late 1990s designing cantilevers to sense the tiny forces created by two-dimensional electron gases.

The new results,[5] shown in figure 2, illustrate a nearly perfect agreement with a model of noninteracting electrons, a model that requires just one fitting parameter—the electron diffusion constant of Al. The direction of the persistent current in each ring depends on details of its defects and the number of electrons and thus varies randomly from ring to ring. The total signal measured from an array of rings scales as the square root of the number of rings, reflecting the randomness.

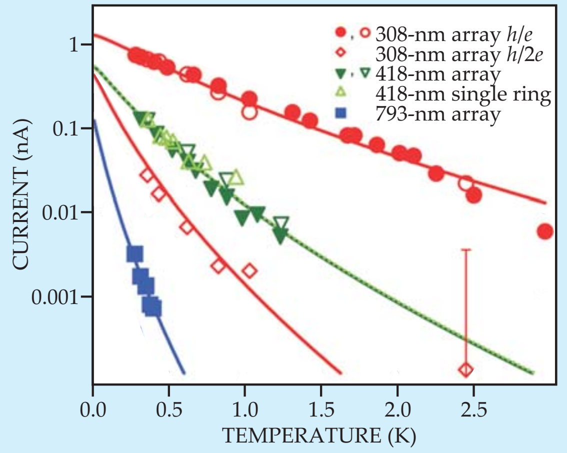

Figure 2. Temperature dependence of the persistent current—or, more precisely, the root-mean-square value of the *h*/*e* and first-harmonic *h*/2*e* Fourier components of that current. The data include variations in five different parameters—the size and number of rings in the array, the magnetic-field strength and orientation (open and solid data points were taken with angle θ equal to 45° and 6°, respectively), and temperature. Each plot precisely follows the trend (solid line) expected from a noninteracting electron model. (Note that the harmonic *h*/2*e* signal here is unrelated to coherent backscattering, which has the same periodicity.) (Adapted from ref. 5.)

Interacting electrons

It's perhaps no surprise that the current's properties depend just on temperature and resistivity of the metal in a regime where the independent-electron approximation reigns. But the Yale group's quantitative account offers a proof of principle for the technique and sets the stage for work at low magnetic fields, where richer physics lies. There, as Imry puts it, "electron–electron interactions turn on and all hell breaks loose."

The interactions and screening effects are manifest in a component of the current whose period is half the magnetic flux quantum, or *h*/2*e*. The component's origin lies in a two-particle version of coherent backscattering. To every zigzagged path an electron might take as it circles the ring there corresponds a precise, time-reversed path through the same scattering centers. Those equivalent pairs of trajectories reinforce each other constructively, which adds the factor of two to the phase shift. Because the effect is a delicate interference involving a sum over relatively few coherent terms, it's easily upset by any significant magnetic field in the metal.

Lévy's group detected the *h*/2*e* signal in its early 1990 study on copper,[2] though with a magnitude at least five times the theoretical value and a sign that indicated attractive electron interactions. That's a surprise for a metal not found to superconduct even at temperatures as low as 10 μK. Last year Imry and collaborators proposed an intriguing explanation:[7] Copper would be a superconductor, they argue, were it not for the influence of tiny part-per-million (or less) levels of magnetic impurities. The impurities break electron pairs and suppress the phase transition but hardly affect the persistent current, which is determined on a larger energy scale.

Once the torque magnetometer is optimized for low fields, Harris plans to address that idea experimentally. He also wants to explore circuits more complicated than the simple metal ring. One can envision, for example, engineering a ring coupled to a quantum dot or grain of superconducting material; that configuration would set normal and persistent currents in competition with each other.

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New technique probes structural elements of folded chromosomes

Chromosomes in a cell nucleus aren't randomly arranged. Studying their twists and turns reveals organization on several length scales.

Stretched to its full length, a human chromosome would be several centimeters long. It is packed, along with its 45 companions, into a cell nucleus just a few microns across in such a way that all the necessary genes are readily accessible to RNA transcription. Figuring out how that packing is done has been a puzzle.

By staining certain chromosomes or genes and looking at them under a microscope, researchers have gained some insight. They've found that chromosomes tend not to be tangled together; rather, each one stakes out its own territory. And there are patterns in the arrangement of those territories: Certain pairs of chromosomes tend to prefer to be near each other. But microscopy offers far from a complete picture. The structures of the individual chromosomes are just too small and too complicated.

Now a research team led by Eric Lander of MIT and Job Dekker of the University of Massachusetts Medical School in Worcester has developed a method, called Hi-C, for examining chromosomes' folded conformations.[1] Dekker's postdoc Nynke van Berkum tackled the biochemical technique, and Lander's student Erez Lieberman-Aiden took care of the mathematical analysis. Together, they've found that chromosomes behave very differently from tangled polymers in equilibrium.

