

points (Fig. 1). Strikingly, the stage classically viewed as the phylotypic stage in zebrafish is marked by the expression of the evolutionarily oldest transcriptome set, whereas earlier and later stages (including adult stages) express comparatively younger transcriptomes. Importantly, the authors identified a similar pattern in published microarray data for other organisms (fruitfly, mosquito and nematode), suggesting that their findings are generally applicable.

By revisiting the subjective anatomical comparisons of classical embryology using quantitative genomics, these two studies<sup>1,2</sup> have revived the concept of the phylotypic stage with much-needed objectivity. Although they take very different approaches, it is remarkable that both studies identify genomics signatures of the phylotypic stage — in short, the phylotypic stage sees expression of the oldest gene set, which is maximally conserved across species. These results reinforce the notion that animal body plans emerged using novel signalling and regulatory genes that arose at the inception of multicellular animal life, and that, once established, the gene-expression patterns underlying the specification of the different body plans have remained fairly invariant.

This newly acquired molecular legitimacy does not, however, explain what establishes and maintains the hourglass pattern. Kalinka *et al.*<sup>1</sup> found that the hourglass pattern of gene-expression variation is best explained by the action of natural selection. This echoes the proposition that mechanistic constraints pertaining to the building of a shared body plan might explain the conservation observed at the phylotypic stage<sup>4,5</sup>.

A body plan is a particular organization of anatomical rudiments. The early embryonic specification of these rudiments, independently of one another, might take different evolutionary roads. But the assembly of these elements into a functional body plan might require a tight and constrained orchestration of gene expression, reflected in the hourglass waist. Once coherently assembled, the connected elements make a stable evolutionary substrate for an organism to explore new morphogenetic directions within the realm of the established body plan.

With this work<sup>1,2</sup>, new avenues open up in addressing a long-standing debate. Future comparative studies of the gene-regulatory networks and developmental events underlying the phylotypic stage will certainly shed light on the *raison d'être* of this peculiar embryonic period. ■

**Benjamin Prud'homme and Nicolas Gompel** are at the Institut de Biologie du Développement de Marseille-Luminy, Parc scientifique de Luminy, case 907, 13288 Marseille cedex 9, France. e-mails: benjamin.prudhomme@univmed.fr; nicolas.gompel@univmed.fr

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## QUANTUM PHYSICS

# Hot entanglement

**Quantum entanglement has been observed at low temperatures in both microscopic and macroscopic systems. It now seems that the effect can also occur at high temperatures if the systems are not in thermal equilibrium.**

VLATKO VEDRAL

Quantum physics is usually thought to apply to small systems at low temperatures. A standard example would be the quantum dynamics of an electron in a hydrogen atom. Atomic orbits of electrons are roughly an ångström in size — that is, comparable with electronic de Broglie wavelengths, which characterize the extent over which electrons display a quantum wave-like behaviour. More importantly, at low temperatures, the typical energies characterizing electronic jumps are hundreds of times larger than the thermal energy of the environment to which the system is exposed. This, in turn, means that the noise due to the environmental temperature is negligible compared with the typical electronic-jump energies, and therefore that the noise does not spoil the system's quantum behaviour. Writing in *Physical Review Letters*, Galve *et al.*<sup>1</sup> show that, contrary to the common view, a macroscopic system at high temperatures can also sustain quantum features.

It is interesting that similar considerations about the restriction of quantum phenomena to small systems at low temperatures can be made about the most quantum of all quantum effects: quantum entanglement. The term entanglement was coined by Erwin Schrödinger, who described it as “the characteristic trait of quantum mechanics”. It refers to a state of two or more quantum systems in which the systems are so intertwined that they behave like one — it is actually a mistake to think of the subsystems separately. Quantum systems become entangled when they interact with one another. In the past decade, extensive theoretical and experimental research<sup>2</sup> has shown that, no matter what systems we look at, a general rule says that if the interaction strength between the subsystems is larger

than the thermal energy due to their coupling to the environment, entanglement should exist between these subsystems provided that they are in thermal equilibrium with the environment.

Now Galve *et al.*<sup>1</sup> prove that this relationship between temperature and entanglement is not valid for systems that are not in thermal equilibrium. Here, in fact, the news is very good for entanglement. The authors predict that nanomechanical oscillators can be entangled at much higher temperatures than previously thought possible.

The basic intuition behind this result is as follows. When a system is not in thermal equilibrium, the temperature no longer provides the relevant energy scale against which to compare the system's quantum behaviour. What matters instead is an effective temperature, which can be much lower than the absolute one. This effective temperature is obtained by multiplying the absolute temperature by the rate at which the system approaches equilibrium divided by the driving frequency, the frequency of the signal with which the system is made to oscillate. Galve and colleagues demonstrate that this new condition for entanglement — that the interaction between subsystems should be compared with the thermal energy at the effective temperature — holds quite generally and is intuitively pleasing. It says that if we can drive the system to oscillate within a shorter timescale than the time it takes to reach thermal equilibrium, then an entangled steady state can be attained at higher temperatures than the absolute one.

The actual system that Galve *et al.* investigate — two macroscopic (harmonic) oscillators coupled to each other — is important because a number of laboratories are currently working with similar systems. For instance, Aspelmeyer and colleagues<sup>3</sup> have created quantum states

in a movable nanomechanical mirror that is a microgram in weight. The high-temperature entanglement envisaged by Galve *et al.* could be achieved by coupling two such mirrors to one another. I and colleagues<sup>4</sup> have shown, using a different theoretical approach to that of the present study<sup>1</sup>, that such nanomechanical entanglement should persist at temperatures of about 20 kelvin. The hope now is that, by using Galve and colleagues' new ideas, the temperature can be pushed upwards to, say, 100 kelvin. This would eliminate the current need for expensive and elaborate cryogenics to cool the oscillators.

