HUMAN GENOME PROJECT

Draft Genome Map Debuts on Internet

When Daniel Cohen of the Centre d'Etude du Polymorphisme Humain (CEPH) in Paris and his colleagues announced completion of the first draft map of the human genome in the 16 December *Nature*, every geneticist's fantasy—a profound understanding of each human gene—may have come one small step closer to reality. But the new map also points to the immensity of the Human Genome Project—the international drive to identify all of the estimated 100,000 human genes by the year 2005—and shows just how essential computers are going to be for handling the mountains of information produced by the endeavor.

Cohen and his colleagues plotted their map with the help of mega-YACs, yeast artificial chromosomes that can carry huge segments of human DNA. Mega-YACs bearing their human genetic cargo can be inserted into yeast cells, where they are copied each time the cells divide. The researchers created copies, or clones, of enough human DNA segments to ensure that almost the whole genome was covered, and that each segment overlapped with its neighbors. Then, by identifying biochemical markers common to two segments, they lined up the cloned segments end-to-end to create a map—albeit still a rough one—of the human genome. That map reportedly includes more than 20,750 overlapping segments of genome from 10 different humans; covers an estimated 87% of the human genome; and bears 2000 markers that serve as signposts for specific regions of the genome.

In their *Nature* paper, Cohen and his colleagues provide only a short "guidebook" to this information, along with an invitation to gene hunters to obtain the full map via Internet, the international electronic network that users access with their computers. "The sheer size of the project made [Internet] the only option" for disseminating the information, says Cohen. Even a condensed version of the data would completely fill several issues of *Nature*. The unabridged version, if printed on paper, "would create a pile several hundred meters high," he says.

But although the new map seems big, just like the first cartographic attempts by any explorer of uncharted territories, it still lacks all but the grossest detail and undoubtedly contains many errors. "The map still needs to be refined, but it is not so bad," says Cohen. "We decided to release the data now, because we believe its good enough to be very useful to the scientific community." Elke Jordan, deputy director of the National Center for Human Genome Research in Bethesda, agrees: "It's a rough map so you have to use it with some caution, but it will be very valuable for making finer maps."

Gene mapper. CEPH's Daniel Cohen.

That effort will be aided, Cohen predicts, by the plans already put into operation for the rapid dissemination of the map coordinates through Internet and of the chromosome segments, which can be ordered from more than 20 labs worldwide. To probe the segments of the new map for disease-causing genes, geneticists must first break the segments into even smaller clones and identify new markers. As they do so, they will spot errors in the map and fill gaps. Eventually, that group effort should help yield detailed maps that geneticists can use to locate new genes rapidly and better understand the structure and function of the genome.

Cohen's map may be rough, but the genome community is anxious to get a look at it. "We received 64 requests for map information [on the first day of publication of the paper]," says Cohen. That's proved to be something of a mixed blessing. "We have a logistics problem that we did not anticipate," Cohen explains "We have only one person at any one time sending out [the files on Internet]." Cohen anticipates that, even by training new people to send out data, it will take weeks to answer all requests.

–Rachel Nowak

MATHEMATICS

Fermat Proof Hits a Stumbling Block

For weeks, rumors have been circulating in the mathematics community that Princeton University mathematician Andrew Wiles has run into trouble nailing down parts of his proof of Fermat's Last Theorem, announced last June at a conference in Cambridge, England (*Science*, 2 July, p. 32). On 4 December, Wiles confirmed that the rumors are at least partly true. He sent his colleagues an e-mail notice acknowledging that a problem had cropped up in the manuscript, which he had submitted to *Inventiones Mathematicae*, but expressing confidence he will resolve it. Experts are uncertain how long the problem will take to fix.

"During the review process a number of problems emerged, most of which have been resolved, but one in particular I have not yet settled," Wiles' statement says. The sticking point is a calculation that is "not yet complete as it stands," he says. "I believe that I will be able to finish this in the near future using the ideas explained in my Cambridge lectures." He plans to give "a full account" of the work in a course at Princeton in February.

