

gene encoding enhanced green fluorescent protein to the repressor gene, and quantify expression of the resulting protein by fluorescence microscopy. They then compare this feedback network with control networks that contain the same promoter but lack negative feedback.

Their results show a more than threefold decrease in the variability of gene expression in the feedback network, compared with the control networks. They also show that the improved stability in the feedback network can be reduced incrementally by applying increasing concentrations of anhydrotetracycline — a chemical inhibitor of TetR.

In past theoretical studies of gene-regulatory networks, researchers have typically adopted a reverse-engineering approach, in which principles and mechanisms of function are extrapolated from data about naturally occurring gene networks. A few well-defined natural gene circuits, such as those involved in bacterial chemotaxis<sup>8</sup> and in the bacteriophage lambda<sup>9</sup>, have emerged as models for theoretical study. But the magnitude and complexity of natural gene networks have, in general, limited researchers' ability to verify their predictions experimentally.

The work of Becskei and Serrano, on the other hand, exemplifies a forward-engineering approach to the study of gene expression. This approach, also adopted in refs 3 and 4, makes use of synthetic gene networks to attain more complete control of the system parameters. Precise perturbations can be introduced to the system without interference to, or from, ancillary processes in the cell. Thus, synthetic gene networks allow

the accurate comparison of theoretical and experimental results, and can, in theory, quickly reveal possible principles and motifs of cellular regulatory processes.

Synthetic gene networks are rapidly emerging as a valuable tool for the identification, analysis and understanding of cell regulatory processes. But it remains to be shown whether observations of a synthetic gene network apply in the context of natural networks. In the case of Becskei and Serrano's work<sup>1</sup>, it is still not clear whether *E. coli* or other organisms do exploit negative feedback to stabilize gene expression. When this question is answered, it may not only solve the mystery of biology's extraordinary precision, but may also reveal the full value of the forward-engineering approach to the study of biological systems. ■

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## Glass transition

# Hard knock for thermodynamics

Salvatore Torquato

It was once thought that relatively few materials could be prepared as amorphous (or disordered) solids. It is now widely believed that the amorphous state is a universal property of condensed matter, whether ceramic, polymeric or metallic<sup>1</sup>. The amorphous solid known as a 'glass' can be achieved by quenching (cooling) a liquid sufficiently rapidly to below its glass transition temperature,  $T_g$ , to avoid crystallization (Fig. 1). Roughly speaking, a glass is a material that is out of equilibrium, having the disordered molecular structure of a liquid and the rigidity of a solid. But the underlying physics of the glass transition remains one of the most fascinating open questions in materials science and condensed-matter physics. A hotly debated issue is whether the glass transition involves an underlying

thermodynamic (static) or kinetic (dynamic) phase transition. On page 550 of this issue, Santen and Krauth<sup>2</sup> provide further evidence that the glass transition is not thermodynamic in origin.

A thermodynamic phase transition must involve abrupt changes in certain thermodynamic properties, such as volume. According to the thermodynamic viewpoint, the experimentally observable glass transition is a kinetically controlled manifestation of an underlying thermodynamic transition. This explanation originates with the famous work of Kauzmann<sup>3</sup>. He observed that the entropy (structural disorder) of a supercooled liquid would fall below that of the corresponding crystal structure — which is expected to have the lowest entropy — if cooled below what is referred to as the Kauzmann temperature,

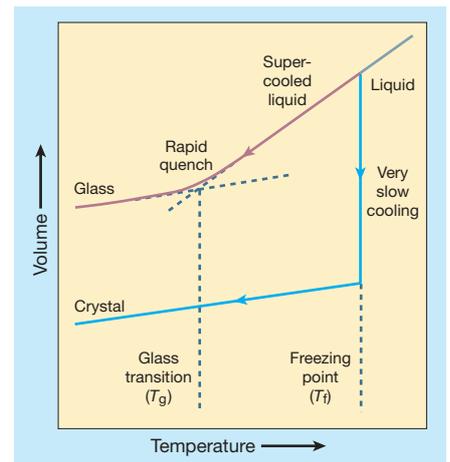


Figure 1 Two cooling paths by which a liquid may solidify. A very slow cooling rate leads to a discontinuous change in volume to a crystal state (purple curve). A rapid quench leads to a continuous change in volume to a glass (blue curve). For a model system of hard spheres, Santen and Krauth<sup>1</sup> have shown that the glass transition does not involve an underlying thermodynamic phase transition.

creating an 'entropy crisis'. The crisis is averted in practice by the intervention of the glass transition. In contrast, the kinetic viewpoint explains the observed structural changes as the consequence of a dynamic transition in the relaxation of the supercooled liquid, which is not accompanied by abrupt changes in thermodynamic properties.

To understand the glass transition, investigators (including Santen and Krauth) have studied idealized models in which the atoms, represented by spheres or disks, interact through hard-core repulsions only<sup>4</sup>. Because the interaction potential is either zero or infinite, such systems are athermal — that is, the thermodynamic and kinetic properties are (after a trivial rescaling) independent of temperature. One might well question whether such a simplified model can shed any light on the nature of the glass transition in real materials. Interestingly, identical hard spheres are known to undergo a transition from a disordered, liquid-like state to an ordered, crystal-like state at a high enough density<sup>5</sup>. Thus, increasing the density in hard-sphere systems plays the same role as decreasing the temperature in thermal systems. Indeed, by increasing the density of hard-sphere systems quickly enough, crystallization can be avoided (albeit only for short periods of time<sup>6</sup>), in analogy with the 'supercooled' branch of the thermal system in Fig. 1.

