from awake mice whose heads are restrained and whose feet rest on a large spherical treadmill (picture a very large ping-pong ball). The speed and direction of treadmill rotation, induced by the animal's leg movements, is integrated and used to move the mouse through a virtual-reality environment presented on screens shaped to cover much of its visual field (Fig. 1). Effectively, the animal moves through an environment of its own volition, a known requirement for normal place-specific activity[6].

The effort and patience involved in developing such a difficult technique are to be applauded, especially given the risk of failure involved. Lacking the normal vestibular inputs from movements of its head that help an animal monitor its own motion during actual running, it was not at all a given that place-specific activity would be observed. And yet, under these conditions, normal-sized, trajectory-dependent, 'virtual' place fields were indeed apparent. Traversal through such fields was consistently accompanied by phase precession, albeit to a lesser degree than seen in freely moving rodents.

Having shown this, the authors[1] deliver a first payment on the promise of the technique. Virtual movement of the animal through a given neuron's place field is accompanied by a ramp-like depolarization of the cell's membrane potential that spans the length of that field. Moreover, the depolarization envelope carries a theta-frequency rhythm that is much more prominent than when the animal moves outside the place field of the recorded neuron. Considered together, these results are consistent with the predictions of a set of explanations for phase precession[7,8]. A feature of such 'somato-dendritic interference models' is the interaction of theta-rhythmic excitatory and inhibitory oscillations between different compartments of the cell. This is an exciting result in that it may prove generalizable to other brain structures, in particular the cerebral cortex[9].

There are many other similar, as well as qualitatively different, questions that may be addressed using this technique. The technique features a great degree of control over what the animal sees at any given time, and so it will probably permit in-depth studies of how the complex arrangements of visual stimuli that define environmental positions drive hippocampal firing. The observation of robust place-field activity in a virtual-reality environment sets the stage for more direct comparisons between hippocampal function in rodents and primates. Finally, the initial development of the technique in mice suggests that the authors may in the future conduct experiments in genetically modified animals. The impact of excitation or inhibition of specific components of the hippocampus on intracellular dynamics could then be assessed. ■

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1. Harvey, C. D., Collman, F., Dombeck, D. A. & Tank, D. W. *Nature* **461,** 941–946 (2009).
2. Sohal, V. S., Zhang, F., Yizhar, O. & Deisseroth, K. *Nature* **459,** 698–702 (2009).
3. Izhikevich, E. M. & Edelman, G. M. *Proc. Natl Acad. Sci. USA* **105,** 3593–3598 (2008).
4. O'Keefe, J. & Dostrovsky, J. *Brain Res.* **34,** 171–175 (1971).
5. O'Keefe, J. & Recce, M. L. *Hippocampus* **3,** 317–330 (1993).
6. Foster, T. C., Castro, C. A. & McNaughton, B. L. *Science* **244,** 1580–1582 (1989).
7. Magee, J. C. *J. Neurophysiol.* **86,** 528–532 (2001).
8. Harris, K. D. *et al. Nature* **417,** 738–741 (2002).
9. Klausberger, T. & Somogyi, P. *Science* **321,** 53–57 (2009).

ANALYTICAL CHEMISTRY

The matrix neutralized

Ilia Fishbein and Robert J. Levy

Many of the best methods available for monitoring biological binding events can't be used in a diverse range of clinical samples. An ultrasensitive assay based on magnetic signals overcomes this problem.

The Matrix and its two sequel films explore the complex reality of an eponymous cyber-generated world that allows machines to dominate humans. This science-fiction trilogy was famous for its distinctive visual effects, which were generated using innovative combinations of previously existing photographic techniques. In *Nature Medicine*, Gaster *et al.*[1] report how they have used a similar strategy — the combination of established techniques — to devise an ultra-sensitive assay that detects biomarker proteins associated with disease or metabolic states. Their pioneering approach uses magnetic signals to overcome the effects of the biological matrix, the host of compounds found in all biological samples that cause interference in assays. The sensitivity of the authors' technique is 1,000 times better than the current gold-standard method, the enzyme-linked immunosorbent assay (ELISA).

