the structure of the liquid could be gained from these studies.

Experimental elucidation of the atomic structure of the liquid-solid interface is inherently difficult. Embedded between the liquid and the contacting surface, the interface is not easily accessible, and the amount of material contained in the interface is extremely small and limited to a few atomic layers. Lead is well suited to liquid surface and interface studies under ultrahigh-vacuum conditions, because it is easy to keep clean, and its vapor pressure is very low even at the melting point. It was used in the pioneering work by Frenken and van der Veen (*10*), who by means of medium-energy ion channeling showed that non-close-packed crystal facets of lead display disordering of the top few surface layers at temperatures well below the bulk melting point. Computer simulations (*11*) for aluminum confirmed the phenomenon of premelting, which is now accepted as a general property of non-close-packed surfaces. A degree of layer ordering is retained in the premelted material (*11*), providing a key to understanding the liquid-solid interface.

With the advent of x-ray synchrotron radiation facilities of extremely high brilliance, instruments have become available for studies of monolayers. These tools have been used to demonstrate lateral anisotropy in a monolayer of liquid lead on germanium (*12*) and layer ordering in the interface between liquid gallium and diamond (*13*). Recently, Reichert *et al.* (*14*) have shown distinct layer ordering in liquid lead on a silicon surface and demonstrated that the in-plane ordering has fivefold symmetry, representative for the building blocks used to describe liquid structures.

Atomic-resolution TEM instruments are not normally associated with studies of liquid-solid interfaces, with some notable exceptions. A few years ago, Howe (*15*) presented a well-designed TEM study that mimicked a liquid-solid interface. He studied the interface between amorphous $Pd_{80}Si_{20}$ and crystalline Pd_3Si, arguing that layer ordering in the amorphous phase may reflect an analogous ordering in the liquid-solid interface. Also using TEM, Sasaki and Saka (*16*) have shown how the solid alumina phase grows layer by layer from the liquid at the solid-liquid alumina interface. The work by Donnelly *et al.* (*1*) follows in this tradition, clearly demonstrating that very detailed information on structures in liquids can be achieved by TEM on carefully chosen systems.

The work by Donnelly *et al.* (*1*) sets a new standard for the use of TEM in the study of liquids in contact with solids. Together with the works by Howe (*15*) and Sasaki and Saka (*16*), it presents the TEM community with new challenges for designing and investigating liquid-solid interface systems and using TEM to obtain information that is otherwise only accessible by use of large-scale x-ray synchrotron facilities.

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Published online 21 March 2002;
10.1126/science.1070400
Include this information when citing this paper.

PERSPECTIVES: COMPUTING

Successes and Challenges

John H. Reif

In the last few years, the idea of a molecular computer that could execute computational steps at the scale of a single molecule has moved from the realm of science fiction into that of scientific publications. Eight years ago, Adleman (*1*) demonstrated the first small-scale molecular computation. From this ground-breaking experiment sprang the rapidly evolving field of DNA computation, or biomolecular computing (*2*), which uses biotechnological techniques to do computation.

On page 499 of this issue, Braich *et al.* (*3*) report by far the largest scale demonstration to date of the capabilities of DNA computation. This landmark study proves that molecular computation is not a far-fetched possibility, but a quickly evolving discipline that may have major impact on more established disciplines such as biotechnology.

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DNA provides a compact means of data storage and a degree of parallelism far beyond that of conventional silicon-based computers. In principle, more than 10^{21} bits of information are packed into each gram of dehydrated DNA. Routine recombinant DNA techniques for detection, amplification, and editing of DNA can be used for massively parallel molecular computation, because they simultaneously operate on each strand of DNA in a test tube. A single recombinant DNA operation can take up to 20 minutes or so, but the high degree of molecular parallelism still provides immense capabilities for efficient computation, because even routine experiments can involve between 10^{15} and 10^{17} strands of DNA in a small test tube. The rapid evolution of biotechnology and use of automation also provides increased scaling capabilities.

Braich *et al.* (*3*) use DNA computing to solve a satisfiability (SAT) problem—a combinatorial search problem where we are given an expression that defines a logical relationship between two or more items (a Boolean formula) and wish to find a truth assignment to the variables to satisfy the formula. As a very simple example, the Boolean formula "($\sim x_1$ or x_2 or x_3) and (x_1 or $\sim x_2$ or x_3) and (x_1 or x_2 or $\sim x_3$) and ($\sim x_1$ or $\sim x_2$ or $\sim x_3$)," where "~" denotes logical "not," has a truth assignment of all the variables to false. SAT is known to be a NP-hard problem, which computer scientists view as unlikely to have a fast solution on a conventional computer for large instances of the problem.

