of amplifiers and logic devices based on graphene, actually enables a new class of nonlinear radiofrequency electronic devices. Frequency multipliers[5,6], high-frequency mixers[7] and digital modulators[8,9] have all been recently demonstrated using this principle, with operating frequencies as high as 16 GHz and radiofrequency efficiencies in excess of 90% (ref. 10).

Infrared photodetectors are another class of graphene device that shows higher performance than its silicon counterpart today, despite its relative immaturity[11,12]. Again, these devices benefit from the zero bandgap of graphene, which allows them to absorb light from the infrared to the ultraviolet with almost equal strength. Graphene photodetectors have already been fabricated at very high frequencies and at wavelengths that cannot be accessed with silicon-based devices. These devices will have an important role in the next generation of infrared night-vision systems, optical communications and chemical analysis.

Finally, a key property of graphene, which is often forgotten, is its ability to integrate with almost any substrate. This means that it does not need to replace silicon to be useful: rather, graphene can complement silicon. In the near future, it will be possible to transfer a variety of graphene-based devices onto a prefabricated silicon chip and connect the devices to the chip through the top-level metallization (Fig. 1). In an early demonstration of this concept[13], a silicon chip was covered with a graphene layer that was patterned to form interconnections and delay lines that were controlled by the chip. A huge amount of research has been devoted to the development of methods for integrating new materials (such as III–V semiconductors) with silicon: with graphene, the integration is remarkably simple.

Graphene is an amazing material looking for an application. Meanwhile, the electronics industry is a trillion-dollar giant looking for the next switch. Although graphene may very well provide that switch, it is important to keep our eyes open to other opportunities, particularly those that result naturally from the properties of graphene. Ambipolar nonlinear electronics, broadband photodetectors and advanced sensors are some of them, and they can be easily integrated onto silicon platforms. It is tempting to try to fit any new material into existing technologies and needs. However, we should never forget the words of the semiconductor pioneer and Nobel Prize winner, Herb Kroemer, which he calls his lemma on new technology: "The principal applications of any sufficiently new and innovative technology have always been — and will continue to be — applications created by that technology."[14] There are many applications that benefit from today's graphene, but the best are still to come. ❐

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BIOCOMPUTING

DNA computes a square root

Complex molecular circuits with reliable digital behaviour can be created using DNA strands.

Yaakov Benenson

The field of molecular computing will shortly enter its third decade, but basic terms used by its practitioners are still the subject of lively debate. The terms 'logic' and 'digital', for example, are frequently objected to on the grounds that molecules cannot be reduced to zeros and ones. However, it is only habit that allows electronic switches to be viewed as a 'natural' fit for abstract models of computation, but not molecules. In fact, such models can be projected onto any physical system; the ultimate test is whether the projection is useful. Writing in *Science*, Lulu Qian and Erik Winfree of the California Institute of Technology now report how digital abstraction can guide the design of DNA-based molecular circuits of unprecedented complexity[1].

In molecular logic, analogy is often drawn between the concentration of a molecule and logic values: low concentrations represent 'false' or '0' and high concentrations 'true' or '1'. To launch a computation, concentrations of molecules designated as inputs are adjusted to set their values to true or false as desired; this triggers downstream processes that eventually generate products designated as outputs. In a well-designed digital molecular circuit, the outputs depend on inputs in a Boolean fashion, for example, an AND logic function is implemented by a process in which the output is high only if input 1 is high and input 2 is high.

The more complex these Boolean relations become, the more difficult it is to implement corresponding circuits because the high/low distinction between the inputs tends to disappear, particularly in multistep reactions. Counteracting these natural trends with the experimental construction of large 'digital' networks is of value for two reasons. First, it might help to unravel the 'mystery of life', suggesting how information processing in cells (including seemingly Boolean transformations[2]) could be implemented in practice. Second, it can clarify whether the digital paradigm is in fact the best approach to molecular computing.

