animal's head was oriented in that direction. With its longer neck and slower swimming, the Imperial cormorant moves its head over a wider range in order to maximize foraging efficiency. Reprinted in part with permission from Wilson, R. P.; Gómez-Laich, A.; Sala, J.-E.; Dell'Omo, G.; Holton, M. D.; Quintana, F. Long necks enhance and constrain foraging capacity in aquatic vertebrates. *Proc. R. Soc. B Biol. Sci.* **2017**, *284* (1867), 20172072. DOI: 10.1098/rspb.2017.2072. Copyright 2017 Royal Society.⁴

insights from these experiences both interesting and informative with respect to the IoT and human medicine.

To begin, we suggest that one key learning is that a sensor attached to an organism can inform seemingly disconnected behaviors in surprising ways. An early example from the marine biology field was the invention of a jaw motion sensor for penguins, dolphins, turtles, sea lions, and other terrestrial mammals.^{8,9} The device was a simple combination of a magnetic field sensor and a neodymium boron-rare earth magnet placed on opposing jaws (Figure 1a), and one might mistakenly assume that its only use was to study some esoteric facial–cranial aspect of shark anatomy. But this device, and others like it, taught us an amazing amount about animal diets, including the mass and type of ingested food, duration of feeding, and general feeding behavior. By observing the amplitude and frequency of magnetic pulses, individual jaw movements could be identified as prey capture, food mastication, and swallowing. Together with the knowledge of whether a given animal was a carnivore, herbivore, or omnivore, these jaw movement sensors significantly informed our understanding of feeding behavior for a wide range of animals (Figure 1b). It may be useful to note that in these studies, biologists have had to be creative in instrument design so as to not introduce confounding factors that disrupt the behavior targeted for study. It is probably not surprising that fish and humans alike require comfortable, nonintrusive, and sturdy sensors to achieve these results. The connection between marine animal physiology and human health is already an emerging subject of investigation, especially among our authors. One example is a new oral insulin delivery capsule which solves the problem of biomacromolecular delivery through the gastrointestinal tract by self-orientation along the stomach lining and injection of insulin.¹⁰ The design of the pill was directly inspired by the shell of the leopard tortoise, which possesses an upper shell with high curvature, a shifted center of mass, and a low curvature underside, which all together enable passive self-righting. These insights into self-righting were obtained by studying the self-righting movements of 30 turtles of 17 different species and correlating the self-righting strategies with shell geometry.¹¹ Generalizing these examples, the take-home message is that a biomedical device to measure some aspect of our own human physiology may be seemingly disconnected but actually inform a surprising range of variables simultaneously, as marine animals have underscored for us.

Among the authors, we have taken to calling this general concept the “partial encoding hypothesis” for the not yet rigorously proven assertion that each physiological state within an organism can be partially described, or encoded, in a given sensor used to monitor it. To what extent does your daily activity, the rate, and quantity of steps that you take “partially

encode” markers of your health like blood sugar or cancer risk? One observes many experiments and projects in data science currently underway that are exploring this partial encoding. Our experience with biologging, however, should be highly encouraging, but within limits. The span of these limits has enormous implications for the IoT as applied to human health. The partial encoding hypothesis is perfect for a modern age where we have seen a dramatic transformation of the very definition of the sensor itself. Sensors have evolved from merely physical hardware and wires to a much broader definition of algorithms and machine learning that may piece together quite disparate data sets, but for the measurement of a single desired variable. We might qualify these new forms as “virtual sensors” or “meta-sensors”, but they nonetheless seem poised to make great use of this partial encoding hypothesis.

Are there limits to this partial encoding? In the Tagging of Pacific Pelagics program (TOPP), a massive data set was produced by tagging 23 species (including whales, sharks, sea lions, seals, tuna, and squid) with 4306 sensors over the course of a decade.^{12,13} In total, using various types of location tracking devices, location data from 265,386 tracking days throughout the Pacific Ocean were collected (Figure 1c). The data produced were voluminous and led to a wide range of important findings. For example, the data elucidated migratory patterns and residency hubs among predator and prey.¹² Combining these movement data with parallel data sets such as average sea surface temperature and density of photosynthetic activity, aquatic animals are predicted to shift their habitats northward by up to 35% due to climate change.¹⁴ Furthermore, the effect of human activities, such as fishing, pollution, and shipping, as well as other environmental stressors (Figure 1d), have been quantified by combining TOPP data with orthogonal data sets.¹⁵ Despite these key insights, however, as a field, we acknowledge some important shortcomings of note that prevented us from learning everything we could have from this tagging effort. Although the location data itself were valuable, the nuanced physiological and behavioral information that we discovered from the jaw position sensor was notably absent. The selection of sensors and information collected focused on a macro, global scale but may have missed an opportunity to cross-correlate or extend this information into local information on behavior for specific animals. The examples above illustrate that location data were most insightful when combined with orthogonal data sets, demonstrating a key lesson when applying this informal partial encoding hypothesis: each sensor forms a *partial* but ultimately incomplete picture of an organism's physical state, necessitating the use of multiple sensors, and some thought on the degree of orthogonality. To yield the most illuminating insights, it seems that at least a few authentically orthogonal

