were small with a few much larger ones. This pattern often arises in processes in which cell growth or loss are interconnected. Using techniques to monitor cell division (a proliferation assay and intravital microscopy), the authors observed how the network of mammary ducts undergoes local formation and loss of side branches of the ducts, which was consistent with the cyclic turnover of the mammary stem cells and correlated with the various stages of the oestrous cycle of each mouse. The mathematical model generated by the group estimated that each stem cell supports only a few non-renewing progenitor cells, consistent with the early loss of many clones.

Some mutant clones survive by chance and expand beyond the stem-cell unit, forming cohesive fields of mutant cells that span large parts of the ductal epithelial network. This expansion predisposes the tissue to tumour transformation.

However, the linear, ribbon-like organization of the cells in the ducts eventually restricts further clone expansion. This architecture limits the space available for mutant cells to spread and forces them into a narrow, confined area, which makes it more difficult for these clones to outcompete neighbouring cells and colonize larger regions of the epithelium. The turnover of side branches mediated by the oestrous cycle acts as a geometric constraint, further limiting the ability of mutant clones to expand, thereby providing another layer of protection against uncontrolled colonization by mutant cells.

Ciwinska and colleagues' findings suggest that following the acquisition of neutral or oncogenic mutations, surviving clones from the stem-cell compartment undergo limited short-term spread, largely restricted to the stem-cell descendant cells. However, the influence of the oestrous cycle drives rapid clonal expansion and increases susceptibility to tumour formation, highlighting the key role of hormonal influences and tissue dynamics in breast-cancer susceptibility.

Clinically, this discovery underscores the importance of early detection of clones that carry oncogenic mutations and the monitoring of their expansion trends across menstrual cycles, particularly in at-risk individuals. Integrating current hormonal profiles with the detection of oncogenic mutations in DNA from cancer cells that are shed into the bloodstream, called circulating tumour DNA, or potentially from cells shed in breast milk, might enhance risk assessment and improve treatment outcomes.

Furthermore, Ciwinska and colleagues' findings extend beyond the mammary gland, providing insights into how hormonal regulation might influence clonal dynamics in other reproductive organs such as the endometrium, uterus and ovaries. The authors' research highlights the interaction between oncogenic mutations and cyclic oestrogen levels — a factor that has a key role in these tissues.

However, translating these findings from mouse models to human breast tissue requires a consideration of several key differences. Crucially, the structure of the mammary gland varies notably between mice and humans. Mouse mammary glands are relatively simple, consisting of a branched ductal system without extensive components called lobuloalveolar structures. By contrast, human breast tissue is more complex, featuring lobules and alveoli that differentiate into milk-producing cells[8]. Hormonal regulation and the oestrous or menstrual cycle also differ markedly between mice and humans, because oestrogen fluctuations during the mouse oestrous cycle are less pronounced than those in humans. Differences in progesterone levels might also affect the cellular dynamics of the mutated clones.

Validating these observations in human studies is therefore crucial. In the future, integrating data on hormonal cycles at the time of tissue collection with the presence and behaviour of oncogenic clones in breast-tissue samples detected by techniques such as genome sequencing would aid in characterizing these clones over time and offer insights into their potential for tumour transformation.

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The author declares competing interests; see go.nature.com/475wsds for details.

Metrology

Countdown to a nuclear clock

Adriana Pálffy & José R. Crespo López-Urrutia

An ultra-precise laser synchronized to one of the world's most precise clocks has been used to excite rapid nuclear oscillations — promising a timekeeper that could help to tackle fundamental questions about the Universe. **See p.63**

The electrons in atoms can transition between different energy levels, often emitting or absorbing radiation, and the frequency of this radiation can be used to measure time. This principle is the basis for atomic clocks, the incredible timekeeping precision of which is made possible by specialized lasers known as frequency combs. Transitions in atomic nuclei could enable even more precise timing, but the range of frequency combs does not extend to nuclear transitions — with the notable exception of one in the isotope thorium-229. On page 63, Zhang *et al.*[1] report that they have driven this unique transition with a custom-built frequency comb, taking a giant step towards nuclear clocks that could track even the slowest drifts in the fundamental constants that govern the physical world.

