conventional ordering and the system features non-zero entropy even at zero temperature, in contrast to the naive expectation from the third law of thermodynamics. Quantum superposition of degenerate states leads to the emergence of exotic many-body phenomena[2–6], from spin ice and quantum spin liquids to high-temperature superconductivity.

A key characteristic of frustrated systems is a large number of degenerate ground states. This high degeneracy is very sensitive to perturbations: any slight asymmetry in the system will reduce the number of degenerate ground states. This instability leads to rich physical behaviour. Understanding the fundamental mechanisms and principles underlying the variety of quantum phenomena that arise from highly degenerate ground states is of conceptual importance in condensed-matter physics. Both the development of numerical-simulation techniques and the increasing ability to experimentally engineer systems in which magnetic, charge or vibrational degrees of freedom interact, have a central role in addressing this problem. In particular, optical lattices (arrays of interfering laser beams) of cold atoms[7–9] provide model systems for strongly interacting many-body systems.

Quantum dots (artificial atoms) provide a promising platform for investigating non-equilibrium charge transport, and in particular how it is affected by geometrical frustration. Advanced techniques for fabricating nanoscale devices allow detailed modelling and flexible tuning of parameters. In semiconductor quantum dots, the potential in which the dots are confined and the number of electrons, as well as the interaction between them, are controlled by metallic 'gate' electrodes.

In their study, Seo *et al.* report the first observation of geometrical frustration in quantum dots. Because of the difficulties in building highly symmetrical devices, this had not been achievable previously. Their frustrated quantum system consists of three quantum dots arranged in a triangle (Fig. 1). Antiferromagnetic interactions between the dots' electron spins lead to a frustrated ground state, which results from the competition of the six degenerate, three-spin configurations out of eight possible spin arrangements. Because controlling electron spins in quantum dots is difficult, the authors used an alternative way of studying geometrical frustration: degenerate charge states. The advantage of this approach is that these charge states (isospins) are defined by the parity of the number of charge carriers in the dots and can be precisely controlled by metallic gate electrodes. The authors' measurements of charge transport revealed the six-fold degeneracy of the isospin configurations in the maximum electrical conductance induced by the fluctuations between the states.

Seo and colleagues' work sheds light on the impact of frustration on charge transport and its characteristic signatures, and motivates further experimental as well as theoretical studies, including analysis of the time evolution of frustrated quantum systems. Quantum dots have been suggested as potential platforms for implementing spin or charge quantum bits[10–14] for quantum computation and information processing. Control of magnetism on the atomic scale is also becoming essential as data-storage devices are miniaturized. In particular, switchable nanoscale antiferromagnets are being discussed as candidate building blocks for future memory, storage and 'spintronic' applications[15]. Understanding the underlying physics will be crucial for the development of these technologies. The challenge is the scalability to large systems — to explore complex many-body phenomena, identify novel quantum phases and design interesting quantum materials. ■

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MOLECULAR BIOLOGY

Circles reshape the RNA world

The versatility of RNA seems limitless. The latest surprise comes from circular RNAs, which are found to counteract the function of another class of regulatory RNA — the microRNAs. **SEE ARTICLE P.333 & LETTER P.384**

KENNETH S. KOSIK

miRNA下调基因表达--对此调控机制的一种管理方式

The protein-coding function of messenger RNAs can be suppressed by the binding of short microRNA sequences. But how microRNA-induced suppression is itself inhibited is poorly understood. In this issue, Memczak *et al.*[1] (page 333) and Hansen *et al.*[2] (page 384) describe highly stable, circular RNAs that bind several copies of a microRNA to terminate suppression of mRNA targets*.

The circular RNA (circRNA) reported, called CDR1as by Memczak *et al.* and ciRS-7 by Hansen *et al.*, contains roughly 70 evolutionarily conserved binding sites for microRNA-7 (miR-7) and forms a complex with AGO proteins. The latter are part of the RNA-induced silencing complex, which allows miRNAs to recognize their target mRNAs. When Memczak and colleagues expressed human CDR1as/ciRS-7 in zebrafish embryos, its effects were the same as those seen when miR-7 expression was reduced — impaired midbrain development. Moreover, the authors' bioinformatic predictions indicated that thousands of circRNAs reside in the genome, consistent with previous reports[3,4].