Qian and Winfree build on rich previous work that has explored DNA–DNA interactions and the resulting interconversion of single-stranded (ss), as well as partially and fully double-stranded DNA species, without any chemical change to the DNA oligomers themselves[3–5]. The key to their design lies in a systematic

use of signal restoration, which cancels out the signal deterioration in molecular circuits. Without restoration, two parallel experiments with a specific input set to 1.0 and 0.0 may lead, for example, to outputs of 0.7 and 0.3, or even 0.5 in both cases.

The restoration step resets deviating values back to the extremes of 1 and 0, allowing the signal to propagate indefinitely. It is implemented at strategic points in a reaction chain by letting incoming ssDNA molecules partake in two different processes, one fast and one slow. In the fast reaction, the ssDNA bind to a specially designed DNA partner (the 'threshold') and are removed from the cascade. Unbound ssDNA, if such molecules are left, react in a slow, reversible process, catalytically releasing much larger amounts of outgoing ssDNA, leading to a dramatic amplification of the residual signal (Fig. 1a).

The threshold mechanism is also used to perform logic operations. This is carried out in two steps. The first adds all the incoming molecules, generating, in the case of N different inputs, a single outgoing molecule with a concentration between 0 and N. This molecule is channelled into the second step where its concentration has to overcome a preset threshold. In an OR gate the threshold is a little less than 1 so that the gate will generate an output if at least one of the original inputs was 1. In an AND gate the threshold is a little lower than N and this gate will 'fire' when all N inputs are equal to 1. OR and AND gates are sufficient to enable arbitrary logic in a dual-rail approach[6] when each input of an abstract logic computation, such as $Z = X$ AND Y, is represented by two physical signals. For example, $X = 0$ and $X = 1$ are encoded by high levels of two distinct value-zero and value-one molecules. With this approach, the researchers are able to create various digital logic circuits, the most complex of which can calculate the integer part of a square root of a four-bit binary number. In this circuit, the input is encoded in eight DNA molecules and the output in four molecules, with twelve logic gates in between.

Taken together, the work of the Caltech team gets very close to the 'molecular transistor': a simple device that can be reused many times to construct arbitrarily complex circuits. Of course, individual DNA transistors must be chemically distinct from each other, unlike in an electronic circuit where distinction is achieved by judicious placement and wiring of individual parts. However, it is relatively easy to design large sets of DNA molecules that combine both chemical distinction and chemical connectivity: communication between individual gates is implemented by molecules that contain on one end a sequence 'source motif' specific to the gate from which they come, and at the other end a 'destination motif' indicating which gate they are going to (Fig. 1b). In this way, many distinct incoming molecules that share a destination motif can converge on the same gate (fan-in), and one gate can generate outgoing signals for many downstream gates (fan-out).

Despite this impressive progress, challenges remain. Qian and Winfree are concerned with slow processing times in the gates, but the distinction between the fast threshold setting and slow signal conversion is the key design feature, meaning that both steps would have to be accelerated. Furthermore, dual-rail logic requires signals from the real world to be channelled through an additional interface that generates mutually exclusive value-zero and value-one molecular bits. This will entail a complex chain of molecular transformations because the real-world signal (for example, a growth factor or a metabolite) may not be a nucleic acid and because its concentration might differ by orders of magnitude from the standard levels used in the circuit.

