Computing with molecules

From possible next-generation electronic devices to the detailed workings of living cells, molecules can process information in many different ways, as **Richard Jones** reports.

The idea of individual molecules acting as the basic elements of computers is a central strand in most visions of nanotechnology. The individual transistors in conventional integrated circuits are at the nanoscale already, of course, but they are made by processing multiple layers of semiconductors, metals and insulators in a top-down approach. What if one could make the transistors by joining together individual molecules from the bottom up? This idea, which goes by the name of molecular electronics, is an old idea that actually predates the widespread use of the term nanotechnology. The origin of this field can be traced back to 1973, and possibly earlier, and it has had a colourful history of big promises, together with waves of enthusiasm and disillusionment[1].

Molecular electronics, though, is not the only way of using molecules to compute, as biology shows us. In an influential review article published in 1995, Dennis Bray pointed out that the fundamental purpose of many proteins in cells seems to be more to process information than to effect chemical transformations or make materials[2]. Mechanisms such as allostery (in which the behaviour of an enzyme or protein can be regulated by a molecule binding to a site other than the active site) permit individual protein molecules to behave as individual logic gates; one or more regulatory molecules bind to the protein, and thereby turn on or off its ability to catalyse a reaction. If the product of that reaction itself regulates the activity of another protein, one can think of the result as an operation that converts an input signal conveyed by one molecule into an output conveyed by another — by linking together many such reactions into a network one builds a chemical 'circuit' that can, in effect, perform computational tasks. The classical example of such a network is the one underlying the ability of bacteria to swim towards food or away from toxins. In bacterial chemotaxis, information from sensors about many different chemical species in the environment is integrated to produce the signals that control the motors in bacteria, resulting in apparently purposeful behaviour.

The broader notion that much cellular activity can be thought of in terms of the processing of information by complex networks (such as those involved in gene regulation and cell signalling) has had a far-reaching impact in biology. The unravelling of these networks is the major concern of systems biology, whereas synthetic biology seeks to re-engineer them to make new products. The analogies between electronics and systems thinking and biological systems are made very explicit in much writing about synthetic biology[3], with its discussions of molecular network diagrams, engineered gene circuits and interchangeable modules.

But this alternative view of molecular computing has yet to make much impact in nanotechnology. Molecular logic gates have been demonstrated in several organic compounds[4], in which ingenious molecular design can allow several input signals, represented by the presence or absence of different ions or other species, to be logically combined to produce outputs represented by optical fluorescence signals at different wavelengths. In one approach, a molecule consists of a fluorescent group attached by a spacer unit to receptor groups; in the absence of bound species at the receptors, electron transfer from the receptor group to the fluorophore suppresses its fluorescence.

Other approaches use molecules called rotaxanes as 'shuttles': the molecular components in these shuttles are physically linked together, but they are still mobile, which means they can move to different positions in response to changes in their chemical environment. These molecular engineering approaches are leading to sensors of increasing sophistication. However, because the output is in the form of fluorescence rather than a molecule, it is not possible to link many such logic gates into a network.

At the moment, the most promising materials for the development of such networks are nucleic acids, particularly DNA. Like other branches of DNA nanotechnology, progress here is being driven by the growing ease and cheapness with which it is possible to synthesize specified sequences of DNA, and the relative ease with which molecular interactions based on the base-pair interaction can be designed and modelled. One recent demonstration uses this base-pair interaction to design logic gates based on DNA molecules[5]. These accept inputs in the form of short RNA strands, producing DNA strands as outputs according to the logical operations OR, AND or NOT. The output strands can themselves be used as inputs for further logical operations, and it is this that would make it possible in principle to develop complex information-processing networks.

So what might molecular computing be used for? The molecular electronics approach has a very definite target: to complement or replace conventional CMOS-based electronics, thus ensuring the continuation of Moore's law beyond the point at which physical limitations prevent any further miniaturization of silicon-based devices. The inclusion of molecular electronics in the latest *International Technology Roadmap for Semiconductors* indicates the seriousness of this challenge, and molecular electronics and other related approaches, such as graphene-based electronics, will undoubtedly continue to be pursued enthusiastically.

But these are probably not appropriate goals for molecular computing with chemical inputs and outputs, which is more likely to be used in applications that exploit its unique selling point — the ability to interface directly with the biochemical processes of the cell. It has been suggested, for example, that molecular logic could be used to control the actions of sophisticated drug-delivery devices. An even more powerful possibility is suggested by recent work in which an RNA construct controls the *in vivo* expression of a particular gene in response to this kind of molecular logic[6]. This suggests the creation of what could be called 'molecular cyborgs' as a result of synthetic molecular logic merging directly with the cell's own control systems.

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