Scaling Up DNA Computation
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BIOCHEMISTRY

Scaling Up DNA Computation

A technique uses DNA strands to perform calculations that can be scaled up in complexity.

John H. Reif

Computation is increasingly pervasive. Silicon-based computing devices are embedded in a wide variety of manufactured goods and appliances, increasing functionality, communication, and control. An analogous development of molecular-scale computing devices could allow similar advantages at vastly smaller scale. For example, embedding molecular-scale computing devices in biological materials such as serum, cells, or tissues could be used to detect, and possibly treat, disease. On page 1196 of this issue, Qian and Winfree (*1*) show how such molecular-scale computing devices might be engineered.

One increasingly promising approach, known as DNA-based computation, makes use of DNA in conjunction with biochemical reactions to do molecular computation. The advantage of this approach is that DNA is very stable, and biochemical reactions involving DNA have been very well developed for over a decade. The DNA hybridization reaction occurs when single strands of complementary DNA form double-stranded DNA in a double-helix conformation. DNA can self-assemble via hybridizations into secondary structures known as DNA nanostructures (*2*). DNA computations can be performed by self-assembly of DNA strands (*3*) and self-assembly of static DNA nanostructures (tiles) (*4*). Thus, DNA is used as an engineering material; the interactions that hold a DNA structure together are encoded in the base sequences of the strands. Computation can be incorporated into the assembly of the strands into DNA arrays and nanostructures. Alternatively, DNA-based computations often use dynamic DNA nanostructures to encode computational state, and computational steps are executed using biochemical reactions that manipulate these DNA nanostructures, changing the encoded state.

The approach adopted by Qian and Winfree marks an important advance in DNA-based computations. The authors make use of dynamic DNA nanostructures called seesaw gates (*5*) and thresholding gates, within which DNA strands can hybridize in certain positions to encode Boolean values ("True" and "False"). There are multiple advantages to this approach. One is its simplicity. Their method uses only DNA hybridization reactions. Logical operations (AND and OR) are executed by seesaw gates, and restoration to the digital values is through thresholding gates followed by catalytic amplification of any leftover signal. Another advantage of the approach used by Qian and Winfree is that logical operations are executed autonomously—that is, without external control. The DNA hybridization reactions form chain reactions, whereby DNA hybridizations executed by seesaw gates cause further DNA hybridizations in other seesaw gates. The authors use toehold-mediated strand displacement (*6*) to initiate DNA hybridizations that displace previously hybridized DNA strands, and they drive the operations through transitions of "fuel" strands (*7*, *8*) to lower energy states.

A further advantage of the method is its universality. The ability to evaluate a Boolean circuit with multiple Boolean gates provides universal computation power, because any digital computation can be executed by Boolean circuit evaluation. Moderate scalability provides yet another advantage of this approach. The modularity of seesaw gates allows composition of multiple gates independently to a much larger scale than permitted by most previous DNA-based computations. The scalability is indicated by the authors' demonstration of error-free computation of square roots of four-bit numbers.

A multidisciplinary approach including computer science and biochemistry was key to the project's success. In addition to biochemistry laboratory techniques, computer science techniques were essential. Dual rail logic converted arbitrary Boolean logic (NOT, AND, and OR) into seesaw gates executing only AND and OR operations. Computer simulations of seesaw gate circuitry optimized the design and correlated experimental data. Design compilers for DNA sequences of seesaw gates were developed.

Two limitations of the work by Qian and Winfree present further challenges. The speed of execution of seesaw gates is a major obstacle to scalability and usability of seesaw circuits for biological applications. Each seesaw gate takes 30 to 60 min. Their computation of four-bit square roots has a circuit depth (the maximum number of Boolean operations that need to be sequentially executed) of 7 and takes 6 to 10 hours. By contrast, biological regulatory circuits can respond much faster, often in less than a second. Another limitation is the number of molecules used in computations. Qian and Winfree executed a seesaw circuit computation simultaneously on a vast number (trillions) of DNA molecules within a test tube, whereas biological regulatory circuits make use of relatively small numbers of molecules for a given task.

Why these limitations? A molecular computation is defined as global if its state is spatially distributed (i.e., determined by averaging concentration and configuration of spatially distributed molecules defining the state), and transitions of state are executed

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through multiple distributed interactions. Seesaw circuits are global, and their logical operations require long durations for diffusion of DNA signals between gates. One approach to solving such challenges is to exploit locality, a technique extensively used in modern conventional computing devices. A molecular computation is considered to be local if its state is encoded by a spatially contiguous set of molecules (i.e., the state of each computing element is explicitly determined by the configuration of these molecules), and transitions of state are executed through interactions between local computing elements. By avoiding delays due to diffusion, local molecular computations may execute more rapidly. Also, due to locality, the number of molecules involved in a single computation is vastly reduced. Biological regulatory circuits are usually local, operating within a confined region such as a cell wall or cell organelle, and this may contribute to their generally more rapid rates. Whiplash polymerase chain reaction (*9*) is a local DNA computation in which polymerization reactions execute state transitions on a single DNA molecule. It remains a challenge to develop DNA-based computational methods that are local and only make use of DNA hybridization operations (and do not require enzymes). A promising approach is to tether together strands and gates used in a hybridization reaction to ensure locality.

