

cortex. In other words, the animals ‘see’ with what was their auditory cortex. The ferrets were given the option of receiving a reward from a spout to their right following a light stimulus, or to their left after a sound stimulus. After visual stimulation of their rewired cortex, the animals always behaved as though they had been stimulated by light. So, in these rewired animals, the experience of sight appears to arise from visual inputs to the auditory cortex area. The sensory qualities associated with seeing appear to be determined by how visual inputs drive visual-input-specific organization of the structure of the visual cortex.

This is an important extension of issues addressed by Aristotle, John Locke, Charles Bell, Johannes Müller and others. Each of these added to a progressively more convincing and more complete argument that the sources of input signals to the brain, and the activation of specific brain regions by those signals, underlie sensory qualities and functions⁵. Von Melchner *et al.*² now argue that source-specific input activities generate input-specific representational structure. This, in turn, accounts for the sensory or perceptual experiences that are specific to a particular system — visual or auditory, for example.

This is a modification of a widely held view derived from two centuries of studies of functional localization within the brain. William James⁶, rather colourfully, put it this way: if we could splice the nerves so that the excitation of the ear fed the brain centre concerned with seeing, and vice versa, we would “hear the lightning and see the thunder”. Sur

and colleagues’ results^{1,2} stand in contradiction to this prediction, because the different characteristics of inputs to the visual (and presumably auditory) system actually create a new visual (or auditory) cortex, and hence its appropriate, source-specific sensory and perceptual qualities.

The studies by Sur and collaborators^{1,2} present a direct challenge to the increasing number of claims that the development of visual orientation columns and topography of the V1 region is not dependent upon input activity^{7–9}. From the new papers, we can see that retinal inputs into the auditory thalamus are sufficient to account for a V1 pattern of development. It would be a peculiar world indeed if the developmental plasticity at the root of this remarkable emergence of V1 structure in A1 cortex does not also underlie the development of visual cortex under normal conditions.

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Ceramic technology

Oxide-ion conductors by design

John B. Goodenough

Oxide-ion conductors are solid oxides that contain highly mobile oxide ions. Some, the oxide-ion electrolytes, are electronic insulators; others are mixed oxide-ion/electronic conductors. These materials form the basis of devices that have a huge market potential. The solid-oxide fuel cell, for example, uses an oxide-ion electrolyte as a separator between air and fuel; combustion using mobile oxide ions in the electrolyte generates clean electric power. Mixed conductors are of interest as oxygen-separation membranes or for partial-oxidation reactions in the production of value-added products from fossil fuels. However, oxide-ion conduction is poor below 1,000 °C in commercially available materials.

The challenge for the chemist is to design a solid material that will allow oxide-ion

conduction at a low enough temperature to be technically useful. For example, the design of an oxide-ion electrolyte that would allow operation of a solid oxide fuel cell at 600–700 °C has motivated chemists for a number of years; the goal has not yet been reached, and new design concepts are needed. On page 856 of this issue, Lacorre *et al.*¹ report a novel oxide-ion electrolyte that introduces a large structural family to be explored.

In 1839, Faraday observed fast fluoride-ion conduction at high temperatures in lead fluoride, which led early investigators to explore oxide-ion conduction in the fluorite structure of Fig. 1. Good oxide-ion conductivity requires only partial occupancy of an energetically equivalent set of oxide-ion lattice sites, such as the anion sites of the fluorite structure. The oxide ions can then move

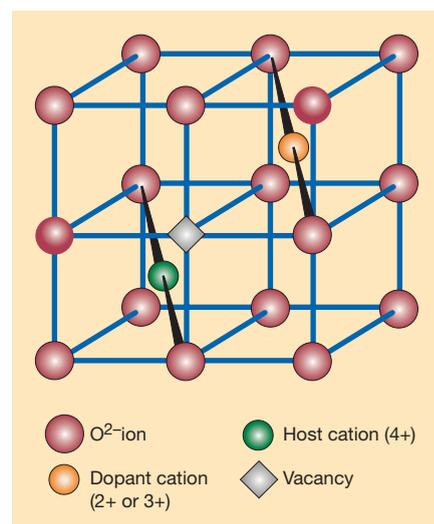


Figure 1 The fluorite structure of solid oxides. Oxides with this structure have high ionic conductivity when the host cations (such as Zr^{4+}) are replaced by lower-valent cations such as Y^{3+} . The missing charge is balanced by the formation of oxygen vacancies in the oxide-ion sublattice, resulting in impressive ionic conductivity. Lacorre *et al.*¹ report a new family of solid oxides (not based on any of the existing structure types), which may offer an alternative strategy for designing new oxide-ion conductors.

