

extended helical rod, much like a DNA double helix. Consequently, the cytoplasmic domain can function as both a kinase and an endonuclease. The authors' structural models are provocative, as they suggest that supra-molecular organization is necessary for Ire1p transition to an active, stress-signalling state.

The structure of Ire1p was also reported by another group last year<sup>6</sup>. Although there are clear similarities in the two structures<sup>3,6</sup>, the differences are substantial. Unlike Korennykh and colleagues' proposal that higher-order oligomerization is required for activation of the Ire1p cytoplasmic domain, the earlier structure indicated a requirement for a back-to-back dimer arrangement. This inconsistency probably reflects relatively modest differences in the precise domains selected in each study, although Korennykh *et al.* provide mechanistic support for the validity of their model with detailed biochemical studies. In the rest of my article, however, I will focus on the biology of the cellular response to stress-associated accumulation of unfolded proteins.

Aragón *et al.*<sup>4</sup> demonstrate that, on sensing unfolded proteins in the lumen of the endoplasmic reticulum, Ire1p molecules coalesce into large, interacting clusters, and at the same time their cytoplasmic domain becomes active. But captivating questions in the story of the unfolded-protein response are manifold, and the authors provide a surprising answer to one of the more vexing ones: how do Ire1p clusters interact with the *HAC1* mRNA?

The first clue came with the observation that regions in *HAC1* mRNA outside the sites cleaved by Ire1p are necessary for the stress response *in vivo*, but not for mRNA processing *in vitro*. The authors<sup>4</sup> identify one such key region, which they call the 3' bipartite element (Fig. 1). They find that, in stressed yeast cells, *HAC1* mRNA lacking the 3' bipartite element interacts with Ire1p clusters only weakly, if at all. Consequently, a rather dismal unfolded-protein response is elicited and the stressed cells cannot sustain growth.

Intriguingly, for the 3' bipartite element to direct *HAC1* mRNA to the clusters of activated Ire1p, translation of *HAC1* mRNA must be repressed. Aragón *et al.*<sup>4</sup> provide a satisfying answer to why this might be so: with mRNA processing linked to translational repression, only those mRNAs that contain the inhibitory domain find their way to Ire1p clusters. This paradigm provides the first example of mRNA localization serving as a crucial regulatory switch.

As for the remaining questions, perhaps the most compelling is how *HAC1* mRNAs find their way to activated Ire1p signalling clusters. Aragón *et al.* speculate that *HAC1* mRNAs travel from their cytoplasmic location along cytoskeletal filaments to these signalling sites at the endoplasmic reticulum. This is an attractive idea, and regulation of mRNA localization by the cytoskeleton and molecular motors certainly has ample precedent. But would it mean

that activated Ire1p clusters also serve as sites for the attachment of cytoskeletal filaments?

And, once on the endoplasmic reticulum, what serves as the binding partner for *HAC1* mRNA? After all, the vast majority of mRNA localization signals are recognized by proteins that contain evolutionarily conserved RNA recognition motifs. So it is the complex of mRNA and RNA-binding protein that directs the localization event. Korennykh *et al.*<sup>3</sup> provide intriguing speculation on this question. They propose that conformational changes in Ire1p that allow its clustering and activation also create a direct binding site for *HAC1* mRNA — potentially another remarkable twist in the biology of mRNA localization.

But if activated Ire1p provides both the binding site for the 3' bipartite element and the enzymatic function necessary for the *HAC1* mRNA processing upstream of this element, how do unprocessed *HAC1* mRNAs gain access to activated signalling centres? One possibility is that Ire1p-processed *HAC1* mRNAs are poor Ire1p binding partners, and simply diffuse away. Yet the data presented<sup>4</sup> indicate seemingly stable co-localization of *HAC1* mRNAs with the active Ire1p clusters. Perhaps there are other binding partners for the *HAC1* mRNA on the endoplasmic reticulum. Many mRNAs that don't encode secretory or membrane proteins are localized to the endoplasmic reticulum and are translated on ribosomes bound to this organelle<sup>7</sup>. Given this precedent, might the

unprocessed *HAC1* mRNAs initially bind to separate sites on the endoplasmic reticulum membrane and be rapidly, and reversibly, transferred to Ire1p signalling clusters? The kinetics of surface chemistry would favour this latter possibility, as reactions occur significantly faster when constrained to a two-dimensional surface rather than in the three dimensions of a solution.

