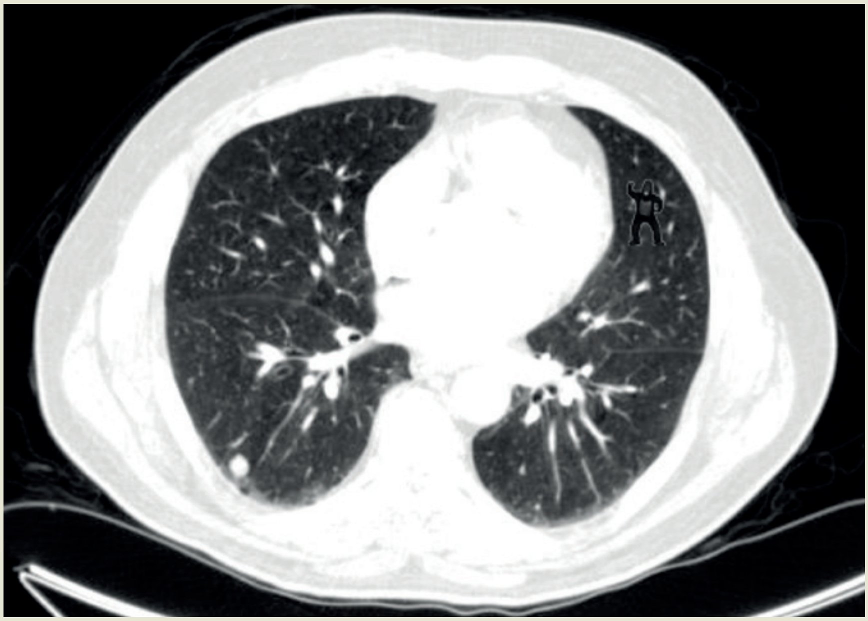
PSYCHOLOGY

Spot the gorilla



PSYCHOL. SCI.

If it's not relevant you may miss it. This phenomenon of inattentional blindness is well documented; in a classic study, most observers asked to monitor a video of a ball game missed a gorilla on the court. But would experts also miss a gorilla? Yes, according to a study on the subject (T. Drew *et al. Psychol. Sci.* http://doi.org/m9s; 2013).

The authors asked 24 radiologists to search for lung nodules (small, bright circles) in several chest scans; the final scan (pictured) contained the image of a gorilla, 48 times larger than an average nodule. Surprisingly, and perhaps worryingly, 83% of the experts missed the gorilla. It is somewhat reassuring that the miss rate among non-medical observers performing the same task was even higher. **Sadaf Shadan**

NANOTECHNOLOGY

Tiny thermometers used in living cells

Nanometre-scale thermometers that operate with millikelvin sensitivity have now been made from diamond crystals. The devices have been used to measure temperature gradients in living cells. SEE LETTER P.54

KONSTANTIN SOKOLOV

Despite many promising studies, taking temperature measurements of environments at nanometre-scale resolution remains a formidable challenge. On page 54 of this issue, Kucsko *et al.*[1] report a precious solution to this problem: a thermometer based on diamond nanocrystals, also known as nanodiamonds. This sensing tool could have many applications, ranging from studies of cell biology to measurements of nanoscale chemical reactions.

Temperature affects diverse physical phenomena. For example, changes in Earth's temperature patterns can lead to the formation of severe storms, droughts and floods. Temperature governs the kinetics, activation and equilibrium states of chemical reactions. And in humans, body temperature is precisely controlled, so that any deviation from the normal range triggers a cascade of biomolecular mechanisms to restore the body's equilibrium. Scientists have therefore developed a range of precise temperature-measuring tools — from satellites to infrared cameras, and a variety of more familiar thermometers — to measure temperature over length scales from multiple kilometres to submillimetres. But how can we measure temperature at length scales of a few micrometres, or a few tens of nanometres?