Target suppression by miRNAs is highly nuanced. On the one hand, these sequences can induce AGO-mediated endonucleolytic mRNA cleavage triggered by complementarity between the mRNA and the miRNA at nucleotides 10 and 11. The destruction of the target, which follows, frees the miRNA to bind to its next target in a catalytic manner. On the other hand, miRNAs can inhibit protein translation by binding more stably to a target mRNA in a stoichiometric manner. This makes the target a 'reservoir' that prevents the miRNA from inhibiting other mRNA targets. The latter mechanism is an indication of the way in which competing endogenous RNAs (ceRNAs) act. These are mRNAs that share miRNA-response elements (MREs) with other mRNAs and so compete for binding to those miRNAs with which they also share MREs[5].

Like ceRNAs, circRNAs serve as miRNA reservoirs. However, circRNAs have numerous binding sites for a specific miRNA and so are completely dedicated to their role of harbouring miRNAs. Binding of a miRNA to a ceRNA not only prevents that miRNA from binding to

*This article and the papers under discussion[1,2] were published online on 27 February 2013.

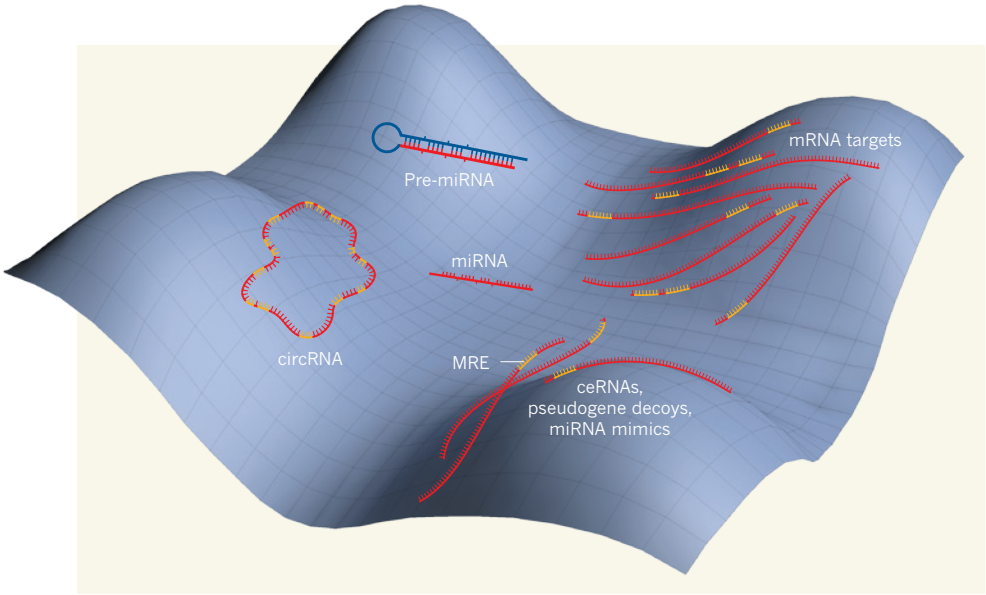

Figure 1 | Constraints on evolutionary change in microRNAs. MicroRNAs (miRNAs) lie in a fitness valley constrained by their numerous interactions, which include those with the hairpin structure of the precursor miRNA (pre-miRNA), the many target mRNAs and other RNAs that terminate or modulate miRNA binding to target sequences by competing against them. The latter category includes competing endogenous RNAs (ceRNAs), pseudogene decoys and miRNA mimics. Two studies[1,2] introduce circular RNAs (circRNAs) as another constraining factor. MRE, miRNA-response element.

other MREs, but can also suppress translation from the coding portion of the ceRNA. Hence, compared with circRNAs, ceRNAs operate in a more complex weave of interacting molecules that constrains translation. Other reservoirs of target sites also reside on distinct molecules. These include target mimics such as the *IPS1* gene in the plant *Arabidopsis thaliana*[6], decoys within pseudogenes such as *PTENP1* (ref. 7) and possibly 3′-untranslated regions of mRNA that are expressed separately from their associated protein-coding sequences[8].

