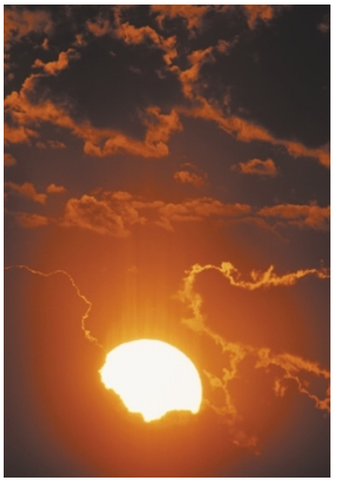
TECHNOLOGY

The dawn of biocomputing?

Although computers have solved some of the most complex problems of the past 60 years, rumour has it that they are running out of steam — it seems that silicon cannot physically meet our growing demands for computational power. But there's one computer that is based on a technology that has been perfecting itself for three billion years — the 'DNA computer'. It runs on materials that are cheap, plentiful, energy efficient and can store a vast amount of information in an extremely small space. But can it solve complex problems? Yes, according to Leonard Adleman's group, who have shown that a DNA computer can select the right answer out of one million possibilities — the most complex problem that has been solved by non-electronic means — so demonstrating that biological molecules might provide the computing power of the future.

Conventional computers store information in a memory using a binary code — 'on' or 'off' — and manipulate this information by using a microchip. Eight years ago it was realized that a DNA computer could store information in DNA using its four-base code, and could manipulate this information by exploiting the speed and specificity with which nucleotides bind to their complementary partners. If the solution to a problem were expressed as a unique sequence of DNA, then the solution could be found by weeding out all the alternative solutions (sequences) that were not complementary. DNA binding allows alternative solutions to be tested in parallel, rather than one at a time, which speeds up the operation.



The logic problem described in Braich *et al.*'s paper illustrates the point. A DNA computer was asked to identify the correct solution to a complex logic problem with 20 variables that were related to each other by 24 conditions, or clauses. This is a mind-boggling problem that has over a million possible solutions to it. Adleman and colleagues built a DNA computer in which each possible solution was represented by a 300-bp DNA molecule. These were run through an electrophoretic chamber, in which they were allowed to bind to a set of 15-nucleotide probes selected in such a way that only those strands that satisfied the first clause would bind (this clause might specify, for example, that the solution bind to oligos 1 and 2 but not to oligo 3). The library strands that were not captured were washed away, whereas those that had bound were used in a second hybridization reaction with oligonucleotides selected in such a way that only those strands that satisfied the second clause would bind. The process was repeated until all 24 clauses were satisfied. The one in 2^{20} correct solution to the problem was the only library strand that satisfied all 24 clauses (the only one that was not washed away). Such a strand could be amplified by PCR and visualized on a standard DNA gel.

So, should electronic computer technology developers be trembling in their boots? Well, not just yet; although this work has shown that DNA computing can do harder maths than it ever has before, an electronic digital computer could have solved the same problem in just a few seconds.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Braich, R. S. *et al*. Solution of a 20-variable 3-SAT problem on a DNA computer. *Science* 14 March 2002 (DOI 10.1126/science1069197)

FURTHER READING Adleman, L. Molecular computation of solutions to combinatorial problems. *Science* **266**, 1021–1024 (1994)

WEB SITE

Len Adleman's lab: http://www.usc.edu/dept/molecular-science/fm-adleman.htm

IN BRIEF

CLONING

Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy.

Rideout III, W. M. *et al*. *Cell* **109**, 17–27 (2002)

In this proof-of-principle study, Rideout *et al.* have tested whether a genetic defect in somatic cells can be corrected using a combination of therapeutic cloning and gene therapy. They began by deriving ES cells from cloned blastocysts generated from the transferred nuclei of *Rag2*$^{-/-}$ mice. The *Rag2* defect in these cells was then corrected by gene targeting, and mice were derived from the corrected cells by tetraploid complementation. These mice developed with normal B- and T-cell populations; moreover, when their bone marrow cells were transferred to *Rag2*$^{-/-}$ mice, they restored immune function in the transplanted mice. However, haematopoietic stem cells derived *in vitro* from the corrected ES cells were unable to repopulate the haematopoietic compartment in *Rag2*$^{-/-}$ mice because of natural-killer-cell-mediated graft rejection, raising the point that even genetically identical cells derived by therapeutic cloning can still face host-mediated transplantation barriers.

COMPLEX DISEASE

A polymorphism in the β1 adrenergic receptor is associated with resting heart rate.

Ranade, K. *et al. Am. J. Hum. Genet*. **70**, 935–942 (2002)

Resting heart rate is positively correlated with cardiovascular and coronary mortality, and so understanding the environmental and genetic factors that influence variation in resting heart rate in human populations could help to identify people at risk. By genotyping >1,000 individuals for two polymorphisms (Ser49Gly and Arg389Gly) in the β1 adrenergic receptor gene — which is required for cardiac function — the authors have shown that the Ser49Gly substitution is significantly associated with resting heart rate. This is the first time a specific polymorphism has been associated with this trait. Furthermore, the two alleles seem to be acting additively, with the heterozygote individuals having a mean resting heart rate intermediate to either homozygote.

GENE EXPRESSION

A molecular link between gene-specific and chromosome-wide transcriptional repression.

Chu, D. S. *et al. Genes Dev.* **16**, 786–805 (2002)

A combination of local and global mechanisms of transcription regulation ensures appropriate gene expression. Although, in most cases, distinct proteins are responsible for each mechanism, *Caenorhabditis elegans* SDC-2 can bring about both. It triggers dosage compensation — a process in which a specialized protein complex associates with hermaphrodite X chromosomes to bring about a twofold reduction in X-linked gene expression. It also specifically downregulates *her-1*, an autosomal gene that directs male development. The authors show that it does so by recruiting the dosage-compensation machinery to the *her-1* locus, and it seems that whether the mode of repression is local or global depends on the DNA target sites with which the complex interacts.