Interference by biological matrices is a real problem in immunoassays, which rely on the binding of an antibody to its target antigen. Such interference has been defined as "the sum of the effects of all of the components [in a sample], qualitative and quantitative, with the exception of the analyte to be measured"[2]. It occurs ubiquitously, both at the stage of specific antigen–antibody binding and during the detection phase, when the amount of antigen–antibody coupling is quantitatively translated into a measurable signal (such as light absorption or fluorescence). The intrinsic, non-zero light absorption and/or fluorescence of biological milieux hinder accurate measurements of analytes (antigens), especially at lower concentrations.

Gaster and colleagues' approach[1] is based on the fundamental observation that even the most complex biological matrices lack a detectable magnetic signal, and would therefore not interfere with a magnetic-field-based detection method. Their assay uses magnetic nanoparticles, bound with high affinity specifically to the biomarkers of interest, as the basis of its detection system. To generate an electronic readout of the assay, they adapted the magnetic-sensing capabilities of giant magnetoresistive (GMR) sensors, devices that were originally developed for use in the read heads of computer hard drives.

So how exactly does Gaster and colleagues' assay work? The authors first attach specific antibodies for a target biomarker to the surface of a GMR sensor, and expose the surface to a fluid sample containing that biomarker, whereupon the target molecules bind to the immobilized antibodies (Fig. 1). The authors then wash the sensor with a second set of antibodies that have been labelled with a compound called biotin; these antibodies also bind

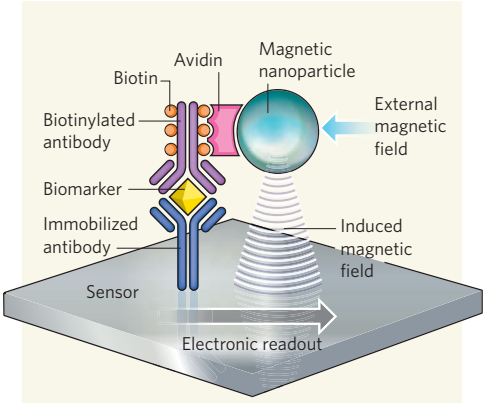

Figure 1 | Mechanism of a magneto-biosensor. Gaster *et al.*[1] describe an ultra-sensitive nanoscale sensor that detects biomarker proteins. Antibodies on the surface of the sensor specifically trap the biomarker of interest from a sample. The sensor is then washed with a solution containing more antibodies, which also bind specifically to the biomarker. These antibodies are tagged with biotin molecules, which bind to the protein avidin. When avidin-coated magnetic nanoparticles are passed over the sensor, they bind to the biotinylated antibody. The sensor is activated by applying an external magnetic field. This induces a magnetic field in the nanoparticles, which causes an electronic response in the sensor that correlates with the number of bound nanoparticles.

specifically to the trapped biomarkers. The next step is to treat the sensor with an aqueous suspension of magnetic nanoparticles — tiny spheres containing iron oxide — to which the protein avidin has been attached. Avidin binds with high affinity to biotin, and so the magnetic nanoparticles become strongly linked to the biomarker–antibody complexes on the surface of the sensor. Finally, the authors activate the sensor by exposing it to a magnetic field. The resulting electronic readout is proportional to the extent of nanoparticle binding, and thus provides a quantitative measure of the amount of biomarker bound to the sensor's surface.

Bioassays that use GMR sensors to detect molecules sandwiched between a pair of antibodies (one immobilized and the other introduced in solution) have been reported previously[3,4]. But there are two factors that distinguish Gaster and colleagues' results[1] from the others. First, they have meticulously characterized their approach for several candidate analytes to prove its generality and its superiority to ELISA. And second, they demonstrate that their nanosensor can be used for multiplexing, so that as many as 64 assays can be performed on the same device. This capability is possible because of the specificity and sensitivity of their design, and because of the lack of biological-matrix interference.

The authors showed that their nanosensor assay system works in all biological fluids studied, including blood, urine, saliva and cell lysates — although the signal strength in saliva is less than that in other media, perhaps because the viscosity of saliva affects the binding kinetics of the assay. The authors also demonstrated that real-time readouts of binding are possible with their system, and that it can be used *in vivo* to follow the earliest stages of tumour progression by monitoring appropriate biomarkers. Turbidity and sample pH do not significantly affect the assay, but Gaster *et al.* found that the output signal is affected by temperature, so that hot or cold samples create undesirable spikes in the baseline of the electronic readout before they equilibrate to room temperature. The authors were able to correct for this, however, by processing the data using a mathematical algorithm. No other assay system, including ELISA, has such a combination of broad applicability, high sensitivity and low background 'noise' caused by biological-matrix interference.