diffusively, providing that they can overcome a small energy barrier E_a to hop to a vacant site in the solid. The oxide-ion conductivity is given by $\sigma_0 = (A/T)\exp(-E_a/kT)$, where k is the Boltzmann constant. The factor A in σ_0 increases with the fraction of anion sites that are vacant. The problem for the designer of an oxide-ion conductor is to maximize A and minimize E_a .

Faraday’s discovery suggested that E_a is relatively small in the fluorite structure; Schultz and Thiemann² proved this to be the case, and commercial oxide-ion electrolytes have the fluorite structure with anion vacancies. Two strategies for introducing anion vacancies have been investigated: one way is to choose an oxide with an intrinsic vacancy concentration; the other substitutes cations that have a different valency (aliovalent) to the host ion in the cation array, thereby creating an extrinsic vacancy concentration.

Intrinsic vacancy concentrations are high, and electrostatic interactions between the mobile ions order the vacancies below a transition temperature T_i . This is the temperature at which many oxide-ion conductors go through a structural transition that produces a sudden increase in conductivity. Long-range vacancy ordering produces unacceptable structural changes for operating temperatures greater than T_i and, below T_i , distinguishes energetically the occupied and empty lattice sites, which increases E_a . The electrostatic interactions between oxide ions are relatively large, so T_i is well above

room temperature in intrinsic-vacancy oxides.

On the other hand, doping with an aliovalent cation perturbs the periodic potential of the oxide-ion array so as to trap the vacancies at the aliovalent ions that introduce them, thereby increasing E_a . Nonetheless, doping ZrO_2 with yttria or calcia stabilizes zirconia in the fluorite structure and introduces extrinsic oxide-ion vacancies. Yttria-stabilized zirconia (YSZ) is the electrolyte of choice of the US Department of Energy for the development of a solid-oxide fuel cell (SOFC). But an SOFC operating below 800 °C requires ceramic membranes only 10 μm thick. Similarly, lanthanide-doped ceria is a good oxide-ion conductor, but it becomes a mixed electronic/oxide-ion conductor in the fuel-rich atmosphere of an SOFC where Ce^{4+} is partially reduced to Ce^{3+} .

The ABO_3 perovskites offer an alternative AB cation framework with the CuAu structure. $BaInO_{2.5}$ contains intrinsic oxygen vacancies, and fast oxide-ion conduction was demonstrated in this oxide above $T_t = 930$ °C (ref. 3). Subsequently, Ishihara *et al.*⁴ reported fast oxide-ion conduction in the extrinsic-vacancy perovskite $La_{1-x}Sr_xGa_{1-y}Mg_yO_{3-0.5(x+y)}$ (LSGM), and this oxide has been optimized and investigated for use in an SOFC⁵; it has an oxide-ion conductivity superior to that of YSZ and could reach an operating temperature of about 700 °C. Condensation of mobile oxygen vacancies into ordered clusters sets in below a $T_t^* \approx 600$ °C in LSGM; there is no long-range order below a T_t .

Two-dimensional oxide-ion conduction in a layered oxide has also been investigated, particularly in the oxides $Bi_4V_{2-x}M_xO_{11-y}$ first studied by Abraham *et al.*⁶⁻⁸. Substitution of aliovalent cations M for V in $Bi_4V_2O_N$ suppresses a $T_t \approx 570$ °C, changing the transition from long-range order below T_t to short-range order below a lower T_t^* . This oxide is an excellent solid electrolyte for applications in an oxidizing atmosphere, but it is subject to reduction by the fuel of an SOFC.

