Earth science

Putting the squeeze on oxidation

Michael J. Walter

The results of experiments conducted under the extreme temperature and pressure conditions of Earth's lower mantle suggest that, at these depths, low oxygen content is no barrier to iron oxidation.

The oxidation of iron is a process with which we are all familiar. The surface of Mars, the rust on our cars, the blood in our veins — all bear the conspicuous red colour that marks the oxidation of iron from its metallic (Fe), or divalent (Fe^{2+}), form to a trivalent cationic species (Fe^{3+}). At atmospheric pressure, the process of iron oxidation in the presence of oxygen depends on the partial pressure of gaseous oxygen (often referred to in geological literature as oxygen fugacity). Earth scientists have used the same thermodynamic formulations, with great success, to calibrate the oxidation state of iron in the rocks and minerals of Earth's upper mantle, at much higher pressures and temperatures[1]. Now Frost *et al.*[2] (page 409 of this issue) show that, when it comes to the more extreme pressure conditions in the lower mantle, we must abandon our conventional thinking about oxidation state.

Geology students are taught that certain minerals — such as $(Mg,Fe)Al_2O_4$, or 'spinel' — serve as sensors of oxidation state because their Fe^{3+}/Fe^{2+} ratios are known, experimentally and thermochemically, to depend on oxygen partial pressure. From such 'geobarometry', we have learnt that Earth's upper mantle is much too oxidized to be in chemical equilibrium with metallic iron[1] — the abundance of Fe^{3+} is too great for metallic iron to be stable. In contrast, we are quite confident that the mantle as a whole was in chemical equilibrium with metallic iron as the planet's core formed (when Earth was less than 50 million years old)[3]. How the uppermost mantle, the part we can sample, became so oxidized is unknown.

The portion of the mantle at depths greater than 660 km, referred to as the lower mantle, is thought to be dominated (70–80% by weight) by a dense, magnesium–iron silicate, $(Mg,Fe,Al)(Si,Al)O_3$. This mineral has a stable 'perovskite' crystal structure (a structure well known in ceramics to have an array of rich and unusual properties). The oxygen content of the lower mantle is unknown because we have no direct rock samples, but it is usually assumed to be similar to that of the upper mantle. In 1997, McCammon[4] reported the surprising discovery that magnesium–silicate perovskites synthesized in the laboratory can have very high Fe^{3+}/Fe^{2+} ratios — much higher, for example, than are preserved by spinel in the relatively oxidized upper mantle. However, the relationship between the oxygen partial pressure and the Fe^{3+}/Fe^{2+} ratio in perovskite remained unclear because of the difficulty of knowing (let alone controlling) the oxygen content in experiments at extreme conditions.

Frost *et al.*[2] have performed experiments in which they brought magnesium perovskite into chemical equilibrium with metallic iron under pressure–temperature conditions typical of the uppermost lower mantle. They made the remarkable discovery that, with very low oxygen content in their samples, the perovskite synthesized can have surprisingly high Fe^{3+}/Fe^{2+} ratios — similar, in fact, to the ratios measured in perovskites synthesized at very high oxygen contents. This decoupling of oxygen content from the Fe^{3+}/Fe^{2+} ratio shatters our traditional view of oxidation state based on oxygen partial pressure.

This result leads Frost *et al.*[2] to predict that a free iron-metal phase should exist in Earth's lower mantle — only 1% by weight, but nevertheless an important component. Ironically, this metal phase forms because of the high Fe^{3+}/Fe^{2+} ratio in perovskite, rather than being excluded by it. For a mineral to achieve a high Fe^{3+}/Fe^{2+} ratio, oxygen must be available to convert FeO into Fe_2O_3 (Fe^{2+} to Fe^{3+}). This could happen in the mantle if some chemical reaction serves as an oxygen pump: for example, the reduction of CO_2 to form C and O_2. An alternative mechanism proposed by Frost *et al.* is that magnesium perovskite has such an affinity for Fe^{3+} that it is energetically favourable for FeO in perovskite to 'self-reduce' by the reaction $3Fe^{2+}O \rightarrow Fe\ (metal) + 2Fe^{3+}O_{1.5}$. In this case, no external oxygen pump is needed and a free iron-metal phase forms out of the necessity for mass balance.

