Applied Physics: Toward a Universal Memory

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Arabidopsis—is not known because validated *rcr3*-null mutant plants are not available (*9*). Thus, we can infer two possible modes of Cf-2 activation (see the figure). Secretion of Avr2 during pathogenesis may sequester Rcr3 away from constitutive Cf-2–Rcr3 complexes, thereby derepressing Cf-2 activity. Alternatively, formation of Avr2–Rcr3 complexes may trigger a conformational change in Rcr3, enabling it to bind to and activate Cf-2. In either case, Cf-2–dependent recognition of Avr2 is likely to be indirect, taking place without physical interaction between the fungal effector protein and the plant host R protein.

Work on other plant resistance responses mediated by pairs of host resistance and pathogen effector proteins supports an indirect mode of nonself recognition (*10, 11*). Of particular note is the recognition of the *P. syringae* effector AvrRpm1 by the intracellular and plasma membrane–associated RPM1 receptor of *Arabidopsis*. Both proteins were found to physically associate with *Arabidopsis* RIN4 rather than interacting directly with each other. Thus, RIN4 appears to be a host target for multiple *Pseudomonas* effector proteins (*11*). However, RIN4 does not disappear upon delivery of AvrRpm1 into plant cells. The exact biochemical alteration in RIN4 mediated by AvrRpm1 is poorly understood, but a change in RIN4 phosphorylation seems likely to be involved in RPM1 activation (*11*). An indirect mode of recognition appears to be the common theme in these cases, and clearly plant immune receptors are capable of recognizing biochemically diverse alterations of effector targets, including phosphorylation status, proteolytic cleavage, and conformational changes.

Indirect recognition of nonself in plants is an elegant alternative solution to direct nonself recognition by the adaptive immune systems of vertebrates. Vertebrates evolved dedicated somatic recombination systems for the generation of receptor diversity and specialized immune cells to recognize any potentially harmful nonself molecular structures (*12*). Indirect pathogen detection in plants appears to be as effective as direct nonself recognition in vertebrates. However, fewer receptors are needed—for example, there are only ~120 nucleotide binding LRR-type receptors in the *Arabidopsis* genome (*13*)—and specialized immune cells are not required. R protein–mediated surveillance of only those host protein assemblies that are critical for successful invasion by parasites may have been an important step in helping plants, with their limited set of receptors, to survive. Indeed, it is conceivable that *Arabidopsis* RIN4 and tomato Rcr3 are virulence targets. However, the roles of these two host proteins in cellular reprogramming during pathogenesis remain mysterious. In addition, although conformational changes in R proteins are likely to be critical for their activation (*14*), we do not have detailed insights into this process owing to a lack of R protein crystal structures. Such structures might help to identify the immediate targets of activated R proteins, which are as yet unknown. Finally, it will be important for future studies to compare the current findings with the recognition mechanics of a second nonself perception system in plants, the so-called PAMP (pathogen-associated molecular pattern) receptors. These receptors detect conserved pathogen-derived molecular structures present in multiple microbial species, such as a peptide derived from the bacterial motor protein flagellin (*15*) .

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APPLIED PHYSICS

Toward a Universal Memory

Johan Åkerman

When it comes to computers, mp3 players, digital cameras, and other electronic gadgets, there is no such thing as too much memory. Whether it is more Flash memory for taking high-resolution digital pictures, a bigger hard drive for digital video files, or more random access memory (RAM) to view them on the computer, the appetite for ever more memory at ever-increasing densities appears insatiable. An emerging technology, magnetoresistive RAM, promises additional functionality and improved memory performance that will enable yet more applications and open up system designs that are not possible today.

Today's dominant solid-state memory technologies—static RAM, dynamic RAM, and Flash—have been around for a long time, with Flash the youngest at 21 years (*1*). Their longevity can be explained in part by mutually beneficial differentiation. Each technology does a single thing very well, but many systems need all three memory types to deliver overall good performance at reasonable cost. However, the gain from differentiation comes at the cost of increased system and fabrication complexity, particularly in so-called embedded applications, where an entire electronic system is implemented on a single chip with static RAM, dynamic RAM, and Flash often used side-by-side.

All three technologies have advantages and disadvantages. Static RAM has excellent read and write speeds, integrates readily into the process technology of embedded applications, and requires little power for data retention. However, its large cell size (a typical memory bit requires six transistors) makes it impractical for embedded applications that require a lot of memory. Embedded static RAM is used for cache memory in microprocessors, where high speed is more important than large amounts of memory.