It should be noted that Gaster and colleagues' approach does not actually prevent the biological matrix from physically interfering with antigen–antibody interactions. Nevertheless, such interference can be minimized by carefully screening antibodies to find those that don't interact with components of the biological matrix[2]. The assay could also be adversely affected by inadvertent exposure to strong magnetic fields, such as those present in nuclear magnetic resonance imaging scanners, but this can be prevented by appropriate shielding.

Gaster *et al.* speculate that their assay will be useful for several applications, such as studying protein–protein interactions and screening compounds for biological activity in drug-discovery programmes. Furthermore, the sensitivity and rapid responsiveness of the system permit biomarker monitoring with both high spatial and temporal resolution. This might open up exciting medical applications — for example, by tracking appropriate biomarkers, tumour responses to therapy could be anticipated before any effect becomes apparent. That could reduce the risk of untoward drug effects, and allow adjustments to be made to medication in a more timely way than is currently possible. ■

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1. Gaster, R. S. *et al. Nature Med.* doi:10.1038/nm2032 (2009).
2. Selby, C. *Ann. Clin. Biochem.* **36,** 704–721 (1999).
3. Dittmer, W. U. *et al. J. Immunol. Meth.* **338,** 40–46 (2008).
4. Osterfeld, S. J. *et al. Proc. Natl Acad. Sci. USA* **105,** 20637–20640 (2008).

STEM CELLS

A fateful age gap

Tim Stearns

When a stem cell divides, one sister cell differentiates and the other retains its stem-cell identity. Differences in the age of an organelle — the centriole — inherited at cell division may determine these differing fates.

One of the enduring mysteries of biology is how two genetically identical sister cells become different from each other after cell division. Stem cells are particularly interesting in this respect because they can divide so that one of the two resulting cells remains an undifferentiated stem cell while the other becomes a differentiated cell type. It has long been thought that such asymmetric cell division may reflect an underlying asymmetry in the segregation of a cellular component at division; the asymmetrically inherited component would have properties that allow it to control the fate of its recipient cell. In this issue (page 947), Wang *et al.*[1] present evidence that the centrosome, a multifunctional organelle that is common to all animal cells, might be such a determinant.

The centrosome is an ancient organelle[2] and is one of the cell structures that distinguishes eukaryotic cells (animal and plant cells) from prokaryotes (bacteria and archaea). It helps to form the microtubule cytoskeleton, a network of protein filaments that serve as tracks for moving cellular cargo. It also organizes the primary cilium, a whip-like structure that extends from the surface of cells. In most cells the primary cilium is non-motile, in contrast to the beating cilium of sperm cells, but it is responsive to chemical and mechanical signals outside the cell. For more than a century, the main function of the centrosome was thought to be organization of the mitotic spindle — the filamentous network that carries out the segregation of chromosomes at cell division. But it is now clear that the spindle can form without the centrosome, and that formation of a cilium is actually the centrosome's essential function[3]. This revelation is particularly exciting because it has coincided with the recognition that the primary cilium is a key signalling centre in vertebrate organisms, thereby placing it, and the centrosome, in the thick of important regulatory processes[4].

Each centrosome consists of a pair of cylindrical centrioles and associated microtubule-organizing material. The two centrioles in a pair usually lie in close association at right angles to each other. One centriole, the mother, has structural appendages that confer the ability to anchor microtubules and to organize a cilium; the other centriole, the daughter, lacks these appendages.

The centrosome duplicates once during the cell cycle, and it derives an intrinsic asymmetry from its mechanism of duplication. Centriole duplication is initiated by disengagement of the centriole pair at the end of mitosis, followed in S phase (the phase of DNA synthesis) by assembly of two new daughter centrioles, each adjacent to one of the existing centrioles. This pattern of duplication and segregation results in an age difference in the two centrosomes that are segregated to sister cells at division. One sister cell receives a centrosome containing a newly minted mother centriole (one that was a daughter centriole before duplication and cell division), and the other sister cell receives a centrosome containing the older mother centriole.

Might there be a correlation between the asymmetric fates of dividing stem cells and differences in the age of the centrioles inherited at cell division? Wang *et al.*[1] addressed this question by studying the asymmetric divisions of radial glial cells, a type of neural stem cell that is important for the development of the mammalian cerebral cortex. These cells are highly polarized, stretching between the epithelial surface of the cerebral ventricles