complex suggests that FOXP3 can act as a tether that pulls together two stretches of $T_n$G repeats that are otherwise far apart, thereby creating and stabilizing long-distance DNA interactions. Indeed, Zhang *et al.* found that $T_n$G repeats appear frequently in FOXP3-bound long-distance DNA-to-DNA contact sites, many of which are near $T_{reg}$ signature genes. The positions of $T_n$G repeats also correlate with regions of DNA bound by FOXP3, where 'enhancer' and 'promoter' DNA sequences are thought to interact to allow gene transcription[11,12].

To test whether the ladder-like complex is essential for the function of FOXP3 in $T_{reg}$ cells, Zhang and colleagues introduced mutations into *FOXP3* that would disrupt interactions between pairs of proteins that make up the 'rungs' of the ladder, and thus prevent DNA bridging. $T_{reg}$ cells carrying these mutations showed a reduction in the expression of $T_{reg}$ signature genes, and so a weaker immune-suppressive function, than did cells in which *FOXP3* was not mutated – suggesting that long-distance DNA-to-DNA interactions facilitated by FOXP3 are important for normal $T_{reg}$ cell function. This finding aligns with previous studies, which suggested that DNA-to-DNA interactions fail to emerge during $T_{reg}$ cell development in cells that had been engineered to lack the *FOXP3* gene[11,12].

Zhang *et al.* also found that FOXP3 in mice, zebrafish (*Danio rerio*), platypus (*Ornithorhynchus anatinus*) and humans all show similar binding to $T_n$G repeats and DNA-bridging activity, suggesting that the ladder-like assembly of FOXP3 and DNA is evolutionarily conserved – and probably appeared at the same time as $T_{reg}$ cells and FOXP3 evolved in fish[13]. The authors assessed other forkhead-box proteins for their capacity to bind to $T_n$G repeats and found that three more FOXP family members (FOXP1, FOXP2 and FOXP4) share this ability, suggesting that the function of FOXP proteins as tethers is conserved.

Two roles for FOXP3 are becoming apparent. The first is as a classic transcription factor that turns gene expression on or off. The second is as a tether that brings two molecules of DNA into close proximity. This might help to shape the 3D structure of chromatin (the packaged form of nuclear DNA in a complex with supporting proteins) and thus enable remote enhancer sequences to interact closely with promoter sequences to regulate gene expression. More studies are needed to tease out how each of these roles of FOXP3 contributes to the development and function of $T_{reg}$ cells.

The study by Zhang and colleagues focuses on the structure of FOXP3 itself. However, FOXP3 forms large multi-protein complexes in $T_{reg}$ cells[14]. It remains to be determined how other proteins that interact with FOXP3 are involved in the DNA-tethering activity. Moreover, this work would benefit from a further study using a mouse model carrying mutations that prevent FOXP3 from being able to tether DNA, to explore the consequences for $T_{reg}$ cells and the balance of the immune system *in vivo*.

This study will also rekindle curiosity about the function of DNA repeats. Short DNA sequences that are repeated multiple times (such as $T_n$G) are called microsatellite sequences, and occupy around 3% of the human genome[15]. Because microsatellites have a higher mutation rate than do other regions of DNA (for example, those that code for proteins)[16], differences between the sequences of microsatellites in the genomes of individual humans can be used for genetic fingerprinting in forensics and analyses of genetic variation in populations. The biological functions of microsatellites are not widely studied. Zhang and colleagues' finding that FOXP3 and other FOXP family members can recognize $T_n$G repeats to bridge DNA molecules suggests that microsatellites could be key regulators of gene expression.

**Zhi Liu** is in the Shanghai Immune Therapy Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China. **Ye Zheng** is in the NOMIS Center for Immunobiology and Microbial Pathogenesis, the Salk Institute for Biological Studies, La Jolla, California 92037, USA.
e-mails: zhiliu@sjtu.edu.cn; yzheng@salk.edu

1. Zhang, W. *et al. Nature* **624**, 433–441 (2023).
2. Sakaguchi, S., Yamaguchi, T., Nomura, T. & Ono, M. *Cell* **133**, 775–787 (2008).
3. Josefowicz, S. Z., Lu, L.-F. & Rudensky, A. Y. *Annu. Rev. Immunol.* **30**, 531–564 (2012).
4. Bennett, C. L. *et al. Nature Genet.* **27**, 20–21 (2001).
5. Brunkow, M. E. *et al. Nature Genet.* **27**, 68–73 (2001).
6. Bandukwala, H. S. *et al. Immunity* **34**, 479–491 (2011).
7. Leng, F. *et al. Immunity* **55**, 1354–1369 (2022).
8. van der Veeken, J. *et al. Immunity* **53**, 971–984 (2020).
9. Kitagawa, Y. *et al. Nature Immunol.* **18**, 173–183 (2017).
10. Samstein, R. M. *et al. Cell* **151**, 153–166 (2012).
11. Liu, Z., Lee, D. S., Liang, Y., Zheng, Y. & Dixon, J. *Nature Commun.* **14**, 6943 (2023).
12. Ramirez, R. N., Chowdhary, K., Leon, J., Mathis, D. & Benoist, C. *Sci. Immunol.* **7**, eabj9836 (2022).
13. Quintana, F. J. *et al. PLoS ONE* **5**, e9478 (2010).
14. Rudra, D. *et al. Nature Immunol.* **13**, 1010–1019 (2012).
15. Subramanian, S., Mishra, R. K. & Singh, L. *Genome Biol.* **4**, R13 (2003).
16. Li, Y.-C., Korol, A. B., Fahima, T., Beiles, A. & Nevo, E. *Mol. Ecol.* **11**, 2453–2465 (2002).