So, OK, we can in principle entangle nanomechanical oscillators at high temperatures. Physicists will no doubt get excited because this realization will strengthen the evidence for the universality of quantum mechanics. But why should anybody else care?

The most exciting macroscopic and 'hot' non-equilibrium systems we know are, of course, the living ones. We can, in fact, view any living system as a Maxwell's demon, maintaining life by keeping its entropy low against the environmental noise — that is, by being

far from equilibrium. The father of thermodynamics, Ludwig Boltzmann, himself viewed living systems in this way. Here is what he said on the matter: "The general struggle for existence of living beings is therefore not a fight for energy, which is plentiful in the form of heat, unfortunately untransformable, in every body. Rather, it is a struggle for entropy that becomes available through the flow of energy from the hot Sun to the cold Earth. To make the fullest use of this energy, the plants spread out the immeasurable areas of their leaves and harness the Sun's energy by a process as yet unexplored, before it sinks down to the temperature level of our Earth, to drive chemical syntheses of which one has no inkling as yet in our laboratories."

We have actually learnt a little bit about that "unexplored" process — photosynthesis — since Boltzmann. And as it happens, recent experiments<sup>5</sup> show a quantum effect leading to entanglement<sup>6</sup> in some photosynthetic complexes. Such entanglement might yield an increased efficiency in the transfer and processing of energy in photosynthesis. The overall mystery of photosynthesis remains, but there is now evidence that quantum physics has

something to do with it in a profound way. And there are other instances in biology in which quantum entanglement could be important<sup>7</sup>. If this is a general trend in the biological world (and it is a big 'if'), maybe Boltzmann was only half right: could it be that life does not just keep its entropy low, but rather, also aims to keep its quantum entanglement high if and when needed for an increased efficiency of energy transport? For now, the jury is still out. ■

**Vlatko Vedral** is at the Clarendon Laboratory, University of Oxford, Oxford OX1 3PU, UK, and the Centre for Quantum Technologies, National University of Singapore, 117543 Singapore.

e-mail: vlatko.vedral@qubit.org

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themselves (Fig. 1). For instance, a comparable proportion of a cell population expressing endothelial-cell markers and a population of neighbouring tumour cells harboured three or more copies of either the *EGFR* gene or other parts of chromosome 7. Such cell populations also shared a mutated version of the oncogene *p53*. Another indicator of the tumour origin of some tumour-vessel endothelial cells is that, as well as expressing characteristic endothelial-cell markers — such as von Willebrand factor and VE-cadherin — they expressed the non-endothelial, tumour marker GFAP.

The researchers also present evidence that tumour-derived endothelial cells arise from tumour stem-like cells. They find that a glioblastoma cell population that could differentiate into endothelial cells and form blood vessels *in vitro* was enriched in cells expressing the tumour-stem-cell marker CD133. Moreover, Wang and colleagues show that a clone of cells derived from a single tumour cell, which expressed CD133 but not VE-cadherin, was multipotent: *in vitro*, the cells differentiated into both neural cells (which eventually form tumour cells) and endothelial cells.

On being grafted into mice, these cells formed highly vascularized tumours. Moreover, even the progenitor cells from these tumours continued to form tumours and tumour-derived endothelial cells, suggesting that the multipotential characteristic had been maintained. Ricci-Vitiani *et al.* gained further insights by generating undifferentiated cell aggregates from human tumour-derived CD133-expressing cells and grafting them into mice. The internal vessels of the resulting tumours expressed human vascular markers,

## CANCER

# Tumour stem cells switch sides

**Tumour stem cells are proposed to be the source of tumour cells. It now emerges that they also give rise to the endothelial cells that line the tumour vasculature, mediating tumour growth and metastasis. SEE LETTERS P.824 & P.829**

VICTORIA L. BAUTCH

To grow, solid tumours need a blood supply. They recruit new blood vessels mainly by inducing the sprouting of endothelial cells from external vessels and promoting the cells' migration into the tumour. This ability, called the angiogenic switch, is required for tumour cells to invade surrounding tissue and metastasize to distant sites — the deadly hallmarks of cancer<sup>1</sup>. In this issue, Wang *et al.*<sup>2</sup> and Ricci-Vitiani *et al.*<sup>3</sup> show that, in addition to recruiting vessels from outside, brain tumours produce endothelial cells for vessel formation from within.

Recent research in tumour biology has focused on two main concepts. According to the first concept — vasculogenic mimicry — some tumour cells take on certain characteristics of vascular endothelial cells and line the tumour's blood vessels<sup>4</sup>. The origin of such tumour cells is ill-defined: whereas one study<sup>5</sup> suggested that tumour stem cells show vasculogenic mimicry, it is generally thought that

tumour cells in the immediate environment of the nascent vessel are co-opted for the purpose. The co-opted cells are thought to retain most of their tumour-cell characteristics while acquiring a limited number of endothelial-cell features.

The second concept — that some tumours originate from a tumour stem cell — has been controversial. According to this idea, tumour stem cells are both refractory to most traditional therapies and capable of regenerating the tumour following treatment. The deadly brain tumour glioblastoma is thought to arise from tumour stem cells<sup>6</sup>.

Wang *et al.*<sup>2</sup> (page 829) and Ricci-Vitiani *et al.*<sup>3</sup> (page 824) now reveal data that are relevant to both concepts, and provide strong evidence that a proportion of the endothelial cells that contribute to blood vessels in glioblastoma originate from the tumour itself, having differentiated from tumour stem-like cells.

Both groups note that a subset of endothelial cells lining tumour vessels carry genetic abnormalities found in the tumour cells