Counting at the Nanoscale: Molecules performing Simple Logic Operations

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ABSTRACT

An overview of recent advances in the design and the characterization of nanosystems, able to perform simple logic operations in solution, is reported. Rather than a detailed and comprehensive update for the specialists, this brief review is intended to give the nonspecialists and the readers currently involved on all aspects of nanocomputing a flavor of the challenges and the opportunities presented by designing simple organic molecules or more complex biological systems operating as switches in response to an external stimuli, and, more importantly, operating as "wet" devices capable to perform simple logic operations and computations.

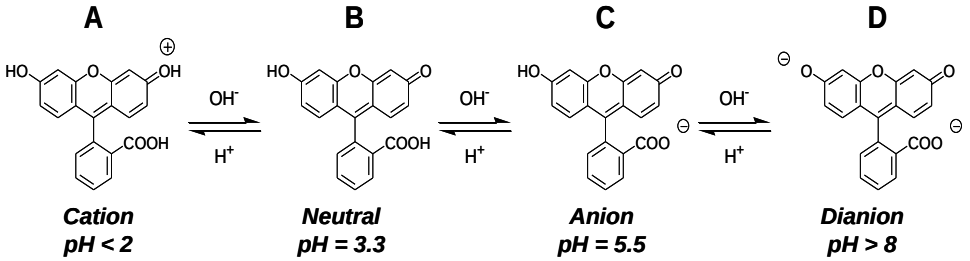
1. Introduction

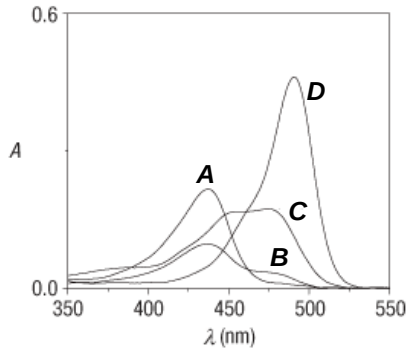
The discovery of a silicon-based switch - the transistor - in 1948 initiated the rapid development of different electronic devices able to perform computations. Although the demand for bigger memories and faster processors, requiring smaller and smaller transistors and other components, has been admirably satisfied by the microelectronic industry up to date, it is widely accepted by the scientific community that the integration scale of electronic components will soon reach its physical limit and further reduction will not be possible. As in some ways anticipated by Richard Feynman in his 60's highly cited speech "there's plenty of room at the bottom" (Drexler 1992), the possible extension of this limit will go through the development of single molecules and molecular systems capable of achieving data acquisition, storage, transfer and computing. Any chemical or biological system, which can exist in at least two different forms with different detectable properties and which can be turned on and off with some chemical or physical stimuli (light, redox potential, pH), can be viewed as a molecular switch. When it is possible to sense more than one different state in response to more than one switching stimuli the system can in

principle act as a molecular logic gate. As in electronic logic gates, the input and output signals have only two values: 0 (OFF, FALSE) or 1 (ON, TRUE), and the output signal is a Boolean function of input signals; as such, molecular logic gates have been shown to be able to perform the basic logic operations AND, NOT, and OR, as well as their combinations (Raymo 2002; Credi 2007). In the following sections, selected recent examples of nanosystems behaving as molecular logic gates, whose chemical structure can be very simple (such as in chemical systems) or in the form of more complex biopolymers, will be briefly reviewed.

2. Chemical Systems

Since the report of small organic molecules behaving as the AND logic gate (de Silva 1993), a series of other Boolean functions have been demonstrated to be processed on the molecular scale, and synthetic molecular species have been proved capable to execute algebraic operations, such as additions and subtractions. Shanzer et al. have recently reported a very simple molecular species capable of addition and subtraction operations (Margulies 2005). The system can be chemically reset after each computation (Figure 1).





Input		Output	
a: OH^-	b: OH^-	447 nm: XOR Sum	501 nm: AND Carry
0	0	0 (low, 0.073)	0 (low, 0.006)
0	1	1 (high, 0.158)	0 (low, 0.048)
1	0	1 (high, 0.158)	0 (low, 0.048)
1	1	0 (low, 0.084)	1 (high, 0.319)

Figure 1. A four-state molecular switch operating as an half-adder.