Kucsko and co-workers' approach is to use the unique properties of electron spins associated with single-nitrogen-atom impurities in diamonds. The presence of a nitrogen atom in a diamond's carbon-atom lattice creates a point defect called a nitrogen vacancy (NV) centre, in which the nitrogen and a vacancy replace two neighbouring carbons. The ground state of an NV centre is split into two energy levels: the spin state of the lower level is 0, whereas that of the higher level is 1. The energy difference between the levels, known as the ground-state energy gap, is highly sensitive to temperature because it varies in response to thermally induced lattice strains. The principle of diamond thermometry is based on accurate measurement of changes in the transition frequency associated with this energy gap — the microwave frequency that corresponds to the energy difference between the lower and higher levels.

In their technique, Kucsko and colleagues used green light to excite electrons in NV centres, which then decayed to the ground state by emitting red fluorescence. The intensity of the fluorescence depends on the spin state of the NV centres. The authors also irradiated their nanodiamonds with microwaves to modulate the electron occupancy of the ground spin states 0 and 1, and determined the occupancy of the states from the observed fluorescence. They then used this information to work out the changes in the ground-state energy gap that are associated with temperature variations.

The researchers first used an isotopically pure (carbon-12 isotope) bulk diamond sample to determine the ultimate sensitivity of their NV-based thermometry. In this system, they detected temperature changes with an accuracy of up to 1.8 millikelvins under ideal experimental conditions. Similar sensitivity has just been reported by other groups[2,3] using analogous experimental techniques and conditions.

However, Kucsko *et al.* went further by demonstrating how nanodiamond thermometers can measure the temperatures in living cells (Fig. 1). They used a clever nanowire-assisted delivery method[4] to position nanodiamonds and gold nanoparticles inside the cells. When excited by laser light, the gold nanoparticles acted as localized heat sources. By using their technique to measure sub-kelvin temperature changes inside a single cell, the authors directly monitored the amount of heat generated by a single gold nanoparticle that was required to kill the cell.

Kucsko and colleagues' nanodiamond temperature sensors have high spatial resolution together with sub-kelvin thermal sensitivity, chemical inertness, biocompatibility and the