One rationale behind making complex molecular circuits is their eventual integration with live cells to modify or augment natural pathways[7]. Until now, logic circuits in cells 'hijacked' natural regulatory mechanisms to implement new

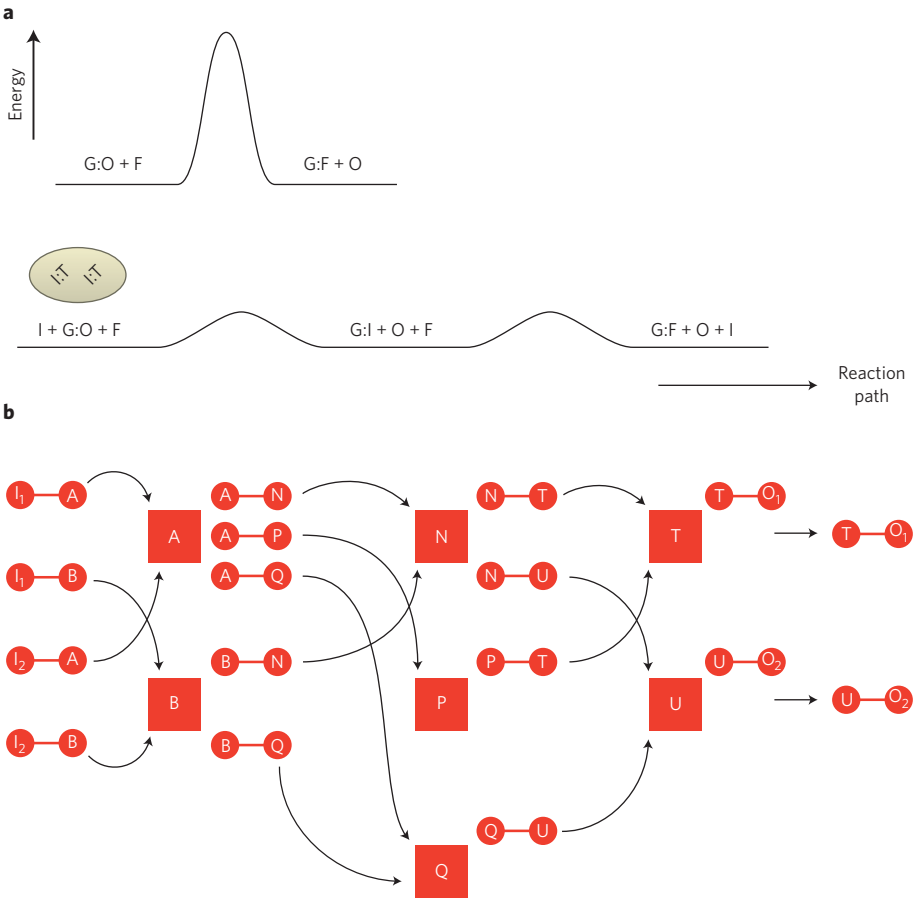

Figure 1 | Key features of the DNA circuits made by Qian and Winfree[1]. **a**, Signal transmission through a gate. Output (O) is bound to a 'gate' molecule (G). A helper 'fuel' molecule (F) can in principle bind to the gate and displace the output, but this process is kinetically very slow (top). However, in equilibrium, the higher the fuel concentration the higher the free output. This is exploited (bottom) by adding an 'input' (I) strand. A certain amount of input is sequestered by the threshold component (T), but the excess can catalyse strand exchange between fuel and output by lowering the activation energy of the transition. **b**, Implementation of complex wiring schemes in the circuits. Each ssDNA signal contains two specific domains indicated by encircled capital letters. The left-hand domain is specific to the gate of origin and the right-hand domain is specific to the gate of destination. The various gates are represented by squares. Letters I and O indicate the original inputs and the final outputs of the computation, respectively.

functions[8]. Taking DNA gates, or even their RNA analogues[9], into cells may create delivery and compatibility challenges. Replacing DNA components with engineered proteins or peptides[10], while preserving the high-level organization of the chemical network, might be an interesting alternative.

Ultimately, the work of Qian and Winfree[1] illustrates how the interaction between natural and information sciences can lead to the development of new molecular computing species. Continuation of such efforts, in conjunction with recent progress in systems and synthetic biology, will further advance the development of a common language to describe information processing both in machines and animate matter. ❐

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SILICON NANOPARTICLES

Isolation leads to change

Nanoindentation experiments and atomistic modelling show that the nanoscale plasticity of silicon changes when the material is no longer connected to the bulk.

