Interestingly, the current studies[1,2] show that the degree of coordination in dynein stepping depends on the head-to-head distance: the stepping pattern is random when the distance is small, but becomes coordinated when the distance is large. This implies a tension-based coordination mechanism similar to the mechanical coupling seen in kinesin-1, but less pronounced.

To further test for the necessity of coordination to dynein motility, DeWitt *et al.*[1] generated a dynein motor in which one of the two heads could not hydrolyse ATP. This head associated only weakly with the microtubule track, probably because transition to a strong binding state requires ATP hydrolysis. This motor moved reliably along microtubules, however, suggesting that coordination is not required for long-range transport.

The high accuracy with which both groups[1,2] managed to track dynein's motion on the surface of microtubules allowed them to make yet another discovery: the two heads exhibit an inherent left–right asymmetry, with the right head more likely to be in the lead. Thus, dynein can be described as staggering sideways along the microtubule.

In light of the two papers' unexpected findings, several exciting questions and ideas for follow-up experiments arise. First, the observed effect of the suggested tension-based mechanism for head coordination is rather small; however, because both groups used modified dyneins, the effect might be more pronounced in normal dynein. It is known[10] that slight modifications to the tail domains, which help to link dynein's two subunits, affect the protein's stepping pattern. Full coordination might thus rely on full-length tail domains and additional subunits, both of which are present in wild-type dynein but lacking in the artificially linked constructs analysed here.

Second, the regulatory ATP-binding sites should not be neglected. It is possible that the disordered stepping patterns observed by the authors are the result of limited ATP binding to the regulatory ATP-binding sites, because all experiments were performed at low concentrations of ATP.

And, third, the highly variable step sizes of the dynein heads — smaller than 16 nm on average — suggest that the centre of mass of the motor dimers tends to move less than 8 nm per step. But it is not clear how this can be reconciled with the aforementioned results of previous studies[5,6] of similar dynein constructs, which were found to take 8-nm steps.

Further development of optical technologies — towards even faster image-acquisition rates at tracking accuracies similar to the outstanding ones presented by DeWitt *et al.*[1] and Qiu *et al.*[2] — will, step by step, allow for fascinating insight into the functioning of dynein and other molecular motors under physiological conditions. Knowledge about the flexibility in the stepping behaviours of various motors might allow us to explain their astonishing ability to move along crowded microtubules in a dense cytoplasmic environment. ■

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PRECISION MEASUREMENT

A comb in the extreme ultraviolet

A 'comb' of photons at evenly spaced frequencies in the extreme ultraviolet has been generated. It will allow a more precise search for variation in the fine-structure constant, which sets the strength of the electromagnetic force. SEE LETTER P.68

LINDA YOUNG

That improved measurement precision yields new physics is axiomatic. In the case of optical spectroscopy, the quest for ultimate precision was revolutionized around the turn of the century by the realization of the optical frequency comb[1–3]. This elegant invention, which was honoured by the 2005 Nobel Prize in Physics[4,5], provides a direct link between radio and optical frequencies, allowing one to count cycles of an electromagnetic field at near-petahertz frequencies (1 petahertz is 10^{15} Hz). On page 68 of this issue, Cingöz *et al.*[6] extend the frequency range of combs to the extreme-ultraviolet spectral regime.

An optical frequency comb is produced by a mode-locked ultra-fast laser in which a light pulse of sub-picosecond duration (1 picosecond is 10^{-12} s) circulates inside an optical cavity made up of a set of highly reflective mirrors. The laser emits an infinite train of pulses at a certain repetition rate (f_{rep}) that is determined by the time the pulses take to make a round trip of the cavity's mirrors[7,8]. This train of pulses has two distinguishing properties: the pulses are equally spaced in time, and the phase (where a wave's peaks and troughs lie) of the electromagnetic field in each pulse is precisely shifted from that in the subsequent pulse (the locked-phase relationship).The train produces a comb of sharp spectral lines uniformly spaced in frequency.

