NEWS & VIEWS

NANOTECHNOLOGY

Molecular robots on the move

Lloyd M. Smith

Robots have to store lots of information in order to coordinate their actions, but how can this be done for nanometre-scale robots? One answer is to program data into the robots' environment instead.

The idea of tiny machines that can execute complex functions has been a mainstay of science fiction for many decades. In the 1966 movie *Fantastic Voyage* (Fig. 1), a micrometre-sized shrunken submarine is injected into a human to find and destroy a life-threatening blood clot; and in Michael Crichton's 2002 novel *Prey*, swarming nanorobotic devices threaten global destruction. Such events remain a fantasy, but 'nanobots' are not so far-fetched. In this issue, two papers[1,2] describe the latest steps in attempts to implement an autonomous, programmable molecular robot.

20TH CENTURY FOX/THE KOBAL COLLECTION

Figure 1 | Nanomachines in science fiction. A miniaturized submarine was injected into a man in the film *Fantastic Voyage*. Although such machines are still a fantasy, molecular 'robots' made of DNA are under development[1,2].

Both papers trace their origins to the field of DNA computing, which began in 1994 with Leonard Adleman's seminal paper[3] describing the use of DNA molecules to solve a small example of the travelling-salesman problem — a task that involves calculating the shortest possible route between several locations, visiting each location only once. Since then, DNA computing has slowly morphed into the field of DNA nanotechnology, in which increasingly complex and sophisticated examples of DNA-based nanostructures are imbued with various logical, chemical and physical properties.

In the past decade, two fascinating developments have occurred in this field. First, motile molecules, known as DNA walkers, have been designed and built[4]. These molecules are powered by energy derived from DNA hybridization (the process in which complementary single strands of DNA form a duplex), consuming 'fuel' oligonucleotides[5] as they move from one binding site to another on a DNA-modified surface. Then, in 2006, Paul Rothemund[6] showed how one could fold DNA molecules into any desired two-dimensional shape to make so-called DNA origami. The two papers[1,2] in this issue now show how to integrate DNA walkers, DNA origami and other nanoscale technologies to program the behaviour of nanomachines on surfaces. Lund *et al.*[1] (page 206) describe how one can control and direct the motion of the walkers along a desired path, whereas Gu *et al.*[2] (page 202) have put together a nanoscale 'assembly line' that serves as a prototype molecular factory.

Lund *et al.*[1] report a system in which the movement of a DNA walker known as a molecular spider[7] is directed across a surface. The spider consists of a streptavidin protein adorned with four single-stranded DNAs, three of which are 'DNAzymes' that act as the legs of the machine. DNAzymes are DNA molecules that catalyse a chemical reaction; in this case, the reaction cleaves a DNA strand on the surface, a process that shortens the length of that strand. The role of the fourth DNA strand on the spider is to anchor the beast at its starting point on the surface. Once the spider starts to move, the anchor strand goes along for the ride.

The surface traversed by the spider is a sheet of DNA origami, designed by Lund *et al.* to contain cleavable DNA strands whose base sequences are complementary to those of the spider's legs. Each step taken by the spider occurs as follows. First, the legs form duplexes with complementary surface strands. One of these strands is then cleaved by the DNAzymes in the legs, weakening the interaction of the spider with that strand. The spider therefore desorbs from the strand, forming a new duplex at another site farther down the track. By repeating this cycle over and over, the spider moves from one binding site to another along a path 'programmed' into the DNA origami surface. The spider comes to a halt when it binds to uncleavable DNA strands at the end of the track.

Gu *et al.*[2] bring a third component into the mix. In addition to an origami track and a DNA walker, their system incorporates DNA machines[8] that hold nanoparticle cargoes. These machines can be set up either to donate their cargoes to a passing walker or to keep their load. The authors used three machines in their systems, each bearing a different nanoparticle cargo. There are therefore eight (2^3) possible ways in which a walker can be loaded with cargo as it passes down this 'assembly

line' of loading devices. This is the first time that systems of nanomachines, rather than individual devices, have been used to perform operations, constituting a crucial advance in the evolution of DNA nanotechnology.

The cargo-carrying DNA walkers[2] differ from Lund and colleagues' spiders[1] in that they have seven single-stranded DNAs appended: four 'feet' that move along the specially constructed surface, and three 'arms' to pick up nanoparticle cargoes. What's more, the feet are not DNAzymes. Instead, the walker's locomotion depends on single strands of DNA (anchor strands) that join together other single strands on the walker's feet and on the surface. When fuel strands are added to the system, they preferentially hybridize to these anchor strands, displacing the walker's feet and thereby freeing them. The authors thus control the binding and release of their walker's feet simply by adding anchor or fuel strands.

There are several interesting concepts lurking in these papers[1,2]. Lund *et al.*[1] point out that macroscopic robots generally have to store a fair amount of information to provide "internal representations of their goals and environment and to coordinate sensing and any actuating of [their] components". Molecular robots, however, have limited ability to store such complex information. In both devices[1,2], the motion of the walkers is thus programmed into the DNA surface, rather than into the walkers themselves. Similarly, by setting the cargo-donating machines into predetermined loading or non-loading states, Gu *et al.*[2] also use information stored in the walker's environment to control the outcome of their system.