The procedure of patching up a proof while revising a manuscript is entirely normal, experts say—especially when the proof is as long as this one, which runs approximately 200 pages. But in this case, the stakes are high because proving Fermat's Last Theorem—the assertion that the equation $x^n + y^n = z^n$ has no solutions in positive integers x, y and z for exponents greater than 2—has for centuries been one of the unconquered peaks of mathematics. Wiles' surprise announcement in June was greeted with immediate worldwide acclaim, making any mistake all the more serious.

But even if there is an unfixable flaw, say colleagues, the surviving parts of the proof will stand as a major advance in number theory. "When people finally see this manuscript, they're just going to be bowled over completely," says Ken Ribet of the University of California, Berkeley. Most mathematicians are happy when they write a paper with a single idea in it, he notes, but in Wiles' manuscript, "there are several ideas on every page."

The proof is actually an advance in the theory of elliptic curves, which can be loosely described as the study of rational solutions of cubic equations. In 1986, Ribet proved that Fermat's Last Theorem is true if an assertion known as the Taniyama-Shimura conjecture (until recently known as the Taniyama-Weil conjecture) holds for certain elliptic curves. The heart of Wiles' proof is a mathematical theory that allows him to prove the Taniyama-Shimura conjecture for a large class of elliptic curves, and that part of the proof is independent of the current sticking point.

What's still at issue is whether Wiles has succeeded in proving the Taniyama-Shimura conjecture for the specific curves needed to prove Fermat's Last Theorem. His key result says that one can prove the Taniyama-Shimura conjecture for particular elliptic curves provided one can calculate precise upper bounds for the sizes of algebraic structures known as Selmer groups. This by itself is a "fantastic new result," says Karl Rubin, a number theorist at Ohio State University. That's because the calculation can be carried out easily for a large number of elliptic curves. The calculation is not so easy, however, for the curves connected to Fermat's Last Theorem.

The approach Wiles takes relies on theoretical machinery introduced in the late 1980s by Victor Kolyvagin, now at the Steklov Institute in Moscow. "The input needed for this machinery is what Kolyvagin calls an Euler system," Rubin explains. "If you can construct an Euler system with the right properties, then you can apply Kolyvagin's machinery, and out comes a bound on the order of the Selmer group." The problem is, it's not clear that the system Wiles constructed in his original manuscript has all the right properties for the Selmer groups relevant to Fermat's Last Theorem.

Ribet thinks Wiles' strategy is sound, even if the result so far isn't airtight. "This upper bound for the Selmer group is something that people believe is true, and they also think that this Kolyvagin method is the appropriate method to prove it," Ribet says. To nail down the proof, he notes, Wiles could prove his original Euler system does indeed have the requisite properties. Or he could modify the system—"jiggle" it, as Ribet puts it—to make one that works. One way or another, Ribet thinks, "he should be able to do it."

–Barry Cipra

RADIATION EXPOSURE

Scientists Study 'Cold War' Fallout

A dirty secret of the early cold war years made headlines last week, when the General Accounting Office (GAO) reported that Americans were deliberately exposed to radiation, without their knowledge or consent, in a dozen experiments conducted between 1948 and 1952. The experiments, in which radionuclides were released into the environment, were part of an effort to explore the feasibility of radiological weapons. Experts such as nuclear engineer John Till, who's overseeing a study of radiation releases from the Hanford (Washington) Reservation, say these experiments reveal a cavalier attitude toward radioactivity in the early postwar years that permeated the entire weapons program. Indeed, Till points out that these deliberate releases were relatively trivial compared with the amounts of radioactivity emitted into the atmosphere from accidents and routine operations at the nation's weapons plants in the 1940s and '50s.

