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elephants, wild boars, and walruses. Finally, the distinction of saber teeth and tusks from ordinary large canines appears to be vague and primarily based on length. *Tiarajudens* seems to further blur this distinction, since anomodonts evolved both approaches (saber teeth and tusks) to enlarge their canines, even though they might have had similar functions, such as deterring predators and intra-specific display or combat (2, 17).

The discovery of extraordinary fossils such as *Tiarajudens eccentricus* provides new insights into the dental diversification and early evolution of herbivory in tetrapods and the complex evolutionary

history of synapsids. Nonetheless, future research applying integrative and quantitative approaches to the study of herbivory will be needed to further investigate its significance for the evolution of terrestrial vertebrate ecosystems.

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MATERIALS SCIENCE

Electronic Bonding Revealed by Electron Diffraction

Paul A. Midgley

When atoms come together to form a crystal, a redistribution of electron charge creates bonds that govern almost all of the crystal's physical and chemical properties. Ab initio calculations can provide theoretical determination of the bonding charge density, but experimental verification can be fraught with difficulty because the change in the total charge density, as measured via diffraction experiments, is very small. For example, in aluminum (Al), most of the electrons are highly delocalized and

form a free electron gas, but some of the electron density forms highly directional bonds. On page 1583 of this issue, Nakashima *et al.* (1) demonstrate the use of ultrasensitive convergent-beam electron diffraction (CBED) to map the bonding charge density of Al to an unrivaled accuracy. These results lead to a greater understanding of this metal's mechanical properties.

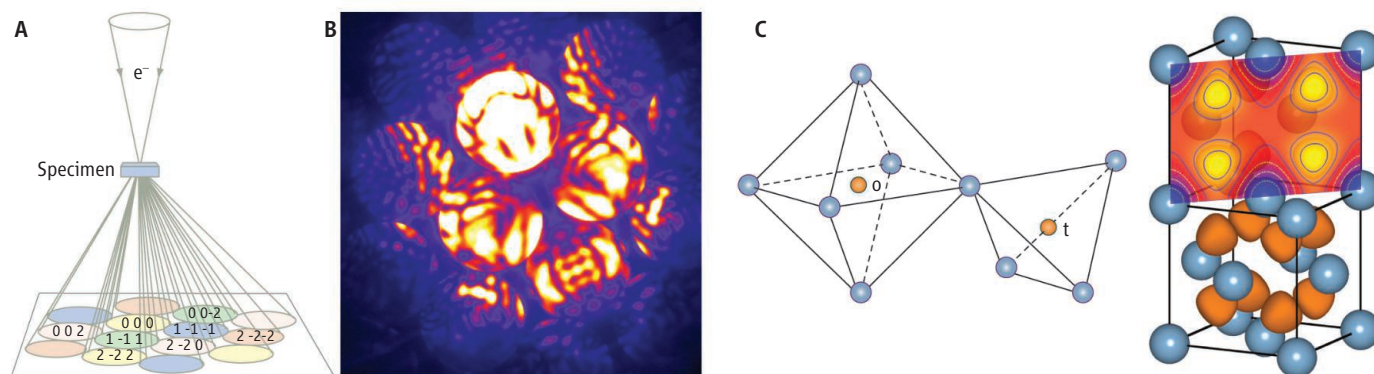
For many decades, efforts have been made to determine bonding charge density with both x-ray and electron diffraction. Crystallographic studies measure the pattern of different intensities of the scattered reflections. These patterns are modeled by determining structure factors, which sum up the individual

A new electron diffraction method reveals a tetrahedral bond network in aluminum that can account for the directional nature of its mechanical properties.

scattering contributions of each atom that is positioned in the unit cell, the repeating block within the crystal. For x-rays, the structure factors are associated with the electron charge density; for electrons, they are associated with the electrostatic potential, which can yield the charge density via Poisson's equation.

The charged nature of the electron ensures that the interaction between the electron and the crystal is far stronger than the equivalent x-ray interaction (by a factor of 100 to 1000), and that charge-density effects are more likely to be observed. The stronger interaction means that electrons scatter many times before exiting the crystal. Unlike most x-ray diffraction data, electron diffraction patterns

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Making a difference with diffraction. (A) Schematic representation of convergent-beam electron diffraction (CBED) showing the formation of pattern-containing disks of different diffraction beams (the beam order is given by the three-digit Miller indices). (B) An experimental CBED pattern from aluminum

determined by Nakashima *et al.* (C) The corresponding bonding charge density they determined using a differential form of the CBED pattern, along with an illustration of the octahedral (o) and tetrahedral (t) sites in the lattice (the latter is the bond position that matches the pattern of excess charge density).

can be interpreted fully only by a complex dynamical theory that takes multiple scattering events into account. When determining an unknown structure, the effects of dynamical scattering can be minimized by using, for example, only the high-order reflections at high scattering angles (2), very thin or weakly scattering crystals (3), or special geometries, as seen with precession electron diffraction (4).