The frequencies of the comb teeth are defined by a simple formula: $f_n = nf_{rep} + f_o$, where f_{rep} and f_o are radio frequencies, f_n is optical frequency and n is an integer of the order of 10^6–10^7 (Fig. 1). With one comb tooth, f_n, referenced to an absolute standard such as the frequency of a caesium atomic clock, the absolute frequency of an unknown optical laser may be counted as a beat note relative to another comb tooth with an accuracy at the level of one part in 10^{14}. This greatly exceeds the accuracy achievable using conventional wavelength-based measurements, which are limited by wavefront distortion to an accuracy at the 10^{-10} level.

A prominent early example of the application of the frequency comb was the measurement[1] of a two-photon transition in hydrogen to an accuracy of more than 2×10^{-14}. This measurement, combined with one performed about four years later[9], placed a limit on the variability of the fine-structure constant — a fundamental constant that characterizes the strength of the electromagnetic interaction and whose variation in time informs the standard model of particle physics. Beyond precision spectroscopy, the optical frequency comb has fostered a multitude of applications, including a clock based on optical frequencies, massively parallel multi-wavelength spectroscopy of unknown chemicals, and long-distance transmission of ultra-stable clock signals, which are useful for next-generation telescope arrays or accelerator systems.

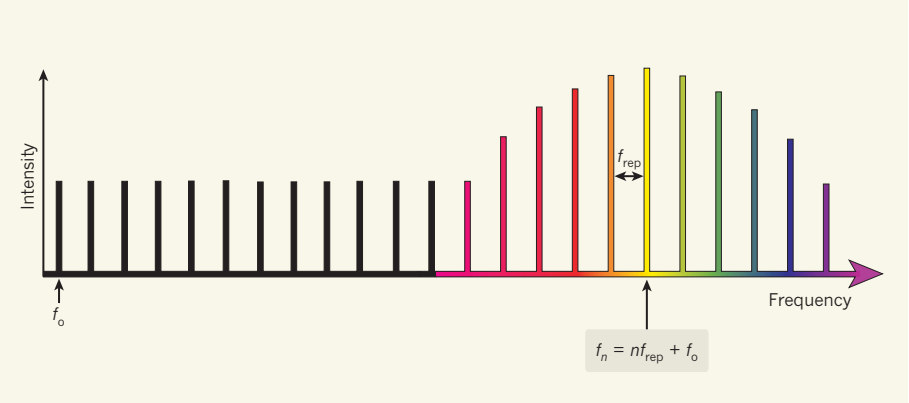

Figure 1 | Frequency comb. The intensity spectrum of a frequency comb consists of an array of sharp lines uniformly spaced in frequency by f_{rep}. The frequencies of the lines, f_n, are determined by a simple relationship, $f_n = nf_{rep} + f_o$, where f_o is an offset frequency and n is an integer. Cingöz *et al.*[6] demonstrate a frequency comb in the extreme-ultraviolet frequency range.

A question that naturally arises is whether frequency-comb technology can be extended to wavelengths shorter than those of the optical spectral range: to the ultraviolet or even the X-ray regime. A route to generating short-wavelength frequency combs that is directly linked to optical frequencies was pioneered by the ultra-fast-laser community, namely by researchers who study high-harmonic generation (HHG). HHG is the process of generating light of frequencies that are multiples (high harmonics) of a fundamental frequency, and is achieved by focusing intense optical pulses into a gaseous target.

In the case of a single atom, HHG involves three steps: ionization of the atom by a laser field; propagation of the resulting electron in the laser field; and recombination of the electron with the parent ion in a process that is accompanied by the emission of high-harmonic light. Although this model captures most of the underlying physics, a complete picture requires an understanding of how waves propagate through partially ionized media[10]. Because the laser intensity required for this extreme nonlinear process to occur is high (more than 10^{13} watts per square centimetre), amplified femtosecond lasers at low repetition rates (10 Hz to 100 kHz) with 10^{-3} joules per pulse are typically used. The 10^{-8}-joule pulses of a typical 100-MHz optical frequency comb are simply not powerful enough for HHG.

