dinates with close to atomic resolution (= 0.3 nm). The instrument consists of an extremely sharp, needle-shaped specimen and a time-of-flight mass spectrometer equipped with a single atom–sensitive detector. The surface atoms of a cryogenically cooled specimen are individually ionized by the application of a short (10 ns), high-voltage pulse and then radially projected from the specimen toward a position-sensitive detector. Typically, the specimen surface is magnified by a factor of about 5 million at the single-atom detector. The identities of the ions are determined from their flight times in the mass spectrometer, which has sufficient mass-resolving power to distinguish the isotopes of all elements. The specimen volume that may be analyzed typically has an area of about 10 to 20 nm^2 and is about 100 to 250 nm deep, containing up to about 1 million atoms. The compositions of small volumes are determined by simply counting the number of atoms of each type within that volume, and thus the technique provides a fundamental measure of local concentrations.

This powerful microanalytical technique, also known as atom probe tomography (APT), enables unique information about the distribution of elements to be experimentally obtained at the atomic level. This information can be used to provide experimental verification of theoretical models, as evidenced by Blavette *et al.*'s (*2*) verification of a Cottrell atmosphere. The atomic level distribution of elements also provides valuable insights into the earliest stages of decomposition of metals (*11*) and may lead to the design of new and improved alloys, by suggesting alterations in alloy composition and thermal treatments. For example, substantial improvements in the fuel efficiency and the environmental impact of gas turbines should be possible based on the results of APT investigations of the distribution of alloying elements in the high-temperature superalloys used in these turbines.

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PERSPECTIVES: DEVICE PHYSICS

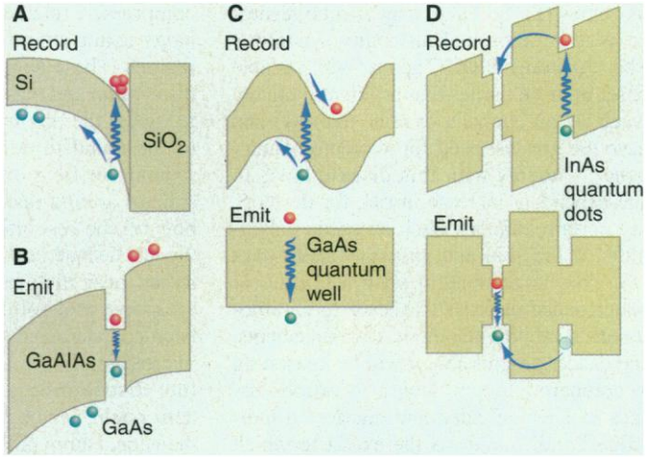
Toward Efficient Smart Pixels

Jörg P. Kotthaus

Much of information technology revolves around the analysis, storage, and processing of visual images and patterns. Usually an image is recorded with a charge-coupled device (CCD) camera in the form of pixels, that is, points of varying color and intensity, thus converting the image into a series of digital electronic signals. These are stored and processed by a computer, often transmitted through fiber optic networks, and finally converted back into visual images on a display consisting of light-emitting diodes (LEDs). A more direct way of image processing uses so-called smart pixels (*1*, *2*): arrays of active devices fabricated on the same chip that operate in parallel to detect, process, and emit photonic signals. By combining the world of image detection and processing with that of electronics on a single chip, smart pixels have the potential to process visual images more efficiently than present technologies.

Today's smart pixels are rather complex, and their image resolution cannot match that of a CCD camera. But a clever device reported by Lundstrom *et al.* (*3*) on page 2312 of this issue may help to make smart pixels more competitive. The device detects light pulses through photogenerated charges, stores its intensity information for up to seconds, and reemits it again as a light pulse. Such a storage device for photonic signals might be developed into a smart pixel that can easily be fabricated in large numbers on a single chip.

The device aims to combine the sensitivity of a CCD camera with the efficient emission of an LED in a single device. It relies on controlling the lifetime of light-generated electron-hole pairs by spatially separating them in a reversible manner (*4*–*6*). In a CCD camera (see panel A in the figure), an individual photon lifts an electron from an occupied state in the so-called valence band of silicon across an energy gap into the conduction band, leaving behind a positively charged empty state called a hole. Strong electric potential gradients generated by external electrodes spatially separate the electron from this hole and trap it in a potential pocket at the Si-SiO_2 interface. Such potential pockets generated by time-dependent voltages can accumulate many photogenerated electrons and move them like a conveyor belt (*5*) to the outside circuit. The astonishing recording sensitivity of a CCD camera is a result of the rather long natural lifetime of a photoexcited electron-hole pair in silicon, which allows efficient electron trapping. The opposite happens in an LED (see panel B in the figure): Electrons and holes are injected from different contacts into the active region of a suitable semiconductor, where they quickly recombine, emitting photons with



Processing of photonic signals in semiconductor devices. In a CCD camera (**A**), photons (blue arrows) excite electrons (red) across the band gap (yellow) of silicon that are trapped at the Si-SiO_2 interface. In an LED (**B**), a photon is generated when a conduction band electron recombines with a valence band hole (green). Reversible storage of photogenerated electron-hole pairs becomes possible in devices that spatially separate the electron and hole by trapping each of them either in an electrostatically deformed quantum well (**C**) or a pair of quantum dots tilted by an electrostatic seesaw (**D**) that can be switched to induce fast recombination.

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band gap energy. This is very efficient if one traps the electron and hole in a narrow quantum well of a material such as gallium arsenide (GaAs), with short radiative recombination lifetimes of typically 10^{-9} s.