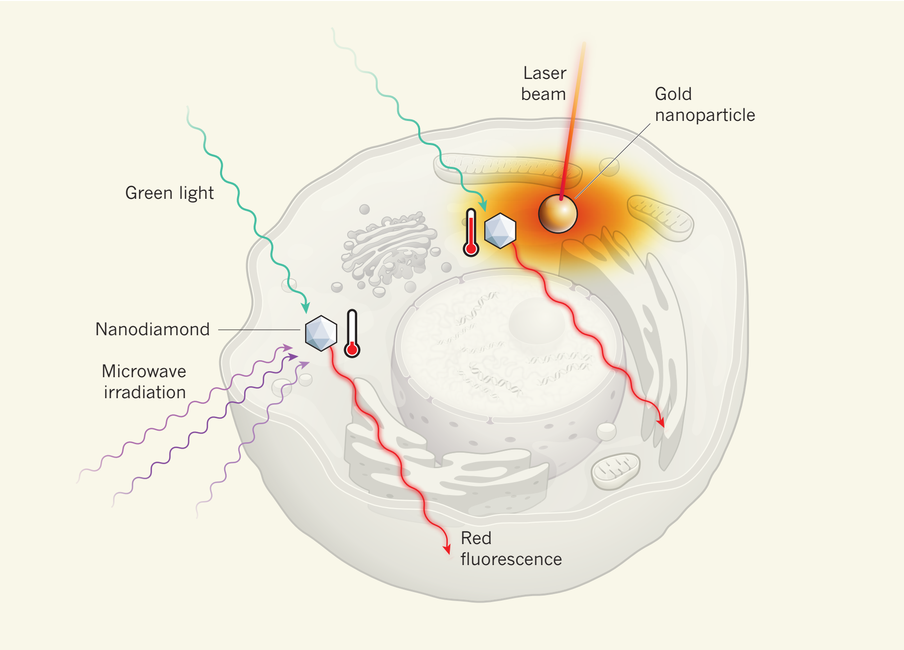


Figure 1 | Temperature measurements in living cells. When diamond-lattice defects known as nitrogen vacancy (NV) centres are excited by green light, they emit red fluorescence. Kucsko *et al.*[1] inserted nanodiamonds into single living cells, and irradiated them with microwaves to modulate the electron occupancy of spin states in NV centres, and with green light. By measuring the fluorescence from these centres, the authors established the electron occupancy of the spin states, and so determined changes in the ground-state energy gap (the microwave frequency that corresponds to the energy difference between spin states) that are associated with temperature variations. In this way, they measured the temperature gradient generated when a gold nanoparticle in the cell was heated by a laser beam, achieving sub-kelvin sensitivity.

best-known thermal conductivity of all solid materials. This is an ideal blend for a nanothermometer. Furthermore, temperature sensing with nanodiamonds could be extended to *in vivo* applications if a different method for fluorescence excitation were adopted: microwave excitation of electronic spin states has already been carried out in animals[5], and the use of 'two-photon' excitation would allow the analysis of deeper tissue than could be achieved with the present method.

Because nanodiamonds are discrete objects, however, the authors' method can take measurements only at distinct locations, rather than taking continuous measurements of a temperature field. Furthermore, the method monitors temperature variations rather than absolute temperature. The authors suggest that this limitation could be overcome by using ensembles of nanodiamonds or diamond samples in which the lattices have low strain, either of which would reduce the experimental variations that currently limit absolute temperature from being measured. At present, the technique also has a fairly low temporal resolution of tens of seconds. This is sufficient for measurements of many biological processes, such as changes in gene expression, but is too slow for studies of temperature effects in faster processes, for example the initial steps of signal transduction, or neural activity.

How might this new tool further our understanding of human cell biology, or enable biomedical advances? Most human cells are 10–20 micrometres in size and are highly compartmentalized by internal membranes that separate cellular organelles. These organelles create multiple micrometre-sized reactors in which a plethora of energy-producing and energy-absorbing reactions occur. The reactions generate intracellular temperature gradients on micrometre and submicrometre scales that, in turn, influence other cellular biochemical reactions. Furthermore, external biochemical signalling and environmental changes activate molecular responses inside cells that can lead to corresponding changes in intracellular temperature gradients. The ability to measure intracellular temperature precisely would therefore provide an invaluable tool for cellular biophysicists, potentially allowing cellular behaviour and characteristics to be manipulated by controlling the temperature within, or close to, cellular organelles.

Kucsko and co-workers' technique could also open up many other intriguing topics for research, including the thermal modulation of immune responses[6], molecular mechanisms of therapeutic tissue preservation induced by local cooling[7], the role of subcellular temperature gradients in cell function[8], and cell resistance to hyperthermia treatment[9] (deliberately induced elevated body temperature, used, for example, as anticancer therapy). When it comes to measuring temperature, it may be that diamonds are a scientist's best friend. ■

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CANCER

Angiogenic awakening

Metastatic tumour cells often remain dormant for years. New findings suggest that endothelial cells lining blood vessels have a central role in regulating the transition from dormancy to metastatic growth.

NETA EREZ

The primary cause of cancer-associated deaths is the metastasis of a tumour to distant organs. Advanced metastatic cancers are mostly incurable, and available therapies can only prolong life to a limited extent. In many tumour types there is a long lag between the arrival of cancerous cells at distant locations and their colonization of an organ, such that the formation of clinically evident metastases can take months to decades. This prolonged dormancy suggests that disseminated tumour cells must overcome growth-inhibiting signals from their new local environment in order to take over the metastatic organ[1,2]. The role of the microenvironment in supporting tumour growth at the primary site is well documented[3], but the role of the metastatic microenvironment