The molecule used is fluorescein, probably the most common fluorescent probe in the biosciences; it exists, at varying pH, in different forms (cation A, neutral B, anion C, and dianion D), possessing distinct spectral properties (Figure 1, bottom left). Each form can be easily obtained by addition of the appropriate amount of

strong acid (HCl) or base (NaOH), and each step can be reversed by addition of the complimentary acid or base. As such, the system is a fully reversible, four state molecular switch. The signal transduction is determined by the measured absorbance at a certain wavelength, which depends on the state (A, B, C or D) the switch is at. A positive logic convention is applied to all inputs (no addition = 0, addition = 1) and outputs (low absorbance = 0, high absorbance = 1, as defined by a common threshold). Once the system is set on the fluorescein neutral form B, it is ready to operate without further modifications; the system is able to perform both as a half-adder and a half-subtractor. The table in Figure 1 illustrates the principle of the half-adder. The molecule signals the algebraic operation of the addition of two inputs, in the form of two identical sodium hydroxide solutions, by means of two outputs, that is the monitoring the absorbance at 447 and 501 nm. The solutions (0.013 M NaOH) are calibrated in such a way that, for example, when both inputs are added the switch adopts a certain state which correspond to a high absorbance at a certain wavelength. The algebraic operation gives, using the binary code, two digits: the sum digit is the result of an XOR logic gate (447 nm), whereas the carry digit is the result of an AND logic gate (501 nm). As an example, we follow the case of both inputs are 1 (both solutions of NaOH are added), entry 4 in the table. The result is 10 (which is 2 using the binary code), obtained by reading the absorbances at 447 nm (low) and 501 nm (high). A simple fluorescein dye can therefore function to encode numbers and reset, just by using only two chemical species (acid, used for reset, or for the half-subtractor in a related way, and base).

3. Biological systems

Nucleic acids (DNA and RNA) have proven to be highly useful building blocks for the construction of molecular logic gates and computational devices (Gianneschi 2007). Artificially designed DNA or RNA sequences can fold into well-ordered, three-dimensional structures that can recognize corresponding ligands or catalyze specific chemical reactions. In the case of RNA-cleaving deoxyribozymes, the corresponding substrates must be either RNA or chimeric DNA (an oligodeoxynucleotide containing at least one ribonucleotide base). This prerequisite leads to high synthesis costs and stability issues, thus is desirable to develop ribonucleotide-free molecular logic gates. Zhan, Fan, He and coworkers (Chen 2006) have recently reported molecular logic gates by using Cu^{2+}-dependent DNA-cleaving deoxyribozymes as the building blocks. These robust molecular logic gates are based on inexpensive, chemically stable DNA oligonucleotides.

In figure 2A the general structure of the deoxyribozymes and substrates used in the study are shown; adaptations of these basic structures, in the form of commercially available DNA sequences as the substrates and of DNAzymes of various forms, also commercially available, allowed the demonstration of their

applicability as an AND logic gate, a NOT logic gate and a complex logic gate made of their combination. The signal transduction is based on the catalytic activity of DNAzymes towards specific substrates, which are also short DNA sequences; in particular, these enzymes are able to cleave specific sequences in the presence of catalytic Cu^{2+} via a mechanism involving the generation of hydroxyl radicals through metal-ion mediated redox reactions, creating oxidative DNA modifications, and subsequent substrate fragmentation and release. These catalyzed reactions could be conveniently monitored by fluorescence detection of the released substrate fragment, which contains a fluorescent dye (FD, in red, figure 2A).

