Genome Projects Ready to Go

A third major report on the human genome project has just been published as momentum in research is growing; the time now seems ripe for decisive action

THE Office of Technology Assessment (OTA) this week released its report on the Human Genome Project, the principal aim of which was to map and sequence the entire complement of human genetic material. The report is the third major publication by governmental and nongovernmental agencies on the topic, the first being that by the Department of Energy (DOE) last April and the second by the National Research Council (NRC) in February. The OTA's document brings a further development in the maturation of discussions about the enterprise: specifically, in further broadening the goals, to encompass advances in genetic analysis in general, not just focusing on the human genome.

In addition, the new report adds a degree of sophistication in Washington ways absent from previous publications, so that it is able to outline various options of how the project might be administered. Of the several possibilities available, the one most favored is an interagency task force that would direct and coordinate activities in the key agencies involved, namely the National Institutes of Health (NIH) and DOE. The chief advantage of this arrangement, notes the report, "is that it builds on existing research programs and planning efforts in different agencies and does not require a single lead agency."

Congressional interest in the genome project has been swelling of late. For instance, earlier this month the Senate Committee on Labor and Human Resources reported out a bill that would establish a National Biotechnology Policy Board and Advisory Panel. The Senate Energy Committee is likely soon to give approval to a similar bill. However, for reasons of intercommittee politics, not lack of interest, prospects for these bills in the House are uncertain.

Meanwhile, the House Committee on Energy and Commerce held hearings this week which addressed "the scientific and technical needs of the genome project, its funding and coordination, and ethical and social issues." In addition, the hearings marked the formal release of the OTA report. "We are ready to make some decisive moves," notes OTA's Robert Cook-Deegan.

The genome project began life almost 3 years ago, the brainchild of Charles DeLisi, director of the DOE's Office of Health and Environmental Research. Initially conceived of as a goal-directed endeavor aimed ultimately at charting the complete sequence of the 3 billion nucleotides in the human genome, the project excited both enthusiasm and fear among biologists. Enthusiasm, because it seemed to promise access to the very basis of *Homo sapiens*—the "holy grail of biology," as Harvard's Walter Gilbert once put it. And fear, because such a massive project seemed to threaten to divert manpower and financial resources from other areas of biology.

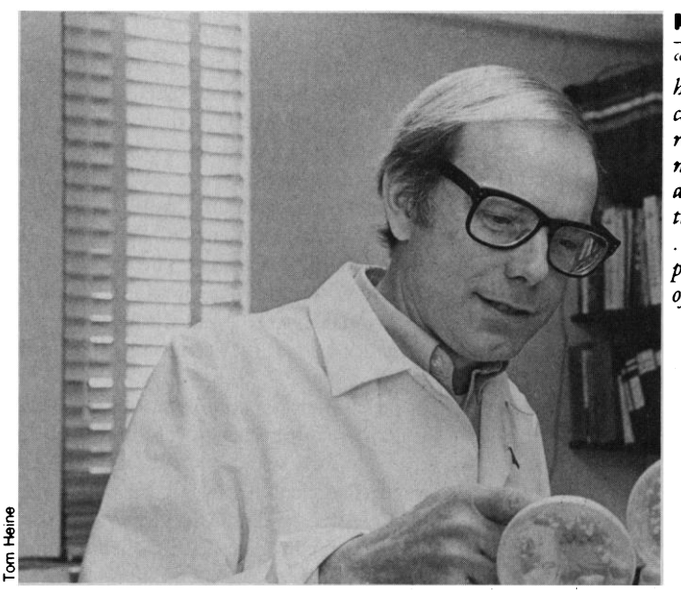
Three areas of concern developed, and were aired at seemingly countless public and private gatherings. First, what should the scope of the enterprise be? Second, how should a project of this scale—Big Science—be organized? And third, how would it be financed?

