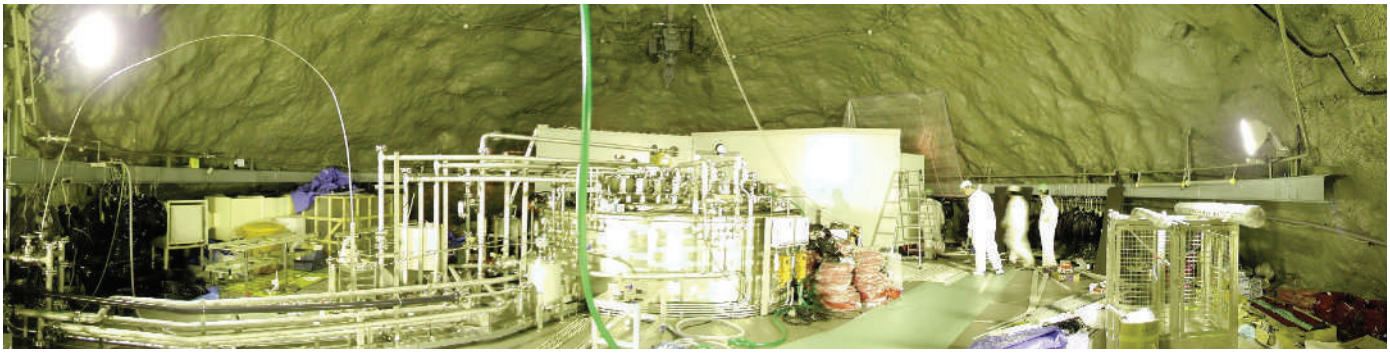
NEWS & VIEWS



KAMLAND/LBNL

EARTH SCIENCES

Ghosts from within

William F. McDonough

The first detection of geoneutrinos from beneath our feet is a landmark result. It will allow better estimation of the abundances and distributions of radioactive elements in the Earth, and of the Earth's overall heat budget.

The decay of unstable isotopes of chemical elements within the Earth produces heat that contributes to its overall energy output — a fact recognized shortly after Henri Becquerel first discovered radioactivity in 1896. More than 100 years on, Araki *et al.* (page 499 of this issue)[1] report the first measurement of antineutrinos produced by radioactive β^--decay at the heart of the Earth. The results obtained from these so-called geoneutrinos are consistent with geochemical and geophysical models of the planet, and provide a new way of determining where the unstable isotopes — radionuclides — are stored inside the Earth, and in what concentrations.

Antineutrinos, like their counterpart neutrinos, come in three varieties, each named after the charged particle with which they are paired: electron, muon and tau. Electron antineutrinos are produced in β^--decays of an atomic nucleus that occur, for example, when potassium (^{40}K) is transformed to the calcium isotope ^{40}Ca, and also in the decay series of uranium (U) and thorium (Th). Neutrinos and antineutrinos are ghostly particles — they have no charge and almost no mass, and pass through most matter without interacting with it at all. Detecting them is thus extremely difficult.

The KamLAND (Kamioka Liquid-scintillator Anti-Neutrino Detector) apparatus was purpose-built to catch a glimpse of these elusive particles (see Fig. 5 on page 502). The detector is situated in the centre of the largest Japanese island, Honshu, in a mine one kilometre below the summit of Mt Ikenoyama, to reduce the effects of cosmic rays formed from particles other than antineutrinos. Antineutrinos are occasionally captured by protons in KamLAND's 1-kilotonne, 13-metre-diameter scintillation detector (pictured above) in a process known as inverse β-decay. This produces a neutron, which combines with a proton to form a deuteron and produces a characteristic γ-ray ('scintillation light') with an energy of 2.2 MeV. The light that this reaction produces is detected as an electrical signal by an array of photomultiplier devices surrounding the detector.