The lower mantle constitutes a large volume of the Earth, about 58%, so even a small amount of metallic iron represents a substantial reservoir — several per cent of all metallic iron in the planet. The lower mantle may first have formed because of the increase in pressure as the solid Earth grew, or it may have crystallized from a deep magma ocean. The core formed very early in Earth's history by the segregation of metal from silicate, a large-scale differentiation event that substantially decreased the Fe/O ratio of the silicate mantle. This ratio, dictated by metal–silicate equilibrium, would have been considerably higher than the current Fe/O ratio in the upper mantle. Frost *et al.*[2] calculate that if about 10% of the perovskite-manufactured free-metal phase were mechanically removed from the lower mantle through interaction with descending plumes of iron during core segregation, the mantle could have acquired its present Fe/O ratio. Thus, Frost and colleagues' discovery may explain the vexing question of why the upper mantle seems to have had such a high oxidation state for the past 4 billion years[5]. ■

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Medicine

Profile of a tumour

Olli Kallioniemi

Molecular profiling — the comprehensive analysis of genes, RNAs and proteins — is having a radical effect on our understanding of cancer. The next step is to convert these findings into better diagnosis and treatment.

The scale of cancer research projects has increased enormously over the past decade or so, presenting scientists with the opportunity to investigate the role of all human genes in cancer. This change has been wrought largely by advances in high-throughput technologies for analysing the human genome, transcriptome and proteome — genes, messenger RNAs and proteins — and in bioinformatic and statistical methods for exploring the gigabytes of data that are generated. As more is learnt about the genes and signalling pathways that promote the proliferation of cancer cells, prevent their death or allow their spread to other organs, it should become feasible to develop new methods of diagnosis, as well as treatments that are tailor-made to fit the specific molecular patterns of individual patients. But realizing these ideas is proving a challenge, as a recent meeting* made clear.

In one approach for converting the

**CNIO Symposium: The Molecular Taxonomy of Cancer.* Madrid, Spain, 3–6 February 2004.

knowledge obtained from 'omics' techniques into clinical application, researchers are attempting to use microarrays — a means of analysing patterns of gene expression by looking at the mRNAs present — to determine the appropriate treatment for different patients. For instance, microarray profiling of breast tumours, using a set of 70 informative genes, has revealed gene-expression signatures that are associated with a good or a poor prognosis[1,2]. In these studies, roughly 40% of early-stage breast cancers turned out to have a 'good' signature, associated with only a 15% risk of metastasis (the spread of tumour cells) and a 5% risk of death by 10 years after diagnosis. According to current clinical practice, most patients with early-stage breast cancer receive adjuvant therapy (chemotherapy or endocrine therapy after surgery). But less than 1% of the patients with a 'good prognosis' signature would be likely to benefit, and the treatments often have harmful side effects (discussed by L. Van't Veer, Netherlands Cancer Institute, Amsterdam)[2]. So researchers now suggest using the 'poor' signature to guide the administration of adjuvant therapy to those for whom it would be most useful.

Indeed, gene-expression profiling is already being introduced clinically as a diagnostic procedure in academic centres in the Netherlands (L. Van't Veer), with similar programmes being launched in the United States. The profiles have been validated retrospectively in several cohorts of patients. Prospective validation, however, can only be achieved after 5–10 years. Also — as several speakers discussed — some technical issues have yet to be resolved, including how to procure and process samples and to ensure reproducibility and quality control. Nevertheless, various analysis platforms and short lists of diagnostic genes are being developed to predict the prognosis associated with other types of tumours, such as lymphomas (L. Staudt, NCI, Bethesda, and M. Piris, CNIO, Madrid), or to predict the likelihood of particular endpoints, such as metastasis (T. Golub, Broad Institute, Cambridge, Massachusetts). Predicting a patient's response to specific types of treatment would, of course, be the most important application. But it may take years for the approach to meet with regulatory approval and be extended from academic centres to mainstream practice.

Another strand of research involves the proteomic profiling of blood serum. This could soon complement — if not replace — the use of established tumour 'markers' in cancer screening and early diagnosis (E. Petricoin, FDA, Bethesda). Whereas specific tumour markers are often used singly, proteomic serum profiling involves the use of mass spectrometry to identify up to 15,000 peaks, representing proteins and protein fragments that are defined by their mass-to-charge ratios[3]. The sensitivity and specificity of such profiles has exceeded 90% for the diagnosis of lung cancer, and approached 100% for ovarian cancer (E. Petricoin). Most of the peaks have still to be identified, and several investigators argued that panels of specific immunoassays, which use antibodies that recognize particular proteins, should be developed for diagnosis instead. But it is the fragments, not intact proteins, that are often the most informative diagnostically, and there may be dozens — if not hundreds — of such fragments, possibly existing in complexes with one another and with other serum proteins. That makes the development of specific assays demanding.