To put the intentional releases in perspective, Till points to studies under way of accidental and routine emissions at Hanford and at Oak Ridge (Tennessee) weapons laboratory, two Department of Energy (DOE) facilities founded during World War II. Data from the Hanford Dose Reconstruction Study indicate that between 1944 and 1947—the years of heaviest release—some 270,000 people were exposed to a total of 685,000 curies of iodine-131. That's nearly 100 times the amount released deliberately in a 1949 experiment known as Green Run that was the initial focus of the GAO study. The experiment studied how radioactive materials spread through the air.

So far there's no firm evidence that any of these releases have harmed human health, but the Hanford and Oak Ridge studies are trying to determine the extent of the health risks. The studies grew out of public reaction to information in 20,000 documents DOE released in 1986.

In the Hanford study, begun in 1988 and cofunded by the Centers for Disease Control and Prevention (CDC), preliminary findings point to the milk of cows that ate iodine-laced vegetation as the most likely source of human exposure. Some 1400 infants and young children were estimated to have received the highest dose, ranging from 15 to 650 rad, mainly to the thyroid, which absorbs iodine. But doses have to be reconstructed from estimates of fallout patterns and milk consumption because iodine-131 has a half life of only 8 days and leaves no radioactive fingerprints that would permit researchers to determine individual exposures.

A similar situation exists at Oak Ridge, where the GAO discovered two previously unreported intentional releases in 1948. "Given the information we have, [the intentional releases at Oak Ridge] are not where our biggest concern would lie," says Mary Yarbrough, director of environmental epidemiology at the Tennessee Health Department, which has just completed a pilot study of accidental and routine radiation releases from the Oak Ridge lab. In a worst-case scenario, the amount of radiation released from Oak Ridge in routine operations and accidents during the 1940s and '50s "could match the numbers at Hanford," Yarbrough says. A dose reconstruction project at Oak Ridge is examining possible health effects from releases of iodine-131 and iodine-133 from a lanthanum processing facility that operated between 1944 and 1956. It is also looking into releases of cesium-137 from 1943 to the mid-1960s during chemical separations of nuclear weapons, and emissions of nonradioactive toxicants such as mercury compounds and polychlorinated biphenyls.

"Given the information we have, the intentional releases are not where our biggest concern would lie."

—Mary Yarbrough

A dose reconstruction study is also under way at the Fernauld (Ohio) Feed Materials Production Center. Preliminary results indicate this weapons facility released 465 kilograms of uranium from 1952 to 1989, about twice as much as previously estimated, says Till, whose firm, Radiological Assessments Corp. of Neeces, South Carolina, is conducting the study. Till's company has just begun dose studies at two other DOE facilities—the Rocky Flats plant outside Denver and the Savannah (Georgia) River site. Till estimates that in the next 2 years his team will analyze 40,000 boxes of records at Savannah River alone. "That's tedious work," Till says, "but it's the only way to get an accurate picture of what radiation was released."

The amount of radiation in these releases from normal operations of the weapons complex in the early cold war appears to be much greater than the intentional releases that made headlines last week. The GAO report, requested by Senator John Glenn (D–OH), was political dynamite, however, because it revealed deliberate practices that would be totally unacceptable today. GAO found evidence of a dozen intentional releases at three DOE facilities—Hanford, Oak Ridge, and Los Alamos National Laboratory—and a U.S. Army depot in Dugway, Utah. The releases were discovered in the course of studying the Green Run experiment, in which researchers dispersed a ton of dissolved nuclear fuel into the air, releasing 7800 curies of iodine-131. The GAO stated that it could not determine whether the test "exceeded present limits for off-site radiation doses and emissions."

Much more needs to be known about the health effects of exposure to either the routine and accidental radiation releases or the intentional experiments. CDC hopes to learn more from a study of thyroid cancer rates in the most highly exposed people who lived near Hanford, and next month a team of Vanderbilt epidemiologists will begin to look for illnesses that may have resulted from releases at the Oak Ridge lab. In addition, DOE is investigating six studies it funded between the mid-1940s and early 1970s that exposed prisoners and other captive populations to such radiation sources as plutonium injected into the body or x-rays to study tumor growth, fetal development, and sperm production.

–Richard Stone