A further challenge is to execute molecular computations within biological materials (e.g, serum, cells, or tissues) where the use of DNA-based computational methods is limited by the presence of DNA-binding and DNA-cutting proteins. Possible approaches include using DNA with nonstandard bases or short RNA, both of which may be less susceptible to these proteins.

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PLANETARY SCIENCE

Io's Tortured Interior

Magnetic measurements made by the Galileo spacecraft reveal an ocean of magma under Io's frozen surface.

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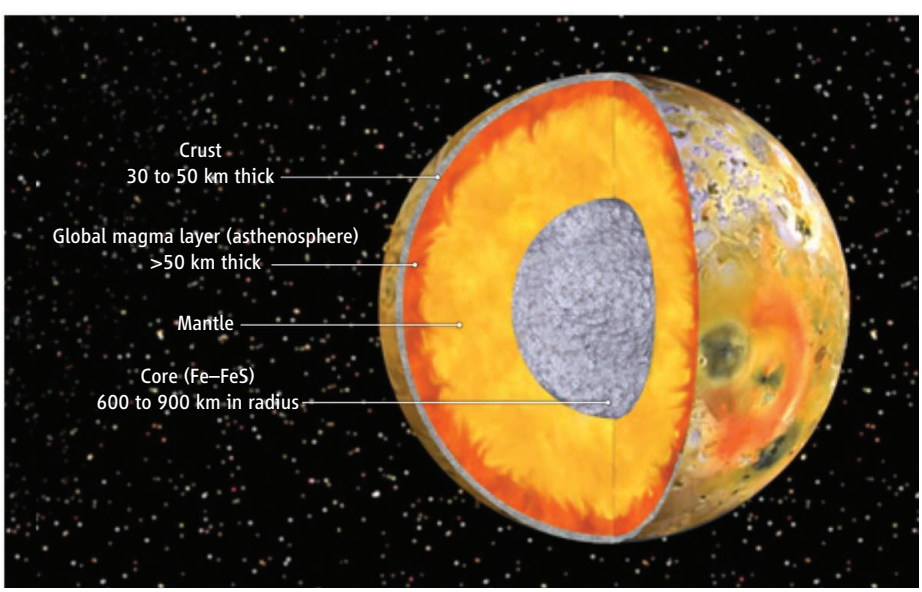
Jupiter's moon Io is the most volcanic object in the solar system, injecting about a metric ton per second of sulfurous material into Jupiter's magnetic environment. Images and movies from spacecraft have caught Io's volcanoes in the act of erupting since their discovery by Voyager in 1979. This prolific activity hints at a tortured inner structure. On page 1186 of this issue, Khurana *et al*. (*1*) report magnetometer data obtained by the Galileo spacecraft and use it to infer the presence of a global magma ocean at least 50 km thick under Io's icy, pock-marked, and colorful surface. This result makes Io stand out as unique among its icy satellite siblings at Jupiter, Saturn, and beyond, where the other subsurface oceans are water-rich. It also confirms the importance of magnetic field and plasma instruments in probing the internal structure of solar system bodies.

Techniques such as gravity measurements, ground-penetrating radar, radar to provide body shape, and seismometers on the surface can probe the internal structure of icy satellites from relatively brief spacecraft flybys and detect oceans of magma or of water. However, these capabilities were either unavailable or not precise enough to be definitive on Galileo. The Galileo team used magnetic field measurements from close flybys of Europa and other moons, combined with modeling of the interior conductivity (*2*, *3*). The idea is to use Jupiter's rapidly rotating (9-hour 55-min period) magnetic field as it overtakes the slower-orbiting moon. If the moon in question is conducting, a magnetic field is induced, the effects of which can be measured by the onboard magnetometer as the spacecraft flies past. Detailed modeling of subsurface conducting regions and the plasma environment, using concepts from geology and external plasma interactions, is then used to understand the measured magnetic field and its time variation (*2*, *3*). The technique emphasizes the coupled nature of icy satellite interactions, from the interior structure through the surface and exosphere to the surrounding plasma environment, and requires exchanges of material and momentum at all the interfaces.

A technique similar to that used at Europa (*2*, *3*) was used to discover subsurface water



Probing inside. Khurana *et al*. modeled magnetometer data to unveil the inner structure of Io with a thick magma ocean beneath the frozen surface.

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