potential lensing galaxies. Furthermore, its optical image appears to be slightly elongated[2]. This can be explained if the source is a pair of almost equally bright lensed images with a separation of 0.33 arcsec, blurred into one by the atmosphere — exactly as expected for a strongly magnified quasar. When a correction is applied for the estimated lensing magnification, the source becomes fainter, and so less unusual.

The higher 0.1-arcsec spatial resolution of the Hubble Space Telescope should confirm or refute the lensing hypothesis. Another quasar, H1413+117 — 'the Cloverleaf', is lensed by an elliptical galaxy into four images of comparable brightness[7] (Fig. 1). The Cloverleaf is also a bright IRAS source, and has been observed in detail over a wide range of wavelengths. It is to be hoped that observations of comparable quality for APM08279, which is brighter than the Cloverleaf, will be available soon.

The identification of APM08279 is more strong evidence that luminous dusty galaxies and quasars exist in the distant Universe. Many more such sources should still be lurking unconfirmed in the IRAS catalogue[2]. In fact, it is quite plausible that IRAS sources as dusty and luminous as APM08279, but with more heavily obscured spectra similar to that of F10214, lie in the surveyed field[2], but were not observed because they are missing from the optically selected APM catalogue. Accounting for this class of source would increase the numbers of high-redshift, high-luminosity galaxies even further.

The existence of sources such as APM08279 is consistent with the results of the first direct systematic survey that is sensitive to very distant dusty galaxies and quasars[8]. This survey was carried out in the submillimetre waveband, to detect the redshifted radiation from distant dusty star-forming galaxies and quasars. Submillimetre-selected sources are almost all located at high redshifts, at which gravitational lensing is most likely to occur. It is difficult to build the sensitive instruments required for submillimetre surveys[9], but they are now becoming available[10], and the planned all-sky survey by ESA's Planck Surveyor satellite will be of particular interest. Planck Surveyor will not only map the cosmic microwave background radiation with unprecedented precision, but will also detect a large number of extremely distant and luminous gravitationally lensed galaxies and quasars[11]. The identification of APM08279 is an excellent omen for this systematic survey of the distant Universe. □

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Thermodynamics

Liquid landscape

Austen Angell

Supercooled liquids — that is, liquids at temperatures below their normal freezing point — can undergo a subtle transition to a microscopically fixed, yet amorphous state: a glass. The temperature of this transition depends on how quickly the liquid is cooled, so it has seemed more natural to describe the process in terms of kinetics, rather than some immutable thermodynamics. But on page 554 of this issue[1] Sastry, Debenedetti and Stillinger show how changes in the dynamic properties of glass-forming liquids[2,3] can be related to changes in the nature of the system's underlying energy landscape.

'Landscape paradigms' are used to describe the qualitative behaviour of complex systems[4]. In such systems there are many metastable states, and many possible transitions between the different states. The system's state is represented by a point which moves on or above a surface, according to rules decided by the problem under consideration. The types of system described by the landscape model range from economics and evolution, through neural networks, spin glasses and proteins, to molecular clusters and viscous liquids. For each problem, the height of the surface may correspond to a different parameter — 'fitness' is to be maximized for an evolving species, for example; and some energy is to be minimized for a system of molecules. For the latter, the landscape topology controls the kinetics[5], and the average energy of the minima visited at temperature T reflects the thermodynamics.

For viscous liquids and glasses, the system point depends on how a collection of N particles are arranged, because the system's energy is determined by the exact positions of all the particles. The energy landscape is a surface with $3N+1$ dimensions, and impossible to conceptualize properly. Nevertheless, a two-dimensional representation (Fig. 1a) is useful, and can illustrate the distinctions between liquid, crystal and glass.

In equilibrium, the liquid moves between minima in a region of energy determined by the temperature. When the temperature is increased, the system will spend most of its time 'higher up' on the energy landscape, gaining access to more possible states. This is in accordance with the principle that fixed-volume systems in equilibrium should minimize their free energy (the Helmholtz free energy $A = E - TS$, where E is the internal energy and S is the entropy). S is large when the number of states that the system can visit is large. The relation is that inscribed on Boltzmann's tomb, $S = k_B \ln W$ where W is the number of possible states (here, energy minima on the landscape; vibrational states equilibrate far more quickly, and so can be treated separately).