Circularizing RNA enhances its stability by obviating a role for RNA exonuclease enzymes, which act on free 3′ and 5′ ends of an RNA molecule to cleave it. Moreover, with several binding sites dedicated to antagonizing a single miRNA, a circRNA can capture miRNAs from numerous targets in one fell swoop. Likewise, circRNA destruction could release a shower of miRNAs that target multiple mRNAs with the shared MRE. In fact, Hansen *et al.* outline a circRNA-destruction mechanism in which miR-671 binds CDR1as/ciRS-7 with greater complementarity than miR-7 and induces AGO-mediated cleavage of this circRNA.

Snapshot approaches to profiling miRNAs reveal that the greatest changes in their expression levels occur at transition points in development, cell differentiation or carcinogenesis[9]. Clearance of the mRNA–miRNA duplexes at these points and their replacement with different miRNAs could operate through circRNAs. For instance, as a brute means of vacuuming up miRNAs, circRNAs could increase in expression as cell differentiation from stem cells proceeds, to capture the exceedingly high levels of miRNAs expressed in stem cells. They could also clean up the opposite strands of mature miRNAs, which can be present in surprisingly large numbers[10], or potentially function therapeutically to divert cancer-associated miRNAs from promoting an oncogenic pathway. In all these cases, however, the circRNAs sequester miRNAs, and so a knowledge gap remains regarding how miRNAs are destroyed.

To function optimally, the number of miRNA-binding sites on each circRNA is probably under selection pressure to attract nearly all of a specific miRNA population from all of its target sites. If so, the number of miRNA-binding sites on a circRNA multiplied by the number of copies of the circRNA in a single cell will inform us about the collective strength of all MREs for a particular miRNA. Many miRNAs operate at copy numbers of 10^3 per cell — a likely lower boundary for the number of circRNA sites required to mop them all up. However, for circRNAs to win out against mRNA targets in the competition for miRNA binding, they must have a greater affinity for the miRNAs. High affinity can be thermodynamically built into the circRNA sequence, but may also require an excess of circRNA-encoded miRNA-binding sites relative to the total number of other relevant MREs in the cell. Certainly, modellers will soon be romping through this territory.

The fitness 'landscape' that has contributed to maintaining each of the roughly 21-nucleotide miRNAs unchanged over major parts of evolution includes circRNAs (Fig. 1). The selection pressure on each miRNA nucleotide is undoubtedly high: an miRNA sequence must base-pair to itself to form the hairpin-shaped precursor miRNA; it must pair with a host of target mRNAs; and it must pair with

binding sites that terminate or modulate target interaction. Despite the enormous number of possible miRNA sequences, the small amount of change in miRNAs implies that the remaining evolutionary space for innovation is limited; in other words, miRNAs have approached molecular perfection. Throughout animal evolution, nature has tinkered with the sequences of a relatively constant set of coding genes, whereas miRNA innovation, in general, is more reliant on the invention of completely novel sequences[11]. Perhaps the ease with which hairpin-shaped miRNA precursors can arise as potential regulatory elements — and fit 'digitally' into a wealth of genomic non-coding sequence, including circRNAs — could serve as a driver of evolution.

As a footnote, a better naming system for circRNAs is needed. 'ciRS-7' denotes binding to miR-7, and therefore assumes that other circRNAs in this category will also neatly align with a single miRNA. 'CDR1as' assumes that circRNAs will bear some relationship to a named gene — in this case, an antisense sequence to the cerebellar degeneration-related gene. With thousands of these circRNAs in the genome, they require their own numbering system. My suggestion is that this one is called circR-1. ■

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ASTRONOMY

The ALMA telescope shows its true colours

Bright, gravitationally magnified galaxies have been found across a wide span of cosmic time. The first results from the still-growing ALMA telescope show its power to reveal these galaxies' redshifts and internal structure. SEE LETTER P.344

