Precision measurement

Quantum engineering for optical clocks

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Atomic clocks known as optical clocks are more accurate and stable than current timekeepers. Two quantum-engineering approaches could improve the performance of optical clocks even further and extend their applications. **See p.408 & p.414**

Today's most accurate clocks mark the passage of time using transitions of electrons between two energy states in an atom. Such clock transitions are typically induced by the oscillating light wave of a laser that has long-term and ultrahigh frequency stability. In the case of atomic clocks called optical-lattice clocks, ensembles of atoms that have two outer electrons are trapped in a lattice-like pattern of superimposed optical waves, known as a standing wave. The frequency of the optical-lattice light is chosen to be 'magic', which means that the light has minimal impact on the frequency of the electronic transitions used for timekeeping. On pages 414 and 408, respectively, Pedrozo-Peñafiel *et al.*[1] and Young *et al.*[2] demonstrate how concepts in modern quantum technology could aid the development of next-generation optical-lattice clocks.

In the past decade, optical-lattice clocks have undergone improvement at a tremendous rate. However, at least three challenges remain. First, the magic-frequency trap still has a slight effect on the electronic-transition frequency. Second, the clock stability is degraded by clock dead times — periods in which the atoms are being prepared for use, rather than used for timekeeping. And third, quantum fluctuations pose a limit to clock stability. This limit can be surpassed only by the production of a quantum phenomenon called squeezing.

Pedrozo-Peñafiel and colleagues transferred squeezing in an ensemble of ytterbium-171 atoms from a transition between two sublevels of the lowest-energy electronic state of the atoms to the clock transition (Fig. 1a). How does this squeezing help the clock's performance? Typically, atomic clocks use atoms that are simultaneously in the lower and upper electronic states of the clock transition — a situation known as a quantum superposition. For optical-lattice clocks, many such atoms are prepared in parallel.

If the lower and upper states contribute equally to each superposition, the atomic clock ticks at the correct rate. In a clock measurement, each superposition is randomly and individually reduced to either the lower or upper state. These random outcomes add up to the quantum fluctuations mentioned earlier, and degrade the clock stability. But if a squeezed state is used in the clock, the atoms no longer act individually, and the quantum fluctuations are suppressed.

Pedrozo-Peñafiel *et al.* achieved such suppression in a realistic clock measurement sequence, albeit with a short, millisecond-long probe time for the squeezed state. For high-performance clock operation, this interrogation time would need to be extended by a factor of 1,000, to about one second — a long time for such a fragile system to exist. However, the authors found that their squeezed state could persist for nearly that long.

These measurements indicate that quantum correlations can be combined with the second-long interrogation times that are accessible in optical clocks. But before these clocks can benefit from the demonstrated squeezing, a further technical challenge must be overcome. Often, clock stability is limited by the combination of tiny frequency fluctuations in the ultrastable laser that excites the superposition state and of the dead times for atom preparation.

Young *et al.* devised an approach to mitigate this challenge. They added an ensemble of about 150 neutral clock atoms to a 16 × 20 array of magic-frequency laser traps known as tweezers (Fig. 1b). The array was loaded with the atoms extremely quickly by an optical potential (potential-energy profile) that was much stronger than that of the tweezer array. The main achievement of the work presented here is the engineering of the array, which enables a high-performance clock operation.

The authors minimized dead time by combining such high performance with long interrogation times of more than 20 seconds. They then made use of the fact that the tweezers in the system can be read out individually to carry out simultaneous clock measurements on two sub-ensembles in the array. They observed a relative stability of the clocks operating on the sub-ensembles that is close to the current record for optical-lattice clocks[3–5].

The geometry of the tweezer array can be chosen at will. For instance, increased distances between tweezers suppress undesirable hopping of atoms between the tweezers and frequency shifts called Doppler shifts. Furthermore, the clock can be operated with much lower intensities of the trapping lasers than when the distances are not increased. Therefore, Young and colleagues' approach provides an alternative to the use of traps that have high potential-energy barriers between tweezers to prevent hopping, or of gravity-assisted hopping inhibition in optical-lattice clocks[6]. Moreover, the concept opens a path for a new type of neutral-atom clock based on individually controlled atoms.

Although Young *et al.* have achieved

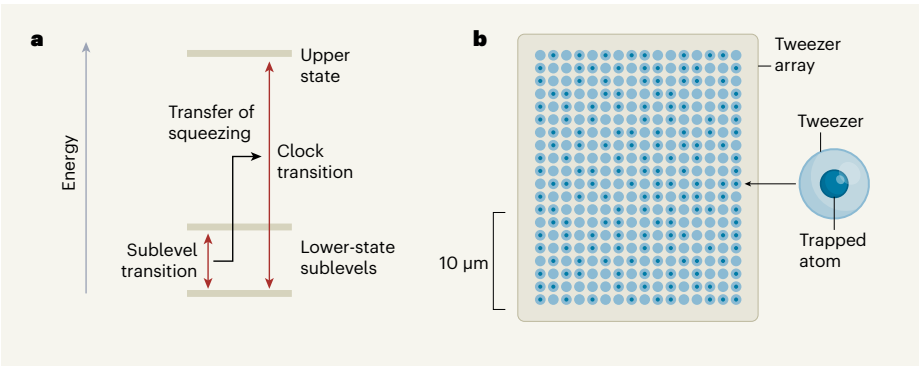

Figure 1 | Improvements to optical-lattice clocks. a, Precise timekeepers called optical-lattice clocks fine-tune the frequency of laser light so that it can drive transitions of electrons between a lower energy state and an upper energy state in an atom (the clock transition); the fine-tuned light waves thus act as a precise 'pendulum' for the clock. Pedrozo-Peñafiel *et al.*[1] demonstrated that a quantum phenomenon known as squeezing can be transferred from a transition between two sublevels of the lower state to the clock transition. Such squeezing can improve the stability of optical-lattice clocks. **b**, Young *et al.*[2] made a 16 × 20 array of laser traps called tweezers, and trapped about 150 neutral atoms for clock measurements. They found that this set-up enables a highly stable clock operation.

excellent clock stability, the characterization of the frequency uncertainty in the clock transition is the next step to realizing a fully operational optical-tweezer clock. For example, the method used to form the tweezer array causes frequency shifts across the array that must be controlled.