**The authors declare no competing interests.**

---

Metrology

# The trick that could put an optical clock on a chip

**Mengxi Tan & David J. Moss**

Researchers have made a key breakthrough in how light is used to control time signals from the world's most precise clocks. The technique marks a crucial step in bringing this technology into everyday life. **See p.267**

As technology has become ever more precise, so too have the tools for measuring time – from the shadows cast by ancient sundials to the digital displays of modern wristwatches. Enter the exciting world of optical clocks, sophisticated devices so accurate and precise that they might soon redefine the second. On page 267, Moille *et al.*[1] report an ingenious method of controlling miniature devices known as optical frequency combs. These combs could be the key to fabricating chip-based optical clocks that are small, ultraprecise and reliable, with low power requirements and transformative real-world applications in timekeeping and navigation.

Any clock must operate in synchrony with an external reference – for example, Earth's rotation is the reference that marks the length of a day. And a clock's accuracy is determined by how precisely it can move in step with this reference. For optical clocks, the reference is the frequency of electromagnetic radiation that is absorbed by electrons when they transition between discrete energy levels in an atom. An optical clock measures time by synchronizing the frequency of a laser with this specific frequency. The higher the frequency, the more precise the time standard.

The problem is that these highly precise optical signals ultimately need to be counted by electronics, and even the most advanced electronic devices operate at frequencies that are thousands of times too slow. Optical frequency combs offer a solution by forming a kind of gear network that converts optical frequencies to electronic ones[2]. These combs are frequency spectra, produced by specialized lasers, that comprise regularly spaced spectral lines resembling the teeth of a comb.

In 2000, scientists reported the first optical comb spanning an octave (factor of two) in frequency – from violet frequencies all the way to infrared[3]. This advance enabled a Nobel-winning technique known as f-to-2f self-referencing, in which two comb lines at opposite ends of the spectrum are made to beat in time with each other through a doubling of the lower frequency[4,5]. The resulting microwave signal has a frequency that matches the absolute offset of the comb. The advent of f-to-2f self-referencing made it possible to 'count' at optical speeds[2] – 10,000 times faster, and more accurately, than could the microwave-frequency clocks of the time.

However, this was just the beginning. Initially, these combs were so difficult to build that they could be produced by only the world's most advanced photonics laboratories. But in 2007, researchers succeeded in generating an optical frequency comb on a chip, by confining light to a circular structure called a microresonator[6]. This raised the exciting prospect of building an entire optical clock on a chip, particularly when chip-based frequency combs became compatible with standard silicon computer technology[7,8], and 'microcombs' became a focus of cutting-edge metrology research[9].

The spectrum that is produced when light travels around a microresonator resembles the equally spaced teeth generated by a frequency comb. One of these teeth (at the high-frequency end) is matched to the frequency of the external reference laser, which has been locked to the stable atomic transition. The comb enables the translation of this highly precise frequency into a microwave frequency that is suitable for transmitting timing information electronically.

However, these systems are far from being fully integrated into a single chip. This is mainly because the frequency of the reference laser doesn't perfectly align with the teeth of the comb, so the comb must be tuned until the frequencies match (Fig. 1a). This requires multiple devices and highly advanced laboratory equipment. And although microcombs themselves have undergone tremendous improvements, from increased spectral stability[10] to self-initiated operation[11], the challenges of tuning and locking them to the reference laser frequency have persisted.

Moille *et al.*[1] have simplified this process markedly by devising a simple method for linking a microcomb to well-established frequency standards in a way that is all-optical – meaning that no electronics are required to actively tune the comb. The authors' innovation was to inject the reference laser directly into the microresonator itself, thus automatically synchronizing the laser with the frequency comb (Fig. 1b).