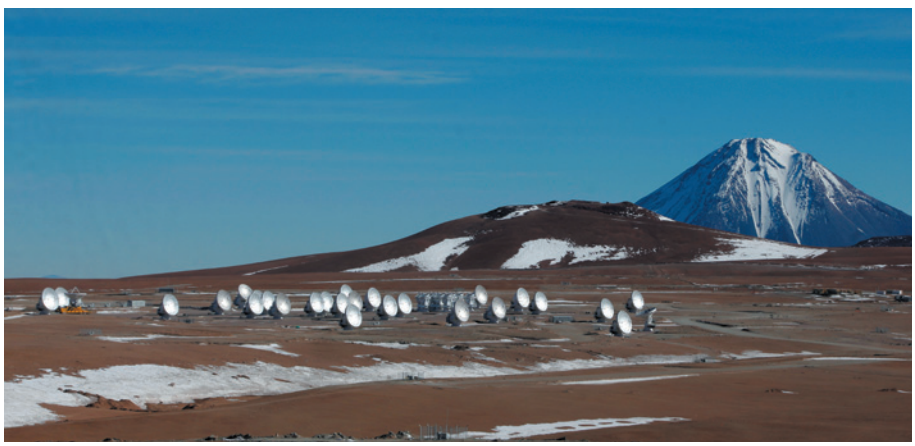
ANDREW W. BLAIN

The Atacama Large Millimeter/submillimeter Array (ALMA) interferometer, which is nearing completion in Chile[1], is revolutionizing observational astronomy. It provides precise views of the internal workings of galaxies by imaging the gas and dust in their interstellar medium at wavelengths of 0.3–3 millimetres. On page 344 of this issue, Vieira *et al.*[2] present some of the first detailed images and measurements of redshifts of distant galaxies obtained by ALMA (Fig. 1). The authors targeted galaxies discovered in a wide-field survey using the South Pole Telescope[3], to find those that are magnified — and so made unusually easy to study — by the 'gravitational lensing' effect of foreground objects*.

The steady discovery of new classes of galaxy, as different windows on the cosmos have become accessible, has been a highlight of astrophysics for decades. The radio, X-ray and far-infrared windows have opened to reveal ever more about the processes at work in both long-known and previously unappreciated types of galaxy. By combining the power of wide-field surveys to discover galaxies and the ability to dissect the galaxies' nature using high-resolution imaging and spectroscopy, an improved understanding of their properties can be obtained rapidly and efficiently.

The heritage of this process dates back to the 1920s with the spectroscopy of diffuse nebulae obtained using the largest optical telescope then available, which led to the measurement of the expansion rate of the Universe. Then came the recognition of radio sources and other active galactic nuclei (AGN) in the 1960s, unambiguously showing cosmic evolution taking place. Wide-field, space-based surveys using the IRAS infrared and ROSAT X-ray satellites several decades ago, and more recently the far-infrared Herschel Space Observatory, mid-infrared WISE and millimetre-wavelength Planck spacecraft, have found classes of unusual and rare galaxies, and clear clues to the general process of galaxy formation and evolution. Ambitious wide-field surveys from the ground, ranging from the Sloan Digital Sky Survey to the recently started Dark Energy Survey, are also driving our view of the properties of galaxies, and enabling unprecedentedly accurate and complete statistical studies.

A fresh opportunity to discover unusual galaxies, magnified by the gravitational influence of foreground objects, has just been provided by a combination of the wide-area, millimetre-wavelength surveys obtained with the South Pole Telescope (SPT) and the imaging and spectroscopic power of ALMA at the galaxies' pinpointed locations. Vieira and colleagues take this opportunity in their study. Their results come from an SPT survey of 1,300 square degrees, an area of sky that blocks out about the same angle as that subtended by a laptop screen in front of its user. The SPT takes images of the sky at three wavebands in the millimetre range, with the primary objective of identifying distant clusters of galaxies by means of the Sunyaev-Zel'dovich effect — the characteristic spectral signal imprinted in these bands on the cosmic microwave background relic radiation from the Big Bang, due to the scattering of this radiation by hot electrons in the clusters[4].



C. PADILLA/ALMA (ESO/NAOJ/NRAO)

Figure 1 | The ALMA array in the Atacama Desert of northern Chile.

*This article and the paper under discussion[2] were published online on 13 March 2013.