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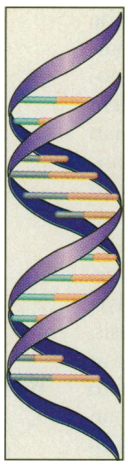
LETTERS

On the Potential of Molecular Computing



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DNA computing. Tracking the traveling salesman through molecular solutions.

In his report "Molecular computation of solutions to combinatorial problems" (11 Nov., p. 1021), Leonard M. Adleman describes a method for finding Hamiltonian paths in directed graphs that is based on molecular biological tools. This approach is demonstrated on a particular graph with seven vertices and 13 edges. Adleman and David K. Gifford, in his Perspective "On the path to computation with DNA" (p. 993), speculate on the possibility of performing difficult computational tasks by operating at the molecular level. We consider the applicability of this intriguing idea in light of the fact that the type of problem solved in the report, called an NP-hard problem, becomes exceedingly difficult as the size of the problem grows. It is known that sparse directed graphs (that is, graphs with few edges) almost surely have no Hamiltonian path, while, for graphs with many edges (dense graphs), almost surely one exists. On the basis of this fact from random graph theory, simple algorithms were designed for finding Hamiltonian paths in graphs that are either very sparse or very dense (*1*). Therefore, the power of any computational technique for this problem should be tested on "middle-ground" graphs, with n vertices and about $n \log n$ edges. Step 1 in Adleman's experiment calls for expanding all paths on n vertices—a total of $(\log n)^n$ in this case. Each path consists of a $(20n)$-mer oligonucleotide. Therefore, such an experiment involves at least $20\ n\ (\log n)^n$ base pairs. If Adleman's method is to be expanded one order of magnitude, to deal with graphs on 70 vertices, the total mass of nucleotides involved in the experiment would reach 10^{25} kilograms (on the basis of the average molecular mass of a nucleotide). These quantities get much higher with any further increase in the number of edges.

Other inherent limitations further reduce the size, n, of graphs to which Adleman's method is applicable: "Coupon-collector" bounds from statistics (*2*) should be observed so that every path type is generated in the random ligation step. Cost, labor, experimental errors, and reaction time further reduce this number. In fact, it seems impossible for graphs with more than 30 vertices to be handled by this approach.

Conventional state-of-the-art algorithmic techniques fare much better: The related, but even harder "traveling salesman" problem is currently solved for graphs on a few thousand vertices, the largest instance being a specific graph with 7397 vertices (*3*). These conventional computers perform so well because of the advanced algorithms they use. For the dream of a molecular biological computer to materialize, a much richer set of instructions than those employed by Adleman may have to be emulated.

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2. W. Feller, *An Introduction to Probability Theory and Its Applications* (Wiley, New York, 1968).
3. D. Applegate, B. Bixby, V. Chvátal, W. Cook, "Finding cuts in the TSP (a preliminary report)" (DIMACS Technical Report 95-05, Center for Discrete Mathematics and Theoretical Computer Science, New Brunswick, NJ, 1995).

Adleman proposes a new approach to computing using DNA molecules which may have implications for certain demanding computing applications. He uses the directed Hamiltonian path problem as an example and shows that it can be solved by using a combination of several well-known molecular biological techniques. This approach has enormous potential for further development. For example, Adleman's system can be modified to find the shortest Hamiltonian cycle in a particular system and thus can be used to solve the well-known "traveling salesman" problem (*1*). This can be accomplished by encoding path length information using oligonucleotides of different lengths. After ligation and amplification by polymerase chain reaction (PCR), affinity purification can be applied directly to the PCR products. Gel electrophoresis will then reveal the shortest PCR product