Dynamic RAM uses a single transistor and a storage capacitor per cell and thus provides a denser architecture than static RAM, at the expense of increased embedded-process complexity. Because the stored charge tends to leak out of the capacitor, dynamic RAM requires constant power to refresh its bit state every few milliseconds. Because of its high power consumption, large amounts of dynamic RAM are impractical for portable electronics with limited battery life.

In contrast to static and dynamic RAM, Flash memory offers nonvolatile data storage; that is, its information is not lost when the power is turned off. Nonvolatility is highly desirable in portable electronics, because nonvolatile data retention does not consume any battery power. Flash also has high density and moderately fast read access time, but its write mode is too slow and its write endurance far too limited for many applications. In addition, embedded Flash needs its own high-voltage drivers, complicating the design and manufacturing process.

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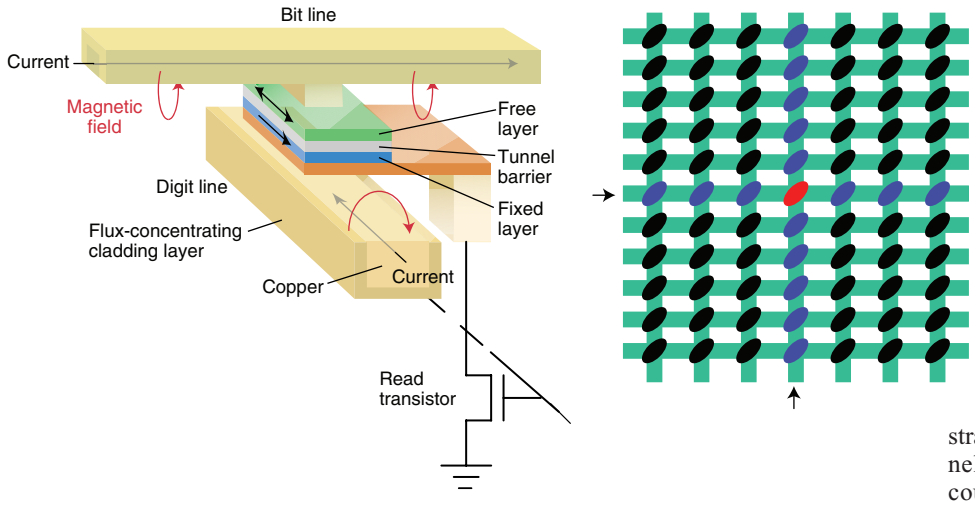
For some time, researchers have tried to devise nonvolatile alternatives to Flash. The goal is a "universal memory" that combines the best attributes of static RAM, dynamic RAM, and Flash. Such a memory would eliminate the need for multiple memories in many applications, would improve system performance and reliability by avoiding data transfer between multiple memories, and would reduce overall system cost.

Magnetoresistive RAM (MRAM) is currently the most promising contender for a memory with such universal characteristics. It combines nonvolatility with relatively high read and write speeds and unlimited endurance. Furthermore, the MRAM storage element resides in the metal interconnect layers, well above the silicon, allowing its process to be optimized independently from the underlying semiconductor process. MRAM is therefore cost effective to integrate and is ideally suited for embedded-memory applications.



2D write selection with MRAM. (Left) MRAM bit cell with a magnetic tunnel junction in series with a transistor for bit read selection. Perpendicular write lines above and below the magnetic tunnel junction select a single tunnel junction during programming. **(Right)** Top view of an MRAM array, highlighting the fully selected bit (red) in the center and 1/2-selected bits (blue) along each current-carrying write line. In toggle-MRAM, all bits are oriented at 45° with respect to the write lines.

State-of-the-art MRAM combines a magnetoresistive magnetic tunnel junction with a single-pass transistor for bit selection during read (see the figure) (*2*). The tunnel junction has a free magnetic layer, a tunneling barrier, and a fixed magnetic layer. The magnetization of the fixed layer is prevented from rotating, whereas the magnetization orientation of the free layer can be switched and is used for information storage. The resistance of the tunnel junction depends on the relative magnetization orientation of the free layer with respect to the fixed layer. For tunnel junctions with a NiFe free layer and an aluminum oxide tunneling barrier, the maximum difference in resistance (the magnetoresistance) is about 40 to 50%.