Perfect crystals occupy just one deep minimum, and melt in order to lower their free energy by gaining access to all the minima of the landscape — for melting at fixed volume, the entropy change $T\mathrm{d}S$ just balances the internal energy change $\mathrm{d}E$. Glass-formers are liquids that fail to find their way back to the crystal minimum on cooling, and hence wander down among the myriad minima of the landscape as they supercool ('down'

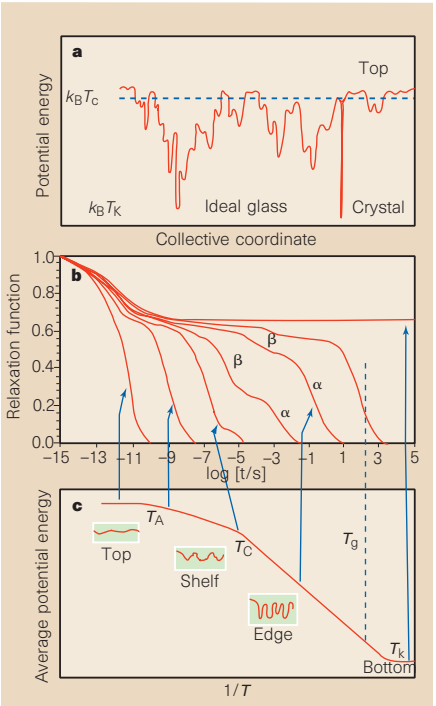

Figure 1 **Three angles on glass.** a, **In the energy-landscape depiction, the internal energy of a system depends on the configuration of all its particles (here simplified to one dimension).** b, **The relaxation function shows the approach to equilibrium over time.** c, **The average energy of the energy-landscape slice sampled at different temperatures, with an indication (in boxes) of the form of the minima in each energy range.**

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because there are then fewer minima accessible, and S is smaller). Eventually the system gets stuck in one of the lower minima — not as low as for the crystal — and we have a glass.

The system gets stuck because the vibrational energy (which adds on to the landscape energy to 'float' the system a little above the bottom of any minimum it occupies) becomes insufficient to activate the system from one minimum to the next. Bringing the temperature up a little allows the system to slowly explore the surrounding minima, hence to restore an equilibrium state (minimum in A). This is called relaxation, annealing or ageing depending on whether one works on liquids, glasses or polymers.

To ferret out the details of this picture for a model potential, Sastry *et al.*[1] have used a system containing a few hundred argon atoms of two different sizes, which interact in a way that stabilizes the liquid and makes it impossible to find any crystal minimum[3,5,6]. Sastry *et al.* equilibrate the system at various temperatures, keeping the volume constant. Then, to determine the internal energy of the 'inherent structure' (the structure sampled most frequently by the system at a given temperature), they quench the system, removing the vibrational energy by a technique that ensures a direct descent to the bottom of the energy minimum above which the system was oscillating at the moment chosen. If all minima have the same depth, then the final energy should be independent of temperature. Indeed, that is what is found, within close limits, for high temperatures — such as those above normal melting points. This means that there can't be a statistically interesting number of higher-energy states anywhere on the landscape, or else the TS factor would drive the system to sample them.

But for supercooled liquids below a well-defined temperature (T_A in Fig. 1), the energy of the inherent structure starts to decrease as the temperature of equilibration is lowered. T_A turns out to be just the temperature at which earlier simulations[3] found a departure from exponential relaxation (and the development of a second stage in the total relaxation process; Fig. 1) and the onset of a special temperature-dependence considered characteristic of viscous liquids. This regime is described well by the much-studied and highly mathematical 'mode-coupling theory'[7], which predicts a power-law variation of relaxation time with T. The physical picture is one of particles 'caged' by their neighbours but eventually escaping on the relaxation timescale.

More interesting is the landscape 'slice' visited as the temperature decreases further, to where mode-coupling theory starts to break down. The breakdown is so far not seen in the simulations because of computing speed limitations, but is known from laboratory studies. Sastry *et al.*[1] found that, although their system also got stuck in this range, the landscape where it stuck was characterized by suddenly deeper minima, and, moreover, minima of a simpler form (Fig. 1c).

A break in the 'average energy sampled' versus T, such as occurs near T_c in Fig. 1c, must mean a break in the number density of the energy minima, as it is entropy that drives the system upward in energy as T increases. We use a $1/T$ scale to simplify the drawing of connections between the slice of landscape frequented by the system at temperature T and the character of the relaxation process.