As mentioned earlier, the scope of the project has been gradually broadening as technical reality and practical utility dawned. Various approaches to genetic and physical mapping have been encompassed, and the drive for a complete sequence tempered. Most significant, *Homo sapiens* is no longer the only experimental subject in the project: other organisms are now included too. This shift of emphasis already was evident in the NRC document and is fully developed in the latest report. As the OTA report makes clear, "There is no single human genome project, but instead many projects."

Maynard Olson of Washington University regards this altered perception as crucial. "If we could analyze the human genome by the close of the century, the real significance would not so much be in the database itself, but in the capability of doing it," he says. "This would have a profound impact on all of biology."

By including other organisms in the genome projects, the genetic data from *Homo sapiens* is placed in wider biological context. To some, this is a more scientific. But to others it robs the project of its most visible and politically attractive appeal, a point that exercised members at a recent Ad Hoc Advisory Committee on Complex Genomes, convened by NIH. "The human element is a natural centerpiece to the project," observes Olson, "but, alone, it stands very poorly."

The second area of concern, that of organization, has also undergone considerable evolution, not least because the project is rapidly moving to de facto implementation. Recognizing that an enterprise of this great scope would require extensive coordination, some proponents urged that it should be the



Tom Heine

Maynard Olson

"If we could analyze the human genome by the close of the century, the real significance would not so much be in the database itself, but in the capability of doing it. . . . This would have a profound impact on all of biology."

property of the DOE, which is well experienced in managing large projects. Moreover, the enterprise had been conceived in that agency, and several projects were already underway. Others considered that NIH would be more appropriate, mainly because human genetics fits naturally within the agency's mandate, but also because peer review was felt to be better developed there.

Perhaps not surprisingly, in its report last year the DOE concluded that the agency would indeed be well suited to running the project. The NRC report agreed that a single agency should take the lead, but it was specific about neither which agency nor exactly how the system would operate. The OTA report recognizes that Congress could designate a single lead agency and notes that "NIH is the natural choice for lead agency." Its mandate and extensive involvement in genetics research are cited in support of such a conclusion.

Although there would be clear advantages in the single lead agency arrangement—"accountability through clear authority"—there are disadvantages too. Not least of these is that "researchers supported by DOE, NSF, and other organizations have important contributions to make," notes the report, "and some projects fall outside the mainstream of research supported by NIH"

The OTA report repeatedly emphasizes the pluralistic nature of the research and its products, which is cogent argument for a broadly organized approach: namely, an interagency task force. "This type of arrangement would certainly be the most flexible structure," says Cook-Deegan. It also recognizes that several different agencies are already actively involved in different aspects of the work. The chief disadvantage, however, is that "no one agency is accountable for the conduct of the genome projects."

Such a task force could be constituted like an interagency committee, with principals from participating agencies, notes the report. In addition, it would include scientists and, possibly, ethicists. Such a group is written into the provisions of the Biotechnology Bill that recently went through the Senate Committee on Labor and Human Resources. NIH might already be a step ahead in this direction, as a result of the recent meeting of its ad hoc committee.

The committee considered and unanimously approved a proposal, drafted by NIH director James Wyngaarden, that an Office of Human Genome Research be established within the director's office. The office will have close links with DOE and other agencies and, notes Cook-Deegan, could provide the focus for establishing a broadly based committee of the sort envisaged in the OTA report.

Chance and Repetition

With some kind of concerted effort to map and sequence the entire human genome now appearing to be inevitable (see page 602), there will be much excitement at the prospect of discovering what is encoded in the 3-billion-base "message." There are certain to be some surprises, perhaps even equivalent in magnitude to the discovery a decade ago of long, noncoding sequences that interrupt the great majority of eukaryotic genes. But there are many biologists who expect large parts of the genome to be devoid of any function at all: "We face the prospect of trudging through huge tracts of junk DNA," remarked British molecular biologist Sydney Brenner during one of the many recent panel discussions on the project. William Loomis and Michael Gilpin of the University of California, San Diego, think that Brenner has it just about right, because they have looked inside many genomes and have seen lots of junk DNA.

