from damaged lysosomes, the generation of reactive oxygen species, and the release of DNA from damaged mitochondria have all been linked to NLRP3 activation (*8*–*10*).

By carefully ruling out potential upstream mechanisms, Shenoy *et al.* suggest that GBP5 acts at a level proximal to the caspase-1 constituent of the inflammasome. GBP5, but not GBP1 (a related paralog), binds to the NLRP3-pyrin domain and thereby promotes oligomerization of NLRP3. The authors generated mutant forms of GBP5 [by modeling GBP5 to the known structure of GBP1 (*11*)] and found mutants that favored the formation of a tetrameric GBP5 complex. They propose that these "activated tetramers of GBP5" subsequently stimulate NLRP3 inflammasome assembly. A regulatory switch mechanism likely exists to convert GBP5 to this tetrameric form to promote NLRP3 complex assembly.

Why is GBP5 required for some but not all NLRP3 agonists to promote inflammasome assembly? Perhaps other GBP family members promote the assembly of NLRP3 in response to particulate ligands or aid in the assembly of other NLRs. Another question is how the GBP5 "switch" is activated. ATP and nigericin cause the oxidation and release of DNA from mitochondria (mtDNA) into the cytoplasm (*9*, *10*). Binding of oxidized DNA to NLRP3 then promotes assembly and oligomerization of the NLRP3 inflammasome (*10*). Future studies should determine if and how the work of Shenoy *et al.* fits with this model.

GBP5-dependent assembly of the NLRP3 inflammasome likely occurs in situations where IFN-γ is present. Whether GBP5 facilitates the initial wave of NLRP3 activation or acts to amplify these events when IFN-γ is released from natural killer and T cells at sites of inflammation or infection remains to be clarified. Shenoy *et al.* identify GBP5 as a positive regulator of IFN-γ–dependent inflammasome signaling, whereas IFN-α/β and IFN-γ can apparently restrain NLRP3-driven inflammation by antagonizing pro–IL-1β production and caspase-1 activation (*12*, *13*). Whether IFN-γ exerts positive GBP5-dependent or negative regulatory effects likely depends on the cellular context. Regardless, the identification of GBP5 raises the intriguing possibility that mutations in GBP5 could contribute to human inflammatory and infectious diseases linked to dysregulation of the NLRP3 inflammasome.

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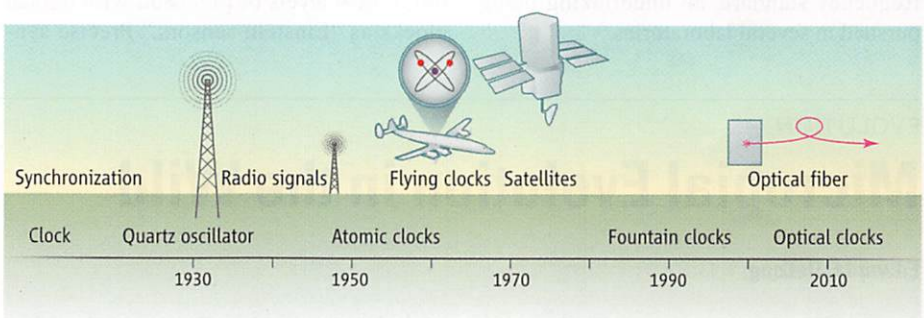
PHYSICS

Two Atomic Clocks Ticking as One

Optical fiber networks allow synchronization of distant optical clocks, which tick too fast to be linked via satellite signals.

Bruce Warrington

How do you set your watch? Perhaps you set it from a radio broadcast, or your computer, or your mobile phone. Each of these devices gets its time in turn from a hierarchy of clocks, typically terminating at a national institute that keeps the reference standards of measurement in your country. If your watch is stable, how well you can rely on it depends on how well you can set it, and thus on propagation delays and "jitter" (phase noise) in the propagation of the reference timing signal itself—whether by radio or over a computer or telecommunication network. In practice, your wristwatch is not stable enough for this to matter, but it is a problem for the best atomic clocks in the national institutes. These are now so stable that they cannot be compared by any of these means, or even by satellite, without noise in the comparison swamping the stability of the clocks. Without new techniques, such as long-range transfer over optical fiber reported on page 441 of this issue by Predehl *et al.* (*1*), we will not be able to take full advantage of these clocks in international timekeeping, and the amazing progress of atomic clocks may grind to a halt.



A timeline of timekeeping. Two problems in timekeeping—improving the accuracy of measuring time and synchronizing time pieces—are intimately related. The timeline illustrates some of the developments in both of these fields.

This problem is not new. Historically, the ability to keep time with a single clock has always been separate from the ability to compare two distant clocks, with technical advances leapfrogging each in turn into the lead (see the figure). In the mid-20th century, the advent of atomic clocks separated time from the rotation of Earth; a new definition of the second was determined by comparing atomic time with astronomical time (*2*), linking laboratories in the United Kingdom and the United States by radio transmission. The new clocks became more and more stable, until radio could no longer transfer time signals without degrading their stability.

