LETTERS

"The excitement of science"

How Harvard undergraduates reacted to the announcement that Harold Varmus (at right) would be their commencement speaker—and what he actually said—are discussed by readers. A "low-tech" solution to the famous Hamiltonian cycle problem is proposed. Researchers describe the "dilemma of resampling" that can arise when one uses PCR to estimate the genetic diversity of an organism or a virus. In a continuing discussion, events leading up to a gene therapy trial are detailed. And how many people died in a plague, possibly caused by the Ebola virus, in Athens in 430 B.C.?

RICK KOZAK

Varmus at Harvard

It is sad, but not surprising, that the Harvard University student population ridiculed the choice of Harold Varmus, director of the National Institutes of Health (NIH), as their 1996 commencement speaker (Random Samples, 21 June, p. 1747). I was hoping that times were changing. When I graduated from the University of Pennsylvania in 1986, the commencement speaker was Michael S. Brown, who won with Joseph Goldstein the 1985 Nobel Prize in Medicine and Physiology for their discoveries in cholesterol metabolism. I planned to enter a graduate program in biology in the fall, so Brown's excellent speech was personally inspiring. However, the majority of Penn's undergraduate population (including the hundreds of Wharton business school, pre-law, and even pre-med undergraduates) moaned, fidgeted, and rolled eyes during the speech. I suppose we can all aspire to be scientists who somehow contribute to the body of scientific knowledge in such a way that we are appreciated by our peers, but even the stars of our community are not going to be heroes to many.

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I was disappointed by the coverage of Harold Varmus's commencement address at Harvard. The contents of the speech itself were not described. Instead, the piece mocked precommencement undergraduate reaction to the selection of an NIH director as speaker. The address confirmed the wisdom of that selection. Varmus spoke directly to the graduates, their families, and other alumni, reminding them of the excitement of science and of its ability to bring about change. He placed dramatic advances in medicine in the context of creative curiosity about fundamental biology. Many of us concerned with undergraduate science education and biomedical research at Harvard found the address inspiring. An account of the talk might have allowed readers to also take pleasure and pride in what Varmus had to say.

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Editor's note: The full text of Harold Varmus's Harvard commencement address can be found at the *Harvard Magazine* home page—http://www.harvard-magazine.com/cg/varmusaddress.html

Finding Hamiltonian Cycles

L. Adleman has proposed and demonstrated a highly novel approach using DNA and the tools of molecular biology to solve the famous Hamiltonian cycle problem (HCP) of computer science: Given a directed graph on N vertices (N cities and a set of $R \leq N^2$ one-way roads connecting the cities), does there exist a subset of the roads using which a tour of the cities can be made beginning and ending at the same city and stopping at each city exactly once (a Hamiltonian cycle)? The HCP has applications in operations research, cryptography, and other fields. Because the HCP is very hard computationally—indeed, the HCP belongs to the NP-complete class of problems which have no known general polynomial time deterministic solution algorithm—novel approaches to the HCP are important to consider. In theory, because Adleman's method exploits the parallelism inherent in solutions containing DNA to check all possible tours, it solves the HCP for any graph. However, it has recently been noted that practical considerations may limit the use of Adleman's method to graphs with less than 30 cities (*1*). Given this finding, we were curious to see what size HCPs could be done on conventional computers. The difficult range for finding Hamiltonian cycles seems to be in the range where $R \sim N *\ln N$ (*1*). We have found that the method of simulated annealing (SA) (*2*) can be modified (*3*) to effectively find Hamiltonian cycles in graphs with up to at least 100 cities in only minutes or seconds on a conventional computer (Table 1). As Adleman states, improvements in enzyme and other technologies will make his method more useful practically. Until then, SA is a good alternative for the HCP which can be run quickly and cheaply on a conventional computer. Our results using SA for the HCP set a standard for Adleman's method. Also, because a near infinite number of HCPs of increasing size containing at least one Hamiltonian cycle can easily be constructed, the success of SA for the HCP establishes the HCP as an excellent problem with which to benchmark optimization methods. With an effective method (SA) for finding Hamiltonian cycles in hand, further study of the complexity of the HCP, and of the power of SA, should now be possible.

Table 1. Number of trials out of 100 in which simulated annealing found a Hamiltonian cycle in a graph into which one had been inserted.

Number of cities (N)	Number of roads (R)			
	$0.5N*\ln N$	$N*\ln N$	$1.5N*\ln N$	$2N*\ln N$
20	100	100	100	100
30	100	100	100	100
40	98	99	100	100
50	88	99	100	100
60	81	100	100	100
70	72	99	100	100
80	41	99	100	100
90	33	100	100	100
100	24	100	100	100

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References and Notes

1. M. Linial and N. Linial, *Science* **268**, 481 (1995).
2. S. Kirpatrick, C. D. Gelatt Jr., M. P. Vecchi, *ibid.* **220**, 671 (1983).
3. As for the traveling salesperson problem (TSP) (*2, 4*), for the HCP we took a tour as a permutation of the numbers 1, 2, 3, . . . , *N*. We took the distance between two cities to be 0 if there exists a road between the cities, and 1 if not. A tour of length 0 thus corresponds to a Hamiltonian cycle. Instead of the Lin-Kernighan reversal move, we substituted a "swap" move in which two randomly chosen cities switch places on the tour. We tried to minimize the length of the tour. As we expected numerous tours to have the same length, we augmented the length of a trial tour by a small additive constant $\delta > 0$ to bias the algorithm to seek shorter paths. We annealed according to the schedule $T = T_0(T_1)^M$, with $T_0 = 0.5$ and $T_1 = 0.9$ (*M* an Integer). We used $\delta = 0.2$. We used $125N^2$ tours at each temperature, lowering the temperature if $12.5N^2$ successful moves had been accepted at a given temperature. Most of the tours appeared to be needed for the HCP near $T = 0$ to find the last few roads. N^2 paths are needed at each temperature for the HCP, but only *N* paths at each temperature for the TSP. A 100-city HCP was beginning to be difficult for SA, while a 100-city TSP was easy. These may reflect the increased complexity introduced by the "distance" function for the HCP over the 2-D Euclidean distance function of the TSP.
4. W. H. Press, S. A. Teukolsky, W. T. Vetterling, B. P. Flannery, *Numerical Recipes* (Cambridge Univ. Press, Cambridge, UK, 1992).
5. Work at Lawrence Livermore National Laboratory was performed under U.S. Department of Energy contract W-7405-Eng-48.