From these lines of questioning, one point should be clear. These ground-breaking studies<sup>3,4</sup> have created both fertile territory for research into the regulation of mRNA localization and mRNA-mediated signalling, and opportunities to gain insights into the fundamental mysteries of the cellular response to environmental stress. The unfolding story of the stress response in the endoplasmic reticulum has yielded many a new paradigm; these latest findings give every indication that the store of surprises is far from exhausted. ■

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## CLIMATE CHANGE

# Snakes tell a torrid tale

Matthew Huber

**The discovery in Colombia of a giant species of fossil snake is news in itself. But a wider, more controversial inference to be drawn is that tropical climate in the past was not buffered from global warming.**

As the world uneasily eyes a warmer future, a large community of researchers is investigating the past for the insights it might provide into the likely magnitude of climatic and ecological change. Time intervals in Earth's past, such as the early Palaeogene (between 65 million and 40 million years ago), are known to have been much warmer than today. The presence of fossil crocodiles<sup>1</sup> and palm trees<sup>2</sup> ringing the Arctic and in the hinterlands of Wyoming and Siberia, combined with quantitative records of palaeoclimate, indicate<sup>1–5</sup> above-freezing winter conditions and annual average temperatures in these regions that were often at least 15 °C. But if the extratropics were this warm, how hot were the tropics? Head *et al.* (page 715 of this issue) provide tantalizing clues from an unusual source<sup>6</sup>.

Establishing the magnitude of past variation in tropical climate is a formidable challenge.

Twenty years ago we thought that the tropics cooled as the world warmed (and vice versa)<sup>7</sup>. Ten years ago the consensus became that, compared with modern values, tropical temperatures were at most only slightly warmer during the various hot, 'greenhouse' climates that have occurred over the past 145 million years<sup>8</sup> and that they cooled by at most a couple of degrees during the ice ages. This muted variation in tropical climate is a puzzle: mechanisms that drive climate change at higher latitudes should also substantially affect lower latitudes. In the early Palaeogene, how could the poles be 30 °C or more warmer than they are today if the tropics were only 2 °C warmer?

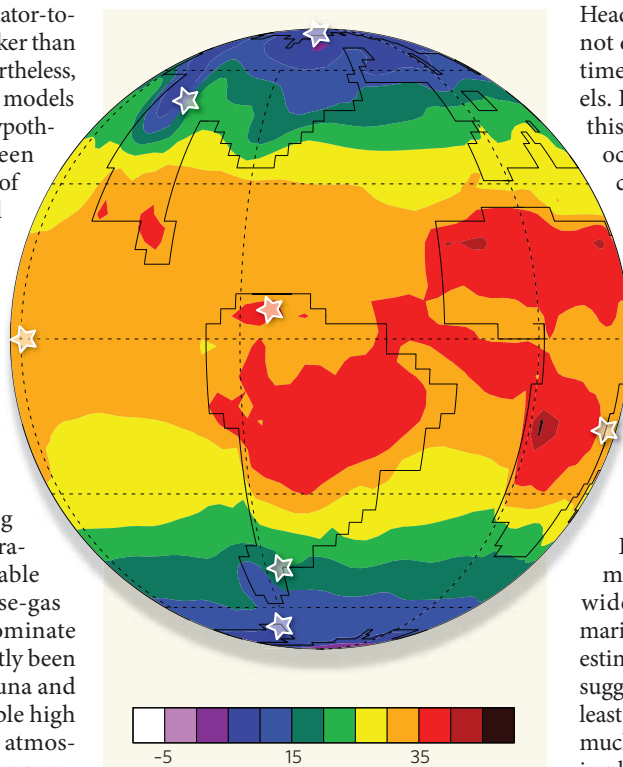
For their part, climate modellers have concluded that hot tropical temperatures, and the high concentrations of greenhouse gases that cause them, are required to reproduce warm extratropics, because standard models and