To read a single bit, the transistor is turned on, a bias of ~0.3 V is applied to the bit, and the memory state is determined by measuring the amount of current that flows through the bit. Programming is achieved by passing current through two perpendicular write lines, one above and the other below the selected bit; these are respectively termed the "bit line" and the "digit line" (see the figure). The lines are clad with magnetic material to focus the applied field to the bit for improved write selectivity and increase the field magnitude by a factor of ~2, reducing the write power consumption by a factor of ~4.

MRAM faces several challenges before it can be introduced to the market on a large scale. The first challenge relates to the switching current distribution. The two-dimensional (2D) write selection scheme outlined above requires tight and uniform switching current distributions. Successful programming of the selected bit requires that the combined write field from both write lines must be greater than the bit's switching field. In addition to the selected bit, thousands of bits along the two write lines (called 1/2-selected bits) see 71% of the write field. As a consequence, a 4-Mb memory will suffer 1/2-select disturbs, unless the standard deviation of the bit-to-bit switching current due to inevitable material and processing variations is less than 6%. Because the 1/2-select disturb process is thermally activated, the actual distribution must be even tighter to ensure proper operation over the life of the memory (typically 10 years).

As a solution to the 1/2-select problem, the late Leonid Savtchenko of Motorola proposed a novel free-layer structure and a phase-sensitive write pulse scheme, in which the free layer rotates rather than switches (*3*). A full rotation takes place only if a bit sees both field pulses; as a result, 1/2-selected bits are less susceptible to thermal activation than are unselected bits. Because the free-layer rotation toggles the bit state, unipolar write currents can be used, further simplifying the design. A necessary pre-read before write effectively reduces the number of write pulses by 50%. This toggle-write method is used in the 4-Mb MRAM under development at Freescale Semiconductor (*4*).

A different approach is taken by Cypress Semiconductor, whose 256-kb lower density MRAM avoids the 1/2-select problem altogether by having individual write transistors for each bit. This design can also reduce the overall write current, but it comes at the cost of increased cell size.

The second concern for MRAM is its relatively small readout signal, which effectively limits its read speed. The available signal is roughly proportional to the magnetoresistance divided by the bit-to-bit resistance distribution. IBM has obtained read times of 3 ns (3×10^{-9} s) in 1-kb research memories, Freescale has demonstrated a 25-ns cycle time for its 4-Mb MRAM (*5*), and Cypress Semiconductor is targeting a 70-ns cycle time for its 256-kb MRAM (*6*). However, a magnetoresistance of more than 230% was recently demonstrated in junctions that use MgO as the tunneling barrier (*7*, *8*). Use of this material could lead to much faster MRAM operation, provided the resistance distributions are as tight as for aluminum oxide barriers.

As with any new technology, customers will worry about its long-term reliability. The most obvious concerns relate to the long-term stability of the ultrathin tunneling barrier, the stability of the magnetic layers in the free layer, and data retention. Accelerated tests show that these mechanisms have negligible impact on memory performance at operating conditions.

The tunneling barrier is likely to be highly stable, because aluminum oxide has a high breakdown voltage even at very small thicknesses, MRAM uses a low operating voltage, and only the magnetic tunnel junctions that are being read are subject to any voltage stress. Accelerated dielectric breakdown studies indeed show barrier lifetimes far greater than 10 years (*9*). Interdiffusion between the magnetic layers may affect the switching performance over time, but accelerated tests indicate that over 10 years of use, virtually no change in switching performance at operating temperatures would occur. MRAM data retention is inversely proportional to the thermal flip rate of the free layer, but at present bit dimensions, accelerated tests predict no observable

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thermal flip rate at operating conditions.

Future generations of MRAM will use smaller tunnel junctions and will thus have to readdress the above challenges. Going toward smaller dimensions must not introduce more bit-to-bit variations or jeopardize data retention. The switching current will not substantially increase with reduced bit size (provided that other dimensions, such as the proximity to the write lines and their width, also decrease). But the current density will scale inversely with the conductor area, and electromigration may therefore become an issue. At that point, spin momentum transfer (*10*)—switching by a spin-polarized current through the bit—might become a viable alternative to 2D write selection.

This year, Cypress Semiconductor became the second company (after Freescale Semiconductor) to announce that it has shipped fully functional MRAM samples to potential customers. Many other companies have demonstrated multi-Mb MRAM prototypes. It is now only a matter of time before the first volume shipments of MRAM devices take place.