Another neat idea is Lund and colleagues' use of surface DNA strands[1] to control their spider's direction of movement, without which the spider would only randomly wander around on the surface. With shorter, cleaved binding sites behind it, and longer, uncleaved binding sites in front of it, the spider's time-averaged, net motion is weighted in the forward direction because its legs spend more time on the longer binding sites. The device thus creates a chemical gradient that controls its own behaviour.

Although both papers[1,2] integrate DNA walkers with origami landscapes, they differ in one important respect. Lund and colleagues' device[1] is autonomous — no external intervention is required for it to execute the program built into the system. By contrast, Gu and colleagues' device[2] relies heavily on external interventions, most importantly the addition of new DNA strands to drive the movements of the walkers and the operation of the cargo-carrying DNA machines. The reward for this lack of autonomy is greater complexity of behaviour: whereas Lund and colleagues' robot is currently limited to walks along a path, Gu and colleagues' robot can pick up cargo while walking, and can adopt eight states that correspond to different manufacturing possibilities. Future work will seek to maintain autonomy while ramping up the attainable complexity of behaviour programmed into molecular systems.

Although we remain far away from the possibilities imagined for nanotechnology by science fiction, it is inspiring nonetheless to see such creativity and rapid progress in the development of autonomous molecular systems that can execute complex actions. This is undoubtedly a field to watch. ■

Lloyd M. Smith is in the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, USA.
e-mail: smith@chem.wisc.edu

1. Lund, K. *et al. Nature* **465,** 206–210 (2010).
2. Gu, H., Chao, J., Xiao, S.-J. & Seeman, N. C. *Nature* **465,** 202–205 (2010).
3. Adleman, L. M. *Science* **266,** 1021–1024 (1994).
4. Bath, J. & Turberfield, A. J. *Nature Nanotechnol.* **2,** 275–284 (2007).
5. Yurke, B., Turberfield, A. J., Mills, A. P. Jr, Simmel, F. C. & Neumann, J. L. *Nature* **406,** 605–608 (2000).
6. Rothemund, P. W. K. *Nature* **440,** 297–302 (2006).
7. Pei, R. *et al. J. Am. Chem. Soc.* **128,** 12693–12699 (2006).
8. Yan, H., Zhang, X., Shen, Z. & Seeman, N. C. *Nature* **415,** 62–65 (2002).

ORIGINS OF LIFE

Common ancestry put to the test

Mike Steel and David Penny

The question of whether or not all life on Earth has an ultimate common origin is a subtle one, complicated by the phenomenon of lateral gene transfer. It has now been tackled with a formal statistical analysis.

Charles Darwin predicted and biologists accept the theory that all extant life traces back to a common ancestor. But how can we formally test the idea? There is a compelling list of circumstantial evidence — for instance, the 'universal' genetic code. However, addressing the question of common origin by applying formal statistical tests to the vast array of molecular sequences now available from all domains of life has long been a challenge. On page 219 of this issue, Theobald[1] does just this, and concludes that the accepted view holds.

His approach starts with amino-acid sequences from 23 highly conserved proteins taken from groups that span the three domains of life (eukaryotes, bacteria and archaea). He then applies standard programs for inferring evolutionary trees (or networks) from the protein sequences. The third step is to compare the likelihood values of different models of sequence evolution, and thus different ancestry hypotheses, adjusting for the principle that larger numbers of free parameters are expected to give arbitrary improvement to how well a particular model fits the data. However, taking that into account, Theobald finds strong support for the unity of life compared with even two independent origins.

Perhaps the most interesting aspect of Theobald's work[1] is not the conclusion — common ancestry is the default view in science. But a formal test of evolution itself requires considerable ingenuity. Amino-acid sequence similarity alone does not imply common ancestry, because it might be due to convergent evolution. Lateral gene transfer between organisms and uncertainty about the best model of sequence evolution also confound statistical testing of common ancestry.

Theobald's paper reports strong support for the common-ancestry hypothesis over alternatives proposing that any one of the three domains of life had a separate origin (including, for example, some archaea that seem to be genetically and morphologically distinct from other life forms). The findings are in line with a phrase from the much-quoted final paragraph of *On the Origin of Species* that "probably all organic beings which have ever lived on this earth have descended from some one primordial form".

Does this mean that life arose just once, more than 3.5 billion years ago? Not necessarily — logically, it is possible that life arose more than once, but that only one of these original life forms has descendants that survive today[2]. It is also possible that there could have been more than one origin of life that has extant surviving descendants. The claim is simply that all known life has at least one common ancestor, a last universal common ancestor (LUCA). Such a LUCA may also not have been the first organism on Earth. These subtleties concerning origins have recently been discussed by the philosopher Elliot Sober[3].

Theobald's analysis[1] is definitely not an argument for a 'tree of life' in place of a reticulate network that shows extensive lateral gene transfer, particularly in early life and in bacteria and archaea[4,5]. Indeed, Theobald considers networks, and 9 of the 23 proteins he analyses are thought to have undergone horizontal transfer early in evolution. There is nothing here that is new. Darwin himself always referred to his "theory of descent with modification", a phrase that allows for gene transfer between an endosymbiotic organism (such as the mitochondrion precursor) and its host, or laterally between free-living organisms — it is the test of ultimate common origin that is the important part of the current paper.

For decades, biologists have been using