A parallel process

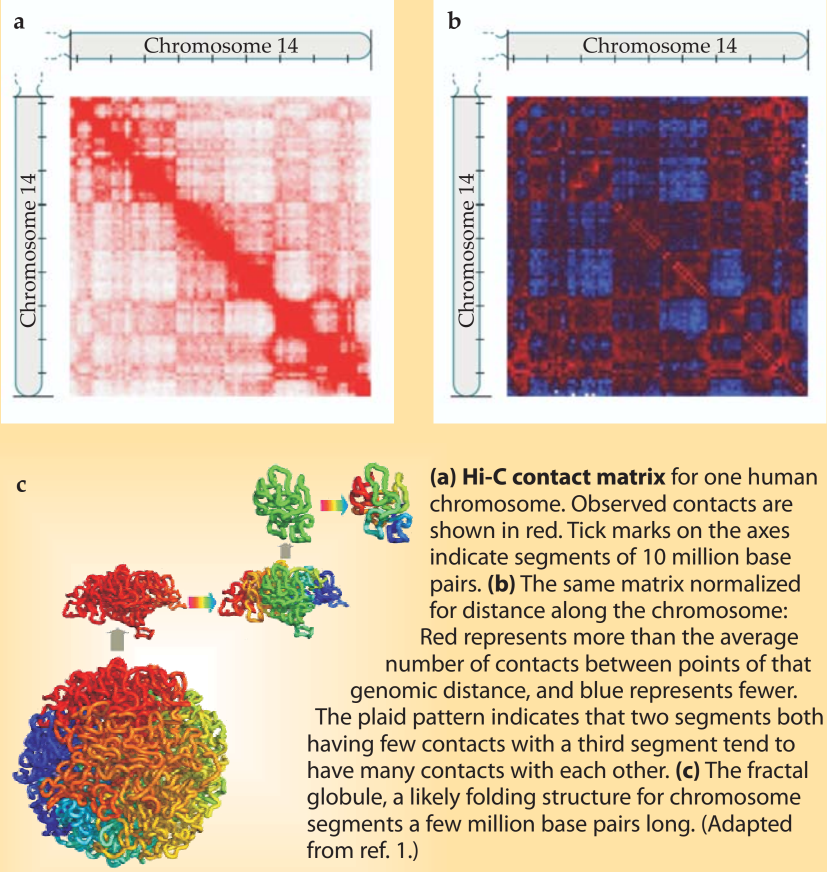
Hi-C is an extension of an earlier technique—called chromosome conformation capture, or 3C—that Dekker helped to develop while he was a postdoc with Nancy Kleckner at Harvard University.[2] In 3C, researchers use formaldehyde to chemically link parts of a chromosome that are close in space. Then, with an enzyme, they cut away the DNA on either side of the cross-link. By sequencing the linked segments of DNA and comparing the sequences with known genome data, they learn which parts of which chromosome they linked.

But 3C could only detect contacts a few at a time—for a folded chromosome with tens or hundreds of millions of base pairs, the method offers only a very coarse view. Hi-C, on the other hand, allows the observation of many more contacts in a short time. Two advances were necessary for that development. The first was the vast improvement in parallel DNA sequencing that has taken place in the past two years. The second was finding a way to isolate and purify so many DNA strands of interest.

The researchers verified that their new method could confirm the results that were already known from microscopy. Fortunately, it could. Hi-C found many fewer contacts between different chromosomes than within the same chromosome, as expected of chromosomes that aren't intertwined. And there were more interchromosomal contacts between pairs that microscopy indicates tend to cluster together.

Pretty in plaid

Plotting a matrix of contacts within a chromosome yields a plaid pattern, as shown in panel a in the figure. Not surprisingly, points that are near each other on the stretched-out chromosome are more likely to be in contact in the folded structure than are points at opposite ends of the chromosome. Still, the off-diagonal regions of the matrix aren't a uniform pale pink: Some pairs of points are more likely to be in contact than one might expect given their linear distance along the chromosome. To sharpen those features, the researchers created a contact matrix normalized for that linear distance (shown in panel b) and a correlation matrix of points that share many common neighbors. From those, they found that two segments that were both far from a third segment tended to be close to each other—that is, the chromosome was segregated into two so-called compartments. Especially interesting was that most of the DNA that was known to be active in that particular cell type fell into one compartment, and most of the inactive DNA into the other.



(a) Hi-C contact matrix for one human chromosome. Observed contacts are shown in red. Tick marks on the axes indicate segments of 10 million base pairs. **(b)** The same matrix normalized for distance along the chromosome: Red represents more than the average number of contacts between points of that genomic distance, and blue represents fewer. The plaid pattern indicates that two segments both having few contacts with a third segment tend to have many contacts with each other. **(c)** The fractal globule, a likely folding structure for chromosome segments a few million base pairs long. (Adapted from ref. 1.)

Zooming in further, the researchers examined the structure of chromosome segments a few million base pairs long. They had no reason to expect chromosomes on that scale to behave much differently from any other tangled polymer. But the Hi-C data told them otherwise: The relationship between contact frequency of points and their distance along the chromosome was different from what widely used polymer models would predict.

Delving into the literature, they found a two-decade-old paper proposing that chromosome segments might form structures called fractal globules.[3] An example is shown in panel c of the figure. The colors represent contiguous segments of the stretched-out chromosome; they also form separate, compact regions in the globule. Each of those regions is structured the same way, as is each of the region's regions, and so on.

The fractal globule fits the Hi-C data better than any other structure the researchers considered—although they can't rule out the possibility that a different structure they haven't considered works just as well. But if the fractal globule structure is correct, it hints at a solution to how the folded chromosomes can be so compact and yet so accessible, since unraveling part of a fractal globule does not cause much disruption to the rest.

To your health

So far, Hi-C has been applied only to cultured cell lines. Those are human cells, but they're far removed from healthy cells in a human body. One of the lines was derived from cancer cells, and another has been modified by a virus. The researchers would like to apply the method to healthy cells to see, for instance, whether there's a difference in chromosome structure in different types of tissue. It's difficult, though, to obtain from healthy tissue the 10 million to 20 million cells necessary for a Hi-C analysis.

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