A further application of proteomics concerns the analysis of signalling pathways, for example by studying the levels of specific phosphorylated proteins — a key feature of many pathways — in tumour samples (E. Petricoin). Analysis of these signalling profiles is being incorporated into many clinical trials to identify biological markers that indicate which tumours are likely to respond to treatment. Proteomic tumour profiling is often carried out from specific cell types, acquired by microdissection of the tumours. Such studies could also help us to understand the tumour microenvironment, where many different cell types and interactions may affect tumour behaviour. For example, in breast cancer, characteristics of the stromal fibroblast cells adjacent to the tumour might change, and contribute to, cancer progression (R. Weinberg, MIT) — much as does the growth of new blood vessels.

Moving on to studies of gene sequence (genomics), mutations in roughly 1% of human genes (291 genes in total) were reported to contribute to cancer (M. Stratton, Sanger Centre, Hinxton)[4]. Twenty-seven of these genes, more than would be expected by chance, encode protein kinases — enzymes that phosphorylate other pro-

Planetary science

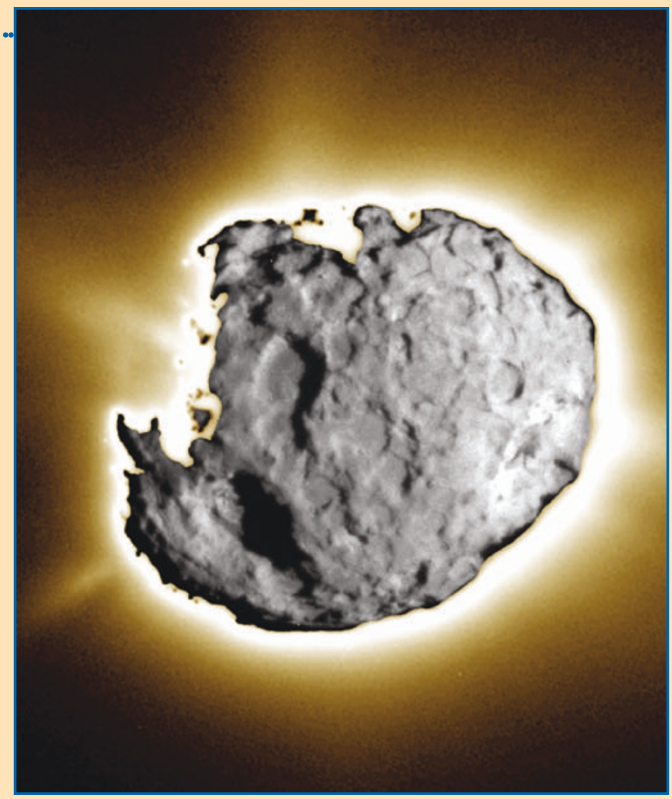
Stardust's comet memories

In January this year, NASA's Stardust spacecraft flew within 237 km of the comet Wild2. Stardust took 72 close-up shots during the flyby, described as an "unqualified success" at the Lunar and Planetary Science Conference in Houston, Texas, last week. After a few months' analysis, the Stardust team has now released stunning pictures of the comet's 5-km nucleus.

The Wild2 comet is 'fresh'. It is believed to have spent billions of years in the Kuiper belt, out beyond Neptune, until gravitational encounters kicked it into orbit closer to the Sun. In 1974, a close encounter with Jupiter knocked Wild2 into its present orbit, inside that planet's. Since then, Wild2 has passed close to the Sun only five times and so has suffered less exposure to solar radiation than other comets. Its surface bears a well-preserved record of its early history in the Kuiper belt.

The short-exposure image at the centre of this composite shows the cometary surface. The surface is markedly different from those of the comets Halley and Borrelly, and of Jupiter's ice-rich moons Callisto and Ganymede: instead of a continuum of crater size, Wild2's craters are mostly large; some are likely to be impact craters, others not. A long-exposure image taken 10 seconds later reveals a glowing halo of gas, thrown out from the nucleus in as many as 20 highly collimated jets.

Stardust's mission doesn't end there. The spacecraft is now heading for Earth once more, carrying particles from the comet's coma that were trapped during the flyby in centimetre-size aerogel cells. The samples will arrive on 15 January 2006. **Alison Wright**



NASA/JPL

teins. As several approved cancer drugs are inhibitors of tumour-associated kinases, such as BCR/ABL, KIT, HER-2 and the epidermal growth factor receptor, the search for mutated kinases is important. Another mutated kinase is BRAF, identified in a large-scale DNA-sequencing project to be altered in melanomas (reviewed in ref. 4). But an ongoing project to sequence the genes encoding 478 kinases in a panel of breast cancers has yet to replicate the success of the BRAF example (M. Stratton).

