the main experimental load of the Human Genome Project. Raw data produced by these instruments, however, require extensive processing before they are ready for biological analysis.

Large-scale sequencing involves a "divide-and-conquer" strategy in which the huge DNA molecules present in human cells are broken into smaller pieces that can be propagated by recombinant-DNA methods. Individual analyses ultimately are carried out on segments of less than 1000 bases. Many such analyses, each of which still contains numerous errors, must be melded together to obtain finished sequence. During the melding, errors in individual analyses must be recognized and corrected. In typical large-scale sequencing projects, the results of thousands of analyses are melded to produce highly accurate sequence (less than one error in 10,000 bases) that is continuous in blocks of 100,000 or more bases. The UW Genome Center is playing a major role in developing software that allows this process to be carried out automatically with little need for expert intervention. Software developed in the UW center is used in more than 50 sequencing laboratories around the world, including most of the large-scale sequencing centers producing data for the Human Genome Project.

High-Resolution Physical Mapping

The UW Genome Center also is developing improved software that addresses a higher-level problem in large-scale sequencing. The starting point for large-scale sequencing typically is a recombinant-DNA molecule that allows propagation of a particular human genomic segment spanning 50,000 to 200,000 bases. Much effort during the last decade has gone into the physical mapping of such molecules, a process that allows huge regions of chromosomes to be defined in terms of sets of overlapping recombinant-DNA molecules whose precise positions along the chromosome are known. However, the precision required for knowing relationships of recombinant-DNA molecules derived from neighboring chromosomal portions increases as the Human Genome Project shifts its emphasis from mapping to sequencing.

High-resolution maps both guide the orderly sequencing of chromosomes and play a critical role in quality control. Only by mapping recombinant-DNA molecules at high resolution can subtle defects in particular molecules be recognized. Such defective human DNA sources, which are not faithful replicas of the human genome, must be weeded out before sequencing can begin. The UW Genome Center has a major program in high-resolution physical mapping which, like the work on sequencing itself, uses advanced computing tools. The center is producing maps of regions targeted for sequencing on a just-in-time basis. These highly detailed maps are proving extremely valuable in facilitating the production of high-quality sequence.

Ultimate Goal

Although many challenges currently posed by the Human Genome Project are highly technical, the ultimate goal is biological. The project will deliver immense amounts of high-quality, continuous DNA sequence into publicly accessible databases. These data will be annotated so that biologists who use them will know the most likely positions of genes and have convenient access to the best available clues about the probable function of these genes. The better the technical solutions to current challenges, the better the center will be able to serve future users of the human genome sequence.