modes of sensing must be connected, whether there is partial encoding or not.

This point was again highlighted in a recent study where we used a composite device that employed accelerometers, video cameras, water depth, magnetometers for position, speed sensors, and GPS.⁵ The combined data sets allowed the mapping of georeferenced 3D swimming trajectory of each whale shark and tracking of the frequency and amplitude of the shark's fin strokes (Figure 1e). This combined data set was remarkable in the overall picture that it provided. The study elucidated the swimming strategies whale sharks use to balance its energy expenditures while swimming and its energy consumption while foraging (Figure 1f). We discovered that the whale shark's swimming patterns, along with its underlying physiology, allowed the animal to retain its body heat when diving during feeding. In this demonstration of the partial encoding hypothesis, composite sensors collected mundane, seemingly unrelated data sets, but the combination identified key drivers of fish behavior.

Another point to make is the importance of the form-factor. The attachment of sensors to huge whale sharks is of course different from tagging a human being. Obviously, sensors have to be noninvasive and leave normal human behavior intact. This does not require complexity, however. An instructive case of this is a more recent example of aquatic bird monitoring, whereby the ultimate goal was to measure feeding behavior among the physiologically distinct Magellanic penguin and Imperial cormorant.⁴ Although both species of birds are warm-blooded and forage in cold waters, their physiologies are markedly different, with the cormorant exhibiting a much longer neck than the penguin. How do these physiological differences translate to changes in feeding behavior? We designed a small, lightweight neck sensor comprising simply two accelerometers, with one mounted on its back and the other on its head. In this way, both whole body movements and head position and orientation relative to the vertebrae could be monitored. As the birds dove into the water for feeding, the swim trajectory and feeding behavior were both discernible. The penguin swims quickly with little movement of its head, a strategy which seems reasonable in order to preserve body heat during foraging activity. However, the cormorant would swim slowly while moving its head over a range four times as wide to capture prey, allowing it to preserve energy and compensate for its larger body surface area losing heat more quickly (Figure 1g,h). These insights were collected from simple sensor devices that were designed to not impact the natural behavior of the animals. A key challenge moving forward for human medicine, however, is how to package these sensors in clever ways to collect data reliably without behavioral artifacts, to process the data thoughtfully to study human health robustly, and to identify specific conditions among those that share common signals.

Translating this into the case for human medicine, we can imagine simple devices that clip onto clothing that inform us about our eating habits, social interactions, respiration, sleep–wake cycles, heart rate, and oxygen levels. Coupled with location data from our cell phones, environmental data about various parameters such as pollutants, and medical history data, the risk of events such as asthma attacks and heart attacks can be quantified, the most vulnerable populations could be identified, and preventative interventions could be implemented earlier to improve outcomes and minimize the cost of treatment. The smartphone plays multiple roles as location

sensor, computational machine of local data, and hub between individuals' local data and the cloud aggregating population-level data. Furthermore, roughly 3 billion people owned smartphones in 2018, effectively already being tagged with a subset of sensors already connected to the Internet.¹⁶

While a number of these sensors already exist or are in development, the integration of molecular biomarker sensors specifically should provide critical, orthogonal data sets that could yield more nuanced diagnoses when combined with advances in computational algorithms and machine learning.¹⁷ The most developed of such biomarker sensors is the continuous glucose monitor. However, several emerging technologies measure other circulating small molecules and proteins and can provide this orthogonality.¹⁸ With the vast network of chemicals underlying the human body, machine learning may play a central role in utilizing this information.¹⁹ Data sets would be massive once aggregating millions of patients' data, with each individual contributing dozens of datastreams. The sheer volume of the data represents not only a challenge in that machine learning may be required to find patterns to gain insights but also an opportunity in that those insights may not have been observable through single datastreams alone.