These two studies impressively demonstrate how quantum-technology developments and precision metrology benefit each other. For optical clocks, sophisticated tools and platforms are now at hand. And in turn, squeezed ensembles of individually detectable clock atoms constitute exciting systems for further applications in the fields of quantum simulation and quantum information.

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Immunology

Engineered antibodies to combat viral threats

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As the COVID-19 pandemic rages globally, interest in antiviral treatments has never been higher. Antibodies are key defence components, and engineering them to better exploit their natural functions might boost therapeutic options. **See p.485**

The use of antibodies to combat human disease dates back to the 1890s. At that time, the physiologist Emil von Behring used blood extracts from rabbits infected with the bacterium that causes diphtheria to tackle that infection. It was discovered only later that antibodies targeting the bacterium were the active ingredient. Amazingly, such serum therapy is still practised today. For example, blood (described as convalescent plasma) donated by people who have recovered from COVID-19, which contains antibodies targeting the SARS-CoV-2 virus, is used as a treatment for people with coronavirus infection. On page 485, Bournazos *et al.*[1] report progress in efforts to aid antiviral responses by engineering human antibodies to enhance their antiviral activity.

Antibodies are a key component of what is called the adaptive branch of the immune system. They can recognize a part of a foreign molecule called an antigen and mobilize various immune processes to neutralize the threat posed by the disease-causing agent. From the work in this area since von Behring's discovery, punctuated by multiple Nobel prizes, we have learnt much about the regulation, structure and function of antibodies, and their use in the clinic has grown exponentially (see go.nature.com/3kltoq7) . Nevertheless, efforts to manipulate, engineer and improve antibodies remain highly topical.

The Fab domain and the Fc domain (Fig. 1) are the two evolutionarily conserved structural components of antibodies. The Fab domain has a variable antigen-binding region, which is different in every antibody, whereas the Fc domain is a constant structure that is largely similar in different antibodies. The Fc domain engages with other elements of the immune system, including a family of what are called Fc receptors, found on a range of immune and non-immune cells[2]. A type of antibody known as IgG engages a subfamily of Fc receptors called the FcγRs. The FcγRs fall into two main classes: activating FcγRs (including the proteins FcγRI, FcγRIIa and FcγRIIIa) and the sole inhibitory FcγR, FcγRIIb. FcγR engagement stimulates or inhibits immune cells, respectively, and the balance of activating to inhibitory engagement determines the responses of cell types that have both activating and inhibitory FcγRs[2].

> **"Efforts to manipulate, engineer and improve antibodies remain highly topical."**

Although antibodies first entered the clinic for use against infection, so far, it has been mainly in combating cancer and autoimmunity that monoclonal antibodies (those with specificity for a single antigen) have had their greatest medical impact. Blockbuster drugs such as trastuzumab (Herceptin; for the treatment of breast cancer), rituximab (for autoimmune diseases and blood cancers) and adalimumab (Humira; for rheumatoid arthritis) have transformed patient outcomes. These advances have been followed by the use of antibodies called immune-checkpoint blockers, which help to unleash immune responses against tumour cells. Such successes have resulted in seven of the top ten global bestselling drugs in 2019 being antibodies[3].

These clinical achievements have fuelled efforts to learn more about the mechanisms underlying antibody action. This led to the rapid realization that FcγRs have pivotal roles in many IgG-mediated functions. Yet it soon became clear that not all patients respond optimally, and there is a need to develop more-effective antibodies for therapeutic purposes. This ushered in the era of Fc engineering, in which key amino-acid residues and sugars in the Fc domain were identified and modified to selectively enhance or reduce their interaction with different FcγRs[4,5].

As the use of monoclonal antibodies has grown, it has been found that different classes of monoclonal antibody require engagement with different FcγRs for optimal activity. For example, antibodies that target tumour cells directly for deletion require activating FcγRs on tumour-killing immune cells, whereas immunostimulatory antibodies that are often directed to receptors of the TNF receptor family on immune cells require inhibitory FcγRs[6]. Yet other types of antibody work optimally without FcγR interaction. In the realm of cancer, this knowledge has guided the development of next-generation antibodies that carry modified Fc domains, such as the antibody drugs atezolizumab and durvalumab, which are engineered for minimal engagement with FcγRs, and the drugs mogamulizumab and obinutuzumab, in which the Fc domain is engineered to increase its binding affinity for FcγRIIIa (ref. 4).

By contrast, the role of FcγRs in affecting antiviral antibody therapies remains relatively under-examined[7]. Indeed, for many researchers, the drive has been to optimize the Fab domain — developing it to serve as a way to tag the virus and prevent its entry into the cell, thus halting transmission and viral replication. However, studies using different viral models have shown that the Fc domain is needed for optimal antiviral therapy[7]. Bournazos *et al.* used mice in which the mouse FcγR was replaced with human FcγR. They found that anti-influenza antibodies directed to bind to various antigens on the viral surface provide an enhanced antiviral therapy if the Fc domain