Figure 1 shows how the energy landscape discussed by Sastry *et al.* relates to the relaxation function[2,3]. Short-timescale relaxation data[2,3], and energy 'slice' data from the present study, are joined with the longer-timescale findings of experimentalists at lower temperatures down to and below the glass transition. Part c shows how the average sampled energy bottoms out at a temperature characteristic of the energy of the lowest minimum on the landscape of part a. This is the Kauzmann temperature (T_K), where the non-vibrational entropy vanishes for infinitely slow cooling — the 'ideal glass temperature' of theory[8,9]. Figure 1b shows how two-step relaxation begins at about the same temperature as a weakly sloping energy profile begins. Arrival at the end of this 'continental shelf' (at T_c) is accompanied not only by the onset of ruggedness (Fig. 1c), but by a new complexity in the relaxation function. This is the little-understood splitting of the de-caging relaxation into two parts (α and β) of very different T dependence, as predicted by Goldstein[10]. Is this, and the shelf edge, due to cage–cage percolation[11] to give a domain structure? The simulations are not yet fast enough to resolve this question.

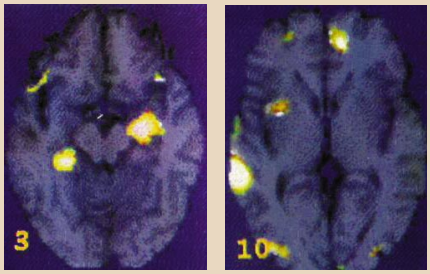
In the meantime, we need to understand liquid 'fragility' (sensitivity to temperature change) in landscape terms[12]. Comparable

Neurobiology

Brain, heart and stress

Positron emission tomography (PET) brain scanning is being used to tackle ever more subtle scientific and medical questions. Witness the two images here, which come from work carried out by Robert Soufer and colleagues of Yale University and are reported in *Proceedings of the National Academy of Sciences* (95, 6454–6459; 1998). They respectively show hyperactivation (left) and deactivation of certain parts of the brain, as measured by blood flow, in subjects with coronary artery disease when under mental stress.

The rationale behind this work is that although stress is associated with heart attacks and other cardiac problems in people with coronary artery disease, research has hitherto centred on the vascular and psychological aspects. The brain is undoubtedly involved in some way — through stress-induced activation of certain regions leading, perhaps, to a response from hormones or the sympathetic nervous system that affects heart function. An end result can be



myocardial ischaemia, with the heart muscle being provided with inadequate oxygen to function properly.

Soufer *et al.* took PET scans of patients with coronary artery disease, controlled against healthy people, when under mental stress and not under stress. They monitored heart function at the same time. The stress involved mental arithmetic, serial subtraction of numbers, the subjects being prompted for ever faster performance and their mistakes being corrected in no uncertain terms.

The resulting differences in patterns of blood flow and therefore brain activation or deactivation were highly complicated and are open to various interpretations. Most notably, however, as depicted in the images shown here, in three of the ten patients with coronary artery disease significant differences in activation/deactivation when under stress were associated with indications of myocardial ischaemia. For instance, the image on the left here shows hyperactivation in the left hippocampus and right parahippocampal regions; that on the right, deactivation in the cingulate gyrus among other areas.

This work can only be considered as a pilot study, but it does show that particular parts of the brain mediate the effects of stress on heart function in people suffering from coronary artery disease. The implications for devising possible treatments of the disease with drugs or changes in behaviour or lifestyle are clear. Realizing those prospects is a distant goal, but a start has been made.

Tim Lincoln

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simulations should show whether the sparser minima of non-fragile systems 'eat up' the shelf seen in the fragile-liquid sampled-energy profile (Fig. 1c), or simply push the Kauzmann temperature to lower values. Fragility is minimized in open networks, so can probably be 'tuned down' by adding variable-strength tetrahedral potentials (as in tin and silicon) to the simple atomic potentials of the present study. That should increase liquid 'strength' and yet maintain low crystallization probability. Such studies may provide the key to filling in the rest of the picture for systems with covalent, metallic or ionic interactions. □

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Physiology

Chemokines beyond inflammation

Richard Horuk

The old adage "don't judge a book by its cover" is certainly apt when applied to chemokines. Although they were originally defined as host defence proteins, chemokines clearly have other functions — growth-regulatory and angiogenic properties, for example — that extend well beyond the regulation of leukocyte migration[1,2]. Moreover, chemokine receptors such as CXCR4 are important[1] in the pathogenesis of the human immunodeficiency virus, HIV-1. A further level of complexity in chemokine biology is now revealed by Tachibana *et al.*[3] and Zou *et al.*[4] on pages 591 and 595 of this issue. They report that deletion of the *CXCR4* gene is embryologically lethal in mice, producing a multiplicity of effects including serious developmental defects in the immune, circulatory and central nervous systems. These studies expand the biological importance of chemokines, from that of simple immune modulators to a much broader biological role than was at first appreciated (Fig. 1).