Lundstrom *et al.* trick nature by developing an efficient handle on the recombination lifetime of an electron-hole pair. Previous schemes to control recombination have spatially separated and trapped both electrons and holes in tilted double quantum wells (*4*), in the piezoelectric potential pockets of a surface acoustic wave travelling along a quantum well (*5*), or in potential pockets of a quantum well created electrostatically by small electrodes (*6*) (see panel C of the figure). These devices can store photogenerated electron-hole pairs for tens of microseconds, more than four orders of magnitude longer than their natural lifetime. Lundstrom *et al.* combine coupled quantum dots with a tiny electrostatic seesaw to trap photogenerated electron-hole pairs in fully confining cages (see panel D in the figure), increasing their storage time to seconds at low temperature before photon emission is induced.

Such devices may potentially be fabricated into large pixel arrays capable of high-resolution image processing. However, quite a few obstacles must be overcome before this intriguingly simple concept becomes a useful and competitive device. Reversible and effective storage of electron-hole pairs at room temperature remains to be demonstrated; similar to a CCD, this appears to be essentially a matter of proper choice and cleanliness of materials. Long storage time as realized by Lundstrom *et al.* in enclosing electron and holes in the cages of quantum dots should ideally be combined with fast and efficient release of photons. Here, the electrostatic devices (see panel C of the figure) appear to have an advantage over the seesaw-like devices (see panel D of the figure), because they do not need fast tunneling of carriers for both the recording and the emitting mode. A third problem is how to efficiently reemit the radiation into a preferential direction. Here the combination of electron-hole pair storage with the already well-established concepts of optical microcavities (*7*) and photonic band gap structures (*8*) appears to be the most promising route to a solution.

Most likely it will still take several years to transfer the elegant concept of reversible storage of photogenerated electron-hole pairs into practical photonic processing devices. At present, one can only speculate whether such devices will eventually be able to compete with conventional digital image processing or other smart pixel arrays. But the potential of doing so makes them an attractive subject for further investigations and improvements.

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PERSPECTIVES: MOLECULAR BIOLOGY

DNA Methylation de Novo

Adrian Bird

In an ideal world, biological processes would be understood at the molecular level by first identifying all the participating components and then by deducing their roles in the system through experiment. In reality, knowledge of each component is hard-won, and the temptation to assume that the key players are those that are currently known, ever-present. Fortunately, as human cDNA sequencing approaches saturation, candidate components in mammalian systems are becoming easier to find. One beneficiary is the field of DNA methylation in which researchers study the shutting down of gene expression through the addition of methyl groups to cytosine (C) bases in the DNA. Few players are more important in this arena than DNA methyltransferases (Dnmts), the enzymes responsible for methylating DNA. Thanks to DNA sequence databases, a clutch of new Dnmts as well as proteins that bind methylated C bases have recently been uncovered (*1*). Three recent papers (*2*–*4*) make clear that several of these newly recognized Dnmts are capable of de novo DNA methylation (that is, addition of methyl groups to DNA that has not been methylated before). The new work demonstrates the crucial importance of an appropriately methylated genome for successful embryonic development.

In vertebrates, the DNA targets for modification through methylation are C bases adjacent to guanine (G) bases. These sites can be methylated to very high levels. In most human somatic cells, for example, about 80% of CGs are methylated, with introns, exons, satellite DNAs, transposons (plus their inert relics), and other "nongenic" DNA all being affected. The distribution of methylated and nonmethylated CGs is not random, but conforms to a pattern. The most obvious features of the pattern are CpG islands at the promoters of many genes. These are clusters of nonmethylated CGs that form gaps between long methylated domains. Both the pattern of methylation and its overall level can sometimes vary. In early mouse embryos, for example, the amount of global methylation plummets, only to be restored at implantation of the blastocyst in the uterine wall. Even the resistance of CpG islands to methylation is not universal. They become methylated in large numbers on the inactive X chromosome (Xi), whereas equivalent CpG islands on the active X chromosome remain methylation-free. What determines whether a specific CG is methylated or not? Does specificity lie in the selective addition of methyl groups to certain chromosomal regions? Or, is methylation applied indiscriminately and patterned by judicious demethylation? The new work promises some answers to these important questions.

Until 2 years ago we knew of only one Dnmt (Dnmt1), and this seemed to be enough (*5*). Dnmt1 can "maintain" CG methylation after DNA replication by methylating the daughter DNA strand using the methylation pattern of the parental strand as a template (see the figure). Also, at least in vitro, Dnmt1 can methylate unmodified DNA de novo. The first evidence that Dnmt1 by itself could not explain de novo methylation in vivo arose when mouse embryonic stem (ES) cells lacking the enzyme nevertheless proved capable of methylating a retroviral provirus (*6*). Trawls of the EST (expressed sequence tag) database (which contains large numbers of unidentified cDNA sequences) revealed two novel proteins (called Dnmt3a and 3b) that looked like Dnmts and could transfer methyl groups to DNA in vitro (*7*). Were these the missing de novo methyltransferases?

To answer this question, Okano *et al.* disrupted the mouse genes and examined the consequences (*2*). Mutations in either gene that resulted in nonfunctioning proteins prevented normal development. Mouse embryos that lacked Dnmt3a were runts and died 3 to 4 weeks after birth; those deficient in Dnmt3b did not develop further than 9.5 days after fertilization. Animals with mutations in both genes (double mutants) were

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