However, once a structure is known, dynamical effects can yield diffraction data that are very sensitive to changes in the electrostatic scattering potential, and the lowest-order reflections in the diffraction pattern are the ones most sensitive to the bonding charge density. The wavelength of the diffracting electron depends on the energy imparted by an accelerating voltage, and at so-called “critical voltages,” distinct diffraction features (intensity minima in diffracted disks) persist at every crystal thickness (5). By matching these data to simulations, or through analytical methods, the ratios of structure factor magnitudes can be determined. However, for many materials, such critical voltages lie beyond the usable range of most microscopes.

With the advent of greater computer power, best-fit CBED pattern matching that can use full dynamical theory (rather than making assumptions about scattering) has become the preferred way to determine structure factors. The basic geometry of a CBED pattern (see the figure, panel A) focuses electrons to a spot on the sample perhaps only a few nanometers wide. The CBED pattern is composed of reflections in the form of disks, the detail within each being a “map” of diffracted intensity as a function of beam orientation (see the figure, panel B).

Dynamical simulations of the electrons in a CBED pattern that undergo elastic scattering (which preserves their energy) are relatively straightforward, but inelastically scattered electrons that have lost energy when scattered are also present and are much harder to incorporate accurately into simulations. Energy filters can be used to remove inelastic scattering from experimental patterns, and experiments in the 1990s yielded some success in determining the bonding charge densities of semiconductors (6), oxides (7), and metals (8).

Nakashima *et al.* introduced a new approach in which a difference CBED pattern (derived with respect to orientation) is constructed and a dynamical simulation fitted to that difference pattern. Commercial energy filters can remove the majority of inelastic scattering (arising primarily from plasmon excitations), but they cannot filter out the

electrons that have lost only a small amount of energy (on the order of tens of millielectron volts) associated with scattering from lattice vibrations (phonons). Such “thermal diffuse scattering” is seen over the whole diffraction pattern, predominantly as a slowly varying background. The differential method removes this background and allows elastic simulations to be matched to a remarkably accurate level. Moreover, by using this differential method, Nakashima and Muddle had previously shown that in many cases, energy filtering is not needed at all (9).

In the present work, Nakashima *et al.* recorded more than 100 unfiltered CBED patterns comprising $\sim 10^6$ data points to determine 14 structure factors. The result of this enormous overdetermination is high accuracy and confidence in the structure factor values obtained and in the uniqueness of the solution. For the lowest-order structure factor in Al, this accuracy approaches 1 part in 1000 (better than equivalent x-ray data by a factor of ~ 10). Using these highly accurate structure factors, they found the excess electron charge (the “bond”) to be in the tetrahedral “hole” between the Al atoms (see the figure, panel C). Much of the previous work, both theory and experiment, had indicated that the bond would be (at least in part) octahedral in nature. Nakashima *et al.* show how this tetrahedral

bond can be related to the mechanical properties of Al by equating the “shape” of the bond to the anisotropy of the elastic constants.

In studies of bonding charge, electron experiments have two advantages over x-rays: sensitivity and spatial resolution. Nakashima *et al.* have illustrated beautifully that highly accurate structure factors can be obtained from volumes of material much smaller than is possible even with synchrotron x-rays. This powerful combination offers the possibility of mapping bonding characteristics across heterogeneous samples (e.g., composites or quantum wells) that may not be achievable with any other method.

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CELL BIOLOGY

Selective Insulin Sensitizers

Ja Young Kim-Muller and Domenico Accili

Can the liver’s insensitivity to insulin in diabetes be overcome with another hormone?

Type 2 diabetes mellitus and its complications are, with cardiovascular diseases, leading threats to public health in the 21st century. In the United States, type 2 diabetes care accounts for a third of federal health insurance (Medicare) expenditures—nearly half of it to treat associated macrovascular problems (1). The cornerstone of type 2 diabetes is insulin resistance—a decreased sensitivity of tissues and organs, such as the liver, to the metabolic effects of the hormone insulin (the other major cause is failure of the pancreas to produce insulin). Yet, except for thiazolidinediones—whose checkered safety history, troublesome side effects, and regulatory setbacks stifled widespread adop-

tion by clinicians—treatment options for insulin resistance have generally remained unchanged since the 1940s. Although insulin signaling pathways in cells have been largely deciphered (2), the key mediators of insulin signaling are poor drug targets because they either lack a suitable ligand-binding domain, or are shared with other cellular pathways that regulate cell growth and proliferation. This realization spawned research into “alternative pathways” that control insulin resistance. On page 1621 of this issue, Kir *et al.* (3) find that human fibroblast growth factor 19 (FGF19) can boost certain effects of insulin on the mammalian liver, raising interest and questions about possible therapies involving this molecule.

After food intake, blood glucose concentration increases, triggering the secretion of insulin. Glucose is taken up by liver cells

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