Fallacious claims for HGP

SIR — Maddox has argued[1] for the value of the Human Genome Project (HGP). Although his case is largely based on the obvious ability of the project to generate enthusiasm in the molecular biology community, he also argues that it will (1) provide important medical benefits in the form of significantly enhanced diagnostic abilities and (2) help understanding of the evolution of the genome itself. These last claims are unwarranted at present[2].

The argument that medical benefits would be obtained by a comparison between any arbitrary sequence and a "presumably representative" sequence of the human genome is flawed. Divergences would presumably be indicative of genetic abnormality, perhaps even disease. The "representative sequence" would thus be used for diagnostic purposes.

The trouble with this argument is that there simply is no such entity as a "representative sequence" of the human (or any) genome; the amount of variability without loss of function in the DNA sequence of any natural population is far too great. Consider, for example, the DNA sequence of a haemoglobin, perhaps the best characterized of human proteins[3]; of 2,583 possible base substitutions of the DNA coding for the α- and β-chains of haemoglobin, only 1,690 would result in amino-acid substitutions because of the degeneracy of the code. Of these, only 575 (about 45 per cent) would result in a change that could be detected by electrophoresis. This has already led to the detection of about 450 variants, almost half of which are fully functional and, therefore, physiologically silent.

The true amount of protein polymorphism (not revealed by electrophoresis) without loss of function is, presumably, even higher. DNA polymorphism, the relevant factor when considering genomic sequences, exceeds protein polymorphism by at least another order of magnitude because of random nucleotide polymorphism, the degeneracy of the genetic code and variability of tandem repeat sequences that generate highly variable regions.[4].

Among all these fully functional sequence variants, it is fallacious and even dangerous to call any one "normal", simply because any notion of normalcy that goes beyond functionality has no scientific, medical or philosophical basis. Further, there is simply no known way in which the highly irregular DNA sequence information can be "averaged" to provide a "representative sequence" for storage in a database and used for normative comparison. All that can be done, if a single sequence is to be stored, is to choose one of the many normal sequences, perhaps the most common. But such a sequence would be of little diagnostic value. A sequence that diverges from it at many different points could yet code for a fully functional protein whereas even a single difference at a critical site might destroy function (as in the case of the sickle-cell haemoglobin). If accurate medical diagnosis is the purpose of the use of sequence information, each arbitrary sequence will have to be independently judged for functionality.

This argument does not even take into account that many of the genes implicated in disease have low or highly variable expressivity[4]. In such circumstances an extragenetic factor is critical to the aetiology of the disease and there is no reason to believe that such an environmental component is in general due to the epistatic effect of genes at other loci. Sequence information is of little value in these cases, since what has to be understood are the interactions with the environment which, at least to a first approximation, consist of, or are mediated by, biological entities at higher levels of organization than the DNA sequence. Once again the quest for DNA sequences offers little direct hope for therapeutic intervention.

These criticisms of the goals of HGP are pertinent only insofar as that project pursues the blind quest for complete sequences. They do not argue against the limited goal of linkage mapping that would locate the relative position of functionally relevant loci on chromosomes. There is little reason to doubt that such a linkage map, and limited sequencing of these and other regions of interest, will provide both medical and evolutionary insights of value. Perhaps this is where the genetics community has shown most wisdom in adopting the two-stage approach to HGP. During the first stage, such linkage maps will be constructed while sequencing techniques are honed. These goals are uncontroversially worthwhile; it is the second stage of complete sequencing (which Maddox correctly identifies as the core of HGP) that remains suspect.

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1. *Nature* **352**, 11 (1991).
2. Tauber, A. I. & Sarkar, S. *Perspectives in Biology and Medicine* (in the press).
3. Bunn, H. F. & Forget, B. F. *Haemoglobin; Molecular, Genetic and Clinical Aspects, 381–451* (Saunders, Philadelphia, 1986).
4. Vogel, F. & Motulsky, A. G. *Human Genetics: Problems and Approaches*, 2nd edn, 435–446 (Springer, Berlin, 1986).

Figures in dispute

SIR — Referring to indirect costs at the University of Michigan (*Nature* **353**,196, 1991) you state: "This is not a dispute about minor errors in a scientific manuscript, but one in which millions of dollars have been lost to scientific research. The disputed charges in Michigan alone add up to $8.3 million." This statement is false. The charges being disputed are 15 per cent of about $2 million, and the government has not yet been charged any of this, neither $300,000 nor $8.3 million. The issue of allowable costs has arisen during negotiation prior to the setting of overhead rates, not over indirect costs already billed. In the course of these negotiations, government auditors questioned $8.3 million in university expenditure of which the university proposed to charge government grants and contracts 15 per cent as overhead. The university volunteered to withdraw more than $6 million, leaving 15 per cent of $2 million in dispute. The cost of the Rose Bowl tickets is not in that $2 million.

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Science in India

SIR — Your report (*Nature* **352**, 465; 1991) of the plan to broadcast a series of 130 radio programmes about evolution on All India Radio (AIR) should have made it clear that the National Council for Science and Technology Communication (which is supported by the Government of India) is an equal partner in the venture with AIR and, in particular, has been responsible for producing the wall charts and kits that will be distributed to registered listeners as the programmes unfold.

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Parking fine

SIR — A better solution to the parking problem than that recently proposed by Daedalus (*Nature* **353**, 216; 1991) would be to adopt the method used by supermarket trolleys, giving a new meaning to the word 'hatchback'.

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