The only solution was to bring the clocks physically together for comparison. Elaborate "flying clock" campaigns circulated a portable atomic clock by air (*3*) for international comparisons of clocks in national

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institutes (*4*). The advent of satellite techniques (*5*) restored the ability to compare clocks remotely without degradation, and the balance remained essentially this way through the remainder of the 20th century. This ability enabled first the coordination of national time signals (*6*) and eventually the generation of International Atomic Time (TAI) and Coordinated Universal Time (UTC). These time scales are now the basis of international timekeeping, drawing on and linking together hundreds of atomic clocks around the world (*7*) and in turn supporting global applications from electricity distribution to financial markets.

Today, the best atomic clocks tick at optical frequencies (~10^{15} Hz), and are orders of magnitude more stable again than their microwave forebears (~10^{10} Hz). Two optical clocks in the same laboratory can be compared (*8*) with exquisite precision. General relativity predicts that if a clock on Earth is elevated, it runs faster (because of its higher gravitational potential), and this effect has been resolved for a change in height of only 33 cm or a fractional frequency shift at the 10^{-17} level (*9*). However, for distant clocks, even the best satellite comparisons stop well short of this resolution, by a factor of ~100 after 1 day of averaging (*10*). Without new techniques, we must return to the flying clock comparisons of 50 years ago, and await the development of a portable optical frequency standard, an undertaking being pursued in several laboratories.

Transfer of signals by optical fiber is one possible solution. A number of links have been successfully demonstrated for distances of around 100 km, and, with active stabilization of fluctuations in length, can transfer the full performance of optical standards within practical averaging times. The goal is now to reach longer distances: 1000 km or more to link laboratories around Europe, several thousand kilometers to span the United States or Australia, and even longer for intercontinental links. The work of Predehl *et al.* sets a new distance record (920 km), but more importantly, it shows that the practical challenges such as attenuation and remote operation can be met on this distance scale. Separately, it has also been shown that these comparisons can be performed in parallel with data transfer over the same "lit" fiber—that is, one already in use on other wavelength channels (*11*). This capability is important, as it extends the reach of networks where "dark" fiber (installed in anticipation of future capacity increases) proves impractical or prohibitively expensive.

Together, these technologies are working toward a new international network of time and frequency standards. This network is not just for metrologists, but supports a whole range of applications, just as did earlier networks linked by telegraph, radio, or satellite. One example is precision geodesy, measuring Earth's gravitational potential to new levels of precision with optical clocks as "Einstein sensors." Precise synchronization is also needed for very long baseline interferometry in radio astronomy, with antenna systems such as the proposed Square Kilometre Array extending over continental scales. Here the same fiber network that transfers data can also transfer time; in future, the same can be true for research, industry, and even our homes, with unprecedented access to accurate and reliable time.

In the 60 years or so since the development of the atomic clock, technological infrastructure from telecommunications networks to satellite navigation systems has come to depend intimately not only on the performance of these clocks but also on the ability to compare them. This history tells us to expect the revolution to continue during the next 50 years of timekeeping.

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EVOLUTION

Microbial Evolution in the Wild

A genetic study of microbes in an acid mine drainage site provide evolutionary rate estimates for wild microbe populations.

Edward F. DeLong

Microbial species thrive in every corner of Earth's biosphere. Their rapid growth rates and promiscuous gene swapping provide ample grist for the evolutionary mill over relatively short time spans. In ocean surface waters, for example, microbial doubling times of about 1 day result in an estimated production of around 10^{30} new cells per year (*1*). (This number exceeds that of all individual grains of sand on Earth by about 10 orders of magnitude.) These cells are not static entities, but rather the products and perpetuators of dynamic evolutionary processes. But exactly how fast, to what degree, and by what mechanisms, do free-living microbes change and evolve over time in natural settings? On page 462 of this issue, Denef and Banfield (*2*) report evolutionary rate estimates from free-living microbial species in the wild.

Measuring evolutionary rates of individual species in complex natural microbial assemblages is a daunting task. Yet Denef and Banfield faced even more formidable challenges. The hot, humid, acidic, low-oxygen conditions found at their acid mine drainage (AMD) study site is, as the authors put it, "close to the limit of human endurance" (*2*). This would seem an unlikely place for conducting detailed evolutionary studies—but in some ways it is ideal. The AMD site harbors a very simple ecosystem containing only a handful of microbial species (*3*). *Leptospirillum*, a hardy and versatile bacterium that can live in sulfuric acid, eat iron, and fix carbon dioxide, often dominates AMD biofilms (*3*, *4*). The very low diversity and complexity of the AMD biofilm allowed Denef and Banfield to directly follow the succession of genotypes in *Leptospirillum* populations over time, and to track recombination events and the accumulation of genomic nucleotide substitutions in populations collected over the course of 5 years (see the figure).

By comparing assembled genomes from different genotypes against total population DNA, the authors found that the AMD bio-

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