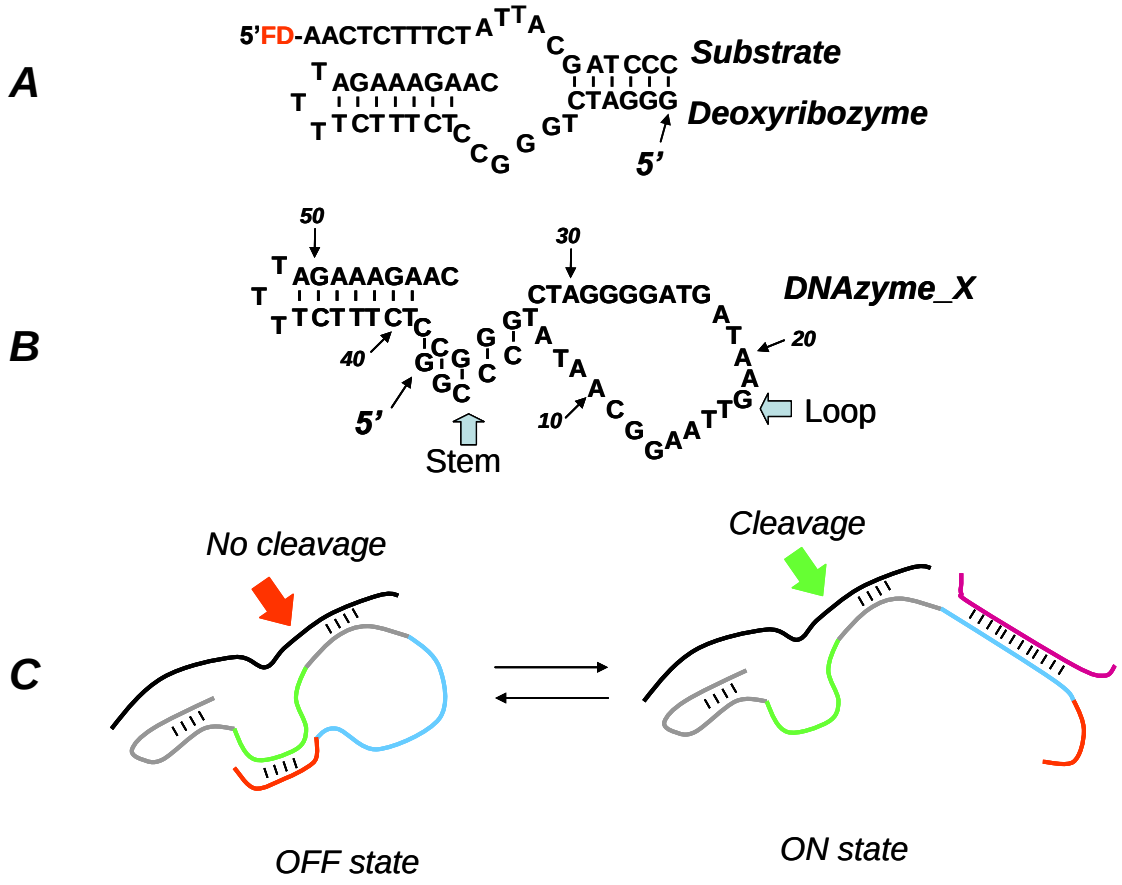


Figure 2. Molecular Logic Gates with a DNA-cleaving Deoxyribozyme.

An "AND" logic gate could be demonstrated by using DNAzyme_X, in which two modules are appended sequentially to the 5' end of the deoxyribozyme (figure 2B). The modules have different purposes: the proximal module function as a flexible loop (loop in Figure 2B, light blue in 2C), whereas the distal module is complementary to the catalytic core of the enzyme (stem in Figure 2B, red in 2C). The latter module interferes with the active enzyme site (green in 2C) and therefore inhibits its catalytic ability to cleave the substrate. The system is therefore in the OFF state (Figure 2C). In the presence of an effector (purple

segment in figure 2C), which is also a DNA fragment with a sequence complementary to the loop, a structural perturbation occurs, and the stem is no longer able to bind the active site, thus completely reactivating the enzyme catalytic activity towards the substrate. The Boolean logic is respected since only when *both* inputs are added (DNAzyme_X and the effector), the output is 1 (i.e. kinetics for substrate cleavage are high), with an ON/OFF ratio factor of about 10:1. These robust molecular logic gates, entirely based on DNA fragments, could be the basis of computing devices that are essentially free of RNA, which is more susceptible to oligonucleotide degradation.

The research described above is certainly an useful and clarifying example of the flurry of research activity dealing with biochemical logic gates. It is worth mentioning, however, that Stojanovic, Macdonald and coworkers, following a strategy similar, in its conception, to that just described, have previously reported the assembly of molecular automata performing complex tasks. Their second-generation deoxyribozyme-based automaton, MAYA-II, was shown to be able to play games according to a well-defined strategy. The system integrates 128 deoxyribozyme-based logic gates, 32 input DNA molecules, and 8 two-channel fluorescent outputs (Macdonald 2006). DNA computing has been successfully utilized to solve complex algebraic problems, such as a 20-variable instance of a three-satisfiability problem, using (excluding input and output) DNA pairing and melting as the sole chemical operations (Braich 2002).

4. Conclusions

Elegant strategies to execute logic operations, based either on chemical or biochemical systems, have emerged in the last decade, as a consequence of the interest for unconventional answers to the fabrication of the new generation of faster computers and communication devices. Optical, electrical or chemical stimuli have all been transduced into output signals through a controlled manipulation of the molecular components. One of the main challenges of the nanocomputing era (Shukla 2004) remains, however, the incorporation of these functional molecules in solid-state devices. Robust computing system design is confronted with quantum physical and probabilistic phenomena, and guaranteeing high reliability is a very complicated task. Recent striking examples in molecular electronics, however, have proven how switching molecules can be assembled in operating, functional and competitive memory devices, by using the combination of ingenious molecular machines and defect-tolerant hardware architectures (Green 2007).

The complexity of the most powerful computer ever made, a "wet" biological device (i.e. the human brain), is still clearly unreachable. The practical applications of the massive parallel integration achieved in biological systems are more likely to be found at the present stage in oligonucleotide analysis and sensing rather than in competition with silicon computing; novel enzyme therapeutics could be in

principle envisaged in which enzyme activation can be "logically" programmed to take place in response to a set of biological inputs. Complex computational problems, such as hypercomputation, often defined as transcending Turing machines in being able to process a larger class of functions, are likely to be addressed more vigorously in the near future with chemical/biochemical systems (Calude 2001).

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