Measuring time has a long history of ingenuity: from counting phases of the Moon to the inventions of the pendulum and the quartz oscillator. The current global standard for timekeeping is a type of atomic clock that is based on a microwave-frequency transition in a caesium atom. These exquisite machines are synchronized precisely across continents to at least the sixteenth digit, enabling space missions and helping people to navigate using GPS that is accurate to within one metre.

A different type of atomic clock uses transitions that emit light in the optical — rather than the microwave — range. Optical clocks offer more precise timekeeping than is possible with a caesium clock. Transitions in different ions and atoms are used for optical clocks, and their oscillation frequencies are compared with each other and with the caesium clock by means of frequency combs. These are laser systems that synchronously emit light at millions of discrete frequencies, such that their spectra resemble long combs with teeth that have even, precisely known spacing. The spectra are similar to the sound spectrum produced by simultaneously hitting one million keys on an enormous,

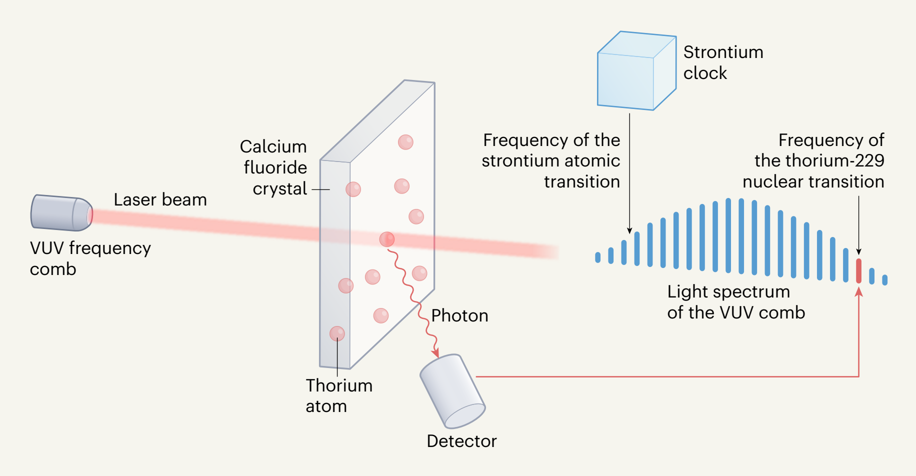

Figure 1 | Synchronized timekeepers. Atomic nuclei of the isotope thorium-229 embedded in a transparent calcium fluoride crystal are excited at precise energies by vacuum ultraviolet (VUV) light from a custom-built VUV 'frequency comb' designed by Zhang and colleagues[1]. Frequency combs are specialized lasers that produce light spectra made up of equidistant, precisely known frequencies. When excited, the thorium nuclei emit photons, producing a signal that can be detected, and that could stabilize the world's most accurate clock. The authors tuned their comb to excite the thorium-229 nuclear transition and to compare the frequency of this transition with that of an optical clock based on strontium atoms[2].

perfectly tuned grand piano. Any optical frequency can be tuned to the nearest comb tooth.

The record for the most accurate clock is currently held by an optical clock that is made from strontium atoms and that is largely insensitive to external perturbations[2]. At present, this is about 100 times more precise than the standard caesium clock.

If atomic transitions are so successful as timekeepers, what about the atomic nucleus, which is 100,000 times smaller than the average atom and therefore less susceptible to the effects of its environment? Nuclear transition frequencies are typically at least 10,000 times higher than those of atomic transitions, but thorium-229 is the exception: with a slight rearrangement of its protons and neutrons, it needs just 8.4 electronvolts (eV) to jump from the lowest energy (ground) state to a long-lived excited state. This energy is uniquely small in terms of the nuclear and electromagnetic forces that keep nuclei together. Thus, once operating, an ultra-precise nuclear clock could reveal one of the Universe's secrets as follows. Are nuclear and electromagnetic forces always constant, or do they slowly drift in time[3] owing to mechanisms that have not yet been determined?