Actually obtaining biomarker data, however, offers unique technical challenges. Unlike the movement sensors described above, whose components require only external mounting to an animal, wearable biosensors must access biological fluid and thus require at least one component to be internal, either the sensing element itself or a vehicle to sample biological fluid. Implantable devices, however, have thus far been limited in lifetime, with the glucose sensor having the most longevity at a mere 2 weeks,²⁰ due to fibrotic processes impeding bioanalyte transport to the sensor and fouling of the sensor's chemical integrity.²¹ Furthermore, measurement techniques of key biomarkers of health and behavior besides glucose, including cortisol, dopamine, and serotonin, among many others, remain as laboratory assays often requiring decoupled sampling and analysis, standing in stark contrast to the instantaneous feedback given by some of the biologging devices described above. Furthermore, some state-of-the-art biomarker sensors operate using optical or electrochemical techniques and are probed using specialized instrumentation. Here, we encounter a critical dilemma. The value of partial encoding relies on the orthogonality of the collected data. However, each data stream may require its own set of instruments, increasing the payload and power requirements of the tags, which may ultimately make the devices less convenient to use and decrease patient compliance. Biologging engineers again offer insights, having fabricated tags that not only collect and transmit multiple types of data but can also operate for several years without needing to change or recharge a battery. Even so, the incorporation of biomarker sensors into biologging tags remains an unsolved problem. A dialogue between the biologging and chemosensor communities would accelerate the development of wearable biosensors for human applications and also advance biologging efforts beyond mere physical parameter sensors.

Among the authors, we are ourselves still engaged in an interdisciplinary debate about the limits of this “partial encoding hypothesis” in medicine and marine biologging alike. However, one thing is clear: the historical record shows that its impact on the scientific biologging of animals is uncontested. We offer that the implications for human health are likewise clear. We need more than our smartphones to

make the biggest impact in this space. However, the peripheral sensors that we need for medicine need not be large or intrusive. They may in fact seem to measure esoteric or disconnected aspects of behavior or physiology. The analogy with biologging can allow us to assert with some confidence that we stand to learn more than what is listed on the packaging. Turning this Internet of Things (IoT) into an Internet of Health stands to benefit everyone if we think carefully about the machine/organism interface, regardless of whether one has legs or fins.

AUTHOR INFORMATION

Corresponding Author

*E-mail: strano@mit.edu.

ORCID

Víctor M. Eguíluz: [0000-0003-1133-1289](https://orcid.org/0000-0003-1133-1289)

Daniel A. Heller: [0000-0002-6866-0000](https://orcid.org/0000-0002-6866-0000)

Robert Langer: [0000-0003-4255-0492](https://orcid.org/0000-0003-4255-0492)

Hadley D. Sikes: [0000-0002-7096-138X](https://orcid.org/0000-0002-7096-138X)

Michael S. Strano: [0000-0003-2944-808X](https://orcid.org/0000-0003-2944-808X)

Notes

The authors declare no competing financial interest.

