Shrinking the building block

The nanowire may bring in the next order of miniature electronics, says s ananthanarayanan

THE emerging science of nanotechnology consists of using materials shaped and assembled not by dies and fasteners but through the use of atomic and molecular forces that help the formation of crystals and natural materials. The simplest nanomaterials are sheets, tubes and shells of carbon atoms and these have powerful electrical properties that are finding application in connecting electronic or optical components in computer circuits to enable miniaturisation and speed that is not feasible with normal connecting elements. But a further level of miniaturisation is that the electronic components themselves be made up of nanomaterials, which has been described by Charles Lieber of Harvard University and colleagues in their paper in the journal *Nature*.

The great leap forward was when the vacuum tube was replaced by the transistor. The latter used a property of semi-conductor materials to create junctions that could pass electricity only in one direction, or allow a greater current to flow if a tiny voltage at one terminal was varied. The property of allowing only one-direction flow could be assembled into logic circuits and the other property could amplify the variations in the tiny voltage applied at one terminal by mimicking the variation in a much larger current flow through the device.

Semi-conductors are materials that have an atomic structure similar to the carbon atom and form regular crystalline lattices. If such a crystal of silicon, which has an electronic structure that bonds with four other carbon neighbours, is "doped" with an impurity of a material like *boron*, which bonds with only three neighbours, then wherever boron replaces silicon in the lattice one of the neighbours will have no bond! This free bond becomes a carrier of charge and helps the silicon crystal, which barely conducts electricity, to become a conductor. Another type of "doping" is to add an impurity like phosphorus that has an extra bond. This fifth bond then has no neighbour to connect to and is again free to help pass an electric current.

Now, when two such materials, one of each type, are brought together, the "extra" bond from one material can jump to the other that is looking for bonds, but the "lack of a bond" in the second material cannot cross over to the other material because there is nothing, really, to cross over. The result is that the current of bonds, which is the electric current, can move from one side to the other, but not the other way.

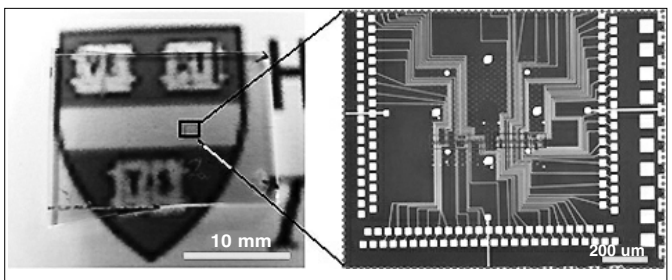
This principle enabled the bulky vacuum tube to be replaced by the handy transistor, and the semi-conductor diode to miniaturise radio sets with wide impact and, equally important, the digital computer.

Integrated circuits

The next phase of miniaturising was the integrated circuit, where a brace of semi-conductor devices was built side by side on the same semi-conductor base. Single crystals of silicon were grown and sliced into wafers.

Dopants were deposited to create the two kinds of semi-conducting materials, with junctions and connectors all built on to the same dime-sized silicon chip. Chips could then be designed to have electronic circuits for a whole function, like providing a wave of some frequency or generating a particular voltage or for amplifying signals, and so on, all on a tiny, prefabricated chip. Once the templates for the processes were ready, the chip could be mass-produced and this lowered the costs substantially.

The integration of circuits has made great progress and the main processor of present day computers is a massive integration of millions of components that allow for the performance of all the complex functions. The limitation to increasing the complexity, in fact, is to soon be that components would start being the size of a crystal or molecular structure and the distances over which information is passed would be of the size of the wavelength of signals employed. It does look like some built-in "size limit" will soon be encountered.



A pair of miniature, programmable logic circuit building blocks

Nanotechnology

The group of scientists at Harvard made use of electronic components created from nanowires.


Charles M Lieber and colleagues have reported on their achieving a marriage of nanowires and neurons.

Nanowires of silicon or germanium, the main semi-conducting materials, are of the order of a billionth of a metre in thickness, for whose production techniques have now become available. The most successful methods are growing the wires from the "bottom up", or by allowing a combination of atoms in the form of vapour or in a solution to build from a nucleus. Adding the dopants to the source then creates nanowires of doped semi-conductors. Wires of different materials can be joined or the same wire doped differently at different places to yield an electronic component within itself.