The genomes in question are computer generated, the products of a program called GENESIS into which are built rules for sequence duplications, deletions, and various kinds of mutations. Two years ago Loomis and Gilpin showed that, starting with just one or a few "genes," selectively advantageous mutations operating in combination with deletions and duplications can "give rise to genomes with many different genes embedded in a large amount of dispensable DNA sequences." In more recent work these workers have focused on the role of neutral mutations in generating certain classes of repetitive sequences. "Our simulations suggest that most middle repetitive DNA sequences are unavoidable products of duplication and divergence of inactive portions of genes that serve no purpose but are too insignificant to be removed from genomes."

Loomis and Gilpin are concerned only with those sequence families that might be generated by stochastic duplications and neutral mutations, not those that, by the nature of their structure, proliferate extensively to form enormous families of sometimes rather short sequences. At least some proportion of the DNA in the genomes of most organisms is in the form of these so-called middle repetitive sequences, ranging from 3% to as much as 70%: typically, the bigger the genome, the more repetitive DNA. There is a long tradition in biology that, seeing structures as extensive as these, argues that there must be a functional explanation for them. Not necessarily so, say Loomis and Gilpin.

The GENESIS program is set so that sequence divergence can occur only in vestigial genes and genes for which there is more than one copy: the effect is therefore functionally neutral. By altering the rate of sequence divergence in relation to duplication and deletion events, it is possible to generate either a small number of highly populous families (low divergence rate) or a large number of less populous families (high divergence rate.) When sequence divergence occurred at each duplication/deletion event, 17% of the families had three or less members while 63% had ten or more. With higher rates of sequence divergence the mean copy number decreases. "The characteristics of genomes generated at these rates of sequence divergence resemble those of organisms with respect to repetitive DNA."

Family members may be complete genes or parts of genes, depending on how they were affected by duplication and deletion events. And the number of members in a family can fluctuate markedly as "time" passes. The effect of such fluctuations is that most families are of relatively recent origin. Family members are therefore "more closely related to each other than they are to the same gene in an independent genome," say Loomis and Gilpin. "Such a 'founder effect' may account for the observation that members of multigene families are often more similar to each other than they are to homologous genes in separate species."

Biologists have long speculated about the function of middle repetitive sequences, with regulation of gene expression being one popular notion. Loomis and Gilpin's perspective, however, is that, although some middle repetitive sequences may have acquired a function once they have formed, there is no need to invoke function as a selective pressure for their origin. ■ **ROGER LEWIN**

ADDITIONAL READING

W. F. Loomis and M. E. Gilpin, "Neutral mutations and repetitive DNA, *BioSci. Rep.* 7, 599 (1987).

Although the structure implied by the interagency task force concept builds on established activities, and recognizes the pluralism of genome research, it leaves unattended some of the worries already expressed. Specifically, as Leroy Hood of the California Institute of Technology notes: "There is still a strong concern about how DOE spends its funds. The national labs have still not got the required skills in molecular biology, and the issue of peer review has not been settled to the satisfaction of many people."

DOE recently made a commitment to submit all such research to peer review, both intramural as well as extramural. Nevertheless, there is still some skepticism about how well this will work.

The third area of concern is that of funding. A frequently expressed sentiment is that, important though the genome project is, it should not bleed other areas of biology in sustaining itself. In fact, this was often used as an argument for having DOE, not NIH, run the projects.

New money, this was what was required. "The difference between old money and new money is not meaningful in the political context," observes Cook-Deegan. "These projects will be funded as line items in the budget year by year, so long as Congress is persuaded they are valuable. You can't insulate budgets into the future, no matter which agency they are in." Researchers have seen biomedical research funds diverted into the AIDS effort, and the same thing is probably inevitable with the genome projects.

Previous estimates on the overall cost of the genome project have varied from $3 billion to several hundred million, depending on assumptions about advances in technology. The OTA report gives estimates for the first 5 years, which begins at $47 million for the first year and rises steadily to $228 million for year five. Unlike the NRC panel, which projected costs over 15 years, the OTA group argued that uncertainties beyond 5 years were just too great to extrapolate further.