The parent compound of the solid oxides studied by Lacorre *et al.*¹ is $La_2Mo_2O_9$, which shows a first-order structural transition at $T_t = 580$ °C to a cubic structure containing cations in the same positions as those of $\beta\text{-SnWO}_4$. In $\beta\text{-SnWO}_4$, the outer electrons of the Sn^{2+} ions form 'lone electron pairs' that are projected into an oxide-ion vacancy. In $La_2Mo_2O_9$, the La^{3+} ions that replace the Sn^{2+} of $\beta\text{-SnWO}_4$ have no lone-pair electrons, but half the sites into which the Sn^{2+} lone pairs are projected in $\beta\text{-SnWO}_4$ are occupied by oxide ions. The oxide-ion conductivity above T_t is between those of YSZ and LSGM, which makes it a competitive oxide-ion electrolyte; however, it has not been tested in a reducing atmosphere. In this case also, cation substitutions on the La

and/or Mo sites suppress the first-order, long-range character of the vacancy ordering below T_t .

The authors further point out that the extra oxygen atom per formula unit in $La_2Mo_2O_9$ replaces only half the lone pairs of the Sn^{2+} ions in $\beta\text{-SnWO}_4$, which makes it an intrinsic-vacancy oxide-ion electrolyte. They make the interesting suggestion that partial substitution of oxygen for vacancies occupied by lone pairs may be an excellent design strategy for finding new intrinsic-vacancy oxide-ion conductors.

Technical applications would all benefit from oxide ceramics that have a higher oxide-ion conductivity at lower temperatures than those now available. Such materials would lower the cost of both fabrication and operation as well as extend the life of a

device. Expansion of the number of host structures to be explored for improved oxide-ion conduction is a promising step towards realization of the commercial potential of oxide-ion conductors. ■

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Cancer

New guardians of the genome

David B. Roth and Martin Gellert

DNA is vulnerable to many types of damage resulting from environmental insults or intrinsic cellular processes. So it is not surprising that cells possess a variety of DNA-repair systems. Several of these systems — referred to as 'caretakers' — are essential for maintaining genomic stability, offering protection from cancer-causing (oncogenic) mutations or chromosome rearrangements¹.

Numbered among known caretaker proteins are those involved in repairing a variety of different types of DNA breaks, but conspicuous for their absence were the non-homologous-end-joining (NHEJ) proteins. These proteins are important for resolving both random DNA breaks produced by environmental agents (such as ionizing radiation) and specific breaks introduced during lymphocyte differentiation by programmed rearrangements of the genes encoding antigen receptors. Thanks to recent work, however — including that of Difilippantonio and colleagues² (published a few weeks ago in *Nature*) and Gao and others³ (writing on page 897 of this issue) — we can add NHEJ proteins to the list of genome guardians.

Proteins in the NHEJ DNA-repair pathway include XRCC4, DNA-PK (the DNA-dependent protein kinase), the Ku proteins and DNA ligase IV. If these proteins are indeed caretakers, one would expect mutations that inactivate the genes encoding them to cause genomic instability and to lead to an increased incidence of cancer in many tissues¹. One of these predictions was recently verified: cells from mice lacking Ku do exhibit genomic instability⁴. And now, Difilippantonio *et al.*² and Gao *et al.*³ have

found that two lines of mice that lack both an NHEJ protein (Ku80 or XRCC4) and p53 — a well-known tumour-suppressor protein — exhibit striking genomic instability and develop B-cell lymphoma tumours at an early age. (Such tumours also occur in mice lacking both p53 and DNA-PK^{5,6}, but chromosome instability has not been seen in these animals.) It seems that the NHEJ machinery indeed functions as a caretaker, guarding against oncogenic DNA rearrangements.

The two NHEJ proteins studied by Difilippantonio *et al.* and Gao *et al.* — Ku80 and XRCC4, respectively — have essential but incompletely understood roles in the joining of dissimilar, or non-homologous, DNA ends. Mice missing only Ku80 are viable, but exhibit a severe immunodeficiency because of a fault in joining the breaks made during $V(D)J$ recombination^{7,8}, the programmed shuffling of segments of antigen-receptor genes. XRCC4-deficient mice (like mice lacking DNA ligase IV) show severely defective lymphoid development, but have more pressing problems⁹. They suffer widespread death (apoptosis) of newly generated neurons and die late in embryonic development. Less severe neuronal apoptosis has also been described in mice lacking Ku¹⁰. Gao *et al.*³ have now shown that a lack of p53 rescues XRCC4-deficient mice from neuronal apoptosis and embryonic death. But this reprieve is short-lived, as B-cell lymphomas cause the untimely demise of these animals within three months after birth.

Interestingly, both groups^{2,3} find that the B-cell lymphomas in their doubly mutant mice resemble human Burkitt's lymphoma,