Simple "logic gates", using individually assembled semi-conductor nanowires and carbon nanotubes have been developed over the past 15 years. But these devices had 16 components at the most and could perform only one predestined function. Lieber and colleagues have gone further, to build circuits of interconnected transistors whose working can be controlled by passing pulses of electric current that allow individual transistors in an array to be switched between inactive and active states. A group of such components, which could perform some logic function, form a *logic tile*, with an area of only ~960 square micrometres, and include 496 of the configurable transistors in two interconnected arrays. Each tile can be programmed to perform a specific digital logic operation and it can be connected to other tiles, with sufficient power to drive other tiles in a cascading sequence.

A series of such tiles, which are so called because they can be laid side by side and interconnect with each other, could then be used to assemble a complete processor, with the ability of addressing the cells of a computer memory and providing outputs to peripheral devices. Being composed of nanomaterials, the parts of the assembly would be microscopic and may be the dream solution for dealing with problems that are arising in miniaturising in the conventional way. The capability to build processors for different purposes with the logic tile building blocks opens the possibility of miniature embedded systems, including devices for medical uses.

The writer can be contacted at simplescience@gmail.com

Decoding differences

The study of the transcription process — its initiation, control and termination — is one of the most active and exciting areas in modern genetics, writes tapan kumar maitra

ALTHOUGH all aspects of transcription differ to some extent between prokaryotes and eukaryotes, we will look at two major differences here — the coupling of transcription and translation that is possible in prokaryotes, and the extensive post-transcriptional modifications that occur in eukaryotic messenger RNA.

In E. coli, translation of the newly transcribed messenger RNA into a protein can take place before transcription is complete. The messenger RNA is synthesised in the 5' à 3' direction, and it is near the 5' end that translation begins. As soon as the 5' end of the RNA is available, a ribosome can attach to the messenger RNA and move along it in the 5' à 3' direction, lengthening the growing polypeptide as it moves.

When the first ribosome moves away from the 5' end of the transcript, a second ribosome can attach and begin translation. These processes are repetitive, as electron micrographs clearly show. In eukaryotes, however, messenger RNA is synthesised in the nucleus, but protein synthesis takes place in the cytoplasm. Before a eukaryotic messenger RNA leaves the nucleus, it is highly modified by processes that generally do not occur in prokaryotes.

Promoters

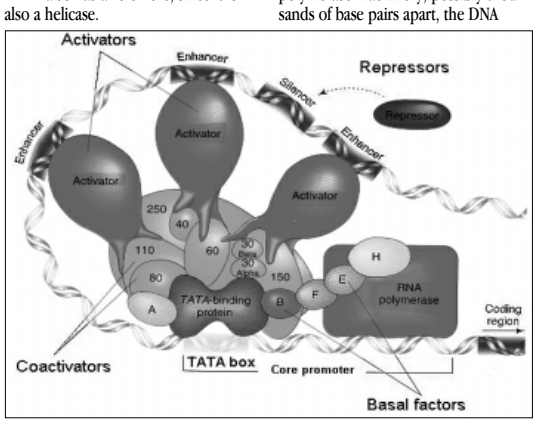
Eukaryotic promoters are somewhat similar to prokaryotic promoters; both are regions of DNA at the beginnings of genes with signals that allow RNA polymerase to attach and begin transcription. In eukaryotes, however, more proteins are involved in promoter recognition and more proteins are involved in the control of transcription, many recognising signals thousands of base pairs away.

All three eukaryotic RNA polymerases recognise a seven-base sequence, TATAAAA, located at about -25 on the promoter DNA. It is similar to the - 10 sequence in prokaryotes and is called the TATA box (or Hogness box after its discoverer. D Hogness.)

Among the large number of promoters that have been sequenced, a few lack the TATA box, yet are still transcribed. Transcription initiation in these promoters appears to be controlled by a CT-rich area, called the initiator element (Inr), at + 1 of the transcript — close to the transcription start site — coupled with a down stream promoter element (DPE) at about + 28 to + 34 of the transcript. In TATA-less promoters, a protein called TFIID requires both these elements to bind. The initiator element has a consensus sequence of TCA (G or T) T (T or C) and the downstream promoter element has the consensus sequence of (A or G) G (A or T) CGTG.