Computer simulations have led to two schools of thought concerning the glass transition in systems of equal-sized hard spheres. One proposes that the transition is thermodynamic<sup>4,7</sup> because there are indications of a discontinuity in the slope of the equation of state along the supercooled branch. The



## 100 YEARS AGO

A remarkable paper, by Mr. Nikola Tesla, appears in the June number of the *Century Magazine*. The subject is "The Problem of Increasing Human Energy, with Special Reference to the Harnessing of the Sun's Energy"; and though metaphysical and sociological questions receive a large share of attention, the article contains an account of some very interesting electrical experiments... Electrical discharges capable of making atmospheric nitrogen combine with oxygen have recently been produced. Experiments made since 1891 showed that the chemical activity of the electrical discharge was very considerably increased by using currents of extremely high frequency or rate of vibration... The flame grew larger and larger, and its oxidising action more and more intense. From an insignificant brush discharge a few inches long it developed into a marvellous electrical phenomenon, a roaring blaze, devouring the nitrogen of the atmosphere and measuring sixty or seventy feet across. The flame-like discharge visible is produced by the intense electrical oscillations which pass through the coil and violently agitate the electrified molecules of the air. By this means a strong affinity is created between the two normally indifferent constituents of the atmosphere, and they combine readily, even if no further provision is made for intensifying the chemical action of the discharge.

From *Nature* 31 May 1900.

## 50 YEARS AGO

The subject of population growth or decline has been in the forefront since the Royal Commission on Population began its investigations and deliberations in 1944. Last year its final report was published, and one of its main conclusions was that the slackening of population growth was due to a change in respect of average family size. The Royal Commission outlined the historical background against which the small family came into being: the decline in the importance of the family as a productive unit, the lengthening period during which children remained dependent upon their parents, the advantages of small family size for those struggling for social security and promotion, the increasing and more widely spread knowledge of the techniques of controlled fertility, the changing status of women and the increased opportunities for the enjoyment of leisure outside the home.

From *Nature* 3 June 1950.

other claims that there is no evidence for a thermodynamic glass transition because no such discontinuities are perceivable and the system always crystallizes along the super-cooled branch<sup>6</sup>, implying that (if it exists) the glass transition can only be a dynamical or kinetic phenomenon. Recent experimental work on colloidal hard spheres<sup>8</sup> supports the second claim.

Adding to the view that glass formation is not a thermodynamic phase transition is the Monte Carlo simulation of Santen and Krauth<sup>2</sup>. They cleverly chose to study two-dimensional systems of hard disks in which each particle has a different size to ensure that the systems do not crystallize. By eliminating any crystallization effects, they can focus exclusively on the nature of the disordered branch. Along this branch, they define the glass transition density to be the point at which the diffusion coefficient (a measure of the mobility of the atoms) becomes vanishingly small — below this density the atoms are mobile (equilibrium liquid), and above this point they are immobile (glass).

An underlying thermodynamic phase transition would be reflected in a discontinuous change in certain thermodynamic properties in crossing this density. In doing these calculations, one must ensure that all of the phase space is sampled without bias (that is, sampling is ergodic). But standard Monte Carlo techniques are known to be non-ergodic when the dynamics slow down near phase transitions. To circumvent this problem, Santen and Krauth use a 'cluster' Monte Carlo algorithm — a method originally introduced to study so-called spin systems

near their critical points<sup>9,10</sup>. In particular, by a non-local swapping of large clusters of disks, they avoid the problems that conventional Monte Carlo methods have near critical points and find no evidence for a thermodynamic glass transition. Although the specific case studied here does not settle the issue once and for all (for example, other realistic models for glass formation might behave differently), it is another piece of evidence that adherents of the thermodynamic phase-transition theory will find difficult to discount.

There are several ways in which this work can be taken forward. For example, it could be extended to less idealized systems, such as those in which crystallization is not explicitly suppressed and systems with more realistic interaction potentials (allowing for temperature dependence). The possibility of combining the non-local character of the cluster Monte Carlo method with molecular dynamics simulations in order to study the true dynamics of glasses is tantalizing. ■

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## Cognitive neuroscience

## Learning how the brain learns

Eilon Vaadia

Methods for monitoring brain activity in behaving animals and humans are being developed with increasing pace. But we are still far from understanding the processes in the brain that give rise to even simple types of behaviour. On page 567 of this issue<sup>1</sup>, Laubach and colleagues address the problem by recording the activity of many nerve cells as rats learn a simple task, and combine this approach with sophisticated analytical algorithms.

It is widely accepted that large areas of cortex are involved in any behavioural process, and that these areas contain many modules, each consisting of groups of cells that process specific information. It is often assumed that, once the brain matures, each module and each cell fulfils one specific function. But accumulating evidence indicates

that this may not be so. Instead it is likely that each cell participates in several different processes. The brain is also constantly changing, and each cell's effects may be rapidly modified<sup>2</sup>. So it is essential to study a large number of neurons simultaneously to understand how cells communicate and how neuronal interactions are modified in relation to learning and behaviour.

These ideas have been evolving for many years<sup>3–5</sup>, but concrete facts have been hard to come by. For a start, it is difficult to record the activity of a large number of neurons while still identifying and isolating each cell. Other problems stem from the limited capacity of computer hardware and a lack of suitable data-analysis algorithms. The study by Laubach *et al.*<sup>1</sup> reflects the intense work being done worldwide to tackle these issues.