REFERENCES

- (1) Wilmers, C. C.; Nickel, B.; Bryce, C. M.; Smith, J. A.; Wheat, R. E.; Yovovich, V.; Hebblewhite, M. The golden age of bio-logging: How animal-borne sensors are advancing the frontiers of ecology. *Ecology* **2015**, *96* (7), 1741–1753.
- (2) Zhang, J.; Landry, M. P.; Barone, P. W.; Kim, J.-H.; Lin, S.; Ulissi, Z. W.; Lin, D.; Mu, B.; Boghossian, A. A.; Hilmer, A. J.; et al. Molecular recognition using corona phase complexes made of synthetic polymers adsorbed on carbon nanotubes. *Nat. Nanotechnol.* **2013**, *8* (12), 959–968.
- (3) Shen, C.; Ho, B. J.; Srivastava, M. MiLift: Efficient Smartwatch-Based Workout Tracking Using Automatic Segmentation. *IEEE Trans. Mob. Comput.* **2018**, *17* (7), 1609–1622.
- (4) Wilson, R. P.; Gómez-Laich, A.; Sala, J.-E.; Dell’Omo, G.; Holton, M. D.; Quintana, F. Long necks enhance and constrain foraging capacity in aquatic vertebrates. *Proc. R. Soc. London, Ser. B* **2017**, *284* (1867), 20172072.
- (5) Meekan, M. G.; Fuiman, L. A.; Davis, R.; Berger, Y.; Thums, M. Swimming strategy and body plan of the world’s largest fish: implications for foraging efficiency and thermoregulation. *Front. Mar. Sci.* **2015**, *2*, 1–8.
- (6) Xiao, X.; Agusti, S.; Lin, F.; Li, K.; Pan, Y.; Yu, Y.; Zheng, Y.; Wu, J.; Duarte, C. M. Nutrient removal from Chinese coastal waters by large-scale seaweed aquaculture. *Sci. Rep.* **2017**, *7*, 46613.
- (7) Grabowicz, P. A.; Ramasco, J. J.; Moro, E.; Pujol, J. M.; Eguíluz, V. M. Social Features of Online Networks: The Strength of Intermediary Ties in Online Social Media. *PLoS One* **2012**, *7* (1), No. e29358.
- (8) Ropert-Coudert, Y.; Kato, A.; Liebsch, N.; Wilson, R.; Müller, G.; Baubet, E. Monitoring jaw movements: a cue to feeding activity. *Game Wildl. Sci.* **2004**, *20* (4), 1–19.
- (9) Wilson, R.; Steinfurth, A.; Ropert-Coudert, Y.; Kato, A.; Kurita, M. Lip-reading in remote subjects: an attempt to quantify and separate ingestion, breathing and vocalisation in free-living animals using penguins as a model. *Mar. Biol.* **2002**, *140* (1), 17–27.
- (10) Abramson, A.; Caffarel-Salvador, E.; Khang, M.; Dellal, D.; Silverstein, D.; Gao, Y.; Frederiksen, M. R.; Vegge, A.; Hubálek, F.; Water, J. J.; et al. An ingestible self-orienting system for oral delivery of macromolecules. *Science (Washington, DC, U. S.)* **2019**, *363* (6427), 611–615.
- (11) Domokos, G.; Varkonyi, P. L. Geometry and self-righting of turtles. *Proc. R. Soc. London, Ser. B* **2008**, *275* (1630), 11–17.
- (12) Block, B. A.; Jonsen, I. D.; Jorgensen, S. J.; Winship, A. J.; Shaffer, S. A.; Bograd, S. J.; Hazen, E. L.; Foley, D. G.; Breed, G. A.; Harrison, A. L.; et al. Tracking apex marine predator movements in a dynamic ocean. *Nature* **2011**, *475* (7354), 86–90.
- (13) Block, B. A.; Costa, D. P.; Boehlert, G. W.; Kochevar, R. E. Revealing pelagic habitat use: the tagging of Pacific pelagics program/ Idées sur l’ utilisation de l’ habitat pélagique: le programme de marquage de pélagiques dans le Pacifique. *Oceanol. Acta* **2002**, *25*, 255–266.
- (14) Hazen, E. L.; Jorgensen, S.; Rykaczewski, R. R.; Bograd, S. J.; Foley, D. G.; Jonsen, I. D.; Shaffer, S. A.; Dunne, J. P.; Costa, D. P.; Crowder, L. B.; et al. Predicted habitat shifts of Pacific top predators in a changing climate. *Nat. Clim. Change* **2013**, *3* (3), 234–238.
- (15) Maxwell, S.; Hazen, E.; Bograd, S.; Halpern, B. Cumulative human impacts on marine predators. *Nat. Commun.* **2013**, *4*, 1–9.
- (16) GSM Association. *Mobile Economy*; 2019.
- (17) Wu, D.; Sedgwick, A. C.; Gunnlaugsson, T.; Akkaya, E. U.; Yoon, J.; James, T. D. Fluorescent chemosensors: the past, present and future. *Chem. Soc. Rev.* **2017**, *46* (23), 7105–7123.
- (18) Zhang, D.; Liu, Q. Biosensors and bioelectronics on smartphone for portable biochemical detection. *Biosens. Bioelectron.* **2016**, *75*, 273–284.
- (19) McRae, M. P.; Simmons, G.; Wong, J.; McDevitt, J. T. Programmable Bio-nanochip Platform: A Point-of-Care Biosensor System with the Capacity To Learn. *Acc. Chem. Res.* **2016**, *49* (7), 1359–1368.
- (20) Abbott. FreeStyle Libre 14 day system. <https://www.freestylelibre.us/system-overview/freestyle-14-day.html>.
- (21) Bakh, N. A.; Bisker, G.; Lee, M. A.; Gong, X.; Strano, M. S. Rational Design of Glucose-Responsive Insulin Using Pharmacokinetic Modeling. *Adv. Healthcare Mater.* **2017**, *6* (22), 1700601.