When researchers first started to investigate whether such questions could be answered using this transition, they based their studies on previous measurements[4,5] suggesting that the required energy was 3.5 eV, which implied that the shift could be driven by conventional lasers. Subsequent measurements[6] instead inferred a difference of approximately 7.8 eV, an energy that falls in the vacuum ultraviolet (VUV) spectral region and could also trigger the atom to release an electron instead of radiation (electron release being a much faster, and unwanted, process). Moreover, reaching this energy with lasers is extremely tricky. Yet the prospect of a nuclear clock remained tantalizing.

As part of this endeavour, Zhang and colleagues' impressive feat is the result of a truly global collaboration. One of the first steps involved finding a material in which to embed the thorium-229 nuclei — ideally one that was transparent to VUV radiation and which evaded the unwanted electron emission. At least two teams were working towards this goal, one of which was in Austria, including three of the authors involved in the present paper. Through dedicated crystal-growing expertise, this group succeeded in making calcium fluoride crystals fulfil the brief.

These crystals were used last year in an experiment at CERN, Europe's particle-physics laboratory near Geneva, Switzerland[7]. The team there implanted excited thorium-229 ions into the calcium fluoride crystals in sufficient quantities for the emitted photons to be detected directly using a VUV spectrometer. This study improved the accuracy of the photon energy estimate, putting it at 8.3 eV — and accelerating the race for the development of a laser that could excite this transition.

During this time, a German group had built a powerful VUV laser capable of this task, and these scientists came together with the Austrian team of crystal-growers to achieve the first laser excitation of the nuclear transition in thorium-229 (ref. 8). In doing so, they reached an accuracy that brought them one step closer to optical frequency metrology.

In the meantime, other authors involved in the present work had developed a VUV frequency comb that could excite the nuclear transition and be simultaneously synchronized with a nearby optical clock paced by strontium atoms[2]. Zhang and colleagues brought the Austrian crystal set-up to the United States, where they drove the excitation with their VUV frequency comb — and history was made. The authors showed through repeated experiments that this frequency comb could excite the nuclear transition and read out its frequency in relation to that of the strontium transition (Fig. 1). The nuclear-excited state they observed had a lifetime of about 10 minutes, which implies that the system could be used to produce a clock ticking with 2-petahertz frequency (1 PHz is 10^{15} Hz) but with microhertz uncertainties.

Zhang *et al.* found seven transitions in total, five of which were expected, owing to an energy-level splitting that arises from the charge distribution of the nucleus interacting with the strong intrinsic electric fields of the crystal. These transitions were centred around a frequency of 2 PHz, which the authors could pinpoint with 12-digit accuracy — 6 digits short of the strontium record. Any hope of higher accuracy is currently complicated by the width of the comb teeth, which are broadened by the procedure through which they are generated. For metrology purposes, further improvements will be necessary to narrow these teeth, possibly by transferring existing techniques[9] from the optical to the VUV frequency range.

What's next? Although the exact transition frequency might depend on the properties of the calcium fluoride host, even the tiniest crystals can accommodate a large number of thorium-229 atoms. This makes it possible to take an average over many of their nuclear transitions and obtain reproducible frequency values. More-compact VUV frequency combs than those reported by Zhang and colleagues could enable the fabrication of small, stable clocks that have many potential applications. The excited thorium-229 nucleus could also be used as a quantum bit (qubit) to store and process quantum information.

A single, trapped thorium-229 ion could also be used to build a VUV nuclear clock that would be less sensitive to its environment than are analogous existing optical atomic clocks. One exciting prospect involves monitoring how the transition frequency of the nuclear clock varies over time. This could reveal hypothetical tiny changes in the fine structure constant (quantifying the strength of the electromagnetic interaction between charged particles) as well as in the coupling between nuclear particles, all of which will motivate searches for new physics[2,3]. Zhang and colleagues' astonishing achievement therefore promises many fascinating future finds – and caps three decades of fantastic research.

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The authors declare no competing interests.