In 2003, KamLAND played a fundamental role in documenting the phenomenon known as antineutrino oscillation[2], in which the varieties of antineutrino are thought to change spontaneously into one another. That result demonstrated that antineutrinos have a mass (albeit a small one), and reinforced the discovery of oscillation among neutrino types from the Sun by the Sudbury Neutrino Observatory in Canada[3]. The oscillating antineutrinos detected by KamLAND were produced in nuclear reactors on average some 180 kilometres away. Now the detector has seen antineutrinos from an even more distant source — geoneutrinos, key to understanding where the energy output of the Earth comes from.

The total power dissipated by the Earth's interior is estimated to be between 30 and 44 terawatts (1 TW is 10^{12} watts)[4,5]. The spread in values stems from differences between global models of heat flow at the Earth's surface on the one hand, and estimates of heat dissipation at mid-ocean ridges, corrected for the effects of hydrothermal circulation in the oceans themselves, on the other. Several compositional models for the Earth find that the amount of K, U and Th in the planet contributes only around 19 TW of power[6,7] to the total. These observations result in a Urey ratio (an assessment of the amount of heat produced by radioactive decay to total heat flow on the surface of a planet) of 0.4–0.6. The remaining heat must come from other potential contributors, such as core segregation, inner-core crystallization, accretion energy or extinct radionuclides — for example, the gravitational energy gained by metal accumulating at the centre of the Earth, which is converted to thermal energy, and the energy added by impacts during the Earth's initial growth.

Alternative models suggest that there is also K in the Earth's core[8,9], and predict a higher Urey ratio. These models are, however, accompanied by geochemical consequences that limit their acceptability (see ref. 4 for a review). The heat flux across the core–mantle boundary and the nature of heat sources in the core are also subject to considerable speculation[10]. The KamLAND results[1] show an upper limit (at the 99% confidence level) of radiogenic heat power from Th and U of 60 TW, and a central value of 16 TW that is consistent with model predictions.

The KamLAND results were not straightforward to obtain, and are not simple to interpret. Various 'pollutants' must be removed from the energy spectrum of the antineutrinos to achieve a pure signal: of a total of 152 events that were potentially from geoneutrinos, only 20–25 were considered true candidate geoneutrinos. The remaining, 'background' antineutrinos came from nearby nuclear power reactors (more than 50% of the total signal)

and radioactive contamination in the detector (around 28%). Moreover, geoneutrinos produced from K decays are not — yet — detected at KamLAND, because their energies are below the threshold of 1.8 MeV required to trigger the existing detector system.

The data reported by Araki *et al.*[1] are the results from their first experiment, which comprised just over two years of counting. Future observations at KamLAND, and at the Borexino detector under the Gran Sasso mountain in central Italy, which begins operation in 2006, will generate more data and provide greater sensitivity in testing the nature and sources of geoneutrinos. A crucial advance will be to confirm that the geoneutrino heat flux moving radially outwards from the Earth is directly proportional to the radiogenic heat flux. This will, however, require an exact knowledge of the abundance and distribution of K, Th and U in the Earth.

To this end, a first detailed assessment has been made[11] of the predicted geoneutrino flux relative to the distribution of radioactive elements in the regional crust and underlying mantle near KamLAND, and throughout the Earth's interior. Further in the future, combining angle-integrated geoneutrino fluxes at different detector sites[12] with element distribution maps will enable us to construct geoneutrino tomographic maps of the Earth that will tell us more about the planet-wide distribution of K, Th and U. Proposed sites for future (anti)neutrino detectors must therefore be sure to include areas beneath both continental regions rich in K, Th and U and oceanic regions where the three radionuclides are depleted.

The pioneering results from KamLAND presented by Araki *et al.*[1], along with data from future work, will provide a fundamental constraint for the Earth's U and Th budget (and, it is to be hoped, shortly for that of K), and define the fractional contribution of radioactive heating to the total energy budget. Later this year, particle physicists and Earth scientists will gather to discuss these exciting and common areas of research at a meeting on Hawaii[13]. ■

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CANCER

One step at a time

David Mooney

Traditional chemotherapy kills tumour cells directly; some newer drugs work instead by cutting the tumour's blood supply. An innovative approach combines these strategies sequentially to pack a double whammy.