Yeast RNA polymerase H is a protein of 12 subunits. This enzyme cannot locate promoters or attach to DNA in a stable fashion. To attach at the beginnings of genes, RNA polymerase II must interact with several proteins called general transcription factors. In eukaryotes, general transcription factors are named after the polymerase they work with. Thus, the transcription factor that recognises the TATA box for polymerase if genes is called TFIID — D being the fourth letter of the alphabet for the fourth transcription factor so named. TFIID is composed of one subunit that recognises the TATA sequence, called TATA-binding protein (TBP) and up to a dozen other proteins called TBP-associated factors (TAFs), which recognise the initiator element, when present, and aid in regulating transcription. TFIID is, in essence, similar to the sigma factors of prokaryotic RNA polymerase. One interesting aspect of the binding of TBP is that it causes a significant bending and opening of the DNA. This bending may be an important signal for other binding proteins.

Once TFIID binds to the TATA box, a cascade of recruitment (binding) of other transcription factors takes place. Transcription factors HA, JIB, and IIF bind, as does RNA polymerase II in an unphosphorylated state. Then transcription factors IIE and IIH bind, forming a pre-initiation complex (PIC), equivalent to the E. coli holoenzyme. The RNA polymerase II is then phosphorylated, presumably by TFIIH, which is a kinase; at this point, most of the transcription factors drop off, leaving the elongation complex, which carries out a basal rate of transcription. TFIIH also has a role here, since it is also a helicase.



The TATA box or Hogness box named after its discoverer D Hogness.

For activated transcription to take place, other factors are needed that are involved in controlling which promoters are actively transcribed. These other factors are activators or specific transcription factors that bind to DNA sequences called enhancers. Enhancers are often hundreds or thousands of base pairs upstream from the promoter. Note that much of this information has been gathered by footprinting, mutational studies, cloning and isolating the genes and proteins involved, and then reconstituting various purified combinations in the test tube. These studies are combined with kinetic research to determine which arrangements are stable, immunological research to isolate various components with antibodies, and photocrosslinking studies to determine which moities are in contact with each other.

These specific transcriptional activators have domains (regions) that recognise their specific enhancer sequences, regions that recognise proteins associated with the polymerase (general transcription factors) and regions that allow the joint attachment of other transcription factors. Similar to activators and enhancers, repressors can bind to silencer regions of DNA, often far upstream of the promoters, to repress transcription. Thus, many genes are associated with numerous and complex arrangements of transcription factors, providing elaborate control of transcription.

For specific transcription factors to attach to both enhancers and the polymerase machinery, possibly thousands of base pairs apart, the DNA must bend to allow them to come into the range of the polymerase. Electron micrographs clearly show this DNA bending and looping.

Although RNA polymerases I and III seem to have termination signals similar to rho-independent promoters in prokaryotes, termination of transcription of RNA polymerase II genes is more complex, coupled with further processing of the mRNA.

Unlike prokaryotic RNA polymerases, eukaryotic RNA polymerases do proofread (showing 3' à 5' exonuclease activity). Also, eukaryotic DNA is complexed with histone proteins that can interfere with transcription. In turn, part of the RNA polymerase II complex is made up of proteins that can disrupt the histones bound to the DNA.

In addition, the RNA polymerase II complex contains proteins that act as mediators between activators and the polymerase holoenzyme. This complex coordination of the initiation of transcription in eukaryotes has been termed combinatorial control; the huge initiation complex may contain 85 or more different polypeptides. And transcription in the archaea — although under much simpler control than in the eukaryotes — resembles transcription in eukaryotes rather than prokaryotes.

The study of the details of the transcription process — its initiation, control and termination — is one of the most active and exciting areas in modern genetics.

Caps and tails

Eukaryotic transcription results in a primary transcript. In contrast to most prokaryotic transcripts that contain information from several genes, virtually all transcripts from higher eukaryotes contain the information from just one genie. (Transcripts from several genes are found in some lower eukaryotes, such as nematode worms.) Three major changes occur in primary transcripts of RNA polymerase II before transport into the cytoplasm — modifications to the 5' and 3' ends and removal of intervening sequences. We refer to these changes as post-transcriptional modifications.