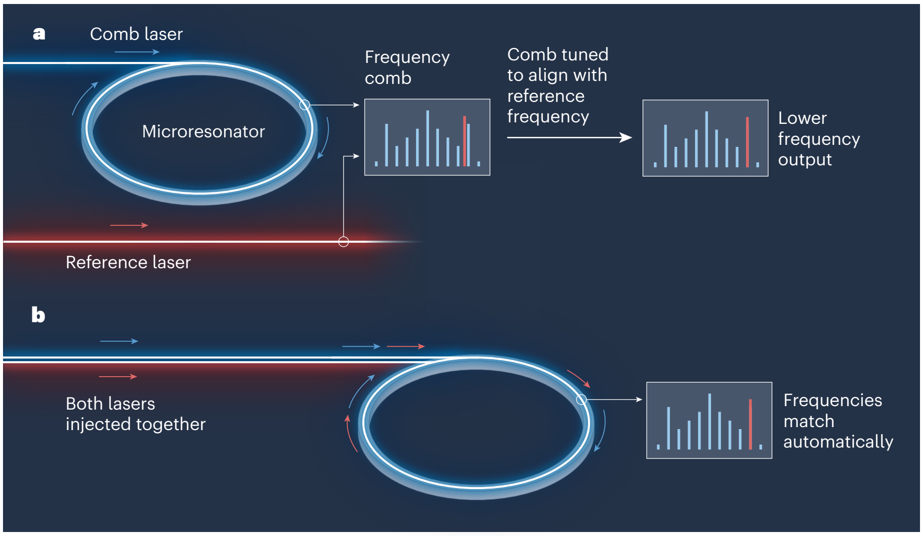

**Figure 1 | Translating ultraprecise time signals into functional frequencies.** Optical clocks measure time on the basis of the ultra-precise frequency of a 'reference' laser. This high frequency is translated into lower frequencies suitable for electronic applications with the help of a frequency comb, which is a spectrum featuring equally spaced lines. **a**, Such a comb can be made by confining laser light to a circular structure called a microresonator, but the teeth of the comb don't necessarily match the frequency of the reference laser, and specialized equipment is required to tune the comb to align these frequencies. **b**, Moille *et al.*[1] showed that the frequencies can be synchronized automatically by injecting the reference laser directly into the microresonator. This innovation could make it possible to build fully integrated chip-cased optical clocks. (Adapted from Fig. 1 of ref. 1.)

They derived a theoretical framework behind this idea, and then verified it experimentally, testing their approach meticulously under a range of conditions to establish its robustness and adaptability. The team also showed the versatility of the approach, which can be tailored to meet diverse technological requirements – including those of optical clocks, but also of frequency references used in astronomy, for example. This process could be the key to finally eliminating the need for any benchtop laboratory equipment, giving rise to the first truly integrated optical clocks on a chip.

This research is bound to have a ripple effect beyond the realm of metrology studies. Imagine a world in which everyday technologies operate with unthinkable accuracy. Fully integrated chip-based clocks could be placed on satellites to improve GPS accuracy, or even embedded in personal smartphones to replace GPS entirely. The improved precision of optical clocks – combined with the extraordinary simplicity of Moille and colleagues' synchronization method – could redefine the limitations of everything from telecommunications to high-speed computing and beyond.

> **"Fully integrated chip-based clocks could be placed on satellites to improve GPS accuracy."**

But perhaps the most profound implication of Moille and colleagues' work is more philosophical. The world is inching closer to a future in which the understanding of time itself might undergo a transformation. Advances in optical clocks could pave the way for a deeper comprehension of time's very fabric, influencing not just science but also how the world is perceived. And with every tick of this clock-on-a-chip, there's the promise of a future in which precision isn't just a luxury but a norm.

**Mengxi Tan** is at the School of Electronic and Information Engineering, Beihang University, Beijing 100191, China, and at the Integrated Photonics and Applications Centre (InPAC), RMIT University, Melbourne, Victoria, Australia. **David J. Moss** is at the Optical Sciences Centre, Swinburne University of Technology, Hawthorn, Victoria 3122, Australia.
e-mails: simtan@buaa.edu.cn; dmoss@swin.edu.au

1. Moille, G. *et al. Nature* **624**, 267–274 (2023).
2. Diddams, S. A., Vahala, K. & Udem, T. *Science* **369**, eaay3676 (2020).
3. Ranka, J. K., Windeler, R. S. & Stentz, A. J. *Opt. Lett.* **25**, 25–27 (2000).
4. Hänsch T. W. *Rev. Mod. Phys.* **78**, 1297–1309 (2006).
5. Hall, J. L. *Rev. Mod. Phys.* **78**, 1279–1295 (2006)..
6. Del'Haye, P. *et al. Nature* **450**, 1214–1217 (2007).
7. Razzari, L. *et al. Nature Photon.* **4**, 41–45 (2010).
8. Levy, J. S. *et al. Nature Photon.* **4**, 37–40 (2010).
9. Spencer, D. T. *et al. Nature* **557**, 81–85 (2018).
10. Herr, T. *et al. Nature Photon.* **8**, 145–152 (2014).
11. Rowley, M. *et al. Nature* **608**, 303–309 (2022).

**The authors declare no competing interests.**