A new way to discover the roles of particular genes in cancer is to use cultured cancer cells and the technology of RNA interference to decrease gene expression. Several academic centres and corporations are developing libraries of RNA interference reagents that reduce the expression of any of the 30,000 human genes (G. Hannon, Cold Spring Harbor Laboratory; see also page 375). These libraries will make it possible to identify the functions of genes that control crucial properties of cancer, and could therefore be attractive drug targets. Moreover, several other approaches to the development of cancer treatments are being launched. When specific target proteins are not known, gene-expression profiles may be used to screen for drugs that modulate cancer-cell behaviour (T. Golub)[5]. For example, the expression pattern of five genes distinguishes leukaemic cells from normal blood cells and can be used as a readout to search for drugs that induce leukaemic cells to differentiate[5].

Roughly 500 new anticancer drugs are in clinical trials, and many more should soon be under development as a result of new technologies. At the same time, advances in the molecular profiling of tumours could help to define diagnostic patterns that identify those patients most likely to benefit from the new treatments. Although numerous challenges still lie ahead, the future of personalized cancer treatment looks promising. ■

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Signal processing

Neural coding by correlation?

Arun V. Holden

Noise limits the efficiency of information transfer. But correlations of the intervals between signal pulses can reduce low-frequency noise and thereby increase the transfer of information.

A nerve cell is an example of a system whose excitation codes and transmits dynamic information. When a stimulus is above a given threshold, the neuron responds by generating an action potential, so that over time it fires irregular sequences of all-or-nothing spike responses. The ionic cell mechanisms that generate the spike are understood, but there are many mechanisms for coding the spike train, and our knowledge of these mechanisms ranges from well established to speculative. In *Physical Review Letters*, Chacron *et al.*[1] show, using a simple action-potential model, that correlations between sequential interspike intervals can shape the noise spectrum — and that this shaping can increase the transmission of information, because it reduces the noise spectrum at low frequencies.

Information theory is essentially linear[2]: a reaction is directly proportional to an action. So it might be expected that the constraints imposed by interval correlations would reduce the transmission of information. However, spike generation is a strongly nonlinear, excitable process with a threshold, and such systems can behave counter-intuitively. A good example is stochastic resonance[3], in which additive noise can increase, rather than decrease, the efficiency of information transmission.

A spike train can be represented by the sequence of intervals between spikes; this is characterized by the interval statistics (in the time domain by probability distributions and correlations, and in the frequency domain by spectral densities). Chacron *et al.*[1] consider two schemes of spike generation. The first produces a 'renewal process' that has no memory of the excitation because the system resets itself each time a spike is generated. Here, there is no correlation between successive spike intervals. The probability distributions for higher-order intervals (say, between one spike and the third spike following) and the 'autocorrelation' (the probability of a spike occurring after some other spike, irrespective of how many intervening spikes there were) can be calculated directly from the interspike-interval probability density.

The second scheme generates a non-renewal spike train, with correlations between adjacent intervals. Spike trains of sensory neurons[4] with a constant stimulus often show dependencies between neighbouring intervals; such dependencies are produced either by fluctuations in an oscillatory spike-generator or by activity-dependent changes in threshold. Long intervals followed by short ones (and vice versa) result in negative interval correlations.

The essence of spike generation is that inputs too weak to trigger a response are summed, giving a potential; when the potential reaches a threshold, a spike is generated. Chacron *et al.*[1] use a 'perfect integrator model'[5] for both spike-generation schemes, with a random threshold drawn from a uniform distribution. When the threshold is reached the potential is reset, either by an amount dependent on the magnitude of the threshold just reached (to produce serial correlation), or by a random amount (to generate a spike train with the same inter-spike-interval density but no correlation).

The advantage of using this simple model is that the spectra, coherence and information transmission rates (mutual information rates) can all be calculated, as well as estimated through computer simulation. Chacron *et al.* demonstrate that a negative serial correlation between spikes reduces the spike-train spectrum and coherence at very low frequencies, although at middle-range frequencies the coherence is increased. Serial correlation also enhances the ability of the model to transmit information by reducing low-frequency noise compared with the renewal process. Such effects have been seen in more realistic neural models[6], and can be quantified in real neural spike trains; but the complexity of both of these situations had meant that the mechanism for improved information transfer was unclear.

Whether or not this increase in the information transmission rate is exploited in neural systems is an open question, as biological evolution produces systems that work well enough and are robust, without necessarily being optimally efficient. The nervous system responds to a spike train in real time and does not process it as an indefinite sequence. But the effect of correlation on the transmission rate in a single spike train might transfer to correlations between multiple spike trains: variability between different neurons could be correlated, through common inputs and feedback[7], and coupling within a population could lead to a similar reduction in variability by noise shaping[8]. ■

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