The CXCR4 chemokine receptor is expressed throughout the body, and is a co-receptor[5] for cellular entry by T-cell-tropic but not macrophage-tropic strains of HIV-1. Its ligand is the stromal derived factor SDF-1 (ref. 6), which is known to be important in embryonic development[7]. Mice that lack the *SDF-1* gene die *in utero*, with severe defects in the ventricular septum of the heart. They also have fewer B-lymphocyte progenitors in the liver and bone marrow, suggesting defects in the formation of red and white blood cells. An obvious question is whether deletion of the CXCR4 receptor would produce a similar profile of deficiencies, and this is now addressed by Tachibana *et al.* and Zou *et al.* Although they find that CXCR4-deficient mice have a similar phenotype to the SDF-1 knockouts, the results also hold some surprises.

The two groups show that when both copies of the CXCR4 gene are knocked out, around half the mice die *in utero* by the 18th day of embryological development (E18.5), the remainder dying within one hour of birth. The similarity of this phenotype to that of the SDF-1-knockout mice confirms that CXCR4 and SDF-1 are a specific receptor–ligand pair that act in cardiac and blood-cell development. But the real surprise to come from the knockout mice is that CXCR4 is involved in the embryological development of neuronal networks in the central nervous system (CNS) and in the development of blood vessels in the gastrointestinal tract.

Zou *et al.*[4] compared brains from normal and CXCR4-deficient mice, and found abnormalities in the architecture of the cerebellum in the knockout mice. Specifically, cells from the external granule layer prematurely migrated into the internal granule layer — a process that normally does not occur until after birth. The generation of precisely formed neural networks, also called neuronal patterning, is important for proper functioning of the entire CNS, ensuring cell-to-cell communication through a system of correctly formed cellular synapses. During normal development, neurons migrate from the germinal matrix to specific positions within the CNS. Cells in the external granule layer migrate from the surface of the cerebellum, through the molecular and Purkinje-cell layers, to form the internal granule layer. Scaffolding provided by radial glia helps these granular neurons in their migration. In the CXCR4-deficient mice, however, the authors found that this orderly process is severely disrupted by the premature migration and abnormal clustering of neurons, despite the presence of intact radial glia.

Thus, the work of Zou *et al.* greatly extends previous studies that have shown neuronal expression of CXCR4. This receptor is clearly important in the development of the CNS, but what role could it play? There are several possibilities. First, there is compelling evidence for cross-talk between serpentine receptors[8] (the superfamily to which CXCR4 belongs). Signals generated from one receptor can either stimulate or inhibit signalling by another. Thus, CXCR4 may regulate migration of cells from the external granule layer by inhibiting their ability to respond to other chemoattractants — in fact, neurons can migrate in response to chemokines[9]. Alternatively, SDF-1 has been shown[10] to induce apoptosis in a human neuronal cell line through CXCR4, so perhaps CXCR4 aids in the apoptotic elimination of cells that have migrated incorrectly in the CNS. This would help to ensure correct neuronal patterning. To learn more, however, we need to identify the cell types in the CNS that express CXCR4 during development.

The formation of new blood vessels can be divided into three stages: vasculogenesis, which involves the maturation of mesodermal precursor cells into haemangioblasts; angiogenesis, in which these cells develop into an initial capillary network; and, finally, pruning and remodelling to form a functional circulatory network. Tachibana *et al.*[3] show that part of this process is defective in the gastrointestinal tract of CXCR4-deficient mice. Development of the vascular system in the gastrointestinal tract of both normal and CXCR4-knockout embryos was identical initially, and a highly vascularized network was observed at E11.5. However, at E13.5 there were clear differences in the circulatory networks of the two groups. The normal embryos developed large and small branches of the superior mesenteric arteries and veins, whereas in the CXCR4-knockout animals the larger branches of these vessels were missing, even though the vessels themselves were normal. Although these deficiencies did not affect development of the gastrointestinal tract, the abnormal circulatory system in the knockout embryos led to haemorrhaging and intestinal obstruction. As expected, SDF-1-knockout animals had a similar phenotype.

The CXCR4 receptor seems to be involved in vascular development in an organ-specific way, because the vasculature of other organs — including the brain and heart — was normal. In contrast to tyrosine kinase receptors such as vascular endothelial-cell growth factor and TIE-1, which seem to be important throughout vascular development, the CXCR4 receptor has a more restricted role. It remodels and prunes vessels, leading to the formation of a correctly branched gastrointestinal circulatory network. The discovery that SDF-1 acts in vascular development is not totally surprising, because other chemokines from the

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