

frequently includes two or three water molecules. Prompted by a Lewis acid-base relationship with the metal ion, water molecules often produce OH^- , which then goes on to attack other molecules in close proximity to the metal (9). An example is Zn^{2+} in carbonic anhydrase where the resultant OH^- attacks CO_2 . The coordination of these molecules is more likely to resemble

the molecular arrangement determined from cluster studies than the time-averaged picture derived from ions in solution.

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PERSPECTIVES: NANOTECHNOLOGY

Toward Nanocomputers

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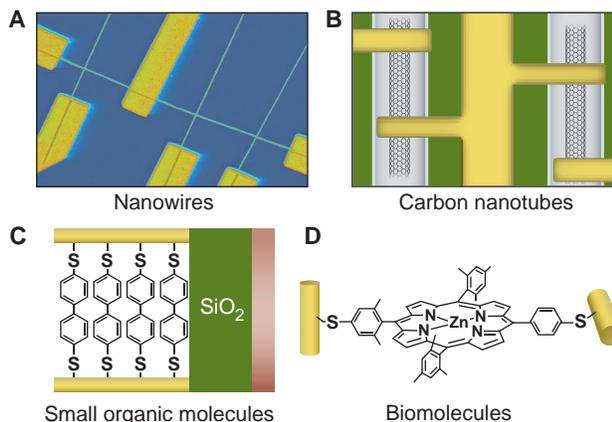
The rapid miniaturization of electronics to the micrometer scale has been a key force driving scientific and economic progress over the past 25 years. Nanometer-scale electronics (nanoelectronics) is the closely watched next frontier (1–5). Two reports in this issue describe dramatic steps toward the realization of electronic nanocomputers. Bachtold *et al.* (page 1317) demonstrate logic circuits constructed from individual carbon nanotube molecules (6). Huang *et al.* (page 1313) have assembled logic circuits from semiconductor nanowires (7).

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In recent years, researchers have reported a variety of molecular-scale wires and switches (8–21), including molecular-scale transistors based on carbon nanotubes (8) and semiconductor nanowires (9). However, the two reports in this issue are the first to advance molecular-scale electronics fully from the single-device level to the circuit level. Both groups developed new methods to meet two key device requirements that previously prevented the realization of transistor circuits. First, the component transistors must produce signal amplification or “power gain” with an output to input ratio much greater than 1. Second, each transistor must be controlled by its own local “gate” contact.

Bachtold *et al.*'s study builds on the same group's earlier discovery that individual semiconducting nanotubes adsorbed between two metal contacts on a silicon substrate behave like the field-effect transistors in today's microcomputers (8). However, the controlling gate contact in that experiment consisted of the entire supporting silicon chip. In such a layout, multiple nan-

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Approaches to molecular-scale electronics. (A) Diodes and transistors based on semiconductor nanowires are assembled with microfluidics to form logic AND, OR, NOR, and XOR circuits and logic functions such as a half adder (7). (B) Carbon nanotube transistors (8) are connected by gold interconnects to construct logic circuits such as a NOT circuit, NOR circuit, static random access memory (RAM) cell, and ring oscillator (6). (C) Field-effect transistors based on self-assembled monolayers of polyphenylene molecules are combined to create a NOT circuit (11, 12). (D) Porphyrin molecules store digital information as electrical charges like dynamic RAM cells (20).

otube devices placed on a chip all must be switched simultaneously. Furthermore, the power gain was less than 1 because the silicon oxide insulator between the gate contact and nanotube was relatively thick, preventing sufficient capacitive coupling between the gate contact and nanotube.

To construct nanotube circuits, the group has now used electron beam lithography to pattern local aluminum gate contacts and exposed them to air to form very thin insulating layers on the aluminum leads (6). Insulator thickness is reduced substantially, enabling the new nanotube transistors to operate independently with a gain ratio in excess of 10, a remarkable increase. By wiring nanotube transistors together with gold interconnects made by lithography, the authors have constructed a range of logic circuits.

Huang *et al.* also build on their earlier achievements in devices to achieve circuits. Earlier this year, the group demon-

strated diodes and bipolar transistors made from nanowires in a crossed geometry (9). In the present work, they assemble OR and AND logic circuits with only diodes, but to construct other circuits required the development of nanowire field-effect transistors.

The new nanowire transistors are formed by placing two nanowires in a crossed geometry and using thermal heating to generate an insulating oxide between the nanowires. As with Bachtold *et al.*'s nanotube transistors, the nanowire transistors feature local gate contacts with thin insulators and are thus easily integrated into transistor circuits.

With the exception of the contacts, Huang *et al.*'s nanowire circuits are assembled without “top-down” methods such as lithography. Instead, “bottom-up” parallel assembly tools such as microfluidics are used. This feature enables them to build and test relatively large numbers of devices and demonstrate readily reproducible behavior in them. Furthermore, Huang *et al.*'s circuits incorporate at least one natural nanometer-scale metric—the constant, small dimension of the crossing points of the nanowires—suggesting that the entire circuits might be shrunk in a straightforward way to the nanometer scale. This capability is important given that the circuits in both studies are still micrometer-scale systems.