dynamical theory do not produce Equator-to-pole temperature gradients much weaker than they have been in modern times<sup>9</sup>. Nevertheless, on the basis of the supposition that the models are missing important physics, many hypotheses and novel mechanisms have been proposed that centre on the existence of a 'thermostat' that maintains tropical temperatures at a fixed level<sup>10,11</sup>. These attempts to include new feedbacks have illuminated many dark alleys of climate dynamics, but so far all have been dead ends<sup>10</sup>.

Whether a tropical thermostat exists is fundamentally important for three reasons. The tropics, defined broadly (30° N to 30° S), make up half of Earth's surface area and so play an outsized part in determining past variations in global mean temperature and the sensitivity of this variable to forcing factors such as greenhouse-gas concentrations. The tropics also dominate global biodiversity, and have frequently been considered stable, safe havens for fauna and flora compared with the more variable high latitudes. Finally, because the global atmosphere-ocean circulation is driven by temperature gradients, tropical temperatures provide a linchpin on which the rest of the general circulation depends.

In the past few years, studies<sup>12-14</sup> based on new temperature proxy measurements, and on better-preserved records from established proxies, have produced warmer estimates for the tropics (5–10 °C warmer than modern values) than those drawn from previous work. Debate continues about whether earlier estimates were systematically biased to cool values. One independent line of evidence for an unchanging tropical climate comes from terrestrial palaeotemperature proxies derived from leaf shape, which support the idea that tropical temperatures were near modern values (24–26 °C)<sup>7</sup>. Of course, leaf-derived tropical temperatures could be wrong as well. Head and colleagues<sup>6</sup> show that this may be the case.

In the Cerrejón Formation of Colombia, South America, Head *et al.* have discovered fossil vertebrae aged between 58 million and 60 million years old, estimated to be from eight individuals of the largest species of snake ever found. But what makes the study so intriguing is that the authors relate the animal's immense projected size — 13 metres long and more than 1 tonne in weight — to a minimum annual mean temperature. To do this, they use an empirical relationship between temperature and size derived from modern organisms. The method has a biophysical grounding in the metabolism of large, air-breathing, terrestrial poikilotherms (animals whose internal temperature varies with ambient temperature). Essentially, poikilothermic animals must sustain a minimal metabolism to survive and, making the standard assumption that this metabolic rate scales with temperature, larger



**Figure 1 | Simulation of annual average surface temperatures about 58 million years ago.** Stars indicate the localities for which temperature estimates exist with ages close to those of Head and colleagues' discoveries<sup>6</sup> in the Cerrejón Formation. In each locality, simulated temperatures match well with those estimated from temperature proxy estimates, suggesting that, with reasonable atmospheric concentrations of greenhouse gases, current models can simulate climate at this time. The simulation was carried out with the National Center for Atmospheric Research Community Climate System model (version 3), with boundary conditions for the early Palaeogene and an atmospheric CO<sub>2</sub> concentration of 2,240 parts per million. Temperature proxy reconstructions are from refs 3–6, 12 and 14. Sea surface temperatures derived from oxygen isotopes in planktonic foraminifera that have not been proven to be as well preserved as those reported in refs 12 and 13 have been omitted from the comparison.

poikilotherms must live in warmer environments. This is the case with snakes today. Head *et al.* estimate that the giant snake required minimum temperatures of 32–33 °C, which is 6–8 °C warmer than temperatures reconstructed from floras within the same formation, and much warmer than modern values.

If we assume that Head and colleagues' temperature estimates are accurate, and it is a big assumption, there are major implications. First, there is no tropical thermostat: although negative feedbacks may slow or inhibit tropical warming, they do not provide a hard limit, and theories that predict the existence of thermostats<sup>11</sup> are invalid. Second, by comparing their snake-derived estimate with a palaeotemperature estimate from high-latitude Patagonia,

Head *et al.* find that temperature gradients did not depart markedly from those of modern times, verifying the results of climate models. Indeed, temperatures reconstructed for this age can now be reproduced by coupled ocean-atmosphere models, provided tropical temperatures are as hot as indicated by the new results<sup>6</sup> (Fig. 1).