In 1971, Judah Folkman proposed that the progression of cancer might be halted by preventing tumours from recruiting new blood vessels (a process called angiogenesis) to provide them with oxygen and nutrients. Last year, this theory bore fruit with the approval by the US Food and Drug Administration of the first anti-angiogenic cancer treatment, Avastin (also known as bevacizumab)[1]. Sengupta and colleagues (page 568 of this issue)[2] advance this concept by designing a drug-delivery vehicle that sequentially releases an anti-angiogenic drug and a traditional chemotherapeutic drug at high concentrations specifically into a tumour. They report that their strategy can slow tumour growth in mice more than can either drug alone or the two drugs delivered at the same time.

Traditional chemotherapeutic agents kill all rapidly growing cells in the body — both cancer cells and other cells that divide quickly (for example, blood, hair and cells lining the intestine). This leads to the distressing side effects of chemotherapy, and limits the practical dose and frequency of application of the drugs. One tactic to avoid these effects is to target the drug specifically to the tumour, and approaches being tested include the incorporation of drugs into materials or complexes that can either be placed in, or directed to, tumours[3].

A second issue, however, is that some tumours develop resistance to a particular drug, so efforts to identify targets that are not prone to developing resistance continue. Endothelial cells, which line blood vessels, may provide an attractive target, as they are thought to be genetically more stable than cancer cells and so less likely to develop mutations that might promote resistance. A number of drugs that kill endothelial cells or prevent their growth are proving effective in phase III clinical trials for treating colon, kidney and lung cancer, and gastrointestinal stromal tumours[1,4–6]. These drugs can be useful alone, but they are commonly combined with traditional chemotherapy to prevent blood-vessel growth while also killing cancerous cells.

Simultaneous delivery of chemotherapeutic and anti-angiogenic drugs is clearly beneficial, but because chemotherapy is blood-borne, shutting down the tumour's blood supply with anti-angiogenic drugs may decrease the delivery of drugs designed to kill the tumour cells. Sengupta *et al.*[2] hypothesized that a more effective strategy would be to use a delivery vehicle that became concentrated in tumours before the vasculature shut down, and allowed the staged release of the two drugs. More specifically, the delivery of the anti-angiogenic factor could lead to a collapse of the vascular network and imprison the vehicle — still bearing its second payload of chemotherapeutic drug — in the tumour. The subsequent release of the latter drug within the tumour would kill the cancer cells.

The authors exploited the fact that the blood vessels of tumours are 'leaky'[7], so tumour tissue can take up larger particles than can normal tissues, promoting selectivity. They created composite vehicle particles of 80–120 nm, consisting of a solid biodegradable polymer core surrounded by a lipid membrane (Fig. 1). The anti-angiogenic drug combretastatin was dissolved in the lipid layer, from which it rapidly escaped. This drug attacks the internal skeleton of cells, and quickly disrupts blood vessels. The chemotherapeutic drug doxorubicin was bound chemically to the inner core of the particle, and so was released more slowly as the bond holding the drug to the polymer broke down. Doxorubicin is a common chemotherapeutic agent, and its structure consists of chemical groups that are amenable to attachment to polymers.

Sengupta *et al.* examined the effects of the drugs on two types of tumour in mice, and showed that, unsurprisingly, either drug alone slowed tumour growth, and that when the drugs were delivered simultaneously there was an additive effect. Strikingly, however, the staged release of the two drugs using the new delivery vehicle improved the outcome still further — survival time increased from approximately 30 days when the drugs were delivered simultaneously to more than 60 days when they were released sequentially. The delivery vehicles tended to accumulate in the tumours, rather than in other body tissues, and the drugs they transported killed both endothelial and cancer cells.

The effect of the sequential delivery of these two drugs on tumour growth is dramatic, but we cannot assume a quick translation of these results to therapy for humans. The biological differences between mice and humans prevent direct comparison between the systems, and it will also be important to extend these studies to longer time periods. Moreover, it has been speculated that anti-angiogenic drugs may actually promote the spread of tumours to other tissues, owing to a complex feedback loop, although there is no evidence of this in