The two reports use very different types of nanometer-scale structures and different techniques for assembly, thus pursuing different routes to building electronic nanocomputers. In the variety and complexity of the circuits they have demonstrated, both surpass two other important results in nanoelectronics announced very recently by Derycke *et al.* (10) and Schön *et al.* (11, 12). Derycke *et al.* demonstrated a NOT logic circuit or

"inverter" built from chemically doped nanotubes on a silicon substrate. Schön *et al.* also demonstrated an inverter assembled from field-effect transistors based on a monolayer of small organic molecules (11) and even on single molecules (12), each only 2 nm long.

As impressive as these four very recent demonstrations of molecular circuits are, they build on a long series of important steps by a number of researchers striving to make molecular-scale computers (2–4). The concept for molecular electronic devices and circuits dates back to the seminal 1974 work of Aviram and Ratner (13). Only in the past few years have scientists realized key experimental demonstrations of molecules that serve as wires and switches, which may be divided into four broad categories, according to the type of molecule or molecular-scale structure used to make the devices. The categories (see the figure) are semiconductor and metal nanowires (7, 9), carbon nanotubes and fullerenes (6, 8, 14), small organic molecules (11, 12, 15–19), and biomolecules (20, 21). Structures from three of these categories are used in the recent advances described above.

Despite the broadly based and encouraging recent progress, a set of technical challenges still must be overcome to make a robust, commercially viable computer integrated on the molecular scale. Circuits must be produced that are molecular scale

in their entirety, not just incorporating molecular-scale components. Developing intrinsic metrics (see above) or other means for readily establishing molecular spacing between components and devices would be an important step in that direction. Advances in the chemistry of nanotubes may make it faster and easier to manipulate them and to produce or select nanotubes with specific structures and electrical properties. The nanotube-based circuits discussed above still require selection and placement through time-consuming, arduous nanomanipulation.

The very small sizes of molecules make it possible, in principle, to fit a trillion molecular devices in a square centimeter. What does one do with a trillion devices? Even if the problem of heat dissipation can be overcome for so many densely spaced electrical devices, how can they be harnessed for useful computation? At this level of integration, geometric and dynamic bottlenecks from the proliferation of interconnects, as well as intrinsic latencies, which have been observed even in less densely integrated highly parallel processors, will present new challenges unless innovative architectural approaches can be found. Finally, how does one assemble a trillion devices per square centimeter quickly, inexpensively, and with molecular precision? This facility seems necessary to fulfill the promise of molecular electronics and would have revolutionary implications for nanotechnology.

Until now, though, one of the major challenges facing molecular electronics investigators was the assembly of individual molecules or molecular-scale structures into functioning logic circuits. The fact that four groups have achieved this goal almost simultaneously is an indicator of how far molecular electronics and nanotechnology have come and is very encouraging concerning their robust promise for the future.

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PERSPECTIVES: IMMUNOLOGY

Antigen Presentation—Losing Its Shine in the Absence of GILT

Colin Watts

Before CD4⁺ T cells of the immune system can be activated, they must engage specific class II major histocompatibility (MHC)/peptide complexes on the surface of antigen presenting cells (APCs) such as dendritic cells and B lymphocytes. The T cell then decides whether to proliferate based on the amount and quality of these complexes and the presence on the APCs of other so-called costimulatory signals. Class II MHC/peptide complexes are assembled within the endosomes and lysosomes of APCs prior to their expression on the cell surface. Both the secretory and endocytic pathways furnish these endosomes and lysosomes with newly synthesized class

II MHC molecules, antigen captured by endocytosis, proteolytic enzymes, and other dedicated chaperone proteins. Add the acidic environment required for everything to work optimally, and you have the complete specification for a "reaction vessel" designed to load class II MHC molecules with diverse antigenic peptide species.

Well, not quite. On page 1361 of this issue, Maric *et al.* reveal a new element of the antigen presentation machinery in the guise of an enzyme called GILT (1). As its name implies, GILT (γ interferon-inducible lysosomal thiol reductase) catalyzes the reduction of disulfide (S-S) bonds in protein substrates endocytosed by APCs. To assess GILT's involvement in class II MHC-restricted presentation of antigenic proteins containing disulfide bonds, Maric *et al.* generated a GILT-deficient mouse. So far, they have tested only a

limited set of antigens in their mouse, but for the principal test case, hen egg lysozyme (also called HEL), the results are clear-cut: In the absence of GILT, presentation of two major lysozyme antigenic epitopes to T cells is partially or completely abrogated. These data provide the first demonstration that the battery of proteolytic enzymes found in the endocytic pathway is not always sufficient to release the full spectrum of peptides for T cells to scrutinize.

A requirement for disulfide bond reduction in antigen processing was demonstrated some years ago. This disulfide bond reduction allows improved access of proteases to the antigen substrate (2) and is an evident requirement for those T cell epitopes that contain cysteine residues, which participate in S-S bridges in the native protein (3, 4). But how is this reduction achieved? Although reductants such as free cysteine are known to be transported into lysosomes (5), the acidic conditions found there, although optimal for proteolysis, are unfavorable for disulfide bond reduction and exchange (6). This finding has led to the suggestion that the reduction step may need to be catalyzed in a fashion analogous to, but the reverse of, protein

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