Cardiovascular biology

Heart is put at rupture risk by damage-bordering cells

Kory Lavine

After a heart attack, cardiac muscle cells at the border between injured and healthy tissue instigate an inflammatory response, which spreads to neighbouring cells and makes the heart wall vulnerable to tearing. **See p.174**

Cardiovascular diseases are among the top causes of illness and death worldwide. Heart attacks (myocardial infarction), and the heart failure that results owing to a loss of blood supply (ischaemia) and injury to cardiac tissue, remain the main causes of cardiovascular disease and have been increasing in frequency and severity over the past five years[1]. A devastating complication of myocardial infarction is the rupture of the heart's muscular wall, which is associated with a more than 50% chance of dying[2]. On page 174, Ninh *et al.*[3] identify the sequence of mechanical and cellular events that lead to cardiac rupture, providing clues to how this life-threatening scenario can be prevented.

Anatomically, cardiac rupture occurs at the intersection between injured and healthy cardiac tissue. This region is referred to as the borderzone. The conventional view is that increased mechanical stress, inflammation and defective wound healing in the borderzone and adjacent injured cardiac tissue promote rupture[4]. However, the molecular mechanisms and signalling pathways that explain why mechanical stress triggers rupture are not fully understood. Moreover, it remains unclear how inflammatory pathways are activated in the borderzone, whether they differ from what occurs in injured tissue, and whether these events might be linked to increases in mechanical stress.

Ninh and colleagues investigated the signalling pathways that are activated in the borderzone using spatial transcriptomics, an emerging technology that measures gene-expression profiles in defined regions of space across a tissue specimen. The researchers used existing data from human heart specimens[5] and new data from mouse models of myocardial infarction and other types of heart injury. Spatial transcriptomics techniques have the capacity to survey thousands of RNA transcripts, and can achieve spatial resolutions ranging from 100 square micrometres (to capture information in cellular neighbourhoods) to less than 2 square micrometres (sufficient to capture information in single cells). The researchers used two complementary approaches to detect unbiased changes in gene expression in cellular neighbourhoods and to measure the expression of predefined transcripts at a subcellular resolution.

Across each of these technologies and pathologies, the authors consistently observed a gene-expression signature in the borderzone that was indicative of activation of type 1 interferon signalling – a pathway belonging to the innate branch of the immune system. This spatially restricted pattern of interferon signalling differed from other markers of innate immune activation found throughout areas of cardiac damage. Clusters of interferon activation that span several tens of cells emerged early after myocardial infarction and persisted for several weeks. The clusters encompassed several cell types, including cardiomyocytes (cardiac muscle cells); immune cells; cells involved in tissue repair, called fibroblasts; and endothelial cells that line blood vessels.

From the archive

A fairground-style festival of physics, and a tasting menu for a hungry carnivorous plant.

50 years ago

Westfield College of the University of London held a carnival of science … The idea for this feast of fun grew out of a similar but larger event held at Aix-en-Provence … Professor Elliot Leader, of Westfield College, was one of the participants in the Aix event, and was sufficiently enthusiastic about the idea to organise something along the same lines in north-west London. The event was widely publicised locally by means of posters in fairground style offering such treats as "See your friends bombarded by cosmic rays!" and "Watch the amazing lasers in action". And further publicity was lavishly provided by the local newspaper, which allowed Professor Leader space for three feature articles about physics and the festival.
From *Nature* 6 September 1974

150 years ago

I have chosen for the subject of my address to you … the carnivorous habits of some of our brother-organisms — Plants. Various observers have described with more or less accuracy the habits of such vegetable sportsmen as the Sundew, the Venus's Fly-trap, and the Pitcher-plants … I will now give the results of Mrs. Treat's experiments, in her own words: — "Fifteen minutes past ten I placed bits of raw beef on some of the most vigorous leaves of *Drosera longifolia* [the great sundew]. Ten minutes past twelve two of the leaves had folded around the beef, hiding it from sight. Half-past eleven on the same day, I placed living flies on the leaves of *D. longifolia*. At twelve o'clock and forty-eight minutes, one of the leaves had folded entirely round its victim, and the other leaves had partially folded, and the flies had ceased to struggle. By half-past two, four leaves had each folded around a fly … I tried mineral substances, bits of dried chalk, magnesia, and pebbles. In twenty-four hours neither the leaves nor the bristles had made any move in clasping these articles."
From *Nature* 3 September 1874