OPINION

The Gift-Wrapped Genome

For other articles on sequencing see THE SCIENTIST, October 20, pp. 11-12.

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Mapping the human genome (let's call it MHG!), is being popularized as the attention-focusing Big Science Project for the 1990s. Like another technological big fix in the military field, MHG! means different things to different people, which is why much of the debate is at cross-purposes.

One extreme technocratic version (or is it a caricature?) would suspend all other DNA research in favor of a single centralized machine. For a few billion dollars—"hardly the cost of an aircraft carrier"—this center could displace all of the diverse laboratories doing molecular biology, and provide a computer tape with the 3×10^9 characters of the human genome. I am not sure just who is espousing this version today, but something like it may be in some minds, and perhaps it should be analyzed.

MHG! is a striking metaphor that tells us a good deal about the contemporary position of biological science. For some years, it has been evident that 3×10^9 is a metric for the complexity of biological systems of a kind never before accessible. Having the sequence in hand will be a necessary precondition for understanding the biology of the cell in molecular terms.

But it will scarcely be sufficient. Each of the 10^5 gene products spoken for by/sequence will deserve many tomes each—such as we have today in approximate measure for individual examples like hemoglobin, the immunoglobulins and interferons. We then have to deal with the interactions of the molecules with one another, not to mention the regulatory systems, the total metabolism of cellular and organismic structure.

One question is whether there exists either the human ingenuity or the computational horsepower to cope with conceptual structures of such complexity. At the very least we have to be thinking about building the necessary mathematical, along with the biochemical, instrumentation. Nevertheless, as large as these constructs are, they are finite and describable. That is the sense in which we have had for the first time a metric of the complexity of human nature.

The MHG! metaphor teaches us about the strategic objective of contemporary biology. What about our tactics?

We face at once a problem of definition: what is THE human genome that is to be sequenced? Presumably a clonal cell-line will be selected as a standard. Whatever it is, can it fairly be labeled as the paradigm of humanity? Even setting aside the certainty that the very process of laboratory cultivation has induced changes in the genotype, and that adventitious mutations will have crept in, we must reconsider the underlying assumptions of a standard genome.

For one thing, we already know that the uniformity of the DNA among all somatic cells is violated, at least for specialized systems like immunogenesis. Diversification of DNA may well play a part in other aspects of ontogeny; we already know of examples of gene amplification. Some somatic cell lines almost surely have deleted or otherwise altered gratuitous DNA sequences. We would be wisest to select a guaranteed totipotent, germline-related cell clone as a standard, but what is that to be?

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Beyond these questions, we must consider the pervasive polymorphism that distinguishes every person's DNA from every other (possibly barring monozygotic twins). Any standard we adopt is arbitrary. More importantly, is it more efficient to spend resources on the exhaustive sequencing of one genome, or to focus on a limited sample of genes? Those selected for deeper examination would be of the greatest medical and biological interest, and they already recruit the most ancillary information about the gene products, and about their polymorphism within the human population.

Will we learn so much more by sequencing all 22 autosomes plus X plus Y, compared to exhausting one chromosome, plus a more broadly integrated study of a roster of genes as these are diversified among tissues and among individuals in the human population? The latter program is just that of contemporary molecular biology and medical genetics, with reasonable assist from advances in the automation of laboratory procedures that do indeed deserve substantial investment.

The mainstream proposals for MHG! are not much more controversial than that. They would entail a necessarily concerted effort to inventory large overlapping DNA fragments from the chromosome set. That library would not be very costly, and would simplify many individual efforts at gene mapping. They would also fund the development of and broad access to new automated instrumentation for DNA sequencing. Priorities for the execution of such machinery should be subject to peer review like that for other regional resources.

It thus appears that MHG!, in any practically supportable version, is chiefly a repackaging of the central research program of molecular biology as it is now pursued. Too bad that it needs such fancy wrappings to attract public attention for an obvious good. ■

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