for the fall of the Roman Empire — a decay of civic virtue.

Without kin discrimination, relatedness in supercolonies becomes indistinguishable from zero[8], which has two consequences. First, workers that can no longer aid close relatives may evolve more selfish strategies. It may not be coincidental that the best example of ultraselfish 'greenbeard genes' comes from another ant with unicolonial characteristics[9]. Here, workers possessing one allele at a genetic locus selectively murder queens lacking that allele.

Whether or not workers evolve selfish strategies, the second, larger problem is that they cannot improve or even sustain their cooperative behaviour[10]. Without relatedness, adaptive modifications of cooperative worker behaviour cannot be favoured and maladaptive ones cannot be disfavoured. Random drift will become important again, this time because of the absence of any opposing force rather than a small population size. The ants are like a casino gambler who is lucky once but cannot quit: chance got them their stake, but over the long run it can only lead to ruin.

Either way, Argentine ants may evolve to control themselves, with their Pax Argentinica falling under an assault of unbridled nepotism, or with their society suffering the lingering death of decay by drift. Of course, either process could take a very long time. As to the question of controlling the ants in California, Tsutsui *et al.*[1] suggest a counterintuitive strategy that might give the ants a push down the nepotistic path. If the main enemies the ants left behind are themselves, perhaps we should introduce more of them. The resulting increase in genetic variation could re-establish the lost kin discrimination. If so, the ants can return to battling among themselves, giving native species a fighting chance. ■

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Gene regulation

Neutralizing noise in gene networks

Timothy S. Gardner and James J. Collins

The thousands of chemical reactions that sustain living cells involve interactions between individual molecules. Such interactions are stochastic, happening discretely and randomly. This so-called noise is inherent in every molecular event that takes place in a cell. In particular, it can cause sizeable, random fluctuations in the concentrations of expressed proteins and RNA. But often the events in an individual cell, or even a whole organism, are not at all unpredictable. The gestation of multicellular organisms, for instance, follows a pattern and time course so predictable it could be used to set a watch. And all too familiar to the frequent traveller is the circadian rhythm, which is driven by a molecular clock with a precise period of oscillation. For years, researchers have wondered how biology achieves such predictability despite its inherent noisiness.

On page 590 of this issue[1], Becskei and Serrano provide insight into a possible mechanism by which cells may accomplish this impressive task. They show, using a synthetic gene circuit, that negative feedback can dramatically reduce variability in gene expression.

Earlier modelling studies[2] showed that noise in gene expression could lead to qualitative differences in a cell's phenotype if the expressed genes act as inputs to downstream regulatory thresholds. Recent experiments — including our own[3] — have also shown that internal noise can lead to premature switching between stable states[3] and irregular oscillations[4,5] in synthetic gene-regulatory networks. It has been suggested that the inclusion of feedback in gene-regulatory circuits could improve their robustness to internal noise[3–6]. Until now, that suggestion has remained unverified by direct experimentation.

The steady state of a noisy system can be characterized as a competition between stabilizing system dynamics and destabilizing random fluctuations. The addition of negative feedback counteracts the internal noise by enhancing the stabilizing action of the system dynamics. This effect can be visualized using a simple physical analogy. A ball (representing the level of gene expression) rolling in a salad bowl (representing the gene network) will ultimately come to rest at the bottom of the bowl. Shaking the bowl (the internal noise) will push the ball away from the bottom, while the shape of the bowl will push the ball back towards the bottom. Adding negative feedback to a gene network is equivalent to making the sides of the salad bowl steeper.

Becskei and Serrano[1] use linear stability analysis of a mathematical model to show that negative feedback can double the stability of gene expression in a simple gene network. They confirm this effect with simulations that show a reduction in the variability of gene expression. To test their predictions experimentally, Becskei and Serrano construct a synthetic gene network in the bacterium *Escherichia coli*. The network includes a TetR (tetracycline repressor)-regulated promoter region[7] placed upstream of the gene encoding the tetracycline repressor itself (Fig. 1). This system constitutes a negative feedback loop, because the promoter is inhibited by the repressor whose expression it drives. To measure the output of the system, Becskei and Serrano fuse the

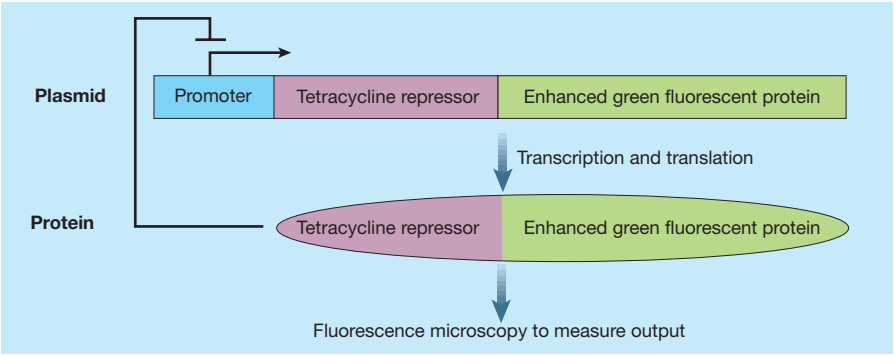

Figure 1 **Controlling noise by negative feedback. The synthetic gene network used by Becskei and Serrano[1] includes a tetracycline-repressor-regulated gene promoter to direct transcription of the repressor gene itself. The repressor protein then inhibits transcription from the promoter. The resulting negative feedback stabilizes expression of the repressor around a particular steady-state level. If the repressor exceeds this level, it will strongly inhibit its own synthesis, and repressor levels will decline. Conversely, when the repressor falls below the steady-state level, it will reduce the inhibition and repressor synthesis will increase. The gene encoding enhanced green fluorescent protein is also fused to the gene construct, allowing quantification of the output of the network.**

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[8] and in the bacteriophage lambda[9], 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[1], 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[1]. 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[2] 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[3]. 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,

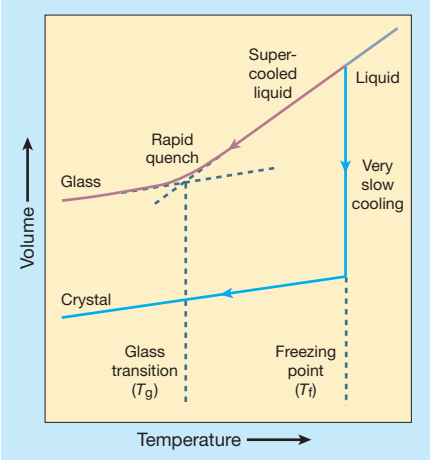

Figure 1 **Two cooling paths by which a liquid may solidify. A very slow cooling rate leads to a discontinuous change in volume to a crystal state (purple curve). A rapid quench leads to a continuous change in volume to a glass (blue curve). For a model system of hard spheres, Santen and Krauth[1] have 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[4]. 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[5]. 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[6]), 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[4,7] because there are indications of a discontinuity in the slope of the equation of state along the supercooled branch. The