In 2005, researchers reported[11,12] that the requisite intensity for HHG could be obtained by adding pulses from an optical frequency comb using an 'enhancement' or 'power build-up' cavity, in which successive pulses add constructively because the phases of the pulses' electromagnetic waves are locked. In such a cavity, the pulse energy can be multiplied nearly 1,000-fold. In addition, it is essential for the HHG process to retain the locked-phase relationship over many consecutive pulses to preserve the underlying comb structure (about 10^5 teeth spaced by f_{rep} for each harmonic) and effectively make the resulting HHG a shorter-wavelength comb. In these two early experiments[11,12], the frequency comb originating from a mode-locked titanium–sapphire laser (with a power of 1 W, repetition rate of about 100 MHz and pulses of roughly 50 fs) was fed into an enhancement cavity containing a jet of xenon gas located at an intracavity focus to produce HHG, in one case[11] up to the 15th harmonic.

However, simply detecting HHG radiation is not sufficient to verify that comb structure exists. Therefore, both groups[11,12] mixed third-harmonic radiation at a wavelength of 266 nm with an independently derived reference signal to observe beat signals that have a spectral linewidth of a few hertz, much less than the roughly 10^{12} Hz expected from the uncertainty principle for 50-fs pulses. These demonstrations were a solid first step towards realizing extreme-ultraviolet combs. But the extracted power per comb tooth was insufficient for applications such as precision spectroscopy, and comb structure was verified up to only the third harmonic.

In their study, Cingöz *et al.*[6] lift these barriers to a more widespread application of extreme-ultraviolet-frequency combs. In contrast to the early demonstrations, the authors show comb structure out to the 13th harmonic (82 nm), and with enough power (200 μW per harmonic) for applications. They achieved these results by using the highest-power near-infrared frequency comb, which is based on an 80-W, 120-fs ytterbium-fibre laser[13] coupled into an enhancement cavity of novel design. The design strategy was informed by a better understanding of the intracavity HHG process[14]. Nonlinearities in the HHG process at the intracavity focus clamp the peak power of the circulating pulses and lead to instabilities that make the constructive addition of the pulses difficult[15]. Cingöz *et al.* used an enhancement cavity that is more robust but loses more power. In this cavity, pulses are amplified only 200-fold, compared with the original 600-fold used by the same group[12].

Cingöz and colleagues went on to perform single-photon spectroscopy of an argon transition using an individual comb tooth (with a linewidth of 11 MHz) with an unprecedentedly high accuracy for the extreme-ultraviolet spectral region.They repeated this measurement as a function of f_{rep}, unambiguously establishing the comb structure at the 13th harmonic. However, single-photon spectroscopy is limited to probing narrow, well-isolated absorption lines; here it was performed with a single comb tooth containing about 10 pW of power. Notably, spectroscopy of two-photon transitions with a frequency comb can use a much larger fraction of the total comb power because pairs of comb teeth whose frequencies sum to the transition frequency also drive the transition.

The authors' demonstration of an extreme-ultraviolet frequency comb, which allows robust linkage between the radio and extreme-ultraviolet spectral regions, ushers in an era of precision metrology in the extreme ultraviolet. A recognized application of their extreme-ultraviolet comb is the aforementioned search for variability in the fine-structure constant: transitions in highly charged ions that have energy in the extreme ultraviolet range are calculated[16] to have higher sensitivity to variations in the fine-structure constant than do optical transitions. As powerful extreme-ultraviolet frequency combs[6,17] are developed that enable a higher precision than that achieved by the optical frequency comb, it will be exciting to see what other applications might emerge. ■

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