PERs and two CRYs, and in some cases—such as that of the CRYs—the proteins play different roles in the two clocks. In mammals, CYC's counterpart is a protein called BMAL, and it is BMAL whose levels cycle in counterpoint to PER's. To get a better fix on how the mammalian cycling works, Reppert collaborated with two research teams that had produced mice with mutant clock genes. Gijsbertus van der Horst of Erasmus University in Rotterdam, the Netherlands, and his co-workers brought to the collaboration a strain of mice that lacks functional *cry* genes, and Cheng Chi Lee of Baylor College of Medicine in Houston contributed mice with a mutant *per2* gene.

Neither strain has a working clock, but the clocks are not identically broken. It's like "hitting a clock with a sledgehammer in different ways," Reppert says. By examining how the clockworks have failed, the researchers gained clues to the function of the protein encoded by the mutant genes. For example, results with mice that have a mutation in the *per2* gene suggest that its protein acts as a positive gene regulator, switching on a key clock gene. Reppert's Harvard colleagues Lauren Shearman and David Weaver deduced that from their observation that, in *per2* mutants, the *bmal* gene is expressed at lower levels than in normal mice, implying that PER2 normally turns *bmal* on.

Work with the *cry* mutants showed that the CRY proteins normally turn off the *per* and *cry* genes. Van der Horst's team had already shown that *per* gene activity is high in the *cry* mutant mice. Now, Sathyanarayanan Sriram, a postdoc with Reppert, has confirmed in cell culture studies that CRY protein alone can turn the genes off, without any help from PER. CRY apparently down-regulates the genes much as PER and TIM do in flies—by binding to CLK and BMAL and taking them out of action.

Experiments with the *cry* mutant mice also suggested a second role for CRY: It seems to stabilize PER2. That conclusion came out of the fact that despite all the *per* gene activity in the clock cells of the mutants, the researchers could find no PER protein there. That suggests PER protein is quickly degraded in the absence of CRY. The *bmal* gene's activity was also low in the mutants, as PER is needed to turn the gene on.

Putting it all together, the team came up with two interlocking loops by which proteins feed back on the expression of their own and other genes. In one loop, PER2 turns on the *bmal* gene. BMAL, after a delay, returns to turn on the *cry* and *per* genes, triggering the second loop. In that loop, CRY and PER proteins accumulate and then pair up and enter the nucleus, where CRY turns off the *cry* and *per* genes and PER2 once again turns on *bmal*. This picture is similar to what Hardin's team found last year in fruit flies, although in the fruit fly clock both PER and its partner, TIM, seem to work together to turn off their own genes and turn on *Clk* (*Science*, 22 October 1999, p. 766).

The paper "is a great move in the right direction," says Scripps's Kay. "It is doing what needs to be done, which is to work out the real mechanics of the clock" in mammals. Many questions remain, such as how PER regulates the *bmal* gene, says Kay, but with the studies moving along like clockwork, those answers are sure to follow soon.

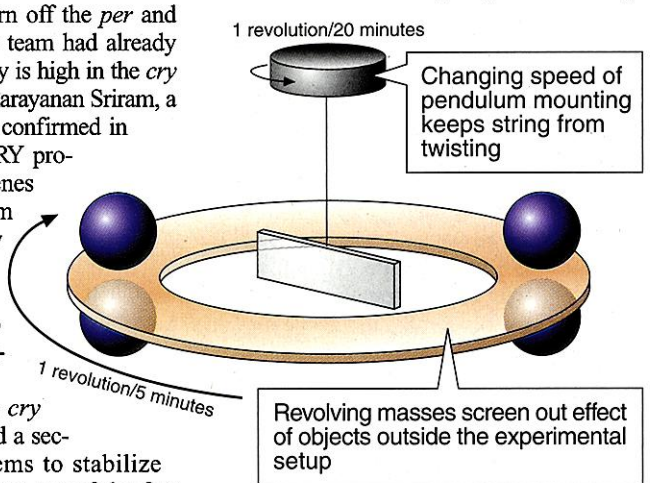
–MARCIA BARINAGA

PHYSICS

A Slow Carousel Ride Gauges Gravity's Pull

Sometimes progress starts with a big step backward. After 14 years of gravitational confusion, physicists at the University of Washington, Seattle, have released the most precise measurement yet of the strength of gravity, thanks to a clever new device.

Although scientists have been studying gravity since the time of Newton, they have had little luck measuring its pull. The strength of gravity, represented by a universal constant nicknamed "big G," is puny; huge amounts of mass exert only a small gravitational attraction. As a result, seismic disturbances, minute electric and magnetic fields, and even the mass of a nearby graduate student can mess up laboratory measurements of G.



Such measurements date back to the end of the 18th century, when the English physicist Henry Cavendish dangled a dumbbell-shaped pendulum from a thread and placed heavy masses nearby. By measuring how much the dumbbell twisted under the attraction of the masses, Cavendish obtained a fairly good measurement of big G. Over the years, Cavendish-like torsion pendulums and other devices yielded better and better values. In 1986, the National Institute of Standards and Technology (NIST) published a value with an uncertainty of only 1.3 parts in 10,000.

Then things started to go downhill. Also in 1986, the PTB, the German equivalent of NIST, performed a technically exquisite experiment that yielded a value 42 standard deviations away from other measurements. "That was quite startling," says NIST's Peter Mohr. "Nobody knows quite what was wrong with it." To make matters worse, in 1995, physicists realized that, because the pendulum wires in Cavendish-style torsion devices are not perfectly elastic, they don't twist in quite the way that scientists had assumed. "[It] should have been obvious," says Randy Newman, a physicist at the University of California, Irvine. "You get a version of G which is too big." NIST hiked its uncertainty about big G by a factor of 12, to a mortifying 15 parts in 10,000.

Enter the big G whizzes of Seattle. At last week's meeting of the American Physical Society,* physicist Jens Gundlach announced that he and his colleagues had eliminated the string-twisting bias and measured big G with an error of a mere 14 parts per million—about 10 times better than previous measurements. The key to the newfound precision was keeping their experimental apparatus in constant motion. Gundlach's team mounted the pendulum's support on a turntable that rotates about once every 20 minutes. As the ends of the pendulum approached the attractor masses—four 8-kilogram steel balls—they felt the increased gravitational force. But whenever the pendulum began to twist, a laser sensor triggered a switch that accelerated the turntable, counteracting the torque. "The torsion fiber hardly gets twisted," says Gundlach. "The gravitational acceleration is transferred to the turntable," getting rid of the string-twisting bias.

Meanwhile, the attractor masses rotated in the opposite direction from the turntable with a period of 5 minutes. That second rotation screened out unaccounted-for gravitational influences from the outside world by turning them into a periodic signal that could easily be subtracted from the data. "You can walk up to this thing, and it won't affect the value," Gundlach says.

The result was a value of G (tentatively $6.67423 \pm 0.00009 \times 10^{-11}$ $m^3/kg \cdot s^2$) far more precise than physicists need for practical purposes. "It's one of the fundamental constants," Gundlach says. "Mankind should just know it. It's a philosophical thing."

–CHARLES SEIFE

* 29 April to 3 May, Long Beach, California.