The figure of $47 million is, incidentally, very close to independent, approved budget requests by NIH ($28 million) and DOE ($18.5 million). Both agencies are therefore clearly pushing ahead. One difference is that the prime mover behind the project at DOE, DeLisi, has recently left the agency and is yet to be replaced. Meanwhile at NIH the establishment of the Office of Human Genome Research gives that agency a significant boost. No name has yet surfaced as head of the office, but the choice will be crucial if NIH is to establish itself as the de facto if not actual lead agency. ■ ROGER LEWIN

Advances in Measurement Science

Year after year, physicists measure various quantities with increasing accuracy and see various objects in increasing detail. These advances are vital, because science's understanding of the physical world is necessarily limited by the accuracy with which science can measure that world. The Instrument and Measurement Science Topical Group of the American Physical Society sponsored several symposia at the recent APS March meeting in New Orleans that discussed recent advances in measurement and observation.

A New Standard Volt

A new integrated-circuit device is available that will allow scientists to measure voltage with unprecedented accuracy and free laboratories from sending their voltage standards to the National Bureau of Standards (NBS) to be set. Until now, large research labs have used in-house voltage standards called Weston cells to calibrate their voltage meters, but have had to send the Weston cells to the NBS periodically to be checked against the bureau's standard. The new device, in addition to setting the Weston cells more accurately, is sufficiently easy to use that the labs will no longer need to rely on the NBS to set the Weston cells. Richard Kautz of the NBS in Boulder, Colorado, said industrial laboratories are "clamoring" for the $100,000 device.

The U.S. Legal Volt is defined in terms of the voltage generated when microwave radiation is applied to a Josephson junction, which is a simple electronic device consisting of two layers of a superconducting material separated by an insulating layer. The voltage across the Josephson junction depends very precisely on the frequency of the microwave radiation and, since the radiation's frequency can be determined to great accuracy, this provides a handy definition of the volt.

The normal procedure to fix the voltage standard has been to use one or two Josephson junctions driven by microwaves with a frequency of 10 gigahertz, which produces a reference voltage between 5 and 10 millivolts. The small size of this reference voltage made it very difficult to calibrate precisely the 1.018-volt Weston cells that serve as secondary standard. There is now a way around this problem, Kautz said. He and NBS co-workers Clark Hamilton and Frances Lloyd have used photolithography to etch thousands of Josephson junctions onto a single chip, with the junctions arranged in such a way that their individual voltages combine to give a much larger voltage upon exposure to microwave radiation. In 1985, an array of about 2,000 Josephson junctions turned out reference voltages of more than 1 volt, and Kautz said that now an array with 19,000 Josephson junctions exists that puts out reference voltages up to 10 volts.

Not only does this make it easier to set the 1.018-volt Weston cells, but these arrays make it possible to calibrate and check voltmeters with relative ease. Voltmeters can be checked directly, without the step of calibrating Weston cells. And the voltage of the 19,000-junction chip can be varied continuously between 0.1 volt and 12 to 14 volts, making it possible to test the performance of a voltmeter at different voltages, something that has been much harder before.

Even allowing for the inaccuracies of comparing the Josephson standard with the secondary Weston standard, the new standard allows calibration of Weston cells with a precision of three parts in 10^{10}. This is a factor of 100 better than obtainable with the old standard.

Perhaps best of all, the new voltage standard frees labs from the necessity of sending their secondary standards to the NBS location in Gaithersburg, Maryland, for testing, a procedure that can take a month or more. The NBS sells the 19,000-junction chip for $6,000, and a complete voltage standard can be built for about $100,000, Kautz said. Labs that can afford it will be able to have in-house voltage standards against which to test their Weston cells and voltmeters.

Squeezed Light Muffles Background Noise

When scientists who use laser light in such things as measurement or communications try to improve the precision of their work, they come up against a fundamental limit that has nothing to do with the purity of the light or the accuracy of their machines. The limit stems instead from a "background noise" arising from the quantum mechanical nature of light. Recently, researchers at several labs have successfully