At the 5' end of polymerase II transcripts, 7-methyl guanosine is added in the "wrong" direction, 5' à 5'. This cap allows the ribosome to recognise the beginning of a messenger RNA. At the other end, the 3' end of polymerase II transcripts, a sequence of 20 to 200 adenine-containing nucleotides, known as a poly-A tail, is added by the enzyme poly-A polymerase. Polyadenylation takes place after the 3' end of the transcript is removed by a nuclease that cuts about 20 nucleotides downstream from the signal 5'-AAUAAA-3'. The tail adds stability to the molecule and aids in its transportation from the nucleus.

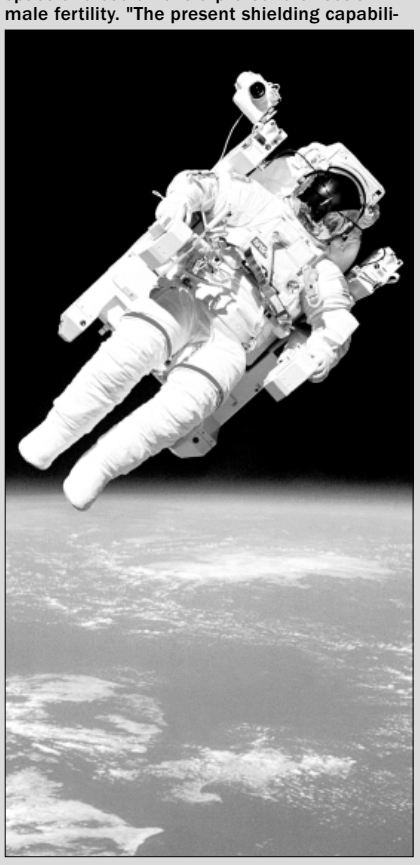
When messenger RNAs were first studied in eukaryotes, the messenger RNAs in the nucleus were found to be much larger than those in the cytoplasm and were called heterogeneous nuclear mRNAs, or hnRNAs. It now turns out that these were primary transcripts, RNAs that had not had any of the major post-transcriptional modifications. In essence, they were pre-messenger RNAs.

The writer is associate professor of botany, Anandamohan College, Kolkata

Why fertility will stop humans colonising in space

Space, it seems, is simply not a good place to have sex, reports jerome taylor

RENOWNED astrophysicist Stephen Hawking once remarked that humankind would need to colonise space within the next century if it was to survive as a species.
"It will be difficult enough to avoid disaster in the next 100 years, let alone the next thousand or million," he said somewhat pessimistically last year. "Our only chance of long-term survival is not to remain inward-looking on planet Earth, but to spread out into space."
The prospect of long-term space travel has led scientists to consider, increasingly seriously, the following conundrum: if travelling to a new home might take thousands of years, would humans be able to successfully procreate along the way? The early indications from Nasa are not encouraging. Space, it seems, is simply not a good place to have sex.
According to a review by three scientists looking into the feasibility of colonising Mars, astronauts would be well advised to avoid getting pregnant along the way because of the high levels of radiation that would bombard their bodies as they travelled through space. Without effective shielding on spaceships, high-energy proton particles would probably sterilise any female foetus conceived in deep space and could have a profound effect on male fertility. "The present shielding capabili-



ties would probably preclude having a pregnancy transited to Mars," said radiation biophysicist Tore Straume of Nasa's Ames Research Center in an essay for the Journal of Cosmology.
The DNA which guides the development of all the cells in the body is easily damaged by the kind of radiation that would assail astronauts as they journeyed through space. Studies on non-human primates have shown that exposure to ionising radiation kills egg cells in a female foetus during the second half of pregnancy. "One would have to be very protective of those cells during gestation, during pregnancy, to make sure that the female didn't become sterile so they could continue the colony," Dr Straume said.
Radiation in space comes from numerous sources but the two types that have Nasa scientists most concerned are solar flares and galactic cosmic rays. Flares are the result of huge explosions in the Sun's atmosphere that catapult highly charged protons across space. The Earth's atmosphere and magnetic field absorbs much of this harmful radiation - but in space astronauts are much more vulnerable. Galactic cosmic rays pose an even greater threat. They are made up of even heavier charged particles. Although Nasa's shields can protect astronauts against most flare radiation, it is unlikely they could do the same against cosmic rays. Until recently, sex had been a taboo subject for Nasa, which has a strict code of conduct stating that "relationships of trust" among astronauts are to be maintained at all times. Only once has a husband and wife been on the same mission ~ Jan Davis and Mark Lee ~ and they have remained tight-lipped over whether they joined the 62-mile high club.

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