patients there is a decreased accumulation of hTR, reduced telomerase activity, and abnormally short tracts of telomeric DNA. Although the investigators could not rule out the possibility that some defect in ribosome biogenesis or other cellular process contributes to the syndrome, a telomere maintenance disorder is sufficient to account for the various disease phenotypes.

How could a mutation in dyskerin cause a deficiency in telomerase? Dysfunctional dyskerin could inhibit the stability or processing of the telomerase hTR, or the assembly, stability, or activity of the telomerase RNP. The investigators observed a reduction in the steady-state levels of hTR in DKC lymphoblasts and fibroblasts, which is consistent with a defect in RNA or RNP stability. Lymphocytes normally express telomerase when stimulated to divide. Activated DKC lymphocytes expressed much lower levels of telomerase than did lymphocytes from healthy individuals. Thus, DKC cells appear to have a relative deficiency in telomerase rather than a total lack of the enzyme. Still to be resolved is whether DKC isoforms act recessively, dominantly, or codominantly with respect to the wild-type protein. If the DKC isoform is recessive, would overexpression of wild-type dyskerin rescue the telomerase RNA deficiency?

Fibroblasts and lymphocytes from DKC-affected individuals demonstrate an age-dependent increase in chromosomal rearrangements that is consistent with telomere shortening. This results in the formation of telomeric fusions (including dicentrics), Robertsonian translocations, and ring chromosomes (*1*). So DKC may also be regarded as a chromosomal instability syndrome. The symptoms of DKC appear with variable onset in those tissues that proliferate rapidly (such as gut epithelia or bone marrow) and have the greatest need for telomere maintenance. Patients with this disease have an age-dependent increase in risk for developing certain cancers, such as epithelial tumors of the skin and gastrointestinal tract (*1*). This is consistent with a telomeric maintenance disorder that leads to chromosomal instability, telomeric rearrangements, and cancer progression. It will be interesting to compare telomere length in various tissues of DKC-affected and unaffected individuals and to address the extent to which telomerase-dependent maintenance of telomeres is required during embryonic development or in response to proliferative demands on specific differentiated cell types. It is now becoming clear that telomere maintenance requirements are likely to be more complex than a simple on/off switch.

The many phenotypes of DKC suggest that telomerase-dependent telomere maintenance is required to provide enough proliferative capacity for multiple types of somatic cells during the human life-span. This leads to the hypothesis that telomere maintenance defects could be causal in certain other human age-related diseases. This is in contrast to the requirement for telomerase in the mouse: in this animal telomere maintenance defects only become apparent after several generations (*4*).

Although we are beginning to identify an increasing number of telomerase and telomere-associated proteins, we need to understand how the telomerase enzyme complex interacts with telomeres, and how telomere maintenance in some tissues and telomere shortening in others affect the intact organism.

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PERSPECTIVES: MATERIALS SCIENCE

Imaging Elusive Solute Atoms

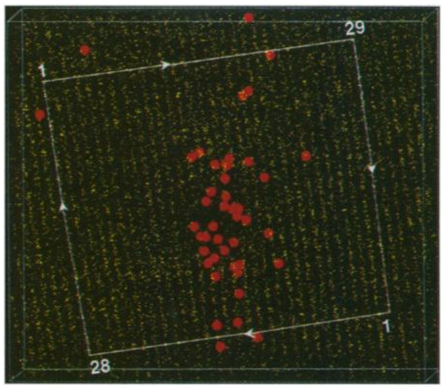
M. K. Miller

In 1948, Cottrell developed a theory in which the strength of iron was explained by the formation of "atmospheres" of carbon atoms around line defects (dislocations) in the crystal lattice (*1*). However, it took more than 50 years for his theory to be verified experimentally. On page 2317 of this issue, Blavette *et al.* (*2*) use a three-dimensional atom probe to determine the distribution of individual boron atoms around a dislocation in FeAl (see the figure), providing the first full experimental description of a Cottrell atmosphere.

According to Cottrell's theory, the smaller solute atoms present in steel, such as carbon, segregate to those regions of the crystal lattice around a dislocation that are compressed relative to the bulk, whereas larger solute atoms segregate to the dilated regions. These solute atmospheres pin the dislocation and make it more difficult for it to move, thereby increasing the resistance of the metal to deformation. The experimental verification of such solute atmospheres around dislocations long remained beyond the resolution of microscopes. In the last decade or so, solutes have been detected near dislocations by field ion microscopy, and solute concentrations have been characterized by atom probe field ion microscopy (*3–5*). However, the precise solute distribution around the dislocation core could not be resolved until three-dimensional atom probes were developed.

The three-dimensional atom probe (3DAP) combines the virtues of the field ion microscope (*6*) with those of the atom probe (*7*). Shortly after the concept and a prototype of the 3DAP were developed at Oak Ridge National Laboratory by the author in 1986 (*8*), substantially improved variants of the instrument were constructed at the University of Oxford by Cerezo *et al.* (*9*) and at the University of Rouen by Blavette *et al.* (*10*). These instruments, known as the position-sensitive atom probe (*9*) and the tomographic atom probe (*10*), respectively, are designed to determine the distribution of all the elements present in a material and have been used to study a wide spectrum of metals ranging from simple model systems to complex commercial alloys.

The 3DAP is the only instrument that can determine the identities of individual atoms in a material and measure their spatial coor-



Atom map of a Cottrell atmosphere. Each dot or sphere denotes the location of an individual atom. The figure has been oriented so that the aluminum (001) planes are visible as the nearly vertical lines of dots. The iron atoms have been omitted for clarity. The presence of a dislocation in this volume is indicated by the extra aluminum plane along the top of the marked box compared with the bottom. The boron atoms (red) are concentrated around the end of the extra plane, that is, the core of the dislocation. [From (*2*)]

CREDIT: FROM (2)

The author is at the Metals and Ceramics Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831–6376, USA. E-mail: millermk@ornl.gov

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

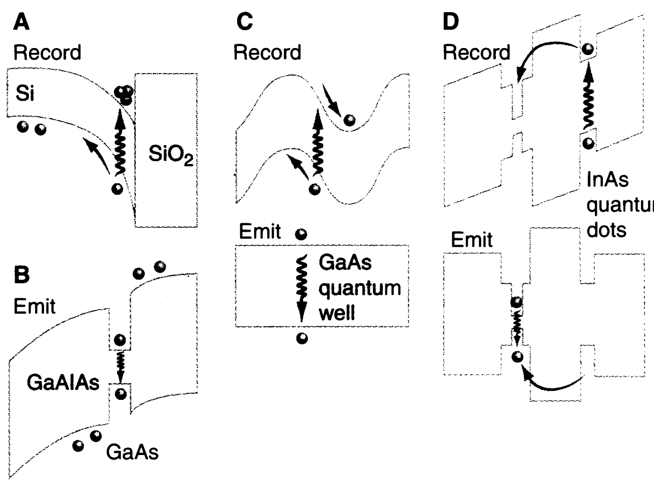
Toward Efficient Smart Pixels

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.

The author is at the Center for NanoScience and the Sektion Physik, Ludwig-Maximilians-University, Geschwister-Scholl-Platz 1, 80539 Munich, Germany. E-mail: kotthaus @cens.de

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