Recent progress on the SAT Problem with DNA computations may lead to unreasonable expectations. The use of DNA computation to solve very large combinatorial search problems such as SAT cannot be scaled up indefinitely. The number of distinct DNA strands generally grows exponentially with the size of the problem statement, and the molecular-scale data storage is eventually swamped by the numbers of DNA strands required for large problems. For the SAT Problem, the likely upper limit is 70 to 80 Boolean variables.

Nevertheless, moderately sized SAT problems have served as a useful test for DNA computation techniques. Generally, these methods involve the generation of a combinatorial library of synthetic DNA

strands, containing short DNA words associated with each of the Boolean variables. A wide variety of biochemical methods have been developed to encode Boolean variable assignments and to separate or identify the strands encoding an assignment of variables satisfying the formula.

Corn, Smith, and co-workers (*4*) have used surface chemistry techniques to solve a 4-variable instance of SAT. They affixed the DNA stands encoding all possible Boolean variable assignments onto a two-dimensional surface, and then applied restriction enzymes to destroy those DNA strands that do not satisfy the Boolean formula. A fluorescent optical readout was used to identify the remaining DNA strands that encode satisfying assignments for the given formula.

Supercomputers in the test tube

Landweber and co-workers (*5*) used a combination of DNA and RNA techniques to solve a 9-variable instance of SAT related to the well-known Knight's Problem in chess. They employed evolutionary methods to determine a set of RNA sequences used to eliminate those strands that do not satisfy the Boolean formula.

The SAT experiments of Adleman and co-workers (*3*) use hybridization of short DNA strands called stickers to encode truth assignments of 20 Boolean variables. Their latest breakthrough was made possible by the use of automated gel electrophoresis to separate out the DNA strands that have stickers encoding satisfying assignments of the Boolean formula.

The above protocols require many laborious separation and detection steps, which will only increase as the scale increases. These problems may be overcome by using autonomous methods for DNA computation, which execute multiple steps of computation without outside intervention. Autonomous DNA computations were first experimentally demonstrated by Hagiya and co-workers (*6*) using techniques similar to the primer extension steps of PCR and by Reif, Seeman, and co-workers (*7*) using the self-assembly of DNA nanostructures (*8*). Recently, Shapiro and co-workers reported the use of restriction enzymes and ligase (*9*).

Known protocols for the solution of medium-scale SAT problems may have useful applications in the biomolecular domain. For example, they may be used to execute Boolean retrieval queries on synthetic DNA tags in a "wet" database consisting of a vast store of genomic DNA (obtained from many organisms, individuals, cell types, and at many distinct dates), each tagged with a synthetic DNA strand that provides binary data such as the sampled individual's identification number, cell type, and date of sampling.

The separation techniques developed by Braich *et al.* for their SAT experiments may be used for exquisitely sensitive and error-resistant separation of a small set of specified molecules from a large combinatorial set of molecules. Quite apart from its use for the SAT problem, the technique may also have many other diverse biotechnology and security applications, such as the detection and tracing of minute amounts of toxic or explosive materials.

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PERSPECTIVES: TRANSCRIPTION

Proteasome Parts at Gene Promoters

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Proteasomes are the protein complexes in eukaryotic cells that direct the degradation of ubiquitin-tagged (ubiquitinated) proteins. The 26*S* proteasome is composed of a 19*S* regulatory subcomplex (comprising a base and a lid) that recognizes polyubiquitinated proteins, and a 20*S* proteolytic subcomplex where these tagged proteins are degraded (see the figure). The proteolysis of ubiquitinated proteins is a feature of many cellular processes including chromosome stabilization, cell division, apoptosis, cell differentiation, and the stress response (*1*). Ubiquitin-tagged proteins are also involved in cellular events that do not require proteolysis, such as endocytosis and the localization of certain proteins in the nucleus (*2*).

Ubiquitin tagging modulates the stability of many transcription factors and even of RNA polymerases, the enzymes that drive gene expression. Intriguingly, the transcriptional activation domains of some transcription factors serve as signals for ubiquitination and degradation (*3*, *4*), suggesting that the proteasome itself is involved in transcription (*4*). In contrast, histone proteins, especially H2A and H2B—which form the nucleosomes around which chromatin is wrapped—are ubiquitinated, but apparently not for purposes of degradation. The participation of ubiquitin in nonproteolytic processes suggests that different components of the proteasome may be involved in proteolytic and nonproteolytic events. This hypothesis gains support from the work of Gonzalez *et al.* (*5*) published on page 548 of this issue. They show that adenosine triphosphatase (ATPase) enzymes of the 19*S* subcomplex (but not the proteases of the 20*S* subcomplex) become associated with genes that are being transcribed.

The roots of this story go back nearly a decade, when Johnston and colleagues discovered that specific alleles of the yeast *SUG1* and *SUG2* genes suppress the phenotype of a defective allele of *GAL4*, which

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