activity of those surfaces. This allows the Oxford team to identify active catalysts and leads them, again, to a silver–palladium core–shell catalyst.

For now the work of Tsang and colleagues suggests that the use of core–shell nanoparticles is a promising approach to the formation of hydrogen through the controlled decomposition of formic acid. With the development of appropriate catalytic processes for the decomposition and formation of formic acid, a hydrogen generation cycle that is carbon dioxide neutral would be possible. Formic acid would then be an attractive material for liquid hydrogen storage, particularly for applications such as portable electric devices. ❐

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BIOSENSORS

# Magnets tackle kinetic questions

Interactions between biomolecules can be probed with the help of technology that was developed for reading data stored on magnetic disk drives.

Shawn P. Mulvaney

Advances in computing power and memory have enabled researchers to handle ever-increasing amounts of data in many areas of science and engineering. In bioinformatics, for example, previously unknown biological interactions have been discovered in the massive datasets gleaned from genomic and proteomic microarrays. It is less well known that advances in computer hardware can also have a vital role in the collection of data. For example, giant magnetoresistive (GMR) wires, which are core components of the read heads for modern hard drives, have been harnessed as transduction elements in various rapid, ultrasensitive and portable biosensor systems[1–5]. Now, writing in *Nature Nanotechnology*, Shan Wang and co-workers[6] at Stanford University, IBM and MagArray, report that GMR-based sensors can also be used to study protein-binding kinetics, such as antibody–antigen interactions.

GMR wires are constructed from alternating layers of magnetic and non-magnetic materials, they change resistance in response to adjacent magnetic materials and they can detect very small changes in field strength (Fig. 1). In the late 1990s, David Baselt of the U.S. Naval Research Laboratory and co-workers developed an approach to biosensing that involved capturing target biomolecules with surface-immobilized antibodies or antigens, labelling the captured biomolecules with magnetic beads, and then sensing the captured beads with GMR-based sensors[7]. Since then, Wang and co-workers at Stanford have developed this technique further, and this group has now demonstrated that GMR sensors can effectively monitor the kinetics of antibody–antigen binding with excellent sensitivity. By monitor the kinetics, we mean measure the values of the rate constants that describe the association and dissociation of the antibody–antigen pairs.

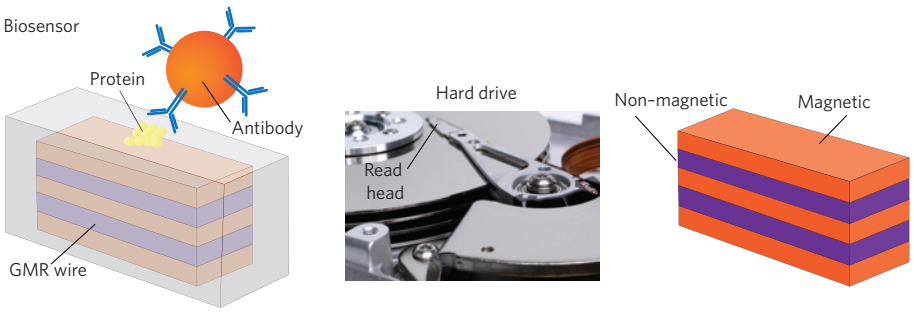


**Figure 1 |** The read heads for most hard drives (centre) rely on GMR wires that contain alternating layers of magnetic and non-magnetic materials (right). GMR sensors can also be used to detect biomolecules that have been labelled with magnetic beads (left). Here one of the four antibodies (blue) attached to a magnetic bead (red) binds to a protein antigen (yellow) immobilized on top of a GMR sensor in a proteomic microarray. The change in the resistance of the GMR wire caused by the magnetic field of the bead allows the kinetics of the protein–antibody interaction to be studied. Centre panel © istockphoto.com/BPalmer.

Binding kinetics is central to clinical diagnostics and drug development, where it is used to identify promising therapeutic candidates. The present gold standard for kinetic analysis is surface plasmon resonance (SPR), but this approach has its limitations. Whereas SPR devices have a limit of detection of ~25 ng ml$^{-1}$ and dynamic range of just 2 logs, GMR biosensors have a limit of detection < 100 fg ml$^{-1}$ (which is 10,000 times more sensitive than the SPR approach) and a much wider dynamic range (~6 logs). Furthermore, the number of channels that can be simultaneously monitored is much higher for a GMR microarray than for an SPR device, and feature densities of 100,000 GMR sensors cm$^{-2}$ have been produced. Consequently, massively multiplexed assays that include redundancy for signal verification are possible with a GMR-sensor chip.

The wide dynamic range enables an array of GMR sensors to sample for low and high abundance targets simultaneously and without the added sample handling, time and cost of serial dilutions. The Wang group confirmed the technique's potential with three clinically relevant protein antigens: epithelial cell adhesion molecule; vascular endothelial growth factor; and carcinoembryonic antigen.

At first it was thought that GMR sensors were not suited to performing kinetic analysis because the assay requires a magnetic label, typically a bead, and because it has been shown many times that any label (such as a fluorophore, electrochemical species or quantum dot) changes biomolecular

interactions owing to steric hindrance, electrostatic repulsion, and/or decreased diffusion[8,9]. These limitations have meant that label-free techniques, such as SPR, have predominated kinetic studies, but the Stanford–IBM–MagArray collaboration has now challenged this state of affairs. Wang and co-workers have developed an analytical model based on their GMR sensing scheme that yields kinetic values for their three protein antigens (and also for the widely studied streptavidin–biotin pair) that are essentially identical to those obtained with SPR.

This breakthrough has been made possible by a new analytical model that takes into account that the antibody is attached to a 45-nm magnetic bead and the protein or antigen is attached to the GMR-sensor surface. While attached to the bead, the diffusion of the antibody becomes negligible and the overall kinetic equations can be greatly simplified. One important requirement is that the proteins bound to the GMR sensor should be sufficiently spaced such that an antibody-labelled bead can interact with the surface at only one point. Another limitation is that custom beads and surfaces must be prepared for every biomolecular interaction of interest.

Small-diameter magnetic beads (45 nm) are atypical for how GMR sensors are used in rapid, diagnostic testing. Instead, larger beads with diameters of between 300 nm and 3 μm are more traditionally used with portable GMR-sensor platforms[1–5]. Fundamentally, larger magnetic beads have more magnetic material and therefore provide more signal per bead. In fact, some GMR device designs are capable of detecting a single bead and therefore a single biological interaction. Moreover, the larger beads can be more easily manipulated by both gravity and magnetic forces for target collection, separation and mass transport to the GMR-sensor surface. Despite these advantages, it is also known that the dissociation constant of the attached biomolecules is suppressed with large-diameter beads[4]. This means that kinetic studies with GMR sensors will be accurate only when the bead diameter is less than a critical value.

The fact that the model developed by Wang and co-workers predicts that kinetic analysis can now be performed with labels is an exciting development. Given the flexibility, multiplexing capabilities and dynamic range possible with GMR sensors, one can imagine rapidly screening large biomolecular libraries. Notably, proteins with significantly different association constants and abundances could be screened in a single experiment. It is expected that such experiments will provide new insights into biology and reveal unanticipated biophysical interactions. GMR wires clearly have uses that go way beyond reading data from hard drives. ❐

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