Third, although the flora and fauna in the Cerrejón Formation were remarkably resilient, and thrived in apparently hotter and wetter conditions than those of any modern rainforest setting, they may have lived near the limit of their tolerance. As Head *et al.*<sup>6</sup> remark, the span of time between 58 million and 60 million years ago was cooler than subsequent intervals, and further warming during the Palaeocene-Eocene Thermal Maximum, around 55.5 million years ago, could have produced widespread heat-death in terrestrial and marine ecosystems<sup>14</sup>. Finally, new temperature estimates from a multiple proxy approach<sup>6,12-14</sup> suggest that global mean temperatures were at least 10 °C warmer than modern temperatures, much warmer than previously estimated. That implies either that global average temperatures were very sensitive to greenhouse-gas forcing, or that concentrations of greenhouse gases were at the upper end of their reconstructed range<sup>15</sup>.

All that said, these implications are based on a new type of proxy: Head and colleagues' findings are the result of probably the first study in 'snake palaeothermometry', and as such must be viewed with caution. Is the empirical link between size and temperature really generalizable and accurate? Could the ability to lose heat be an important limitation for these giant snakes, rendering Head and colleagues' extrapolations moot? Can a few vertebrae truly provide accurate estimates of snake size? Why have similarly giant snakes not been found in other warm intervals?

The findings attest to the resiliency of tropical ecosystems in the face of extreme warming, but more work is clearly necessary. For the moment, however, the burden of proof is on those who argue that the tropics do not warm substantially in a greenhouse world. ■ Matthew Huber is in the Department of Earth and Atmospheric Sciences and the Purdue Climate Change Research Center, 550 Stadium Mall Drive, Purdue University, West Lafayette, Indiana 47907, USA.

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## QUANTUM OPTICS

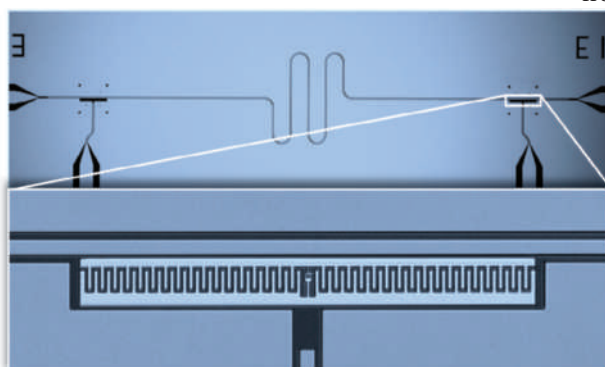
# A shift on a chip

Douglas H. Bradshaw and Peter W. Milonni

**The Lamb shift, a minute change in certain energy levels of quantum systems that was first measured in atomic hydrogen some 60 years ago, has now been observed in a solid-state superconducting system.**

The emission and absorption of light by atoms can be significantly affected by their environment. For many years, physicists have studied how atoms behave in cavities that confine light and restrict the frequencies with which the atoms interact. Cavity quantum electrodynamics (cavity QED) experiments, which examine how light and matter interact in a cavity, can be designed such that an atom is well described as a two-state system (or ‘qubit’) interacting with a single light frequency in a nearly lossless cavity. It has been observed, for instance, that the frequency of the light emitted (or absorbed) in an atomic transition can be altered by a cavity. More recently, similar effects have been observed in circuit QED, in which pieces of solid-state superconducting systems acting as qubits are embedded in on-chip circuits that are, in effect, one-dimensional cavities<sup>1,2</sup>. Writing in *Science*, Fagnier *et al.*<sup>3</sup> now report experiments in which one of the most studied effects of QED in atomic physics — the Lamb shift — has been measured in circuit QED (Fig. 1).