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CELL BIOLOGY

Guiding ATM to Broken DNA

Robert T. Abraham and Randal S. Tibbetts

DNA damage poses a continuous threat to genomic integrity in mammalian cells. To cope with this problem, these cells have evolved an elaborate network of sensor, transducer, and effector proteins that coordinate cell-cycle progression with the repair of the initiating DNA lesion. A particularly lethal form of DNA damage is the DNA double-strand break (DSB). The cellular response to DSBs must be swift and decisive—requirements that are capably fulfilled by a serine-threonine kinase in the nucleus called ATM (ataxia-telangiectasia mutated). This nuclear protein serves as a key signal transducer in the DSB response pathway. ATM is a member of the phosphoinositide 3-kinase related kinase (PIKK) family, which includes several important proteins required for genome surveillance (*1*). Humans that lack functional ATM suffer from a devastating syndrome called ataxia telangiectasia (AT), characterized by cerebellar neurodegeneration, premature aging, immunodeficiency, extreme sensitivity to radiation, and heightened susceptibility to developing cancer. The severe pathologies associated with AT are attributable largely, if not entirely, to defective DSB recognition and repair. Exposure to ionizing radiation or other DSB-inducing agents triggers a prompt increase in ATM kinase activity, suggesting that ATM is a proximal transducer of DNA damage signals (*1*). On page 551 of this issue, Lee and Paull (*2*) offer new insights into the molecular mechanism that relays damage signals from DNA to ATM.

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Seminal studies 2 years ago by Bakkenist and Kastan (*3*) revealed that, in undamaged cells, ATM resides as a catalytically inactive dimer or higher order multimer. DNA damage induced by ionizing radiation triggers the auto- or trans-phosphorylation of the serine amino acid residue at position 1981 (Ser^{1981}) in the ATM polypeptide. This leads, in turn, to the dissociation of inactive ATM complexes into catalytically active ATM monomers. The authors made the striking observation that nearly the entire nuclear pool of ATM molecules was phosphorylated on Ser^{1981} within minutes of cellular exposure to low doses of ionizing radiation that induced only a few DSBs. To explain this highly efficient amplification mechanism, the authors proposed that even a single DSB causes a far broader alteration in chromatin structure that encompasses megabase regions of genomic DNA. This creates a suitable platform for the prompt activation of hundreds of ATM dimers after DSB induction. Consistent with this epigenetic model for ATM activation, the authors demonstrated that treatment of cells with chromatin-disrupting agents provoked widespread phosphorylation of ATM under conditions that did not produce detectable DSBs.

The new study by Lee and Paull (*2*) highlights the Mre11-Rad50-Nbs1 (MRN) complex as an essential mediator of ATM recruitment to and activation by DSBs. The MRN complex has a long history of association with the ATM-dependent checkpoint pathway (*4*). Hypomorphic mutations in the *NBS1* and *MRE11* genes give rise to Nijmegen breakage syndrome (NBS) and an AT-like disorder (ATLD), respectively. The clinical features of ATLD are indistinguishable from those of AT, whereas NBS patients (and cells from these patients) display a somewhat attenuated version of the AT phenotype. Mre11 is a DNA binding protein that possesses 3′,5′-exonuclease activity, as well as an endonuclease activity that cleaves DNA hairpins. Rad50 is a member of the structural maintenance of chromosomes (SMC) family. It forms homodimers that associate with two Mre11 molecules to yield tetrameric Mre11-Rad50 (MR) complexes (see the figure). The two arms of the MR complex allow this structure to form bridges between free DNA ends or between sister chromatids. The contribution of the Nbs1 subunit to the MRN complex is not well understood, although numerous studies show that Nbs1 expression is required for optimal phosphorylation of ATM substrates in cells damaged by ionizing radiation. Bakkenist and Kastan (*5*) recently argued that the partial ATM signaling defects observed in cells from NBS patients indicate that Nbs1 positively influences, but is not essential for, activation of ATM. However, as these authors point out, many NBS cells express a truncated form of Nbs1 that contains an intact carboxyl terminus. It turns out that this region of Nbs1 binds directly to ATM and is important for recruitment of ATM to sites of DNA damage (*6*). Thus, the hypomorphic *NBS1* allele expressed in NBS cells may mask an obligate role for Nbs1 in ATM activation. Earlier findings indicated that the Nbs1 partner protein, Mre11, is equally indispensable for ATM activation after DNA damage (*7*, *8*). Lee and Paull (*2*) now offer compelling biochemical evidence to support the conclusion that the MRN heterotrimer both recruits and activates ATM at DNA damage sites.

Lee and Paull (*9*) earlier demonstrated that the protein kinase activity of purified