Graham L. W. Cross

The mechanical properties of silicon have been crucial to its success in the semiconductor industry because chip designers can improve switching performance by imposing strain to manipulate its bandgap. Recently, discrete forms of silicon such as nanospheres and nanowires have emerged, which could potentially provide an even broader range of applications. However, to successfully develop new devices, it will be important to understand and control the mechanical behaviour of these new isolated forms of silicon, just as was the case with the bulk form of the material.

Nanoindentation — a technique that uses a sharp indenter to probe the mechanical properties of nanoscale volumes of bulk materials[1] — was first developed in the 1980s, and among the first samples to be tested were the silicon wafers used by the semiconductor industry. As the diamond indenter tip was pushed into and out of the sample, curious 'pop-out' events were observed in which the indenter suddenly changed the way it moved out of the material as the force was reduced. It was eventually recognized that the indentation behaviour in silicon often did not follow conventional dislocation-mediated plasticity common to metal crystals. Instead, under the intense contact pressure, the material went through a thermodynamic phase transformation to an amorphous semimetallic phase before deforming[2]. The pop-outs, which signify a reversal of this phase transformation as the pressure is released, have become a hallmark of silicon plasticity in small volumes at the bulk surface.

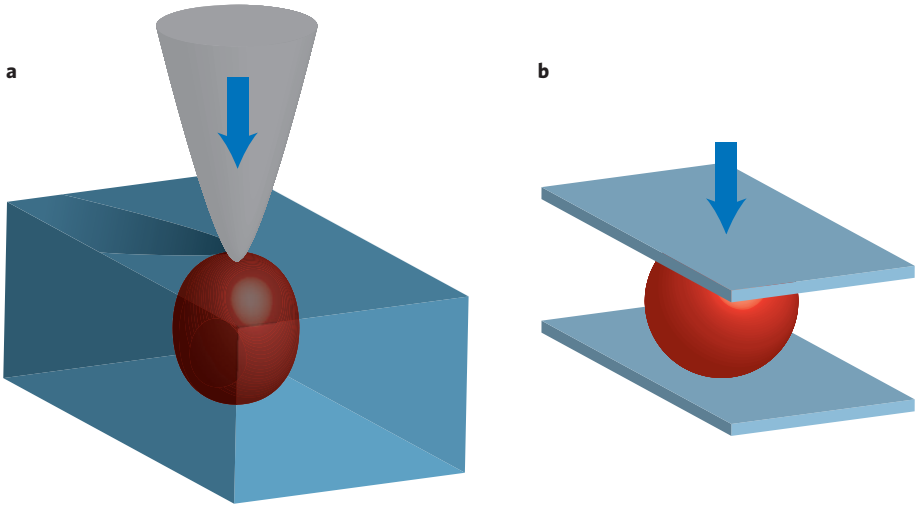

Figure 1 | The plastic behaviour of equivalent small volumes of silicon depends on their surroundings. **a**, In a conventional nanoindentation experiment, a diamond tip pushing against the surface causes stress throughout a small volume of material (red region) that is connected to the bulk. Phase transitions occur in this volume leading to the flow of amorphous material during the indentation. **b**, Conversely, Nowak and colleagues[3] show that when an isolated silicon sample with the same volume is compressed between two parallel plates, deformation proceeds through conventional crystal plasticity with the nucleation and propagation of dislocations. The blue arrow indicates the direction of the applied load.

Writing in *Nature Nanotechnology*, Roman Nowak and colleagues[3] now report a wholesale change in the mechanical behaviour of nanoscale volumes of silicon when the material is no longer connected to the bulk. The researchers — who are based at Aalto University, the University of Silesia, the University of Minnesota and Nagaoka University of Technology — performed compression experiments on silicon nanospheres ranging in size from 20 nm to just under 200 nm. In a process they term 'deconfinement', a qualitative