The Lamb shift in atomic hydrogen was famously measured some 60 years ago<sup>4</sup>. Experiments showed that, in a vacuum, one of the atom’s energy levels is shifted very slightly from the value predicted when the effect on the electron of the electromagnetic vacuum is ignored. The corresponding shift in the frequency of the transition of the electron to the ground state, relative to the unshifted frequency ( $\nu$ ), is only about  $4 \times 10^{-7}$ . This shift can be attributed largely to the interaction of the hydrogen atom with a continuum of electromagnetic frequencies, all in the vacuum state. Quantum fluctuations of this vacuum field, associated with the emission and absorption of ‘virtual’ photons, cause the electron to undergo fluctuations that change its energy level from that predicted when it is assumed to interact only with the nucleus.



**Figure 1 | Lamb shift on a solid qubit.** The image shows the resonator (top) used in the experiments of Fagnier *et al.*<sup>3</sup> to detect a tiny shift in the transition frequency — the Lamb shift — of a solid-state superconducting qubit (bottom). The qubit of dimensions  $0.3 \text{ mm} \times 30 \mu\text{m}$  is embedded in the resonator at the position indicated by the boxed area (top right). (Image taken from ref. 1.)

But cavity QED has allowed for conceptually simpler experiments in which atoms interact with only one electromagnetic-field frequency. If this frequency is exactly tuned to the atomic resonance, a quantum of energy can flow back and forth between an atom and the electromagnetic field at a rate known as the Rabi frequency ( $\Omega$ ). By introducing a ‘detuning’ ( $\Delta$ ) between the atomic-transition frequency and the field frequency, one can change the nature of the atom–field interaction. When the ratio  $\Delta/\Omega$  is large, the observable effect of the field on the atom is to shift the atomic-transition frequency rather than to cause energy to oscillate to and fro between the atom and the field. The shift is proportional to  $(q + 1/2)/\Delta$ , where  $q$  is the number of photons in the cavity. The Lamb shift occurs when the cavity is devoid of photons ( $q = 0$ ), and is thus associated with quantum fluctuations of the vacuum state of the field. This Lamb shift for a two-state atom was first measured in a cavity QED experiment<sup>5</sup>; Lamb shifts amounting to about  $10^{-8} \nu$  were measured for the smallest detunings.

In circuit QED, a qubit is a superconducting two-state system based on the Josephson junction — two superconductors separated by a thin insulator across which electron pairs

can tunnel. In the very simplest approximation, two parallel junctions can form a qubit with a transition frequency controllable by a magnetic field. The cavity resonator in circuit QED is effectively a one-dimensional waveguide formed by a superconducting structure patterned on a silicon chip. An electromagnetic field in such a resonator induces transitions in a qubit inside it if its frequency is close to the qubit transition frequency. Then the system can be described in much the same way as a qubit interacting with a single field frequency in cavity QED.

In their experiments, Fagnier and colleagues<sup>3</sup> measured  $\nu$  and the qubit–field coupling constant, which describes the strength of the interaction and thus determines the Lamb shift. They then determined the Lamb shift from the difference between  $\nu$  and the measured, shifted qubit transition frequency.

The detuning was varied by changing the magnetic flux through the qubit circuit. For the largest detunings, the authors obtained an excellent fit of the measured Lamb shifts to the simplified theoretical predictions based on the two-state model of the parallel Josephson junctions; a more accurate theory that accounts for deviations of the Josephson pair from a two-state system gave an excellent fit for all detunings.

A notable difference between these Lamb shifts and those in cavity QED is their magnitude — approximately  $0.014 \nu$  at the smallest detunings. These relatively large shifts reflect a strong qubit–field interaction resulting from the large electric dipole moment characterizing the qubit as well as the large vacuum-field strengths possible in the micrometre-scale resonators used in circuit QED. The strong coupling (large Rabi frequency) inferred from the Lamb-shift experiments directly illustrates one reason for the growing interest in circuit QED in connection with quantum computing<sup>6–8</sup>, which requires that information between a photon and a qubit be exchanged rapidly compared with the rates at which any other effects, such as the escape of the photon from the resonator, cause information about the qubit state to be lost.

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